



Factors Associated With Latent Tuberculosis Infection Treatment Failure Among Patients With Commercial Health Insurance—United States, 2005–2016

Shareen A. Iqbal, PhD, MPH,

Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention, Atlanta, Georgia

Cheryl J. Isenhour, DVM, MPH,

Division of Health Informatics and Surveillance, Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, Georgia.

Gerald Mazurek, MD,

Division of Tuberculosis Elimination, NCHHSTP, Centers for Disease Control and Prevention, Atlanta, Georgia.

Adam J. Langer, DVM, MPH,

Division of Tuberculosis Elimination, NCHHSTP, Centers for Disease Control and Prevention, Atlanta, Georgia.

Man-Huei Chang, MPH,

Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention, Atlanta, Georgia.

Benedict I. Truman, MD, MPH

Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention, Atlanta, Georgia.

Abstract

Context—Approximately 80% of US tuberculosis (TB) cases verified during 2015–2016 were attributed to untreated latent TB infection (LTBI). Identifying factors associated with LTBI treatment failure might improve treatment effectiveness.

Objective—To identify patients with indicators of isoniazid (INH) LTBI treatment initiation, completion, and failure.

Methods—We searched inpatient and outpatient claims for *International Classification of Diseases (Ninth and Tenth Revisions)*, National Drug, and *Current Procedural Terminology* codes.

Correspondence: Shareen A. Iqbal, PhD, MPH, Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Mailstop E-07, Atlanta, GA 30329 (kqj7@cdc.gov).

The authors have no nongovernmental sources of funding or conflicts of interest to declare for this research.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (<http://www.JPHMP.com>).

We defined treatment completion as 180 days or more of INH therapy during a 9-month period. We defined LTBI treatment failure as an active TB disease diagnosis more than 1 year after starting LTBI treatment among completers and used exact logistic regression to model possible differences between groups. Among treatment completers, we matched 1 patient who failed treatment with 2 control subjects and fit regression models with covariates documented on medical claims paid 6 months or less before INH treatment initiation.

Participants—Commercially insured US patients in a large commercial database with insurance claims paid during 2005–2016.

Main Outcome Measures—(1) Trends in treatment completion; (2) odds ratios (ORs) for factors associated with treatment completion and treatment failure.

Results—Of 21 510 persons who began LTBI therapy during 2005–2016, 10 725 (49.9%) completed therapy. Treatment noncompletion is associated with those younger than 45 years, living in the Northeast or South Census regions, and women. Among persons who completed treatment, 30 (0.3%) progressed to TB disease. Diagnoses of rheumatoid arthritis during the 6 months before treatment initiation and being aged 65 years or older (reference: ages 0–24 years) were significantly associated with INH LTBI treatment failure (adjusted exact OR = 5.1; 95% CI, 1.2–28.2; and adjusted exact OR = 5.1; 95% CI, 1.2–25.3, respectively).

Conclusion—Approximately 50% of persons completed INH LTBI therapy, and of those, treatment failure was associated with rheumatoid arthritis and persons 65 years or older among a cohort of US LTBI patients with commercial health insurance.

Keywords

administrative data; arthritis; claims data; epidemiology; failure; health service delivery; isoniazid; latent; latent tuberculosis infection; LTBI; medication adherence; *Mycobacterium tuberculosis* infection; public health practice; rheumatoid; treatment; treatment completion; treatment failures; tuberculosis infection

An estimated 12.4 million US residents have latent *Mycobacterium tuberculosis* infection (LTBI), with the majority of those persons being aged 25 to 64 years.¹ The prevalence of LTBI overall and by age group has remained steady since 1999–2000.² Approximately 5% to 10% of those with newly detected *M tuberculosis* infection will experience active tuberculosis (TB) caused by the bacterial reactivation during their lifetime.³ Approximately 80% of the 13777 cases of TB disease verified and genotyped in the United States during 2015–2016 were attributed to reactivation of LTBI acquired 2 years or more earlier.⁴

Isoniazid (INH) preventive therapy administered for 6 to 9 months has been a standard regimen for LTBI treatment and has been demonstrated to substantially reduce the risk for experiencing TB disease.⁵ Longitudinal studies have demonstrated INH effectiveness in preventing TB disease in the first 5 years after treatment initiation among persons who completed 6 months or more of INH therapy.^{6–8} Although lifetime risk for reactivation is low,³ clinical trials have demonstrated that persons with certain conditions (eg, HIV infection at the time of LTBI therapy initiation) have higher rates of TB disease.^{9,10} Prior studies regarding LTBI preventive therapy among US commercially insured persons have focused primarily on patient characteristics associated with the completion of LTBI

treatment but not on preexisting comorbidities associated with LTBI treatment failure (ie, TB disease after treatment completion).^{11,12}

We conducted this study to identify trends in LTBI treatment completion preexisting comorbidities recognized at the time of treatment initiation that are associated with LTBI treatment failure among a US cohort of commercially insured persons during 2005–2016.

Methods

Cohort selection and data source

Using methods previously developed for claims data,¹² we selected a cohort of persons who filled an INH prescription for possible LTBI from the IBM Watson Health MarketScan (IBM Corporation, Ann Arbor, Michigan) Commercial and Medicare Supplemental Research Databases. These databases contain health insurance claims data for persons with employer-sponsored private health insurance, their spouses, and their dependents, who lived throughout the United States. Medical claims, outpatient prescription drug claims, and individual-level enrollment data are linked by unique enrollee identification numbers, which facilitates longitudinal analyses.

