MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **5**, Number **1**, January **2008**

http://www.mbejournal.org/

pp. **145–174**

MATHEMATICAL ANALYSIS OF THE TRANSMISSION DYNAMICS OF HIV/TB COINFECTION IN THE PRESENCE OF TREATMENT

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(Communicated by Zhilan Feng)

Abstract. This paper addresses the synergistic interaction between HIV and mycobacterium tuberculosis using a deterministic model, which incorporates many of the essential biological and epidemiological features of the two diseases. In the absence of TB infection, the model (*HIV-only model*) is shown to have a globally asymptotically stable, disease-free equilibrium whenever the associated *reproduction number* is less than unity and has a unique endemic equilibrium whenever this number exceeds unity. On the other hand, the model with TB alone (*TB-only model)* undergoes the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium when the associated reproduction threshold is less than unity. The analysis of the respective reproduction thresholds shows that the use of a targeted HIV treatment (using anti-retroviral drugs) strategy can lead to effective control of HIV provided it reduces the relative infectiousness of individuals treated (in comparison to untreated HIV-infected individuals) below a certain threshold. The full model, with both HIV and TB, is simulated to evaluate the impact of the various treatment strategies. It is shown that the HIV-only treatment strategy saves more cases of the mixed infection than the TB-only strategy. Further, for low treatment rates, the mixed-only strategy saves the least number of cases (of HIV, TB, and the mixed infection) in comparison to the other strategies. Thus, this study shows that if resources are limited, then targeting such resources to treating one of the diseases is more beneficial in reducing new cases of the mixed infection than targeting the mixed infection only diseases. Finally, the universal strategy saves more cases of the mixed infection than any of the other strategies.

1. **Introduction.** The inextricably linked pathogenesis and epidemiology of mycobacterium tuberculosis (TB) and the human immuno-deficiency syndrome (HIV) are well known [18, 23, 24, 36]. The two diseases exhibit some sort of synergistic relationship, where each accelerates the progression of the other. For instance, since its emergence in the 1980s, the HIV/AIDS pandemic continues to play a major role in the resurgence of TB, resulting in increased morbidity and mortality worldwide.

2000 *Mathematics Subject Classification.* Primary: 92D30; Secondary: 92B05; 34D23.
Key words and phrases. HIV/TB, equilibria, stability, bifurcation, treatment.
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Additionally, HIV fuels progression to active disease in people infected with TB [23, 40]. Rates of recurrence of TB, both due to endogenous reactivation and exogenous re-infection, are increased among people infected with HIV [19, 23, 40]. For instance, in many countries of eastern and southern Africa, the rates of TB notification have increased by five or more times as a result of HIV infection [37, 38]. Similarly, HIV infection increases the likelihood that a person will develop active TB [40].

The current statistics associated with the two diseases are staggering. While HIV accounts for 30-46 million infections (and resulted in over 20 million deaths) globally since its inception in the 1980s [39], TB affects at least 2 billion people (one-third of the world's population) and is the second greatest contributor of adult mortality amongst infectious diseases, causing approximately two million deaths a year worldwide [39]. Currently, approximately 8% of global TB cases are attributable to HIV infection, but this proportion is expected to increase in the future. For instance, the number of HIV positives in India is estimated to be 3.97 million cases, and nearly 60% of the reported cases of AIDS had TB [19].

The largest number of TB cases occurs in Southeast Asia, which in 2004 accounted for an estimated 3 million new cases (one-third of the global total) for that year [39]. However, the estimated incidence per capita in sub-Saharan Africa is nearly twice that of Southeast Asia, at 356 cases per 100,000 population in 2004. Also, the countries of Eastern Europe faced a serious epidemic in 2004, there were an estimated 166,000 new cases in Russia alone.

Thankfully, effective treatment does exist for each of these deadly diseases. For HIV, the use of anti-retroviral drugs (ARVs), notably the highly active antiretroviral therapy (HAART), has proven to be effective in curtailing its spread and AIDS-related mortality [14, 21, 28, 29]. However, these life-saving drugs are still not widely available in some resource-poor nations with high HIV incidence and prevalence. Tuberculosis, on the other hand, can be cured using drug therapy, such as DOTS (directly observed treatment short course). DOTS cures TB in 95% of cases, and a six-month supply of DOTS costs as little as $10 per person in some parts of the world [3].

The enormous public health burden inflicted by these two diseases necessitates the use of mathematical modelling to gain insights into their transmission dynamics and to determine effective control strategies. Unfortunately, not much has been done in terms of modelling the dynamics of HIV-TB coinfection at a population level. A few modelling studies, such as those in [27, 30, 35], have provided basic framework (using simplified models) for modelling the complex HIV-TB interaction in a community. The purpose of the current study is to complement the aforementioned studies, by designing and qualitatively analysing a new and more comprehensive deterministic model for gaining insights into the transmission dynamics and control of the two diseases in a population. The model allows for the assessment of treatment strategies for each disease (including the mixed infection). The robust model will be used to assess the public health (epidemiological) impact of four main treatment strategies, namely: (*i*) treating people infected with HIV only (*HIV-only strategy*), (*ii*) treating people infected with TB only (*TB-only strategy*), (*iii*) treating people infected with the mixed infection only (*mixed-only strategy*) and treating individuals infecetd with HIV, TB or the HIV-TB coinfection (*universal strategy*).

It is worth emphasizing that the two diseases differ in their modes of transmission. Whilst TB is an airborne disease (a susceptible individual may become infected with TB if he or she inhales bacilli, the causative agent of TB, in the air), HIV is transmitted predominantly via sexual contact or needle sharing (particularly among IV drug users). Thus, whilst HIV transmission almost exclusively involves sexually-active people (except for cases of vertical transmission), everyone (children and adults) is susceptible to TB infection. Children can acquire TB infection by having close contact with infected adults (usually family members). However, data from Health Canada [5] suggests that pediatric TB is on the decline. For instance, the number of reported TB cases in Canada in children under 15 years of age declined from 430 in 1970 to 109 in 2001 (the incidence of TB in children also decreased from 6.6 per 100,000 in 1970 to 1.9 per 100,000 in 2001). Although pediatric TB may be a factor in some nations, this study does not include children in the compartment of people susceptible to TB or HIV; rather, we consider sexually-active individuals only.

The paper is organized as follows. The model is formulated in Section 2. Two sub-models of the full model (HIV-only and TB-only) are analyzed in Section 3. The full model is analyzed (for the stability of the associated disease-free equilibrium) in Section 4, and numerical simulations are carried out in Section 5.

2. **Model formulation and basic properties.** The total sexually-active population at time t, denoted by $N(t)$, is subdivided into mutually-exclusive compartments, namely susceptible ($S(t)$), newly- and asymptomatically-infected individuals with HIV ($H_1(t)$), HIV-infected individuals with clinical symptoms of AIDS ($H_2(t)$), individuals infected with TB in latent (asymptomatic) stage ($L(t)$), individuals infected with TB in the active stage ($T(t)$), untreated dually-infected individuals (with both diseases) having latent TB and in the asymptomatic stage of HIV infection ($I^1_{HL}(t)$), untreated dually-infected individuals with active TB and in the asymptomatic stage of HIV infection ($I^1_{HT}(t)$), untreated dually-infected individuals with latent TB and showing symptoms of AIDS ($I^2_{HL}(t)$), untreated dually-infected individuals with active TB and showing symptoms of AIDS ($I^2_{HT}(t)$), treated individuals infected with HIV only ($W_H(t)$), treated individuals infected with TB only ($W_T(t)$), dually-infected individuals with latent TB treated of HIV ($W^H_{HL}(t)$), dually-infected individuals with active TB treated of HIV only ($W^H_{HT}(t)$), individuals infected with both diseases treated of TB ($W^T_{HT}(t)$) and those treated of both HIV and TB only ($W^M_{HT}(t)$), so that

$$\begin{aligned} N(t) &= S(t) + H_1(t) + H_2(t) + L(t) + T(t) + I^1_{HL}(t) + I^1_{HT}(t) + I^2_{HL}(t) \\ &+ I^2_{HT}(t) + W_H(t) + W_T(t) + W^H_{HL}(t) + W^H_{HT}(t) + W^T_{HT}(t) + W^M_{HT}(t). \end{aligned}$$

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population, at a rate Π. Both singly- and dually-infected individuals transmit either HIV or TB infection as follows (note that we split the disease transmission process into those generated by singly-infected and dually-infected individuals to make the formulation easier to follow).

2.1. **Transmission by singly-infected individuals.** Susceptible individuals acquire HIV infection, following effective contact with people infected with HIV only (i.e., those in the H_1, H_2 and W_H classes) at a rate λ_H, given by

$$\lambda_H = \frac{\beta_H(H_1 + \eta_2 H_2 + \eta_H W_H)}{N}, \tag{1}$$

where, β_H is the effective contact rate for HIV transmission. Further, the modification parameters $\eta_2 \geq 1$ and $\eta_H < 1$ account for the relative infectiousness of individuals in the H_2 (AIDS) and W_H (treated HIV-infected individuals) classes in comparison to those in the H_1 (asymptomatic HIV) class. That is, individuals in the H_2 class are more infectious than those in the H_1 class (because of their higher viral load); and, likewise, treated HIV-infected individuals are less infectious than those in the H_1 class (because the use of treatment significantly reduces the viral load in those treated).

Similarly, susceptible individuals acquire TB infection from individuals with active TB only at a rate λ_T, given by

$$\lambda_T = \frac{\beta_T(T + \eta_T W_T)}{N}, \tag{2}$$

where, β_T is the effective contact rate for TB infection, and the parameter $\eta_T < 1$ accounts for the reduction in infectiousness among individuals with active TB who are treated (in comparison to those who are not treated). A fraction, l, of susceptible individuals who acquire TB infection moves to the latent TB class (L) at the rate λ_T, and the remaining fraction, $1 - l$, moves to the active TB class T. It is assumed that individuals in the latent TB class do not transmit infection.

2.2. **Transmission by dually-infected individuals.**

2.2.1. *Untreated individuals.* Dually-infected individuals are assumed capable of transmiting either HIV or TB, but not the mixed infection. Untreated dually-infected individuals (i.e., those in the $I^1_{HL}, I^1_{HT}, I^2_{HL}$, and I^2_{HT} classes) transmit HIV at a rate λ^1_{HT}, where

$$\lambda^1_{HT} = \frac{\beta_H[I^1_{HL} + \eta_D I^1_{HT} + c_2\eta_2(I^2_{HL} + \eta_D I^2_{HT})]}{N}. \tag{3}$$

In (3), $c_2\eta_2$ (with $c_2 \geq 1$) accounts for the assumed increase in infectiousness for dually-infected individuals in the AIDS stage compared to dually-infected individuals in the asymptomatic HIV stage; while the modification parameter $\eta_D > 1$ accounts for the assumption that dually-infected individuals with active TB transmit HIV at a higher rate than the corresponding dually-infected individuals with latent TB (in other words, it is assumed that dually-infected people with active TB transmit HIV at a rate higher than that of dually-infected individuals (W^T_{HT}) with latent TB, since it is known that active TB accelerates HIV progression in people infected with both diseases).

