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Risk factors for treatment default in close contacts with latent tuberculosis infection

Christina T. Fiske, M.D. M.P.H.¹, Fengxia Yan, M.D.², Yael Hirsch-Moverman, Ph.D., M.P.H.³, Timothy R. Sterling, M.D.^{1,4}, Mary R. Reichler, M.D.², and the Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team

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

²Centers for Disease Control and Prevention, Atlanta, GA

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

⁴Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

Abstract

Objective—To characterize risk factors for non-completion of treatment for latent tuberculosis infection (LTBI). Secondly, to assess the impact of LTBI treatment regimen on subsequent risk of tuberculosis.

Methods—Close contacts of adults (≥ 15 years) with pulmonary tuberculosis were prospectively enrolled in a multi-center study in the U.S. and Canada from January 2002–December 2006. Close contacts to TB patients were screened and cross-matched with tuberculosis registries to identify those who developed active tuberculosis.

Results—Of the 3,238 contacts screened, 1,714 (53%) were diagnosed with LTBI. Preventive therapy was recommended in 1,371 (80%); 1,147 contacts (84%) initiated therapy, of whom 723 (63%) completed treatment. In multivariate analysis, study site, initial interview sites other than a home or healthcare setting, and treatment with isoniazid were significantly associated with LTBI treatment non-completion. Fourteen tuberculosis cases were identified in contacts, all of whom

#Corresponding author/author for reprint requests: Christina T. Fiske, M.D. M.P.H., A2200 MCN, 1161 21st Ave S, Nashville TN, 37232 USA, Phone +1 615 322 2035, Fax +1 615 343 6160, christina.fiske@vanderbilt.edu.

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Dr. Christina Fiske contributed to data analysis and interpretation and writing of the manuscript.

Dr. Fengxia Yan contributed to data analysis and interpretation and writing of the manuscript.

Dr. Yael Hirsch-Moverman contributed to data interpretation and writing of the manuscript

Dr. Tim Sterling contributed to data analysis and interpretation and writing of the manuscript.

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initiated isoniazid. There were two cases among persons who received six or more months of isoniazid (66 cases/100,000 person-years), and nine cases among persons who received 0–5 months (median 2 months) of isoniazid (792 cases/100,000 person-years; $p < 0.001$); data on duration of isoniazid for three cases were not available.

Conclusion—Only 53% (723 of 1,371) of close contacts for whom preventive therapy was recommended actually completed treatment. Close contacts of TB patients were significantly less likely to complete LTBI treatment if they took isoniazid. Less than six months of isoniazid therapy was associated with increased risk of active TB.

Keywords

latent tuberculosis infection; treatment non-completion; treatment effectiveness

INTRODUCTION

Approximately 5–10% of persons latently infected with *M. tuberculosis* will develop active tuberculosis (TB) disease. Identification and treatment of the large reservoir of individuals in the U.S. with latent tuberculosis infection (LTBI) is critical to sustain a continued decline in TB incidence rates and achieve TB elimination.^{1–3} Roughly 50–60% of contacts to persons with TB who initiate treatment for LTBI complete therapy.^{4–7} Multiple risk factors for LTBI treatment non-completion have been identified including age, sex, country of origin, substance abuse and treatment regimen.^{6, 8–11}

Isoniazid was first recommended in the U.S. in 1965 as a treatment for LTBI.¹² While many randomized controlled clinical trials have evaluated the efficacy of isoniazid in preventing active TB disease, few clinical trials have studied various durations of isoniazid. In one trial, five-year TB incidence rates were lowest in the group that received 12 months of isoniazid (compared to placebo, 3 months, and 6 months).¹³ Recent studies in HIV-infected individuals with LTBI suggest that longer courses of isoniazid are more efficacious in preventing TB compared to shorter durations.^{14, 15} A post-hoc analysis of data from studies of compliance with isoniazid therapy concluded that 9 months of isoniazid was more effective than 6 months but that there was no significant benefit in extending therapy to 12 months.¹⁶

Close contacts to TB patients with subsequent LTBI have high rates of progression to active TB.^{17, 18} We report findings from a large, multi-site, prospective evaluation of close contacts to persons with culture-positive pulmonary TB. Our primary aim was to characterize factors associated with LTBI treatment non-completion. Secondarily, we used prospectively collected data to describe the frequency of use and effectiveness of different chemoprophylaxis regimens for LTBI, including different durations of isoniazid, in preventing active TB disease. A separate paper will describe epidemiologic and clinical risk factors for LTBI and tuberculosis and the impact of LTBI treatment in preventing TB in close contacts in this study population.

