

Management of Hepatotoxicity and Utilization of Antitubercular Drugs in Chronic Liver Disease: A Narrative Review

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ABSTRACT

The World Health Organization's "End TB strategy" envisions a world free of tuberculosis (TB), emphasizing early diagnosis, effective treatment, and prevention. The Government of Nepal has incorporated innovative activities into its National Strategic Plan and the "TB Free Initiative." Despite these initiatives, significant challenges remain, particularly concerning hepatotoxicity during antitubercular therapy, its management, and the treatment of tuberculosis in patients with chronic liver disease (CLD). Drug-induced liver injury (DILI) is a leading cause of treatment interruption, nonadherence, and therapeutic failure. Among these, antitubercular drug-induced liver injury (ATT-DILI) represents a distinct and clinically significant concern that requires focused attention. In patients with chronic liver disease, appropriate selection of antitubercular regimens based on the severity of liver disease is essential for successful TB treatment. A tailored approach that balances efficacy and safety is necessary. This article proposes a strategy based on monitoring and modification to assist clinicians in managing hepatotoxicity associated with antitubercular agents in patients with chronic liver disease.



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INTRODUCTION

Tuberculosis (TB) remains one of the most formidable infectious diseases, caused by the bacterium *Mycobacterium tuberculosis*. In 2024 alone, it claimed the lives of approximately 1.23 million people, including 150,000 individuals living with HIV. Despite decades of medical progress, TB continues to stand as the world's leading killer from a single infectious agent and ranks among the top ten causes of death globally. That same year, an estimated 10.7 million people developed the disease. 5.8 million men, 3.7 million women, and 1.2 million children underscoring its relentless impact across all ages and communities. TB is present in all countries and age groups. The WHO's "End TB strategy" aims for a world free of TB.¹ The Government of Nepal has integrated several innovative activities into its National Strategic Plan (2021/22–2025/26), among which the TB Free Initiative stands out as a flagship effort to accelerate progress toward eliminating tuberculosis.²

Despite much progress in the management of TB, there are still visible and hidden hurdles in combating tuberculosis. The issues

related to hepatotoxicity during treatment, its management, and the inclusion of patients with chronic liver disease (CLD) in the high-risk group are among a few concerns. This article aims to review some of these issues.

ANTITUBERCULAR DRUGS AND HEPATO-TOXICITY

Drug-induced liver injury (DILI) is one of the most important reasons for discontinuation of drugs and treatment failures. Drug-induced liver injury (DILI) represents a significant clinical challenge, accounting for nearly 7% of all reported adverse drug reactions, 2% of hospital-based jaundice cases, and about 30% of acute liver failure (ALF).³ Notably, DILI has now surpassed viral hepatitis as the leading cause of ALF, underscoring its growing importance in hepatology and patient safety.⁴

The preferred term for drug-induced liver injury caused by anti-tubercular drugs is ATT-DILI (antitubercular drug-induced

liver injury). ATT-DILI can lead to nonadherence, treatment failure, and could negatively impact the treatment outcome.⁵ Data with wide variations have been found regarding the incidence of ATT-DILI from different countries, ranging from 5 to 28 %.⁴

The manifestation of ATT-DILI can range from asymptomatic elevations in liver enzymes to ALF. Two Studies from Nepal have reported that ATT-DILI occurs in 8%⁶ and 48.2%⁷, respectively. Such a discrepancy is likely due to variation in definitions, enrolled study populations, ethnicity, and treatment regimens. Moreover, DILI can cause acute liver failure (ATT-ALF) in 30 % of cases⁸ and the mortality rate among patients with ATT-ALF is 67.1%.⁹

Recurrence of ATT-induced DILI occurs in approximately 10% of cases.¹⁰ Anti-tubercular therapy containing isoniazid (H), rifampicin (R), and pyrazinamide (Z) is highly effective; however, these agents are hepatotoxic,¹¹ and the risk increase with combination regimens. Fluoroquinolones can also rarely cause hepatitis.¹² Among the first-line anti-tubercular therapy (ATT) drugs, isoniazid, rifampicin, and pyrazinamide have a high hepatotoxic potential, whereas ethambutol and fluoroquinolones have a low hepatotoxic potential.

