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Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI

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SUMMARY

SETTING—Nine months of daily isoniazid (9H) and 3 months of once-weekly rifapentine plus isoniazid (3HP) are recommended treatments for latent tuberculous infection (LTBI). The risk profile for 3HP and the contribution of hepatitis C virus (HCV) infection to hepatotoxicity are unclear.

OBJECTIVES—To evaluate the hepatotoxicity risk associated with 3HP compared to 9H, and factors associated with hepatotoxicity

DESIGN—Hepatotoxicity was defined as aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) with symptoms (nausea, vomiting, jaundice, or fatigue), or AST >5 × ULN. We analyzed risk factors among adults who took at least 1 dose of their assigned treatment. A nested case-control study assessed the role of HCV.

RESULTS—Of 6862 participants, 77 (1.1%) developed hepatotoxicity; 52 (0.8%) were symptomatic; 1.8% (61/3317) were on 9H and 0.4% (15/3545) were on 3HP ($P < 0.0001$). Risk factors for hepatotoxicity were age, female sex, white race, non-Hispanic ethnicity, decreased body mass index, elevated baseline AST, and 9H. In the case-control study, HCV infection was associated with hepatotoxicity when controlling for other factors.

CONCLUSION—The risk of hepatotoxicity during LTBI treatment with 3HP was lower than the risk with 9H. HCV and elevated baseline AST were risk factors for hepatotoxicity. For persons with these risk factors, 3HP may be preferred.

Keywords

isoniazid; hepatitis C; aspartate aminotransferases

APPROXIMATELY ONE THIRD of the world's population is infected with latent *Mycobacterium tuberculosis*.[1] One of the main strategies for tuberculosis (TB) control and elimination is the treatment of latent tuberculous infection (LTBI) among persons at highest risk for progression to TB disease.[2–5] While LTBI treatment is generally safe and well-

tolerated, hepatotoxicity occurs in 0.1–4% of persons after initiating treatment.[6] Documented risk factors for hepatotoxicity include increasing age, elevated baseline transaminases, underlying liver disease, alcohol consumption, malnutrition, and being pregnant or in the immediate post-partum period.[6] Hepatotoxicity may occur with all LTBI treatment regimens.[6] Previous studies have found no consistent association between co-infection with hepatitis B or C virus and increased hepatotoxicity incidence during LTBI treatment.[7] The incidence of hepatotoxicity associated with 3 months of rifapentine (P, RPT) +isoniazid (H, INH) in PREVENT TB was 0.4%;[8] however, risk factors for hepatotoxicity among persons receiving this regimen have not been previously reported.

To provide a more complete picture of the hepatotoxicity risk associated with LTBI treatment, including the hepatotoxicity-specific safety profile of 3 months of directly observed once-weekly RPT + INH (3HP), we examined treatment interruptions or discontinuations associated with LTBI treatment among adults enrolled in the Tuberculosis Trials Consortium's PREVENT TB study. We also conducted a nested case-control study to evaluate the role of co-infection with chronic hepatitis C virus (HCV) in treatment-limiting hepatotoxicity.

METHODS

Definition of hepatotoxicity and clinical monitoring

Methods and primary findings for the PREVENT TB study have been published previously.[8] Analytic decisions made in determining risk factors (e.g., differentiating race from ethnicity) were similar between the main PREVENT TB study publication and this report to ensure comparability of published results. Study participants were enrolled from clinical trial sites in Brazil, Canada, Spain, and the United States. Participants from one PREVENT TB study site were excluded from this analysis due to discrepancies regarding receipt of study drug and directly observed therapy.

Monitoring for hepatotoxicity in the PREVENT TB study was primarily symptom-driven. Baseline and routine liver chemistries were drawn at the discretion of individual investigators per local guidelines and for participants at risk for hepatotoxicity.[6] Participants were queried monthly about symptoms of nausea, vomiting, fatigue, or jaundice during study treatment. If hepatotoxicity was suspected, investigators were encouraged to query participants about alcohol use, and testing for viral hepatitis was suggested. Suspected hepatotoxicity events meeting the criteria of AST >3 times the upper limit of normal (ULN) with symptoms of nausea, vomiting, fatigue or jaundice, or AST >5 × ULN were systematically reported to the PREVENT TB study team at the US Centers for Disease Control and Prevention (CDC) via standardized adverse event case report forms. Toxicities were graded by local clinicians according to the Common Toxicity Criteria Version 2.[9] Events of AST >3 × ULN with symptoms were considered grade 3 toxicities. Treatment-limiting hepatotoxicity was defined as the interruption of any study drug(s) for any length of time, including permanent discontinuation, as a result of suspected hepatotoxicity.

Nested case-control study methods

For the nested case-control study, eligible case participants were those in the PREVENT TB study aged >18 years who experienced treatment-limiting hepatotoxicity. The primary objective of the nested study was to assess the effect of HCV co-infection on the discontinuation of LTBI treatment due to hepatotoxicity.