Similarly, untreated dually-infected individuals with active TB (i.e., those in the I^1_{HT} and I^2_{HT} classes) transmit TB at a rate λ^2_{HT}, with

$$\lambda^2_{HT} = \frac{\beta_T(I^1_{HT} + I^2_{HT})}{N}. \tag{4}$$

2.2.2. *Treated individuals.* Here, too, treated individuals with the dual infection transmit both diseases (but not the mixed infection) to susceptible individuals, where the transmission of the disease being treated is assumed to occur at a lower rate in comparison to the transmission by the corresponding class of dually-infected individuals who are not treated; while the transmission of the other disease occurs

at the same rate as that of the corresponding singly-infected untreated individuals. For instance, treated individuals with the mixed infection (i.e., those in the $W_{HL}^H, W_{HT}^H, W_{HT}^T$ and W_{HT}^M classes) transmit HIV at a rate λ_M^H, where

$$\lambda_M^H = \frac{\beta_H[W_{HT}^T + \eta_H(W_{HL}^H + W_{HT}^H + W_{HT}^M)]}{N}. \tag{5}$$

In other words, equation (5) shows that dually-infected individuals treated of TB (W_{HT}^T) transmit HIV at the same rate (β_H) as the corresponding (untreated) HIV-infected individuals with HIV infection only (in the H_1 class), while dually-infected individuals treated of HIV with latent and active TB (W_{HL}^H and W_{HT}^H), and dually-infected individuals treated of both diseases (W_{HT}^M) transmit HIV at the reduced rate, $\eta_H\beta_H$ (in comparison to the untreated HIV-infected individuals in the H_1 class). Thus, treating dually-infected individuals of one disease (only) does not limit (or reduce) their ability to transmit the other disease.

Similarly, treated individuals with mixed infection (involving active TB) transmit TB at a rate λ_M^T, where

$$\lambda_M^T = \frac{\beta_T[W_{HT}^H + \eta_T(W_{HT}^T + W_{HT}^M)]}{N}. \tag{6}$$

2.3. **Derivation of model equations.** The populations of individuals in the H_1 and H_2 classes are reduced due to TB infection (following effective contact with individuals in the $T, I_{HT}^1, I_{HT}^2, W_T, W_{HT}^H, W_{HT}^T$, and W_{HT}^M classes). Further, individuals in the H_1 class progress to the AIDS class (H_2), at a rate σ. The parameters ψ_1 and ψ_2 (with $\psi_2 > \psi_1 > 1$) account for the assumed increase in probability of acquiring TB infection for HIV-infected individuals; the parameter ψ_2 is associated with those with clinical symptoms of AIDS (H_2) while ψ_1 is associated with those without symptoms (H_1). That is, it is assumed that individuals with HIV infection are more prone to TB infection than wholly-susceptible individuals. Further, those with AIDS acquire TB infection at a higher rate than those in the asymptomatic stage of HIV infection owing to the weaker immune status of the former. The population of individuals infected with TB only (in the L or T class) is reduced following acquisition of HIV-infection, which can result following effective contact with individuals infected with HIV (in the $H_1, H_2, W_H, I_{HL}^1, I_{HT}^1, I_{HL}^2, I_{HT}^2, W_{HL}^H, W_{HT}^H, W_{HT}^T$ and W_{HT}^M classes). Further, individuals in the latent TB class (L) progress to the active TB class (T) at a rate α, and become re-infected (exogenously) after effective contact with individuals in the active TB class (at a rate λ_R) or with individuals having mixed infection involving active TB (at a rate λ_{R1}). The rates λ_R and λ_{R1} are, respectively, given by

$$\lambda_R = \frac{\beta_T\eta_r T}{N} \text{ and } \lambda_{R1} = \frac{\beta_T\eta_r(I_{HT}^1 + I_{HT}^2 + W_{HT}^H)}{N},$$

where $\beta_T\eta_r$ (with $\eta_r > 0$ being the modification parameter for exogenous re-infection) is the contact rate associated with the exogenous re-infection. Individuals in the I_{HL}^1 class undergo exogenous re-infection at a rate λ_{R2}, where

$$\lambda_{R2} = \frac{\beta_T\eta_r(T + I_{HT}^1 + I_{HT}^2 + W_{HT}^H)}{N}.$$

A fraction, l, of susceptible individuals who acquire TB infection from untreated dually-infected individuals (at the rate λ_{HT}^2) move to the latent TB class, while the

remaining fraction, $1-l$, move to the active TB class. Susceptible individuals who had effective contact with dually-infected individuals treated of TB can acquire either TB or HIV infection. Those who acquire HIV move to the H_1 class (at the rate β_H), and, on the other hand a fraction, l, of those who acquire TB infection move to the latent TB class (L), while the remaining fraction, $1-l$, move to the active TB class (T). Similarly, susceptible individuals who acquire infection from dually-infected individuals treated of HIV alone can become infected with TB at the rate β_T (where a fraction, l, move to the latent class; and the remaining fraction, $1-l$, move to the active TB class), and those infected with HIV move to H_1 class at the reduced rate $\eta_H\beta_H$. Dually-infected individuals treated of both diseases transmit HIV infection at the reduced rate $\eta_H\beta_H$, and TB infection at the reduced rate $\eta_T\beta_T$ (where a fraction, l, of the TB cases move to the latent class and the remaining fraction, $1-l$, move to the active TB class). Note that, since we have no data to show that the aforementioned fractions (that move to the latent TB class) are distinct, we assume that they are all equal (to l).

Further, individuals in the I^1_{HL} class progress to the I^1_{HT} class at an increased rate $\theta_1\alpha$, where $\theta_1 \geq 1$ (this is to account for the fact that HIV infection accelerates TB progression in dually-infected individuals); and are treated for HIV at a rate τ_1. Finally, a fraction, ξ, of individuals in the I^1_{HL} class progress to active TB and AIDS stage (I^2_{HT}) at a rate γ_{HT}, and the remaining fraction, $1-\xi$, moves to the I^2_{HL} at the same rate γ_{HT}.

As noted earlier, individuals with latent TB (only) are re-infected (exogenously) at a rate λ_R or λ_{R1}. A fraction, ϕ, of those individuals re-infected at the rate λ_{R1} progress to active TB, and the remaining fraction, $1-\phi$, acquire HIV infection and move to the I^1_{HT} class. Individuals in this I^1_{HT} class are treated for HIV at the rate τ_1 and for active TB at a rate τ_3. Finally, I^1_{HT} individuals progress to I^2_{HT} at an increased rate $\eta_1\sigma$, with $\eta_1 \geq 1$. In other words, this study assumes that the presence of mixed infection accelerates progression of both diseases (to either active TB or AIDS stage).

Similarly, individuals with AIDS and latent TB (I^2_{HL}) are re-infected (exogenously) at the rate λ_{R2}. Individuals in this class are treated for HIV at the rate τ_2, progress to I^2_{HT} class at the rate $\theta_2\alpha$ ($\theta_2 \geq 1$) and die due to the two diseases at a rate δ_{HT}. Finally, individuals in the I^2_{HT} class are treated for HIV at the rate τ_2 and active TB at the rate τ_3; and they die at an increased rate $\omega\delta_{HT}$, with $\omega > 1$. Treatment for HIV, using ARVs, is administered to individuals in both H_1 and H_2 classes, at the rate τ_1 and τ_2, respectively; while individuals with active TB are treated at the rate τ_3.

Individuals successfully treated for HIV are assumed to eventually (after long period of time, lasting decades) succumb to the disease (due to the failure of treatment or resistance development) and progress to AIDS at a reduced rate $\theta_t\sigma_1$, where $0 < \theta_t < 1$. Individuals successfully treated of TB return to the latent TB stage at a rate ρ. Finally, dually-infected individuals treated of HIV can further be treated for TB; while dually-infected individuals treated of TB can similarly be treated for HIV. Dually-infected individuals who have received treatment for both diseases (W^M_{HT} class) and dually-infected individuals treated of TB (W^T_{HT} class) eventually progress to the final stage of HIV disease and latent TB (I^2_{HL}) at rates σ_{HT} and σ_T, respectively. On the other hand, dually-infected individuals treated of HIV with latent TB (W^H_{HL} class) progress to the class of dually-infected individuals treated of HIV with active TB (I^1_{HT}) at the rate $\theta_1\alpha$ and/or to the untreated dually-infected

individuals with AIDS and latent TB at a rate $\theta_t\sigma$. Dually-infected individuals treated of HIV with active TB (W_{HT}^H) progress to the class of individuals with AIDS and active TB (I_{HT}^2) at a rate σ_H. Further, natural mortality occurs in all classes at a rate μ, while individuals in the AIDS (H_2) and active TB (T) classes suffer an additional disease-induced death at rates δ_H and δ_T, respectively.

Combining all the aforementioned assumptions and definitions, the model for the transmission dynamics of HIV and TB in a sexually-active population is given by the following system of differential equations:

