Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial

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Summary

Background Preventive therapy for tuberculosis in patients with HIV is effective, but it has not been widely implemented in moderate or high-burden settings. We assessed the effect of widespread use of isoniazid preventive therapy on rates of tuberculosis and death in people with HIV in Brazil.

Methods We did a stepped wedge, cluster-randomised trial with patients actively enrolled in 29 HIV clinics in Rio de Janeiro. Clinic staff were trained in tuberculosis screening, use of tuberculin skin tests, and use of isoniazid preventive therapy. Clinics were randomly allocated a date to begin the intervention period, with two clinics beginning the intervention every 2 months starting from Sept 1, 2005. The primary outcome was tuberculosis incidence alone or combined with death in the control versus intervention periods until Aug 31, 2009. This trial is registered at ClinicalTrials.gov, number NCT00107887.

Results Of 17 413 patients in the cohort, 12 816 were eligible for the intervention. Overall, there were 475 tuberculosis cases and 838 deaths. The intervention increased the rate of patients receiving skin tests from 19 per 100 person-years to 59 per 100 person-years, and from 36 per 100 person-years to 144 per 100 person-years for those eligible for isoniazid preventive therapy. In the control period, 221 cases of tuberculosis were diagnosed (1·31 per 100 person-years) compared with 254 (1·10 per 100 person-years) in the intervention period (unadjusted hazard ratio [HR] 0·87; 95% CI 0·69–1·10). Rates of tuberculosis incidence or death were 3·64 and 3·04 per 100 person-years, respectively (0·76; 95% CI 0·66–0·87). When adjusted for age, sex, entry CD4 count, and use of antiretroviral therapy, the HR for tuberculosis was 0·73 (95% CI 0·54–0·99) and for tuberculosis or death was 0·69 (0·57–0·83).

Interpretation Operational training aimed at increasing tuberculosis screening, provision of tuberculin skin tests, and use of isoniazid preventive therapy in Brazilian HIV clinics significantly reduced incident tuberculosis and death. Thus, scale-up of preventive therapy for HIV-infected patients in settings of moderate tuberculosis incidence is achievable and should be widely implemented in Brazil and elsewhere.

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Introduction

Isoniazid preventive therapy has long been recognised as an effective intervention for reducing the risk of tuberculosis at the individual and population level.[1] Studies in people with HIV infection show that preventive therapy reduces tuberculosis rates, particularly in those with positive tuberculin skin tests.[2] Evidence from observational studies in Brazil and South Africa have shown substantial reductions in tuberculosis risk in patients with HIV who received both isoniazid and antiretroviral therapy.[3,4] Although use of isoniazid preventive therapy has been recommended by WHO since 1998,[5] uptake of this intervention in countries with high burdens of HIV and tuberculosis has been extremely poor.[6] Brazil has a moderate tuberculosis rate (38 per 100 000 in 2011),[6] and in Rio de Janeiro, a city where 10% of cases are co-infected with HIV, the prevalence was 95·3 per 100 000 in 2009. Tuberculosis continues to be a leading cause of illness and death in people with HIV infection.[7] We sought to determine the effect of an intervention to increase use of isoniazid preventive therapy, and to assess the subsequent effect on rates of tuberculosis and death in HIV-infected individuals in Brazil, where antiretroviral therapy has been freely available through the public sector since 1996.

Methods

Study design and participants

The design of the Tuberculosis/HIV in Rio de Janeiro (THRio) study has been previously described.[8] It was a stepped-wedge, cluster randomised trial in which 29 of the 51 clinics providing antiretroviral therapy in Rio de Janeiro (representing 57% of all HIV-infected patients in the region) were randomly assigned to the date when a training intervention would be introduced. Clinics ranged in size from 121 to 1749 patients, and were chosen

because they were under the administrative control of the city health department and were geographically dispersed throughout the city. A stepped-wedge design was chosen for operational simplicity and to ensure that all patients eventually received the intervention.