What is the concern regarding the use of ATT in patients with CLD?

Over 90% of TB cases are reactivations of latent infection, typically occurring in patients with some degree of immunodeficiency or immunosuppression. As CLD represents an immunodeficient state, patients with CLD exhibit a significantly higher prevalence of tuberculosis compared with the general population.

CLD- a risk factor for tuberculosis

Mycobacterium tuberculosis can infect individuals across all demographic backgrounds; however, the risk of progressing to active disease is substantially higher among those with specific predisposing factors, particularly conditions associated with immune suppression. Risk factors for tuberculosis extend beyond traditional exposures and include a broad spectrum of conditions that compromise immunity. These encompass HIV/AIDS, diabetes mellitus, end-stage renal disease, cancer chemotherapy, and immunosuppressive therapy following organ transplantation. Certain medications used in autoimmune disorders such as rheumatoid arthritis, Crohn's disease, and psoriasis also heighten susceptibility. In addition, malnutrition and advanced age remain essential contributors.¹³ More recently, end-stage liver disease has been recognized as an independent risk factor, further broadening the clinical contexts in which TB may emerge.

A Danish population-based study demonstrated a 14-fold higher incidence of tuberculosis among patients with chronic liver disease (CLD) compared with the general population (168.6 vs. 7.8 per 100,000 person-years). The highest incidence, 246

per 100,000 person-years, was observed in men aged 65 years and older. Mortality was considerable, with a 30-day case-fatality rate of 27.3% and a 1-year case-fatality rate of 47.7%. These findings highlight that patients with CLD not only face a markedly elevated risk of tuberculosis but also suffer from poor clinical outcomes.¹⁴

Studies from India have reported comparable findings. In a study from Mumbai, Baijal et al. demonstrated that the prevalence of tuberculosis among patients with chronic liver disease (CLD) was 15 times higher than in the general population, with particularly elevated rates in those with alcohol-related liver disease.¹⁵ In contrast, Wu et al. found no evidence of an increased risk of pulmonary tuberculosis in patients with CLD.¹⁶

CLD- a state of immune system dysfunction

Patients with chronic liver disease (CLD) demonstrate profound impairments in immune competence, particularly within cell-mediated immunity. Cirrhosis-associated immune dysfunction syndrome represents a complex, multifactorial state characterized by diminished clearance of cytokines, bacteria, and endotoxins from the circulation. The liver ordinarily harbours nearly 90% of the reticuloendothelial system cells principally Kupffer cells and sinusoidal endothelial cells which are pivotal to bacterial clearance and immune surveillance. In cirrhosis, portosystemic shunting together with a reduction in reticuloendothelial cell mass permits bacteria and endotoxins to bypass hepatic filtration and gain access to the systemic circulation, underscoring the critical role of hepatic immune surveillance in maintaining host defence.¹⁷

Reticuloendothelial system dysfunction is a well-recognized feature of cirrhosis, characterized by marked reductions in monocyte spreading, chemotaxis, phagocytosis, and bacterial killing compared with healthy individuals. Neutrophil mobilization and phagocytic activity are also impaired, and the severity of these defects correlates closely with the progression of liver disease. Metabolic disturbances such as hyperammonaemia and hyponatremia further disrupt neutrophil volume regulation and diminish phagocytic capacity. Malnutrition, exposure to immunosuppressive therapies, and alcohol consumption further compound the immune dysfunction seen in cirrhosis. Both acute and chronic alcohol intake are associated with reductions in T lymphocytes, B lymphocytes, natural killer cells, and monocytes, accompanied by heightened production of pro-inflammatory cytokines. Collectively, these alterations underscore the profound disruption of innate and adaptive immune responses in cirrhosis, highlighting the population's vulnerability to infectious complications.

