

The incidence of hepatotoxicity due to anti-tubercular treatment and its associated risk factors in patients with tuberculosis: an analytical cross-sectional study

Anil Sontakke MD, Riya Pati MBBS, Saood Ali MD, Nidhi Girdhar MD

ABSTRACT

Introduction: Tuberculosis (TB), primarily a pulmonary disease, requires a 6-month regimen of anti-tuberculous drugs. While effective, this treatment can lead to adverse effects, particularly drug-induced liver injury (DILI). This study investigates the incidence, severity, and associated risk factors of hepatotoxicity in TB patients undergoing anti-tubercular treatment (ATT).

Methods: This analytical cross-sectional study was conducted at a tertiary healthcare center over six months. A total of 125 adult TB patients were selected through convenience sampling. Patient number; demographic data, clinical history, and laboratory results were recorded. Hepatotoxicity was graded based on WHO criteria, and correlations with alanine transaminase (ALT) and bilirubin levels were analyzed using SPSS version 22.

Results: The study revealed that 18.4% of patients developed hepatotoxicity, with 5.6% experiencing mild, 4% moderate, 4.8% severe, and 4% life-threatening levels. A moderate positive correlation ($r = 0.56$) was found between ALT levels and hepatotoxicity grades, while a strong correlation ($r = 0.67$) was observed with total bilirubin levels.

Statistical Analysis: Significant correlations between liver function markers and hepatotoxicity severity underscore the importance of regular monitoring in TB patients on ATT.

Conclusions: The study highlights the high incidence of hepatotoxicity in TB patients, emphasizing the need for regular liver function monitoring to minimize severe outcomes and optimize treatment strategies.

Keywords: Tuberculosis, anti-tubercular treatment, drug-induced liver injury, hepatitis, adverse drug reactions

INTRODUCTION

Tuberculosis (TB) is a chronic bacterial infection caused by Mycobacterium tuberculosis complex, predominantly Mycobacterium tuberculosis, often characterized by granuloma formation. Although primarily affecting the lungs, TB can also involve other organs like the kidney, spine, brain, and skin. The cornerstone

of TB treatment is a 6-month regimen of anti-TB drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol, aimed at ensuring patient compliance and successful management. However, adverse effects, particularly anti-TB drug-induced hepatotoxicity, can compromise treatment outcomes.¹

Hepatotoxicity induced by anti-tuberculous drugs is typically diagnosed through jaundice or elevated liver function markers like AST, ALT, APT, or total bilirubin. ALT elevation exceeding three times the upper limit of normal (ULN) in symptomatic cases or five times the ULN in asymptomatic cases warrants treatment interruption.²⁻⁵ Hepatotoxicity is the most common of all adverse effect leading to drug discontinuation in 11%

Corresponding author: Anil Sontakke
Contact Information: Anilsontakke66@gmail.com
DOI: 10.12746/swjm.v13i56.1511

of patients treated with a combination of isoniazid, rifampicin and pyrazinamide.²⁻⁵

Drug-induced liver injury (DILI) from ATT drugs ranges from transient enzyme elevations to acute liver failure, with mortality rates post-jaundice reported between 4% to 12%.⁶ The prevalence of DILI varies due to factors like liver disease, alcoholism, and advanced TB.⁶

Studies highlight isoniazid and rifampicin as primary contributors to DILI, with distinct mechanisms. Rifampicin, especially in multidrug regimens, elevates DILI prevalence, while pyrazinamide significantly heightens liver injury risks. Up to 20% of the patients receiving isoniazid either in single or combination therapy develop transient asymptomatic elevation in liver enzymes, which settle with continued use of the drug.⁵ Manifestation of the anti-tuberculous drug induced hepatotoxicity can vary from asymptomatic elevations in the liver enzymes to fulminant liver failure. Drug-induced liver injury generally has a hepatocellular pattern. The burden of anti-tuberculous drug related hepatotoxicity is based not only on its prevalence or incidence, but also on its severity and outcome. The median interval from treatment initiation of the drug to development of clinical symptoms is 16 weeks (range 6 weeks–6 months).⁶

