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Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil

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Abstract

Background/Objective—The risk of recurrent tuberculosis may increase in HIV-infected patients due to exogenous re-infection. We measured the frequency of and determined risk factors for recurrent tuberculosis in a cohort of HIV-infected patients in Rio de Janeiro, Brazil.

Methods—Data were abstracted from medical records of HIV-infected patients attending 29 HIV clinics between 1998 and 2007. Patients analyzed were those who had no tuberculosis history prior to their first HIV clinic visit and who had at least one episode of tuberculosis after entry. Incidence rate ratios compared incidence rates between risk groups and Cox proportional hazards regression models evaluated unadjusted and adjusted associations.

Results—Among 1,080 HIV-infected patients with tuberculosis, 96(8.9%) developed a recurrent diagnosis. The median time between diagnoses was 2.4 years. Fewer patients with recurrent tuberculosis had completed their initial 6-month course of tuberculosis treatment compared to patients without recurrence (78% versus 86%; $p=0.02$). For patients who completed therapy, the incidence rate of recurrence was 2.5/100 person years (PYs) versus 9.0/100PYs for non-completers (Incidence Rate Ratio (IRR)=3.60(95%CI:1.92-6.32). In multivariate modeling, initial tuberculosis treatment completion, receipt of antiretroviral therapy (ART) and CD4 cell count $>200/\text{mm}^3$ any time after the initial diagnosis were associated with a significantly decreased hazard of recurrence.

Conclusions—Tuberculosis recurrence rates were high in this HIV-infected population. Completion of initial tuberculosis therapy, use of ART and increases in CD4 cell counts were associated with lower recurrence rates. Use of secondary preventive therapy might be warranted to reduce the burden of tuberculosis in patients with HIV infection.

Keywords

HIV; tuberculosis; recurrence; antiretroviral therapy; Brazil

Introduction

Tuberculosis is a major opportunistic infection in persons infected with human immunodeficiency virus (HIV) (1). Following treatment with short-course chemotherapy, patients have a small risk for developing recurrent tuberculosis as a result of a relapse or exogenous re-infection (2;3).

Recurrent tuberculosis is a significant problem for tuberculosis control programs, as treatment for recurrent episodes is often associated with drug resistance and low cure rates (4-6). Recent evidence suggests that rates of recurrent disease can be significantly greater than rates of new tuberculosis in high incidence areas, even among patients who successfully complete therapy (7-9).

Risk factors for recurrence due to relapse include poor tuberculosis treatment adherence at initial diagnosis (10), residual cavitation on chest radiograph (2;3) and positive sputum culture at 2 months of treatment (11;12). A primary risk factor for both relapse and re-infection is HIV-infection (2;3;10;13). Among HIV-infected populations, low initial CD4 count (13) and receiving less than 37 weeks of anti-tuberculosis therapy (10;13) have been observed to increase recurrence.

The frequency of and risk factors for recurrent tuberculosis in HIV-infected populations with access to antiretroviral therapy (ART) have not been determined. While ART reduces the risk of initial episodes of tuberculosis (14) and decreases rates of recurrence of other HIV-related opportunistic infections, its impact on subsequent tuberculosis is not known. The aim of this analysis was to measure the magnitude of and determine risk factors associated with tuberculosis recurrence in a cohort of HIV-infected patients in Rio de Janeiro, Brazil.

Methods

The study was conducted within the Tuberculosis and HIV in Rio (THRio) study, as previously described (14;15). In brief, data were abstracted from medical records of HIV-infected patients attending 29 HIV clinics in Rio de Janeiro who had at least one clinic visit between September 2003 and September 2005. Chart abstractions are conducted semi-annually at all participating clinics. Information routinely collected includes demographic data, dates of HIV diagnosis, opportunistic infections including tuberculosis, treatment history for HIV and tuberculosis, and results of diagnostic tests including CD4 counts, HIV viral loads and tuberculin skin tests. Although patients were required to have had a clinic visit in the 2003-2005 time period, all clinical information from the date of the first clinic visit, which may have occurred years earlier, were collected. Analysis of the baseline data collected as part of the THRio study have been reported (14). The data for this analysis were updated through February, 2008.

