Tropical Gastroenterology 2011;32(3):167–174

Quarterly Review

Antituberculous drug-induced liver injury: current perspective

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ABSTRACT

Drug-induced liver injury (DILI) is a minor but significant cause of liver injury across all regions. Antituberculosis drug-induced liver injury (TB DILI) is a leading cause of DILI and drug-induced acute liver failure (DIALF) in India and much of the developing world. Single center registries of DILI continue to highlight the high incidence of DILI and DIALF, much of it due to diagnostic errors and inappropriate prescriptions. The clinical spectrum includes asymptomatic elevation in liver tests to acute hepatitis and acute liver failure. TB DILI can occur across all age groups including children with significant morbidity and mortality. Although TB DILI develops more commonly in males, ALF is noted to be commoner in females with a worse prognosis. Contrasting reports on the role of genetic and environmental factors continue to be published. Since DILI is a diagnosis of exclusion, acute viral hepatitis particularly hepatitis E needs to be excluded in such cases. The presence of jaundice, hypoalbuminemia, ascites, encephalopathy and high prothrombin time are poor prognostic markers. Recent reports of the beneficial role of N-acetylcysteine in DIALF and in preventing TB DILI in elderly individuals needs further investigation. Reintroduction of antitubercular therapy must be balanced with the knowledge of adaptation a common occurrence with antituberculosis drugs. Although monitoring and rechallenge practices vary greatly, the importance of early clinical symptoms cannot be underestimated. Simultaneous rechallenge with combination drugs or sequential treatment have similar incidence of DILI, although increasing reports about the role of pyrazinamide in DILI and on rechallenge warrants its careful use. The combined affliction of HIV or chronic hepatitis B or C and tuberculosis poses multiple challenges including the greatly increased risks of DILI.

KEYWORDS: antituberculosis drugs, DILI, liver injury, isoniazid, rifampicin, pyrazinamide

"I took so much medicine, that I was ill for a long time, after I got well" - Carl Sandbera.

Tuberculosis continues to remain a significant infectious disease across much of the developing world. It exacts a significant socioeconomic burden on the individual and society. India is home to a fifth (21%) of the world's TB population and is the country with the highest TB burden.[1] The incidence of TB in India is 1.96 million cases annually, contributing to >300,000 deaths annually, including 1000 deaths every day.[1] Although the western world has seen a declining trend in the incidence and prevalence of tuberculosis, the emergence of HIV/AIDS has complicated the efforts of controlling the disease, particularly in developing countries. Co-infection with

HIV increases the risk of tuberculosis 6-50 fold.[2] Indeed both TB and HIV coexist in the same population making it a "cursed duet".[3] Although newer and safer drugs are continuously being sought after and used in the treatment of HIV, the mainstay of drugs used in the treatment of tuberculosis still includes the first line drugs identified more than 5-6 decades ago. These include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZY) and ethambutol (EMB). Although a vast majority of patients tolerate the drugs, some develop adverse effects of which hepatotoxicity is the most significant.[4] Twenty percent of patients develop asymptomatic elevation of liver enzymes which is self limiting (as a result of adaptation or discontinuance) in a majority of patients[4-7] but the outlook may be less favorable in those with develop jaundice, ascites, encephalopathy or acute liver failure.[8,9] Furthermore, the ripple effects of hepatotoxicity include disruption of treatment with potential for prolongation of treatment, genesis of drug resistance and suboptimal cure. Hepatotoxicity or DILI due to antituberculosis drug-induced liver injury (DILI) encompasses a wide spectrum of liver injury ranging from asymptomatic minimal elevation of liver enzymes to acute liver failure, often leading to death or liver transplantation. Indeed, it is a leading cause of drug-induced liver injury in India and of drug-induced acute liver failure leading to death (DIALF).[8-10] In contrast, non-TB antibiotics and paracetamol are the commonest causes of DILI and drug-induced ALF in western countries.[11-13] In a single center registry of 303 patients from Bangalore, antituberculosis drugs contributed to 58% cases of DILI.[10] In another large series investigating acute liver failure in New Delhi, anti-TB drugs contributed to 5.7% patients with ALF(70/1223), with 67% mortality.[8] This review examines the current perspectives of TB DILI. For a complete and exhaustive overview of TB DILI, excellent reviews have been published.[5-7]

