Published in final edited form as:

Int J Tuberc Lung Dis. 2011 July ; 15(7): 906–911. doi:10.5588/ijtld.10.0448.

Chronic lung disease and HIV infection are risk factors for recurrent tuberculosis in a low-incidence setting

A. C. Pettit^{*}, L. A. Kaltenbach[†], F. Maruri^{*}, J. Cummins[‡], T. R. Smith[‡], J. V. Warkentin[‡], M. R. Griffin^{§,¶}, and T. R. Sterling^{*,#}

^{*}Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

[†]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina

[‡]Tennessee Department of Health, Nashville, Tennessee

[§]Department of Preventive Medicine and Center for Education and Research on Therapeutics, Vanderbilt University School of Medicine and the Mid-South Geriatric Research Education and Clinical Center, VA Tennessee Valley Health Care System, Nashville, Tennessee

[¶]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[#]Center for Health Services Research, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Abstract

SETTING—Programmatic data from the United States on tuberculosis (TB) recurrence are limited.

OBJECTIVES—To determine the TB recurrence rate and to determine if chronic lung disease (CLD) and human immunodeficiency virus (HIV) infection are risk factors for recurrence in this population.

DESIGN—Nested case-control study among TB cases reported to the Tennessee Department of Health between 1 January 2000 and 31 December 2006. Time at risk for recurrence was through 31 December 2007. Multiple imputation accounted for missing data.

RESULTS—Of 1431 TB cases, 20 cases recurred (1.4%, 95% CI 0.9–2.1). Median time at risk for recurrence was 4.5 years (interquartile range 2.7–6.1). Initial and recurrent *Mycobacterium tuberculosis* isolates were available for genotyping for 15 patients; 12 were consistent with relapse (0.8%, 95% CI 0.4–1.5) and three with re-infection (0.2%, 95% CI 0.04–0.6). HIV infection (OR 5.01, $P = 0.04$) and CLD (OR 5.28, $P = 0.03$) were independently associated with recurrent TB, after adjusting for a disease risk score. HIV infection was a risk factor for TB re-infection ($P < 0.001$).

CONCLUSIONS—In this low-incidence US population, the TB recurrence rate was low, but CLD and HIV were independent risk factors for recurrence. HIV infection was also a risk factor for TB re-infection.

© 2011 The Union

Correspondence to: April C Pettit, Vanderbilt University Medical Center, 1161 21st Avenue South, A2209 Medical Center North, Nashville, TN 37232-2582, USA. Tel: (+1) 615 322 0574. Fax: (+1) 615 343 6160. april.pettit@vanderbilt.edu.

These results were presented in part at the 2009 American Thoracic Society International Conference: 15–20 May 2009, San Diego, California, Abstract #3676.

Keywords

tuberculosis; recurrence; relapse; re-infection; human immunodeficiency virus infection

Recurrent tuberculosis (TB) is due to exogenous re-infection with a new *Mycobacterium tuberculosis* strain or relapse with the initial strain. Genotyping can distinguish between genotypically identical (relapse) and dissimilar (re-infection) strains. In high TB incidence areas, recurrences are likely due to re-infection (assuming treatment guideline adherence and subsequent low relapse rates). However, in low-incidence areas, recurrences are likely due to relapse, provided infection control is adequate.¹ Recurrent TB has been associated with treatment failure,² drug resistance,^{3–5} and more complicated and expensive treatment regimens. Effectiveness of TB control programs is assessed in part by TB recurrence rates; however, programmatic data from the United States are limited.^{6–8}

TB relapse rates vary from 2% to 6%,^{9–11} but are higher without appropriate treatment dosing,¹² rifamycin-based therapy,^{13–15} or directly observed therapy (DOT).¹⁶ In TB Trials Consortium (TBTC) Study 22, non-Hispanic white race, low body weight, bilateral pulmonary or cavitary disease and positive sputum cultures after 2 months of treatment were all independent predictors of relapse.^{7,17}