Patients who made at least one visit to any of the 29 clinics between Sept 1, 2003, and Sept 1, 2005, or those making their first clinic visit between Sept 1, 2005, and Aug 31, 2009, were eligible for inclusion in our analysis. The Brazilian policy for isoniazid preventive therapy recommends that patients with HIV who have had no history of tuberculosis diagnosis, treatment, or preventive therapy should undergo tuberculin skin testing and, if positive, receive isoniazid.[9] Patients were eligible for inclusion if they had not been diagnosed with tuberculosis or completed isoniazid preventive therapy before the study. Approval was granted by the *Comite de Etica em Pesquisa* of the Municipal Health Secretariat of Rio de Janeiro and the Johns Hopkins Medicine Institutional Review Board (Baltimore, MD, USA). The need for informed consent was waived because the intervention under study was training clinic staff to better undertake practices that were already the recommended standard in these clinics. Approval for the study was also obtained from the director of each clinic. An independent data safety and monitoring board reviewed the protocol and interim results every year.

Randomisation and masking

The unit of randomisation was the HIV clinic. Clinics were randomly allocated a date to begin the intervention period, with two clinics beginning the intervention every 2 months starting from Sept 1, 2005. Randomisation was done using a highly restricted design to achieve close balance with respect to clinic-level covariates including mean CD4 count, clinic size, average education, tuberculosis treatment levels, existence of a supervised tuberculosis therapy programme, and geography.[10–12] All study investigators and personnel other than the study statistician were masked to allocation order.

Procedures

The intervention tested was training of clinic staff to screen and to treat HIV-infected patients for tuberculosis, to do tuberculin skin tests, and to treat latent tuberculosis infection with isoniazid preventive therapy. These staff members included physicians, nurses, social workers, nutritionists, and psychologists. All clinics received the study intervention at a randomly assigned time during a 2·5 year implementation period. Staff training began around a month before the intervention start date at each site. Clinics were then provided with updated lists of patients eligible for testing and isoniazid preventive therapy at least once a year. Annual meetings were held to provide indicators of clinic performance for tuberculin skin tests and initiation of isoniazid preventive therapy.

Staff were instructed to screen all patients with HIV for tuberculosis symptoms and to do annual skin testing using PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark) for eligible individuals. Patients with skin test reactions of 5 mm or larger were asked about tuberculosis symptoms and given a chest radiograph. Those who tested positive were to be given isoniazid 300 mg with pyridoxine 25 mg a day for 6 months, refilled at 30 days or 90 days depending on the clinic, as were patients with chest radiographic scars compatible with previous healed tuberculosis and no documented anti-tuberculosis therapy. Physicians made a record of "completion" when patients reported taking 180 doses of isoniazid preventive therapy.

Medical record data for all patients were abstracted onto standardised forms at baseline and at roughly 9-month intervals by trained study personnel uninvolved in clinical care. Completed forms were mailed to the data management centre for entry. Seven data abstraction visits were done during the study and for 9 months after study conclusion to ensure complete data capture. Information collected included HIV-related diagnoses, CD4 cell counts, HIV viral loads, antiretroviral therapy use, and all diagnostic and treatment data for both active and latent tuberculosis. Supervisors abstracted 5% of records again for quality control and an external study monitor consistently reported less than 1% of randomly reviewed records had minor inconsistencies. To ensure all tuberculosis cases and deaths were captured, we cross-matched the THRio registry with the Rio de Janeiro tuberculosis and mortality surveillance databases.

Statistical analysis

With a type I error of 0·05, and a coefficient of variation of 0·2 for tuberculosis incidence rates across clinics (based on a sample of 240 patients in ten clinics[10]), we