Study enrollment for the nested case-control study was open from March 2002 to November 2009; 5.5% of adults enrolled in the PREVENT TB study were systematically selected as potential controls on enrollment into the PREVENT TB study. Age of potential control participants was evaluated for selection such that the mean age for all controls would be 45 years, as isoniazid (INH) associated hepatotoxicity increases with age. If a selected control developed treatment-limiting hepatotoxicity, the participant was no longer considered a control and could instead be enrolled as a case.

All cases and controls provided written informed consent. The study was approved by the institutional review boards (IRBs) at all study sites and the CDC, Atlanta, GA, USA. One site was not IRB approved for the nested study and contributed no cases or controls.

Both case and control participants in the nested study were queried regarding alcohol use and concomitant medications in the month prior to enrollment; blood samples of all participants were collected for viral hepatitis serological testing at CDC. Blood specimens were tested for immunoglobulin (Ig) M antibody to hepatitis A virus (IgM anti-HAV), hepatitis B virus (HBV) surface antigen (HB_sAg), total and IgM antibody to hepatitis B core (anti-HB_C), and antibody to hepatitis C virus (anti-HCV). All positive anti-HCV specimens were subsequently tested using a nucleic acid test for HCV RNA (AMPLICOR® Hepatitis C Virus Test, v2.0; Roche Molecular Systems Inc, Branchburg, NJ, USA) to ascertain current unresolved HCV infection. HBV infection was defined as a positive HB_sAg and negative IgM anti-HB_C. Current (acute or chronic) HCV infection was defined as a positive anti-HCV antibody and HCV RNA, if available.

Statistical methods

For the analysis of incidence and risk factors for treatment-limiting hepatotoxicity, all participants aged ≥18 years enrolled in the PREVENT TB study between June 2001 and February 2008 who took at least one dose of the study drug were included. Statistical analyses were performed using SAS version 9.2 (Statistical Analysis System Institute, Cary, NC, USA). Race was reported by all trial participants, whereas ethnicity was reported only by participants in the United States or Canada. For descriptive analyses, all races were included; however, for modeling analyses, Asian/Pacific Islander, Black, and White were separate and North American Indian and other races were combined due to small numbers of North American Indian participants. Alcohol use was defined as self-reported current or past drinking of beer, wine or other alcoholic beverage in any amount. Alcohol abuse was defined as any affirmative response to the CAGE alcohol assessment questionnaire.[10] History of chronic liver disease was defined as any self-reported hepatitis B or C, hepatitis due to alcohol use, or hepatitis or cirrhosis of unknown cause.

We calculated hepatotoxicity incidence proportions and 95% confidence intervals (CIs) among adults in the PREVENT TB study. Incidence proportions were statistically compared using CIs. Using a Wilcoxon-Gehan test, Kaplan-Meier survival analysis was performed to compare days from treatment start to hepatotoxicity event. For comparisons of persons with and without hepatotoxicity, dichotomous variables were compared using Pearson's χ^2 or Fisher's exact test. Multiplicative interactions of treatment regimen and participant factors were explored; none were statistically significant. Continuous variables were compared using Student's *t*-test. For the analysis of risk factors for hepatotoxicity among adults in PREVENT TB, risk ratios (RRs) and 95%CIs were estimated using log-binomial regression. For the nested study, odds ratios (ORs) and 95%CIs were estimated using logistic regression. For multivariable modeling, all variables with $P < 0.20$ were entered into an initial model, and only those with $P \leq 0.05$, through backwards selection, were retained in the final model. The multivariable model for the PREVENT TB study cohort omitted HCV co-infection, as these data were routinely collected only for nested study participants. The multivariable model for the case-control study excluded age because control participants were weighted by age and elevated baseline AST. Baseline AST was missing for 24% of the study population. We tested for co-linearity of risk factors included in multivariable models, and found that factors describing liver health (history of chronic liver disease, elevated baseline AST, and HCV co-infection) were co-linear. Final multivariable models included only the predictors that contributed to the best model fit as determined by the minimized Akaike information criterion. We estimated attributable risk percentages for statistically significant predictors in our multivariable logistic regression models.

RESULTS

A total of 6862 adult participants in the PREVENT TB study took at least one dose of the study treatment: respectively 3317 (48%) and 3545 (52%) were prescribed 9H (9 months of daily INH) and 3HP. Baseline AST evaluation was conducted for 76% of all study participants, regardless of study regimen, with baseline AST results reported for the majority of participants from all trial sites except Brazil and California, USA (data not shown). Repeated AST monitoring (i.e., at least two AST results reported) during the study phase was conducted for 37% of participants (2558/6862), 40% of those on 9H (1312/3317) and 35% of those on 3HP (1246/3545, RR 1.25, 95%CI 1.06–1.20; χ^2 $P = 0.0002$).

Treatment-limiting hepatotoxicity occurred four times more frequently in those receiving 9H than 3HP among all participants (9H 1.9% vs. 3HP 0.4%, RR 4.42, 95%CI 2.52–7.75, χ^2 $P < 0.001$), as well as among those with symptomatic (9H 1.3% vs. 3HP 0.3%, RR 4.51, 95%CI 2.27–8.97, χ^2 $P < 0.001$) and asymptomatic (9H 0.6% vs. 3HP 0.1%, RR 4.10, 95%CI 1.53–11.0, χ^2 $P = 0.002$) hepatotoxicity. In the nested study, there were 49 cases, of whom 35 were symptomatic (27 on 9H, 8 on 3HP) and 14 were asymptomatic (all on 9H), and 243 controls. No hospitalizations or deaths were associated with hepatotoxicity.

