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The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil

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Abstract

Background—Tuberculosis is a common complication and leading cause of death in HIV infection. Antiretroviral therapy (ART) lowers the risk of tuberculosis, but may not be sufficient to control HIV-related tuberculosis. Isoniazid preventive therapy (IPT) reduces tuberculosis incidence significantly, but is not widely used.

Methods—We analysed tuberculosis incidence in 11 026 HIV-infected patients receiving medical care at 29 public clinics in Rio de Janeiro, Brazil, between 1 September 2003 and 1 September 2005. Data were collected through a retrospective medical record review. We determined rates of tuberculosis in patients who received neither ART nor IPT, only ART, only IPT, or both ART and IPT.

Results—The overall tuberculosis incidence was 2.28 cases/100 person-years (PY) [95% confidence interval (CI) 2.06–2.52]. Among patients who received neither ART nor IPT, incidence was 4.01/100 PY. Patients who received ART had an incidence of 1.90/100 PY (95% CI 1.66–2.17) and those treated with IPT had a rate of 1.27/100 PY (95% CI 0.41–2.95). The incidence among patients who received ART and IPT was 0.80/100 PY (95% CI 0.38–1.47). Multivariate Cox proportional hazards modeling revealed a 76% reduction in tuberculosis risk among patients receiving both ART and IPT (adjusted relative hazard 0.24; $P < 0.001$) after adjusting for age, previous tuberculosis diagnosis, and CD4 cell counts at baseline.

Conclusion—The use of both IPT and ART in HIV-infected patients is associated with significantly reduced tuberculosis incidence. In conjunction with expanded access to ART, the wider use of IPT in patients with HIV will improve tuberculosis control in high burden areas.

Keywords

antiretroviral therapy; Brazil; HIV; isoniazid; tuberculosis

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Introduction

Tuberculosis is one of the most common opportunistic complications of HIV infection, and is a leading cause of death [1–3]. Preventive therapy for tuberculosis with isoniazid has been known to reduce incidence in high-risk individuals for more than 40 years [4,5], and preventive therapy in HIV co-infected patients lowers incidence by 70–90% [6–11]. Despite the confirmed efficacy of preventive therapy, concerns about the durability of protection, toxicity, drug resistance and adherence have limited uptake [12–14]. Conversely, antiretroviral therapy (ART) is associated with reduced tuberculosis incidence in several cohort studies, and the scale-up of ART is being widely pursued [15–17]. The incidence of tuberculosis, however, remains unacceptably high after ART is initiated [15,18,19], and many individuals develop tuberculosis before being eligible to receive ART.

Global policy regarding isoniazid preventive therapy (IPT) in patients with HIV infection has been ambivalent. The World Health Organization and UNAIDS recommended in 1998 that IPT be offered to HIV-infected patients with or at risk of latent tuberculosis infection as part of a package of care for the ‘personal health benefit’ the treatment may provide, but did not endorse IPT for public health purposes [20]. As a result, IPT has been rarely implemented, particularly in countries where the tremendous HIV or tuberculosis burden is primarily concerned with the first tenet of tuberculosis control: the detection and treatment of active cases. More recently, a policy endorsing the use of IPT in HIV-infected patients has been promoted [21], but uptake has been very limited.

Brazilian policies for the treatment of HIV-infected individuals are among the most progressive in the world, and the country stands as a model for implementing ART in a relatively resource-poor setting. Brazil provides combination ART free of charge to an estimated 170 000 patients, and maintains an extensive clinic and laboratory system for the appropriate prescription and monitoring of therapy [22,23]. Brazilian national tuberculosis and HIV guidelines emphasize the need to conduct tuberculin skin tests (TST) in all HIV-infected patients, and to provide IPT to those who have latent infection, but uptake of these policies is unknown.

The TB/HIV no Rio study (THRio) is a cluster-randomized trial to determine whether routine screening for and treatment of latent tuberculosis in patients receiving HIV care, including antiretroviral drugs, in 29 HIV clinics in Rio de Janeiro, Brazil, will reduce tuberculosis incidence at the clinic level [24]. In preparation for this trial, we analysed baseline medical records and assessed the association between a history of ART or IPT, or both, and the risk of active tuberculosis during a 2-year period before introducing our intervention.

