International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Reintroduction of Anti-Tubercular Therapy After Hepatotoxicity: Comparative Outcomes of World Health Organization, American Thoracic Society, and British Thoracic Society Protocols

Dr Ajaz Nabi Koul[1], Dr Ishrath Syeed[2], Dr Qayoom Yousuf[3]

[1]Professor and Head, Infectious Disease Division, Department of Internal Medicine, SKIMS Srinagar, India
[2]Senior Resident, Department of Internal Medicine, SKIMS MCH Srinagar, India
[3]Senior Resident, Department of Cardiology, SKIMS Srinagar, India

OPEN ACCESS

Corresponding Author:

Dr Qayoom Yousuf
Senior Resident, Department of Cardiology, SKIMS Srinagar, India

Received: 21-12-2025
Accepted: 11-01-2026
Available online: 21-01-2026

ABSTRACT

Background: Anti-tubercular therapy (ATT) is frequently complicated by drug-induced hepatotoxicity. Following the development of drug-induced hepatitis, multiple guidelines exist for reintroducing first-line ATT drugs, but comparative data are limited. This study sought to evaluate and compare the outcomes of different reinstitution strategies in patients recovering from ATT-induced hepatotoxicity.

Methods: In this prospective observational study, 98 patients with ATT-induced hepatitis were randomized to one of three reintroduction protocols: World Health Organization (WHO, Arm 1), American Thoracic Society (ATS, Arm 2), or British Thoracic Society (BTS, Arm 3). Baseline demographics, liver function tests, and clinical features were recorded. Patients were followed for recurrence of hepatitis after re-exposure.

Results: The mean age was 44.9 years; 55 (56.1%) patients were females. The predominant presenting symptoms were vomiting in 66 (67.3%), nausea in 60 (61.2%), and abdominal pain in 57 (58.1%) of patients. 18 (18.4%) patients developed recurrent hepatitis, including five (15.2%) in the WHO arm, six (18.2%) in the ATS arm, and seven (21.9%) in the BTS arm (p = 0.78). Recurrence was more likely in patients with higher baseline bilirubin and alkaline phosphatase (ALP); and lower albumin at the first hepatitis episode.

Conclusion: Recurrence rates did not differ significantly across the three regimens. However, the WHO protocol, which employs full-dose reintroduction from the first day, was simpler to implement, associated with shorter hospital stay, and better suited to high-burden, resource-limited settings.

Keywords*: Tuberculosis (TB), ATS/BTS/WHO , Hepatotoxicity, Anti-Tubercular.*

INTRODUCTION

Tuberculosis (TB) continues to be a significant global health challenge and, in 2023, was the leading infectious cause of death worldwide, exceeding HIV/AIDS. An estimated 10.8 million people developed TB that year, and 1.25 million died of it.Although TB can affect anyone anywhere, most people who develop the disease (nearly 90%) are adults; with more cases occurring among men than women (55% vs. 33%). Of those who fell sick with TB in 2023, about 87% were concentrated in 30 high TB burden countries with India accounting for nearly one-fourth of the global tuberculosis burden (26%), making it the country with the highest number of TB cases worldwide [1-2]. Individuals with HIV have a 6-50 fold higher risk of developing tuberculosis [3].This overlap in population with both TB and HIV has led to the characterization of TB and HIV as “cursed duet” [4]. The COVID-19 pandemic has likely reshaped TB trends. While distancing may have limited spread, its benefits were offset by late diagnosis, longer infectious periods, increased household exposure, and worsening socioeconomic conditions that collectively impaired treatment outcomes.

The treatment of tuberculosis still relies on the classic first-line agents—isoniazid, rifampicin, pyrazinamide, and ethambutol - introduced more than fifty years ago. Among their side effects, hepatotoxicity (drug-induced liver injury,

DILI) is of greatest concern. Multiple organizations, including the World Health Organization (WHO) [1], American Thoracic Society (ATS) [5],British Thoracic Society (BTS) [6] and the International Union Against Tuberculosis and Lung Disease have published guidelines on managing this complication. Our study aimed to evaluate the safety and effectiveness of three anti-TB drug reintroduction protocols (WHO, ATS, and BTS), in patients who developed drug-induced hepatitis.