Anti-TB drug-induced fulminant liver failure appears to have a worse outcome when compared with that related to acute viral hepatitis with a case fatality rate between 0.042 and 0.07 per 1000 persons at any given time during therapy. Liver biopsy specimens, when available, reveal lobular hepatitis, sub massive to massive necrosis, and hydropic degeneration of hepatocytes in severe cases. In cases associated with rifampicin hepatotoxicity, focal hepatocellular necrosis and apoptosis in zone 3 and cholestasis have been noted on histology. This study assesses DILI prevalence in TB patients and identifies factors like alcohol consumption, hepatitis, and drug regimens influencing hepatotoxicity.⁷⁻¹¹ The study was conducted in a tertiary healthcare center to assess the severity and frequency of hepatotoxicity caused by antituberculosis (ATT) drugs and to evaluate whether concurrence of risk factors influence the antituberculosis drug induced hepatotoxicity.

OBJECTIVES

1. To study the incidence of hepatotoxicity caused by antituberculosis (ATT) drugs
2. To study the severity of hepatotoxicity caused by antituberculosis (ATT) drugs
3. To study the various risk factors associated with hepatotoxicity in TB patients taking ATT

METHODS

This analytical cross-sectional study was conducted at a tertiary healthcare center, focusing on all patients diagnosed with tuberculosis and undergoing antituberculosis (ATT) drug treatment who visited the department of respiratory medicine. The study included participants meeting the inclusion criteria, after obtaining approval from the institutional ethical committee and consent from the participants. The study duration was 6 months.

A convenience sampling method was used to enroll the study subjects who met the inclusion criteria during the study duration. Based on the article by Molla et al., the incidence of hepatotoxicity was estimated at 8.9%. Using this information, the required sample size was calculated to be 125 subjects.¹²

The sample consisted of consecutive subjects who met all eligibility criteria, consented to participate, and were receiving anti-tubercular treatment and care at the study hospital. These subjects were selected from the respiratory medicine department, inpatient department (IPD), outpatient department (OPD), and intensive care unit (ICU) using a convenience sampling method.

SELECTION CRITERIA FOR STUDY SUBJECTS

Inclusion Criteria: All adult patients (>18 years) diagnosed with TB (pulmonary, extrapulmonary, or both) who tested positive for the first time and started anti-TB medication (First Line Drugs) were included.

Exclusion Criteria: Patients with baseline ALT and AST values greater than two times the upper limit of normal (ULN) were excluded from the study.

Methods: The study began after receiving institutional ethical committee approval and obtaining written informed consent from the participants. Over the study duration of 6 months, demographic information, clinical history, and examination findings were recorded using a standard, semi-structured, pre-validated case record. Hepatotoxicity was categorized into different grades based on the WHO grading system using ALT and/or AST levels. Treatment plans for patients with hepatotoxicity were determined by their respective physicians based on laboratory findings and individual patient complaints.

Grade & Level	Toxicity
1 – Mild	Transient or mild discomfort; no limitation in (in activity; no medical intervention or therapy required.
2 – Moderate	Mild to moderate limitation in activity, some assistance may be needed; none or minimal medical intervention or therapy required.
3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization is possible.
4 – Life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care are probable.

GRADES OF TOXICITY RESULTING FROM TB TREATMENT

Statistical Analysis: Data were coded and analyzed using SPSS version 22. Descriptive statistics included summary measures such as mean and standard deviation for quantitative variables (e.g., age) and frequency and percentages for categorical variables. The Chi-square test or Fisher’s exact test was used to evaluate associations between qualitative variables, with a p-value <0.05 considered statistically significant for all comparisons.

Ethical Considerations: Patient participation was kept confidential, and data privacy was maintained. Data were anonymized and securely stored to restrict access to only the study team members, the ethics committee, and representatives of national and local health authorities. Patient names were accessible only to the study doctor and staff, authorized study representatives, designated study monitors, and auditors. The study was initiated after IEC approval.