The clinical and demographic characteristics of the 6862 persons in the study population and the 292 participants enrolled in the nested study are shown in Appendix Table A.1.* Among the PREVENT TB study participants, those who developed any hepatotoxicity or symptomatic hepatotoxicity tended to be older, female, white, and non-Hispanic. In addition,

most had elevated baseline AST, a history of chronic liver disease or alcohol abuse, reported current injection drug use or cigarette smoking, and were receiving 9H (Appendix Table A. 1). Both cases and controls in the nested study were similar to non-enrolled cases and controls on all medical and social factors assessed (data not shown).

Within various clinical or demographic strata, persons who received 3HP consistently had a lower cumulative incidence of hepatotoxicity than those who received 9H (Appendix Table A.2). Persons administered 9H who developed hepatotoxicity received a median 4.5 mg/kg dose of INH compared to a 4.0 mg/kg dose received by those without hepatotoxicity (Wilcoxon signed-rank test $P = 0.001$). There were no significant differences in median mg/kg weekly dose of INH or RPT stratified by hepatotoxicity among persons on 3HP (hepatotoxicity, 10.9 mg/kg each of INH and RPT; no hepatotoxicity, 12.1 mg/kg each of INH and RPT, Wilcoxon signed-rank test $P = 0.59$).

The median number of days to the onset of treatment-limiting hepatotoxicity differed according to treatment regimen (9H median 101 days, inter-quartile range [IQR] 62–161; 3HP median 22 days, IQR 19–49; Wilcoxon-Gehan $P < 0.001$). Similarly, days to the onset of treatment-limiting symptomatic or asymptomatic hepatotoxicity also differed by treatment regimen (symptomatic 9H 97 days, IQR 62–155; 3HP 23 days, IQR 19–40, Wilcoxon-Gehan $P < 0.001$; asymptomatic 9H 105 days, IQR 59–183; 3HP 21 days, IQR 20–49, Wilcoxon-Gehan $P < 0.001$).

Permanent discontinuation of study treatment due to hepatotoxicity occurred more than five times more frequently among those taking 9H than 3HP (9H 1.7%, 3HP 0.3%, RR 5.54, 95%CI 2.91–10.5, χ^2 $P < 0.001$). Among those who restarted treatment, the median length of treatment interruption in days did not vary by treatment regimen (9H 36 days, IQR 21–44; 3HP 15 days, IQR 13–30; Student's t-test $P = 0.48$).

In the nested study, most cases (29/49, 59%) developed an AST 5–10 × ULN, and all events but one were grade 3 toxicities. The one serious adverse event (i.e., grade 4 toxicity) was in a Hispanic female participant assigned to 9H. She developed elevated AST (1025 U/l, 26× ULN), alanine aminotransferase (1468 U/l, 37× ULN) and bilirubin (2.9 mg/dl, 2.4× ULN) levels, with nausea, dark urine and pruritus after 89 doses of 9H; LTBI treatment was permanently discontinued. The majority of the cases presented with at least one symptom (37/49, 76%), of which fatigue was the most common (29/37, 76%).

In both the PREVENT TB and the nested study, female sex, history of chronic liver disease, elevated AST at LTBI treatment start, current or past alcohol use, and treatment with 9H were significantly associated with hepatotoxicity or symptomatic hepatotoxicity (Appendix Tables A.3 and A.4) on univariable analyses. Furthermore, increasing age and current or past injection drug use were associated with hepatotoxicity and symptomatic hepatotoxicity, ethnicity was associated with hepatotoxicity, and race with symptomatic hepatotoxicity in the PREVENT TB study, and with HCV co-infection with treatment-limiting hepatotoxicity in the nested study (Appendix Tables A.3 and A.4).

*The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000009/art00008

In a multivariable analysis of risk factors for hepatotoxicity in the PREVENT TB study, increasing age, female sex, White race, non-Hispanic ethnicity, low body mass index (BMI), history of chronic liver disease, elevated AST at LTBI treatment start, and receipt of 9H were independently associated with an increased risk of hepatotoxicity (Appendix Table A. 2). The combined attributable risk for the presence of any of these factors was 56% (95%CI 50–61). In an analysis of symptomatic hepatotoxicity, the same risk factors were associated with hepatotoxicity, except low BMI (Table), with a combined attributable risk of 61% (95%CI 54–66). In a multivariable analysis of risk factors in the nested study, when controlling for factors significant in the parent study except for age, HCV co-infection was an independent risk factor for hepatotoxicity, with an attributable risk of 51% (Appendix Table A.4).

