An Optimal Treatment Control of TB-HIV Coinfection

Fatmawati and Hengki Tasman

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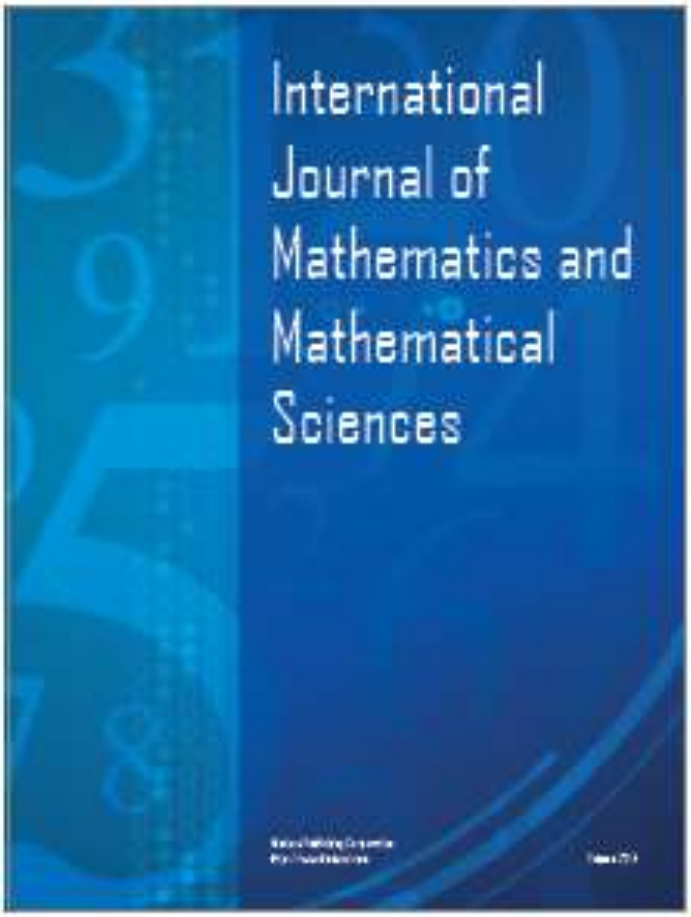

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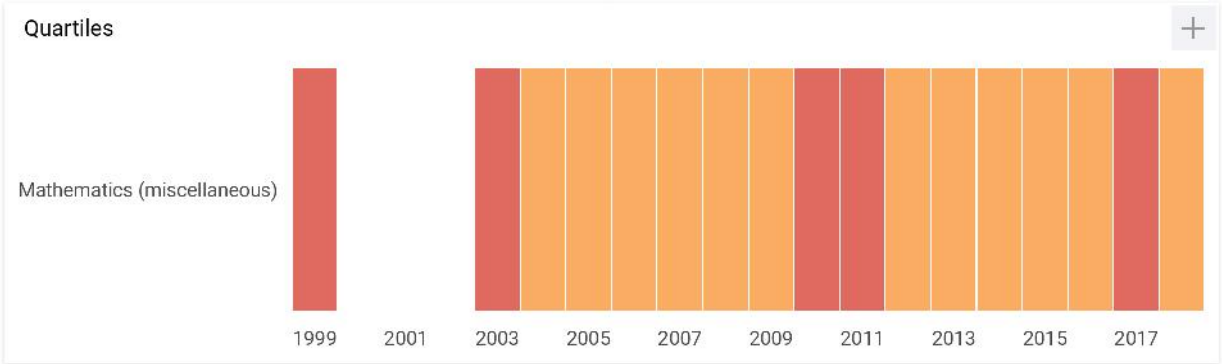