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_H S - \lambda_T S - \lambda_{HT}^1 S - \lambda_{HT}^2 S - \lambda_M^H S - \lambda_M^T S - \mu S,\\
\frac{dH_1}{dt} &= \lambda_H S + \lambda_{HT}^1 S + \lambda_M^H S - \lambda_T \psi_1 H_1 - \lambda_{HT}^2 \psi_1 H_1 - \lambda_M^T \psi_1 H_1 - K_1 H_1,\\
\frac{dH_2}{dt} &= \sigma H_1 + \theta_t \sigma W_H - \lambda_T \psi_2 H_2 - \lambda_{HT}^2 \psi_2 H_2 - \lambda_M^T \psi_2 H_2 - K_2 H_2,\\
\frac{dL}{dt} &= l\lambda_T S + l\lambda_{HT}^2 S + l\lambda_M^T S + \rho W_T - \lambda_H L - \lambda_{HT}^1 L - \lambda_M^H L - \lambda_R L - \lambda_{R1} L - K_3 L,\\
\frac{dT}{dt} &= (1-l)\lambda_T S + (1-l)\lambda_{HT}^2 S + (1-l)\lambda_M^T S + \lambda_R L + \alpha L - \lambda_H T + \phi\lambda_{R1} L - \lambda_M^H T -\\
&\quad \lambda_{HT}^1 T - K_4 T,\\
\frac{dI_{HL}^1}{dt} &= \lambda_T \psi_1 H_1 + \lambda_{HT}^2 \psi_1 H_1 + \lambda_M^T \psi_1 H_1 + \lambda_H L + \lambda_{HT}^1 L + l(\lambda_{HT}^2 W_H + \lambda_T W_H +\\
&\quad \lambda_M^T W_H) + \lambda_M^H L + \lambda_{HT}^1 W_T + \lambda_H W_T + \lambda_M^H W_T - \lambda_{R2} I_{HL}^1 - K_5 I_{HL}^1,\\
\frac{dI_{HT}^1}{dt} &= \lambda_H T + \lambda_{HT}^1 T + \lambda_M^H T + (1-l)(\lambda_{HT}^2 W_H + \lambda_T W_H + \lambda_M^T W_H) + \lambda_{R2} I_{HL}^1 +\\
&\quad \theta_1 \alpha I_{HL}^1 + (1-\phi)\lambda_{R1} L - K_6 I_{HT}^1,\\
\frac{dI_{HL}^2}{dt} &= \lambda_T \psi_2 H_2 + \lambda_{HT}^2 \psi_2 H_2 + \lambda_M^T \psi_2 H_2 - \lambda_{R2} I_{HL}^2 + (1-\xi)\gamma_{HT} I_{HL}^1 + \theta_t \sigma W_{HL}^H +\\
&\quad \sigma_{HT} W_{HT}^M + \sigma_T W_{HT}^T - K_7 I_{HL}^2,\\
\frac{dI_{HT}^2}{dt} &= \lambda_{R2} I_{HL}^2 + \theta_2 \alpha I_{HL}^2 + \xi\gamma_{HT} I_{HL}^1 + \eta_1 \sigma I_{HT}^1 + \sigma_H W_{HT}^H - K_8 I_{HT}^2,\\
\frac{dW_H}{dt} &= \tau_1 H_1 + \tau_2 H_2 - \lambda_{HT}^2 W_H - \lambda_T W_H - \lambda_M^T W_H - K_9 W_H,\\
\frac{dW_T}{dt} &= \tau_3 T - \lambda_{HT}^1 W_T - \lambda_H W_T - \lambda_M^H W_T - K_{10} W_T,\\
\frac{dW_{HL}^H}{dt} &= \tau_1 I_{HL}^1 + \tau_2 I_{HL}^2 - \lambda_{R2} W_{HL}^H - K_{11} W_{HL}^H,\\
\frac{dW_{HT}^H}{dt} &= \tau_1 I_{HT}^1 + \tau_2 I_{HT}^2 + \theta_1 \alpha W_{HL}^H + \lambda_{R2} W_{HL}^H - K_{12} W_{HT}^H,\\
\frac{dW_{HT}^T}{dt} &= \tau_3 (I_{HT}^1 + I_{HT}^2) - K_{13} W_{HT}^T,\\
\frac{dW_{HT}^M}{dt} &= \tau_3 W_{HT}^H + \tau_2 W_{HT}^T - K_{14} W_{HT}^M,
\end{aligned}
\tag{7}
$$

where,

$$
\begin{aligned}
K_1 &= \mu + \sigma + \tau_1,\ \ K_2 = \mu + \delta_H + \tau_2,\quad K_3 = \mu + \alpha,\ \ K_4 = \mu + \delta_T + \tau_3,\\
K_5 &= \mu + \theta_1\alpha + \tau_1 + \gamma_{HT},\ K_6 = \mu + \tau_1 + \tau_3 + \eta_1\sigma,\ K_7 = \mu + \theta_2\alpha + \tau_2 + \delta_{HT},\\
K_8 &= \mu + \tau_2 + \tau_3 + \omega\delta_{HT},\ K_9 = \mu + \theta_t\sigma,\ K_{10} = \mu + \rho,\ K_{11} = \mu + \theta_1\alpha + \theta_t\sigma,\\
K_{12} &= \mu + \sigma_H + \tau_3,\ \ K_{13} = \mu + \sigma_T + \tau_2,\ K_{14} = \mu + \sigma_{HT}.
\end{aligned}
$$

Table 1: Description of variables and parameters for the treatment model with staged-progression (7)

Variable	Description
$S(t)$	Susceptible individuals
$H_1(t)$	New- and asymptomatically-infected individuals
$H_2(t)$	HIV-infected individuals with clinical symptoms of AIDS
$L(t)$	TB-infected individuals in latent stage
$T(t)$	TB-infected individuals in active stage
$I^1_{HL}(t)$	Dually-infected individuals with latent TB and in the asymptomatic stage of HIV infection
$I^1_{HT}(t)$	Dually-infected individuals with active TB and in the asymptomatic stage of HIV infection
$I^2_{HL}(t)$	Dually-infected individuals with latent TB and showing symptoms of AIDS
$I^2_{HT}(t)$	Dually-infected individuals with active TB and showing symptoms of AIDS
$W_H(t)$	Treated individuals with HIV
$W_T(t)$	Treated individuals with TB
$W^H_{HL}(t)$	Dually-infected individuals treated of HIV with latent TB
$W^H_{HT}(t)$	Dually-infected individuals treated of HIV with active TB
$W^T_{HT}(t)$	Dually-infected individuals treated of TB
$W^M_{HT}(t)$	Dually-infected individuals treated of both diseases

Parameter	Description
Π	Recruitment rate into the population
μ	Natural death rate
$\delta_H, \delta_T, \delta_{HT}$	Disease-induced mortality for HIV, TB and mixed infections
θ_t	Modification factor for progression to AIDS for treated HIV-infected people
σ	Progression rates to AIDS and active TB classes for untreated singly-infected individuals of individuals with HIV and latent TB, respectively
γ_{HT}	Progression rates to symptomatic stages of dual infection of individuals latent TB in the asymptomatic stage of HIV disease
α	Progression rate to active TB of individuals with latent TB
ρ	Progression rate to latent TB of individuals treated for TB
$\eta_1, \eta_2, c_2, \eta_H, \eta_T, \eta_D$	
$\omega, \theta_1, \theta_2$	Modification parameters
$\sigma_H, \sigma_T, \sigma_{HT}$	Progression rates to AIDS or active TB or both by dually-infected treated individuals
η_r	Re-infection parameter
ϕ	Fraction of individuals with latent TB only who are reinfected with TB
ξ	Fraction of dually-infected individuals showing symptoms of AIDS and latent TB who are reinfected with TB
l	Fraction of newly-infected individuals with latent TB
$1-l$	Fraction of newly-infected individuals with active TB
τ_1, τ_2, τ_3	Treatment rates for H_1, H_2 and T classes
ψ_1, ψ_2	Modification parameter for increased TB susceptibility for people in H_1 and H_2 classes
β_H, β_T	Effective contact rates for HIV and TB

Since the model (7) monitors human populations, all the variables and parameters of the model are non-negative. Consider the biologically-feasible region

$$\begin{aligned}\mathcal{D} &= \{(S, H_1, H_2, L, T, I^1_{HL}, I^1_{HT}, I^2_{HL}, I^2_{HT}, W_H, W_T, W^H_{HL}, W^H_{HT}, W^T_{HT}, W^M_{HT}) \\ &\quad \in \mathbb{R}^{15}_+ : N \leq \Pi/\mu\}.\end{aligned}$$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e., all solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all time). The rate of change of the total population, obtained by adding all the equations in model (7), is given by

$$\frac{dN}{dt} = \Pi - \mu N - \delta_H H_2 - \delta_T T - \delta_{HT} I^2_{HL} - \omega\delta_{HT} I^2_{HT}. \tag{8}$$

It is easy to see that whenever $N > \Pi/\mu$, then $dN/dt < 0$. Since dN/dt is bounded by $\Pi - \mu N$, a standard comparison theorem [25] can be used to show that $N(t) \leq N(0)e^{-\mu t} + \dfrac{\Pi}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \dfrac{\Pi}{\mu}$ if $N(0) \leq \dfrac{\Pi}{\mu}$. Thus, every solution of the model (7) with initial conditions in $\mathcal{D}$ remains there for $t > 0$ (the ω-limit sets of the system (7) are contained in $\mathcal{D}$). Thus, $\mathcal{D}$ is positive-invariant and attracting. Hence, it is sufficient to consider the dynamics of the flow generated by (7) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed [17].

3. **Analysis of the sub-models.**

Before analyzing the full model (7), it is instructive to gain insights into the dynamics of the models for HIV only (*HIV-only model*) and TB only (*TB-only model*).

3.1. **HIV-only model.**

The model with HIV only (obtained by setting $L = T = I^1_{HL} = I^1_{HT} = I^2_{HL} = I^2_{HT} = W_T = W^H_{HL} = W^H_{HT} = W^T_{HT} = W^M_{HT} = 0$ in (7)) is given by

$$\begin{aligned}\frac{dS}{dt} &= \Pi - \lambda_H S - \mu S, \\ \frac{dH_1}{dt} &= \lambda_H S - K_1 H_1, \\ \frac{dH_2}{dt} &= \sigma H_1 + \theta_t \sigma W_H - K_2 H_2, \\ \frac{dW_H}{dt} &= \tau_1 H_1 + \tau_2 H_2 - K_9 W_H,\end{aligned} \tag{9}$$

where,

$$\lambda_H = \frac{\beta_H(H_1 + \eta_2 H_2 + \eta_H W_H)}{N} \text{ and, now, } N = S + H_1 + H_2 + W_H.$$

For this model, it can be shown that the region,

$$\mathcal{D}_1 = \{(S, H_1, H_2, W_H) \in \mathbb{R}^4_+ : N \leq \Pi/\mu\},$$

is positively-invariant and attracting. Thus, the dynamics of the HIV-only model will be considered in $\mathcal{D}_1$.

3.1.1. *Local stability of disease-free equilibrium (DFE).* The model (9) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\mathcal{E}_0 = (S^*, H_1^*, H_2^*, W_H^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right). \tag{10}$$

The linear stability of $\mathcal{E}_0$ can be established using the next- generation operator method on the system (9). Using the notation in [33], the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are, respectively, given by (noting that $S^* = N^*$ at the DFE $\mathcal{E}_0$)

$$F = \begin{pmatrix} \beta_H & \beta_H\eta_2 & \beta_H\eta_H \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} K_1 & 0 & 0 \\ -\sigma & K_2 & -\theta_t\sigma \\ -\tau_1 & -\tau_2 & K_9 \end{pmatrix}.$$

Thus,

$$\mathcal{R}_H = \beta_H \frac{\left[(\mu+\delta_H)K_9 + \mu\tau_2 + \eta_2\sigma(K_9 + \theta_t\tau_1) + \eta_H(\sigma\tau_2 + K_2\tau_1)\right]}{K_1\left[(\mu+\delta_H)K_9 + \mu\tau_2\right]}. \tag{11}$$

The following result follows from Theorem 2 of [33].

Lemma 3.1. *The DFE of the HIV-only model* (9)*, given by* (10)*, is locally asymptotically stable (LAS) if* $\mathcal{R}_H < 1$*, and unstable if* $\mathcal{R}_H > 1$*.*

The threshold quantity $\mathcal{R}_H$ is the *reproduction number* for HIV [1]. It measures the average number of new HIV infections generated by a single HIV-infected individual in a population where a certain fraction of infected individuals are treated.

