Impact of Isoniazid Preventive Therapy for HIV-Infected Adults in South Africa: A Compartmental Epidemiological Model

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Supplemental Digital Content 1:

Model Description, Equations, and Supplementary Analysis

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1 Model Description

This compartmental model evaluates the impacts of different strategies to provide isoniazid preventive therapy (IPT) to prevent tuberculosis (TB) among people living with HIV (PLHIV). The model was developed in the context of rural KwaZulu-Natal, South Africa for the Delivery Optimization for Antiretroviral Therapy study (DO ART). This model was adapted from Dowdy, David W., et al. (2014) who developed a similar model for application in Rio de Janeiro, Brazil [1].

1.1 Model Compartments

For the purpose of this model we introduce a total of 8 TB, 2 Drug Resistance (DR), 4 HIV compartments, and 2 gender compartments resulting in a total of $(8 \times 2 \times 4 \times 2) = 128$ compartments. In 2 of the 8 TB compartments, where the population is uninfected, it is not possible to distinguish by drug resistance. Even though these compartments are not distinguishable, this model keeps the compartments for consistency in matrix notation.

Set of Tuberculosis Compartments - $t \in TB$

The model consists of uninfected (susceptible), latent TB infection (LTBI/exposed), active (infectious), and recovered/treated TB compartments similar to a SEIR model. These compartments are duplicated when appropriate to account for current status of IPT. Furthermore, since the risk for rapid progression from LTBI to active varies for recently and remotely infected populations we separate these compartments accordingly. This yields eight total TB compartments. We define the set of TB compartments as:

1. Uninfected, not on IPT
2. Uninfected, on IPT
3. LTBI, infected recently (within the past two-years)
4. LTBI, infected remotely (more than two-years ago)
5. LTBI, on IPT
6. Active
7. Recovered/Treated
8. LTBI, after IPT

Set of Tuberculosis Drug Resistance Compartments - $r \in DR$

This model incorporates transmission of drug susceptible and multidrug-resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin. Populations with LTBI due to MDR-TB strains may receive IPT in this model, as there would not be a way to distinguish these populations clinically in the absence of a strong exposure history for MDR-TB. Populations with latent MDR-TB do not experience a TB prevention benefit from IPT in the model. As such we introduce an indicator variable that disallows MDR-TB infected populations to move into TB compartment 8, LTBI, after TB, by setting the transition rate into that compartment to zero, thereby forcing TB compartment 8 to have zero population for MDR-TB compartments. We define the set of DR compartments as:

1. Drug-susceptible (DS)
2. Multidrug-resistant (MDR-TB)

Set of HIV Compartments - $h \in HIV$

The purpose of this model is to test the impact on offering IPT to PLHIV persons. The model consists of four HIV compartments. We define the set of HIV compartments as:

1. HIV-negative
2. PLHIV not on ART, CD4 > 200
3. PLHIV not on ART, CD4 ≤ 200
4. PLHIV and on ART

Set of Gender Compartments - $g \in G$

The model accounts for gender, which has shown in previous studies to have an impact on transmission (contact), IPT initiation and mortality rates []. We define the set of gender compartments as:

1. Male
2. Female

1.2 Policy Description

We evaluate three policy scenarios using data from the DO ART study. The baseline policy is called "Standard of care", and reflects the levels of ART and IPT initiation observed among participants in the standard clinic-based care arm of the DO ART study. Policy 2 reflects the mobile van intervention arm of the DO ART study, which tested this community-based strategy to enhance ART initiation [2]. Policy 3 reflects a nested IPT trial tested community-based IPT delivery in the setting of community-based ART [3]. The independent effect of community-based IPT delivery without community-based ART is not tested. Thus we define the set of all polices as:

1. Standard of care, only facility-based ART and IPT delivery offered
2. Community-based ART delivery, only facility-based IPT delivery offered
3. Community-based ART and IPT delivery

