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Tumor Necrosis Factor-Antagonist Therapy Exposure Associated with Sputum Conversion by Eight Weeks among United States Tuberculosis Patients, 2010-2015

By

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Degree to be awarded: Master of Public Health

Epidemiology

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Abstract

Tumor Necrosis Factor-Antagonist Therapy Exposure Associated with Sputum Conversion by Eight Weeks among United States Tuberculosis Patients, 2010-2015

By Jessica R. Probst

Immunosuppressive therapy through the use of Tumor Necrosis Factor (TNF) antagonists has been linked to activation of latent Tuberculosis (TB) infection to active TB disease. Less is known, however, about the effect of anti-TNF therapy on TB disease presentation, and on the course of TB disease after patients start on anti-TB therapy. Sputum culture conversion after the 2-month intensive phase of TB treatment serves as a biomarker of long-term cure and of contagiousness. We reviewed Reports of Verified Cases of Tuberculosis for all patients diagnosed in the United States and its territories from 2010-2015 through the National Tuberculosis Surveillance System (NTSS), which collects clinical and demographic patient data. Logistic models were used to estimate the odds ratios (ORs) for sputum conversion by 2 months or after. In the study population (n=26,861), sputum conversion by 8 weeks was observed in 15,915 (59.2%) patients. Anti-TNF exposure was significantly associated with a reduction in sputum conversion after 8 weeks among US-born patients (aOR: 0.2624, 95% confidence interval: (0.01, 0.70), p-value: 0.0067), adjusting for other clinical and demographic factors. This data may serve to reassure TB patients on anti-TNF therapy that their TB outcomes will likely be better than their other TB counterparts, and could also have implications on contagiousness of anti-TNF patients.

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Table of Contents

Background

Tuberculosis remains one of the world's deadliest communicable diseases (1). The World Health Organization (WHO) monitors and tracks the global occurrence of TB disease. The WHO estimates that 10.4 million people contracted TB in the year 2015 worldwide, and that there were 1.8 million TB-related deaths (2). In contrast, nearly 10,000 cases of TB were reported in the United States that year, a 1.6% increase from 2014 (3). Key aspects of a successful TB control program include case-finding, patient care, and proactive methods to prevent transmission. Tuberculosis is transmitted from person-to-person when someone with pulmonary TB disease coughs or sneezes and a susceptible close contact inhales the aerosolized bacilli.

Caused by infection by M*ycobacterium tuberculosis*, the clinical manifestation of tuberculosis can be described as either active disease or latent infection. In active disease state, patients experience symptoms such as fever, night sweats, and persistent cough, which can be productive (4). In patients with robust immune systems, infection with *M. tuberculosis* can manifest as latent TB infection (LTBI), a non-contagious state; it has been reported that 1/3 of the world's population experiences infection from TB bacilli either in the form of latent infection or in active disease (5).

Certain immunosuppressive conditions or treatments can accelerate progression from LTBI to active TB disease, including HIV co-infection or diabetes mellitus as a co-morbid condition (6, 7). One such treatment is the use of a class of biologic medications known as tumor necrosis factor-antagonists. The inflammatory cytokine tumor necrosis

factor (TNF) and its receptor sites are key players along the regulatory pathway of the human immune system (8). Biologic antagonists of TNF inhibit its regulation and output and are most often used in therapeutic efforts to return an over-active immune system to a baseline state (9). Worldwide, patients are prescribed TNF inhibitors (TNF-antagonists) for a variety of immune-mediated inflammatory diseases (IMIDs) including psoriasis, irritable bowel syndrome, Crohn's disease, and rheumatoid arthritis (9). These drugs come in two classes, anti-TNFmAbs including infliximab and adalimumab, and soluble TNF-receptor fusion proteins like etanercept (10).

Early animal studies showed that antibodies against TNF caused a reactivation of latent tuberculosis infection and suggested that TNF plays a central part in the host response against tuberculosis, including granuloma formation and containment of disease (11). Granuloma formation and regulation is a key mechanism for controlling bacterial growth and thus transitioning active TB disease into latent TB disease (10). In humans, both observational studies and clinical trials have shown that patients on TNF antagonists have difficulties mounting an immune response strong enough to stave off infectious agents, which can allow latent infection with *Mycobacterium tuberculosis* to develop into active TB disease (12). It has been observed that undergoing TNF antagonist therapy is a statistically significant predictor for development of TB (13). As such, patients in the United States undergoing TNF antagonist therapy face an over 4-fold relative risk of developing TB disease (14). Rates for development of active tuberculosis among anti-TNF users were reported as 49 cases per 100,000 person-years, compared to 4.1 cases per 100,000 person-years background rate (15).