DISCUSSION

Our study provides contemporary estimates of the incidence of and risk factors for hepatotoxicity during treatment for LTBI with 9H or 3HP under clinical trial conditions, and suggests that 3HP is less hepatotoxic than 9H and may be preferred in persons at increased risk of hepatotoxicity. The incidence of hepatotoxicity in persons treated with 9H was comparable to rates previously reported for daily INH.[11,12] In contrast, the incidence of any hepatotoxicity or symptomatic hepatotoxicity among persons treated with 3HP in this study was significantly lower than that among those who received 9H. Although rare, severe liver injury and death are well-documented adverse effects of anti-tuberculosis drugs used for LTBI treatment, particularly INH.[12,13] The participants in the PREVENT TB clinical trial had frequent interactions with health care providers, which may explain why more severe toxicity was not observed.[14]

The data from the PREVENT TB study allowed us to characterize the incidence of treatment-limiting hepatotoxicity and associated risk factors. The case-control study allowed us to focus on the specific role of HCV co-infection in treatment-limiting hepatotoxicity. Data from the PREVENT TB study demonstrated that participants with a history of chronic liver disease or elevated AST upon initiating LTBI treatment have an increased incidence of hepatotoxicity. This incidence was substantial for patients receiving 9H, but lower among those receiving 3HP. Also consistent with other studies, we found hepatotoxicity to be associated with increasing age, elevated AST at LTBI treatment start, and 9H.[2,6] The nested study demonstrated that HCV co-infection was independently associated with hepatotoxicity. This association had been previously documented only among injection drug users, but even among this population the association has not been a consistent finding.[15,16] Furthermore, female sex, white race, and non-Hispanic ethnicity were identified as risk factors for hepatotoxicity, findings that have not been commonly described.[17]

Our results, combined with this prior work, suggest that close clinical monitoring is required, not only of persons of increased age and those with a history of chronic liver disease, but also of women and persons of White race and non-Hispanic ethnicity. Although lower BMI was found to be a risk factor, the median BMI of 26 kg/m^2 among persons with hepatotoxicity was not consistent with malnutrition.

Our study had two main limitations. First, AST monitoring differed by treatment regimen, with those on 9H being more likely to have two or more AST evaluations. There was thus potential for undetected asymptomatic hepatotoxicity, particularly among those on 3HP. Our RR estimates for 9H with any hepatotoxicity may therefore have been an overestimation. However, the RR estimates for 9H with any or symptomatic hepatotoxicity are very similar, suggesting minimal overestimation of the RR in our study. Second, this study was conducted in the context of a clinical trial. As patient selection (and self-selection) and monitoring may not reflect populations treated in operational settings, our observed incidence of hepatotoxicity might not accurately represent findings in program conditions.

LTBI treatment in all patients should include a discussion and evaluation of the risk of drug-induced liver injury including hepatotoxicity, including chronic ethanol consumption, known viral hepatitis, pre-existing liver disease, post-partum within 3 months, concomitant hepatotoxic medication and previous abnormal liver enzymes.[6] Furthermore, evaluation of AST at treatment initiation may help identify persons at increased risk of hepatotoxicity.

The possibility of severe hepatitis and liver dysfunction should be considered when deciding whether a patient with HCV is a candidate for LTBI treatment. If treatment is initiated, an adverse event clinical monitoring plan should be put in place. Given that 3HP is as effective as 9H,[8,18] these results add to the growing body of evidence that 3HP may be a preferred choice for the treatment of LTBI, particularly among those patients who are at high risk of hepatotoxicity.

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APPENDIX

Table A.1

Demographic and clinical characteristics of adults enrolled in PREVENT TB and the nested case-control study

	PREVENT TB				Case-control study	
	Hepatotoxicity* **(*n* = 77)†** ***n* (%)**	**Symptomatic hepatotoxicity*** **(*n* = 52)** ***n* (%)**	**Asymptomatic hepatotoxicity*** **(*n* = 24)** ***n* (%)**	**No hepatotoxicity*** **(*n* = 6785)** ***n* (%)**	**Cases (*n* = 49)** ***n* (%)**	**Controls (*n* = 243)** ***n* (%)**
Demographic factors						
Age, years, median [IQR]	44 [34–52]	44 [33–52]	47 [37–50]	37 [28–48]	44 [33–52]	46 [32–53]
Female sex	49 (64)	36 (69)	12 (50)	3065 (45)	33 (67)	107 (44)
Race						
White	52 (68)	39 (75)	13 (54)	3799 (56)	35 (67)	121 (60)
Black	13 (17)	8 (15)	5 (21)	1780 (26)	10 (20)	76 (31)
Asian/Pacific Islander	6 (7.8)	2 (3.9)	4 (17)	887 (13)	4 (8.2)	32 (13)
North American Indian	2 (2.6)	1 (1.9)	0 (0)	109 (1.6)	0 (0)	7 (2.9)
Other	4 (5.2)	2 (3.9)	2 (8.3)	210 (3.1)	2 (4.1)	7 (2.9)

