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Original Research Paper

Respiratory Medicine

EVALUATION OF FIRST LINE ANTI-TUBERCULAR THERAPY INDUCED ADVERSE DRUG REACTIONS

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ABSTRACT Standard anti-TB treatment (ATT) is highly effective and one of the great challenges for ATT success is management of TB drugs toxicity. This toxicity is manifested through adverse drug reactions (ADR)[4]. NTEP, the then RNTCP had adopted thrice weekly regimen for treatment of drug sensitive TB until the year 2016. Various research studies have shown that relapse rates were higher with intermittent regimen. Hence the programme has now shifted to daily regimen for treatment of all drug sensitive TB patients. The adverse drug reactions with daily regimen may be higher compared to intermittent regimen, therefore, it is necessary to clinically monitor the patients on treatment. **Objectives:** To estimate the proportion of ADR among patients receiving first line antitubercular drugs in Respiratory Medicine department of AGMC and also to determine the factors associated with ADR in different phases of DOTS therapy. **Methodology:** Cross-sectional study hospital-based observational study and was conducted for a period of 18 months from Jan 2022 to June 2024 at AGMC & GB Pant Hospital in the department of Respiratory Medicine, among newly diagnosed drug sensitive tuberculosis patients of both pulmonary and extra-pulmonary registered for first-line ATT during the study period **Results:** In the present study, 105 tuberculosis patients were included. There were 81 male and 24 female patients. Out of total 105 cases diagnosed with Tuberculosis, 60 cases (57.1%) developed ADR and 45 cases (42.8%) did not develop any ADR to First line ATT. It was found that majority of the patients suffered from Liver dysfunction (55%) followed by Gastrointestinal symptoms (20%), Fever (11.67%), Neurological symptoms (6.67%), generalised weakness and allergic drug reactions (3.33% each). **Conclusion:** A majority of these ADRs occurred during the intensive phase of treatment. Significant risk factors for developing adverse reactions to antitubercular drugs include male sex, malnutrition, alcohol consumption, cigarette smoking, co-morbidities and having pulmonary tuberculosis. Therefore, healthcare providers treating tuberculosis must identify these vulnerable patient groups to prevent, diagnose, and manage these ADRs. By doing so, patients can adhere to treatment and achieve higher cure rates.

KEYWORDS : RNTCP (Revised National Tuberculosis Control Program), NTEP (National tuberculosis eradication program), Firstline Anti-tubercular Therapy, Adverse Drug Reaction.

INTRODUCTION:

Tuberculosis (TB) is an airborne infectious disease caused predominantly by Mycobacterium tuberculosis species of pathogenic bacteria, first discovered in 1882 by Robert Koch. TB is caused by one of several mycobacterial species that belong to the Mycobacterium tuberculosis complex. Patients suffering from Microbiologically confirmed pulmonary TB (PTB) constitutes the most important source of infection. The infection occurs most commonly through droplet nuclei generated by coughing, sneezing etc., inhaled via the respiratory route. Drug treatment is fundamental for controlling TB, promoting the cure of the patient and breaking the chain of transmission when the anti-tubercular drug regimen is completely and correctly followed[2]. Adverse reactions to these agents are common and cause significant morbidity and even sometimes mortality if not detected early[3]. The National Tuberculosis Control Programme (NTP) of India was initiated in 1962. A comprehensive review of the NTP in 1992 found that the NTP had not achieved its aims or targets. Based on the recommendations of the 1992 review, the Revised National Tuberculosis Control Programme (RNTCP), incorporating the components of the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy for the control of TB, was developed with nationwide coverage in March 2006. India accounts for more than one fourth of the global TB burden i.e. 27 lakhs out of 1 crore new cases annually. In India, more than 40% of population is infected (prevalence of infection) with Mycobacterium tuberculosis. Standard anti-TB treatment (ATT) is highly effective and one of the great challenges for ATT success is management of TB drugs toxicity. This toxicity is manifested through adverse drug reactions (ADR)[4]. The NTEP had adopted thrice weekly regimen for treatment of drug sensitive TB until the year 2016. Various research studies have shown that relapse rates were higher with intermittent regimen. Hence the programme has now shifted to daily regimen for treatment of all drug sensitive TB patients. The adverse drug reactions with daily regimen may be higher compared to intermittent regimen, therefore, it is necessary to clinically monitor the patients on treatment. Treatment is given in two phases: Intensive phase (IP) consists of 8 weeks (56 doses) of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given under direct observation in daily dosages as per weight band categories and continuation phase (CP), consists of 16 weeks (112 doses) of isoniazid, rifampicin and ethambutol in daily dosages. Only pyrazinamide will be stopped in the continuation phase. The CP may be extended by 12-24 weeks in certain forms of TB like CNS TB, Skeletal TB, Disseminated TB etc. based on clinical decision of the treating physician on case-to-case basis. Rather than concentrating only on the treatment, the adverse effects of the drugs should also be looked upon for achieving better patient compliance. Identifying the drugs causing ADRs is an important responsibility of the medical professionals and could help in educating patient along with preventing the occurrence of similar ADRs in future. It is essential for the medical professionals to educate the patients regarding the early identification of ADRs in the first few weeks. Identification of the ADR profile of drugs is considered useful for the prevention, early detection and treatment of ADRs. Hence there is a need to study the safety profile of patients on DOTS through monitoring of ADRs in a clinical set up.

