Mathematical Analysis of the Tuberculosis and Human Immunodeficiency Virus Syndemic

Malachi Vaughn[*], Kwabena Agyemang[†], Jada Onwuta[‡]

Tamantha Pizzarro[*], Claudia P. Ferreira[§]

Arizona State University[*], Lorain County Community College[†], Wellesley College[‡]

São Paulo State University[§]

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1 Abstract

In this work, we propose a continuous deterministic model to explore the interaction between human immunodeficiency virus (HIV) and pulmonary tuberculosis (TB). The model consists of six epidemiological classes, namely susceptible individuals, latent TB cases, active TB cases, undiagnosed HIV cases, diagnosed HIV cases, and individuals with AIDS. It includes death, progression, recovery, and diagnosis rates, as well as proportional treatment coverage. In the model, co-infection results in immediate transferral to the AIDS class. Depending on the parameter space, we found four possible equilibria: disease-free, TB-only, HIV-only, and disease coexistence. The single-disease equilibria's existence and stability primarily depend on thresholds R_{TB} and R_{HIV}. We obtain these by analyzing the two single-disease submodels. The disease-free equilibrium is locally asymptotically stable given that $\max\{R_{TB}, R_{HIV}\} < 1$. The exact nature of the disease interactions has high importance for the existence of the coexistence equilibrium. When such an equilibrium exists, however, it is always unstable. Finally, sensitivity analysis indicates that increasing treatment for either disease reduces the *per capita* transition rate to AIDS due to co-infection, with treatment for TB having the stronger influence of the two.

2 Introduction

Pulmonary Tuberculosis (TB) is an airborne bacterial infection caused by the bacteria *Mycobacterium tuberculosis* (*Mtb*). Tuberculosis can be divided into two categories: latent tuberculosis (LTBI) and active tuberculosis. *Mtb* infects susceptible individuals when they breathe in particles from an individual with active TB. When the bacteria enters the body, it triggers an immune response. An individual with LTBI may be asymptomatic and cannot transmit the infection due to Mtb being dormant in the body. When Mtb proliferates within the body, the individual develops

active TB, and gains the ability to transmit the bacteria. Symptoms include coughing, weakness, and fever. Individuals with latent TB can develop active TB, some faster than others. Both LTBI and active TB are treatable and curable [1].

Human immunodeficiency virus (HIV) is a retrovirus that causes HIV infections. Individuals become infected with HIV by coming into contact with the blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, or breast milk of an infected individual. The main target for HIV is the CD4 T lymphocytes (CD4 cells). These cells help to coordinate the body's immune response. By attacking and destroying CD4 cells, HIV jeopardizes the immune response preventing the body from fighting off infectious agents such as viruses and bacteria. Without proper treatment, HIV infection can progress to acquired immunodeficiency syndrome (AIDS). HIV-positive individuals can become diagnosed with AIDS by meeting one of two criteria: having a CD4 count of less than 200 cells per mm^3, or by contracting an opportunistic infection. Both HIV and AIDS are incurable, but treatment exists to slow the progression from HIV to AIDS [2].

TB is endemic to and most prevalent in low and middle-income countries and regions. Overall, the spread of HIV is higher in sub-Saharan Africa, with other regions containing a number of high-burden countries. It has been shown that the existence of HIV in a given population can influence the existence of TB within that same population, and vice-versa [3]. Therefore, it is logical to classify the interaction between HIV and TB in a population as a syndemic, where the term syndemic refers to a situation in which the interaction between different health conditions contributes to a higher burden of disease within a population [4].

Immunological and epidemiological mathematical models have been used to combat HIV and TB by providing a guide for controlling mechanisms such as treatment and screening. These models can support public health programs to promote action that reduces deaths caused by both diseases. Here, we present some continuous deterministic epidemiological models focused on the HIV/TB

syndemic. In Naresh *et al.*, a nonlinear ordinary differential model (ODE) is proposed to study the effect of TB on the spread of HIV infection in a logistically growing human population. The population is divided into susceptibles, TB infectives, HIV infectives (with or without TB) and AIDS individuals. It is considered that interaction between TB and HIV individuals moves individuals from the TB compartment to the HIV compartment. The model exhibits four equilibria: a disease-free, a TB-only, a HIV-only, and a coexistence equilibrium. The disease-free equilibrium is locally asymptotically stable if $R_0 = \max\{R_{TB}, R_{HIV}\} < 1$, otherwise, at least one of the infections will persist. The R_{TB} and R_{HIV} are the basic reproduction numbers for TB and HIV diseases, respectively. The coexistence equilibrium exists if $R_0 > 1$ and it is globally stable under certain conditions (given by a Lyapunov function). Focusing on the effect of TB on HIV infectives, the increase of TB promotes the increase in HIV and AIDS infectives [5]. If new individuals enter the population at a constant rate, then the TB-only and HIV-only equilibria are unstable [6].

Sharomi *et al.* used a nonlinear ODE model with fifteen equations that describe the epidemiological status of individuals as susceptible, single-infected and co-infected individuals, asymptomatic and symptomatic HIV individuals, latent and active TB individuals, treated and untreated individuals. The aim is to study the synergistic interaction between TB and HIV in a sexually active population. Transmission of either HIV or TB occurs through contact with a singly-infected individual or through contact with a co-infected individual. A co-infected individual can not transmit the mixed infection. Furthermore, for individuals in treatment, disease transmission occurs at a lower rate compared to the untreated one. Analysis of the full model supports the conclusion that HIV-targeted treatment reduces co-infection cases more than TB-targeted treatment. So if resources are limited, the results of the model support the targeted treatment of one disease rather than the targeted treatment of the co-infection [7].

In the following sections, we present a six-dimensional ODE system that models the transmission

of TB and HIV in a population, and conduct various mathematical analyses on said system. We aimed to construct a model that combined a balance of simplicity along with essential characteristics of interactions inspired by previous work [5] [6] [7] . The existence and stability of equilibrium points are determined either analytically or numerically. A sensitivity analysis is conducted and highlights the particular importance of treatment to stop the progression of HIV infection to the stage called AIDS.

3 Objective

Our goal is to propose a mathematical model that captures the main characteristics of the HIV and Tuberculosis syndemic in order to understand the interaction of these diseases and whose outcome contributes to AIDS. Therefore, based on epidemiological and mathematical literature about HIV and TB transmission and progression, we formulated the following questions:

1. Which disease plays the most important role in coexistence?
2. Which parameters play the most important role for each disease threshold?
3. How does HIV and TB treatment impact the transmission and prevalence of each disease?
4. How do HIV diagnosis rates influence the prevalence of AIDS?

4 Mathematical Model

The model was formulated taking into account the following assumptions. First, individuals with latent TB cannot transmit the disease to others. In addition, treatment for latent TB only prevents individuals from advancing to active TB [8]. Therefore, the only mode for transitioning back to the

susceptible class from the latent TB class in our model is natural recovery. Treatment of individuals with active TB has the additional effect of lowering the disease's additional death rate, increasing their recovery rate, and eliminating their ability to transmit TB to others [9]. Individuals with HIV do not move back to the susceptible population under any circumstances [10]. Treatment of HIV has a twofold function: lessening of transmission of HIV to others, and lessening the transition rate to AIDS [11]. Also, individuals in the AIDS class do not transmit either disease and do not recover from TB.

Based on the epidemiological knowledge of TB and HIV, how they interact, and the objective of the work, we split the individuals with tuberculosis into two classes because of the unique nature of latent TB with respect to active TB. We also split the HIV-positive individuals into two classes supposing that those who know they are infected will behave differently compared to those who are unaware of their infection, highly impacting the degree to which they spread HIV. Finally, a single AIDS class comprises individuals with and without TB (Table 1).

Table 1: Description of the compartments of the mathematical model that divides the population into epidemiological classes.

Variable	Definition
S	Susceptible
L, T	Latent TB, Active TB
U, D	Undiagnosed HIV, Diagnosed HIV
A	AIDS (include HIV/TB)

4.1 Ordinary differential equation model for TB/HIV syndemic

Here we describe step by step the construction of the mathematical model. It is an ordinary differential equation (ODE) model. Therefore, the instantaneous change in a compartment is calcu-

lated by the difference between the entrance and exit of individuals in this compartment (see Table 1). A homogeneous mixing pattern of transmission is assumed for both infections.

