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Pharma Research

An International Peer Reviewed, Indexed Journal

[10.62655/s-epub.2026.v18.i01.pp63-70](https://s-epub.in/index.php/trp/index)

HEPATOTOXICITY OF ANTITUBERCULAR DRUGS: INCIDENCE AND RISK FACTORS

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Article info

Received date:05-08-2025

Accepted date:08-12-2025

Published date:21-04-2026

ISSN;0975-8216

Keywords:

Antitubercular drugs, Hepatotoxicity, Isoniazid, Risk factors, Drug-induced liver injury

1. INTRODUCTION

Tuberculosis treatment is long, and its first-line drugs are not gentle on the liver. A standard regimen of isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by isoniazid and rifampicin for four, has cured millions of patients [1, 2]. It also produces drug-induced liver injury in a meaningful minority. Most affected patients have only a rise in serum transaminases that settles, but a few develop jaundice or acute liver failure, and in them the damage can be fatal [3, 4]. Because injury often leads

Abstract

Drug-induced liver injury is the most frequent serious adverse effect of first-line antitubercular therapy and a common reason for interrupted treatment. This narrative review, which reports no new data, summarises what published studies say about the hepatotoxic mechanisms of isoniazid, rifampicin and pyrazinamide, the reported incidence of injury, and the patient, genetic and disease-related risk factors. Reported incidence varies widely with definitions and populations. Older age, slow acetylator status, malnutrition, alcohol use and chronic viral hepatitis recur as risk factors, though effect sizes differ between cohorts. Monitoring, prompt interruption and structured reintroduction protect most patients. Inconsistent case definitions and scarce prospective data limit comparison across studies.

clinicians to stop the very drugs that keep the patient alive, it carries a cost far beyond the

liver. This review summarises what the literature reports on incidence and risk factors, with no new data presented.

The scale of the problem is worth stating plainly. Tuberculosis remains one of the largest infectious causes of death worldwide, and treatment must be taken for at least six months to prevent relapse and resistance. Every interruption raises the chance of failure, and every substitute regimen is longer, costlier and often more toxic [1, 2]. In settings where malnutrition, alcohol use and viral hepatitis are common, the same populations most exposed to tuberculosis are also those most vulnerable to hepatic injury, which makes the intersection of the two diseases a practical concern for national programmes as well as a topic for pharmacology [5, 6].

The material here is organised from mechanism to practice. Mechanisms of injury for each drug come first, then incidence and presentation, then the patient and genetic features that raise or lower risk, summarised in table 1 and counted by category in fig. 1. Management strategies follow, and the review closes with limits in the current evidence. Throughout, attention is given to how a study defined hepatotoxicity, since a threshold of three times the upper limit of normal for alanine aminotransferase yields very different figures from a requirement for symptoms or jaundice [7]. Without that context, published rates cannot be compared.

2. MECHANISMS OF INJURY

Isoniazid is the main suspect in most cases. The drug is acetylated in the liver by N-acetyltransferase 2 to acetylisoniazid, which is hydrolysed to acetylhydrazine, and further oxidation by cytochrome P450 enzymes, notably CYP2E1, can generate reactive acetyl species that bind covalently to hepatic proteins [8, 9]. Isoniazid is also hydrolysed directly to hydrazine, itself hepatotoxic. For many years the dominant model held that toxic metabolites accumulate in people who metabolise isoniazid in a particular way, though the exact species responsible has been debated for decades [4, 5]. The model explains why injury tracks with host metabolism better than with simple dose.

Mitochondria have gained prominence as a target. Isoniazid and its metabolites impair mitochondrial function in hepatocytes, depleting glutathione, increasing oxidative stress and opening the permeability transition pore in vulnerable cells, and this combination may tip a cell towards necrosis only when another stressor is present [9, 10]. Immune mechanisms have also been proposed because some patients develop injury after weeks and not days, occasionally with fever, rash or eosinophilia, and because rechallenge may bring faster recurrence. Evidence for a true adaptive immune reaction is circumstantial, however, and the idiosyncratic nature of the injury means that no single mechanism accounts for every case [9, 11].