The parameters that are impacted by policy are summarised in Table 3. Table 1 provides a high-level summary of how different policies impact parameterization of these rates. In the Model Transition Figures, Figure 1 and Figure 2 the transition rates that are directly impacted by policy and presented in Table 1 are highlighted in red. The Rate of populations moving from HIV compartment i to HIV compartment h for gender g, per year, under policy p is denoted $\eta_{i,h,g}(p)$, $\forall (i,h) \in HIV$, $g \in G, p \in P$. As highlighted in Table 1 policy impacts the rate of ART initiation into HIV compartment 4 (PLHIV on ART). The rate of populations initializing IPT from TB compartment t, HIV compartment h for gender compartment g under policy p is denoted $\kappa_{t,h,g}(p)$, $\forall t \in \{1,3,4\} \subset TB, h \in HIV, g \in G, p \in P$. The IPT adherence parameter denoted $\varpi_g(p)$ accounts for the impact of adherence to IPT regimens on the treatment success in preventing an individual from getting active TB for gender g under policy p, $\forall g \in G, p \in P$.

As you can see in Table 1, Policy 1, clinic-based care alone includes lower levels of ART and IPT initiation and greater disparity in ART initiation between men and women. Policy 2, community-based ART delivery, has a higher ART use than Policy 1, the standard of care. In Policy 3, where both ART and IPT are delivered in the community, both men and women have higher rate of uptake than in Policy 1.

Table 1: Impact of policies to IPT and ART initiation, and adherence

Policy set ID	Policy name	Gender	Gender set ID	ART initiation %	IPT initiation %	IPT adherence %
1	Standard of Care	Male	1	Lowest	6	<6
		Female	2	Low	6	<6
2	Community ART delivery	Male	1	High	6	<6
		Female	2	High	6	<6
3	Community ART and IPT delivery	Male	1	High	91 (50-100)	75?
		Female	2	High	91 (50-100)	75?

1.3 Model's Time Horizon

Time Interval - $0 \leq \tau \leq TT$

The model is solved over a five-year time horizon ($TT = 5$).

1.4 Population

We use $N(\tau, p)$ to denote the size of the full population at time $0 \leq \tau \leq TT$ under policy $p \in P$, summing over all compartments, $t \in TB$, $r \in DR$, $h \in HIV$, $g \in G$. We define $N_{t,r,h,g}(\tau, p)$ as the total population in LTBI, active, or recovered TB compartment t, DR compartment r, HIV compartment h, gender compartment g at time τ under policy p, $t \in TB$, $r \in DR$, $h \in HIV$, $g \in G$, $0 \leq \tau \leq TT$, $p \in P$. For uninfected TB compartments in $N_{t,r,h,g}(\tau, p)$, $t \in \{1, 2\} \subset TB$, it is not possible to distinguish by drug resistance so we do not differentiate by DR compartments when referencing the total population in these TB states. We track movements in population using multi-dimensional matrices that will be used in the supplementary analysis to evaluate the model outputs. The initial population at time $\tau = 0$ is the same for all policies. Table 2 lists the ways the states of population movements are tracked, as well as the notation for force of infection as it changes over time intervals. We use $\lambda(\tau, p)$ to denote the total force of infection at time $0 \leq \tau \leq TT$ under policy $p \in P$. Force of infection calculations are discussed further in Section 2.1.

Notation	Description
$N_{t,r,h,g}(\tau, p)$	Total population in LTBI, active, or recovered TB compartment t, DR compartment r, HIV compartment h, gender compartment g at time τ under policy p, $t \in TB$, $r \in DR$, $h \in HIV$, $g \in G$, $0 \leq \tau \leq TT$, $p \in P$
$\lambda_{r,g}(\tau, p)$	Force of infection for populations in DR compartment r, gender compartment g, at time τ under policy p, $r \in DR$, $g \in G$, $p \in P$, $0 \leq \tau \leq TT$, $p \in P$

