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Risk factors for tuberculin skin test conversion among HIV-infected patients in New York City

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SUMMARY

Background: We assessed the incidence of and risk factors for tuberculin skin test (TST) conversion among HIV-infected adults at a New York City clinic.
Methods: All adult HIV-infected patients were eligible for inclusion if they had a negative baseline TST result and at least one subsequent documented TST test result.
Results: A total of 414 HIV-infected patients had a negative baseline TST result; 288 (69.6%) were male. Among 348 patients who had a place of birth documented, 50% were born outside of mainland USA. Twenty-two (5.3%) of 414 patients had documented TST conversions, giving a crude incidence rate of 1.77 per 100 person-years. Being a foreign-born Asian individual ($p = 0.02$), having lived in a shelter ($p = 0.004$), and having an increase in CD4 cell count ($p = 0.02$) while under care were independent risk factors for TST conversion.
Conclusions: We found a high TST conversion rate among HIV-infected patients attending an urban clinic. Annual TST testing is particularly important for patients who are foreign-born from high-endemic countries, those with a history of homelessness, and those with an increase in CD4 cell count since the baseline negative TST test.

1. Introduction

HIV-infected individuals are 10 times more likely than HIV-uninfected individuals to progress from latent tuberculosis infection (LTBI) to active tuberculosis (TB).[1] Due to the high rate of progression and greater severity of TB disease among HIV-infected individuals, diagnosis and treatment of LTBI in this population is critical.[2] Despite many limitations, the tuberculin skin test (TST) remains the primary diagnostic tool for LTBI, including for HIV-infected persons.

The New York State Department of Health AIDS Institute's HIV Quality of Care Program (HIVQUAL) is responsible for the systematic monitoring of the quality of medical care provided to people with HIV infection in New York's hospitals, chronic care facilities, and community-based organizations.[3] One quality indicator required of clinics that receive funding from Ryan White grants is an annual TST for all HIV-infected patients.[3] However, few data exist on the incidence of TST conversion and associated risk factors in HIV-infected patients,[4] and none in a non-study clinic setting. The aim of this study was to assess the incidence of TST conversion and to identify risk factors for conversion among patients attending our HIV clinic in New York City.

2. Methods

All adult HIV-infected patients (age ≥18 years) were eligible for inclusion if they had attended the Bellevue Hospital Center's Virology Clinic at least twice between January 1, 1995 and December 31, 2006. The initial cohort identified from this search included 1047 patients. This research protocol was reviewed by the New York University School of Medicine Institutional Review Board and ruled exempt because it was a retrospective chart review conducted in such a way that the subjects could not be identified directly or through identifiers linked to the subjects.

We reviewed paper and electronic charts, including clinic, emergency room, and inpatient visits, using a standardized data collection form. Fifty-nine charts (5.6%) were unavailable for review and therefore excluded. Among the patients with available charts ($n = 988$), patients were excluded if they had no record of a TST test result in their medical chart ($n = 286$, 28.9%), had an initial

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positive TST result (n = 101, 10.2%), or had a history of active TB (n = 18, 1.8%). Of the remaining 583 patients with a negative initial TST result, 169 (29.0%) were excluded because they had no further TST testing. The remaining 414 patients who had a negative baseline TST result and at least one subsequent TST test documented were included in this analysis.

Data abstracted included gender, age, race, birthplace, and year of arrival to the USA (if foreign-born). History of vaccination with bacillus Calmette–Guérin (BCG) was not routinely recorded and therefore not included in the study. Information was collected at baseline and again at the time of each subsequent TST test on: (a) HIV history, including CD4 cell count, HIV viral load, and receipt of antiretroviral therapy, and (b) known risk factors for TST conversion, including history of living in a shelter, history of incarceration, history of living in a group home, history of being a home health aide or healthcare provider, exposure to a person with known active TB, and alcohol or drug dependence.