RESULTS

The study included a diverse group of patients categorized based on various parameters. The patients’ ages had a mean of 47.66 ± 14.50 years. The ages ranged in a broad distribution from 23 to 83 years. Seventy-six patients (60.8%) were male, and 49 patients (39.2%) were female.

The body mass index (BMI) of the study participants had a mean of 21.40, ±3.02; values ranged from 15.2 to 28.4 (Table 1).

Some patients had comorbidities: 11 patients (8.8%) had diabetes mellitus (DM), 15 patients (12%) had hypertension, 4 patients (3.2%) had ischemic heart disease (IHD), and 1 patient (0.8%) had tuberculosis. Eighty-eight patients (70.4%) had pulmonary TB, and 37 patients (29.6%) had extrapulmonary TB. Sixteen patients (12.8%) were alcoholics, and 14 patients (11.2%) were smokers. These distributions provide a comprehensive overview of the study population’s demographics and health-related characteristics, essential for understanding the context and implications of the research findings.

The clinical presentations of the study participants included various symptoms and conditions. A reduced diet was observed in 19 subjects (15.2%), while 20 subjects (16%) experienced easy fatiguability. Breathlessness affected 8 subjects (6.4%), and swelling of the feet (pedal edema) was seen in 4 subjects (3.2%). Oliguria and vomiting were each reported by 3 subjects (2.4%) (Table 2).

Generalized weakness was a symptom in 17 patients (13.6%), and poor nutrition was noted in 14 subjects (11.2%). Pruritus was experienced by 3 patients (2.4%), while anuria was observed in

Table 1. Demographic Information

Parameters	Number	Number	Percentage
Age distribution	Less than 35 years	29	23.2
	36 to 45 years	25	20
	46 to 55 years	28	22.4
	56 to 65 years	25	20
	More than 65 years	18	14.4
Gender distribution	Males	76	60.8
	Females	49	39.2
BMI	Less than 18.5	29	23.2
	18.5 to 22.9	55	44
	23 to 24.9	28	22.4
	More than 25	11	8.8
Comorbidities	DM	11	8.8
	Hypertension	15	12
	IHD	4	3.2
	Tuberculosis	1	0.8
Extent of TB	Pulmonary	88	70.4
	Extrapulmonary	37	29.6
Addictions	Alcoholism	16	12.8
	Smoking	14	11.2

Table 2. Clinical Presentation

Clinical Presentation	Number	Percentage
Reduced Diet	19	15.2
Easy Fatiguability	20	16
Pallor	17	13.6
Icterus	7	5.6
Breathlessness	8	6.4
Swelling of feet (pedal edema)	4	3.2
Oligouria	3	2.4
Vomiting	3	2.4
Generalised weakness	17	13.6
Poor Nutrition	14	11.2
Pruritis	3	2.4
Anuria	2	1.6
Hematuria	1	0.8
Jaundice	5	4
H/O Liver cirrhosis	2	1.6
H/O Kidney disease	3	2.4

2 patients (1.6%). Hematuria was reported in 1 patient (0.8%), and jaundice was present in 5 subjects (4%). A history of liver cirrhosis was reported by 2 patients (1.6%), and a history of kidney disease was noted in 3 patients (2.4%).

The study assessed the grades of hepatotoxicity among the participants. It was found that 102 subjects (81.6%) experienced no hepatotoxicity (Grade 0). Mild hepatotoxicity (Grade 1) was observed in 7 subjects (5.6%), moderate hepatotoxicity (Grade 2) in 5 patients (4%), and severe hepatotoxicity (Grade 3) in 6 patients (4.8%). The most severe grade of hepatotoxicity (Grade 4) was seen in 5 patients (4%). In total, 125 patients were included in the study, encompassing the entire population assessed (Figure 1).