AIMS & OBJECTIVES.

1. To estimate the proportion of ADR among patients receiving first line antitubercular drugs in Respiratory Medicine department of AGMC.
2. To determine the factors associated with ADR in different

phases of DOTS therapy.

MATERIALS & METHODS.

The present study was a Cross-sectional Hospital based observational Study carried out in Respiratory Medicine department, AGMC & GB Pant Hospital, Agartala, Tripura foe a period one and half years. The study included all newly diagnosed drug sensitive tuberculosis patients registered for first-line ATT during the study period.

Sample Size:

As per admission register and OPD register, in the year 2018,2019 & 2020. 97, 107 & 111 new TB cases were diagnosed respectively. So, on an average 105 new drug sensitive TB cases were diagnosed per year, accordingly sample size was decided as 105.

Sampling Technique: Census sampling technique.

Inclusion Criteria:

1. All newly diagnosed cases of TB (PTB & EPTB) during my study period admitted in the chest ward or attending OPD with first-line ATT at AGMC & GBPH.

Exclusion Criteria:

1. Patients who did not give valid consent.
2. Drug resistant Tuberculosis patients.

Study Tools:

1. A pre-designed case record proforma was used to collect relevant information, medical history, clinical features, demographic data, for each individual patient
2. ADR reporting form.

METHOD OF DATA COLLECTION:

All newly diagnosed cases of tuberculosis (PTB & EPTB) admitted in the chest ward or attending OPD and under ATT with the first line anti-tubercular drugs were included in this study and these patients were subjected to detailed clinical evaluation and blood investigation including viral markers for HIV and hepatitis virus for baseline and diagnosis of any co-morbid conditions and also Chest X ray of these patients done routinely. Past history of tuberculosis and anti-tubercular treatment was recorded. All details of every individual case selected were registered and analysed at the end and the final conclusion was made thereafter. All patients were followed-up till the complete duration of treatment with first-line ATT as per treatment guidelines under NTEP. Patients recruited for 1 year till 31.12.2023, as all patients were followed up till completion of treatment for 6 months. ADRs were defined and categorized as per the definition of Edwards & Aronson - "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" and also WHO's definition of an adverse drug reaction: - "A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [22] and a rescue treatment arranged for treating the patients presenting with ADR either on OPD basis or patients were admitted in Respiratory Medicine ward if required for which a conservative and symptomatic management was provided or admitting and stopping of the offending drug.

Detailed information about ADR were recorded as per the standard operative procedure of Indian pharmacopeia commission on suspected ADR reporting form 1.4 version and this information was sent to ADR monitoring centre of AGMC for causality assessment. The data were collected and analysed.

The suspected ADRs were classified in terms of causality using WHO-UMC

RESULTS:

In the present study, 105 cases suffering from any form of Tuberculosis were studied. The results and observations are as given below.