	PREVENT TB				Case-control study	
	Hepatotoxicity* (*n* = 77)† *n* (%)	Symptomatic hepatotoxicity* (*n* = 52) *n* (%)	Asymptomatic hepatotoxicity* (*n* = 24) *n* (%)	No hepatotoxicity* (*n* = 6785) *n* (%)	Cases (*n* = 49) *n* (%)	Controls (*n* = 243) *n* (%)
Ethnicity						
Hispanic	25 (32)	16 (31)	9 (37)	2666 (39)	11 (22)	62 (25)
Non-Hispanic	51 (66)	36 (69)	14 (58)	3591 (53)	37 (76)	144 (59)
Not applicable (not in the United States or Canada)	1 (1.3)	0 (0)	1 (4.2)	528 (7.8)	1 (2.0)	37 (15)
Health factors						
BMI, kg/m^2, median [IQR]	26 [23–28]	26 [23–28]	25 [23–28]	27 [24–31]	26 [23–30]	28 [24–31]
HIV status						
Non-infected	41 (53)	25 (48)	15 (63)	3366 (50)	31 (63)	132 (54)
Infected	2 (2.6)	1 (1.9)	1 (4.2)	149 (2.2)	2 (4.1)	9 (3.7)
Unknown	34 (44)	26 (50)	8 (33)	3270 (48)	16 (33)	102 (42)
History of chronic liver disease	15 (19)	10 (19)	5 (21)	322 (4.8)	11 (20)	16 (6.6)
Elevated baseline AST	21/72 (29)	9/48 (19)	12/23 (52)	369/5151 (7.2)	11/46 (24)	15/168 (8.9)
Hepatitis serology results‡						
Hepatitis B virus co-infection	—	—	—	—	0 (0)	3 (1.2)
Hepatitis C virus co-infection	—	—	—	—	12 (24)	23 (9.5)
Self-reported social factors						
Homeless >6 months	6 (7.8)	5 (9.6)	1 (4.2)	495 (7.3)	4 (8.2)	24 (9.9)
Unemployed >12 months	10 (13)	7 (13)	3 (13)	769 (11)	7 (14)	25 (10)
Correctional institute >1 month	7 (9.1)	3 (5.8)	4 (17)	377 (5.6)	3 (6.1)	18 (7.4)
Current or past alcohol use						
None	28 (36)	22 (42)	6 (25)	3107/6777 (46)	17 (35)	119 (49)
Use	36 (47)	21 (40)	14 (58)	3147/6777 (47)	24 (49)	110 (45)
Abuse	13 (17)	9 (17)	4 (17)	469/6777 (6.9)	8 (16)	14 (5.8)
Current or past IDU	10 (13)	8 (15)	2 (8.3)	254/6776 (3.8)	5 (10)	15 (6.2)
Current cigarette smoker	28 (36)	18 (35)	10 (42)	1977 (29)	19 (39)	89 (35)
Anti-tuberculosis treatment factors						
Indication for TLTBI§						
Close contact	50 (65)	31 (60)	19 (79)	4711 (69)	29 (59)	181 (74)
Recent converter	25 (32)	19 (37)	5 (21)	1798 (27)	18 (37)	50 (21)
HIV-infected	0 (0)	0 (0)	—	107 (1.6)	0 (0)	8 (3.3)
Fibrosis on chest X-ray	2 (2.6)	2 (3.9)	—	169 (2.5)	2 (4.1)	4 (1.7)
9H	62 (81)	42 (81)	19 (80)	3353 (48)	41 (84)	95 (39)

*Hepatotoxicity was defined as serum AST >3 × ULN with symptoms of nausea, vomiting, jaundice or fatigue, or AST >5 × ULN regardless of symptoms.

†Symptoms were not assessed for one participant.

‡Hepatitis B and C serological and NAT tests were performed systematically only for participants in the nested case-control study.

§Subjects were counted only once in the order presented. The total number of HIV-infected persons who were enrolled is listed separately in this table.

BMI = body mass index; HIV = human immunodeficiency virus; AST = aspartate aminotransferase; IDU = injection drug user; TLTBI = treatment for latent tuberculous infection; 9H =9 months of self-administered daily isoniazid at 5–15 mg/kg rounded to the nearest 50 mg, with a maximum dose of 300 mg; ULN = upper limit of normal; NAT = nucleic acid testing.

Table A.2

Treatment-limiting hepatotoxicity cumulative incidence (95%CI) by treatment arm among adults enrolled in the Tuberculosis Trials Consortium PREVENT TB study