Definitions

Eligible patients were those who were diagnosed with a first episode of tuberculosis after their initial clinic visit. According to Brazilian surveillance definitions, tuberculosis is diagnosed in patients presenting with signs and symptoms compatible with the disease on the basis of chest radiographs, sputum acid-fast bacilli smears, and response to anti-tuberculosis therapy (16). Sputum smear results were not regularly recorded and have not been included in analyses.

Recurrent tuberculosis was defined according to the Brazilian national guidelines as a subsequent diagnosis of tuberculosis at least 9 months after the initial diagnosis (16). Patients who had less than 270 days of follow-up after their initial tuberculosis diagnosis were excluded because they did not have enough follow-up time to record a recurrent tuberculosis event. Beginning with the latter of January 1, 1998 or their initial visit to the HIV clinic, patients with

a recorded tuberculosis diagnosis were followed to the earlier of date of a second tuberculosis diagnosis or last recorded clinic visit date. Because an individual was not at risk for a recurrent tuberculosis diagnosis until at least 270 days following their initial tuberculosis diagnosis and to allow equal time for patients to have completed their anti-tuberculosis therapy, person-time was calculated beginning 270 days after the initial tuberculosis diagnosis through a second tuberculosis event or the last recorded date in their medical record. All recurrent tuberculosis diagnoses reported in the medical records were abstracted, but only the first recurrent tuberculosis diagnosis was evaluated in the current analysis. We calculated recurrent tuberculosis rates for population subgroups and determined risk factors associated with recurrence.

Baseline and follow up CD4 data were those reported closest in time to the initial episode of tuberculosis and the time of a recurrent tuberculosis diagnosis, respectively. CD4 counts are routinely determined between 3 and 4 times per year for HIV-infected patients in Rio de Janeiro, thus patients had as many as 34 recorded CD4 counts. All CD4 counts were used in the analyses as discussed below. Antiretroviral therapy was treated as a time-dependent covariate, coded as zero until the initiation of treatment and coded as one thereafter.

Statistical Analysis

Differences in categorical variables were assessed by χ^2 tests. The Mann-Whitney U Test was used to compare between-group distributions for unpaired data and the Wilcoxon Signed-Rank Test for paired data. Exact confidence intervals for incidence rates were calculated based on the Poisson distribution. Follow-up time started at 270 days following first tuberculosis diagnosis and ended on the earliest of date of a second recorded tuberculosis diagnosis (recurrence) or last recorded clinic date (censored without recurrence). Kaplan-Meier curves for the primary outcome were generated. Cox proportional hazards regression models evaluated unadjusted and adjusted associations of outcome of initial tuberculosis treatment, antiretroviral therapy, time on antiretroviral therapy as a time-dependent variable, age at initial tuberculosis diagnosis, sex, baseline and time-dependent CD4 counts.

Unadjusted proportional hazards models were fit using each risk factor of interest as the only variable in the model. Using covariates significant at the 0.10 level in the unadjusted models, we generated two fully adjusted proportional hazards models. In Model 1, CD4 at initial tuberculosis diagnosis was included and in Model 2, CD4 was included as a time-dependent variable. All analyses were conducted using SAS (Version 9.1, Cary, NC) and Stata (Version 9.1, College Station, Texas).

Results

There were 15,252 HIV-infected patients in the THRio database as of December 31, 2007. Of these, 1,961 had a tuberculosis diagnosis prior to their first recorded clinic date and were excluded from the current analysis. Among the remaining 13,291 patients (60,713 person-years [PYs]), there were 1,396 patients with at least one incident tuberculosis diagnosis for an incidence rate of 2.3 per 100 PYs.

316 tuberculosis patients were excluded because they had fewer than 270 days of follow-up after their initial tuberculosis diagnosis. Among the remaining 1,080 tuberculosis patients, 96 (8.9%) developed a recurrent diagnosis at least 270 days later. The median time between diagnoses was 2.4 years (IQR=1.5-4.1 years). Multiple recurrent diagnoses were made in 18 patients (14 patients had 2 recurrences; 4 patients had 3 recurrences), but analyses were limited to first recurrent tuberculosis diagnosis.

