# Preventing tuberculosis with community-based care in an HIV-endemic setting: a modeling analysis

**Supplemental Digital Content 1**

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## Contents

# 1 Model Description

We developed a dynamic transmission model for tuberculosis (TB) and human immunodeficiency virus (HIV) disease progression that is compartmentalized by TB stage, HIV stage, TB and HIV treatment status, TB drug resistance status, and gender. We use the model to evaluate the impacts of increased uptake of antiretroviral therapy (ART) and isoniazid preventive therapy (IPT) observed in the community-based intervention of the Delivery Optimization for Antiretroviral Therapy (DO ART) trial [4], compared to standard facility-based care. The model projects health outcomes, including TB incidence, TB mortality, TB and HIV prevalence, and disability-adjusted life years. We developed a cost model that uses projections from the dynamic transmission model to generate costs of TB and HIV care from the program perspective. We use these metrics to calculate incremental health outcomes and costs, and cost-effectiveness ratios to evaluate the cost-effectiveness of community-based programs compared to standard facility-based care.

## 1.1 Dynamic Transmission Model

The model considers eight TB compartments, two TB drug resistance (DR) compartments, four HIV compartments, and two gender compartments described in Section 1.1.1. The model considers a population of 100,000 adults ages 15-59 in Kwazulu-Natal, South Africa, as described in Section 1.1.2. Rates of flow between each compartment that reflect TB and HIV disease progression and entries and exits from the model are summarised in Section 1.1.3. Outputs generated by the model are described in Section 1.1.4.

### 1.1.1 Model Compartments

*Set of Tuberculosis (TB) Compartments*: $t \in TB$

The model consists of uninfected, latent TB infection (LTBI), active TB, and recovered/treated TB compartments. We separate LTBI compartments into recent (less than two years since exposure) and remote (at least two years after exposure to TB) to account for the difference in risk of progression [8, 11, 13, 23]. Those who are uninfected or have LTBI can initiate IPT. We include a compartment for LTBI after IPT to account for the reduced risk of progression to active TB after completion of IPT [1, 9, 26]. This yields eight TB compartments. We define the set of TB compartments as:

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

*Set of Tuberculosis Drug Resistance (DR) Compartments*: $r \in DR$

The model differentiates drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB) infections. We define MDR-TB as resistant to IPT and rifampicin. Uninfected individuals on IPT have a reduced risk of acquiring DS LTBI [10], but we assume no reduced risk of acquiring

MDR LTBI. Individuals with DS LTBI on IPT have a reduced risk of progression to active TB [2, 3, 6, 20, 30, 33], but we assume those with MDR LTBI on IPT do not benefit from a reduced risk of progression to active TB. We define the set of DR compartments as:

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

For individuals who are uninfected (TB compartments 1 or 2), it is not possible to distinguish by DR status, so all individuals in TB compartments 1 and 2 are assigned to DR compartment 1. We only allow individuals with DS LTBI (TB compartments 3 or 4 and DR compartment 1) to enter LTBI on IPT (TB compartment 5) and subsequently LTBI after IPT (TB compartment 8). As such, the possible combinations of TB and DR compartments are:

TB compartment 1, DR compartment $r = 1$ only
TB compartment 2, DR compartment $r = 1$ only
TB compartment 3, both DR compartments $r = 1$ and $r = 2$
TB compartment 4, both DR compartments $r = 1$ and $r = 2$
TB compartment 5, DR compartment $r = 1$ only
TB compartment 6, both DR compartments $r = 1$ and $r = 2$
TB compartment 7, both DR compartments $r = 1$ and $r = 2$
TB compartment 8, DR compartment $r = 1$ only

*Set of HIV Compartments*: $h \in HIV$

The model consists of four HIV compartments that are differentiated by their relative transmissibility of TB, risk of progression from LTBI to active TB, duration of active TB and mortality rates [2, 3, 6, 16, 20, 24, 30, 33] cite(missing mort references). Only people living with HIV (PLWH) are eligible to initiate ART, and only those on ART initiate IPT treatment [4]. We define the set of HIV compartments as:

1. HIV-
2. HIV+, not on ART, CD4 $>$ 200
3. HIV+, not on ART, CD4 $\leq$ 200
4. HIV+, and on ART

*Set of Gender Compartments*: $g \in G$

The model consists of two gender compartments that are differentiated by effective contact rates, rate of IPT and ART initiation, HIV infection and CD4 decline and mortality rates [14, 15, 19, 22, 27, 28]. We define the set of gender compartments as:

1. Male
2. Female

### 1.1.2 Population

The model includes an adult population between the ages of 15 and 59 with no immigration or emigration. We define $N_{t,r,h,g}(\tau)$ as the total population in TB compartment $t$, DR compartment

$r$, HIV compartment $h$, and gender compartment $g$ at time $\tau$. For the purpose of this model, we keep the size of the population constant at all time steps such that

$$\sum_{t \in TB} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} N_{t,r,h,g}(\tau) = 100,000.$$

We keep the population constant by setting the total amount of population entering the model to the total amount exiting the model (due to aging out or dying). Some proportion of the population aging into the model ages into TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, infected recently), 4 (LTBI, infected remotely), and 6 (active TB), both DR compartments, HIV compartments 1 (HIV-) and 2 (HIV+, not on ART, CD4>200), and both gender compartments. We account for changes in population characteristics of those aging into the model over time by adjusting the proportion of the population aging into each TB, HIV, and gender according to yearly estimates from the 2019 Global Burden of Disease (GBD) study for Kwazulu-Natal, SA, and dynamic parameters (e.g., HIV infection rates) [12].

### 1.1.3 Model Transitions

Rates of flow between each compartment are governed by differential equations as described in Section 2.2. Transitions that describe TB and HIV disease progression are illustrated in Figure 1 and Figure 2. Although not depicted in Figure 1 and Figure 2, there are entries to reflect those aging into the model and exits in the model due to aging out or dying as described at the end of this section. The description and notation for the parameters used in these transitions are summarized in Table 1, where time-varying parameters are indicated by $\tau$. The time-varying parameters in Table 1 that are calculated using population states, specifically TB force of infection rates for populations in DR compartment $r$ at time $\tau$, $\lambda_r(\tau)$, ART initiation rates for gender $g$, $\eta_{2,4,g}(\tau)$ and $\eta_{3,4,g}(\tau)$, the total population entering the model, $B(\tau)$, and rates of exits from mortality and aging-out, $\alpha^{out}_{t,r,h,g}(\tau)$, are calculated using the equations defined in Section 2.1. The parameters that are directly impacted by care delivery programs (ART and IPT initiation rates) are highlighted in green in Figure 1, Figure 2, Table 1 and Table 2. The equations used to describe model transitions are described in Section 2.2.

*TB disease progression*

Figure 1 illustrates transitions to and from each TB compartment with words and mathematical notation as in Table 1. Care delivery programs that directly impact IPT initiation rates are highlighted in green. The primary focus of the analysis is the impact of different programs on active TB (TB compartment 6), as highlighted in red, including TB incidence rates (the number of individuals moving into the active TB compartment per year) and TB mortality rates (the number of individuals who die in active TB compartment, per year).

Individuals exit TB compartment 1 (uninfected, not on IPT) through TB infection or IPT initiation. While all individuals in TB compartment 1 are arbitrarily assigned to DR compartment 1 ($r = 1$), when transitioning to TB compartment 3 (LTBI, infected recently), the force of infection is differentiated by drug resistance status ($\lambda_r(\tau)$), which is based on a proportion of those infected with DS-TB and MDR-TB. Uninfected individuals who initiate IPT enter TB compartment 2 (uninfected, on IPT) and DR compartment 1 ($r = 1$). Individuals in TB compartment 2 (uninfected, on IPT) that contract TB while on IPT and transition to TB compartment 3 (LTBI, infected recently) are differentiated by drug resistance status according to the force of infection ($\lambda_r(\tau)$) and a parameter that accounts for the reduced risk of infection of DS-TB while on IPT ($\iota_r$).

| Notation | Description |
|---|---|
| **Parameters that impact TB infection** | |
| $\lambda_r(\tau)$ | The force of infection for populations in DR compartment $r$ at time $\tau$ |
| $\iota_r$ | Diminished risk of acquiring a latent TB infection for those exposed to DS-TB while on IPT, such that $0 < \iota_1 < 1$ and $\iota_2 = 1$. |
| $\xi$ | Increased risk of reinfection after recovery/treatment of active TB |
| $\zeta$ | Partially-protective effect of LTBI against acquiring a new TB infection |
| **Parameters that describe TB progression** | |
| $\omega$ | Rate of moving off of IPT, per year |
| $\gamma_r$ | Indicator to reflect that those infected with MDR LTBI do not yield benefits of IPT, such that $\gamma_1 = 1, \gamma_2 = 0$ |
| $\pi_{3,4}$ | Rate of TB progression from recent LTBI to remote LTBI, per year |
| $\pi_{3,6}$ | Rate of TB progression from recent LTBI to active TB, per year |
| $\pi_{4,6}$ | Rate of TB progression from remote LTBI to active TB, per year |
| $\theta_h$ | Relative risk for TB progression from LTBI to active TB by HIV compartment $h$, where those who are HIV negative ($h = 1$) progress at the base rate, $\theta_1 = 1$, and $\theta_h$ for $h = 2, 3, 4$ accounts for an increased risk of TB progression, $\theta_h > 1$ |
| $\pi_{5,6}$ | Rate of TB progression from LTBI on IPT to active TB, per year |
| $\pi_{7,6}$ | Rate of relapse from recovered/treated to active TB, per year |
| $\pi_{8,6}$ | Rate of TB progression from LTBI after IPT to active TB, per year |
| $\pi_{6,7}$ | Rate of recovery/treatment from active TB, per year |
| $\upsilon_h$ | Relative reduction of recovery/treatment rate by HIV compartment $h$, to reflect delays in TB treatment, $0 < \upsilon_h \leq 1$ |
| $\kappa_{h,g}(\tau)$ | Rate of IPT initiation from HIV compartment $h$ for gender $g$ at time $\tau$, per year, where only PLWH and on ART initiate IPT, such that $\kappa_{h,g} = 0$ for $h = \{1, 2, 3\}$ and for all $g$ |
| **Parameters that describe HIV progression** | |
| $\eta_{1,2,g}(\tau)$ | HIV incidence rate for gender $g$ at time $\tau$, per year, HIV compartment 1 (HIV-) to 2 (HIV+, not on ART, CD4 $>$ 200) |
| $\eta_{2,3,g}$ | Rate of HIV progression from HIV compartment 2 (HIV+, not on ART, CD4 $>$ 200 to HIV compartment 3 (HIV+, not on ART, CD4 $\leq$ 200 for gender $g$ |
| $\eta_{2,4,g}(\tau)$ | ART initiation rate from HIV compartment 2 (HIV+, not on ART, CD4 $>$ 200) to HIV compartment 4 (HIV+, on ART) for gender $g$ at time $\tau$, per year. |
| $\eta_{3,4,g}(\tau)$ | ART initiation rate from HIV compartment 3 (HIV+, not on ART, CD4 $\leq$ 200) to HIV compartment 4 (HIV+, on ART) for gender $g$ at time $\tau$, per year. |
| **Parameters that describe entries and exits from the population** | |
| $B(\tau)$ | Population aging into the model at time $\tau$ |
| $\alpha^{out}_{t,h,g}(\tau)$ | Rate of the population exiting the model due to mortality or aging out in TB compartment $t$, HIV compartment $h$, and gender compartment $g$ at time $\tau$, per year. |
| $\alpha^{in}_{t,r,h,g}(\tau)$ | Proportion of population that enters into TB compartment $t$, DR compartment $r$, HIV compartment $h$, and gender compartment $g$ at time $\tau$ due to aging in. |

Table 1: Description and notation for parameters used in the equations that describe TB and HIV disease progression, treatment rates, and entries and exits from the model. Time-varying parameters are notated as functions of $\tau$. Parameters that depend on the care delivery program are highlighted in green.

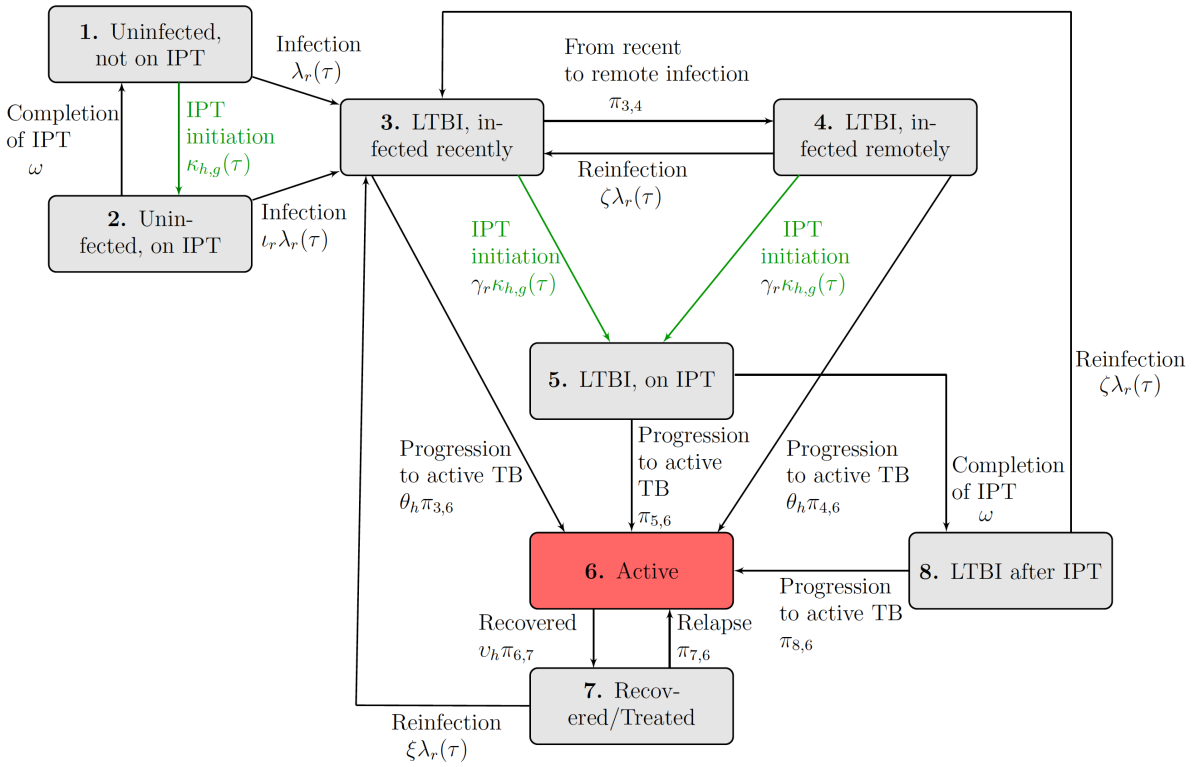



Figure 1: Illustration of TB transition rates for each DR compartment $r$, HIV compartment $h$, and gender compartment $g$ at time $\tau$, with model parameters in mathematical notation as defined in Table 1. Although not visualized here, each TB compartment is stratified across two TB drug-resistance, four HIV, and two gender compartments. Care delivery programs directly impact the rate of IPT initiation rates (highlighted in green). TB compartment 6 (active TB) is highlighted in red to emphasize the compartment capturing key model outputs of TB incidence and mortality.

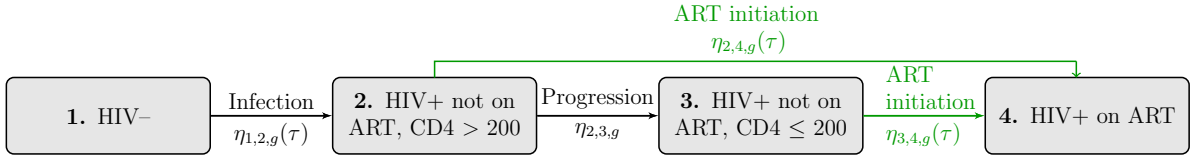



Figure 2: Illustration of HIV transitions between HIV compartments for each gender compartment $g$ at time $\tau$. ART initiation rates (highlighted in green) are directly impacted by ART coverage for each care delivery program. Although not visualized here, each HIV compartment is stratified across eight TB, two TB drug resistance, four HIV, and two gender compartments.

The transition rate for all those that move into TB compartment 3 (LTBI, infected recently) by reinfection (from TB compartments 4, 7, and 8) accounts for the individual's most recent TB strain type. Those in TB compartments 4 and 8 (LTBI, infected remotely, and LTBI after IPT) may be infected by DS-TB ($r = 1$) or MDR-TB ($r = 2$). The force of infection determines the transition rate of reinfection $\lambda_r(\tau)$ and the partially-protective effect of LTBI against acquiring a new TB infection ($\zeta$). However, individuals in TB compartment 7 (Recovered/Treated) have an increased

risk of reinfection, where the force of infection is modified by an increased risk of reinfection ($\xi$).