Table 2: Model States

1.5 Description of Model Parameters

Notation	Description
	Parameters that impact force of infection
β_g	Number of effective contact for TB transmission per infectious year for gender g, $\forall g \in G$
ϕ_h	Relative transmissibility of TB in populations living in HIV compartment h $\forall h \in HIV$
ε_g	Fraction of new TB infections that are MDR-TB, $\forall g \in G$
ι_r	Indicator for whether infection with given TB strain can occur while on IPT for populations in DR compartment r, $\forall r \in DR$
υ	Indicator the diminished force of infection due to partially-protective effects of IPT after moving off of IPT for populations with LTBI
ζ	Indicator that diminishes force of infection due to the partially-protective effect of LTBI infection and acquiring a new TB infection
	Parameters that describe TB progression
$\kappa_{t,h,g}(p)$	Rate of IPT initiation *from* TB compartment t and HIV compartment h for gender g under policy p, per year, $t \in \{1,3,4\} \subset TB$, $h \in HIV, g \in G, p \in P$
$\varpi_g(p)$	IPT adherence for gender g under policy p, $g \in G, p \in P$
ω	Rate rate of moving off of IPT, per year
$\pi_{i,t}$	Base rates of TB progression of infected populations from TB compartment i to TB compartment t, per year $(i,t) \in TB$ (set to zero where not applicable and not included in equations, as shown in Figure 2 and Section 2 respectively)
θ_h	Relative risk for TB progression from LTBI to Active for HIV compartment h, $h \in HIV$
γ_r	1 if in drug-susceptible, DR compartment $r \in 1 \subset DR$, 0 if in MDR-TB, DR compartment $r \in 2 \subset DR$ to indicate that populations with MDR-TB cannot move into LTBI after IPT
	Parameters that describe HIV progression
$\eta_{i,h,g}(p)$	Rate of populations moving from HIV compartment i to HIV compartment h for gender $g \in G$, per year, $(i,h) \in HIV$ under policy $p \in P$ (set to zero where not applicable, as shown in Figure 1)
	Parameters for death and aging rates
$\mu_{t,h,g}$	Mortality rates from populations in TB compartment t and HIV compartment h and gender compartment g, per year, $\forall t \in TB, \forall h \in HIV, g \in G$
$\alpha^{in}_{t,r,h,g}$	Rate of entry into the population due to aging into TB compartment t, DR compartment r HIV compartment h and gender compartment g, per year, $\forall t \in \{1,3,4,5\} \subset TB, r \in DR, h \in \{1,2\} \subset HIV, g \in G$
α^{out}	Rate of exit from the population due to aging

Table 3: Model Parameters

1.6 Description of Model Transitions: HIV

Transitions between HIV compartments are described in Figure 1. All $\eta_{i,h}$ not illustrated in the figure are set to zero, $\forall(i,h) \in HIV$. Transitions between HIV compartments that are impacted by policy highlighted in Table 1 are highlighted in red.

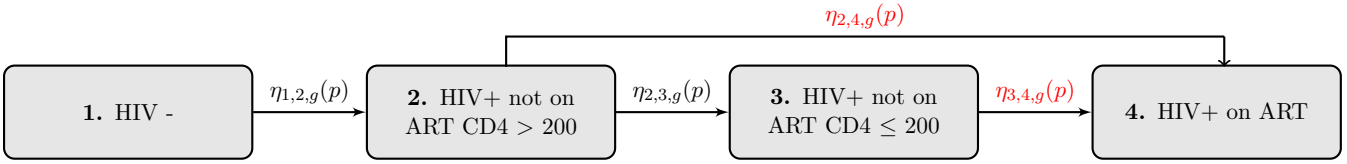

Figure 1: Rates between HIV Compartments

1.7 Description of Model Transitions: TB

Figure 2 illustrates transitions to and from in each TB compartments. The parameters used in the graph are summarised in Table 3, and the notation for the rate the force of infection is described in Table 2. Force of infection calculations are presented in Section 2.1. Transitions between TB compartments that are impacted by policy highlighted in Table 1 are highlighted in red. Transitions that are dependent on DR compartment are highlighted in blue. The transitions that are depended on DR compartment are double lined if this transition can result in populations transitioning between DR compartments (DS and MDR). Active TB TB compartment 6, is highlighted in green because the transitions in and out of this compartment will be the primary focus of the analysis as presented in Section 3.

