Original Article

Burden of comorbidities and their treatment in patients with active tuberculosis: A prospective study

Venkat Manolasya[1], D. T. Katyarmal[1], T. Muni Suneel Babu[2], T. Sreeja Prasad[2], T. Preethi[2], B. Priyanka[2], G. Robin[2]

[1]Department of Medicine, Sri Venkateswara Institute of Medical Sciences, [2]Department of Pharmacology, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, India

Abstract

Background: Patients diagnosed to have active tuberculosis (TB) may have co-existing comorbid conditions. Treatment for both conditions may lead to possible drug-related problems. Hence, the present study was designed to understand the incidence and pattern of drug-related problems. This knowledge gives a scope to minimise the occurrence and help patients to adhere to treatment.

Methods: A prospective observational study was carried out for a period of 6 months. A pre-designed data collection form was used for this study that was used to document clinical data including brief history, laboratory investigations, treatment details and drug-drug interactions (DIs).

Results: One hundred and five TB patients were enrolled in the study. Their mean age was 43.7 ± 16.8 years. Sixty patients were found to have comorbidities. One hundred and fifty-eight drug-related problems between comorbidities' treatment regimens and ATT were documented. DIs were the most common drug-related problems. Seventy-nine major DIs and 74 moderate DIs were documented. Nine patients had adverse drug reactions which were ATT-induced hepatotoxicity, thrombocytopenia and anaemia.

Conclusions: Co-existence of comorbidities and their treatment resulted in a significant burden on patients who are diagnosed positive for TB. This can lead to treatment delay or failure or default. Strategies and programmes to tackle the burden of comorbid conditions on TB-positive patients are to be developed and implemented aggressively.

Keywords: Comorbidities, drug interaction, drug-related problems, tuberculosis

Address for correspondence: Dr Venkat Manolasya, Assistant Professor, Department of Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati 517 507, Andhra Pradesh, India.
E-mail: manolasya.13@gmail.com

Submitted: 11-Jan-2021 **Accepted:** 07-Jul-2021 **Published:** 25-Oct-2021

INTRODUCTION

Tuberculosis (TB) is a devastating disease that is a major global health problem. As per the World Health Organization (WHO) global TB report 2020, India has approximately 26% of the global TB incidence.[1] Even though the current preventive efforts against the incidence and the spread of TB have decreased, the problem is yet far from over. In recent decades, there has been an increasing concern over patients' adherence to anti-TB treatment (ATT). One of the glaring problems is gradual rise in comorbid conditions such as diabetes mellitus, systemic hypertension, coronary artery disease (CAD), chronic kidney disease (CKD) and cerebrovascular

Access this article online	
Quick Response Code:	Website: www.jcsr.co.in
	DOI: 10.4103/jcsr.jcsr_8_21

How to cite this article: Manolasya V, Katyarmal DT, Babu TMS, Prasad TS, Preethi T, Priyanka B, *et al*. Burden of comorbidities and their treatment in patients with active tuberculosis: A prospective study. J Clin Sci Res 2021;10:202-7.

accident (CVA). Co-existing comorbid conditions may worsen the existing infection or even increase its risk of spread. The comorbid condition may decrease or impair the immune response; this in result can increase the chance of tubercular infection. It is a challenge for healthcare systems to deal with this sort of double trouble. Thus, the focus of the study is shifted to the untargeted comorbidities that play a role in increase in spread and severity of TB. Therefore, traditional approaches need to be re-assessed. A multidisciplinary collaboration and integrated strategies must be opted.

In our study, we have focused on the burden of existing comorbidities on the patients who are diagnosed with TB, the effects of treatment for both the conditions and probable drug-related problems. It assesses the status of burden and close relationship between the anti-tubercular treatment and comorbid conditions' treatment. The present study, hopefully, provides the evidence to support the need for the management of drug-drug interactions (DIs) and adverse drug reaction (ADR)-related problems. It emphasises the evidence for causation of drug-related problems. Therefore, this study will help to improve the quality of treatment in a TB-positive patient and thus hopefully a better outcome.

MATERIAL AND METHODS

Adult (>18 years) patients presenting to medicine outpatient departments, admitted to the medical wards and the medical intensive care unit at Sri Venkateswara Institute of Medical Sciences, a tertiary care teaching hospital, in Tirupati, South India, between August 2018 and January 2019, who were diagnosed with TB as per Revised National TB Control Programme (RNTCP) guidelines and were started on treatment were studied. Pregnant women, lactating women, patients with malignancy and those who were not willing to participate in the study were excluded.