Some proportion of individuals in TB compartment 3 (LTBI, infected recently) will progress to TB compartment 4 (LTBI, infected remotely) after two years, TB compartment 6 (active TB), or TB compartment 5 (LTBI, on IPT). We assume only PLWH on ART will initiate IPT, which is captured by the IPT initiation rates. We assume individuals with MDR LTBI do not benefit from a reduced risk of progression to active TB (TB compartment 6) by disallowing those with MDR LTBI to move into TB compartment 5 (LTBI, on IPT) and subsequently TB compartment 8 (LTBI, after IPT). Those with LTBI who complete their course of IPT move into TB compartment 8 (LTBI after IPT) to account for the reduced risk of progression even after completing their IPT course.

Individuals who progress to TB compartment 4 (LTBI, infected remotely) have a reduced risk of progression to active TB compared to those in TB compartment 3 (LTBI, infected recently). PLWH have an increased risk of progression to TB compartment 6 (active TB). Rates of recovery are differentiated by HIV status to represent varying expected delays to treatment. A proportion of those who recover from active TB will relapse or become reinfected.

*HIV disease progression*

Figure 2 illustrates transitions to and from each HIV compartment in words and with mathematical notation as defined in Table 1. ART initiation rates are highlighted in green to indicate that the care delivery program directly impacts them. Those in HIV compartment 1 (HIV-) are infected according to infection rate estimates over time for each gender. Some proportion of those in HIV compartment 2 (HIV+, not on ART, CD4 $>$ 200) will initiate ART and transition into HIV compartment 4 (HIV+, on ART), and others experience CD4 decline and transition into HIV compartment 3 (HIV+, not on ART, CD4 $\leq$ 200). Net ART initiations from HIV compartment 2 (HIV+, not on ART, CD4 $>$ 200) and HIV compartment 3 (HIV+, not on ART, CD4 $\leq$ 200) are based on ART coverage estimates over time by gender and the guidance on eligibility for PLWH to initiate ART based on their CD4 count.

*Entries and exits*

Although not depicted in Figure 1 and Figure 2, transitions for entries and exits to the model are used to maintain constant population size. We keep the size of the population constant by setting entries from aging-in equal to exits from aging-out or dying. Individuals can age into the model into TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, infected recently), 4 (LTBI, infected remotely), and 6 (active TB), both DR compartments, HIV compartments 1 (HIV-) and 2 (HIV+, not on ART, CD4 $>$ 200), and both gender compartments. All compartments include exit transitions from aging out or dying.

### 1.1.4 Model Outputs

The model projects TB incidence, TB mortality, TB and HIV prevalence, and disability-adjusted life years (DALYs) based on population states and transition rates. DALYs are representative of years of life lost (YLL) and years lived with disability (YLD) for TB and HIV disease. The equations used to calculate these metrics are described in Section 4. During the intervention period, we generate model outputs for three care delivery programs described in the next section, Section 1.2.

## 1.2 Care Delivery Programs

We executed the model for three care delivery programs including:

- *Program 1:* Standard facility-based ART and IPT care
- *Program 2:* Community-based ART care delivery with standard facility-based IPT care, and
- *Program 3:* Community-based ART and IPT care delivery.

The parameters that depend on the care delivery program are IPT initiation rates and ART coverage. These parameters are estimated using observational data from the DO ART trial [4]. Community-based care delivery programs aim to increase ART coverage and IPT initiation [4]. While all PLWH in the DO ART trial were diagnosed with HIV, in our model we include PLWH who do not know their status. We assume that only those who are virally suppressed experience the benefits of ART.

We evaluate these programs over a 10-year intervention period. We assume that programs take full effect at the start of the 10-year intervention period, such that ART coverage and IPT initiation assumptions for each program immediately increase at the beginning of the intervention period and are held constant over the 10-year intervention period. Only PLWH not on ART (in HIV compartments 2 and 3) initiate ART, and only PLWH on ART (in HIV compartment 4) initiate IPT.

The standard of care, Program 1, reflects the levels of ART coverage and IPT initiation observed among participants in the standard facility-based care arm of the DO ART trial [4]. Community-based ART was tested in the DO ART trial with a community-based IPT delivery program (Program 3); however, we additionally test community-based ART without community-based IPT (Program 2) by setting IPT initiation rates among all PLWH to the same rate as the IPT standard of care scenario.

In Figure 1, Figure 2, and Table 1, parameters that are directly impacted by the care delivery program are highlighted in green. ART initiation rates are calculated based on ART coverage observations using the equations described in Section 2.1.

## 1.3 Cost Model

The cost model generates costs of TB and HIV care, including costs to administer ART, IPT, TB, and HIV care. The cost to distribute ART is based on the number of individuals in HIV compartment 4 (HIV+, on ART) and the yearly cost to provide ART under community-based and facility-based programs. Costs for community-based ART care delivery are higher than costs for standard facility-based ART care delivery to reflect additional costs for the additional cadre of health workers and other resources needed to deliver community-based care. The annual cost of community ART delivery is based on a micro-costing study conducted during the DO ART trial under the "efficient at scale" scenario (cite).

The cost to administer IPT is based on the number of individuals on IPT (TB compartments 2 and 5), the medication costs, provider time for counseling, and provider laboratory costs associated with drug-induced liver injury from IPT over a six-month course of IPT. Since community-based IPT is delivered in conjunction with community-based ART (Program 3), the additional costs for community-based care are reflected in ART community-based costs. We assume costs to administer IPT through facility-based and community-based care are the same.

TB care costs are based on the number of individuals with active TB (TB compartment 6) and are differentiated by TB drug-resistance status to reflect different treatment regimens for DS-TB and MDR-TB. HIV care costs are based on the number of PLWH (HIV compartments 2, 3, and 4)

without TB (not in TB compartment 6) and are differentiated by HIV compartment to reflect the difference in projected inpatient and outpatient care costs based on CD4 count and ART status. As TB is a leading cause of hospitalization of PLWH in South Africa, we subtract the costs of TB-related hospitalization from the total reported HIV inpatient care costs to generate estimates of the annual cost of inpatient care for causes other than TB. The cost model for each care delivery program is described in Section 4.5.

### 1.4 Incremental Health Outcomes and Costs

We quantify discounted and undiscounted health outcomes, including TB incident cases, TB deaths, and DALYs, and costs for each program over the 10-year intervention period. We use these metrics to generate incremental cost-effectiveness ratios (ICERs) to assess the undiscounted and discounted per-dollar cost per incident TB case averted, TB death averted, and DALY averted of community-based programs compared to facility-based programs, including:

- Community-based ART with standard facility-based IPT (Program 2) to standard facility-based ART and IPT (Program 1) to quantify incremental health gains and additional costs of a community-based ART intervention,
- Community-based ART with IPT (Program 3) compared to standard facility-based ART and IPT (Program 1) to quantify incremental health gains and additional costs of a community-based ART and IPT intervention, and
- Community-based ART with IPT (Program 3) compared to community-based ART with standard facility-based IPT (Program 2) to quantify incremental health gains and additional costs of a community-based IPT intervention (assuming community-based ART is already implemented).

The equations used to generate ICERs are described in Section 4.6.

## 2 Dynamic Transmission Model Equations

Time-varying parameters that are calculated based on current population states at each time step $\tau$, including TB force of infection calculations, ART initiations, and population entries and exits, are governed by the equations described in Section 2.1. Rates of flow between compartments are governed by the system of ordinary differential equations defined in Section 2.2.

### 2.1 Time-Varying Parameters Impacted by Population States

A description of the parameters used in the calculations of TB force of infection calculations, ART initiation rates, and entries to and exits from the population is given in Table 2. These parameters are calculated based on the total population in TB compartment $t$, DR compartment $r$, HIV compartment $h$, and gender compartment $g$ at time $\tau$ denoted $N_{t,r,h,g}(\tau)$.

#### 2.1.1 TB Force of Infection

The TB force of infection for DR compartment $r$ at time $\tau$ is denoted $\lambda_r(\tau)$, and is calculated at each time step using Equations (A) through (C). The number of individuals infected with active DS-TB (in HIV compartment 6 and DR compartment 1), HIV compartment $h$, and gender $g$ at time $\tau$ is indicated by $N_{6,1,h,g}(\tau)$. Relative transmissibility varies by HIV compartment $h$, and is represented by the parameter $\phi_h$ [16, 24]. The estimated fraction of new TB infections that are

| Notation | Description |
|---|---|
| **Parameters that impact TB force of infection ($\lambda_r(\tau)$)** | |
| $\beta_g$ | Number of effective contacts for TB transmission per year for gender $g$ |
| $\phi_h$ | Relative transmissibility of TB in populations in HIV compartment $h$, such that $\phi_1 = 1$ and $\phi_h < 1$ for $h = 2, 3$, or 4 |
| $\varepsilon$ | Fraction of new TB infections that are MDR-TB |
| **Parameters that impact ART initiation ($\eta_{2,4,g}(\tau)$ and $\eta_{3,4,g}(\tau)$)** | |
| $\sigma_g(\tau)$ | ART coverage for gender $g$ at time $\tau$. |
| $\varrho_g(\tau)$ | Proportion of the population in HIV compartment 2 (HIV+, not on ART, CD4 > 200) eligible to initiate ART by gender $g$ at time $\tau$. |
| **Parameters that impact entries ($B(\tau)$) and exits ($\alpha^{out}_{t,h,g}(\tau)$) from the population** | |
| $\mu_{t,h,g}(\tau)$ | Mortality rates from populations in TB compartment $t$, HIV compartment $h$, and gender compartment $g$ at time $\tau$, per year |
| $\alpha^{\text{ageout}}$ | Rate of exit from the population due to aging, $\alpha^{\text{ageout}} = 1/(60-15)$ |

Table 2: Description and notation for parameters used in calculations impacted by population states.

projected to be MDR are represented by the parameter $\varepsilon$. These parameters are used to calculate the TB force of infection for each DR compartment $r$ at each time step $\tau$, as follows

$$\lambda_{1,g}(\tau) = \left(\frac{\beta_g}{100,000}\right) \sum_{h \in HIV} \phi_h N_{6,1,h,g}(\tau) \qquad \forall g \in G \qquad \text{(A)}$$

$$\lambda_{2,g}(\tau) = \frac{\varepsilon \lambda_{1,g}(\tau)}{(1-\varepsilon)} \qquad \forall g \in G \qquad \text{(B)}$$

$$\lambda_r(\tau) = \sum_{g \in G} \lambda_{r,g}(\tau) \qquad \forall r \in DR. \qquad \text{(C)}$$

Equation (A) calculates the TB force of infection for DS-TB ($r = 1$) for each gender $g$. Equation (B) uses the estimated fraction of new TB infections that are projected to be MDR to calculate the TB force of infection for MDR-TB strains ($r = 2$) by gender $g$. Finally, Equation (C) sums over gender $g$ to get the total TB force of infection for each DR compartment $r$.

### 2.1.2 ART Initiation Rates

This section describes how ART initiation rates from HIV compartment 2 (HIV+, not on ART, CD4 > 200) and HIV compartment 3 (HIV+, not on ART, CD4 ≤ 200) at time $\tau$ denoted $\eta_{2,4,g}(\tau)$ and $\eta_{3,4,g}(\tau)$, respectively, are calculated at each time step $\tau$. ART initiation rates are calculated based on ART coverage, $\sigma_g(\tau)$, and the proportion of those in HIV compartment 2 (HIV+, not on ART, CD4 > 200) that are eligible to initiate ART, by gender $g$, $\varrho_g(\tau)$. We assume all those eligible to initiate ART, initiate at the same rate. There are four distinct time periods that impact these parameters (need ref from Jenn),

1. Before 2004: ART did not exist.

2. Between 2004-2010: ART was developed and available to all individuals who were HIV positive with CD4 $\leq 200$.
3. Between 2011-2015: CD4 eligibility levels were increased to 350 for all individuals who were HIV positive.
4. After 2016: All individuals who are HIV positive are eligible for ART.

Before 2004, all ART initiation rates are set to zero, i.e. $\eta_{2,4,g}(\tau) = \eta_{3,4,g}(\tau) = 0$, to represent that ART is not available before 2004. After 2004, when ART becomes available, ART initiation rates are estimated based on: ART coverage by gender $g$ at time $\tau$, denoted $\sigma_g(\tau)$; the proportion of those who are in HIV compartment 2 (HIV+, not on ART, CD4 $> 200$) and are eligible to initiate ART by gender $g$ at time $\tau$, denoted $\varrho_g(\tau)$; and the current proportion of those who are HIV positive in each HIV compartment $h \in HIV\{2,3,4\}$, by gender $g$ at time $\tau$. These rates are calculated using Equation (D) – Equation (G).

First we calculate $V_{h,g}(\tau)$ to represent the proportion of HIV positive population by gender $g$ in the model in each HIV compartment $h$ at time $\tau$ as:

$$V_{h,g}(\tau) = \frac{\sum_{t \in TB} \sum_{r \in DR} N_{t,r,h,g}(\tau)}{\sum_{t \in TB} \sum_{r \in DR} \sum_{\substack{i \in HIV \\ \{2,3,4\}}} N_{t,r,i,g}(\tau)} \qquad \forall h \in HIV\{2,3,4\}, g \in G. \tag{D}$$

Equation (E) provides an expression for a general ART initiation rate for all HIV positive persons eligible to initiate ART (according to the associated program) by gender, denoted $\eta_g^{all}(\tau)$. The numerator represents the difference in ART coverage for gender $g$ at time $\tau$ with $\sigma_g(\tau)$ and model projected ART coverage for gender $g$ at time $\tau$, $V_{4,g}(\tau)$. The denominator represents the proportion of the HIV positive population eligible to initiate ART at time $\tau$ by gender $g$.

$$\eta_g^{all}(\tau) = \frac{\sigma_g(\tau) - V_{4,g}(\tau)}{\varrho_g(\tau) V_{2,g}(\tau) + V_{3,g}(\tau)} \qquad \forall g \in G \tag{E}$$

Note that ART coverage $\sigma_g(\tau)$ for time steps $\tau$ associated with years in the intervention period depends on the care delivery program, as in Table 6. In the years between 2004 and 2010, no individuals in HIV compartment 2 (HIV+, not on ART, CD4 $> 200$) were eligible to initiate ART, so $\varrho_g(\tau) = 0$ for all $\tau$ associated with the years between 2004 and 2010. For all times $\tau$ associated with the years between 2011 and 2015, $0 < \varrho_g(\tau) < 1$ to indicate that some individuals who are in HIV compartment 2 (HIV+, not on ART, CD4 $> 200$) were eligible to initiate ART. For times $\tau$ associated with 2016 and the years thereafter, $\varrho_g(\tau) = 1$ to indicate that all those who are HIV positive are eligible to initiate ART.

Finally, Equation (F) provides ART initiation rates from HIV compartment 2 (HIV+, not on ART, CD4 $> 200$) to HIV compartment 4 (HIV+, on ART), by gender at time $\tau$, and Equation (G) provides ART initiation rates from HIV compartment 3 (HIV+, not on ART, CD4 $\leq 200$) to HIV compartment 4 (HIV+, on ART), by gender at time $\tau$.

$$\eta_{2,4,g}(\tau) = \eta_g^{all}(\tau) \qquad \forall g \in G \tag{F}$$

$$\eta_{3,4,g}(\tau) = \varrho_g(\tau) \eta_g^{all}(\tau) \qquad \forall g \in G \tag{G}$$

### 2.1.3 Population Entering and Exiting the Model

This section describes how we calculate the rate of population exiting the model based on aging-out rates and mortality rates at time $\tau$, $\alpha^{out}_{t,h,g}(\tau)$ for TB compartment $t$, DR compartment $r$, HIV compartment $h$ and gender compartment $g$ in Equation (H) and the total population aging into the model at time $\tau$, $B(\tau)$ in Equation (I).

Exits from the model can occur due to mortality at a rate of $\mu_{t,h,g}(\tau)$ for TB compartment $t$, HIV compartment $h$ and gender compartment $g$ at time $\tau$ or aging-out at a rate of $\alpha^{\text{ageout}}$. We only consider populations with ages between 15 and 59, that is, they enter on their 15th birthday and exit on their 60th birthday so we assume aging-out of the population occurs at a rate of $1/(60-15)$ per year which is the inverse of the duration of time between population entry at age 15 and exit at age 60. So, we set $\alpha^{\text{ageout}} = 1/(60-15)$. Note that $\mu_{t,h,g}(\tau)\alpha^{\text{ageout}}$ is subtracted to ensure an individual can only age out or die, but cannot both age out and die. For the purpose of this model, we assume a constant population size of 100,000. In order to keep the population size constant, the entries to the population are set to the total population leaving the model from aging out or dying.

$$\alpha^{out}_{t,h,g}(\tau) = \mu_{t,h,g}(\tau) + \alpha^{\text{ageout}}(1-\mu_{t,h,g}(\tau)) \qquad \forall t \in TB, h \in HIV, g \in G \qquad \text{(H)}$$

$$B(\tau) = \sum_{t\in TB}\sum_{r\in DR}\sum_{h\in HIV}\sum_{g\in G}\alpha^{out}_{t,h,g}(\tau)N_{t,r,h,g}(\tau). \qquad \text{(I)}$$

New entries are assigned to TB uninfected, latent TB, and active TB compartments, $t \in TB\{1,3,6\}$, HIV- and HIV+, not on ART, CD4 $>$ 200, $h \in HIV\{1,2\}$, as well as all DR $r$ compartments and gender $g$ compartments at time $\tau$ with the parameter $\alpha^{in}_{t,r,h,g}(\tau)$.

