Long-term Protection From Isoniazid Preventive Therapy for Tuberculosis in HIV-Infected Patients in a Medium-Burden Tuberculosis Setting: The TB/HIV in Rio (THRio) Study

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Background. The duration of protection against tuberculosis provided by isoniazid preventive therapy is not known for human immunodeficiency virus (HIV)-infected individuals living in settings of medium tuberculosis incidence.

Methods. We conducted an individual-level analysis of participants in a cluster-randomized, phased-implementation trial of isoniazid preventive therapy. HIV-infected patients who had positive tuberculin skin tests (TSTs) were followed until tuberculosis diagnosis, death, or administrative censoring. Nelson–Aalen cumulative hazard plots were generated and hazards were compared using the log-rank test. Cox proportional hazards models were fitted to investigate factors associated with tuberculosis diagnosis.

Results. Between 2003 and 2009, 1954 patients with a positive TST were studied. Among these, 1601 (82%) initiated isoniazid. Overall tuberculosis incidence was 1.39 per 100 person-years (PY); 0.53 per 100 PY in those who initiated isoniazid and 6.52 per 100 PY for those who did not (adjusted hazard ratio [aHR], 0.17; 95% confidence interval [CI], .11–.25). Receiving antiretroviral therapy at time of a positive TST was associated with a reduced risk of tuberculosis (aHR, 0.69; 95% CI, .48–1.00). Nelson–Aalen plots of tuberculosis incidence showed a constant risk, with no acceleration in 7 years of follow-up for those initiating isoniazid preventive therapy.

Conclusions. Isoniazid preventive therapy significantly reduced tuberculosis risk among HIV-infected patients with a positive TST. In a medium-prevalence setting, 6 months of isoniazid in HIV-infected patients with positive TST reduces tuberculosis risk over 7 years of follow-up, in contrast to results of studies in higher-burden settings in Africa.

Keywords. tuberculosis; isoniazid; preventive therapy; HIV; durability.

Isoniazid preventive therapy (IPT) has long been used to prevent development of tuberculosis in high-risk populations [1], with efficacy ranging from 60% to 90% [2]. Prior to the human immunodeficiency virus (HIV) epidemic, IPT reduced tuberculosis incidence substantially in Alaska Natives in the 1950s where incidence rates (IRs) were similar to those in settings with high HIV prevalence, such as southern Africa today [1,3], and the incidence remained low for at least 20 years [1].

In the HIV era, IPT has proved effective in reducing tuberculosis rates among HIV-infected patients, particularly among those with a positive tuberculin skin test (TST) result [4–12]. Trials in Botswana and South Africa, however, show that although IPT significantly reduces tuberculosis risk for HIV-infected individuals and gold miners while they are receiving the drug, once IPT is stopped risk quickly elevates toward the level of persons who never received IPT [11, 12].

Received 16 July 2014; accepted 19 October 2014; electronically published 2 November 2014.

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Clinical Infectious Diseases® 2015;60(4):639–45

DOI: 10.1093/cid/ciu849

These recent results add to the growing evidence [11–14] that lifetime preventive therapy may be required in these settings where reinfection with tuberculosis is presumed to be common. However, in settings of medium tuberculosis incidence, such as Brazil, it is not known if the currently recommended 6-month IPT regimen for HIV-infected patients with a positive TST is effective against tuberculosis over the long term.

We report tuberculosis rates among patients with positive tuberculin skin tests in the TB/HIV in Rio (THRio) study, a cluster-randomized, phased implementation trial that showed that implementing IPT resulted in reductions in the incidence of tuberculosis and death among all patients in participating HIV clinics in Rio de Janeiro, Brazil [15]. In the current analysis, we have examined the long-term individual-level impact of IPT on tuberculosis risk in TST-positive patients for up to 7 years.

