Published in final edited form as:

J Infect. 2013 November ; 67(5): 424–432. doi:10.1016/j.jinf.2013.07.015.

FEMALE SEX AND DISCONTINUATION OF ISONIAZID DUE TO ADVERSE EFFECTS DURING THE TREATMENT OF LATENT TUBERCULOSIS

April C. Pettit, M.D., M.P.H.¹, James Bethel, Ph.D.², Yael Hirsch-Moverman, Ph.D.³, Paul W. Colson, Ph.D.³, Timothy R. Sterling, M.D.^{1,4}, and the Tuberculosis Epidemiologic Studies Consortium (TBESC)

¹Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

²Westat, Rockville, MD

³Charles P. Felton National Tuberculosis Center, ICAP, Mailman School of Public Health, Columbia University, New York, NY

⁴Center for Health Services Research, Vanderbilt University School of Medicine, Nashville, TN

© 2013 The British Infection Society. Published by Elsevier Ltd. All rights reserved.

Corresponding Author Information: April C. Pettit, M.D., M.P.H., Vanderbilt University School of Medicine, 1161 21st Avenue South, A2200 Medical Center North, Nashville, TN 37232-2582, Phone: (615) 353-0574, Fax: (615) 343-6160, april.pettit@vanderbilt.edu.

Notation of Prior Abstract Presentation: These results were presented in part at IDWeek 2012, October 17-21, 2012, San Diego, CA, Abstract #36105.

Author Contributions: A.C.P. had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: A.C.P., J.B., P.W.C., Y.H., T.R.S. Acquisition of data: J.B., P.W.C., Y.H., T.R.S. Analysis and interpretation of data: A.C.P., J.B., P.W.C., Y.H., T.R.S. Drafting of the manuscript: A.C.P. All authors were involved in critical revision of interim drafts and approved the final version of the manuscript.

Financial/nonfinancial disclosures: All authors report no conflicts of interest relevant to this article. Dr. Sterling reports receiving research grant funding from Bristol-Myers Squibb and Pfizer for HIV observational studies. Dr. Sterling is also a member of a data safety monitoring board for Otsuka.

Other Contributions: The authors thank the Tuberculosis Epidemiologic Studies Consortium (TBESC) and the Centers for Disease Control and Prevention, which supported this study. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

We also thank the investigators and staff at all the participating TBESC sites: James McAuley, (Principal Investigator [PI]), Judith Beison (Project Coordinator [PC]), Respiratory Health Association of Metropolitan Chicago; Jennifer Flood (PI), Katya Salcedo (PC), California Department of Health Services; Randall Reves (PI), Kirsten Wall (PC), Juanita Lovato (Research Assistant [RA]), Alessandra Pereira (RA), Denver Public Health and Hospital Authority; Henry Blumberg (PI), Jane Tapia (PC), Lily Singha (RA), Emory University; Paul Colson (PI), Yael Hirsch-Moverman (PC), Joyce Ann Thomas (RA), Hugo Ortega (RA), Columbia University/Charles P. Felton National TB Center at Harlem Hospital; Thara Venkatappa (PC), Hawaii Department of Health; Wendy Cronin (PI), Susan Collins (PC), Heather Rutz (PC), Maryland Department of Health and Mental Hygiene; Robert Horsburgh (PI), Sue Etkind (PI), Sharon Sharnprapai (PC), Arnaud Barbosa (RA), Massachusetts Department of Health; Steven Hughes (PI), Wilson Miranda (PC), Mary Freely (Site quality assurance and data entry), New York State Department of Health; Timothy Sterling (PI), Trudy Stein-Hart (PC), Katie Gordon (PC), Tennessee Department of Health; Monika Naus (PI), Kadria Alasaly (PC), University of British Columbia; Stephen Weis (PI), Guadalupe Bayona (PC), Jotam Pasipanodya (RA), Edgar Vecino (RA), University of North Texas.

In addition, we thank the Task Order #13 Phase 3 Protocol Team: Robert Horsburgh, MD, MUS (Chair), Robin Shrestha-Kuwahara, MPH (CDC Co-Project Officer), Stefan Goldberg, MD (CDC Co-Project Officer), Jim Bethel, PhD, Henry Blumberg, MD, Paul Colson, PhD, Carol Dukes-Hamilton, MD, Eduard Eduardo, MPH Yael Hirsch-Moverman, PhD, Stephen Hughes, PhD, Heather Joseph MPH, Maya Nakajima, MPH, Rick O'Brien, MD, Barbara Roche, BScN, MPH, Katya Salcedo, MPH, Nandini Selvam, MPH, Timothy Sterling, MD, Kirsten Wall, MHS, Paul Weinfurter, MPH, and Lourdes Yun, MPH.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

SUMMARY

Objectives—To determine the rate of and risk factors for discontinuation of isoniazid due to adverse effects during the treatment of latent tuberculosis infection in a large, multi-site study.

