Risk Factors for Tuberculosis After Highly Active Antiretroviral Therapy Initiation in the United States and Canada: Implications for Tuberculosis Screening

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Background. Screening for tuberculosis prior to highly active antiretroviral therapy (HAART) initiation is not routinely performed in low-incidence settings. Identifying factors associated with developing tuberculosis after HAART initiation could focus screening efforts.

Methods. Sixteen cohorts in the United States and Canada contributed data on persons infected with human immunodeficiency virus (HIV) who initiated HAART December 1995–August 2009. Parametric survival models identified factors associated with tuberculosis occurrence.

Results. Of 37 845 persons in the study, 145 were diagnosed with tuberculosis after HAART initiation. Tuberculosis risk was highest in the first 3 months of HAART (20 cases; 215 cases per 100 000 person-years; 95% confidence interval [CI]: 131–333 per 100 000 person-years). In a multivariate Weibull proportional hazards model, baseline CD4+ lymphocyte count <200, black race, other nonwhite race, Hispanic ethnicity, and history of injection drug use were independently associated with tuberculosis risk. In addition, in a piece-wise Weibull model, increased baseline HIV-1 RNA was associated with increased tuberculosis risk in the first 3 months; male sex tended to be associated with increased risk.

Conclusions. Screening for active tuberculosis prior to HAART initiation should be targeted to persons with baseline CD4 <200 lymphocytes/mm^3 or increased HIV-1 RNA, persons of nonwhite race or Hispanic ethnicity, history of injection drug use, and possibly male sex.

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The risk of developing tuberculosis among persons infected with human immunodeficiency virus (HIV) has been reported to be extremely high in the first 3 months after initiation of highly active antiretroviral therapy (HAART), with rates ranging from 1300 to 1700 per 100 000 person-years in developed countries [1, 2] and from 10 700 to 23 000 per 100 000 person-years in developing countries [2, 3]. Tuberculosis diagnosed after HAART initiation may represent previously undiagnosed prevalent disease, newly acquired tuberculosis (ie, acquired since HAART initiation), or progression of subclinical tuberculosis that was not recognized prior to initiation of antiretroviral therapy (so-called tuberculosis unmasking) [4]. A subset of persons in the latter group may have immune reconstitution inflammatory syndrome, with a severe and/or pronounced clinical presentation [5–7]. With continued use of HAART, tuberculosis risk decreases over time, although the risk remains higher than in HIV-seronegative persons [1–3]. Tuberculosis rates shortly after HAART initiation could potentially be decreased if screening for active tuberculosis prior to HAART initiation were optimized. In the United States, it is recommended that persons infected with HIV undergo screening for latent *Mycobacterium tuberculosis* infection at the time of HIV diagnosis, and annually thereafter if they are at high risk for exposure to tuberculosis [8]. However, the guidelines do not address screening prior to HAART initiation—for either latent *M. tuberculosis* infection or active disease. Screening for tuberculosis prior to HAART initiation is not routinely performed in the United States and Canada [9, 10].

Risk factors for developing tuberculosis shortly after HAART initiation are incompletely understood. Predisposing factors in developed countries include low CD4+ lymphocyte count prior to HAART initiation and HIV transmission risk factors of heterosexual sex and injection drug use [1, 2]. In developing countries, risk factors include low CD4+ lymphocyte count, younger age, and male sex [2]. However, in a study from South Africa, only low CD4+ lymphocyte count in the 4 months prior to tuberculosis diagnosis was significantly associated with increased tuberculosis risk during antiretroviral therapy [3]. Low CD4+ lymphocyte count prior to antiretroviral therapy initiation also appears to be associated with ''tuberculosis unmasking'' [5, 7, 11].