The study was approved by the Institute's Ethics Committee. Written informed consent was obtained from all the patients participating in the study. For all the patients included in the study, a detailed history was obtained focusing on comorbid conditions, drug history pertaining to medications used for comorbid conditions' management and ATT regimen. History pertaining to personal habits such as tobacco usage and alcohol consumption was taken. Laboratory investigations such as complete haemogram, renal function tests, liver function tests (LFTs), chest X-ray, thyroid function test and blood sugar test were done as deemed fit by the treating physician. Based on the details collected, further assessment was done.

Statistical analysis

Data were recorded on a pre-designed pro forma and managed using Microsoft Excel worksheet (Microsoft Corp, Redmond, WA). All the entries were double checked for any possible error. Descriptive statistics for categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of distribution was assessed. Variables following normal distribution were summarised by mean ± standard deviation; the remaining variables were summarised as median (interquartile range). The statistical software IBM SPSS Statistics version 26 (IBM Corp. Somers NY, USA) was used for statistical calculations.

RESULTS

A total of 105 patients presenting to the medical outpatient department and inpatient department diagnosed with TB were recruited for the study between August 2018 and January 2019. In our study, patients were between 18 years and 75 years of age, of which the highest number of patients fell between 18–24 years and 45–64 years. The mean age was 43.7 ± 16.8. Males (n = 59, 56.2%) outnumbered females (n = 46, 43.8%), marginally. When social habits were taken into account, majority were teetotalers (n = 76, 72.4%). Eleven (10.4%) had a history of tobacco usage along with alcohol consumption, 5 (4.8%) had the habit of alcohol consumption alone and 13 (12.4%) were plain tobacco users. Extrapulmonary TB (n = 54, 51.42%) was more frequently seen than pulmonary TB (n = 51, 48.58%) cases. Amongst the extrapulmonary TB, TB meningitis (n = 26, 48.1%) was the most frequent followed by skeletal TB (n = 8, 14.8%), TB lymphadenitis (n = 7, 13%), TB pleural effusion (n = 7, 12.9%), gastro-intestinal TB (n = 3), peritoneal TB (n = 2) and genito-urinary TB (n = 1). Most patients had received new patient (Category I) treatment (n = 72, 62.6%), the remaining received category II regimen (n = 30, 28.6%) and drug-resistant TB regimen (n = 3). Of the 105 cases, TB-positive patients with comorbid conditions were higher (n = 60, 57.1%) compared to TB-positive patients without comorbid conditions (n = 45, 42.9%). Amongst the 60 TB-positive patients with comorbid conditions, comorbidities such as systemic hypertension, CAD, type 2 diabetes mellitus, type 1 diabetes mellitus, bronchial asthma, chronic obstructive pulmonary disease (COPD), seizures, hemiplegia, CKD and malnutrition were noted. Amongst all the comorbid conditions, type 2 diabetes mellitus and occurrence of type 2 diabetes

mellitus along with systemic hypertension were recorded to be more common (*n* = 7), followed by systemic hypertension and seizure disorder (*n* = 6 each), systemic hypertension with CAD (*n* = 5 each), history of bronchial asthma (*n* = 4), COPD and seizures along with history of hemiplegia (*n* = 3 each), type 2 diabetes mellitus with systemic hypertension along with CVA, hypertension with CKD, hypothyroidism (*n* = 2 each) and rheumatoid arthritis, CVA, CKD, bronchial asthma-COPD overlap syndrome, seizure with obsessive-compulsive disorder, HIV, type I diabetes mellitus, systemic hypertension with CAD and type 2 diabetes mellitus, systemic hypertension with type 2 diabetes mellitus and seizures (*n* = 1 each). A total 158 drug-related problems were documented and categorised as ADRs (*n* = 9) and DIs (94.5%). Of the nine patients who were identified with ADRs, four were found to have elevated LFTs due to isoniazid (H), rifampicin (R) and pyrazinamide (Z). Drug-induced anaemia due to H, R and Z was found in three female patients. Drug-induced thrombocytopenia was found in two patients. A total of 149 DIs were documented, of which 79 (53%) were major interactions and 70 (47%) were moderate DIs. The major DIs (*n* = 79, 53%) were observed in TB patients with type 2 diabetes mellitus, systemic hypertension, epilepsy, CAD and other concomitant treatment drugs. Major DIs and moderate DIs along with the respective drugs and number of patients who were on the said drugs along with percentages are depicted in Tables 1a and b, respectively.

