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

Kojo Amoakwa,[1] Neil A. Martinson,[2,3] Lawrence H. Moulton,[1] Grace L. Barnes,[3] Reginah Msandiwa,[2] and Richard E. Chaisson[1,3]

[1]Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; [2]Perinatal HIV Research Unit, University of Witwatersrand, Johannesburg, South Africa; and [3]Johns Hopkins University Center for Tuberculosis Research, Baltimore, Maryland

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.

Tuberculosis is the leading cause of death among persons infected with human immunodeficiency virus (HIV) especially in developing countries [1]. A meta-analysis of recent clinical trials showed that isoniazid preventive therapy reduced the risk of active tuberculosis by 64% among adults infected with HIV, as demonstrated by a positive tuberculin skin test (TST) [2].

The Soweto/Johns Hopkins Novel Tuberculosis Prevention Regimens Trial showed that shorter directly observed combination regimens of rifapentine and isoniazid (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.

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 disease as determined by a symptom review, chest radiograph, and sputum culture if indicated, (4) had a CD4 count of at least 200 cells/mm^3, (5) had no history of tuberculosis treatment for more than 2 months, and (6) were not currently on anti-tuberculosis or antiretroviral therapy (ART). Incident tuberculosis was ascertained actively through follow up of participants and passively through review of clinical records and death certificates whenever possible. Incident tuberculosis was classified as confirmed, probable, or possible. Confirmed cases had signs and symptoms and were culture-positive. Probable cases had signs and symptoms and were sputum smear-positive. Possible cases had signs and symptoms without microbiologic or histologic evidence but had a clinical response to antituberculosis therapy.

Received 27 March 2014; accepted 16 December 2014.

Correspondence: Kojo Amoakwa, MBChB, MPH, Number 5 Bernadotte Court Parkville Baltimore, MD 21234 (kojojnr@gmail.com).

Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofu120

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/mm^3 (IQR, 348–677) and 4.2 $\log_{10}$ copies/mL (IQR, 3.5–4.7), respectively. The median baseline BMI was 25 kg/m^2 (IQR, 22–29). One hundred sixty-seven participants initiated ART, and ART use made up 10% of the total follow-up time.

Independent risk factors for incident tuberculosis from multivariate analysis were the following: TST induration size of >15 mm vs 5–9 mm (hazard ratio [HR], 2.74; CI, 1.06–7.06; $P = .037$); self-reported alcohol consumption (HR, 2.08; CI, 1.21–3.50; $P = .007$) and alcohol consumption >10 units per week (HR, 2.87 CI, 1.14–7.23; $P = .025$); baseline viral load greater than the median, ie, 14 600 (4.2 $\log_{10}$) copies/mL (HR, 3.13; CI, 1.64–5.97; $P = .001$); and baseline CD4 cell count <500 cell/mm^3 (HR, 1.94; CI, 1.07–3.49; $P = .028$). Other factors did not have a statistically significant association with incident tuberculosis in either univariate or multivariate analysis. Smoking (past or present) was associated with an increased hazard of incident tuberculosis in univariate analysis (HR, 1.60; CI, 0.95–2.72), but the association was mitigated in multivariate analysis (HR, 0.98; CI, 0.49–1.98). A second multivariate analysis that included only variables with a $P < .2$ from the first multivariate analysis showed almost identical results (Table 1).

DISCUSSION

We have identified several characteristics associated with progression from latent tuberculosis infection to active tuberculosis disease in HIV-infected adults treated with preventive therapy. 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.

Several cross-sectional and prospective studies have established the association between low CD4 cell count and the risk of tuberculosis. A CD4 cell count of below 200 cells/mm^3 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/mm^3 was an exclusion criterion; however, we found that a CD4 cell count below 500 cell/mm^3 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

Table 1. Relative Frequencies and Univariate and Multivariate Hazard Ratios for Incident Tuberculosis[a]

Variable	Frequency (N = 908)	Univariate Analysis HR (95% CI)	*P* Value	Multivariate Analysis HR (95% CI)[b]	*P* Value	Multivariate Analysis HR (95% CI)[c]	*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		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		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		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		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		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		REF		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		REF		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		REF		REF	
Baseline Viral Load (log_{10} copies/mL)							
≤14 600 (4.2 log_{10}) copies/mL	454 (50.00)	REF		REF		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		REF		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		REF		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 (0.52–1.89)	.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		REF		REF	

Table 1 continued.

Variable	Frequency (N = 908)	Univariate Analysis HR (95% CI)	*P* Value	Multivariate Analysis HR (95% CI)[b]	*P* Value	Multivariate Analysis HR (95% CI)[c]	*P* Value
ART Start							
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.

[a] 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.

[b] 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.

[c] 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.

predictor of incident tuberculosis. Mellors et al [11, 12] also found from the Multicenter AIDS Cohort Study that baseline CD4 cell count and baseline HIV viral load were strong predictors of progression to acquired immune deficiency syndrome (AIDS) and death from opportunistic infections in HIV-infected adults, with baseline HIV viral load being a stronger predictor of HIV progression to AIDS and death than baseline CD4 cell count.

CONCLUSIONS

Our results may be generalizable to HIV-infected adults in other high-burden settings with CD4 cell counts above 200 cells/mm^3. Modifying the baseline independent risk factors of alcohol consumption, high viral load, and low CD4 cell count could reduce the tuberculosis risk profile in HIV-infected adults. Performing a TST before tuberculosis preventive therapy may also be useful for risk stratification in adults infected with HIV.

Acknowledgments

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. This research has been facilitated by the infrastructure and resources provided by the Johns Hopkins University Center for AIDS Research, a National Institute of Health (NIH)-funded program (Grant 1P30AI094189), which is supported by the following NIH Co-Funding and Participating Institutes and Centers: National Institute of Allergy and Infectious Diseases, National Cancer Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, the National Institute of Mental Health, National Institute on Aging, Fogarty International Center, and Office of AIDS Research.

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

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

References

1. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med **2003**; 163:1009–21.
2. Akolo C, Adetifa I, Shepperd S, et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev **2010**; 1: CD000171.
3. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med **2011**; 365:11–20.
4. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol **1974**; 99:131–8.
5. Leung CC, Yew WW, Au KF, et al. A strong tuberculin reaction in primary school children predicts tuberculosis in adolescence. Pediatr Infect Dis J **2012**; 31:150–3.
6. Larson EM, O'Donnell M, Chamblee S, et al. Dual skin tests with *Mycobacterium avium* sensitin and PPD to detect misdiagnosis of latent tuberculosis infection. Int J Tuberc Lung Dis **2011**; 15:1504–9, i.
7. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med **2011**; 365:2155–66.
8. Narasimhan P, Wood J, Macintyre CR, et al. Risk factors for tuberculosis. Pulm Med **2013**; 2013:828939.
9. Hanrahan CF, Golub JE, Mohapic L, et al. Body mass index and risk of tuberculosis and death. AIDS **2009**; 424:1501–8.
10. Zenteno-Cuevas R, Montes-Villasenor E, Morales-Romero J, et al. Co-infection and risk factors of tuberculosis in a Mexican HIV+ population. Rev Soc Bras Med Trop **2011**; 44:282–5.
11. Mellors JW, Kingsley LA, Rinaldo CR Jr, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med **1995**; 122:573–9.
12. Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science **1996**; 272:1167–70.