Unmasked tuberculosis can become acid-fast bacillus smear-positive and therefore perhaps more readily transmitted to others than subclinical disease [7]. In one study, tuberculosis diagnosed in AIDS patients during the first 3 months of antiretroviral therapy was also associated with a 3-fold higher mortality rate than when diagnosed before or more than 3 months after antiretroviral therapy initiation [12]. The authors suggested that patients with tuberculosis unmasking have a higher mortality rate due to delays in tuberculosis diagnosis and initiation of antituberculosis therapy. A better understanding of the risk factors for developing tuberculosis in the first few months after antiretroviral therapy initiation—the objective of the present analysis—can help inform screening strategies to target patients at highest risk, both before and shortly after antiretroviral therapy initiation.

METHODS

Study Population

Data were collected as part of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International epidemiological Databases to Evaluate AIDS (IeDEA) initiative. The NA-ACCORD was established in 2006 as a regional collaboration of existing single-site and multisite cohorts from the United States and Canada. Details on the collaboration and participating sites have been published elsewhere [13, 14]. Both interval and clinical cohorts were included, sites used methods to eliminate duplicate participants in more than one study cohort, and each cohort used standardized data collection methods. The participating cohorts and this study were approved by local institutional review boards.

For the current study, we identified persons infected with HIV from 16 cohorts who initiated HAART after cohort enrollment. The study period was from 1 December 1995 through 1 August 2009, although not all cohorts contributed data throughout the entire study period. Requirements for inclusion in this analysis were as follows: (1) confirmed HIV infection as evidenced by documented positive HIV antibody test, detectable plasma HIV-1 RNA, or a confirmed AIDS-defining event [15]; (2) known sex and year of birth; (3) available historical data prior to first study visit, including AIDS-defining events, use of antiretroviral therapy, CD4+ lymphocyte counts, and HIV-1 RNA; (4) at least 1 follow-up visit within 12 months of the initial study visit; and (5) initiation of a HAART regimen prior to 1 August 2009.

The primary endpoint for this study was tuberculosis diagnosed after HAART initiation. Individuals with tuberculosis diagnosed prior to HAART initiation were excluded. Persons with AIDS-defining events other than tuberculosis and persons who received non-HAART antiretroviral therapy prior to HAART initiation were included in the study population.

Study Definitions

HAART was defined as a regimen of at least 30 days duration that contained at least 3 antiretroviral drugs, one of which had to be a protease inhibitor (PI; with or without ritonavir boosting), a nonnucleoside reverse transcriptase inhibitor (NNRTI), one of the nucleoside reverse transcriptase inhibitors (NRTI) abacavir or tenofovir, an integrase inhibitor (eg, raltegravir), or an entry inhibitor (eg, maraviroc or enfuvirtide). Persons who received 3 drugs, of which 2 were zidovudine and stavudine, were excluded. The months that individual antiretroviral drugs were started and stopped were collected to construct the

treatment periods. Baseline CD4+ lymphocyte counts and HIV-1 RNA were within 12 months prior to HAART initiation. Black race in the Canadian cohorts included some persons from indigenous populations, and thus was characterized separately from black race in US cohorts.

All tuberculosis cases were confirmed by local investigators. For all tuberculosis cases diagnosed <3 months after HAART initiation, both the date of antiretroviral therapy initiation and tuberculosis diagnosis date were reconfirmed by local site investigators. In general, tuberculosis diagnosis date was defined as the date of anti-tuberculosis therapy initiation. Pulmonary tuberculosis was defined as disease affecting the pulmonary parenchyma. Extrapulmonary disease included disease of the pleura or any extra-thoracic site. Culture-negative tuberculosis was established by signs, symptoms, and chest radiography consistent with tuberculosis, pathology with necrotizing granulomas and acid-fast bacilli, positive nucleic acid amplification test, and/or clinical response to antituberculosis therapy.

To assess the risk of tuberculosis recurrence, person-time accumulation began at the end of antituberculosis treatment. Persons without information on start and stop dates of tuberculosis treatment were assumed to receive 6 months of treatment (the standard of care) [16] from the time of tuberculosis diagnosis.