## 2.2 Model Transitions

This section describes the differential equations used to represent transitions between the eight TB compartments, two DR compartments, four HIV compartments, and two gender compartments.

*TB compartment 1: Uninfected, not on IPT**

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

$$\forall h \in HIV, g \in G$$

**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 all exits and entries*

*into TB uninfected compartments are from DR compartment 1.*

*Equation* (1) *Description*
The first line in Equation (1) calculates the entries into TB compartment 1 as a proportion of the population enters at age 15. The second line calculates the population leaving the compartment from aging out or dying. The third and fourth lines calculate the total population leaving and entering compartment 1 from initiation (only those who are HIV+ and on ART) and completion of IPT, respectively. The fifth line calculates the population leaving after being infected with TB. The last two lines calculate entries and exits between HIV compartments.

*TB compartment 2: Uninfected, on IPT**

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

$$\forall h \in HIV, g \in G$$

**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 all exits and entries into TB uninfected compartments are from DR compartment 1.*

*Equation* (2) *Description*
The first line in Equation (2) calculates the population leaving the compartment from aging out or dying (note: we do not let individuals age into IPT compartments). The second and third lines calculate the total population entering and leaving compartment 2 from initiation and completion of IPT. The fourth line calculates the population leaving after being infected with TB, diminished for those infected with DS TB to represent the partially protective effects of becoming infected with TB while on IPT. The last two lines calculate entries and exits between HIV compartments.

*TB compartment 3: LTBI, infected recently*

$$\begin{aligned}\frac{dN_{3,r,h,g}(\tau)}{dt} = \quad & \alpha^{in}_{3,r,h,g}(\tau)B(\tau) \\ & -\alpha^{out}_{3,h,g}(\tau)N_{3,r,h,g}(\tau) \\ & +\lambda_r(\tau)N_{1,1,h,g}(\tau) \\ & +\iota_r\lambda_r(\tau)N_{2,1,h,g}(\tau) \\ & +\zeta\lambda_r(\tau)\sum_{r\in DR}N_{4,r,h,g}(\tau)\end{aligned}$$

$$
\begin{aligned}
&+ \xi\lambda_r(\tau) \sum_{r\in DR} N_{7,r,h,g}(\tau) \\
&+ \zeta\lambda_r(\tau) \sum_{r\in DR} N_{8,r,h,g}(\tau) \\
&- \pi_{3,4} N_{3,r,h,g}(\tau) \\
&- \gamma_r \kappa_{h,g}(\tau) N_{3,r,h,g}(\tau) \\
&- \theta_h \pi_{3,6} N_{3,r,h,g}(\tau) \\
&+ \sum_{i\in HIV, i\neq h} \eta_{i,h,g}(\tau) N_{3,r,i,g}(\tau) \\
&- \sum_{i\in HIV, i\neq h} \eta_{h,i,g}(\tau) N_{3,r,h,g}(\tau) \qquad (3)
\end{aligned}
$$

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (3) *Description*
Line one in Equation (3) calculates entries into TB compartment 3 as a proportion of the population enters at age 15. Line two calculates the population leaving the compartment from aging out or dying. Lines three through seven calculate entries from infections (and re-infections) from TB compartments 1 (uninfected, not on IPT), 2 (uninfected, on IPT), 4 (LTBI, remote), 8 (LTBI, on IPT), and 7 (recovered/treated). 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). For individuals in TB compartments 4 and 8, re-infection is diminished by the partially protective effect of previous infections on reinfection. For individuals in TB compartment 8, infection rates are increased to account for the increased risk of reinfection after active TB. Lines eight through ten calculate exits due to movements from recent to remote, going onto IPT, and progression to active TB. We only allow individuals with DS LTBI and HIV+ and on ART to move into TB compartment 5, we assume those with MDR LTBI on IPT continue to progress according to the annual risk of progression for recent LTBI. The last two lines calculate transitions between HIV compartments for entries and exits.

*TB compartment 4: LTBI, infected remotely*

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

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (4) *Description*
Line one in Equation (4) calculates entries into TB compartment 4 as a proportion of the population enters at age 15. Line two calculates the population leaving the compartment from aging out or dying. Line three calculates entries from LTBI, recent to remote, two years after the initial LTBI. Lines three to six calculate exits due to re-infection, which is diminished for the partially-protective effect of previous LTBI infections against acquiring a new TB infection, going onto IPT, and progression to active TB. We only allow individuals with DS LTBI and HIV+ and on ART to move into TB compartment 5. We assume those with MDR LTBI on IPT continue to progress according to the annual risk of progression for remote LTBI. The last two lines calculate transitions between HIV compartments.

*TB compartment 5: LTBI, on IPT*

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

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (5) *Description*
Line one in Equation (5) calculates the population leaving the compartment from aging out or dying (note: we do not let individuals age into IPT compartments). Line two calculates the rate at which populations move onto IPT from the LTBI, infected recently, and LTBI, infected remotely compartments, respectively. Lines three and four calculate exits due to active TB progression and completion of IPT. The last two lines calculate transitions between HIV compartments for entries and exits.

*TB compartment 6: Active TB*

$$\begin{aligned}\frac{dN_{6,r,h,g}(\tau)}{dt} = \quad & \alpha^{in}_{6,r,h,g}(\tau)B(\tau) \\ & -\alpha^{out}_{6,h,g}N_{6,r,h,g}(\tau) \\ & +\theta_h\pi_{3,6}N_{3,r,h,g}(\tau) \\ & +\theta_h\pi_{4,6}N_{4,r,h,g}(\tau) \\ & +\pi_{5,6}N_{5,r,h,g}(\tau) \\ & +\pi_{8,6}N_{8,r,h,g}(\tau) \\ & +\pi_{7,6}N_{7,r,h,g}(\tau) \\ & -\upsilon_h\pi_{6,7}N_{6,r,h,g}(\tau) \end{aligned}$$

$$
\begin{aligned}
&+ \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(\tau) N_{6,r,i,g}(\tau) \\
&- \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(\tau) N_{6,r,h,g}(\tau) \qquad (6)
\end{aligned}
$$

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (6) *Description*
Line one in Equation (6) calculates entries into TB compartment 6 as a proportion of the population enters at age 15. Line two calculates the population leaving the compartment from aging out or dying. Lines three through six calculate the rate at which populations with LTBI who are recently and remotely infected (relative to HIV state), on IPT, and after IPT (for those who are HIV+ and on ART) progress to active TB. Line seven calculates entries from relapse. Line eight calculates exits from recovery and accounts for the increased duration of active TB due to delays in treatment. The last two lines calculate transitions between HIV compartments for entries and exits.

*TB compartment 7: Recovered/Treated*

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

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (7) *Description*
Line one in Equation (7) calculates the population leaving the compartment from aging out or dying (note: we do not let individuals age into the TB recovered/treated compartment). Line two calculates entries from recovery/treatment and accounts for the increased duration of active TB due to delays in treatment. Line three calculates exits from reinfection, which accounts for the increased risk of acquiring a new TB infection after active TB. Line four calculates exits from relapse. The last two lines calculate transitions between HIV compartments.

*TB compartment 8: LTBI after IPT*

$$
\begin{aligned}
\frac{dN_{8,r,h,g}(\tau)}{dt} = \quad & - \alpha^{out}_{8,h,g} N_{8,r,h,g}(\tau) \\
& + \omega N_{5,r,h,g}(\tau) \\
& - \pi_{8,6} N_{8,r,h,g}(\tau) \\
& - \zeta \lambda(\tau) \sum_{r \in DR} N_{8,r,h,g}(\tau)
\end{aligned}
$$

$$+ \sum_{i \in HIV, i \neq h} \eta_{i,h,g}(\tau) N_{8,r,i,g}(\tau)$$
$$- \sum_{i \in HIV, i \neq h} \eta_{h,i,g}(\tau) N_{8,r,h,g}(\tau) \quad (8)$$

$$\forall r \in DR, h \in HIV, g \in G$$

*Equation* (8) *Description*
Line one in Equation (8) calculates the population leaving the compartment from aging out or dying (note: we do not let individuals age into IPT compartments). Line two calculates the total population entering TB compartment 8 after completing IPT with LTBI. Lines three and four calculate exits due to progression to active TB and reinfection, which is diminished for the partially-protective effect of LTBI from TB against acquiring a new TB infection. The last two lines calculate transitions between HIV compartments for entries and exits.

# 3 Model Execution

The dynamic transmission model was programmed in R version 3.5.2 and the system of differential equations was solved with the deSolve package (cite). We run our code on Hyak, the University of Washington's supercomputing system, to allow for computations at scale [17]. The code and parameters used to run the model are available at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/tree/master/model_execution`. We start the dynamic transmission model at the beginning of 1940 at time $\tau = 1940.0$ to allow for the slow propagation of TB. We initiate population states into TB compartments 1, 3, 4, and 6, DR compartments 1 and 2, HIV compartment 1 (HIV negative only), and both gender compartments 1 and 2. We introduce HIV through HIV incidence rates at the beginning of 1980 at time $\tau = 1980.0$.

We solve the system of differential equations using a time step $\tau$ of one month or 1/12 (0.083) of a year. Each time step $\tau$ is associated with a year, *year* $Y$. For example time steps $\tau \in \{1990.0, 1990.083, \ldots, 1990.833, 1990.917\}$ are associated with the year 1990 or *year* $Y = 1990$. Time-varying parameters are notated as a function of $\tau$ in Table 1.

To calibrate parameters used in the dynamic transmission model, we generate a set of parameter sets from a range of values as described in Section 5 that correspond to findings from the DO ART trial and scientific literature for each parameter included in the calibration. We run the model for each parameter set assuming standard facility-based ART and IPT care (Program 1) for the calibration period, from the beginning of 1940 to the end of 2017. We evaluate the model outputs for each parameter set against calibration targets as described in Section 5.4 to determine whether to accept or reject a parameter set. The source code to generate the set of parameter sets can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/9_sample_gen.R`. The source code for the model for the warm-up and calibration period is available at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/model_execution/calibration_runs/warmup_calibration_for_loop_Rscript.R`. The script used to evaluate which parameter sets are accepted or rejected can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/model_execution/calibration_runs/calibration_analysis_Rscript.R`. The results from the calibration can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/results/calibration_analysis/`.

Then, we continue to execute the model for the three care delivery programs and each of the accepted parameter sets over the intervention period, from the beginning of 2018 until the end of 2027.

The population states at the beginning of 2018 for each accepted parameter set are used to initiate each of the three care delivery programs. We modify parameters that depend on the care delivery program starting at the beginning of 2018 and hold them constant over the intervention period. The source code for the model intervention period is available at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/model_execution/program_runs/program_runs_for_loop_Rscript.R`. This code generates model outputs used in the cost model and to calculate program health metrics.

We calculate program health outcome metrics for each parameter set and care delivery program, based on the equations in Section 4. The equations for the program health outcome metrics related to population states and transition rates are described in Section 1.1.4. The code used to generate program heath outcomes and graphs can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/model_execution/program_runs/program_analysis_Rscript.R`.

# 4 Program Health Outcomes and Costs

Program health outcomes and costs are summarized in Table 3. The metrics related to TB incidence, TB mortality, TB and HIV prevalence, and DALYs, are based on population states and transition rates from the dynamic transmission model. The equations used to generate these metrics are described in Section 4.2 to Section 4.4. The cost model generates costs for each program as described in Section 4.5. We calculate discounted and undiscounted incremental health outcomes, incremental costs, and cost-effectiveness ratios over the 10-year intervention period from the start of 2018 to the end of 2027, as described in Section 4.6.

| Notation | Description |
|---|---|
| | **TB Incidence** |
| $TBinc\_per(Y,p)$ | TB incidence rate in *year* $Y$, per 100,000 individuals for program $p$ |
| $TBinc\_per_g^{HIV+}(Y,p)$ | TB incidence rate for the HIV positive population in *year* $Y$ by gender $g$, per 100,000 males or females for program $p$ |
| $TBinc\_per_g^{HIV-}(Y,p)$ | TB incidence rate for the HIV negative population in *year* $Y$ by gender $g$, per 100,000 males or females for program $p$ |
| | **TB Mortality** |
| $TBmort\_per(Y,p)$ | TB mortality rate per 100,000 individuals in *year* $Y$ for program $p$ |
| $TBmort\_per_g^{HIV+}(Y,p)$ | TB mortality rate for the HIV positive population in *year* $Y$ by gender $g$ per 100,000 males or females for program $p$ |
| $TBmort\_per_g^{HIV-}(Y,p)$ | TB mortality rate for the HIV negative population in *year* $Y$ by gender $g$, per 100,000 males or females for program $p$ |
| | **TB and HIV prevalence** |
| $TBprev\_per(Y,p)$ | TB prevalence rate in *year* $Y$, per 100,000 individuals for program $p$ |
| $HIVprev\_per_g(Y,p)$ | HIV prevalence rate in *year* $Y$, for gender $g$ per 100,000 males or females for program $p$ |
| | **Disability-Adjusted Life Years** |
| $YLL\_per(Y,p)$ | YLL in *year* $Y$, per 100,000 individuals for program $p$ |
| $YLD\_per(Y,p)$ | YLD in *year* $Y$, per 100,000 individuals for program $p$ |
| $DALY\_per(Y,p)$ | DALYs in *year* $Y$, per 100,000 individuals for program $p$ |

Continued on next page

**Table 3 – continued from previous page**

| Notation | Description |
|---|---|
| **Costs** | |
| $Cost\_per(Y, p)$ | Costs in *year* $Y$ per 100,000 individuals for program $p$ |
| **Incremental Health Outcomes and Costs (Undiscounted)** | |
| $UTBinc\_total(p)$ | Total undiscounted incident TB cases over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $UTBmort\_total(p)$ | Total undiscounted TB deaths over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $UDALY\_total(p)$ | Total undiscounted DALYs over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $UCost\_total(p)$ | Total undiscounted costs over the 10-year intervention period from 2018 to 2027 for program $p$ |
| **Incremental Health Outcomes and Costs (Discounted)** | |
| $DTBinc\_total(p)$ | Total discounted incident TB cases over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $DTBmort\_total(p)$ | Total discounted TB deaths over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $DDALY\_total(p)$ | Total discounted DALYs over the 10-year intervention period from 2018 to 2027 for program $p$ |
| $DCost\_total(p)$ | Total discounted costs over the 10-year intervention period from 2018 to 2027 for program $p$ |
| **Incremental Cost-Effectiveness Ratios (Undiscounted)** | |
| $UICER^{TBinc}(\tilde{p}, p)$ | Undiscounted incremental cost per TB incidence case averted from 2018 to 2027 between the intervention program $\tilde{p}$ and the standard program $p$ |
| $UICER^{TBmort}(\tilde{p}, p)$ | Undiscounted incremental cost per TB death averted from 2018 to 2027 between the intervention program $\tilde{p}$ and the standard program $p$ |
| $UICER^{DALY}(\tilde{p}, p)$ | Undiscounted incremental cost per DALY from 2018 to 2027 between the intervention program $\tilde{p}$ and the standard program $p$ |
| **Incremental Cost-Effectiveness Ratios (Discounted)** | |
| $DICER^{TBinc}(\tilde{p}, p)$ | Discounted incremental cost per TB incidence case averted over the intervention period between the intervention program $\tilde{p}$ and the standard program $p$ |
| $DICER^{TBmort}(\tilde{p}, p)$ | Discounted incremental cost per TB death averted over the intervention period between the intervention program $\tilde{p}$ and the standard program $p$ |
| $DICER^{DALY}(\tilde{p}, p)$ | Discounted incremental cost per DALY averted over the intervention period between the intervention program $\tilde{p}$ and the standard program $p$ |

Table 3: Description and notation for program health outcomes and costs.

Metrics that are scaled per 100,000 individuals contain *per* in the notation. Metrics are aggregated at different levels, where a subscript $g$ in the notation represents gender ($g = 1$ for males and

$g = 2$ for females). TB incidence rates and TB mortality with a superscript of $HIV+$ aggregate those in HIV positive compartments (HIV compartments 2, 3, and 4), and a superscript of $HIV-$ represents the HIV negative population (HIV compartment 1).

Metrics that are noted as a function of $Y$ provide annual estimates by summing model projections over times that are associated with *year* $Y$, where $Y$ takes on values from 2018 to 2027. There are 12 values of $\tau$ in each year; for example, year 2018 or $Y = 2018$ sums over time steps $\tau \in \{2018.0, 2018.083, \ldots, 2018.833, 2018.917\}$. Estimates that are cumulative over the 10-year intervention period contain *total* in the notation.

Metrics pertaining to a care delivery program during the intervention period are notated as a function of $p$, for Programs $p = 1, 2$, and 3. Discounted and undiscounted incremental cost-effectiveness ratios (ICERs) compare community-based intervention programs $\tilde{p}$ to standard, facility-based programs $p$. They are generated using corresponding incremental health outcomes and cost metrics.

