Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 6, Issue, 12, pp.10637-10642, December, 2014

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A STUDY OF ADVERSE DRUG REACTIONS IN TUBERCULOSIS PATIENTS DUE TO DIRECTLY OBSERVED TREATMENT THERAPY AT GOVERNMENT HOSPITAL IN THE CITY OF WARANGAL, TELANGANA, INDIA

Rashmi Pusunoori, Manjari Bodasu, Spandana Adepu and *Sangram Vurumadla

Department of Pharmacy Practice, St. Peter's Institute of Pharmaceutical Sciences, Hanamkonda, Warangal, Telangana, India

ARTICLE INFO

Article History:
Received 10th September, 2014
Received in revised form
25th October, 2014
Accepted 15th November, 2014
Published online 27th December, 2014

Key words:
Adverse drug reactions,
Anti-TB therapy,
Directly observed treatment,
Short course,
Severity,
Tuberculosis.

ABSTRACT

Background: As with the profile of adverse drug reactions (ADRs) due to directly observe treatment, short course (DOTS), there is no report available in patients receiving anti tuberculosis (anti–TB) chemotherapy in Warangal region, Telangana, India. One of the main reasons for non-adherence to anti–TB therapy (ATT) is adverse drug reactions (ADRs), even under DOTS.

Objective: This main objective of the study was to determine the incidence and prognosis of ADRs due to DOTS therapy, and to evaluate their impact on anti-TB treatment in Warangal district, Telangana State.

Methods: A prospective population-based study was performed from January 2014-August 2014. Sputum smear positive pulmonary tuberculosis patients who received DOTS therapy were included and followed up for six months. The suspected ADRs were recorded.

Results: A total of 120 Tuberculosis patients were included in this study. 70 patients (58.3%) showed at least one ADR due to anti tubercular regimens. The incidence (count) of ADR based on affected organ was: gastrointestinal disorders in 35 patients (41.17%), anemia in 30 patients (42.85%), ototoxicity and giddiness in 19 patients (27.14%), Liver dysfunction in 17 patients (24.28%), allergic reactions in 12 patients (17.14%), Muscle weakness in 11 patients (12.94%). No ADRs were observed in CVS. Most cases of ADRs (53%) had a good clinical outcome.

Conclusions: The incidence of ADRs due to DOTS therapy was 58.3%. These ADRs had a substantial impact on TB control in Warangal. This highlighted the importance of developing strategies to ameliorate ADRs both to improve the quality of patient care and to control TB safely.

INTRODUCTION

Tuberculosis (TB) caused by Mycobacterium has been understood to afflict human beings since ancient period. It continues to rank among the world's most serious health issues despite the greatest medical achievements of discovering effective diagnostic and treatment measures (Central TB Division and National AIDS Control Organization, 2005). Directly discovered treatment, short course (DOTS) was introduced in India in 1993 as a part of the Revised National Tuberculosis Control Program (RNTCP), following a review of India's NTP a year earlier (Balasubramanian *et al*., 2000). The key part of DOTS therapy is the traditional anti-TB short course therapy program, which needs regularly taking drug combinations of INH (INH), Rifampicin (RFP), Pyrazinamide (PZA), Ethambutol (EMB), and/or Streptomycin each different day for 6-9 months (World Health Organization, 2002). Despite the optimistic therapeutic effects, several studies have shown that multidrug regimens will cause unwanted adverse drug reactions (ADRs) of varied degrees of severity, like hepatotoxicity, gastrointestinal (GI) disorders, CNS disorders, hypersensitive reactions and so on (Yee *et al*., 2003; Vieira *et al*., 2008; Zaka *et al* 2008; Marra *et al*., 2007 and Chhetri *et al*., 2008). Studies have advocated that over five percent of the patients on anti-tubercular medication (ATD) develop ADRs (Dhingra *et al*., 2004, Chukanov *et al*., 2004). None of the anti-TB drug is without adverse reaction and seldom is the adverse reaction life threatening. ADRs are considered one among the main causes of non-adherence to anti-TB treatment (Awofeso *et al*., 2008). At the same time, various other drugs might have bigger issues with toxicity, and are usually less effective. As a result, ADRs might eventually contribute to the extension of treatment length, final termination, drug resistance and treatment failure (Kaona *et al*., 2004). It may additionally increase the TB cases, and more seldom deaths of TB patients, posing a challenge to the management of TB patients. The occurrence, severity and also anti-TB drugs

Corresponding author: Sangram Vurumadla
Department of Pharmacy Practice, St. Peter's Institute of Pharmaceutical Sciences, Hanamkonda, Warangal, Telangana, India

elicited ADRs have always been a matter of concern. With the prevalence of ADRs caused by anti-TB drugs, no agreement has been reached worldwide, with the frequency of ADRs starting from 5.1% to 83.5% (Xiaozhen *et al*., 2013). In this study our main objective was to get an outline of ADRs owing to DOTS therapy in Warangal district population.