Among the 96 patients with recurrent tuberculosis, 63 (66%) were male and the median age at first tuberculosis diagnosis was 33.9 years (Table 1). Patients without a recurrent event were slightly older (median age = 36.8 years; $p=0.004$). Fewer patients with recurrence received ART prior to their recurrent diagnosis compared to patients without recurrence ($p<0.001$). Treatment of the initial episode of tuberculosis was completed by fewer patients with recurrence compared to patients without recurrent tuberculosis ($p=0.02$).

The 1,080 patients contributed 3,370 years of follow-up and the incidence rate of recurrent tuberculosis was 2.8/100PYs. Incidence did not differ by sex, though older patients had decreased rates of recurrence compared to younger patients (Table 2). Patients receiving ART had half the risk of recurrence compared to those not receiving ART (IRR=0.51; 95% CI: 0.29-0.93). Patients with incomplete treatment at their initial tuberculosis diagnosis had an incidence of recurrence of 9.0/100PYs (95% CI: 5.0-14.8) and were three times as likely to have a recurrent diagnosis (IRR=3.60; 95% CI: 1.92-6.33) compared to those who completed treatment at initial diagnosis (Figure 1). Patients whose tuberculosis treatment status was unknown had similar rates of recurrence (IR=3.1/100PYs) compared to those with treatment completion (IR=2.5/100PYs; IRR=1.25; 95% CI: 0.44-2.85).

We investigated the association between CD4 cell count and recurrent tuberculosis in several ways. The median CD4 cell count at first tuberculosis diagnosis for patients who had a recurrent diagnosis was 197/mm³ (IQR: 108-366) compared to 192/mm³ (IQR: 91-341) for patients who did not experience a recurrence ($p=0.99$). For those with recurrence, there was no change between the median baseline CD4 cell counts and median CD4 cell count at the time of their recurrent diagnosis ($p=0.80$) (Table 3). Among patients who did not have a recurrent tuberculosis diagnosis, the median CD4 cell count doubled from 192/mm³ (IQR 91-341) at initial tuberculosis diagnosis to 382/mm³ (IQR=221-579) at the end of follow-up ($p<0.001$). Patients whose CD4 cell counts declined or remained the same were more than five times as likely to have a recurrent diagnosis compared to patients with an increasing CD4 cell count (IRR=5.61; 95% CI: 3.55-9.08).

Multivariate Cox proportional hazards modeling was consistent with the univariate results (Table 4). In Model 1, CD4 cell count measured at first tuberculosis diagnosis was not predictive of increased risk of recurrence. With CD4 cell count observed as a time-dependent variable in Model 2, a CD4 cell count between 200 and 349 reduced recurrence 65% compared to those with a CD4 < 200 (aHR=0.35; 95% CI: 0.20-0.60). Similar trends were seen with a CD4 cell count between 350 and 499 (aHR=0.42; 95% CI: 0.24-0.74) and CD4 greater than 500 (aHR=0.25; 95% CI: 0.14-0.48). Use of ART reduced recurrence by 50% in both models. Patients with incomplete treatment at initial tuberculosis diagnosis had a 3-fold increased risk of recurrence in both models, while those with unknown treatment results had a minimal increase that was not statistically significant in either model.

Discussion

We found recurrent tuberculosis occurred in 8.9% of HIV-infected patients in Rio de Janeiro, at a rate of 2.8 per 100 person-years. This rate was slightly higher than the overall tuberculosis incidence in all HIV-infected patients in this cohort (14). The major predictors of recurrent tuberculosis were failure to complete initial tuberculosis therapy, not receiving ART and lower CD4 cell counts. Older age (40-49 years) was associated with reduced risk of recurrence.