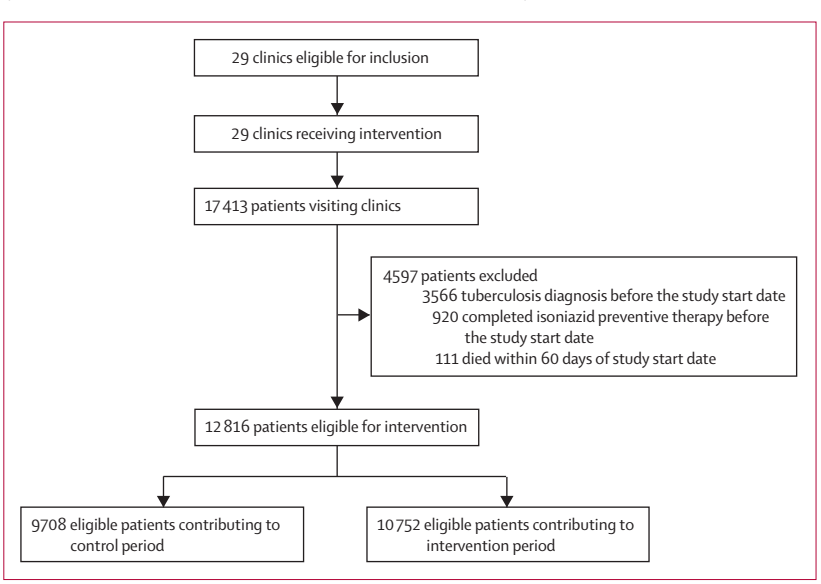

Figure: **Trial profile**

	Control period (n=9708; person-years=16 830)	Intervention period (n=10752; person-years=23 093)	Unadjusted		Adjusted	
			Hazard ratio (95% CI)	p	Hazard ratio* (95% CI)	p
Tuberculosis	221	254	..	..	..	..
Incidence (per 100 person-years)	1·31	1·10	0·87 (0·69–1·10)	0·24	0·73 (0·54–0·99)	0·04
Tuberculosis or death	612	701	..	..	..	..
Incidence rate (per 100 person-years)	3·64	3·04	0·76 (0·66–0·87)	<0·0001	0·69 (0·57–0·83)	<0·0001

*Adjusted model excludes 1982 patients because they did not have a CD4 count; the adjusted model includes 345 tuberculosis cases and 891 tuberculosis cases and deaths for the two models, respectively. Model is adjusted for age, sex, highly active antiretroviral therapy at baseline, and time-varying CD4 count.

Table 1: **Incidence rates during control and intervention periods, and Cox proportional hazards model results for primary outcomes**

estimated the study would have 80% power to detect a 40% reduction in tuberculosis incidence.

The primary outcomes were crude and adjusted incidence of active tuberculosis and incidence of active tuberculosis or death before and after exposure to the intervention.[13] Tuberculosis was defined according to the Brazilian guidelines[14] as: at least one positive culture for *Mycobacterium tuberculosis*, positive acid-fast bacilli smear, or clinical and radiographic presentation consistent with tuberculosis and response to treatment.

Rates of tuberculin skin testing and initiation of isoniazid preventive therapy were compared between control and intervention periods across clinics using a Poisson regression accounting for within-clinic correlation via inclusion of a scale parameter for overdispersion. The denominator time for the skin test rates started at entry into the cohort and for isoniazid preventive therapy rates on the date of a first positive skin test. Incidence rates were calculated for both primary outcomes with total person-time in each period as the denominator, and either all tuberculosis events or all tuberculosis events and deaths as the numerator, standardised to 100 person-years of observation. The start of follow-up was on Sept 1, 2005, or the date of first clinic visit for patients who enrolled in care after the study began. Patients were followed up until death, tuberculosis diagnosis, or Aug 31, 2009 (administrative censoring). Person-time was allocated to the control period from the time of study entry until the patient attended their clinic after the intervention was introduced. Patients who died or were diagnosed with tuberculosis within 60 days of their first clinic visit, whether that visit was during the clinic's control or intervention period, were excluded from the analysis.

In the primary intention-to-treat analysis, all patients eligible to receive either a tuberculin skin test or isoniazid preventive therapy were included. We considered patients as exposed to the intervention once they attended a clinic that had entered the intervention period of the trial, whether or not they received skin testing or isoniazid. Patients who transferred clinics contributed follow-up time to each clinic during the time they attended it. However, once a patient had observation time in a clinic in the intervention period, they were analysed as having received the intervention. Tuberculosis incidence and mortality rates on each day were compared between patients who had been exposed to the intervention and those who had not. Because this study had a stepped-wedge design, clinics spent different lengths of time in the control and intervention periods.

