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Tuberculosis incidence and risk factors among patients living with HIV/AIDS in public health service institutions in Brasilia, Federal District

Incidência e fatores de risco para tuberculose em pacientes vivendo com HIV/AIDS atendidos nos serviços públicos de saúde em Brasília, Distrito Federal

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ABSTRACT

In order to estimate the incidence of and risk factors for developing tuberculosis, the clinical charts of a retrospective cohort of 281 HIV-positive adults, who were notified to the AIDS Program of the Health Department of Brasilia in 1998, were reviewed in 2003. All the patients were treatment-naive regarding antiretroviral therapy at the time of inclusion in the cohort. Twenty-nine patients were identified as having tuberculosis at the start of the study. Thirteen incident tuberculosis cases were identified during the 60 months of follow-up, with an incidence density rate of 1.24/100 person-years. Tuberculosis incidence was highest among patients with baseline CD4+ T-lymphocyte counts ≤ 200 cells/µl who were not using antiretroviral therapy (incidence = 5.47; 95% CI = 2.73 to 10.94). Multivariate analysis showed that baseline CD4+ T-lymphocyte counts ≤ 200 cells/µl (adjusted hazard ratio [AHR] = 5.09; 95% CI = 1.27 to 20.37; p = 0.02) and non-use of antiretroviral therapy (AHR = 12.17; 95% CI = 2.6 to 56.90; p = 0.001) were independently associated with increased risk of tuberculosis.

Key-words: Tuberculosis. Incidence. Human immunodeficiency virus. Acquired immunodeficiency syndrome. Risk factors. Survival.

RESUMO

Para estimar a incidência e os fatores de risco para desenvolver tuberculose foram revisados em 2003 os ≤prontuários de uma coorte retrospectiva de 281 adultos infectados pelo HIV que foram notificados ao Programa de AIDS da Secretaria de Saúde de Brasília em 1998. Todos os pacientes eram virgens de tratamento anti-retroviral no momento da inclusão na coorte. Vinte e nove pacientes foram identificados com tuberculose na avaliação basal. Treze casos incidentes de tuberculose foram identificados durante os 60 meses de seguimento com densidade de incidência de 1,24/100 pessoas-ano. A incidência de tuberculose foi maior em pacientes com contagens basal de linfócitos T CD4+ ≤ 200 células/µl que não se encontravam em uso de terapia anti-retroviral 5,47 (IC95%=2,73 a 10,94). A análise multivariada demonstrou que a contagem basal de linfócitos T CD4+ ≤ 200 células/µl (a*djusted hazard ratio* [AHR] =5,09; IC95%=1,27 to 20,37; p =0,02) e o não uso de terapia anti-retroviral (AHR=12,17; IC95%=2,6 to 56,90; p=0,001) estiveram independentemente associados a um risco maior de tuberculose.

Palavras-chaves: Tuberculose. Incidência. Vírus da imunodeficiência humana. Síndrome da imunodeficiência adquirida. Fatores de risco. Sobrevivência.

The emergence and dissemination of human immunodeficiency virus (HIV) in the 1980s promoted increased tuberculosis (TB) incidence around the world, even though in developed countries it had been considered under control[6 9 10 25].

TB is one of the most common causes of morbidity and mortality among HIV patients living in low-income countries[10]. Some estimates have shown that 30 to 60% of HIV patients are carriers of *Mycobacterium tuberculosis* with an 8 to 10% likelihood per year of developing the disease, whereas among immunocompetent individuals, the lifetime risk of TB reaches 10%[1 39]. HIV increases the risk of progression from latent *Mycobacterium tuberculosis* infection, early infection or reinfection to active disease[8 10]. Previous studies have demonstrated that patients living with HIV/AIDS have a poor prognosis when

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they have TB that is also associated with low CD4+ T-lymphocyte counts and limited access to highly active antiretroviral therapy (HAART)[2 11 20 31 45].

