

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

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Background/objective: The risk of recurrent tuberculosis may increase in HIV-infected patients due to exogenous reinfection. 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 1080 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 with patients without recurrence (78 versus 86%; $P = 0.02$). For patients who completed therapy, the incidence rate of recurrence was 2.5/100 versus 9.0/100 person-years for noncompleters (incidence rate ratio, 3.60; 95% confidence interval, 1.92–6.32). In multivariate modeling, initial tuberculosis treatment completion, receipt of antiretroviral therapy, and CD4 cell count more than 200 mm^{-3} any time after the initial diagnosis were associated with a significantly decreased hazard of recurrence.

Conclusion: Tuberculosis recurrence rates were high in this HIV-infected population. Completion of initial tuberculosis therapy, use of antiretroviral therapy, 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.

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Introduction

Tuberculosis is a major opportunistic infection in persons infected with 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 reinfection [2,3].

Recurrent tuberculosis is a significant problem for tuberculosis control programs, as treatment for recurrent

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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 reinfection is HIV-infection [2,3,10,13]. Among HIV-infected populations, low initial CD4 cell count [13] and receiving less than 37 weeks of antituberculosis 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. Although 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 semiannually 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 cell 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, was collected. Analysis of the baseline data collected as part of the THRio study has 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 antituberculosis 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 1 January 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 individuals are 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 antituberculosis 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 cell counts are routinely determined between three and four times per year for HIV-infected patients in Rio de Janeiro, thus patients had as many as 34 recorded CD4 cell counts. All CD4 cell counts were used in the analyses as discussed below. ART 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 (CI) 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, ART, time on ART as a time-dependent variable, age at initial tuberculosis diagnosis, sex, and baseline, and time-dependent CD4 cell 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; SAS Institute Inc., Cary, North Carolina, USA) and Stata (Version 9.1; STATA Corp., College Station, Texas, USA).

Results

There were 15 252 HIV-infected patients in the THRio database as of 31 December 2007. Of these, 1961 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), there were 1396 patients with at least one incident tuberculosis diagnosis for an incidence rate of 2.3/100 person years.

Three hundred and sixteen tuberculosis patients were excluded because they had fewer than 270 days of follow-up after their initial tuberculosis diagnosis. Among the remaining 1080 tuberculosis patients, 96 (8.9%) developed a recurrent diagnosis at least 270 days later. The median time between diagnoses was 2.4 years [interquartile range (IQR), 1.5–4.1 years]. Multiple recurrent diagnoses were made in 18 patients (14 patients had two recurrences; four patients had three 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 with patients without recurrence ($P<0.001$). Treatment of the initial episode of tuberculosis was completed by fewer patients with recurrence compared with patients without recurrent tuberculosis ($P=0.02$).

The 1080 patients contributed 3370 years of follow-up and the incidence rate of recurrent tuberculosis was 2.8/100 person years. Incidence did not differ by sex, though older patients had decreased rates of recurrence compared with younger patients (Table 2). Patients receiving ART had half the risk of recurrence compared with those not receiving ART [incidence rate ratio (IRR), 0.51; 95% CI, 0.29–0.93]. Patients with incomplete treatment at their initial tuberculosis diagnosis had an incidence of recurrence of 9.0/100 person years (95% CI 5.0–14.8) and were three times as likely to have a recurrent diagnosis

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
Sex			
Male	63 (65.6)	652 (66.3)	0.90
Female	33 (34.4)	332 (33.7)	
Age at first TB diagnosis (years)			
<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)	
ART at any time during follow-up			
Yes	80 (83.3)	923 (93.8)	<0.001
No	16 (16.7)	61 (6.2)	
CD4 at first TB diagnosis ^a (cells mm ⁻³)			
<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 first 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)	

ART, antiretroviral therapy; TB, tuberculosis.

^aData unknown for 33 patients.

(IRR, 3.60; 95% CI 1.92–6.33) compared with those who completed treatment at initial diagnosis (Fig. 1). Patients whose tuberculosis treatment status was unknown had similar rates of recurrence [incidence rate (IR), 3.1/100 person years] compared with those with treatment completion (IR, 2.5/100 person years; 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 mm⁻³ (IQR, 108–366) compared with 192 mm⁻³ (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 mm⁻³ (IQR, 91–341) at initial tuberculosis diagnosis to 382 mm⁻³ (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 with patients with an increasing CD4 cell count (IRR, 5.61; 95% CI 3.55–9.08).

Multivariate Cox proportional hazard 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

Table 2. Incidence rates and incident rate ratios for recurrent tuberculosis.