### 4.1 TB Incidence

TB incidence rates per 100,000 individuals are calculated by summing those progressing to active TB (TB compartment 6) from TB compartments 3, 4, 5, and 8 (note: only those in HIV compartment 4, HIV+ and on ART, can initiate IPT and enter TB compartments 5 and 8) for all time steps $\tau$ in *year* $Y$ (e.g., *year* $Y = 2018$ sums $\tau$ from 2018.0 to 2018.917) for each program $p$ and is calculated as,

$$\begin{aligned} TBinc\_per(Y,p) = &\sum_{\tau \in year\ Y} \sum_{\substack{t \in TB \\ \{3,4\}}} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} \theta_h \pi_{t,6} N_{t,r,h,g}(\tau) \\ &+ \sum_{\tau \in year\ Y} \sum_{\substack{t \in TB \\ \{5,8\}}} \sum_{r \in DR} \sum_{g \in G} \pi_{t,6} N_{t,r,4,g}(\tau). \end{aligned} \tag{9}$$

We also generate TB incidence rates by year and by gender (per 100,000 males or females) for those who are HIV positive and HIV negative in Equation (11) and Equation (12), respectively. In order to scale rates by gender, we use population estimates for each gender compartment $g$ at time $\tau$ for the program $p$ denoted $POP_g(\tau, p)$. Population estimates gender compartment $g$ at time $\tau$ for program $p$ is calculated as,

$$POP_g(\tau, p) = \sum_{t \in TB} \sum_{r \in DR} \sum_{h \in HIV} N_{t,r,h,g}(\tau) \qquad \forall g \in G. \tag{10}$$

Equation (11) calculates the number of TB incident cases for the HIV positive population by gender $g$ at time $\tau$, then scales TB incidence rates for those who are HIV positive per 100,000 males $g = 1$ and 100,000 females $g = 2$ by dividing by population estimates for each gender $g$, summing over all time steps $\tau$ in *year* $Y$ and multiplying by 100,000,

$$TBinc\_per_g^{HIV+}(Y,p) = 100,000 \sum_{\tau \in year\ Y} \left( \frac{\sum\limits_{\substack{t \in TB \\ \{3,4\}}} \sum\limits_{r \in DR} \sum\limits_{\substack{h \in HIV \\ \{2,3,4\}}} \theta_h \pi_{t,6} N_{t,r,h,g}(\tau)}{POP_g(\tau, p)} \right) \tag{11}$$

$$+ 100,000 \sum_{\tau \in year\ Y} \left( \frac{\sum_{\substack{t \in TB \\ \{5,8\}}} \sum_{r \in DR} \pi_{t,6} N_{t,r,4,g}(\tau)}{POP_g(\tau, p)} \right) \qquad \forall g \in G.$$

Similarly, Equation (12) calculates the number of TB incident cases for the HIV negative population by gender $g$ at time $\tau$ in program $p$, and divides by population estimates for each gender $g$, then summing over all time steps $\tau$ in *year* $Y$ and multiplying by 100,000,

$$TBinc\_per_g^{HIV-}(Y, p) = 100,000 \sum_{\tau \in year\ Y} \left( \frac{\sum_{\substack{t \in TB \\ \{3,4\}}} \sum_{r \in DR} \pi_{t,6}\ N_{t,r,1,g}(\tau)}{POP_g(\tau, p)} \right) \qquad \forall g \in G. \tag{12}$$

The aggregated TB incidence rate in *year* $Y$, per 100,000 individuals for program $p$, is equal to the sum of $TBinc\_per_g^{HIV+}(Y, p)$ plus $TBinc\_per_g^{HIV-}(Y, p)$ over each gender $g$.

### 4.2 TB Mortality

TB mortality per 100,000 individuals projected by the model for program $p$ are calculated by summing those departing the active TB compartment (TB compartment 6) due to death for all time steps $\tau$ in *year* $Y$ and are calculated as,

$$TBmort\_per(Y, p) = \sum_{\tau \in year\ Y} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} \mu_{6,h,g}(\tau)\ N_{6,r,h,g}(\tau). \tag{13}$$

We also generate TB mortality in program $p$ by gender (per 100,000 males or females) for those who are HIV positive and HIV negative in Equation (14) and Equation (15), respectively. We use $POP_g(\tau, p)$ as described in Equation (10) to scale TB mortality by gender. Equation (14) calculates the number of HIV positive individuals who died at time $\tau$, divided by the number of individuals who are HIV positive by population estimates for each gender $g$, and summed over all time steps $\tau$ in *year* $Y$ and multiplied by 100,000,

$$TBmort\_per_g^{HIV+}(Y, p) = 100,000 \sum_{\tau \in year\ Y} \left( \frac{\sum_{r \in DR} \sum_{\substack{h \in HIV \\ \{2,3,4\}}} \mu_{6,h,g}(\tau)\ N_{6,r,h,g}(\tau)}{POP_g(\tau, p)} \right). \tag{14}$$

Similarly, Equation (15) calculates the number of individuals who died that are HIV negative by gender $g$ at time $\tau$, scaled by population estimates for each gender $g$, summed over all time steps $\tau$ in *year* $Y$, and multiplied by 100,000,

$$TBmort\_per_g^{HIV-}(Y, p) = 100,000 \sum_{\tau \in year\ Y} \left( \frac{\sum_{r \in DR} \mu_{6,1,g}(\tau)\ N_{6,r,1,g}(\tau)}{POP_g(\tau, p)} \right) \qquad \forall g \in G. \tag{15}$$

Note that $TBmort\_per(Y, p)$ in (13) is equivalent to summing $TBmort\_per_g^{HIV+}(Y, p)$ and $TBmort\_per_g^{HIV-}(Y, p)$ for *year* $Y$ and program $p$.

### 4.3 TB and HIV Prevalence

Prevalence represents the proportion of the population in the model that is infected with TB and/or HIV. We provide TB prevalence by year per 100,000 individuals in Equation (16). Equation (16) calculates the number of individuals infected with TB (in TB compartment 6), then sets TB prevalence for *year* $Y$ in program $p$ based on the average TB prevalence over time steps $\tau$ in *year* $Y$,

$$TBprev\_per(Y,p) = \frac{1}{12} \sum_{\tau \in year\ Y} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} N_{6,r,h,g}(\tau). \tag{16}$$

Why do you do HIV prevalence by gender, but not TB prevalence? Do you ever report TB prevalence by gender?

HIV prevalence represents the proportion of the population who are infected with HIV (in HIV compartments 2, 3, and 4). We provide HIV prevalence by gender (per 100,000 males and per 100,000 females) and year in Equation (17). Equation (17) calculates the number of HIV positive individuals at time $\tau$, divided by population estimates for each gender $g$ and multiplied by 100,000, and taking the average over all time steps $\tau$ in *year* $Y$,

$$HIVprev\_per_g(Y,p) = 100,000 \left(\frac{1}{12}\right) \sum_{\tau \in year\ Y} \left( \frac{\sum_{t \in TB} \sum_{r \in DR} \sum_{\substack{h \in HIV \\ \{2,3,4\}}} N_{t,r,h,g}(\tau)}{POP_g(\tau,p)} \right) \quad \forall g \in G. \tag{17}$$

### 4.4 Disability-Adjusted Life Years

Disability-adjusted life years (DALYs) are calculated based on years of life lost (YLL) and years lived with disability (YLD) per 100,000 individuals. The years of life lost in *year* $Y$ per 100,000 individuals for program $p$, $YLL\_per(Y,p)$, is calculated in Equation (18) as a measure that represents the number of years lost from premature mortality as a result of TB and/or HIV infection. Since individuals age out at 60 years old, we assume that any individual who died from HIV/TB infection would have lived or aged out by the end of the intervention period (in 2028) if they did not die from a TB and/or HIV infection. Equation (18) calculates YLL projected by the model in *year* $Y$ for the program $p$, per 100,000 individuals based on the number of individuals departing the active TB compartment (TB compartment 6) and/or HIV positive compartments (HIV 2, 3 and 4). We multiply the number of deaths at time $\tau$ by the time left until the end of the intervention period $(2028 - \tau)$ to represent the number of years each person who died would have lived if they lived to the end of the intervention period,

$$\begin{aligned} YLL\_per(Y,p) = & \sum_{\tau \in year Y} \sum_{r \in DR} \sum_{h \in HIV} \sum_{g \in G} (2028 - \tau)(\mu_{6,h,g}(\tau)\ N_{6,r,h,g}(\tau)) \\ & + \sum_{\tau \in year Y} \sum_{\substack{t \in TB \\ t \neq 6}} \sum_{r \in DR} \sum_{\substack{h \in HIV \\ \{2,3,4\}}} \sum_{g \in G} (2028 - \tau)(\mu_{t,h,g}(\tau)\ N_{h,r,h,g}(\tau)). \end{aligned} \tag{18}$$

The years lived with disability in *year* $Y$ per 100,000 individuals for program $p$, $YLD\_per(Y,p)$, is calculated in Equation (19) to quantify the impact of TB and HIV infections on quality of life for those infected with TB and HIV using disability weights.

The parameter $D_{t,h}$ is the disability weight for those in TB compartment $t$ and HIV compartment $h$. Input parameter values for disability weights $D_{t,h}$ are defined for a year living with TB and/or HIV [12], and are given in Table 7. To convert disability weights to monthly estimates, we multiply disability weights by 1/12,

$$YLD\_per(Y,p) = \sum_{\tau \in year Y} \left( \sum_{t \in TB} \sum_{h \in HIV} \frac{1}{12} D_{t,h} \sum_{r \in DR} \sum_{g \in G} N_{t,r,h,g}(\tau) \right). \tag{19}$$

We calculate disability-adjusted life years (DALYs) for each program $p$ by year $Y$, per 100,000 individuals, as the sum of years of life lost (YLL) and years lived with disability (YLD) for each program $p$ by year $Y$ such that,

$$DALY\_per(Y,p) = YLL\_per(Y,p) + YLD\_per(Y,p). \tag{20}$$

### 4.5 Program Costs

Costs include costs to administer ART, HIV care, IPT, and TB care. These costs are generated by combining TB and HIV prevalence estimates from the model with the cost parameters summarised in Table 4.

| Notation | Description |
|---|---|
| | **Costs** |
| $ART^{COST}$ | Costs to provide ART, per year |
| $Ocare_h^{COST}$ | Costs for inpatient and outpatient treatment for individuals without active TB and in HIV compartment $h$, for $h \in HIV\{2,3,4\}$, per year |
| $IPT^{COST}$ | Costs to provide a full course of IPT |
| $TBcare_r^{COST}$ | Costs to provide a course of inpatient and outpatient TB treatment for those with active TB in DR compartment $r$ |

Table 4: Description and notation for parameters used in the cost model. Parameters that depend on the care delivery program are highlighted in green.

Equation (21) calculates costs in *year* $Y$ projected under program $p$ per 100,000 individuals, $Cost\_per(Y,p)$. Projected ART costs are calculated in the first line of the equation and are based on monthly costs to administer ART per person multiplied by the number of individuals on ART (in HIV compartment 4) at time $\tau$. The second line calculates the inpatient and outpatient cost of care for causes other than TB for those who are not infected with TB (not in TB compartment 6) and in an HIV positive compartment $h$ (in HIV compartments 2, 3, and 4) at a yearly rate of $Ocare_h^{COST}$. The assumptions regarding the proportion of time those in HIV compartment $h$ are actively receiving inpatient and outpatient treatment for diseases other than HIV are accounted for in the parameter $Ocare_h^{COST}$. We multiply annual costs, $ART^{COST}$ and $Ocare_h^{COST}$, by 1/12 to convert yearly costs to monthly costs. The cost to provide IPT is calculated in the third line of Equation (21) and is based on the monthly cost of administer IPT per person multiplied by the number of individuals on IPT (in TB compartments 2 and 5) at time $\tau$. Note: our model assumes only those on ART (in HIV compartment 4) can initiate IPT. CHELSEA: in Table 5, $1/\omega$ is already in months, not years. The equation below is correct, I'm fixing the wording. Since the IPT cost, $IPT^{COST}$, is defined for an entire course of IPT, we multiply $IPT^{COST}$ by $1/\omega$ to get

monthly costs, where $1/\omega$ represents the duration of an IPT course in months. Line four calculates the inpatient and outpatient cost of TB care for those with active TB (in TB compartment 6) and DR compartment $r$. The TB care cost, $TBcare_r^{COST}$, is defined for a course of TB treatment. We multiply TB treatment costs by $1/(\upsilon_h \pi_{6,7})$ to get monthly costs, where $1/(\upsilon_h \pi_{6,7})$ represents the duration of recovery/treatment in months. To get yearly costs, we sum monthly costs for each time $\tau$ in *year* $Y$,

$$\begin{aligned} Cost\_per(Y,p) = & \sum_{\tau \in yearY} \frac{1}{12} ART^{COST} \sum_{t \in TB} \sum_{r \in DR} \sum_{g \in G} N_{t,r,4,g}(\tau) \\ & + \sum_{\tau \in yearY} \sum_{\substack{h \in HIV \\ \{2,3,4\}}} \frac{1}{12} Ocare_h^{COST} \sum_{\substack{t \in TB \\ t \neq 6}} \sum_{r \in DR} \sum_{g \in G} N_{t,r,h,g}(\tau) \\ & + \sum_{\tau \in yearY} \frac{1}{\omega} IPT^{COST} \sum_{\substack{t \in TB \\ \{2,5\}}} \sum_{r \in DR} \sum_{g \in G} N_{t,r,4,g}(\tau) \\ & + \sum_{\tau \in yearY} \sum_{r \in DR} \sum_{h \in HIV} \frac{1}{\upsilon_h \pi_{6,7}} TBcare_r^{COST} \sum_{g \in G} N_{6,r,h,g}(\tau). \end{aligned} \tag{21}$$

### 4.6 Incremental Health Outcomes, Costs, and Cost-effectiveness Ratios

We calculate discounted and undiscounted health outcomes and costs including: TB incident cases, TB deaths, DALYs, and program costs. Undiscounted incident TB cases, TB deaths, DALYs, and costs are accumulated over the 10-year intervention period from 2018 to 2027 for each program $p$, and are specified in Equation (22), Equation (23), Equation (24), and Equation (25), respectively,

$$UTBinc\_total(p) = \sum_{Y \in [2018,2027]} TBinc\_per(Y,p) \tag{22}$$

$$UTBmort\_total(p) = \sum_{Y \in [2018,2027]} TBmort\_per(Y,p) \tag{23}$$

$$UDALY\_total(p) = \sum_{Y \in [2018,2027]} DALY\_per(Y,p) \tag{24}$$

$$UCost\_total(p) = \sum_{Y \in [2018,2027]} Cost\_per(Y,p). \tag{25}$$

Discounted health outcomes and costs are calculated similarly but are multiplied by a discounting factor, $F(Y)$. We discount metrics at a rate of 3% or 0.03 to the present value at the start of the intervention period in 2018 for each year in the intervention period, *year* $Y \in [2018, 2027]$ as,

$$F(Y) = \frac{1}{(1+0.03)^{(Y-2018)}}. \tag{26}$$

Discounted incident TB cases, TB deaths, DALYs, and costs over the 10-year intervention period from 2018 to 2027 are calculated for each program $p$ and converted to 2018 present values with the discounting factor $F(Y)$ in Equation (27), Equation (28), Equation (29), and Equation (30), respectively,

$$DTBinc\_total(p) = \sum_{Y \in [2018,2027]} F(Y)\ TBinc\_per(Y,p) \tag{27}$$

$$DTBmort\_total(p) = \sum_{Y \in [2018,2027]} F(Y)\ TBmort\_per(Y,p) \tag{28}$$

$$DDALY\_total(p) = \sum_{Y \in [2018,2027]} F(Y)\ DALY\_per(Y,p) \tag{29}$$

$$DCost\_total(p) = \sum_{Y \in [2018,2027]} F(Y)\ Cost\_per(Y,p). \tag{30}$$

We use these metrics to generate undiscounted and discounted incremental cost-effectiveness ratios (ICERs) to assess the per-dollar cost per incident TB case averted, TB death averted and DALY averted to compare community-based care delivery intervention programs $\tilde{p}$ to programs $p$ including:

1. Program 2 ($\tilde{p} = 2$) to Program 1 ($p = 1$) to evaluate the incremental benefit of a community-based ART intervention,
2. Program 3 ($\tilde{p} = 3$) to Program 1 ($p = 1$) to evaluate the incremental benefit of a community-based ART and IPT intervention and
3. Program 3 ($\tilde{p} = 3$) to Program 2 ($p = 2$) to evaluate the incremental benefit of a nested community-based IPT intervention (assuming community-based ART is already implemented)

We calculate undiscounted ICERs for incident TB cases averted, TB deaths, and DALYs as in Equation (31), Equation (32), and Equation (33), respectively,

$$UICER^{TBinc}(\tilde{p},p) = \frac{UCost\_total(\tilde{p}) - UCost\_total(p)}{UTBinc\_total(\tilde{p}) - UTBinc\_total(p)} \tag{31}$$

$$UICER^{TBmort}(\tilde{p},p) = \frac{UCost\_total(\tilde{p}) - UCost\_total(p)}{UTBmort\_total(\tilde{p}) - UTBmort\_total(p)} \tag{32}$$

$$UICER^{DALY}(\tilde{p},p) = \frac{UCost\_total(\tilde{p}) - UCost\_total(p)}{UDALY\_total(\tilde{p}) - UDALY\_total(p)}. \tag{33}$$

Discounted ICERs are calculated for incident TB cases averted, TB deaths, and DALYs as in Equation (34), Equation (35) and Equation (36), respectively.

$$DICER^{TBinc}(\tilde{p},p) = \frac{DCost\_total(\tilde{p}) - DCost\_total(p)}{DTBinc\_total(\tilde{p}) - DTBinc\_total(p)} \tag{34}$$

$$DICER^{TBmort}(\tilde{p},p) = \frac{DCost\_total(\tilde{p}) - DCost\_total(p)}{DTBmort\_total(\tilde{p}) - DTBmort\_total(p)} \tag{35}$$

$$DICER^{DALY}(\tilde{p},p) = \frac{DCost\_total(\tilde{p}) - DCost\_total(p)}{DDALY\_total(\tilde{p}) - DDALY\_total(p)}. \tag{36}$$

# 5 Description of Input Data

This section describes the input data needed to execute the dynamic transmission model and evaluate each program. All the input parameters described in this section can be found at `https://`

github.com/cgreene3/epi_model_HIV_TB_KZN_SA/tree/master/param_files/input_parameters. Section 5.1 describes how we initialize the population in 1940, and how individuals age in and out of the model. Section 5.2 describes the input parameter values and calibration ranges for the parameters that describe TB and HIV disease progression as summarised in Table 1 and Table 2. Parameter values for care delivery programs, including ART coverage and IPT initiation, are calculated based on findings from the DO ART trial and are described in Section 5.3. Section 5.4 describes how we calibrate the model and illustrates calibration results. Section 5.5 provides disability weights, and finally, Section 5.6 describes the parameter values needed in the cost model.