RISK FACTORS

Why some patients who receive anti-tubercular treatment develop hepatitis is not clear. Incidence data indicate that hepatotoxicity is more common in patients of Asian origin, suggesting that ethnicity and environmental factors also contribute. Several

studies have examined host factors, genetic factors such as HLA typing¹⁸, cytochrome P450 2E1¹⁹ and acetylator status.²⁰ Risk factors for ATT drug-induced liver injury (ATT-DILI) include advanced age,²¹⁻²⁷ female gender,^{23,27-29} extrapulmonary tuberculosis,^{27,28} greater disease severity on chest radiograph,^{27,30} poor nutritional status,^{26,27,31,32} protein-energy malnutrition (PEM),³³ mid-upper arm circumference (MAC) < 20 cm, and hypoalbuminemia.²⁷

Note: It is noteworthy that patients with chronic liver disease frequently harbour several predisposing risk factors, including advanced age, poor nutritional status, and hypoalbuminemia.³⁴

DEFINITION OF HEPATOTOXICITY

The definition of hepatotoxicity in patients with chronic liver disease remains controversial, mainly due to the difficulty in distinguishing drug-induced injury from the natural progression of the underlying condition. Current recommendations consider ATT-DILI when aminotransferase (AT) levels rise to more than three times the upper limit of normal (ULN) following initiation of therapy. However, this threshold is unclear in patients with elevated baseline AT levels at treatment initiation.⁴⁶ This is of concern in patients with CLD, as they already can have elevated transaminase levels before the treatment.

Making a diagnosis

Diagnosing ATT-DILI involves a combination of clinical symptoms, excluding other causes, and biochemical tests. Anti-tuberculosis treatment-related drug-induced liver injury (ATT-DILI) is ultimately a diagnosis of exclusion, because liver histology is rarely obtained.

The International DILI Expert Working Group criteria are a standard for diagnosis.⁴⁷

a. Biochemical markers:

- ALT >5 times the upper limit of normal (ULN).
- ALT >3 times the ULN with total bilirubin >2 times the ULN (Hy's Law).
- Alkaline Phosphatase (ALP) >2 times the ULN.

b. Clinical presentation: Patients may present with symptoms like jaundice, fatigue, nausea, brown urine, or loss of appetite.

c. Exclusion of other causes: It is crucial to rule out other potential reasons for liver damage.

Consider these few points before diagnosing ATT-DILI.

- As CLD can already have elevated AT, it is essential to know whether the patient has CLD or non-CLD.
- Other causes of hepatic dysfunction, such as acute viral hepatitis, alcohol use, metabolic dysfunction-associated steatotic liver disease, or other drugs, should be checked.
- Tuberculosis itself may involve the liver (hepatic tuberculosis) and cause abnormal liver function.

Table 3. Studies on hepatotoxicity of ATT drugs in combination therapy

Studies/ year	Definition of hepatotoxicity	Incide- nce(%)	Risk Factors
Dossing et al 1996 ²³	AST > 6X ULN	2.0	Female sex, advanced age
Ormerod et al 1996 ²¹	ALT > 5X ULN	2.3	Advanced age
Tost et al 2005 ³⁵	ALT/AST > 10X ULN	2.6	Alcoholism, HBsAg carrier, other drugs
Yee et al 2003 ²²	ALT > 3X ULN	3.0	Female sex, advanced age, Asian, HIV positive
Van Hest et al 2004 ³⁶	ALT > 5X ULN	3.4	Female sex
Teleman et al 2002 ²⁴	ALT/AST > 3X ULN	5.3	Female sex, advanced age, abnormal baseline values
Fernandez-villar et al 2004 ³⁷	ALT/AST > 5X ULN	8.1	Abnormal baseline values, low BMI, HBV/HCV, other drugs
Pukenyte et al 2007 ³⁸	ALT > 5X ULN	10.7	T Bilirubin >0.8 mg/dl, ALT>51 IU/L
Schaberg et al 1996 ³⁹	ALT/AST > 3X ULN	11.0	Advanced age, past history of hepatitis, female sex
Saigal et al 2001 ⁴⁰	AST/ALT > 5X ULN or >400 IU/ ml, Total bilirubin>2.5 mg/dl	12.9	Advanced child-Pugh score
Breen et al 2006 ⁴¹	ALT/AST > 5X ULN	13	HIV infection, Asian
Huang et al 2003 ⁴²	ALT > 3X ULN	15	Advanced age, low BMI
Sharma et al 2002 ¹⁸	ALT/AST > 5X ULN, or any increase plus symptoms	16.1	Advanced age
Park et al 2010 ⁴³	ALT > 3X ULN	17.0	Female sex, total number of hepatotoxic drugs, baseline ALP
Ungo et al 1998 ⁴⁴	ALT/AST > 3X ULN	19.0	HIV or HCV infection
Sharifzadeh et al 2005 ⁴⁵	ALT > 3X ULN with or AST > 5X ULN without symptoms	27.7	No significant risk factors
Pande et al 1996 ³⁰	AST > 3X ULN	ND	Advanced age, high alcohol intake