Though recurrence was greatest among those who did not complete treatment at initial diagnosis (17.2%) in our study, recurrent tuberculosis occurred frequently in treatment completers (8.1%) and those whose treatment status was unknown (8.5%) as well. Our overall recurrence rate of 2.8/100PYs and subgroup rate of 2.5/100PYs in patients with known

treatment completion are one-fourth of that detected in a cohort of South African mineworkers (3). However, tuberculosis rates in South African gold-mine workers are considerably higher than those of HIV-infected patients in Rio de Janeiro, Brazil primarily due to pulmonary fibrosis. A community study in Cape Town, South Africa where tuberculosis incidence was 313/100,000, reported recurrence rates of 2.7/100PYs following successful treatment and 6.5/100PYs among treatment failures, though HIV status was unknown for most patients. These rates compare with our rates in Brazil, though our recurrence among treatment failures was even higher (9.0/100PYs).

A study in the US found that tuberculosis patients who were treated with suboptimal regimens had a 6-fold increased risk of recurrence compared to those completing an optimal regimen (17), though few of their patients had HIV/AIDS and HIV/AIDS was not associated with recurrence. Another US study in the pre-HIV era reported that 77% of patients with recurrent tuberculosis did not initially receive anti-tuberculosis therapy, had been prescribed inadequate or inappropriate therapy or had been non-adherent to their prescribed regimen (18). In this study, all patients started therapy with the standard Brazilian 3-drug regimen, which is effective for drug-susceptible disease but may not be adequate for drug-resistant tuberculosis. While directly observed therapy has been increasingly used in Rio de Janeiro, not all patients would have had access to this modality and we cannot calculate the proportion of doses that individual patients may have missed, though we are able to determine which patients completed treatment.

The use of ART and increases in CD4 cell count were both strongly associated with protection against recurrence. ART has been shown to reduce the incidence of first episodes of tuberculosis in HIV-infected patients(14;19-22), and it also clearly reduces the risk of recurrence of other opportunistic diseases, such as *Mycobacterium avium*(23;24), cryptococcosis(24), and *Pneumocystis jirovecii*(23;24). In the present study, CD4 counts at the time of initial tuberculosis diagnosis did not predict the likelihood of recurrence. Rather, change in median CD4 count after the initial diagnosis was important. For those who experienced a recurrence, the median CD4 counts were essentially unchanged, while for those who did not have recurrent disease the median CD4 count during follow up doubled. Lawn et al. found that among HIV-infected patients receiving ART in Cape Town, those who developed tuberculosis had significantly impaired CD4 cell responses compared to patients who remained free of tuberculosis(25). These results underscore the importance of restoration of cellular immunity as a mechanism for reducing the risk of tuberculosis and other opportunistic diseases. We did not have sufficient numbers of viral load determinations to assess the impact of changes in viral burden on risk of recurrence, but others have suggested that this may be an important factor in the probability of experiencing opportunistic infections while receiving ART(26).

A substantial proportion of recurrent tuberculosis in HIV-infected patients and in high-incidence countries has been attributed to exogenous reinfection.(8) We did not have the capacity to investigate the extent of exogenous reinfection in our cohort, as *M. tuberculosis* isolates were not available for genotyping. However, based on the increased risk seen in patients who failed to complete their initial treatment regimen, we expect that many cases were relapses rather than reinfections. Nonetheless, a proportion of our recurrent cases could have been due to reinfection, and it is likely that ART and higher CD4 counts protect against progression of a new infection to active disease.

Provision of secondary isoniazid preventive therapy after treatment completion has been shown to reduce a subsequent tuberculosis diagnosis among HIV-infected populations in high incidence settings (27-29). In our population, rate of recurrent tuberculosis was higher than the rate of initial tuberculosis (2.8 vs 2.3/100PYs). These results suggest that secondary preventive therapy may also be warranted in this setting to reduce the overall tuberculosis burden. Churchyard et al suggest that secondary preventive therapy may only be effective for persons

with only one previous episode of tuberculosis due to the increased risk of drug resistance after multiple recurrences (28). We do not have drug resistance data for our patients, but levels of resistance are likely higher in retreatment cases than in new cases. However, in another study in Rio de Janeiro, treatment success in retreatment cases given community-based directly observed therapy was 83%, suggesting that the prevalence of drug resistance is not extremely high (30). Research on the role of resistance in recurrent tuberculosis in this setting would be useful.