Materials and methods

This prospective observational study was carried out at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS), a tertiary care center in northern India, over a period of two years. Eligible participants included patients attending the Infectious Diseases outpatient clinic, as well as those admitted to the General Medicine ward with a diagnosis of TB, who subsequently developed ATT-induced hepatitis. In total, 103 patients with clinical and/or laboratory evidence of drug-induced hepatitis during anti-tubercular therapy were enrolled, of which five patients not meeting the inclusion criteria were excluded, leaving 98 patients for the final analysis.

Inclusion and exclusion criteria:

The study population comprised individuals who developed hepatitis while on anti-tubercular therapy (ATT) and met at least one of the primary inclusion criteria: Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) on a single occasion, or ≥3 times ULN on three consecutive tests; or an increase in transaminases above baseline accompanied by symptoms of hepatotoxicity (for example nausea, anorexia, vomiting, or jaundice); or a total bilirubin level of > 1.5 mg/dL. Supporting evidence included a negative serology for hepatitis A, B, C, and E; and improvement in liver function tests after withdrawal of ATT.[5]

Patients were excluded if they had serological evidence of active viral hepatitis (A, B, C, or E), established chronic liver disease, pregnancy and baseline liver function abnormalities unrelated to ATT.

Data Collection

Data were collected about the symptoms of tuberculosis, the type of tuberculosis whether (pulmonary, extra-pulmonary or disseminated), past history of tuberculosis, family history of tuberculosis and the use of other hepatotoxic drugs were recorded. History about other comorbid conditions like Type 2 Diabetes Mellitus, other liver conditions was noted. Nutritional status was evaluated using body mass index (BMI). Laboratory assessments included complete blood counts (CBC), serial liver function tests (LFTs), as well as serum protein and albumin levels.

Study Protocol

This was a prospective, observational clinical study conducted to evaluate the safety and efficacy of three reintroduction strategies for anti-tubercular therapy (ATT) following drug-induced hepatitis. The principal outcome measure was recurrence of hepatitis after re-exposure to first-line drugs.

After fulfilling eligibility criteria, patients with ATT-related hepatitis had all first-line drugs discontinued. They were temporarily managed with second-line non-hepatotoxic agents, including ethambutol, fluoroquinolones, and streptomycin. Clinical status and liver function tests were reviewed weekly until the normalization. Once stable, patients were randomized using computer-generated block randomization (blocks of three) into one of three reintroduction strategies. In the WHO regimen (Arm 1), isoniazid, rifampicin, and pyrazinamide were reintroduced simultaneously at full therapeutic doses from the first day. In the ATS regimen (Arm 2), rifampicin was restarted at full dose on Day 1, followed by isoniazid at full dose on Day 8 and pyrazinamide at full dose on Day 15. In contrast, the BTS regimen (Arm 3) involved a stepwise titration beginning with low-dose isoniazid (100 mg/day) on Day 1, escalated to full dose by Day 4; rifampicin 150 mg/day on Day 8, escalated to full dose by Day 11; and pyrazinamide 500 mg/day on Day 15, escalated to full dose by Day 18.

Lab monitoring

All patients were screened for markers of active viral hepatitis, and abdominal ultrasonography was performed to assess for hepatitis, fatty liver, or chronic liver disease. During reintroduction of ATT, LFTs were obtained prior to adding a new drug or escalating the dose, and subsequently monitored to detect recurrence of hepatotoxicity - weekly during the first month, every two weeks in the second month, and once at the end of the third month.

