Safety of 3 Different Reintroduction Regimens of Antituberculosis Drugs after Development of Antituberculosis Treatment–Induced Hepatotoxicity

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(See the editorial commentary by Saukkonen, on pages 840–842.)

Background. Drug-induced hepatotoxicity (DIH) is the most common adverse drug reaction leading to interruption of antituberculosis treatment. Worldwide, different reintroduction regimens have been advocated, but no consensus guidelines are available. Reintroduction of antituberculosis drugs in patients with DIH has never been studied systematically. We aimed to compare the safety of 3 different reintroduction regimens of antituberculosis drugs in patients with antituberculosis DIH.

Methods. A total of 175 patients with a diagnosis of antituberculosis DIH were randomized to receive 1 of 3 different predefined reintroduction regimens of antituberculosis drugs and were evaluated prospectively. Patients in arm I were given isoniazid, rifampicin, and pyrazinamide simultaneously at full dosage from day 1. In arm II, drugs were administered in a manner similar to that recommended in the American Thoracic Society guidelines for reintroduction. In arm III, drugs were administered in accordance with British Thoracic Society guidelines.

Results. Nineteen patients (10.9%) had recurrence of DIH during follow-up. Eight, 6, and 5 patients had recurrence of hepatitis in arms I, II, and III, respectively (P = .69). Of all the clinical and laboratory parameters, pretreatment serum albumin level was the only statistically significant predictor of future recurrence of DIH on reintroduction of antituberculosis drugs (P < .01).

Conclusions. The recurrence rate of hepatotoxicity was not significantly different between the 3 groups. According to the findings of the present study, all 3 of the potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) can be reintroduced simultaneously at full dosage safely from day 1, especially for patients with bilateral extensive pulmonary tuberculosis, to halt disease transmission or to treat patients with life-threatening tuberculosis.

Trial registration. ClinicalTrials.gov identifier number: NCT00405301.

Tuberculosis (TB) continues to be a major health problem in both developing and developed countries because of its resurgence among immunosuppressed patients. Short-course chemotherapy comprising isoniazid, rifampicin, and pyrazinamide has proved to be highly effective in the treatment of TB. The most common adverse effect leading to interruption of therapy is hepatotoxicity [1]. Anti-TB drug–induced hepatotoxicity (DIH) is associated with a mortality of 6%–12% if these drugs are continued after the onset of symptoms [2]. The risk of hepatotoxicity is increased when the drugs are combined.

The treatment of underlying TB after occurrence of hepatitis is difficult and controversial. In a limited number of published studies, different reintroduction regimens have been advocated with variable success [3–5], but consensus guidelines for managing anti-TB DIH are yet to be developed. Reintroduction of anti-TB drugs following anti-TB DIH has never been studied systematically. With the exception of 1 small study [4], there is little empirical evidence comparing different reintroduction regimens of anti-TB drugs.

The present study was designed to compare 3 dif-
ferent predefined regimens of reintroduction of anti-TB drugs in patients with DIH with respect to safety and risk of recurrence of hepatotoxicity. In brief, in the first reintroduction regimen (arm I), all 3 drugs were introduced together at full dosages. In the other 2 reintroduction regimens (arms II and III), the drugs were introduced sequentially, as advocated by the American Thoracic Society (ATS) and British Thoracic Society (BTS) guidelines, respectively.

**PATIENTS, MATERIALS, AND METHODS**

**Patients.** The study included patients with a diagnosis of DIH who attended the outpatient department or were admitted to the All India Institute of Medical Sciences Hospital (New Delhi, India) and Sri Venkateswara Institute of Medical Sciences Hospital (Tirupati, Andhra Pradesh, India). The study period was 2004–2009. We recruited 237 consecutive patients who developed clinical and/or laboratory features suggestive of DIH while receiving anti-TB treatment. Patients who met the following diagnostic criteria for DIH were enrolled: (1) an increase \( \geq 5 \) times the upper limit of the normal levels (50 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) on 1 occasion or \( > 3 \) times the upper limit of normal (\( > 150 \) IU/L) on 3 consecutive occasions; (2) an increase in serum total bilirubin \( > 1.5 \) mg/dL; (3) any increase in serum AST and or ALT level above pretreatment values together with anorexia, nausea, vomiting, and jaundice; (4) absence of serological evidence of infection with hepatitis A, B, C, or E virus; and (5) improvement in liver function test results (serum bilirubin level, AST level, ALT level, alkaline phosphatase [ALP] level, serum total protein, and serum albumin level) on 3 consecutive occasions; (2) an increase in serum total bilirubin \( > 1.5 \) mg/dL; (3) any increase in serum AST and or ALT level above pretreatment values together with anorexia, nausea, vomiting, and jaundice; (4) absence of serological evidence of infection with hepatitis A, B, C, or E virus; and (5) improvement in liver function test results (serum bilirubin level \( < 1 \) mg/dL; AST and ALT level \( < 100 \) IU/L) after withdrawal of anti-TB drugs [6, 7]. DIH was diagnosed if criteria 1, 2, or 3 were present in combination with criteria 4 and 5.