### 5.1 Population

Initial population state values in 1940 at $\tau = 1940.0$ are assigned to TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, recent), 4 (LTBI, remote), and 6 (active TB), both DR compartments, HIV compartment 1 (HIV-) and HIV compartment 2 (HIV+, not on ART, CD4 > 200) and both gender compartments according to 1990 GBD estimates for 15 to 59-year-olds from Kwazulu-Natal, SA (cite). Chelsea: I thought there was no DR $r = 2$ in 1940. I am rewriting this paragraph in green. Initial population state values in 1940 at $\tau = 1940.0$ are assigned according to 1990 GBD estimates for 15 to 59-year-olds from Kwazulu-Natal, SA (cite). The non-zero population compartments include: drug-susceptible (DR $r = 1$) TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, recent), 4 (LTBI, remote), and 6 (active TB), HIV compartment 2 (HIV+, not on ART, CD4 > 200), and both gender compartments. The code used to generate initial population estimates at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/4_births_perc_overtime_and_pop_init_calc.R`.

The population ages out of the model at a rate of $\alpha^{out} = 1/(60\text{-}15)$ per year, which represents the inverse of the duration of time between the age at which individuals enter the model at 15 years old and exit at 60 years old.

I'll rewrite this paragraph too. See below in green. A proportion of the population aging into the model is assigned to TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, recent), 4 (LTBI, remote), and 6 (active TB), both DR compartments, HIV compartment 1 (HIV-) and HIV compartment 2 (HIV+, not on ART, CD4 > 200) and both gender compartments with the parameter $\alpha^{in}_{t,r,h,g}(\tau)$. Aging in rates change over time according to yearly estimates from the Global Burden of Disease Study 2019 for 15 to 19-year-olds in Kwazulu-Natal, South Africa [12]. We assume all PLWH age into HIV compartment 2 (HIV+, not on ART, CD4 > 200). Compartments where we do not allow individuals to enter from aging in are set to zero. Between 1940 and 1979, before HIV infections are introduced, new entries are only assigned to HIV compartment 1 (HIV-) according to 1990 proportions. For the time steps, $\tau$ associated with the years between 1980 and 1989 aging in proportions are set to 1990 estimates. For time steps $\tau$ associated with the years between 2018 and 2028, aging in proportions are set to 2017 estimates. Aging in proportion yearly estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/input_parameters/birth_perc_df_overtime.csv`. The source code used to generate these estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/4_births_perc_overtime_and_pop_init_calc.R`.

The aging in parameter $\alpha^{in}_{t,r,h,g}(\tau)$ changes over time and is set according to yearly estimates from the Global Burden of Disease Study 2019 for 15 to 19-year-olds in Kwazulu-Natal, South Africa [12]. A proportion of the population aging into the model is assigned to TB compartments 1 (Uninfected, not on IPT), 3 (LTBI, recent), 4 (LTBI, remote), and 6 (active TB), both DR compartments, HIV compartment 1 (HIV-) and HIV compartment 2 (HIV+, not on ART, CD4 >

200) and both gender compartments. The aging in parameter $\alpha^{in}_{t,r,h,g}(\tau)$ is set to zero for compartments where we do not allow individuals to enter. Between 1940 and 1979, before HIV infections are introduced, new entries are only assigned to HIV compartment 1 (HIV-) according to 1990 proportions. Between 1980 and 1989, aging in proportions are set to 1990 estimates. For the years between 2018 and 2028, aging in proportions are set to 2017 estimates. Aging in proportion yearly estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/input_parameters/birth_perc_df_overtime.csv`. The source code used to generate these estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/4_births_perc_overtime_and_pop_init_calc.R`.

## 5.2 Parameter Values that Describe Disease Progression

Table 5 includes the input parameter values and calibration ranges for the parameters that describe TB and HIV disease progression as summarised in Table 1 and Table 2. For parameters that are calibrated, we used a range of 25% above and below the mean value from cited sources. We calibrate a total of 34 parameters.

Most of the input parameters that describe disease progression are calibrated and are not time-dependent. Time-varying input parameters are notated as functions of $\tau$ in Table 5. Time-varying input parameter values related to the care delivery program are described in Section 5.3. Time-varying input parameter values related to disease progression, including mortality rates ($\mu_{t,h,g}(\tau)$) and HIV incidence rates ($\eta_{1,2,g}(\tau)$), are calculated based on cited sources and are described in Section 5.2.2 and Section 5.2.1.

Table 5: Dynamic transmission model input parameters. The mean value for the 34 calibrated parameters is given, with the 25% calibration range used in calibration. Care delivery program-specific parameters are highlighted in green.

| Parameter description | Value [Calibration Range] | Reference |
|---|---|---|
| **Parameters that Impact TB Force of Infection** | | |
| $\beta_g$ Number of effective contacts for TB transmission per year for: | | [Need ref] |
| Males, $\beta_1$ | 14 [10.5, 17.5] | |
| Females, $\beta_2$ | 14 [10.5, 17.5] | |
| $\phi_h$ Relative transmissibility of TB for those: | | [16, 24] |
| HIV−, $\phi_1$ | 1 (base rate) | |
| HIV+, Not on ART, CV4 $>$ 200, $\phi_2$ | 0.9 [0.675, 1.125] | |
| HIV+, Not on ART, CV4 $\leq$ 200, $\phi_3$ | 0.6 [0.45, 0.75] | |
| HIV+, On ART, $\phi_4$ | 0.9 [0.675, 1.125] | |
| $\varepsilon$ Fraction of new TB infections that are MDR-TB | 0.037 [0.02775, 0.04625] | [34] |
| Diminished risk of acquiring a latent TB infection for those exposed to DS-TB while on IPT, such that, | | |
| DS-TB, $\iota_1$ | 0.43 [0.3225, 0.5375] | [10] |
| MDR-TB, $\iota_2$ | 1 (fixed value) | |

Continued on next page

**Table 5 – continued from previous page**

| Parameter description | Value [Calibration Range] | Reference |
|---|---|---|
| $\xi$ Increased risk of reinfection after recovering/treatment of active TB | 4 [3, 5] | [31] |
| $\zeta$ Partially protective effect of LTBI against acquiring a new TB infection | 0.4 [0.3, 0.5] | [10, 16, 21, 31] |
| **Parameters that Describe TB Progression** | | |
| $1/\omega$ Duration of IPT course (months) | 6 (fixed value) | [4] |
| $\gamma_r$ Indicator to reflect that those infected with MDR-TB do not yield benefits of IPT, such that: | | |
| Drug-Susceptible strain, $\gamma_1$ | 1 (fixed value) | |
| MDR strain, $\gamma_2$ | 0 (fixed value) | |
| $1/\pi_{3,4}$ Duration of LTBI recently infected period (years) | 2 (fixed value) | [32] |
| $\pi_{i,6}$ Rates of TB progression from: | | |
| Recent LTBI to active TB, $\pi_{3,6}$ | 0.025 [0.01875, 0.03125] | [11, 23] |
| Remote LTBI to active TB, $\pi_{4,6}$ | 0.001 [0.00075, 0.00125] | [8, 13] |
| LTBI on IPT to active TB, $\pi_{5,6}$ | 0.0033 [0.002475, 0.004125] | [26] |
| Recovered/Treated to active TB, $\pi_{7,6}$ | 0.01 [0.0075, 0.0125] | [7] |
| LTBI after IPT to active TB, $\pi_{8,6}$ | 0.0033 [0.002475, 0.004125] | [26] |
| $\theta_h$ Relative risk of TB progression for individuals that are: | | [2, 3, 6, 20, 30, 33] |
| HIV−, $\theta_1$ | 1 (fixed value) | |
| HIV+, not on ART, CD4 $>$ 200, $\theta_2$ | 10 [7.5, 12.5] | |
| HIV+, not on ART, CD4 $\leq$ 200, $\theta_3$ | 17 [12.75, 21.25] | |
| HIV+, on ART, $\theta_4$ | 3 [2.25, 5.25] | |
| $1/\pi_{6,7}$ Duration of treatment/recovery (months) | 6 (fixed value) | [18] |
| $1/(\upsilon_h\pi_{6,7})$ Duration of active TB (years) that reflect delays in treatment for: | | [18] |
| HIV−, $1/(\upsilon_1\pi_{6,7})$ | 2.0 [1.6, 2.7] | |
| HIV+, not on ART, CD4 $>$ 200, $1/(\upsilon_2\pi_{6,7})$ | 1.5 [1.2, 2] | |
| HIV+, not on ART, CD4 $\leq$ 200, $1/(\upsilon_3\pi_{6,7})$ | 1.5 [1.2, 2] | |
| HIV+, on ART, $1/(\upsilon_4\pi_{6,7})$ | 1.5 [1.2, 2] | |
| **Parameters that Describe HIV Progression** | | |
| $\eta_{1,2,g}(\tau)$ HIV incidence time-varying rates for gender $g$ at time $\tau$ are calculated using the calibrated factor $\eta_{1,2,g}^{FACTOR}$ for: | | [12] |
| Males $\eta_{1,2,1}^{FACTOR}$ | 1 [0.75, 1.25] | |
| Females $\eta_{1,2,2}^{FACTOR}$ | 1 [0.75, 1.25] | |
| $1/\eta_{2,3,g}$ Duration from HIV infection to CD4 $<$ 200 (years) for: | | [27] |
| Males $1/\eta_{2,3,1}$ | 7.72 [5.79, 9.65] | |
| Females $1/\eta_{2,3,2}$ | 10.25 [7.6875, 12.8125] | |
| **Parameters that Describe Morality Rates** | | |

Continued on next page

**Table 5 – continued from previous page**

| Parameter description | Value [Calibration Range] | Reference |
|---|---|---|
| $\mu_g^{BASELINE}(\tau)$ Baseline mortality time-varying rates for gender $g$ at time $\tau$ calculated using the calibration factor $\mu_g^{FACTOR}$ for: | | [12] |
| Males $\mu_1^{FACTOR}$ | 1 [0.75,1.25] | |
| Females $\mu_2^{FACTOR}$ | 1 [0.75,1.25] | |
| $R_{t,h}$ Increased risk of mortality for those in TB compartment $t$ and HIV compartment $h$ | | need ref |
| No active TB and HIV-, $R_{t,1}, t \neq 6$ | 1 (base rate) | |
| Active TB and HIV-, $R_{6,1}$ | 15.5 [11.625, 19.375] | |
| Active TB and HIV+, not on ART, CD4 $> 200$, $R_{6,2}$ | 26 [19.5, 32.5] | |
| Active TB and HIV+, not on ART, CD4 $\leq 200$, $R_{6,3}$ | 50 [37.5, 62.5] | |
| Active TB and HIV+, on ART, $R_{6,4}$ | 18.5 [13.875, 23.125] | |
| No active TB and HIV+, not on ART, CD4 $> 200$, $R_{t,2}, t \neq 6$ | 8 [6, 10] | |
| No active TB and HIV+, not on ART, CD4 $\leq 200$, $R_{t,3}, t \neq 6$ | 26 [19.5, 32.5] | |
| No active TB and HIV+, on ART, $R_{t,4}, t \neq 6$ | 1.35 [1.2, 1.5] | |

### 5.2.1 HIV Incidence Rates

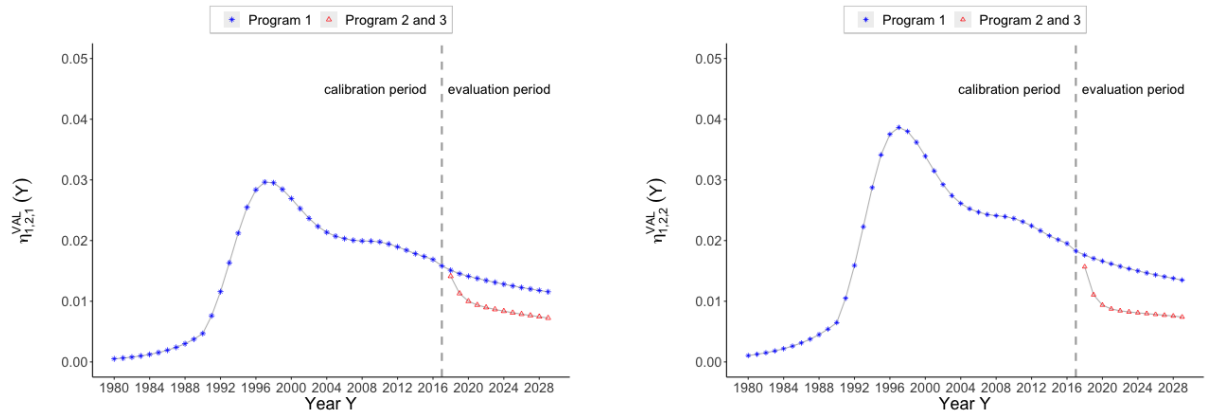
HIV incidence rates, $\eta_{1,2,g}(\tau)$ for gender $g$ at time $\tau$, are calibrated using a multiplication factor denoted $\eta_{1,2,g}^{FACTOR}$ for each gender $g$, and yearly mean HIV incidence estimates denoted $\eta_{1,2,g}^{VAL}(Y)$ for each year $Y$ for each gender $g$. We calculate yearly mean HIV incidence estimates denoted $\eta_{1,2,g}^{VAL}(Y)$ based on the mean number of HIV incidence cases for gender $g$ in *year* $Y$ from the Global Burden of Disease Study 2019 for Kwazulu-Natal, SA [12], denoted $GBD_g^{NHIVinc}(Y)$, and population estimates $GBD_g^{NPOP}(Y)$ projected by the Global Burden of Disease Study 2019 [12] such that,

$$\eta_{1,2,g}^{VAL}(Y) = \frac{GBD_g^{NHIVinc}(Y)}{GBD_g^{NPOP}(Y)}.$$

HIV incidence yearly estimates for males $\eta_{1,2,1}^{VAL}(Y)$ and females $\eta_{1,2,2}^{VAL}(Y)$ are represented in Figure 3. HIV incidence yearly estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/input_parameters/hiv_inc_df.csv`. The source code used to generate these estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/3_hiv_incidence_rate_gen.R`.

Chelsea, Figure 3 says it is for $\eta_{1,2,g}^{VAL}(Y)$, yet it also graphs something for Programs 2 and 3. Are you really graphing $\eta_{1,2,g}(\tau)$?