Little is known, however, about the effect of anti-TNF therapy on TB disease presentation, and on the course of TB disease after patients start on anti-TB therapy. An observational study by Keane et. al. described the unique pattern of TB related to TNF-inhibitor therapy, stating that extrapulmonary TB and disseminated disease, forms of tuberculosis disease that are associated generally with severe immunosuppression, were observed at increased rates (11, 16). TNF-antagonist therapy is a clinical effort to induce immunosuppression, which traditionally is associated with prolonged treatment periods (17, 18). Because TNF-antagonist therapy causes a specific disseminated form of disease, tracking clinical progression and outcome among patients with this exposure is important in tailoring care.

In countries like the United States where there are relatively greater resources to care for TB patients, diagnosis is most often based on positive sputum cultures of *M. tuberculosis*, and treatment success is measured by conversion to no growth on sputum culture (19). Sputum culture conversion after the 2-month intensive phase of TB treatment serves as a biomarker of long-term cure and of contagiousness (20, 21). Conversely, non-conversion of a sputum smear at the end of this period has been documented to be associated with unfavorable outcomes, more specifically with default and failure (1). Delayed sputum conversion has also been linked to prolonged infectiousness (22).

Methods

Study Sample

This retrospective cohort study included all patients age 15 years and older with culture-confirmed TB diagnosed in 2010-2015 in the United States. These cases were identified using the National Tuberculosis Surveillance System (NTSS). TB disease is a nationally notifiable condition; cases are required to be reported by all 50 states and territories of the United States to the Centers for Disease Control and Prevention and entered into the NTSS (3). Data in the NTSS are collected via Reports of Verified Tuberculosis (RVCT) submitted from state and/or county health departments. Patients were excluded from the study if they were ineligible for the outcome due to: (1) absence of a positive baseline diagnostic sputum culture for *Mycobacterium tuberculosis*; (2) date of sputum conversion not recorded; or (3) extrapulmonary-only manifestation of disease.

Variable Definition and Collection Methods

Primary outcome was delayed sputum conversion, defined as absence of culture conversion at 2 months. The outcome was calculated from initial positive sputum collection to date of first of three consistently negative sputum cultures and dichotomized as being 56 days or less, or over 56 days.

We identified a list of potential covariates based on a review of the published literature, medical and biological disease processes, and topical expertise.

Statistical Methods

Variables with excessive missing data, defined as 20% or greater, were not further pursued. Univariate analysis was performed on each covariate in relation to delayed sputum conversion, and those with p-values less than .05 were considered for the multivariable model (Table 3). We performed backwards elimination of variables with the highest p-values from the model until all remaining covariates had p-values less than .05 or were part of interaction terms whose p-values were less than .05. All data were analyzed by using SAS for Windows, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Missing data were not replaced or imputed. This analysis was considered as nonhuman subjects research by the Emory University Institutional Review Board.

Results

During the study period from January 1, 2010 through December 31, 2015, 62,239 patients were reported by states and territories of the United States to CDC as meeting the established case definition for TB. Ultimately, our study included all 26,861 patients who met the study inclusion criteria and had complete data regarding exposures, demographic status, and outcome.

A total of 17,474 (65.1%) of reported TB patients in the United States between 2010-2015 who met our study criteria were male, and 9,621 (35.8%) were born in the United States (Table 1). Among the 17,222 foreign-born individuals, 1,507 (8.75%) had arrived in the United States within 1 year of their diagnosis. Of reported TB cases who met study inclusion criteria, 1,580 (5.9%) were HIV co-infected, and 4,426 (16.5%), had diabetes mellitus listed as a co-morbid condition. These two co-morbidities have been documented as having significant effects on TB outcomes, and both had p-values of <0.0001 in relation to our outcome of delayed time until sputum conversion on univariate analysis (23-25). Cavitation was present on chest X-ray (CXR) or chest CT-scan in 12,254 (45.6%) of patients, while miliary disease manifestation was present in 1,095 (4.1%).

Overall, 10,603 patients (39.5%) did not convert their sputum within the 8-week intensive phase of therapy (Table 2). Men comprised 68.3% of late converters, versus 65% of overall TB patients (chi-square p-value <0.0001). While 24.3% of late converters

were white, only 17.9% of those who converted within 8 weeks were white (chi-square p-value = 0.04). Compared with TB patients reported with sputum conversion documented by 8 weeks, patients with delayed sputum conversion were statistically more likely to have cavitation on CXR or CT scan (41.0% versus 52.7% respectively, chi-square p-value <0.0001) and less likely to have extrapulmonary involvement (12.2% versus 7.0% respectively, chi-square p-value <0.0001). Foreign-born patients were less likely to have delayed sputum conversion than U.S. born (Relative Risk (RR) 0.7928, 95% Confidence Interval (CI) 0.77, 0.82).

