Impact of Isoniazid Preventive Therapy for HIV-Infected Adults in Rio de Janeiro, Brazil:

An Epidemiological Model

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Supplemental Digital Content 1:

Model Description, Equations, and Supplementary Analyses

Model Description

Model Compartments

The mathematical model consists of five tuberculosis (TB) compartments, three of which are duplicated by drug resistance status (drug-susceptible or multidrug-resistant, MDR), yielding eight TB compartments overall. Each TB compartment is then subdivided into four HIV states (the post-IPT state into three, as IPT is not offered to people without HIV in this model), for a total of 31 total compartments. The TB compartments are:

- U_h, Uninfected

- $L_{h,r}$, Latently infected

- I_h, Post-isoniazid preventive therapy (IPT) with drug-susceptible TB

- $A_{h,r}$, Active TB

- $R_{h,r}$, Recovered/Treated

where the subscript h denotes HIV status according to the following strata:

- HIV-negative ($h = 0$)

- HIV-positive with CD4$^+$ T-cell count >350 cells/mm^3 ($h = 1$)

- HIV-positive with CD4$^+$ T-cell count ≤350 cells/mm^3 but not on antiretroviral therapy [ART] ($h = 2$), and

- HIV-positive with CD4$^+$ T-cell count ≤350 cells/mm^3 and on antiretroviral therapy [ART] ($h = 3$).

The subscript r denotes drug resistance status as drug-susceptible ($d = 0$) or MDR-TB ($d = 1$). We use $N(t)$ to denote the size of the full population at time t, summing over all compartments.

Population

The model assumes an adult population (the catchment population of a given set of clinics), with no immigration or emigration. We include only individuals between the ages of 15 and 59 (to match available data in Brazil), assuming that deaths or exits (reaching one's 60th birthday) are replaced by entries (reaching ones 15th birthday). Entries occur primarily into the HIV uninfected, TB uninfected compartment (U_0), though a small number are assumed to have latent infection. The proportion entering the latently infected compartment $L_{0,r}$ is estimated at baseline/equilibrium as $(1 - e^{-15*\lambda})$, where λ is the force of infection as below. For model simplicity (and given the relatively low force of infection), this proportion is held constant throughout the rest of the model's time horizon. Similarly, the proportion of individuals entering with latent MDR-TB infection is modeled as the relative force of infection for MDR-TB relative to drug-susceptible TB at baseline.

Description of Model Transitions: TB

Individuals exit the uninfected compartment U_h at a rate that is determined by the per-person TB transmission rate, number of infectious TB cases, and the relative transmission rate σ for individuals with HIV-associated TB. A proportion of these individuals progress rapidly to active disease $A_{h,r}$; the remainder become latently infected ($L_{h,r}$), from which reactivation as well as reinfection and subsequent rapid progression to active disease (at a reduced rate) are both allowed. Individuals with latent TB infection (due to drug-susceptible TB) may also progress to the post-IPT state I_h according to the "IPT initiation rate." Incomplete courses of IPT are modeled as having no effect; completed courses of IPT result in transition to the post-IPT state for the duration of the five-year analytic horizon. (As described in the main text, sensitivity

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analysis is performed for durations of protection as short as 6 months.) Although the duration of IPT effectiveness among HIV-infected individuals in settings of high TB transmission and/or low ART coverage is a matter of debate, we do not see any evidence of waning effectiveness in THRio trial data, and the average duration of the post-IPT state in this model (given a five-year analytic horizon with continuous deployment of IPT throughout the time period) was less than three years. Note that IPT may also be delivered to individuals without latent TB infection (e.g., false-positive tuberculin skin test), or with latent TB infection due to MDR-TB, but these individuals are assumed to receive no benefit from IPT and thus do not change their TB status. The post-IPT state is characterized by a reduced risk of TB reactivation (assuming that one's latent TB strain is drug-susceptible), but no change in the risk of reinfection – although as described in the main text, we perform sensitivity analysis to relax this assumption as well.

