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 $\leq$ 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 $\eta_{i,h,g}(p)$. 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 $\kappa_{t,h,g}(p)$. 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.

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

For the purpose of this model we keep the size of the population constant over all policies and model's time horizon, $N = 100,000$. 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. In order to keep the population constant we set the total population aging into the model denoted $B(\tau, p)$ to the total population leaving the model due to aging or death. We describe the equations to calculate $B(\tau, p)$ in Section 2.1.

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 initiate all all uninfected populations to DR compartment 1, and only allow entries and exits from DR compartment 1, so that,

$$N_{t,2,h,g}(\tau, p) = 0 \qquad \forall t \in \{1, 2\} \subset TB, h \in HIV, g \in G, 0 \leq \tau \leq TT, p \in P$$

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 is a function of the proportion of the population that has active TB, adjusted by rate of effective contacts, and relative transmissibility of TB by HIV compartment. The equations to calculate $\lambda(\tau, p)$ is described in Section 2.2.

Notation	Description
N	Total population size ($N = 100{,}000$)
$N_{t,r,h,g}(\tau, p)$	Total population in LTBI, active, or recovered TB compartment t, DR compartment r, HIV compartment h, gender compartment g at time τ under policy $p,\ t \in TB,\ r \in DR,\ h \in HIV,\ g \in G,\ 0 \leq \tau \leq TT,\ p \in P$
$B(\tau, p)$	Total population aging into the model $\ 0 \leq \tau \leq TT,\ p \in P$
$\lambda_{r,g}(\tau, p)$	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, $\forall r \in DR$
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, $\forall t \in TB, \forall h \in HIV, g \in G$
$\alpha^{in}_{t,r,h,g}$	Proportion of population that enters into TB compartment t, DR compartment r HIV compartment h and gender compartment g, due to aging, $\forall t \in \{1,3,4,6\} \subset TB, r \in DR, h \in \{1,2\} \subset HIV, g \in G$
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. Transitions between HIV compartments that are impacted by policy highlighted in Table 1 are highlighted in red.

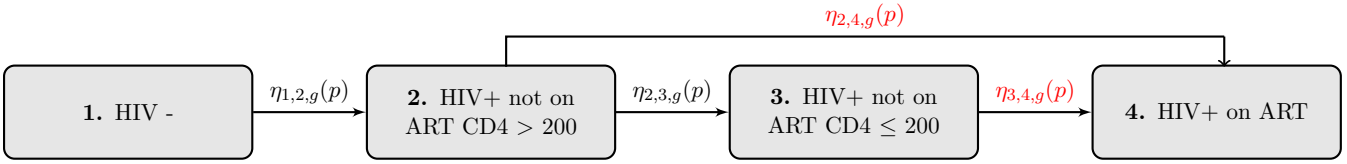

Figure 1: Rates between HIV Compartments

1.7 Description of Model Transitions: TB

Figure 2 illustrates transitions to and from each TB compartment. 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 2.2. Transitions between TB compartments that are impacted by policy highlighted in Table 1 are highlighted in red. Transitions that represent infection from uninfected compartments (compartments 1 and 2) and re-infection from LTBI, and recovered/treated compartments (compartments 4, 7, and 8) are highlighted in blue. For the purpose of this model, we assume in regards to reinfection, that the most recent TB strain type determines an individual's associated DR compartment. 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 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