Patients of either sex who were 16–65 years of age were recruited. Patients outside this age range were excluded, because the risk of DIH increases at both extremes of age [8–13]. Written informed consent was obtained from all patients. The Institutional Ethics Committee approved the study.

**Data collection.** The site of TB involvement, the method of establishing the diagnosis of TB, history of liver disease, history of concomitant use of other hepatotoxic drugs, and alcohol intake were recorded. The details of anti-TB drugs (nature of drugs, dosages, duration of treatment, and patient compliance) were noted. The pretreatment liver function test results (serum bilirubin level, AST level, ALT level, alkaline phosphatase [ALP] level, serum total protein, and serum albumin level) were recorded. The extent of disease as determined by examination of a chest radiograph was recorded and categorized as minimal, moderately advanced, and far advanced [14], as defined by the US National Tuberculosis Association in 1961. Patient history and family history of TB was also recorded. Nutritional status was estimated by calculating the body mass index (BMI, defined as the weight in kilograms divided by the square of height in meters) and mid-arm circumference. Time interval from initiation of anti-TB drugs to occurrence of DIH was taken as the latency period.

**Study design.** We conducted a prospective, randomized trial to evaluate the hepatotoxic potential of 3 different predefined anti-TB drug reintroduction regimens after the occurrence of anti-TB DIH. The primary end point was recurrence of DIH, which was defined using the criteria stated above. Exclusion criteria observed were serological evidence of acute viral hepatitis, ultrasonographic evidence of chronic liver disease, human immunodeficiency virus (HIV) infection, long-term alcoholism (defined as consumption of \( > 48 \) g of alcohol per day for at least 1 year [7]), concomitant consumption of other potentially hepatotoxic drugs (eg, methotrexate, phenytoin, valproate, and fluconazole), pregnancy, and failure to give written informed consent.

Patients with DIH who satisfied the inclusion criteria were enrolled into the study. Treatment with the hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) was immediately stopped. Patients were administered a modified anti-TB drug regimen consisting of ethambutol, streptomycin, and 1 of the fluoroquinolones. Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized (ie, absence of vomiting and abdominal pain, both AST and ALT levels \( < 100 \) IU/L, and serum bilirubin level \( < 1.0 \) mg/dL). Time interval between stopping isoniazid, rifampicin, and pyrazinamide and achieving these parameters was taken as the normalization period.

After stabilization of liver functions, the patients were randomized into 1 of the 3 arms with use of computer-generated random numbers, blocked in groups of 3. These numbers were kept in sealed opaque envelopes. The envelopes were in the possession of an individual who was not involved in the conduct of study. Each arm had a different reintroduction protocol for anti-TB drugs (Table 1). There was no crossover of patients between study arms. Adherence to treatment protocol was established at each visit. Patients in arm I were given isoniazid, rifampicin, and pyrazinamide simultaneously at the full dosage. This strategy for reintroduction of anti-TB drugs is not recommended by any of the existing guidelines because of fear of increased hepatotoxicity. In arm II, anti-TB drugs were introduced in a manner similar to that recommended by ATS guidelines [15], and in arm III, drugs were administered in accordance with BTS guidelines [16]. Figure 1 summarizes the study.