	All		9H		3HP	
	n*/*N	**% (95%CI)**	***n*/*N***	**% (95%CI)**	***n*/*N***	**% (95%CI)**
Overall *	77/6862	1.1 (0.9–1.4)	61/3317	1.8 (1.4–2.3)	15/3545	0.4 (0.2–0.6)
Treatment permanently discontinued	68/6862	1.0 (0.8–1.2)	57/3317	1.7 (1.3–2.2)	11/3545	0.3 (0.1–0.5)
Symptomatic	52/6862	0.8 (0.6–1.0)	42/3317	1.3 (0.9–1.6)	10/3545	0.3 (0.1–0.5)
Asymptomatic	24/6862	0.3 (0.2–0.5)	19/3317	0.6 (0.3–0.8)	5/3545	0.1 (0.02–0.3)
Demographic factors						
Female sex	49/3114	1.6 (1.1–2.0)	40/1528	2.6 (1.8–3.4)	9/1586	0.6 (0.2–0.9)
Male sex	28/3748	0.7 (0.5–1.0)	22/1789	1.2 (0.7–1.7)	6/1959	0.3 (0.1–0.6)
Race						
White	52/3851	1.4 (1.0–1.7)	44/1873	2.3 (1.7–3.0)	8/1978	0.4 (0.1–0.7)
Black	13/1793	0.7 (0.3–1.1)	8/873	0.9 (0.3–1.5)	5/920	0.5 (0.1–1.0)
Asian/Pacific Islander	6/893	0.7 (0.1–1.2)	5/443	1.1 (0.1–2.1)	1/450	0.2 (0–0.7)
North American Indian	2/111	1.8 (0–4.3)	2/31	6.5 (0–15)	0/80	0
Other	4/214	1.9 (0–3.7)	3/97	3.1 (0–6.5)	1/117	0.9 (0–2.5)
Ethnicity						
Hispanic	25/2691	0.9 (0.6–1.3)	21/1283	1.6 (0.9–3.0)	4/1408	0.3 (0–0.6)
Not Hispanic	51/3642	1.4 (1.0–1.8)	40/1770	2.3 (1.6–3.0)	11/1872	0.6 (0.2–0.9)
Not applicable (not US or Canada)	1/529	0.2 (0–0.6)	1/264	0.4 (0–1.1)	0/265	0
Health factors						
HIV status						
Non-infected	41/3407	1.2 (0.8–1.5)	32/1688	1.9 (1.2–2.5)	9/1719	0.5 (0.2–0.9)
Infected	2/151	1.3 (0–3.1)	1/78	1.3 (0–3.8)	1/73	1.4 (0–4.0)
Unknown	34/3304	1.0 (0.7–1.4)	29/1551	1.9 (1.2–2.5)	5/1753	0.3 (0–0.5)
History of chronic liver disease	15/337	4.5 (2.2–6.7)	13/171	7.6 (3.6–12)	2/166	1.2 (0–2.9)
Elevated baseline AST	21/390	5.4 (3.1–7.6)	17/188	9.0 (4.9–13.0)	4/202	2.0 (0.1–3.9)
Self-reported social factors						
Homeless >6 months	6/501	1.2 (0.2–2.2)	6/214	2.8 (0.6–5.0)	0/287	0
Unemployed >12 months	10/779	1.3 (0.5–2.1)	9/369	2.4 (0.9–4.0)	1/410	0.2 (0–0.7)
Correctional institute >1 month	7/384	1.8 (0.5–3.2)	6/169	3.6 (0.8–6.3)	1/215	0.5 (0–1.4)
Current or past alcohol use						
None	28/3135	0.9 (0.6–1.2)	21/1475	1.4 (0.8–2.0)	7/1660	0.4 (0.1–0.7)
Use	36/3210	1.1 (0.8–1.5)	30/1616	1.9 (1.2–2.5)	6/1594	0.4 (0.1–0.7)
Abuse	13/509	2.6 (1.2–3.9)	11/222	5.0 (2.1–7.8)	2/287	0.7 (0–1.7)

	All		9H		3HP	
	n/*N*	% (95%CI)	*n*/*N*	% (95%CI)	*n*/*N*	% (95%CI)
Current or past IDU	10/264	4.0 (1.7–6.3)	8/130	6.2 (2.0–10)	2/134	1.5 (0–3.5)
Current cigarette smoker	28/2005	1.4 (0.9–1.9)	24/959	2.5 (1.5–3.5)	4/1046	0.4 (0–0.8)
TB treatment factors						
Indication for TLTBI[†]						
Close contact	50/4761	1.1 (0.8–1.3)	42/2252	1.9 (1.3–2.4)	8/2506	0.3 (0.1–0.5)
Recent converter	25/1823	1.4 (0.8–1.9)	18/924	1.9 (1.1–2.8)	7/899	0.8 (0.2–1.4)
HIV-infected	0/107	0	0/52	0	0/55	0
Fibrosis on chest X-ray	2/171	1.2 (0–2.8)	2/89	2.2 (0–5.3)	0/82	0

[*] Symptoms were not assessed for one participant.

[†] Subjects were counted only once in the order presented. The total number of HIV-infected persons who were enrolled is listed separately in this table.

CI=confidence interval; 9H=9 months of self-administered daily isoniazid at 5–15 mg/kg rounded to the nearest 50 mg, with a maximum dose of 300 mg; 3HP= 3 months of directly-observed once weekly 900 mg rifapentine plus isoniazid at 15–25 mg/kg rounded to the nearest 50 mg, with a maximum dose of 900 mg; HIV = human immunodeficiency virus; AST =aspartate aminotransferase; IDU = injection drug user; TLTBI = treatment for latent tuberculous infection.

