

Original article:

Adverse Drug Reactions in patients with first line Anti-Tuberculosis

Treatment

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ABSTRACT

Objective: To study adverse drug reactions in patients of tuberculosis started on first line anti-tuberculosis drugs at Dehuroad Cantonment Hospital, Pune.

Results: Of 89 cases receiving directly observed anti-tuberculosis treatment with mean age 34.3 ± 13.8 years. Of 89 cases studied, 60 (67.4%) did not have any adverse effects, while 29 (32.6%) presented with adverse drug reactions; 10 (11.2%) had hyperuricemia, 7 (7.9%) had gastritis, 3 (3.4%) had Gastritis with hyperuricemia, 3 (3.4%) had Drug induced hepatitis, 3 (3.4%) had skin rash, 1 (1.1%) had neuritis, 1 (1.1%) had ototoxicity and 1 (1.1%) had thrombocytopenia in the study group. More number of females (45.7%, n=89, females=46) presented with adverse drug reactions compared to male (18.6%, n=89, males=43).

Conclusion: It is very important to closely observe all patients started on anti-tuberculosis treatment for adverse drug reactions and interfere with these to avoid non-adherence to treatment.

Key words: Tuberculosis, Primary Anti-TB drugs, Adverse drug reactions

INTRODUCTION:

Tuberculosis continues to be a major cause of morbidity and mortality worldwide. It is a mycobacterium disease, treatable with anti-tubercular therapy (ATT), commonly used drugs are, Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as first line drugs¹. Injectable Streptomycin is used for primary drug sensitive relapse, failure and default cases of TB. Isoniazid, Rifampicin and Pyrazinamide are essential components, cost effective of DOTS strategy to break the chain of transmission in tuberculosis, endorsed by world health organization (WHO)². All these drugs used in combination for minimum 6 months. Currently available first line anti-tuberculosis drugs are effective against active and latent tuberculosis but have side effects of cognizance as these lead to treatment default³.

Insignificant side effects such as orange discoloration of urine from Rifampicin as well as symptoms of potentially serious side effects are known. Common adverse effects or side of these drugs are; Isoniazid causes peripheral neuropathy and hepatotoxicity (elevated serum transaminases and serum bilirubin), Rifampicin causes immune-allergic reactions and hepatotoxicity (elevated serum transaminases, alkaline phosphates and serum bilirubin). Immune thrombocytopenia is a rare side effect of Rifampicin. Drug induced immune thrombocytopenia (DTTP) is caused by drug dependent and antibody mediated platelet destruction. To confirm DTTP, the patient's serum is analyzed for drug-dependent platelet antibodies with immunofluorescence by flow cytometry⁴.

Pyrazinamide and Ethambutol are two anti-tuberculosis drugs reported to induce hyperuricemia causing joint pain, swelling and renal failure in severe cases. (Increased serum uric acid more than 6.8 mg/dl) and hepatotoxicity (elevated serum transaminases and serum bilirubin), Pyrazinamide is strong agent causing urate retention. Ethambutol can cause blindness. Streptomycin can cause adverse effects of ototoxicity, gluteal abscess.

MATERIALS AND METHODS:

This is an observational study done in patients receiving anti-tuberculosis treatment. Study was done at Dehuroad Cantonment Board Hospital, Pune, Maharashtra, India. Diagnosis of Tuberculosis was done based on the World Health Organization definitions⁵. Patients with confirmed diagnosis of tuberculosis started on anti-tuberculosis treatment from April 2017-April 2018 were studied prospectively. All newly diagnosed Tuberculosis patients and drug sensitive relapse, failure and default patients were started on RNTCP DOTS category I and II regimen respectively. Patients started on ATT screened for baseline measurements of hepatic enzymes, bilirubin, serum creatinine and blood urea nitrogen, complete blood cell count including platelet count, serum uric acid, and vision test. These cases enrolled in study with informed consent. Counseling was done regarding side effects of anti-tuberculosis drugs-epigastric burning sensation, nausea, vomiting, skin rashes, joint pain, decreased vision, burning pain of soles, orange discoloration of urine. . Follow up assessments were done at 2, 4, 8 and 24 weeks regularly. Patients were informed to report immediately for any symptom, at any time other than scheduled follow up visits. During the treatment duration patients with symptoms pertaining to adverse drug reactions were recorded, investigated and treated.