The study examined the correlation between grades of hepatotoxicity and two biochemical markers: ALT and total bilirubin (Table 3). The correlation coefficient (r-value) between ALT and the grades of hepatotoxicity

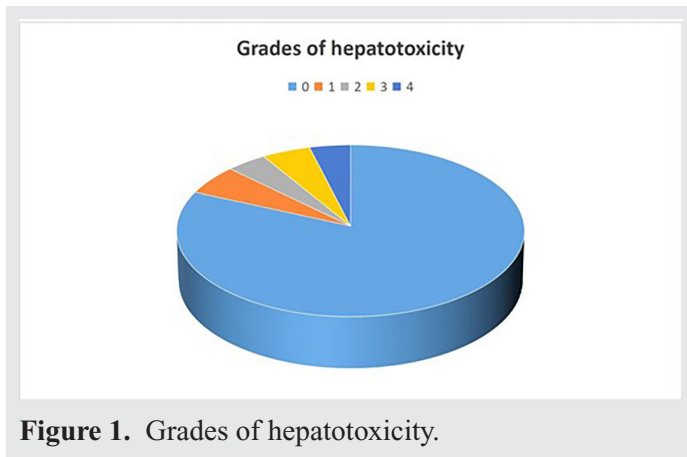


Figure 1. Grades of hepatotoxicity.

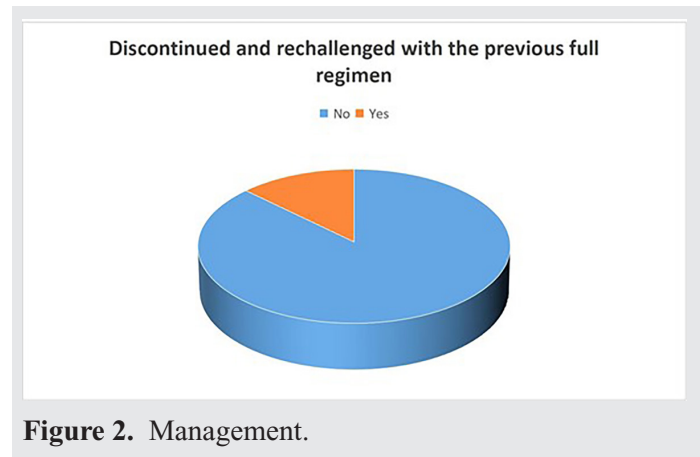


Figure 2. Management.

was 0.56, with a highly significant p-value of less than 0.0001. This indicates a moderate positive correlation, suggesting that higher ALT levels are associated with higher grades of hepatotoxicity.

Similarly, the correlation coefficient (r-value) between total bilirubin and the grades of hepatotoxicity was 0.67, with a p-value also less than 0.0001. This indicates a strong positive correlation, suggesting that higher total bilirubin levels are strongly associated with higher grades of hepatotoxicity.

These findings highlight the significant relationship between these biochemical markers and the severity of hepatotoxicity in patients undergoing antituberculosis treatment.

Regarding the management of patients who developed hepatotoxicity, 109 subjects (87.2%) did not need to discontinue their treatment and were given symptomatic treatment for their adverse drug reactions. However, for the 16 subjects (12.8%) who developed severe adverse effects, ATT was discontinued, and they later were rechallenged with the previous regimen once LFT returned to normal levels (Figure 2).

Table 3. Correlation Between Grades of Hepatotoxicity and Liver Function Parameters

Correlation Between	Grades of Hepatotoxicity
ALT	0.56 (p-value: <0.0001)
Total Bilirubin	0.67 (p-value: <0.0001)

DISCUSSION

The present study provides a comprehensive analysis of the incidence and severity of hepatotoxicity due to anti-tubercular treatment in a diverse cohort of tuberculosis patients, as well as the associated risk factors.

The study population had a mean age of 47.66 ± 14.50 years, and ranged from 23 to 83 years, demonstrating a wide age distribution. The gender distribution was skewed towards males, with 60.8% of the participants being male. This male predominance aligns with the global epidemiology of TB, which often shows higher rates in males compared to females.