After progressing to active TB, individuals can enter the recovered compartment $R_{h,r}$ through diagnosis and treatment or spontaneous recovery. We assume that diagnosis and treatment occur at a constant annual rate; for simplicity, we assume that individuals with MDR-TB are successfully diagnosed and treated at the same rate as those with drug-susceptible TB. Since the relative infectiousness of MDR-TB is fit to the prevalence of MDR-TB in Brazil, lowering the MDR-TB treatment rate simply results in a lower relative infectiousness of MDR-TB in this model (i.e., to maintain a constant MDR-TB prevalence at equilibrium), with little impact on model outcomes related to IPT effectiveness (data not shown). Subsequent relapse from $R_{h,r}$ to $A_{h,r}$ is allowed (encompassing both "relapse" and "reactivation" in a single parameter), as is reinfection.

Description of Model Transitions: HIV

Since the purpose of this model is to evaluate the impact of IPT on TB incidence and mortality in an HIV epidemic that is essentially at steady-state over the five-year model duration, we do not explicitly model HIV incidence as transmission events over sexual or drug-use networks. Rather, we adopt a simplified approach that considers a constant HIV incidence rate from $X_{0,r}$ to $X_{1,r}$, where X represents any of the five TB states listed above. Following HIV infection, people then progress to CD4 count $\leq$350 cells/mm^3 at a mean rate informed by natural history studies in the pre-ART era. Once people reach a CD4 nadir $\leq$350 cells/mm^3, we assume that they are started on ART at a rate that results in population ART coverage consistent with estimates in Brazil. We also assume that people on ART discontinue or are lost to follow-up at a rate of 0.2/year; we vary this parameter widely in sensitivity analysis. The Table below shows all model parameters in their symbolic form.

Table. Model Parameters – Symbolic Representations

Parameter	Representation
Transmission rate (transmission events per infectious person-year)	β
Rate of diagnosis and treatment (including spontaneous cure), per year	τ
TB-specific mortality rate, per year:	μ_{TBh}
Rate of exit plus non-TB (including HIV) mortality, per year	μ_h
Proportion of recent infections resulting in rapid progression	π_h
Reactivation rate after latent infection, per year	ε_h
Rate of ART initiation, per year	α_{in}
Rate of ART discontinuation, per year	α_{out}
HIV incidence rate, per year	η
Relapse rate after successful treatment, per year	ρ
Relative infectiousness of MDR-TB	ξ
Relative infectiousness of HIV-associated TB	σ
Partial immunity to reinfection in people with latent TB infection	ψ_0
IPT initiation rate, per year	κ
Protective efficacy of IPT against reinfection TB	ι
Proportion of recovery events resulting in acquisition of resistance	φ
Rate of CD4 progression to ≤ 350 cells/mm^3, per year	γ
Proportion of individuals at age 15 with latent TB infection	χ

Values of each parameter, with corresponding sensitivity/uncertainty ranges and references, are found in Table 1 of the main text.

Model Equations

Rates of flow between compartments are governed by the system of ordinary differential equations listed in Equations 1-9. We first define the force of infection, total mortality rate, and rates of successful treatment for simplicity. The model was programmed in R version 3.0.0 (R Foundation for Statistical Computing, 2013), and differential equations were solved with the deSolve package at time steps of 0.1 years. The source code for the model is available at https://github.com/ddowdy/THRio-model.

Force of Infection *(λ)*

$$\lambda_0(t) = \beta * \left(A_{0,0} + \sigma * \sum_{h>0} [A_{h,0}(t)] \right) / N(t)$$

$$\lambda_1(t) = \beta * \left(\xi * A_{0,1} + \xi * \sigma * \sum_{h>0} [A_{h,1}(t)] \right) / N(t)$$

$$\lambda_{tot}(t) = \lambda_0(t) + \lambda_1(t)$$

TB infection is therefore modeled as a density-dependent process, a function of the transmission rate (β) and relative transmissibility according to drug resistance status. This transmission rate is multiplied by the number of individuals with infectious TB [$A(t)$], with HIV-coinfected individuals being somewhat less infectious (represented by the weight σ) as seen in earlier studies in Rio de Janeiro.