3.1.2. *Analysis of* $\mathcal{R}_H$*.* The objective here is to determine, using the threshold quantity $\mathcal{R}_H$, whether or not treating individuals with HIV, either those in the asymptomatic stage (modelled by the rate τ_1) or AIDS stage (modelled by the rate τ_2), can lead to HIV elimination in the community. It is evident from (11) that

$$\lim_{\tau_1\to\infty} \mathcal{R}_H = \frac{\beta_H(\eta_2\sigma\theta_t + \eta_H K_2)}{(\mu+\delta_H)K_9 + \mu\tau_2} > 0, \tag{12}$$

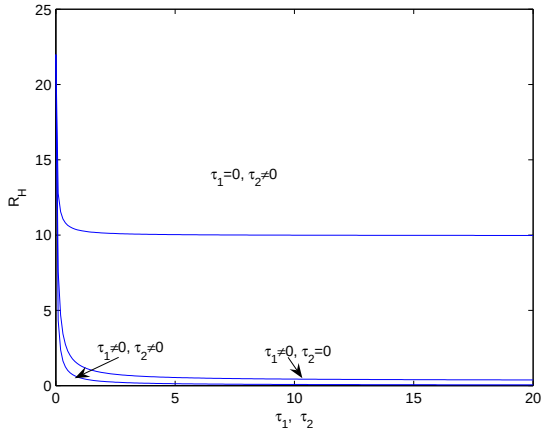
and,

$$\lim_{\tau_2\longrightarrow\infty} \mathcal{R}_H = \frac{\beta_H}{K_1}\left[1 + \frac{\eta_H(\sigma+\tau_1)}{\mu}\right] > 0. \tag{13}$$

Thus, a sufficiently effective HIV treatment program that focusses on treating infected individuals in the asymptomatic stage (at a high rate, $\tau_1 \to \infty$) or those with AIDS symptoms (at a rate $\tau_2 \to \infty$) can lead to effective disease control if it results in making the respective right-hand side of (12) or (13) less than unity. The profiles of $\mathcal{R}_H$, as a function of treatment rates τ_1 and τ_2, are depicted in Figure 1A. For the set of parameters used in these simulations, it is evident from this figure that while a strategy that focuses on treating asymptomatic individuals alone can dramatically reduce $\mathcal{R}_H$ from around $\mathcal{R}_H = 17$ to a value of $\mathcal{R}_H$ less than unity ($\mathcal{R}_H = 0.523$), the strategy that focuses on treating AIDS individuals only reduces $\mathcal{R}_H$ from $\mathcal{R}_H = 17$ to $\mathcal{R}_H = 10$ (thus, HIV cannot be eliminated in the

latter case, but will be in the former). It was further shown, in Figure 1A, that the combined treatment of HIV-infected individuals with or without AIDS symptoms reduces $\mathcal{R}_H$ to values less than unity faster than a strategy that targets individuals without AIDS symptoms.

(A)



(B)

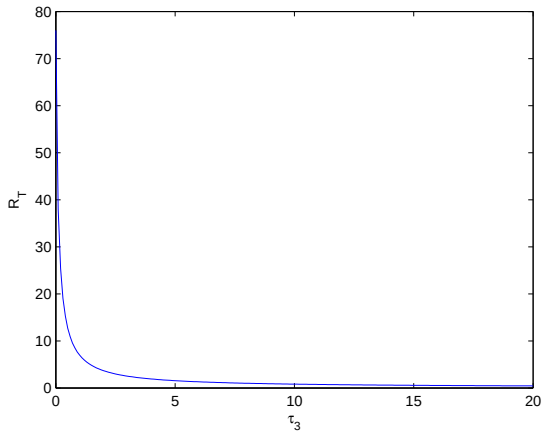


FIGURE 1. Reproduction numbers as a function of treatment rates. (A) $\mathcal{R}_H$, (B) $\mathcal{R}_T$

Further sensitivity analysis on the treatment parameters is carried out by computing the partial derivatives of $\mathcal{R}_H$ with respect to the treatment parameters (τ_1 and τ_2), giving,

$$\frac{\partial \mathcal{R}_H}{\partial \tau_1} = \frac{\beta_H\{[(\mu+\sigma)(\mu+\delta_H)+\mu\tau_2]\,\eta_H - \eta_2\sigma\mu(1-\theta_t) - (\mu+\delta_H)(\mu+\theta_t\sigma) - \mu\tau_2\}}{(\mu+\sigma+\tau_1)^2\,[(\mu+\delta_H)K_9+\mu\tau_2]}, \tag{14}$$

and,

$$\frac{\partial \mathcal{R}_H}{\partial \tau_2} = \frac{\beta_H\sigma\,[\eta_H\delta_H+\mu(\eta_H-\eta_2)]\,[\mu+\theta_t(\sigma+\tau_1)]}{(\mu+\sigma+\tau_1)\,[(\mu+\delta_H)K_9+\mu\tau_2]^2}. \tag{15}$$

Consider the case $\tau_2 = 0$ (that is, only HIV-infected individuals with no AIDS symptoms being treated). It follows from (14) that $\frac{\partial \mathcal{R}_H}{\partial \tau_1} < 0$ if

$$\eta_H < \Delta_I = \frac{\eta_2 \sigma \mu (1-\theta_t) + (\mu + \delta_H)(\mu + \theta_t \sigma)}{(\mu + \sigma)(\mu + \delta_H)}. \tag{16}$$

Thus, the targeted treatment of HIV-infected individuals in the asymptomatic stage will have positive impact in reducing HIV burden only if $\eta_H < \Delta_I$. Such a treatment will fail to reduce the HIV burden if $\eta_H = \Delta_I$, and will have a detrimental impact in the community (increase $\mathcal{R}_H$) if $\eta_H > \Delta_I$. This result is summarized below.

Lemma 3.2. *The targeted treatment of HIV-infected individuals in the asymptomatic stage will have positive impact if $\eta_H < \Delta_I$, no impact if $\eta_H = \Delta_I$ and will have detrimental impact if $\eta_H > \Delta_I$.*

Similarly, it follows from (15) that $\frac{\partial \mathcal{R}_H}{\partial \tau_2} < 0$ if

$$\eta_H < \Delta_A = \frac{\mu \eta_2}{\mu + \delta_H}, \tag{17}$$

giving the following result.

Lemma 3.3. *The targeted treatment of HIV-infected individuals with AIDS symptoms will have positive impact if $\eta_H < \Delta_A$, no impact if $\eta_H = \Delta_A$ and negative impact if $\eta_H > \Delta_A$.*

It is worth emphasizing that if Condition (16) or (17) does not hold, then the use of the corresponding targeted treatment strategy would increase HIV burden in the community (since it increases $\mathcal{R}_H$), although such treatment may be beneficial to those HIV-infected (individuals) treated. That is, the use of ARVs will increase disease burden if it fails to reduce the infectiousness of those treated below a certain threshold ($\eta_H < \Delta_I$ if asymptomatic HIV-infected individuals are targeted; or $\eta_H < \Delta_A$ if individuals with AIDS symptoms are targeted).

Returning back to Lemma 1. Biologically speaking, this lemma implies that HIV can be eliminated from the community (when $\mathcal{R}_H < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of $\mathcal{E}_0$. To ensure that elimination of the virus is independent of the initial sizes of the sub-populations, it is necessary to show that the DFE is globally asymptotically stable. This is established below.

3.1.3. *Global stability of DFE.*

Theorem 3.4. *The DFE of the HIV-only model* (9)*, given by* (10)*, is globally asymptotically stable (GAS) in $\mathcal{D}_1$ whenever $\mathcal{R}_H \leq 1$.*

Proof. Consider the following Lyapunov function:

$$\mathcal{F} = b_1 H_1 + b_2 H_2 + b_3 W_H,$$

where,

$$\begin{aligned} b_1 &= (\mu + \delta_H) K_9 + \mu \tau_2 + \eta_2 \sigma (K_9 + \theta_t K_3) + \eta_H (\sigma \tau_2 + K_2 K_3), \\ b_2 &= K_1 (\eta_2 K_9 + \eta_H \tau_2), \\ b_3 &= K_1 (\eta_2 \sigma \theta_t + \eta_H K_2), \end{aligned}$$

with Lyapunov derivative (where a dot represents differentiation with respect to t),

$$\begin{aligned}
\dot{\mathcal{F}} &= b_1\dot{H}_1 + b_2\dot{H}_2 + b_3\dot{W}_H, \\
&= b_1(\lambda_H S - K_1 H_1) + b_2(\sigma H_1 + \theta_t \sigma W_H - K_2 H_2) + b_3(\tau_1 H_1 + \tau_2 H_2 - K_9 W_H), \\
&= b_1\lambda_H S - K_1[(\mu+\delta_H)K_9 + \mu\tau_2](H_1 + \eta_2 H_2 + \eta_H W_H), \\
&= b_1\lambda_H S - \frac{\lambda_H N K_1[(\mu+\delta_H)K_9 + \mu\tau_2]}{\beta_H}, \\
&= \frac{\lambda_H N K_1[(\mu+\delta_H)K_9 + \mu\tau_2]}{\beta_H}\left\{\frac{b_1 S\beta_H}{NK_1[(\mu+\delta_H)K_9 + \mu\tau_2]} - 1\right\}, \\
&\leq \frac{\lambda_H N K_1[(\mu+\delta_H)K_9 + \mu\tau_2]}{\beta_H}\left\{\frac{b_1\beta_H}{K_1[(\mu+\delta_H)K_9 + \mu\tau_2]} - 1\right\}, \text{ (since } S \leq N) \\
&= \frac{\lambda_H N K_1[(\mu+\delta_H)K_9 + \mu\tau_2]}{\beta_H}(\mathcal{R}_H - 1) \leq 0 \text{ for } \mathcal{R}_H \leq 1.
\end{aligned}$$

Since all the model parameters are nonnegative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_H \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $H_1 = H_2 = W_H = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on $\mathcal{D}_1$; and the largest compact invariant set in $\{(S, H_1, H_2, W_H) \in \mathcal{D}_1 : \dot{\mathcal{F}} = 0\}$ is the singleton $\{\mathcal{E}_0\}$. Therefore, by the LaSalle's Invariance Principle [26], every solution to the equations of the model (9), with initial conditions in $\mathcal{D}_1$, approaches $\mathcal{E}_0$ as $t \to \infty$, whenever $\mathcal{R}_H \leq 1$ (note that substituting $H_1 = H_2 = W_H = 0$ in the first equation of (9) shows that $S \to S^*$ as $t \to \infty$). □

The above result shows that HIV will be eliminated from the community if the epidemiological threshold, $\mathcal{R}_H$, can be brought to a value less than unity.