Statistical Analysis

Groups were defined according to when tuberculosis was diagnosed in relation to HAART initiation. Continuous variables were compared with the Wilcoxon rank-sum test. Categorical variables were compared with the Fisher exact test. Persons with missing CD4+ lymphocyte and HIV-1 RNA measurements had values imputed multiple times (20 iterations) using multiple imputation by chained equations [17, 18], and measurements underwent Box-Cox transformation to ensure approximately normal distributions for the multiple imputation [19]. Multiple imputation was conducted in SAS 9.2 using the IVEware package for SAS [20]. In addition, race/ethnicity and injection drug use were also imputed for persons in whom such data were missing (Supplementary Table 1). All variables (age, sex, race, injection drug use, HAART regimen type, antiretroviral therapy naive, CD4+ lymphocytes, $\log_{10}$HIV-1 RNA, year of HAART start, cohort) including time (time from HAART initiation) and outcome (tuberculosis) were included in the imputation process.

Tuberculosis incidence rates were determined per 100 000 person-years of follow up; 95% confidence intervals (CI) were calculated using exact Poisson probabilities. To determine risk factors for tuberculosis after HAART initiation, univariate and multivariate Weibull proportional hazards models were performed. Graphical plots assessed Weibull assumptions and demonstrated that the Weibull distribution was appropriate. To assess whether covariates had different relationships to tuberculosis risk <3 months versus ≥3 months after HAART initiation, a piece-wise Weibull model was used, allowing for a change in the underlying hazard starting at 3 months [21]. We first compared whether this change-point model fit better than the standard Weibull model with all covariates included using Akaike's Information Criterion (AIC). Interaction terms between covariates and time interval were added until the AIC was minimized. Then a process of removing main effect terms and addition of remaining interaction terms was assessed for improving model fit until a final model was identified by AIC.

RESULTS

There were 37 845 persons included in the study, of whom 145 (0.4%) were diagnosed with tuberculosis after HAART initiation. The demographic and clinical characteristics of the study population are in Table 1. The median length of follow up was 4.7 years (IQR: 2.0–8.3 years). There were 22 459 (59%) patients who were antiretroviral therapy-naive at the time of HAART

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Number	Denominator[a]	% or IQR
Median age, years	39		33–45
Male sex	28 980		77
Race		32 142	
White	13 860		43
Black	12 360		38
Hispanic	4735		15
Other[b]	1187		4
Injection drug use as HIV risk factor[c]	6253	32 973	19
HAART type			
PI-based	21 023		56
NNRTI-based	12 302		33
PI + NNRTI or ≥ 3 NRTI	4520		12
Median CD4+ lymphocytes/mm^3			
Prior to HAART[c]	207	24 642	77–346
Median HIV-1 RNA (copies/mL)			
Prior to HAART[c]	48 312	22 989	6432–183 677
Developed confirmed diagnosis of TB after HAART initiation	145		0.4
Died prior to 1 August 2009	4913		13

NOTE. There were 37 845 persons in the study. Data presented pertain to those persons for whom data were available. HAART, highly active antiretroviral therapy; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase; PI, HIV-1 protease inhibitor; TB, tuberculosis.

[a] Number of persons with available data is 37 845 unless otherwise noted.

[b] Includes American Indian, Asian, Pacific Islander, and multiracial.

[c] Within 12 months prior to HAART initiation.

Table 2. Demographic and Clinical Characteristics of Persons Diagnosed With Tuberculosis, Stratified by Timing of Tuberculosis Diagnosis in Relation to Antiretroviral Therapy Initiation