METHODS

Close contacts of adults (≥ 15 years old) with culture-positive pulmonary TB were prospectively enrolled in a multi-center study from January 2002 to December 2006 at nine health departments (seven U.S. and two Canadian). Close contacts were defined as persons who had shared airspace with a person with pulmonary TB for at least 15 hours per week for one or more weeks, or 180 total hours during an infectious period defined as three months prior to collection of the first culture-positive sputum or the date of cough onset (whichever was longer) until two weeks after the initiation of appropriate anti-tuberculosis therapy.

Contacts were screened as soon as possible after they were identified by interviewing the TB patient and again 10–12 weeks after their last exposure to the patient.¹⁹ Screening consisted of a standardized interview and tuberculin skin testing (TST); a positive TST result was ≥ 5mm.¹⁹ Any person with a history of LTBI or previous TB was excluded from analysis. Chest radiograph was performed if contacts had a positive TST, were less than 6 years of age, or at high risk for TB (immunosuppressive disorders or therapy with oral or injectable steroids) with an initial negative TST (<5mm). While a standard protocol was used for conducting the contact investigations, the staff at the study sites did not use a standard protocol for patient management.

Contacts were cross-matched with TB registries at the end of the enrollment period, and annually for four years with the exception of one study site that cross-matched contacts annually for two years. Testing for HIV was offered on a voluntary basis to all cases and contacts included in the study, regardless of TST result. The Centers for Disease Control and Prevention Institutional Review Board “A” approved the study protocol (protocol number 2456).

Statistically significant differences in categorical variables were assessed using the Pearson’s chi-squared test. The denominator for those subjects completing therapy was the number initiating therapy. Risk factors for non-completion of LTBI therapy were determined *a priori* and included in a univariate logistic regression model. Variables significant at $p \leq 0.2$ were included in the multivariate logistic regression model. TB incidence rates were calculated by dividing the total number of TB cases by the person-years of follow-up and compared using the chi-squared test. Final registry match date was used to determine person-years of follow-up, and any TB events between enrollment and registry match were counted. All statistical analyses were performed using SAS 9.2, SAS Institute Inc, Cary, NC, USA.

RESULTS

A total of 3,238 contacts were identified and screened, of whom 1,714 (53%) were diagnosed with LTBI. Demographic characteristics of these infected contacts are found in Table 1.

Table 2 describes the characteristics of the 1,714 infected contacts according to three groups: 1) the proportion in whom LTBI treatment was recommended, 2) of those in whom it was recommended, the proportion initiating LTBI treatment, and 3) of those who initiated

treatment, the proportion completing treatment. The most common reason why LTBI treatment was not recommended was prior treatment of TB or LTBI (n=106, 35%). Other reasons included: the contact was lost to follow-up (n=90, 30%), greater than 35 years of age (n=40, 13%), had received BCG (n=24, 8%), used excess alcohol (n=1; 0.3%), or was pregnant (n=5, 2%). Close contacts of smear positive TB patients and men were more likely to be recommended treatment. Whites were more likely and Asians less likely to be recommended treatment compared with blacks.

Hispanics and persons born outside the U.S. and Canada were less likely to initiate treatment compared to blacks and persons born in the U.S. and Canada respectively. The most common regimen among contacts initiating LTBI treatment was isoniazid (n=807, 70%), followed by combination therapy of isoniazid and rifapentine (n=150, 13%). Because the latter regimen was administered under direct observation as part of a clinical trial,²⁰ it was excluded from further analysis. Other LTBI regimens included four months of rifampin (n=98, 9%), three months of isoniazid and rifampin (n=34, 3%), two months of four drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol (n=16, 1%), a fluoroquinolone-containing regimen (n=9, 0.9%), and “other” (n=8, 0.7%). Information about the treatment regimen was unknown for 18 contacts initiating LTBI treatment.

