

Incidence of Tuberculosis among HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy in Europe and North America

The Antiretroviral Therapy Cohort Collaboration^a

(See the editorial commentary by Lawn and Wood on pages 1783–6)

Background. We obtained estimates of the incidence of tuberculosis (TB) among patients receiving HAART and identified determinants of the incidence.

Methods. We analyzed the incidence of TB during the first 3 years after initiation of HAART among 17,142 treatment-naïve, AIDS-free persons starting HAART who were enrolled in 12 cohorts from Europe and North America. We used univariable and multivariable Poisson regression models to identify factors associated with the incidence.

Results. During the first 3 years (36,906 person-years), 173 patients developed TB (incidence, 4.69 cases per 1000 person-years). In multivariable analysis, the incidence rate was lower for men who have sex with men, compared with injection drug users (relative rate, 2.46; 95% confidence interval [CI], 1.51–4.01), heterosexuals (relative rate, 2.42; 95% CI, 1.64–3.59), those with other suspected modes of transmission (relative rate, 1.66; 95% CI, 0.91–3.06), and those with a higher CD4⁺ count at the time of HAART initiation (relative rate per log₂ cells/ μ L, 0.87; 95% CI, 0.84–0.91). During 28,846 person-years of follow-up after the first 6 months of HAART, 88 patients developed TB (incidence, 3.1 cases per 1000 person-years of follow-up). In multivariable analyses, a low baseline CD4⁺ count (relative rate per log₂ cells/ μ L, 0.89; 95% CI, 0.83–0.96), 6-month CD4⁺ count (relative rate per log₂ cells/ μ L, 0.90; 95% CI, 0.81–0.99), and a 6-month HIV RNA level >400 copies/mL (relative rate, 2.21; 95% CI, 1.33–3.67) were significantly associated with the risk of acquiring TB after 6 months of HAART.

Conclusion. The level of immunodeficiency at which HAART is initiated and the response to HAART are important determinants of the risk of TB. However, this risk remains appreciable even among those with a good response to HAART, suggesting that other interventions may be needed to control the TB epidemic in the HIV-infected population.

Infection with HIV is an important risk factor for tuberculosis (TB). Approximately a half-million cases of TB attributable to HIV infection occur worldwide each year, and TB accounts for ~10% of all AIDS-related deaths among adults [1]. HIV infection may also have an indirect effect on the incidence of TB by increasing transmission rates of *Mycobacterium tuberculosis*, with

negative consequences for both HIV-negative and HIV-positive persons [2, 3].

Although the risk of developing TB is reduced by 70%–90% among HIV-infected persons receiving HAART, compared with untreated individuals [4–7], TB continues to occur [8]. Furthermore, TB has become relatively more common when considered as a proportion of all AIDS-associated opportunistic infections [9]. Whether the occurrence of TB among HAART-treated patients is caused by a lack of response to HAART, whether it is linked to an inability of HAART to completely reconstitute the immune system, or whether these cases would have occurred anyway in the absence of HIV infection is unclear.

Our understanding of the possible impact of HAART on HIV-associated TB remains limited. Although the incidence of TB after starting HAART has been estimated, little information is available on the relationship

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between the risk of TB after starting HAART and either pre-existing immunodeficiency or virological and immunological responses to HAART. We analyzed data from the Antiretroviral Therapy (ART) Cohort Collaboration [10] to obtain estimates of the incidence of TB among patients receiving HAART and to identify potential determinants of this incidence.

METHODS

The ART Cohort Collaboration is an international collaboration of cohort studies from Europe and North America set up to describe the prognosis of antiretroviral-naïve patients starting HAART for the first time. The study has been described in detail elsewhere [10]. Prospective cohort studies were eligible for inclusion if they had enrolled at least 100 antiretroviral-naïve patients with HIV-1 infection aged ≥ 16 years who had started HAART with at least 3 drugs, including nucleoside reverse-transcriptase inhibitors, protease inhibitors, and/or non-nucleoside reverse-transcriptase inhibitors. The data set utilized in the current analysis was collected at the start of 2003 and includes data for patients starting HAART between 1996 and early 2003 from 12 cohorts: the AIDS Therapy Evaluation Project–Netherlands, the Aquitaine Cohort, the HAART Observational Medical Evaluation and Research cohort study from the British Columbia Centre for Excellence in HIV/AIDS, Collaborations in HIV Outcomes Research, EuroSIDA, the Frankfurt HIV Cohort, the French Hospital Database on HIV, the Italian Cohort of Antiretroviral-Naïve Patients, the Köln/Bonn Cohort, the Royal Free Hospital Cohort, the South Alberta Clinic Cohort, and the Swiss HIV Cohort Study.