Note: Uninfected compartments are not distinguished by DR

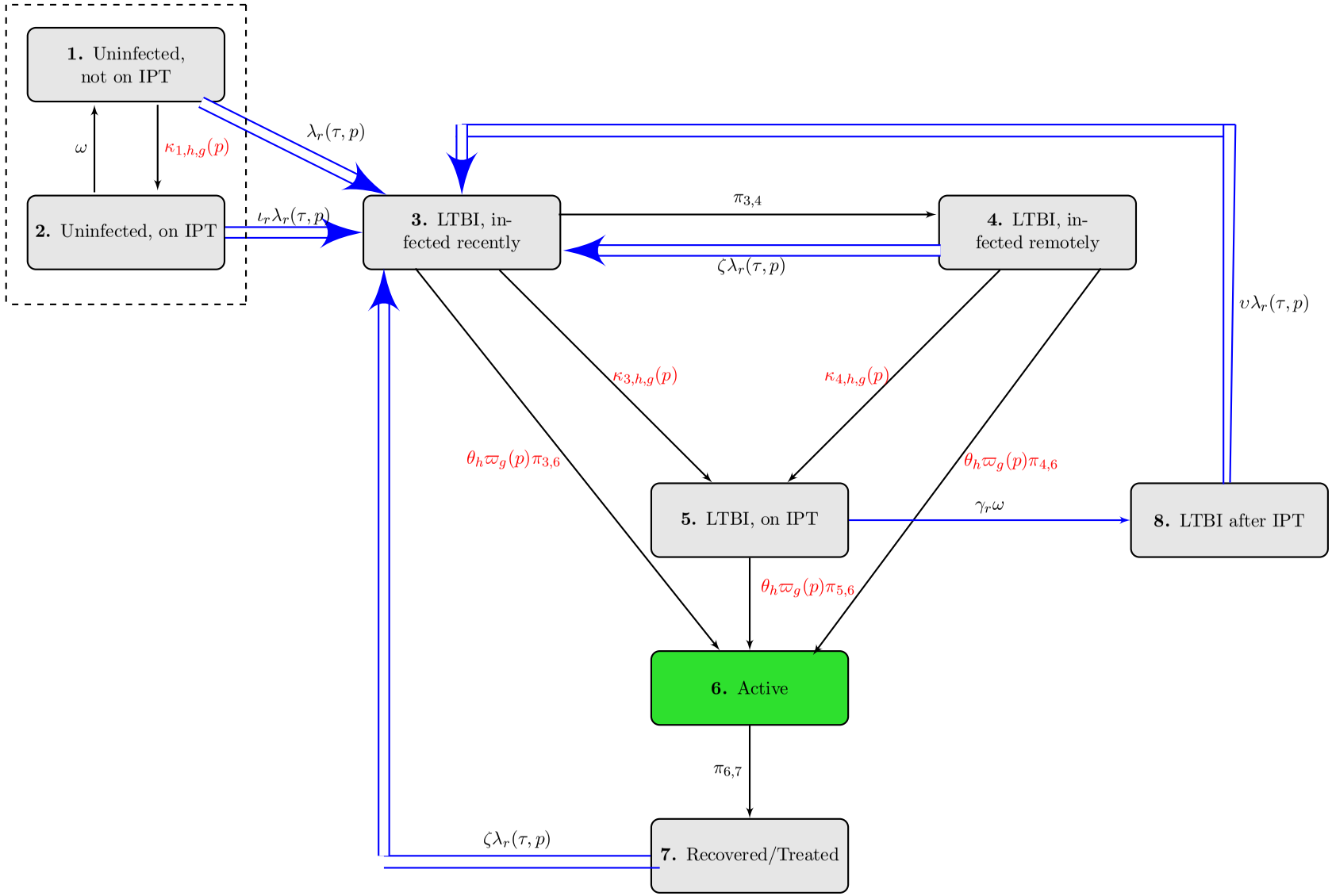

Figure 2: Rates between TB compartments, for each DR compartment r, HIV compartment h, gender compartment g, policy p, and evaluation time interval τ, $r \in DR, h \in HIV, g \in G, p \in P, 0 \leq \tau \leq TT$