Statistical Analysis

Categorical variables were compared using Pearson's chi-square test. Continuous variables were analyzed with one-way analysis of variance (ANOVA) and independent samples t-test, as appropriate. A p-value <0.05 was taken as the threshold for statistical significance. Data processing and analysis were performed using SPSS software, version 22 (IBM Corp., Armonk, NY, USA).

Results

Of the initial 103 enrolled patients who developed clinical and biochemical features of ATT-induced hepatitis, five were excluded: two had underlying chronic liver disease, one was on concomitant hepatotoxic medication, one tested positive

for active hepatitis C infection, and one died before reintroduction of therapy. The remaining 98 patients achieved stabilization of liver function and were subsequently randomized into one of the three treatment arms.

Patient Characteristics

Among the 98 patients, 23 (23.5%) patients had pulmonary tuberculosis, while the remaining had extra-pulmonary tuberculosis. Among extra-pulmonary forms, pleural tuberculosis was the most frequent, occurring in 18 patients (18.36%), followed by tuberculous meningitis in 12 patients (12.2%), intestinal tuberculosis and Pott's disease in 11 patients each (11.2%), genitourinary and lymph node tuberculosis in 6 patients each (6.1%), peritoneal tuberculosis in 3 patients (3.1%), pericardial involvement in 1 patient (1%), and 7 patients (7.14%) had other forms. The most common presenting symptoms in our study were vomiting in 66 (67.3%), nausea in 60 (61.2%), abdominal pain in 57 (58.1%), anorexia in 49 (50%), jaundice in 28 (28.5%), dizziness in 26 (26.5%) and altered sensorium in 18 (18.36%) patients. The patients were evenly distributed among the three arms. Table 1 and 2 compare the baseline parameters of the three arms of patients. The mean age of our study cohort was 44.9 years$\pm$19.02. Patients in Arm-2 were significantly older (p = 0.003) than Arm-1 and Arm-3. Females represented 55 (56.1%) of patients in the study. The mean BMI of the study population was 22.1 ± 3.3 kg/m², while the average hemoglobin level was 11.5 ± 0.7 g/dL. Liver function parameters were largely comparable across the three groups, except for AST, which was elevated in Arm 1, and serum protein, which was significantly lower in Arm 2.

A total of 18 (18.4%) patients experienced recurrence of hepatitis in our study. 5 patients (15.2%) in Arm-1, 6 (18.2%) in Arm-2 and 7 (21.9%) in Arm-3 developed recurrence; although without any statistical difference across the arms (0.78). The maximum derangement of serum Bilirubin, AST, ALT and ALP was similar in all the three Arms (Table 4). Patients who had recurrence were compared with other patients who tolerated ATT with respect to clinical and lab parameters and with respect to the severity of the first episode of hepatitis. Mean pre-treatment serum albumin level in patients with recurrence was 3.32±0.50 mg/dL as compared to 3.58 ± 0.41 mg/dL in patients who tolerated ATT (p = 0.04). Bilirubin and ALP of recurrence patients was high at the time of first episode as compared to non-recurrence patients. Bilirubin 3.20 ±2.79 mg/dL in recurrence patients as compared to bilirubin 1.70±1.91 mg/dL in non-recurrence patients (p value 0.007) and ALP 269.66 ± 332.79 IU/L as compared to 203.43 ± 116.26 IU/L in non-recurrence patients (p = 0.01). In our study, the severity of the initial hepatitis episode was found to influence the likelihood of recurrence. Overall, 12 patients (12.2%) died during the study period, with causes including disseminated tuberculosis, underlying comorbidities, multiorgan dysfunction, and acute liver failure.

Table 1. Baseline demographic and clinical characteristics of the study population across the three reintroduction arms. Continuous variables were compared using one-way analysis of variance (ANOVA). Categorical variables were compared using the Pearson Chi-square test.