Definition

Earlier definitions were plagued by inconsistencies in elevation of numerical levels of transaminases needed for a diagnosis of DILI. Presently, there is a fair amount of consistency in the criteria used for diagnosing DILI including TB DILI. In the absence of symptoms, elevation of transaminases up to 5 times the upper limit of normal (ULN) and in the presence of symptoms up to three times the ULN or twice the ULN of bilirubin constitutes DILI,[6,14,15] provided competing causes such as acute viral hepatitis, autoimmune hepatitis and others liver diseases are ruled out. Although physicians often use elevation of transaminases or bilirubin as default criteria for diagnosing TB DILI, recent studies underscore the importance of concomitant viral hepatitis A-E as a reason for elevation in liver biochemical tests. A recent study by Sarda and colleagues[16] identified acute viral hepatitis as a competing cause in 14.7% of patients. Routine use of causality assessment scores such as Roussel Uclaf Causality Assessment Method (RUCAM) or Drug Induced Liver Injury Network (DILIN) criteria will bring some objectivity to the likelihood/probability scores of DILI and minimize errors.[14,15] Besides the above definition in patients with HIV, the AIDS Clinical Trials Group criteria is used, which is as follows: Grade 1: transaminases 1.25 - 2.5 × upper limit of normal (ULN); Grade 2: 2.6 - 5 × ULN; Grade 3: 5.1 - 10 × ULN; and Grade 4: >10 × ULN.[17]

Incidence, interactive toxicity and mechanism of toxicity

The overall incidence of TB DILI in the population is unknown and is probably unrecognized. Toxicity occurs both during primary prophylaxis (preventive therapy) and treatment of tuberculosis; and is dependent on the dynamics of drugs, drug-disease and drug-host interactions.

Among the first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), the first three have the potential for hepatotoxicity with pyrazinamide being the most hepatotoxic followed by isoniazid and rifampicin.[18,19] Rifampicin combined with PZA is more hepatotoxic than with INH.[20,21] Pyrazinamide contributes significantly to ALF.[22] There is some evidence to suggest the protective effect of isoniazid on hepatotoxicity of RIF and PZA in combination regimens.[23,24] However, when DILI occurs following the use of 4-drug combination regimen, it is impossible to quantify the contribution of each drug in the development of DILI.

Pathogenesis and mechanisms

Most cases of DILI are idiosyncratic in nature, meaning it is the characteristics of the host and not the characteristic of the drug which are responsible for the liver injury. Idiosyncratic reactions may be hypersensitive or metabolic.[25] Hypersensitive idiosyncrasy is often associated with skin rashes, fever, eosinophilia and/or lymphadenopathy. This is uncommon in anti-TB drugs, being more common with antiepileptics and sulfonomides.[26] More commonly, TB DILI is due to metabolic

idiosyncrasy due to the metabolites released or accumulated during the metabolic process. Recent evidence indicates that drugs taken in quantities of >50 grams/day[27]are more likely to produce hepatotoxicity, which results from the formation or reduced clearance of toxic metabolites.[28] This may be facilitated by genetic factors or polymorphism of drug metabolizing enzymes (see section on genetic polymorphism).