Thus, do LFTs before initiating ATT for baseline assessment, because patients with abnormal baseline AT levels are at

increased risk of developing hepatic injury.

ATT-DILI should be suspected (after initiating ATT) when:

- ALT > 3 x ULN (or increase from previous values in cases of patients with CLD)

ATT-ALF should be suspected (after initiating ATT):

ATT-ALF is diagnosed if the patient with ALF had a history of consumption of at least two of the three first-line hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) for a minimum period of 1 week and if the patient is tested negative for evidence of known hepatitis virus infection and absence of any other identifiable cause of acute liver injury.⁴⁸

Note: ALF is defined by occurrence of encephalopathy within 4 weeks of symptoms in absence of preexisting liver disease.

HOW TO MANAGE?

If ATT-DILI is suspected, temporarily discontinue ATT. Discontinuation leading to a fall in AT and/or Bilirubin (to normal or close to the previous value) is the strongest confirmation of the diagnosis.⁴⁹

Section 1: Non-CLD patients with ATT-DILI

Basic Principles of safe ATT Therapy in patients include:
a) Monitoring, b) Modification.

a. Monitoring

Liver function tests should be repeated every week for the first 2 weeks, and then once every two weeks during that initial two-month period.⁵⁰

Note: Usually, the time of onset of ATT-DILI is within months of initiating a drug.

- If needed urgent ATT, while standard regimen is on hold: Change to non-hepatotoxic drugs (fluroquinolones, preferably Moxifloxacin plus Ethambutol plus Linezolid) and repeat LFT in 1 week (modified from ICMR-22⁴⁹, Note: We omitted Aminoglycoside because the National Tuberculosis Management guidelines 2019⁵¹ state that “there is no room for addition of an injectable agent”

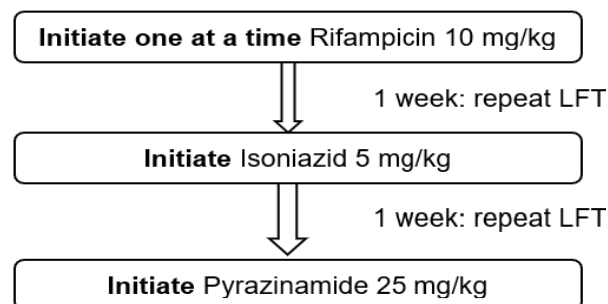
b. Modification

Modification refers to reintroducing drugs. Re-introduction is performed once AT < 2x ULN, as AT levels will fall if it is ATT-DILI. Note: *Start full-dose ethambutol on Day 1, as it is non-hepatotoxic.* Clinicians should also consider gastrointestinal features like nausea, vomiting, jaundice, and abdominal pain. It is worthwhile to wait for the resolution of gastrointestinal symptoms before reintroducing the drugs.

Clinicians can reintroduce using one of three approaches.