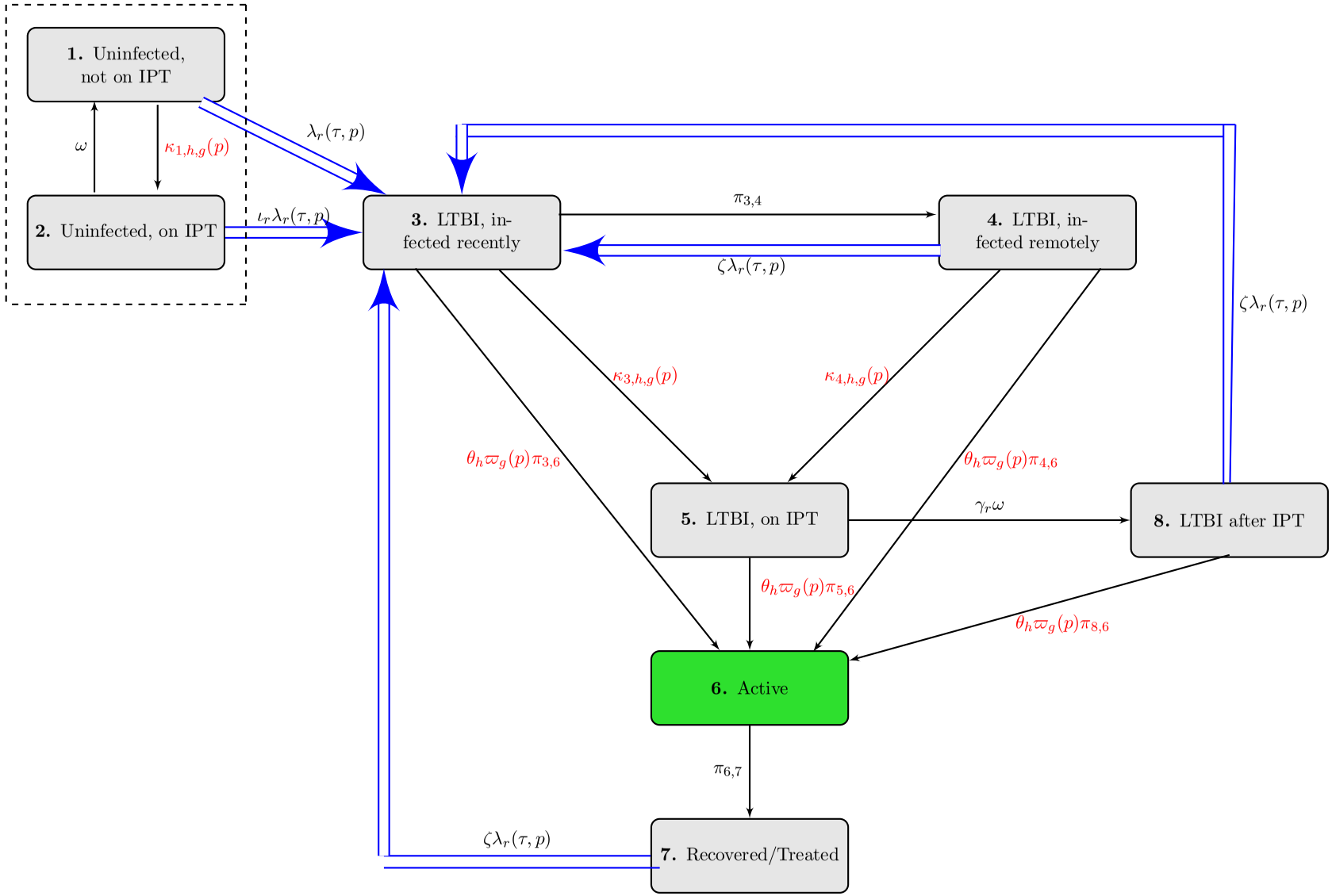

Figure 2: Rates between TB compartments, for each DR compartment r, HIV compartment h, gender compartment g, policy p, and evaluation time interval τ, $r \in DR, h \in HIV, g \in G, p \in P, 0 \leq \tau \leq TT$

2 Model Equations

Entries and exits from the population and force of infection rates are governed by Equation 1b and Equations 2a - 2d respectively. Rates of flow between compartments are governed by the system of ordinary differential equations listed in Equations (3) to (10). 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 Entries and Exits from the Population

For the purpose of this model we assume a constant population of 100,000 denoted by N. Death rates include the annual background death rate is differentiated by gender. Note here that $\mu_{t,h,g}$ for TB compartment t, HIV compartment HIV and gender compartment 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.