The standard operating procedure was to perform an annual TST on all HIV-infected persons during their comprehensive exam, regardless of risk of TB infection, and after a possible exposure to a person with active TB. The two-step TST was not routinely conducted. TSTs were performed by intra-dermal injection using 5 TU intermediate strength purified protein derivative. Induration was measured 48–72 h after inoculation. A physician confirmed all skin reactions suspected to be positive. Induration with a transverse diameter of 5 mm or greater was considered positive. Patient-read results were not counted. A TST conversion was defined by the development of a TST with $\geq$5 mm induration after a previously negative test ($<$5 mm).[4]

For non-converters, the time at risk for TST conversion was estimated as the interval between the first and last tests. For the converters, the time at risk was the interval from the first to last negative test plus half the interval from the last negative to the first positive test. The impact of a rise in CD4 cell count on risk of conversion during the period of observation was assessed by computing the change from the first to last CD4 count for all persons who had at least two CD4 cell counts taken at least 90 days apart. The last CD4 count used in the analysis was the most recent test for non-converters and the test closest to the date of conversion for the converters.

Final analyses were done using either SPSS v.12 (IBM-SPSS, Chicago, IL, USA) or the statistical environment 'R' (http://www.r-project.com). Survival curves were estimated by the method of Kaplan and Meier, and hazard ratios were estimated using Cox proportional hazards regression. Baseline risks were considered as time-invariant factors and interval risks recorded at the time of each TST were considered as time-dependent factors. The curves and ratios were compared using the log rank test. Nested regression models containing both time-invariant and time-dependant factors were compared to reduced models by assessing the change in deviance using an F ratio or Chi-square test. Means of continuous variables were compared using the Student's t-test and medians were compared using the Wilcoxon signed-rank test.

3. Results

Among the 414 HIV-infected patients with a negative baseline TST result, 288 (69.6%) were male (Table 1). The median age was 42 years (interquartile range (IQR) 36–50 years), and men were significantly older than women (means 43.9 vs. 40.2 years, p = 0.0005). Of the 394 patients with a race or ethnicity recorded, 172 (43.7%) were identified as Hispanic, 150 (38.1%) as black, 42 (10.6%) as white, and 30 (7.6%) as Asian (Table 1). Among 348 patients who had place of birth documented, 174 (50%) were born outside of mainland USA.

Table 1
Baseline characteristics of patients with negative baseline tuberculin skin testing (n = 414)

Characteristic	
Male sex, n (%)	288 (70)
Median age, years (range)	42 (19–71)
Race, n (%)	
Black	150 (36)
Hispanic	172 (42)
Asian/Pacific Islander	30 (7)
White	42 (10)
Unknown	20 (5)
Birthplace, n (%)	
Mainland USA (not including Puerto Rico)	174 (42)
Outside of mainland USA (including Puerto Rico)	174 (42)
Unknown	66 (16)

3.1. TST conversion

Twenty-two (5.3%) of 414 patients had documented TST conversions. The 22 patients who converted were at risk for 47.99 person-years and the 392 non-converters were at risk for 1193.48 person-years. Overall, the incidence of TST conversion was 1.77 per 100 person-years at risk. The incidence of TST conversion among men was 1.73 conversions per 100 person-years observation (15 conversions in 865.05 person-years) and among women was 1.88 conversions per 100 person-years observation (7 conversions in 371.82 person-years). Twenty-five percent of patients were observed for more than 3.9 years, 50% for 2.8 years or more, and 75% for 1.6 years or more. Among the 22 persons who converted their TST, nine (41%) converted on their second TST, nine (41%) on their third TST, two (9%) on their fourth TST, one (5%) on their fifth TST, and one (5%) on their sixth TST. The median interval between tests was 412 days (IQR 330–611) and there was no evidence that this interval changed as the number of prior TSTs increased.

3.2. Risk factors for TST conversion

Patients who identified themselves as Asian had a higher rate of TST conversion (Table 2, Figure 1A). The omnibus log rank test for race was significant (log rank Chi-square = 14.2, degree of freedom (df) = 4, p = 0.007) and became non-significant when Asians were removed from the analysis. Being foreign-born was also a significant risk factor (log rank Chi-square = 5.5, df = 1, p = 0.019) and became non-significant when Asians, all of whom were foreign-born, were removed from the analysis (log rank Chi-square = 3.0, df = 1, p = 0.08).