We apply the calibrated multiplication factor for gender $g$, $\eta_{1,2,g}^{FACTOR}$, to the yearly mean HIV incidence projection $\eta_{1,2,g}^{VAL}(Y)$ to generate annual HIV incidence rates. However, the dynamic




(a) Mean HIV incidence rate, for year $Y$ and males, $\eta^{VAL}_{1,2,1}(Y)$

(b) Mean HIV incidence rate, for year $Y$ and females, $\eta^{VAL}_{1,2,2}(Y)$

Figure 3: Yearly mean HIV incidence estimates for males, $\eta^{VAL}_{1,2,1}(Y)$, and females, $\eta^{VAL}_{1,2,2}(Y)$ from 1980 to 2028 [12]. Over the intervention period between 2018 and 2027, HIV estimates are differentiated by program. HIV incidence rate estimates for Program 1 are in blue and incidence rate estimates for Programs 2 and 3 are in red.

transition model uses monthly incidence rates, so we assume the monthly incidence rate is the same for all months within the year, that is,

$$\eta_{1,2,g}(\tau) = \eta^{FACTOR}_{1,2,g}\eta^{VAL}_{1,2,g}(Y) \quad \text{for} \quad g \in G,\ \tau \in year\ Y, \text{and for } Y\ [1990, 2017]. \tag{37}$$

For all $\eta_{1,2,g}\tau$ associated with years prior to 1980, we set $\eta_{1,2,g}\tau = 0$. We introduce HIV incidence at the beginning of 1980. Since the Global Burden of Disease Study 2019 for Kwazulu-Natal, SA does not estimate HIV incidence before 1990 [12], we assume a linear scale-up of HIV incidence rate estimates from zero in 1980 to the GBD value at 1990. Chelsea, is this for $\eta_{1,2,g}(\tau)$ or for $\eta^{VAL}_{1,2,g}(Y)$? For the time between 1990 and 2017, the HIV incidence rate is calculated using Equation (37). In 2018 we apply the annual rate of change to 2017 estimates. From 2018 through 2027, during the intervention period, we apply the annual rate of change HIV incidence projections for the standard facility-based care program (Program 1) and community-based ART care programs (Program 2 and Program 3) based on Cara et al. [**?**]. Chelsea, it is not clear how you get values for Programs 2 and 3. HIV incidence rates over the intervention period are less for community-based ART programs (Program 2 and Program 3) compared to the standard facility-based care program (Program 1) to represent the impact of increased ART coverage on the risk of HIV transmission for those who are HIV positive, and on ART [4]. Chelsea, it appears that $\eta_{1,2,g}\tau$ depends on the care delivery program. Is that true? Then it should be highlighted in green and discussed in the section on parameter values for care delivery programs.

### 5.2.2 Mortality Rates by TB and HIV Compartments

Mortality rates for populations in TB compartment $t$, HIV compartment $h$ for gender $g$ at time $\tau$ denoted $\mu_{t,h,g}(\tau)$ are calculated from mortality base rate estimates for each gender $g$ for each year $Y$ denoted $\mu^{BASELINE}_g(Y)$, increased risk of mortality for those in TB compartment $t$ and HIV compartment $h$ denoted $R_{t,h}$.

Chelsea, I cannot understand this. Why do you have both $\mu^{BASELINE}_g(Y)$ and $\mu^{BASELINE}_g(\tau)$, when the equation for $\mu_{t,h,g}(\tau)$ only uses $\mu^{BASELINE}_g(\tau)$ and $R_{t,h}$? It seems that something is

wrong here.

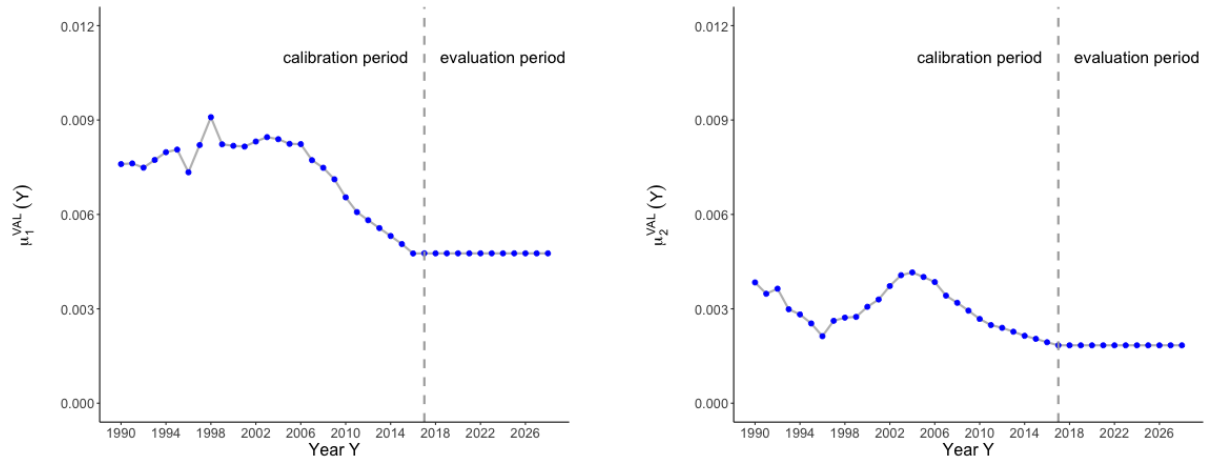
Baseline mortality rates $\mu_g^{BASELINE}(Y)$ for each gender $g$ for year $Y$ are provided in Figure 4. Baseline mortality rates are based on mortality rates for all causes other than TB and/or HIV for males and females between the ages of 15 and 59 from the Global Burden of Disease Study 2019 for Kwazulu-Natal, SA [12]. We calculate yearly baseline mortality rates denoted $\mu_g^{BASELINE}(Y)$ for time steps $\tau$ associated with the years 1990 and 2017 based on the number of all-cause mortality lets call this $GBD_g^{NALLMORT}(Y)$, TB related mortality lets call this $GBD^{NTBMORT}(Y)$ and HIV related mortality for causes other than TB lets call this $GBD^{NHIVMORT}(Y)$ and population estimates $GBD_g^{NPOP}(Y)$ projected by the Global Burden of Disease Study 2019 for for males and females between the ages of 15 and 59 for Kwazulu-Natal, SA [12] such that,

$$\mu_g^{BASELINE}(Y) = \frac{GBD_g^{NALLMORT}(Y) - GBD^{NTBMORT}(Y) - GBD^{NHIVMORT}(Y)}{GBD_g^{NPOP}(Y)}$$

We introduce two baseline mortality calibration factors, $\mu_g^{FACTOR}$ for each gender $g$. Baseline mortality rates $\mu_g^{BASELINE}(\tau)$ for gender $g$ at time $\tau$ change according to the data from year $Y$ associated with time $\tau$. For $\tau$ associated with year $Y$ between 1990 and 2017,

$$\mu_g^{BASELINE}(\tau) = \mu_g^{FACTOR}\mu_g^{VAL}(Y) \quad \text{for} \quad g \in G,\ \tau \in year\ Y$$

For $\tau$ associated with *year* $Y$ between 1940 and 1989 baseline mortality rates are set to 1990 calibrated values. For $\tau$ associated with *year* $Y$ between 2018 and 2028 baseline mortality rates are set to 2017 calibrated values. Baseline mortality values are available at `https://github.com/cgreene3/epi_model_HIV_TB/south_africa/param_files/baseline_mortality.csv`.




(a) Mean baseline mortality rates, for year $Y$ and males, $\mu_1^{VAL}(Y)$

(b) Mean baseline mortality rates, for year $Y$ and females, $\mu_2^{VAL}(Y)$

Figure 4: Yearly mean baseline mortality rate estimates for males, $\mu_1^{VAL}(Y)$, and females, $\mu_2^{VAL}(Y)$ [12] from 1990 to 2028.

We multiply baseline mortality rates $\mu_g^{BASELINE}(\tau)$ with multipliers that represent the increased risk of mortality for those in TB compartment $t$ and HIV compartment $h$, $R_{t,h}$ to calculate mortality rates as,

$$\mu_{t,h,g}(\tau) = R_{t,h}\mu_g^{BASELINE}(\tau) \quad \text{for} \quad g \in G$$

Where $R_{t,h}$ for TB compartments and HIV compartments associated with TB and HIV infections $R_{t,h} > 1$ and $R_{t,h}$ is a calibrated parameter with ranges specified in Table 5. The source code used to generate these estimates can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/2_base_mort_rate_gen.R`. These yearly estimate rates are calculated at each time step while executing the model according to the calibrated base rate for the current year associated with the current time step and increased risk of disease-related mortality.

### 5.3 Parameter Values for Care Delivery Programs

The model parameters that depend on the care delivery program are ART initiation rates from HIV compartments 2 and 3 for gender $g$ at time $\tau$, $\eta_{2,4,g}(\tau)$, $\eta_{3,4,g}(\tau)$, and IPT initiation rates $\kappa_{h,g}(\tau)$ for HIV compartment $h$ and gender $g$ at time $\tau$ as indicated in green in Table 5. ART coverage for year $Y$ denoted $\sigma_g(Y)$ is used to calculate ART initiation rates, $\eta_{2,4,g}(\tau)$, $\eta_{3,4,g}(\tau)$, for each gender $g$ at each time-step $\tau$ using the equations in Section 2.1.

We assume only those in HIV compartment 2 (HIV+, not on ART, CD4>200) and HIV compartment 3 (HIV+, not on ART, CD4≤200) initiate ART and only those in HIV compartment 4 (HIV+, on ART) initiate IPT. Table 6 describes the impact of the three programs by gender on ART coverage and IPT initiation over the program intervention period from the beginning of 2018 to the end of 2027. We provide input parameter values for ART coverage and IPT initiation for the care delivery programs using data from the DO ART trial [4] in Table 6.

| Program Number and Name | ART Coverage %, $\sigma_g(\tau)$, to calculate $\eta_{h,4,g}(\tau), h \in HIV\{2,3\}$ | | IPT Initiation % for $\kappa_{h,g}(\tau), h \in HIV\{4\}$ | |
|---|---|---|---|---|
| | Male g = 1 | Female g = 2 | Male g = 1 | Female g = 2 |
| 1. Standard facility-based ART and IPT care delivery | 49 | 69 | 29 | 28 |
| 2. Community-based ART with standard facility-based care delivery | 82 | 83 | 17 | 23 |
| 3. Community-based ART and IPT care delivery | 82 | 83 | 70 | 75 |

Table 6: Parameter values used for the three programs over the intervention period.

Participants of the DO ART trial were recruited through HIV testing at clinics, community locations, and at home and were diagnosed with HIV. A dried blood spot was collected from each participant to assess HIV viral load at baseline. Then, eligible participants were randomly assigned to either standard facility-based care or community-based ART delivery.

#### 5.3.1 ART Coverage

ART coverage estimates $\sigma_g(\tau)$ are generated based on observations from the DO ART trial [4] and the 2017 South African national HIV prevalence, incidence, behaviour and communication survey [29]. The percent of males and females that achieve viral suppression, let's call this $VS_g$ is from observations from the DO ART trial [4]. While all individuals in the DO ART trial knew their status, we assume not everyone who is HIV positive is diagnosed. We assume only those who are on

ART and virally suppressed experience the benefits of ART (e.g., reduced risk of TB progression). The proportion of males and females diagnosed with HIV, let's call this $DH_g$ and virally suppressed given they are on ART treatment let's call this $AT_g$ is from the 2017 South African national HIV prevalence, incidence, behaviour, and communication survey [29]. We use these values to calculate ART coverage for each gender over the intervention period using the following equation:

$$\sigma_g(\tau) = DH_g \left( \frac{VS_g}{AT_g} \right) \qquad \forall g \in G, \tau \in Year\ Y[2018, 2027].$$

Findings from the DO ART trial indicate that under the baseline Program 1, 51% and 70% of males and females, $VS_1 = 51\%, VS_2 = 70\%$ on ART achieved viral suppression, and under community ART delivery, Program 2 and Program 3, 72% and 73% of males and females who are on ART achieved viral suppression, $VS_1 = 72\%, VS_2 = 73\%$ [4].

One of the findings from the DO ART trial was that the enhanced community-based ART care delivery (compared to the standard care) closed the gender gap in terms of the proportion of individuals virally suppressed given they are on ART treatment [4]. To account for this finding, we assume under facility-based ART care, Program 1, the proportion of individuals virally suppressed given they know their status and are on ART differ by gender, whereas under community-ART care delivery programs, we assume this value is the same for both genders. The 2017 South African national HIV prevalence, incidence, behaviour, and communication survey [29] indicates that 82%, 90%, and 88% of males, females, and both, respectively are virally suppressed given they know their status and on ART. Under the facility-based ART care delivery program (Program 1), we assume the proportion of individuals virally suppressed given they know their status is differentiated by gender, such that $AT_1 = 82\%, AT_2 = 90\%$, whereas under the community-based ART care delivery programs (Program 2 and Program 3) we assume the same value for both genders, such that $AT_1 = AT_2 = 88\%$.

Under the facility-based ART care delivery program (Program 1), we assume 78% and 90% of males and females do not know their status according to findings from the 2017 South African national HIV prevalence, incidence, behaviour and communication survey [29], such that $DH_1 = 78\%, DH_2 = 90\%$. We assume in the community-ART delivery, all individuals in the community will know their status, such that $DH_1 = DH_2 = 100\%$.

These values were used to generate the ART coverage estimates as presented in Table 6 for Program 1 for males ($78\% \times \frac{51\%}{82\%} = 49\%$) and females ($89\% \times \frac{70\%}{90\%} = 69\%$); and Program 2 and Program 3 for males ($100\% \times \frac{72\%}{88\%} = 82\%$) and females ($100\% \times \frac{73\%}{88\%} = 83\%$).

ART coverage is scaled up linearly between 2004 (when ART becomes available) to the start of the intervention period in 2018 for each gender. For all time steps $\tau$ associated with years prior to 2004, ART coverage, $\sigma_g(\tau) = 0$ is set to zero for both genders $g$ to indicate that ART did not exist. From 2004 to 2017, ART coverage is assumed to increase by 3.4% and 4.9% for males and females every year until 2018, so that ART coverage under the standard clinic-based care program is 48% and 69% for males and females. Over the intervention period from the beginning of 2018 to the end of 2027, we assume ART coverage is held constant under each program. The source code used to scale up ART coverage rates is available at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/calculated_param_gen/7_ART_coverage_calc.R` and the input parameters are available at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/input_parameters/art_coverage_df.csv`.

### 5.3.2 IPT Initiation Rates

IPT initiation rates $\kappa_{h,g}(\tau)$ are generated based on direct observations of the proportion of those on ART who initiated IPT from the DO ART trial [4]. In our model, we assume only those who are HIV positive and on ART initiate IPT such that $\kappa_{h,g}(\tau) = 0$ for $h \in \{1, 2, 3\}$ and all $g$ and $\tau$. The independent effect of community-based IPT delivery without community-based ART is not tested within the DO ART trial; however, we test community-based ART delivery with facility-based IPT care by assuming the same ART coverage as seen in community based-delivery trial and the same IPT initiation as seen in the standard of care, Program 1. In Program 1, the proportion of males who are on ART and initiate IPT is ($49\% \times 29\% = 14\%$), and females who are on ART and initiate IPT is ($69\% \times 28\% = 19\%$). In Program 2, the proportion of males and females who are on ART and initiate IPT to 14% and 19%, respectively, such that ($82\% \times 17\% = 14\%$) and ($83\% \times 22\% = 19\%$).

IPT initiation rates are scaled up linearly between 2005 (when IPT becomes widely available) to the start of the intervention period in 2018 for each gender. For all time steps $\tau$ associated with years prior to 2005, IPT initiation rates, $\kappa_{4,g}(\tau) = 0$ is set to zero for both genders $g$ to indicate that IPT was not widely available. After 2005 IPT initiation rates for individuals HIV+, on ART in HIV compartment $h \in HIV\{4\}$ is scaled up linearly between 2005 (when IPT becomes widely available) to 2018 under the standard facility-based ART and IPT care delivery scenario, Program 1. From 2005 to 2018, IPT is assumed to increase by 2.2% for males and 2.1% for females, HIV+ and on ART, every year until 2018. Over the intervention period from 2018 to 2028, we assume IPT initiation is held constant under each program.

## 5.4 Calibration

We generate 100,000 unique parameter sets using latin hypercube sampling in a uniform distribution defined by the ranges of the 34 calibrated parameters in Table 5. The 100,000 parameter sets can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/param_files/input_parameters/calibration_sets_df.csv`. Then, we run the model from 1940 to 2018 for all 100,000 parameter sets in the standard of care, facility-based ART and IPT care scenario (Program 1). For each of these parameter sets we calculate: (1) HIV prevalence per 100,000 males by year denoted $HIVprev\_per_1(Y,\ p = 1)$; (2) HIV prevalence per 100,000 females by year denoted $HIVprev\_per_2(Y,\ p = 1)$, (3) TB incidence per 100,000 males that are HIV positive by year denoted $TBinc\_per_1^{HIV+}(Y,\ p = 1)$, (4) TB incidence per 100,000 females that are HIV positive by year denoted $TBinc\_per_2^{HIV+}(Y,\ p = 1)$, (5) TB incidence per 100,000 males that are HIV negative by year denoted $TBinc\_per_1^{HIV-}(Y,\ p = 1)$, (6) TB incidence per 100,000 females that are HIV negative by year denoted $TBinc\_per_2^{HIV-}(Y,\ p = 1)$, (7) TB mortality per 100,000 males that are HIV positive by year denoted $TBmort\_per_1^{HIV+}(Y,\ p = 1)$, (8) TB mortality per 100,000 females that are HIV positive by year denoted $TBmort\_per_2^{HIV+}(Y,\ p = 1)$, (9) TB mortality per 100,000 males that are HIV negative by year denoted $TBmort\_per_1^{HIV-}(Y,\ p = 1)$, (10) TB mortality per 100,000 females that are HIV negative by year denoted $TBmort\_per_2^{HIV-}(Y,\ p = 1)$. The calculations for these metrics are provided in Section 4. We evaluate each of these ten metrics for 2005 ($year\ Y = 2005$) at the height of the HIV epidemic and 2017 ($year\ Y = 2017$), the last year before the model intervention period, for a total of 20 metrics used in calibration.