Chronic lung disease (CLD), including chronic obstructive pulmonary disease (COPD),^{18–20} asthma,²¹ and interstitial lung disease (particularly silicosis),²² are risk factors for developing TB, but have not been evaluated as risk factors for recurrence. In high TB incidence countries, human immunodeficiency virus (HIV) infection is a risk factor for TB re-infection.^{23–25} This association has not been shown in low-incidence areas, possibly due to lower likelihood of repeat exposure.²⁶ Previous studies report conflicting results regarding HIV infection as a risk factor for TB relapse.^{8,26}

TB relapse rates are used to determine optimal treatment duration, with desired rates of <2–5%. National and international guidelines for treatment of drug-susceptible TB recommend a 6-month rifamycin-based regimen.^{27,28} In the United States, treatment is extended to 9 months in patients with cavitary pulmonary TB and a positive sputum culture after 2 months or silicotuberculosis. The optimal treatment duration in HIV-infected persons is unclear, although current recommendations are for the same duration as non-HIV-infected persons, with possible extension if clinical response is slow or suboptimal. Treatment duration is not extended for patients with CLD not due to silicosis.

METHODS

Patient population

We conducted a nested case-control study among drug-susceptible TB cases reported to the Tennessee Department of Health from 1 January 2000 to 31 December 2006. Time at risk for recurrence was through 31 December 2007. Patients were excluded if they moved, died or were lost to follow-up during TB treatment, did not receive isoniazid, a rifamycin and pyrazinamide (HRZ), had drug-resistant disease, had central nervous system (CNS) or bone/joint disease, or did not complete therapy.

This study was approved by the Vanderbilt University, Tennessee Department of Health, and Metro Public Health Department Institutional Review Boards.

Study definitions

Time at risk for recurrence began at completion of therapy and ended at initiation of therapy for recurrence or at the end of the study period (31 December 2007). Patients were assumed not to have moved to another state or to have died during time at risk. DOT is mandated in the State of Tennessee.

TB cases were defined according to Centers for Disease Control and Prevention (CDC) guidelines.²⁹ Initial cases were identified using the Tuberculosis Information Management System (TIMS). Recurrent TB was defined as re-initiation of therapy for a diagnosis of TB following an adequate response to a completed course of anti-tuberculosis treatment. In TIMS, a recurrent case is counted separately if it occurred >12 months following completion of therapy; therefore, chart review was performed for all persons treated for >12 months. An adequate response was defined as conversion of cultures to negative for pulmonary disease and an appropriate clinical response. Therapy was considered complete if the reason for stopping therapy in TIMS was due to successful completion of the prescribed course of therapy.

Four controls per case were randomly selected from those without TB recurrence and individually matched by age $\pm$ 10 years, TB diagnosed before/after 20 June 2003, and health department region.³⁰ Patients were matched by diagnosis date before/after 20 June 2003 to reflect changes in treatment guidelines.²⁷

Demographic and laboratory data were obtained via TIMS. Charts were reviewed using a standardized abstraction form to gather data not available in TIMS (bilateral disease, height, weight, CLD, tobacco use). A patient was noted to have CLD if he/she reported being diagnosed with COPD ($n = 11$), asthma ($n = 3$), interstitial lung disease ($n = 1$) or pulmonary sarcoidosis ($n = 1$). Tobacco use was defined as any cigarette smoking at the time of TB diagnosis.

Laboratory methods

Prior to the CDC TB Genotyping Program, restriction fragment length polymorphism (RFLP) was performed by the CDC,³¹ with additional genotyping (spoligotyping and mycobacterial interspersed repetitive unit [MIRU]) performed for cases with <6 bands. Following this, spoligotyping and MIRU typing were performed by the Michigan Department of Community Health.³² Isolates were considered identical if they differed by no more than one band on RFLP and if they matched completely on spoligotyping/MIRU. Identical results were considered to be due to relapse and dissimilar results due to re-infection.

Statistical analysis

Statistical analyses were conducted using STATA IC version 10.1 (Stata Corp, College Station, TX, USA) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Fisher's exact and Wilcoxon rank-sum tests compared categorical and continuous variables, respectively. The odds ratio (OR) for TB recurrence was determined using conditional logistic regression. All P values were two-sided and were considered statistically significant if <0.05 .

Multiple imputation was used to impute missing height ($n = 29$) and tobacco use ($n = 4$).³³ Height was imputed using sex, age, weight and an interaction term between sex and weight. Tobacco use was imputed using all the variables for height plus HIV infection status, homelessness and CLD.