The mean BMI was $21.40, \pm 3.02$, indicating a generally healthy weight range among the participants. However, the presence of comorbidities such as diabetes mellitus (8.8%), hypertension (12%), and ischemic heart disease (3.2%) highlights the complex health profiles of the TB patients in this study. The majority of the participants had pulmonary TB (70.4%), with the remaining having extrapulmonary TB (29.6%).

In their study, Saha et al. observed that the following risk factors were prevalent: chronic alcohol consumption in 26 patients, Hepatitis B infection in 2 patients, Hepatitis C infection in 1 patient, HIV infection in 37 patients, and chronic TB in 21 patients.¹³

The clinical symptoms reported by the patients included reduced diet (15.2%), easy fatiguability

(16%), and generalized weakness (13.6%). These symptoms are commonly associated with TB and can be exacerbated by ATT. The presence of icterus (5.6%) and jaundice (4%) in a subset of patients suggests potential liver dysfunction, which is a known side effect of ATT. The study found that 81.6% of the subjects experienced no hepatotoxicity (Grade 0), indicating that the majority of patients tolerate ATT well. However, a significant minority experienced varying degrees of hepatotoxicity, with 5.6% having mild (Grade 1), 4% moderate (Grade 2), 4.8% severe (Grade 3), and 4% very severe (Grade 4) hepatotoxicity. These findings underscore the importance of monitoring liver function in patients undergoing ATT.

A study in Taiwan by Shang and colleagues reported a prevalence of drug-induced liver injury (DILI) from tuberculosis treatment at 12% (111/926) within a median of 38 days from the start of treatment, with 3.5% developing severe DILI. In China, the prevalence was 10.4% (267/2457) within the first 2 months of treatment.¹⁴ Independent risk factors for DILI identified in a study from Peru by Chung-Delgado et al. included overweight/obesity and smoking,¹⁵ while Pande et al. in India found advanced age, hypoalbuminemia, high alcohol intake, slow acetylator phenotype, and associated chronic diseases to be significant risk factors.¹⁶ Previous Indian studies by Ungo et al.¹⁷ and Sulkowski et al.¹⁸ demonstrated that HIV coinfection, due to the concomitant use of protease inhibitors, and HBV coinfection are also associated with increased DILI risk. Similarly, the study by Saha et al. reported a prevalence of DILI at 9.48%, but without any associated risk factors.¹³

The correlation analysis revealed a moderate positive correlation between ALT levels and the grades of hepatotoxicity ($r = 0.56$, $p < 0.0001$), and a strong positive correlation between total bilirubin levels and the grades of hepatotoxicity ($r = 0.67$, $p < 0.0001$). These significant correlations indicate that both ALT and total bilirubin are valuable markers for assessing the severity of hepatotoxicity in TB patients receiving ATT.

The therapeutic approach to managing drug-induced liver injury is quite challenging. Current recommendations suggest withholding anti-TB drugs until liver function normalizes. The American Thoracic Society

advises starting a new treatment regimen once liver enzyme levels are below twice the upper limit of normal. The reintroduction of hepatotoxic ATT drugs must be carefully balanced against their benefits, necessitating thorough supervision and close monitoring. Baseline laboratory testing and ongoing monitoring should be ensured throughout the ATT treatment process.¹⁹⁻²¹

In managing hepatotoxicity, the majority of patients (87.2%) did not need to discontinue their treatment and were given symptomatic treatment for their adverse drug reactions. However, for the 16 subjects (12.8%) who developed severe adverse effects, ATT was discontinued and they later were rechallenged with the previous regimen once liver enzymes returned to normal levels, highlighting the necessity for individualized treatment strategies and close monitoring to mitigate adverse effects while maintaining therapeutic efficacy.

These findings highlight the critical need for regular monitoring of liver function tests, including ALT and total bilirubin, in TB patients undergoing ATT to detect and manage hepatotoxicity promptly. Additionally, the identification of risk factors such as comorbidities and specific clinical symptoms can aid in early intervention and tailored treatment plans to improve patient outcomes.

