

Reduced Risk of Tuberculosis among Brazilian Patients with Advanced Human Immunodeficiency Virus Infection Treated with Highly Active Antiretroviral Therapy

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This observational study assessed the effect of combination antiretroviral therapy on the risk of tuberculosis among 255 patients with human immunodeficiency virus (HIV) infection and advanced immunodeficiency who were living in an area of Brazil with a high incidence of tuberculosis. The use of highly active antiretroviral therapy in regions with a high prevalence of coinfection with HIV and *Mycobacterium tuberculosis* may contribute to a lower incidence of tuberculosis.

The use of highly active antiretroviral therapy (HAART) for the treatment of HIV infection has been associated with a marked reduction in the incidence of most opportunistic infections [1, 2]. Although a reduction in the risk of tuberculosis (TB) was not initially apparent [3], recent reports from large observational studies performed in Europe [4, 5] and the United States [6] have suggested that antiretroviral therapy has a protective effect.

TB is the most common opportunistic infection among patients with HIV infection in many developing countries [7]. It is uncertain whether the benefit of antiretroviral regimens in regions with a low prevalence of latent TB infection and low risk of transmission of *Mycobacterium tuberculosis* in the community can be generalized to populations of developing coun-

tries where coinfection with HIV and *M. tuberculosis* is very common.

To our knowledge, no published data exist on the effectiveness of combination antiretroviral therapy in reducing the risk of TB in developing countries. This lack of data likely reflects the fact that antiretroviral therapy is generally not available in resource-poor countries. Brazil, the first developing country to provide free access to antiretroviral therapy for patients with HIV infection, provides a unique opportunity to study this issue. In this observational study, we analyzed the impact of combination antiretroviral therapy on the risk of TB in a cohort of HIV-infected persons who have advanced immunodeficiency and who reside in Rio de Janeiro, the city with the highest incidence of TB in Brazil.

Patients included in this study were selected from a prospective seroprevalent HIV cohort observed at the outpatient clinic of Hospital Universitário Clementino Fraga Filho [8]. The original objective of this cohort was to validate the 1990 World Health Organization staging system for HIV infection [9]. Patients were admitted to the cohort from January 1991 through December 1994. In Brazil, HAART was generally reserved for patients with advanced HIV infection, in accordance with contemporary recommendations of the Brazilian Ministry of Health [10]. Thus, only patients with advanced immunodeficiency (defined as ≥ 1 CD4⁺ lymphocyte differential count of <15%) were included in this study. We used CD4 percentages rather than absolute CD4 counts to define the occurrence of advanced immunodeficiency because the percentages have lower intraindividual variability. Patients with a previous diagnosis of TB were excluded. The start of the follow-up period was defined as the date of the first CD4 lymphocyte differential count of <15%. The follow-up period ended on 30 September 1998. Patients whose last visit took place >6 months before this date were considered lost to follow-up.

Baseline data that were collected included age, sex, risk factor for HIV infection, level of education, and the results of cutaneous delayed type hypersensitivity (DTH) tests that were performed closest to the date of the first CD4 lymphocyte differential count of <15%. The median time between DTH testing and the start of the follow-up period was 1 month (range, 0–6 months). DTH tests included the intradermal injection of tuberculin (PPD), *Candida*, and *Trichophyton* antigens. A positive reaction to PPD was defined as a cutaneous induration of ≥ 5 mm in diameter. Patients were classified as anergic if they did not display a reaction to any of the DTH antigens. Follow-up data included the clinical manifestations observed at each visit

Received 7 May 2001; revised 17 September 2001; electronically published 7 January 2002.

Financial support: PETROBRAS S.A. and Fundação do Amparo à Pesquisa do Rio de Janeiro (FAPERJ).

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Clinical Infectious Diseases 2002;34:543–6

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1058-4838/2002/3404-0019\$03.00

and the use of antiretroviral drugs. The diagnosis of TB was made if culture yielded *M. tuberculosis*, or, for patients who had suggestive clinical manifestations, if there was a favorable response to anti-TB therapy, in association with the presence of acid-fast bacilli in sputum or biopsy samples or with radiological findings compatible with pulmonary TB. A “favorable response” was defined as the resolution of fever and other signs and symptoms associated with presumed TB within 60 days of the initiation of therapy.