Table 1: Selected published findings on risk factors for hepatotoxicity during antitubercular therapy

Factor or setting	Reported finding	Ref.
Isoniazid NAT2 slow acetylators	Higher risk of hepatitis in slow acetylators, supported by meta-analysis.	[12, 13]
CYP2E1 c1/c1 genotype Taiwan	Higher-activity genotype linked to injury, with added risk in combination with NAT2 status.	[14]
Genotype-guided dosing NAT2	Randomised trial reported less liver injury with genotype-adjusted isoniazid dose.	[15]
Age above 60 years older adults	Greater risk of injury and severe outcomes in older patients across reviews.	[16, 17]
Malnutrition low albumin	Low weight and hypoalbuminaemia associated with injury in Indian case-control data.	[18, 19]
Alcohol use daily intake	Associated with higher injury rates through shared pathways and poorer adherence.	[20, 21]
Chronic hepatitis B carriers	Higher rates of aminotransferase elevation than in uninfected patients.	[22, 23]
Chronic hepatitis C carriers	Increased risk reported during treatment of latent infection.	[24]
Pyrazinamide dose regimen	Dose-related hepatotoxicity, with higher risk in some cohorts than with isoniazid.	[25]

Factor or setting	Reported finding	Ref.
Isoniazid with rifampicin combination	Combination hepatitis rate higher than either drug alone in pooled analysis.	[26]
Acute liver failure outcomes	Antitubercular drugs a leading cause with high mortality without transplantation.	[3, 27]

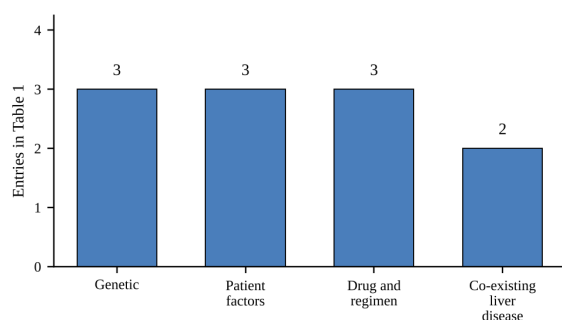


Fig. 1: Number of entries in table 1 by category of risk factor

Rifampicin adds its own effects. It is a potent inducer of hepatic enzymes, including CYP2E1 and others involved in isoniazid handling, and it is thought to increase the generation of hydrazine from isoniazid, which explains why the combination appears more hepatotoxic than either drug alone [8, 26]. Rifampicin can also compete for hepatic uptake and excretion of bilirubin and bile salts, producing a cholestatic picture and benign unconjugated hyperbilirubinaemia without hepatocellular damage. The distinction is clinically useful, since an isolated rise in bilirubin soon after starting treatment need not signal severe injury, while a rising ALT with symptoms does [4, 5].

Experimental models have been disappointing, and that limits what can be said about mechanism. Isoniazid given alone rarely produces overt liver injury in standard rodents, and rabbit and mouse studies that do show toxicity usually involve very high doses, co-treatment with rifampicin, or genetic manipulation of antioxidant defences [9, 10]. Even then, the histology often fails to match the human picture of centrilobular or submassive necrosis. Because of this, much of what is believed about mechanism has been inferred from human metabolite data, genetic association studies and case reports. That is a weaker evidential footing than one might wish for the most important hepatotoxic drug in a global treatment

programme [4, 8].

Pyrazinamide is dose related in a way that isoniazid is not. At the higher doses used in older regimens, hepatotoxicity was common enough to alter prescribing, and the lower doses now recommended have reduced the problem without eliminating it [8, 25]. A cohort and case-control study from Hong Kong reported that pyrazinamide was associated with a higher risk of injury than isoniazid or rifampicin in the regimens analysed, while other series find the three drugs roughly comparable [20, 25]. Its metabolite, pyrazinoic acid, and the downstream compounds hydroxylated in the liver are candidate toxins, though human proof is limited. Ethambutol is rarely implicated and is usually kept in the regimen when others are withdrawn [5].