METHODS

The THRio study has been previously described [15, 16]. In brief, THRio was a cluster-randomized trial in 29 HIV clinics in Rio de Janeiro, Brazil, evaluating the impact of an intervention to increase TST and use of IPT on tuberculosis incidence and mortality [15]. In the 12 816 patients included in the primary analysis, 2135 had a positive TST result. In this analysis, we included patients with a positive TST result after September 2003 and excluded patients with tuberculosis diagnosed within 30 days of a positive TST result, as this likely represented prevalent tuberculosis. We collected information on dates of TST results, start of IPT treatment, start of antiretroviral therapy (ART), and dates of tuberculosis diagnosis and deaths through medical record review during the study data collection period between 1 September 2003 and 31 August 2010. Physicians recorded "completion" when patients reported taking 180 doses of IPT. Tuberculosis and death dates were also obtained by cross-matching with the Rio de Janeiro mortality registry and tuberculosis registry through 31 October 2012 [17, 18].

TST was performed with purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) by trained nurses, and results were read in the clinic within 2–7 days. After ruling out active tuberculosis disease with a clinical history and chest radiography, patients with a positive TST result were prescribed isoniazid 300 mg with pyridoxine 25 mg per day for 6 months, refilled at 30- or 90-day intervals. Brazilian national guidelines up to 2006 recommended ART for HIV-infected patients with a CD4 count <200 cells/μL [19]. In 2007, the guidelines changed to recommend ART to patients with a CD4 count <350 cells/μL [20] and were changed again to CD4 <500 cells/μL in 2010 [21].

The primary endpoint was development of incident tuberculosis, defined according to Brazilian guidelines as at least 1 positive culture for *Mycobacterium tuberculosis*, positive acid-fast bacilli smear, or clinical and radiographic presentation consistent with tuberculosis and response to treatment [22]. We calculated IRs and compared risk of tuberculosis in 2 ways: (1) for all TST-positive patients beginning 30 days after the date of the positive test and (2) for TST-positive patients beginning on the date that IPT began. We followed patients for up to 7 years and censored follow-up at the first of tuberculosis diagnosis, death, or the last matching date with the tuberculosis and mortality registries (31 October 2012). We calculated IRs per 100 person-years (PY), and 95% confidence intervals (CIs) based on the Poisson distribution. Cox proportional hazards regression models were fitted to investigate factors associated with tuberculosis. Nelson–Aalen cumulative hazard plots were fitted and hazards were compared using the log-rank test. We also calculated tuberculosis IRs in 6-month increments starting at initiation of IPT.

For the analysis of all TST-positive patients, the primary exposure variable was IPT initiation. IPT was treated as a time-dependent variable. Time from TST positive until start of IPT was considered "no IPT" time, and changed to "IPT" time when treatment was initiated. Patients treated for <15 days were considered to have not initiated IPT. Other covariates were receipt of ART, CD4 cell count and age at the time of a positive TST result, and sex. For the analysis restricted to IPT initiators, covariates of interest were receipt of ART at or prior to IPT start date, CD4 cell count and age at IPT start date, and sex. Sensitivity analyses removed patients who died or were diagnosed with active tuberculosis disease within 60 and 90 days after a positive TST result.

RESULTS

Among 2135 patients with a positive TST result in the THRio study, 181 were excluded for this analysis for the following reasons: had a positive TST prior to 2003 (n = 123), tuberculosis was diagnosed within 30 days of initiating IPT (n = 43), first recorded positive TST result was after the IPT start date (n = 9), or the recorded IPT start date was the same as the recorded IPT end date (n = 6). Among the 1954 patients who met the inclusion criteria for our analysis, 1601 (82%) started IPT and 353 did not (18%). Median time to start IPT treatment was 35 days following a positive TST result (interquartile range [IQR], 9–99 days). Among the 1601 initiating IPT, 1330 (83%) were reported to have completed 6 months of treatment, and the median length of IPT among those who completed treatment was 185 days (IQR, 181–216 days). Median follow-up was 4.8 years (IQR, 3.6–6.0 years) from time of positive TST result and 4.7 years (IQR, 3.7–5.6 years) from time of IPT initiation. Tuberculosis IRs and hazard ratios (HRs) for all patients with a positive TST and for those with a positive TST who started IPT are shown in Tables 1 and 2, respectively. Patients initiating IPT

Table 1. Tuberculosis Incidence Rates and Cox Proportional Hazards Model for HIV-Infected Patients With a Positive Tuberculin Skin Test (TST), Followed for up to 7 Years After Positive TST