Total Rate of Mortality and Exit from the Population Due to Aging *(M)*

$$M(t) = \sum_{h,0} \{\mu_h * [U_h(t) + L_{h,0}(t) + I_h(t) * + A_{h,0}(t) + R_{h,0}(t)] + \mu_{TBh} * A_{h,0}(t)\}$$

$$+ \sum_{h,1} \{\mu_h * [L_{h,1}(t) + A_{h,1}(t) + R_{h,1}(t)] + \mu_{TBh} * A_{h,1}(t)\}$$

Total mortality is the sum of baseline mortality across all compartments, plus TB-specific

mortality across the compartments that correspond to active TB. Note that μ_h here includes non-

specific mortality, HIV-specific mortality among those with HIV, and aging from the population

at a rate of 1/(60-15) per year – i.e., the inverse of the duration of time between population entry

(15th birthday) and exit (60th birthday).

In the following equations, equation (a) corresponds to HIV-uninfected, equation (b) to HIV with

CD4 count >350, equation (c) to HIV with CD4 count ≤350 not on ART, and equation (d) to

HIV on ART:

Equations 1a-1d. Uninfected Compartments (U_h)

$$a) \quad \frac{dU_0(t)}{dt} = (1 - \chi) * M(t) - (\lambda_{tot} + \mu_0) * U_0(t) - \eta * U_0(t)$$

$$b) \quad \frac{dU_1(t)}{dt} = -(\lambda_{tot} + \mu_1) * U_1(t) + \eta * U_0(t) - \gamma * U_1(t)$$

$$c) \quad \frac{dU_2(t)}{dt} = -(\lambda_{tot} + \mu_2) * U_2(t) + \gamma * U_1(t) - \alpha_{in} * U_2(t) + \alpha_{out} * U_3(t)$$

$$d) \quad \frac{dU_3(t)}{dt} = -(\lambda_{tot} + \mu_3) * U_3(t) + \alpha_{in} * U_2(t) - \alpha_{out} * U_3(t)$$

where χ is the proportion of 15-year-olds who are latently infected, *M(t)* represents total

mortality and aging as above, λ_{tot} denotes the total force of infection (drug-sensitive plus MDR),

μ_h represents background mortality and aging, η represents HIV infection, γ represents

progression of HIV disease, α_{in} the initiation of ART, and α_{out} the discontinuation of ART. Thus,

uninfected individuals leave this compartment through infection, death, and aging; and they

move through HIV strata according to HIV infection, disease progression, and ART

initiation/discontinuation, with entries into U_0 (plus latent compartments below) matching exits

due to mortality or aging.

Equations 2a-2d. Latently Infected Compartments ($L_{h,r}$)

$$a) \quad \frac{dL_{0,r}(t)}{dt} = \left[\chi * \frac{\lambda_r(t)}{\lambda_{tot}(t)} \right] * M(t) + \lambda_r * (1 - \pi_0) * U_0(t)$$

$$-[\lambda_{tot} * (1 - \psi_0) * \pi_0 + \varepsilon_0 + \mu_0 + \eta] * L_{0,r}(t)$$

$$b) \quad \frac{dL_{1,r}(t)}{dt} = \lambda_r * (1 - \pi_1) * U_1(t) + \eta * L_{0,r}(t)$$

$$-[\lambda_{tot} * \pi_1 + \kappa * (1 - \varphi) * \mathbb{I}_{r=0} + \varepsilon_1 + \mu_1 + \gamma] * L_{1,r}(t)$$

$$c) \quad \frac{dL_{2,r}(t)}{dt} = \lambda_r * (1 - \pi_2) * U_2(t) + \gamma * L_{1,r}(t) + \alpha_{out} * L_{3,r}(t)$$

$$- [\lambda_{tot} * \pi_2 + \kappa * (1 - \varphi) * \mathbb{I}_{r=0} + \varepsilon_2 + \mu_2 + \alpha_{in}] * L_{2,r}(t)$$

$$d) \quad \frac{dL_{3,r}(t)}{dt} = \lambda_r * (1 - \pi_3) * U_3(t) + \alpha_{in} * L_{2,r}(t)$$

$$-[\lambda_{tot} * \pi_3 + \kappa * (1 - \varphi) * \mathbb{I}_{r=0} + \varepsilon_3 + \mu_3 + \alpha_{out}] * L_{3,r}(t)$$

where χ is the proportion of 15-year-olds who are latently infected, *M(t)* represents total

mortality and aging as above, λ_r denotes the resistance-specific force of infection while λ_{tot}