The introduction of HAART has markedly changed the natural history of HIV infection in both developed and developing countries, with a notable reduction in the risk of contracting opportunistic infections (OI) such as *Pneumocystis jirovecii* pneumonia, *Mycobacterium avium* complex infection and cytomegalovirus retinitis[35]. In Brazil, access to HAART has been available since 1996, with the introduction of protease inhibitors and other potent drugs such as non-nucleoside analogues of reverse transcriptase. These drugs have promoted a significant reduction in overall OI, prolonged patient survival and improved quality of life for the patients. In addition, HAART has produced changes in the clinical characteristics[28] and prognosis among HIV/TB coinfected patients[1].

In this study, we addressed the issues of incidence, survival and risk of TB disease among HIV-infected patients who were notified to the AIDS Program of the Health Department of Brasilia, Federal District.

PATIENTS AND METHODS

Retrospective cohort. We identified TB-naive adult patients among all the HIV/AIDS cases notified to the AIDS Program of the Health Department of Brasilia, Federal District, during 1998. The exclusion criteria for our study included lack of clinical records, healthcare at private hospitals and death within the first month after HIV diagnosis.

The patients were followed up for 60 months at any of the seven health centers in Brasilia that were able to care for people living with HIV/AIDS and TB. Enrolment was independent of disease stage and degree of immunodeficiency. Data were collected from clinical records according to standardized criteria on structured forms at registration, and again every six months until December 2003. AIDS was defined according to the 1993 revised classification system for HIV infection of the Centers for Disease Control and Prevention[7] and the Rio de Janeiro/Caracas criteria[37]. HIV and TB infection were defined in accordance with the Brazilian Ministry of Health guidelines for TB and HIV/AIDS. These guidelines included:

Tuberculosis diagnosis: identification of *Mycobacterium tuberculosis* in cultures or acid-fast smears in sputum or other tissues, compatible histological findings from tissue biopsies or compatible clinical features[13]. When this last criterion was positive, the TB diagnosis was confirmed by means of a good response to specific anti-TB treatment maintained for at least two months.

The TB-free group was formed by patients without these features in spite of regular clinical and laboratory evaluations as advocated by the Brazilian National Sexually Transmitted Diseases/AIDS Program[39], as well as absence of any clinical records of TB.

Hunan immunodeficiency virus diagnosis: positive enzyme-linked immunosorbent assay (ELISA) confirmed by either immunofluorescence or the western blot test[37].

Initial use of HAART was defined when the patient had used antiretroviral drugs for at least three uninterrupted months starting from the cohort inception date.

Patients who did not complete the follow-up period and remained TB-free were censored at the last medical evaluation available before death, as were those who transferred to health units outside of the study area or who were lost from the follow-up.

Tuberculosis incidence and risk estimates. Patients who were diagnosed as having TB between January 1998 and December 2003 were included in the analysis.

Incidence rate: the incidence density of TB was calculated by dividing the number of patients with TB by the person-years of follow-up of all patients at risk. Only the first detected episode of TB was considered for calculating the incidence rate. For a large number of patients, the diagnosis of HIV infection was concomitant with the TB diagnosis. Therefore, the incidence density was calculated for two groups according to the time of TB diagnosis: first, for patients who developed TB after the cohort inception, and second, for all patients including those having both HIV and TB diagnosis at the inception of the cohort. This approach was chosen because it better represented the influence of TB as a serious reason for focusing on persons with unknown HIV infections.

Risk estimates and survival analysis: we estimated the mean TB-free survival time and probability by means of a Kaplan-Meier curve. The incidence density and strength of association were estimated by means of the hazard ratio, using the Cox proportional hazards regression model. The patients were stratified according to their baseline CD4+ T-lymphocyte count (≤ 200 and > 200 cells/µl) and the use of HAART. The Cox proportional hazards regression model was run in relation to sex, age, transmission risk group, CD4+ T-lymphocyte count, viral load and use of HAART, to obtain the adjusted hazard ratio. Patients with simultaneous diagnoses of TB and HIV infection were excluded from the survival and Cox proportional hazards regression analysis.