3.1.4. *Existence of endemic equilibria.* To find conditions for the existence of an equilibrium for which HIV is endemic in the population (i.e., at least one of H_1^{**}, H_2^{**} and W_H^{**} is non-zero), denoted by $\mathcal{E}_1 = (S^{**}, H_1^{**}, H_2^{**}, W_H^{**})$, the equations in (9) are solved in terms of the force of infection at steady-state (λ_H^{**}), given by

$$\lambda_H^{**} = \frac{\beta_H(H_1^{**} + \eta_2 H_2^{**} + \eta_H W_H^{**})}{N^{**}}. \tag{18}$$

Setting the right hand sides of the model to zero (and noting that $\lambda_H = \lambda_H^{**}$ at equilibrium) gives

$$\begin{aligned}
S^{**} &= \frac{\Pi}{\mu + \lambda_H^{**}},\ H_1^{**} = \frac{\lambda_H^{**}\Pi}{K_1(\mu + \lambda_H^{**})},\ H_2^{**} = \frac{\sigma\lambda_H^{**}\Pi(K_9 + \theta_t\tau_1)}{K_1(\mu + \lambda_H^{**})[(\mu+\delta_H)K_9 + \mu\tau_2]}, \\
W_H^{**} &= \frac{\lambda_H^{**}\Pi(K_2\tau_1 + \sigma\tau_2)}{K_1(\mu + \lambda_H^{**})[(\mu+\delta_H)K_9 + \mu\tau_2]}.
\end{aligned} \tag{19}$$

Using (19) in the expression for λ_H^{**} in (18) shows that the nonzero (endemic) equilibria of the model satisfy

$$a_{11}\lambda_H^{**} - a_{12} = 0, \tag{20}$$

where,

$$a_{11} = \frac{1}{K_1}\left[1+\frac{\sigma(K_9+\theta_t\tau_1)}{(\mu+\delta_H)K_9+\mu\tau_2}+\frac{\sigma\tau_2+K_2\tau_1}{(\mu+\delta_H)K_9+\mu\tau_2}\right] \text{ and } a_{12}=\mathcal{R}_H-1.$$

It is clear that $a_{11} > 0$, and $a_{12} > 0$ for $\mathcal{R}_H > 1$. Thus, the linear system (20) has a unique positive solution, given by $\lambda_H^{**} = a_{12}/a_{11}$, whenever $\mathcal{R}_H > 1$. The components of the endemic equilibrium, $\mathcal{E}_1$, are then determined by substituting $\lambda_H^{**} = a_{12}/a_{11}$ into (19). Noting that $\mathcal{R}_H < 1$ implies that $a_{12} < 0$. Thus, for $\mathcal{R}_H < 1$, the force of infection at steady-state (λ_H^{**}) is negative (which is biologically meaningless). Hence, the model has no positive equilibria in this case. These results are summarized below.

Lemma 3.5. *The HIV-only model* (9) *has a unique endemic equilibrium whenever* $\mathcal{R}_H > 1$, *and no endemic equilibrium otherwise.*

3.1.5. *Local stability of endemic equilibrium.* Using standard linearization of the HIV-only model around the endemic equilibrium is laborious and not really tractable mathematically. Here, the center manifold theory [6], as described in [9] (Theorem 4.1), will be used to establish the local asymptotic stability of the endemic equilibrium (see also [10, 33]). To apply this method, the following simplification and change of variables are made first. Let $S = x_1, H_1 = x_2, H_2 = x_3$, and , $W_H = x_4$, so that $N = x_1+x_2+x_3+x_4$. Further, by using vector notation $X = (x_1, x_2, x_3, x_4)^T$, the HIV-only model (9) can be written in the form $\frac{dX}{dt} = (f_1, f_2, f_3, f_4)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Pi - \frac{\beta_H(x_2+\eta_2x_3+\eta_Hx_4)}{(x_1+x_2+x_3+x_4)}x_1 - \mu x_1,\\
\frac{dx_2}{dt} &= f_2 = \frac{\beta_H(x_2+\eta_2x_3+\eta_Hx_4)}{(x_1+x_2+x_3+x_4)}x_1 - K_1x_2,\\
\frac{dx_3}{dt} &= f_3 = \sigma x_2 + \theta_t\sigma x_4 - K_2x_3,\\
\frac{dx_4}{dt} &= f_4 = \tau_1x_2 + \tau_2x_3 - K_9x_4.
\end{aligned} \tag{21}$$

The Jacobian of the system (21), at $\mathcal{E}_0$, is given by

$$J(\mathcal{E}_0) = \begin{pmatrix} -\mu & -\beta_H & -\beta_H\eta_2 & -\beta_H\eta_H \\ 0 & \beta_H - K_1 & \beta_H\eta_2 & \beta_H\eta_H \\ 0 & \sigma & -K_2 & \theta_t\sigma \\ 0 & \tau_1 & \tau_2 & -K_9 \end{pmatrix},$$

from which it can be shown that

$$\mathcal{R}_H = \frac{\beta_H}{K_1}\left[1+\frac{\eta_2\sigma(K_9+\theta_t\tau_1)}{(\mu+\delta_H)K_9+\mu\tau_2}+\frac{\eta_H(\sigma\tau_2+K_2\tau_1)}{(\mu+\delta_H)K_9+\mu\tau_2}\right]. \tag{22}$$

Consider the case when $\mathcal{R}_H = 1$. Suppose, further, that β_H is chosen as a bifurcation parameter. Solving (22) for β_H gives $\mathcal{R}_H = 1$ when

$$\beta_H = \beta^* = \frac{K_1}{1+\frac{\eta_2\sigma(K_9+\theta_t\tau_1)}{(\mu+\delta_H)K_9+\mu\tau_2}+\frac{\eta_H(\sigma\tau_2+K_2\tau_1)}{(\mu+\delta_H)K_9+\mu\tau_2}}. \tag{23}$$

Note that the above linearized system, of the transformed system (21) with $\beta_H = \beta^*$, has a zero eigenvalue which is simple. Hence, the center manifold theory [6]

can be used to analyze the dynamics of (21) near $\beta_H = \beta^*$. In particular, Theorem 4.1 in [9] will be used to show the LAS of the endemic equilibrium point of (21) (which is the same as the endemic equilibrium point of the original system (9)), for β_H near β^*.

Eigenvectors of $J(\mathcal{E}_0)\Big|_{\beta_H=\beta^*}$

It can be shown that the Jacobian of (21) at $\beta_H = \beta^*$ (denoted by J_{β^*}) has a right eigenvector (associated with the zero eigenvalue) given by $w = [w_1, w_2, w_3, w_4]^T$, where

$$\begin{aligned} w_1 &= -\frac{(\beta^* w_2 + \beta^* \eta_2 w_3 + \beta^* \eta_H w_4)}{\mu}, \\ w_2 &= \frac{\beta^*(\eta_2 w_3 + \eta_H w_4)}{K_1 - \beta^*}, \\ w_3 &= w_3 > 0, \quad w_4 = \frac{K_2\tau_1 + \tau_2\sigma}{\tau_2\theta_t\sigma + K_9\sigma} w_3. \end{aligned}$$

The denominator $K_1 - \beta^* > 0$ since it follows from (23) that $K_1 > \beta^*$. Further, J_{β^*} has a left eigenvector $v = [v_1, v_2, v_3, v_4]$ (associated with the zero eigenvalue), where

$$\begin{aligned} v_1 &= 0, \quad v_2 = \frac{\sigma\tau_2 + K_2\tau_1}{(K_1 - \beta^*)\tau_2 + \beta^*\eta_2\tau_1} v_3, \quad v_3 = v_3 > 0, \\ v_4 &= \frac{\beta^*\eta_H v_2 + \theta_t\sigma v_3}{K_9}. \end{aligned}$$

For convenience, the theorem in [9] (see also [6, 10, 33]) is reproduced below.

Theorem 3.6 (Castillo-Chavez & Song [9])**.** *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{24}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ *for all* ϕ*) and assume*

- **A1:** $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of the system* (24) *around the equilibrium 0 with* ϕ *evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*
- **A2:** *Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).*

Let f_k *be the kth component of f and*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

The local dynamics of the system around 0 is totally determined by the signs of a and b.

i: $a > 0, b > 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, *0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*

ii: $a < 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable; when* $0 < \phi \ll 1$, *0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;*

iii: $a > 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, *0 is stable, and a positive unstable equilibrium appears;*

iv: $a < 0, b > 0$. *When* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\phi = 0$.

Computations of a and b :
For the system (21), the associated non-zero partial derivatives of F (at the DFE) are given by

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_2^2} &= -\frac{2\beta^*\mu}{\Pi}, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\frac{\beta^*\mu(1+\eta_2)}{\Pi}, \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_4} &= -\frac{\beta^*\mu(1+\eta_H)}{\Pi}, \quad \frac{\partial^2 f_2}{\partial x_3^2} = -\frac{2\beta^*\mu\nu_2}{\Pi}, \\
\frac{\partial^2 f_2}{\partial x_3 \partial x_4} &= -\frac{\beta^*\nu_2\eta\mu(\nu_2+\nu_H)}{\Pi}, \quad \frac{\partial^2 f_2}{\partial x_4^2} = \frac{2\beta^*\mu\eta_H}{\Pi}.
\end{aligned}$$

It follows from the above expressions that

$$a = -\frac{2v_2\beta^*\mu(w_2+w_3+w_4)(w_2+w_4\eta_H+w_3\eta_2)}{\Pi} < 0.$$

For the sign of b, it can be shown that the associated non-vanishing partial derivatives of F are

$$\begin{aligned}
\frac{\partial^2 f_1}{\partial x_2 \partial \beta^*} &= -1, \quad \frac{\partial^2 f_1}{\partial x_3 \partial \beta^*} = -\eta_2, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} = -\eta_H, \\
\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*} &= 1, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = \eta_2, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} = \eta_H.
\end{aligned}$$

It also follows from the above expressions that

$$b = v_2(w_2 + w_3\eta_2 + w_4\eta_H) > 0.$$

Thus, $a < 0$ and $b > 0$. So (by Theorem 2, Item (iv)), we have established the following result (note that this result holds for $\mathcal{R}_H > 1$ but close to 1):

Theorem 3.7. *The unique endemic equilibrium guaranteed by Theorem 2 is LAS for* $\mathcal{R}_H$ *near 1.*

In summary, the HIV-only model (9) has a globally-asymptotically stable DFE whenever $\mathcal{R}_H \leq 1$, and a unique endemic equilibrium point whenever $\mathcal{R}_H > 1$. The unique endemic equilibrium point is LAS at least near $\mathcal{R}_H = 1$. The dynamics of TB-only is also explored as below.

3.2. **TB-only model.** The model for the transmission dynamics of TB only (obtained by setting $H_1 = H_2 = I^1_{HL} = I^1_{HT} = I^2_{HL} = I^2_{HT} = W_H = W^H_{HL} = W^H_{HT} = W^T_{HT} = W^M_{HT} = 0$ in (7)), given by

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda_T S - \mu S, \\ \frac{dL}{dt} &= l\lambda_T S + \rho W_T - \lambda_R L - K_3 L, \\ \frac{dT}{dt} &= (1-l)\lambda_T S + \lambda_R L + \alpha L - K_4 T, \\ \frac{dW_T}{dt} &= \tau_3 T - K_{10} W_T, \end{aligned} \tag{25}$$

with,

$$\lambda_T = \frac{\beta_T(T + \eta_T W_T)}{N}, \ \ \lambda_R = \frac{\beta \eta_r T}{N} \ \text{ with } \ N = S + L + T + W_T.$$

The TB-only model (25) is formulated along the lines of the model in Feng et al. [12], but with the additional features of (i) newly-infected individuals can have either latent or active TB ($0 < l < 1$) and (ii) treated (TB-infected) individuals can transmit TB ($\eta_T \neq 0$).