Patients who experienced a TST conversion had a non-significantly lower baseline median CD4 cell count compared to non-converters: 100 cells/ml (IQR 0–564) vs. 278 cells/ml (IQR 80–460) (p = 0.21). Among the converters, by the time of TST conversion, the median CD4 cell count had risen to 482 cells/ml (IQR 323–662). Three hundred and seventy-three persons had at least two CD4 tests conducted 90 or more days apart (median interval from first to last CD4 test was 995 days (IQR 558–1361)). Among these 373 persons, 124 (33.2%) had a decline or no change in the CD4 cell count from baseline (mean −134.4 (SD 139.9)) and 249 (66.8%) had an increase (mean 203.7 (SD 171)). Patients with increases in the CD4 cell count had a significantly higher TST conversion rate compared to those with no increase or a decrease in CD4 cell count (relative hazard 7.64, log rank Chi-square = 5.4, df = 1, p = 0. 02) (Figure 1B). The median increase in CD4 count for converters was 223 (IQR 113–275) and for non-converters it was 63.5 (IQR −36.5–214.5) (p = 0.009).

Patients with a history of having ever lived in a shelter had a higher rate of conversion (relative hazard = 3.49, p = 0.004)

Table 2
Tuberculin skin test (TST) conversion rates and risk factors for conversion

Risk factor for TST conversion	Conversions/ at risk	HR (95% CI)	*p*-Value
Ever lived in shelter?			
Yes	7/48	3.49 (1.42–8.57)	0.004
No	15/366		
Race			0.007
White	1/42	1	
Hispanic	6/172	1.03 (0.124–8.63)	
Black	9/150	1.90 (0.24–15.13)	
Asian/Pacific Islander	6/30	6.05 (0.7–50.35)	
Born in USA (including Asian race)			
Not mainland USA	15/174	3.46 (1.15–10.4)	0.019
Mainland USA	4/174		
Change in CD4 cell count			
Increased during period	16/249	7.64 (1.01–57.7)	0.020
Decreased during period	1/124		
Born in USA (excluding Asian race)			
Not USA	10/147	2.67 (0.837–8.54)	0.084
USA (not Puerto Rico)	4/174		
Initial viral load			
<50 copies/ml	5/118	2.71 (0.725–10.1)	0.123
≥50 copies/ml	4/211		
Any alcohol dependence?			
Yes	3/103	0.48 (0.14–1.62)	0.219
No	19/311		
Any recreational drug use?			
Yes	7/181	0.60 (0.25–1.47)	0.261
No	15/233		
Ever lived in a group home?			
Yes	1/23	0.74 (0.1–5.48)	0.765
No	21/391		
Age by quartile, years			0.382
19–36	10/117	1	
37–42	5/93	0.76 (0.26–2.25)	
43–50	5/105	0.63 (0.22–1.88)	
51–71	2/99	0.28 (0.061–1.30)	
Sex			
Female	7/126	1.09 (0.45–2.68)	0.846
Male	15/288		
Ever incarcerated?			
Yes	3/51	1.10 (0.32–3.71)	0.883
No	19/363		

HR, hazard ratio; 95% CI, 95% confidence interval.

compared to those who had not (Table 2, Figure 1C). Adding the time-dependant information to the baseline information on shelter residence increased the hazard ratio slightly (to 3.6), but the increase was not significant (deviance = 0.364, df = 1, $p = 0.50$).

Age, gender, prior or interval of intravenous drug use, alcohol dependence, incarceration, living in a group home, exposure to a person with known tuberculosis, receiving antiretroviral therapy at the time of initial visit, and having an undetectable HIV viral load (<50 copies per ml) at the time of the initial visit were not associated with an increased risk of TST conversion.