Characteristics of patients with tuberculosis. The clinical and epidemiological characteristics of patients during their TB episodes were obtained from clinical records. The characteristics recorded included age, sex, CD4+ T-lymphocyte count, HIV viral load, use of HAART and clinical presentation of TB.

Statistical analysis. Stata software (version 8; Stata Corporation, College Station, Texas, USA) was used for calculating the incidence and confidence intervals (95% CI), assuming a Poisson distribution of events. The survival analysis was performed by means of a Kaplan-Meier life table method to assess the equality of the survival function using the log-rank test, and by means of the Cox proportional hazards regression model. Variables associated with TB development with $p < 0.5$ in the crude analysis were included in the multivariate approach in the initial model. Variables were removed from the model if the value of alpha was greater than 0.05.

RESULTS

During 1998, 484 naive adult patients were reported as having HIV/AIDS. Of these, 173 were excluded: 85 did not have

clinical records available, 26 attended private hospitals and 62 died within the first month after HIV diagnosis. Therefore, a total of 281 (58%) HIV-infected persons were enrolled in the study. Among them, 29 were diagnosed as having simultaneous HIV and TB infection at the cohort inception.

The other 252 patients enrolled in the study were 59% male. The main HIV transmission routes were: unprotected sex (56% heterosexual and 21% men who had sex with men [MSM]), intravenous drug use (IDU) in 14% of the patients and unknown cause in 9% of the patients. At diagnosis, the median age (with P25 – P75) was 31 years (25-37). The median (P25 – P75) baseline for the CD4+ T-lymphocyte count was 196 cells/µl (59-418) and the viral load was 5.1 log RNA copies/µl (4.4-5.5).

Tuberculosis incidence. Thirteen patients were diagnosed as having TB during follow-up. All of the HIV-infected patients contributed 1048 person-years of follow-up. Those TB cases yielded an incidence density of 1.24 (95% CI: 0.66 to 2.12) events per 100 person-years of observation (PYO). The incidence density for the 42 coinfected patients after including 29 patients with simultaneous TB and HIV infection at the cohort inception was 4.01 (95% CI: 3.13 to 5.75) events per 100 PYO.

Among these patients, six showed clinical findings and radiographic images that were compatible with TB, four had positive sputum for acid-fast bacilli (AFB), two had positive cultures for *Mycobacterium tuberculosis* and one showed compatible histological findings in tissue biopsies.

Survival. Twenty-nine TB patients diagnosed at the inception were excluded from the survival analysis. Two-hundred and fifty-two patients were thus included. Figure 1 shows the Kaplan-Meier estimates of TB-free survival proportion after diagnosis of HIV infection, in the overall cohort and among patients with CD4+ T-lymphocyte counts categorized as ≤ 200 and > 200 cells/µl, as stratified by the use of HAART. Survival was significantly worse ($p < 0.001$ using the log-rank test) among the patients with CD4+ T-lymphocyte counts ≤200 and among those who were not using HAART. Patients who showed both of these characteristics had the worst mean survival and highest hazard ratio for developing TB (Table 1). The Cox proportional hazards model including sex, baseline CD4+ T-lymphocyte counts, HIV baseline viral load and use of HAART was used to assess and correct for confounding factors. After adjustments were done, CD4 count ≤ 200 and non-use of HAART remained the most powerful predictors of poor survival (Table 2).