Because the primary aim of this analysis was to describe the incidence of new cases of TB in this cohort, individuals with a prior diagnosis of AIDS (who may have experienced TB before starting HAART) were excluded (information on specific AIDS-related events previously experienced was not included in the data set). We considered the incidence of TB during the first 3 years after starting HAART and investigated factors associated with this incidence. Person-years of follow-up (PYFU) were calculated from the date of starting HAART until the date of death, the date of last follow-up visit at the clinic, or 3 years after starting HAART, whichever occurred first. The following baseline factors were considered: sex, risk group (men who have sex with men, injection drug user, heterosexual, or other/not known), year of starting HAART (1997 or earlier, 1998, 1999, 2000, and 2001 or after), CD4⁺ cell count at baseline (stratified as <50, 50–199, 200–349, 350–499, and ≥ 500 cells/ μ L, and also treated as a continuous variable after a log₂ transformation, so that relative rates reflect the impact of a doubling in the CD4⁺ count on the TB rate), HIV RNA level at baseline (either <5 or ≥ 5 log₁₀ copies/mL), type of HAART regimen (fitted as binary variables indicating patients who received regimens including protease inhibitors, nonnucleoside reverse-transcrip-

tase inhibitors, or nucleoside reverse-transcriptase inhibitors only; those patients receiving regimens including both protease inhibitors and nonnucleoside reverse-transcriptase inhibitors were included in both groups), age (either ≤ 37 or >37 years), and time since starting HAART (0–3, 4–6, 7–12, 13–24, and 25–36 months after start of HAART, but modelled as a continuous variable by taking the midpoint of each interval [11]). All analyses were adjusted for cohort to indirectly account for geographical region. Univariable and multivariable Poisson regression models were used to identify factors independently associated with the incidence of TB using the GenMod procedure in the SAS software, version 8 (SAS).

We then considered the incidence of TB in relation to response to HAART. For this analysis, because CD4⁺ cell counts were only available in the data set at 6 months after starting HAART (the nearest CD4⁺ cell count within the window of 3–9 months after starting HAART), events and PYFU were only considered after this time point. Poisson regression models were used to identify whether the incidence of TB over this time period was associated with the immunological and virological response to HAART at 6 months after controlling for baseline disease status and for the other risk factors identified in the first analysis. Because analyses that considered the incidence of TB in relation to the baseline CD4⁺ cell count suggested that the risk of TB increased in an exponential way with a decreasing CD4⁺ cell count, the final multivariable model included the CD4⁺ cell counts at baseline and at 6 months as continuous measurements after a log₂ transformation.

RESULTS

In total, 17,142 (77.2%) of the 22,217 patients had no prior AIDS event at the time of starting HAART. The majority of patients were male (74%), were infected with HIV through sexual transmission (75%), and had a CD4⁺ cell count <350 cells/ μ L at the time of starting HAART (64%). The majority (63.1%) started a HAART regimen including ≥ 1 protease inhibitors (table 1). The median duration of follow-up for patients in the cohort after starting HAART was 2.8 years (range, 0–7.9 years).

Baseline factors associated with the incidence of TB during the first 3 years of follow-up. During the first 3 years (36,906 PYFU), 173 patients developed a first episode of TB (incidence, 4.69 cases per 1000 PYFU; 95% CI, 3.99–5.39 cases per 1000 PYFU). Two patients died within 2 months after receiving their TB diagnosis; these cases occurred at 2 weeks and 2 years after starting HAART. The TB rate was highest in the first 3 months after starting HAART but decreased with increased exposure to HAART (table 2). TB rates were higher among women than among men; higher among those infected via heterosexual sex, injection drug users, and those with other or unknown risk factors, compared with men who have sex with men; higher

Table 1. Demographic and clinical characteristics of patients included in an analysis of tuberculosis incidence, Antiretroviral Therapy Cohort Collaboration, 1996–2003.