Given the low event rate, a disease risk score was estimated for each patient^{34,35} using a conditional logistic regression model relating TB recurrence to all other variables in the model on the subset of unexposed patients. Tobacco use was excluded from the disease risk score due to collinearity with CLD. Variables were chosen for the adjusted analysis if they were significant in the unadjusted analysis, significant in previous studies, or clinically important.

RESULTS

Study population baseline characteristics

From 1 January 2000 to 31 December 2006, 1999 TB cases were reported to TDOH. Patients were excluded if they moved ($n = 8$), died ($n = 200$) or were lost to follow-up during treatment ($n = 47$), did not initiate HRZ ($n = 191$), had drug-resistant disease ($n = 61$), had CNS or bone/joint disease ($n = 89$) or did not complete therapy ($n = 61$). Of 1431 eligible TB cases, 20 developed recurrent TB during their time at risk. Characteristics of the study population are listed in Table 1.

All persons with recurrent TB had HIV results available at baseline, and HIV status did not change for those who were non-infected. The characteristics of persons with missing and non-missing HIV status are listed in Table 2. Analyses were conducted with the HIV-unknown cohort included as non-HIV-infected and then excluded, and there were no significant changes (Table 3). Persons with unknown HIV results were therefore considered to be non-infected.

Cohort results

Each patient had at least 1 year at risk for recurrence (median = 4.5 years, interquartile range [IQR] 2.7–6.1). TB recurred in 20/1431 (1.4%, 95% confidence interval [CI] 0.9–2.1). TB relapse occurred in 12/1431 (0.8%, 95%CI 0.4–1.5); the median time to TB relapse was 412 days (IQR 203–885). TB re-infection occurred in 3/1431 (0.2%, 95%CI 0.04–0.6); the time to TB re-infection was 112, 158 and 218 days, respectively. All three cases of TB re-infection occurred among HIV-infected, homeless men who used tobacco. TB recurrence and re-infection rates were significantly higher among HIV-infected persons; however, the relapse rate did not differ significantly based on HIV infection status (Table 3). Five recurrent cases did not undergo genotyping because the initial ($n = 1$) or recurrent ($n = 3$) case was culture-negative or because the initial isolate was missing ($n = 1$). Sensitivity analyses were performed in which all missing cases were assumed to be relapses or re-infections, and this did not alter the results (Table 4). Specific genotyping information for each case is listed in Table 5.

Case-control results

Each case was matched with four controls, except for two cases for which only three matched controls were identified. CLD (OR 5.28, 95%CI 1.16–24.04, $P = 0.03$), HIV infection (OR 5.01, 95%CI 1.07–23.39, $P = 0.04$), and non-Hispanic, white race (OR 4.62, 95%CI 1.28–16.68, $P = 0.02$) increased the TB recurrence risk after controlling for the disease risk score (Table 6). An adjusted analysis was not performed for the remaining variables due to requirements of the disease risk score or assumptions of the conditional logistic regression model. These analyses were not repeated for relapse ($n = 12$) or re-infection ($n = 3$) because the model would have been over-fit due to low event rates.

DISCUSSION

TB recurrence risk in this cohort was low (1.4%, 95%CI 0.9–2.1), suggesting that the programmatic treatment approach was effective. This rate is lower than those reported from cohorts in New York City (123/4571, 2.7%, 95%CI 2.2–3.2),⁶ Baltimore (14/407, 3.4%, 95%CI 1.9–5.7),⁷ and San Francisco (16/700, 2.3%, 95%CI 1.3–3.7).⁸ All three studies were observational, and all patients had >1 year at risk for TB recurrence; however, in San Francisco patients were actively assessed for TB recurrence at 6 and 12 months following completion of therapy. Advances in TB diagnostics, control, and treatment may have led to the lower recurrence rate in this contemporary cohort.