3. INCIDENCE AND PRESENTATION

Reported incidence depends heavily on the definition and the population. Early US surveillance of isoniazid preventive therapy found clinical hepatitis in a small percentage of treated adults, with a clear rise with age, while later public health clinic series with closer monitoring reported lower rates [16, 28]. A meta-analysis of regimens in the 1980s found rates between one and three per cent depending on whether isoniazid, rifampicin or their combination was given [26]. Studies that count any laboratory abnormality report far higher figures, sometimes more than one patient in five, with the largest values coming from Asian and African cohorts and from hospital populations with advanced disease [5, 8]. The quoted figure therefore reflects methods at least as much as biology.

Timing offers a useful clue. Most cases arise within the first two months of treatment, and many in the first few weeks, though isoniazid injury can appear later, including after months on preventive therapy [8, 21]. Symptoms are non-specific: nausea, loss of appetite, fatigue, abdominal discomfort and dark urine, often attributed to the tuberculosis itself. Jaundice is a late sign. Because the earliest symptoms overlap with those of the disease and of the drugs, laboratory monitoring finds many patients before they report anything, and clinicians who rely on symptoms alone will

miss the early part of the picture [4, 8].

Injury during treatment of latent infection deserves separate comment. These patients are well, take a single drug for many months, and are especially vulnerable to stopping treatment at the first sign of symptoms. Surveys of public health clinics reported that hepatotoxicity was uncommon but occasionally severe, and that some deaths followed continued use of isoniazid despite symptoms [16, 28]. Chronic viral hepatitis appears to raise the likelihood of enzyme elevation in this setting as well [24]. Because the benefit in an individual patient with latent infection is a reduced chance of future disease and not cure of present illness, the tolerance for liver injury is lower, and monitoring protocols are correspondingly stricter [29].

Severity ranges from transient enzyme elevation, termed adaptation, to acute liver failure. In an Indian series, antitubercular drugs accounted for a leading share of drug-induced acute liver failure in adults, with high mortality unless transplantation was available, and prognosis was worse with encephalopathy, higher bilirubin and prolonged prothrombin time [3, 27]. A British hospital cohort found that injury was relatively uncommon but resulted in treatment modification for a substantial proportion of those affected, with consequences for duration of therapy [30]. The picture is similar across countries: most injuries resolve on stopping the drugs, and a small number are life threatening [11, 31].

Geography adds a further layer. Hospital series from India report antitubercular drugs as a leading cause of drug-induced liver injury and acute liver failure, in part because tuberculosis treatment is so widely used and because nutritional and viral risk factors are common [3, 27]. Reports from the United Kingdom describe lower frequency and a different case mix, with more injury recognised through routine blood tests than through symptoms [30]. Differences in dosing per kilogram, in the proportion of patients who are malnourished, in the prevalence of hepatitis B and in the intensity of monitoring all complicate direct comparison. A single global incidence figure would hide more than it would reveal [5, 21].

4. PATIENT AND GENETIC RISK FACTORS

Age is the most consistent single factor. In the early surveillance studies, hepatitis was rare in the young and became progressively more common in the fifth decade and beyond [16, 28]. A systematic review in older patients concluded that those aged above sixty to sixty-five are at greater risk of injury and of severe outcomes than younger adults, although the heterogeneity between studies was large [17]. Reduced hepatic blood flow, lower glutathione reserves, polypharmacy and comorbidity are plausible explanations. Whatever the cause, close monitoring is warranted in older people, and some programmes use lower threshold values for intervention in this group [2, 17].

Nutritional status and sex also matter. Low body weight, hypoalbuminaemia and undernutrition have been linked to hepatotoxicity in case-control and cohort studies from India and elsewhere, as has female sex in several but not all series [18, 19]. Low albumin probably acts as a marker of reduced hepatic reserve and poor nutrition, which impairs glutathione synthesis, rather than as a cause in itself. Alcohol use, even at moderate levels, adds to the burden through shared pathways and reduced adherence to follow-up [20, 21]. Taken individually, the associations are modest, but they cluster in the same patients, which probably explains why combined models perform better than any single factor [19, 32].