Patients with abnormal baseline screening reports, alcoholic liver disease, neuropathy, and nephropathy were excluded from study.

Statistical Methods:

The data on categorical variables is shown as n (% of cases). Being an observational non-comparative study, we did not compare the distributions of several categorical variables studied statistically. The entire data was entered and cleaned in MS Excel before its statistical analysis. All results are shown in tabular as well as graphical format to visualize the frequency distributions of variables studied more clearly.

The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS version 21.0, IBM Corporation, USA) for MS Windows.

RESULTS

Total 89 diagnosed patients of Tuberculosis were included in study.

Distribution of mean \pm SD of age of cases studied was 34.3 ± 13.8 years with minimum – maximum age range 12 – 71 years.

Table 1) Age distribution of cases studied.

Age Group (years)	No. of cases	% of cases
11 – 20	12	13.5
21 – 30	33	37.1
31 – 40	22	24.7
41 – 50	7	7.9
51 – 60	10	11.2
>60	5	5.6
Total	89	100.0

Of 89 cases studied, 12 (13.5%) had age between 11 – 20 years, 33 (37.1%) had age between 21 – 30 years, 22 (24.7%) had age between 31 – 40 years, 7 (7.9%) had age between 41 – 50 years, 10 (11.2%) had age between 51 – 60 years, 5 (5.6%) had age more than 60 years.

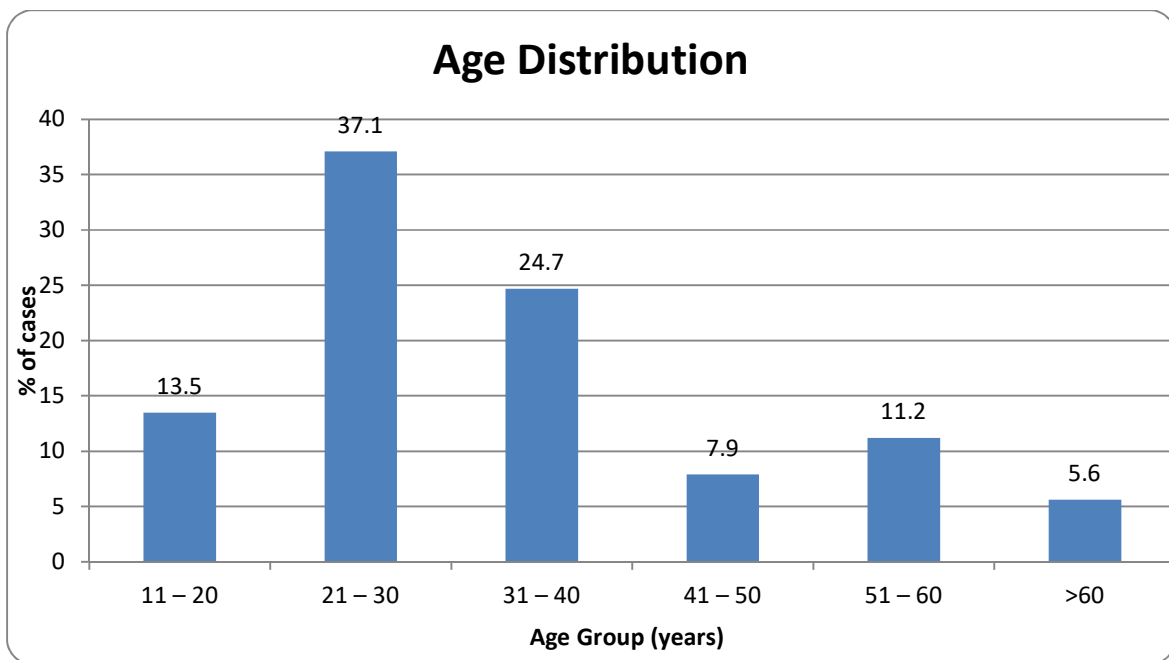


Figure 1) Age distribution of cases studied.

Table 2) Sex distribution of cases studied.

Sex	No. of cases	% of cases
Male	43	48.3
Female	46	51.7
Total	89	100.0

Of 89 cases studied, 43 (48.3%) were males and 46 (51.7%) were females. Male to female sex ratio was 0.93:1.00.