Methods

Data collection

The THRio study design and methodology have been described in detail [24]. In brief, 29 public primary care clinics treating HIV-infected patients with ART and other care have been randomly assigned a date to begin implementing tuberculosis screening procedures and IPT for tuberculosis/HIV co-infected patients, starting in September 2005. To obtain complete ascertainment and baseline data on all HIV-infected patients registered at the 29 HIV study clinics, medical record abstractions were conducted for all HIV-infected patients who visited the clinics between 1 September 2003 and 1 September 2005. Data were abstracted from individual patient records at each clinic using customized data collection forms, adapted from a long-standing HIV clinical cohort study [25]. Abstraction forms were extensively piloted before implementation and a team of data abstractors was trained to

collect the data. Information collected included age, sex, date of HIV diagnosis, treatment history (antiretroviral drugs, IPT), dates of opportunistic diseases including tuberculosis, and results of diagnostic tests including CD4 cell counts, HIV viral loads and TST. All forms were reviewed for completeness, and then data were double entered into a PostgreSQL/Delphi server database. Standardized queries were used to conduct range and logic checks, and discrepant entries were rectified by a study supervisor after a re-review of medical records.

Patients eligible for inclusion in this analysis were those who had made at least one visit to one of the THRio clinics between the dates of 1 September 2003 and 1 September 2005, and who received their primary care from the clinics. Patients who only attended the clinic to collect antiretroviral medications prescribed by a private physician were excluded, as were patients who were known to be dead before 1 September 2003. Institutional review board approval was granted from Johns Hopkins School of Medicine and the Comite de Etica em Pesquisa of the Municipal Health Secretariat of Rio de Janeiro.

Definitions

All exposures and outcomes were abstracted from patient medical records. The main outcome for this analysis was tuberculosis diagnosis according to Brazilian surveillance definitions [26]. Tuberculosis is diagnosed in patients presenting with signs and symptoms compatible with tuberculosis on the basis of chest radiographs, sputum acid-fast bacilli smears, and response to antituberculosis therapy. For this analysis, patients with a tuberculosis diagnosis listed in the medical record were included; pulmonary and extrapulmonary tuberculosis were included. The HIV diagnosis date was defined as the earliest of the following variables: positive serological test for HIV, first CD4 cell count result, or first date of ART. HIV diagnosis in Brazil is based on a positive enzyme-linked immunosorbent assay confirmed by a second positive enzyme-linked immunosorbent assay and a Western blot. Tuberculin testing in Brazil uses 2 U of purified protein derivative RT-23. The recommended duration of IPT for HIV-infected patients with a tuberculin reaction of ≥5 mm induration is 6 months.

Tuberculosis was defined as the first tuberculosis diagnosis recorded between 1 September 2003 and 1 September 2005. A patient's follow-up time ended either at the date of tuberculosis diagnosis or the earlier of either their last visit to an HIV clinic or the date of administrative censoring, 1 September 2005. Patients who died during follow-up were censored on the date of their last clinic visit, as we could not verify the exact dates of death. Each patient's individual follow-up time was divided into time on no therapy, time after starting IPT, time after starting ART, and time after starting both IPT and ART, the four primary exposures of interest. Patients who had received ART or IPT before 1 September 2003 were considered to be exposed throughout follow-up. ART and IPT were treated as time-dependent exposures, coded as zero until the initiation of treatment, and coded as one thereafter. Patients who began either medication within the 2-year study follow-up period thus contributed person-time to both pre and posttreatment intervals. Patients who received ART or IPT but for whom the date (month and year) of starting treatment was unknown were excluded. Person-time was used as the denominator for measuring incidence rates. CD4 cell count and viral load data were those reported closest in time to the reference variable. For participants for whom the initial CD4 cell count or viral load was greater than 12 months earlier or later than entry date to the study, the data points for these variables were recorded as missing. A secondary analysis had the IPT variable coded as zero until the initiation of IPT for patients who completed 6 months of IPT, and one thereafter.