Discrete variables are given as absolute counts and percentages. Continuous variables are given as the median and interquartile range. Cox regression models were used to study the impact of antiretroviral therapy and the studied covariates on the risk of developing TB. Antiretroviral regimens that combined 2 nucleoside analog reverse-transcriptase inhibitors (NRTIs) or 2 NRTIs plus 1 protease inhibitor (HAART) were

modeled as time-dependent variables in intention-to-treat analyses. Patients who received anti-TB preventive therapy had their follow-up data censored on the date of the start of preventive therapy. Variables associated with a *P* value of <.15 in univariate regression models were included in an adjusted regression model. Significance levels are given by the results of the log-likelihood ratio test.

Of the 617 persons originally admitted to the cohort, 284 (46%) had CD4 lymphocyte differential counts of <15% during follow-up. Thirteen of these patients were excluded from the study because of a previous diagnosis of TB. Sixteen patients who started receiving anti-TB preventive therapy before the date of their first CD4 lymphocyte differential count of <15% were also excluded.

For the 255 patients included in this study, the median duration of follow-up was 22 months (range, 12.9–39.5 months).

Table 1. Frequency of tuberculosis (TB), according to the studied covariates and results of Cox regression crude analyses, among 255 HIV-infected patients included in the study.

Characteristic	No. (%) of patients		Crude hazard ratio (95% CI)	<i>P</i>
	Total	With TB		
Sex				.19
Female	75 (29)	9	1.0	
Male	180 (71)	39	1.59 (0.77–3.27)	
Level of education, years				.99
≤8	113 (44)	22	1.0	
>8	140 (55)	26	1.0 (0.56–1.78)	
Age, years				.23
<35	128 (50)	30	1.0	
≥35	127 (50)	18	0.70 (0.39–1.26)	
Risk factors for HIV				.51
Male homosexuality/bisexuality	135 (53)	30	1.0	
Heterosexual contact	69 (27)	9	0.54 (0.17–1.79)	
Transfusion or injection drug use	20 (8)	3	0.64 (0.30–1.34)	
Unknown	31 (12)	6	0.79 (0.33–1.90)	
DTH skin test results				.01
PPD nonreactive	133 (52)	19	1.0	
PPD reactive	86 (34)	19	2.17 (1.15–4.11)	
Anergic	36 (14)	10	2.89 (1.34–6.24)	
CD4 ⁺ lymphocyte percentage				.44
≤7%	59 (23)	9	1.0	
>7%	196 (77)	39	0.74 (0.35–1.56)	
Antiretroviral therapy received ^a				
None or NRTI monotherapy	195		1.0	
Dual-NRTI therapy	42	5	0.86 (0.32–2.32)	.80
Two NRTIs plus 1 PI	41	1	0.19 (0.03–1.09)	.051

NOTE. DTH, delayed type hypersensitivity; NRTI, nucleoside analog reverse-transcriptase inhibitor; PI, protease inhibitor; PPD, intradermal injection of tuberculin antigen.

^a Data are the number of patients who were included in 1 of the categories at any time during follow-up.

Thirty-eight patients (15%) had their follow-up data censored when they started to receive preventive therapy with isoniazid. The frequency of loss to follow-up was lower among the 41 patients treated with HAART (4 patients [10%] were lost to follow-up) than it was among the other 214 patients (47 patients [22%]; $P = .073$). Death was also less common among patients treated with HAART (3 patients [7%] died) than it was among the others (44 patients [21%]; $P = .045$). None of these patients had a diagnosis of TB at the time of death. However, autopsies were not performed to rule out the possibility that some of them died with undiagnosed TB.