Table 1:

Parameter	Arm-1 (n = 33)	Arm-2 (n = 33)	Arm-3 (n = 32)	Statistical test used	p-value
Age (years), mean ± SD	42.48 ± 19.02	51.63 ± 15.09	40.50 ± 21.19	ANOVA	0.03
Female sex, n (%)	16 (48.5%)	20 (60.6%)	19 (59.4%)	Chi-square	0.55
BMI (kg/m²), mean ± SD	22.64 ± 3.60	21.92 ± 2.93	21.63 ± 3.19	ANOVA	0.43
Hemoglobin (g/dL), mean ± SD	12.00 ± 0.70	11.16 ± 0.70	11.22 ± 0.70	ANOVA	0.09
Rural residence, n (%)	26 (78.8%)	27 (81.8%)	27 (84.4%)	Chi-square	0.83
Urban residence, n (%)	7 (21.2%)	6 (18.2%)	5 (15.6%)	Chi-square	—
Family history of TB, n (%)	1 (3.0%)	3 (9.1%)	3 (9.4%)	Chi-square	0.53
Past history of TB, n (%)	1 (3.0%)	3 (9.1%)	3 (9.4%)	Chi-square	0.53

Table 2. Baseline liver function parameters before initiation of ATT among the three study arms.Comparisons were performed using one-way ANOVA.

AST = Aspartate aminotransferase; ALT = Alanine, aminotransferase; ALP = Alkaline phosphatase; IU = International Units.

Table 2:

Baseline LFT	Arm-1	Arm-2	Arm-3	Statistical test used	p- value
Sr. Bilirubin, mg/dL	0.76 ± 0.22	0.74 ± 0.24	0.66 ± 0.28	ANOVA	0.22
AST, IU/L	42.3 ± 14.64	31.21± 22.99	35.25 ± 14.86	ANOVA	0.04
ALT, IU/L	45.03 ± 19.66	33.72 ± 22.27	40.75 ± 16.52	ANOVA	0.06
ALP, IU/L	108.63 ± 30.83	125.72 ± 38.51	106.65 ± 42.48	ANOVA	0.08
Sr. Protein, g/dL	6.94 ± 0.89	6.47± 0.67	6.99 ± 0.78	ANOVA	0.017
Sr. Albumin, g/dL	3.43 ± 0.48	3.43 ± 0.42	3.49 ± 0.51	ANOVA	0.85

Table 3 compares the maximum derangement of LFT in the three study arms. The average stabilization period in our study was 15$\pm$7 days. Liver function test profiles were comparable across the three arms, and all patients were monitored

with serial LFTs during follow-up.Maximum liver function derangements prior to reintroduction of ATT in the three study arms. Comparisons were performed using one-way ANOVA.

Table 3

Parameter	Arm-1	Arm-2	Arm-3	Statistical test used	p-value
Sr. Bilirubin (mg/dL)	1.68 ± 1.23	1.83 ± 2.43	2.43 ± 2.58	ANOVA	0.34
AST level (IU/L)	176 ± 132.23	177.30 ± 122.86	175.31 ± 122.0	ANOVA	0.99
ALT level (IU/L)	247.0 ± 191.81	209.57 ± 135.02	238.18 ± 205.70	ANOVA	0.67
ALP level (IU/L)	210.75 ± 192.01	184.57 ± 155.73	266.96 ± 338.12	ANOVA	0.37
Sr. Protein (g/dL)	6.89 ± 0.95	6.51 ± 0.62	6.77 ± 0.73	ANOVA	0.13
Sr. Albumin (g/dL)	3.36 ± 0.53	3.33 ± 0.51	3.25 ± 0.75	ANOVA	0.73
Stabilization Period (Median Days)	15 ± 7 (5-37)	15 ± 5 (5-25)	16 ± 7 (5-39)	ANOVA	0.83

Table 4. Comparative liver function derangements in patients with recurrence of ATT induced hepatitis after rechallenge across the three study arms. Continuous LFT parameters were compared using one-way ANOVA. Recurrence of hepatitis (categorical variable) was compared using the Pearson Chi-square test.