In total, 126 (0.47%) of all U.S. TB patients in this cohort had documented history of TNF-antagonist therapy, and 35 (27.8%) of them experienced delayed sputum conversion, compared to 39.5% of overall TB cases (chi-square p-value = 0.01). Among those who had TNF-antagonist therapy, 13 (10.3%) were black; in contrast, persons who were black made up 20.2% of overall TB cases. Conversely, 32 (25.4%) of those with a history of TNF-inhibitor therapy were persons who were white, while 3,894 whites comprised just 14.5% of all TB patients. Thirty-two patients with a history of TNF-inhibitor therapy who were aged 65 years or older represented 29.6% of this group. In contrast, 4,492 (20.6%) TB cases reported from 2010-2015 were among patients over age 65. Sixty-six women made up 52.4% of the patients with TNF-antagonist exposure, yet there were 9,384 (34.9%) women in the entire cohort of TB patients (p-value <0.0001). Patients with a history of TNF-antagonist therapy were more likely than those without this history to visit private healthcare providers for their TB care (38.9% vs. 25.3%, p-value 0.002).

While 17,953 (66.8%) of all TB cases had positive initial sputum smear results, only 71 (56.3%) of those with a history of TNF-inhibitory therapy had positive initial smears (p-value 0.01). Results of clinical scans showed significantly more miliary disease among TNF-antagonist exposed patients than those without exposure (27.8% vs. 4.1%, p-value <0.0001). Likewise, cavitation was present in 12,254 (45.6%) of overall TB cases, but only 15 (11.9%) of TB case-patients who received TNF-antagonist therapy had radiographic evidence of cavitation (p-value <0.0001). Compared with reported TB cases who did not receive TNF-alpha antagonists, those who did receive such therapy appeared more likely to exhibit resistance to first-line anti-TB drugs (18.3% vs 12.4%), but this difference was of borderline statistical significance (p = 0.051)

TNF-alpha antagonist therapy was associated with lower odds of delayed sputum conversion among domestic U.S. TB cases, after adjusting for significant demographic and clinical factors (OR: 0.2624, 95% CI: (0.01, 0.70), p-value = 0.0067). However, this relationship was not observed in foreign-born TB cases.

Discussion

The significance of TNF-antagonist therapy as a predictor of sputum conversion within eight weeks has important public health implications. Because these patients sterilize their sputum cultures in a timely way, they may be less likely to have prolonged periods of infectiousness (22).

US-born TNF-antagonist patients in this cohort suffer from more disseminated disease in the form of extrapulmonary involvement and miliary manifestation, and their pulmonary disease appears to respond to treatment and resolve quicker than in other patients with pulmonary TB. This observation is probably influenced by the finding that reported TB case-patients who did not receive TNF-antagonist therapy were also more likely to have a high bacillary load, reflected by more extensive cavitary disease than TB patients who received TNF-alpha antagonist therapy. This observation was also noted by Keane et al (11), and is thought to be correlated to the functionality of TNF in disease progression and containment. More broadly, TNF-antagonist therapy exposure may be a marker of patients with absence of other risk factors associated with worse clinical outcomes. The results of this study suggest that, through the use of sputum conversion by 8 weeks as a proxy for long-term treatment success, US-born patients with prior TNF-antagonist therapy exposure are at reduced risk for complications in treatment.

Resolution of infectious pulmonary TB disease has important implications for TB control programs. These programs target early identification and initiation of appropriate therapy in these patients by prompt linkage into care as a way to reduce risk of TB

contagion among contacts. TB patients with a history of TNF-alpha antagonist therapy should be readily identified by proper documentation of medical history. TB patients who have a medical history of TNF- alpha inhibitory therapy present a small but significant pool of easy-to-locate targets for treatment as a way to reduce suffering, morbidity, and adverse outcomes – including death.

The retrospective nature of this study could introduce bias in terms of reporting patterns of patient outcomes; those with poorer clinical outcomes may have more missing data. Sputum sample frequency was not documented and health departments or private providers in local jurisdictions performed sampling, thus timing was not consistently verified. This leads to possible variation in time to culture conversion: it is possible that sputum conversion occurred between sampling sessions and was not captured until later than it occurred, though this misclassification cannot be measured with the available data. Exposure status to TNF-alpha inhibitor therapy was collected only as a checkbox on the RVCT. There is a possibility that some TB patients with this exposure could be misclassified as unexposed, leading to underreporting of exposure status in the study population.