Table 1: Gender- Wise Distribution Of Cases

Gender	Frequency	Percent
M	81	77.0
F	24	23.0
Total	105	

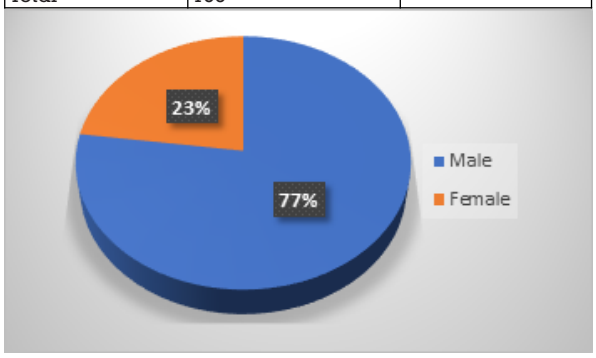

Figure 1: Gender- wise distribution of cases

Table 1 and Figure 1 show that the males outnumbered the females in the present study.

Table 2: Age Wise Distribution Of Cases:

Age group	Male N (%)	Female N (%)	Total
≤20	3 (2.85)	1 (0.95)	04
21-30	5 (4.76)	6 (5.71)	11
31-40	12 (11.43)	4 (3.81)	16
41-50	19 (18.0)	4 (3.81)	23
51-60	22 (20.95)	5 (4.76)	27
61-70	18 (17.14)	3 (2.86)	21
>70	3 (2.86)	0	3

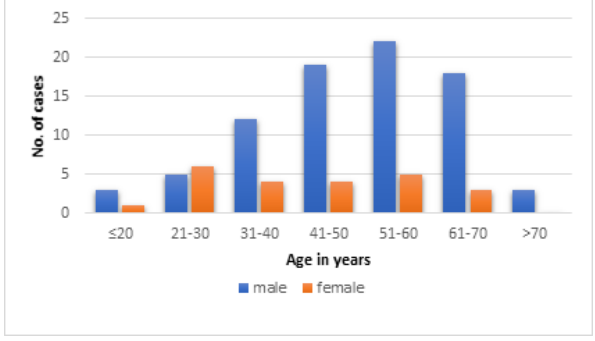

Figure 2: Age Wise Distribution Of Cases

It is evident from Table-2 and Figure-2 that the majority of Study (27) cases occurred in the Age Group of 51-60 years followed by in the age group of 41-50 years (23), in the Age group of 61-70 years (21), in the age group of 31-40 years (16), ≤20 years (04), >70 years (03).

Table-3: Mean Age ± SD in cases

Number of patients	Age (mean ± SD)
105	49.26 ± 14.84

Table-3 shows that the mean age in years(±SD) in cases is 49.26 ± 14.84

Table-4: Distribution Of Cases According To Weight

Weight in Kg	Number of cases (n)	%
≤50	85	80.95

>50	20	19.05

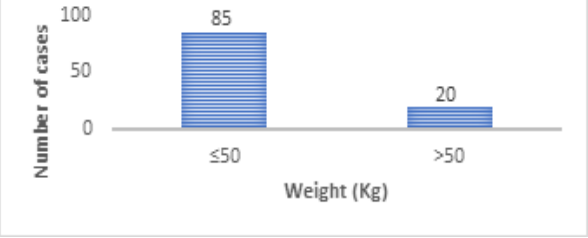

Figure-3: Distribution Of Cases According To Weight

Table-3 Shows That The Mean Age In Years(±SD) In Cases Is 49.26 ± 14.84

Table-5: Mean Weight (± SD kg) Among The Cases

Number of cases	Minimum	Maximum	Mean	SD
105	30.0	65.0	43.943	7.6156

Table-5 shows that Mean Weight (±SD kg) among the cases was 43.943(±7.6156 kg)

Table-6: Mean weight (±SD) among the different genders

Gender	Mean (±SD)	P-value
Male	44.61 ± 9.14	<0.001
Female	44.60 ± 6.55	

Table-6 shows that the mean weight (±SD kg) of the male cases was 44.61 ± 9.14 and the females was 44.60 ± 6.55 and the difference between these two genders was statistically significant.