2 Model Equations

Force of Infection rates are governed by the set of FOI equations listed in the sub-equations 0. Rates of flow between compartments are governed by the system of ordinary differential equations listed in Equations (1) to (8). The model was programmed in R version 3.5.2, and differential equations were solved with the deSolve package at time steps of one month, or $\frac{1}{12}$ years. The source code for the model is available at `https://github.com/cgreene3/epi_model_HIV_TB`.

2.1 Force of Infection Calculations

The total *Force of Infection* for the entire population at time $0 \leq \tau \leq TT$ under policy $p \in P$ is denoted in the mathematical model as $\lambda(\tau, p)$. We denote $\lambda_{r,g}(\tau, p)$ as the force of infection for the population in gender compartment g, DR compartment r, at time τ under policy p, $\forall g \in G, r \in DR, \tau \in TT, p \in P$. In this mathematical model we distinguish the number of effective contacts for TB transmission, and relative transmissibility of TB by HIV status.

$$\lambda_{1,g}(\tau, p) = \beta_g \left(\frac{\sum_{h \in HIV} \phi_h N_{6,1,h,g}(\tau, p)}{N(\tau)} \right) \qquad \forall g \in G, \tau \in TT, p \in P \qquad \text{(0a)}$$

$$\lambda_{2,g}(\tau, p) = \frac{\varepsilon_g \lambda_{1,g}(\tau, p)}{1 - \varepsilon_g} \qquad \forall g \in G, \tau \in TT, p \in P \qquad \text{(0b)}$$

$$\lambda_r(\tau, p) = \sum_{g \in G} \lambda_{r,g}(\tau, p) \qquad \forall r \in DR, \tau \in TT, p \in P \qquad \text{(0c)}$$

$$\lambda(\tau, p) = \sum_{r \in DR} \lambda_r(\tau, p) \qquad \forall \tau \in TT, p \in P \qquad \text{(0d)}$$

Equation (0a) calculates the force of infection for DS populations, $\{1\} \subset DR$, for each gender. Equation (0b) calculates the force of infection for MDR-TB populations, $\{2\} \subset DR$, by gender. Equation (0c) calculates the force of infection by DR compartment. Equation (0d) calculates the total force of infection.

2.2 Total Rate of Mortality and Exits from the Population Due to Aging

The annual background death rate is differentiated by gender. Since we only evaluate populations between the age of 15 and 65, we also include a parameters $\alpha^{in}_{t,r,h,g}$ and α^{out} to represent aging in and out of the population. We assume aging into the population occurs at a are of $\frac{1}{65-15}$ per year which is the inverse of the duration of time between population entry at age 15 and exit at age 65. We then distribute the entries into the population due to aging into uninfected and latently infected TB compartments($t \in \{1, 3, 4, 5\} \subset TB$), HIV negative and PLHIV not on ART, CD4 > 200 ($h \in \{1, 2\} \subset HIV$) as well as all DR r compartments and gender g compartments, $\forall r \in DR, g \in G$ based on the relative proportion of the initial populations (based on 2017 numbers) from those compartments. We adjust α^{out} to account for the populations that died between the population entry at age 15 and exit at age 65. Note here that $\mu_{t,h,g}, \forall t \in TB, h \in HIV, g \in G$, includes the annual background death rate as well as TB and HIV specific mortality rates. For the purpose of this study, we will focus our analysis as presented in Section 3 on the impact to death rates for populations with Active TB.