denotes the total force of infection (drug-sensitive plus MDR), π_h is the proportion of recent

infections that progress rapidly to active TB, ψ_0 is the relative reduction in rapid progression

after reinfection among people with latent TB and no HIV infection, ε_h represents the

endogenous reactivation rate, μ_h represents background mortality and aging, η represents HIV infection, γ represents progression of HIV disease, α_{in} the initiation of ART, and α_{out} the discontinuation of ART. The term $\kappa * (1 - \varphi) * \mathbb{I}_{r=0}$ is the IPT initiation rate among people with HIV and without MDR-TB, the expression $\mathbb{I}_{r=0}$ equaling 1 when $r = 0$ and 0 when $r = 1$, and φ denoting the proportion of IPT treatments that result in new resistance, set pessimistically in the base case as equal to the number of recovery events from active TB that result in MDR-TB. Not shown for simplicity in the equations above is acquisition of resistance during IPT (i.e., rate of $\kappa * \varphi * L_{h,0}$ from each HIV-infected compartment with $r=0$ into each compartment with $r=1$).

Thus, uninfected individuals who do not progress rapidly are modeled as developing latent infection, and latently infected individuals leave this compartment through TB reinfection (followed by rapid progression), IPT initiation, endogenous reactivation, and death. They move through HIV strata according to HIV infection, disease progression, and ART initiation/discontinuation. Note that, in this model using a 5-year time horizon, we do not explicitly model superinfection of individuals with latent TB (e.g., movement from latent/drug-resistant to latent/drug-susceptible after superinfection with a susceptible strain) unless that superinfection is followed by rapid progression to active TB – as superinfection followed by progression within 5 years would, by our definition, be considered rapid progression.

Equations 3a-3c. Post-IPT Compartments (I_h)

Note that IPT is only offered to those with HIV (i.e., no compartment for $h=0$) and is assumed to have no effect in those with MDR-TB (i.e., no compartments for $r=1$).

b) $\dfrac{dI_1(t)}{dt} = \kappa * (1-\varphi) * L_{1,0}(t) - [\lambda_{tot} * \pi_1 + \varepsilon_1 * (1-\iota) + \mu_1 + \gamma] * I_1(t)$

c) $\dfrac{dI_2(t)}{dt} = \kappa * (1-\varphi) * L_{2,0}(t) + \gamma * I_1(t) + \alpha_{out} * I_3(t)$

$- [\lambda_{tot} * \pi_2 + \varepsilon_2 * (1-\iota) + \mu_2 + \alpha_{in}] * I_2(t)$

d) $\dfrac{dI_3(t)}{dt} = \kappa * (1-\varphi) * L_{3,0}(t) + \alpha_{in} * I_2(t)$

$-[\lambda_{tot} * \pi_3 + \varepsilon_3 * (1-\iota) + \mu_3 + \alpha_{out}] * I_3(t)$

where κ is the IPT initiation rate, φ is the proportion of IPT treatments resulting in acquisition of resistance, λ_{tot} denotes the total force of infection (drug-sensitive plus MDR), ι is the protective efficacy of IPT, π_h is the proportion of recent infections that progress rapidly to active TB, ε_h represents the endogenous reactivation rate, μ_h represents background mortality and aging, γ represents progression of HIV disease, α_{in} the initiation of ART, and α_{out} the discontinuation of ART.

Thus, latently infected individuals may be placed on IPT, at which time they enter a compartment, exit from which resembles latent infection except for a degree of protection against endogenous reactivation (if the infection is drug-sensitive).

Equations 4a-4d. Active TB Compartments ($A_{h,r}$)

a) $$\frac{dA_{0,r}(t)}{dt} = \lambda_r * \pi_0 * \left\{ U_0(t) + \sum_r [(1 - \psi_0) * L_{0,r}(t) + R_{0,r}(t)] \right\}$$

$$+ \varepsilon_0 * L_{0,r}(t) + \rho * R_{0,r}(t) + \varphi * \tau * A_{0,0}(t) * (\mathbb{I}_{r=1} - \mathbb{I}_{r=0})$$

$$- [\tau * (1 - \varphi * \mathbb{I}_{r=0}) + \mu_0 + \mu_{TB0} + \eta] * A_{0,r}(t)$$