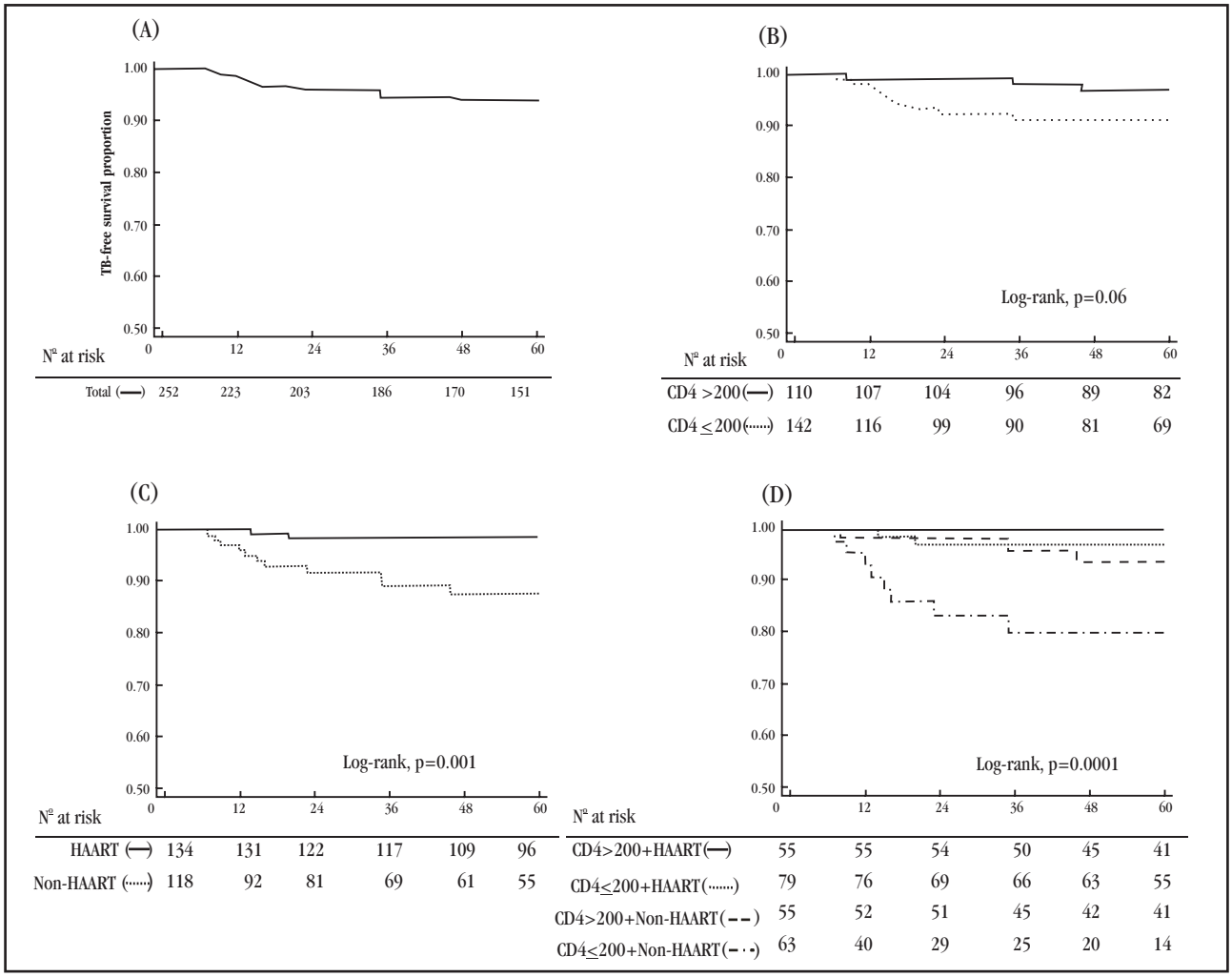

Figure 1 - Kaplan-Meier plots of TB-free survival proportion: (A) ***in the overall cohort;*** (B) ***among patients stratified according to baseline CD4+ T-lymphocyte count;*** (C) ***among patients stratified according to use of HAART;*** (D) ***among patients stratified according to baseline CD4+ T-lymphocyte count and use of bigly active anti-retroviral therapy.***

Table 1 - Effect of baseline CD4+ T-lymphocyte cell counts and higly active anti-retroviral therapy use on the risk of tuberculosis disease among 252 patients living with HIV/AIDS in Brasilia, Federal District.