Using outpatient pharmacy claims paid January 1, 2005, through December 31, 2016, we identified filled prescriptions for INH by National Drug Codes (NDCs). For each patient, we used the date on which the first prescription was filled for at least a 28-day supply as the INH treatment initiation index date. Patients had variable times for continuous enrollment, but all were required to be enrolled continuously for 6 months or more before and 12 months or more after the INH treatment initiation index date. We used the *Current Procedural Terminology (CPT)* codes,¹³ Healthcare Common Procedure Coding System (HCPC)¹⁴ codes, and the *International Classification of Diseases Clinical Modifications (Ninth and Tenth Revision)* diagnosis codes (*ICD-9-CM* and *ICD-10-CM*)¹⁵ to identify and exclude persons with evidence of INH-treated conditions other than LTBI during the 18-month period of continuous enrollment before and after the INH treatment initiation index date. These conditions include non-TB mycobacterial infection, multiple sclerosis, nystagmus, or tremor. We also identified and excluded patients with diagnosis codes associated with TB disease and patients with pharmacy claims for other drugs approved for treating TB disease, including rifampin, rifapentine, rifabutin, ethambutol, and pyrazinamide, during the 18 months of continuous enrollment before and after the index date. For a detailed description of the methods and the NDC, *ICD*, *CPT*, and HCPC codes used to select the LTBI cohort, readers should refer to Stockbridge et al.¹⁰ Because the files with pharmacy claims paid in 2016 were released to the CDC in 2017, close to 100% of the paid claims for pharmacy services were in the 2016 file analyzed.

Data analyses

Trends in LTBI treatment—We defined completion of LTBI treatment as having claims for filled prescriptions for 180 or more doses of INH received within 9 consecutive months. Completed treatments were then categorized as 9 to 12 months (ie, 270 doses in 12 consecutive months) and 6 to less than 9 months (ie, 180 doses in 6 to <9 months, but <270

doses in 12 months). The percentage of patients in the LTBI cohort who completed LTBI treatment with INH was calculated as the number of patients who completed INH treatment among those who met the LTBI cohort selection criteria.

We defined treatment failure as patients who completed treatment and had evidence of TB disease for more than 1 year after LTBI treatment initiation. Evidence of TB disease was defined as 1 inpatient claim or 2 outpatient claims on different service dates with *ICD* codes for TB disease, or 1 outpatient *ICD* code for 2 or more anti-TB drugs, including INH, rifampin, ethambutol, or pyrazinamide for 2 weeks or less after a TB disease-related *ICD* code. Patients who failed treatment had to have continuous enrollment up to the date of TB diagnosis.

Association between patient characteristics and incomplete treatment—We assessed the association between patient characteristics and treatment completion status. We considered patient demographics (eg, age, sex, US region, and TB diagnosis >1 year after treatment initiation) as possible confounders.

Association between patient characteristics and treatment failure—To assess the association between patient characteristics and a diagnosis of TB disease more than 1 year after treatment initiation, we restricted the analysis to patients who met our criteria for treatment completion. Covariates included age, sex, US region, and category of treatment duration.

Association between comorbidities and treatment failure—A matched case-control analysis—To identify risk factors associated with LTBI treatment failure among patients completing treatment, we conducted a matched case-control analysis of case-patients with an indication of LTBI treatment failure and control subjects without an indication of failure. A case was defined as completion of INH treatment and a patient claim for TB disease more than 1 year after treatment initiation. Two control subjects were matched with each case-patient from a sampling frame of potential control subjects by using probability sampling by age (± 5 years), sex, year of treatment initiation (or closest year of treatment initiation), INH treatment duration, and continuous enrollment. Control subjects had the same or shorter duration of INH treatment and the same or greater number of days of continuous enrollment. Of note, 2 case-patients had control subjects with a different year of treatment initiation because control subjects with the same year of treatment initiation were unavailable. The same control subject was not matched to different case-patients. All diagnostic codes listed for case-patients and control subjects during the 6 months before the INH treatment initiation index date were captured, and relevant codes were categorized into the following variables: diabetes, cancer, rheumatoid arthritis, renal insufficiency, excessive alcohol use, tobacco use, nontuberculous respiratory conditions, abnormal chest radiograph without a respiratory disorder, HIV/AIDS, prior TB, other immunocompromising conditions, and surgery (see Supplemental Digital Content Table 1, available at <http://links.lww.com/JPHMP/A611>). Among patients with rheumatoid arthritis included in the case-control analysis, we examined claims for anti-TNF- α therapy (see Supplemental Table 2, available at <http://links.lww.com/JPHMP/A611>) 6 months before treatment and during the treatment year.

Statistical analyses

We used Joinpoint regression (version 4.5.0.1; National Institutes of Health/National Cancer Institute, Bethesda, Maryland) from 2005 to 2015 to identify years at which statistically significant changes in the percentage of treatment completion occurred and to estimate the annual percentage change and corresponding 95% confidence interval (CI) for each trend segment in the model. We allowed for a maximum number of 3 Joinpoints. Wald's χ^2 2-tailed t test was used to determine statistical significance of the differences in population attributes between case-patients and control subjects. We excluded 2016 from the trend analysis because only 1 patient had initiated INH treatment.