This study included a total sample size of 26,861 patients, including all confirmed cases of TB disease from the United States and its territories that fit inclusionary criteria. Because TB is a nationally notifiable condition, we can be confident that we have captured all cases within the jurisdiction, creating a robust sample size.

Conclusions from this study expand the body of knowledge and offer additional contributions to the understanding of the epidemiology of TB disease among patients with a history of TNF-alpha inhibitory therapy. These observations provide insight to healthcare providers and policymakers to inform prescribing habits for immunosuppressive therapies, as well as to TB control programs. Additionally, these data could be used to reassure TB patients on anti-TNF therapy that their clinical outcomes will likely be better than their other TB counterparts.

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Tables

Table 1. Characteristics of a Cohort of U.S. TB Patients by TNF-Therapy Status, 2010-2015

	Eligible Cases (n=26,861)		TNF-Therapy (n=126)		No TNF-Therapy (n=26,735)		P-Value[c]
	No.	%	No.	%	No.	%	
Delayed Sputum Conversion[a]							
No	15,915	59.2%	88	69.8%	15,827	59.2%	0.009
Yes	10,603	39.5%	35	27.8%	10,568	39.5%	
Missing	343	1.3%	3	2.4%	340	1.3%	
Race/Ethnicity							
Hispanic	7,886	29.4%	30	23.8%	7,856	29.4%	0.0004
Non-Hispanic							
White[b]	3,894	14.5%	32	25.4%	3,862	14.4%	
Black	5,417	20.2%	13	10.3%	5,404	20.2%	
Asian	8,147	30.3%	46	36.5%	8,101	30.3%	
Other	1,464	5.5%	4	3.2%	1,460	5.5%	
Missing	53	0.2%	1	0.8%	52	0.2%	
Sex							
Male	17,474	65.1%	60	47.6%	17,414	65.1%	<.0001
Female	9,384	34.9%	66	52.4%	9,318	34.9%	
Missing	3	0.0%	0	0.0%	3	0.0%	
Age at Diagnosis							
15-24[b]	2,602	11.9%	8	7.4%	2,594	12.0%	0.009
25-44	7,277	33.4%	31	28.7%	7,246	33.4%	
45-64	7,405	34.0%	37	34.3%	7,368	34.0%	
65+	4,492	20.6%	32	29.6%	4,460	20.6%	
Missing	1	0.0%	0	0.0%	1	0.0%	
Place of Birth							
US Born	9,621	35.8%	41	32.5%	9,580	35.8%	0.439
Foreign Born	17,222	64.1%	85	67.5%	17,137	64.1%	
Missing	18	0.1%	0	0.0%	18	0.1%	
Initial Smear							
Negative	8,833	32.9%	55	43.7%	8,778	32.8%	0.011
Positive	17,953	66.8%	71	56.3%	17,882	66.9%	
Missing	75	0.3%	0	0.0%	75	0.3%	
Cavitation							
Absent	13,662	50.9%	109	86.5%	13,553	50.7%	<.0001
Present	12,254	45.6%	15	11.9%	12,239	45.8%	
Missing	945	3.5%	2	1.6%	943	3.5%	

Site of TB Disease							
Pulmonary Only	24,141	89.9%	83	65.9%	24,058	90.0%	<.0001
Pulmonary & Extrapulmonary	2,720	10.1%	43	34.1%	2,677	10.0%	
HIV Status							
Negative	22,350	83.2%	111	88.1%	22,239	83.2%	0.015
Positive	1,580	5.9%	1	0.8%	1,579	5.9%	
Missing	2,931	10.9%	14	11.1%	2,917	10.9%	
Diabetes Status							
Non-Diabetic	22,435	83.5%	111	88.1%	22,324	83.5%	0.168
Diabetic	4,426	16.5%	15	11.9%	4,411	16.5%	
Recent Immigration							
Yes	1,507	5.6%	2	1.6%	1,505	5.6%	0.043
No	7,345	27.3%	38	30.2%	7,307	27.3%	
Missing/Not Applicable	18,009	67.0%	86	68.3%	17,923	67.0%	
Evidence of Miliary Disease							
Yes	1,095	4.1%	35	27.8%	1,060	4.0%	<.0001
No	25,275	94.1%	91	72.2%	25,184	94.2%	
Unknown	491	1.8%	0	0.0%	491	1.8%	
Reason for Initial Evaluation							
Abnormal X-ray	5,489	20.4%	23	18.3%	5,466	20.4%	0.045
TB Symptoms	17,199	64.0%	93	73.8%	17,106	64.0%	
Other	3,986	14.8%	10	7.9%	3,976	14.9%	
Missing	187	0.7%	0	0.0%	187	0.7%	
Homeless Within Past Year							
Yes	1,892	7.0%	1	0.8%	1,891	7.1%	0.006
No	24,844	92.5%	125	99.2%	24,719	92.5%	
Missing	125	0.5%	0	0.0%	125	0.5%	
Resident of Correctional Facility							
Yes	976	3.6%	0	0.0%	976	3.7%	0.999
No	25,794	96.0%	126	100.0%	25,668	96.0%	
Missing	91	0.3%	0	0.0%	91	0.3%	
Resident of Long-term Care Facility							
Yes	387	1.4%	1	0.8%	386	1.4%	0.841
No	26,435	98.4%	125	99.2%	26,310	98.4%	
Missing	39	0.1%	0	0.0%	39	0.1%	
Employment Status							
Employed	11,172	41.6%	59	46.8%	11,113	41.6%	0.327
Not Employed	15,107	56.2%	67	53.2%	15,040	56.3%	
Missing	582	2.2%	0	0.0%	582	2.2%	
Drug Use Within Past Year							
Yes	2,539	9.5%	5	4.0%	2,534	9.5%	0.033