Characteristic	<3 months (n = 20) n (%)	≥3 months (n = 125) n (%)	*P* value[3]
Median age, years (IQR)[1]	41 (36–45)	37 (31–42)	.03
Male sex	18 (90)	86 (69)	.06
White	6/17 (35)	23/104 (22)	.27[6]
Black (US and Canada)	6/17 (35)	55/104 (53)	
Hispanic	3/17 (18)	21/104 (20)	
Other	2/17 (12)	5/104 (5)	
IDU	6/17 (35)	32/113 (28)	.57[6]
HAART type			
PI-based	13 (65)	71 (57)	.82
NNRTI-based	6 (30)	42 (34)	
PI + NNRTI or > 3 NRTI	1 (5)	12 (10)	
TB culture			
Positive	16 (80)	82 (66)	.36
Negative	3 (15)	36 (29)	
Unknown	1 (5)	7 (5)	
Site of TB disease			
Pulmonary	9 (45)	81 (65)	.26
Extrapulmonary	6 (30)	21 (17)	
Both	3 (15)	11 (9)	
Unknown	2 (10)	12 (10)	
Median CD4 prior to HAART (IQR)[2]	61 (32–150)	134 (57–234)	.04
Mean CD4 (95% CI) including imputed values	82 (41, 142)	135 (104, 171)	.05
Median HIV-1 RNA prior to HAART (IQR)[3]	217 344 (77 473–291 594)	64 069 (14 399–184 291)	.05
Mean HIV-1 RNA (95% CI) including imputed values	135 026 (56 252–290 805)	50 536 (29 107–83 871)	.06
Died	6 (30)	24 (19)	.39[7]
Time in care before HAART initiation (days)[5]	22 (1–350)	173 (17–829)	.06
Median year of HAART initiation	2002 (1999–2004)	1999.5 (1998–2002)	.11

NOTE. When data were not available for the entire group, the number of persons with data available is provided. CI, confidence interval; HAART, highly active antiretroviral therapy; IDU, injection drug use as HIV risk factor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI; nucleoside reverse transcriptase inhibitor; PI, HIV-1 protease inhibitor; TB, tuberculosis.

[1] At time of HAART initiation.

[2] Median and IQR prior to multiple imputation; 7 individuals with TB diagnosed <3 months and 44 individuals diagnosed ≥3 months had no CD4 within 12 months prior to HAART initiation.

[3] Median and IQR prior to multiple imputation; 9 individuals with TB diagnosed <3 months and 54 individuals diagnosed ≥3 months after HAART start were missing a HIV-1 RNA measurement within 12 months prior to HAART initiation.

[4] Tests were either Fisher's exact or Wilcoxon rank-sum test as appropriate.

[5] Time in care before HAART initiation is defined as time from first CD4 measurement to initiation of HAART among those with a CD4 prior to HAART initiation.

[6] Comparison of race and IDU by timing of TB remained insignificant after imputation ($P = .31$ and .44, respectively).

[7] *P* value is from a Cox proportional hazards model, comparing time to death from TB diagnosis among those with <3 months between HAART initiation and TB diagnosis versus those with ≥3 months.

initiation; the remaining 15 386 (41%) had received non-HAART antiretroviral therapy prior to HAART initiation. Characteristics of the 145 persons who developed tuberculosis are in Table 2, stratified by timing of diagnosis following HAART initiation. Compared with persons diagnosed ≥3 months after initiation, the 20 patients who developed tuberculosis <3 months after HAART initiation were older, tended to be male, have lower median baseline CD4+ lymphocyte count, higher median baseline HIV-1 RNA, and less time in care prior to HAART initiation. There was no statistically significant difference in the risk of time to death after tuberculosis diagnosis. The relative hazard was 1.48 (95% CI: 0.61–3.63; $P = .39$) for persons with tuberculosis diagnosed in the first 3 months of HAART compared with ≥3 months after HAART initiation.

The risk of tuberculosis was highest in the first 3 months after HAART initiation and highest in the first month (Table 3). The tuberculosis incidence rate declined after the first month on HAART, but it became significantly lower than during the first 3 months only after persons had been on antiretroviral therapy for >6 months.