The regimen with the highest completion rate was four drug therapy with isoniazid, rifampin, ethambutol, and pyrazinamide (15/16, 94% completed therapy). This high completion rate may reflect directly observed therapy because these contacts were considered potential TB cases. Although isoniazid mono-therapy was the most frequently prescribed LTBI regimen, it had the second lowest completion rate (456/807, 57%). Similar proportions of contacts completed four months of rifampin and three months of isoniazid and rifampin (71% and 74%, respectively). The most common reasons for treatment non-completion were loss-to-follow-up (228/495, 46%) and non-adherence (122/495, 25%). Other reasons for non-completion included refusal (40/495, 8%), side effects of LTBI therapy (19/495, 4%), and development of active TB (6/495, 1%) (data not shown).

In a univariate logistic regression analysis, factors associated with non-completion of LTBI therapy included black race, study site, birth in the U.S. or Canada, being initially interviewed at a site other than a healthcare setting or home (“other interview places” such as workplace, parking lot, or telephone contact only), and skin test reaction size of 10–19mm (Table 3). Treatment with rifampin and four-drug therapy were significantly associated with increased treatment completion rates. In a multivariate analysis, significant factors associated with LTBI treatment non-completion included study site, initial interview of the contact at “other interview places,” and isoniazid mono-therapy.

Among 1147 close contacts with LTBI who initiated isoniazid therapy 14 developed TB during follow-up (Table 4). Data on the duration of INH for three of these individuals were not available. One hundred and ninety-one close contacts with LTBI completed <6 months (median 2 months) of isoniazid; nine of these contacts subsequently developed TB (792 cases/100,000 person-years). There were two cases among persons who received six or more months of isoniazid (66 cases/100,000 person-years; $p<0.001$ compared to persons completing less).

DISCUSSION

In a large prospective study of close contacts to persons with pulmonary TB, we found that only 63% of persons initiating therapy for LTBI completed treatment (and only 53% of close contacts for whom preventive therapy was recommended completed treatment). The completion rate we observed in the current study is only slightly higher than rates reported from previous studies. Reichler, et al conducted a retrospective study of close contacts with LTBI from five U.S. health departments in 1996; two of these health departments were included in the current study.⁶ Of those contacts who initiated LTBI treatment, 51% completed a 6 month course of isoniazid. Another retrospective analysis of 68 public and private clinics in the U.S. and Canada conducted in 2002 found that only 47% of 1,994 persons with LTBI who initiated treatment actually completed the course of therapy.²¹ Our findings indicate that further research on novel interventions to promote adherence to LTBI treatment is needed. One area of ongoing research that may be applicable to LTBI treatment is healthcare communication via mobile technology.²²

We found that race, sex, age, and place of birth were not significantly associated with LTBI treatment completion in a multivariate analysis. Previous studies have found inconsistent associations between adherence to LTBI treatment and these factors.^{8–10} Also, while the study by Reichler, et al found that recent TST converters were most likely to complete LTBI treatment,⁶ this was not a significant factor associated with treatment completion in the current study. Interestingly, study sites differed significantly in treatment completion. Specifically site 1 had lower while site 4 had higher odds of treatment completion. Previous studies have found differences in completion rates of LTBI treatment by study site, perhaps due to regional population differences and variation in practices in administering treatment for LTBI.^{6, 23} Additionally, persons at site 4 had increased odds of treatment completion after controlling for risk factors for non-completion in the multivariate analysis, suggesting that an unmeasured factor may be contributing to treatment completion at that site. Initial interview of close contacts at a site other than a healthcare setting or home was associated with LTBI treatment non-completion. This finding suggests that every effort should be made to meet close contacts of TB cases in as stable an environment as possible so that a focused and detailed interview can take place.

Similar to previous studies, we found that isoniazid mono-therapy was associated with less LTBI treatment completion compared to other regimens. Two retrospective analyses found that significantly fewer latently infected individuals completed 9 months of isoniazid compared to 4 months of rifampin.^{24, 25} Similarly, an open-label randomized trial found that significantly more individuals completed 4 months of rifampin for LTBI treatment compared with 9 months of isoniazid.²⁶ Isoniazid was more likely to be discontinued in these studies because of adverse reactions compared to rifampin. Only 19 (5%) of contacts in our study reported treatment discontinuation (of any regimen) because of adverse events. However, there was a large proportion of discontinuing patients for whom there was no reason recorded for therapy discontinuation. The longer duration of isoniazid regimens (six or nine months) compared to shorter durations of regimens such as rifampin may also be a barrier to completion. This suggests that regimens of shorter duration, such as three months of isoniazid/rifampentine, may achieve higher rates of treatment completion. Studies are

ongoing to determine the efficacy of this regimen in preventing active TB when it is self-administered.