MATERIALS AND METHODS

Study design and sample selection

This observational prospective study was carried out in the department of respiratory medicine, Government Tuberculosis (TB) Hospital, Hanamkonda, Telangana, India from January 2014 to August 2014. The study included 140 diagnosed TB patients attending outdoor of the department. The patients were selected irrespective of age and sex. Patients receiving different treatment regimens were excluded, as were people who were human immunodeficiency virus (HIV) positive, people who were transferred and people who abandoned treatment, those whose diagnosis was modified during the course of the treatment and died because of reasons other than ADRs during the monitoring. Patients were divided according to the class of treatment (I, II or MDR) they were receiving underneath DOTS. Before anti-tubercular therapy (ATT), patients recruited were asked to complete the baseline form and receive many laboratory examinations like blood tests, urine test, liver, kidney function tests, and hepatitis B (HBsAg) test. Blood, urine and liver and renal function test were measured again within 2 months after anti-TB treatment initiation. The participants were asked to record any signs or symptoms of ADRs and to report back to the clinic if they had discomfort or adverse reactions.

Once a suspected ADR was known, they were recorded and followed-up till resolution or finish of TB therapy. ADR experienced patients changed their DOTS therapy and/or received symptomatic medical care consistent with the seriousness of the ADR. ADR was defined as "an appreciably harmful or unpleasant reaction, following from an intervention associated with the utilization of a medication product, that predicts hazard from future administration and warrants interference or specific treatment, or alteration of the dose regime, or withdrawal of the drugs causing ADRs and as resultant modifications within the treatment, were recorded" (Sinha K *et al*., 2013). Severity of the ADRs were classified as (Hartwig *et al*., 1992) (i) Mild reactions that were self-limiting and ready to resolve over time without treatment and did not contribute to prolongation of length of stay, (ii) Moderate ADR's were outlined as people who needed therapeutic intervention and hospitalization prolonged by one day however resolved in less than 24 hour or change in drug therapy or specific treatment to stop an extra outcome, and (iii) Severe ADR's were those that were life-threatening, produce disability and those that prolong hospital stay or lead to the death of the patient.

RESULTS

Gender distribution in Tuberculosis patients: A total of 140 patients were enrolled in our study during period of eight months. Among those, 8 patients transferred out during monitoring, 4 patients died other than ADR's, 3 patients diagnosis was changed and five patients abandoned treatment. As a result, a total of 120 patients were included in the study. The males outnumbered the females (73.33 vs. 26.66%) in the present study. Age of the patients ranged from 13 to 75 years with a mean of 39.3 years. Out of 120 patients, 70 patients experienced ADR's and were analyzed in our study. Out of 70 tubercular patients with ADR's, 53 (75.7%) were males and 17 (24.3%) were females as shown in Table 1.

Table 1. Distribution of ADR Occurred Patients Based on Gender

Sex	No of patients (%)
Males	53 (75.7%)
Females	17 (24.3%)

Age wise distribution in ADR reported tuberculosis patients: The incidence of ADR's was higher in the age group around 50-59 years age group which comprised 25.71% of the patients followed by the age group of 30-39 years which comprised 21.42% of the entire study population. The results are shown in Table 2.

Table 2. Distribution of ADR Reported Patients Based on age group

Age	10-19 yrs	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-70 yrs
Number	1	12	15	14	18	10
Percentage	1.42%	17.14%	21.42%	20%	25.71%	14.28%

Previous TB course in ADR occurred individuals: Out of 70 patients experiencing ADR, 31 (44.28%) patients were newly diagnosed with tuberculosis, 11 (15.71%) patients had already completed tuberculosis treatment and 28 (40%) patients discontinued their treatment due to various reasons. Data regarding treatment course is shown in Table 3 and Fig 1.