We only evaluate populations between the age of 15 and 59, that enter in on their 15th birthday and exit on their 60th birthday, we also include a parameter α^{out} to represent aging in and out of the population. We assume aging into the population occurs at a rate of $\frac{1}{60-15}$ per year which is the inverse of the duration of time between population entry at age 15 and exit at age 65. So we calculate the total population leaving each compartment, by setting it to the total population leaving the model due to death or aging out as in equation (1a) and total population leaving at each time interval τ and policy p as in equation (1b) and set that to the total population aging in.

$$\alpha^{out}_{t,r,h,g} = \mu_{t,h,g} + \alpha^{out} - (\mu_{t,h,g}\alpha^{out}) \qquad \forall t \in TB, r \in DR, h \in HIV, g \in G \qquad (1a)$$

$$B(\tau, p) = \sum_{t \in TB} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} \alpha^{out}_{t,r,h,g} N_{t,r,h,g} \qquad \forall 0 \leq \tau \leq TT, p \in P \qquad (1b)$$

Note: the equation (1a) subtracts $\mu_{t,h,g}\alpha^{out}$ to ensure an individual can only age out, die, but cannot both age out and die. We then distribute the entries into the population due to aging into uninfected and latently infected TB compartments, $t \in \{1, 3, 4, 6\} \subset TB$, 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, based on the relative proportion of the initial populations (based on 2017 numbers) from those compartments, denoted $\alpha^{in}_{t,r,h,g}$.

2.2 Force of Infection Calculations

The total *force of infection* for the entire population at time τ 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. In this mathematical model we distinguish the number of effective contacts for TB transmission, and relative transmissibility of TB by HIV status.

$$\lambda_{1,g}(\tau,p) = \beta_g \left(\frac{\sum_{h \in HIV} \phi_h N_{6,1,h,g}(\tau,p)}{N(\tau)} \right) \qquad \forall g \in G, \tau \in TT, p \in P \tag{2a}$$

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

$$\lambda_r(\tau,p) = \sum_{g \in G} \lambda_{r,g}(\tau,p) \qquad \forall r \in DR, \tau \in TT, p \in P \tag{2c}$$

$$\lambda(\tau,p) = \sum_{r \in DR} \lambda_r(\tau,p) \qquad \forall \tau \in TT, p \in P \tag{2d}$$

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

2.3 TB Compartment Equations

2.3.1 TB compartment 1 - Uninfected, not on IPT

$$\begin{aligned} \frac{dN_{1,1,h,g}(\tau,p)*}{dt} &= \alpha^{in}_{1,r,h,g} B(\tau,p) \\ &+ \omega N_{2,r,h,g}(\tau,p) \\ &- \alpha^{out}_{1,1,h,g} N_{1,1,h,g}(\tau,p) \\ &- \lambda(\tau,p) N_{1,1,h,g}(\tau,p) \\ &- \kappa_{1,h,g}(p) N_{1,1,h,g}(\tau,p) \\ &+ \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(p) N_{1,1,i,g}(\tau,p) \\ &- \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(p) N_{1,1,h,g}(\tau,p) \end{aligned} \tag{3}$$

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

**it is important to note, we do not distinguish TB Uninfected, not on IPT compartments by drug resistance, and as such, all initial uninfected populations are assigned to DR compartment 1, and and all exits and entries into TB Uninfected compartments are from DR compartment 1.*

Equation (3) *Description*
The first line in Equation (3) 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. Drug resistance status is not assigned in TB compartment 1 because its population is TB uninfected. The second line calculates the population returning to compartment 1 from TB compartment 2 as they stop taking IPT. The third, forth and fifth line of the equation calculates the total population leaving from deaths and

aging out, from infection and going onto IPT respectively. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.2 TB compartment 2 - Uninfected, on IPT

$$\begin{aligned}\frac{dN_{2,1,h,g}(\tau,p)*}{dt} &= \kappa_{1,h,g}(p)N_{1,1,h,g}(\tau,p) \\ &- \alpha^{out}_{2,1,h,g}N_{2,1,h,g}(\tau,p) \\ &- \omega N_{2,1,h,g}(\tau,p) \\ &- \sum_{r\in DR} \iota_r \lambda_r(\tau,p)N_{2,1,h,g}(\tau,p) \\ &+ \sum_{i\in HIV, i\neq h} \eta_{i,h,g}(p)N_{2,1,i,g}(\tau,p) \\ &- \sum_{i\in HIV, i\neq h} \eta_{h,i,g}(p)N_{2,1,h,g}(\tau,p) \end{aligned} \tag{4}$$