Table 3. Tuberculosis Incidence Rates According to Time Since Antiretroviral Therapy Initiation

Time Interval[1]	TB diagnoses	Person-years	Incidence rate per 100 000 (PY)	95% CI[2]	Cumulative incidence rate per 100 000 PY	95% CI[2]
HAART initiation <1 month	8	3152	254	109–500	254	109–500
>1 month–< 3 months	12	6137	196	101–342	215	131–333
>3 months–≤ 6 months	13	8906	146	78–250	181	125–255
>6 months–≤ 1 year	16	16 801	95	54–155	140	103–185
>1 year–≤ 2 years	21	30 298	69	43–106	107	84–136
>2 years–≤ 3 years	23	26 450	87	55–131	101	82–124
>3 years–≤ 4 years	17	22 923	74	43–119	96	79–116
>4 years–≤ 5 years	7	19 580	36	14–74	87	72–104
>5 years–≤12 years	28	64 675	43	29–62	73	61–86

NOTE. CI, confidence interval; HAART, highly active antiretroviral therapy. *P* values for the comparison of the incidence rate for the indicated time interval versus the first 3 months after HAART initiation using a Poisson model: 3–6 months, .28; 6 months–1 year, .02; 1–2 years, <.001; 2–3 years, .003; 3–4 years, .001; 4–5 years, <.001; 5–12 years, <.001.

[1] For persons with less than 1 month, 1 month accumulated.

[2] 95% CI determined via exact Poisson probabilities.

Tuberculosis risk was not constant over time after HAART initiation (Table 3), motivating the use of Weibull proportional hazards models to identify risk factors for tuberculosis over the duration of follow up after HAART initiation (Table 4). In univariate analyses, black race, other nonwhite race, Hispanic ethnicity, history of injection drug use, being antiretroviral therapy-naive, baseline CD4+ lymphocyte count <200 cells/mm^3, and increased baseline HIV-1 RNA were all associated with a significantly increased risk of tuberculosis. In a multivariate model, black and other nonwhite race, Hispanic ethnicity, history of injection drug use, and baseline CD4+ lymphocyte count <200 cells/mm^3 remained significantly associated with tuberculosis risk after adjusting for cohort and other remaining variables in the model (Table 4). Tuberculosis risk was not significantly different among persons with baseline CD4+ lymphocyte count 200–350 versus >350 cells/mm^3 (relative hazard = 1.16; 95% CI: 0.57–2.35; $P = .68$), so these strata were combined to simplify the model.

To assess for predictors of tuberculosis risk in the first 3 months after HAART initiation, a multivariate piece-wise Weibull model was performed, evaluating interactions between tuberculosis predictor variables and time after HAART initiation (<3 months vs. ≥3 months). The model with the best fit is presented in Table 5. Baseline HIV-1 RNA and sex both had an interaction with time, although the interaction with sex was of borderline significance ($P = .09$). For every 1 log increase in baseline HIV-1 RNA, the relative hazard of tuberculosis was 1.93 in the first 3 months, but 0.99 ≥3 months after HAART initiation. Compared to women, men had a relative hazard of tuberculosis of 3.13 in the first 3 months, but 0.78 ≥3 months after HAART initiation. The other variables in the model had no interaction with time, and therefore similar relative hazards throughout the entire follow-up period. Results were similar when the analysis was limited to persons with complete data (ie, no multiple imputation), although the 95% confidence intervals were wider due to the lower number of tuberculosis cases (Supplementary Table 2).

Of the 145 tuberculosis cases diagnosed after HAART start, 137 contributed follow-up time after tuberculosis diagnosis (6 individuals died while on tuberculosis treatment or within 6 months of tuberculosis diagnosis, and 2 did not contribute follow up). There were 93 individuals with both start and stop dates of anti-tuberculosis therapy available, among whom the median time to complete treatment was 9.1 months (IQR: 7.3–12.0). The median duration of follow up after completion of anti-tuberculosis therapy was 43 months (IQR: 17–65). Of the 137 tuberculosis patients, 2 (1.5%) developed recurrent disease (incidence rate: 390 per 100 000 person-years of follow up (95% CI: 50–1410 per 100 000 person-years). Of the 2 patients with recurrent tuberculosis, one had a third tuberculosis episode.