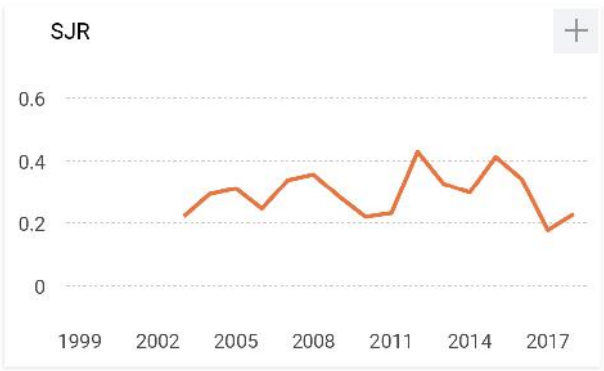

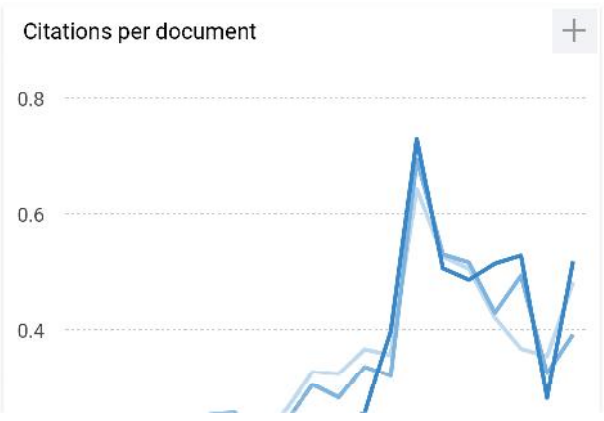

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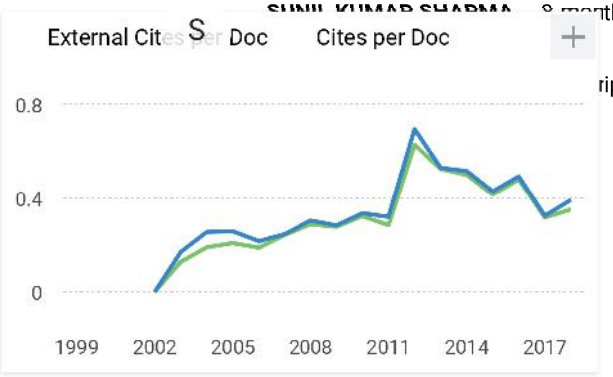

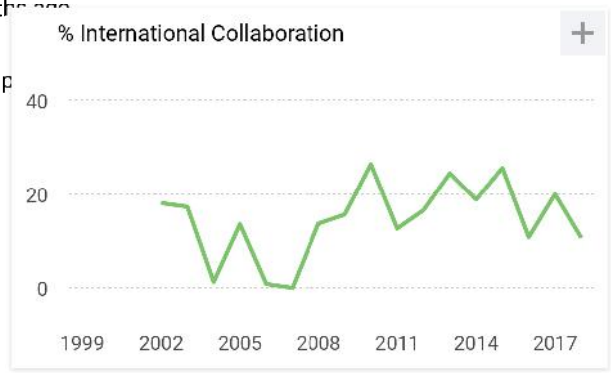

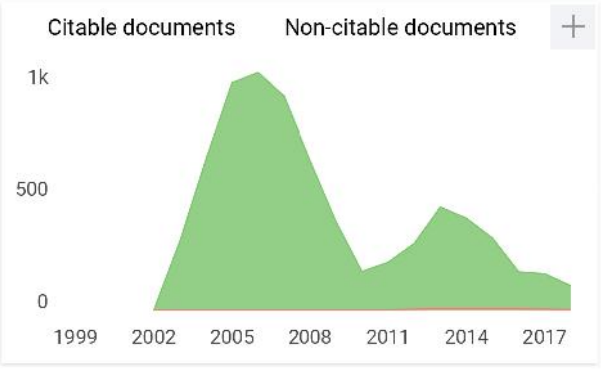

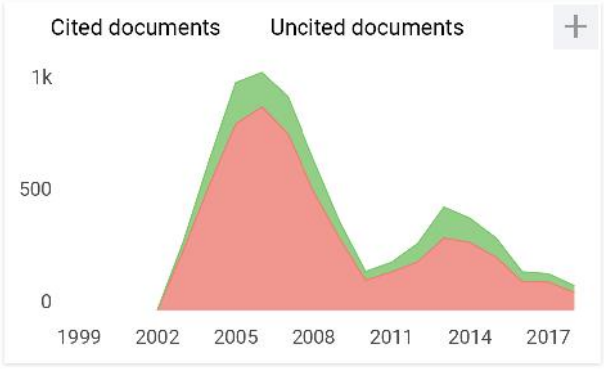

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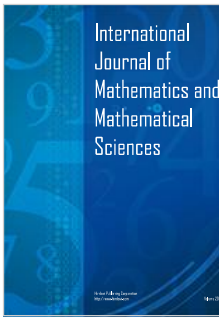