Methods—The Tuberculosis Epidemiologic Studies Consortium (TBESC) conducted a prospective study from March 2007–September 2008 among adults initiating isoniazid for treatment of LTBI at 12 sites in the US and Canada. The relative risk for isoniazid discontinuation due to adverse effects was determined using negative binomial regression. Adjusted models were constructed using forward stepwise regression.

Results—Of 1,306 persons initiating isoniazid, 617 (47.2%, 95% CI 44.5–50.0%) completed treatment and 196 (15.0%, 95% CI 13.1–17.1%) discontinued due to adverse effects. In multivariable analysis, female sex (RR 1.67, 95% CI 1.32–2.10, $p < 0.001$) and current alcohol use (RR 1.41, 95% CI 1.13–1.77, $p = 0.003$) were independently associated with isoniazid discontinuation due to adverse effects.

Conclusions—The rate of discontinuation of isoniazid due to adverse effects was substantially higher than reported earlier. Women were at increased risk of discontinuing isoniazid due to adverse effects; close monitoring of women for adverse effects may be warranted. Current alcohol use was also associated with isoniazid discontinuation; counseling patients to abstain from alcohol could decrease discontinuation due to adverse effects.

Keywords

Mycobacterium tuberculosis; latent tuberculosis infection; female sex; alcohol use; adverse effects

INTRODUCTION

There are an estimated 11 million people living with latent tuberculosis infection (LTBI) in the United States (US).¹ Reactivation of LTBI accounts for approximately 70% of tuberculosis (TB) cases in this country.^{2, 3} Therefore, targeted testing and successful completion of treatment for LTBI is a critical component of TB elimination in the US.⁴ The current standard treatment regimen for LTBI is daily isoniazid for 9 months.⁴ Completion rates for this regimen are low, ranging 30–64%, which is due in part to the long duration of the regimen as well as drug-related adverse effects.^{4–9}

One well-characterized adverse effect due to isoniazid is liver injury. A previous meta-analysis reported a rate of liver injury of 0.6% among patients taking isoniazid for LTBI treatment.¹⁰ More recent, large studies have reported lower rates of 0.1–0.3%.^{7, 11} However, fatalities due to isoniazid-associated liver injury have been reported.^{12, 13} Risk factors for isoniazid-associated liver injury include older age,^{7, 11, 13} regular alcohol use,¹³ chronic viral hepatitis,^{14, 15} and pregnancy or the post-partum period (particularly among Hispanic women).¹⁶ There is no clear evidence for a sex-related difference in the incidence of isoniazid-associated liver injury;¹⁷ however, women may be at increased risk of death due to isoniazid-associated liver injury.¹⁸

Peripheral neuropathy is another adverse effect described during treatment with isoniazid. The incidence is dose-related and uncommon (<2%) with conventional dosing of 5 milligrams (mg)/kilogram (kg) daily.¹⁹ Risk factors include other conditions associated with nutritional deficiency including malnourishment, human immunodeficiency virus (HIV) infection, diabetes mellitus, renal failure, alcoholism, and pregnancy or breastfeeding.¹⁹ Pyridoxine supplementation is recommended during therapy with isoniazid among these high-risk groups.⁴

There is less known about the rate of and risk factors for the occurrence of other adverse effects during isoniazid LTBI treatment, particularly from programmatic field settings. In a retrospective study of 3,788 patients starting isoniazid for LTBI treatment in San Diego County's TB Control Program, 52 (1.4%) stopped treatment early due to adverse effects.⁷ These included hepatotoxicity (50%), dizziness (35%), nausea or vomiting (9%), abdominal pain (5%), rash (4.6%), headache (2.4%), paresthesias (2.2%), and pruritus (1.7%). In adjusted analyses, female sex, increasing age, homelessness, and time spent in a correctional facility were associated with the occurrence of ≥ 1 adverse effect. The occurrence of ≥ 1 adverse effect, in turn, was associated with lower rates of completion of LTBI treatment. Excess alcohol use and injection drug use were not associated with adverse effects, although excess alcohol use was associated with lower completion rates. However, this study was retrospective and did not assess more detailed information on the timing, severity, or type of alcohol and substance use. Additionally, 19.3% of patients in this study were lost to follow-up and had no treatment outcome documented.