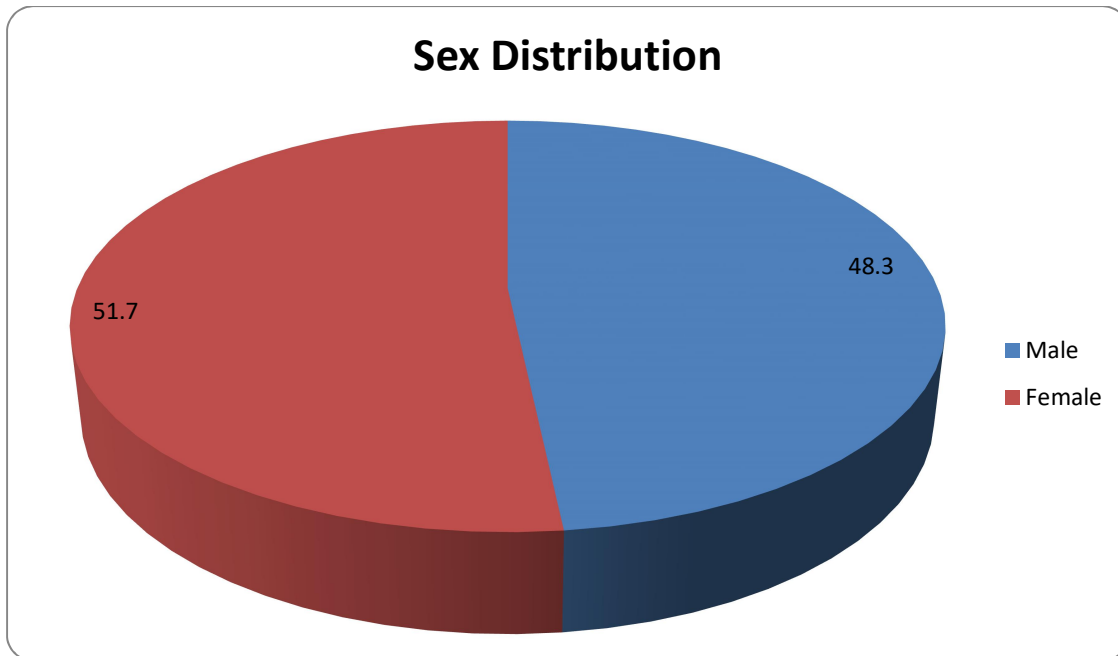


Figure 2) Sex distribution of cases studied.

Table 3) Distribution of symptoms after ATT among the cases studied.

Symptoms	No. of cases	% of cases
Nil	58	65.2
Joint pain (Arthralgia)	14	15.7
Nausea, vomiting	10	11.2
Itching, Rash	3	3.4
Other	4	4.4
Total	89	100.0

Of 89 cases studied, 58 (65.2%) did not have any symptoms, 14 (15.7%) had arthralgia, 10 (11.2%) had nausea and vomiting, 3 (3.4%) had itching, 4 (4.4%) had other symptoms in the study group.