Table 3. Distribution of ADR reported patients based on TB course of treatment

Previous Course	Newly Diagnosed	Completed	Defaulted
No of patients (%)	31 (44.28%)	11 (15.71%)	28 (40%)

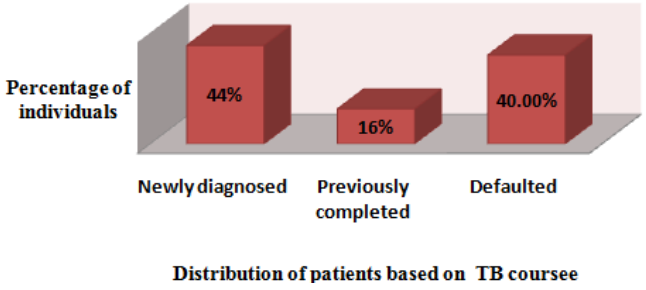

Fig. 1. Distribution of patients with ADR based on previous TB course of treatment

Social History: Out of total ADR reported cases, tuberculosis was recorded mostly in alcoholics in 39 patients (55.71%), followed by smokers in 19 (27.14 %) patients, decreased appetite in 22 (31.42%) patients. Low effect of tuberculosis was seen in tobacco chewers in 3 patients (4.28%) as shown in Table 4.

Table 4. Distribution of ADR reported patients based on social history

Parameters	Smokers	Alcoholics	Decreased Appetite	Tobacco Chewers
No of patients (%)	19 (27.14%)	39 (55.71%)	22 (31.42%)	3 (4.28%)

Type of Tuberculosis: Out of 70 ADR reported patients, all patients recruited were of pulmonary tuberculosis and no extra pulmonary tuberculosis patient was identified.

Type of DOTS (Directly Observed Treatment Strategy): Table 5 says that out of 70 ADR reported patients enrolled in the study, 27 (38.5%) patients have undergone CAT 1 treatment, 25 (35.75%) patients have undergone CAT 2 treatment and 18 (25.71%) patients have undergone MDR treatment.

Table 5. Distribution of ADR reported patients based on treatment

DOTS	CAT1	CAT 2	MDR
No of patients (%)	27 (38.51%)	25 (35.75%)	18 (25.71%)

Incomplete course reasons in 28 defaulted patients: Out of 70 patients experiencing ADR, 28 patients didn't complete the tuberculosis treatment course due to following reasons: 4 patients had interruptions recorded, 20 patients discontinued the treatment and 4 patients have withdrawn the treatment due to resistance or sensitivity to drugs as shown in Table 6 and Fig 2.

Table 6. Distribution of patients based on incomplete courses

Reasons	Interruptions	Discontinued	Withdrawal
No of patients (%)	4 (14.28%)	20 (71.42%)	4 (14.28%)

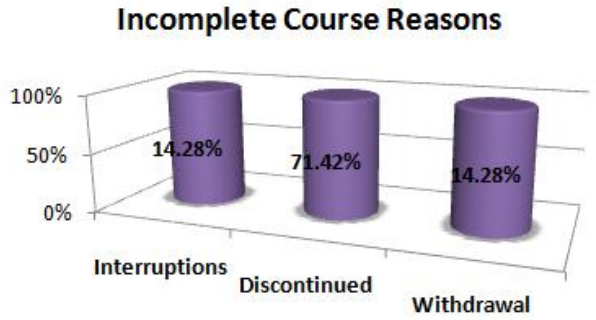

Fig. 2. Distribution of patients based on incomplete courses

Adverse drug reactions: 70 patients recorded several adverse drug reactions, in which vomiting's recorded highest percentage in 35 (30.70%) patients followed by anemia in 30 (42.8%) patients, abdominal pain in 16 (22.8%) patients, giddiness in 14 (20%) patients and dermatitis in 12 (17.1%) patients. Data regarding ADRS were shown in Table 7 and Fig 3.