- I. Sequential order:** Re-introduce one drug at a time (helps identify the culprit)
- II. Incremental order (rapid):** Re-introduce a low dose of one drug, followed by the full dose after three days
- III. Incremental order (slow):** Re-introduce a low dose of one drug, followed by a gradual increase in the dose every three days
- IV. Case-by-case basis** (in exceptional circumstances)

I. Sequential order (ICMR-22)⁴⁹



Scenario 1:

After you introduce rifampicin, if the LFTs at 1 week show rising transaminases, consider rifampicin the likely culprit for ATT-DILI. Discontinue rifampicin and wait for transaminases to normalize. Once liver enzymes return to baseline, initiate isoniazid and repeat the LFT after 1 week.

Note: Introducing rifampicin first is not mandatory. However, clinicians commonly do so, as supported by several studies. Although both isoniazid and rifampicin can cause ATT-DILI, isoniazid is generally considered more hepatotoxic than rifampicin.

In a meta-analysis, isoniazid was more likely to be associated with hepatotoxicity (odds ratio (OR) 1.6) even in the absence of rifampicin. Still, the combination of these two drugs was associated with a higher rate of hepatotoxicity (OR 2.6) when compared to each drug on its own.⁵² It is also important to note that up to 20% of the patients who received isoniazid either in single or combination therapy develop transient asymptomatic elevation in liver enzymes, which settle with continued use of the drug.^{53,54} Thus, decision-making by a clinician can be crucial at times.

II. Incremental order (rapid): (National Tuberculosis Management guidelines 2019)⁵¹

Day 1-3: E + H (1/3rd-full dose)

Start Isoniazid and increase the dose in subsequent days, i.e., 1/3rd, 2/3rd, then full dose

Perform LFT at Day 3

Day 4-6: E + H + R (1/3rd-full dose)

Start Rifampicin and increase the dose in subsequent days, i.e., 1/3rd, 2/3rd, then full dose

Perform LFT at Day 6

Day 7-9: E + H + R + Z (1/3rd-full dose)

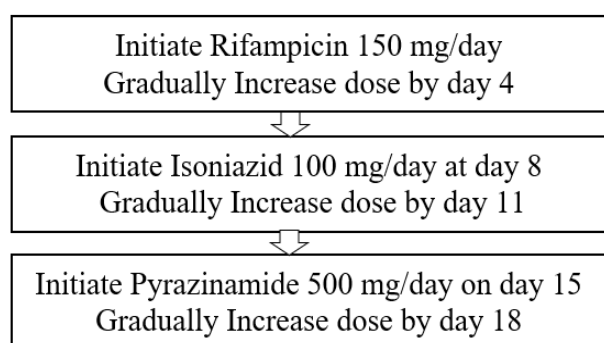
Start Pyrazinamide and increase the dose in subsequent days, i.e., 1/3rd, 2/3rd, then full dose

Perform LFT at Day 9

If the patient is symptomatic or LFT is deranged at any stage, stop the offending drug.

Note: As mentioned above, it is not necessary to introduce Isoniazid initially. One can also start with Rifampicin; the above Incremental order is shown as an example.

III. Incremental order (slow):



IV. Case-by-case basis:

When a single tablet is unavailable, we have been using the HRE tablet, starting with a single tablet (75/150/275) and increasing the dose weekly until the full dose per kg is required, while monitoring ATs weekly and as tolerated.

If a second episode of ATT-DILI occurs after full reintroduction of ATT, stop all hepatotoxic drugs. Provide an extended-duration ATT regimen that excludes potentially hepatotoxic agents, or discontinue only the most recently added drug.

Section 2: Using ATT in CLD patients

Treating TB in patients with CLD, who are already in an immunodeficient state and have additional risk factors, presents a significant challenge. The treatment of TB in decompensated CLD is particularly challenging because it involves a delicate balance. On one hand, the treatment itself may lead to hepatotoxicity, while on the other hand, the progression of tuberculosis may result in liver decompensation. However, the actual clinical scenario is less alarming than the description suggests. When clinicians implement appropriate precautions, they can safely administer anti-tubercular drugs to patients with CLD.