Injection drug use increases the risk for recent *M. tuberculosis* infection^{20, 21} and progression to active disease.²² Therefore, injection drug users are a group of persons in whom the Centers for Disease Control and Prevention (CDC) recommends targeted testing and treatment for LTBI.⁴ Persons who use injection drugs are less likely to complete treatment for LTBI with rifampin and pyrazinamide,²³ but associations with isoniazid regimens have not been shown. It is unknown if the non-completion among this group is due to drug-related adverse effects, non-adherence, or both.

Regular alcohol use may increase the risk of infection with *M. tuberculosis* or progression to active disease; however, given the prevalence of other known risk factors among persons who abuse alcohol (e.g. tobacco use), it has been difficult to identify alcohol use as an independent risk factor.⁴ Persons who regularly use alcohol are less likely to complete isoniazid treatment for LTBI.^{7, 24} Regular alcohol use has also been shown to be a risk factor for isoniazid-associated liver injury,¹³ but has not been evaluated as a risk factor for non-hepatotoxic adverse effects.

It is important to determine the rates of discontinuation of isoniazid treatment for LTBI due to all adverse effects, not just liver injury. Moreover, identification of risk factors for adverse effects may lead to the identification of persons in need of closer monitoring or persons in whom interventions such as treatment for alcohol or substance abuse should be pursued in conjunction with treatment for LTBI. We report data from a large, prospective, multi-site study to determine the rate of adverse effects resulting in drug discontinuation during isoniazid treatment for LTBI. We also examine risk factors for discontinuation of isoniazid due to adverse effects, including the severity, timing, and type of alcohol and substance use.

PATIENTS AND METHODS

Patient Population

The Tuberculosis Epidemiologic Studies Consortium (TBESC) conducted a prospective cohort study from March 2007–September 2008 among adults initiating isoniazid for LTBI treatment at 12 sites in the US and Canada. Details regarding this consortium are described elsewhere²⁵. Participants were eligible if they were ≥ 18 years old, tested positive for LTBI by a tuberculin skin test, and accepted self-administered isoniazid as treatment for LTBI. Participants were ineligible for study enrollment if they were incarcerated at the time treatment was offered, received directly observed therapy for LTBI, had previously been treated for LTBI or TB disease, initiated a regimen other than isoniazid for LTBI, or participated in other LTBI treatment studies. The methods are described in more detail

elsewhere²⁶. Eligible participants were excluded from this analysis if they accepted, but never initiated isoniazid treatment. The institutional review board at the CDC and at each study site approved the protocol. All study participants signed a written informed consent and received the standard of care at each study site.

Study Definitions

Latent TB infection was defined as a positive tuberculin skin test (TST) using criteria for positivity defined by the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC). Completion of treatment was defined by the number of doses received within a specified time period according to ATS and CDC guidelines.⁴ A 9-month regimen of isoniazid was considered complete if 270 doses were received within 12 months; for a 6-month regimen 180 doses of isoniazid were required within 9 months. Completion of treatment was defined based on the initial recommended regimen. Therefore, if an individual completed a 6-month regimen of isoniazid, but a 9-month regimen was initially recommended then that participant was not considered to have completed treatment. Participants switched to rifampin were classified as non-completers of isoniazid treatment, even if they completed the rifampin regimen.

Reasons for treatment cessation were determined by chart review and included treatment completion, the participant moving, adverse effects, loss to follow-up, incarceration, or other reasons. A participant was determined to discontinue treatment due to drug adverse effects if the reason for cessation noted in the medical chart was due to adverse effects. Participants who were switched to rifampin due to adverse effects of isoniazid were classified as discontinuing isoniazid due to adverse effects, even if they completed the rifampin regimen.

Alcohol use was defined as the use of beer, wine, or liquor in any quantity with or without intoxication. Problematic alcohol use was defined as any reported occurrence of treatment for alcohol abuse, delirium tremens (shaking, severe confusion, fever, or hallucinations 1–2 days after a drink or after a significant decrease in alcohol intake), or alcohol related problems (hangover, craving, withdrawal symptoms, disturbing effects of use, or wanting to stop and being unable). Alcohol use was determined to be current if it occurred < 30 days prior to the initial interview.

Substance use was defined as use of heroin, methadone, cocaine, amphetamines, cannabis, or other substances (hallucinogens, inhalants, or barbiturates) in any quantity. Problematic substance use was defined as any reported occurrence of treatment for drug abuse or drug related problems (cravings, withdrawal symptoms, disturbing effects of use, or wanting to stop and being unable). Substance use was determined to be current if it occurred < 30 days prior to the initial interview.