Following was the recorded descending order of ADR's in recruited 70 patients

Vomitings > Anemia>abdominal pain> giddiness> dermatitis> arthritis >nausea > hearing disturbances = peripheral neuropathy> hepatitis> generalized weakness> blurred vision > seizures = psychosis= insomnia

Table 7. Percentage of patients with different Adverse Drug Reactions

S. No	ADRs	No of patients (%)
1	Vomiting's	35 (50%)
2	Anemia	30 (42.85%)
3	Abdominal pain	16 (22.8%)
4	Giddiness	14 (20.0%)
5	Dermatitis	12 (17.1%)
6	Arthritis	8 (11.4%)
7	Nausea	6 (8.56%)
8	Hearing disturbances	5 (7.14%)
9	Peripheral neuropathy	5 (7.14%)
10	Hepatitis	4 (4.3%)
11	Generalized weakness	3 (4.28%)
12	Blurred vision	2 (2.85%)
13	Seizures	1 (1.4%)
14	Psychosis	1 (1.4%)
15	Insomnia	1 (1.4%)

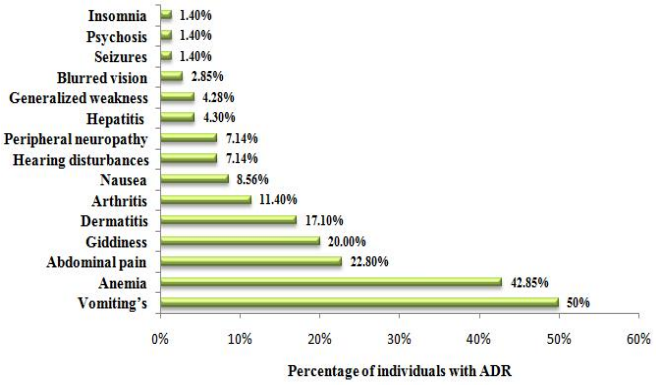

Fig. 3. Proportion of individuals with various adverse drug reactions

Toxicities of anti-tubercular drugs: Out of 70 patients experiencing ADR's, several physiological systems involved in the production of ADR's.

Gastrointestinal system has a higher incidence of ADRs in 35 (41.17%) patients followed by blood and lymphatic system in 30 patients (42.85%) vestibular system in 19 patients (27.14%), Hepatic system involvement in 17 patients (24.28%), allergic reactions in 12 patients (17.14%), Musculoskeletal system involvement in 11 (12.94%) patients.

No ADRs were observed in CVS. Data about ADR's involvement system are shown in Table 8 and Figure 4.

Following is the descending order of systems involved in the production of ADRs

GI System> blood and lymphatic system> vestibular system>hepatic system> skin> musculoskeletal system > CNS > ocular system=Renal system

Table 8. Distribution of adverse drug reactions based on the systems involved

Toxicities due to anti-tubercular drugs	Number of Patients (Percentage)
GI toxicities	57 (81.4%)
Hematologic toxicities	30 (42.85%)
Ototoxicities	19 (27.14%)
Hepatotoxicity	17 (24.28%)
Allergic reactions	12 (17.14%)
Musculoskeletal toxicities	11 (15.71%)
Neurological toxicities	8 (11.42%)
Renal toxicities	2 (2.85%)
Ocular toxicities	2 (2.85%)

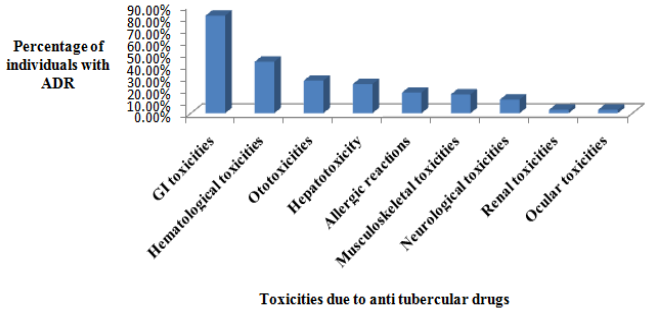

Fig. 4. Distribution of adverse drug reactions based on the systems involved due to anti tubercular drugs

Adverse drug reaction classification based on severity: Based on severity of ADR's in patients, ADR's were classified into mild ADR's, moderate ADR's and severe ADR's as shown in Table 9.

Table 9. Adverse drug reaction classification based on severe drug reactions

Mild ADR'S	Moderate ADR'S	Severe ADR'S
Nausea	Dermatitis	Hepatotoxicity
Generalized weakness	Visual disturbances	Ototoxicity
Giddiness	Anemia	Seizures
Vomiting	Psychosis	Hepatitis
Abdominal pain	Peripheral neuropathy	
Arthritis	Nephrotoxicity	
Insomnia		

Drugs causing Adverse reactions: 9 drugs were causing different ADRs in 70 subjects; of which rifampicin has a higher incidence rate (31.4%) followed by other drugs as follows. Data is shown in Table 10 and Figure 5.