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

**it is important to note, we do not distinguish TB Uninfected, not on IPT compartments by drug resistance, and as such, all initial uninfected populations are assigned to DR compartment 1, and and all exits and entries into TB Uninfected compartments are from DR compartment 1.*

Equation (4) *Description*
The first line in Equation (4) calculates the entries from the TB uninfected population in TB compartment 1 as they initiate IPT. The second, third and forth lines calculate exists from aging out and dying, going off of IPT, and infection. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.3 TB compartment 3 - LTBI, infected recently

$$
\begin{aligned}
\frac{dN_{3,r,h,g}(\tau,p)}{dt} \quad &= \alpha^{in}_{3,r,h,g} B(\tau,p) \\
&+ \lambda_r(\tau,p) N_{1,1,h,g}(\tau,p) \\
&+ \iota_r \lambda_r(\tau,p) N_{2,1,h,g}(\tau,p) \\
&+ \zeta \lambda_r(\tau,p) \sum_{r \in DR} (N_{4,r,h,g}(\tau,p) + N_{7,r,h,g}(\tau,p)) \\
&+ \upsilon \lambda_r(\tau,p) \sum_{r \in DR} N_{8,r,h,g}(\tau,p) \\
&- \alpha^{out}_{3,r,h,g} N_{3,r,h,g}(\tau,p) \\
&- \pi_{3,4} N_{3,r,h,g}(\tau,p) \\
&- \kappa_{3,h,g}(p) N_{3,r,h,g}(\tau,p) \\
&- \theta_h \varpi_g(p) \pi_{3,6} N_{3,r,h,g}(\tau,p) \\
&+ \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(p) N_{3,r,i,g}(\tau,p) \\
&- \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(p) N_{3,r,h,g}(\tau,p) \qquad (5)
\end{aligned}
$$

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

Equation (5) *Description*
Line one in Equation (5) calculates entries into TB compartment 3 as a proportion of the population enters at age 15. Lines two through five calculate entries from infections (and re-infections) from compartments 1,2,4,7, and 8 diminished for the partially protective effects of IPT from compartment 2, and LTBI infection from compartments 4,7, and 8. For the purpose of this model, we assume in regards to reinfection, that the most recent TB strain type determines the DR compartment. As such, we sum the total populations from compartments 4,7, and 8 over drug-resistant compartments to allow populations to transition between DR compartments (DS and MDR). Lines three to six calculate exits due to aging out and dying, from recent to remote, going onto IPT, and progression to active TB, respectively. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.4 TB compartment 4 - LTBI, infected remotely

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

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

Equation (6) *Description*
Line one in Equation (6) calculates entries into TB compartment 4 as a proportion of the population enters at age 15. Line two calculates entries from LTBI, recent to remote. Lines three to six calculate exits due to infection, which is diminished for the partially-protective effect of LTBI recovery from TB against acquiring a new TB infection, going onto IPT and progression to active TB, respectively. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.5 TB compartment 5 - LTBI, on IPT

$$\begin{aligned}\frac{dN_{5,r,h,g}(\tau,p)}{dt} &= \kappa_{3,h,g}(p)N_{3,r,h,g}(\tau,p)\\ &+ \kappa_{4,h,g}(p)N_{4,r,h,g}(\tau,p)\\ &- \alpha^{out}_{5,r,h,g}N_{5,r,h,g}(\tau,p)\\ &- \theta_h\varpi_g(p)\pi_{5,6}N_{5,r,h,g}(\tau,p)\\ &- \gamma_r\omega N_{5,r,h,g}(\tau,p)\\ &+ \sum_{i\in HIV,i\neq h}\eta_{i,h,g}(p)N_{5,r,i,g}(\tau,p)\\ &- \sum_{i\in HIV,i\neq h}\eta_{h,i,g}(p)N_{5,r,h,g}(\tau,p) \qquad (7)\end{aligned}$$

