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# Potentially preventable tuberculosis among HIV-infected persons in the era of highly active antiretroviral treatment

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## SUMMARY

**OBJECTIVE—**To characterize the proportion of tuberculosis (TB) cases that could have been prevented among human immunodeficiency virus (HIV) infected persons receiving care in the era of highly active antiretroviral treatment (HAART).

**DESIGN—**We conducted an observational cohort study among HIV-infected patients with ≥2 out-patient visits at the Comprehensive Care Center, Nashville, Tennessee, USA, between 1 January 1998 and 31 December 2005.

**METHODS—**A potentially preventable TB case was defined as a case in which the patient received no screening tuberculin skin test (TST) prior to TB diagnosis or a case in which a patient with a positive screening TST did not complete treatment for latent infection.

**RESULTS—**Of 3601 HIV-infected persons in care (13 905 person-years [p-y] of follow-up), 29 developed TB (230/100 000 p-y). Of the 29, 20 (69%) had not had TST performed as part of routine screening. Of the nine patients screened, four had a positive test, three of whom completed treatment for latent TB infection. Of 29 TB cases, 21 (72%) were therefore potentially preventable.

**CONCLUSIONS—**Most TB cases in this cohort were potentially preventable had the patients undergone a screening TST followed by treatment of latent infection if they had a positive TST.

### Keywords

tuberculosis; *M. tuberculosis* infection; tuberculin skin testing; human immunodeficiency virus; highly active antiretroviral treatment

THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) increases the risk of tuberculosis (TB) disease among persons infected with *Mycobacterium tuberculosis*.[1] Treatment of latent TB infection (LTBI) reduces this risk, but tuberculin skin testing (TST) and other tests for *M. tuberculosis* infection are not routinely performed.2,[3] Highly active antiretroviral treatment (HAART) reduces the risk of TB,[4] but it can also 'unmask' undiagnosed TB via immune



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reconstitution, potentially increasing the risk of transmission.5 It is important to diagnose and treat LTBI in HIV-infected persons, and to identify sub-clinical TB prior to the initiation of HAART.

## METHODS

### Patient population

We conducted an observational cohort study among patients in care at the Comprehensive Care Center (CCC), a multidisciplinary HIV clinic in Nashville, Tennessee, USA. HIV-1 seropositive patients with two or more provider visits between 1 January 1998 and 31 December 2005 were included.

This study was approved by the Vanderbilt Institutional Review Board.

### Study definitions

Patients with TB diagnosed after the first CCC visit were included. Diagnoses were classified as culture-positive or -negative. Culture-negative TB was diagnosed based on the provider's clinical judgment, with or without a specimen with caseating/necrotizing granulomas and/or acid-fast bacilli. Date of TB diagnosis was the date of initiation of anti-tuberculosis treatment. For patients with recurrent TB, both TB episodes were included in the case rate analysis. For all other analyses, only the first episode was included. A potentially preventable TB case was defined as a case in which the patient received no screening TST before TB diagnosis or a case in which a patient with a positive screening TST did not complete treatment for LTBI.

Demographic and laboratory data were obtained via electronic medical records. Charts were reviewed to validate electronic data and fill in missing data. For both CD4+ lymphocytes and HIV-1 RNA, baseline values were defined as the first available values within 120 days before or up to 365 days after the first study visit.

TST was considered part of routine screening if performed >90 days before TB diagnosis, and part of the TB diagnostic work-up if performed <90 days before diagnosis.

HAART utilization was validated by chart review for all study patients. HAART was defined as regimens that contained ≥3 nucleoside reverse-transcriptase inhibitors (NRTIs), ≥2 NRTIs plus either ≥1 one non-nucleoside reverse-transcriptase inhibitor (NNRTI) or ≥1 protease inhibitor (PI), ≥1 NRTI and ≥1 NNRTI and ≥1 PI, or one fusion inhibitor (enfuvirtide or T-20) and either ≥1 NRTI or ≥1 NNRTI or ≥1 PI. Time on HAART prior to TB diagnosis was the time since HAART initiation in naïve patients, or the most recent HAART regimen change in non-naïve patients. Antiretroviral treatment data (including regimen start and stop dates) were entered into an electronic medical record by medical providers at the time of the patient encounter and validated by systematic chart review. If the chart noted that the patient had not taken the prescribed antiretroviral treatment, the patient was coded as not taking antiretroviral treatment during that time period.

### Laboratory methods

HIV-1 RNA in plasma was quantified by reverse transcriptase polymerase chain reaction. CD4 + lymphocytes were quantified by flow cytometry.