3.2.1. *Local stability of DFE.* The TB-only model (25) has a DFE given by

$$\mathcal{E}_{0t} = (S^*, L^*, T^*, W^*_T) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right). \tag{26}$$

Here, the F and V matrices are given, respectively, by

$$F = \begin{pmatrix} 0 & l\beta_T & l\beta_T\eta_T \\ 0 & (1-l)\beta_T & (1-l)\beta_T\eta_T \\ 0 & 0 & 0 \end{pmatrix}, \ V = \begin{pmatrix} K_3 & 0 & -\rho \\ -\alpha & K_4 & 0 \\ 0 & -\tau_3 & K_{10} \end{pmatrix}.$$

It follows that

$$\mathcal{R}_T \ = \ \frac{(1-l)K_3\beta_T(K_{10} + \eta_T\tau_3) + \beta_T l\alpha(K_{10} + \eta_T\tau_3)}{K_3K_4K_{10} - \alpha\rho\tau_3}, \tag{27}$$

where, $K_3K_4K_{10} - \alpha\rho\tau_3 = \mu(\mu + \rho + \alpha)(\mu + \delta_T + \tau_3) + \alpha\rho(\mu + \delta_T) > 0$. Thus, the following result is established (from Theorem 2 of [33]).

Lemma 3.8. *The DFE of the model* (25)*, given by* (26)*, is LAS if* $\mathcal{R}_T < 1$*, and unstable if* $\mathcal{R}_T > 1$.

The threshold quantity, $\mathcal{R}_T$, is the *reproduction number* for TB.

3.2.2. *Analysis of* $\mathcal{R}_T$. Here, the reproduction threshold, $\mathcal{R}_T$, will be analyzed to determine whether or not treating people with active TB (modelled by the rate τ_3) can lead to the effective control or elimination of TB in the population. It follows from (27), that

$$\lim_{\tau_3 \to \infty} \mathcal{R}_T = \frac{(1-l)\beta_T K_3 \eta_T + l\beta_T \alpha \eta_T}{\mu(\mu + \rho + \alpha)} = \frac{\beta_T \eta_T[\mu(1-l) + \alpha]}{\mu(\mu + \rho + \alpha)} > 0,$$

from which it is evident that the parameters β_T and η_T play an important role in determining the value of $\mathcal{R}_T$. A plot of $\mathcal{R}_T$ as a function of τ_3 is depicted in Figure 1B. This figure shows that, for the set of parameters used in the simulations, an effective strategy for treating people with active TB may not be adequate to eliminate TB in the community, since it only brings $\mathcal{R}_T$ down to about $\mathcal{R}_T = 5$ at

steady state (and the condition $\mathcal{R}_T < 1$ is needed for effective control of TB in a population).

Biologically speaking, Lemma (3.8) implies that TB can be eliminated from the community (when $\mathcal{R}_T < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of $\mathcal{E}_{0t}$. Since TB models are often shown to exhibit the phenomenon of backward bifurcation [9, 12], where the stable DFE co-exists with a stable endemic equilibrium when the associated reproduction threshold ($\mathcal{R}_T$) is less than unity, it is instructive to determine whether or not the TB-only model (25) exhibits this feature. This is done below.

3.2.3. *Bifurcation analysis.* Models of TB dynamics with exogenous re-infection are known to exhibit the phenomenon of backward bifurcation [9, 12], where the stable DFE co-exists with a stable endemic equilibrium. Here, the model (25) will be analysed to see whether or not the new features ($l \neq 1$ and $\eta_T \neq 0$) added to some of the earlier TB models (e.g., the model in [12]) would have any effect on the expected reinfection-induced backward bifurcation property of TB disease. Here, too, the Centre Manifold theory will be used on the model system (25). Let $S = x_1, L = x_2, T = x_3$, and $W_T = x_4$, so that $N = x_1 + x_2 + x_3 + x_4$, so that the model (25) is re-written in the form:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Pi - \frac{\beta_T(x_3 + \eta_t x_4)x_1}{x_1 + x_2 + x_3 + x_4} - \mu x_1, \\
\frac{dx_2}{dt} &= f_2 = l\frac{\beta_T(x_3 + \eta_t x_4)x_1}{x_1 + x_2 + x_3 + x_4} + \rho x_4 - \frac{\beta_T \eta_r x_3 x_2}{x_1 + x_2 + x_3 + x_4} - K_3 x_2, \\
\frac{dx_3}{dt} &= f_3 = (1-l)\frac{\beta_T(x_3 + \eta_t x_4)x_1}{x_1 + x_2 + x_3 + x_4} + \frac{\beta_T \eta_r x_3 x_2}{x_1 + x_2 + x_3 + x_4} + \alpha x_2 - K_4 x_3, \\
\frac{dx_4}{dt} &= f_4 = \tau_3 x_3 - K_{10} x_4.
\end{aligned} \tag{28}$$

The Jacobian of the system (28), at the DFE (26), is given by

$$J(\mathcal{E}_{0t}) = \begin{pmatrix} -\mu & 0 & -\beta_T & -\beta_T \eta_T \\ 0 & -K_3 & l\beta_T & l\beta_T \eta_T + \rho \\ 0 & \alpha & (1-l)\beta_T - K_4 & (1-l)\beta_T \eta_T \\ 0 & 0 & \tau_3 & -K_{10} \end{pmatrix},$$

from which it can also be shown that

$$\mathcal{R}_T = \frac{\beta_T[(1-l)K_3(K_{10} + \eta_T \tau_3) + l\alpha(K_{10} + \eta_T \tau_3)]}{K_3 K_4 K_{10} - \alpha\rho\tau_3}. \tag{29}$$

Suppose β_T is chosen as a bifurcation parameter. Solving (29) for $\mathcal{R}_T = 1$, gives

$$\beta_T = \beta^* = \frac{K_3 K_4 K_{10} - \alpha\rho\tau_3}{(1-l)K_3(K_{10} + \eta_T \tau_3) + l\alpha(K_{10} + \eta_T \tau_3)}.$$

Eigenvectors of $J(\mathcal{E}_{0t})\Big|_{\beta_T = \beta^*}$

It can be shown that the Jacobian of (28) at $\beta_T = \beta^*$ (denoted by $J(\mathcal{E}_{0t})\Big|_{\beta_T = \beta^*} = J_{\beta^*}$) has a right eigenvector (corresponding to the zero eigenvalue) given by $w =$

$[w_1, w_2, w_3, w_4]^T$, where

$$\begin{aligned} w_1 &= \frac{-\beta^* w_3 - \beta^* \eta_t w_4}{\mu}, \\ w_2 &= \frac{l\beta^* w_3 + (l\beta^* \eta_T + \rho) w_4}{K_3}, \\ w_3 &= w_3, \\ w_4 &= \frac{\tau_3 w_3}{K_{10}}. \end{aligned}$$

Further, the Jacobian J_{β^*} has a left eigenvector (associated with the zero eigenvalue) given by $v = [v_1, v_2, v_3, v_4]$, where

$$\begin{aligned} v_1 &= 0, \\ v_2 &= \frac{\alpha}{K_3} v_3, \\ v_3 &= v_3, \\ v_4 &= \frac{(l\beta^* \eta_T + \rho) v_2 + (1-l)\beta^* \eta_t v_3}{K_{10}}. \end{aligned}$$

Theorem 2 will be used to establish the presence of backward bifurcation in the TB-only model (25).

Computations of a and b :

For the system (28), the associated non-zero partial derivatives of F (at the DFE) are given by

$$\begin{aligned} \frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= -\frac{\beta^* \mu}{\Pi}(l + \eta_r), \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_4} = -\frac{l\beta^* \eta_T \mu}{\Pi}, \quad \frac{\partial^2 f_2}{\partial x_3^2} = -\frac{2l\beta^* \mu}{\Pi}, \\ \frac{\partial^2 f_2}{\partial x_3 \partial x_4} &= -\frac{l\beta^* \mu}{\Pi}(1 + \eta_T), \quad \frac{\partial^2 f_2}{\partial x_4^2} = \frac{-2l\beta^* \eta_T \mu}{\Pi}, \quad \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = -\frac{\beta^* \mu}{\Pi}(1 - l - \eta_r), \\ \frac{\partial^2 f_3}{\partial x_2 \partial x_4} &= -\frac{(1-l)\beta^* \eta_T \mu}{\Pi}, \quad \frac{\partial^2 f_3}{\partial x_3^2} = -\frac{2(1-l)\beta^* \mu}{\Pi}, \\ \frac{\partial^2 f_3}{\partial x_3 \partial x_4} &= -\frac{(1-l)\beta^* \mu}{\Pi}(1 + \eta_T), \quad \frac{\partial^2 f_3}{\partial x_4^2} = \frac{-2(1-l)\beta^* \eta_T \mu}{\Pi}. \end{aligned}$$

It follows from the above expressions that

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^{4} w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{4} w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j}, \\ &= -\frac{2\beta^* \mu}{\Pi}[A_{11} l + A_{12}(1-l) - (v_3 - v_2) w_2 w_3 \eta_r], \end{aligned}$$

from which it can be shown that $a > 0$ iff

$$w_2 w_3 \eta_r (v_3 - v_2) > A_{11} l + A_{12}(1-l),$$

where,

$$A_{11} = v_2(w_2 + w_3 + w_4)(w_3 + w_4 \eta_T), \quad A_{12} = \frac{v_3 A_{11}}{v_2}.$$

Hence, $a > 0$ whenever (note that $v_3 - v_2 = \mu v_3 > 0$)

$$\eta_r \quad > \quad \frac{A_{11}l + A_{12}(1-l)}{w_2 w_3 (v_3 - v_2)}.$$

For the sign of b, it can be shown that the associated non-vanishing partial derivatives of F are

$$\frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} \quad = \quad l, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} = l\eta_T, \quad \frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} = 1 - l, \quad \frac{\partial^2 f_3}{\partial x_4 \partial \beta^*} = (1-l)\eta_T,$$

so that,

$$\begin{aligned} b &= v_2 \sum_{i=1}^{4} w_i \frac{\partial^2 f_2}{\partial x_i \partial \beta^*} + v_3 \sum_{i=1}^{4} w_i \frac{\partial^2 f_3}{\partial x_i \partial \beta^*} \\ &= (w_3 + w_4 \eta_T)[v_2 l + v_3(1-l)] > 0. \end{aligned}$$

Thus, we have established the following result:

Theorem 3.9. *If*

$$\eta_r \quad > \quad \frac{A_{11}l + A_{12}(1-l)}{w_2 w_3 (v_3 - v_2)},$$

with $v_3 - v_2 > 0$, then the TB-only model (28) *undergoes a backward bifurcation at $\mathcal{R}_T = 1$.*

It should be noted that the inequality in Theorem 4 does not hold if $\eta_r = 0$ (since the right hand side of the inequality is positive). Thus, the backward bifurcation phenomenon of the TB-only model (28) will not occur if $\eta_r = 0$ (i.e., the TB-only model will not undergo backward bifurcation in the absence of exogenous re-infection).

Numerical simulations are carried out, using an appropriate set of parameter values (satisfying the inequality in Theorem 4), to illustrate the backward bifurcation phenomenon of model (28) (see Figure 2).