We performed regression analyses with SAS (version 9.4; SAS Institute, Inc, Cary, North Carolina) by using the logistic procedure, and we set the level of significance at $P < .05$. We used logistic regression to create models to differentiate INH treatment completion status (completed or not completed). Because of small cell size, we used exact logistic regression for models differentiating between treatment failure and success. For the logistic adjusted analysis, we included all variables initially, conducted backward elimination, and excluded from the adjusted analysis subcategories of variables that had 1 or more cells for either outcome with no data. We used the likelihood ratio test as a goodness of fit between backward elimination iterations with $P < .05$.

We used exact logistic regression to estimate the odds ratios (ORs) for variables with treatment failure as the outcome. We included the variables associated with treatment failure with $P < .30$ in the multivariable analyses. Thus, we calculated the association between treatment failure and age, sex, census region, and year of INH treatment initiation. For our matched case-control exact logistic regression, we calculated the association between treatment failure and prior TB, rheumatoid arthritis, and non-TB respiratory diagnoses.

Results

Among 69285 enrollees treated with INH during 2005–2016, 29458 (43%) met the 18-month continuous enrollment requirement. As displayed in the Figure, after applying the additional exclusion criteria, the LTBI treatment initiation cohort included 21510 patients. Of these, 49.9% ($n = 10725$) completed 6 months or more of INH treatment.

Sample characteristics

Of the 21 510 patients included in the INH LTBI treatment cohort, the highest percentages were those who were aged 25 to 44 years ($n = 7411$; 34.5%), resided in the West census region ($n = 8939$; 41.6%), were women ($n = 12 180$; 56.6%), did not complete treatment ($n = 10 785$; 50.1%), and did not have a diagnosis of TB disease ($n = 21 436$; 99.7%) (Table 1). During 2005–2015 (2016 was excluded because only 1 patient had initiated INH treatment), the percentage of patients completing treatment increased, with an annual percentage change of 1.9% (95% CI, 1.0–2.8; $P < .05$).

Incomplete LTBI treatment

Of the 10785 noncompleters included in the LTBI treatment cohort, the highest percentage started treatment during 2009–2012 ($n = 5287$; 49.0%), were aged 25 to 44 years ($n = 4007$; 37.2%), resided in the West census region ($n = 4376$; 40.6%), and were women ($n = 6252$; 58.0%) (Table 2). After INH initiation, noncompleters had a median enrollment of 2.8 years (interquartile range [IQR]: 1.7–4.8 years) and a median time to TB disease of 1.8 years (IQR: 1.3–3.1) (Table 2; see Supplemental Digital Content Figure, available at <http://links.lww.com/JPHMP/A611>). Two patients who experienced TB disease for 1 year or more after INH initiation had gaps in continuous enrollment; 1 was a completer with a 13-day gap, and 1 was a noncompleter with a 146-day gap. Continuous enrollment for the 2 patients was calculated from INH LTBI treatment initiation to the first period of disenrollment.

Compared with patients who completed treatment, noncompleters had greater adjusted odds of beginning treatment during 2005–2012 (reference, 2013–2016), being 44 years or younger (reference, 65 years), residing in the Northeast or South census regions (reference, West), or being women (reference, men) (Table 2). Length of continuous enrollment and time to TB disease were similar, regardless of treatment completion.

LTBI treatment failure

Among patients who completed LTBI treatment ($n = 10\,725$), 0.3% ($n = 30$) had a diagnosis of TB disease 1 year or more after INH initiation. The greatest proportion of patients who failed treatment were aged 25 to 44 years and 45 to 64 years (for both age groups, $n = 10$; 33.3%), resided in the West census region ($n = 11$; 36.7%), were men ($n = 17$; 56.7%), and had initiated therapy in 2009–2012 ($n = 22$; 73.3%). In the adjusted analyses, patients who failed treatment had greater adjusted exact odds of beginning treatment in 2009–2012 (reference, 2013–2016) and being 65 years or older (reference, 0–24 years) compared with patients who had not failed therapy (Table 2).

Matched case-control study results

Case-patients and control subjects had no statistically significant differences before treatment initiation, except for rheumatoid arthritis (Table 3). In the adjusted analysis, rheumatoid arthritis and TB treatment failure had a matched association of exact OR = 5.1 (95% CI, 1.2–28.2).

We further investigated the characteristics of patients with an indication of rheumatoid arthritis. Among case-patients ($n = 9$), the majority were women ($n = 5$; 55.6%), aged 45 to 64 years ($n = 5$; 55.6%), started treatment in 2009–2012 ($n = 6$; 66.7%), and resided in the Midwest or South census regions (for both regions, $n = 4$; 44.4%) (Table 4). In comparison, among control subjects ($n = 7$), the majority were male ($n = 4$; 57.1%), aged 45 to 64 years ($n = 4$; 57.1%), started treatment in 2009–2012 ($n = 7$; 100.0%), and resided in the South census region ($n = 6$; 85.7%). Before INH initiation, 33.3% ($n = 3$) of case-patients and 14.3% ($n = 1$) of control subjects with rheumatoid arthritis had a prescription filled for anti-TNF- α therapy. During INH treatment, 44.4% ($n = 4$) of case-patients and 85.7% ($n = 6$) of control subjects had evidence of anti-TNF- α therapy.