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

Equation (7) *Description*
Line one and two in Equation (7) calculates the rate at which populations move onto IPT from the LTBI, infected recently and LTBI, infected remotely compartments. Lines three to five calculates

exits due to aging out and dying, active TB progression, and going onto IPT, respectively. 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. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.6 TB compartment 6 - Active TB

$$\begin{aligned}\frac{dN_{6,r,h,g}(\tau,p)}{dt} &= \alpha^{in}_{6,r,h,g}B(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{3,6}N_{3,r,h,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{4,6}N_{4,r,h,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{5,6}N_{5,r,h,g}(\tau,p)\\ &+ \theta_h\varpi_g(p)\pi_{8,6}N_{8,r,h,g}(\tau,p)\\ &- \alpha^{out}_{6,r,h,g}N_{6,r,h,g}(\tau,p)\\ &- \pi_{6,7}N_{6,r,h,g}(\tau,p)\\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{6,r,i,g}(\tau,p)\\ &- \sum_{i\in HIV, i\neq h}\eta_{h,i,g}(p)N_{6,r,h,g}(\tau,p) \qquad (8)\end{aligned}$$

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

Equation (8) *Description*
Line one in Equation (8) calculates entries into TB compartment 8 as a proportion of the population enters at age 15. Line two to five calculate 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). Lines six and seven calculate exits due to aging out and dying, and from recovery, respectively. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.7 TB compartment 7 - Recovered/Treated

$$\begin{aligned}\frac{dN_{7,r,h,g}(\tau,p)}{dt} &= \pi_{6,7}N_{6,r,h,g}(\tau,p)\\ &- \alpha^{out}_{7,r,h,g}N_{7,r,h,g}(\tau,p)\\ &- \zeta\lambda N_{7,r,h,g}(\tau,p)\\ &+ \sum_{i\in HIV, i\neq h}\eta_{i,h,g}(p)N_{7,r,i,g}(\tau,p)\\ &- \sum_{i\in HIV, i\neq h}\eta_{h,i,g}(p)N_{7,r,h,g}(\tau,p) \qquad (9)\end{aligned}$$

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

Equation (9) *Description*
Line one calculates entries into recovered/treated, at the rate at which populations with active TB are treated and recover. Lines two and three calculate exits due to aging out and dying, and from re-infection, which is diminished for the partially-protective effect of LTBI recovery from TB against acquiring a new TB infection. The last two lines calculate transitions between HIV compartments, for entries and exits.

2.3.8 TB compartment 8 - LTBI after IPT

$$\begin{aligned}\frac{dN_{8,r,h,g}(\tau,p)}{dt} &= \gamma_r \omega N_{5,r,h,g}(\tau,p) \\ &- \theta_h \varpi_g(p) \pi_{8,6} N_{8,r,h,g}(\tau,p) \\ &- \alpha^{out}_{8,r,h,g} N_{8,r,h,g}(\tau,p) \\ &- \zeta \lambda(\tau,p) N_{8,r,h,g}(\tau,p) \\ &+ \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(p) N_{8,r,i,g}(\tau,p) \\ &- \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(p) N_{8,r,h,g}(\tau,p) \end{aligned} \tag{10}$$

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

Entries
Line one 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. Lines three through six calculate exits due to progression to active TB, from aging out and dying, and from re-infection, which is diminished for the partially-protective effect of LTBI recovery from TB against acquiring a new TB infection. The last two lines calculate transitions between HIV compartments, for entries and exits.

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.

[2] "COMMUNITY ART INCREASES VIRAL SUPPRESSION AND ELIMINATES DISPARITIES FOR AFRICAN MEN". 2020. https://www.croiconference.org/abstract/community-art-increases-viral-suppression-and-eliminates-disparities-for-african-men/

[3] "TB PREVENTIVE THERAPY UPTAKE IS HIGH WITH COMMUNITY ART DELIVERY IN SOUTH AFRICA" https://www.croiconference.org/abstract/tb-preventive-therapy-uptake-high-community-art-delivery-south-africa/. 2020.