Table 1a: The major drug interactions along with drugs and number and percentage of patients who were affected

Interacting drugs	No. (%)
Insulin with H and R	1 (0.7)
Glibenclamide with R	1 (0.7)
Metformin with H/R	15 (10.1)
Glimepiride with R	5 (3.4)
Amlodipine with R	20 (13.4)
Phenytoin with H	2 (1.3)
Phenytoin with R	2 (1.3)
Atorvastatin with R	3 (2.0)
Ivabradine with R	2 (1.3)
Pantoprazole with R	16 (10.7)
Ondansetron with R	2 (1.3)
Dexamethasone with R	15 (10.1)
Cilnidipine with R	2 (1.3)
Mannitol with injection streptomycin	1 (0.7)

R=Rifampicin

Table 1b: Moderate drug interactions along with drugs, number and percentage of patients who were affected

Interacting drugs	No. (%)
Metoprolol with R	2 (1.3)
Losartan with R	1 (0.7)
Theophylline with H, R	5 (3.4)
Carbamazepine with H	4 (2.7)
Clopidogrel with R	2 (1.3)
Clopidogrel+aspirin with R	1 (0.7)
Propranolol with R	1 (0.7)
Carvedilol with R	2 (1.3)
Acenocoumarin with R	1 (0.7)
Aspirin with injection streptomycin	1 (0.7)
Levothyroxine with R	4 (2.7)
Ranitidine with R	4 (2.7)
Acetaminophen with H	11 (7.4)
Tramadol with R	1 (0.7)

R=Rifampicin

DISCUSSION

A significant number of patients experienced drug-related problems that could have been preventable. This may result in reduced quality of life, morbidity and at times even mortality. In our study, we reviewed complete clinical profiles of 105 TB patients to assess the burden of comorbidities and their treatment for a period of 6 months (August 2018–January 2019). Of the 105 TB-positive patients, 60 had comorbid conditions and experienced several drug-related problems.

Regarding demographic data of the cases, out of 105 patients, 59 (56.2%) were males and 49 (43.8%) were females. These data reveal that males are relatively at more risk when compared to females in contracting TB. This is due to testosterone hormone in males which may decrease immune response to *M. tuberculosis*. Meanwhile, in females, oestrogen helps in triggering an immune response against the invading pathogen. Furthermore, proximal risk factors for TB, such as tobacco smoking and alcohol abuse, tend to be more common in men. While in a study,[2] the male-to-female ratio in patients of TB was found to be 2:1. In our study, we found that the male-to-female ratio was 1.28, which is less in comparison to the global ratio being 1.5–2.1:1. The mean age of TB patients was 43.7 ± 16.8 years. The mean age of males and females was 46.2 ± 16.7 years and 40.5 ± 16.5 years respectively. Elderly males (65 years and beyond) and younger females (18–24 years) are infected more when compared to other age groups. Amongst patients from Asia, 25–44 and 45–64 years of age were more likely to have TB.[3]

Of the 105 cases, 13 (12.4%) were tobacco users, 5 (4.8%) were alcoholics and 11 (10.4%) were both tobacco users and alcoholics. Most of the patients, i.e., 76 (72.4%), were tee-totalers. Many recent studies[4,5] elucidated that tobacco is an independent risk factor causing approximately a twofold increase not only in active TB disease but also in latent TB infection and mortality. A prospective cohort study conducted in 591 laboratory-diagnosed TB-positive adults, from Georgia, suggested that smokers had an increased risk of poor treatment outcome.[4] Compared to

those who never smoked, current smokers had an increased risk of poor treatment outcome. Cigarette smokers were 3.1 times more frequent to contract TB when compared with controls.[5] Biological mechanisms related to smoking that impair host defences and increase the risk of *M. tuberculosis* infection probably contribute to the relatively poor results of TB treatment amongst smokers. Smoking can have an irreversible inhibitory effect on nitric oxide synthase – the enzyme needed by alveolar macrophages to form nitric oxide to inhibit the multiplication of *M. tuberculosis*. Smoking cessation measures during and after therapy, which has so far received insufficient attention in TB programs, therefore should include them in order to achieve the WHO TB elimination target. Isoniazid is found to be metabolised more rapidly in chronic alcohol abuse patients. Therefore, optimising drug dosing for TB with the potential to improve therapeutics for patients is to be considered. In chronic alcoholic individuals, risk of hepatotoxicity is aggravated with isoniazid treatment.[6] Hence, TB patients with chronic alcohol abuse should be counselled properly about the effects of alcohol abuse and should be encouraged for cessation alcohol consumption.