Discussion

Our study addressed the association between certain characteristics and LTBI therapy completion or failure in a longitudinal study design among commercially insured persons. We determined that approximately half of insured persons who initiated INH for LTBI completed treatment. We also identified an association between INH treatment failure and rheumatoid arthritis and being 65 years or older among those completing INH treatment.

Overall, half of patients in our cohort who initiated LTBI treatment completed it, and our trend analysis indicated that completion rates are increasing. Our results also indicate that age, sex, geographic location, and year of INH initiation were significantly associated with treatment completion. Practitioners should aim to increase treatment completion among patients who are statistically associated with noncompletion, such as patients who are younger than 65 years, live in the Northeast or South Census regions, and are female.

Our associations differed from a previous study of commercially insured persons in the United States.¹¹ Although overall completion rates were similar, the previous study determined that patients 14 years or younger were more likely to complete treatment and no association existed with sex, geographic region, or year of INH initiation and treatment completion. Multiple factors might have contributed to outcome differences; our study had a larger cohort (21510 vs 1072 persons), a longer study period (2005–2016 vs 2011–2015), a greater age range (all ages vs 0–64 years), and used a different insurance claims database (MarketScan Commercial and Medicare Supplemental Research Databases vs Optum Impact National Research Database, Optum Corporation, Eden Prairie, Minnesota).

Among our cohort, INH treatment failure was rare, approximately 0.3%, and was associated with either being 65 years or older or having rheumatoid arthritis. In the United States, persons 65 years or older have been associated with LTBI reactivation, but the association of prior LTBI treatment completion on reducing reactivation was not measured.¹⁶ Rheumatoid arthritis and treatment with immunosuppressants are known risks for progression to TB disease after becoming infected with *M tuberculosis*, and LTBI treatment reduces that risk.¹⁷ Despite recommendations to delay anti-TNF- α therapy until 4 weeks after initiation of LTBI treatment,¹⁸ we identified a proportion of case-patients (33.3%) and a lower proportion of unmatched control subjects with rheumatoid arthritis (14.3%) who had begun anti-TNF- α therapy before initiating INH treatment. Further analyses are needed to assess the association between the timing of anti-TNF- α therapy and LTBI treatment failure. Our findings support recommendations that clinicians caring for persons with rheumatoid arthritis should test for and treat LTBI early and before initiation of anti-TNF- α therapy. Additional studies using more detailed health records might provide information regarding whether other comorbidities increase patients' risk for LTBI treatment failure.

Strengths and Limitations

Use of a large, national data source of commercially insured patients strengthens our study because it provides results regarding private-sector treatment completion and failure for persons with LTBI in the United States. Another strength is in the use of longitudinal data,

which capture timing for diagnostic, procedural, and pharmaceutical therapy, thus allowing temporal adjustment for individual characteristics.

Despite the large data source, INH treatment failure was rare. Studies with more detailed data are needed to confirm our findings and to quantify the associations of INH treatment failure with anti-TNF- α therapy timing or age. Another limitation is that the data were a convenience sample of commercially insured patients and are not generalizable to the entire US population. The MarketScan database primarily comprises information from large employers in higher populated cities,¹⁹ and, consequently, states with larger urban populations might have overrepresented data. The databases do not include information about uninsured patients, cash payers, and Medicare beneficiaries without employer-sponsored supplemental insurance. Information gaps exist for persons who had covered services but without an insured amount, financial data that were withheld, or uncovered services. The data are subject to coding misclassification by health care providers or administrators or by insurance administrators. Finally, the data lack information regarding the intention of the listed diagnostic code, either as a rule-out or as a diagnosis code, resulting in the possibility of misclassification. Detailed demographic information, particularly information pertinent to groups at a higher risk for LTBI (eg, certain racial/ethnic groups or non-US-born persons¹), is also unavailable.

Our analysis was limited in multiple ways. To be identified as a patient with LTBI, a person must have filled 1 or more INH prescriptions. The analysis was unable to identify patients who did not accept INH treatment, failed to fill their first prescription, failed to take the medication as instructed, or did not ingest the medication after filling the prescription. Also unknown is whether those identified as having LTBI and who later received a diagnosis of TB during the therapy period were originally misdiagnosed or progressed to TB disease during treatment. The study did not distinguish between patients who had a new TB infection that progressed to TB disease and patients with treatment failure. Patients with LTBI might have been excluded from the analysis because health care providers misdiagnosed them as having TB disease and referred them for further testing or presumptively misdiagnosed patients' TB disease. The outcome of TB disease was based on *ICD* codes and not verified by laboratory tests, resulting in the possibility of treatment failure misclassification. Selection bias might have been introduced in our study by requiring persons to have had 18 months or more of continuous insurance enrollment. Because the majority of persons in our cohort had less than 5 years of follow-up data, we were unable to identify patients with treatment failure who developed TB 5 years or more after treatment completion. However, those cases, if reported, would have been reflected in the incidence of TB, which decreases with time after infection.²⁰

Finally, whether INH resistance might account for the treatment failures identified in our study is unknown. Resistance to INH among US TB patients remained steady at 8% to 9% during our study period.⁴ However, among persons with exposure to a patient with INH resistance, the American Thoracic Society and the Centers for Disease Control and Prevention recommend non-INH chemoprophylaxis²¹ and therefore these persons were most likely not represented in our data set because included patients were identified by first INH treatment.