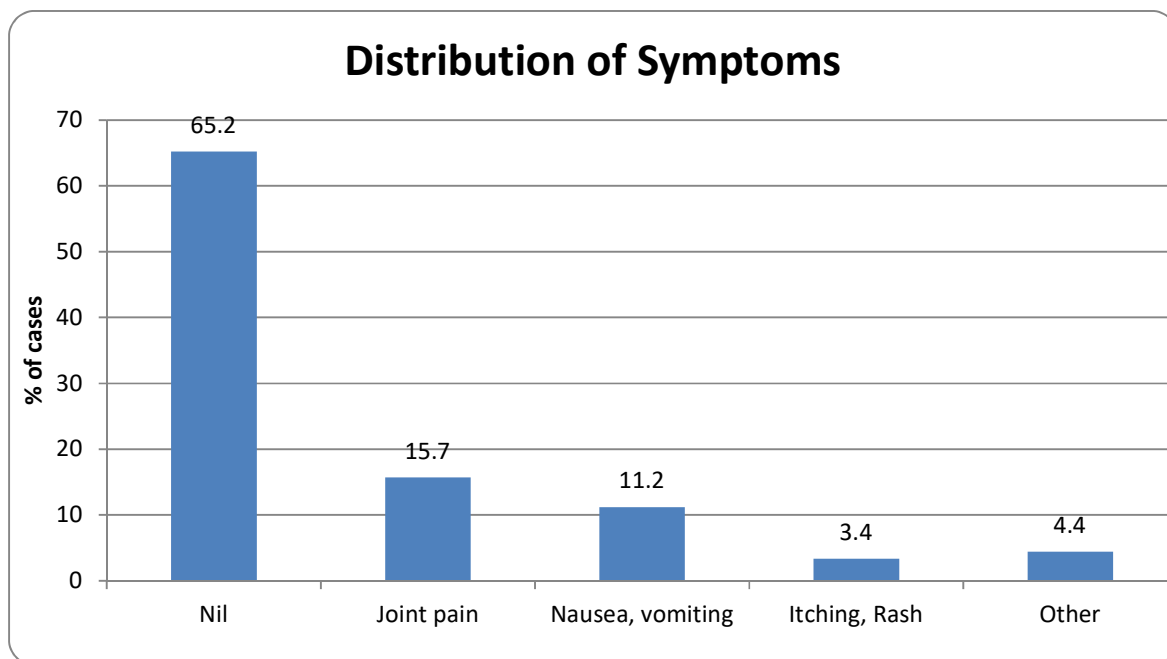


Figure 3) Distribution of symptoms after ATT among the cases studied.

Table 4) Distribution of adverse effects of ATT among the cases studied.

Adverse effects	No. of cases	% of cases
Nil	60	67.4
Hyperuricemia	10	11.2
Gastritis	7	7.9
Gastritis with hyperuricemia	3	3.4
Drug induced hepatitis	3	3.4
Skin rash	3	3.4
Peripheral Neuritis	1	1.1
Ototoxicity	1	1.1
Thrombocytopenia	1	1.1
Total	89	100.0

Of 89 cases studied, 60 (67.4%) did not have any adverse effects, while 29 (32.6%) presented with adverse drug reactions; 10 (11.2%) had hyperuricemia, 7 (7.9%) had gastritis, 3 (3.4%) had Gastritis and hyperuricemia, 3 (3.4%) had Drug induced hepatitis, 3 (3.4%) had skin rash, 1 (1.1%) had neuritis, 1 (1.1%) had hearing loss (ototoxicity) and 1 (1.1%) had Thrombocytopenia in the study group.