Table A.3

Univariable analyses of risk factors for treatment-limiting hepatotoxicity in the PREVENT TB study

	All hepatotoxicity[*]		Symptomatic hepatotoxicity[*]	
	RR (95%CI)[†]	*P* value[†]	RR (95%CI)[†]	*P* value[†]
Demographic factors				
Age, per year increase	1.03 (1.01–1.04)	<0.0001	1.03 (1.01–1.04)	0.002
Female sex	2.11 (1.33–3.34)	0.002	2.71 (1.51–4.88)	0.009
Race		0.07		0.04
White	1.00 (reference)		1.00 (reference)	
Black	0.54 (0.30–0.98)		0.44 (0.21–0.94)	
Asian	0.50 (0.21–1.15)		0.22 (0.05–0.92)	
Other	1.37 (0.59–3.16)		0.92 (0.28–2.95)	
Ethnicity		0.04		0.09
Hispanic	1.00 (reference)		1.00 (reference)	
Non-Hispanic	1.51 (0.94–2.42)		1.66 (0.92–3.00)	
Not applicable (not US or Canada)	0.20 (0.03–1.50)			
Health factors				
BMI, per kg/m^2 increase	0.97 (0.93–1.01)	0.10	0.97 (0.93–1.02)	0.24
HIV status		0.77		0.96
Non-infected	1.00 (reference)		1.00 (reference)	
Infected	1.10 (0.27–4.51)		0.90 (0.12–6.63)	
Unknown	0.86 (0.54–1.34)		1.07 (0.62–1.85)	
History of chronic liver disease	4.68 (2.69–8.15)	<0.0001	4.67 (2.36–9.22)	<0.0001
Elevated baseline AST	5.10 (3.10–8.39)	<0.0001	2.94 (1.44–6.03)	0.003
Social factors				

	All hepatotoxicity*		Symptomatic hepatotoxicity*	
	RR (95%CI)†	*P* value†	RR (95%CI)†	*P* value†
Homeless >6 months	1.07 (0.47–2.46)	0.87	1.34 (0.54–3.37)	0.52
Unemployed >12 months	1.17 (0.60–2.26)	0.65	1.22 (0.54–2.68)	0.63
Correctional institute >1 month	1.69 (0.78–3.64)	0.18	1.04 (0.33–3.32)	0.95
Current or past alcohol use		0.006		0.03
None	1.00 (reference)		1.00 (reference)	
Use	1.26 (0.77–2.05)		0.93 (0.52–1.70)	
Abuse	2.86 (1.49–5.48)		2.53 (1.17–5.47)	
Current or past IDU	3.73 (1.94–7.16)	<0.0001	4.56 (2.17–9.58)	<0.0001
Current cigarette smoker	1.38 (0.87–2.20)	0.17	1.28 (0.72–2.27)	0.39
TB treatment factors				
Indication for TLTBI‡		0.55		0.23
Close contact	1.00 (reference)		1.00 (reference)	
Recent converter	1.31 (0.81–2.10)		1.60 (0.91–2.82)	
Fibrosis on chest X-ray	1.11 (0.27–4.54)		1.79 (0.43–7.41)	
Treatment with 9H	4.42 (2.52–7.75)	<0.0001	4.51 (2.27–8.97)	<0.0001

*Hepatotoxicity was defined as serum AST >3 × ULN with symptoms of nausea, vomiting, jaundice or fatigue or AST >5 × ULN regardless of symptoms.

†*P* values are from the Wald χ^2 test. RRs are estimated through log-binomial regression.

‡Subjects were counted only once in the order presented. The total number of HIV-infected persons who were enrolled is listed separately in this table.

RR =risk ratio; CI =confidence interval; BMI =body mass index; HIV =human immunodeficiency virus; AST =aspartate aminotransferase; IDU =injection drug user; TLTBI =treatment for latent tuberculous infection; 9H =9 months of self-administered daily isoniazid at 5–15 mg/kg rounded to the nearest 50 mg, with a maximum dose of 300 mg; ULN = upper limit of normal.

Table A.4

Univariable and multivariable analyses of risk factors for treatment-limiting hepatotoxicity* in the nested case-control study

	Univariable analysis		Multivariable analysis		
	OR (95%CI)†	*P* value†	OR (95%CI)†	*P* value†	Attributable risk‡ %
Demographic factors					
Age, per year increase	1.00 (0.98–1.02)	0.97			
Female sex	2.62 (1.37–5.01)	0.003	2.75 (1.28–5.91)	0.001	50
Race		0.18		0.01	
White	1.00 (reference)		1.00 (reference)		41
Black	0.48 (0.23–1.04)		0.23 (0.08–0.63)		
Asian	0.46 (0.15–1.39)		0.19 (0.05–0.72)		
Other	0.52 (0.11–2.42)		0.97 (0.15–6.47)		
Ethnicity		0.07		0.005	
Hispanic	1.00 (reference)		1.00 (reference)		43
Non-Hispanic	1.45 (0.69–3.02)		2.97 (1.13–7.86)		