Table: Distribution According Anatomical Site Involvement (PTB/EPTB)

	Frequency	Percent
EPTB	17	16.2
PTB	88	83.8
Total	105	100.0

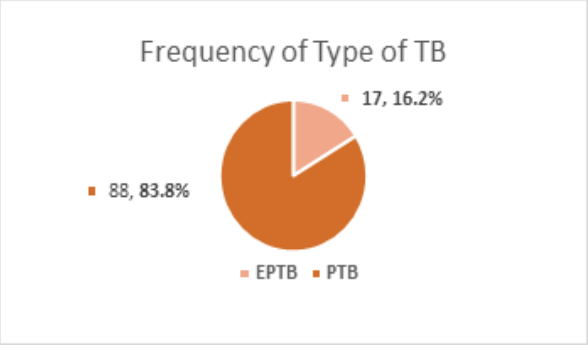

Figure: Distribution According Anatomical Site Involvement (PTB/EPTB)

Table- and Figure- shows that 83.8% cases were diagnosed as PTB and 16.2% were diagnosed as EPTB

Table-: Distribution Of Cases Presenting With And Without Adverse Drug Reactions Following First-line ATT

	Frequency	Percent
Absent	62	59.05
Present	43	40.95

The present study shows out of total 105 cases diagnosed with Tuberculosis, 43 cases (40.95%) developed ADR and 62 cases (59.05%) did not develop any ADR to First line ATT.

Majority of the patients suffered from Liver dysfunction (42%) followed by Gastrointestinal symptoms (28%), Fever (11.6%), Neurological symptoms (9.3%), generalised weakness and allergic drug reactions (4.7% each). In the present study, 59.05% did not experience any adverse drug reactions.

Table-: Distribution Of Adverse Drug Reactions

Type	Number of patients	Frequency %
Gastrointestinal (Anorexia/ Vomiting/Nausea/Burning epigastrium)	12	28%
Generalized weakness	02	4.7%
Liver disfunction	18	42%
Allergic drug reactions	02	4.7%
Neurological	04	9.3%
Fever	05	11.6%

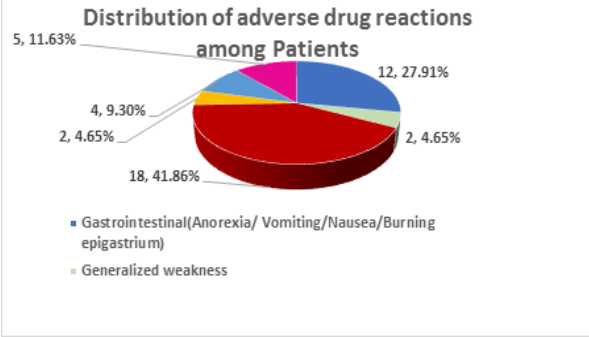

Figure-: Distribution Of Adverse Drug Reactions Among Patients

Table -: Association Of Adverse Drug Reactions With Age

Age group	Number of cases			*P*-value
	Total	Developed ADR	Not Developed ADR	
≤20	04	0	04	>0.05
21-30	11	02	09	
31-40	16	06	10	
41-50	23	11	12	
51-60	27	10	17	
61-70	21	13	08	
>70	03	01	02	

The present study shows that maximum number of ADRs were reported in cases that belong to the age group of 51-60 years (17 cases), followed by 41-50 years (12 cases), 31-40 years (10 cases), 21-30 years, ≤ 20 years, > 70 years. The adverse drug reactions, when compared with the different age groups was not statistically significant (P>0.05).

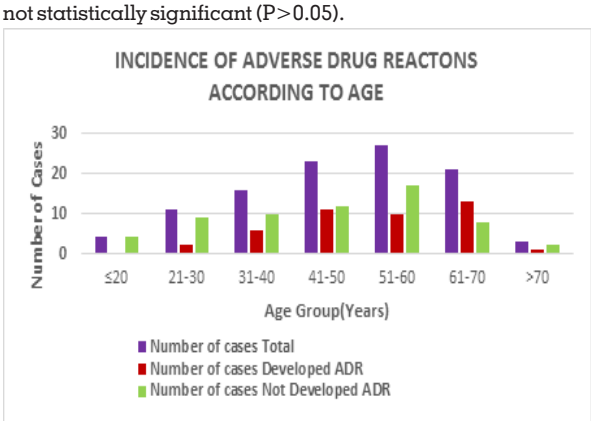

Figure -: Association Of Adverse Drug Reactions With Age

Table-: Incidence Pattern Distribution Based On Gender Of Patients

ADR	Male	Female
Present	35 (33.3%)	08 (33.3%)
Absent	46 (66.7%)	16 (66.7%)
Total	81	24