**Laboratory monitoring.** Tests to detect markers of acute viral hepatitis (immunoglobulin M [IgM] anti–hepatitis A virus, IgM anti–hepatitis B core antigen and/or hepatitis B surface antigen, IgM anti–hepatitis C virus antibodies, and IgM anti–
Table 1. Three Different Regimens for Reintroduction of Anti-Tuberculosis Drugs

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>H, R, and Z at maximum dosages from day 1</td>
</tr>
<tr>
<td>Arm II</td>
<td>R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15</td>
</tr>
<tr>
<td>Arm III</td>
<td>H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 18</td>
</tr>
</tbody>
</table>

**NOTE.** Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg. H, isoniazid; R, rifampicin; Z, pyrazinamide.

Statistical analysis. We assumed that the risk of recurrence of hepatotoxicity associated with the simultaneous reintroduction of isoniazid, rifampicin, and pyrazinamide at a full dosage (as in arm I) was 24%, as reported by Tahaoglu et al [4]. Also, we assumed that the risk of recurrence of hepatotoxicity associated with a reintroduction regimen in which isoniazid, rifampicin, and pyrazinamide were introduced sequentially in the same order in gradually escalating dosages (as in arm III) was 6.8%, as reported by Singh et al [3]. To our knowledge, no study has previously evaluated the risk of recurrence of hepatotoxicity associated with a reintroduction schedule in which rifampicin, isoniazid, and pyrazinamide are reintroduced sequentially at full dosage (as in arm II). We assumed that such a reintroduction schedule would be noninferior to the one used in arm III, and therefore, the risk of recurrence of hepatotoxicity associated with such a regimen was assumed to be 7%. To detect a difference in the risk of recurrence of hepatotoxicity with 80% power using a \( \chi^2 \) test with a 5% level of significance, 56 subjects in each arm were required.

We analyzed group mean values by means of the Student’s \( t \) test and analysis of variance (ANOVA), and the proportions were compared with use of the \( \chi^2 \) test and Fisher’s exact test.

Figure 1. Summary of the study. DIH, drug-induced hepatotoxicity; HIV, human immunodeficiency virus; TB, tuberculosis.
The Bonferroni correction was applied for multiple comparisons among the 3 groups when ANOVA indicated a statistically significant difference. Associations with a $P$ value $<.05$ were considered to have statistical significance. Stata, version 9.2 (StataCorp), was used for data analysis.

**RESULTS**

A total of 237 patients who developed clinical and/or laboratory features suggestive of DIH while receiving anti-TB drugs were recruited. Four patients died before they could be randomized into any of the 3 arms (3 patients died due to acute liver failure, and 1 patient died due to progressive pulmonary TB leading to acute respiratory failure). A total of 58 patients were excluded for various reasons; 11 had long-term alcoholism, 5 were taking hepatotoxic drugs (chiefly phenytoin), and 17 had HIV infection. Serological evidence confirmed recent acquisition of acute viral hepatitis in 25 patients, of whom 4 (16%) had hepatitis A, 4 (16%) had hepatitis B, 3 (12%) had hepatitis C, and 14 (56%) had hepatitis E. None of the patients had multidrug-resistant or extensively drug-resistant TB. The remaining 175 patients were randomized to 1 of the 3 arms after stabilization of liver functions. Of these 175 patients, 12 (6.9%) were asymptomatic and received a diagnosis on the basis of elevated transaminase levels alone. Most of the patients experienced nausea (90.2%), vomiting (65.7%), abdominal pain (28%), or jaundice (43.4%). Forty five (25.7%) had pulmonary TB, 97 (55.4%) had extrapulmonary TB, and 33 (18.9%) had disseminated or miliary TB. Only 25 (14.3%) of the patients were receiving antiretroviral therapy, and 20 (11.4%) had received antiretroviral therapy in the past.

**Table 2. Baseline Clinical and Laboratory Characteristics of Study Patients**

| Parameter                                      | Arm I          | Arm II         | Arm III         | $P$  
|------------------------------------------------|----------------|----------------|-----------------|------
| Age, years                                     | 37.36 ± 12.75  | 33.68 ± 12.73  | 34.29 ± 13.19   | .26  
| Female sex, %                                  | 41.38          | 57.63          | 55.17           | .17  
| History of TB, %                               | 12.07          | 15.25          | 6.90            | .38  
| History of jaundice, %                         | 5.17           | 6.78           | 0               | .16  
| BMI                                            | 19.55 ± 3.29   | 19.28 ± 3.01   | 19.28 ± 3.06    | .87  
| MAC, cm                                        | 21.93 ± 3.85   | 22.12 ± 3.58   | 21.29 ± 2.66    | .39  