Among the study population, patients with recurrent TB were more likely to have cavitary disease and positive cultures after 2 months of therapy. In the unadjusted and adjusted case-control analysis, non-Hispanic white race was associated with TB recurrence. These findings are consistent with those from TBTC Study 22.^{7,17}

CLD has been associated with TB disease in other settings.^{18–22} We found an increased risk of TB recurrence with CLD (OR 5.28, 95%CI 1.16–24.04, $P = 0.03$). To our knowledge, this is the first study to demonstrate this association. This highlights the importance of efforts aimed at prevention of CLD, such as smoking cessation, and close monitoring of these patients for an appropriate response to therapy.

TB recurrence was significantly higher among HIV-infected persons (OR 5.01, 95%CI 1.07–23.39, $P = 0.04$). Observational cohorts from New York City, Baltimore and San Francisco all found that HIV-infected persons were more likely to develop TB recurrence.^{6–8} In contrast, combined data from TBTC Studies 22 and 23 found no difference in TB recurrence based on HIV status.²⁶ It is possible that observational studies, in contrast to randomized controlled trials, have not controlled for confounders related to TB recurrence and HIV infection.

All three cases of re-infection occurred among HIV-infected, homeless men who used tobacco. Given the low incidence of TB in Tennessee (approximately 5/100 000),³⁶ the possibility of exposure to another strain is lower than the probability of relapse. Therefore, the higher rate of re-infection among HIV-infected persons may be related to an increase in exposure and subsequent increased risk for progression to disease. To our knowledge, our study is the first to show a difference in re-infection rates based on HIV infection status in a US population.

TB relapse rates were not significantly different based on HIV infection status. Combined data from TBTC Studies 22 and 23 found no difference in relapse rates between HIV-infected and non-HIV-infected persons.²⁶ In contrast, in San Francisco, the rate of TB relapse was higher in non-HIV-infected persons.⁸ Currently, no recommendation to extend therapy among all HIV-infected persons has yet been made.³⁷

The median time to TB relapse was 412 days (IQR 203–885 days); the two HIV-infected persons had the shortest time to relapse, at 151 and 181 days. In our study, one (8%) of the relapses occurred within 6 months and 6 (50%) within 12 months of treatment completion. Jasmer et al. reported that 51 (71%) of their relapses occurred within 6 months and 64 (89%) within 12 months. Similarly, Nunn et al. reported that 447 (78%) relapses occurred within 6 months and 525 (91%) within 12 months.³⁸ These data suggest that 2 years of follow-up after treatment completion in clinical trials would likely capture most relapses. However, the diagnosis of TB relapse may take longer in a programmatic setting outside the structure of a clinical trial.

All three cases of re-infection occurred within 12 months, suggesting that re-exposure and progression to active disease was more likely to occur in the first year following completion of treatment. Furthermore, the epidemiologic characteristics of persons with TB re-infection highlight the importance of contact investigation and social network analysis. Other studies have not reported time to diagnosis of TB re-infection.

The main limitation of this study is that the number of recurrent TB cases was low. Our ascertainment of recurrent TB was complete based on available data. Twelve cases were identified by a second entry in TIMS; the remainder ($n = 8$) were identified by chart review. While it is possible that some recurrent cases were not identified and misclassified as controls, this would seem unlikely given that TB is a reportable disease and that clinicians would likely seek expertise when treating recurrent TB. If an initial TB case treated in Tennessee had TB recurrence treated in another state, the recurrent case would not have been captured; however, we did not have access to TIMS data from other states. Regardless, this type of misclassification would bias towards the null hypothesis. Alternatively, it is possible that the low rate of recurrence in this population reflects a high rate of early initiation and completion of therapy. During the study period, 97% of TB cases completed therapy (unpublished data).

A second limitation is in the interpretation of genotyping results. It is possible that some cases of relapse are actually cases of re-infection with the same strain of *M. tuberculosis*. Conversely, it is possible that some cases of re-infection are actually cases of relapse. However, genotypic data suggest that the genetic distance between paired isolates for re-infection cases is great, making the possibility that they actually represent relapse unlikely (Table 5).

Finally, two potential confounders for HIV-infected patients are worth noting. First, CD4+ lymphocyte count and antiretroviral therapy use were not controlled for because this information was not routinely recorded in TB clinic charts. Second, we could not control for extension of therapy in HIV-infected persons with a slow or suboptimal response. HIV-infected persons took longer to complete therapy than non-HIV-infected persons (39 weeks, IQR 30–49 vs. 30 weeks, IQR 27–40, $P < 0.001$). It is unclear if this reflects a longer planned course of therapy, more non-adherence or both.