No	24,116	89.8%	121	96.0%	23,995	89.8%	
Missing	206	0.8%	0	0.0%	206	0.8%	
Excess Alcohol Within Past Year							
Yes	4,046	15.1%	4	3.2%	4,042	15.1%	0.000
No	22,601	84.1%	122	96.8%	22,479	84.1%	
Missing	214	0.8%	0	0.0%	214	0.8%	
End-Stage Renal Failure							
Yes	292	1.1%	1	0.8%	291	1.1%	0.601
No/Missing	26,569	98.9%	125	99.2%	26,444	98.9%	
Post-Organ Transplant							
Yes	92	0.3%	0	0.0%	92	0.3%	0.648
No/Missing	26,769	99.7%	126	100.0%	26,643	99.7%	
First Line Drug Resistance							
Yes	3,349	12.5%	23	18.3%	3,326	12.4%	0.051
No	23,512	87.5%	103	81.7%	23,409	87.6%	
Directly Observed Therapy							
Self-Administered	879	3.3%	3	2.4%	876	3.3%	0.351
Both	7,763	28.9%	43	34.1%	7,720	28.9%	
Directly Observed	17,455	65.0%	75	59.5%	17,380	65.0%	
Missing	764	2.8%	5	4.0%	759	2.8%	
Provider Type							
Health Department	18,610	69.3%	71	56.3%	18,539	69.3%	0.002
Any Private Provider Use	6,815	25.4%	49	38.9%	6,766	25.3%	
Missing	1,436	5.3%	6	4.8%	1,430	5.3%	

[a]Only patients alive at diagnosis were eligible

[b]Reference group

[b]P-values calculated using chi-square test of independence or Fischer's exact test

Table 2. Characteristics of a Cohort of US TB Patients by Sputum Conversion Status, 2010-2015

	Eligible Cases[a] (n=26,861)		Delayed Conversion[b] (n=10,603)		Normal Conversion (n=15,915)		P-Value[d]
	No.	%	No.	%	No.	%	
TNF-antagonist Therapy							
No	26,395	99.5%	10,568	99.7%	15,827	99.4%	0.01
Yes	123	0.5%	35	0.3%	88	0.6%	
Race/Ethnicity							
Hispanic	7,816	41.9%	3,119	41.8%	4,697	42.0%	0.04
Non-Hispanic							
White[c]	3,828	20.5%	1,822	24.3%	2,006	17.9%	
Black	5,332	35.8%	2,088	36.9%	3,244	35.2%	
Asian	8,051	30.1%	2,790	25.8%	5,261	32.9%	
Other	1,439	5.1%	757	6.6%	682	4.1%	
Missing	52		27		25		
Sex							
Male	17,246	65.0%	7,246	68.3%	10,000	62.8%	<.0001
Female	9,269	35.0%	3,356	31.7%	5,913	37.2%	
Missing	3	0.0%	1	0.0%	2	0.0%	
Age at Diagnosis							
15-24[c]	3,230	12.2%	1,134	10.7%	2,096	13.2%	0.01
25-44	8,899	33.6%	3,406	32.1%	5,493	34.5%	
45-64	9,026	34.0%	4,055	38.2%	4,971	31.2%	
65+	5,362	20.2%	2,007	18.9%	3,355	21.1%	
Missing	1	0.0%	1	0.0%	0	0.0%	
Place of Birth							
US Born	9,477	35.7%	4,368	41.2%	5,109	32.1%	<.0001
Foreign Born	17,023	64.2%	6,220	58.7%	10,803	67.9%	
Missing	18	0.1%	15	0.1%	3	0.0%	
Initial Smear							
Negative	8,682	32.7%	2,918	27.5%	5,764	36.2%	<.0001
Positive	17,764	67.0%	7,656	72.2%	10,108	63.5%	
Missing	72	0.3%	29	0.3%	43	0.3%	
Cavitation							
Absent	13,465	50.8%	4,690	44.2%	8,775	55.1%	<.0001
Present	12,119	45.7%	5,588	52.7%	6,531	41.0%	
Missing	934	3.5%	325	3.1%	609	3.8%	
Site of TB Disease							
Pulmonary Only	23,834	89.9%	9,858	93.0%	13,976	87.8%	<.0001