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Research Article

An Optimal Treatment Control of TB-HIV Coinfection

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An optimal control on the treatment of the transmission of tuberculosis-HIV coinfection model is proposed in this paper. We use two treatments, that is, anti-TB and antiretroviral, to control the spread of TB and HIV infections, respectively. We first present an uncontrolled TB-HIV coinfection model. The model exhibits four equilibria, namely, the disease-free, the HIV-free, the TB-free, and the coinfection equilibria. We further obtain two basic reproduction ratios corresponding to TB and HIV infections. These ratios determine the existence and stability of the equilibria of the model. The optimal control theory is then derived analytically by applying the Pontryagin Maximum Principle. The optimality system is performed numerically to illustrate the effectiveness of the treatments.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria *Mycobacterium tuberculosis* that most often attack the lungs. The bacteria are spread through air from one person to another when the people with active TB cough, sneeze, speak, or sing. People nearby may breathe in these bacteria and become infected. According to the World Health Organization (WHO), one-third of the world's population is infected with TB [1]. In 2013, 9 million people around the world became sick with TB disease and around 1.5 million TB-related deaths worldwide were reported. TB is the most common opportunistic disease that affects people infected with HIV [2].

HIV stands for human immunodeficiency virus that can lead to acquired immunodeficiency syndrome (AIDS). HIV can be transmitted via the exchange of a variety of body fluids from infected individuals, such as blood, breast milk, semen, and vaginal secretions. There is no cure for HIV infection. However, effective treatment with antiretroviral (ARV) drugs can control the virus so that people with HIV can enjoy healthy and productive lives [3]. As reported in WHO fact sheet (2013), at least one-third of the 34 million people living with HIV worldwide are infected with TB. HIV and TB form a lethal combination, each speeding the other's progress. TB is one of the leading causes of death among people living with HIV. Almost 25% of deaths among people with HIV are due to TB [1]. Therefore, an effective strategy is needed to control the transmission of TB-HIV coinfection in the population.

Mathematical models provide an important tool in understanding the spread and control of TB-HIV coinfection diseases. The dynamics of the transmission of TB-HIV coinfection model have been studied by many researchers [4–7]. Gakkhar and Chavda [4] formulated the dynamics of TB-HIV coinfection model with the population divided into four subclasses: the susceptible class, the TB infective class, the HIV infective class, and the TB-HIV coinfection class. They found the basic reproduction number for each of the diseases and checked the stability results for the equilibrium points. Naresh et al. [5] proposed a model to study the effect of tuberculosis on the transmission dynamics of HIV in a logistically growing human population. Roeger et al. [6] focus on the joint dynamics of HIV and TB in a pseudocompetitive environment, at the population level. Sharomi et al. [7] discussed the synergistic interaction between HIV and *Mycobacterium tuberculosis* using a deterministic model, with many of the essential biological and epidemiological features of the two infections.

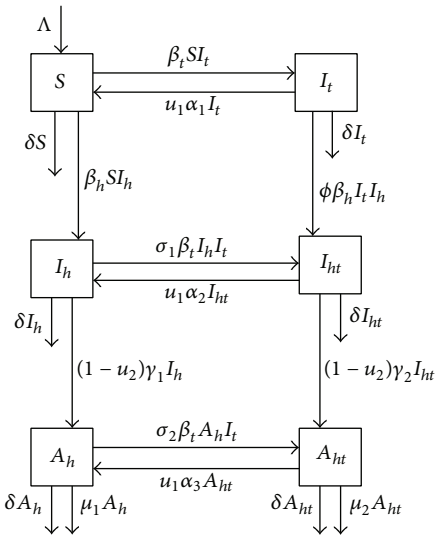

Figure 1: TB-HIV coinfection transmission diagram.

In this paper, mathematical model with an optimal control on the treatment of TB-HIV coinfection is proposed. The optimal control strategies have been applied to the studies on epidemiological models such as HIV, TB, Hepatitis C, Malaria, coinfection Malaria-Cholera, and HIV-Malaria diseases dynamics [8–16]. Very few studies have been applied in the area of optimal control theory to TB-HIV coinfection models. Recently, Agusto and Adekunle [17] have used optimal control strategies associated with treating symptomatic individuals with TB using the two-strain TB-HIV/AIDS transmission model. The aim of this study is to analyze the effect of two treatment scenarios, that is, anti-TB and ARV, to control the spread of TB-HIV coinfection diseases.

The organization of this paper is as follows. In Section 2, we derive a model of tuberculosis-HIV coinfection transmission with controls on anti-TB and ARV treatment. The model is analyzed in Section 3. In Section 4, we show the numerical simulations to illustrate the effectiveness of the treatments. The conclusion of this paper could be seen in Section 5.