A secondary analysis was done to assess the effect of the intervention on patients retained in care (stayers analysis), because several patients eligible to receive tuberculosis testing and isoniazid preventive therapy never returned to the clinic after implementation of the intervention. This post-hoc analysis was designed before initiation of data analysis and included those patients who had consistent contact with a clinic, defined as receiving at least one CD4 determination per year. In principle, patients should be seen at clinic, with routine CD4 testing, three times a year. Thus, patient time was censored 1 year after the last CD4 result in these analyses.

We did Cox proportional hazards modelling on a calendar time axis to account for secular trends with gamma-distributed random effects for clinic-level shared frailty to compare instantaneous risk of outcomes of those in intervention status to those in control status. Crude Cox models were done for the primary analysis and adjusted models were generated that accounted for important covariates potentially associated with the intervention and the outcomes. These factors were sex, age at entry, antiretroviral therapy at baseline, and time-varying (last observation carried forward) CD4 count.[15] A time-varying binary covariate tracking intervention status was fitted with definitions of times-at-risk in each period. These analyses were done with R version 2, and fitted separately in Stata/MP version 12.1 for verification.

This trial is registered with ClinicalTrials.gov, number NCT00107887.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Control period (n=9087; person-time=11 307)	Intervention period (n=9743; person-time=18 008)	Unadjusted		Adjusted	
			Hazard ratio (95% CI)	p	Hazard ratio* (95% CI)	p
Tuberculosis	200	199	..	..	..	..
Incidence rate (per 100 person-years)	1·77	1·11	0·42 (0·31–0·58)	<0·0001	0·42 (0·29–0·60)	<0·0001
Tuberculosis or death	502	553	..	..	..	..
Incidence rate (per 100 person-years)	4·44	3·07	0·50 (0·41–0·60)	<0·0001	0·45 (0·35–0·56)	<0·0001

*Adjusted model includes 293 tuberculosis cases and 763 tuberculosis cases and deaths for the two models, respectively. Model is adjusted for age, sex, highly active antiretroviral therapy at baseline, and time-varying CD4 count.

Table 2: **Incidence rates during control and intervention periods, and Cox proportional hazards model results for secondary stayers analysis**

Results

The initial THRio cohort consisted of 17 413 patients with HIV, 11 629 who had visited study clinics before the trial started and 5784 who entered clinical care between Sept 1, 2005, and Aug 31, 2009 (figure). 4597 (26%) patients were excluded from the analysis for the following reasons: diagnosis of tuberculosis before the study start date plus 60 days (n=3566), had isoniazid preventive therapy before the study plus 60 days (n=920), or died within 60 days of study start (n=111). After these exclusions, 12 816 patients remained in our study sample.

Patients were aged between 16 and 84 years (median 37 [IQR 30–45] years). 7789 (61%) were men, the median CD4 count was 408 cells per μL (IQR 248–598), and 7657 (60%) were receiving combination antiretroviral therapy at baseline (table 1); 2319 patients (18%), had no CD4 result available within 180 days of entry. At first visit in the intervention period, the median CD4 count was 426 cells per μL (IQR 268–619); 2813 patients (22%) had no CD4 result available within 180 days of intervention.

Of 12 816 eligible patients, 472 had a positive tuberculin skin test before the THRio start date and were eligible for isoniazid preventive therapy. Of the remaining 12 344, 7361 (60%) had at least one tuberculin skin test placed and read. Of the 6224 patients eligible for a second test, 2919 (47%) received at least one additional test. 1455 (20%) of 7361 patients receiving at least one test had a positive result. Of all tuberculin-positives, 1186 (82%) started isoniazid preventive therapy and 1003 (85%) completed treatment. Rates of tuberculin skin tests were significantly greater during the intervention period (59 per 100 person-years) than in the control period (19 per 100 person-years, p<0·0001), as were rates for initiation of isoniazid preventive therapy for those with a positive tuberculin skin test (144 *vs* 36 per 100 person-years, p<0·0001). An additional 286 patients initiated isoniazid preventive therapy for reasons other than a new positive tuberculin skin test: 211 had a previous positive tuberculin skin test, 70 had a previous positive chest radiograph, and five had both a previous positive tuberculin skin test and chest radiograph. Treatment completion was 83% in these patients. Of the patients initiating preventive therapy, 22 (1·5%) reported adverse events leading to therapy interruption, mostly pruritis (n=7) and gastrointestinal disturbances (n=5), with only three patients experiencing liver toxicity.