Pulmonary & Extrapulmonary	2,684	10.1%	745	7.0%	1,939	12.2%	
HIV Status							
Negative	22,076	83.2%	8,885	83.8%	13,191	82.9%	<.0001
Positive	1,560	5.9%	493	4.6%	1,067	6.7%	
Missing	2,882	10.9%	1,225	11.6%	1,657	10.4%	
Diabetes Status							
Non-Diabetic	22,149	83.5%	8,716	82.2%	13,433	84.4%	<.0001
Diabetic	4,369	16.5%	1,887	17.8%	2,482	15.6%	
Recent Immigration							
Yes	1,482	5.6%	520	4.9%	962	6.0%	0.12
No	7,251	27.3%	2,700	25.5%	4,551	28.6%	
Missing/Not Applicable	17,785	67.1%	7,383	69.6%	10,402	65.4%	
Evidence of Miliary Disease							
Yes	1,079	4.1%	365	3.4%	714	4.5%	<.0001
No	24,962	94.1%	10,040	94.7%	14,922	93.8%	
Unknown	477	1.8%	198	1.9%	279	1.8%	
Reason for Evaluation							
Abnormal X-ray	5,397	20.4%	2,014	19.0%	3,383	21.3%	<.0001
TB Symptoms	16,999	64.1%	7,052	66.5%	9,947	62.5%	
Other	3,941	14.9%	1,453	13.7%	2,488	15.6%	
Missing	181	0.7%	84	0.8%	97	0.6%	
Homeless Within Past Year							
Yes	1,873	7.1%	879	8.3%	994	6.2%	<.0001
No	24,526	92.5%	9,677	91.3%	14,849	93.3%	
Missing	119	0.4%	47	0.4%	72	0.5%	
Resident of Correctional Facility							
Yes	959	3.6%	370	3.5%	589	3.7%	0.36
No	25,470	96.0%	10,204	96.2%	15,266	95.9%	
Missing	89	0.3%	29	0.3%	60	0.4%	
Resident of Long-Term Care Facility							
Yes	384	1.5%	145	1.4%	239	1.5%	0.37
No	26,096	98.5%	10,441	98.6%	15,655	98.5%	
Missing	38	0.1%	17	0.2%	21	0.1%	
Employment Status							
Employed	11,051	42.6%	4,415	42.6%	6,636	42.6%	1.00
Not Employed	14,900	57.4%	5,953	57.4%	8,947	57.4%	
Missing	567	2.2%	235	2.3%	332	2.1%	
Drug Use Within Past Year							
Yes	2,509	9.7%	1,198	11.6%	1,311	8.4%	<.0001
No	23,815	91.8%	9,327	90.0%	14,488	93.0%	
Missing	194	0.7%	78	0.8%	116	0.7%	

Excess Alcohol Within Past Year							
Yes	3,992	15.4%	1,967	19.0%	2,025	13.0%	<.0001
No	22,323	86.0%	8,549	82.5%	13,774	88.4%	
Missing	203	0.8%	87	0.8%	116	0.7%	
End-Stage Renal Failure							
Yes	290	1.1%	96	0.9%	194	1.2%	0.02
No/Missing	26,228	98.9%	10,507	99.1%	15,721	98.8%	
Post-Organ Transplant							
Yes	90	0.3%	27	0.3%	63	0.4%	0.05
No/Missing	26,428	99.7%	10,576	99.7%	15,852	99.6%	
First Line Drug Resistance							
Yes	3,308	12.5%	1,323	12.5%	1,985	12.5%	0.99
No	23,210	87.5%	9,280	87.5%	13,930	87.5%	
Directly Observed Therapy							
Self-Administered	868	3.4%	368	3.6%	500	3.2%	0.08
Both Methods	7,666	29.8%	3,101	30.1%	4,565	29.5%	
Directly Observed Only	17,231	66.9%	6,841	66.4%	10,390	67.2%	
Missing	753	2.9%	293	2.8%	460	3.0%	
Provider Type							
Health Department Only	18,363	69.2%	7,188	67.8%	11,175	70.2%	<.0001
Any Private Provider Use	6,745	25.4%	2,886	27.2%	3,859	24.2%	
Missing	1,410	5.3%	529	5.0%	881	5.5%	