2. Model Formulation

We assume that human population is homogeneous and closed. The total population, denoted by N, is classified into six classes, namely, the susceptible class (S), the infected with TB only and susceptible to HIV class (I_t), the infected with HIV only and susceptible to TB class (I_h), the infected with TB and HIV both class (I_{ht}), the infected with AIDS only and susceptible to TB class (A_h), and the infected with TB and AIDS both class (A_{ht}). We also assume that the susceptible cannot get TB and HIV infection simultaneously at the same time.

We consider the anti-TB treatment control u_1 and the ARV control u_2. The control functions u_1 and u_2 are defined on interval $[0, t_f]$, where $0 \le u_i(t) \le 1$, $t \in [0, t_f]$, $i = 1, 2$, and t_f denotes the end time of the controls.

We use the transmission diagram as in Figure 1 for deriving our model.

The model is as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda + u_1\alpha_1 I_t - \beta_t SI_t - \beta_h SI_h - \delta S,\\
\frac{dI_t}{dt} &= \beta_t SI_t - u_1\alpha_1 I_t - \delta I_t - \phi\beta_h I_t I_h,\\
\frac{dI_h}{dt} &= \beta_h SI_h + u_1\alpha_2 I_{ht} - \sigma_1\beta_t I_h I_t - (1-u_2)\gamma_1 I_h\\
&\quad - \delta I_h,\\
\frac{dI_{ht}}{dt} &= \sigma_1\beta_t I_h I_t - u_1\alpha_2 I_{ht} - (1-u_2)\gamma_2 I_{ht} - \delta I_{ht}\\
&\quad + \phi\beta_h I_t I_h,\\
\frac{dA_h}{dt} &= (1-u_2)\gamma_1 I_h + u_1\alpha_3 A_{ht} - \sigma_2\beta_t A_h I_t\\
&\quad - (\delta+\mu_1) A_h,\\
\frac{dA_{ht}}{dt} &= (1-u_2)\gamma_2 I_{ht} + \sigma_2\beta_t A_h I_t - u_1\alpha_3 A_{ht}\\
&\quad - (\delta+\mu_2) A_{ht}.
\end{aligned} \tag{1}$$

The region of biological interest of model (1) is

$$\Omega = \left\{(S, I_t, I_h, I_{ht}, A_h, A_{ht}) \in \mathbb{R}_+^6 : 0 \le N \le \frac{\Lambda}{\delta}\right\}, \tag{2}$$

and all of the parameters used in model (1) are nonnegative. The description of the parameters is given below.

Parameters of Model (1). Consider the following:

Λ: recruitment rate into the population.

δ: natural death rate.

β_t: infection rate for TB.

β_h: infection rate for HIV.

σ_1: progression rate from HIV only to TB infection.

σ_2: progression rate from AIDS only to TB infection.

ϕ: progression rate from TB only to HIV infection.

α_1: recovery rate from TB.

α_2: recovery rate from TB of TB-HIV coinfection.

α_3: recovery rate from TB of TB-AIDS coinfection.

μ_1: AIDS disease induced death rate.

μ_2: TB-AIDS disease induced death rate.

γ_1: progression rate from HIV only to AIDS infection.

γ_2: progression rate from TB-HIV coinfection to TB-AIDS coinfection.

Model (1) is well posed in the nonnegative region $\mathbb{R}^6_+$ because the vector field on the boundary does not point to the exterior. So, if it is given an initial condition in the region, then the solution is defined for all time $t \geq 0$ and remains in the region.

We seek to minimize the number of TB-HIV/AIDS coinfections while keeping the costs of applying anti-TB and ARV treatment controls as low as possible. We consider an optimal control problem with the objective function given by

$$J(u_1, u_2) = \int_0^{t_f} \left(I_t + I_{ht} + A_h + A_{ht} + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 \right) dt, \tag{3}$$

where c_1 and c_2 are the weighting constants for anti-TB and ARV treatment efforts, respectively. We take a quadratic form for measuring the control cost [12, 13, 17]. The terms $c_1u_1^2$ and $c_2u_2^2$ describe the cost associated with the anti-TB and ARV treatment controls, respectively. Larger values of c_1 and c_2 will imply more expensive implementation cost for anti-TB and ARV treatment efforts.

Our goal is to find an optimal control pair u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \min_{\Gamma} J(u_1, u_2), \tag{4}$$

where $\Gamma = \{(u_1, u_2) \mid 0 \leq u_i \leq 1,\ i = 1, 2\}$.

3. Model and Sensitivity Analysis

Consider model (1) without the control functions u_1 and u_2. Let

$$R_t = \frac{\Lambda\beta_t}{\delta^2}$$
$$R_h = \frac{\Lambda\beta_h}{\delta(\gamma_1 + \delta)}. \tag{5}$$

The parameters R_t and R_h are basic reproduction ratios for TB infection and HIV infection, respectively. These ratios describe the number of secondary cases of primary case during the infectious period due to the type of infection [18, 19].