Susceptible class S receives new members through influx Ω as well as through the recovery of individuals from latent L and active T tuberculosis classes. Individuals leave the susceptible class through infection to TB via contact with an untreated individual from T, or infection to HIV via contact with an individual from undiagnosed HIV class U or someone from diagnosed HIV class D who is not in treatment. Individuals can also leave this class through natural death. The first equation in our system is thus

$$S' = \Omega + L\rho_L + T\rho_T - S(\Lambda_{ST}(1-\tau_T) + \Lambda_{SU} + \Lambda_{SD}(1-\tau_D) + \mu).$$

Latent TB class L receives new individuals through a member of the S class becoming infected with TB through contact with individuals from T not receiving treatment. Individuals can leave the L class through progression to T, through HIV infection via contact with individuals from U and individuals from D not in treatment, through natural recovery to S, and through natural death. The second equation in our system is thus

$$L' = S\Lambda_{ST}(1-\tau_T) - L(\gamma_L(1-\tau_L) + \Lambda_{LU} + \Lambda_{LD}(1-\tau_D) + \rho_L + \mu).$$

Active TB class T receives new individuals only through the natural progression of individuals in L. Individuals can leave T by recovering and moving to S, through dying due to their TB infection, or through natural death. Thus the third equation in our system is

$$T' = L\gamma_L(1-\tau_L) - T(\rho_T + \delta_T + \mu).$$

Undiagnosed HIV class U receives new members through a member of S becoming infected with HIV via contact with a member of U or a member of D not receiving treatment. Members can leave U through natural progression to AIDS, through accelerated progression to AIDS through a

TB infection arising from contact with an untreated member of T, through becoming diagnosed with HIV and therefore moving to D, or through natural death. Thus the fourth equation in our system is

$$U' = S(\Lambda_{SU} + \Lambda_{SD}(1 - \tau_D)) - U(\gamma_H + \Lambda_{UT}(1 - \tau_T) + \psi + \mu).$$

Diagnosed HIV class D receives new members through the diagnosis of individuals in U with HIV. Members can leave by progressing naturally to AIDS (if not in treatment)[1], through accelerated progression to AIDS from a TB infection resulting from contact from an untreated individual in T (regardless of the recipient's treatment status[1]), as well as through natural death. The fifth equation in our system is thus

$$D' = U\psi - D(\gamma_H(1 - \tau_D) + \Lambda_{DT}(1 - \tau_T) + \mu).$$

AIDS class A receives new members from a variety of avenues. A member of L may transition to AIDS by contacting and being infected by a member of U or a member of D not receiving treatment. Members of U and D may progress to AIDS naturally (given that the individual in D is not in treatment), or they may experience accelerated progression to AIDS through coming into contact with and being infected by an untreated member of T. Members of A can leave only through an accelerated death due to their AIDS or through natural death. Thus the sixth and final equation in our system is

$$A' = L(\Lambda_{LU} + \Lambda_{LD}(1 - \tau_D)) + U(\gamma_H + \Lambda_{UT}(1 - \tau_T)) + D(\gamma_H(1 - \tau_D) + \Lambda_{DT}(1 - \tau_T)) - A(\delta_A + \mu).$$

Figure 1 shows the diagram of the proposed compartmental model, and Table 2 describes its parameters.

[1]See model assumptions

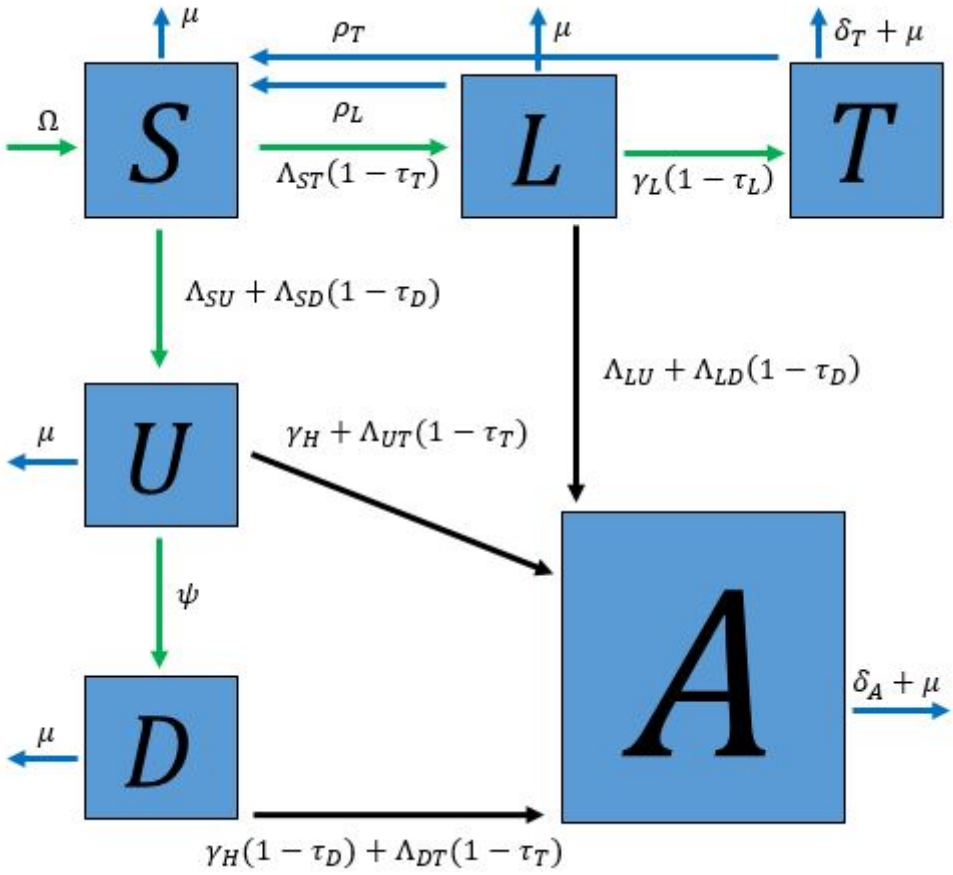

Figure 1: Diagram of the compartmental model. The epidemiological classes are susceptible (S), latent TB (L), active TB (T), undiagnosed HIV (U), diagnosed HIV (D), and AIDS (A). The arrows show the flux between compartments. The parameters are described in Table 2 with $\Lambda_{XY} = \beta_{XY} Y$, and $X \in \{S, L, U, D\}, Y \in \{T, U, D\}$.

Table 2: Description of model parameters and their units. The subscripts X or Y identify the epidemiological class S, L, T, U, D or A.

Parameter	Definition	Units
Ω	new susceptibles arrival rate	[individual][time]$^{-1}$
μ	*per capita* natural mortality rate	[time]$^{-1}$
γ_X	*per capita* progression rate	[time]$^{-1}$
δ_X	additional *per capita* mortality rate	[time]$^{-1}$
β_{XY}	*per capita* transmission rate	[time×individual]$^{-1}$
ψ	*per capita* diagnosis rate of HIV	[time]$^{-1}$
ρ_X	*per capita* recovery rate	[time]$^{-1}$
τ_X	proportion of individuals in treatment	–

Putting together the six equations described before into a single system yields the following ODE system:

$$
\begin{aligned}
S' &= \Omega + L\rho_L + T\rho_T - S(\Lambda_{ST}(1-\tau_T) + \Lambda_{SU} + \Lambda_{SD}(1-\tau_D) + \mu) \\
L' &= S\Lambda_{ST}(1-\tau_T) - L(\gamma_L(1-\tau_L) + \Lambda_{LU} + \Lambda_{LD}(1-\tau_D) + \rho_L + \mu) \\
T' &= L\gamma_L(1-\tau_L) - T(\rho_T + \delta_T + \mu) \\
U' &= S(\Lambda_{SU} + \Lambda_{SD}(1-\tau_D)) - U(\gamma_H + \Lambda_{UT}(1-\tau_T) + \psi + \mu) \\
D' &= U\psi - D(\gamma_H(1-\tau_D) + \Lambda_{DT}(1-\tau_T) + \mu) \\
A' &= L(\Lambda_{LU} + \Lambda_{LD}(1-\tau_D)) + U(\gamma_H + \Lambda_{UT}(1-\tau_T)) - A(\delta_A + \mu) \\
&\quad + D(\gamma_H(1-\tau_D) + \Lambda_{DT}(1-\tau_T))
\end{aligned}
$$

where

$$\delta_T = \delta_{T1}(1-\tau_T) + \delta_{T2}\tau_T, \quad \delta_A = \delta_{A1}(1-\tau_A) + \delta_{A2}\tau_A \quad \text{and} \quad \rho_T = \rho_{T1}(1-\tau_T) + \rho_{T2}\tau_T.$$

The additional mortality to members of T and A, as well as the recovery rate of individuals in T, is adjusted by weighing the overall value according to whether individuals are in treatment or not, and the corresponding values for each type of individual.

The total population can be represented by

$$N = S + L + T + U + D + A.$$

It is convenient to define $z = \frac{\Omega}{\mu}$, and normalize the model by dividing each population by z

$$s = \frac{S}{z},\ \ell = \frac{L}{z},\ t = \frac{T}{z},\ u = \frac{U}{z},\ d = \frac{D}{z},\ a = \frac{A}{z}.$$

Therefore,

$$N' = \Omega - \mu N - T\delta_T - A\delta_A,$$

and the ODE system can now be rewritten as:

$$
\begin{aligned}
s' &= \mu + \bar{\ell}\rho_L + \bar{t}\rho_T - \bar{s}(\bar{t}\tilde{\beta}_{ST} + \bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD} + \mu) \\
\ell' &= \bar{s}\bar{t}\tilde{\beta}_{ST} - \bar{\ell}(\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD} + \gamma_L(1-\tau_L) + \rho_L + \mu) \\
t' &= \bar{\ell}\gamma_L(1-\tau_L) - \bar{t}(\rho_T + \delta_T + \mu) \\
u' &= \bar{s}(\bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD}) - \bar{u}(\gamma_H + \bar{t}\tilde{\beta}_{UT} + \psi + \mu) \\
d' &= \bar{u}\psi - \bar{d}(\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT} + \mu) \\
a' &= \bar{\ell}(\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD}) + \bar{u}(\gamma_H + \bar{t}\tilde{\beta}_{UT}) + \bar{d}(\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT}) - \bar{a}(\delta_A + \mu)
\end{aligned}
$$

with

$$
\begin{aligned}
&\tilde{\beta}_{SU} = z\beta_{SU}, \quad \tilde{\beta}_{ST} = z\beta_{ST}(1-\tau_T), \quad \tilde{\beta}_{SD} = z\beta_{SD}(1-\tau_D), \quad \tilde{\beta}_{LU} = \chi_{HIV}\ z\beta_{SU}, \\
&\tilde{\beta}_{LD} = \chi_{HIV}\ z\beta_{SD}(1-\tau_D), \quad \tilde{\beta}_{UT} = \chi_{TB}\ z\beta_{ST}(1-\tau_T), \quad \tilde{\beta}_{DT} = \chi_{TB}\ z\beta_{ST}(1-\tau_T).
\end{aligned}
$$

The parameters χ_{TB} and χ_{HIV} represent the co-infection transmissibility factors for TB and HIV, respectively. These two factors increase the rate of transition to the A class for individuals who are initially infected with one disease compared to those in the S class. When χ_{HIV} (χ_{TB}) is in the interval $[0, 1)$, TB-infected individuals (HIV-infected individuals) after getting infected by HIV (TB), progress slower to AIDS compared with susceptible individuals that become infected with HIV. When χ_{HIV} (χ_{TB}) is bigger than 1, (TB/HIV)-infected individuals progress faster to AIDS after getting infected by (HIV/TB). In particular, $\chi_{HIV} = 0$ ($\chi_{TB} = 0$) means that TB-infected individuals (HIV-infected individuals) do not get infected by HIV (TB), and $\chi_{HIV} = \chi_{TB} = 1$ means that co-infection does not accelerate the rate at which individual progress to A.