Statistical analysis

Exact confidence intervals for rates were calculated based on the Poisson distribution. Differences in categorical variables were assessed by χ^2 tests and continuous variables by *t*-tests. Cox proportional hazards regression models evaluated unadjusted and adjusted associations of ART, IPT, age at start of follow-up, sex, baseline CD4 cell count and previous tuberculosis diagnosis. Follow-up time started at 1 September 2003 or the date at first clinic visit, whichever was later. Unadjusted proportional hazards models were fit using each of the primary exposure variables and other covariates as the only variable in the model. Fully adjusted models were constructed using both fixed and time-dependent covariates significant in the unadjusted analyses at the 0.10 level. Adjusted models excluded viral load despite univariate significance levels because over 40% had missing data. All analyses were conducted using SAS (version 9.1; Cary, North Carolina, USA) and Stata (version 9.1; College Station, Texas, USA).

Results

Data were collected from the medical records of 12 129 HIV-infected patients. We excluded from analysis patients with no HIV diagnosis date (76), an HIV diagnosis date after 1 September 2005 (405), those who received ART, but for whom the start date was unknown (387), those who received IPT, but for whom the start date was unknown (22), and those with prevalent tuberculosis diagnosed at time of HIV diagnosis during the follow-up period (213, Fig. 1). Baseline characteristics of the remaining 11 026 HIV-infected patients are shown in Table 1. The median age was 35 years, 62% were men, the median CD4 cell count at entry to the study was 365 cells/μl [interquartile range (IQR) 210–534] and the median $\log_{10}$ HIV viral load was 3.89 copies/ml. ART had been received by 56% of patients at the start of follow-up and an additional 18% started during follow-up. IPT was received by 10%; 7% began before the start and an additional 3% began during follow-up. A previous diagnosis of tuberculosis was noted for 17% of patients.

Tuberculin skin testing and isoniazid preventive therapy

Of the 11 026 patients, 5492 (49.8%) received at least one TST, of whom 1363 (24.8%) had a positive result. IPT was started in 815 of tuberculin-positive patients (59.8%), and 6 months of treatment was completed in 631 of those starting (77.4%), or 46% of those who were TST positive. Among the 4129 patients who were TST negative, 190 (4.6%) began IPT and 143 (75.3%) completed at least 6 months. An additional 91 HIV-infected patients who had no record of receiving a TST began IPT, and 60 (65.9%) completed at least 6 months. In total, 1096 patients (10%) started IPT and 834 (76.1%) completed 6 months.

Tuberculosis during follow-up

During the 2-year follow-up period, 391 individuals were diagnosed with tuberculosis [incidence rate 2.28 cases per 100 person-years (PY), 95% confidence interval (CI) 2.06–2.52]. Compared with those who did not have tuberculosis during the 2-year period, patients with an episode of tuberculosis were younger (mean age 36.3 versus 38.7 years; $P < 0.01$), had a lower median baseline CD4 cell count (172 versus 369; $P < 0.01$) and a mean viral load one $\log_{10}$ greater (4.09 versus 3.45; $P < 0.01$). There were 15 cases (1.4%) of tuberculosis diagnosed among the 1096 who started IPT compared with 376 cases out of 9930 (3.8%) among those who did not receive IPT ($P < 0.01$). Among patients with a positive TST, 13 tuberculosis cases were diagnosed among 815 patients starting IPT (1.6%) versus 63 of 548 patients not starting treatment (11.5%; $P < 0.01$).

ART was received by 8128 patients (73.7%) at some point before the end of follow-up, of whom 6142 (75.6%) began on or before 1 September 2003, and the remaining 1986 began

ART after 1 September 2003. A total of 231 tuberculosis cases were diagnosed among the 8128 patients receiving ART (2.8%) compared with 160 cases among those who never received ART (5.5%; $P < 0.01$). Of the 231 tuberculosis cases among ART users, 76 (32.9%) were diagnosed with tuberculosis within 6 months of beginning ART.