Conclusions

Approximately half of commercially insured persons who initiated INH for LTBI completed treatment, and completion rates are increasing in the United States. Among commercially insured persons, rheumatoid arthritis and being 65 years or older are associated with INH treatment failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the assistance of CDC Data Hub in data acquisition and the contributions of C. Kay Smith for editorial assistance. 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.

References

1. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The prevalence of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med*. 2016;194(4):501–509. [PubMed: 26866439]
2. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. *PLoS One*. 2015;10(11):e0140881. [PubMed: 26536035]
3. World Health Organization. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. Geneva, Switzerland: World Health Organization; 2018 <https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en>. Accessed May 1, 2019.
4. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2016 Atlanta, GA: US Department of Health and Human Services, CDC; 2017. <https://www.cdc.gov/tb/statistics/reports/2016/default.htm>. Accessed May 1, 2019.
5. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev*. 2000;(2):CD001363. [PubMed: 10796642]
6. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet*. 1993;342(8866):268–272. [PubMed: 8101302]
7. Falk A, Fuchs GF. Prophylaxis with isoniazid in inactive tuberculosis. A Veterans Administration Cooperative Study XII. *Chest*. 1978; 73(1):44–48. [PubMed: 340155]
8. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ*. 1982;60(4):555–564. [PubMed: 6754120]
9. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapen-tine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155–2166. [PubMed: 22150035]
10. Chaisson RE, Clermont HC, Holt EA, et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med*. 1996;154(4, pt 1):1034–1038. [PubMed: 8887603]
11. Stockbridge EL, Miller TL, Carlson EK, Ho C. Predictors of latent tuberculosis infection treatment completion in the US private sector: an analysis of administrative claims data. *BMC Public Health*. 2018;18(1):662. [PubMed: 29843664]
12. Stockbridge EL, Miller TL, Carlson EK, Ho C. Tuberculosis prevention in the private sector: using claims-based methods to identify and evaluate latent tuberculosis infection treatment with isoniazid among the commercially insured. *J Public Health Manag Pract*. 2018;24(4):E25–E33.
13. American Medical Association. CPT 2017, Professional Edition. Chicago, IL: American Medical Association Press; 2016.

14. American Medical Association. HCPCS Level II 2018, Professional Edition. Chicago, IL: American Medical Association Press; 2017.
15. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, Switzerland: World Health Organization; 2016.
16. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR Jr. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol.* 2014;179(2):216–225. [PubMed: 24142915]
17. Ai JW, Zhang S, Ruan QL, et al. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor alpha antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. *J Rheumatol.* 2015;42(12):2229–2237. [PubMed: 26472414]
18. Iannone F, Cantini F, Lapadula G. Diagnosis of latent tuberculosis and prevention of reactivation in rheumatic patients receiving biologic therapy: international recommendations. *J Rheumatol Suppl* 2014;91:41–46.
19. Hansen LG, Stella C. Health Research Data for the Real World: the MarketScan Databases. Ann Arbor, MI: Truven Health Analytics; 2011.
20. Grzybowski SM, Neil E, Tuters L, Pinkus G, Philipps R. Reactivations in inactive pulmonary tuberculosis. *Am Rev Respir Dis.* 1966; 93:352–361.
21. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med.* 2000;161(4, pt 2):S221–S247. [PubMed: 10764341]

Implications for Policy & Practice

- TB controllers and others can use commercially available data to conduct longitudinal analyses of LTBI treatment outcomes.
- Because incomplete LTBI treatment is associated with being younger than 65 years, living in the Northeast or South Census regions, and being female, practitioners should monitor those patients more closely and provide incentives to ensure adherence to and completion of LTBI treatment.
- Because patients who completed LTBI treatment, are 65 years or older, or have a diagnosis of rheumatoid arthritis are at high risk for LTBI treatment failure, practitioners can avoid that outcome by closer monitoring during treatment and follow-up of older patients and by delaying use of anti-TNF- α immunosuppressive therapy for rheumatoid arthritis.