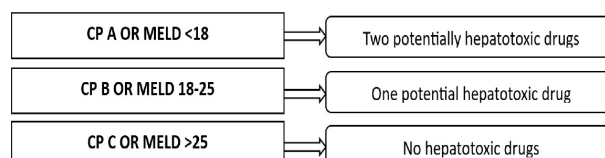
Basic Principles of safe ATT Therapy in patients with CLD include: a) **Monitoring**, b) **Modification**.

a. Monitoring

- Liver function tests should be repeated twice weekly for the first 2 weeks, then weekly for the next 2 months, and then monthly until the end of treatment.⁵⁰

b. Modification

- First, risk-stratify the patient according to the Child Pugh Score⁵⁵ or the MELD score⁵⁶.
- Choose the drug regimen according to Child Pugh class (example CP -A, B, or C) or MELD score⁵⁷



Two hepatotoxic drugs REGIMEN:

- 9 months HRE [preferred]
- 2 months HRE followed by 7 months HR
- 6 Months HZE with F
- 6 Months RZE with or without F (Regime without isoniazid)

One hepatotoxic drug REGIMEN:

- 2 months REF followed by 10 RE (CDC 2003)
- 12-18 months R/H plus EF [preferred]
- 2 months H/R + E & aminoglycoside, followed by 10 months H/R + E (ICMR 2022)

(Note: F=fluoroquinolone= Moxifloxacin 400 mg PO OD.)

No hepatotoxic drugs REGIMEN:

- 18–24 months using a combination of E, F, cycloserine & capreomycin

Note: Cycloserine and capreomycin are unavailable in our setting; therefore, add linezolid. However, if the patient's condition improves, consider transitioning to a single hepatotoxic regimen.

Points to consider:

However, in certain situations, such as in early stages of CLD, patients may fall under Class B despite having relatively preserved liver function. In such cases, it may not be necessary to strictly adhere to guidelines based on Child-Pugh class or MELD score. Instead, initiate the first-line drugs like HRZE with close monitoring. Furthermore, it may be more appropriate to approach each case individually and assess the specific circumstances. *For example, although Pyrazinamide is a weak bactericidal agent, its strong sterilizing properties can be beneficial in the treatment of tuberculosis.*⁵⁸

Case-by-case basis: review

For example, if a CLD patient with CP-B is started on 12 REF

and, after 1 month, the patient's liver disease status improves, and their CP score improves to CP-A, isoniazid can be added, monitored, and continued if tolerated.

*Note: The proven efficacy of isoniazid and, especially, rifampicin underscores the importance of their use and retention whenever feasible, even in the presence of preexisting liver disease.*⁵⁹

Case-by-case basis: review

When a single tablet is not available, use the HRE tablet (as it is readily available in our context), starting from a single tablet (75/150/275) and increasing the dose subsequently every week until the full dosage is required as per kg, while monitoring ATs every week and as tolerated.

For patients with ATT-ALF:

Deal on a case-by-case basis using drug combinations like Ethambutol, Fluoroquinolone, and Linezolid for a longer duration, i.e., 18 to 24 months. However, if the patient's condition improves, consider introducing first-line drugs.

Progression of anti-tuberculosis treatment-related drug-induced liver injury (ATT-DILI) to acute liver failure (ATT-ALF) is

associated with poor survival when managed with medical therapy alone. Emergency liver transplantation has emerged as an effective therapeutic option for ATT-ALF, although post-transplant outcomes are generally inferior to those achieved with elective transplantation.

Few strategies have been employed to prevent antitubercular therapy-induced liver injury (ATT-DILI). For instance, co-administration of N-acetylcysteine (NAC) has demonstrated protective effects against DILI in animal models treated with hepatotoxic doses of isoniazid and rifampicin.⁶⁰ However, further studies are necessary to draw definitive conclusions. Similarly, specific herbal formulations have been investigated and shown potential to reduce the incidence and severity of hepatotoxicity associated with antitubercular drugs.⁶¹ Nonetheless, large-scale clinical trials are required to substantiate these findings.

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