Rifampicin > Isoniazid >Pyrazinamide > Ethionamide= Streptomycin > Kanamycin > Ethambutol > Cycloserine > Levofloxacin

Table 10. Distribution of patients based on drugs causing ADRs

S.No	Drug	No of patients (%)
1	Rifampicin	22 (31.4%)
2	Isoniazid	19 (27.14%)
3	Pyrazinamide	17 (24.2%)
4	Streptomycin	9 (12.85%)
5	Ethionamide	9 (12.85%)
6	Kanamycin	5 (7.1%)
7	Ethambutol	2 (2.8%)
8	Cycloserine	1 (1.42%)
9	Levofloxacin	1 (1.42%)

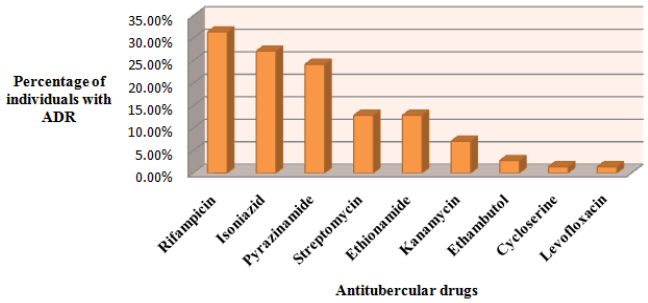

Fig. 5. Distribution of patients based on drugs causing ADRs

DISCUSSION

Tuberculosis that had a high rate of mortality need better understandings regarding the demographics, socioeconomics, family and social history, treatment courses and risk factors for the event of the infection or for the worsening from better treatment outcomes. The present study was undertaken to find out the ADRs of anti-TB drugs due to DOTS therapy among the tuberculosis patients in a hospital setting. Of all tuberculosis patients, males constitute the major population of the study group, that is, 73.33% against 26.66% females. People of age above 30 years were at high risk to be affected by tuberculosis, which is in accordance with many studies done globally and also in South Indian population (Shetty *et al*., 2006). Male sex and age above 30 years are mostly prone to the development of infection than females and the reason for this is that socioeconomic factors or social habits like alcohol consumption, smoking, tobacco use and working environment may provoke them to the exposure of tuberculosis which turned out to be true form our study where patients with habits of alcohol consumption (56%) followed by smokers (27%) and tobacco chewing (4.23%) were more prone to tuberculosis and development of ADR'S (Joanna d'Arc Lyra, 2008; Per Gustafson, 2004; Grzegorz, 2014).

70 (58.3%) patients out of 120 patients in our study developed one or more adverse drug reactions which were found to be higher than the study conducted by Pravat Kumar and Chhetri Anupa in Nepal (Pravat Kumar *et al*., 2013; Chhetri *et al*., 2008) and 41.66% of the patients in our study did not experience any ADRs. It has been found that ADRS were more prevalent among individuals in the age group 50-59 years (25.71%) followed by age group 30-39 years (21.42%). Sinha, *et al* also found that ADRs were more prevalent among the age group 31-40 years (82.4%) and 50-70 years (77.7%). This is probably because the people in this age group are involved in TB infectious activities like alcohol intake, smoking, etc., which results in the weakening of immunity (Sinha *et al*., 2013). A study conducted in Ethiopia (Begna *et al*., 2014) reported that there is an increase in the risk of acquiring tuberculosis infection up to 6% if they are in contact with active tuberculosis people in their vicinities which was in contrast with our studies which reported the incidence of 4.28%. Reason behind this might be due to the awareness campaign conducted throughout the country by various government bodies on the spread of the disease. Our results depicted 44% of newly diagnosed and 40% of defaulted patients among ADR experienced patients. The reasons for

course default are illiteracy, development of adverse drug reactions, employment and socioeconomic status. Our study showed that most of the TB people were defaulted because of discontinuation of the DOTS treatment, reason for this was known through patient counseling which included that patients were not aware of the treatment course, their outcomes by incompletion of course and also because of lack of remembrance, work busy, functions, travelling etc (Vijay *et al*., 2010). 14% of people defaulted because of interruptions due to development of adverse drug reactions like vomiting, abdominal pain, dermatitis and the results of our study were in cordinance with study conducted by Jaggarajamma *et al* in South India (Jaggarajamma *et al.*, 2007). Majority of the cases belonged to the category I (38.51%), 35.75% were in category II, and 25.71% were in category IV (MDR) in our study. It may be due to the fact that majority of TB cases in our study were new sputum positive cases and most of the cases were defaulted due to lack of adherence. (Mittal and Gupta, 2011) also found in their study that the majority of the TB patients belonged to the category I (42.8%).