Table 4:

Parameter	Arm-1	Arm-2	Arm-3	Statistical test used	p- value
Sr. Bilirubin (mg/dL)	3.14 ± 61.8	3.32 ± 4.38	3.13 ± 2.14	ANOVA	0.99
ALT level (IU/L)	130.0 ± 61.8	150.0 ± 65.97	258.85 ± 341.56	ANOVA	0.55
AST level (IU/L)	83.2 ± 24.9	143.3 ± 56.8	129.2 ± 87.8	ANOVA	0.32
ALP level (IU/L)	174 ± 70.4	162.6 ± 42.8	429.7 ± 509.8	ANOVA	0.28
No. of patients with recurrence	5	6	7	Chi-square	0.78
Time period of recurrence (days)	50 (9-175)	37 (17-91)	58 (6-164)	ANOVA	0.78

Discussion

Anti-tubercular therapy (ATT) is linked to multiple adverse effects, the most frequent and clinically significant being hepatotoxicity, which often results in interruption of treatment. Among the first line agents, Isoniazid and Rifampicin are the most commonly used drugs in the treatment of tuberculosis of any part of the body. The incidence of hepatotoxicity by combined Isoniazid and Rifampicin therapy is approximately 2.6%, compared to 1.1% and 1.6% with monotherapy, respectively [6-7].

In our study, 103 patients who developed ATT-related drug-induced hepatitis were enrolled initially. With the exclusion of 5 patients from the study, ATT was reintroduced in 98 patients after randomization into three groups to evaluate the different reintroduction strategies. Out of these patients, 18 (18.4%) experienced recurrence of hepatitis. In Arm 1, 5 (15.2%) patients had recurrence, 6 (18.2%) and 7 (21.9%) patients had recurrence in Arm 2 and Arm 3 respectively. Although the difference was not statistically significant ($p > 0.05$), recurrence appeared slightly higher in the BTS arm. This finding carries clinical relevance in high-burden settings such as India, where early initiation of all three drugs can facilitate faster sputum conversion, thereby reducing transmission in patients with smear-positive pulmonary tuberculosis.

Overall mortality in the study cohort was 12 patients (12.2%). This mortality is at the higher end of the range reported in earlier series on ATT-induced hepatotoxicity (6–12%) [8-11], and is substantially greater than that observed in general tuberculosis cohorts. In our study - advanced disease at baseline, disseminated TB, and severe comorbidities likely contributed, with two deaths directly due to acute liver failure.

In our study patients with recurrence had high bilirubin and ALP at the time of first episode of hepatitis, suggesting that the severity of the initial hepatitis episode may predict recurrence risk. Our findings are in line with those of Gaude et al. [7], who reported a 14% recurrence rate of DILI. In their study, prior hepatitis episodes, previous anti-TB therapy, age over 60 years, extensive disease, hypoalbuminemia, and alcohol use were identified as significant risk factors for recurrence.

Patient compliance and the practicality of implementing each regimen were important considerations. Overall, the WHO protocol was perceived as the easiest to administer, followed by the ATS and then the BTS regimens. All the three guidelines for reintroduction differ in their duration of time. WHO full dose, same day regimen after the recovery of LFT was easier to administer and follow. Also administration of all drugs simultaneously limits the spread of tuberculosis. It also facilitated shorter hospital stays and improved treatment adherence. In contrast, the stepwise escalation protocols recommended by ATS and BTS are more difficult to implement There is no weekly follow up in WHO protocol compared to ATS and BTS. BTS guidelines are more difficult to follow especially in rural areas where most of the

patients with drug induced hepatitis belong to far off places and frequent monitoring and follow ups are challenging. And if these guidelines are followed during the period of admission - the approach will prolong hospitalization, thereby increasing financial costs and psychosocial stress for patients, while also heightening the risk of hospital-acquired infections.This aligns with the work by Sharma et al. [8], who evaluated the safety and efficacy of three reintroduction strategies for anti-tubercular drugs in patients with ATT-induced hepatitis. In their trial, 175 patients were randomized, and 19 (10.9%) experienced recurrence. The authors concluded that isoniazid, rifampicin, and pyrazinamide can be safely reintroduced at full therapeutic doses from Day 1, a strategy that may help limit disease transmission.Zuberi et al. [9] compared the BTS and ATS reintroduction protocols and reported no significant difference in outcomes between the two. While the BTS approach involves slow, incremental dose escalation, the ATS regimen was considered simpler and more practical to implement.