We found differences by race and sex in those recommended to start LTBI treatment. These results suggest there may be bias in recommending treatment to different demographic groups and should be studied further. Similar to previous studies, we found that close contacts to persons with smear positive TB were more likely to be recommended for treatment compared with contacts to persons with smear negative TB.⁶ We also found in several instances that health departments deviated from current guidelines in choosing not to recommend LTBI treatment to individuals who were greater than 35 years old, had a history of BCG receipt, or were pregnant.¹ Previous studies have also found low adherence to guidelines for testing and treatment of LTBI.^{27, 28} Continued education of healthcare providers is needed to improve adherence with published guidelines for LTBI treatment.

We identified 14 TB cases among close contacts who initiated isoniazid therapy for LTBI. Not surprisingly, the greatest TB incidence was in those contacts who failed to complete a full course of isoniazid. Six persons discontinued isoniazid because they developed TB and were not excluded from the study. Results from this and other studies suggest that longer durations of isoniazid are more efficacious compared to shorter durations in preventing active TB in persons with LTBI. While one recent clinical trial suggested that isoniazid given for three years was more efficacious than a six month course in preventing active TB, a separate study did not find additional benefit of “continuous INH” (six years duration).^{14, 15} The latter finding may have resulted from the open-label nature of the study and increased drop-out of participants in the “continuous isoniazid” arm. These trials were performed in HIV-infected persons and it is not clear if the same benefit would exist for HIV-negative persons. Also, the risk of adverse events and drug resistant *M. tuberculosis* isolates in persons that are non-adherent with longer courses of isoniazid should be studied further.

The strengths of the current study are the large number of close contacts that were enrolled and the prospective study design. Our study did have several limitations. Missing data on HIV status and the duration of isoniazid might have affected our results. This study was observational and was not designed with the intent of examining differences in TB rates by LTBI treatment regimen. Also, regimen selection at individual study sites may have affected completion rates as well as rates of subsequent TB; we were unable to control for this. In addition, the risk of progression from LTBI to active TB is not constant over time and potential confounding of our results by the duration of follow-up per patient at each site could have affected the results. However, only one site had less than four years of follow-up (2 years) and this should not affect our results because this site contributed very few subjects. Finally, directly observed therapy for LTBI has been shown to increase LTBI treatment completion^{29–31} but we were unable to assess its effect in the current study.

CONCLUSIONS

We found in a large prospective study that close contacts of TB patients were significantly less likely to complete therapy for LTBI if they were prescribed isoniazid versus other LTBI

regimens. Our findings suggest that further research is needed on novel interventions to promote adherence to LTBI treatment. The findings also suggest that shorter LTBI regimens, such as rifampin, or combination therapy with isoniazid and rifapentine given by directly observed therapy, are associated with higher rates of treatment completion than longer regimens of isoniazid. We found significant deviations from established treatment guidelines for LTBI, suggesting that ongoing education about current guidelines for LTBI should be undertaken.

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Appendix

The Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team was composed of:

1. TBESC Task Order 2 study sites, investigators, and study coordinators:

- Arkansas Dept. of Health (I. Bakhtawar, C. LeDoux)
- Respiratory Health Association of Metropolitan Chicago and Rush Univ. (J. McAuley, J. Beison)
- Univ. of British Columbia (M. Fitzgerald, M. Naus, M. Nakajima)
- Columbia Univ. (N. Schluger, Y. Hirsch-Moverman, J. Moran)
- Emory Univ. (H. Blumberg, J. Tapia, L. Singha)
- Univ. of Manitoba (E. Hershfeld, B. Roche)
- New Jersey Medical School National Tuberculosis Center (B. Mangura, A. Sevilla)
- Vanderbilt Univ. and TN Dept. of Health (T. Sterling, T. Chavez-Lindell, F. Maruri)
- Maryland Dept. of Health (S. Dorman, W. Cronin, E. Munk);

2. CDC Data management team:

- B. Chen, Y. Yuan, F. Yan, Y. Shen, H. Zhao, H. Zhang, M. Fagley, M. Reichler

3. Task Order 2 Protocol Team:

- M. Reichler (Chair), T. Sterling (Co-chair), J. Tapia, C. Hirsch, C. Luo

Abbreviations

TB Tuberculosis

LTBI	Latent tuberculosis infection
TST	tuberculin skin test
HIV	Human immunodeficiency virus
BCG	Bacille Calmette Guerin