Our study found that the gastric system (57%) was highly involved in the development of adverse drug reactions followed by hematological system (42.85%), vestibular system (27%), hepatic system (24.28%), skin reactions (17.14%) and musculoskeletal system (15.7%).The drugs, which are responsible for GI system, vestibular and musculoskeletal side effects, may be PZA and RFP. The drugs that are responsible for the side effect hepatic dysfunction may be PZA, RFP, and INH (Sinha *et al*., 2013). The drugs, which are responsible for allergic skin manifestations, may be PZA, RFP, and INH and drug, which is responsible for hematological toxicities, may be INH. Most of the ADRs in our study were mild and the results of the systems involved in ADR were identical to that of the study done by Glauciene *et al*., on people of Brazil (Glauciene Santana Damasceno *et al*., 2013) and Kheirollah Gholami within hospitalized patients (Kheirollah Gholam *et al*., 2006).

Adverse drug reaction caused by Rifampin was of higher incidence (31.4%) followed by Isoniazid (27.4%), Pyrazinamide (24.2%), Ethionamide (12.4%), Streptomycin (12.4%), Kanamycin (7.1%) Ethambutol (2.8%), Cycloserine and Levofloxacin (1.42%). Our study slightly differed from the study conducted by (Daphne Yee *et al*., 2003), which stated that adverse drug reactions caused by Pyrazinamide were higher followed by Isoniazid and Rifampicin. Patient education played a major role in the beneficial clinical outcome of therapy; this has been proved from our results which showed 53% of them improved from the condition as previous studies (Xiaozhen *et al*., 2013). 47% of them were not up to the mark in the treatment outcome, this was due to the negligence of the patients and domination of their illiteracy or due to financial drawback or due to interruptions or family problems.

Conclusion

This study showed that 58.03% of TB patients who received DOTS therapy developed one or more ADRs. ADRs were more prevalent among males with the number of patients more in the 31-40 years age group and 50-59 years age group. Most common ADRs were GI symptoms, but most were mild and CAT-I drugs were mainly involved in development of ADR. ADRs could lead to a rise in health care services and have an effect on the anti-TB treatment pattern. Patients with ADRs were more of vulnerable to develop unfavorable anti-TB outcomes. Given the incidence of ADRs and the size of the TB population in Warangal the negative impact of ADRs on anti-TB treatment would be substantial. This highlighted the importance of developing ways to ameliorate ADRs, each to boost the standard of patient care and to regulate TB safely.

Abbreviations

ADR-Adverse Drug Reaction
TB-Tuberculosis
GI-Gastro intestinal
DOTS-Directly Observed Treatment Strategy

REFERENCES

Awofeso, N. 2008. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bull World Health Organ.*, 86: B–D.

Balasubramanian, VN., Oommen, K. and Samuel, R. 2000. DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State. *India. Int J Tuberc Lung Dis*., 4:409-13.

Begna, T., Nagasa, D., Yibeltal, K. and Biruhalem, T. 2014. Smear positive pulmonary tuberculosis and its risk factors among tuberculosis suspect in South East Ethiopia; a hospital based cross-sectional study. *BMC Medicine*., 7:285, 1-6.

Central, TB. 2005. Division and National AIDS Control Organization, New Delhi. Programme objectives. Training module for medical officers on TB/HIV., 14-8.

Chhetri, AK., Saha, A., Verma, SC., Palaian, S., Mishra, P. and Shankar, PR. 2008. 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*., 58:531-6.

Chukanov, VI., Kaminskaia, GO. and Livchane, E. 2004. Frequency and pattern of adverse reactions due to treatment of patients with pulmonary tuberculosis with antitubercular reserve drugs. *Probl Tuberk Bolezn Legk*., 10:6-10.

Daphne Yee, Chantal, V., Marthe, P., Isabelle, P., Isabelle, R. and Dick, M. 2003. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory and Critical Care Medicine*., 67. 1472–1477.