4. Discussion

Conversion of a TST from a negative to a positive in an HIV-infected patient may occur because of new TB infection, a boosting effect, or improved TB-specific immune responses.[2] We found that among HIV-infected patients attending a municipal clinic in New York City, the incidence of TST conversion was 1.77 cases per 100 person-years at risk. Being a foreign-born person of Asian ethnicity, having ever lived in a homeless shelter, and having an increase in CD4 cell count were each an independent risk factor for TST conversion.

The incidence of TB cases in the USA decreased by 45% between 1993 and 2006.[5] This decline has occurred disproportionately among the US-born population; in 2006, 57% of all reported TB cases were among foreign-born persons.[5] A recent study found that 53% of TB cases among foreign-born persons occurred in persons from sub-Saharan Africa and Southeast Asia.[6] Our study found that being Asian was a significant risk factor for TST conversion. Furthermore, when Asians were taken out of the analysis, being foreign-born was no longer an independent risk factor. This and the previously cited data[6] support the recommendation that annual testing be administered to persons born in countries with a high burden of TB rather than all foreign-born individuals.[2]

Many persons born in TB-endemic countries receive BCG vaccination during childhood and therefore may react to a TST even without exposure to *Mycobacterium tuberculosis*.[7] The tuberculin reactivity in BCG-vaccinated individuals does wane over time but can be boosted by the TST. A two-step TST entails a second test conducted 1 to 4 weeks after the first negative TST to identify those who have an attenuated but existing immunologic recall of the tuberculosis antigen. A positive result after an initial negative result in a two-step test is referred to as the 'booster phenomenon'. A subsequent positive TST result after a negative two-step TST result is assumed to represent a true conversion. In the present study, because BCG vaccination history was not recorded and two-step testing was not systematically recorded, we cannot confidently rule out a boosting effect as a contributing factor to the higher rates of conversion we observed among foreign-born patients. Nevertheless, the high incidence of active TB infection among foreign-born persons places them at great risk of being exposed to TB. Therefore, foreign-born HIV-infected patients with a new TST conversion would require LTBI treatment regardless of BCG vaccination history.

Homelessness and living in shelters are known risks for TB.[2,8,9] Our findings support recommendations for annual TST testing in

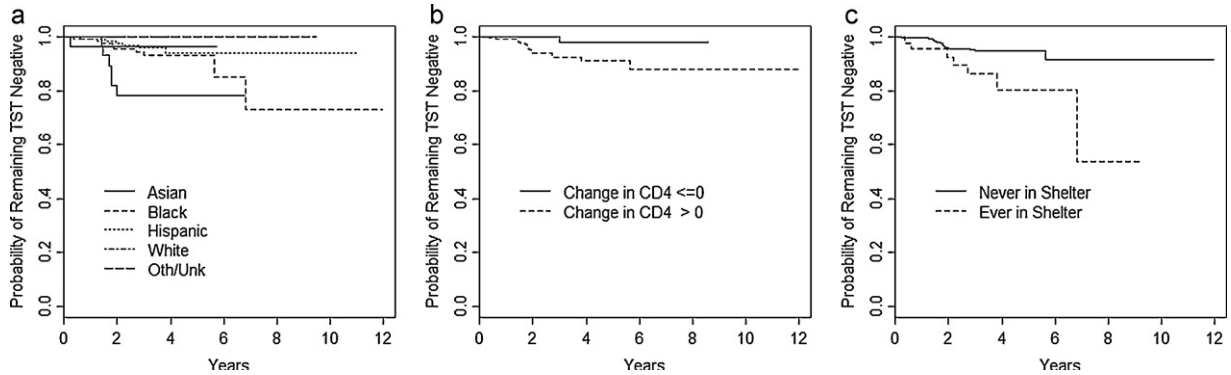

Figure 1. Kaplan–Meier estimates of the probability of remaining tuberculin skin test (TST)-negative for HIV-infected patients by (A) race, (B) change in CD4 cell count, and (C) history of living in a homeless shelter.

HIV-infected patients who have a history of homelessness. In practice, this would include conducting annual TST testing not only in those who are currently homeless or living in shelters, but in patients who have a history of homelessness or are intermittently homeless.