Presentation, adaptation and clinical evaluation of DILI

Antituberculosis DILI has a wide spectrum of presentations, ranging from asymptomatic mild rise in liver biochemical tests to acute hepatitis and acute liver failure. The mild increase in aminotransferases experienced by ~20% of patients is usually asymptomatic.[5] Clinical hepatitis is seen in 1-6% of patients taking isoniazid prophylaxis or combination drugs.[29] A feature peculiar to anti-TB drugs is the development of adaptation or tolerance to the drugs. Indeed, adaptation during INH or anti-TB use is an illustrative example for adaptation. This is defined as elevation of transaminases and or bilirubin, without any symptoms, which resolves with continuation of the drugs. Rarely, despite marked rise in transaminases and bilirubin, patients may still be asymptomatic.[30] Awareness of the phenomenon of adaptation is critical in tuberculosis to prevent inadvertent discontinuation of antitubercular drugs which are critical for successful treatment of TB patients. Since liver biochemical tests are not routinely monitored in TB patients on the 4 antitubercular drugs, the actual incidence of this condition remains unknown but is believed to be in the order of ~20%.[5] When elevated liver enzymes are noted in a TB patient on ATT, the major challenge for the treating physician is to determine whether the elevation is a sign of adaptation or a sign of incipient liver injury. The current recommended diagnostic criteria laid down by the DILIN and other groups may assist in resolving this issue. TB drugs can be continued till AST/ALT is 5 × ULN, in the absence of hyperbilirubinemia or symptoms; or up to 3 × ULN in the presence of symptoms or hyperbilirubinemia (bilirubin 2 × ULN). Competing etiologies particularly acute viral hepatitis may need to be excluded.

Risk factors for TB DILI

Interactions between genetic, host and environmental factors contribute towards the development of TB DILI. The following is a summary of the most important factors.

Age: Recent studies have noted patients older than 35 years are at 4 times increased risk to develop TB DILI.[31] Other studies on latent disease indicate that 1.7% of those >35 years developed TB DILI compared to 0.2% in those younger than 35. However in their meta-analysis, Steele et al[29] observed hepatitis in 1 - 6.9% of children compared to 1.6 - 2.5% of adults taking INH and RIF combination; implying that all age groups are at risk for DILI. Roy et al[32] observed an incidence of 8% in children while Devrim noted an incidence of 1.7% in Turkey.[33] Indeed, the fatal effects of the 4 drug ATT combination is marked with 50% mortality in those with TB DILI, including >80% mortality in those with TB DILI ALF,[26] which is higher than the mortality of 67% reported in adults.[8,9]

Gender: Although women have traditionally been considered more susceptible to develop TB DILI, recent reports suggests that men outnumber women in the incidence of TB DILI.[9,10] This likely reflects the demographic disparity where more men than women are under treatment for tuberculosis. However, female gender is a positive predictor of more severe liver disease including death.[10]

Organ involvement / extent of TB disease: The extent of tuberculosis including cavitory disease, multibacillary TB and extrapulmonary organ involvement have been incriminated as positive predictors for TB DILI by some authors,[34,35] while others have failed to note any significant association[36] In a study from south India, TB DILI was detected in 16-39% of children with tuberculous meningitis, compared to 10% in spinal tuberculosis and 2-8% in pulmonary tuberculosis.[34] The strikingly high 39% DILI in the above study was also attributed to the high dose of pyrazinamide (20 mg/kg body weight) compared to 16% in those who received a 12 mg/kg dose. Interestingly, a recent meta-analysis of 29 studies did not find any significant hepatotoxicity between high-dose pyrazinamide (60 mg/kg) compared to medium (40 mg/kg) and low dose (30 mg/kg) regimens.[37]

Malnutrition: Recent reports continue to confirm the relevance of hypoalbuminemia as a surrogate marker of malnutrition and a risk factor for TB DILI. Singla et al and Sharma et al demonstrated that patients with low albumin (<3.5 mg/dl) had three fold higher risk of developing TB DILI.[31,35] A recent report incriminated weight loss as an important risk factor for DILI.[38]

Alcohol: The influence of alcohol as a risk factor is equivocal. Patients who drink frequently often underestimate the quantity consumed and continue to drink despite recommendations to the contrary. Alcohol as a risk factor has

been ascribed to under-nutrition and depleted glutathione stores.[7]

Hepatitis B: The risk of DILI is increased 4 fold in HBsAg carriers compared to non-carriers (34.9% vs. 9.4%, p<0.001). Replicating status (HBeAg) may play a pathophysiological role although even inactive carriers are at risk to develop DILI.[39] A recent study found high baseline HBV DNA in patient samples to be a risk factor for DILI.[36] The probability of an acute flare should be considered during the time of raised transaminases.[36]

Hepatitis C: Combination chemotherapy and isoniazid monotherapy is associated with a 5 fold increased risk of DILI. Similar to hepatitis B, the HCV viral count may play a critical role during transaminase elevation.[40]

Dosing schedules: The role of daily vs. intermittent high dose schedules including DOTS (directly observed therapy, short-course) continues to be debated. Chang and associated did not find a link between dosing schedule and hepatotoxicity.[41] Many of the patients in a recent series from India developed TB DILI while receiving DOTS therapy.[9,42] The role of an overstretched health care system and workers who disregard or ignore minimal signs and symptoms of DILI may be a contributing factor.