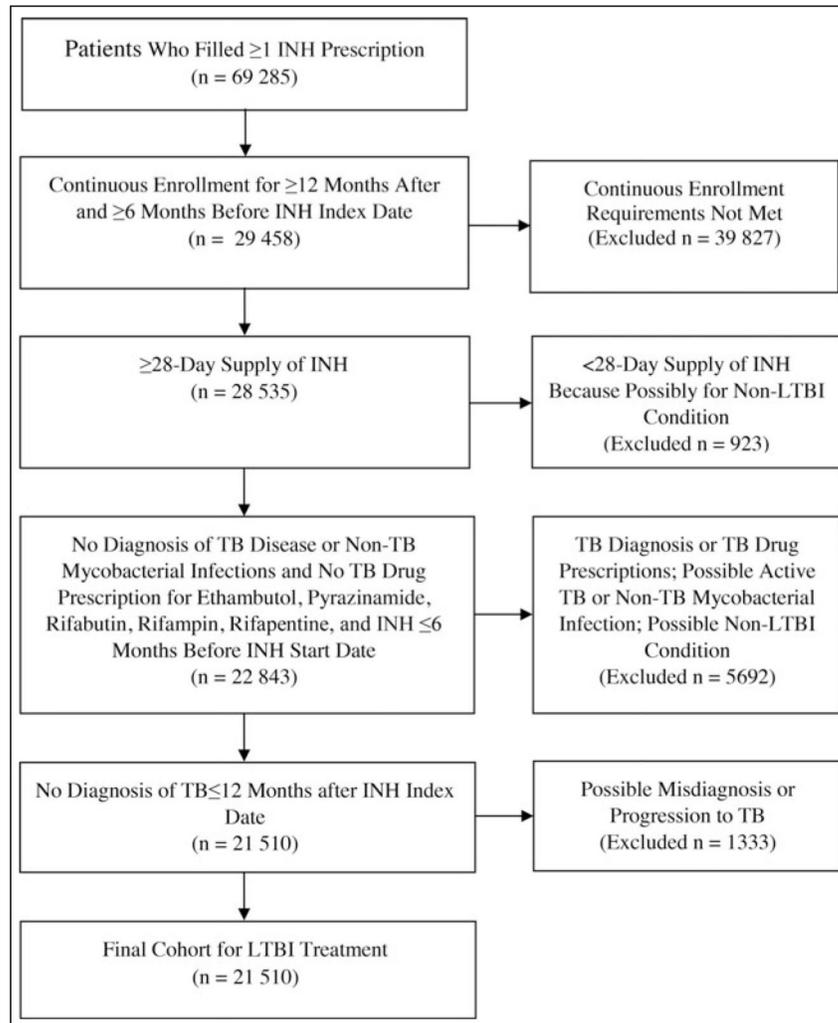


FIGURE. Patient Inclusion and Exclusion Criteria for the LTBI Treatment Cohort, 2005–2016
Abbreviations: INH, isoniazid; LTBI, latent tuberculosis infection; TB, tuberculosis.

TABLE 1
Trends and Characteristics Among Persons Who Had Initiated INH LTBI Therapy During 2005–2016

Characteristics	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Treatment cohort, 18-mo continuous enrollment													
Non-INH treated, year of first enrollment ^a	9 675 314	3 428 453	8 559 843	5 810 679	5 955 572	8 228 078	7 257 443	4 957 402	6 132 236	3 886 253	2 754 525	...	66 645 798
Among INH-treated in LTBI cohort ^b	692	1 398	1 902	2 329	2 400	2 695	2 872	2 356	2 020	1 526	1 319	1	21 510
Age group, %													
0–24 y	29.6	28.4	29.6	29.5	27.8	30.8	31.1	30.2	33.6	28.2	25.7	...	29.8
25–44 y	35.6	36.2	36.1	36.9	37.6	34.9	33.2	33.5	31.0	32.1	31.3	...	34.5
45–64 y	26.5	26.7	26.9	28.5	29.3	28.6	29.8	29.7	30.5	33.4	37.6	100	29.7
65 y	8.4	8.7	7.5	5.1	5.3	5.7	5.9	6.7	5.0	6.3	5.4	...	6.1
Census region, %													
Northeast	12.0	12.7	11.9	10.2	14.0	14.5	14.6	15.2	22.5	25.4	25.6	...	15.8
Midwest	18.5	18.3	15.9	13.1	16.7	16.0	14.1	10.8	11.8	14.4	13.9	...	14.5
South	19.7	19.7	29.5	32.6	28.1	26.6	25.9	24.7	27.6	31.5	30.0	100.0	27.4
West	49.6	49.2	42.4	43.6	41.0	42.8	44.2	48.3	35.1	28.4	30.3	...	41.6
Missing	0.3	0.1	0.3	0.5	0.2	0.2	1.2	1.0	3.1	0.3	0.2	...	0.7
Sex, %													
Women	56.5	57.2	56.6	56.1	56.2	57.4	55.9	57.5	56.2	57.3	56.3	100.0	56.6
Men	43.5	42.9	43.4	43.9	43.8	42.6	44.2	42.5	43.8	42.7	43.7	...	43.4
Treatment completion, %													
Yes	44.1	49.6	48.7	47.5	47.9	48.6	49.7	48.7	52.0	56.1	56.8	100.0	49.9
No	55.9	50.4	51.3	52.5	52.1	51.4	50.3	51.3	48.0	43.9	43.2	...	50.1
TB diagnosis, % ^c													
Yes	0.3	0.2	0.3	0.4	0.5	0.5	0.3	0.6	0	0.4	0	0	0.3
No	99.7	99.8	99.7	99.6	99.5	99.5	99.7	99.4	100.0	99.6	100.0	100.0	99.7

Abbreviations: INH, isoniazid; LTBI, latent tuberculosis infection; TB, tuberculosis.

^aData ended in 2016. A person starting enrollment in 2016 would not qualify for 18 months' continuous enrollment.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^b Persons in 2005 were eligible starting in July 2005 as a result of a 6-month look-back period. Persons in 2016 were eligible only if they began treatment on January 1, 2016, as a result of a 1-year continuous enrollment period from treatment start.

^c By year of treatment initiation. Diagnosis of TB more than 1 year from treatment initiation by 1 inpatient diagnosis, 2 outpatient diagnoses, or 1 outpatient diagnosis with prescriptions for ethambutol and pyrazinamide within 2 weeks of TB diagnosis.