| Distribution of DIH cases with respect to site of TB, % | Arm I | Arm II | Arm III | $P$  
|---------------------------------------------------------|-------|--------|---------|------
| Pulmonary TB                                            | 29.3  | 22.0   | 25.9    |      
| Extrapulmonary TB                                       | 56.9  | 55.9   | 53.5    |      
| Miliary/disseminated TB                                 | 13.8  | 22.0   | 20.7    | .96  
| Moderately/far advanced TB on chest radiograph, %       | 29.3  | 25.4   | 27.5    | .76  

| Parameter                                      | Arm I          | Arm II         | Arm III         | $P$  
|------------------------------------------------|----------------|----------------|-----------------|------
| Serum bilirubin level, mg/dL                   | 0.65 ± 0.12    | 0.69 ± 0.16    | 0.65 ± 0.14     | .13  
| Serum protein level, g/dL                      | 7.76 ± 0.60    | 7.57 ± 0.77    | 7.43 ± 0.64     | .03  
| Serum albumin level, g/dL                      | 4.03 ± 0.66    | 3.77 ± 0.60    | 3.75 ± 0.59     | .03  
| AST level, IU/L                                | 36.5 ± 10.14   | 35.6 ± 13.21   | 36.4 ± 10.78    | .90  
| ALT level, IU/L                                | 35.7 ± 12.01   | 32.4 ± 12.96   | 36.2 ± 12.73    | .21  
| ALP level, IU/L                                | 201.0 ± 103.8  | 178.1 ± 71.8   | 170.9 ± 50.3    | .11  

**Table 3. Comparison of Maximum Derangement of Liver Function Test Results and Normalization Period in the 3 Study Arms Prior to Reintroduction of Anti-Tuberculosis Drugs**

| Parameter                                      | Arm I          | Arm II         | Arm III         | $P$  
|------------------------------------------------|----------------|----------------|-----------------|------
| Serum bilirubin level, mg/dL                   | 2.31 ± 1.93    | 2.9 ± 3.02     | 2.1 ± 1.72      | .18  
| AST level, IU/L                                | 318.3 ± 268.3  | 399.7 ± 427.1  | 274.9 ± 157.9   | .11  
| ALT level, IU/L                                | 344.4 ± 255.7  | 361.4 ± 356.7  | 288.2 ± 206.4   | .34  
| Serum albumin level, g/dL                      | 3.73 ± 0.66    | 3.57 ± 0.60    | 3.59 ± 0.59     | .21  
| ALP level, IU/L                                | 294.7 ± 143.1  | 274.2 ± 165.7  | 255.2 ± 133.6   | .36  
| Normalization period, median days (range)       | 21 (7–53)      | 18 (6–97)      | 17 (5–53)       | .62  

**NOTE.** Data are mean value (± standard deviation), unless otherwise indicated. Arms I, II, and III are defined in Table 1. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by the square of the height in meters; MAC, mid-arm circumference; TB, tuberculosis.
with the Revised National Tuberculosis Control Programme guidelines [17]. The remaining 150 patients (85.7%) were taking daily treatment as prescribed by their physician.

Fifty-eight, 59, and 58 patients were randomized to arms I, II, and III, respectively. The median latency period was 23 days (interquartile range [IQR], 14–44 days), and the median normalization time was 18 days (IQR, 14–28 days).

Table 2 and Table 3 show a comparison of the baseline characteristics of patients and the severity of DIH, respectively, among the 3 arms. Except for pretreatment serum albumin level, which was found to be significantly higher in arm I, all other parameters were similar among the 3 arms.

Nineteen patients (10.9%) had recurrence of DIH during the follow-up period. None of these patients had serological evidence of acute viral hepatitis on retesting. Eight, 6, and 5 patients had recurrence of DIH in arms I, II, and III, respectively (Table 4). The maximum serum bilirubin level, AST level, and ALT level observed in each of the 3 arms was also similar (Table 4). No deaths were observed in any of the 3 arms. All the other patients were followed up with regular liver function monitoring, as described above, for a period of 3 months after experiencing successful reintroduction of all 3 hepatotoxic drugs. None of the patients reported any deviation from the prescribed treatment protocol during the follow-up period.

Nineteen patients who had recurrence of DIH were compared with the remaining patients who tolerated reintroduction of anti-TB drugs with respect to clinical characteristics, baseline laboratory parameters, and severity of the first episode of hepatitis. Of the clinical and baseline laboratory parameters analyzed, pretreatment serum albumin level was the only statistically significant predictor of future recurrence of DIH. Patients with recurrence of DIH had mean pretreatment serum albumin levels (± standard deviation) of 3.39 ± 0.17 g/dL, compared with 3.91 ± 0.05 g/dL in the remaining patients who tolerated reintroduction of anti-TB drugs (P < .01). In the present study, the severity of the first episode of DIH did not affect the risk of recurrence of DIH.