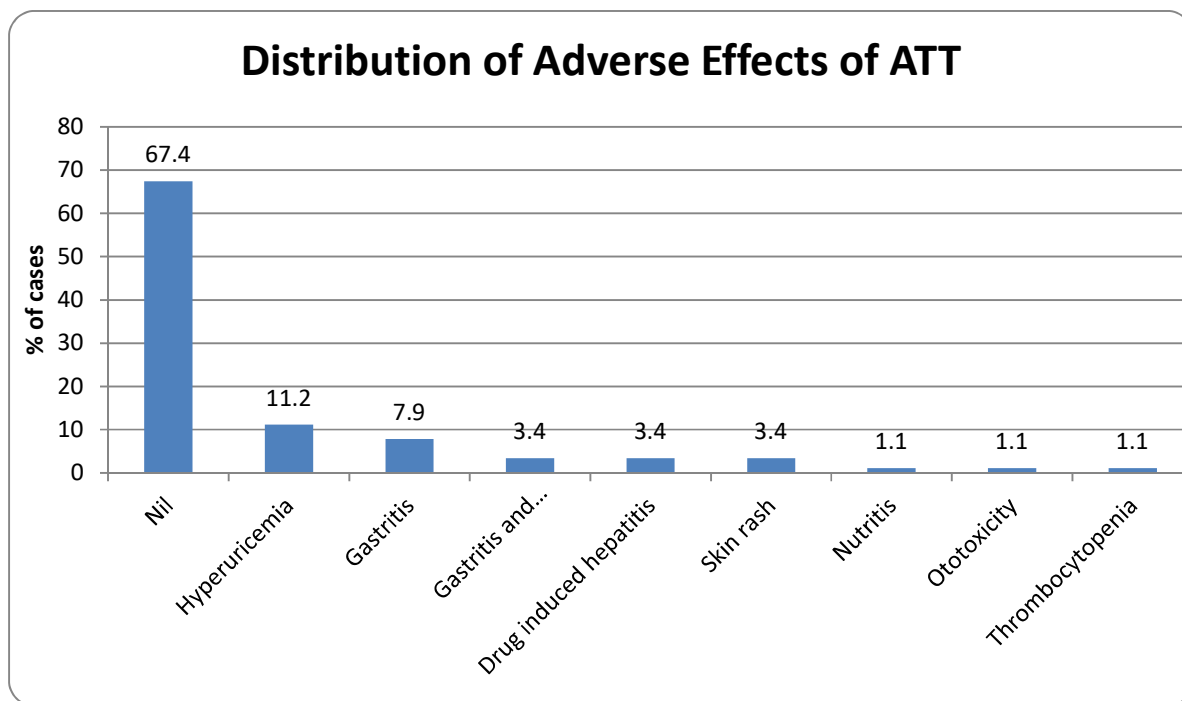


Figure 4) Distribution of adverse effects of ATT among the cases studied.

Table 5) Distribution of adverse effects of ATT according to sex in the study group.

Adverse effects	Sex				Total (n=89)		P-value
	Male (n=43)		Female (n=46)		n	%	
	n	%	n	%	n	%	
Nil	35	81.4	25	54.3	60	67.4	0.019*
Hyperuricemia	4	9.3	6	13.0	10	11.2	
Gastritis	0	0.0	7	15.2	7	7.9	
Gastritis with hyperuricemia	1	2.3	2	4.3	3	3.4	
Drug induced hepatitis	0	0.0	3	6.5	3	3.4	
Skin rash	0	0.0	3	6.5	3	3.4	
Peripheral Neuritis	1	2.3	0	0.0	1	1.1	
Ototoxicity	1	2.3	0	0.0	1	1.1	
Thrombocytopenia	1	2.3	0	0.0	1	1.1	
Total	43	100.0	46	100.0	89	100.0	

P-value by Chi-Square test. P-value<0.05 is considered to be statistically significant. *P-value<0.05.

Of 43 male cases studied, the most common adverse effect was Hyperuricemia which was observed in 4 cases (9.3% of total males), followed by Gastritis and hyperuricemia, Neuritis, Hearing loss and Thrombocytopenia which was observed in one case each.

Of 46 female cases studied, the most common adverse effect was Gastritis was observed in 7 cases (15.2% of total females), followed by Hyperuricemia in 6 cases (13.0% of total females), followed by Gastritis and hyperuricemia, Drug induced hepatitis and Skin rash which was observed in three cases each.

Distribution of incidence of adverse effect of ATT differs significantly between group of male and group of female cases studied (P-value<0.05).