Characteristic	Value (n = 17,142)
Female sex	4457 (26.0)
Age, median years (IQR)	36 (31–42)
Risk group	
MSM	6689 (39.0)
Injection drug user	2890 (16.9)
Heterosexual	6129 (35.8)
Blood product recipient	132 (0.8)
Other/not known	1302 (7.6)
CD4 ⁺ cell count at HAART initiation, cells/ μ L	
Median value (IQR), cells/ μ L	280 (160–419)
<50	1289 (7.5)
50–199	4307 (25.1)
200–349	5358 (31.3)
350–499	3572 (20.8)
\geq 500	2616 (15.3)
HIV RNA level at HAART initiation, copies/mL	
Median value (IQR), copies/mL	59,770 (15,000–180,000)
<100,000	10,592 (61.8)
\geq 100,000	6550 (38.2)
Year of HAART initiation	
1997 or before	4672 (27.3)
1998	3613 (21.1)
1999	2874 (16.8)
2000	2434 (14.2)
2001 or after	3549 (20.7)
Type of HAART received	
PI-based	10,815 (63.1)
NNRTI-based	4511 (26.3)
PI and NNRTI	332 (1.9)
NRTI only	1484 (8.7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

in recent calendar years than earlier; and higher in patients with low CD4⁺ cell counts and high HIV RNA levels at the time of HAART initiation. Of the 173 cases of TB, 86 (49.7%) were pulmonary and 87 (50.3%) were extrapulmonary; the ratio of pulmonary to extrapulmonary cases did not vary greatly by calendar time, CD4⁺ cell count, or duration of HAART exposure.

Results from the multivariable Poisson regression analyses (table 3) suggested that rates were lower in men who have sex with men compared with other risk groups and in those starting HAART in 1998 or earlier compared with those starting HAART in later years. In addition, a higher CD4⁺ cell count

at the time of starting HAART was independently associated with a reduced incidence of TB. There was no independent relationship between the baseline HIV RNA level and the incidence of TB after adjustment.

Incidence of TB in relation to response to HAART.

Of the 17,142 patients included in the study, 15,243 (88.9%) and 14,930 (87.1%) had a CD4⁺ cell count and an HIV RNA measurement, respectively, 6 months after starting HAART. CD4⁺ cell counts had increased by a median of 107 cells/ μ L (interquartile range [IQR], 30–200 cells/ μ L) over this period to a median of 397 cells/ μ L (IQR, 251–571 cells/ μ L), and HIV RNA levels were <400 copies/mL in 9993 patients (66.9%). Of the patients included in the study, 3781 (24.8%) had experienced a CD4⁺ cell count increase of >200 cells/ μ L, 4096 (26.9%) had experienced an increase of 101–200 cells/ μ L, and 7366 (48.3%) had experienced an increase of <100 cells/ μ L (including 2615 patients who experienced a decrease in CD4⁺ cell count). CD4⁺ cell count increases during the first 6 months of HAART were not significantly different between individuals who developed TB during the first 6 months and those who developed TB subsequently, whether change was considered in absolute ($P = .58$, by the Mann-Whitney U test) or relative terms ($P = .30$).

During the subsequent 28,846 PYFU following the 6 month time point, 88 patients developed a new case of TB (3.05 cases per 1000 PYFU; 95% CI, 2.41–3.69 cases per 1000 PYFU). TB rates during this period were again highest in those with a low CD4⁺ cell count, either at baseline or at 6 months after HAART initiation (table 4). Those patients who experienced the smallest increases in CD4⁺ cell count during the first 6 months of HAART had a higher TB rate from 6 months onward than did individuals who experienced larger increases in CD4⁺ cell count. TB rates were also higher from 6 months onward in those whose baseline and 6-month RNA levels were higher. In multivariable analyses (table 3), the CD4⁺ cell count at 6 months and the baseline CD4⁺ cell count both remained associated with the incidence of TB from 6 months onward. Individuals with an HIV RNA level >400 copies/mL at 6 months were at twice the risk of a subsequent TB event, compared with those with lower HIV RNA levels, but an HIV RNA level \geq 100,000 copies/mL at the start of HAART was not significantly associated with the incidence of TB after controlling for the 6-month level and for CD4⁺ cell counts at the 2 time points (adjusted relative rate, 0.87; 95% CI, 0.53–1.45; $P = .60$). The relative rates associated with the CD4⁺ cell count at baseline and at 6-months were similar when the analysis was restricted to those with an HIV RNA level <400 copies/mL at 6 months (relative rates, 0.90 and 0.92, respectively), although the estimate for the 6-month value was no longer statistically significant, because of the reduced number of individuals in this analysis.