CONCLUSIONS

The incidence of hepatotoxicity is relatively high among TB patients taking first-line anti-TB drugs. The high incidence of ATT drug-induced liver injury emphasizes the public health importance of this side effect. The results emphasize the importance of acquired risk factors in the development of DILI and require careful monitoring in the first 2 months.

Thus, the liver function of patients should be regularly monitored to reduce the severity of drug-induced hepatotoxicity, possibly shortening treatment interruption and reducing mortality.

The combination of risk factors of extensive TB disease, HIV infection, chronic liver disease, and under nutrition increases the vulnerability to DILI, particularly with daily treatment regimen, emphasizing the role of acquired risk factors in the development of DILI.

Article citation: Songtakke A, Pati R, Ali S, et al. The incidence of hepatotoxicity due to anti-tubercular treatment and its associated risk factors in patients with tuberculosis: An analytical cross-sectional study. *The Southwest Journal of Medicine* 2025;13(56):1–7

From: Department of Respiratory Medicine (AS, RP, SA, NG), NKPSIMS & Lata Mangeshkar Hospita, Hingna, Nagpur, Maharashtra, India

Submitted: 4/8/2025

Accepted: 6/29/2025

Conflicts of interest: none

This work is licensed under a Creative Commons Attribution-ShareAlike 4.0 International License.

REFERENCES

- Adigun R, Singh R. Tuberculosis. [Updated 2023 Jul 11]. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441916/>
- Saukkonen JJ, Cohn DL, Jasmer RM. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935–52.
- Younossian AB, Rochat T, Ketterer JP. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis. *Eur Respir J* 2005;26:462–4.
- Papastavros T, Dolovich LR, Holbrook A. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. *CMAJ*. 2002; 167:131–6.
- Prince MI, Burt AD, Jones DE. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002;50:436–9.
- Verma R, Khanna P, Mehta B. Revised national tuberculosis control program in India: the need to strengthen. *Int J Prev Med* 2013 Jan;4(1):1–5.
- LoBue PA, Moser KS. Isoniazid- and rifampin-resistant tuberculosis in San Diego County, California, United States, 1993–2002. *Int J Tuberc Lung Dis* 2005;9:501–6.
- Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *J Am Med Assoc*. 1999; 281:1014–18.
- Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis* 1992; 145:494–7.
- Steele MA, Burk, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991;99: 465–71.
- Chang KC, Leung CC, Yew WW. Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? *Eur Respir J* 2007; 29:347–51.
- Molla Y, Wubetu M, Dessie B. Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. *Hepat Med*. 2021 Jan 28;13:1–8. doi: 10.2147/HMER.S290542.
- Saha A, Shanthi FXM, Winston AB, et al. Prevalence of Hepatotoxicity From Antituberculosis Therapy: A Five-Year Experience From South India. *J Prim Care Community Health* 2016 Jul;7(3):171–4.
- Shang P, Xia Y, Liu F, et al. Prevalence, clinical features and impact on anti-tuberculosis Treatment of anti-tuberculosis drug induced liver injury (ATLI) in China. *PLoS One* 2011;6:e21836.
- Chung-Delgado K, Revilla-Montag A, Guillen-Bravo S, et al. Factors associated with anti-tuberculosis medication adverse effects: a case-control study in Lima, Peru. *PLoS One* 2011;6:e27610.
- Pande JN, Singh SP, Khilnani GC, et al. Risk factor for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996;5:132–6.
- Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med* 1998;157:1871–6.
- Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000;283:74–80.
- Wong WM, Wu PC, Yuen MF, et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000;31:201–6.
- World Health Organization Treatment of tuberculosis guidelines. http://apps.who.int/iris/bitstream/10665/44165/1/9789241547833_eng.pdf. Accessed November 6, 2015.
- Jong E, Conradie F, Berhanu R, et al. Consensus statement: management of drug induced liver injury in HIV positive patients treated for TB. *S Afr. J HIV Med* 2013;14: 113–19.