Amongst 105 TB cases, pulmonary TB cases were 51 (48.5%) and extrapulmonary cases were 54 (51.5%). In a study of conducted at Lucknow, a retrospective analysis of 552 TB patients revealed that majority had extrapulmonary TB, amongst which pleural TB was the most common presentation.[7] Of the 54 extrapulmonary TB cases, TB meningitis was most common form (n = 26, 48.1%), followed by skeletal TB (n = 8), TB lymphadenitis (n = 7), TB pleural effusion (n = 7), gastro-intestinal TB (n = 3), peritoneal TB (n = 2) and genito-urinary TB (n = 1). In the present study, majority of patients, i.e., 72 (68.6%), were under category I treatment regimen of ATT, 30 (28.6%) were under category II and 3 were under drug-resistant TB regimen.

Several medical conditions are risk factors for TB, which may also result in poor treatment outcomes, as TB can complicate the course of some diseases and vice versa. Therefore, it is important to identify these comorbidities in patients with TB in order to ensure early diagnosis and improve co-management. Comorbid conditions can drastically weaken the immune system and cause more severe illness. In our study, out of 105 TB patients, 58 patients had various comorbid conditions.

Total 158 drug-related problems were identified and categorised as ADRs and DIs. Patients who experienced ADRs (n = 9, 5.5%); patients who experienced DIs (n = 149, 94.5%). In our study, we found that the majority of drug-related problems occurred in patients with comorbidities when compared to TB alone. As these chronic comorbid conditions require multidrug treatment as a part of their management, they are the major contributors to drug-related problems. Nine (5.5%) patients were identified with ADRs, out of which four patients had elevated LFT values due to H, R and Z. The first-line anti-TB drugs are potentially hepatotoxic, mainly H, R and Z.

The rate of ATT-induced hepatotoxicity was found to be 2%–28%.[8] The risk factors for ATT-induced hepatotoxicity include chronic alcohol abuse, pre-existing liver diseases and viral infection of liver.[9] Drug-induced anaemia was found in three female patients. The reduction in haemoglobin levels is due to H, R and Z. Drug-induced thrombocytopenia was found in two patients. Thrombocytopenia was caused due to the additive risk of thrombocytopenia by rifampicin. Drug-induced thrombocytopenia was confirmed after ruling out idiopathic thrombocytopenic purpura by bone marrow aspiration. In a study conducted in Northwest Ethiopia, there was a significant ($P < 0.05$) difference in haematological parameters before and after completing intensive phase of ATT.[10]

In this study, the major contributor of drug-related problems is DI between ATT regimens and concomitant drugs used to treat comorbidities. A total of 149 DIs were documented, of which 79 (53.03%) were major DIs and 70 (46.97%) were moderate DIs. As minor DIs were not clinically significant. Hence, we excluded them.

Management of diabetes mellitus (both type 1 and type 2) in TB patients should be aggressive. Diabetes mellitus itself can cause an increased incidence of TB.[11] An optimal glycaemic control results in a better disease outcome. Oral hyperglycaemic agent (OHA) usage should be closely monitored in the severe form of TB. The efficacy of insulin and OHAs may be altered by isoniazid and rifampicin. Rifampicin and metformin interact, thus enhancing the glucose-lowering effect of metformin. Rifampicin and glyburide interact, decreasing its glucose-lowering effects.[12] Close clinical monitoring of glycaemic control is recommended during intensive phase and continuation phase of ATT and doses of concomitant oral hypoglycaemic agents can be adjusted as necessary. Hepatotoxicity has also been seen in the combination of isoniazid and acetaminophen. It was observed in a higher incidence in patients who have taken 4 g of acetaminophen daily, occasionally in those taking normal doses.[13] Although several studies state about hepatotoxicity caused by acetaminophen and