Because we found that recurrent tuberculosis was more common in patients whose CD4 counts did not increase, targeting these individuals for secondary preventive therapy might be an efficient strategy. One potential strategy for secondary preventive therapy would be to provide secondary IPT to those persons with declining CD4 counts over a 6 month period following treatment completion for initial tuberculosis diagnosis. Timing of secondary IPT needs further investigation, as does determining the longevity of protection provided by secondary IPT in various populations and settings.

Interestingly, in our study population, tuberculosis incidence rates among those with a negative TST (2.0/100PYs) or an unknown TST result (2.4/100PYs) were similar to the entire population, suggesting that isoniazid preventive therapy should not be limited to those with a known positive TST.(31-36). The World Health Organization recommends IPT for HIV-infected patients in regions with high tuberculosis prevalence regardless of TST results(37; 38).

Despite the success of ART in reducing tuberculosis incidence in HIV-infected populations, rates remain unacceptably high. Tuberculosis recurrence is an important contributor to the overall tuberculosis burden in settings where co-infection is common, even where ART is available. Interventions to reduce initial and recurrent tuberculosis in HIV-infected populations are crucial if the burden of HIV-associated tuberculosis is to significantly decline.

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Figure 1. Kaplan-Meier survival estimates, stratified by treatment completion status at 1st tuberculosis diagnosis

X-axis: Time to recurrent tuberculosis diagnosis (days)

Kaplan-Meier survival estimates describing survival among patients who completed treatment at first tuberculosis diagnosis (—), did not complete treatment (---), and whose treatment status was unknown (-----).

Table 1
Characteristics of patients with a recurrent tuberculosis diagnosis versus those with no recurrent diagnosis

	Recurrent TB diagnosis (N=96) n (%)	No recurrent diagnosis (N=984) n (%)	p-value
Sex			
Male	63 (65.6)	652 (66.3)	0.90
Female	33 (34.4)	332 (33.7)	
Age at 1 st TB diagnosis			
< 30	24 (25.0)	209 (21.2)	0.03
30-39	52 (54.2)	422 (42.9)	
40-49	16 (16.7)	262 (26.6)	
> 49	4 (4.2)	91 (19.3)	
Antiretroviral therapy at any time during follow-up			
Yes	80 (83.3)	923 (93.8)	< 0.001
No	16 (16.7)	61 (6.2)	
CD4 at 1 st TB diagnosis*			
< 200	50 (53.2)	485 (50.9)	0.79
200-349	25 (26.6)	244 (25.6)	
350-499	12 (12.8)	121 (12.7)	
> 500	7 (7.5)	103 (10.8)	
Treatment at 1 st TB diagnosis			
Complete	75 (78.1)	847 (86.1)	0.02
Incomplete	15 (15.6)	72 (7.3)	
Unknown	6 (6.3)	65 (6.6)	