b) $$\frac{dA_{1,r}(t)}{dt} = \lambda_r * \pi_1 * \left\{ U_1(t) + \sum_r [L_{1,r}(t) + I_{1,r}(t) + R_{1,r}(t)] \right\}$$

$$+ \varepsilon_1 * [L_{1,r}(t) + (1 - \iota) * I_1(t) * \mathbb{I}_{r=0}] + \rho * R_{1,r}(t) + \varphi * \tau * A_{1,0}(t) * (\mathbb{I}_{r=1} - \mathbb{I}_{r=0})$$

$$+ \eta * A_{0,r}(t) - [\tau * (1 - \varphi * \mathbb{I}_{r=0}) + \mu_1 + \mu_{TB1} + \gamma] * A_{1,r}(t)$$

c) $$\frac{dA_{2,r}(t)}{dt} = \lambda_r * \pi_2 * \left\{ U_2(t) + \sum_r [L_{2,r}(t) + I_{2,r}(t) + R_{2,r}(t)] \right\}$$

$$+ \varepsilon_2 * [L_{2,r}(t) + (1 - \iota) * I_2(t) * \mathbb{I}_{r=0}] + \rho * R_{2,r}(t) + \varphi * \tau * A_{2,0}(t) * (\mathbb{I}_{r=1} - \mathbb{I}_{r=0})$$

$$+ \gamma * A_{1,r}(t) + \alpha_{out} * A_{3,r}(t) - [\tau * (1 - \varphi * \mathbb{I}_{r=0}) + \mu_2 + \mu_{TB2} + \alpha_{in}] * A_{2,r}(t)$$

d) $$\frac{dA_{3,r}(t)}{dt} = \lambda_r * \pi_3 * \left\{ U_3(t) + \sum_r [L_{3,r}(t) + I_{3,r}(t) + R_{3,r}(t)] \right\}$$

$$+ \varepsilon_3 * [L_{3,r}(t) + (1 - \iota) * I_3(t) * \mathbb{I}_{r=0}] + \rho * R_{3,r}(t) + \varphi * \tau * A_{3,0}(t) * (\mathbb{I}_{r=1} - \mathbb{I}_{r=0})$$

$$+ \alpha_{in} * A_{2,r}(t) - [\tau * (1 - \varphi * \mathbb{I}_{r=0}) + \mu_3 + \mu_{TB3} + \alpha_{out}] * A_{3,r}(t)$$

where λ_r denotes the resistance-specific force of infection while λ_{tot} denotes the total force of infection (drug-sensitive plus MDR), π_h is the proportion of recent infections that progress rapidly to active TB, ψ_0 is the relative reduction in rapid progression after infection among people with latent TB and no HIV infection, ε_h represents the endogenous reactivation rate, ρ denotes the relapse rate after successful treatment, φ is the proportion of recovery events

resulting in acquisition of resistance, τ represents the combined rate of treatment and spontaneous resolution, μ_h represents background mortality and aging, μ_{TBh} represents TB-specific mortality, η represents HIV infection, γ represents progression of HIV disease, α_{in} the initiation of ART, and α_{out} the discontinuation of ART. The expression $\mathbb{I}_{fxn}$ denotes an indicator function that equals 1 when fxn is true and 0 when fxn is false.

Thus, active TB arises through infection of uninfected individuals, reinfection of people with latent TB infection (with or without IPT, at the same rate), reinfection after recovery, endogenous reactivation from latent infection (with some protection from IPT if drug-susceptible), and relapse after successful treatment/resolution. Drug resistance may be acquired during treatment (in the reference scenario, at the same rate as during IPT). Note that, since spontaneous and treatment-induced recovery are not modeled separately here, the probability of acquiring drug resistance on therapy is somewhat higher than the value of φ, depending on the proportion of recovery events that reflect spontaneous recovery (e.g., if 25% of all recoveries occur without selective drug pressure, then the probability of acquiring resistance on therapy is $\varphi/0.75$). People leave this compartment through death (background or TB-specific) or successful treatment/resolution (which includes spontaneous cure). They move through HIV strata according to HIV infection, disease progression, and ART initiation/discontinuation.