	Univariable analysis		Multivariable analysis		
	OR (95%CI)†	*P* value†	OR (95%CI)†	*P* value†	Attributable risk‡ %
Not applicable (not US or Canada)	0.15 (0.02–1.23)		0.14 (0.02–1.30)		
Health factors					
BMI, per kg/m^2 increase	0.95 (0.90–1.01)	0.08	0.92 (0.86–0.99)	0.02	
HIV status		0.48			
Non-infected	1.00 (reference)				
Infected	0.95 (0.20–4.60)				
Unknown	0.68 (0.35–1.29)				
History of chronic liver disease	3.64 (1.54–8.60)	0.005	—	0.79	
Elevated baseline AST	3.21 (1.36–7.58)	0.006			
Hepatitis B virus co-infection	0.69 (0.04–13.7)	1.00			
Hepatitis C virus co-infection	3.10 (1.42–6.77)	0.003	3.24 (1.12–9.34)	0.03	51
Social factors					
Homeless >6 months	0.81 (0.27–2.45)	0.71			
Unemployed >12 months	1.45 (0.59–3.58)	0.42			
Correctional institute >1 month	0.82 (0.25–2.88)	0.75			
Current or past alcohol use		0.03	—	0.06	
None	1.00 (reference)		—		
Use	1.57 (0.78–2.99)		—		
Abuse	4.00 (1.46–10.9)		—		
Current or past IDU	1.72 (0.59–4.98)	0.31	—	0.10	
Current cigarette smoker	1.16 (0.61–2.18)	0.65			
Anti-tuberculosis treatment factors					
Indication for TLTBI§		0.04	—	0.94	
Close contact	1.00 (reference)		—		
Recent converter	2.25 (1.15–4.38)		—		
Fibrosis on chest X-ray	3.12 (0.55–17.8)		—		
Treatment with 9H	7.98 (3.59–17.8)	<0.0001	9.20 (3.79–22.4)	<0.0001	79

*Hepatotoxicity was defined as serum AST >3 × ULN with symptoms of nausea, vomiting, jaundice or fatigue or AST >5 × ULN regardless of symptoms.

†*P* values are from the Wald χ^2 test. ORs are estimated through logistic regression. Only participant factors with a univariable $P < 0.20$ were entered into the multivariable model, and only factors with a $P \leq 0.05$ were retained in the final multivariable model. For the multivariable model, *P* values without an OR indicate terms that were entered into the model but not retained in the final model. Elevated baseline ASTwas not included in the multivariable model as data were missing in 27% of case-control participants.

‡Calculated for White race and non-Hispanic ethnicity only, not all races and ethnicities.

§Subjects were counted only once in the order presented. The total number of HIV-infected persons who were enrolled is listed separately in this table.

OR =odds ratio; CI =confidence interval; BMI =body mass index; HIV =human immunodeficiency virus; AST =aspartate aminotransferase; IDU =injection drug user; TLTBI =treatment for latent tuberculous infection; 9H =9 months of self-administered daily isoniazid at 5–15 mg/kg rounded to the nearest 50 mg, with a maximum dose of 300 mg; ULN = upper limit of normal.

Table

Multivariable analyses of risk factors for treatment-limiting hepatotoxicity* in the PREVENT TB study

	All hepatotoxicity			Symptomatic hepatotoxicity		
	RR (95%CI)†	***P* value†**	**Attributable risk %**	**RR (95%CI)†**	***P* value†**	**Attributable risk %**
Demographic factors						
Age, per year increase	1.03 (1.02–1.05)	<0.0001	—	1.03 (1.01–1.05)	0.002	
Female sex	2.70 (1.65–4.42)	0.0001	52	3.34 (1.70–6.28)	0.0003	64
Race		<0.0001			0.008	
White	1.00 (reference)		38	1.00 (reference)		57
Black	0.32 (0.17–0.62)			0.25 (0.11–0.55)		
Asian	0.13 (0.04–0.43)			Not estimated		
Other	1.32 (0.60–3.22)			0.87 (0.27–2.87)		
Ethnicity		0.01			0.001	
Hispanic	1.00 (reference)			1.00 (reference)		
Non-Hispanic	2.22 (1.28–3.85)		42	3.57 (1.86–6.88)		40
Not applicable (not US or Canada)	0.87 (0.11–6.76)			Not estimated		
Health factors						
BMI, per km/m^2 increase	0.94 (0.91–0.99)	0.008	—	—	—	—
Elevated baseline AST	5.57 (3.31–9.37)	<0.0001	80	3.19 (1.53–6.63)	0.002	66
Anti-tuberculosis treatment factors						
Treatment with 9H	4.55 (2.53–8.18)	<0.0001	77	4.22 (2.10–8.47)	<0.0001	78

*Hepatotoxicity was defined as serum AST >3 × ULN with symptoms of nausea, vomiting, jaundice or fatigue or AST >5 × ULN regardless of symptoms.

†*P* values are from the Wald χ^2 test. RRs are estimated through log-binomial regression. Only participant factors with a univariable $P < 0.20$ were entered into the multivariable model, and only factors with a $P \leq 0.05$ were retained in the final multivariable model. For the multivariable model, *P* values without a RR indicate terms that were entered into the model but not retained in the final model.

RR =risk ratio; CI =confidence interval; BMI =body mass index; AST =aspartate aminotransferase; 9H =9 months of self-administered daily isoniazid at 5–15 mg/kg rounded to the nearest 50 mg, with a maximum dose of 300 mg; ULN = upper limit of normal.