It should be emphasized that these parameter values are chosen only to illustrate the backward bifurcation phenomenon of model (28), and may not all be realistic epidemiologically. With the chosen set of parameter values, the ratio $\frac{A_{11}l + A_{12}(1-l)}{w_2 w_3 (v_3 - v_2)} = 2$. Thus, the inequality in Theorem 4 will hold by choosing a value of $\eta_r > 2$, such as $\eta_r = 3$. Thus, it follows from Theorem 4 (and Figure 2) that the additional features $l = 1$ (i.e., all newly-infected individuals have latent TB) and $\eta_T = 0$ (i.e., treated people do not transmit the disease) do not affect the backward bifurcation property of the TB disease (since, the inequality in Theorem 4 still holds if $l = 1$ and $\eta_T = 0$ with $\eta_r = 3$).

In summary, unlike the HIV-only model (9), the TB-only model (28) undergoes backward bifurcation, where multiple stable equilibria co-exist when $\mathcal{R}_T < 1$. Backward bifurcations have been observed in a number of epidemiological settings, such as those associated with behavioral responses to perceived risks [10, 15], multi-group models [7, 8, 20, 31], vaccination models [2, 4, 11, 22, 32], disease treatment [34] and models of the transmission of TB with exogenous re-infection [9, 12] and HTLV-I [13].

Having analysed the dynamics of the two sub-models, the full HIV-TB model (7) will now be anlysed.

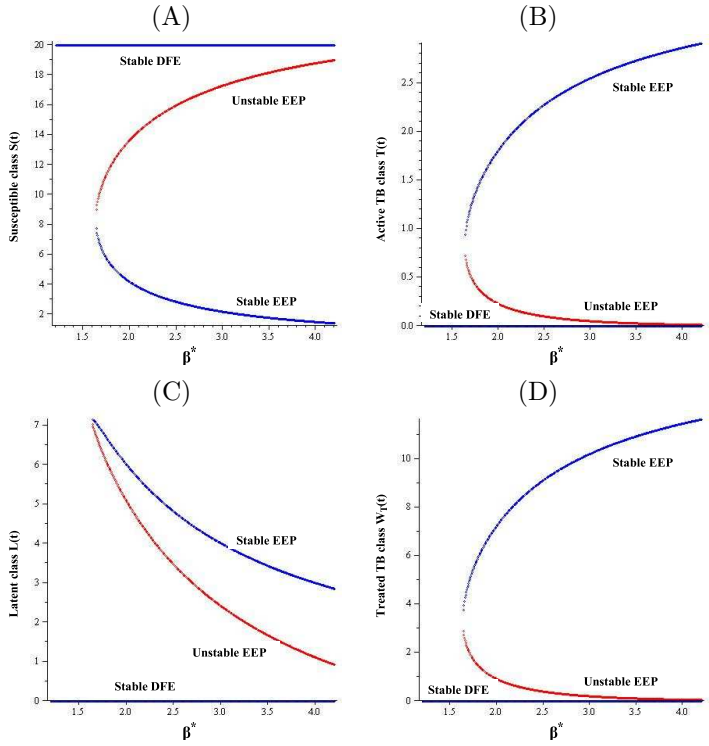


FIGURE 2. Simulations of the TB-only model (25). Backward bifurcation diagrams for (A) susceptible, (B) active TB, (C) latent TB and (D) treated TB classes using $\beta = 0.56, \eta_T = 0.001, \alpha = 0.03, \mu = 0.03, \rho = 0.1, \delta_t = 0.02, \tau_3 = 0.5, l = 0.6$ and $\eta_r = 3$.

4. **Analysis of the full model.** Consider, now, the full model (7), with DFE given by

$$\begin{aligned}\mathcal{E}_1 &= (S^*, H_1^*, H_2^*, L^*, T^*, I_{HL}^{1*}, I_{HT}^{1*}, I_{HL}^{2*}, I_{HT}^{2*}, W_H^*, W_T^*, W_{HL}^{H*}, W_{HT}^{H*}, W_{HT}^{T*}, W_{HT}^{M*}) \\ &= (\Pi/\mu, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0),\end{aligned}$$

and the associated matrices F and V, are given, respectively, by

$$F = \begin{bmatrix} F_1 & F_2 \\ \mathbf{0}_{10\times 8} & \mathbf{0}_{10\times 6} \end{bmatrix},$$

where,

$$F_1 = \begin{pmatrix} \beta_H & \beta_H\eta_2 & 0 & 0 & \beta_H & \beta_H\eta_D & \beta_H c_2\eta_2 & \beta_H c_2\eta_2\eta_D \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & l\beta_T & 0 & l\beta_T & 0 & l\beta_T \\ 0 & 0 & 0 & (1-l)\beta_T & 0 & (1-l)\beta_T & 0 & (1-l)\beta_T \end{pmatrix},$$

$$F_2 = \begin{pmatrix} \beta_H\eta_H & 0 & \beta_H\eta_H & \beta_H\eta_H & \beta_H & \beta_H\eta_H \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & l\beta_T\eta_T & 0 & l\beta_T & l\beta_T\eta_T & l\beta_T\eta_T \\ 0 & (1-l)\beta_T\eta_T & 0 & (1-l)\beta_T & (1-l)\beta_T\eta_T & (1-l)\beta_T\eta_T \end{pmatrix},$$

and,

$$V = \begin{bmatrix} V_1 & V_2 \\ V_3 & V_4 \end{bmatrix},$$

with,

$$V_1 = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 & 0 \\ -\sigma & K_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & K_3 & 0 & 0 & 0 \\ 0 & 0 & -\alpha & K_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_5 & 0 \\ 0 & 0 & 0 & 0 & -\theta_1\alpha & K_6 \end{pmatrix},$$

$$V_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_t\sigma & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\rho & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V_3 = \begin{pmatrix} 0 & 0 & 0 & 0 & -(1-\xi)\gamma_{HT} & 0 \\ 0 & 0 & 0 & 0 & -\xi\gamma_{HT} & -\eta_1\sigma \\ -\tau_1 & -\tau_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\tau_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\tau_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\tau_1 \\ 0 & 0 & 0 & 0 & 0 & -\tau_3 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V_4 = \begin{pmatrix} K_7 & 0 & 0 & 0 & -\theta_t\sigma & 0 & -\sigma_T & -\sigma_{HT} \\ -\theta_2\alpha & K_8 & 0 & 0 & 0 & -\sigma_H & 0 & 0 \\ 0 & 0 & K_9 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & K_{10} & 0 & 0 & 0 & 0 \\ -\tau_2 & 0 & 0 & 0 & K_{11} & 0 & 0 & 0 \\ 0 & -\tau_2 & 0 & 0 & -\theta_1\alpha & K_{12} & 0 & 0 \\ 0 & -\tau_3 & 0 & 0 & 0 & 0 & K_{13} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\tau_3 & -\tau_2 & K_{14} \end{pmatrix}.$$

Here, it is shown that the associated *reproduction number* is given by,

$$\mathcal{R}_c = \max\{\mathcal{R}_H, \mathcal{R}_T\},$$

where, $\mathcal{R}_H$ and $\mathcal{R}_T$ are as defined before. Using Theorem 2 in [33], the following result is established.

Lemma 4.1. *The DFE of the full HIV-TB model* (7)*, given by* $\mathcal{E}_1$*, is LAS if* $\mathcal{R}_c < 1$*, and unstable if* $\mathcal{R}_c > 1$*.*

It can be shown, using similar approach as in Section 3.2.3, that the full model (7) will exhibit backward bifurcation for $\mathcal{R}_c < 1$.

5. **Simulations.** The full model (7) is now simulated, using the parameter estimates in Table 2 (unless otherwise stated), to assess the potential impact of treatment strategies against HIV and TB, as follows.
Table 2: Parameter Values

Parameter	Nominal value	References
Π	50,000	
μ	0.02	
β_H, β_T	variable	
$\theta_1, \theta_2, \theta_t$	6, 6, 0.01	
ρ	0.1	[9]
α	0.03	
σ	1/33	[9]
$\delta_H, \delta_T, \delta_{HT}$	0.01, 0.02, 0.03	
l	0.7	
τ_1, τ_2, τ_3	variable	
$\eta_1, \eta_D, \eta_r, \eta_2, \eta_T, \eta_H$	1.2, 1.2, 1, 1.2, 0.001, 0.001	
c_2	1	
ψ_1, ψ_2	1.2, 1.4	
ω	1.4	
$\sigma_H, \sigma_T, \sigma_{HT}$	0.1,0.2,1/15	
γ_{HT}	0.4	
ξ	0.5	
ϕ	0.7	

5.1. **Threshold simulations.** Simulations are carried out to monitor the dynamics of the full model (7) for various values of the associated reproduction thresholds ($\mathcal{R}_H$ and $\mathcal{R}_T$). For the case when $\mathcal{R}_H < 1$ and $\mathcal{R}_T < 1$, (that is, $\mathcal{R}_c < 1$), the solution profiles can converge to the DFE or the EEP owing to the phenomenon of backward bifurcation in the full model (7). Figure 3 shows convergence of the solutions to the DFE for $\mathcal{R}_c < 1$ (in line with Lemma 6), whereas Figure 4 illustrates the backward bifurcation phenomenon of the full model (7), with some solutions converging to an EEP and others to a DFE when the threshold quantity $\mathcal{R}_c$ is less than unity. Note that, for the set of parameter values used, the simulations have to be run for long time periods (in hundreds of years) to generate the backward bifurcation pictures depicted in Figure 4.

5.2. **Evaluation of treatment strategies.** As stated earlier, the paper offers four main treatment strategies namely the, (*i*) HIV-only strategy, (*ii*) TB-only strategy, (*iii*) mixed-only strategy, and (*iv*) universal strategy. The full model (7) is now simulated (for a four-year period) to assess these strategies as follows:

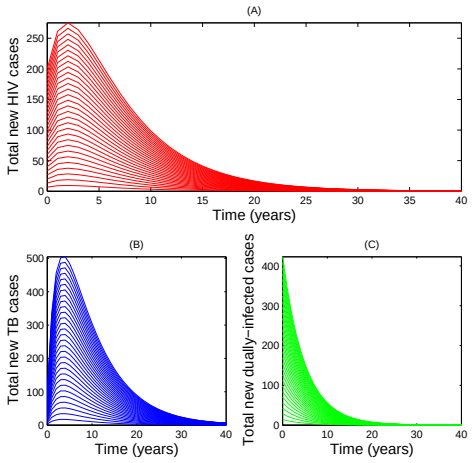


FIGURE 3. Simulations of the full model (7). Total infectives as a function of time using different initial conditions, with $\mathcal{R}_H = 0.29, \mathcal{R}_T = 0.50$; so that $\mathcal{R}_c = 0.50$. (A) HIV cases, (B) TB cases, and (C) HIV-TB cases. All other parameters as in Table 2.