Genetic polymorphism: The role of three enzymes important for metabolism of INH has been extensively investigated. They include, N-acetyltransferase 2 (NAT2), CYP 2E1 and glutathione S-transferase.[43,44]

Increasing number of studies are reporting the plausible impact of N-acetyltransferase 2 (NAT2) gene/enzyme polymorphisms on the metabolism of isoniazid and susceptibility to DILI. While early reports linked fast acetylators (normal level of NAT2 enzyme) with susceptibility to TB DILI, later studies have uniformly incriminated slow acetylators lacking NAT2 activity with TB DILI.[45] Bose and colleagues demonstrated NAT2 slow-acetylator genotype in 71% patients with TB DILI compared to 45% patients without DILI (p<0.05).[46] This is consistent with similar results reported by Huang YS et al[47] who found a higher risk of hepatotoxicity in slow acetylators than rapid acetylators (26.4% vs. 11.1%; p=0.013), and also demonstrated that slow acetylators were at higher risk for developing severe liver injury.[47] In contrast, Roy et al[48] did not find any association between NAT2 slow acetylators and DILI, or CYP 2E1 *1A/*1A and DILI. However a subgroup analysis found an association of CYP 2E1 DraI in children with DILI.[49] This was confirmed by a recent study by Bose et al[46] which found an association of DraI polymorphism of CYP 2E1 gene with DILI (85% DILI vs. 64% non-DILI, p<0.05). Vuilleumier et al[50] also concluded that CYP 2E *1A/*1A was a risk factor for INH induced hepatitis in patients with latent tuberculosis.

In another study Roy and associates[48] observed an increased risk of TB DILI in individuals with glutathione S-transferase M1"null" mutation, a result similar to that reported by Huang et al in an Asian population.[51] Leiro and colleagues concluded similar results among Caucasians with regard to GSTT1 homozygous null mutation and anti-TB DILI.[52] Paradoxically, a recent study by Chatterjee et al did not show any association with either GSTT1 or GSTM1 gene deletion in TB DILI.[53] The reasons for such discordant findings are unclear, but could be due to the variability in small patient cohorts and the limited impact of these polymorphisms on DILI.

Role of HLA on DILI

Antituberculous class of drugs are among the growing list of drugs linked to human leukocyte antigen (HLA) class II. Sharma et al reported the presence of HLA-DQB1*0201 and the absence of HLA-DQA1*0102 with AT DILI with odds ratio of 1.9 and 4.0 respectively.[42] The low odds ratio is in marked contrast to the odds ratio of 80.6 with flucloxacillin in patients with HLA B*5701.[54] HLA B*5701 is also linked strongly with abacavir induced hypersensitivity reactions. Given the modest increase in the risk of developing TB DILI, the role of pharmacogenetics particularly for drugs such as antituberculous agents will be limited given the global burden of disease, the absence of potent second line drugs and the costs associated with pharmacogenomic testing. The importance of host and environmental factors such as weight based dosage, appropriate indications, concomitant drug history and stopping drugs at the first sign of hepatic injury will likely make greater contribution towards minimizing the incidence and progression of DILI.