DISCUSSION

Analyses of the incidence of TB among individuals receiving HAART have been hampered, even in large cohorts, by the small number of individuals developing the disease. We addressed this issue by analyzing data from patients starting HAART who were enrolled in several cohorts in Europe and North America. The majority of patients were enrolled in countries where annual TB incidence rates in the general population are <20 cases per 100,000 population [12]. Among these patients, we found an overall incidence of TB of 4.7 cases per 1000 PYFU. The CD4⁺ cell count at the time of starting HAART and the immunological response to treatment measured after 6 months of therapy were both independently associated with the risk of TB over the subsequent 2.5-year period. Although a virological response to HAART was associated with a reduced risk of TB, the baseline HIV RNA level was not. Thus, those at higher risk of TB are those with poorer immunological or virological responses to HAART and those starting HAART with more-advanced immuno-suppression.

Previous European and North American studies conducted in the pre-HAART era reported an increased risk of TB for those with HIV infection, ranging from 1% to 9% per year [13]. In the present analysis, we observed an incidence of 13.1 cases per 1000 PYFU during the first 3 months after starting HAART, a figure approaching that seen for untreated HIV-infected individuals. This observation is consistent with reports that the risk of developing an opportunistic infection may be only slightly reduced in the first months after initiation of HAART [14]. It is possible that this high rate may reflect delayed diagnosis in those whose symptoms were being investigated at the time of initiation of HAART. It is also possible that the high rate may reflect the impact of immune reconstitution [15], although increases in CD4⁺ cell count during the first 6 months were similar for patients who developed TB in the first 6 months and patients who developed TB later, suggesting that this explanation was unlikely. Although a striking reduction in incidence of TB was achieved in the first 6 months after starting HAART, the risk of TB continued to decrease over the period of observation among those patients remaining under follow-up. This decrease in risk may reflect a progressive restoration of the ability of the immune system to control *M. tuberculosis* infection, and it is in agreement with in vitro studies suggesting that restoration of cellular immunity against TB may be delayed after initiation of HAART [16].

The incidence of TB was associated with the CD4⁺ cell count before starting HAART, which is consistent with results from studies involving untreated patients [17]. The baseline CD4⁺ cell count remained associated with the incidence of TB from 6 months after initiation of HAART, even after controlling for the 6-month CD4⁺ cell count, which was also predictive of the subsequent incidence of TB. These findings are in contrast to

Table 2. Incidence of tuberculosis per 1000 person-years of follow-up (PYFU) during the first 3 years after HAART initiation according to baseline characteristics, Antiretroviral Therapy Cohort Collaboration, 1996–2003.

Baseline characteristic	No. of cases of tuberculosis	No. of PYFU	Incidence rate of tuberculosis, cases per 1000 PYFU (95% CI)
Duration of HAART, months			
0–3	55	4208	13.1 (9.6–17.7)
4–6	30	3852	7.8 (5.0–10.6)
7–12	34	7322	4.6 (3.1–6.2)
13–24	40	12,210	3.3 (2.3–4.3)
25–36	14	9314	1.5 (0.8–2.5)
Sex			
Male	120	27,727	4.3 (3.6–5.1)
Female	53	9179	5.8 (4.2–7.3)
Risk group			
MSM	37	15,233	2.4 (1.7–3.2)
Injection drug user	32	6084	5.3 (3.4–7.1)
Heterosexual	89	12,772	7.0 (5.5–8.4)
Other/not known	15	2817	5.3 (3.0–8.8)
Year of HAART initiation			
1997 or before	33	12,341	2.7 (1.8–3.6)
1998	27	9127	3.0 (1.8–4.1)
1999	37	7126	5.2 (3.5–6.9)
2000	40	4892	8.2 (5.6–10.7)
2001 or after	36	3420	10.5 (7.1–14.0)
CD4 ⁺ cell count at HAART initiation, cells/ μ L			
<50	34	2543	13.4 (8.9–17.9)
50–199	61	8789	6.9 (5.2–8.7)
200–349	52	11,287	4.6 (3.4–5.9)
350–499	16	8263	1.9 (1.1–3.1)
\geq 500	10	6023	1.7 (0.8–3.1)
HIV RNA level at HAART initiation, copies/mL			
<100,000	90	22,910	3.9 (3.1–4.7)
\geq 100,000	83	13,996	5.9 (4.7–7.2)
Type of HAART			
PI-based	110	25,256	4.4 (3.5–5.2)
NNRTI-based	51	8412	6.1 (4.4–7.7)
PI and NNRTI	3	691	4.3 (0.9–12.7)
NRTI only	9	2547	3.5 (1.6–6.7)
Age, years			
\leq 37	100	21,283	4.7 (3.8–5.6)
>37	73	15,623	4.7 (3.6–5.7)