Genetic features have received the most attention. N-acetyltransferase 2 slow acetylators have been found to have a higher risk of antitubercular hepatitis in a number of studies and a meta-analysis, and the difference is largest for isoniazid [12, 13]. The CYP2E1 c1/c1 genotype, which is associated with higher enzyme activity, was linked to injury in a Taiwanese cohort, and combined genotypes seemed to carry even higher risk [14]. Glutathione S-transferase deletions and human leukocyte antigen alleles have also been investigated, with less consistent results across populations [11, 32]. Effects are real but moderate, and population differences in allele frequency make direct transfer of findings hazardous.

The concept of pharmacogenetic guidance is the logical next step. In a Japanese randomised trial, patients assigned to doses of isoniazid adjusted for NAT2 genotype had fewer cases of liver injury and less early treatment failure than those given standard doses, with slow acetylators receiving lower doses and rapid acetylators higher ones [15]. The finding is encouraging but comes from a single population, and routine genotyping is not yet part of guideline-recommended practice [2, 13]. Costs, turnaround time and access to testing will determine whether it becomes feasible in the high-burden settings in which most tuberculosis occurs.

Underlying liver disease and co-infection form the final cluster. Chronic hepatitis B virus (HBV) and hepatitis C virus infections raise the likelihood of aminotransferase elevations during treatment, with several studies reporting rates two to several times higher in carriers than in uninfected patients, although most carriers complete treatment safely under monitoring [22, 23, 24]. Coinfection with the human immunodeficiency virus (HIV) complicates the picture further by adding antiretroviral toxicity and drug interactions [4, 27]. Existing cirrhosis or alcoholic liver disease limits the choice of regimen, and expert guidance generally favours regimens with fewer hepatotoxic drugs for those with advanced disease. The summary is given in table 1 [2, 6].

Regimen features contribute independently of the patient. Isoniazid and rifampicin given together are more hepatotoxic than either alone, and adding pyrazinamide increases risk in some but not all studies, so shortened four-drug regimens may confer a higher likelihood of injury than older two-drug regimens [25, 26]. Dose per kilogram matters because fixed-dose combinations deliver a similar amount to patients of different weights, and low-weight patients receive relatively more. For drug-resistant disease, second-line agents such as ethionamide and para-aminosalicylic acid are themselves hepatotoxic, and regimens with several such drugs create a heavier load [4, 8]. Treatment guidelines therefore specify regimens for people with liver disease rather than leaving

the choice to individual prescribers [1, 2].

Gene-environment interaction probably explains part of the variation. A slow acetylator who drinks alcohol, is undernourished and carries hepatitis B may be at much higher risk than any single factor suggests, yet very few studies have the numbers to test such combinations. Where interaction analyses exist, risk appears to be multiplicative rather than additive, though confidence intervals are wide [14, 32]. Risk scores combining clinical and genetic variables have been proposed but are not yet validated for routine use, and a score built in one country may misclassify patients in another where nutrition and hepatitis prevalence differ.

5. MONITORING, MANAGEMENT AND PREVENTION

Monitoring policies differ. The ATS statement recommends baseline liver tests for people with risk factors and regular clinical review for everyone on treatment, with biochemical follow-up added for those with risk factors, such as older age, alcohol use, chronic liver disease or hepatitis infection, while accepting that routine testing of everyone is a matter of local preference [2, 29]. World Health Organization (WHO) guidance leaves more discretion for programmes with limited laboratory capacity and emphasises education of patients about symptoms [1]. Evidence that routine monitoring prevents severe injury is indirect, but early detection of symptoms with prompt cessation appears to improve outcomes, which supports at least symptom-driven review [4, 8].