HIV infection

Tuberculosis and HIV often coexist and are emerging as a global problem of alarming proportions. The ~ 40 million people living with HIV infection are 6-50 times more likely to develop active TB than those without HIV infection.[2] Both diseases need multidrug therapy, resulting in up to 18% incidence of hepatotoxicity.[55] The likely causes include drug-drug and potential drug-disease interactions. In addition, the presence of hepatitis B and hepatitis C complicate and markedly increase

the risk of hepatotoxicity.[7] For example, HIV alone and co-infection with hepatitis C increases the risk of TB DILI 4 and 14 fold respectively, in patients on antituberculous drug therapy.[40]

TB DILI in children

Although DILI occurs less frequently in children than adults, it is by no means uncommon. DILI contributes to 4-8% and 8.7% pediatric cases in the west and India, respectively.[26] The commonest cause among Indian children and adolescents is antituberculous agents used for treatment of tuberculosis usually with a 4-drug combination regimen. In children too, the mortality is substantial, occurring in 50 % of patients with TB DILI, largely due to metabolic idiosyncrasy. In a retrospective study of 99 children from Japan, 8 children developed TB DILI.[56] Younger age and the use of pyrazinamide were factors associated with risk of hepatotoxicity.[56] DILI due to antituberculous agents is seen more commonly due in extensive disease particularly tuberculous meningitis,[57] whereas TB DILI during chemoprophylaxis is distinctly uncommon.[57] However, studies from Bangalore,[26] Japan,[56] and elsewhere[57] remind us that children receiving antituberculosis combination drugs are at risk of TB DILI and should be monitored for hepatotoxicity.

While all the above factors are important and may well contribute towards development of DILI, studies from India suggest that 42-63% of individuals who developed DILI and TB DILAF never required anti-TB drugs in the first place and were being treated empirically for suspected tuberculosis.[8,9]

Management of hepatotoxicity

Prevention of DILI: Various predictive factors have been implicated in DILI and caution should be exercised in such patients. Not all studies have identified the same risk factors. Education of the patient and their family members about the risk of TB drugs and the critical need to stop the drug immediately on development of symptoms should be emphasized. In a study of 11,144 patients on INH chemoprophylaxis, only 0.6% subjects developed clinically relevant DILI without the use of liver biochemical tests.[58] The above study highlights the role played by primary care providers and patient education, and emphasizes the importance of immediate discontinuance of the drug in order to prevent progressive liver disease. Since old age is a risk factor, a recent study concluded that co-prescription with N-acetylcysteine (NAC) in patients above 60 years prevented DILI, when compared to those who did not receive NAC.[59] Further studies are needed to confirm this finding.

Management after diagnosis of DILI: Elevated liver biochemical tests alone are often used as to diagnose DILI and should be discouraged. While it is prudent to discontinue the hepatotoxic drugs, a search for an alternative cause such as acute viral hepatitis A-E should be undertaken before a diagnosis of DILI can be made. Various guidelines for the management of DILI have been propounded by the American Thoracic Society (ATS),[6] British Thoracic Society (BTS),[60] the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease. There are minor variations among these guidelines including the necessity or not of liver biochemical tests. There are no studies validating the utility of liver biochemical tests in prevention of DILI or assessing its severity. Such monitoring is often seen as inconvenient, expensive and inefficient by both patients and doctors, and thus the monitoring recommendations are poorly followed.[61] However, monitoring with liver tests is recommended in the following groups: patients who consume alcohol, individuals with chronic hepatitis B or C, and those on concomitant hepatotoxic drugs, have elevated baseline transaminase levels, suffer from underlying liver disease and those with HIV.[6] Symptoms of DILI are often the first clue to an early diagnosis of the disorder and should not be disregarded. After the diagnosis of DILI, the 3 hepatotoxic drugs, namely INH, RIF and PYZ are to be withheld immediately. Depending upon the urgency of the underlying tuberculous condition second line drugs such as streptomycin or amikacin, ciprofloxacin or ofloxacillin, may be initiated till such time the liver tests return to normal, or jaundice abates or the transaminases drop to $<2 \times$ ULN.[6] Alternatively newer drugs such as moxifloxacillin may be used in lieu of the first line drugs. Although most cases may resolve with omission of the offending drugs (dechallenge), unfortunately a few cases will continue to progress despite drug withdrawal. Reintroduction of the primary agents after DILI has resolved is subject of much debate. The common regimen consisting of sequential treatment, first with rifampicin followed by isoniazid 3-7 days later may be undertaken. If tolerated, pyrazinamide may be started with monitoring of liver tests. Alternatively pyrazinamide may be omitted and both isoniazid and rifampicin may be continued for a longer duration of 9-12 months depending on the underlying disease.