By setting $u_1 = u_2 = 0$, model (1) has four equilibria (with respect to the coordinates $(S, I_t, I_h, I_{ht}, A_h, A_{ht})$); these are as follows:

(i) The disease-free equilibrium $E_0 = (\Lambda/\delta, 0, 0, 0, 0, 0)$. This equilibrium always exists.

(ii) The TB-endemic equilibrium $E_t = (\delta/\beta_t, (\delta/\beta_t)(R_t - 1), 0, 0, 0, 0)$. The equilibrium E_t exists if $R_t > 1$.

(iii) The HIV-endemic equilibrium $E_h = ((\gamma_1 + \delta)/\beta_h, 0, (\delta/\beta_h)(R_h - 1), 0, (\gamma_1\delta/\beta_h(\delta + \mu_1))(R_h - 1), 0)$. The equilibrium E_h exists if $R_h > 1$.

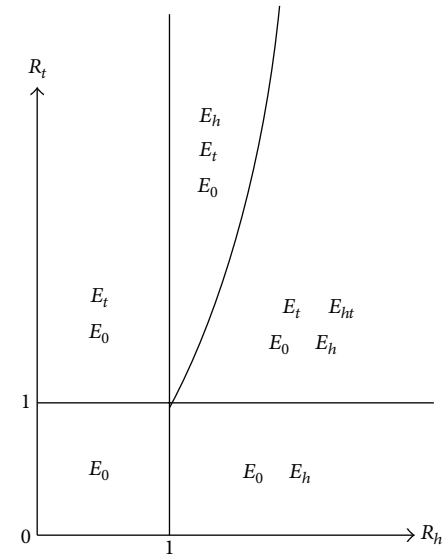

Figure 2: The diagram of equilibria with respect to R_h and R_t.

(iv) The TB-HIV-endemic equilibrium $E_{ht} = (S^*, I_t^*, I_h^*, I_{ht}^*, A_h^*, A_{ht}^*)$, where

$$S^* = \frac{\sigma_1\beta_t I_t^* + \gamma_1 + \delta}{\beta_h},$$
$$I_h^* = \frac{\beta_t^2\sigma_1 I_t^* + \delta\beta_h(R_t/R_h - 1)}{\beta_h^2},$$
$$I_{ht}^* = \frac{(\sigma_1\beta_t + \phi\beta_h)}{(\gamma_2 + \delta)} I_h^* I_t^*, \tag{6}$$
$$A_h^* = \frac{\gamma_1 I_h^*}{\sigma_2\beta_t I_t^* + \delta + \mu_1},$$
$$A_{ht}^* = \frac{\gamma_2 I_{ht}^* + \sigma_2\beta_t A_h^* I_t^*}{\delta + \mu_2},$$

and I_t^* satisfies the quadratic equation

$$A_0 (I_t^*)^2 + A_1 I_t^* + A_2 = 0, \tag{7}$$

where

$$A_0 = \beta_t^2\sigma_1(\beta_t\sigma_1 + \beta_h\phi),$$
$$A_1 = \frac{\delta^3 R_t(\delta + \gamma_1)(\delta\sigma_1 R_h(\phi - 1) + 2\delta\sigma_1 R_t + \phi R_t(\delta + \gamma_1))}{\Lambda^2}, \tag{8}$$
$$A_2 = -\frac{\delta^2(\delta + \gamma_1)^2(R_h - R_t + \phi R_h(R_h - 1))}{\Lambda}.$$

The HIV-TB coinfection equilibrium E_{ht} exists if $R_h, R_t > 1$ and $\phi R_h^2 + R_h(1 - \phi) > R_t$.

Summarizing the above results, we get diagram of existence of equilibria with respect to R_h and R_t as in Figure 2. The

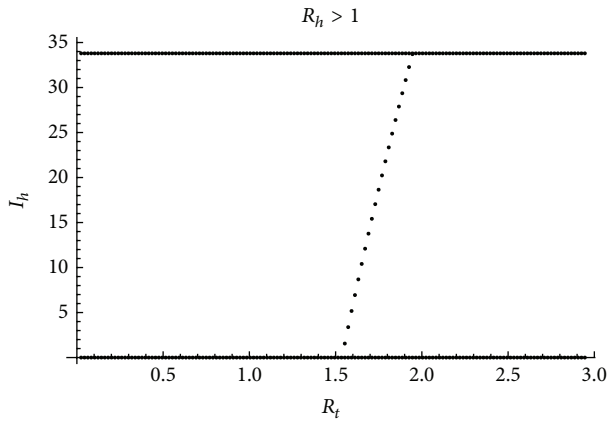

Figure 3: The bifurcation diagram for R_t versus I_h.