2.3 TB Compartment Equations

2.3.1 Uninfected, not on IPT - TB state 1

$$\begin{aligned}\frac{dN_{1,r,h,g}(\tau,p)*}{dt} &= \alpha^{in}_{1,r,h,g}N(\tau,p) \\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{1,r,i,g}(\tau,p) \\ &+ \omega N_{2,r,h,g}(\tau,p) \\ &- \left(\alpha^{out}+\mu_{1,h,g}+\lambda(\tau,p)+\kappa_{1,h,g}(p)+\sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)\right)N_{1,r,h,g}(\tau,p) \qquad (1)\end{aligned}$$

$$\forall r\in DR, h\in HIV, g\in G, 0\leq\tau\leq TT, p\in P$$

**it is important to note, we do not distinguish TB Uninfected, not on IPT compartments by drug resistance.*

Entries
The first line in Equation (1) calculates the entries into TB compartment 1 as a proportion of the population enters at age 15. New entries are assigned to TB uninfected, latent TB, and active TB compartments in proportion to data from population-based surveys []. Similarly, new entries are assigned to HIV compartment h, and gender compartment g, $\forall h\in\{1,2\}\subset HIV, g\in G$. Drug resistance status is not assigned in TB compartment 1 because its population is TB uninfected. The second line in Equation (1) calculates transitions between HIV compartments. The third line in Equation (1) calculates the population returning to compartment 1 from TB compartment 2 as they stop taking IPT.

Exits
The last line in Equation 1 calculates the total population leaving TB compartment 1. Exits from the compartment include aging out, death, TB infection, IPT initiation, and transition between HIV compartments.

2.3.2 Uninfected, on IPT - TB state 2

$$\begin{aligned}\frac{dN_{2,r,h,g}(\tau,p)*}{dt} &= \sum_{i\in HIV,i\neq h}\eta_{i,h,g}(p)N_{2,i,g}(\tau,p) \\ &+ \kappa_{1,h,g}(p)N_{1,h,g}(\tau,p) \\ &- \left(\alpha^{out}+\mu_{2,h,g}+\omega+\sum_{r\in R}\iota_r\lambda_r(\tau,p)+\sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)\right)N_{2,h,g}(\tau,p) \qquad (2)\end{aligned}$$

$$\forall r\in DR, h\in HIV, g\in G, 0\leq\tau\leq TT, p\in P$$

**it is important to note, we do not distinguish TB Uninfected, on IPT compartments by drug resistance.*

Entries
The first line in Equation (2) calculates transitions between HIV compartments. The second line in Equation (2) calculates the entries from the TB uninfected population in TB compartment 1 as they initiate IPT.

Exits
The last line in Equation (2) calculates the total population leaving TB compartment 2. Exits from the compartment include aging out, death, TB infection, movement off of IPT, and transitions between HIV compartments.

2.3.3 LTBI, infected recently - TB state 3

$$\begin{aligned}\frac{dN_{3,r,h,g}(\tau,p)}{dt} &= \alpha^{in}_{3,h,g}N(\tau,p)\\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{3,r,i,g}(\tau,p)\\ &+ \lambda_r(\tau,p)N_{1,r,h,g}(\tau,p)\\ &+ \iota_r\lambda_r(\tau,p)N_{2,r,h,g}(\tau,p)\\ &+ \zeta\lambda_r(\tau,p)(N_{4,r,h,g}(\tau,p)+N_{7,r,h,g}(\tau,p))\\ &+ \upsilon\lambda_r(\tau,p)N_{8,r,h,g}(\tau,p)\\ &- \left(\alpha^{out}+\mu_{3,h,g}+\pi_{3,4}+\kappa_{3,h,g}(p)+\theta_h\varpi_g(p)\pi_{3,6}+\sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)\right)N_{3,r,h,g}(\tau,p)\end{aligned} \tag{3}$$