In conclusion, this study shows that the rate of recurrent TB in this cohort was low. To our knowledge, this is the first study to show that CLD is a risk factor for TB recurrence. Furthermore, we have shown that HIV infection is a risk factor for TB recurrence due to re-infection in a low-incidence setting. However, further studies in larger populations are needed to determine if it is also a risk factor for TB relapse. Lastly, this study illustrates the importance of obtaining genotyping to determine the cause of recurrence. While the TB incidence in this population is low and most recurrences are likely due to relapse, re-infection remains a possible cause of recurrent disease.

Acknowledgments

The authors acknowledge the students and faculty of the Vanderbilt University Masters of Public Health Program for their thoughtful input in the design and analysis of this study. The authors would also like to thank the anonymous reviewers whose thoughtful comments significantly strengthened the manuscript. This research was supported by the National Institutes of Health: NIH 2 T32 AI07474-13 (ACP) and K24 AI065298 (TRS).

References

1. Chiang CY, Riley LW. Exogenous reinfection in tuberculosis. *Lancet Infect Dis*. 2005; 5:629–636. [PubMed: 16183517]

2. World Health Organization. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO; 2009. Global tuberculosis control: epidemiology, strategy, financing.
3. Johnson J, Kagal A, Bharadwaj R. Factors associated with drug resistance in pulmonary tuberculosis. *Indian J Chest Dis Allied Sci.* 2003; 45:105–109. [PubMed: 12715932]
4. Garcia-Garcia ML, Ponce de LA, Jimenez-Corona ME, et al. Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. *Arch Intern Med.* 2000; 160:630–636. [PubMed: 10724048]
5. Fujiwara PI, Cook SV, Rutherford CM, et al. A continuing survey of drug-resistant tuberculosis, New York City, April 1994. *Arch Intern Med.* 1997; 157:531–536. [PubMed: 9066457]
6. Driver CR, Munsiff SS, Li J, Kundamal N, Osahan SS. Relapse in persons treated for drug-susceptible tuberculosis in a population with high coinfection with human immunodeficiency virus in New York City. *Clin Infect Dis.* 2001; 33:1762–1769. [PubMed: 11595988]
7. Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis.* 2004; 38:731–736. [PubMed: 14986259]
8. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med.* 2007; 175:1199–1206. [PubMed: 17290042]
9. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Hong Kong Chest Service/British Medical Research Council. *Am Rev Respir Dis.* 1987; 136:1339–1342. [PubMed: 2891333]
10. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. *Am Rev Respir Dis.* 1991; 143(4 Pt 1):700–706. [PubMed: 1901199]
11. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. *Ann Intern Med.* 1990; 112:397–406. [PubMed: 2155569]
12. Chang KC, Leung CC, Yew WW, Chan SL, Tam CM. Dosing schedules of 6-month regimens and relapse for pulmonary tuberculosis. *Am J Respir Crit Care Med.* 2006; 174:1153–1158. [PubMed: 16908866]
13. Controlled clinical trial comparing a 6-month and a 12-month regimen in the treatment of pulmonary tuberculosis in the Algerian Sahara. Algerian Working Group/British Medical Research Council cooperative study. *Am Rev Respir Dis.* 1984; 129:921–928. [PubMed: 6375490]
14. Short-course chemotherapy in pulmonary tuberculosis. A controlled trial by the British Thoracic and Tuberculosis Association. *Lancet.* 1975; 1:119–124. [PubMed: 46047]
15. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. *Lancet.* 1972; 1:1079–1085. [PubMed: 4112569]
16. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med.* 1994; 330:1179–1184. [PubMed: 8139628]
17. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet.* 2002; 360:528–534. [PubMed: 12241657]
18. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum.* 2006; 55:19–26. [PubMed: 16463407]
19. Inghammar M, Ekblom A, Engstrom G, et al. COPD and the risk of tuberculosis—a population-based cohort study. *PLoS One.* 2010; 5:e10138. [PubMed: 20405056]
20. Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. *Chest.* 2008; 134:46–53. [PubMed: 18403661]
21. Lienhardt C, Fielding K, Sillah JS, et al. Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa. *Int J Epidemiol.* 2005; 34:914–923. [PubMed: 15914505]