NOTE. MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

earlier analyses, in which the 6-month CD4⁺ cell count was a stronger predictor of clinical outcomes (all AIDS-related events) for patients receiving HAART than was the baseline CD4⁺ cell count [18]. Our findings may reflect the fact that

Table 3. Results of multivariable Poisson regression analyses to identify factors independently associated with incidence of tuberculosis (TB) in patients receiving HAART, Antiretroviral Therapy Cohort Collaboration, 1996–2003.

Variable	Incidence of TB from HAART initiation to 3 years after HAART initiation		Incidence of TB from 6 months after HAART initiation to 3 years after HAART initiation	
	Relative rate (95% CI)	P	Relative rate (95% CI)	P
Duration of HAART, per year	0.45 (0.36–0.56)	.0001	0.59 (0.39–0.89)	.009
Risk group				
MSM	1		1	
Injection drug user	2.46 (1.51–4.01)		2.98 (1.37–6.45)	
Heterosexual	2.42 (1.64–3.59)		2.69 (1.41–5.12)	
Other/not known	1.66 (0.91–3.06)	.0001	1.54 (0.55–4.35)	.006
Year of HAART initiation				
1997 or before	0.51 (0.31–0.84)		0.24 (0.11–0.56)	
1998	0.54 (0.32–0.90)		0.36 (0.16–0.80)	
1999	0.87 (0.54–1.39)		0.57 (0.26–1.21)	
2000	1.15 (0.73–1.82)		0.81 (0.39–1.68)	
2001 or after	1	.002	1	.003
CD4 ⁺ cell count, per log ₂ cells/μL				
At HAART initiation	0.87 (0.84–0.91)	.0001	0.89 (0.83–0.96)	.009
At 6 months after HAART initiation	NA		0.90 (0.81–0.99)	.07
HIV RNA level at 6 months after HAART of >400 copies/mL	NA		2.21 (1.33–3.67)	.003

NOTE. MSM, men who have sex with men; NA, not applicable.

patients coinfecting with HIV and TB may show minimal recovery of in vitro immunity to TB when HAART is started at low CD4⁺ cell counts [19]. Thus, we may expect a different relationship when considering TB than when considering all other AIDS-related events. Alternatively, our findings may reflect some degree of residual confounding, either because of the method of incorporation of CD4⁺ cell counts in the model or because of lack of adjustment for other unmeasured confounders.

Unlike other HIV-associated opportunistic infections, TB may occur at relatively high CD4⁺ cell counts [20] and may also occur soon after HIV seroconversion [21]. Our results suggest that HAART may reduce the risk of TB to levels observed in the first phase of infection and that, as also suggested by in vitro studies [16, 19, 22], complete restoration of cellular immunity against TB may not be possible. Some of the cases of TB in individuals with high CD4⁺ cell counts may be among individuals who have recently been infected with *M. tuberculosis*, who may remain at increased risk of developing active disease. Unfortunately, we cannot distinguish between new infections and reactivations of latent TB in this study, and therefore, we are unable to determine which of these explanations is most likely.

In our analysis, men who had sex with men had a lower risk

of TB, compared with other HIV-infected persons, most likely reflecting the different background prevalence of TB infection in different population groups, different ethnicity profiles, adherence patterns, and/or social or lifestyle factors. Furthermore, the incidence of TB appears to have increased over time. This may be due to a change over time in the underlying population of individuals with HIV infection, because the proportion of individuals immigrating from regions with a high TB prevalence into many European countries has increased.

