Risk Factors for Developing Active Tuberculosis After the Treatment of Latent Tuberculosis in Adults Infected With Human Immunodeficiency Virus

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Tuberculosis is the leading cause of death among adults infected with human immunodeficiency virus (HIV), and rates of tuberculosis remain high even after preventive therapy. Among 908 HIV-infected adults in a trial of preventive treatment, we found self-reported alcohol consumption, low baseline CD4 count, high baseline viral load, and tuberculin skin test size >15 mm as independent risk factors for incident tuberculosis.

Keywords. baseline; HIV-infected adults; latent tuberculosis; preventive therapy; risk.

METHODS

Study and Source Population

The study population comprised 908 participants from the Soweto/Johns Hopkins Novel Tuberculosis Prevention Regimens Trial. The trial was an open-label, randomized, controlled trial that compared novel combination tuberculosis preventive regimens to daily isoniazid for 6 months. A fourth arm randomized patients to receive daily isoniazid continuously for up to 6 years; patients in this arm had similar rates of tuberculosis as those in the other arms, but in an “as-treated” analysis had significantly lower rates of tuberculosis or death, and it is excluded from this analysis. The parent trial had 1148 eligible participants randomized to the 4 treatment arms. The participants included in this analysis completed at least 80% of their assigned preventive treatment. The first 2 treatment arms (rifapentine-isoniazid and rifampin-isoniazid arms) had directly observed treatment, whereas the third treatment arm (isoniazid for 6 months) had self-reported adherence.

At entry, all participants had HIV infection confirmed by enzyme-linked immunosorbent assay and Western blot analyses and were TST positive (skin reaction of at least 5 millimeters). All participants (1) were at least 18 years of age, (2) were not pregnant or breastfeeding, (3) had no evidence of active tuberculosis, (4) had a CD4 count (once weekly for 12 weeks), and rifampin and isoniazid (twice weekly for 12 weeks) had similar efficacy as isoniazid (daily for 6 months) in preventing a combined outcome of tuberculosis or death in HIV infected adults with latent tuberculosis infection [3]. In this analysis, we studied risk factors for developing incident tuberculosis after receipt of short-term preventive therapy in this population of HIV-infected adults to identify sociodemographic and potentially modifiable clinical and behavioral variables associated with progression to tuberculosis.
Analysis
We used Cox proportional hazards regression models to estimate hazard ratios for incident tuberculosis. The Stata statistical package version 12 was used (StataCorp LP, College Station, TX). The time origin for this analysis was the date of last treatment dose, and the time metric was follow-up time thereafter. Risk factors for incident tuberculosis assessed included the following: age, sex, employment status, highest educational level attained, current living conditions, smoking status, alcohol consumption, baseline CD4 cell count, baseline viral load, baseline TST induration size, and baseline body mass index (BMI). Multivariate models were adjusted by study arm and ART initiation. We did not use time-varying representations of CD4 and viral load, because we wanted to be able to assess medium- to long-term prognosis based on variables available at initial presentation.

RESULTS
The 908 participants in the 3 included arms were observed for a total of 3032.7 person-years (median follow-up time, 3.73 years). There were 59 cases of incident tuberculosis during follow up (1.95 cases per 100 person-years; 95% confidence interval [CI], 1.51–2.50). The median age of participants was 30 years (interquartile range [IQR], 26–34), 83% were female, and all were black. Their median CD4 and viral load at entry was 489 cells/mm3 (IQR, 348–677) and 4.2 log_{10} copies/mL (IQR, 3.5–4.7), respectively. The median baseline BMI was 25 kg/m2 (IQR, 22–29). One hundred sixty-seven participants initiated ART, and ART was an exclusion criterion from cross-sectional and prospective studies have established the association between low CD4 cell count and the risk of tuberculosis. A CD4 cell count below 200 cells/mm3 was statistically significant with the categories of BMI we used, point estimates indicating increased risk of tuberculosis for those with low BMI and decreased risk for those with higher BMI were in accord with those reported by Hanrahan et al [9] in Soweto, South Africa.

Several cross-sectional and prospective studies have established the association between low CD4 cell count and the risk of tuberculosis. A CD4 cell count below 200 cells/mm3 has been found to be associated with increased risk of tuberculosis in HIV-infected people [8, 10]. In our study, a baseline CD4 cell count of less than 200 cells/mm3 was an exclusion criterion; however, we found that a CD4 cell count below 500 cells/mm3 was statistically significantly associated with an increased risk of tuberculosis. A baseline viral load of greater than 14 600 (4.2 log_{10}) copies/mL was also found to be an independent risk factor for tuberculosis. Our findings suggest that a drop in CD4 cell count below normal is associated with higher hazards of incident tuberculosis and that viral load may be a stronger

Clinical variables associated with risk of tuberculosis included size of TST induration, CD4 cell count, and HIV viral load, whereas the sole behavioral characteristic associated with tuberculosis risk was self-reported alcohol consumption and alcohol consumption >10 units per week.