Characteristics Among Persons Who Initiated INH LTBI Therapy by Treatment Completion, TB Diagnosis, and Treatment Failure During 2005–2016

TABLE 2

Characteristics	Treatment Completion, n (%)		Odds Ratio (95% Confidence Interval)		Treatment Failure ^d Among Treatment Completed, n (%)		Unadjusted ^b Exact OR (95% CI)	Adjusted ^b Exact OR (95% CI)	P	
	Not Complete	Complete	Unadjusted	Adjusted	Failed	Not Fail				
N	10 785 (50.1)	10 725 (49.9)	30 (0.3)	10 695 (99.7)	
Treatment adherence, months										
1–3	7319 (67.9)
4–6	3466 (32.1)
6–9	...	4760 (44.4)	15 (50.0)	4745 (44.4)	1.0 (Ref)	...	(Ref)	...
9	...	5965 (55.6)	15 (50.0)	5950 (55.6)	0.8 (0.4–1.8)659	...
Year of treatment initiation										
2005–2008	3289 (30.5)	3032 (28.3)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	6 (20.0)	3026 (28.3)	2.6 (0.5–26.7)384	2.4 (0.4–24.4)
2009–2012	5287 (49.0)	5036 (47.0)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	22 (73.3)	5014 (46.9)	5.8 (1.4–51.1)007	5.5 (1.3–48.3)
2013–2016	2209 (20.5)	2657 (24.8)	1.0 (Ref)	1.0 (Ref)	2 (6.7)	2655 (24.8)	1.0 (Ref)	...	(Ref)	1.0 (Ref)
Age group, %										
0–24 y	3294 (30.5)	3106 (29.0)	1.3 (1.1–1.4)	1.3 (1.1–1.4)	4 (13.3)	3102 (29.0)	1.0 (Ref)	...	(Ref)	1.0 (Ref)
25–44 y	4007 (37.2)	3404 (31.7)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	10 (33.3)	3394 (31.7)	2.3 (0.7–10.0)242	2.2 (0.6–9.6)
45–64 y	2883 (26.7)	3499 (32.6)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	10 (33.3)	3489 (32.6)	2.2 (0.6–9.7)263	2.1 (0.6–9.0)
65 y	601 (5.6)	716 (6.7)	1.0 (Ref)	1.0 (Ref)	6 (20.0)	710 (6.6)	6.5 (1.5–36.6)009	5.1 (1.2–25.3)
Census region, %										
Northeast	1764 (16.4)	1644 (15.3)	1.1 (1.03–1.2)	1.2 (1.1–1.3)	2 (6.7)	1642 (15.4)	0.5 (0.1–2.3)579	0.6 (0.1–2.7)
Midwest	1501 (13.9)	1625 (15.2)	1.0 (0.9–1.0)	1.0 (0.9–1.1)	10 (33.3)	1615 (15.1)	2.6 (1.0–6.7)057	2.3 (0.9–6.0)
South	3046 (28.2)	2838 (26.5)	1.1 (1.05–1.2)	1.2 (1.1–1.2)	7 (23.3)	2831 (26.4)	1.0 (0.3–2.9)	...	1.000	1.1 (0.4–3.1)
West	4376 (40.6)	4563 (42.6)	1.0 (Ref)	1.0 (Ref)	11 (36.7)	4552 (42.6)	1.0 (Ref)	...	(Ref)	1.0 (Ref)
Missing	98 (0.9)	55 (0.5)	1.9 (1.3–2.6)	2.0 (1.5–2.8)	0 (0)	55 (0.5)
Sex, %										
Women	6252 (58.0)	5928 (55.3)	1.1 (1.1–1.2)	1.1 (1.04–1.2)	13 (43.3)	5915 (55.3)	0.6 (0.3–1.4)258	0.7 (0.3–1.4)
Men	4533 (42.0)	4797 (44.7)	1.0 (Ref)	1.0 (Ref)	17 (56.7)	4780 (44.7)	1.0 (Ref)	...	(Ref)	1.0 (Ref)
TB diagnosis, %										

Characteristics	Treatment Completion, n (%)		Odds Ratio (95% Confidence Interval)		Treatment Failure ^a Among Treatment Completed, n (%)		Unadjusted ^b Exact OR (95% CI)	P	Adjusted ^b Exact OR (95% CI)
	Not Complete	Complete	Unadjusted	Adjusted	Failed	Not Fail			
Yes	44 (0.4)	30 (0.3)	1.5 (0.9–2.3)	
No	10 741 (99.6)	10 695 (99.7)	1.0 (Ref)	
Enrollment period from treatment start, %									
Continuous enrollment, median (Q1-Q3), y	2.8 (1.7–4.8)	3.0 (1.8–4.9)	4.5 (2.7–6.6)	2.9 (1.8–4.8)	
Time to TB diagnosis, median (Q1-Q3), y	1.8 (1.3–3.1)	1.8 (1.4–3.8)	1.8 (1.3–3.3)	

Abbreviations: CI, confidence interval; INH, isoniazid; LTBI, latent tuberculosis infection; OR, odds ratio; TB, tuberculosis.

^aBy year of treatment initiation. Diagnosis of tuberculosis more than 1 year from treatment initiation by 1 inpatient diagnosis, 2 outpatient diagnoses, or 1 outpatient diagnosis with prescriptions for ethambutol and pyrazinamide for 2 weeks or more after TB diagnosis.

^bStrata with 1 cell equal to 0 were excluded from all models. A bivariate analysis was executed for each variable: variables with strata having P < .3 along with variables having biological plausibility were included in the multivariable model.