Patient Characteristics	No. of Patients	No. Tuberculosis Cases/PY	Incidence Rate/ 100 PY (95% CI)	HR[a] (95% CI)	Adjusted HR[a,b] (95% CI)
All TST+ patients	1954	127/9117	1.39 (1.16–1.66)		
Initiated IPT					
Yes	1601 (82%)	41/7798	0.53 (.38–.71)	0.16 (.11–.23)	0.17 (.11–.25)
No	353 (18%)	86/1319	6.52 (5.21–8.05)	Ref	Ref
ART at TST+[c]					
Yes	1186 (61%)	64/5396	1.19 (.91–1.51)	0.67 (.47–.94)	0.69 (.48–1.00)
No	768 (39%)	63/3721	1.69 (1.30–2.17)	Ref	Ref
Sex					
Male	1216 (62%)	78/5652	1.38 (1.09–1.72)	1.03 (.72–1.47)	1.13 (.79–1.63)
Female	738 (38%)	49/3465	1.41 (1.05–1.87)	Ref	Ref
Age at TST+, y					
<30	330 (17%)	28/1608	1.74 (1.16–2.52)	2.10 (1.12–3.93)	1.24 (.65–2.38)
30–39	625 (32%)	36/2998	1.20 (.84–1.66)	1.42 (.78–2.60)	1.03 (.56–1.89)
40–49	617 (32%)	48/2826	1.70 (1.25–2.25)	1.97 (1.10–3.51)	1.55 (.87–2.79)
≥50	382 (19%)	15/1684	0.89 (.50–1.47)	Ref	Ref
CD4 at TST+, cells/μL					
<200	150 (8%)	27/639	4.22 (2.78–6.15)	7.50 (4.38–12.85)	6.35 (3.68–10.95)
200–349	349 (18%)	40/1577	2.54 (1.81–3.45)	4.56 (2.79–7.48)	4.26 (2.59–6.99)
350–499	436 (23%)	32/2077	1.54 (1.05–2.17)	2.81 (1.68–4.72)	2.61 (1.55–4.37)
≥500	987 (51%)	26/4680	0.55 (.36–.81)	Ref	Ref

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IPT, isoniazid preventive therapy; PY, person-years; Ref, reference; TST, tuberculin skin test.

[a] IPT time dependent.

[b] Adjusted for all variables listed.

[c] ART at TST+refers to whether patients were receiving ART at the time that their TST was positive.

were older (median, 40 years [IQR, 33–48 years] vs 37 years [IQR, 30–45 years]; $P < .001$), had higher CD4 counts at time of positive TST (median, 525 cells/μL [IQR, 359–735 cells/μL] vs 447 cells/μL [IQR, 285–648 cells/μL]; $P < .001$), and were more likely to be on ART at time of positive TST (62% vs 53%; $P = .002$) than those who did not start IPT.

During follow-up of all patients with a positive TST, 127 first episodes of tuberculosis were diagnosed (IR, 1.39/100 PY): 86 episodes among the 353 patients who never received IPT (IR, 6.52/100 PY) and 41 episodes among the 1601 who initiated IPT (IR, 0.53/100 PY; HR, 0.16 [95% CI, .11–.23]; Table 1). In the multivariate Cox proportional hazards model comparing IPT vs no IPT, initiating IPT was associated with a 83% reduction in tuberculosis risk (adjusted HR [aHR], 0.17 [95% CI, .11–.25]) and taking ART was associated with a 31% reduced risk (aHR, 0.69 [95% CI, .48–1.00]). There was little evidence of interaction between initiating IPT and taking ART ($P = .50$).

Having a CD4 count ≤200 cells/μL at time of a positive TST result was associated with an increased tuberculosis risk (aHR, 6.35 [95% CI, 3.68–10.95]) compared with having a CD4 count ≥500 cells/μL. Sex and age were not associated with tuberculosis risk (Table 1). Sensitivity analyses allowing for longer periods of time (60 and 90 days) for diagnosing active tuberculosis following a positive TST result revealed HRs nearly identical to those for the primary 30-day analysis.