The median CD4 cell count was 213 cells/μl (IQR 114–330) at the start of ART and 365 cells/μl (IQR 224–564) at the start of IPT. Of 4506 patients with a CD4 cell count of less than 350 cells/μl at the start of follow-up, 223 (4.9%) developed tuberculosis compared with 68 patients (1.4%) with higher baseline CD4 cell counts ($P < 0.01$). Of 1554 patients with no CD4 cell data, 100 (6.4%) developed tuberculosis. Among 291 tuberculosis cases with CD4 cell data, 223 (76.6%) were among those with CD4 cell counts of less than 350 cells/μl.

Tuberculosis incidence rates were calculated using PY of follow-up as the denominator for the entire cohort and among the four primary exposure groups (Table 2). The overall tuberculosis incidence in the cohort was 2.28 cases per 100 PY (95% CI 2.06–2.52). Patients who did not receive ART or IPT had a tuberculosis incidence of 4.01 episodes/100 PY (95% CI 3.40–4.69); those who received only ART had a rate of 1.90/100 PY (95% CI 1.66–2.17); those who received only IPT had a rate of 1.27/100 PY (95% CI 0.41–2.95); and those who received both ART and IPT had a rate of 0.80/100 PY (95% CI 0.38–1.47).

Proportional hazards analyses

Unadjusted proportional hazards analysis revealed that both ART [relative hazard (RH) 0.55; $P < 0.01$] and IPT (RH 0.36; $P < 0.01$) were independently associated with a decreased risk of tuberculosis compared with no treatment (Table 3). Patients receiving both IPT and ART were even less likely to develop tuberculosis than those who received no treatment or either treatment alone (RH 0.23; $P < 0.01$).

Compared with patients less than 30 years old, patients 40–49 years of age had a decreased risk of tuberculosis (RH 0.61; $P < 0.01$) as did those aged 50 years or older (RH 0.42; $P < 0.01$). Sex was not associated with the incidence of tuberculosis (RH 0.89; $P = 0.31$). Using a baseline CD4 lymphocyte count of less than 200 cells/μl as the reference group, a CD4 lymphocyte count between 200 and 349 cells/μl was associated with a 65% decreased risk of tuberculosis (RH 0.34; $P < 0.001$); CD4 cell counts between 350 and 499 cells/μl were associated with a 78% deceased risk of tuberculosis (RH 0.22; $P < 0.001$); and CD4 cell counts greater than 500 cells/μl were associated with an 87% reduction in risk (RH 0.13; $P < 0.001$). A baseline viral load of 10 000–99 999 copies/ml (RH 1.39; $P = 0.04$) and 100 000 copies/ml or greater (RH 4.27; $P < 0.001$) was significantly associated with an increased risk of tuberculosis when compared with patients with viral loads of less than 10 000 copies/ml.

In an adjusted proportional hazards analysis, ART alone was significantly associated with a reduced risk of tuberculosis (aRH 0.41; $P < 0.001$) whereas IPT was no longer significant (aRH 0.57; $P = 0.34$; Table 3). The use of both IPT and ART was associated with a 76% lower risk of tuberculosis compared with no treatment (aRH 0.24; $P < 0.001$). The adjusted model revealed similar estimates for the association between CD4 cell counts and age with tuberculosis incidence.

Separate proportional hazards models were generated according to baseline CD4 cell counts (<or ≥350 cells/μl; Table 4). For patients with CD4 cell counts less than 350 cells/μl, the protective effects of ART alone(aRH0.46; $P < 0.001$) were greater than IPT alone (aRH 0.88; $P = 0.86$) when compared with no treatment. When both ART and IPT were taken, however, there was a 72% decrease in tuberculosis risk (aRH 0.28; $P < 0.001$). There was a trend towards decreasing tuberculosis risk among older patients.