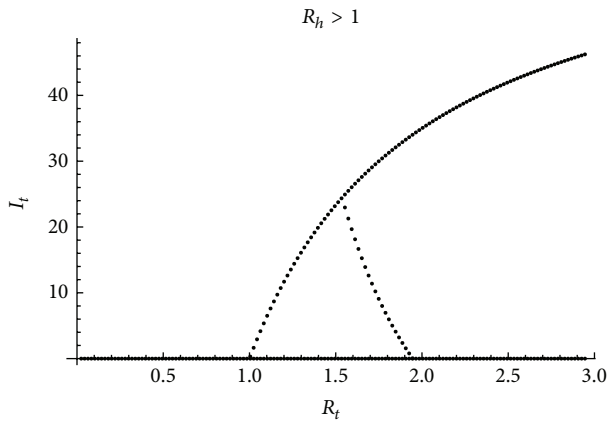

Figure 4: The bifurcation diagram for R_t versus I_t.

numerical bifurcation diagrams for the basic reproduction numbers R_t versus the infective classes I_h, I_t, and I_{ht} are given in Figures 3–5, respectively. In Figures 3–5, R_h is fixed for a value larger than one.

The following theorems give the stability criteria of the equilibriums.

Theorem 1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_t, R_h < 1$ and unstable if $R_t, R_h > 1$.*

Proof. Linearizing model (1) near the equilibrium E_0 gives eigenvalues $-\delta$, $-(\gamma_2 + \delta)$, $-(\mu_1 + \delta)$, $-(\mu_2 + \delta)$, $\delta(R_t - 1)$, and $(\gamma_1 + \delta)(R_h - 1)$. It is clear that all of the eigenvalues are negative if $R_t, R_h < 1$. So, if $R_t, R_h < 1$, the equilibrium E_0 is locally asymptotically stable. Otherwise, it is unstable. □

Theorem 2. *Suppose that the TB-endemic equilibrium E_t exists. It is locally asymptotically stable if $R_h/R_t < 1$; otherwise it is unstable.*

Proof. Linearizing model (1) near the equilibrium E_t gives eigenvalues $-\delta$, $-(\gamma_2 + \delta)$, $-(\delta + \mu_2)$, $\delta(1 - R_t)$, $-\mu_1 - \delta[\sigma_2(R_t - 1) + 1]$, and $(R_h/R_t - 1)(\delta + \gamma_1) - \delta\sigma_1(R_t - 1)$. So, the equilibrium E_t is locally asymptotically stable if $R_t/R_h < 1$; otherwise it is unstable. □

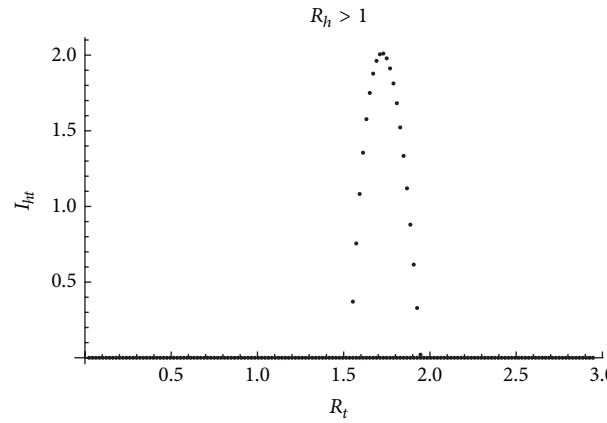

Figure 5: The bifurcation diagram for R_t versus I_{ht}.

Theorem 3. *Suppose that the HIV-endemic equilibrium E_h exists. It is locally asymptotically stable if $R_t/R_h < 1$; otherwise it is unstable.*

Proof. Linearizing model (1) near the equilibrium E_h gives eigenvalues $-(\mu_1 + \delta)$, $-(\mu_2 + \delta)$, $-(\gamma_2 + \delta)$, and $\delta(R_t/R_h - 1 - \phi(R_h - 1))$ and the roots of quadratic equation $x^2 + \delta R_h x + \delta(\delta + \gamma_1)(R_h - 1) = 0$. So, if $R_t/R_h < 1$, then the equilibrium E_h is locally asymptotically stable; otherwise it is unstable. □

In the following we investigate the sensitivity of the basic reproduction numbers R_t and R_h to the parameters in the model. The sensitivity analysis determines the model robustness to parameter values. Here, we could know the parameters that have a high impact on the reproduction numbers (R_t and R_h). Using the approach in [20], we derived the analytical expression for sensitivity index of R_t and R_h to each parameter.