Among patients who completed IPT, there were 31 episodes of tuberculosis (IR, 0.49/100 PY) vs 8 episodes (IR, 0.91/100 PY; HR, 0.54 [95% CI, .24–1.35]) among those who did not complete IPT. Two cases were diagnosed among 68 patients for whom outcome of IPT is not known. Patients completing IPT were older (median, 41 years [IQR, 33–48 years] vs 37 years [IQR, 31–46 years]; $P < .001$) and more likely to be on ART (68% vs 55%; $P < .001$) than patients not completing IPT. In the multivariate model of TST-positive patients who initiated IPT, ART at time of IPT was associated with a 48% reduction in tuberculosis risk (aHR, 0.52 [95% CI, .27–.99]) (Table 2).

We calculated tuberculosis IRs by 6-month intervals (Table 3). Only 1 diagnosis of tuberculosis was made during the 6 months after IPT began, and this case occurred at 162 days from initiation of IPT in a patient who stopped treatment after 116 days. Of the 31 tuberculosis cases diagnosed among patients who completed therapy, 14 (45%) were diagnosed in the first 24 months

Table 2. Tuberculosis Incidence Rates and Cox Proportional Hazards Model for HIV-Infected Patients With a Positive Tuberculin Skin Test Who Received at Least 30 Days of Isoniazid Preventive Therapy (IPT), Followed for up to 7 Years Following Initiation of IPT

Patient Characteristics	No. of Patients	No. Tuberculosis Cases/PY	Incidence Rate, per 100 PY (95% CI)	HR (95% CI)	Adjusted HR[a] (95% CI)
TST+ patients					
Starting IPT	1601	41/7422	0.55 (.40–.75)		
ART at start of IPT					
Yes	1061 (66%)	22/4857	0.45 (.28–.69)	0.60 (.32–1.11)	0.52 (.27–.99)
No	540 (34%)	19/2565	0.74 (.45–1.16)	Ref	Ref
Sex					
Male	988 (62%)	26/4547	0.57 (.37–.84)	0.92 (.49–1.74)	0.93 (.49–1.78)
Female	613 (38%)	15/2875	0.52 (.29–.86)	Ref	Ref
Age at start of IPT, y					
<30	235 (15%)	6/1126	0.53 (.19–1.16)	1.65 (.50–5.40)	1.42 (.42–4.83)
30–39	504 (31%)	14/2391	0.59 (.32–.98)	1.80 (.65–4.99)	1.63 (.58–4.54)
40–49	517 (32%)	16/2401	0.67 (.38–1.08)	2.04 (.75–5.57)	1.87 (.67–5.15)
≥50	345 (22%)	5/1503	0.33 (.11–.78)	Ref	Ref
CD4 at start of IPT, cells/μL					
<200	94 (6%)	6/427	1.41 (.52–3.10)	5.16 (1.91–13.95)	5.91 (2.16–16.18)
200–349	277 (17%)	11/1315	0.84 (.42–1.50)	3.08 (1.34–7.11)	3.14 (1.36–7.27)
350–499	358 (23%)	12/1663	0.72 (.37–1.26)	2.62 (1.15–5.94)	2.58 (1.14–5.86)
≥500	862 (54%)	11/3974	0.28 (.14–.49)	Ref	Ref

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IPT, isoniazid preventive therapy; PY, person-years; Ref, reference; TST, tuberculin skin test.

[a] Adjusted for all variables listed.

following initiation, compared with 6 (75%) of the tuberculosis cases diagnosed among patients who did not complete therapy. Figure 1 shows tuberculosis incidence increasing markedly in the first 2 years following a positive TST result for those who did not initiate IPT, whereas those receiving IPT had a lower hazard of developing disease ($P < .01$, log-rank test). No substantial rise is seen over the 7-year period among those initiating IPT.

DISCUSSION

In this prospective study of HIV-infected patients with positive TST followed for up to 7 years in Rio de Janeiro, Brazil, those receiving 6 months of IPT received durable protection from developing tuberculosis. More than half of the tuberculosis episodes that developed after initiation of IPT were diagnosed within the first 2 years, and 75% of the cases among patients who did not complete IPT occurred during this time period. ART was also independently associated with reduced tuberculosis risk, and tuberculosis risk was significantly greater among patients with lower CD4 counts at time of positive TST and at time of starting IPT, emphasizing the importance of earlier diagnosis of HIV and TST screening in Brazil [23].