During the THRio study period, 725 patients were diagnosed with tuberculosis, 250 (34%) of whom were excluded because the diagnosis was within 60 days of clinic entry. Of the 475 tuberculosis cases included in the analysis, 404 (85%) were identified from medical records and 71 (15%) from the tuberculosis registry. Among 838 deaths, 294 (35%) were found in medical records and 544 (65%) in the mortality registry. During the control period, 221 patients were diagnosed with tuberculosis and 391 deaths occurred during 16 830 person-years of follow-up, for a tuberculosis incidence rate of 1·31 per 100 person-years and a tuberculosis or death incidence rate of 3·64 per 100 person-years. The estimated coefficient of variation of tuberculosis rates, calculated as the square root of the variance of the γ-distributed rate multipliers, was 0·22.[16] In the intervention period, there were 254 patients diagnosed with tuberculosis and 447 deaths during 23 093 person-years of follow-up (table 1). The unadjusted hazard ratio for tuberculosis incidence showed no difference for intervention and control periods, but the unadjusted hazard ratio for death, and adjusted hazard ratios for incidence and death favoured the intervention (table 1 and appendix).

See Online for appendix

In the secondary stayers analysis, 621 patients were excluded and 2083 had their person-time reduced during the control period, and 1009 patients were excluded and 2969 patients had their person-time reduced during the intervention period. A total of 5523 person-years were lost in the control period and 5085 in the intervention period, accounting for 33% and 22% of follow-up time, respectively. In the control period, 200 patients were diagnosed with tuberculosis and 302 deaths were reported during 11 307 person-years of follow-up, for a tuberculosis incidence rate of 1·77 per 100 person-years and a tuberculosis or death incidence rate of 4·44 per 100 person-years (table 2). In the intervention period, 199 tuberculosis cases and 354 deaths were reported among 18 008 person-years, for rates of 1·11 per 100 person-years for tuberculosis incidence and 3·07 per 100 person-years for tuberculosis or death (table 2). In

the secondary analysis, all analyses favoured the intervention period (table 2 and appendix). In the secondary analysis, rates of tuberculin skin tests were significantly greater in the intervention period (74 per 100 person-years) than in the control period (29 per 100 person-years, p<0·0001), as were rates for initiating isoniazid preventive therapy (172 per 100 person-years *vs* 52 per 100 person-years, p<0·0001).

Discussion

The THRio intervention of training clinicians to screen for tuberculosis, to do tuberculin skin testing, and to offer isoniazid preventive therapy had a modest effect on tuberculosis incidence (13% reduction) and a larger and statistically significant effect on tuberculosis or death (24% reduction). After adjustment for important covariates such as age, sex, CD4 count, and receipt of antiretroviral therapy, during the intervention there was a 27% reduction in tuberculosis and a 31% reduction in tuberculosis or death. The effect was even greater in the secondary analysis of patients retained in care, with a 58% reduction in tuberculosis and a 55% reduction in tuberculosis and death.

These effects are noteworthy, since the THRio study included patients with free access to antiretroviral drugs, which can reduce the risk of tuberculosis substantially.[16] The larger effect on tuberculosis and death in the unadjusted analysis could reflect deaths from tuberculosis in the control period that were not diagnosed before death.[17] Thus, our results show that isoniazid given to patients with a positive tuberculin skin test who have access to antiretroviral therapy can have additional benefits for reducing the risk of tuberculosis and death. These benefits are substantial and important, since the risk of tuberculosis remains elevated in patients with HIV receiving antiretroviral therapy compared with those without HIV. Baseline data from this study found individual level effects of isoniazid preventive therapy and antiretroviral therapy, with a multiplicative effect of the two.[3] However, the baseline study revealed many limitations of the current implementation of tuberculin skin testing and isoniazid preventive therapy in patients with HIV. Preliminary results from a recent randomised clinical trial in patients receiving antiretroviral therapy in South Africa[18] reported a 37% reduced risk for tuberculosis in patients receiving 12 months of isoniazid preventive therapy versus placebo (panel).