The normalized forward sensitivity index of a variable, h, that depends differentially on a parameter, l, is defined as

$$\Upsilon_l^h := \frac{\partial h}{\partial l}\frac{l}{h}. \tag{9}$$

Now, using the parameter values in Table 1, we have the following results in Table 2. The sensitivity index of R_t with respect to β_t is

$$\Upsilon_{\beta_t}^{R_t} := \frac{\partial R_t}{\partial \beta_t}\frac{\beta_t}{R_t} = 1. \tag{10}$$

The sensitivity indices of the basic reproduction numbers (R_t and R_h) to parameters (see Table 2), such as recruitment rate of the population (Λ), natural death rate (δ), infection rate for HIV (β_h), and progression rate from HIV only to AIDS infection (γ_1), can be derived in the same way as (10). In the sensitivity indices of R_t, since $\Upsilon_{\beta_t}^{R_t} = 1$, increasing (or decreasing) infection rate for TB, β_t, by 10%, increases (or decreases) the reproduction number R_t by 10%. In the

same way, increasing (or decreasing) recruitment rate of the population Λ by 10% increases (or decreases) R_t by 10% and in like manner, increasing (or decreasing) natural death rate δ by 10% decreases (increases) R_t by 20%.

Similarly, for the sensitivity indices of R_h, since $\Upsilon_{\beta_h}^{R_h} = 1$, increasing (or decreasing) infection rate for HIV, β_h, by 10%, increases (or decreases) the reproduction number R_h by 10%. Thus, increasing (or decreasing) recruitment rate of the population Λ, by 10%, increases (or decreases) R_h by 10%. Also increasing (or decreasing) natural death rate δ by 10% decreases (increases) R_h by 16,67%. In a similar manner, increasing (or decreasing) progression rate from HIV only to AIDS infection γ_1 by 10% decreases (increases) R_h by 3,33%.

4. Analysis of Optimal Control

Next, we analyze model (1) with its control functions u_1 and u_2. Consider the objective function (3) for model (1). The necessary conditions to determine the optimal controls u_1^* and u_2^* such as condition (4) with constraint model (1) could be obtained using the Pontryagin Maximum Principle [21]. The principle converts (1)–(4) into minimizing Hamiltonian function H problem with respect to (u_1, u_2); that is,

$$H\left(S, I_t, I_h, I_{ht}, A_h, A_{ht}, u_1, u_2, \lambda_1, \lambda_2, \ldots, \lambda_6\right) = I_t + I_{ht} + A_h + A_{ht} + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 + \sum_{i=1}^{6}\lambda_i g_i, \tag{11}$$

where g_i denotes the right hand side of model (1) which is the ith state variable equation. The variables λ_i, $i = 1, 2, \ldots, 6$, are called adjoint variables satisfying the following costate equations:

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \left(\lambda_1 - \lambda_2\right)\beta_t I_t + \left(\lambda_1 - \lambda_3\right)\beta_h I_h + \lambda_1\delta,\\
\frac{d\lambda_2}{dt} &= -1 + \left(\lambda_2 - \lambda_1\right)u_1\alpha_1 + \left(\lambda_1 - \lambda_2\right)\beta_t S + \lambda_2\delta\\
&\quad + \left(\lambda_3 - \lambda_4\right)\sigma_1\beta_t I_h + \left(\lambda_2 - \lambda_4\right)\phi\beta_h I_h\\
&\quad + \left(\lambda_5 - \lambda_6\right)\sigma_2\beta_t A_h,\\
\frac{d\lambda_3}{dt} &= \left(\lambda_1 - \lambda_3\right)\beta_h S + \left(\lambda_2 - \lambda_4\right)\phi\beta_h I_t\\
&\quad + \left(\lambda_3 - \lambda_4\right)\sigma_1\beta_t I_t + \left(\lambda_3 - \lambda_5\right)\left(1 - u_2\right)\gamma_1\\
&\quad + \lambda_3\delta,\\
\frac{d\lambda_4}{dt} &= -1 + \left(\lambda_4 - \lambda_3\right)\alpha_2 u_1 + \left(\lambda_4 - \lambda_6\right)\left(1 - u_2\right)\gamma_2\\
&\quad + \lambda_4\delta,\\
\frac{d\lambda_5}{dt} &= -1 + \left(\lambda_5 - \lambda_6\right)\sigma_2\beta_t I_t + \lambda_5\left(\delta + \mu_1\right),\\
\frac{d\lambda_6}{dt} &= -1 + \left(\lambda_6 - \lambda_5\right)u_1\alpha_3 + \lambda_6\left(\delta + \mu_2\right),
\end{aligned} \tag{12}$$

where the transversality conditions $\lambda_i(t_f) = 0$, $i = 1, \ldots, 6$.