Whether IPT provides long-term protection against tuberculosis in HIV-infected individuals has been questioned, as trials

Table 3. Tuberculosis Incidence Rates Following Initiation of Isoniazid Preventive Therapy (IPT) Among Patients With a Positive Tuberculin Skin Test Who Completed and Those Who Did Not Complete 6 Months of IPT

Time From IPT Initiation	IPT Treatment Completed (n = 1330)		IPT Treatment Not Completed (n = 203)	
	Tuberculosis Cases/PY	IR/100 PY(95% CI)	Tuberculosis Cases/PY	IR/100 PY(95% CI)
0–6 mo	1/655	0.15 (.004–.85)	0/99	0
7–12 mo	4/653	0.61 (.17–1.57)	3/97	3.1 (.64–8.77)
13–18 mo	6/647	0.93 (.34–2.02)	2/95	2.1 (.25–7.40)
19–24 mo	3/643	0.47 (.10–1.36)	1/93	1.1 (.03–5.85)

Abbreviations: CI, confidence interval; IPT, isoniazid preventive therapy; IR, incidence rate; PY, person-years.

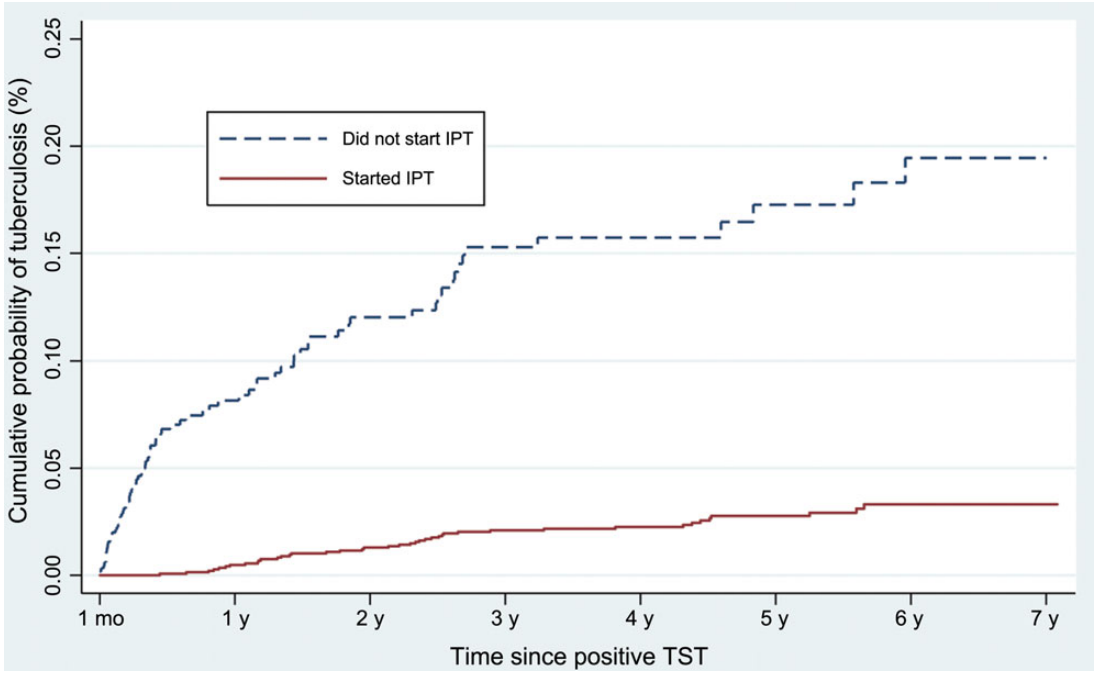

Figure 1. Nelson–Aalen plots of tuberculosis incidence for patients starting and those not starting isoniazid preventive therapy (IPT). Abbreviation: TST, tuberculin skin test.