A recent study evaluated the safety of reintroduction of 3

antituberculosis regimens either as sequential treatment or concomitant treatment in 175 patients with TB DILI.[42] In this study the three treatment arms were as follows: arm I (n=58), patients received maximum doses of INH, RIF, PZA simultaneously, arm II (n=59), patients received treatment as per ATS guidelines, i.e. RIF followed by INH after 7 days, followed by PZA after 7 days, all with maximum doses. In arm III (n=58), patients received sequential treatment with graded doses according to British Society Study (BTS) guidelines. The doses of INH, RIF and PZA were gradually escalated sequentially after the maximum dose of the preceding drugs was achieved. The authors concluded that the recurrence of DILI was similar between the three treatment arms, namely 8, 6, and 5 patients respectively (p=0.69).[42] In contrast, the only other randomized study by Tahaoglu and associates[62] on 45 patients concluded that reintroduction regimens containing maximum dose of antituberculosis drugs including pyrazinamide (group 1, n=25) caused more hepatotoxicity than gradual reintroduction without pyrazinamide, (group 2, n=25).[62] The authors noted hepatotoxicity in 6 (24%) patients in group I, compared to none in group 2 (p=0.021). The differences between the above two studies could be due to a smaller number of patients in the second study and the lower treatment limiting cut-offs in the former study, a number of whom may have had adaptation.[63] The advantage of sequential treatment is its ability to delineate the hepatotoxic drug and the choice of not using pyrazinamide which appears to be the most hepatotoxic drug among the 3. The jury is still out regarding the optimal regimen and dose for reintroduction of anti-TB drugs after hepatotoxicity. However, caution should be exercised while treating patients with chronic liver disease or cirrhosis. Pyrazinamide may be withheld particularly in individuals with cirrhosis and a dual combination consisting of INH and RIF may likely be safer.[64,65]

N-acetylcysteine has been shown to be useful in drug induced liver injury. In the randomized controlled trial assessing the utility of NAC in all forms of acute liver failure, NAC was found useful in coma progression in DILI (p=<0.05).[66] Although further studies are needed to validate this result in AT DILI, indirect evidence of the usefulness of NAC comes from another study by Baniasadi et al[59] demonstrating the usefulness of limiting liver enzyme elevation in patients over 60 years when NAC was used prophylactically along with antituberculosis drugs.

Management in specific setting such as liver or organ transplantation: Patients who undergo liver transplantation for acute liver failure due to TB DILI may need to be on antituberculosis medications. Rifampin's potent induction of CYP 450 system may cause decrease in the concentration of immunosuppressive drugs leading to acute rejection of transplant organs. Therefore caution should be exercised when rifampin is prescribed. Alternatively, drugs such as rifabutin or other second line drugs may be instituted in order to minimize the risk of rejection and maximize the efficacy of treating tuberculosis simultaneously.[67]

Conclusions

Comprehensive case series on DILI in India, including TB DILI and TB DIALF continue to improve our awareness and understanding of the clinical spectrum, natural history, outcome and genetic predictors of TB DILI. The high mortality associated with TB DILI should serve as a caution to minimize diagnostic and prescription errors. While reintroduction regimen after antituberculosis drug hepatotoxicity remain debatable, sequential treatment appears safer. The recent warning from WHO against the use of inaccurate and inconsistent blood tests for tuberculosis may mitigate the occurrence of TB DILI.[68]

References

1. www.tbcindia.org/pdf/keyfactsandconcepts accessed 23 August 2011.
2. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med*. 2003;**163**:1009–21.
3. Nunn P, Reid A, De Cock KM. Tuberculosis and HIV infection: the global setting. *J Infect Dis*. 2007;**196**:S5–14.
4. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin Drug Saf*. 2006;**5**:231–49.
5. 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.
6. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;**174**:935–52.
7. Senousy BE, Belal SI, Draganov PV. Hepatotoxic effects of therapies for tuberculosis. *Nat Rev Gastroenterol Hepatol*. 2010;**7**:543–56.
8. 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.