Data Collection

Data were collected through in-person interviews and through abstraction of information from medical charts. Interviews were performed by study staff using standardized questionnaires. Participants were interviewed at the time treatment was accepted (initial interview) and at the time treatment was ceased (exit interview). Non-English speaking participants were interviewed by bilingual site study staff, in-person interpreters, or via telephone interpreters. The initial interview obtained information on demographics, socioeconomic status, cultural background, immigration history, health status, and alcohol and substance use. The exit interview obtained information on treatment experiences, including adverse effects.

Chart abstraction was performed by site study staff using a standardized abstraction form. Information collected by chart abstraction included dates isoniazid was first and last

prescribed, reasons for isoniazid cessation, total number of months isoniazid was prescribed, total number of monthly isoniazid prescriptions/doses that were picked up, information on receipt of regimens other than isoniazid, information on directly observed therapy, hospitalizations or deaths due to LTBI treatment, and development of active TB disease.

Statistical Analysis

Statistical analyses were conducted using STATA IC version 10.1. Chi-squared and Wilcoxon rank-sum tests compared categorical and continuous variables, respectively. The relative risk (RR) for discontinuation of isoniazid due to adverse effects was determined using negative binomial regression with adjustment for study site. All p-values were two-sided and considered statistically significant if <0.05 . Unadjusted models were adjusted for study site only. Adjusted models were constructed using forward stepwise regression and adjusted for study site.

RESULTS

From March 2007 to September 2008, 1,323 participants were determined eligible and enrolled in this study. Participants were excluded from this analysis if they accepted, but never initiated isoniazid treatment ($n=17$). Of 1,306 who initiated isoniazid, 617 (47.2%, 95% confidence interval [CI] 44.5–50.0%) completed isoniazid treatment; 595 (96.4%) completed a planned 9-month course and 22 (3.6%) a planned 6-month course. There were 196 (15.0%, 95% CI 13.1–17.1%) who discontinued isoniazid due to adverse effects. Of these 196 participants, 52 (26.5%) were switched to rifampin. Among the 52 participants switched to rifampin, 36 (69.2%) completed the rifampin-based regimen and 16 (30.8%) did not complete treatment for LTBI. The remaining 493 participants (37.7%, 95% CI 35.1–40.4%) discontinued isoniazid due to reasons other than adverse effects (Figure 1). These include moving, loss to follow-up, incarceration, pregnancy, pill-related difficulties, financial reasons, conflict with employment and/or family obligations, housing problems, patient attitudes/personal factors, issues with the patient-provider relationship, or issues with health care delivery.

Table 1 presents the clinical and demographic characteristics of the study population. Compared to participants who completed isoniazid, participants who discontinued due to adverse effects were more likely to be female (64.3% versus 49.9%) and more likely to be non-Hispanic white (18.4% versus 9.2%); they were less likely to be Hispanic (19.4% versus 26.3%) or non-Hispanic black (14.3% versus 23.0%). Participants who discontinued isoniazid due to adverse effects were more likely to report current alcohol use (37.8% versus 30.1%, $p=0.04$). The median number of days of alcohol use in the 30 days prior to the initial interview was one day (IQR: 0–4 days) among those who discontinued isoniazid due to adverse effects, compared to zero days (IQR: 0–2 days) among those who completed isoniazid. There was a trend toward participants who discontinued isoniazid due to adverse effects to be more likely to report current substance use (6.1% versus 3.1%, $p=0.05$).

In unadjusted analyses (adjusting for study site only), female sex (RR 1.57, 95% CI 1.22–2.02, $p<0.001$), non-Hispanic white race (RR 1.74, 95% CI 1.14–2.64, $p=0.01$), being US-born (RR 1.22, 95% CI 1.06–1.41, $p=0.005$), having a high school (or equivalent) education (RR 1.33, 95% CI 1.02–1.73, $p=0.03$), being a healthcare worker (RR 1.23, 95% CI 1.02–1.47, $p=0.03$), and current alcohol use (RR 1.29, 95% CI 1.00–1.66, $p=0.05$) were associated with isoniazid discontinuation due to adverse effects. Using forward stepwise progression, study site, female sex, and current alcohol use were adjusted for in the multivariate model. Both female sex (RR 1.67, 95% CI 1.32–2.10, $p<0.001$) and current alcohol use (RR 1.41, 95% CI 1.13–1.77, $p=0.003$) remained independently associated with discontinuation of isoniazid due to adverse effects (Table 2).