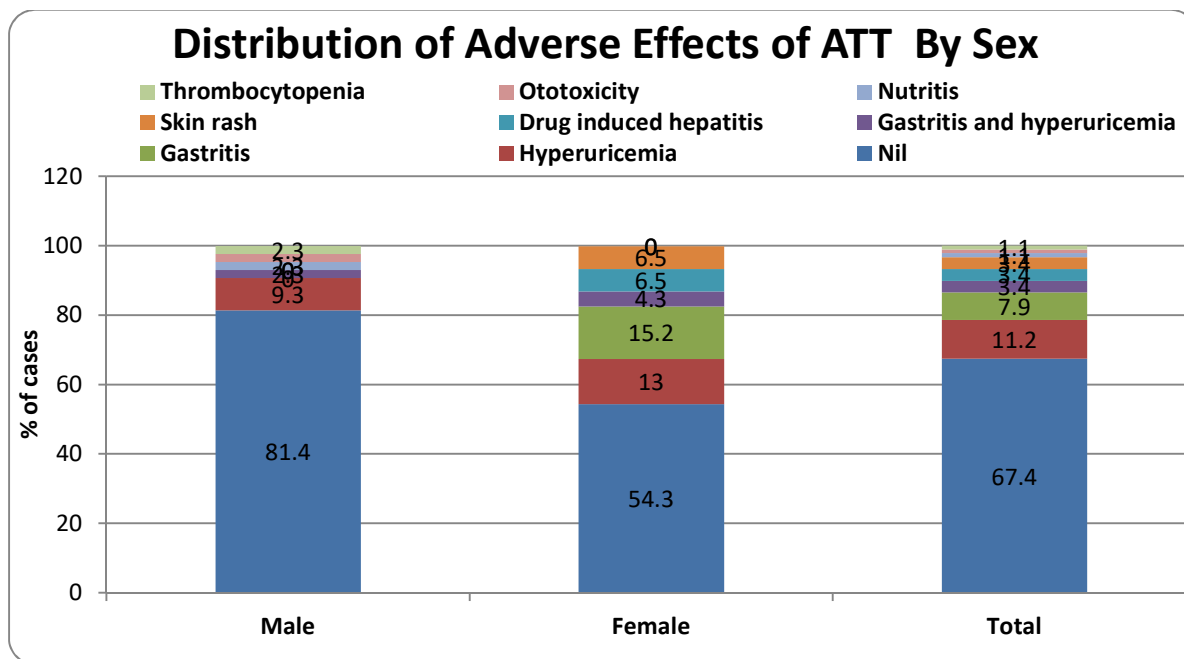


Figure 5) Distribution of adverse effects of ATT according to sex in the study group.

DISCUSSION:

India is the highest TB burden country accounting for one fifth (21%) of the global incidence. Default is one of the unfavorable outcomes for patients on DOTS and represents an important challenge for the Tuberculosis elimination program. In study done by Geeta S Pardeshi reported default rate 10.33%⁶. Non-adherence to tuberculosis therapy leading to prolonged infectiousness continuing chain of transmission, drug resistance and death. In extrinsic factors associated with default important is a side effect of anti-tuberculosis medication⁷.

In this study 31(34.8%) patients of 89 had side effects of primary drugs used to treat tuberculosis. Reported incidence of side effects to anti-TB drugs 8.3% in study done by Banu Eris Gulbay⁸.

In this study females outnumbered males with adverse drug reactions to anti-tuberculosis treatment (females 45.7% compared to males 18.6%).

10 patients (11.2%) of 89 showed hyperuricemia, female affection was more compared to male exhibiting symptomatic raised uric acid levels (6 females and 4 males). 4 patients showed hyperuricemia associated with gastritis (3 female and 1 male) . Total cases of hyperuricemic arthralgia reported were 14 of 89 (15.73%) where female affection was 10.11%. Hyperuricemia has been reported in 43% -100%of patients treated with Pyrazinamide alone or in combination with Ethambutol⁹.

ATT induced hepatotoxicity during standard multidrug TB treatment has been reported to be between 2-28%¹⁰. In this study hepatitis is reported 3.4%. Antituberculosis drugs causing hepatic injury has wide spectrum of presentations, ranging from asymptomatic mild rise in liver biochemical tests to acute hepatitis and acute liver failure. Female gender, old age, malnutrition and Indians, these are positive predictor of more severe liver disease^{11, 12}.

Other side effects observed were gastritis (7 patients- females, 7.9%), skin rash (3 patients, 4.3%), thrombocytopenia (1 patient, 1.1%), ototoxicity (1 patient, 1.1%) and peripheral neuritis (1 patient, 1.1%).

Thrombocytopenia is most common hematological manifestation in patients with HIV and TB¹³. In non-HIV affected TB patients it is an uncommon but potentially fatal adverse effect of rifampicin¹⁴.

Ototoxicity is important adverse effect of streptomycin. In this study observed in one patient (1.1%). In study done by Banu Eris Gulbay ototoxicity reported 1.7%⁸.

Peripheral neuritis observed in one patient (1.1%) in this study. Incidence of polyneuropathy in INH- treated patients revealed 2-44%¹⁵. Likely pathophysiology behind this is nicotinic acid hydrazide interferes with vitamin B6 (pyridoxine) metabolism leading to deficiency in biological active B6 by inhibition of pyridoxine-dependent enzyme systems¹⁶. Increased blood concentration of Isoniazid results in an increased risk of adverse effects¹⁷. This is a rare complication with appropriate doses of Isoniazid (5mg /Kg body weight). High incidence can be observed in malnourished patients receiving anti-TB drugs¹⁸.

CONCLUSION:

Treatment of tuberculosis comprises not only initiation and completion of anti-tuberculosis drugs but also close monitoring of patients for any serious or even insignificant adverse reactions which may cause non-adherence to treatment and management of same.

Counseling of patient diagnosed of tuberculosis regarding side effects of drugs, timely reporting, managing side effects and reassurance to patient with further safe treatment will improve adherence to treatment, success rate and breaking the chain of transmission.

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