We evaluate these 20 metrics against calibration target ranges that represent the 95% confidence interval ranges for males and females between the ages of 15 and 59 from 2019 GBD estimates for Kwazulu-Natal, South Africa [12]. The target calibration ranges can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/tree/master/param_files/target_calibration_estimates`.

We accept a parameter set if all 20 metrics calculated from model outputs fall into the each of the target calibration ranges. 1,708 parameter sets generate model outputs within 100% (20 out of 20) of the calibration target ranges and can be found at `https://github.com/cgreene3/epi_model_HIV_TB_KZN_SA/blob/master/calibration_analysis/accepted_calibration_sets_ref_df.csv`.

Figure 5 illustrates the mean, minimum and maximum values of the 1,708 accepted parameter sets for each of the 10 calibration metrics for the years 1990 to 2017. Metrics generated from model projections that represent the HIV negative and HIV positive populations are shown in red and orange, respectively. The calibration target ranges that represent the HIV negative and HIV positive populations are shown in blue and green, respectively. In the calibration years 2005 and 2017, the calibration target ranges from estimates from the Global Burden of Disease Study 2019 for males and females between the ages of 15 and 59 in Kwazulu-Natal, South Africa [12] are emphasized with lines in the calibration years.

### 5.5 Parameter Values for Disability-Adjusted Life Years

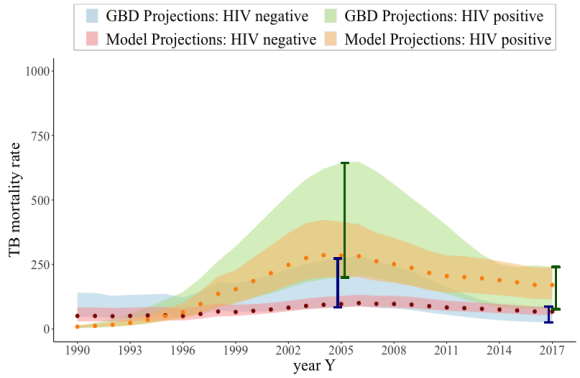
We incorporated disability weights from the Global Burden of Disease Study 2019 [12] to calculate the YLD component of DALYs as summarised in Table 7. Disability weights are associated with disabilities caused by TB and/or HIV infection. In contrast, those without TB infection (not in TB compartment 6) or HIV infection (in TB compartment 1) do not have associated disability weight. The Global Burden of Disease Study 2019 [12] includes stratification over levels of anemia for each associated HIV compartment, but we did not identify data to inform the prevalence and severity of anemia by HIV, TB, and IPT status in South Africa. Since mild anemia is common among people with HIV or HIV-TB co-infection and IPT is not expected to affect anemia prevalence substantially, we applied the disability weight corresponding to mild anemia for all HIV compartments in the analysis. Additionally, the Global Burden of Disease Study 2019 disability weights for an HIV and TB co-infection is not distinguished among levels of HIV disease severity and has a less severe value than AIDS with mild anemia. We substituted the value of AIDS with mild anemia for HIV-TB among PLWH with CD4 $< 200$ (in HIV compartment 3) and active TB (in TB compartment 6).

| Parameter Description | Value | Reference |
|---|---|---|
| $D_{t,h}$ Disability weights for those in TB compartment $t$ and HIV compartment $h$, per year | | [12] |
| No active TB and HIV-, $D_{t,1}, t \neq 6$ | 0 (no disability) | |
| Active TB and HIV-, $D_{6,1}$ | 0.333 | |
| Active TB and HIV+, not on ART, CD4 $> 200$, $D_{6,2}$ | 0.411 | |
| Active TB and HIV+, not on ART, CD4 $\leq 200$, $D_{6,3}$ | 0.583 | |
| Active TB and HIV+, on ART, $D_{6,4}$ | 0.333 | |
| No active TB and HIV+, CD4 $> 200$, $D_{t,2}, t \neq 6$ | 0.016 | |
| No active TB and HIV+, CD4 $\leq 200$, $D_{t,3}, t \neq 6$ | 0.583 | |
| No active TB and HIV+, on ART, $D_{t,4}, t \neq 6$ | 0.081 | |

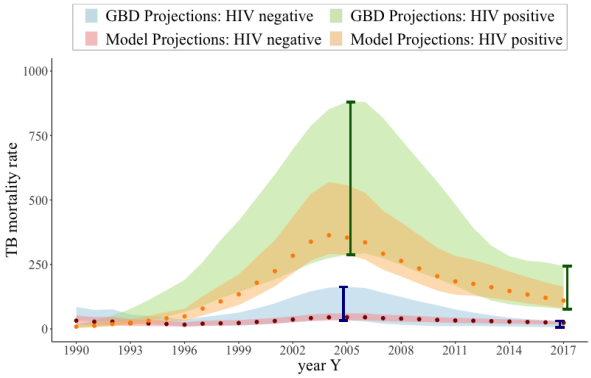
Table 7: Input parameters values for disability weights used to calculate YLD and DALYs

### 5.6 Parameter Values for Program Costs

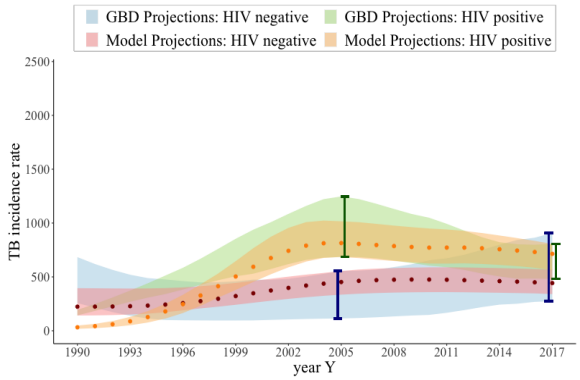
The input parameter values used to generate program costs are summarised in Table 8 and are provided in 2018 US Dollars. Costs for a course of IPT and yearly costs for treatment for PLWH



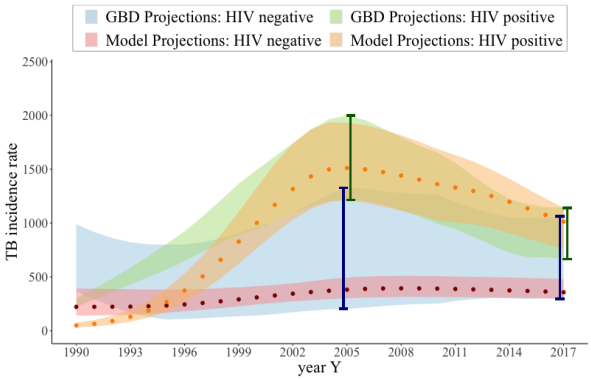

(a) TB mortality rate per 100,000 males in year $Y$ HIV positive $TBmort\_per_1^{HIV+}(Y, p = 1)$ and HIV negative $TBmort\_per_1^{HIV-}(Y, p = 1)$



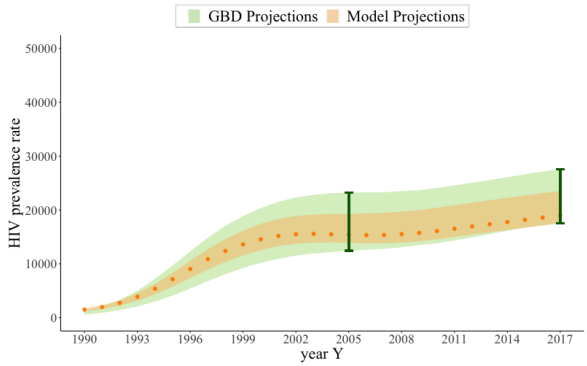

(b) TB mortality rate per 100,000 females in year $Y$ HIV positive $TBmort\_per_2^{HIV+}(Y, p = 1)$ and HIV negative $TBmort\_per_2^{HIV-}(Y, p = 1)$



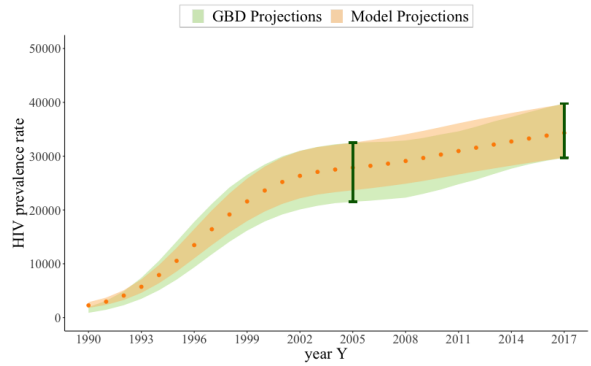

(c) TB incidence rate per 100,00 males in year $Y$ HIV positive $TBinc\_per_1^{HIV+}(Y, p = 1)$ and HIV negative $TBinc\_per_1^{HIV-}(Y, p = 1)$




(d) TB incidence rate per 100,00 females in year $Y$ HIV positive $TBinc\_per_2^{HIV+}(Y, p = 1)$ and HIV negative $TBinc\_per_2^{HIV-}(Y, p = 1)$




(e) HIV prevalence per 100,00 males in year $Y$ $HIVprev\_per_1(Y, p = 1)$




(f) HIV prevalence per 100,00 females in year $Y$ $HIVprev\_per_2(Y, p = 1)$

Figure 5: Maximum, minimum, and mean ranges of TB mortality, TB incidence, and HIV prevalence metrics from accepted parameter sets for each year $Y$ under Program 1, $p = 1$, from 1990 to 2017. Model projections are shown in red and orange for HIV negative and HIV positive populations, respectively. Calibration target ranges from 95% confidence intervals of each metric from the Global Burden of Disease Study 2019 for males and females between the ages of 15 and 59 in Kwazulu-Natal, South Africa [12] are shown in blue and green for HIV negative and HIV positive populations, respectively.

are generated based on multiple factors/sources cited in Table 9.

| Parameter Description | Value | Reference |
|---|---|---|
| **Costs Associated with Preventative Treatments** | | |
| $IPT^{COST}$ Costs for a course of IPT | 20 | [] |
| $ART^{COST}$ Yearly costs to provide ART under | | [4] |
| Program 1 | 249 | |
| Programs 2 and 3 | 310 | |
| **Costs Associated with TB and HIV care** | | |
| $TBcare_r^{COST}$ Costs for a course of TB treatment for those infected with | | |
| DS-TB, $TBcare_1^{COST}$ | 129 | [5] |
| MDR-TB, $TBcare_2^{COST}$ | 1,889 | [25] |
| $Ocare_h^{COST}$ Yearly costs for treatment for HIV positive individuals for causes other than TB for who are | | |
| HIV+, not on ART, CD4 $>$ 200 $Ocare_2^{COST}$ | 168 | |
| HIV+, not on ART, CD4 $\leq$ 200 $Ocare_3^{COST}$ | 222 | |
| HIV+, on ART $Ocare_4^{COST}$ | 81 | |

Table 8: Input parameters values for costs. Costs are provided in 2018 US Dollars.

Costs associated with preventative treatments include costs associated with IPT and ART. Costs of ART delivery, $ART^{COST}$, are defined yearly and differentiated by delivery method to account for additional costs associated with community-based care delivery versus facility-based care [4]. IPT community-based care delivery is nested in the community-based ART care delivery intervention and only provided to those already on ART, so there are no additional costs associated with community-based IPT care delivery versus facility-based care [4]. IPT costs are defined over a six-month course of IPT and are based on multiple references defined in Table 9. IPT costs, $IPT^{COST}$ include the cost of the medication, provider time for counseling [], and provider laboratory costs associated with drug-induced liver injury from IPT [] for a six-month course of IPT as described in Table 9 such that, $20 = 8 + 12 + ((0.00293)(4 + 14))$.

Costs for TB treatment are defined for a course of TB treatment and differentiated by DS-TB and MDR-TB infections to account for differentiated treatment regimen [25]. Costs for treatment for PLWH for causes other than TB $Ocare_h^{COST}$ include outpatient and inpatient care costs and are based on multiple references defined in Table 9. As TB is a leading cause of hospitalization of PLWH in South Africa, we subtracted the costs of TB-related hospitalization from the total reported HIV inpatient care costs to generate estimates of the annual cost of inpatient care for causes other than TB [].

# 6 Results

This section illustrates the results of metrics generated from model outputs, the parameters used in cost model and the equations in Section 4 for each of the three programs over the intervention period from the start of 2018 to the end of 2027 for the years *year* $Y \in [2018, 2027]$. Section 6.1 illustrates results of the metrics including TB mortality, incidence and prevalence. These metrics are derived directly from model outputs (states and transitions) using the equations described in

| Description | Value | Range | Reference |
|---|---|---|---|
| **IPT ($IPT^{COST}$)** | | | |
| Medication cost for 6 months of isoniazid 300mg tabs | $8 | | |
| Provider time cost for delivering 6-month course of IPT | $12 | | |
| Probability of developing IPT-associated drug-induced liver injury (DILI) per month of IPT exposure | 0.00293 | | |
| Cost of outpatient care for IPT-associated DILI (assumes one visit) | $4 | | |
| Laboratory cost for IPT-associated DILI | $14 | | |
| **HIV care ($Ocare_h^{COST}$)** | | | |
| Annual HIV care for people not on ART | $135 | | |
| Annual hospitalization cost for causes other than TB for PLWH not on ART and CD4<200 ($h = 2$) | $87 | | |
| Annual hospitalization cost for causes other than TB for PLWH not on ART and CD4 $\geq$ 200 ($h = 3$) | $34 | | |
| Annual hospitalization cost for causes other than TB for PLWH on ART ($h = 4$) | $81 | | |

Table 9: Components used to generate IPT and HIV care costs. Costs are provided in 2018 US Dollars.

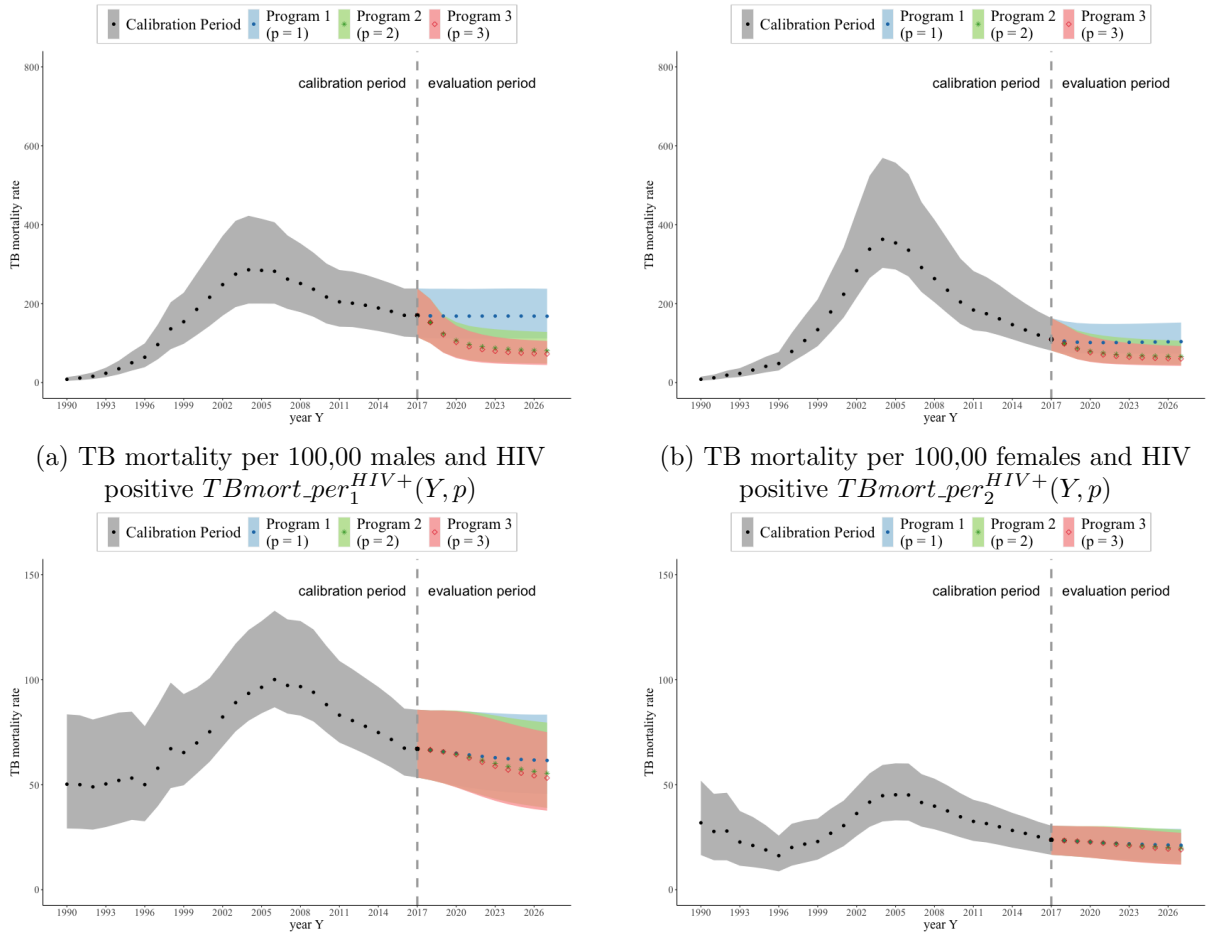
Section 4.2 to Section 4.3. Section 6.2 illustrates results generated from the cost model, including DALYs and costs as well as incremental health gains, additional costs, and cost-effectiveness ratios.