Of 813 persons who either completed isoniazid (n=617) or discontinued due to adverse effects (n=196), 641 (78.8%) completed the exit interview, including questions about symptoms experienced during isoniazid treatment. Symptoms reported among those who completed the exit interview can be found in Table 3. Participants who discontinued due to adverse effects were more likely to report symptoms during isoniazid treatment and were more likely to relate these symptoms to this medication. The most commonly reported symptom was weakness and fatigue (17.5%). There were no hospitalizations due to isoniazid and no deaths related to treatment for LTBI during the study period (Table 3).

DISCUSSION

In this study, the rate of completion of isoniazid for LTBI treatment was 47.2% (95% CI 44.5–50.0%). This isoniazid completion rate is consistent with previously reported rates ranging from 30–64% depending on the population studied.^{4–9}

The rate of discontinuation of isoniazid due to adverse effects was 15.0% (95% CI 13.1–17.1%). In a previous study of 3,788 patients starting isoniazid for LTBI treatment in San Diego County's TB Control Program, there were 672 (17.7%, 95% CI 16.5–19.0%) who experienced >1 adverse effect; only 52 (1.4%, 95% CI 1.0–1.8%) stopped treatment early due to adverse effects, with an additional 41 patients who stopped due to a provider decision (1.1%, 95% CI 0.8–1.5%) and 371 patients due to a patient decision (9.8%, 95% CI 8.9–10.8%). Thus <2% stopped due to adverse effects, in contrast to 15.0% in our study. However, 19.3% were lost to follow-up, some of whom may have stopped therapy due to unreported adverse events.

In multivariate analysis, we found that female sex was independently associated with an increased risk of discontinuation of isoniazid due to adverse effects (RR 1.67, 95% CI 1.32–2.10, $p<0.001$). Similarly, in the study from San Diego's TB Control Program, female sex was also independently associated with the occurrence of ≥ 1 adverse effect during isoniazid treatment (OR 1.6, 95% CI 1.4–2.0, $p<0.01$).

It is possible that there were other unmeasured variables which could account for the sex-related differences in discontinuation of isoniazid due to adverse effects. One example of an unmeasured variable includes a participant's body weight and isoniazid dose. The recommended dose of isoniazid for LTBI treatment is 5 mg/kg daily (maximum dose 300mg daily).⁴ Peripheral neuropathy due to isoniazid is known to be dose-related,¹⁹ but a relationship of isoniazid dose with other adverse effects has not been reported. In the US, isoniazid is available in 100mg and 300mg tablets. Persons weighing < 60 kg may receive 300mg of isoniazid daily due to tablet formulations and preference for single-pill dosing. It is possible that those participants who discontinued isoniazid due to adverse effects were those weighing < 60 kg, and still receiving 300mg daily doses. This may be a more frequent among women, who tend to weigh less than men.

A second example of a possible unmeasured variable which may account for the sex differences in the discontinuation of isoniazid due to adverse effects includes the ascertainment of polymorphisms in genes involved in the metabolism of isoniazid. It is known that isoniazid is metabolized, in large part, by N-acetyltransferase-2 (NAT-2).²⁷ It has been shown that slow acetylators (determined by NAT-2 genotype) have a higher incidence of isoniazid-associated liver injury^{28, 29} and peripheral neuropathy,¹⁹ but associations with other adverse effects have not been reported. However, serum samples for NAT-2 genotyping were not collected as part of this study. Previous studies have not reported a sex difference in NAT-2 genotypes.^{30, 31}

Current alcohol use was also independently associated with an increased risk of discontinuation of isoniazid due to adverse effects (RR 1.41, 95% CI 1.13–1.77, $p=0.003$). Among those who discontinued due to adverse effects, the median number of days of alcohol use in the 30 days prior to the initial interview was low (median: 1 day [IQR: 0–4 days]). Problematic alcohol use was not more likely among participants with isoniazid discontinuation due to adverse effects. However, the number of participants with problematic alcohol use was low, which may make detection of differences between the groups difficult.

We did not find an association of substance use with discontinuation of isoniazid due to adverse effects. This may be due to the low numbers of participants who reported current substance use. Of 813 persons, only 31 (3.8%) reported current substance during the 30 days prior to enrollment. Among the 260 persons who reported current alcohol use, only 18 (6.9%) also reported current substance use.

The main limitation of this study is that the specific adverse effect that led to discontinuation of isoniazid was not collected. Therefore, we cannot determine if isoniazid was discontinued due to liver injury, peripheral neuropathy or due to other adverse effects. However, it is important to determine the rate of discontinuation of isoniazid and to identify risk factors for discontinuation of isoniazid due to all adverse effects.