### DISCUSSION

Hepatotoxicity is the most common adverse effect of anti-TB treatment that leads to interruption of therapy [1]. Retreatment is started only when all biochemical markers of liver injury have returned to normal levels. Although the reintroduction of isoniazid, rifampicin, and pyrazinamide therapy after hepatic injury does involve the risk of additional morbidity, the compelling rationale for doing so is grounded in the fact that non-isoniazid and non-rifampicin anti-TB treatment regimens require a longer duration of administration and lack of proof of clinical efficacy. Worldwide, different schedules for reintroduction of anti-TB drugs after hepatotoxicity has resolved have been advocated [15–18], with variable success. However, no evidence-based guidelines are available, because of the lack of prospective, randomized, controlled trials. Patients with infectious pulmonary TB—especially those with bilateral extensive pulmonary TB and a higher bacillary load—pose a threat of disease transmission in the community and require a timely reintroduction of anti-TB drugs. Furthermore, repeated recurrences of DIH may potentially predispose an individual to develop drug-resistant TB. Therefore, in this context, this topic is of considerable interest.

This study is, to our knowledge, the first to compare 3 different predefined anti-TB drug reintroduction regimens in a fairly large sample population. Such a large sample size, combined with the observed exclusion criteria, would be difficult to attain, especially with the introduction of DOT as an integral part of treatment of TB in several countries (including India) where TB is endemic [19]. This is because the risk of DIH is comparatively lower among patients receiving intermittent, thrice-weekly treatment from DOT centers [20, 21]. In our study, the study team was not aware of the allocation sequence.

### Table 4. Comparison of Maximum Derangement of Liver Function Test Results in the 3 Study Arms after Reintroduction of Anti-Tuberculosis (TB) Drugs and Frequency of Recurrence of Drug-Induced Hepatotoxicity (DIH)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm I (n = 58)</th>
<th>Arm II (n = 59)</th>
<th>Arm III (n = 58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum bilirubin level, mg/dL</td>
<td>0.94 ± 0.64</td>
<td>0.86 ± 0.45</td>
<td>0.82 ± 0.46</td>
<td>.59</td>
</tr>
<tr>
<td>Maximum AST level, IU/L</td>
<td>71.5 ± 58.0</td>
<td>64.7 ± 69.3</td>
<td>63.6 ± 62.7</td>
<td>.84</td>
</tr>
<tr>
<td>Maximum ALT level, IU/L</td>
<td>72.8 ± 79.7</td>
<td>68.2 ± 58.3</td>
<td>60.8 ± 62.1</td>
<td>.73</td>
</tr>
<tr>
<td>No. (%) of patients with recurrence of DIH after reintroduction of anti-TB drugs</td>
<td>8 (13.8)</td>
<td>6 (10.2)</td>
<td>5 (8.6)</td>
<td>.69</td>
</tr>
<tr>
<td>Time period from reintroduction of anti-TB drugs to recurrence of DIH, median days (range)</td>
<td>14 (5–28)</td>
<td>21 (14–28)</td>
<td>21 (14–35)</td>
<td>.69</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean value (± standard deviation), unless otherwise indicated. Arms I, II, and III are defined in Table 1. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* Time period was calculated from the beginning of introduction of the first drug until the occurrence of DIH.
The randomized nature of the intervention, with prospective weekly surveillance and predefined objective criteria for DIH, allowed us to compare the 3 reintroduction regimens with minimal bias. We also excluded pregnant women, individuals with long-term alcoholism, patients with chronic liver disease, and patients who were concomitantly receiving other hepatotoxic drugs. All of the above characteristics are established risk factors for DIH [15]. Also, treating TB in HIV-infected patients is a complicated matter. These patients generally require antiretroviral drugs, which are potentially hepatotoxic and are associated with multiple drug-drug interactions. Also, hepatitis in these patients may be attributable to an opportunistic infection. Therefore, to simplify matters, HIV-infected patients were excluded from the present study. Furthermore, we also investigated all patients for markers of acute viral hepatitis and carefully excluded them from the study.