Of the 145 tuberculosis cases, 92 (63%) were known to have received tuberculin skin testing (TST), of whom 59 (64%) of 92 had a positive TST, and 23 (39%) of 59 received treatment of latent *M. tuberculosis* infection prior to tuberculosis diagnosis.

DISCUSSION

Several aspects of this observational study should be noted. First, it was large and included data from more than 37 000 HIV-infected persons who initiated antiretroviral therapy in 16 cohorts from across the United States and Canada. This enhances the generalizability of the results to this region. Second, tuberculosis risk was highest in the first 3 months of HAART. This finding is consistent with previous studies conducted in both the developed and developing world [1–3]. However, the tuberculosis incidence rate during the first 3 months (215 per 100 000 person-years) was substantially lower than has

Table 4. Weibull Proportional Hazards Model Examining Time to Tuberculosis Diagnosis After HAART Initiation

		Univariate model		Multivariate model adjusted for cohort	
	Events[3] (Person-years)	Relative hazard (95% CI)	*P* value	Relative hazard (95% CI)	*P* value
Age (per year)	145 (199 779)	0.88 (.73–1.05)	.16	0.89 (.73–1.08)	.23
Male sex	104 (152 392)	0.79 (.55–1.13)	.20	0.96 (.64–1.43)	.83
Race					
Black—Canada	13.6 (5232.5)	5.92 (3.05–11.48)	<.001	14.02 (2.73–72.0)	.002
Black—USA	55.0 (60 130.0)	2.07 (1.38–3.09)	<.001	1.57 (.99–2.48)	.053
Hispanic	26.1 (28 606)	2.09 (1.25–3.50)	.005	2.29 (1.35–3.89)	.002
Other	7.8 (6587.6)	2.74 (1.21–6.19)	.015	2.68 (1.17–6.15)	.020
White	42.4 (99 223)	1.0	…	1.0	…
IDU	46.4 (43 910)	1.63 (1.15–2.33)	.007	1.71 (1.15–2.55)	.008
HAART type					
PI based	84 (121 542)	1.0		1.0	…
NNRTI	48 (54 813)	1.16 (.82–1.66)	.40	1.19 (.82–1.73)	.37
Other[2]	13 (23 424)	0.76 (.43–1.37)	.37	0.78 (.43–1.41)	.40
Antiretroviral therapy naive (yes vs no)	92 (104 531)	1.46 (1.03–2.05)	.03	1.23 (.85–1.80)	.28
CD4					
0<CD4≤50	37.1 (34 645)	2.48 (1.47–4.20)	<.001	2.10 (1.21–3.64)	.009
50<CD4≤100	27.2 (22 437)	2.83 (1.60–5.02)	<.001	2.47 (1.36–4.49)	.003
100<CD4≤200	37.6 (41 866)	2.10 (1.29–3.40)	.003	1.90 (1.16–3.12)	.011
CD4 > 200	43.1 (100 831)	1.0	…	1.0	…
$\log_{10}$(HIV RNA)[1]	145 (199 779)	1.26 (1.03–1.53)	.02	1.05 (.85–1.31)	.64
Year of HAART Initiation (per year)	145 (199 779)	1.04 (.98–1.10)	.19	1.01 (.95–1.08)	.74

NOTE. CI, confidence interval; HAART, highly active anitretroviral therapy; IDU, injection drug use as HIV risk factor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, HIV-1 protease inhibitor.

[1] Value prior to HAART initiation. Multiple imputation was used for missing values for CD4 and HIV RNA.

[2] Other corresponds to those who had PI and NNRTI, 3+ NRTI, or an entry/fusion inhibitor based regimen.