### Statistical analysis

Fisher's exact and Wilcoxon rank-sum tests compared categorical and continuous variables, respectively. All *P* values were two-sided. *P* values <0.05 were considered statistically significant.

## RESULTS

Among 3601 HIV-infected patients, there were 32 TB episodes among 29 patients: three patients had two episodes each. Of the three patients with recurrent TB, only one had culture-confirmed disease for both the initial and recurrent episodes. DNA fingerprints of both *M. tuberculosis* isolates were not available, however. TB patients were of similar age and sex as those who did not develop TB, but TB patients were more likely to be Black, have lower median baseline CD4+ lymphocytes, and higher median baseline HIV-1 RNA (Table 1). The median CD4+ lymphocyte count of the 29 TB patients before TB diagnosis was 120 cells/mm$^3$ (interquartile range [IQR] 64–225).

There were 13 905 person-years (p-y) of follow-up for the study population, and a TB case rate of 230 per 100 000 p-y.

Twenty of the 29 (69%) patients did not have TST performed as part of routine screening prior to TB diagnosis. Characteristics of persons with and without TST screening are shown in Table 2; those who were screened tended to have higher median CD4 counts and lower median HIV-1 RNA at baseline, although these differences were not statistically significant. Of the nine patients screened, four had a positive test, three of whom completed treatment for LTBI. One of the four positive screening tests was not documented in millimeters of induration, only as 'positive' but, according to standard guidelines for TST in HIV-infected patients, would have been at least 5 mm.[6] The indurations for the remaining three patients were 20, 20 and 25 mm. The median CD4+ lymphocyte count before screening TST was 171 cells/mm$^3$ (IQR 84–434). Among the five patients with negative TST results, the median CD4+ lymphocyte count prior to TST was 171 cells/mm$^3$ (IQR 40–372). Among the four patients with positive TST results, the median CD4+ lymphocyte count prior to TST was 282 cells/mm$^3$ (IQR 119–499).

Fifteen of the 29 (52%) patients developed TB on HAART. Six of the 15 (40%) cases occurred within 90 days after HAART initiation. Patients who developed TB >90 days after HAART initiation were similar to those who did so <90 days after HAART initiation (Table 3). Fourteen patients were not on HAART at the time of TB diagnosis. The median CD4+ lymphocyte count of those 14 patients was 87 cells/mm$^3$ (IQR 57–179). Among the 15 patients on HAART at the time of TB diagnosis, the median CD4+ lymphocyte count was 150 cells/mm$^3$ (IQR 64–372).

## DISCUSSION

The most important finding of this study was that most TB cases were potentially preventable. Twenty of the 29 patients (69%) did not receive screening TST, and of the four with positive tests only three completed treatment for LTBI. Thus, 21/29 (72%) TB cases were potentially preventable. This suggests that with greater efforts to identify and treat *M. tuberculosis* infection, TB case rates could be dramatically reduced among HIV-infected persons in care.

Several caveats must be noted when determining the number of preventable TB cases. First, TST is insensitive in persons with advanced HIV.7 However, newer diagnostic tests such as ELISpot may be more sensitive in HIV-infected persons.8 Second, the effectiveness of treatment of LTBI is limited by low adherence rates. At most, 21/29 (72%) TB cases in our study could have been prevented. A more conservative estimate would be to assume 70% sensitivity8 of TST in HIV-infected persons and 20–60% effectiveness of treatment of LTBI. 9 Of the 21 cases, the number prevented would therefore range from three (70% × 20% = 14% × 21 = 3) to nine (70% × 60% = 42% × 21 = 9). Of the 29 total patients with TB, 3/29 (10%) to 9/29 (31%) could have been prevented. While much less than 72%, it would still be a substantial reduction in TB burden. A recent study among HIV-infected persons concluded

that TST screening and treatment of patients with positive results reduced TB incidence, even with rates of testing and treatment completion substantially under 100%.10

Half (15/29, 52%) of the patients who developed TB in our cohort did so while receiving HAART. Although HAART reduces the risk of TB in HIV-infected persons,4 and the risk decreases with time on HAART,11 the risk is still significantly higher than in HIV-seronegative persons. This is illustrated by the substantially higher TB incidence in the study population than in the general Tennessee population (5.9/100 000 population) during the study period.12

Six of the 15 (40%) cases occurred within 90 days after HAART initiation. It is possible that patients who develop TB soon after HAART initiation are 'unmasking' a previous infection due to immune reconstitution.[5] However, it is not possible to determine which of the patients in this cohort developed TB due to progression of a previous infection or a recent infection.