In the present study, the majority of patients (156 [89%] of 175) had successful reintroduction of anti-TB drugs without recurrence of DIH. This is similar to the findings of earlier studies [3–5], which observed that ~90% of patients tolerate reintroduction of isoniazid, rifampicin, and pyrazinamide. Although the number of patients with recurrence of DIH appeared to be greater in arm I, this difference was insignificant. This observation has important implications for a country, such as India, that has a high burden of sputum-positive pulmonary TB, in which initiating isoniazid, rifampicin, and pyrazinamide simultaneously will help to achieve faster sputum conversion and reduce the risk of disease transmission. Also, this strategy has obvious merits for treating severe, life-threatening forms of TB and will theoretically reduce the risk of acquisition of drug-resistant TB. However, in accordance with the results, our study lacked sufficient power to detect a difference between the 3 arms. Therefore, there is an urgent need to plan multicenter trials in countries in which TB is endemic to address this important issue.

The only other prospective clinical trial of anti-TB drug reintroduction after DIH was conducted in Turkey by Tahaoglu et al [4]. In that study, 45 patients with DIH were randomized to receive 2 different retreatment protocols. Tahaoglu et al [4] showed that the risk of developing DIH after reintroduction of anti-TB drugs was 24% in the group in which the original regimen, which included pyrazinamide, was given from day 1 during reintroduction, compared with 0% in the group in which drugs were introduced gradually in a sequential manner and in which pyrazinamide was excluded from the regimen. In our study, the risk of recurrence of hepatitis was comparatively lower when the original regimen, including pyrazinamide, was given from day 1 during reintroduction. This could be explained by ethnic differences in the 2 study populations (one in India and the other in Turkey). Also, we had excluded individuals with alcoholism and patients with HIV infection; these individuals face an increased risk of DIH [15]. Furthermore, AST and ALT levels <40 IU/L were considered to be normal by the Turkish study, in contrast with our study, in which the cut off value was 50 IU/L; this could potentially have led to an increase in the frequency of DIH diagnoses in the former study, compared with our study. Unlike Tahaoglu et al [4], we did not study a reintroduction regimen that lacked pyrazinamide.

The present study also revealed pretreatment serum albumin level to be an important predictor of a second recurrence of DIH. Therefore, patients with hypoalbuminemia should be closely monitored for subsequent recurrence of DIH. Also, the nutritional status of these patients should be improved. In the present study, an increased severity of the first episode of DIH did not confer an increased risk of recurrence. This may be explained by the observation made in the present study that individuals with severe cases of DIH present late, after developing symptoms suggestive of DIH. For such patients, anti-TB drugs are modified relatively late, which further accentuates hepatotoxicity. These patients perhaps do not have an intrinsic tendency to develop more severe hepatitis per se. These findings do not support the suggestions of a very small study done at Kathmandu, Nepal [22], in which it was recommended to be more cautious in reintroducing isoniazid, rifampicin, and pyrazinamide after normalization of liver function in patients with more-severe DIH.

Antit-TB DIH is a relatively common problem, especially in resource-limited settings where TB is endemic. Furthermore, acute viral hepatitis is also often endemic in these areas. Our study also shows acute viral hepatitis to be an important confounding factor in DIH [23]. After excluding individuals with alcoholism, those receiving concomitant hepatotoxic drugs, and those with HIV infection, 200 patients were observed who developed acute hepatitis while receiving anti-TB drugs. Of these patients, 25 (12.5%) had acute viral hepatitis; hepatitis E was the most common type of viral hepatitis (found in 14 [56%] of 25 patients). This observation is not surprising, given that hepatitis E virus is hyperendemic in India [24]. In the same study [23], it was shown that patients with acute viral hepatitis, compared with patients with DIH, had later onset of hepatitis, greater elevations in hepatic transaminase levels, and a longer time for normalization of liver function test results. The patient profile outlined above may guide the clinicians to suspect and look for acute viral hepatitis. Also, it must be ensured that adequate resources and good-quality laboratory services should be available to rule out acute viral hepatitis once DIH is suspected.

Anti-TB DIH is a relatively common problem, adding to the morbidity and mortality among patients with TB. No evidence-based guidelines are available for management of these patients. This study provides evidence supporting the safety of intro-
ducing all 3 potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) together, which is a finding that may enable timely therapy for patients with severe disease and limit ongoing transmission of infectious TB.

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