Characteristics of Matched Case-Patients With a TB Diagnosis More Than 1 Year After INH LTBI Treatment Initiation and Control Subjects During 2005–2016

TABLE 3

Characteristics	Case-Patients, n (%)	Control Subjects, n (%)	Exact OR (95% CI)	P	Adjusted Exact OR (95% CI) ^d
Co-diagnoses					
Prior tuberculosis					
Yes	3 (10.0)	1 (1.7)	6.0 (0.5–315.0)	.222 (Ref)	15.8 (0.9 to >999) (Ref)
No/missing	27 (93.3)	59 (98.3)	1.0 (Ref)		
Tobacco use					
Yes	2 (6.7)	1 (1.7)	4.0 (0.2–236.0)	.519 (Ref)	...
No/missing	28 (93.3)	59 (98.3)	1.0 (Ref)		...
Rheumatoid arthritis					
Yes	9 (30.0)	7 (11.7)	3.5 (0.9–16.1)	.064 (Ref)	5.1 (1.2–28.2) (Ref)
No/missing	21 (70.0)	53 (88.3)	1.0 (Ref)		
Abnormal chest radiograph without respiratory disorder					
Yes	4 (13.3)	5 (8.3)	2.2 (0.3–26.4)	.664 (Ref)	...
No/missing	26 (86.7)	55 (91.7)	1.0 (Ref)		...
Respiratory disorder (nontuberculosis)					
Yes	10 (33.3)	12 (20.0)	2.0 (0.7–5.9)	.266 (Ref)	3.1 (0.9–14.0) (Ref)
No/missing	20 (66.7)	48 (80.0)	1.0 (Ref)		
Immunocompromised conditions, other					
Yes	2 (6.7)	2 (3.3)	2.0 (0.1–27.6)	1.000 (Ref)	...
No/missing	28 (93.3)	58 (96.7)	1.0 (Ref)		...
Kidney disorder					
Yes	2 (6.7)	3 (5.0)	1.4 (0.1–21.7)	1.000 (Ref)	...
No/missing	28 (93.3)	57 (95.0)	1.0 (Ref)		...
Cancer					
Yes	2 (6.7)	3 (5.0)	1.3 (0.1–11.6)	1.000 (Ref)	...
No/missing	28 (93.3)	57 (95.0)	1.0 (Ref)		...
HIV infection					
Yes	2 (6.7)	3 (5.0)	1.3 (0.1–11.6)	1.000 (Ref)	...

Characteristics	Case-Patients, n (%)	Control Subjects, n (%)	Exact OR (95% CI)	P	Adjusted Exact OR (95% CI) ^a
No/missing	28 (93.3)	57 (95.0)	1.0 (Ref)	(Ref)	...
Diabetes					
Yes	4 (13.3)	7 (11.7)	1.2 (0.2–7.1)	1.000	...
No/missing	26 (86.7)	53 (88.3)	1.0 (Ref)	(Ref)	...
Recent surgery					
Yes	1 (3.3)	4 (6.7)	0.5 (0.01–5.1)	0.922	...
No/missing	29 (96.7)	56 (93.3)	1.0 (Ref)	(Ref)	...
Alcohol use					
Yes	0 (0)	1 (1.7)
No/missing	30 (100.0)	59 (98.3)

Abbreviations: CI, confidence interval; INH, isoniazid; LTBI, latent tuberculosis infection; OR, odds ratio; TB, tuberculosis.

^a Conditional exact test. A bivariate analysis was executed for each variable; those variables having $P < .3$ along with variables having biologic plausibility were included in the multivariable model.

TABLE 4

Characteristics of Persons With Rheumatoid Arthritis in the Matched Case-Control Study for INH LTBI Treatment Failure During 2005–2016

Rheumatoid Arthritis	Case-Patients (n = 9), n (%)	Control Subjects (n = 7), n (%)
Sex		
Men	4 (44.4)	4 (57.1)
Women	5 (55.6)	3 (42.9)
Age, y		
25–44	1 (11.1)	2 (28.6)
45–64	5 (55.6)	4 (57.1)
65	3 (33.3)	1 (14.3)
Year of treatment initiation		
2005–2008	3 (33.3)	0 (0)
2009–2012	6 (66.7)	7 (100.0)
Census region		
Northeast	0 (0)	1 (14.3)
Midwest	4 (44.4)	0 (0)
South	4 (44.4)	6 (85.7)
West	1 (11.1)	0 (0)
Co-diagnoses		
None	6 (66.7)	6 (85.7)
Surgery	0 (0)	1 (14.3)
Respiratory disorders (non-TB)	1 (11.1)	0 (0)
Respiratory disorders (non-TB) and tobacco use	1 (11.1)	0 (0)
Respiratory disorders (non-TB), diabetes, and renal insufficiency	1 (11.1)	0 (0)
Anti-TNF- α therapy		
0–180 d before INH LTBI treatment initiation		
Yes	3 (33.3)	1 (14.3)
No	6 (66.7)	6 (85.7)
1–365 d after INH LTBI treatment initiation		
Yes	4 (44.4)	6 (85.7)
No	5 (55.6)	1 (14.3)
Median time in years to TB disease after treatment initiation (Q1-Q3)	1.9 (1.4–3.8)	—

Abbreviations: INH, isoniazid; LTBI, latent tuberculosis infection; TB, tuberculosis.