[a]343 patients were missing time to sputum conversion data

[b]Delayed Conversion defined as time until conversion over 65 days, exclusive

[c]Reference group

[d]P-values calculated using chi-square test of independence or Fischer's exact test

Table 3. Univariate Analysis of Characteristics U.S. TB Patients and Sputum Conversion Status, 2010-2015

	Crude Odds Ratio	95% Confidence Interval		P-Value
TNF-antagonist Therapy	0.60	0.402	0.882	0.01
Race/Ethnicity				
White	REF			
Black	0.71	0.65	0.77	<.0001
Asian	0.58	0.54	0.63	<.0001
Hispanic	0.73	0.68	0.79	<.0001
Other	1.22	1.08	1.38	0.0012
Sex	1.28	1.21	1.34	<.0001
Age at Diagnosis				
15-24[c]	REF			
25-44	0.90	0.83	0.99	0.03
45-64	1.04	0.97	1.11	0.31
65+	1.36	1.27	1.46	<.0001
Place of Birth	0.67	0.64	0.71	<.0001
Initial Smear Positivity	1.50	1.42	1.58	<.0001
Cavitation	1.60	1.52	1.68	<.0001
Site of TB Disease	0.54	0.50	0.59	<.0001
HIV Status	0.69	0.61	0.77	<.0001
Diabetes Status	1.17	1.10	1.25	<.0001
Recent Immigration Status	0.91	0.81	1.02	0.12
Evidence of Miliary Disease	0.76	0.67	0.86	<.0001
Reason for Evaluation				
TB Symptoms	REF			
Other	0.82	0.77	0.88	<.0001
Abnormal X-Ray	0.84	0.79	0.89	<.0001
Homeless Within Past Year	1.36	1.23	1.49	<.0001
Resident of Correctional Facility	0.94	0.82	1.07	0.36
Resident of Long-Term Care Facility	0.91	0.74	1.12	0.37
Employment Status	1.00	0.95	1.05	1.00
Drug Use Within Past Year	1.42	1.31	1.54	<.0001
Excess Alcohol Within Past Year	1.57	1.46	1.67	<.0001
End-Stage Renal Failure	0.74	0.58	0.95	0.02
Post-Organ Transplant	0.64	0.41	1.01	0.05
First Line Drug Resistance	1.00	0.93	1.08	0.99
Directly Observed Therapy	1.04	0.99	1.09	0.08
Provider Type				
Health Department Only	REF			
Any Use of Private Provider	1.15	1.08	1.24	<.0001

Table 4. Associations Between TNF Antagonist Therapy and Delayed Sputum Conversion Among US TB Patients, Stratified by Place of Birth

	Crude OR	95% CI		p-value	Adjusted OR*	95% CI		p-value
Domestic	0.33	0.16	0.69	0.003	0.26	0.10	0.69	0.007
Foreign Born	0.81	0.51	1.28	0.363	0.94	0.56	1.58	0.819

*Adjusted for: Site of TB disease, sex at birth, race/ethnicity, age at diagnosis, HIV status at diagnosis, cavitary disease, excess alcohol use within the past year, drug use within the past year, end stage renal failure, post-organ transplant status, homelessness within the past year, and provider type.

Table 5. Associations of Demographic and Clinical Factors with Sputum Conversion, Stratified by Place of Birth

	Domestic		Foreign born	
	n (delayed/ <8 weeks)	OR (95% CI)	n (delayed/ <8 weeks)	OR (95% CI)
TNF-antagonist Therapy				
No	4,359/5,077	1	6,194/10,747	1
Yes	9/32	0.33 (0.16 - 0.69)	26/56	0.81 (0.51 - 1.28)
Race/Ethnicity				
Hispanic	702/904	0.81 (0.72-0.92)	2,415/3,793	0.87 (0.74 - 1.01)
Non-Hispanic				
White	1,507/1,579	1	313/427	1
Black	1,437/1,989	0.76 (0.69 - 0.83)	651/1,255	0.71 (0.59 - 0.84)
Asian	95/162	0.61 (0.47 - 0.80)	2,695/5,095	0.72 (0.62 - 0.84)
Other	612/469	1.37 (1.19 - 1.57)	135/211	0.87 (0.64 - 1.13)
Sex				
Male	3,134/3,402	1.27 (1.17 - 1.39)	4,102/6,596	1.24 (1.16 - 1.32)
Female	1,234/1,706	1	2,117/4,206	1
Age at Diagnosis				
15-24	474/714	1	657/1,380	1
25-44	1,156/1,446	1.20 (1.05 - 1.38)	2243/4,047	1.16 (1.05 - 1.29)
45-64	2,047/1,951	1.58 (1.39 - 1.80)		1.39 (1.25 - 1.55)
65+	691/998	1.04 (.090 - 1.21)	1,316/2,356	1.17 (1.05 -1.32)
Initial Smear				
Negative	1,030/1,795	1	1,885/3,968	1
Positive	3,328/3,300	1.75 (1.60 - 1.92)	4,316/6,806	1.33 (1.25 - 1.43)