22. Corbett EL, Churchyard GJ, Clayton TC, et al. HIV infection and silicosis: the impact of two potent risk factors on the incidence of mycobacterial disease in South African miners. *AIDS*. 2000; 14:2759–2768. [PubMed: 11125895]
23. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. 2001; 358:1687–1693. [PubMed: 11728545]
24. Crampin AC, Mwaungulu JN, Mwaungulu FD, et al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi. *AIDS*. 2010; 24:417–426. [PubMed: 20042847]
25. Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. *J Infect Dis*. 2010; 201:691–703. [PubMed: 20121433]
26. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med*. 2004; 170:1360–1366. [PubMed: 15477492]
27. American Thoracic Society. Treatment of tuberculosis. *Morb Mortal Wkly Rep*. 2003; 52(RR-11): 735–739.
28. World Health Organization. Treatment of tuberculosis guidelines. 4th ed.. Geneva, Switzerland: WHO; 2009.
29. Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recomm Rep*. 1997; 46(RR-10):1–55.
30. Bergstralh, EKJ. Locally written SAS macros. Rochester, MN, USA: Mayo Clinic Division of Biomedical Statistics and Informatics; 2003.
<http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm>
31. Van Embden JD, Cave MD, Crawford JT, et al. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: recommendations for a standardized methodology. *J Clin Microbiol*. 1993; 31:406–409. [PubMed: 8381814]
32. Mazars E, Lesjean S, Banuls AL, et al. High-resolution minisatellite-based typing as a portable approach to global analysis of *Mycobacterium tuberculosis* molecular epidemiology. *Proc Natl Acad Sci U S A*. 2001; 98:1901–1906. [PubMed: 11172048]
33. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999; 18:681–694. [PubMed: 10204197]
34. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res*. 2009; 18:67–80. [PubMed: 18562398]
35. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment for multiple cardiovascular risk factors using a summary risk score. *Epidemiology*. 2008; 19:30–37. [PubMed: 18091000]
36. Holt, E. Epidemiologic profile of tuberculosis in Tennessee, 2005. Nashville, TN, USA: Tennessee Department of Health, Tuberculosis Elimination Program; 2006.
37. Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2010; 50:1288–1299. [PubMed: 20353364]
38. Nunn AJ, Phillips PP, Mitchison DA. Timing of relapse in short-course chemotherapy trials for tuberculosis. *Int J Tuberc Lung Dis*. 2010; 14:241–242. [PubMed: 20074418]

Table 1

Baseline demographic and clinical characteristics of the study population

Characteristic	Persons without TB recurrence (n = 1411) n (%)	Persons with TB recurrence (n = 20) n (%)	P value *
Age at report date, years, median [IQR]	46 [30–62]	39 [35–60]	0.56
Male sex	934 (66)	18 (90)	0.03
White race	635 (45)	12 (60)	0.26
Foreign-born	267 (19)	0	0.04
Homeless	144 (10)	4 (20)	0.15
HIV infection	115 (8)	6 (30)	0.005
Alcohol use	302 (21)	8 (40)	0.06
IDU	32 (2)	0	1.00
Non-IDU	157 (11)	2 (10)	1.00
Extra-pulmonary disease	329 (23)	6 (30)	0.44
Cavitary disease	412 (29)	11 (55)	0.02
Smear-positive	771 (56)	15 (75)	0.07
Culture-positive	1084 (77)	19 (95)	0.06
Culture-positive at 2 months	298 (21)	8 (40)	0.05
Cavitary disease and culture positive at 2 months	169 (12)	7 (35)	0.007
Directly observed therapy	1372 (97)	19 (95)	0.44
Time to completion of therapy, weeks, median [IQR]	30 [27–41]	39 [27–46]	0.45

* Fisher's exact and Wilcoxon rank sum were used to compare categorical and continuous variables, respectively.

TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; IDU = injecting drug use.