Equations 5a-5d. Recovered/Treated Compartments ($R_{h,r}$)

$$a) \quad \frac{dR_{0,r}(t)}{dt} = \tau * (1 - \varphi * \mathbb{I}_{r=0}) * A_{0,r}(t) - [\lambda_{tot} * \pi_0 + \rho + \mu_0 + \eta] * R_{0,r}(t)$$

$$b) \quad \frac{dR_{1,r}(t)}{dt} = \tau * (1 - \varphi * \mathbb{I}_{r=0}) * A_{1,r}(t) + \eta * R_{0,r}(t) - [\lambda_{tot} * \pi_1 + \rho + \mu_1 + \gamma] * R_{1,r}(t)$$

$$c) \quad \frac{dR_{2,r}(t)}{dt} = \tau * (1 - \varphi * \mathbb{I}_{r=0}) * A_{2,r}(t) + \gamma * R_{1,r}(t) + \alpha_{out} * R_{3,r}(t)$$

$$- [\lambda_{tot} * \pi_2 + \rho + \mu_2 + \alpha_{in}] * R_{2,r}(t)$$

$$d) \quad \frac{dR_{3,r}(t)}{dt} = \tau * (1 - \varphi * \mathbb{I}_{r=0}) * A_{3,r}(t) + \alpha_{in} * R_{2,r}(t)$$

$$- [\lambda_{tot} * \pi_3 + \rho + \mu_3 + \alpha_{out}] * R_{3,r}(t)$$

where τ represents the combined rate of treatment and spontaneous resolution, φ is the proportion of recovery events resulting in acquisition of resistance (the indicator function $\mathbb{I}_{r=0}$ implies that recoveries resulting in acquisition of resistance remain in the active compartment), λ_{tot} denotes the total force of infection (drug-sensitive plus MDR), π_h is the proportion of recent infections that progress rapidly to active TB, ρ denotes the relapse rate after successful treatment (which includes both "reactivation" and "relapse"), μ_h represents background mortality and aging, η represents HIV infection, γ represents progression of HIV disease, α_{in} the initiation of ART, and α_{out} the discontinuation of ART.

Thus, individuals enter this compartment through successful treatment or resolution and exit through TB reinfection (followed by rapid progression), relapse, and death. They move through HIV strata according to HIV infection, disease progression, and ART initiation/discontinuation.

Supplementary Analyses

Model Validation by Comparison to Alternative Trial Analysis

We compared our TB incidence projections (using time-to-IPT data – but not TB outcome data – from the trial) to a statistical analysis of THRio outcome data that included all participants in each clinic who were eligible for IPT screening (i.e., HIV-infected and without prior history of TB or IPT), rather than evaluating the effect of IPT among those who contacted the clinic as in the primary adjusted trial analysis. For this analysis, we assumed rates of IPT uptake as in the THRio trial, with IPT providing a persistent 67% protection against reactivation TB. Our statistical analysis utilized an unadjusted Cox proportional hazards model with time to TB diagnosis as the outcome. Over the median follow-up period of 2.8 years, the model projected that IPT would reduce cumulative TB incidence among PLHIV by 3.0% (95%UR: 1.6%, 7.2%); the corresponding population-level hazard ratio for incident TB from the trial data was 0.94 (95%CI: 0.75, 1.18).

Potential Impact of IPT on MDR-TB

We investigated the potential for IPT to generate MDR-TB under two alternative assumptions. In the first ("worst-case") scenario, we assumed that the probability of acquired drug resistance during IPT was the same as the probability of acquired drug resistance during chemotherapy for active TB, i.e., 1 new MDR-TB case generated for every 200 IPT treatments (Table 1, main text). Under this pessimistic assumption, IPT increased the incidence of MDR-TB by 0.3% at the end of year 5 (95%UR: -0.2%, 0.7%), or 1.2 additional cases in the entire city over the full 5-year time course. In the second ("realistic") scenario, we assumed that that the risk of MDR-TB is increased by 45% among those who have taken IPT, as reported by Balcells et al (*Emerg Infect*

Dis. 2006; 12:744-751). In this scenario, IPT actually reduced the population incidence of

MDR-TB by year 5 (i.e., reduction in overall TB incidence outweighed the IPT-associated

increase in MDR-TB incidence).