4.2 Describing steady states of the system

To find steady states for the system, we must solve the normalized equations' associated homogeneous system:

$$0 = \mu + \bar{\ell}\rho_L + \bar{t}\rho_T - \bar{s}(\bar{t}\tilde{\beta}_{ST} + \bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD} + \mu) \tag{1}$$

$$0 = \bar{s}\bar{t}\tilde{\beta}_{ST} - \bar{\ell}(\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD} + \gamma_L(1-\tau_L) + \rho_L + \mu) \tag{2}$$

$$0 = \bar{\ell}\gamma_L(1-\tau_L) - \bar{t}(\rho_T + \delta_T + \mu) \tag{3}$$

$$0 = \bar{s}(\bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD}) - \bar{u}(\gamma_H + \bar{t}\tilde{\beta}_{UT} + \psi + \mu) \tag{4}$$

$$0 = \bar{u}\psi - \bar{d}(\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT} + \mu) \tag{5}$$

$$0 = \bar{\ell}(\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD}) + \bar{u}(\gamma_H + \bar{t}\tilde{\beta}_{UT}) + \bar{d}(\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT}) - \bar{a}(\delta_A + \mu). \tag{6}$$

From (3) we have

$$\bar{t} = \frac{\gamma_L(1-\tau_L)}{\rho_T + \delta_T + \mu}\bar{\ell}. \tag{7}$$

Substituting for $\bar{t}$ in (2), we have

$$0 = \bar{\ell}\left(\bar{s}\frac{\gamma_L(1-\tau_L)\tilde{\beta}_{ST}}{\rho_T + \delta_T + \mu} - (\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD} + \gamma_L(1-\tau_L) + \rho_L + \mu)\right).$$

For this to hold, one of two conditions must be met:

$$\bar{\ell} = 0 \quad \text{or} \quad \bar{s} = (\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD} + \gamma_L(1-\tau_L) + \rho_L + \mu)\left(\frac{\rho_T + \delta_T + \mu}{\gamma_L(1-\tau_L)\tilde{\beta}_{ST}}\right). \tag{8}$$

We will analyze these conditions separately.

4.2.1 Tuberculosis-free equilibria

As stated, $\bar{\ell} = 0 \Longrightarrow \bar{t} = 0$. Substituting into the system then gives us the 4-equation HIV-only subsystem:

$$\begin{aligned} 0 &= \mu - \bar{s}(\bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD} + \mu) && (9)\\ 0 &= \bar{s}(\bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD}) - \bar{u}(\gamma_H + \psi + \mu) && (10)\\ 0 &= \bar{u}\psi - \bar{d}(\gamma_H(1-\tau_D) + \mu) && (11)\\ 0 &= \bar{u}\gamma_H + \bar{d}\gamma_H(1-\tau_D) - \bar{a}(\delta_A + \mu). && (12) \end{aligned}$$

From (11) and (12) we have

$$\bar{d} = \frac{\bar{u}\psi}{\gamma_H(1-\tau_D) + \mu} \quad \text{and} \quad \bar{a} = \frac{\bar{u}\gamma_H + \bar{d}\gamma_H(1-\tau_D)}{\delta_A + \mu}.$$

Substituting these in (10) and factoring for $\bar{u}$, we have

$$\bar{u}\left[\bar{s}\left(\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\mu}\right) - (\gamma_H + \psi + \mu)\right] = 0.$$

This forces one of two possibilities,

$$\bar{u} = 0 \quad \text{or} \quad \bar{s} = \frac{\gamma_H + \psi + \mu}{\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\mu}}.$$

Therefore, we have two steady states.

1. $E_{DF} = (1, 0, 0, 0, 0, 0)$

   This is the disease-free equilibrium, where 100% of our population is in the susceptible class, and 0% of our population is in the latent TB, active TB, undiagnosed HIV, diagnosed HIV,

and AIDS classes.

2. $E_{HIV} = (\bar{s}, 0, 0, \bar{u}, \bar{d}, \bar{a})$

   Considering the second case, we can substitute for $\bar{d}$ in (9), obtaining an expression of $\bar{u}$ in terms of $\bar{s}$:

$$\bar{u} = \frac{\mu(1-\bar{s})}{\bar{s}(\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\mu})} = \frac{\mu(1-\bar{s})}{\gamma_H + \psi + \mu}.$$

   Now that we have $\bar{u}$ in terms of $\bar{s}$, which itself can be expressed in terms of only parameters, we can also express $\bar{d}$, $\bar{a}$, and thereby the entire HIV-only equilibrium in terms of only parameters:

$$\bar{s} = \frac{\gamma_H + \psi + \mu}{\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\mu}}, \quad \bar{u} = \frac{\mu(1-\bar{s})}{\gamma_H + \psi + \mu}, \quad \bar{d} = \frac{\bar{u}\psi}{\gamma_H(1-\tau_D) + \mu}, \quad \bar{a} = \frac{\bar{u}\gamma_H + \bar{d}\gamma_H(1-\tau_D)}{\delta_A + \mu}.$$

4.2.2 Tuberculosis-persistent equilibria

Let's explore the other possibility in (8), which is

$$\bar{s} = (\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD} + \gamma_L(1-\tau_L) + \rho_L + \mu)\left(\frac{\rho_T + \delta_T + \mu}{\gamma_L(1-\tau_L)\tilde{\beta}_{ST}}\right). \tag{13}$$

From (5) we have

$$\bar{d} = \frac{\bar{u}\psi}{\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT} + \mu}. \tag{14}$$

Substituting for $\bar{d}$ in (4) and factoring out $\bar{u}$, we get

$$0 = \bar{u}\left[\bar{s}\left(\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT} + \mu}\right) - (\gamma_H + \bar{t}\tilde{\beta}_{UT} + \psi + \mu)\right]$$

which yields two possibilities,

$$\bar{u} = 0 \quad \text{or} \quad \bar{s} = \frac{\gamma_H + \bar{t}\tilde{\beta}_{UT} + \psi + \mu}{\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\bar{t}\tilde{\beta}_{DT}+\mu}}. \tag{15}$$

Again, we can explore each condition separately.

3. $E_{TB} = (\bar{s}, \bar{\ell}, \bar{t}, 0, 0, 0)$

   Let us assume $\bar{u} = 0$. Since $\bar{u} = 0 \implies \bar{d}, \bar{a} = 0$ (see (14) and (6), respectively), the system becomes

$$\begin{aligned} 0 &= \mu + \bar{\ell}\rho_L + \bar{t}\rho_T - \bar{s}(\bar{t}\tilde{\beta}_{ST} + \mu) && (16)\\ 0 &= \bar{s}\bar{t}\tilde{\beta}_{ST} - \bar{\ell}(\gamma_L(1-\tau_L) + \rho_L + \mu) && (17)\\ 0 &= \bar{\ell}\gamma_L(1-\tau_L) - \bar{t}(\rho_T + \delta_T + \mu) && (18) \end{aligned}$$

   and, putting aside the aforementioned disease-free equilibrium, we arrive at an equilibrium point $(\bar{s}, \bar{\ell}, \bar{t}, 0, 0, 0)$. Using (7) to substitute for $\bar{t}$ in (17), we can then divide both sides of the expression by $\bar{\ell}$ (since $\bar{\ell} \neq 0$), and thereby arrive at an expression for $\bar{s}$ in terms of only parameters:

$$\bar{s} = \frac{(\rho_T + \delta_T + \mu)(\gamma_L(1-\tau_L) + \rho_L + \mu)}{\tilde{\beta}_{ST}\gamma_L(1-\tau_L)}.$$

   Plugging the expression for $\bar{t}$ from (7) into (16) and solving for $\bar{\ell}$, we get

$$\bar{\ell} = \frac{\mu(1-\bar{s})(\rho_T + \delta_T + \mu)}{\gamma_L(1-\tau_L)(\delta_T + \mu) + \mu(\rho_T + \delta_T + \mu)}.$$

We thereby arrive at our third equilibrium state, where

$$\begin{aligned}\bar{s} &= \frac{(\rho_T+\delta_T+\mu)(\gamma_L(1-\tau_L)+\rho_L+\mu)}{\tilde{\beta}_{ST}\gamma_L(1-\tau_L)}, \qquad \bar{\ell} = \frac{\mu(1-\bar{s})(\rho_T+\delta_T+\mu)}{\gamma_L(1-\tau_L)(\delta_T+\mu)+\mu(\rho_T+\delta_T+\mu)},\\ \bar{t} &= \frac{\mu(1-\bar{s})\gamma_L(1-\tau_L)}{\gamma_L(1-\tau_L)(\delta_T+\mu)+\mu(\rho_T+\delta_T+\mu)}.\end{aligned}$$