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Table 1

Characteristics of 1714 Contacts with Newly Documented Latent Tuberculosis Infection

Characteristic	Number (%)
Total	1714
Median age (IQR) (years)	31 (21–46)
Age group (years)	
<15	233 (14)
15–34	728 (43)
35–64	667 (39)
>65	79 (5)
Male sex	972 (57)
Race/ethnicity	
White	644 (37)
Black	752 (44)
Asian	35 (2)
Hispanic	190 (11)
Other	66 (4)
Unknown	26 (2)
Birth Place	
U.S. or Canada	787 (46)
Foreign born	902 (53)
Unknown	25 (1)
BCG Vaccination (per interview)	564 (35)
Resident in homeless shelter	44(2)
Heavy alcohol use ^a	152 (9)
Illicit drug use	134 (8)
Smoked in last 6 months	367 (21)
HIV status	
Positive	6 (0.35)
Negative	601 (35)
Unknown	1112 (65)
Interviewing setting	
TB clinic	571 (36)
Private clinic	7 (0.44)
Hospital	17 (1)
Other public health clinic	27 (2)
Patient home	679 (43)
Other interview places	289 (18)

^aHeavy alcohol use was defined as ≥ 12 beers per week, ≥ 2 bottles of wine per week, and/or ≥ 2 pints of hard liquor per week

Table 2

Characteristics of 1714 contacts who were recommended, initiated, and completed therapy for latent *M. tuberculosis* infection.

	Number (%)	TLTBI Recommended ^a N (%)	p-value	TLTBI Initiated ^b N (%)	p-value	TLTBI Completed ^c N (%)	p-value
Total	1714	1387(81)		1147(83)		723(63)	
Male sex	972(57)	805(84)	0.02	672(85)	0.22	419(62)	0.50
Race/ethnicity							
White	644(37)	555(87)	0.01	461(84)	0.31	296(64)	0.06
Black	752(44)	609(82)	ref	514(85)	ref	299(58)	ref
Asian	35(2)	18(56)	<0.001	15(94)	0.71	10(67)	0.06
Hispanic	190(11)	135(71)	0.001	95(72)	<0.001	71(75)	0.008
Other	66(4)	54(87)	0.032	48(89)	0.34	39(81)	0.001
Unknown	26(2)	15(58)	0.002	13(87)	0.93	7(54)	1.00
Study Site							
1	228(14)	200 (89)	0.11	145(73)	<0.001	31(21)	<0.001
2	601 (35)	506 (84)	ref	436 (87)	ref	306 (70)	ref
3	191 (11)	137 (74)	<0.001	129 (96)	0.01	71 (55)	0.04
4	166 (10)	141 (85)	0.76	118 (87)	0.75	92 (78)	0.06
5	156 (9)	131 (87)	0.38	107 (82)	0.12	74 (69)	0.73
6	103 (6)	62 (61)	<0.001	48 (79)	0.08	42 (88)	0.03
7	51 (3)	40 (78)	0.26	19 (48)	<0.001	10 (53)	0.05
8	162 (9)	146 (92)	0.02	123 (84)	0.39	85 (69)	0.42
9	56 (3)	24 (46)	<0.001	22 (100)	0.07	12 (55)	0.28
Birth place							
US or Canada	787(46)	626(81)	ref	542(88)	ref	315(58)	ref
Foreign born	902(53)	742(83)	0.12	592(80)	<0.001	401(68)	0.02
Unknown	25(1)	19(83)	0.81	13(72)	0.06	7(54)	0.75
BCG Vaccination (per interview)	564(35)	464(83)	0.47	378(82)	0.16	273(72)	<0.001
Heavy alcohol use ^d	152(9)	127(85)	0.39	110(87)	0.38	61(55)	0.10