in Africa suggest that people with HIV are only protected from tuberculosis while receiving isoniazid and that the protection is diminished once the drug is stopped [8–14]. Most recently, the Thibela tuberculosis study suggested that high rates of tuberculosis transmission in gold mines may have led to reinfection immediately following completion of a 9-month regimen of IPT for miners, thus resulting in no impact of IPT in the 12 months after completion of treatment. Earlier studies of IPT in Haiti, the United States, Mexico, and Brazil did not show any diminution of protection, but follow-up was limited and many patients died of AIDS, as the studies were done prior to combination ART [4, 6, 9]. In an individually randomized clinical trial in Cape Town, Rangaka et al report a more gradual increase in tuberculosis rates after cessation of 1 year of IPT [14]. However, a recent modeling analysis utilizing data from 3 preventive therapy trials in Africa [10, 12, 24] concluded that current preventive therapies, including isoniazid, are not sufficient to cure latent tuberculosis in most people with HIV, thus leading to high tuberculosis rates upon cessation of IPT [25].

Whether high rates of tuberculosis after cessation of IPT are due to reinfection or failure to sterilize latent tuberculosis is unclear. In a number of African trials, patients stopping IPT appear to "catch up" with those not treated or given placebo, suggesting that isoniazid may be suppressing, but not sterilizing, latent infection. This was particularly notable in the Thibela tuberculosis trial [13], conducted among gold miners in South Africa who also have high rates of silicosis, which increases the risk of tuberculosis independent of HIV infection [26]. Conversely, annual rates of *M. tuberculosis* infection in African settings are considerably higher than in Brazil, supporting the role of reinfection. A potential unifying hypothesis for the differences observed in our study and in African trials is that rates of infection and reinfection with *M. tuberculosis* result in a larger individual bacillary burden of latent tuberculosis that is more difficult to sterilize, and that this is compounded by reinfection.

If reinfection or lower burden of latent infection are the primary factors influencing tuberculosis risk among those treated with IPT, then in countries with medium or low tuberculosis incidence, a short-course regimen may be sufficient to provide lasting protection. Tuberculosis incidence in Rio de Janeiro is 79.2 per 100 000 [27], twice the Brazilian national rate but less than one-tenth the rate in South Africa. Whereas rates of tuberculosis in Brazilians with HIV infection and a positive TST are similar to those reported elsewhere, the risk of tuberculosis in patients with TST-negative results is substantially lower than in African patients with HIV, indicating that new tuberculosis infections are less common. Our analysis suggests that in settings such as this, IPT given for 6 months provides long-term protection against tuberculosis, and longer courses are not required.

An important limitation of our analysis was that IPT was provided by clinicians in routine practice, and those who did not receive treatment differed significantly from those who did. We have adjusted for these baseline differences in our multivariate analyses, but residual confounding is likely. In addition, we relied on the recording of "complete" or "not complete" in the patients' medical records for determining if 6 months of IPT was received. However, when we plot tuberculosis risk by IPT initiation, we clearly see that tuberculosis risk remains low over 7 years for those receiving IPT. Among the cases of tuberculosis that developed among those who completed therapy, 16% occurred in the year following initiation, and among those who did not complete treatment, 38% of tuberculosis cases were diagnosed in this time frame. Although we cannot rule out reinfection in these patients, our results suggest that lack of cure of infection was the more likely reason for these tuberculosis events [25], whereas reinfection may have been the cause for later events. Another limitation is that we only considered ART at time of IPT initiation and potential later benefits of starting ART would be missed.

In conclusion, we have shown that IPT significantly reduces tuberculosis risk among TST-positive, HIV-infected patients in Brazil independent of ART. Our data suggest that a 6-month regimen of IPT is sufficient to reduce tuberculosis risk for as long as 7 years, but failing to complete the IPT regimen may yield high tuberculosis risk. Better operationalizing of IPT for people with HIV in Brazil is imperative to help curb tuberculosis risk, as too few patients are receiving this beneficial treatment.

Notes

Financial support. This work was supported by the Bill & Melinda Gates Foundation (grant number 19790.01 to the Consortium to Respond Effectively to the AIDS-Tuberculosis Epidemic). Additional support was received from the National Institutes of Health Fogarty International Center (grant number U2RTW006885) and National Institutes of Health (grant numbers AI066994 to J. E. G. and AI001637 to R. E. C.) and the Johns Hopkins University Center for AIDS Research (grant number P30 AI094189). Additional support was received from Conselho Nacional de Desenvolvimento Científico e Tecnológico and Fundação Carlos Chagas Filho de Apoio a Pesquisa do Estado do Rio de Janeiro (to A. G. P.).