$$\forall r\in DR, h\in HIV, g\in G, 0\leq\tau\leq TT, p\in P$$

Entries
Line one in Equation (3) calculates entries into TB compartment 3 as a proportion of the population enters at age 15. Line two calculates transitions between HIV states. Lines three and dour in Equation (3) calculate entries as populations develop LTBI from the Uninfected, not on IPT compartment (1) and Uninfected, on IPT compartment (2) respectively. The only entries from the population taking IPT in compartment 2 are due to MDR-TB infection, as IPT is assumed to fully protect against infection by drug-susceptible TB while an individual is taking it.The population in TB compartment 3 has a drug resistance state $r, \forall r\in DR$ assigned even though clinically it would not be known. Line five in Equation (3) calculates rate of reinfection diminished for the partially-protective effect of LTBI against acquiring a new TB infection. Line five in Equation 3 calculates the rate of reinfection diminished due to partially-protective effects of IPT after moving off of IPT for populations with LTBI. For the purpose of this model, we assume in regards to reinfection, that the most recent TB strain type determines the DR compartment.

Exits
The last line in Equation 3 calculates the rate populations leave TB compartment 3. Exits from

the compartment include aging out, death, progression from infected LTBI to active TB, infected recently to infected remotely, movement onto IPT, movement to active TB (relative to HIV state), and transitions between HIV compartments.

2.3.4 LTBI, infected remotely - TB state 4

$$\begin{aligned}\frac{dN_{4,r,h,g}(\tau,p)}{dt} &= \alpha^{in}_{4,h,g}N(\tau,p) \\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{4,r,i,g}(\tau,p) \\ &+ \pi_{3,4}N_{3,r,h,g}(\tau,p) \\ &- \left(\alpha^{out} + \mu_{4,h,g} + \zeta\lambda_r(\tau,p) + \kappa_{4,h,g}(p) + \theta_h\varpi_g(p)\pi_{4,6} + \sum_{i\in HIV, i\neq h}\eta_{h,i,g}(p)\right)N_{4,r,h,g}(\tau,p) \end{aligned} \tag{4}$$

$$\forall r \in DR, h \in HIV, g \in G, 0 \leq \tau \leq TT, p \in P$$

Entries
Line one in Equation (4) calculates entries into TB compartment 4 as a proportion of the population enters at age 15. Line two calculates transitions between HIV compartments. Line three calculates entries due to population movement over time from recent LTBI infection (compartment 3).

Exits
The last line in Equation (4) calculates the rate populations leave TB compartment 4. Exits from the compartment include aging out, death, progression from infected LTBI to active TB, infected recently to infected remotely, movement onto IPT, movement to active TB (relative to HIV state), and transitions between HIV compartments.

2.3.5 LTBI, on IPT - TB state 5

$$\begin{aligned}\frac{dN_{5,r,h,g}(\tau,p)}{dt} &= \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{5,r,i,g}(\tau,p) \\ &+ \kappa_{3,h,g}(p)N_{3,r,h,g}(\tau,p) \\ &+ \kappa_{4,h,g}(p)N_{4,r,h,g}(\tau,p) \\ &- \left(\alpha^{out} + \mu_{5,h,g} + \theta_h\varpi_g(p)\pi_{5,6} + \gamma_r\omega + \sum_{i\in HIV, i\neq h}\eta_{h,i,g}(p)\right)N_{5,r,h,g}(\tau,p) \end{aligned} \tag{5}$$

$$\forall r \in DR, h \in HIV, g \in G, 0 \leq \tau \leq TT, p \in P$$

Entries
Line one in Equation (5) calculates movements between HIV states. Line two and three in Equation 5 calculates the rate at which populations move onto IPT from the LTBI, infected recently and

LTBI, infected remotely compartments.

Exits
The last line in Equation (5) calculates the rate populations leave TB compartment 5. Exits from the compartment include agining out, death, movement to active TB (relative to HIV state), movement into LTBI after IPT, and transitions between HIV compartments. Populations infected with an MDR strain do not have a protective benefit from IPT, and so they cannot move into LTBI after IPT (compartment 8). The parameter γ_r is set to 0 for the population in the MDR state and 1 for the population in the DS state.