[3] Mean number of events and person-years are presented for categories that are affected by multiple imputation resulting in non-integer values for the number of TB events.

previously been reported, even in developed world settings (1300–1700 per 100 000 person-years) [1, 2]. Although the reason is unclear, it may be due to differences in patient population, tuberculosis prevalence, or implementation of tuberculosis prevention strategies. In addition, we included persons who had previously received non-HAART antiretroviral therapy; tuberculosis risk could be higher among persons naive to antiretroviral therapy. Third, tuberculosis diagnosed in the first 3 months of antiretroviral therapy was not associated with a significantly higher mortality risk than tuberculosis diagnosed subsequently. This finding (from a low-incidence region) differs from findings reported from Haiti [12] but is consistent with a study from Uganda (both high-incidence countries) [22].

Tuberculosis diagnosed within the first 3 months of HAART may be due to incomplete immune reconstitution—insufficient to prevent disease—or unmasking of previously undiagnosed tuberculosis. The latter may be particularly important in a setting with low rates of *M. tuberculosis* transmission, such as the United States and Canada. Such disease was either not clinically apparent prior to the initiation of antiretroviral therapy, or the signs and symptoms were attributed to processes other than tuberculosis. This possibility highlights the importance of determining the risk factors associated with such tuberculosis cases, so that these patient groups can be targeted for tuberculosis screening just prior to antiretroviral therapy initiation or within the initial months of treatment initiation.

In this study, the risk factors independently associated with tuberculosis diagnosis after HAART initiation were black race, other nonwhite race, Hispanic ethnicity, a history of injection drug use, and baseline CD4+ lymphocyte count <200 cells/mm^3. Persons who were antiretroviral therapy-naive tended to have an increased tuberculosis risk, but it was not statistically significant in the multivariate models (Table 4). The piece-wise Weibull model identified an increased tuberculosis risk with HIV-1 RNA levels within the first 3 months of HAART that was ~2-fold increased risk for every 1 log increase in HIV-1 RNA (Table 5). The increased tuberculosis risk among men in the first 3 months of HAART was of borderline statistical significance. The findings were similar when the analysis was limited to persons with complete data (ie, no imputation; Supplementary Table 2), although perhaps

Table 5. Piecewise Weibull Model of Tuberculosis Risk After HAART Initiation

	Multivariate model adjusted for cohort	
	Relative hazard (95% CI)	*P* value
Male sex[2]		
<3 months	3.13 (.65–14.19)	.16
≥3 months	0.78 (.51–1.17)	.23
Race		
Black—Canada	13.51 (2.78–65.67)	.002
Black—USA	1.50 (.97–2.34)	.07
Hispanic	2.18 (1.30–3.66)	.003
Other	2.84 (1.30–6.18)	.009
White	1.0	…
IDU	1.60 (1.11–2.31)	.01
Antiretroviral therapy naive (yes vs no)	1.33 (.94–1.88)	.10
CD4		
0<CD4≤50	1.94 (1.14–3.29)	.02
50<CD4≤100	2.37 (1.34–4.18)	.003
100<CD4≤200	1.91 (1.18–3.08)	.008
CD4 >200	1.0	…
$\log_{10}$(HIV RNA)[1,2]		
<3 months	1.93 (1.39–2.69)	<.001
≥3 months	0.99 (.80–1.23)	.92

NOTE. Tuberculosis risk is dichotomized according to <3 months versus ≥ 3 months after HAART initiation. Shape parameter: <3 months shape = 1.33, ≥3 months space = 0.92. This analysis includes imputed values for missing data. CI, confidence interval; HAART, highly active antiretroviral therapy; IDU, injection drug use as HIV risk factor.

[1] Value prior to HAART initiation. Multiple imputation was used for missing values for CD4 and HIV RNA.

[2] Interaction with time after HAART initiation: male sex *P* value = .09; $\log_{10}$ HIV-1 RNA *P* value < .001.

slightly weaker for HIV-1 RNA and slightly stronger for male sex.