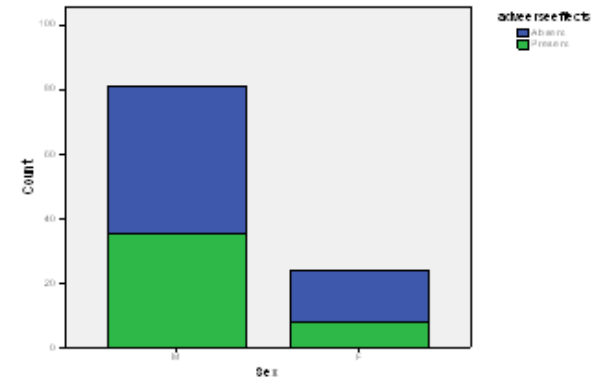

Figure-: Incidence Pattern Distribution Based On Gender Of Patients

The present study shows that incidence of ADR is equal in both the sexes.

Table-: Incidence Pattern Of ADRs In Different Sites Of The Diseases

ADR	Extrapulmonary	Pulmonary	Total
Present	05 (29.4%)	38 (43.2%)	43 (41%)
Absent	12 (70.6%)	50 (56.8%)	62 (59%)
Total	17(100%)	88 (100%)	105

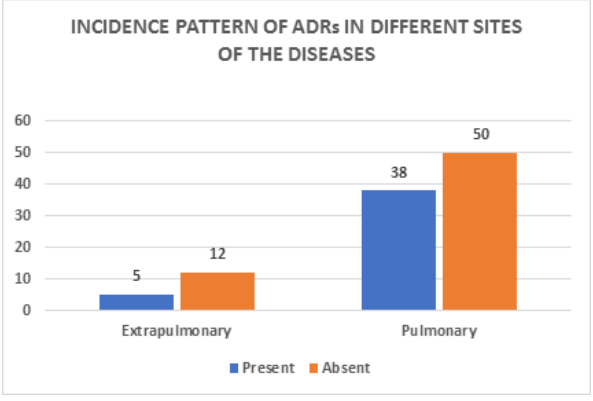

Figure-: Incidence pattern of ADRs in different sites of the Diseases

Table-: Association Of Type Of TB And Adverse Effects

Type of TB	Number of patients	Adverse effects	*p* value
PTB	88	36	
EPTB	17	5	0.001

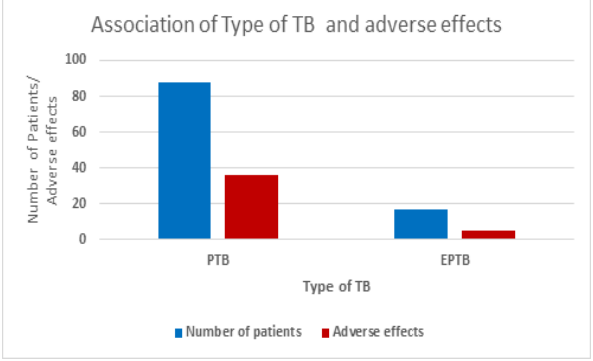

Figure- : Association of Type of TB and adverse effects

The present study shows that 36 patients out of total 88 PTB cases and 5 patients out of total 17 of EPTB cases developed ADR to First-line ATT drugs. The association of type of TB and development of ADR to First-line ATT was found to be statistically significant (p=0.001).

Table-: Distribution Of Patients Who Consume Smoking

Number of cases	Frequency of smokers	%
105	73	69.52

Table-: Association Of Smoking And Adverse Effects

Total number of patients	Number of patients who smoke	Adverse effects	*p* value
105	73	46	0.005

In the present study 73 cases (69.52 %) out of total 105 cases diagnosed with TB are found to be smokers and 46 cases among 73 cases developed ADR. Association of smoking and adverse effects was statistically significant in this study (P=0.005).