When injury occurs, the usual action is to stop hepatotoxic drugs, treat with less hepatotoxic substitutes if the disease is severe, and wait for recovery. Once liver tests fall to near baseline, drugs are reintroduced one at a time, in an order and at intervals set out in guidelines, so that a culprit can be identified [2, 4]. Rifampicin is typically reintroduced first because of its importance and relatively low hepatotoxicity, then isoniazid, with pyrazinamide often left out if it was the likely cause [8, 30]. Some patients are reintroduced without recurrence, which shows that not all

early elevations imply permanent intolerance. N-acetylcysteine has been used in acute liver failure from various drugs, though evidence specific to antitubercular injury is limited [3].

Pharmacists have a practical role at several points. They can screen prescriptions for interacting drugs, including other hepatotoxic agents and enzyme inducers, counsel patients about alcohol and symptoms that should prompt a call, and check that liver tests have been requested when guidelines advise them [6, 8]. In many health systems the pharmacist is also the person who sees the patient most often during treatment, so reinforcing adherence and reporting adverse events falls naturally to them. Pharmacovigilance reports that carry a clear description of timing, laboratory values and rechallenge outcome are particularly useful, because they can help characterise rare injury patterns that single studies cannot detect [11].

Prevention rests on identifying and counselling patients at higher risk and on careful use of co-medications. Alcohol should be avoided, paracetamol and other hepatotoxic drugs minimised, viral hepatitis status checked in people with risk factors, and nutrition supported [5, 6]. Fixed-dose combinations reduce errors in dosing and support adherence, which in turn avoids interrupted treatment and restarts that carry their own risks [1]. Hepatoprotective agents such as silymarin have been tested in small studies with mixed results, and there is no persuasive evidence to recommend routine use [4, 8]. For the present, the best protection remains vigilance, education and timely action.

6. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has several weaknesses. Case definitions vary between studies, with different aminotransferase thresholds, different requirements for symptoms and different treatment of baseline abnormalities, so pooled incidence figures conceal real differences [7, 8]. Many studies are retrospective, single centre and small, and are exposed to selection effects, since hospital cohorts concentrate sicker patients. Adherence to the intended regimen is seldom

verified. Genetic association studies suffer from the usual problems of small samples, population stratification and publication bias, and the meta-analyses that pool them inherit those limits [12, 13]. Reports of severe or fatal cases are also more likely to be published than reports of uneventful treatment.

Interpretation of observational associations calls for restraint. Age, nutrition, alcohol use, hepatitis status and ethnicity are correlated with one another and with the setting in which a patient is treated, so crude associations may overstate the effect of any single feature [19, 32]. Multivariable analyses help, but sample sizes are often too small for the number of variables entered. Treatment of the same patient with several hepatotoxic drugs makes it difficult to assign blame to a particular one. Rechallenge data, though ethically constrained, remain among the best sources of evidence for causality, and well-documented rechallenge sequences should be published routinely [4, 7].

Several developments would improve matters. Prospective, multicentre cohorts using a common definition would allow reliable estimates by age, nutrition, infection status and genotype [7, 11]. More trials of pharmacogenetic-guided dosing, ideally in several populations and settings, would clarify whether genotype-directed therapy can be adopted on a wider scale [15]. Better biomarkers, such as markers of mitochondrial stress or microRNA signatures, could someday predict injury earlier than aminotransferases, though these are experimental [9, 10]. Until then, clinicians must manage risk using clinical features, careful monitoring and the guideline algorithms available [2].

7. CONCLUSION

Hepatotoxicity of antitubercular therapy is common enough to shape practice and serious enough to demand constant attention. Isoniazid, rifampicin and pyrazinamide each contribute through different mechanisms, and the interplay of reactive metabolites, mitochondrial stress and enzyme induction explains much of the observed pattern [9, 10, 25, 26]. Reported incidence ranges from

around one per cent for clinical hepatitis to a fifth or more for laboratory abnormalities, with the figure depending strongly on definition and population [5, 8, 26]. This variation is a warning against quoting any single number without its definition, and it makes comparison between countries and decades uncertain.