other hepatotoxic drugs, the information related to this is limited and further studies in this regard are needed. Isoniazid is an inhibitor of 2C19, cytochrome P450 isoenzyme system, of which antiepileptic drug phenytoin is a substrate. In these patients, increased incidence of phenytoin toxicity was observed. Isoniazid has also been reported to markedly increase levels of carbamazepine, although the mechanism of interaction is less clear.[14] In patients undergoing thyroid replacement therapies, serum TSH increased and free thyroxine levels decreased significantly after the start of rifampicin treatment in patients taking levothyroxine for hypothyroidism. Therefore, close monitoring of thyroid function is required, particularly in patients who have undergone subtotal thyroidectomy and total thyroidectomy.[15] Rifampicin is a powerful inducer of cytochrome P450 isoform inhibitors. Many cardiovascular agents are metabolised via cytochrome P450 enzymatic system in the liver. Rifampicin significantly reduces levels of beta-blockers and calcium channel blockers, regular blood pressure monitoring should be done and dose adjustment should be considered.[16] Clinically significant interactions occur during ATT chemotherapy, principally involving rifampicin, isoniazid and fluoroquinolones. Lipid-lowering agents such as atorvastatin are greatly affected due to rifampicin, as it decreases the serum concentrations of statins. Alternative drugs can be considered to minimise this effect. Rifampicin can cause greater inhibition of platelet aggregation.[12] Monitoring for increased anti-platelet effects such as bruising and bleeding was done.[17] In the management of concurrent TB and COPD or bronchial asthma, isoniazid and rifampicin have mechanisms that are different from each other on cytochrome P1A2, which may alter the disposition of theophylline and it is, therefore, difficult to evaluate theophylline pharmacokinetics when concomitantly administered with ATT. The clearance of theophylline exhibits a tendency to increase at the beginning of ATT and to decrease after 4 weeks. In Patients reeiving anti-TB treatment in whom theophylline is co-administered, therapeutic drug monitoring of theophylline concentrations and the dosage adjustment should be done as per need.[18,19]

Documented higher exposure to acid-suppressive agents is shown to have an increased risk of TB infection or activation.[20] In this study, 16 patients were already on pantoprazole and 4 were on ranitidine. If the patient is experiencing anorexia, nausea and abdominal pain due to ATT, it is advised to give drugs with small meals. Inappropriate prophylactic acid suppression is a major concern and may even be underestimated due to the lack of appropriate guidelines. More data are required to guide the section between proton-pump inhibitors and H2-receptor antagonists.

Isoniazid and rifampicin combined have a higher incidence of hepatotoxicity. In a study, published in 2013, mannitol, an Food and Drug Administration-approved excipient, was found to be a CYP2E1 inhibitor, which may be used as an adjuvant for drugs that have the potential to induce hepatotoxicity.[21] However, renal parameters should be kept in check when combining it with streptomycin, as it might enhance the nephrotoxic effect of aminoglycosides. In our study, one patient was found to require mannitol, as a part of management to decrease the raised intracranial pressure. There was no hepatotoxicity noted before the start of mannitol in our patient. Rifampicin markedly decreases the exposure to tramadol.[22] One patient was documented to be on tramadol.

In the management of comorbidities in patients who are positive for TB, several drugs are required to be given along with ATT. This calls for a close monitoring of drug toxicity and drug-related problems. These are to be identified as soon as possible and appropriate corrective measures should be done. In a rapidly evolving healthcare system of our country, there should be a good understanding amongst physicians, healthcare professionals involved in managing TB cases and patients for the best possible outcomes.

In collaboration with clinical pharmacists, assessment of clinical profiles of the patient is done, ensuring the best possible healthcare by avoiding the recurrence of clinical events due to drug-related problems.

This was a single-centre study conducted over a fixed period of time. Results need to be validated in a larger group of study. In our study, we concluded that drug-related problems are predominant in TB patients with comorbid conditions. This is one of the contributing factors for failure of ATT leading to TB defaulter or drug-resistance TB or multidrug-resistant TB, which further delays the WHO End-TB Strategy. Strategies and programs to tackle the burden of comorbidities on TB are to be developed and implemented aggressively in order to achieve TB-free goal.

We believe that our observational study reports can become an aid to develop strategy for the prevention, management of comorbidities and their drug-related problems with anti-tubercular therapy.

Financial support and sponsorship
Nil.

Conflicts of interest

The authors are faculty members/residents of Sri Venkateswara Institute of Medical sciences, Tirupati, of which Journal of Clinical and Scientific Research is the official Publication. The article was subject to the journal's standard procedures, with peer review handled independently of these faculty and their research groups.