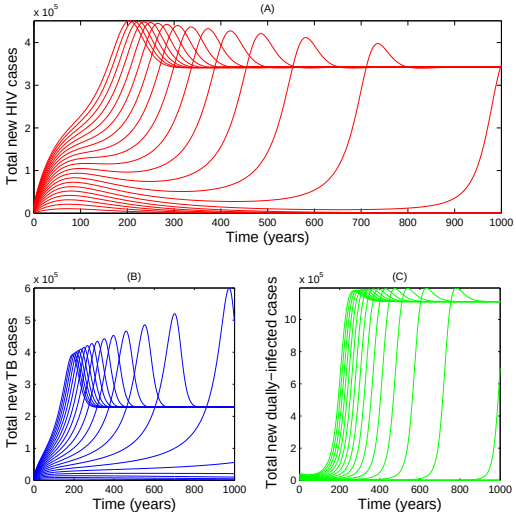


FIGURE 4. Simulations of the full model (7). Backward bifurcation diagrams using different initial conditions and parameter values such that $\mathcal{R}_H = 0.87, \mathcal{R}_T = 0.96$; so that $\mathcal{R}_c = 0.96$. (A) HIV cases, (B) TB cases, and (C) HIV-TB cases. All other parameters as in Table 2.

5.2.1. *HIV-only treatment strategy.* Here, simulations are carried out to monitor the impact of treating for HIV only. That is, singly-infected individuals in the H_1

and H_2 classes are treated at the rates τ_1 and τ_2, respectively; while dually-infected individuals are treated for HIV at the rate τ_2 (i.e., individuals infected with TB, either singly or dually, are not treated for TB, so that $\tau_3 = 0$). Using a modest rate of $\tau_1 = \tau_2 = 0.5$, the results, depicted in Figure 5A, show a significant reduction of the number of new cases of HIV as well as those of the mixed HIV-TB infection (although more new cases of HIV are prevented than those of the mixed infection). Similar trends were observed when the treatment rate was increased by 10-fold (Figure 5B).

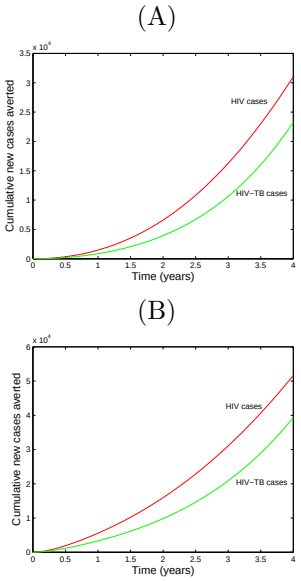


FIGURE 5. Simulations of the full model (7). Cumulative new cases averted using HIV-only treatment strategy with (A) $\tau_1 = \tau_2 = 0.5$ and $\tau_3 = 0$ and (B) $\tau_1 = \tau_2 = 5$ and $\tau_3 = 0$. All other parameters as in Table 2.

5.2.2. *TB-only treatment strategy.* In these simulations, only individuals infected with TB are treated for TB. That is, only individuals in the active TB classes (i.e., those in T, I^1_{HT}, I^2_{HT}, and W^H_{HT}) are treated (at the rate τ_3) and those with HIV or latent TB are not treated (i.e., $\tau_1 = \tau_2 = 0$). Figure 6A shows a significant reduction of the cumulative number of new TB cases followed by that of the mixed infection. It should be stated that the number of TB cases prevented (Figure 6A) exceeds the corresponding number of HIV cases prevented under the HIV-only treatment strategy (Figure 5A). However, more cases of the mixed infection were prevented in the HIV-only treatment strategy than in this (TB-only) treatment scenario. Similar trends were observed when the treatment rate is increased by 10-fold (Figure 6B).

5.2.3. *Mixed-only treatment strategy.* In these simulations, only individuals with the mixed infection are treated for both diseases (HIV infected individuals are treated at the rates τ_1 and τ_2; and those with active TB are treated at the rate τ_3). That is, we set $\tau_1 = \tau_2 = \tau_3 = 0$ in the H_1, H_2, T, W_H and W_T classes but use these

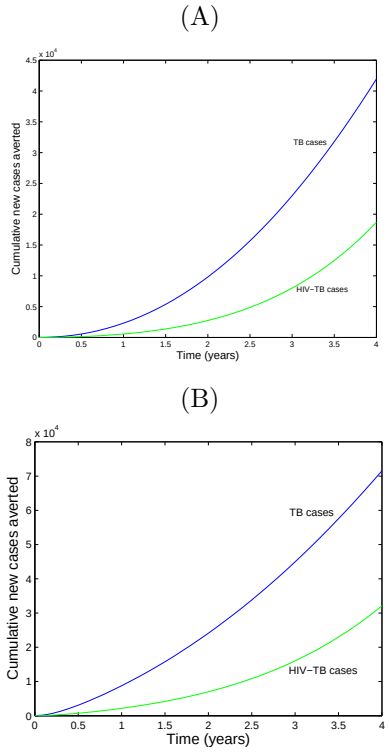


FIGURE 6. Simulations of the full model (7). Cumulative new cases averted using TB-only treatment strategy with (A) $\tau_3 = 0.5, \tau_1 = \tau_2 = 0$ and (B) $\tau_3 = 5$ and $\tau_1 = \tau_2 = 0$. All other parameters as in Table 2.

rates in each of the mixed infection classes. The results obtained for low treatment rate, depicted in Figure 7A, show more reductions of cumulative new cases of HIV followed by those of the mixed infection and then TB. However, this strategy saves far fewer cases than either the HIV-only or TB-only treatment strategy. Increasing the treatment rate by 10-fold shows more savings of the cumulative new cases of TB followed by those of HIV and then the mixed infection (Figure 7B). It should be noted that although the mixed-only strategy saves fewer cumulative cases for low treatment rates (in comparison to the other two strategies discussed above), the mixed-only strategies compares reasonably well with the other (aforementioned) two strategies when the treatment rate is high enough (Figure 7B).

5.2.4. *Universal treatment strategy.* Here, all infected individuals, either those with TB-only, HIV-only or mixed infection-only, are treated for each of the diseases they have. Figure 8A shows that, on average (within the four year period), more cumulative new cases of TB are prevented followed by those of HIV and then the mixed infection if the treatment rate is low (although the number of cases of HIV and the mixed infection prevented are almost identical). Figure 8B shows similar trends when the treatment rate is increased by 10-fold. It is evident from Figure 8B that although the universal strategy saves the same cumulative number of new

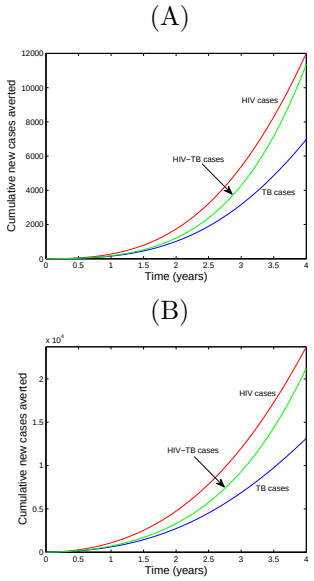


FIGURE 7. Simulations of the full model (7). Cumulative new cases averted using mixed-only treatment strategy with (A) $\tau_1 = \tau_2 = \tau_3 = 0.5$ and (B) $\tau_1 = \tau_2 = \tau_3 = 5$. All other parameters as in Table 2.

cases of HIV and TB as the HIV-only and TB-only strategies, the universal strategy saves more mixed infections than any of the other three strategies.

Conclusions. A realistic deterministic model for the transmission dynamics of HIV and TB in a population is designed and rigorously analysed. The HIV-only model is shown to have a globally-asymptotically stable disease-free equilibrium whenever its associated reproduction number is less than unity; and has a unique and locally-asymptotically stable endemic equilibrium when the number exceeds unity. On the hand, it was shown (using Centre Manifold theory) that the model with TB infection only undergoes the phenomenon of backward bifurcation, when the associated reproduction number is less than unity. The full model has a disease-free equilibrium which is locally-asymptotically stable whenever the maximum of the reproduction numbers of the two sub-models described above is less than unity. Numerical simulations show that the full model, like the TB-only sub-model, also undergoes backward bifurcation. These results have important public health implication, as they govern the elimination and/or persistence of the two diseases in a community. By analyzing the various associated reproduction numbers, it was shown that the targeted use of ARVs for individuals with or without AIDS symptoms can lead to HIV elimination in the community if the (average) relative infectiousness of the individuals treated, in comparison to untreated HIV-infected individuals, does not exceed a certain critical value.

Numerical simulations of the full model were carried out to assess the impact of the associated (four) treatment strategies. Some of main epidemiological findings of this study include:

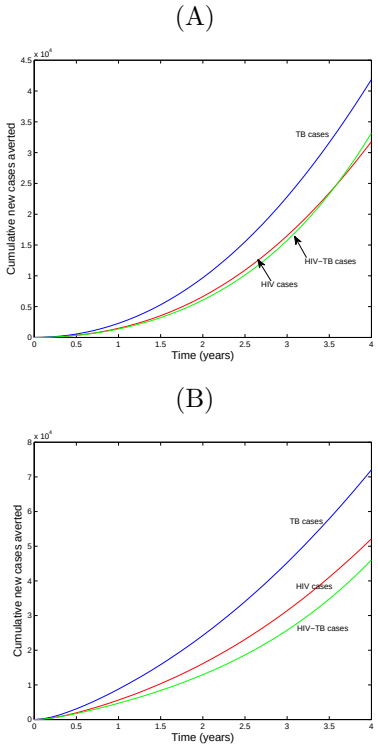


FIGURE 8. Simulations of the full model (7). Cumulative new cases averted using the universal treatment strategy with (A) $\tau_1 = \tau_2 = \tau_3 = 0.5$ and (B) $\tau_1 = \tau_2 = \tau_3 = 5$. All other parameters as in Table 2.

(i) Treating any of the two diseases alone prevents significant number of cumulative new cases of the disease being treated as well as that of the mixed infection (and more cumulative new cases are prevented for higher treatment rates);
(ii) The HIV-only strategy prevents more cumulative new cases of the mixed infection than the TB-only strategy;
(iii) For low treatment rates, the mixed-only strategy saves the least cumulative new cases of HIV, TB and the mixed infection in comparison to the other strategies. That is, if resources are low and the objective is to minimize cases of mixed infection, than such resources should be targeted to treating either HIV or TB but not the mixed HIV-TB infection;
(iv) For high treatment rates, the mixed-only strategy compares reasonably well (in terms of cumulative new cases averted) with the other strategies;
(v) The universal strategy saves more cumulative new cases of the mixed infection than any of the other strategies.

Overall, this study shows that the prospects of effectively controlling the spread of HIV and TB in a community, using effective treatment for both diseases, is bright.

Acknowledgments. One of the authors (ABG) acknowledges, with thanks, the support in part of the Natural Science and Engineering Research Council (NSERC) and Mathematics of Information Technology and Complex Systems (MITACS) of Canada. Two other authors (CNP and OS) gratefully acknowledge the support of the Department of Mathematics and the Institute of Industrial Mathematical Sciences, University of Manitoba. The authors are grateful to the reviewers for their constructive comments. The authors are also very grateful to James Watmough (University of New Brunswick, Canada) for many excellent comments that have enhanced the model as well as the clarity of the paper. The authors are grateful to Zhilan Feng (Purdue University, USA) for very useful comments pertaining to the model design.

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Received on May 23, 2007. Accepted on November 9, 2007.

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