The finding that lower CD4+ lymphocyte count was associated with early tuberculosis risk was consistent with several prior reports [1–3]. Of note in the present study, tuberculosis risk was similarly increased in the 3 categories of baseline CD4+ lymphocytes ≤200 compared with CD4+ lymphocyte count >200 cells/mm^3.

A history of injection drug was also associated with accelerated tuberculosis risk in this study. This finding is consistent with previous studies of tuberculosis risk after antiretroviral therapy initiation [1], as well as reports from the United States demonstrating an association between substance abuse (including injection drug use) and tuberculosis [23].

Black race, other nonwhite race, and Hispanic ethnicity have not previously been associated with increased tuberculosis risk after HAART initiation to our knowledge. However, this finding is not unexpected in the United States and Canada, where such groups have a disproportionately high tuberculosis risk in the general population, irrespective of HIV status [24]. It is unclear why persons of black race in Canada appeared to have a higher tuberculosis risk than blacks in the United States, but this may be due in part to differences in how black race was characterized in these 2 countries.

Although tuberculosis risk was lower than previously reported and decreased with time on HAART, it was still significantly higher than in the general population of the United States and Canada even after >5 years of HAART. The tuberculosis incidence rate in such persons in our study was 43 per 100 000 person years—more than 8-fold higher than the overall tuberculosis incidence rate in the United States and Canada during the study period—approximately 5 per 100 000 population [25, 26]. This finding highlights the importance of continued surveillance for tuberculosis, even after prolonged HAART use.

The rate of recurrent tuberculosis in this study population (1.5%; 390 per 100 000 person-years) was low compared with other studies in North America, even with a long median follow up of 43 months after completion of antituberculosis therapy. Recurrent tuberculosis risk among HIV-infected persons in the United States has been reported as high as 8.3% and 9300 per 100 000 person-years [27, 28]. This suggests a beneficial effect of HAART on recurrence risk, which would be expected given the decreased risk of recurrent tuberculosis with increasing CD4+ lymphocyte count [27]. Of note, however, although the confidence intervals were wide, the tuberculosis recurrence rate in this study was higher than in the "high-risk" first 3 months after HAART initiation (215 per 100 000 person-years). This finding is consistent with studies from high tuberculosis incidence settings without widespread HAART use, in which recurrence rates exceed incidence rates [29–32]. These findings provide additional impetus for prevention of tuberculosis in persons infected with HIV.

Of the tuberculosis cases that had received TST and had a positive test, only 39% received treatment of latent *M. tuberculosis* infection prior to tuberculosis diagnosis. This observation is consistent with other studies that have identified potentially preventable tuberculosis cases among HIV-infected persons [9]. A strategy of screening for and treating latent infection is effective in preventing tuberculosis among persons infected with and adds benefit compared with HAART alone [33, 34].

This study had some limitations. First, it was observational, and tuberculosis was diagnosed not through active screening of all study participants but as part of ongoing health care for individuals. Therefore, some tuberculosis cases could have been missed. However, because patients were in HIV care and tuberculosis is a reportable disease, all cases should have been captured by the individual cohorts. Second, the NA-ACCORD database included only persons with at least 1 follow-up visit within 12 months of entering observation in the current analysis. Tuberculosis cases in any persons without such a follow-up visit would therefore have not been included.

In summary, our study highlights the possible benefit of screening for tuberculosis prior to and shortly after antiretroviral therapy initiation, even in low tuberculosis incidence areas such as the United States and Canada. Screening should be focused on persons with baseline CD4+ <200 lymphocytes/mm^3 or increased HIV-1 RNA, persons of nonwhite race or Hispanic ethnicity, history of injection drug use, and possibly male sex. The tuberculosis recurrence rate of 1.5% among persons receiving HAART illustrates an important paradox: HAART appeared to confer a benefit regarding recurrence risk, but the risk of recurrent tuberculosis was high relative to tuberculosis risk among all HIV-infected persons in this study.

Supplementary Data

Supplementary Data are available at *The Journal of Infectious Diseases* online.

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