The median CD4 lymphocyte differential count before patients started receiving HAART was 6% (range, 3%–13%), and it increased significantly thereafter (median, 11%; interquartile range, 7%–17%; $P < .001$). TB was diagnosed in 48 patients (19%; incidence rate, 8.4 cases per 100 patient-years). Diagnosis was made on the basis of isolation of *M. tuberculosis* in culture for 25 (52%) of these 48 patients. Table 1 shows the distribution of the variables studied and the results of crude Cox regression analyses. The use of HAART was associated with an 81% reduction in the risk of TB ($P = .05$). Results of DTH tests were also associated with the risk of TB ($P < .001$). There was no significant association between TB and all other variables studied, including dual-drug therapy. In the adjusted regression analysis (table 2), the association between the use of HAART and a reduction in the risk of TB were essentially unchanged (hazard ratio, 0.2; $P = .06$).

To our knowledge, this is the first study to suggest that the use of HAART in a region with a high incidence of TB may reduce the risk of this disease among HIV-infected patients. Contrary to the findings of other studies [5, 6], dual-drug therapy was not effective, probably because only patients with advanced immunodeficiency were studied.

The hypothesis tested in this study was that the higher rate of transmission of *M. tuberculosis* associated with concurrent factors that could enhance immunodeficiency in poor populations (e.g., undernourishment and the high prevalence of helminthic infections [11]) could blunt the expected protective effect of HAART on the incidence of HIV-associated TB, especially among patients with advanced immunodeficiency. An incomplete recovery of the immune response against *M. tuberculosis* [12] might still render patients with advanced immunodeficiency highly susceptible to reactivation of TB or to rapid development of disease after a newly acquired infection. Given these assumptions, it is noteworthy that the magnitude of the protective effect associated with HAART among patients with advanced immunodeficiency in this study was similar to that observed in 2 larger studies reported from industrialized countries [5, 6].

Our study has several limitations. The duration of follow-up for patients receiving HAART was short, and, accordingly,

Table 2. Results of adjusted Cox regression analyses.

Variable	Adjusted hazard ratio (95% CI)	P
DTH skin test results		
PPD negative, nonanergic	1.0	.003
PPD positive	2.0 (1.14–3.33)	
Anergic	4.39 (2.19–8.80)	
Antiretroviral therapy received		
All others ^a	1.0	
Two NRTIs plus 1 PI	0.2 (0.04–1.13)	.06

NOTE. DTH, delayed type hypersensitivity; NRTI, nucleoside analog reverse-transcriptase inhibitor; PI, protease inhibitor; PPD, intradermal injection of tuberculin antigen.

^a Patients who did not receive any antiretroviral therapy or who were treated with other antiretroviral drug regimens (mono- or dual-NRTI therapy).

the long-term effect of HAART on TB incidence could not be determined. A precise estimate of the protective effect of HAART for TB was not possible because of the combination of a short follow-up period for patients receiving HAART and the relatively small number of patients treated, which resulted in the wide confidence intervals obtained in our analyses. On the other hand, most patients treated with HAART in this study had previously been treated with monotherapy or dual-NRTI therapy. It is likely that some of these patients were already infected with virus with resistance mutations to some of the drugs used in the combination, which could have caused an underestimation of the potential impact of HAART. Another limitation was that the number of patients who were lost to follow-up or who died was greater than the number of cases of TB. Deaths and losses to follow-up were more common among patients who were not treated with HAART, which may have caused an underestimation of the protective effect of HAART. Finally, our analyses were restricted to patients with advanced disease. Few patients in this cohort started receiving HAART while they had CD4 lymphocyte differential counts of $\geq 15\%$; therefore, we did not have enough statistical power to make conclusions about the impact of HAART on these patients. Results obtained in patients with advanced immunodeficiency cannot be generalized to those with less-advanced HIV disease. Because it has been shown that patients with HIV-related TB in developing countries tend to present with higher CD4 cell counts than do such patients in industrialized countries [13, 14], it is still possible that the benefit of HAART in reducing TB may be less apparent in developing countries than it is in industrialized countries.

Despite these limitations, our data suggest that the policy of providing free access to HAART may contribute to a reduction in the incidence of TB in populations with low socioeconomic level and high prevalence of coinfection with HIV and *M. tuberculosis*. Such a policy, in association with well-structured programs to provide preventive therapy to PPD-positive pa-

tients, should be considered an integral part of public health strategies to control HIV-associated TB in underserved populations. However, large prospective studies in developing countries are needed to confirm these findings.

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