Baseline parameters	Incidence rate cases per 100 PYO (95% CI)	Hazard ratio (95% CI)	Mean survival months (95% CI)
CD4 > 200 + HAART	0	1.0*	60.0
CD4 ≤ 200 + HAART	0.60 (0.15 – 2.37)	4.5 (1.2 – 16.4)	58.8 (57.2 – 60.4)
CD4 > 200 + non-HAART	1.26 (0.41 – 3.90)	10.1 (2.2 – 45.8)	58.2 (55.9 – 60.4)
CD4 ≤ 200 + non-HAART	5.47 (2.73 – 10.94)	44.9 (5.6 – 361.8)	51.5 (46.2 – 56.8)

PYO: person-years of observations, HAART: highly active antiretroviral therapy, 95% CI: 95% confidence interval.

*denominator of hazard ratio.

Table 2 - Hazard ratios for tuberculosis according to the Cox proportional hazards regression model, adjusted for baseline parameters among 252 patients living with HIV/AIDS in Brasilia, Federal District.

Baseline parameters	Crude hazard ratio (95% CI)	*p*	Adjusted hazard ratio (95% CI)	*p*
Male Sex	1.64 (0.50 – 5.32)	0.41		
Age < 30 years	0.88 (0.30 – 2.62)	0.82		
Transmission risk behavior				
intravenous drug use	0.50 (0.07 – 3.85)	0.51		
HIV viral load > 5 log	1.57 (0.43 – 5.72)	0.50		
T-lymphocyte CD4 ≤ 200 cells/µl	3.22 (0.89 – 11.71)	0.07	4.46 (1.21 – 16.35)	0.024
Non-use of antiretroviral treatment	8.06 (1.79 – 36.38)	0.007	10.07 (2.21 – 45.81)	0.003

HIV: human immnunodeficiency virus, 95% CI = 95% confidence interval.

*adjusted for variables with $p < 0.5$ in the crude hazard ratio analysis.

Clinical and epidemiological characteristics of human immunodeficiency virus-tuberculosis coinfected patients. From 1998 to 2003, 42 patients were diagnosed with TB, and 67% of them were male. The types of HIV transmission included heterosexual intercourse for 55% of the subjects, intravenous drug use for 21%, men who had sex with men for 12%, and others for 12%. The median (P25 – P75) baseline CD4+ T-lymphocyte count was 99 (63-260) cells/µl and the HIV viral load was 5.4 (5.0-5.5) log RNA copies/µl. In Table 3, the characteristics of HIV/AIDS patients at the time of TB diagnosis are described.

The TB cases were diagnosed at medians (P25 – P75) of 14 (10-21) and 17 (14-20) months after cohort inception among the patients who did and did not use HAART, respectively. In the group of patients with a baseline CD4+ count > 200 cells/µl, TB cases were diagnosed at a median (P25 – P75) of 35 (8-46) months among patients who did not use HAART, and no cases were identified among HAART users.

Table 3 - Characteristics of 42 HIV-TB coinfected patients diagnosed from 1998 to 2003 in Brasilia, Federal District.

	Detected at cohort inception nº = 29	Detected during follow-up nº = 13
Male sex (%)	66	69
Age (median [P25 – P75] years)	34 (30 - 42)	35 (27 - 36)
Transmission risk behavior to HIV (%)		
unprotected heterosexual contacts	45	77
intravenous drug use	28	8
men who had sex with men	17	0
unknown	10	15
T-lymphocytes CD4+ count (median [P25 – P75] cells/ µl)	96 (65 - 339)	64 (34 - 99)
HIV viral load (median [P25 – P75] log RNA copies/µl)	5.3 (5.0-5.7)	5.0 (3.4 - 5.8)
Non-use of HAART (%)	100*	85
Clinical presentation of TB (%)		
pulmonary	52	62
extrapulmonary	21	23
pulmonary + extrapulmonary	27	15
Extrapulmonary TB presentation (%)		
lymph node	64	40
miliary	14	40
others**	22	20

HIV: human immnunodeficiency virus, RNA: ribonucleic acid, HAART: highly active antiretroviral therapy, TB: tuberculosis,

*These patients did not use antiretroviral treatment, because TB diagnosis was at the same time as HIV diagnosis, ** Pleural, meningeal and genitourinary tuberculosis.