Several individual clinical trials in high incidence settings in southern Africa have shown improved efficacy of extended durations of isoniazid preventive therapy in patients with HIV, and protection waned once patients stopped treatment.[19,23] Brazil's tuberculosis epidemic is much less severe than southern Africa's, thus the durability of a short course of isoniazid preventive therapy for patients with positive tuberculin skin tests seems to be robust, since reinfection is less likely. Whether the combination of antiretroviral therapy and a short course of isoniazid is sufficient for providing durable protection against tuberculosis in high-burden settings is uncertain. Also, treatment of latent tuberculosis with a more sterilising regimen, such as a rifamycin-based regimen, might be more efficacious than treatment with isoniazid alone.[24]

We aimed to do a study under normal clinic conditions in an effort to represent a sustainable model, without the stringent conditions of a clinical trial. Thus, a large number of patients either never attended or had limited attendance at the clinic and were therefore not exposed to the intervention. One marker of attendance is the reporting of CD4 counts, which Brazilian guidelines recommend is done three times a year. However, 1982 (15·5%) patients included in the primary analysis never had a reported CD4 count, and were subsequently excluded from the adjusted analysis. Tuberculosis rates were higher in patients with no CD4 count reported, and these patients tended to be newly diagnosed with HIV during the intervention period and had little or no contact with the clinic after their HIV diagnosis and before their tuberculosis diagnosis. Thus, adjusted analyses reported marginally better protection. When we restricted our analysis to patients who had at least yearly encounters with a study clinic and were therefore more likely to be exposed to the intervention, we saw an even larger and highly significant reduction in the incidence of tuberculosis (58%) and tuberculosis or death (55%). The estimates of the effectiveness of our intervention range from the intention-to-treat results and the results seen in the subset of patients who have regular contact with the clinic—ie, from the 13% and 24% reductions (and their confidence intervals) observed in the intention-to-treat analysis and the more than 50% reductions seen in the secondary stayers analysis. The results of the secondary analysis emphasise the need for strategies to maintain attendance in clinic to improve HIV outcomes.

The overall effect of our intervention was diminished by patients, newly diagnosed with HIV, presenting with tuberculosis before preventive measures could be offered. 21% of all tuberculosis diagnoses during the study period were in patients newly diagnosed with HIV, and were excluded from our analyses a priori because they did not have an opportunity to benefit from the intervention. This finding emphasises the need for strategies to diagnose HIV earlier and start preventive therapy and antiretroviral therapy as soon as possible after diagnosis to reduce tuberculosis risk.

Because tuberculosis deaths are probably under-reported in patients with HIV in Rio de Janeiro, we combined the outcome of tuberculosis and death to capture effects related to prevention of tuberculosis deaths by the intervention.[25] Our finding that the intervention reduces the risk of tuberculosis and death more substantially than it does for tuberculosis alone suggests that there was under-ascertainment of

tuberculosis deaths, consistent with reports from South Africa.[26]

Although the provision of tuberculin skin tests and isoniazid preventive therapy was the primary focus, an increased awareness by all staff receiving the training might have provided additional inestimable benefits, such as earlier tuberculosis diagnosis or earlier initiation of antiretroviral therapy, thus decreasing mortality.[27–29] Our study was only 4 years in duration, but care for patients may have improved over this period (60% receiving antiretroviral therapy at study start compared with 73% at study end), thus providing more benefit to patients in the intervention period. Although only 9% of the population actually received isoniazid preventive therapy, those patients screened for latent and active tuberculosis might have stayed more connected to the clinic and benefited accordingly. The stepped-wedge design was chosen for operational simplicity, although this design did present several challenges. Although the analysis accounted for secular trends, interactions between secular trends and some covariates might have occurred. Finally, increased tuberculosis screening and use of isoniazid preventive therapy could have had secondary benefits, decreasing transmission of *M tuberculosis* in health facilities and thereby decreasing incidence more broadly.