Another limitation is that data collected on alcohol and substance use was obtained by self-report. It is possible that answering questions on alcohol and drug use as part of a research study may produce biased responses. However, there was no collection of serum or urine specimens for confirmation of current use. Additionally, self-reported alcohol and drug use is reflective of information available to local TB control program staff in the programmatic field setting.

The strengths of this study are that the data were collected prospectively, through a large multi-center study. Therefore, these results are generalizable to the population in the US and Canada who receive targeted testing and treatment for LTBI. Additionally, extensive data was collected on alcohol and substance use including timing, severity, and types of use.

In conclusion, in a large, prospective multi-center study we found that the rate of discontinuation of isoniazid due to adverse effects during the treatment for LTBI was 15%, substantially higher than reported earlier. We found that female sex and current alcohol use were independently associated with isoniazid discontinuation due to adverse effects. These findings suggest that close monitoring of women may be warranted to detect and manage adverse effects before they lead to isoniazid discontinuation. Moreover, counseling patients to minimize or abstain from alcohol during isoniazid treatment could potentially decrease discontinuation due to adverse effects.

Acknowledgments

Funding Information: This study was supported by the Centers for Disease Control and Prevention, Contract Number 200-2001-00082 and National Institutes of Health K24 AI 65298 (ACP,TRS).

References

1. Bennett DE, Courval JM, Onorato I, et al. Prevalence of tuberculosis infection in the United States population: the national health and nutrition examination survey, 1999–2000. *Am J Respir Crit Care Med*. 2008; 177(3):348–355. [PubMed: 17989346]
2. Geng E, Kreiswirth B, Driver C, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. *N Engl J Med*. 2002; 346(19):1453–1458. [PubMed: 12000815]

3. Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. *N Engl J Med.* 1994; 330(24): 1703–1709. [PubMed: 7910661]
4. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep.* 2000; 49(RR-6):1–51.
5. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med.* 2004; 350(20):2060–2067. [PubMed: 15141044]
6. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. *Int J Tuberc Lung Dis.* 2003; 7(12 Suppl 3):S384–S390. [PubMed: 14677827]
7. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med.* 2003; 168(4):443–447. [PubMed: 12746255]
8. Horsburgh CR Jr, Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest.* 2010; 137(2):401–409. [PubMed: 19793865]
9. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. *Int J Tuberc Lung Dis.* 2008; 12(11):1235–1254. [PubMed: 18926033]
10. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest.* 1991; 99(2):465–471. [PubMed: 1824929]
11. 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(11):1014–1018. [PubMed: 10086436]
12. Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB. Isoniazid-associated hepatitis. Report of an outbreak. *Am Rev Respir Dis.* 1972; 106(3):357–365. [PubMed: 5080707]
13. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis.* 1978; 117(6):991–1001. [PubMed: 666111]
14. Fernandez-Villar A, Sopena B, Vazquez R, et al. Isoniazid hepatotoxicity among drug users: the role of hepatitis C. *Clin Infect Dis.* 2003; 36(3):293–298. [PubMed: 12539070]
15. Patel PA, Voigt MD. Prevalence and interaction of hepatitis B and latent tuberculosis in Vietnamese immigrants to the United States. *Am J Gastroenterol.* 2002; 97(5):1198–1203. [PubMed: 12014728]
16. Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Public Health Rep.* 1989; 104(2):151–155. [PubMed: 2495549]
17. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006; 174(8):935–952. [PubMed: 17021358]
18. Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis.* 1992; 145(2 Pt 1):494–497. [PubMed: 1736764]
19. Snider DE Jr. Pyridoxine supplementation during isoniazid therapy. *Tubercle.* 1980; 61(4):191–196. [PubMed: 6269259]
20. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. *Am J Respir Crit Care Med.* 1998; 158(6):1797–1803. [PubMed: 9847270]
21. Schluger NW, Huberman R, Wolinsky N, Dooley R, Rom WN, Holzman RS. Tuberculosis infection and disease among persons seeking social services in New York City. *Int J Tuberc Lung Dis.* 1997; 1(1):31–37. [PubMed: 9441056]
22. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA.* 1992; 268(4):504–509. [PubMed: 1619742]
23. Lobato MN, Reves RR, Jasmer RM, et al. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *Chest.* 2005; 127(4):1296–1303. [PubMed: 15821208]
24. Gilroy SA, Rogers MA, Blair DC. Treatment of latent tuberculosis infection in patients aged > or =35 years. *Clin Infect Dis.* 2000; 31(3):826–829. [PubMed: 11017843]