9. Devarbhavi H, Dierkhising R, Kremers WK. Antituberculosis therapy drug-induced liver injury and acute liver failure. *Hepatology*. 2010;**52**:798–9.
10. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol*. 2010;**105**:2396–404.
11. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008;**135**:1924–34.
12. Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology*. 2005;**42**:481–9.
13. Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;**129**:512–21.
14. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;**46**:1323–30.
15. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf*. 2009;**32**:55–68.
16. Sarda P, Sharma SK, Mohan A, Makharia G, Jayaswal A, Pandey RM, et al. Role of acute viral hepatitis as a confounding factor in antituberculosis treatment induced hepatotoxicity. *Indian J Med Res*. 2009;**129**:64–7.
17. AIDS Clinical Trials Group. Table of grading severity of adult adverse experiences. Rockville, MD: Division of AIDS, National Insttute of Allergy and Infectious Diseases; 1996.
18. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003;**167**:1472–7.
19. Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. *Arch Intern Med*. 2006;**166**:1863–70.
20. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med*. 2002;**137**:640–7.
21. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis*. 2002;**6**:995–1000.
22. Durand F, Bernuau J, Pessayre D, Samuel D, Belaiche J, Degott C, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. *Hepatology*. 1995;**21**:929–32.
23. Grosset J, Truffot-Pernot C, Lacroix C, Ji B. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. *Antimicrob Agents Chemother*. 1992;**36**:548–51.
24. Dickinson J, Guy A, Mitchison DA. Bioavailability of rifampin in experimental murine tuberculosis**.** ***Antimicrob Agents Chemother.*** **1992;**36**:2066–7.**
25. Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. *2nd ed. Phiiladelphia: Lippincott, Williams and Williams*; 1999.p.427–56.
26. Devarbhavi H, Karanth D, Prasanna K, Adarsh C, Patil M. Drug-Induced liver injury with hypersensitivity features has a better outcome: A single center experience of 39 children and adolescents. *Hepatology*. 2011;**54**:1344–50.
27. Lammert C, Einarsson S, Saha C, Niklasson A, Bjornsson E, Chalasani N. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. *Hepatology*. 2008;**47**:2003–9.
28. Lammert C, Bjornsson E, Niklasson A, Chalasani N. Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events. *Hepatology*. 2010;**51**:615–20.
29. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. 1991;**99**:465–71.
30. Mitchell JR, Long MW, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventive therapy. *Chest*. 1975;**68**:181–90.
31. 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.
32. Roy B, Ghosh SK, Sutradhar D, Sikdar N, Mazumder S, Barman S. Predisposition of antituberculosis drug induced hepatotoxicity by cytochrome P450 2E1 genotype and haplotype in pediatric patients. *J Gastroenterol Hepatol*. 2006;**21**:784–6.
33. Devrim I, Olukman O, Can D, Dizdarer C. Risk factors for isoniazid hepatotoxicity in children with latent TB and TB: difference from adults. *Chest*. 2010;**137**:737–8.
34. Parthasarathy R, Sarma GR, Janardhanam B, Ramachandran P, Santha T, Sivasubramanian S, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1986;**67**:99–108.
35. 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.
36. Wang JY, Liu CH, Hu FC, Chang HC, Liu JL, Chen JM, et al. Risk factors of hepatitis during anti-tuberculous treatment and implications of hepatitis virus load. *J Infect*. 2011;**62**:448–55.
37. Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than low doses currently used. *Antimicrob Agents Chemother*. 2010;**54**:2847–54.
38. Warmelink I, ten Hacken NH, van der Werf TS, van Altena R. Weight loss during tuberculosis treatment is an important risk factor for drug-induced hepatotoxicity. *Br J Nutr*. 2011;**105**:400–8.