Although most studies show similar recurrence rates in WHO, ATS and BTS reintroduction regimens. However some studies have shown differing results.Tahaoglu et al. [10] in Turkey carried out a prospective study involving 45 patients with ATT-induced hepatotoxicity, which were allocated into two retreatment strategies. In the first protocol, isoniazid, rifampicin, ethambutol, and streptomycin were restarted gradually with stepwise dose escalation, while in the second, isoniazid, rifampicin, pyrazinamide, and ethambutol were reintroduced at full therapeutic doses from the outset. Recurrence of hepatotoxicity was observed in none of the patients managed with the gradual reintroduction approach, compared with 24% in the group that received immediate full doses. The findings, however, are constrained by the limited sample size and the relatively lower biochemical cut-offs employed for defining hepatotoxicity.

Limitations:
This study had several limitations. The cohort size was relatively small, and of patients and many patients had comorbidities requiring drugs which have multiple interactive effects to drug induced liver injury, its recovery and thus hampering reinstitution of drugs. These confounders may have affected the assessment of causality and the comparative efficacy of reintroduction strategies.

Conclusions:
This study demonstrates that most patients recovering from ATT-induced hepatotoxicity can safely resume first-line therapy when reintroduced through structured, guideline-based protocols. Although no statistically significant differences in recurrence or complications were observed among the three reintroduction regimens and none of the three methods of reinstitution score over each, the WHO regimen stood out for its simplicity and ease of implementation, making it especially suitable for high-burden, resource-limited settings. The findings also highlight that patient-specific factors, particularly the severity of the initial hepatic injury, and nutritional status play an important role in determining tolerance to re-exposure. These observations emphasize the need for individualized assessment, careful monitoring, and supportive care during reintroduction. With appropriate supervision, hepatotoxicity should not prevent successful completion of standard ATT, and streamlined protocols may further enhance treatment continuity and outcomes in real-world practice.

References:

1. World Health Organization. Global tuberculosis report 2024. Geneva : World Health Organization; 2024.
2. Hershkovitz I, Donoghue HD, Minnikin DE, et al. Tuberculosis origin: the Neolithic scenario. Tuberculosis. 2015;95 Suppl1:S122–6.
3. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003;163:1009-21.
4. Nunn P, Reid A, De Cock KM. Tuberculosis and HIV infection: the global setting. J Infect Dis. 2007;196:S5–14.
5. Saukkonen JJ, Cohn DL, Jasmer RM, et al; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J RespirCrit Care Med. 2006;174:935–52.
6. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 1998;53:536–48.
7. Gaude GS, Chaudhury A, Hattiholi J. Drug induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. Journal of Family Medicine and Primary Care.2015;4(2)238-43.
8. Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010;50:833–9.
9. Zuberi FF, Bader N, Alvi H, et al. Comparison of British Thoracic Society and American Thoracic Society reintroduction guidelines for antituberculosis therapy induced liver injury. J Pak,Med Assoc.2014; 64:896-9.
10. Tahaoglu K, Atac G, Sevin T, et al. The management of anti-tuberculosis drug induced hepatotoxicity. Int J Tuberc Lung Disc.2001;5:65-9.
11. Agal S, Baijal R, Pramanik S, et al. Monitoring and management of antituberculosis drug-induced hepatotoxicity. J GastroenterolHepatol. 2005 Nov;20(11) :1745-52.