	Recurrent tuberculosis diagnosis <i>N</i> (%)	Person-years	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
All recurrent TB	96 (8.9)	3371	2.8 (2.3–3.5)	–
Sex				
Male	63 (8.7)	2280	2.8 (2.1–3.5)	Ref
Female	33 (9.1)	1091	3.0 (2.1–4.2)	1.09 (0.70–1.69)
Age at first TB diagnosis (years)				
<30	24 (25.0)	674	3.6 (2.3–5.3)	Ref
30–39	52 (54.2)	1512	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)
ART				
No	16 (21.8)	310	5.2 (3.0–8.4)	Ref
Yes	80 (8.0)	3061	2.6 (2.1–3.3)	0.51 (0.29–0.93)
CD4 at first TB diagnosis ^a (cells mm ⁻³)				
<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 first TB diagnosis				
Complete	75 (8.1)	3010	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)

ART, antiretroviral therapy; TB, tuberculosis.

^aData unknown for 33 participants.

model 2, a CD4 cell count between 200 and 349 (cells mm⁻³) reduced recurrence 65% compared with those with a CD4 cell count less than 200 (cells mm⁻³) [adjusted hazard ratio (aHR), 0.35; 95% CI, 0.20–0.60]. Similar trends were seen with a CD4 cell count between 350 and 499 (cells mm⁻³) (aHR, 0.42; 95% CI, 0.24–0.74) and CD4 cell count greater than 500 (cells mm⁻³) (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 three-fold increased risk of recurrence in both models, whereas those with unknown treatment results had a minimal increase that was not statistically significant in either model.

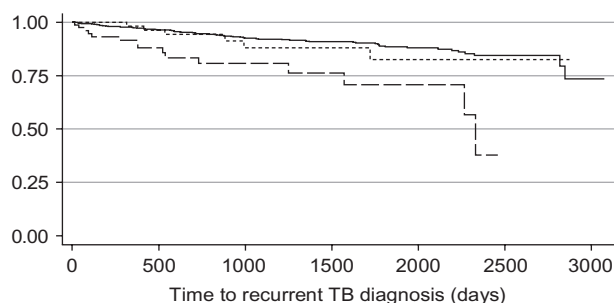


Fig. 1. Kaplan–Meier survival estimates (stratified by treatment completion status at first tuberculosis diagnosis). X-axis: time to recurrent tuberculosis diagnosis (days). Kaplan–Meier survival estimates describing survival among patients who completed treatment at first tuberculosis diagnosis (—), did not complete treatment (---), and whose treatment status was unknown (.....).

Discussion

We found recurrent tuberculosis occurred in 8.9% of HIV-infected patients in Rio de Janeiro, at a rate of 2.8/100 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.

Although 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 2.8/100 person years and subgroup rate of 2.5/100 person years 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

Table 3. Change in CD4 cell count for patients with recurrence.

CD4 category* (cells mm ⁻³)	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%)

TB, tuberculosis.

*CD4 cell count not known for two patients.

***P* = 0.80.

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 2.7/100 person years following successful treatment and 6.5/100 person years 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 (9.0/100 person years).

A study in the United States found that tuberculosis patients who were treated with suboptimal regimens had a six-fold increased risk of recurrence compared with 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 antituberculosis therapy, had been prescribed inadequate or inappropriate therapy, or had been nonadherent to their prescribed regimen [18]. In this study, all patients started therapy with the standard Brazilian three-drug regimen, which is effective for drug-susceptible disease but may not be adequate for drug-resistant tuberculosis. Although 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 jiroveci* [23,24]. In the present study, CD4 cell counts at the time of initial tuberculosis diagnosis did not predict the likelihood of recurrence. Rather, change in median CD4 cell count after the initial diagnosis was important. For those who experienced a recurrence, the median CD4 cell counts were essentially unchanged, whereas for those who did not have recurrent disease the median CD4 cell count during follow-up doubled. Lawn *et al.* [25] found that among HIV-infected patients receiving ART in Cape Town, those who developed tuberculosis had significantly impaired CD4 cell responses compared with patients who remained free of tuberculosis. These results underscore the importance or 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

Table 4. Unadjusted and adjusted Cox proportional hazards models for tuberculosis patients.

Patient characteristic/experience	Unadjusted HR (95% CI)	P	Model 1 adjusted HR (95% CI)	P	Model 2 adjusted HR (95% CI)	P
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 first TB diagnosis (years)						
<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
ART 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 cell count at first TB diagnosis ^a (cells mm ⁻³)						
<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 cell count as a time-dependent variable ^a (cells mm ⁻³)						
<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 first 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

Model 1 includes baseline CD4 and model 2 includes CD4 as a time-dependent variable (N = 1047). ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis.

^aData unknown for 33 participants.

been attributed to exogenous reinfection [8]. We did not have the capacity to investigate the extent of exogenous reinfection in our cohort, as *Mycobacterium 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 cell 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 versus 2.3/100 person years). These results suggest that secondary preventive therapy may also be warranted in this setting to reduce the overall tuberculosis burden. Churchyard *et al.* [28] 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. 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 cell 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 isoniazid preventive therapy (IPT) to those persons with declining CD4 cell 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 tuberculin skin test (TST) (2.0/100 person years) or an unknown TST result (2.4/100 person years) were similar to the entire population, suggesting that IPT 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 in which coinfection 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 decline significantly.

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