* Data unknown for 33 patients

Table 2
Incidence rates and Incident Rate Ratios for recurrent tuberculosis

	Recurrent tuberculosis diagnosis N (%)	Person-years	Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All recurrent TB	96 (8.9)	3,371	2.8 (2.3-3.5)	---
Sex				
Male	63 (8.7)	2,280	2.8 (2.1-3.5)	Ref
Female	33 (9.1)	1,091	3.0 (2.1-4.2)	1.09 (0.70-1.69)
Age at 1 st TB diagnosis				
< 30	24 (25.0)	674	3.6 (2.3-5.3)	Ref
30-39	52 (54.2)	1,512	3.4 (2.6-4.5)	0.97 (0.58-1.64)
40-49	16 (16.7)	921	1.7 (1.0-2.8)	0.49 (0.24-0.96)
> 49	4 (4.2)	263	1.5 (0.4-3.9)	0.43 (0.11-0.89)
Antiretroviral therapy				
No	16 (21.8)	310	5.2 (3.0-8.4)	Ref
Yes	80 (8.0)	3,061	2.6 (2.1-3.3)	0.51 (0.29-0.93)
CD4 at 1 st TB diagnosis*				
< 200	50 (53.2)	1762	2.8 (2.1-3.7)	Ref
200-349	25 (26.6)	811	3.1 (2.0-4.6)	1.09 (0.64-1.79)
350-499	12 (12.8)	401	3.0 (1.5-5.2)	1.05 (0.51-2.01)
> 500	7 (7.5)	348	2.0 (0.8-4.1)	0.71 (0.27-1.57)
Treatment of 1 st TB diagnosis				
Complete	75 (8.1)	3,010	2.5 (2.0-3.1)	Ref
Incomplete	15 (17.2)	167	9.0 (5.0-14.8)	3.60 (1.92-6.33)
Unknown	6 (8.5)	193	3.1 (1.1-6.8)	1.25 (0.44-2.85)

* Data unknown for 33 participants

Table 3**Change in CD4 for patients with recurrence**

CD4 category [*] ^{**}	At initial TB diagnosis	At recurrent TB diagnosis
Median	197 (108-366)	201 (111-355)
< 200	50 (51%)	47 (50%)
200-349	25 (26%)	23 (24%)
350-499	12 (15%)	14 (15%)
> 500	7 (9%)	10 (11%)

*
CD4 not known for 2 patients

**
p=0.80

Table 4

Unadjusted and adjusted Cox proportional hazards models for TB patients. Model 1 includes baseline CD4 and Model 2 includes CD4 as a time-dependent variable (N=1,047)

Patient characteristic/experience	Unadjusted RH (95% CI)	p-value	Model 1 Adjusted RH (95% CI)	p-value	Model 2 Adjusted RH (95% CI)	p-value
Sex						
Male	Ref		Ref		Ref	
Female	1.10 (0.72-1.68)	0.66	1.03 (0.67-1.58)	0.91	1.06 (0.69-1.63)	
Age at 1 st TB diagnosis						
< 30	Ref		Ref		Ref	
30-39	0.97 (0.60-1.58)	0.91	0.90 (0.55-1.47)	0.68	0.97 (0.59-1.59)	0.90
40-49	0.49 (0.26-0.92)	0.03	0.47 (0.25-0.89)	0.02	0.50 (0.27-0.95)	0.04
> 49	0.44 (0.15-1.26)	0.12	0.45 (0.15-1.30)	0.14	0.49 (0.17-1.43)	0.19
Antiretroviral therapy as a time dependent variable						
No	Ref		Ref		Ref	
Yes	0.55 (0.32-0.97)	0.04	0.50 (0.28-0.89)	0.02	0.48 (0.27-0.84)	0.01
CD4 at 1 st TB diagnosis *						
< 200	Ref		Ref		---	---
200-349	1.06 (0.66-1.71)	0.80	1.08 (0.67-1.74)	0.75	---	---
350-499	1.04 (0.55-1.95)	0.91	1.01 (0.53-1.90)	0.99	---	---
> 500	0.71 (0.32-1.57)	0.40	0.61 (0.27-1.37)	0.23	---	---
CD4 as a time dependent variable *						
< 200	Ref		---	---	Ref	
200-349	0.34 (0.20-0.58)	<0.001	---	---	0.35 (0.20-0.60)	<0.001
350-499	0.41 (0.24-0.72)	0.002	---	---	0.42 (0.24-0.74)	0.003
> 500	0.27 (0.14-0.50)	<0.001	---	---	0.25 (0.14-0.48)	<0.001
Treatment of 1 st TB diagnosis						
Complete	Ref		Ref		Ref	
Incomplete	3.56 (2.04-6.22)	<0.001	3.53 (2.01-6.21)	<0.001	3.32 (1.89-5.84)	<0.001
Unknown	1.23 (0.53-2.82)	0.63	1.25 (0.54-2.89)	0.60	1.38 (0.60-3.18)	0.45

* Data unknown for 33 participants