25. Sterling TR, Bethel J, Goldberg S, et al. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. *Am J Respir Crit Care Med*. 2006; 173(8):927–931. [PubMed: 16424442]
26. Colson PW, Hirsch-Moverman Y, Bethel J, et al. Acceptance of treatment for latent tuberculosis infection: prospective cohort study in the United States and Canada. *The International Journal of Tuberculosis and Lung Disease*. 2013; 17(4):473–479. [PubMed: 23485381]
27. Parkin DP, Vandenplas S, Botha FJ, et al. Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. *Am J Respir Crit Care Med*. 1997; 155(5):1717–1722. [PubMed: 9154882]
28. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology*. 2002; 35(4):883–889. [PubMed: 11915035]
29. Ohno M, Yamaguchi I, Yamamoto I, et al. Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2000; 4(3): 256–261. [PubMed: 10751073]
30. Welfare MR, Bassendine MF, Daly AK. The effect of NAT2 genotype and gender on the metabolism of caffeine in nonsmoking subjects. *Br J Clin Pharmacol*. 2000; 49(3):240–243. [PubMed: 10718779]
31. Welfare MR, Cooper J, Bassendine MF, Daly AK. Relationship between acetylator status, smoking, and diet and colorectal cancer risk in the north-east of England. *Carcinogenesis*. 1997; 18(7):1351–1354. [PubMed: 9230278]

Figure 1.
Study Enrollment and Outcomes

Table 1

Clinical and Demographic Characteristics of the Study Population

Characteristic n=1,306	Isoniazid Completed n=617	Isoniazid discontinued due to adverse effects n=196	P-value ^a	Isoniazid discontinued for other reasons N=493	P-value ^b
Age in years-Median (IQR)	35 (28-46)	38 (27-49)	0.09	33 (25-45)	0.04
Female sex-Number (%)	308 (49.9%)	126 (64.3%)	<0.001	272 (55.2%)	0.09
Race/Ethnicity-Number (%)			<0.001		<0.001
White, non-Hispanic	57 (9.2%)	36 (18.4%)		45 (9.26%)	
Black, non-Hispanic	142 (23.0%)	28 (14.3%)		151 (31.1%)	
Asian	215 (34.8%)	68 (34.7%)		99 (20.4%)	
Hispanic	162 (26.3%)	38 (19.4%)		162 (33.3%)	
Other/Unknown	41 (6.6%)	26 (13.3%)		36 (7.3%)	
US Born-Number (%)	139 (22.5%)	54 (27.5%)	0.15	153 (31.0%)	0.002
High school or equivalent education-Number (%)	435 (70.5%)	152 (77.5%)	0.05	337 (68.4%)	0.47
Currently Homeless- Number (%)	10 (1.6%)	2 (1.0%)	0.54	28 (5.7%)	<0.001
Employed-Number (%)	318 (51.5%)	112 (57.1%)	0.17	247 (50.1%)	0.67
Healthcare Worker-Number (%)	39 (6.3%)	16 (8.2%)	0.37	33 (6.7%)	0.81
Household income <\$20,000-Number (%)	235 (51.3%)	70 (44.0%)	0.11	242 (49.1%)	<0.001
Jail >30 days in last 2 years-Number (%)	9 (1.5%)	3 (1.5%)	0.94	29 (5.9%)	<0.001
No health insurance- Number (%)	217 (35.5%)	76 (39.4%)	0.32	228 (47.0%)	<0.001
Current Daily Prescription medication-Number (%)	208 (33.8%)	75 (38.3%)	0.25	148 (30.2%)	0.22
Psychiatric hospitalization or prescription medication- Number (%)	46 (7.5%)	21 (10.7%)	0.16	45 (9.2%)	0.38
HIV infection-Number (%)	17 (2.8%)	2 (1.0%)	0.16	12 (2.5%)	0.85
Alcohol use					
Any Ever-Number (%)	378 (61.3%)	126 (64.3%)	0.45	335 (67.9%)	0.02

Characteristic n=1,306	Isoniazid Completed n=617	Isoniazid discontinued due to adverse effects n=196	P-value ^a	Isoniazid discontinued for other reasons N=493	P-value ^b
Any Current-Number (%)	186 (30.1%)	74 (37.8%)	0.04	177 (35.9%)	0.05
Problematic Ever-Number (%)	20 (3.2%)	6 (3.1%)	0.90	34 (6.9%)	0.007
Problematic Current-Number (%)	8 (1.3%)	3 (1.5%)	0.80	14 (2.8%)	0.08
Past 30 days-Median (IQR)	0 (0-2)	1 (0-4)	0.03	1 (0-3)	0.16
Substance use					
Any Ever-Number (%)	102 (16.5%)	32 (16.3%)	0.74	134 (27.2%)	<0.001
Any Current-Number (%)	19 (3.1%)	12 (6.1%)	0.05	53 (10.7%)	<0.001
Problematic Ever-Number (%)	22 (3.6%)	10 (5.1%)	0.33	65 (13.2%)	<0.001
Problematic Current-Number (%)	14 (2.3%)	7 (3.6%)	0.32	41 (8.3%)	<0.001