Among patients whose baseline CD4 cell counts were greater than 350 cells/μl, the protective effects of ART (aRH 0.39; $P < 0.001$) were again greater than IPT (aRH 0.26; $P = 0.18$) when compared with no treatment. When both were given, a 78% reduction in risk was observed (aRH 0.22; $P = 0.04$). In this CD4 cell stratum, a previous tuberculosis diagnosis increased the risk of tuberculosis twofold (aRH 2.27; $P < 0.01$). The trend in decreasing tuberculosis risk among older patients was not evident in this stratum.

Discussion

Our study confirms that tuberculosis is a common HIV-related complication in this population with high levels of ART, with an incidence of 2.28 cases per 100 PY, more than 20-fold higher than for the general population of Brazil [27]. In univariate analyses of tuberculosis incidence rates, the use of ART, IPT or the combination of both ART and IPT was associated with substantially lower risks. Multivariate analyses confirmed that ART was independently associated with a 59% reduction in tuberculosis incidence, whereas the use of both IPT and ART further reduced the incidence to approximately 24% of the rate of treatment-naive patients. These results suggest that the provision of antiretroviral drugs and tuberculosis preventive therapy could have a more substantial impact on HIV-related tuberculosis than either strategy alone over a minimum of 2 years of follow-up.

The combination of IPT and ART was associated with significant reductions in tuberculosis for patients with both advanced HIV disease and among patients with earlier HIV disease. In the population of patients with more advanced HIV disease (CD4 cell counts <350 cells/μl), over a period of 2 years, ART alone was associated with a significantly reduced tuberculosis incidence, whereas IPT alone was not. In patients with CD4 cell counts greater than 350 cells/μl at baseline, ART significantly reduced tuberculosis risk, IPT reduced the risk but not at a statistically significant level, whereas the combination reduced the risk substantially.

We also found that a previous diagnosis of tuberculosis was associated with a risk of tuberculosis during follow-up for patients with higher CD4 cell counts. HIV infection increases the risk of recurrent tuberculosis as a result of re-infection or relapse by nearly 19-fold [28,29]. Two previous studies have found the recurrence of tuberculosis to be associated with lower CD4 cell counts [30,31]; our analysis found that previous tuberculosis was a significant risk factor for incident tuberculosis in patients with higher CD4 cell counts. This discrepancy could be caused by differences in tuberculosis treatment in Brazil, where higher rates of interruption are noted. Secondary isoniazid prophylaxis has been an effective method of preventing tuberculosis recurrence among HIV-infected patients, although this is not practised in most of the world [32,33]. Our results suggest that patients with previous tuberculosis are at an increased risk of another tuberculosis diagnosis, thus the use of secondary isoniazid prophylaxis in this population should be considered seriously.

Increasing age was associated with a decreased risk of tuberculosis, although the association was considerably stronger in patients with lower baseline CD4 cell counts. This observation is somewhat perplexing, as older age is usually associated with a higher risk of tuberculosis infection and disease. We found an interaction with older age, lower CD4 cell counts and a history of previous tuberculosis, but cannot explain the lower risk of incident tuberculosis with increasing age in this analysis.

It should be noted that we conducted an intention-to-treat analysis, thereby considering all patients who began IPT equally, regardless of their completion status. When we restricted the IPT group to only those patients who completed 6 months of IPT, the incidence rate decreased further, from 1.27/100 PY for all patients starting IPT to 0.62/100 PY for those

completing IPT, whereas the final Cox models remained similar but with an even stronger reduction in tuberculosis risk when both ART and IPT were taken.