The THRio intervention was successful in increasing the use of tuberculin skin tests and isoniazid preventive therapy, as recommended by the Brazilian Ministry of Health. Median times to skin testing and to isoniazid therapy for skin test-positive patients were markedly reduced after the intervention.[24] Nevertheless, 36% of tuberculosis cases diagnosed after the intervention were in patients who had not yet received a tuberculin skin test. Strategies for delivering tuberculosis preventive therapy more expeditiously are urgently needed. Use of interferon-γ release assays linked to routine CD4 cell count might simplify the process of diagnosing latent tuberculosis infection and speed the time to initiation of preventive therapy. Alternatively, providing tuberculosis preventive therapy to all patients with HIV, as recommended by WHO,[5] could ensure broader uptake. Although earlier trials have shown either very modest or no benefit of isoniazid preventive therapy for tuberculin-negative individuals,[2,19] Rangaka and colleagues show that it is highly protective in tuberculin-negative and interferon-γ-negative individuals receiving antiretroviral therapy. However, these results might not be applicable in Brazil, where tuberculosis exposure and transmission are both markedly less than in South Africa.[20]

Despite limitations inherent to a study done in a real-world setting, we showed that tuberculin skin test screening and provision of isoniazid to patients with HIV significantly reduced the risk of tuberculosis and death and should be widely implemented. In settings similar to those of Brazil, where rates of latent tuberculosis infection are reasonably high but repeat re-infection with tuberculosis is uncommon, provision of a 6-month regimen of isoniazid is likely to have lasting protection from tuberculosis. Providing preventive therapy on a large scale through routine HIV clinic care is an effective way to significantly reduce tuberculosis incidence and death in patients with HIV.

Panel: Research in context

Systematic Review

We searched PubMed for articles published in the HIV era with the search terms "isoniazid preventive therapy" or "tuberculosis preventive therapy" or "tuberculin skin test" and "HIV" and "tuberculosis." Only English language titles were included. We also included results reported at recent scientific meetings of the International AIDS Society, Conference on Retroviruses and Opportunistic Infections, and the International Union Against Lung Disease and Tuberculosis. These results were combined with a published systematic review.[2]

Interpretation

Isoniazid preventive therapy reduces tuberculosis risk in HIV-infected individuals,[2] especially those with a positive tuberculin skin test.[2,19] Observational studies show that treatment with isoniazid and antiretroviral agents provide greater protection against tuberculosis than either therapy given alone.[3,4] A recent randomised clinical trial in South Africa among HIV-infected patients receiving highly active antiretroviral therapy found that isoniazid preventive therapy significantly reduced tuberculosis risk compared with placebo, including in patients with negative tuberculin tests or interferon-gamma assays.[18,20] The durability of isoniazid preventive therapy seems to vary according to risk of re-infection with *Mycobacterium tuberculosis*. A recent cluster randomised trial in South African gold miners showed no durable population effect of 9 months of isoniazid preventive therapy in a setting with high HIV prevalence and risk of re-infection, although isoniazid was effective while participants were receiving the drug.[21,22] Studies in Botswana and South Africa found that continuous isoniazid preventive therapy provided durable protection against tuberculosis for HIV-infected patients with latent tuberculosis infection.[19,23] Our study found that isoniazid preventive therapy substantially reduces tuberculosis rates in Brazilian HIV clinic populations where there is excellent access to antiretroviral therapy, and both isoniazid and antiretroviral agents contribute to a significant population effect on tuberculosis risk and mortality. The overall population level effect is modest, however—the result of patients presenting to care with prevalent tuberculosis late in the course of HIV disease and insufficient isoniazid coverage due to both patient and health system lapses.

Contributors

REC, LHM, JEG, BD, and SCC designed the study. BD, VS, SCC, BK, SC, AE, REC, and JEG participated in the implementation of the trial. BD, VS, SCC, and AE participated in administration, and AE, BK, SC in regulatory support. LHM, JEG, VS, BK, SC, and AE participated in data management. VS, BK, and SC participated in data collection. REC, LHM, JEG, VS, AGP, BK, and SC participated in data analysis. JEG wrote the initial draft of the report and all authors revised and approved the final report.

Conflicts of interest

We declare that we have no conflicts of interest.

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