4. $E_{CO} = (\bar{s}, \bar{\ell}, \bar{t}, \bar{u}, \bar{d}, \bar{a})$

The remaining case in (15) is that for which

$$\bar{s} = \frac{\gamma_H + \bar{t}\tilde{\beta}_{UT} + \psi + \mu}{\tilde{\beta}_{SU} + \tilde{\beta}_{SD}\frac{\psi}{\gamma_H(1-\tau_D)+\bar{t}\tilde{\beta}_{DT}+\mu}}.$$

To find the equilibrium, we will write all variables as a function of $\bar{\ell}$ and solve for it. From (7) we know that $\bar{t}$ is expressible as $t(\bar{\ell})$. Substituting (14) for $\bar{d}$ in equation (2), we have

$$0 = \bar{s}\bar{t}\tilde{\beta}_{ST} - \ell\left(\gamma_L(1-\tau_L) + \bar{u}\tilde{\beta}_{LU} + \tilde{\beta}_{LD}\frac{\bar{u}\psi}{\gamma_H(1-\tau_D)+\bar{t}\tilde{\beta}_{DT}+\mu} + \rho_L + \mu\right).$$

Solving for $\bar{u}$, and knowing that $\bar{s}$ and $\bar{t}$ are expressible as functions of $\bar{\ell}$, we get

$$\bar{u}(\bar{\ell}) = \frac{\bar{s}\bar{t}\tilde{\beta}_{ST} - \bar{\ell}(\gamma_L(1-\tau_L)+\rho_L+\mu)}{\bar{\ell}(\tilde{\beta}_{LU} + \tilde{\beta}_{LD}\frac{\psi}{\gamma_H(1-\tau_D)+\bar{t}\tilde{\beta}_{DT}+\mu})}. \tag{19}$$

We can get $\bar{d}(\bar{\ell})$ from (14), since it has now been shown that $\bar{u}$ can be expressed as a function of $\bar{\ell}$:

$$\bar{d}(\bar{\ell}) = \frac{\bar{u}\psi}{\gamma_H(1-\tau_D)+\bar{t}\tilde{\beta}_{DT}+\mu}.$$

Finally, since all other classes can be expressed in terms of $\bar{\ell}$, we can write

$$\bar{a}(\bar{\ell}) = \frac{\bar{\ell}(\bar{u}\tilde{\beta}_{LU} + \bar{d}\tilde{\beta}_{LD}) + \bar{u}(\gamma_H + \bar{t}\tilde{\beta}_{UT}) + \bar{d}(\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT})}{\delta_A + \mu}.$$

Now that we have every normalized class in terms of $\bar{\ell}$, let us take a look back at (1),

$$0 = \mu + \bar{\ell}\rho_L + \bar{t}\rho_T - \bar{s}\left(\bar{t}\tilde{\beta}_{ST} + \bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD} + \mu\right).$$

This is now an expression in terms of $\bar{\ell}$, and this allows us to define two new functions:

$$g(\ell) = \mu + \bar{\ell}\rho_L + \bar{t}\rho_T \quad \text{and} \quad h(\ell) = \bar{s}\left(\bar{t}\tilde{\beta}_{ST} + \bar{u}\tilde{\beta}_{SU} + \bar{d}\tilde{\beta}_{SD} + \mu\right).$$

Where these two expressions are equal, a coexistence equilibrium can exist. To make the solution biologically relevant, however, none of the equilibrium point's six values can be negative. To quantify this, we can look at (19), and set the equation for $\bar{u}$ to be greater than 0:

$$\frac{\bar{s}\bar{t}\tilde{\beta}_{ST} - \bar{\ell}(\gamma_L(1-\tau_L) + \rho_L + \mu)}{\bar{\ell}(\tilde{\beta}_{LU} + \tilde{\beta}_{LD}\frac{\psi}{\gamma_H(1-\tau_D) + \bar{t}\tilde{\beta}_{DT} + \mu})} > 0.$$

Isolating $\bar{s}$ and simplifying the expression yields

$$\bar{s} > \frac{(\gamma_L(1-\tau_L) + \rho_L + \mu)(\rho_T + \delta_T + \mu)}{\gamma_L(1-\tau_L)\tilde{\beta}_{ST}}. \tag{20}$$

Importantly, we can also infer from the denominator of (19) that if χ_{HIV} and χ_{TB} are both equal to zero, the coexistence equilibrium $(\bar{s}, \bar{\ell}, \bar{t}, \bar{u}, \bar{d}, \bar{a})$ does not exist.

4.3 Stability of the steady states

We computed the next-generation matrix (NGM) of each single-disease submodel and of the complete model to conduct a local stability analysis of the disease-free equilibrium.

4.3.1 HIV-only Equilibrium (E_{HIV})

We began our analysis with the HIV-only submodel:

$$\begin{aligned} s' &= \mu - s(u\tilde{\beta}_{SU} + d\tilde{\beta}_{SD} + \mu), \\ u' &= s(u\tilde{\beta}_{SU} + d\tilde{\beta}_{SD}) - u(\gamma_H + \psi + \mu), \qquad (21) \\ d' &= u\psi - d(\gamma_H(1-\tau_D) + \mu), \qquad (22) \\ a' &= u\gamma_H + d\gamma_H(1-\tau_D) - a(\delta_A + \mu). \end{aligned}$$

We used equations (21) and (22) to construct our NGM. First, we constructed the infection-dependent matrix T, and the transition-dependent matrix $-\Sigma$, then evaluated both at the disease-free equilibrium $(1, 0, 0, 0)$:

$$T = \begin{pmatrix} \tilde{\beta}_{SU} & \tilde{\beta}_{SD} \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad -\Sigma = \begin{pmatrix} \gamma_H + \psi + \mu & 0 \\ -\psi & \gamma_H(1-\tau_D) + \mu \end{pmatrix}.$$

The NGM is then $-T\Sigma^{-1}$. To obtain the reproduction number for this subsystem, we found the dominant eigenvalue $\rho(-T\Sigma^{-1})$ and arrived at the following threshold for HIV:

$$R_{HIV} = \frac{\tilde{\beta}_{SU}(\gamma_H(1-\tau_D) + \mu) + \tilde{\beta}_{SD}\psi}{(\gamma_H(1-\tau_D) + \mu)(\gamma_H + \psi + \mu)}.$$

Rewriting the equilibrium solution for this submodel in terms of R_{HIV}, we obtain

$$\begin{aligned}
\bar{s} &= \frac{1}{R_{HIV}} \\
\bar{u} &= \frac{\mu(1-\bar{s})(\gamma_H(1-\tau_D)+\mu)}{\bar{s}\tilde{\beta}_{SU}} \\
\bar{d} &= \frac{\mu(1-\bar{s})}{(\gamma_H(1-\tau_D)+\mu)(\gamma_H+\psi+\mu)} \\
\bar{a} &= \frac{\bar{u}\gamma_H+\bar{d}\gamma_H(1-\tau_D)}{\delta_A+\mu}.
\end{aligned}$$

Biological relevance necessitates that all classes are positive and less than one. We observe that $\bar{s}$ meets these conditions only if $R_{HIV} > 1$. Therefore, the condition for the existence of E_{HIV} is that $R_{HIV} > 1$.

4.3.2 TB-only Equilibrium (E_{TB})

We repeat the process for the TB-only submodel:

$$\begin{aligned}
s' &= \mu + \ell\rho_L + t\rho_T - s(t\tilde{\beta}_{ST}+\mu) \\
\ell' &= st\tilde{\beta}_{ST} - \ell(\gamma_L(1-\tau_L)+\rho_L+\mu) \qquad (23) \\
t' &= \ell\gamma_L(1-\tau_L) - t(\rho_T+\delta_T+\mu). \qquad (24)
\end{aligned}$$

For the infection-dependent matrix, T, and transition matrix $-\Sigma$, evaluating at the disease-free equilibrium $(1, 0, 0)$ gives us

$$T = \begin{pmatrix} 0 & \tilde{\beta}_{ST} \\ \gamma_L(1-\tau_L) & 0 \end{pmatrix} \quad \text{and} \quad -\Sigma = \begin{pmatrix} \gamma_L(1-\tau_L)+\rho_L+\mu & 0 \\ 0 & \rho_T+\delta_T+\mu \end{pmatrix}.$$

Computing the dominant eigenvalue of our NGM, $-T\Sigma^{-1}$, we obtain the following threshold for tuberculosis:

$$\tilde{R}_{TB} = \sqrt{\frac{\gamma_L(1-\tau_L)\tilde{\beta}_{ST}}{(\gamma_L(1-\tau_L)+\rho_L+\mu)(\rho_T+\delta_T+\mu)}}, \qquad R_{TB} = (\tilde{R}_{TB})^2.$$

Using R_{TB}, we rewrite the equilibrium solutions for the tuberculosis submodel in terms of R_{TB} as follows:

$$\begin{aligned}
\bar{s} &= \frac{1}{R_{TB}} \\
\bar{\ell} &= \frac{\mu(1-\bar{s})(\rho_T+\delta_T+\mu)}{\gamma_L(1-\tau_L)(\delta_T+\mu)+\mu(\rho_T+\delta_T+\mu)} \\
\bar{t} &= \frac{\mu(1-\bar{s})\gamma_L(1-\tau_L)}{\gamma_L(1-\tau_L)(\delta_T+\mu)+\mu(\rho_T+\delta_T+\mu)}.
\end{aligned}$$

Again, we observe that $\bar{s}$ is only positive and less than one if $R_{TB} > 1$. Therefore, the condition for the existence of E_{TB} is that $R_{TB} > 1$.