DISCUSSION

Analysis of the incidence of HIV-associated TB infection in the HAART era has always been a difficult task. We approached these issues by analyzing retrospective data from newly diagnosed HIV-patients notified to the AIDS Program in 1998. The patients were from Brasilia, Federal District, which is a medium-level TB transmission area[26] where the annual TB incidence rate in the general population is less than 20 cases per 100,000 inhabitants[38] Meanwhile, the national Brazilian annual incidence reaches up to 60 cases per 100,000 inhabitants[47].

We found an overall TB incidence of 1.24 per 100 PYO. Among patients with advanced immunodeficiency (baseline CD4 ≤ 200 cells/µl) who used HAART, the prognosis for not developing TB disease was better after six years of follow-up, with an incidence rate reduced by around fivefold, compared with patients who did not use HAART. We could not determine the time at which HAART use began to diminish the TB incidence rate, but in a previous large population study, the risk of contracting TB continued to decrease for six months after starting to use HAART[17].

Previous studies have reported that TB incidence among HIV patients varies from one country to another, depending on the country's health policy regarding HAART use and the local TB prevalence rate. In Ethiopia, where the policy on the use of HAART was established in 2002[21] and where TB rates were high, the coinfection incidence reached 3.7 per 100 PYO[47]. However, in India an incidence of 6.9 per 100 PYO was reported[44]. India approved antiretroviral treatment in 2003[41] and implemented it by 2004, and the country has continued to have high TB incidence for many years[47]. Similar numbers could be expected in India at present. In Europe and North America, the use of HAART was approved nearly a decade ago[24 32 35], which has resulted in low reported rates of TB[9 47]. In Italy, the incidence was 0.79 per 100 PYO[14], a figure similar to that from the EuroSIDA cohort, which estimated 0.80 TB cases per 100 PYO[23]. The HAART Cohort Collaboration, an international collaborative study, reported 0.47 TB cases per 100 PYO[17]. Furthermore, the Adult/Adolescent Spectrum of HIV Disease (ASD) project, a North American study, showed 0.50 TB cases per 100 PYO[22]. Our observations were thus consistent with the reported incidences in developed countries. However, when considering all TB cases diagnosed at the cohort inception, the incidence then became elevated by around fourfold, which may have reflected a better estimate if we consider the exposure risk period for *Mycobacterium tuberculosis* infection from seroconversion until HIV diagnosis. The number of simultaneous diagnoses of TB/HIV (69%; 29 out of 42) showed that the patients knew about their HIV status for the first time when they were also diagnosed with TB[18].

Observational studies conducted both in low and in high TB incidence countries have shown that the risk of developing TB has decreased by 70 - 90% for HIV-infected individuals who received HAART, compared with those who were untreated[4 16 22 36]. Consequently, the incidence of HIV-associated TB has generally decreased in countries where HAART has become the care standard for HIV-infected individuals. Although HAART may reduce the incidence of TB, it may not completely eliminate the risk. Estimates have shown that early use of HAART averted TB. However, if HAART were started when the CD4+ T-lymphocyte count reached 200 cells/µl or lower, the drug regimen would only be able to reduce 25% of the TB cases (assuming 85% coverage of the population). If HAART were started with higher CD4+ levels, then the reduction rate for TB cases would be better[46]. Middle-income countries like Brazil that are attempting to manage concomitant epidemics of TB and HIV/AIDS are thus advised to implement broad public strategies with the aims of increasing the coverage and compliance and stimulating the early use of HAART to avert OI and TB in the course of HIV infection[29].

Unlike other OIs that occur when CD4+ T-lymphocyte counts drop to ≤ 200 cells/µl, active TB occurs through a broader spectrum of immunodeficiency[19 33]. The relative proportions of clinical forms of TB in HIV patients with almost intact immune function are similar to those observed in non-HIV infected patients, i.e. 80 to 85% presenting pulmonary forms[42]. Among patients with advanced HIV disease, pulmonary tuberculosis has decreased to 50 to 60%, and the likelihood of extrapulmonary involvement rises as the immunity worsens, thus showing a predominance of lymphadenopathy[15 43]. Most of our patients presented an increased number of extrapulmonary TB forms, with nearly half showing lymph node involvement. These were compatible numbers considering their advanced immunodeficiency.