Restoration of *M. tuberculosis*-specific immune function with antiretroviral therapy occurs[10] and may lead to TST conversion in patients receiving HIV treatment. The current recommendation to re-administer a TST after the CD4 cell count increases to above 200 cells/ml is based on expert opinion.[2] A recent study revealed that recent initiation of highly active antiretroviral therapy (HAART) (within 2 years) and not any specific CD4 threshold was a risk factor for TST conversion.[4] We found that patients who had an increase in CD4 count while under observation were more likely to experience a TST conversion compared to patients whose CD4 count did not increase or decreased since the baseline TST. The median increase in CD4 cell count among converters was 223 cells/ml compared to 63.5 cells/ml among non-converters. Furthermore, the median CD4 count at baseline was 100 cells/ml compared to 482 cells/ml at the time of conversion, supporting the recommendations for repeat TST after CD4 cell counts rise to above 200 cells/ml.

Although the New York State AIDS Institute's HIVQUAL program recommends annual TSTs in all HIV-infected patients, guidelines written by the US Public Health Service and the Infectious Diseases Society of America (IDSA) recommend initial TST for all HIV-infected patients and annual skin testing only for those patients at high risk for exposure to tuberculosis and those whose immune function has improved in response to antiretroviral therapy.[11]

The incidence of TST conversion among women in our study, 1.9 conversions per 100 person-years observation (7 conversions in 371.82 person-years), is significantly higher than the rate of 0.8 conversion per 100 person-years (36 conversions within 4416 person-years observation, $p = 0.037$) previously reported among HIV-infected women enrolled in the Women's Interagency HIV Study (WIHS) cohort.[4] In both studies, two-step skin testing was not performed and the definition of TST conversion was the same, making comparisons more legitimate. Differences in conversion rates between the studies could be due to other factors, including misclassifications of positive TST results in either study, since accurate interpretation of TST is notoriously difficult,[12] and differences in the racial composition of the two cohorts. Although both cohorts are from socio-economically disadvantaged sectors of society, non-white or non-black women made up <2% of the WIHS cohort (listed as 'other'), while 5.6% of our women were Asian.[13] Another possible explanation is that persons enrolled in prospective cohort studies may be at lower risk for TB infection than the population at large.

Several limitations of this observational study require mention. First, as previously noted, two-step testing was not performed at baseline and therefore we could not differentiate between true conversion from new TB infection and a booster phenomenon. Second, induration size was not noted and the TST result was indicated as being 'positive' if ≥5 mm or 'negative' if <5 mm. Therefore, we could not measure changes in induration size. When repeat TST testing is conducted, increases of ≥6 mm are considered to represent a true biological phenomenon (boosting or conversion) rather than inherent variability of the test due to differences in administration and reading or non-specific differences in biological response to tuberculin.[14] The Centers for Disease Control and Prevention (CDC) guidelines define a new conversion in persons undergoing repeat TST testing (generally health workers) as a ≥10 mm increase in induration, although no specific recommendations are made for repeat testing of HIV-infected persons.[15] For these reasons, small increases in induration size (e.g., from 3 mm to 6 mm) may have been misclassified as conversions instead of expected variability of the test. Finally, this study was conducted in a single site located in a New York City public hospital, limiting the generalizability of our data. However, surveillance data in 2006 indicate that 82% of reported AIDS cases were among persons residing in urban areas with a population >500 000, therefore our study is likely to be relevant to the majority of infected patients in the USA.[16]

In summary, among HIV-infected patients attending a municipal HIV clinic in New York City, we found a high TST conversion rate of 1.77 per 100 person-years. Being a foreign-born Asian individual, having a history of living in a shelter or being homeless, and an increase in CD4 cell count were independent risk factors for conversion. Patients in these groups, as well as foreign-born persons from other high-endemic countries, should be targeted for baseline two-step TST and annual TST so that appropriate treatment for LTBI can be prescribed.

Conflict of interest: No competing interest declared.

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