4.3.3 Disease-free Equilibrium (E_{DF})

For the complete model, we use the following equations to construct the next-generation matrix

$$\begin{aligned}
\ell' &= st\tilde{\beta}_{ST} - \ell(\gamma_L(1-\tau_L) + u\tilde{\beta}_{LU} + d\tilde{\beta}_{LD} + \rho_L + \mu) \\
t' &= \ell\gamma_L(1-\tau_L) - t(\rho_T+\delta_T+\mu) \\
u' &= s(u\tilde{\beta}_{SU} + d\tilde{\beta}_{SD}) - u(\gamma_H + t\tilde{\beta}_{UT} + \psi + \mu) \\
d' &= u\psi - d(\gamma_H(1-\tau_D) + t\tilde{\beta}_{DT} + \mu).
\end{aligned}$$

Following the same process, constructing the NGM for the complete model, we obtain

$$R_{DF} = \max\{R_{TB}, R_{HIV}\}.$$

Therefore, we can conclude that if $\max\{R_{TB}, R_{HIV}\} < 1$, the disease-free equilibrium E_{DF} is globally asymptotically stable.

5 Results

We then used Python to solve the ODE systems, run tests on long-term population dynamics, and complete a sensitivity analysis. Table 3 shows the baseline parameter values used in the simulations. Besides showing results from section 4 in action, here we completed our study of this model with a variety numerical simulations.

Table 3: Baseline parameter values and main references.

Parameter	Value	Reference
γ_L, γ_H	0.75±0.25, 0.1048±0.0388	[12], [13]
δ_{T1}, δ_{T2}	0.019, 0.0169	estimated
δ_{A1}, δ_{A2}	0.50, 0.33	estimated
τ_A	0.6645±0.0415	[14], [15]
τ_L, τ_T	0.182, 0.53	[16]
τ_D	0.623	[14]
ρ_L	0.130±0.057	[12]
ρ_{T1}, ρ_{T2}	0.231, 1.33	estimated
ψ	0.091	[17]
μ	0.0159	[18]
$\beta_{SU}, \beta_{SD}, \beta_{ST}$	$[0, \infty)$	variable
χ_{TB}, χ_{HIV}	$[0, \infty)$	variable

5.1 Solving the ODE system and constructing bifurcation diagrams

For each single-disease subsystem, we chose two sets of parameters, one for an R-value greater than 1 and one for an R-value less than 1. We then substituted all the parameters into each subsystem, defined the initial condition, and let the program run over a large timespan. Plotting each population as a function of time allows us to study the behavior of the system for a given parameter set.

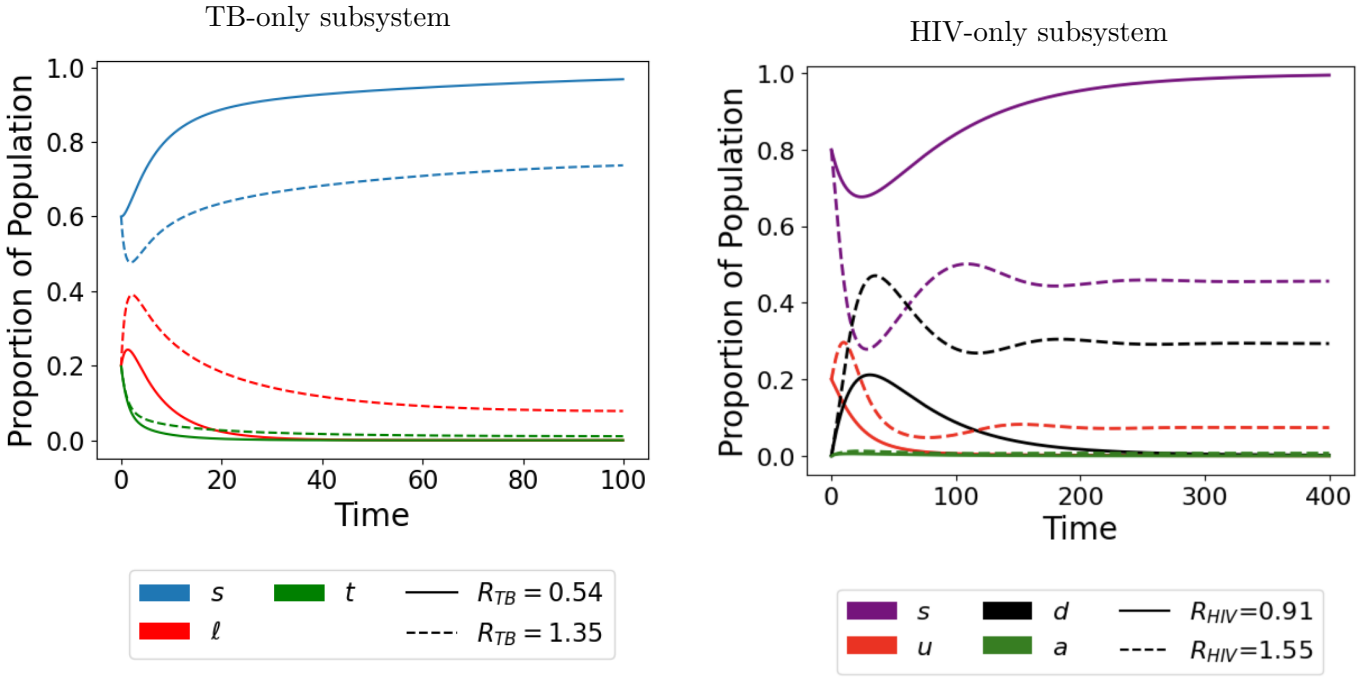

Figure 2: Long-term behavior of each subsystem at different values of R.

Figure 2 shows an example for each subsystem for both the TB and HIV subsystems. For both diagrams, the dashed lines represent a simulation using an R-value greater than 1, and the solid lines represent a simulation using an R-value less than 1. We see that for both submodels, having an R-value less than 1 leads to the disease dying out, and the system falling into E_{DF}. On the

other hand, having an R-value greater than 1 leads to the disease persisting in the population, and the system falling into E_{TB} and E_{HIV}, respectively.

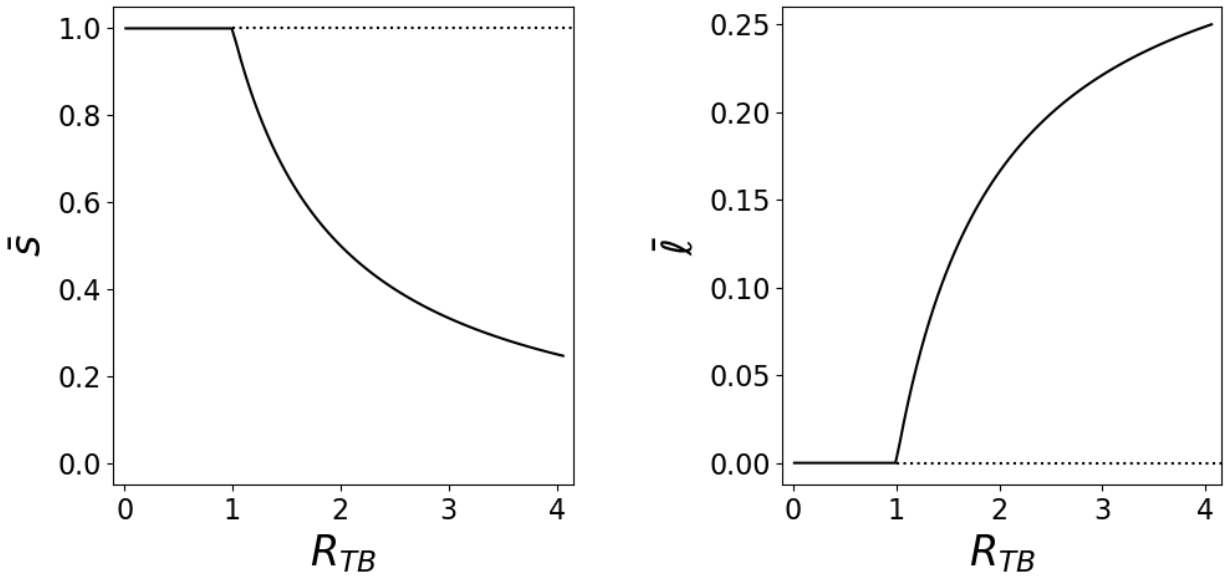

Figure 3: Bifurcation diagrams for TB sub-system. On the left we have the susceptible class and on the right the latent class, both at their steady states for each value of R_{TB}. The behavior of $\bar{t}$ is similar to $\bar{\ell}$.

Figure 3 shows the bifurcation diagrams for the TB subsystem. In this case, a range of $\tilde{\beta}_{ST}$ values were used to obtain a range of values for R_{TB}, our bifurcation parameter. We know from subsections 4.2 and 4.3 that the free-disease equilibrium always exists and it is locally asymptotically stable if $R_{TB} < 1$. When $R_{TB} > 1$, a new equilibrium appears, E_{TB}. The bifurcation diagram shows that this equilibrium is stable given that $R_{TB} > 1$ holds. On the y-axis of the bifurcation diagram, we show the steady state of the compartment $\bar{s}$ and $\bar{\ell}$. Continuous lines indicate stable equilibria and dashed ones unstable equilibria.