	Number (%)	TLTBI Recommended ^a N (%)	p-value	TLTBI Initiated ^b N (%)	p-value	TLTBI Completed ^c N (%)	p-value
Illicit drug use	134(8)	103(78)	0.17	90(90)	0.10	51(57)	0.56
Smoked in last 6 months	367(21)	293(80)	0.16	258(90)	0.01	149(58)	0.11
HIV status							
Positive	6(0.35)	5(83)	1.00	5(100)	0.43	3(50)	1.00
Negative	601(35)	482(82)	ref	423(89)	ref	285(67)	ref
Unknown	1112(65)	900(82)	0.66	719(81)	<0.001	435(61)	0.04
Case smear status							
Smear positive	1521(89)	1243(83)	0.02	1036(84)	0.15	644(62)	0.20
Smear negative	185(11)	137(76)	ref	105(79)	ref	73(70)	ref
Not done	8(0.50)	7(100)	0.14	6(86)	1.00	6(100)	0.18
Skin Test Size							
5–9 mm	94(5)	73(78)	ref	62(87)	ref	47(76)	ref
10–19 mm	827(48)	679(83)	0.20	559(83)	0.40	344(62)	0.05
>=20 mm	554(32)	435(80)	0.68	360(84)	0.42	238(66)	0.17
Unknown	239(14)	200 (87)	0.04	166(85)	0.65	94(57)	0.03
Skin Test Status							
TST converter	237(14)	198(87)	ref	166(86)	ref	93(56)	ref
TST positive	1477(86)	1189(81)	0.05	981(83)	0.39	630(64)	0.12
TLTBI regimen							
INH mono-therapy	807(45)	807(100)	--	807(100)	--	456(57)	ref
RIF	98(7)	98(100)	--	98(100)	--	70(71)	0.02
INH_RIF	34(2)	34(100)	--	34(100)	--	25(74)	0.10
RIPE	16(0.87)	16(100)	--	16(100)	--	15(94)	0.01
RIF_PZA	7(0.36)	7(100)	--	7(100)	--	3(43)	0.45
INH_RPT ^e	150(8)	150(100)	--	150(100)	--	138(92)	<0.001
FQ- containing	9(0.50)	9(100)	--	9(100)	--	6(67)	0.48
Other	8(0.41)	8(100)	--	8(100)	--	5(63)	1.00

^aThe proportion of close contacts with L TBI that was recommended for therapy out of all those identified with L TBI (TLTBI: Treatment of latent tuberculosis infection)

- ^b The proportion of close contacts with LTBI that initiated therapy out of all those who were recommended for LTBI treatment
- ^c The proportion of close contacts with LTBI that completed therapy out of all those who initiated LTBI treatment.
- ^d Heavy alcohol use was defined as ≥ 12 beers per week, ≥ 2 bottles of wine per week, and/or ≥ 2 pints of hard liquor per week
- ^e All INH-RPT patients were part of an ongoing clinical trial, and received DOT as part of the trial.

INH: isoniazid; RIF: rifampin; RIPE: Four drug therapy with rifampin, isoniazid, pyrazinamide, ethambutol; PZA: pyrazinamide; EMB: ethambutol; RPT: rifapentine; FQ: fluoroquinolone

Table 3

Factors associated with LTBI treatment completion

	Completed N=585 (%)	Not Completed N=362 (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Mean age in years (SD)	32.59 (17.94)	33.29 (17.89)	1.0 (0.99–1.01)	0.56	---	---
Male	334 (57)	219 (61)	0.87 (0.67–1.14)	0.30	---	---
Race/ethnicity						
Black	241 (52)	189 (41)	0.64 (0.49–0.84)	0.001	0.97 (0.66–1.43)	0.88
Non-black	343 (48)	173 (59)	ref	n/a	ref	n/a
HIV positive	1 (0.17)	1 (0.28)	0.62 (0.04–9.91)	0.73	---	---
Heavy alcohol use [†]	48 (8)	42 (12)	0.68 (0.44–1.05)	0.08	1.09 (0.63–1.90)	0.76
Illicit drug use	32 (6)	27 (8)	0.72 (0.42–1.23)	0.23	---	---
Smoked (last 6 months)	116 (20)	90 (25)	0.75 (0.55–1.02)	0.07	0.72 (0.48–1.06)	0.10
Site						
1	31 (5)	111 (31)	0.13 (0.08–0.21)	<0.001	0.15 (0.09–0.26)	<0.0001
2	239 (41)	111 (31)	ref	n/a	ref	n/a
3	71 (12)	42 (12)	0.79 (0.50–1.22)	0.28	0.87 (0.50–1.52)	0.62
4	71 (12)	20 (6)	1.65 (0.96–2.84)	0.07	3.26 (1.58–6.75)	0.001
5	58 (10)	26 (7)	1.04 (0.62–1.73)	0.89	0.90 (0.48–1.70)	0.75
6	42 (7)	6 (2)	3.25 (1.34–7.87)	0.009	3.00 (1.15–7.82)	0.02
7	8 (1)	9 (2)	0.41 (0.16–1.10)	0.08	0.58 (0.20–1.69)	0.32
8	60 (10)	37 (10)	0.75 (0.47–1.20)	0.23	0.78 (0.48–1.29)	0.34
Birth Place						
U.S. or Canada	265 (45)	187 (52)	ref	n/a	ref	n/a
Foreign born	318 (54)	172 (48)	1.31 (1.00–1.70)	0.05	1.04 (0.69–1.56)	0.87
Unknown	2 (0.34)	3 (0.83)	0.47 (0.08–2.84)	0.41		
Interviewing setting						
TB clinic	216 (39)	111 (33)	ref	n/a	ref	n/a
Healthcare setting	24 (4)	9 (3)	1.37 (0.62–3.05)	0.44	1.34 (0.53–3.37)	0.53
Home	250 (45)	166 (49)	0.77 (0.57–1.05)	0.10	0.96 (0.67–1.39)	0.84