### 6.1 Impacts of Programs on Health Outcomes

We summarise the impacts of programs on health outcomes at different levels of aggregation by HIV status and gender. Figure 6 and Figure 7 illustrate maximum, minimum, and mean yearly TB mortality and incidence rates, respectively, by HIV status and gender, and program over all 1,708 accepted parameter sets. TB mortality rates for males and females are calculated using Equation 14 and Equation 15 in Section 4, for the HIV+ and HIV- population, respectively. TB incidence rates for males and females are calculated using Equation 11 and Equation 12 in Section 4, for the HIV+ and HIV- population, respectively. In the manuscript, we present the impacts of programs on health outcomes by gender (not disaggregated by HIV status) by summing TB mortality and incidence rates for the HIV positive and HIV negative populations for each year and program.

As expected, community-based ART and IPT programs have the greatest impact on the HIV positive population. However, these programs are also projected to reduce TB mortality and incidence rates for the HIV-negative population. It is projected in the year 2027, we would see a 13.6% [6.6%, 19.4%] and 9.9% [2.6%, 16.0%] reduction in TB mortality rates for the HIV-negative population per 100,000 males and females, respectively. As well as a 17.1% [9.8%, 23.1%] and 13.8% [6.0%, 20.2%] reduction in TB incidence rates for the HIV-negative population per 100,000 males and females, respectively.

Community-based ART programs are projected to have the greatest impact on TB mortality and incidence for males. It is projected that by the year 2027, we would see a 52.0% [28.0%, 40.7%] and 34.2% [23.8%, 43.6%] decrease in TB mortality and incidence rates per 100,000 males in implementing Program 2 compared to Program 1. For females, it is projected that by the year




(a) TB mortality per 100,00 males and HIV positive $TBmort\_per_1^{HIV+}(Y,p)$

(b) TB mortality per 100,00 females and HIV positive $TBmort\_per_2^{HIV+}(Y,p)$

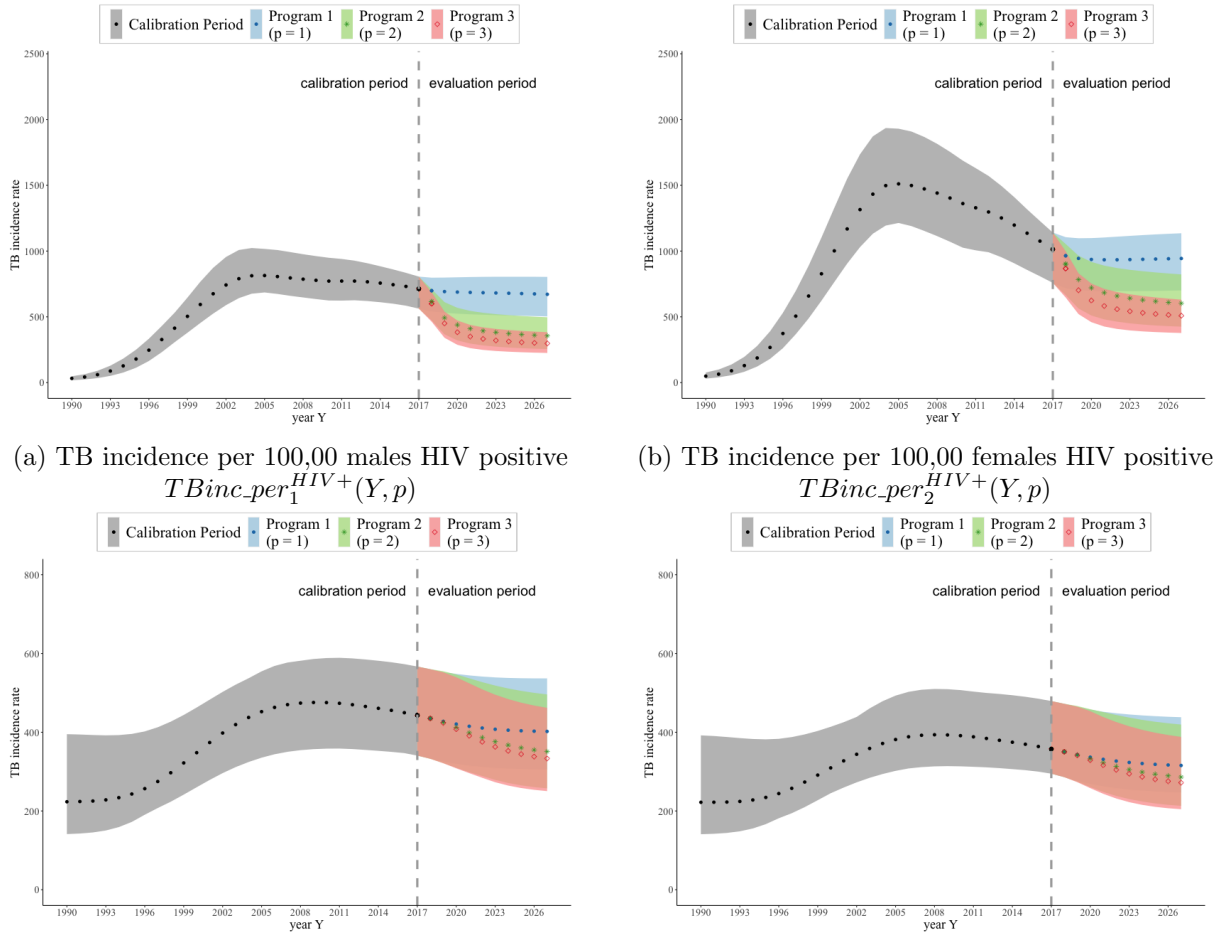
(c) TB mortality per 100,00 males and HIV-negative $TBmort\_per_1^{HIV-}(Y,p)$

(d) TB mortality per 100,00 females and HIV positive $TBmort\_per_2^{HIV-}(Y,p)$

Figure 6: Maximum, minimum, and mean ranges over the 1,708 accepted parameter sets for TB mortality by gender and HIV status. Model projections over the calibration period are shown in grey. Model projections for Program 1, Program 2, and Program 3 are shown in blue, green, and red, respectively.

2027, we would see a 31.4% [21.4%, 40.4%] and 29.5% [20.7%, 37.7%] decrease in TB mortality and TB incidence rates per 100,000 females in implementing Program 2 compared to Program 1. The nested community-based IPT programs further improve TB outcomes for both males and females. It is projected that by the year 2027, we would see a 7.4% [3.2%, 13.6%] and 10.6% [5.3%, 16.8%] decrease in TB mortality and TB incidence rates per 100,000 males in implementing Program 3 compared to Program 2. For females, it is projected that by the year 2027, we would see a 7.2% [3.0%, 14.1%] and 12.1% [6.0%, 19.0%] decrease in TB mortality and TB incidence rates per 100,000 females in implementing Program 3 compared to Program 2.

Figure 8 illustrates yearly TB mortality, TB incidence, and TB prevalence model maximum, minimum and average projections of the 1,708 accepted parameter sets for each program over and year in the intervention period from 2018 to 2027. Population TB mortality, TB incidence, and TB prevalence metrics are calculated using Equation 13, Equation 9, and Equation 16 in Section 4, respectively. By the last year of the intervention period, in 2027, it is projected that we would see




(a) TB incidence per 100,00 males HIV positive $TBinc\_per_1^{HIV+}(Y,p)$

(b) TB incidence per 100,00 females HIV positive $TBinc\_per_2^{HIV+}(Y,p)$

(c) TB incidence per 100,00 males HIV-negative $TBinc\_per_1^{HIV-}(Y,p)$

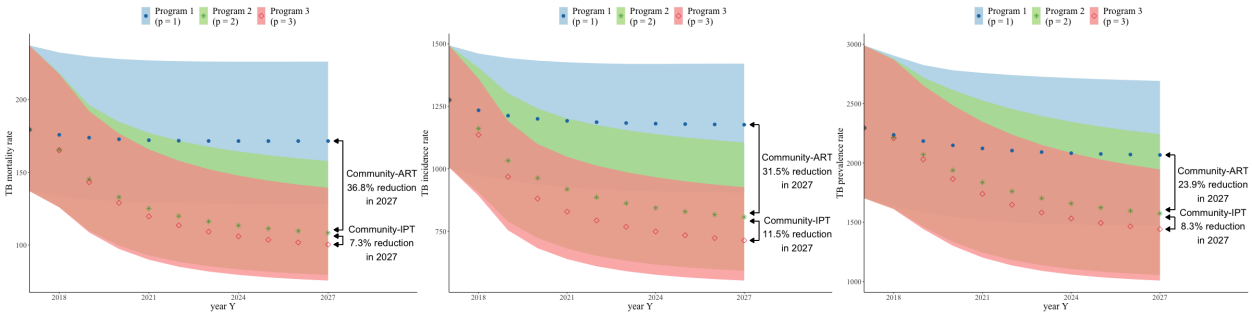
(d) TB incidence per 100,00 females HIV positive $TBinc\_per_2^{HIV-}(Y,p)$

Figure 7: Maximum, minimum, and mean ranges over the 1,708 accepted parameter sets for TB incidence by gender and HIV-status. Model projections over the calibration period are shown in grey. Model projections for Program 1, Program 2, and Program 3 are shown in blue, green, and red, respectively.

36.8% [25.5%, 46.9%] fewer TB deaths with a community-ART intervention compared to facility-based ART (comparing Program 1 to Program 2) and 13.8% [3.1%, 7.3%] fewer TB deaths with a community-IPT intervention compared to facility-based IPT (comparing Program 2 to Program 3). It is projected to see a 31.5% [22.2%, 40.3%] and 11.5% [5.7%, 18.2%] reduction in incident TB cases and a 23.9% [13.0%, 33.1%] and 8.3% [4.0%, 14.4%] reduction in TB prevalence in 2027 with community-based ART and IPT interventions.

## 6.2 Incremental Health Outcomes and Costs

Table 10 summarises the metrics for each program used to calculate the discounted and undiscounted ICERs to assess the per-dollar cost per TB death averted, incident TB case averted, and DALY averted. Discounted metrics are discounted at a rate of 3% to 2018 values using a discounting factor $F(Y)$ as defined in Equation 26 in Section 4. These metrics are summed over all years in the intervention period from the beginning of 2018 to the end of 2027, $Y \in [2018, 2027]$, and are




(a) TB mortality per 100,000 individuals in *year* $Y$ $TBmort\_per(Y,p)$

(b) TB incidence per 100,000 individuals in *year* $Y$ $TBinc\_per(Y,p)$

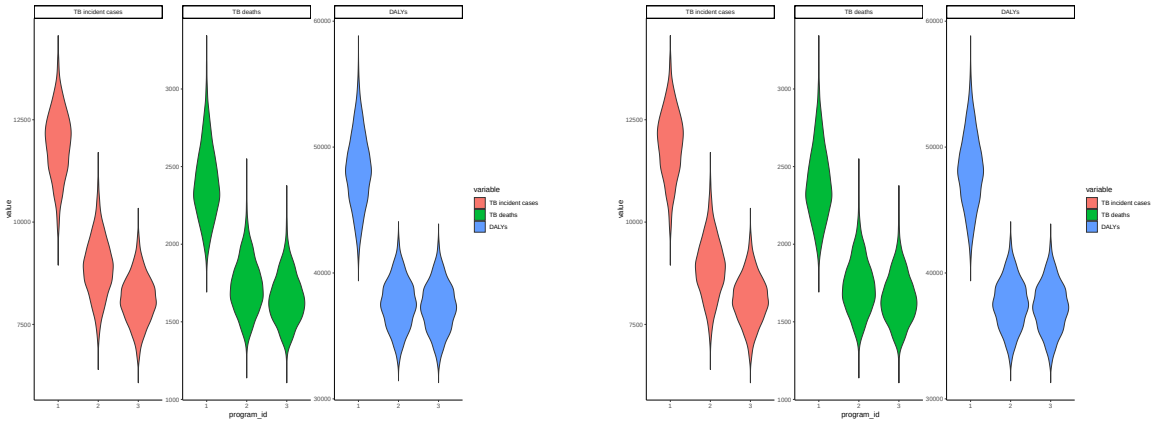
(c) TB prevalence per 100,000 individuals in *year* $Y$ $TBprev\_per(Y,p)$

Figure 8: TB mortality, TB incidence and TB prevalence minimum, maximum, and average projections for each year $Y$ in the intervention period and each program $p$.

calculated for each program and each of the 1,708 accepted parameter sets to generate the average, maximum and minimum of undiscounted and discounted metrics used in the economic evaluation including TB incidence, TB mortality, DALYs and costs summarised in Table 10 and illustrated in Figure 9.

| | **Standard facility-based ART and IPT care delivery (p = 1)** | **Community-based ART care delivery with standard facility-based IPT care (p = 2)** | **Community-based ART and IPT care delivery (p = 3)** |
|---|---|---|---|
| **Undiscounted Metrics** | | | |
| Incident TB cases $UTBinc\_total(p)$ | 12130 [9432, 14521] | 9014 [6724, 11798] | 8189 [6350, 10325] |
| TB mortality $UTBmort\_total(p)$ | 1754 [1319, 2314] | 1233 [917, 1737] | 1177 [888, 1613] |
| DALY $UDALY(p)$ | 48433 [40718, 57471] | 37531 [32482, 43655] | 37281 [32263, 43379] |
| Costs $UCost\_total(p)$ | 38272307 [34153398, 44179116] | 99779331 [88676813, 114979272] | 99946920 [88842986, 115186898] |
| **Discounted Metrics** | | | |
| Incident TB cases $DTBinc\_total(p)$ | | | |
| TB mortality $DTBmort\_total(p)$ | | | |
| DALY $DDALY\_total(p)$ | 42562 [35803,50484] | 33184 [28727,38602] | 32970 [28540,38366] |
| Costs $DCost\_total(p)$ | 33598300 [29989215,38789060] | 87524399 [77791445,100880389] | 87682214 [77946368,101075500] |

Table 10: Discounted metrics are presented in 2018 values. Values are the mean, minimum and maximum values of the 1,708 accepted parameter sets for each program.




(a) Undiscounted Metrics

(b) Discounted Metrics

Figure 9: Discounted and Undiscounted metrics

We use the costs, TB deaths, incident TB cases, and DALY metrics summarised in Table 10 to calculate incremental cost-effectiveness ratios (ICERs) that describe the unit cost per TB death averted, TB incident case averted, and DALYs over the intervention period from the beginning of 2018 to the end of 2027 as summarised in Table 11. The calculations for ICERs are described in Section 4.6. Health outcomes (TB deaths averted, incident TB cases averted, and DALYs) are representative of the numerator in the ICER equations, whereas costs are representative of the denominator in the ICER equations. We compare standard facility-based programs $p$ to community-based care delivery intervention programs $\tilde{p}$ including:

1. Program 1 ($p = 1$) to Program 2 ($\tilde{p} = 2$) to evaluate the incremental benefit of a community-based ART intervention,
2. Program 1 ($p = 1$) compared to Program 3 ($\tilde{p} = 3$) to evaluate the incremental benefit of a community-based ART and IPT intervention and
3. Program 2 ($p = 2$) compared to Program 3 ($\tilde{p} = 3$) to evaluate the incremental benefit of a community-based IPT intervention (assuming community-based ART is already implemented)

| | **Community-based ART, vs Standard of Care** $\tilde{p} = 2$ , $p = 1$ | **Community-based ART and IPT, vs Standard of Care** $\tilde{p} = 3$ $p = 1$ | **Community-based ART and IPT, vs Community-based ART** $\tilde{p} = 3$ $p = 2$ |
|---|---|---|---|
| **Undiscounted health outcomes and costs** | | | |
| TB deaths averted | | | |
| Incident TB cases averted | | | |
| DALYs averted | | | |
| Additional program costs | | | |
| **Discounted health outcomes and costs** | | | |
| TB deaths averted | | | |
| Incident TB cases averted | | | |
| DALYs averted | | | |
| Additional program costs | | | |
| **Undiscounted ICERs** | | | |
| Cost per TB death averted | | | |
| Cost per TB incident case averted | | | |
| Cost per DALY averted | | | |
| **Discounted ICERs** | | | |
| Cost per TB death averted | | | |
| Cost per TB incident case averted | | | |
| Cost per DALY averted | | | |

Table 11: Discounted metrics are presented in 2018 values. Values are the mean, minimum and maximum values over the 1,708 accepted parameter sets. The calculations for ICERs are described in Section 4.6. Undiscounted and discounted health outcomes are representative of the numerator in the ICER equations, where undiscounted and discounted costs are representative of the denominator in the ICER equations. CG: to do add mathematical notation

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