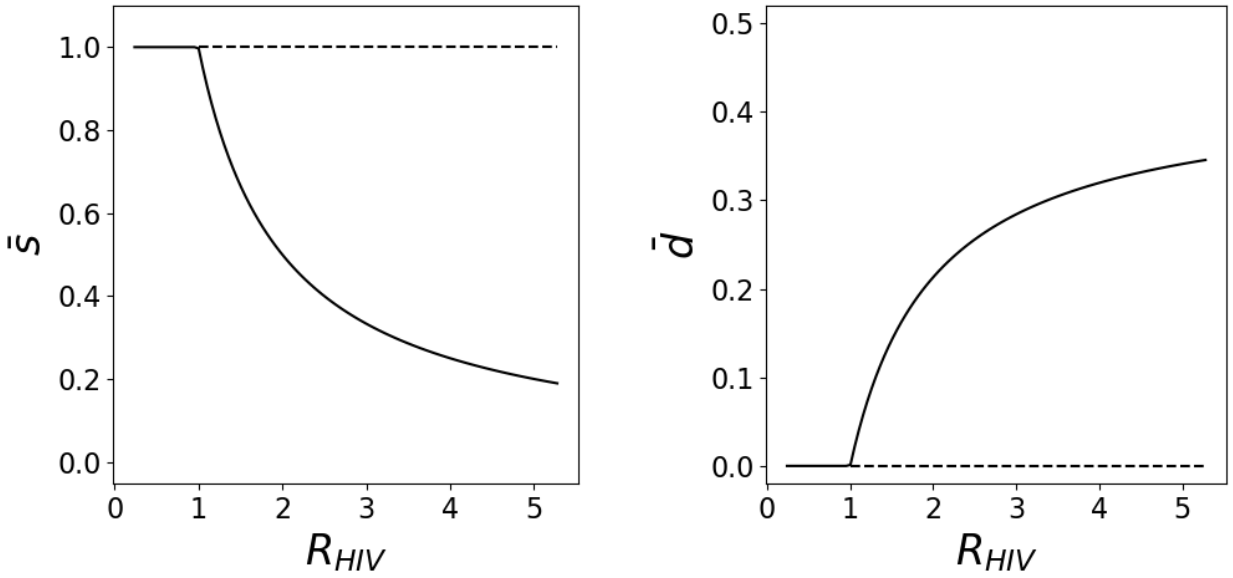

Figure 4: Bifurcation diagrams for HIV-only subsystem. On the left we have the susceptible class and on the right the diagnosed class, both at their steady states for the given R_{HIV}. The behavior of $\bar{u}$ and $\bar{a}$ is similar to $\bar{d}$.

We then did the same for the HIV-only subsystem (Figure 4). In this case, a range of $\tilde{\beta}_{SU}$ values were used to obtain a range of values for R_{HIV}, which we used for our bifurcation parameter. Again, the free-disease equilibrium always exists and it is locally asymptotically stable if $R_{HIV} < 1$. When $R_{HIV} > 1$, a new stable equilibrium appears, E_{HIV}.

5.2 Stability diagrams

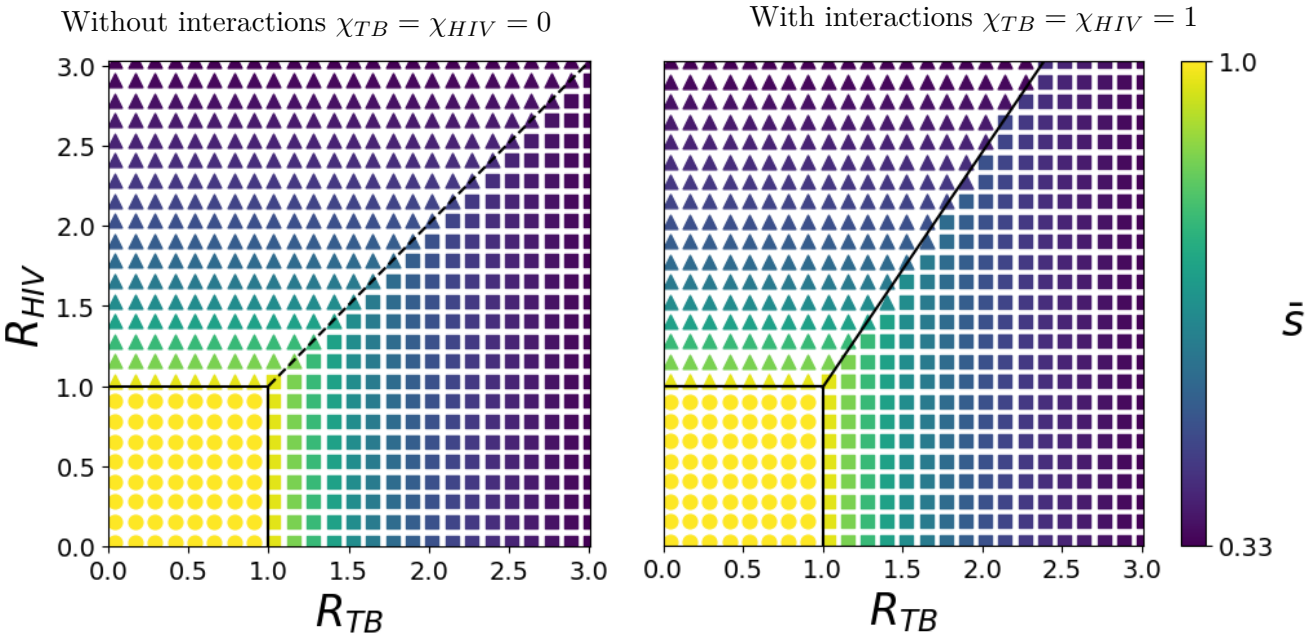

Figure 5: Stability diagrams. The thresholds R_{TB} and R_{HIV} depend on model parameters. Circles represent E_{DF}, triangles represent E_{HIV}, and squares represent E_{TB}. Color represents the proportion of the population in the susceptible class at the steady state.

Figure 5 shows the stability diagrams for the model without and with interactions between HIV and TB. Varying R_{TB} and R_{HIV} in the interval $(0, 3]$, we explore the parameter space looking for the existence and stability of each equilibrium point. Each point in the figure represents the stable equilibrium for the system with a parameter set that results in the given R_{TB} and R_{HIV}. Circles represent E_{DF}, triangles represent E_{HIV}, and squares represent E_{TB}. The color indicates the proportion of the population in the susceptible class at the steady state. The three lines divide the parameter space into three regions. (The dashed line in the second figure is kept for ease of comparison.) Observe that, without disease interactions, the system moves to the disease-free equilibrium if $R_{DF} < 1$. Otherwise, the system can fall into one of two stable endemic equilibria,

E_{HIV} or E_{TB}. The two thresholds R_{HIV} and R_{TB} determine which of these two equilibria the system will go to. If $R_{HIV} > R_{TB}$, then the system moves to the HIV-only equilibrium. If $R_{TB} > R_{HIV}$, then it moves to the TB-only equilibrium. Once disease interactions are turned on, however, the boundary between where the system reaches E_{HIV} and where the system reaches E_{TB} changes. Now, there is a region where $R_{HIV} > R_{TB}$, but the system still falls into E_{TB} regardless. This implies that TB has 'dominance' of sorts over HIV, since with all thresholds equal, the system falls to E_{TB}. We redid this figure using different initial conditions, and it seems that the found equilibria are globally stable. However, more simulations are needed to definitively assert global stability. In addition, analytical work in order to find the boundary between the equilibria.

We then analyzed the existence and stability of coexistence equilibrium E_{CO}. First, we see from equation (20) that

$$\bar{s} > \frac{1}{R_{TB}} \Longrightarrow R_{TB}\bar{s} > 1.$$

Using this inequality, which asserts that all components of the equilibrium point are strictly positive, together with the fact that the equality $g(\bar{\ell}) = h(\bar{\ell})$ has to be satisfied at the equilibrium, and that $\frac{dg}{dl} > 0$ and $\frac{dh}{dl} > 0$ (both $g(l)$ and $h(l)$ are monotonically increasing functions), we can explore, for a given parameter set, the region where a coexistence equilibrium exists (see Figure 6).

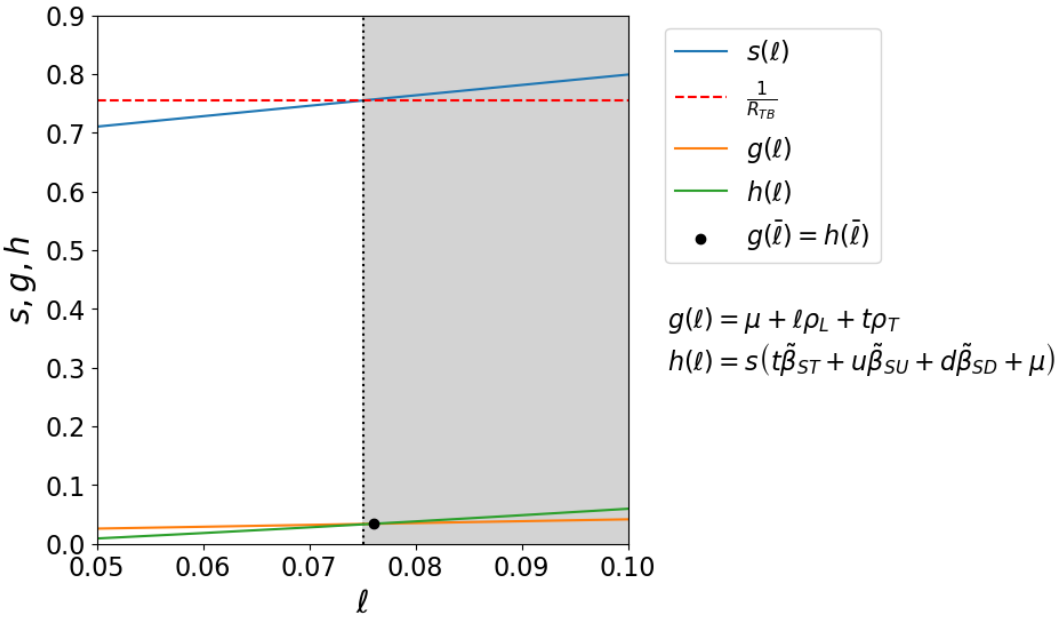

Figure 6: An example E_{CO} is shown as the intersection point of $g(\ell)$ and $h(\ell)$. The shaded region represents where $s(\ell) > \frac{1}{R_{TB}}$. Only when the intersection point is within the shaded region does there exist a valid coexistence equilibrium.