Other limitations of our analysis need to be mentioned. First, we included patients who started HAART as their first regimen, but we have no information on actual receipt of therapy or on the different types of antiretroviral drugs used during follow-up. Because our analysis aimed to provide information on the risk of TB for individuals who had started HAART, this limitation will not have a major impact on our results. Second, our definition of response to HAART was based on the HIV RNA level and CD4⁺ cell count at 6 months after starting HAART. Previous studies have suggested that these values effectively characterize response to HAART in terms of its impact on the risk of developing opportunistic infections [14, 18, 23–25]. Third, and most importantly, the majority of patients in our analysis were enrolled in countries with a low incidence of TB. Thus, our data will not be generalizable to countries with

Table 4. Incidence of tuberculosis (TB) occurring ≥ 6 months after HAART initiation, stratified by CD4⁺ cell count and HIV RNA level as measured at HAART initiation and at 6 months after HAART initiation, Antiretroviral Therapy Cohort Collaboration, 1996–2003.

Variable	No. of cases of TB	No. of PYFU	No. of cases of TB per 1000 PYFU (95% CI)
CD4 ⁺ cell count, cells/ μ L			
At HAART initiation			
<50	18	1961	9.2 (5.4–14.5)
50–199	24	6792	3.5 (2.1–5.0)
200–349	27	8771	3.1 (1.9–4.2)
350–499	11	6552	1.7 (0.8–3.0)
≥ 500	8	4770	1.7 (0.7–3.3)
At 6 months after HAART initiation			
<50	6	303	19.8 (7.3–43.2)
50–199	25	3668	6.8 (4.1–9.5)
200–349	19	6108	3.1 (1.9–4.9)
350–499	16	6613	2.4 (1.4–3.9)
≥ 500	12	9551	1.3 (0.7–2.2)
Increase from baseline value			
>200	12	6949	1.7 (0.9–3.0)
101–200	17	7042	2.4 (1.4–3.9)
≤ 100	49	12,252	4.0 (2.9–5.1)
HIV RNA level, copies/mL			
At HAART initiation			
<100,000	53	17,917	3.0 (2.2–3.8)
$\geq 100,000$	35	10,930	3.2 (2.1–4.3)
At 6 months after HAART initiation			
≤ 400	38	17,022	2.2 (1.5–2.9)
>400	34	8705	3.9 (2.6–5.2)

NOTE. PYFU, person-years of follow-up.

a high incidence of TB. Fourth, because information was not available on the specific AIDS-defining events that individuals had experienced before starting HAART, we only included individuals who were free of AIDS at initiation of HAART. Thus, our results will only reflect the incidence of TB among AIDS-free individuals starting HAART, and we cannot generalize our results to recurrent TB events, for which a prior history of TB may be a strong risk factor [26]. Furthermore, we cannot rule out the possibility that we have included some recurrences in this analysis, because pulmonary TB started to be considered an AIDS-related event only in 1993 [27, 28]. Fifth, we have not performed any analyses on geographical variability of TB in the study. The cohorts included in the collaboration have very different study designs and use their own methods to achieve standardization of AIDS recording and TB diagnoses, and the use of TB treatment and prophylaxis varies from country to country. However, all analyses have been adjusted to take account of any cohort effects that might exist. Finally, even with this large data set, the number of events is too small to inves-

tigate whether the risk factors for TB differ according to the site of TB.

Even with widespread use of HAART, HIV-infected individuals remain at a relatively high risk of developing TB. Interventions to improve adherence to HAART and other TB control interventions may reduce the risk still further. Clinical trials have shown that treatment of latent TB infection reduces the risk of developing TB in HIV-infected persons [29]. Because a significant proportion of cases of HIV-associated TB result from the reactivation of latent infection, this intervention may significantly contribute to control of this disease. The effectiveness of treating latent TB infection may be increased in those receiving HAART. It has been shown that the possibility of identifying HIV-infected persons with an exposure to TB by using the tuberculin skin test may be increased among those with an immunological response to HAART [30], and there is evidence that the protective effect of treatment of latent TB may be greater among those with higher CD4⁺ cell counts [31]. Thus, the preservation or partial reconstitution of immune function

determined by HAART could enhance the protective effect of treatment of latent TB.

In conclusion, our analysis shows that the level of immunodeficiency at which HAART is initiated and the virological and immunological responses to HAART are important determinants of the risk of TB among HIV-infected patients. The use of HAART appears to progressively decrease, but not to abrogate, TB risk. If it is the case, as is also suggested by previous studies [22], that HAART-treated individuals remain at risk of TB over a prolonged life span, then HAART may have only a limited role as a TB-control measure in countries with a high burden of TB and HIV infection.

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