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the Bethel isoniazid studies. Am Rev Respir Dis **1979**; 119:827–30.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev **2010**; CD000171.
3. World Health Organization. Global tuberculosis report 2013. Geneva, Switzerland: WHO, **2013**. WHO/HTM/2013.11.
4. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet **1993**; 342:268–72.
5. de Pinho AM, Santoro-Lopes G, Harrison LH, Schechter M. Chemoprophylaxis for tuberculosis and survival of HIV-infected patients in Brazil. AIDS **2001**; 15:2129–35.
6. Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet **1998**; 351:786–92.
7. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda–Case Western Reserve University Research Collaboration. N Engl J Med **1997**; 337:801–8.
8. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS **1998**; 12:2447–57.
9. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med **1997**; 337:315–20.
10. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. AIDS **2001**; 15:2137–47.
11. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomized, double-blind, placebo-controlled trial. Lancet **2011**; 377:1588–98.
12. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med **2011**; 365:11–20.
13. Churchyard GJ, Fielding KL, Lewis JJ, et al; Thibela TB Study Team. A trial of mass isoniazid preventive therapy for tuberculosis control. N Engl J Med **2014**; 370:301–10.
14. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomized double-blind placebo-controlled trial. Lancet **2014**; 384:682–90.
15. Durovni B, Saraceni V, Moulton LH, et al. Lancet Infect Dis **2013**; 13:852–8.
16. Moulton LH, Golub JE, Durovni B, et al. Statistical design of THRio: a phased implementation clinic-randomized study of a tuberculosis preventive therapy intervention. Clin Trials **2007**; 4:190–9.
17. Sistema de Informação sobre Mortalidade: Brasil. Ministério da Saúde.Sisitema de informações de mortalidade. Available at: http://www2.datasus.gov.br/DATASUS/index.php?area=040701. Accessed 27 November 2012.
18. Sistema Nacional de Agravos de Notificação: Brasil. Ministério da Saúde.Sistema de informação de agravos de notificação. Available at: http://dtr2004.saude.gov.br/sinanweb. Accessed 27 November 2012.
19. Ministério da Saúde. Recomendacoes para terapia anti-retroviral em adultos e adolescents infectados pelo HIV—2004. Brasilia: Ministerio da Saude, Secretaria de Vigilancia em Saude, Programa Nactional de DST e AIDS, **2004**.
20. Ministério da Saúde. Recomendacoes para terapia anti-retroviral em adultos e adolescents infectados pelo HIV—2007/2008. Brasilia: Documento preliminar. Ministerio da Saude, Secretaria de Vigilancia em Saude, Programa Nactional de DST e AIDS, **2008**.
21. Ministério da Saúde. Recomendacoes para terapia antiretroviral em adultos infectados pelo HIV—2008. Supplemento III: Tratamento e prevencao. Brasilia: Ministerio da Saude, Secretaria de Vigilancia em Saude, Depatamento de DST, AIDS e Hepatities Virais, **2010**.
22. Conde MB, Melo FA, Marques AM, et al. III Brazilian Thoracic Association guidelines on tuberculosis. J Bras Pneumol **2009**; 35:1018–48.
23. Saraceni V, Cohn S, Cavalcante SC, et al. Prevalent tuberculosis (TB) at HIV diagnosis in Rio de Janeiro, Brazil: the TB/HIV in Rio (THRio) Cohort. J Acquir Immune Defic Syndr **2014**; 67:98–101.

24. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS **1997**; 11:875–82.
25. Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings. Proc Natl Acad Sci U S A **2014**; 111:5325–30.
26. Corbett EL, Churchyard GJ, Clayton TC, et al. HIV infection and silicosis: the impact of two potent risk factors on the incidence of mycobacterial disease in South African miners. AIDS **2000**; 14: 2759–68.
27. Ministério da Saúde. Secretaria de Vigilância em Saúde. O controle da tuberculosis no Brasil: avancos, inovacoes e desafios. Boletim Epidemiologico **2014**; 44:1–13.