Table 2

Characteristics of persons with missing and non-missing HIV results

Characteristic	HIV result non-missing (<i>n</i> = 1100) <i>n</i> (%)	HIV result missing (<i>n</i> = 331) <i>n</i> (%)	<i>P</i> value*
Male sex	773 (70)	179 (54)	<0.001
White race	468 (43)	179 (54)	<0.001
Age at report date, years, median [IQR]	44 [30–57]	58 [30–76]	<0.001
Foreign-born	227 (21)	40 (12)	<0.001
Homeless	136 (12)	12 (4)	<0.001
IDU	31 (3)	1 (0.3)	0.005
Non-IDU	155 (14)	4 (1)	<0.001
Alcohol use	280 (25)	30 (9)	<0.001

* Fisher's exact and Wilcoxon rank sum tests were used to compare categorical and continuous variables, respectively.

HIV = human immunodeficiency virus; IQR = interquartile range; IDU = injecting drug use.

Table 3

TB incidence rates by HIV infection status

	HIV-infected (n = 121) n (%)	Non-HIV-infected or HIV status unknown (n = 1310) n (%)	P value*
Recurrences	6 (5.0)	14 (1.1)	0.005
Re-infections	3 (2.5)	0	0.001
Relapses	2 (1.7)	10 (0.8)	0.27
		Non-HIV-infected (n = 979)	
Recurrences	6 (5.0)	14 (1.4)	0.02
Re-infections	3 (2.5)	0	0.001
Relapses	2 (1.7)	10 (1.0)	0.63

* Fisher's exact test was used to compare categorical variables.

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 4

Sensitivity analysis of recurrent TB with unknown genotype results

	HIV-infected (<i>n</i> = 121) <i>n</i> (%)	Non-HIV-infected or HIV status unknown (<i>n</i> = 1310) <i>n</i> (%)	<i>P</i> value *
Assumed re-infections	4 (3.3)	4 (0.3)	0.003
Assumed relapses	3 (2.5)	14 (1.1)	0.17

* Fisher's exact test was used to compare categorical variables.

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 5

Genotyping results

Re-infection cases	RFLP	Spoligotyping	MIRU
1-Initial	3219245 (8 bands)		
1-Recurrent	3212615 (20 bands)		
2-Initial		777777777760760	223326153323
2-Recurrent		000000000003771	222325173543
3-Initial		700076760003771	No result
3-Recurrent		777777777760601	223315153324
Relapse cases			
1		776037777760771	223125163324
2		777777777760760	223326153323
3		000000000003771	222325173543
4		000000000003771	223325144523
5		777760016760601	224225153323
6		777767777760771	225325123324
7		776037777760771	223125163324
8	997505 (3 bands)	700076760000011	224325153322
9		700076777760700	224425143324
10		700076760000011	224325153322
11		760001400000171	224326133224
12	337025453 (2 bands)	777767777760601	224325153323

RFLP = restriction fragment length polymorphism; MIRU = mycobacterial interspersed repetitive unit.

Table 6

Conditional logistic regression models for tuberculosis recurrence

Characteristic	Cases (n = 20) n (%)	Controls (n = 78) n (%)	Unadjusted		Adjusted*	
			Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
HIV infection	6 (30)	12 (15)	2.67 (0.77–9.18)	0.12	5.01 (1.07–23.39)	0.04
Chronic lung disease	8 (40)	13 (17)	4.01 (1.15–13.94)	0.03	5.28 (1.16–24.04)	0.03
White race	12 (60)	28 (40)	4.01 (1.15–14.00)	0.03	4.62 (1.28–16.68)	0.02
Male sex	18 (90)	47 (60)	6.47 (1.39–30.26)	0.02		
Body mass index, kg/m ² , median [IQR]	20.0 [18.7–22.1]	21.3 [18.8–24.4]	0.94 [0.83–1.07]	0.38		
Tobacco use	17 (85)	39 (50)	16.85 (2.06–137.76)	0.008		
Cavitary or bilateral disease and culture positive at 2 months	13 (65)	46 (59)	1.33 (0.47–3.71)	0.59		
Time to completion of therapy, weeks, median [IQR]	39 [27–46]	35 [27–41]	1.00 [0.96–1.03]	0.78		

* All covariates in the table were included in the disease risk score except for the exposure of interest and tobacco use, due to collinearity with chronic lung disease.

CI = confidence interval; HIV = human immunodeficiency virus.