Dhingra, VK., Rajpal, S., Aggarwal, N., Aggarwal, JK., Shadab, K. and Jain, SK. 2004. Adverse drug reactions observed during DOTS. *J Commun Dis*., 36:251-9.

Glauciene, SD., Lusiele, G., Elyne, ME., Mariza Miranda, TF., Reinaldo, SS., Ana Gloria, GV. and Suel, R. 2013. Adverse reactions to antituberculosis drugs in Manguinhos, Rio de Janeiro, Brazil. *Clinics*., 68(3):329-337.

Grzegorz, P., Anita, D. and Hanna, T. 2014**.** Alcoholism and other socio-demographic risk factors for adverse TB-drug reactions and unsuccessful tuberculosis treatment- data from ten years' observation at the Regional Center of

Pulmonology, Bydgoszcz, Poland. *Medical Science Monitor*., 20: 444-453.

Hartwig, SC., Siegel, J. and Schneider, PJ. 1992. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*., 49: 2229-32.

Jaggarajamma, K., Sudha, G., Chandrasekaran, V., Nirupa, C., Thomas, A., Santha, T., *et al*. 2007. Reasons for noncompliance among patients treated under Revised national Tuberculosis Control Programme (RNTCP), Tiruvallur District, and South India. *Indian Journal of Tuberculosis*., 54:130-135.

Joanna d'Arc Lyra, B., Maria de Fatima, PMA., Ricardo Arraes de, AX. and Laura Cunha, R. 2008. Smoking increases the risk of Relapse after successful tuberculosis treatment. *International Journal of Epidemiology*., 37:841–851

Kaona, FA., Tuba, M., Siziya, S. and Sikaona, L. 2004. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health*., 4: 68.

Kheirollah Gholami, Elahe, K., Mahboubeh, H. and Gloria, S. 2006. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. *Pharmacy Practice*., 4(3): 134-138

Marra, F., Marra, CA., Bruchet, N., Richardson, K., Moadebi, S., Elwood, RK., *et al*. 2007. Adverse drug reactions associated with first line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis*., 11:868-75.

Mittal, C. and Gupta, SC. 2011. Effect of disease related variables on treatment outcome under DOTS. *JK Science*., 13:15-8.

Per Gustafson. Victor, FG., Cesaltina, SV., Paulo, R., Remonie, S., Peter, J. *et al*. 2004. Tuberculosis in Biassu; Incidence and risk factors in urban community in sub Saharan Africa. *International Journal of Epidemiology*., 33:163–172.

Pravat Kumar, T. and Sagar, K. 2013. Pulmonary Tuberculosis and its haematological correlates, *Transworld Medical Journal*., 1(1):11-13.

Shetty, N. and Shemko, M. 2006. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. *The International Journal of Tuberculosis and Lung Disease.*, 10(1):80–86.

Sinha, K., Marak, IR. and Singh, WA. 2013. 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*., 1:50-3.

Vieira, DE. and Gomes, M. 2008. Adverse effects of tuberculosis treatment: Experience at an outpatient clinic of a teaching hospital in the city of Sao Paulo, Brazil. *J Bras Pneumol*., 34:1049-55.

Vijay, S., Prahlad, K., Lakbir Singh, C., Balasangameshwara, HV., Unnikrishnan, PK. and Sumathi, GR. 2010. Risk Factors Associated with Default among New Smear Positive TB Patients treated under DOTS in India. *Plos one*., 5(4): e10043

World Health Organization, 2002. An expanded DOTS framework for effective tuberculosis control. Stop TB Communicable Diseases. Geneva: WHO Press., 1-20.

Xiaozhen, LV., Shaowen, T., Yinyin, X., Xiaomeng, W., Yanli, Y., *et al*. June 2013.Adverse Reactions due to directly observed treatment strategy therapy in Chinese tuberculosis patients: A Prospective Study. *Plos One*., 8:6.

Yee, D., Valiquette, C., Pelletier, M., Parisien, I., Rocher, I. and Menzies, D. 2003. Incidence of serious side effects from first line anti-tuberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*., 167:1472-7.

Zaka Ur Rehman, Z., Jamshaid, M. and Chaudhry, A. 2008. Clinical evaluation and monitoring of adverse effects for fixed multidose combination against single drug therapy in pulmonary tuberculosis patients. *Pak J Pharm Sci*., 21:185-94.

****