There are several limitations to our analysis, which was observational and retrospective. First, our data were abstracted from medical records, not were prospectively collected, and may suffer from missing information. Records in Rio de Janeiro are not maintained in a standardized fashion and therefore clinical monitoring may not have been conducted uniformly in all study clinics. The data abstraction and collection process was, however, closely monitored by trained supervisors, and extensive quality assurance measures were employed. A second limitation is the potential bias by indication that may have been present in our population. We do not know why some patients underwent TST and why some patients began IPT or ART whereas others did not. The use of antiretroviral drugs generally follows national guidelines, and treatment eligibility is monitored by a central drug distribution programme. Nonetheless, the use of tuberculin testing and IPT is also recommended by national guidelines but is not universally adhered to. Whereas the high proportion of patients receiving TST was higher than anticipated (50%), many patients remained untested. A third limitation is that we studied individuals attending HIV outpatient clinics, and did not include those with undiagnosed HIV infection who may have an increased risk of tuberculosis; thus, we could have underestimated the overall risk of tuberculosis. Adjustment for baseline viral load and CD4 cell count, however, should aid in interpretation. Fourth, the limited number of individuals initiating IPT rendered imprecise the estimates of its effects on tuberculosis incidence. Finally, it should be noted that this was a prevalent cohort, probably with some underrepresentation of patients whose HIV disease progressed rapidly, and thus died before the study start date.

A number of randomized clinical trials have demonstrated that IPT can reduce tuberculosis incidence in HIV-infected patients, and guidelines for the management of HIV-infected patients in many countries endorse the use of IPT, but the uptake of this intervention has been limited. Concerns about the ability to rule out active tuberculosis before starting preventive therapy, adherence with treatment, drug toxicity, and the development of isoniazid resistance have all contributed to low enthusiasm for IPT. Several studies have shown, however, that active tuberculosis can be excluded using relatively simple screening measures [34,35], and there is little evidence that IPT results in the emergence of drug resistance [36]. Although there has been a great and understandable interest in expanding the use of ART, which clearly has benefits beyond the prevention of tuberculosis, IPT has been relatively ignored. Our data indicate that the combined effect of IPT and ART may have an even greater impact on tuberculosis incidence than the use of antiretroviral drugs alone.

Implementing a policy of the widespread use of IPT has the potential to reduce the rates of tuberculosis substantially among HIV-infected populations and to reduce the burden of disease in countries affected by dual epidemics of tuberculosis and HIV/AIDS. Isoniazid is extremely inexpensive, easy to administer and generally well tolerated. The broader use of IPT in conjunction with ART is likely to yield important health benefits for individual patients and for communities, and should be a high priority in the scaling up of treatment for HIV infection in the developing world.

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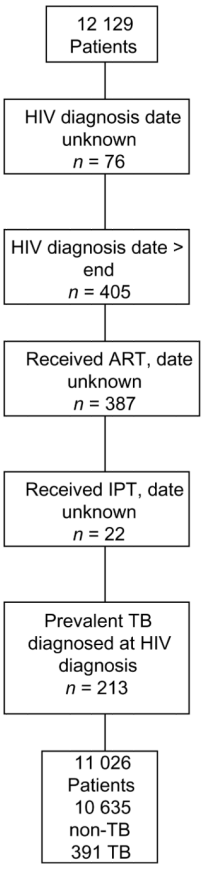

Fig. 1. Details of the original cohort of 12 129 patients, showing the reasons some were excluded from the final study

ART, Antiretroviral therapy; IPT, isoniazid preventive therapy; TB, tuberculosis.

Table 1

Characteristics of 11 026 HIV-infected patients in Rio de Janeiro, Brazil.

	Total
Sex	
Male	6830 (61.8)
Female	4192 (38.1)
Age at baseline	
<30	2386 (21.5)
30–39	4092 (37.1)
40–49	2968 (26.9)
>49	1579 (14.3)
Previous tuberculosis	
No	9173 (83.2)
Yes	1853 (16.8)
CD4 cell count[a] at baseline	
<200	2138 (22.5)
200–349	2368 (24.9)
350–499	2141 (22.5)
≥500	2855 (30.0)
Viral load[a] at baseline	
<10 000	3759 (52.6)
10 000–99 999	2196 (30.7)
≥100 000	1186 (16.6)
IPT before or during follow-up	
No	9930 (90.1)
Yes	1096 (9.9)
ART before or during follow-up	
No	2898 (26.3)
Yes	8129 (73.7)

ART, Antiretroviral therapy; IPT, isoniazid preventive therapy.