2.3.6 Active TB - TB state 6

$$\begin{aligned}\frac{dN_{6,r,h,g}(\tau,p)}{dt} &= \alpha^{in}_{6,r,h,g}N(\tau,p)\\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{6,r,i,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{3,6}N_{3,r,h,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{4,6}N_{4,r,h,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{5,6}N_{5,r,h,g}(\tau,p)\\ &- \left(\alpha^{out}+\mu_{6,h,g}+\pi_{6,7}+\sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)\right)N_{6,r,h,g}(\tau,p) \qquad (6)\\ &\qquad \forall r\in DR, h\in HIV, g\in G, 0\leq\tau\leq TT, p\in P\end{aligned}$$

Entries
Line one in Equation (6) calculates entries into TB compartment 6 as a proportion of the population enters at age 15. Line two calculates transitions between HIV states. Lines three, four, and five calculates the rate at which populations with LTBI who are recently infected, remotely infection, and on IPT, respectively, progress to active TB (relative to HIV state).

Exits
The last line in Equation (6) calculates the rate populations leave TB compartment 6. Exits from the compartment include aging out, death, which includes excess mortality due to TB, recovery/treatment of active TB, and transitions between HIV compartments.

2.3.7 Recovered/Treated - TB state 7

$$\begin{aligned}\frac{dN_{7,r,h,g}(\tau,p)}{dt} &= \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{7,r,i,g}(\tau,p)\\ &+ \pi_{6,7}N_{6,r,h,g}(\tau,p)\\ &- \left(\alpha^{out}+\mu_{7,h,g}+\zeta\lambda_r+\sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)\right)N_{7,r,h,g}(\tau,p) \qquad (7)\end{aligned}$$

$$\forall r \in DR, h \in HIV, g \in G, 0 \leq \tau \leq TT, p \in P$$

Entries
Line one in Equation (7) calculates transitions between HIV compartments. Line two calculates the rate in which populations with active TB are treated and recover.

Exits
The last line in Equation 7 calculates the rate populations leave TB compartment 7. Exits from the compartment include aging out, death, and reinfection, which is diminished for the partially-protective effect of LTBI recovery from TB against acquiring a new TB infection, and transitions between HIV compartments.

2.3.8 LTBI after IPT - TB state 8

$$\begin{aligned}\frac{dN_{8,r,h,g}(\tau,p)}{dt} &= \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(p) N_{8,r,i,g}(\tau,p) \\ &+ \gamma_r \omega N_{5,r,h,g}(\tau,p) \\ &- \left(\alpha^{out} + \mu_{8,h,g} + \upsilon \lambda_r(\tau,p) + \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(p) \right) N_{8,r,h,g}(\tau,p) \end{aligned} \tag{8}$$

$$\forall r \in DR, h \in HIV, g \in G, 0 \leq \tau \leq TT, p \in P$$

Entries
Line one in Equation (8) calculates transitions between HIV states. Line two, calculates the total population that move from the LTBI, on IPT to the LTBI, after IPT compartment based on the rate of populations completing a course of IPT. Populations infected with an MDR strain do not have a protective benefit from IPT, and so they cannot move into LTBI after IPT (compartment 8). The parameter γ_r is set to 0 for the population in the MDR state and 1 for the population in the DS state.

Exits
The last line in Equation (8) calculates the rate populations leave TB compartment 8. Exits from the compartment include aging out, death, the rate at which populations with LTBI after IPT are re-infected with TB, which is diminished due to partially-protective effects of completing a course of IPT, and transitions between HIV compartments.

3 Supplementary Analysis

References

[1] Dowdy, David W., et al. "Impact of isoniazid preventive therapy for HIV-infected adults in Rio de Janeiro, Brazil: an epidemiological model." Journal of acquired immune deficiency syndromes (1999) 66.5 (2014): 552.

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