To find the parameters sets that lead to a coexistence equilibrium, we used Latin Hypercube sampling to construct arrays of fourteen parameter values between 0 and 1, keeping $\beta_{SU}, \beta_{SD}, \beta_{ST}$, χ_{TB}, χ_{HIV}, Ω, and μ constant. We repeated this to produce an array with 1,000,000 parameter combinations. Then, we found the minimum and maximum values for each parameter that allowed for a coexistence equilibrium, using the two conditions described before (see Figure 6). From those minimum and maximum bounds, we then randomly selected parameter values from their respective ranges and created another array of 1,000,000 parameter combinations. We checked all combinations for the existence of the coexistence equilibrium. This process allowed us to find 3,397 coexistence equilibria points, and after collecting eligible parameter values, we plotted the distribution for all 14 parameters (see Figure 7).

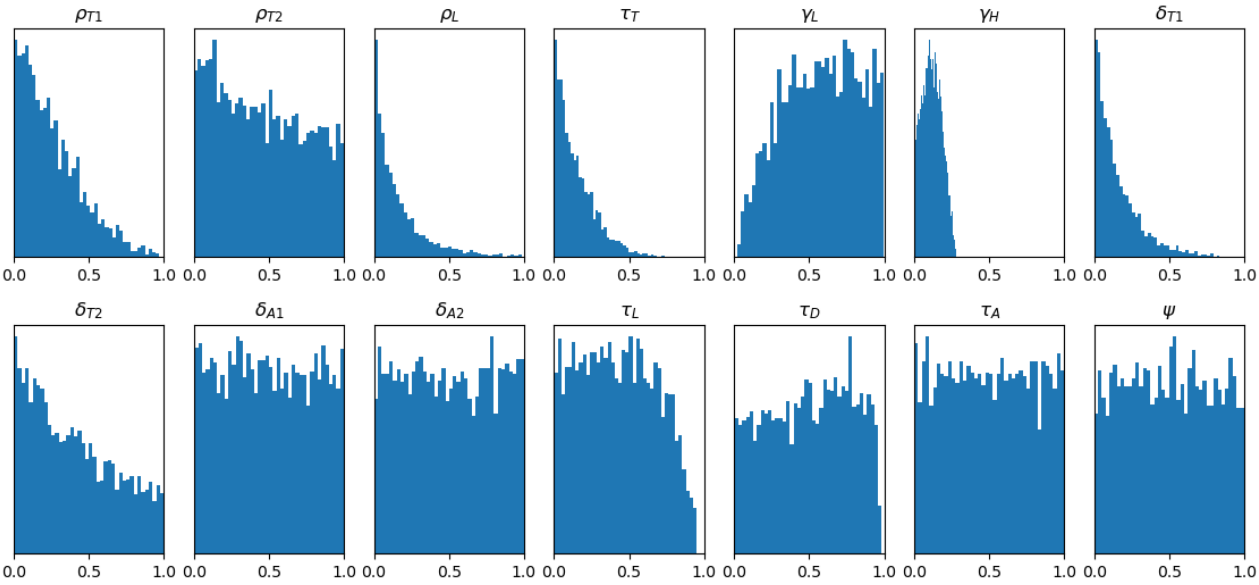

Figure 7: Distribution of parameter values allowing existence of E_{CO}.

Looking at the histograms, we grouped parameters in Table 4 by how much the existence of an E_{CO} seemed to depend on that parameter's value.

Table 4: Qualitative grouping of parameters by value selectivity.

Not Selective	**Selective**	**Strongly Selective**
$\psi, \delta_{A1}, \delta_{A2}, \tau_A$	$\tau_D, \gamma_L, \tau_L, \rho_{T2}$	$\gamma_H, \rho_L, \rho_{T1}, \tau_T, \delta_{T1}, \delta_{T2}$

To study the stability of the coexistence equilibrium numerically, we first constructed the Jacobian of the normalized system and evaluated it at every set of parameters found to lead to an E_{CO}. Then we calculated the eigenvalues of the Jacobian Matrix, sorted the real parts from smallest to largest, and plotted their distribution. Figure 8 shows that for every coexistence equilibrium that was found, one eigenvalue was greater than 0. This means that E_{CO} is unstable regardless of which parameter values were used.

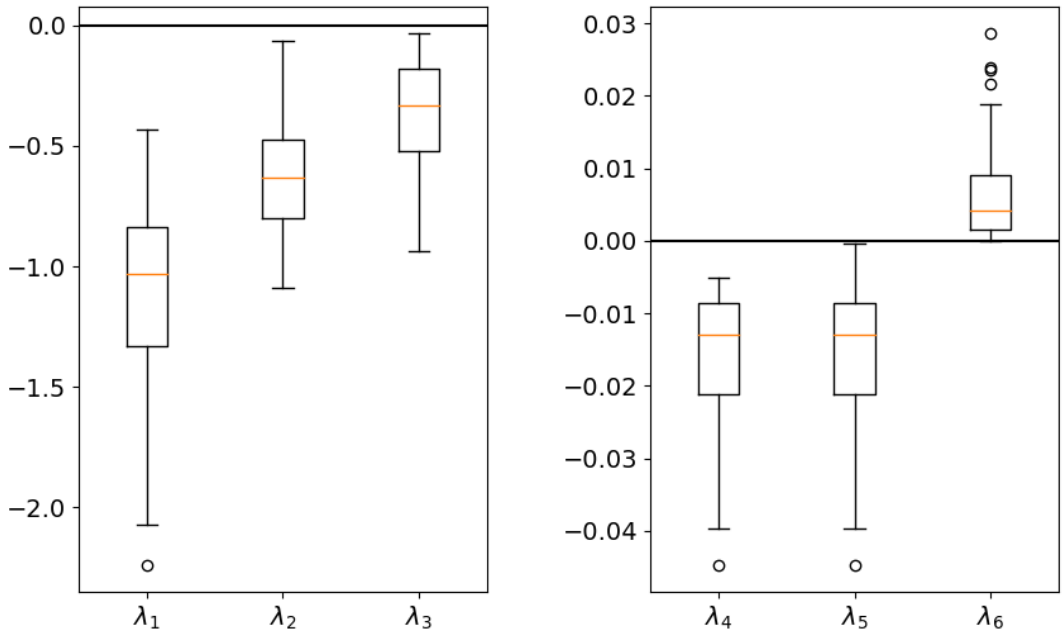

Figure 8: Box plot of the real part of the eigenvalues obtained from the Jacobian Matrix (16,578 unique parameter sets).

5.3 Sensitivity Analysis

We then conducted a sensitivity analysis to determine which parameters have the most impact on our disease thresholds, R_{TB} and R_{HIV}.

5.3.1 R_{TB} threshold

We run a local sensitivity analysis with the following target parameters: proportion of treatment for active tuberculosis (τ_T), recovery for active tuberculosis with and without treatment (ρ_{T1} and ρ_{T2}, respectively), and natural recovery for latent tuberculosis (ρ_L). For this, we take the partial derivative of R_{TB} with respect to our target parameters and then multiply the partial derivative by

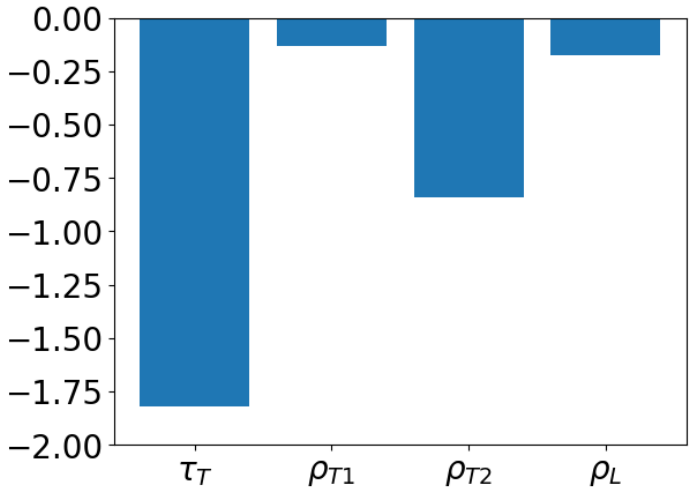

Figure 9: Normalized sensitivity analysis of R_{TB} with respect to τ_T, ρ_{T1}, ρ_{T2}, and ρ_L.

a normalization factor. We rewrite the threshold using each model parameter's explicitly

$$R_{TB} = \frac{\gamma_L(1-\tau_L)\frac{\Omega}{\mu}\beta_{ST}(1-\tau_T)}{(\gamma_L(1-\tau_L)+\rho_L+\mu)(\delta_{T1}(1-\tau_T)+\delta_{T2}\tau_T+\rho_{T1}(1-\tau_T)+\rho_{T2}\tau_T+\mu)}. \tag{25}$$

The normalized sensitivity indices are given by the following equations

$$\begin{aligned}
\frac{\tau_T}{R_{TB}}\frac{\partial R_{TB}}{\partial \tau_T} &= -\frac{\tau_T(\delta_{T2}+\rho_{T2}+\mu)}{(1-\tau_T)(\delta_{T1}(1-\tau_T)+\delta_{T2}\tau_T+\rho_{T1}(1-\tau_T)+\rho_{T2}\tau_T+\mu)} \\
\frac{\rho_{T1}}{R_{TB}}\frac{\partial R_{TB}}{\partial \rho_{T1}} &= -\frac{\rho_{T1}(1-\tau_T)}{\delta_{T1}(1-\tau_T)+\delta_{T2}\tau_T+\rho_{T1}(1-\tau_T)+\rho_{T2}\tau_T+\mu} \\
\frac{\rho_{T2}}{R_{TB}}\frac{\partial R_{TB}}{\partial \rho_{T2}} &= -\frac{\rho_{T2}\tau_T}{\delta_{T1}(1-\tau_T)+\delta_{T2}\tau_T+\rho_{T1}(1-\tau_T)+\rho_{T2}\tau_T+\mu} \\
\frac{\rho_L}{R_{TB}}\frac{\partial R_{TB}}{\partial \rho_L} &= -\frac{\rho_L}{\gamma_L(1-\tau_L)+\rho_L+\mu}.
\end{aligned}$$

For the target parameters, an increase of any one of them results in a decrease of R_{TB}. Using the average of parameter values (see Table 3), Figure 9 shows the impact of each parameter on TB threshold. We can see that τ_T has the greatest impact on the R_{TB} threshold.