REFERENCES

1. World Health Organization. Global Tuberculosis Report. Geneva: World Health Organization; 2020.
2. Rao S. Tuberculosis and patient gender: An analysis and its implications in tuberculosis control. Lung India 2009;26:46-7.
3. Zhang X, Andersen AB, Lillebaek T, Kamper-Jørgensen Z, Thomsen VØ, Ladefoged K, *et al.* Effect of sex, age, and race on the clinical presentation of tuberculosis: A 15-year population-based study. Am J Trop Med Hyg 2011;85:285-90.
4. Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Golub JE, *et al.* Tobacco smoking and tuberculosis treatment outcomes: A prospective cohort study in Georgia. Bull World Health Organ 2015;93:390-9.
5. Alavi-Naini R, Sharifi-Mood B, Metanat M. Association between tuberculosis and smoking. Int J High Risk Behav Addict 2012;1:71-4.
6. Myers B, Bouton TC, Ragan EJ, White LF, McIlleron H, Theron D, *et al.* Impact of alcohol consumption on tuberculosis treatment outcomes: A prospective longitudinal cohort study protocol. BMC Infect Dis 2018;18:488.
7. Gaur PS, Suryakant, Bhaskar R, Singh S, Saxena P, Agnihotri S. Incidence and clinical profiles of pulmonary and extra-pulmonary tuberculosis patients in north Indian population: A hospital based retrospective study. Int J Res Dev Pharmacy Life Sci 2017;6:2773-8.
8. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy. Clinical profile and reintroduction of therapy. J Clin Gastroenterol 1996;22:211-4.
9. Wong W, Wu P, Yuen M, Cheng C, Yew W, Wong P. Antituberculosis drug-related liver dysfunction in chronic hepatitis B inection. Hepatology 2000;31:201-6.
10. Kassa E, Enawgaw B, Gelaw A, Gelaw B. Effect of anti-tuberculosis drugs on hematological profiles of tuberculosis patients attending at University of Gondar Hospital, Northwest Ethiopia. BMC Hematol 2016;16:1.
11. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, *et al.* Diabetes and tuberculosis: The impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health 2007;7:234.
12. Cho SK, Yoon JS, Lee MG, Lee DH, Lim LA, Park K, *et al.* Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. Clin Pharmacol Ther 2011;89:416-21.
13. Bates M, Marais BJ, Zumla A. Tuberculosis comorbidity with communicable and noncommunicable diseases. Cold Spring Harb Perspect Med 2015;5:a017889.
14. Goldstein MA, Harden CL. Infectious states. In: Ettinger AB, Devinsky O, editors. Managing Epilepsy and Co-Existing Disorders. Boston: Butterworth-Heinemann; 2002. p. 83-133.
15. Kim HI, Kim TH, Kim H, Kim YN, Jang HW, Chung JH, *et al.* Effect of rifampin on thyroid function test in patients on levothyroxine medication. PLoS One 2017;12:e0169775.
16. Marais BJ, Lönnroth K, Lawn SD, Migliori GB, Mwaba P, Glaziou P, *et al.* Tuberculosis comorbidity with communicable and non-communicable diseases: Integrating health services and control efforts. Lancet Infect Dis 2013;13:436-48.
17. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin: Clinical relevance. Clin Pharmacokinet 2003;42:819-50.
18. Ahn HC, Lee YC. The clearance of theophylline is increased during the initial period of tuberculosis treatment. Int J Tuberc Lung Dis 2003;7:587-91.
19. Sarkar M, Srinivasa, Madabhavi I, Kumar K. Tuberculosis associated chronic obstructive pulmonary disease. Clin Respir J 2017;11:285-95.
20. Hsu WH, Kuo CH, Wang SS, Lu CY, Liu CJ, Chuah SK, *et al.* Acid suppressive agents and risk of Mycobacterium tuberculosis: Case-control study. BMC Gastroenterol 2014;14:91.
21. Shih TY, Ho SC, Hsiong CH, Huang TY, Hu OY. Selected pharmaceutical excipient prevent isoniazid and rifampicin induced hepatotoxicity. Curr Drug Metab 2013;14:720-8.
22. Saarikoski T, Saari TI, Hagelberg NM, Neuvonen M, Neuvonen PJ, Scheinin M, *et al.* Rifampicin markedly decreases the exposure to oral and intravenous tramadol. Eur J Clin Pharmacol 2013;69:1293-301.