The association between a positive TST and risk of tuberculosis has been studied in HIV-infected and uninfected populations. Individuals with HIV and a positive TST are at higher risk of developing tuberculosis than those with negative TSTs. A few studies have shown an association between larger TST size and risk of tuberculosis [4, 5], but association with size among HIV-infected adults has not been previously reported. A TST size of >15 mm was associated with a higher hazards of incident tuberculosis compared to a TST size of 5–9 mm. If a larger TST induration size reflects greater biological susceptibility to tuberculosis, then a biological dose-response mechanism may explain the increased risk; however, it may just be an issue of misclassification, because HIV-infected adults with a TST size between 5 mm and 10 mm are considered to have latent tuberculosis, whereas immune-competent adults with a similar TST size are not. Our study participants had a high CD4 count at entry, which is close to normal. Misclassification from cross-reaction to Mycobacterium avium is also more likely for TST size <15 mm [6].

Several studies have also observed an association between alcohol consumption and the risk of tuberculosis [7, 8]. Greater alcohol units consumed in 1 week were associated with increased hazards of incident tuberculosis, and our results clearly demonstrate a dose-response relationship (Table 1). Many studies have also shown a positive association between smoking and the risk of tuberculosis [7, 8], but we did not find a statistically significant association between smoking and incident tuberculosis. This may be because our data did not differentiate between ever and current smokers. Although not statistically significant with the categories of BMI we used, point estimates indicating increased risk of tuberculosis for those with low BMI and decreased risk for those with higher BMI were in accord with those reported by Hanrahan et al [9] in Soweto, South Africa.