IQR=Interquartile Range; US=United States; HIV=Human Immunodeficiency Virus

^{a,b} Comparisons made using Pearson's chi-square and Wilcoxon rank sum tests for categorical and continuous variables, respectively.

^a Comparison made between those who discontinued isoniazid due to adverse events and those who completed isoniazid.

^b Comparison made between those who discontinued isoniazid for other reasons and those who completed isoniazid.

Table 2

Binomial Regression Model for Risk of Isoniazid Discontinuation Due to Toxicity

Characteristic n=813	Unadjusted Relative Risk ^a	P-value	Adjusted Relative Risk ^b	P-value
Age (in years)	1.01 (0.99–1.03)	0.40		
Female sex	1.57 (1.22–2.02)	<0.001	1.67 (1.32–2.10)	<0.001
White, non-Hispanic race	1.74 (1.14–2.64)	0.01		
US Born	1.22 (1.06–1.41)	0.005		
High school education or equivalent	1.33 (1.02–1.73)	0.03		
Currently homeless	0.69 (0.17–2.77)	0.60		
Employed	1.19 (1.00–1.42)	0.06		
Healthcare worker	1.23 (1.02–1.47)	0.03		
Household income <\$20,000	0.80 (0.64–1.01)	0.06		
Jail >30 days in last 2 years	1.04 (0.32–3.40)	0.95		
No health insurance	1.14 (0.78–1.65)	0.51		
Current daily prescription medications	1.16 (0.87–1.54)	0.31		
Psychiatric hospitalization or prescription medication	1.33 (0.96–1.82)	0.08		
HIV infection	0.43 (0.13–1.46)	0.17		
Current alcohol use	1.29 (1.00–1.66)	0.05	1.41 (1.13–1.77)	0.003
Current substance use	1.65 (0.93–2.90)	0.08		

HIV=Human Immunodeficiency Virus

^aUnadjusted relative risk is adjusted for study site only.^bAdjusted relative risk is adjusted for study site, sex, and current alcohol use.

Table 3

Symptoms

Characteristic n=641	Isoniazid Completed n=553	Isoniazid discontinued due to adverse effects n=88	P-value ^a
Stomach upset			
Reported	40 (7.2%)	30 (34.1%)	<0.001
Related to meds	14 (35%)	27 (90%)	<0.001
Nausea or vomiting			
Reported	30 (5.4%)	31 (35.2%)	<0.001
Related to meds	14 (46.7%)	30 (96.8%)	<0.001
Skin rash, itchy skin			
Reported	35 (6.3%)	31 (35.2%)	<0.001
Related to meds	7 (20%)	28 (90.3%)	<0.001
Tingling in hands/feet			
Reported	43 (7.8%)	20 (22.7%)	<0.001
Related to meds	19 (44.2%)	17 (85.0%)	0.002
Yellowing of skin/eyes			
Reported	3 (0.5%)	8 (9.1%)	<0.001
Related to meds	2 (66.7%)	8 (100%)	0.09
Headache			
Reported	68 (12.3%)	28 (31.8%)	<0.001
Related to meds	14 (20.6%)	24 (85.7%)	<0.001
Dizziness			
Reported	38 (6.9%)	28 (31.2%)	<0.001
Related to meds	17 (44.7%)	23 (82.1%)	0.002
Weakness/fatigue			
Reported	68 (12.3%)	44 (50%)	<0.001
Related to meds	22 (32.3%)	39 (88.6%)	<0.001
Dark urine			
Reported	19 (3.4%)	24 (27.3%)	<0.001
Related to meds	6 (31.6%)	22 (91.7%)	<0.001
Other			
Reported	43 (7.8%)	30 (34.5%)	<0.001
Related to meds	22 (51.2%)	24 (80.0%)	0.01
1 symptom			
Reported	183 (33.1%)	75 (85.2%)	<0.001
Related to meds	74 (40.4%)	69 (92%)	<0.001

^aComparisons made using Pearson's chi-square and Wilcoxon rank sum tests for categorical and continuous variables, respectively.