[a]1308 patients had unknown CD4 cell counts and viral loads; 216 had unknown CD4 cell counts and 2577 patients had unknown viral loads; CD4 cell counts and viral loads were closest recorded values to the baseline start date.

Table 2

Incidence rate of tuberculosis for primary exposure categories.

Exposure category	Person-years	TB cases	IR (per 100 PY)	Incidence rate ratio
Naive	3865	155	4.01 (3.40–4.69)	1.0
ART only	11 627	221	1.90 (1.66–2.17)	0.48 (0.39–0.59)
IPT only	395	5	1.27 (0.41–2.95)	0.32 (0.10–0.76)
Both	1253	10	0.80 (0.38–1.47)	0.20 (0.09–0.91)
Total	17 140	391	2.28 (2.06–2.52)	

ART, Antiretroviral therapy; IPT, isoniazid preventive therapy; IR, incidence rate; TB, tuberculosis.

Table 3

Cox proportional hazards model for all HIV-infected patients (N = 9502 for adjusted model).[a]

	Unadjusted RH (95% CI)	*P* value	Adjusted RH[b] (95% CI)	*P* value
Naive	1		1	
ART only	0.55 (0.45–0.68)	<0.01	0.41 (0.31–0.54)	<0.001
IPT only	0.36 (0.15–0.89)	0.02	0.57 (0.18–1.82)	0.34
ART and IPT	0.23 (0.12–0.45)	<0.01	0.24 (0.11–0.53)	<0.001
Previous TB	1.26 (0.99–1.60)	0.06	1.19 (0.88–1.60)	0.25
CD4 cell count				
200	1		1	
200–349	0.34 (0.26–0.46)	<0.001	0.34 (0.25–0.45)	<0.001
350–499	0.22 (0.15–0.31)	<0.001	0.19 (0.13–0.27)	<0.001
≥500	0.13 (0.09–0.19)	<0.001	0.10 (0.07–0.15)	<0.001
Age (years)				
<30	1		1	
30–39	0.84 (0.65–1.07)	0.15	0.98 (0.73–1.31)	0.88
40–49	0.61 (0.46–0.81)	<0.01	0.69 (0.49–0.97)	0.03
≥50	0.42 (0.28–0.62)	<0.01	0.53 (0.33–0.83)	<0.01

ART, Antiretroviral therapy; CI, confidence interval; IPT, isoniazid preventive therapy; RH, relative hazard; TB, tuberculosis.

[a] Does not include 1524 patients with unknown CD4 cell counts at baseline.

[b] Adjusted for all other variables in the table.

Table 4

Cox proportional hazards model.

	TB cases (*N*)	Adjusted RH[a] (95% CI)	*P* value
CD4 cell count <350 cells/μl (*n* = 4506)			
Naive	70	1	
ART only	143	0.46 (0.33–0.63)	<0.001
IPT only	2	0.88 (0.22–3.61)	0.86
ART and IPT	8	0.28 (0.14–0.60)	<0.001
Previous TB	42	1.02 (0.72–1.45)	0.90
Age (years)			
<30	58	1	
30–39	99	0.88 (0.63–1.22)	0.43
40–49	48	0.57 (0.39–0.85)	<0.01
≥50	18	0.42 (0.24–0.71)	<0.01
CD4 cell count ≥350 cells/μl (*n* = 4996)			
Naive	33	1	
ART only	32	0.39 (0.23–0.66)	<0.001
IPT only	1	0.26 (0.04–1.90)	0.18
ART and IPT	2	0.22 (0.05–0.91)	0.04
Previous TB	17	2.27 (1.27–4.06)	<0.001
Age (years)			
<30	14	1	
30–39	27	1.21 (0.63–2.35)	0.56
40–49	19	1.19 (0.58–2.43)	0.64
≥50	8	0.93 (0.38–2.28)	0.88

ART, Antiretroviral therapy; CI, confidence interval; IPT, isoniazid preventive therapy; RH, relative hazard; TB, tuberculosis.

[a]Adjusted for all other variables in the table.