Nowadays, TB diagnosis among HIV patients follows specific guidelines[18]. However, in some patients, doubt persists about clinical TB diagnoses in spite of using appropriate means of evaluation[3]. In the present study, patients with no microbiological confirmation were assumed to have had TB if the suspected clinical condition had improved after two months of anti-tuberculosis therapy. This has been possible up to now because Brazil has been considered to be a country with low multidrug-resistance TB prevalence[47]. Until now, there has not been an established period for confirming the TB diagnosis from good responses to anti-TB treatment. Reports on patients with difficult TB diagnoses have suggested that this period could vary from 3 weeks[30] to 3 months[5].

TB was diagnosed earlier in HIV patients with CD4+ T-lymphocyte counts of ≤ 200 cells/µl than in patients with higher CD4+ T-lymphocyte counts. Among patients with good adherence to antiretroviral treatment, the first TB cases appeared more than one year after the cohort inception. Sometimes, the immune reconstitution syndrome (IRIS) increases the number of TB cases within the first month after starting HAART use, among HIV patients with severe immunodeficiency[17], thereby confounding the effectiveness of antiviral treatment for preventing TB. However, we did not have any patients diagnosed with TB because of IRIS after using HAART, since the majority of TB associated with IRIS developed within the first two months of HAART use (usually within the first 2-3 weeks[12]).

We have shown in this study that baseline CD4+ T-lymphocyte counts of ≤ 200 cells/µl and lack of HAART use were both independently associated with increased risk of TB, based on the results from our multivariate analysis. Other risk factors have been reported in other countries. In an adult AIDS cohort

in Cape Town, for individuals aged 33 years or younger, CD4+ T-lymphocyte counts < 100 cells/µl and WHO clinical stages 3 and 4 when HAART was first started were identified as risk factors[27]. In a study cohort in the United States, IDU, heterosexual contact, CD4+ T-lymphocyte counts < 100 cells/µl and lack of any antiretroviral therapy were important risk factors[22]. In Côte d'Ivoire, where TB incidence has been high since the 1990's, a history of TB was an important risk factor for developing HIV-associated TB[40 47]. In Rio de Janeiro, positive PPD (intradermal injection of tuberculin antigen) was identified as an important risk factor among advanced immunodeficiency HIV patients[36]. In our study, the intermediate TB rates in our city and the methodological limitations of our study may have lowered the sensitivity for detecting other risk factors.

One important limitation was the large number of patients seeking medical attention after their first clinical symptoms of advanced immunodeficiency had occurred. This may have caused selection of the patients who were most vulnerable towards developing TB or other OIs in our study. It also yielded a limited estimation of the survival rates when the cohort study began at HIV diagnosis rather than at HIV serological conversion. This resulted in a much higher survival rate among patients with less immunodeficiency, thereby increasing the risk of latent TB progression to active disease. The absence of microbiological confirmation in some patients with TB could be another important limitation. Nonetheless, we could not exclude these cases, because of the known difficulties in confirming TB in HIV/AIDS patients, especially if they are in advanced stages of immunodeficiency. The deaths of some patients from causes other than TB, and patients relocating to another city were also relevant factors to consider. However, we believe that the impact of these factors would have been small because there were many critical patients still at risk by the end of the study period.

In conclusion, our analysis showed that HAART attenuated the increase in TB incidence among HIV patients, especially among severely immunodeficient HIV-infected individuals. Hence, the use of HAART diminished TB risk. Nonetheless, cases of TB appeared several months later in this city, which has low incidence of TB infection. Future prospective adult cohorts need to be established, with the purpose of exploring other risk factors such as social and economic status and TB contact in inpatient or outpatient clinical settings, in order to evaluate their impact on the development of TB among HIV patients.

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