Fourteen patients were not on HAART at the time of TB diagnosis. The median CD4+ lymphocyte count of these 14 patients was 87 cells/mm$^3$ (IQR 57–179). Based on the current HIV treatment guidelines, many of these patients should have been on HAART.[13] If they had been initiated on treatment at the appropriate time, these TB episodes might have been prevented as well.

There were limitations of this study. First, data on TST were not available for the patients who did not develop TB. However, such information was not necessary to investigate our primary outcome: the proportion of potentially preventable TB cases. Second, we did not have data regarding TST performed at institutions other than the CCC. Third, some cases of TB could have been missed if the provider did not enter the diagnosis into the electronic record.

We conclude that screening for and treatment of *M. tuberculosis* infection could substantially reduce the number of TB cases among HIV-infected persons in care. Earlier diagnosis of TB among persons in whom it is unmasked by HAART would also improve the care of such patients.

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## Table 1

Demographic characteristics of the study population (all HIV-infected)

| Characteristic | Entire cohort (*N* = 3601) | TB patients (*n* = 29) | Patients without TB (*n* = 3572) | *P* value |
|---|---|---|---|---|
| Age, years, median (IQR) | 37 (31–43) | 37 (32–41) | 37 (31–43) | 0.74 |
| Male sex, *n* (%) | 2 770 (77) | 26 (90) | 2 744 (77) | 0.12 |
| Black race, *n* (%) | 1 326 (37) | 20 (69) | 1 306 (37) | 0.01 |
| Injection drug use, *n* (%) | 482 (13) | 6 (21) | 476 (13) | 0.27 |
| Baseline CD4+ lymphocytes/mm$^3$, median (IQR)* | 320 (162–513) | 179 (114–372) | 322 (162–513) | 0.02 |
| Baseline CD4%, median (IQR) | 21 (13–30) | 16 (10–26) | 21 (13–30) | 0.15 |
| Baseline HIV-1 RNA, copies/ml, median (IQR) † | 13 266 (1065–72 909) | 37 980 (5577–242 751) | 13 213 (1036–72 209) | 0.03 |

HIV = human immunodeficiency virus; TB = tuberculosis; IQR = interquartile range.

* CD4+ lymphocyte count and per cent were available for 3460 of 3601 patients.

† HIV-1 RNA was available for 3415 of 3601 patients.

## Table 2

Demographic and clinical characteristics according to screening TST

| Characteristic | TB patients who had screening TST (*n* = 9) | TB patients who did not have screening TST (*n* = 20) | *P* value |
|---|---|---|---|
| Age, years, median (IQR) | 39 (29–40) | 37 (32–41) | 0.60 |
| Male sex, *n* (%) | 8 (89) | 18 (90) | 1.00 |
| Black race, *n* (%) | 5 (56) | 15 (75) | 0.40 |
| Intravenous drug use, *n* (%) | 1 (11) | 5 (25) | 0.63 |
| Foreign-born, *n* (%) | 3 (33) | 2 (10) | 0.29 |
| Baseline CD4+ lymphocytes/$mm^3$, median (IQR) | 372 (182–464) | 150 (97–237) | 0.09 |
| Baseline CD4%, median (IQR) | 21 (16–28) | 13 (10–25) | 0.17 |
| Baseline HIV-1 RNA, copies/ml, median (IQR) | 9771 (2795–67 532) | 47 819 (6151-258 862) | 0.33 |

TST = tuberculin skin test; TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus.

## Table 3

Demographic and clinical characteristics according to timing of TB diagnosis in relationship to HAART initiation

| Characteristic | TB diagnosed >90 days from HAART (*n* = 9) | TB diagnosed <90 days from HAART (*n* = 6) | *P* value |
|---|---|---|---|
| Age, years, median (IQR) | 39 (33–46) | 33 (30–40) | 0.16 |
| Male sex, *n* (%) | 8 (89) | 5 (83) | 1.00 |
| Black race, *n* (%) | 7 (78) | 3 (50) | 0.33 |
| Intravenous drug use, *n* (%) | 1 (11) | 2 (33) | 0.53 |
| Foreign-born, *n* (%) | 1 (11) | 1 (17) | 1.00 |
| Baseline CD4+ lymphocytes/mm$^3$, median (IQR) | 120 (85–372) | 160 (108–464) | 0.72 |
| Baseline CD4%, median (IQR) | 19 (8–28) | 16 (11–28) | 0.68 |
| Baseline HIV-1 RNA, copies/ml, median (IQR) | 6695 (2795–40 891) | 11 696 (2000–35 000) | 0.95 |

TB = tuberculosis; HAART = highly active antiretroviral treatment; IQR = interquartile range; HIV = human immunodeficiency virus.