5.3.2 R_{HIV} threshold

We also run a local sensitivity analysis on the following target parameters: diagnosis rate (ψ), treatment for diagnosed HIV (τ_D), and transition rate of individuals in both HIV compartments into the AIDS compartment (γ_H). For this, we take the partial derivative of R_{HIV} with respect to our target parameters and then multiply the partial derivative by a normalization factor. We rewrite the threshold using each model parameter's explicitly

$$R_{HIV} = \frac{\tilde{\beta}_{SU}(\gamma_H(1-\tau_D)+\mu)+\tilde{\beta}_{SD}\psi}{(\gamma_H(1-\tau_D)+\mu)(\gamma_H+\psi+\mu)}. \tag{26}$$

The normalized sensitivity indices are:

$$\frac{\tau_D}{R_{HIV}}\frac{\partial R_{HIV}}{\partial \tau_D} = -\frac{\mu\tau_D(\beta_{SD}\psi+\beta_{SU}\gamma_H)}{(\gamma_H(1-\tau_D)+\mu)(\beta_{SD}\psi(1-\tau_D)+\beta_{SU}\gamma_H(1-\tau_D)+\mu)} \tag{27}$$

$$\frac{\psi}{R_{HIV}}\frac{\partial R_{HIV}}{\partial \psi} = -\frac{(1-\tau_D)\gamma_H(\beta_{SU}-\beta_{SD})+\mu[(1-\tau_D)\beta_{SU}-\beta_{SD}]}{(\gamma_H+\psi+\mu)(\beta_{SD}\psi(1-\tau_D)+\beta_{SU}\gamma_H(1-\tau_D)+\mu)} \tag{28}$$

$$\frac{\gamma_H}{R_{HIV}}\frac{\partial R_{HIV}}{\partial \gamma_H} = \frac{A+B}{(\gamma_H(1-\tau_D)-\mu)[\beta_{SD}\psi(1-\tau_D)+\beta_{SU}(\gamma_H(1-\tau_D)-\mu)(\gamma_H+\mu+\psi)]} \tag{29}$$

where

$$A = (1-\tau_D)(\gamma_H+\mu+\psi)[\gamma_H\beta_{SU}(\gamma_H(1-\tau_D)-\mu)+(\beta_{SD}\psi+\beta_{SU})(1-\tau_D)-\mu]$$

$$B = (\gamma_H(1-\tau_D)-\mu)[(\beta_{SD}\psi+\beta_{SU}\gamma_H)(1-\tau_D)-\beta_{SU}\mu)].$$

In equation (28), supposing that $\beta_{SD} < \beta_{SU}$ we can conclude that $(1-\tau_D)\gamma_H(\beta_{SU}-\beta_{SD}) + \mu[(1-\tau_D)\beta_{SU}-\beta_{SD}] > 0$. Therefore, for any parameter sets, the relationship between τ_D and ψ with R_{HIV} is the same, i.e., an increase of these parameters promotes a decrease on R_{HIV}. We could not easily establish a fixed relationship between γ_H and R_{HIV}. For a fixed parameter set,

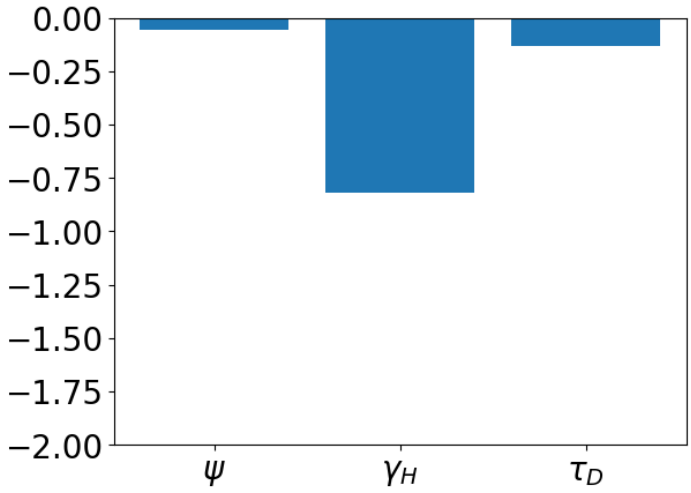

Figure 10: Normalized sensitivity analysis for R_{HIV} with respect to ψ, τ_D, and γ_H.

which was taken from Table 3, Figure 10 shows that an increase of the target parameters results in a decrease of R_{HIV}. We can see that γ_H has the most impact on our R_{HIV} threshold.

6 Discussion

The syndemic between human immunodeficiency virus (HIV) and pulmonary tuberculosis (TB) can be visualized as having a source and sink dynamic. The synergistic relationship between the two diseases is fueled by interactions between those infected with HIV and those infected with TB. With equal, non-zero interaction factors χ_{TB} and χ_{HIV}, a population is more likely to see TB persistence rather than HIV persistence in the long run (see Figure 5). Given that a real-world population has HIV-infected individuals and TB-infected individuals interacting with other individuals equally, a number of steps can be taken to greatly mitigate the HIV/TB syndemic. These include reducing transmission of TB by using preventive measures against airborne diseases, reducing the incidence of risky behaviors with the potential to spread HIV (unsafe sex, needle sharing, etc.), increasing access to TB treatment in TB-endemic regions, and continuously testing TB-infected individuals

for HIV and vice versa. Further research needs to be done to confirm real-world interaction factor values in order to find the most effective region-specific and culture-specific mitigation strategies.

Even though the complexity of Naresh *et al.* and Sharomi *et al.* varies when compared to our model, certain equivalent results were obtained. As in Naresh *et al.*, four equilibria were obtained through analytical work. Other similarities include the disease-free equilibrium, as well as the thresholds that the single-disease equilibria depend on. Furthermore, as in Sharomi *et al.*, treatment for one disease has a detrimental effect on the proliferation of the disease being treated as well as on co-infection.

Through sensitivity analyses, both the propagation of HIV and TB is shown to be decreased by their respective treatments (see Figures 9 and 10). The noticeable impact of R_{TB} on the coexistence equilibrium signifies tuberculosis' role in establishing a coexistence equilibrium is greater than that of HIV (see Figure 6). TB treatment has the greatest effect on reducing the propagation of TB, while our model suggests that the progression to AIDS has the greatest effect on reducing the propagation of HIV, followed by treatment. It is important to note that the natural progression rate to AIDS has this effect solely as a result of the composition of our model and the assumptions that were made. We stress the importance of avoiding policies or actions that restrict access to HIV/AIDS treatment. Treatment access should be increased, as well as HIV/AIDS education. Doing so will not only improve the quality of life of those living with HIV/AIDS, but decrease the prevalence and incidence of the condition. Furthermore, increased diagnosis rates are shown to decrease the propagation of HIV.

Due to the nature of our constructed A compartment, the system failed to produce a stable coexistence equilibrium. In fact, the system behaves as an indirect competitive model. Independent of having or not having interactions between the diseases—in the long run—only one of the diseases persists. In general, disease persistence depends on the fitness of each disease, and in the case

when both χ_{TB} and χ_{HIV} are 0, the fitness is given by the thresholds R_{TB} and R_{HIV} (equations (25) and (26)), for TB and HIV respectively. Both thresholds have a biological interpretation; they measure the average number of new infections produced by one infected individual that arrives in a population with fully susceptible individuals to TB and HIV. Interestingly, one of the criteria to be satisfied in order to obtain a positive coexistence equilibrium is $R_{TB}\bar{s} > 1$, which can be interpreted as an effective number for TB cases, given that $\bar{s}$ measures the size of the susceptible pool at the coexistence equilibrium. Remember that in our model, TB disease is unique in that it is part of a potential positive feedback loop with the susceptible class that permits both diseases to circulate in the long run.

Finally, one challenge we encountered was creating a combination of parameter sets for our simulations, as this required a high amount of computing power. The equipment used to complete the simulations ended up being sufficient for our purposes, but the time taken to achieve results was far from optimal. In the future, we hope to further explore the disease dynamics in order to study coexistence. The next steps are to construct a co-infected compartment in order to track HIV/TB co-infected individuals separately from the rest of the AIDS class, and re-work our assumptions to add a path between individuals in the co-infected class who recover from TB and transition back to the diagnosed HIV class.

7 Conclusion

The model presented in this work does an effective job of capturing essential aspects of TB-HIV interaction as well as maintaining simplicity in order to produce relevant analytic results. We were able to find a threshold for disease coexistence that is related to the effective reproduction number for TB, as well as thresholds for the subsystems where only one disease was present. Conditions

for disease coexistence were also obtained for the complete model. We conclude that treatment for either disease significantly reduces progression to AIDS, with treatment for active tuberculosis having the greater influence of the two.

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