Risk is concentrated in older patients, those who are malnourished or drink alcohol, carriers of chronic hepatitis viruses and slow acetylators [12, 17, 18, 22]. Early recognition, prompt interruption and structured reintroduction allow most patients to complete treatment [2, 30]. Pharmacists, nurses and physicians share the task of counselling and surveillance, and programmes with limited laboratory capacity can still act on symptoms. Treatment should never be stopped on the basis of a single minor enzyme elevation without assessing the patient. Standard definitions, large prospective cohorts and tests of genotype-guided dosing are the main needs for the next stage of research [7, 11, 15].

8. ABBREVIATIONS

ALT-Alanine aminotransferase, ATS-American Thoracic Society, CYP2E1-Cytochrome P450 2E1, DILI-Drug-induced liver injury, HBV-Hepatitis B virus, NAT2-N-acetyltransferase 2, ULN-Upper limit of normal, WHO-World Health Organization, HIV-Human immunodeficiency virus

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. Geneva: WHO; 2010.
2. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, *et al.* American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167:603–62.
3. Kumar R, Shalimar, Bhatia V, Khanal S, Sreenivas V, Gupta SD, *et al.* Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. *Hepatology* 2010;51:1665–74.
4. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. *J Clin Exp Hepatol* 2013;3:37–49.
5. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006;11:699–707.
6. Hussain Z, Kar P, Husain SA. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. *Indian J Exp Biol* 2003;41:1226–32.
7. Maria VAJ, Victorino RMM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997;26:664–9.
8. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008;23:192–202.
9. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. *Br J Clin Pharmacol* 2016;81:1030–6.
10. Boelsterli UA, Lee KK. Mechanisms of isoniazid-induced idiosyncratic liver injury: emerging role of mitochondrial stress. *J Gastroenterol Hepatol* 2014;29:678–87.
11. Chalasani N, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology* 2010;138:1924–34.
12. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, *et al.* Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology* 2002;35:883–9.
13. Wang PY, Xie SY, Hao Q, Zhang C, Jiang BF. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis* 2012;16:589–95.
14. Huang YS, Chern HD, Su WJ, Wu JC, Chang SC, Chiang CH, *et al.* Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology* 2003;37:924–30.
15. Azuma J, Ohno M, Kubota R, Yokota S, Nagai T, Tsuyuguchi K, *et al.* NAT2

- genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol* 2013;69:1091–101.
16. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a US Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978;117:991–1001.
 17. Hosford JD, von Fricken ME, Lauzardo M, Chang M, Dai Y, Lyon JA, *et al.* Hepatotoxicity from antituberculous therapy in the elderly: a systematic review. *Tuberculosis* 2015;95:112–22.
 18. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996;51:132–6.
 19. Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, *et al.* Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. *Indian J Med Res* 2010;132:81–6.
 20. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J* 1996;9:2026–30.
 21. Gaude GS, Chaudhury A, Hattiholi J. Drug-induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. *J Family Med Prim Care* 2015;4:238–43.
 22. Wong WM, Wu PC, Yuen MF, Cheng CC, Yew WW, Wong PC, *et al.* Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000;31:201–6.
 23. Hwang SJ, Wu JC, Lee CN, Yen FS, Lu CL, Lin TP, *et al.* A prospective clinical study of isoniazid-rifampicin-pyrazinamide-induced liver injury in an area endemic for hepatitis B. *J Gastroenterol Hepatol* 1997;12:87–91.
 24. Bliven EE, Podewils LJ. The role of chronic hepatitis in isoniazid hepatotoxicity during treatment for latent tuberculosis infection. *Int J Tuberc Lung Dis* 2009;13:1054–60.
 25. Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. *Am J Respir Crit Care Med* 2008;177:1391–6.
 26. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. *Chest* 1991;99:465–71.
 27. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh AB. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010;105:2396–404.
 28. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;281:1014–8.
 29. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221–47.
 30. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, *et al.* Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infect Dis* 2017;17:231.
 31. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014;89:95–106.
 32. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *Am J Respir Crit Care Med* 2002;166:916–9.