Table-: Distribution Of Patients Who Consume Alcohol

Number of cases	Frequency of alcoholic patients	%
105	17	16.19

Table-: Association Of Alcohol Intake And Adverse Effects

Total number of patients	Number of patients consuming alcohol	Adverse effects	*p* value
105	17	11	0.006

In the present study 17 cases (16.19 %) out of total 105 cases diagnosed with TB were found to be alcoholics and 11cases among 17 cases developed ADR. Association of alcohol intake and adverse effects was statistically significant in this study (P=0.006).

Table-: Mean ± SD Of Serum Bilirubin Among Cases

	N	Mean	SD
Bilirubin	105	0.4778	.65946

Table-: Abnormal mean ±SD Of Serum Bilirubin

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	13 (12.38%)	1.86 ± 1.07

Table-: Total Mean ± SD (U/L) of Serum Alkaline Phosphatase (SALP) among cases.

	N	Mean	SD
S.ALP	105	160.8952	117.86579

Table-: Abnormal mean ± SD of Serum Alkaline Phosphatase (SALP) among cases.

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	09 (8.57 %)	447.67 ± 177.35

Table-: Total mean ± SD (Units) of SGOT among cases

	N	Mean	SD
SGOT	105	58.4286	73.02527

Table-: Abnormal mean ± SD (Units) of SGOT among cases

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	35 (33.33 %)	122.20 ± 99.59

Table-: Total mean ± SD (Units) of SGPT among cases

	N	Mean	SD
SGPT	105	44.4952	51.30192

Table-: Abnormal mean ± SD (Units) of SGPT among cases

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	44 (41.9 %)	78.11 ± 65.80

Table-: Total mean ± SD (mg %) of Serum Urea among cases

	N	Mean	SD
Urea	105	31.0924	20.36631

Table-: Abnormal mean ±SD (mg %) of Serum Urea among cases

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	12 (11.43%)	74.17 ± 34.0

Abnormal mean ±SD of serum creatinine

Total number of cases	Total number of abnormal cases (%)	mean ± SD
105	07 (6.7%)	2.9 ± 1.0

Table-: Total mean ± SD (mg) of Serum Uric acid among cases

	N	Mean	SD
Uric acid	105	5.3276	1.26571

Table-: Abnormal Levels Of Serum Uric Acid

Total number of cases	Total number of abnormal cases (%)
105	01 (0.95%)

Table-: Distribution Of Adverse Effects According To Associated Diseases

Associated diseases	Number of cases (%)	Number of adverse effects	%
Diabetes mellitus	22	15	68.18
HTN	07	04	57.14
HIV	04	01	25
Thyroid disorders	05	02	40
HBsÄg +ve	02	02	100
CKD	06	05	83.33
Ca Lung	01	01	100
COPD	01	01	100

The present study shows out of total 105 cases diagnosed with Tuberculosis, 43 cases (40.95%) developed ADR and 62 cases (59.05%) did not develop any ADR to First line ATT.

Table 1: Gender- Wise Distribution Of Cases

Gender	Frequency	Percent
Male	81	77.0%
Female	24	23.0%
Total	105	100%

DISCUSSION:

In the present study, 105 tuberculosis patients were included. There were 81 male and 24 female patients. Out of total 105 cases diagnosed with Tuberculosis, 60 cases (57.1%) developed ADR and 45 cases (42.8%) did not develop any ADR to First line ATT. This study found that highest percentage of antituberculosis treatment induced adverse effects were observed in the age group of 51-60 years. Majority of male cases are suffering from adverse drug reactions (83.33%, n=50) when compared to female cases (16.66%, n=10). Majority of the patients suffered from Liver dysfunction (55%) followed by Gastrointestinal symptoms (20%), Fever (11.67%), Neurological symptoms (6.67%), generalised weakness and allergic drug reactions (3.33% each). A majority of these ADRs occurred during the intensive phase of treatment. Significant risk factors for developing adverse reactions to antitubercular drugs include male sex, malnutrition, alcohol consumption, cigarette smoking, co-morbidities and having pulmonary tuberculosis.

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