	Completed N=585 (%)	Not Completed N=362 (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Other interview places	61 (11)	54 (16)	0.58 (0.38–0.89)	0.01	0.43 (0.23–0.78)	0.005
Case smear positive	521 (89)	333 (92)	0.71 (0.45–1.12)	0.14	1.0 (0.59–1.70)	1.00
Skin test size						
5–9	39 (6.7)	14 (3.6)	ref	n/a	ref	n/a
10–19	265 (46.2)	184 (52.7)	0.51 (0.27–0.97)	0.04	0.53 (0.25–1.10)	0.09
>=20	199 (33.9)	107 (29.2)	0.67 (0.35–1.29)	0.23	0.64 (0.30–1.36)	0.24
Unknown	82 (13.2)	57 (14.5)	0.52 (0.26–1.04)	0.06	0.47 (0.21–1.05)	0.06
Skin test status						
TST converter	81 (14)	58 (16)	ref	n/a	---	---
Initial TST positive	504 (86)	304 (84)	1.19 (0.82–1.71)	0.36	---	---
LTBI regimen ²						
INH	456 (79)	312 (87)	ref	n/a	ref	n/a
Non-INH	70 (12)	27 (8)	1.77 (1.11–2.83)	0.02	1.64 (1.07–2.52)	0.02
RIF	25 (4)	9 (3)	1.90 (0.88–4.13)	0.10		
INH/RIF	15 (3)	1 (0)	10.26 (1.35–78.06)	0.02		
RIPE	3 (1)	4 (1)	0.51 (0.11–2.31)	0.38		
RIF/PZA	6 (1)	2 (1)	2.05 (0.41–10.24)	0.38		
FQ-containing	5 (1)	3 (1)	1.14 (0.27–4.81)	0.86		
Other						
	70 (12)	27 (8)	1.77 (1.11–2.83)	0.02		
	25 (4)	9 (3)	1.90 (0.88–4.13)	0.10		
	15 (3)	1 (0)	10.26 (1.35–78.06)	0.02		
	3 (1)	4 (1)	0.51 (0.11–2.31)	0.38		
	6 (1)	2 (1)	2.05 (0.41–10.24)	0.38		
	5 (1)	3 (1)	1.14 (0.27–4.81)	0.86		

¹ Heavy alcohol use: defined as ≥ 12 beers per week, ≥ 2 bottles of wine per week, and/or ≥ 2 pints of hard liquor per week

² LTBI regimens other than INH mono-therapy were combined into the group “Non-INH” for the multivariate analysis. Persons taking INH/RPT were excluded from this table.

TST: tuberculin skin test; INH: isoniazid; RIF: rifampin; PZA: pyrazinamide; EMB: ethambutol; RPT: rifapentine; FQ: fluoroquinolone

Table 4

Incidence of active TB in close contacts with LTBI treated with isoniazid (INH)

Duration of INH treatment	Number of persons treated	TB cases	Person-years follow-up	TB cases/100,000 person-years (95% CI)	p-value ²
<6 months ¹	191	9	1136.4	792 (4.2–15.0)	ref
6 months	482	2	3009.4	66 (0.64–0.68)	<0.001
Unknown duration	134	3	903.3	332 (1.1–9.7)	0.18

¹ Median duration of treatment 2 months (IQR, 1–3)² p-value for the comparison of TB incidence rates between <6 months of isoniazid and all other durations.