Cavitation				
Absent	1,698/2,587	1	2,986/6,187	1
Present	2,528/2,282	1.68 (1.55 - 1.83)	3,053/4,247	1.49 (1.40 - 1.59)
Site of TB Disease				
Pulmonary	4,109/4,568	1	5,734/9,405	1
& Extra-pulmonary	259/541	0.53 (0.46 - 0.62)	4,86/1,398	0.57 (0.51 - 0.64)
HIV Status				
Negative	3,717/4,190	1	5,158/8,999	1
Positive	251/502	.056 (0.48 - 0.66)	242/565	0.75 (0.64 - 0.87)
Diabetes				
Non-Diabetic	3,732/4,509	1	4,969/8,921	1
Diabetic	636/600	1.28 (1.14 – 1.44)	1,251/1,882	1.19 (1.10 - 1.29)
Recent Immigration				
Yes	--	--	510/952	0.90 (0.80 - 1.01)
No	--	--	2,664/4,483	1
Evidence of Miliary Disease				
Yes	156/227	0.80 (0.65 – 0.98)	208/486	0.72 (0.62 - 0.87)
No	4,134/4,802	1	5,894/10,118	1
Reason for Evaluation				
Abnormal X-ray	1,001/1,238	0.87 (0.79 – 0.96)	1,009/2,144	0.76 (0.70 – 0.83)
TB Symptoms	2,701/2,920	1	4,342/7,025	1
Other	640/927	0.75 (0.67 – 0.84)	811/1,561	0.84 (0.77 - 0.92)
Homeless Within Past Year				
Yes	648/683	1.13 (1.01 -1.27)	229/311	1.29 (1.08 - 1.53)
No	3,699/4,403	1	5,964/10,444	1
Resident of Correctional Facility				
Yes	176/289	0.70 (0.58 – 0.85)	192/300	1.11 (0.93 - 1.34)
No	4,182/4,804	1	6,009/10,459	1
Resident of Long-term Care Facility				
Yes	92/131	0.82 (0.63 – 1.07)	53/108	0.85 (0.61 - 1.18)
No	4,266/4,972	1	6,160/10,680	1
Employment Status				
Employed	1,428/1,622	1	2,984/5,014	1
Not Employed	2,871/3,407	0.96 (0.88 – 1.04)	3,071/5,538	0.93 (0.87 - 0.99)
Drug use within past year				
Yes	939/977	1.16 (1.05 – 1.28)	259/334	1.36 (1.16 - 1.61)
No	3,401/4,090	1	5,912/10,395	1
Excess alcohol within past year				
Yes	1,325/1,220	1.39 (1.27 – 1.52)	641/804	1.43 (1.29 - 1.60)
No	3,014/3,847	1	5,522/9,925	1
End-Stage Renal Failure				
Yes	30/59	0.59 (0.38 – 0.92)	66/135	0.85 (0.63 - 1.14)

No	4,338/5,050	1	6,154/10,668	1
Post-Organ Transplant				
Yes	8/16	0.58 (0.25 – 1.37)	19/47	0.70 (0.41 - 1.20)
No	4,360/5,093	1	6,201/10,756	1
First Line Drug Resistance				
Yes	346/416	.097 (.084 – 1.13)	977/1,569	1.10 (1.01 - 1.20)
No	4,022/4,693	1	5,243/9,234	1
Directly Observed Therapy				
Self-Administered	110/125	1.04 (.080 – 1.35)	258/375	1.23 (1.04 - 1.45)
Directly Observed	2,968/3,495	1	3,860/6,892	1
Both	1,172/1,349	1.02 (0.93 -1.12)	1,928/3,216	1.07 (1.00 - 1.15)
Provider Type				
Health Department Only	3,073/3,643	1	4,106/7,530	1
Any Private Provider Use	1,099/1,239	1.05 (.096 – 1.16)	1,784/2,619	1.25 (1.16 - 1.34)