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| Variable                                      | Frequency (N = 908) | Univariate Analysis | P Value | Multivariate Analysis | P Value | Multivariate Analysis | P Value |
|-----------------------------------------------|---------------------|---------------------|---------|-----------------------|---------|-----------------------|---------|
| Age (per year increase)                       | 1.03 (0.99–1.07)    | .119                |         | 1.02 (0.98–1.06)      | .335    |                      |         |
| Sex                                           |                     |                     |         |                       |         |                      |         |
| Male                                          | 154 (16.96)         | REF                 |         |                       |         |                      |         |
| Female                                        | 754 (83.04)         | 0.56 (0.31–1.01)    | .055    | 0.99 (0.47–2.12)      | .990    |                      |         |
| Employment Status                             |                     |                     |         |                       |         |                      |         |
| Employment                                    | 127 (13.99)         | REF                 |         |                       |         |                      |         |
| Lack of employment                            | 781 (86.01)         | 1.78 (0.71–4.46)    | .216    | 2.08 (0.82–5.28)      | .122    |                      |         |
| Highest Education Level                       |                     |                     |         |                       |         |                      |         |
| ≥12 years of schooling                        | 293 (32.27)         | REF                 |         |                       |         |                      |         |
| <12 years of schooling                        | 615 (67.73)         | 1.29 (0.72–2.28)    | .391    | 1.04 (0.56–1.94)      | .895    |                      |         |
| Living Conditions                             |                     |                     |         |                       |         |                      |         |
| House/Flat                                    | 575 (63.33)         | REF                 |         |                       |         |                      |         |
| Shack/Shelter/Other                           | 333 (36.67)         | 0.91 (0.52–1.56)    | .723    | 1.03 (0.59–1.79)      | .920    |                      |         |
| Smoking                                       |                     |                     |         |                       |         |                      |         |
| Never                                         | 650 (71.79)         | REF                 |         |                       |         |                      |         |
| Past/Present                                  | 258 (28.21)         | 1.60 (0.95–2.72)    | .079    | 0.98 (0.49–1.98)      | .968    |                      |         |
| Alcohol Use                                   |                     |                     |         |                       |         |                      |         |
| No Use                                        | 659 (72.58)         | REF                 |         |                       |         |                      |         |
| Use                                           | 249 (27.42)         | 1.99 (1.19–3.33)    | .009    | 2.08 (1.14–3.78)      | .016    | 2.06 (1.21–3.50)     | .007    |
| Alcohol units per week                        |                     |                     |         |                       |         |                      |         |
| None                                          | 659 (72.58)         | REF                 |         |                       |         |                      |         |
| 0–4 units per week                            | 135 (14.87)         | 1.64 (0.85–3.17)    | .140    | 1.78 (0.87–3.63)      | .113    | 1.74 (0.89–3.41)     | .108    |
| 5–10 units per week                           | 56 (6.17)           | 2.28 (0.96–5.43)    | .063    | 2.37 (0.93–6.02)      | .070    | 2.30 (0.95–5.55)     | .064    |
| >10 units per week                            | 58 (6.39)           | 2.90 (1.34–6.27)    | .007    | 2.87 (1.14–7.23)      | .025    | 2.87 (1.30–6.32)     | .009    |
| Baseline CD4 count (cells/mm$^3$)             |                     |                     |         |                       |         |                      |         |
| <500                                          | 473 (52.09)         | 2.44 (1.39–4.28)    | .002    | 1.94 (1.07–3.49)      | .028    | 1.95 (1.09–3.50)     | .025    |
| ≥500                                          | 435 (47.91)         | REF                 |         |                       |         |                      |         |
| Baseline Viral Load (log_{10} copies/mL)      |                     |                     |         |                       |         |                      |         |
| ≤14 600 (4.2 log_{10}) copies/mL             | 454 (50.00)         | REF                 |         |                       |         |                      |         |
| >14 600 (4.2 log_{10}) copies/mL             | 454 (50.00)         | 3.84 (2.08–7.11)    | <.001   | 3.13 (1.64–5.97)      | .001    | 3.18 (1.67–6.04)     | <.001   |
| TST induration diameter (mm)                  |                     |                     |         |                       |         |                      |         |
| 5–9 mm                                        | 172 (18.94)         | REF                 |         |                       |         |                      |         |
| 10–15 mm                                      | 348 (38.33)         | 2.15 (0.81–5.69)    | .125    | 1.92 (0.72–5.12)      | .195    | 1.94 (0.73–5.19)     | .185    |
| >15 mm                                        | 388 (42.73)         | 2.90 (1.13–7.42)    | .027    | 2.74 (1.06–7.06)      | .037    | 2.69 (1.04–6.94)     | .04     |
| BMI (kg/m$^2$)                                |                     |                     |         |                       |         |                      |         |
| <18.5                                         | 70 (7.71)           | 2.81 (0.98–8.04)    | .054    | 2.14 (0.85–5.39)      | .105    | 2.16 (0.87–5.37)     | .09     |
| 18.5–24.9                                     | 391 (43.06)         | REF                 |         |                       |         |                      |         |
| 25–29.9                                       | 237 (26.10)         | 0.68 (0.33–1.37)    | .276    | 0.92 (0.47–1.79)      | .807    | 0.87 (0.43–1.72)     | .68     |
| >30                                           | 210 (23.13)         | 0.99 (0.52–1.99)    | .973    | 1.38 (0.61–2.50)      | .350    | 1.45 (0.75–2.78)     | .27     |
| Treatment Arm                                 |                     |                     |         |                       |         |                      |         |
| Rifapentine-Isoniazid                         | 300 (33.04)         | 1.19 (0.61–2.31)    | .610    | 1.22 (0.63–2.36)      | .552    | 1.30 (0.67–2.53)     | .44     |
| Rifampin-Isoniazid                            | 306 (33.70)         | 1.35 (0.71–2.60)    | .357    | 1.22 (0.64–2.33)      | .540    | 1.32 (0.69–2.55)     | .40     |
| Isoniazid for 6 months                        | 302 (33.26)         | REF                 |         |                       |         |                      |         |
Table 1 continued.

| Variable            | Frequency (N = 908) | Univariate Analysis | P Value | Multivariate Analysis | P Value | Multivariate Analysis | P Value |
|---------------------|---------------------|---------------------|---------|-----------------------|---------|-----------------------|---------|
| ART Start           |                     | HR (95% CI)         |         | HR (95% CI)           |         | HR (95% CI)           |         |
| Started ARVs        | 167 (18.39)         | 1.06 (0.56–2.01)    | .845    | 1.05 (0.55–1.98)      | .885    |                      |         |
| No ARV Start        | 741 (81.61)         | REF                 |         | REF                   |         |                       |         |

Hazard ratios of statistically significant risk factors are represented in bold.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; BMI, body mass index; CI, confidence interval; HR, hazard ratio; REF, reference; TST, tuberculin skin test.

* Cox proportional hazard regression used. Complementary log-log plots used to check proportional hazard assumption. Only 1 alcohol variable is used in each multivariate model.

a In multivariate analysis, all models are controlled for age, sex, smoking, alcohol use, baseline viral load, baseline CD4, TST induration size, BMI, ART start, and treatment arm.

b In multivariate analysis, all variables with a P < .2 are taken out in a stepwise manner (excluding treatment arm) to arrive at a final model that includes alcohol use, baseline CD4, baseline viral load, TST induration size, BMI, and treatment arm.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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