39. Lee BH, Koh WJ, Choi MS, Suh GY, Chung MP, Kim H, et al. Inactive hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy. *Chest*. 2005;**127**:1304–11.
40. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, 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.
41. Chang KC, Leung CC, Yew WW, Tam CM. Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? *Eur Respir J*. 2007;**29**:347–51.
42. Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, 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.
43. Huang YS. Genetic polymorphisms of drug-metabolizing enzymes and the susceptibility to antituberculosis drug-induced liver injury. *Expert Opin Drug Metab Toxicol*. 2007;**3**:1–8.
44. Roy PD, Majumder M, Roy B. Pharmacogenomics of anti-TB drugs-related hepatotoxicity. *Pharmacogenomics*. 2008;**9**:311–21.
45. Daly AK. Drug-induced liver injury: past, present and future. *Pharmacogenomics*. 2010;**11**:607–11.
46. Bose PD, Sarma MP, Medhi S, Das BC, Husain SA, Kar P. Role of polymorphic N-acetyl transferase2 and cytochrome P4502E1 gene in antituberculosis treatment-induced hepatitis. *J Gastroenterol Hepatol*. 2011;**26**:312–8.
47. 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.
48. Roy B, Chowdhury A, Kundu S, Santra A, Dey B, Chakraborty M, et al. Increased risk of antituberculosis drug-induced hepatotoxicity in individuals with glutathione S-transferase M1 'null' mutation. *J Gastroenterol Hepatol*. 2001;**16**:1033–7.
49. Roy B, Ghosh SK, Sutradhar D, Sikdar N, Mazumder S, Barman S. Predisposition of antituberculosis drug induced hepatotoxicity by cytochrome P450 2E1 genotype and haplotype in pediatric patients. *J Gastroenterol Hepatol*. 2006;**21**:784–6.
50. Vuilleumier N, Rossier MF, Chiappe A, Degoumois F, Dayer P, Mermillod B, et al. CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. *Eur J Clin Pharmacol*. 2006;**62**:423–9.
51. Huang YS, Su WJ, Huang YH, Chen CY, Chang FY, Lin HC, et al. Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H:quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. *J Hepatol*. 2007;**47**:128–34.
52. Leiro V, Fernández-Villar A, Valverde D, Constenla L, Vázquez R, Piñeiro L, et al. Influence of glutathione S-transferase M1 and T1 homozygous null mutations on the risk of antituberculosis drug-induced hepatotoxicity in a Caucasian population. *Liver Int*. 2008;**28**:835–9.
53. Chatterjee S, Lyle N, Mandal A, Kundu S. GSTT1 and GSTM1 gene deletions are not associated with hepatotoxicity caused by antitubercular drugs. *J Clin Pharm Ther*. 2010;**35**:465–70.
54. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet*. 2009;**41**:816–9.
55. Núñez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J Hepatol*. 2006;**44**:S132–9.
56. Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, et al. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. *Clin Pharmacol Ther*. 2002;**72**:220–6.
57. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. *Pediatr Rep*. 2011;**3**:e16
58. 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.
59. Baniasadi S, Eftekhari P, Tabarsi P, Fahimi F, Raoufy MR, Masjedi MR, et al. Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity. *Eur J Gastroenterol Hepatol*. 2010;**22**:1235–8.
60. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax*. 1998;**53**:536–48.
61. Senior JR. Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests? *Clin Pharmacol Ther*. 2009;**85**:331–4.
62. Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2001;**5**:65–9.
63 Saukkonen J. Challenges in reintroducing tuberculosis medications after hepatotoxicity. *Clin Infect Dis*. 2010;**50**:840–2.
64. Park WB, Kim W, Lee KL, Yim JJ, Kim M, Jung YJ, et al. Antituberculosis drug-induced liver injury in chronic hepatitis and cirrhosis. *J Infect*. 2010;**61**:323–9.
65. Nathwani RA, Kaplowitz N. Drug hepatotoxicity. *Clin Liver Dis*. 2006;**10**:207–17, vii.
66. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*. 2009;**137**:856–64, 864.e.1.
67. Ichai P, Saliba F, Antoun F, Azoulay D, Sebagh M, Antonini TM, et al. Acute liver failure due to antitubercular therapy: Strategy for antitubercular treatment before and after liver transplantation. *Liver Transpl*. 2010;**16**:1136–46.
68. www.who.int/tb/en accessed 23 August 2011.