By applying Pontryagin's Maximum Principle and the existence result for the optimal control pairs, the steps to obtain the optimal controls $u = (u_1^*, u_2^*)$ are as follows [22, 23]:

(1) Minimize the Hamilton function H with respect to u; that is, $\partial H/\partial u = 0$, which is the stationary condition. We obtain

$$\begin{aligned}
u_1^* &= \begin{cases} 0 & \text{for } u_1 \le 0\\ \dfrac{\left(\lambda_4 - \lambda_3\right)\alpha_2 I_{ht} + \left(\lambda_2 - \lambda_1\right)\alpha_1 I_t + \left(\lambda_6 - \lambda_5\right)\alpha_3 A_{ht}}{c_1} & \text{for } 0 < u_1 < 1\\ 1 & \text{for } u_1 \ge 1, \end{cases}\\
u_2^* &= \begin{cases} 0 & \text{for } u_2 \le 0\\ \dfrac{\left(\lambda_6 - \lambda_4\right)\gamma_2 I_{ht} + \left(\lambda_5 - \lambda_3\right)\gamma_1 I_h}{c_2} & \text{for } 0 < u_2 < 1\\ 1 & \text{for } u_2 \ge 1. \end{cases}
\end{aligned} \tag{13}$$

(2) Solve the state system $\dot{x}(t) = \partial H/\partial\lambda$ which is model (1), where $x = (S, I_t, I_h, I_{ht}, A_h, A_{ht})$, $\lambda = (\lambda_1, \lambda_2, \ldots, \lambda_6)$ with initial condition $x(0)$.

(3) Solve the costate system $\dot{\lambda}(t) = -\partial H/\partial x$ which is system (12) with the end condition $\lambda_i(t_f) = 0$, $i = 1, \ldots, 6$.

Hence, we obtain the following theorem.

Theorem 4. *The optimal controls (u_1^*, u_2^*) that minimize the objective function $J(u_1, u_2)$ on Γ are given by*

$$\begin{aligned}
u_1^* &= \max\left\{0, \min\left(1, \frac{\left(\lambda_4 - \lambda_3\right)\alpha_2 I_{ht} + \left(\lambda_2 - \lambda_1\right)\alpha_1 I_t + \left(\lambda_6 - \lambda_5\right)\alpha_3 A_{ht}}{c_1}\right)\right\},\\
u_2^* &= \max\left\{0, \min\left(1, \frac{\left(\lambda_6 - \lambda_4\right)\gamma_2 I_{ht} + \left(\lambda_5 - \lambda_3\right)\gamma_1 I_h}{c_2}\right)\right\},
\end{aligned} \tag{14}$$

Table 1: Parameter values.

Parameter	Value	Reference	Parameter	Value	Reference
Λ	50000/year	[7]	α_1	2/year	Assumed
δ	0.02/year	[7]	α_2	1.2/year	Assumed
β_t	0.00031/year	Assumed	α_3	1/year	Assumed
β_h	0.00045/year	Assumed	μ_1	0.03/year	Assumed
σ_1	1.02/year	Assumed	μ_2	0.06/year	Assumed
σ_2	1.04/year	Assumed	γ_1	0.01/year	Assumed
ϕ	1.0002/year	Assumed	γ_2	0.05/year	Assumed

Table 2: Sensitivity indices to parameter for the TB-HIV model.

Parameter	Sensitivity index (R_t)	Parameter	Sensitivity index (R_h)
Λ	1	Λ	1
β_t	1	β_h	1
δ	−2	δ	−1.667
		γ_1	−0.333

where λ_i, $i = 1, \ldots, 6$, is the solution of the costate equations (12) with the transversality conditions $\lambda_i(t_f) = 0$, $i = 1, \ldots, 6$.

Substituting the optimal controls (u_1^*, u_2^*) which are obtained from the state system (1) and the costate system (12), we obtain the optimal system. The solutions of the optimality system will be solved numerically for some parameter choices. Most of the parameter values are assumed within realistic ranges for a typical scenario due to lack of data.

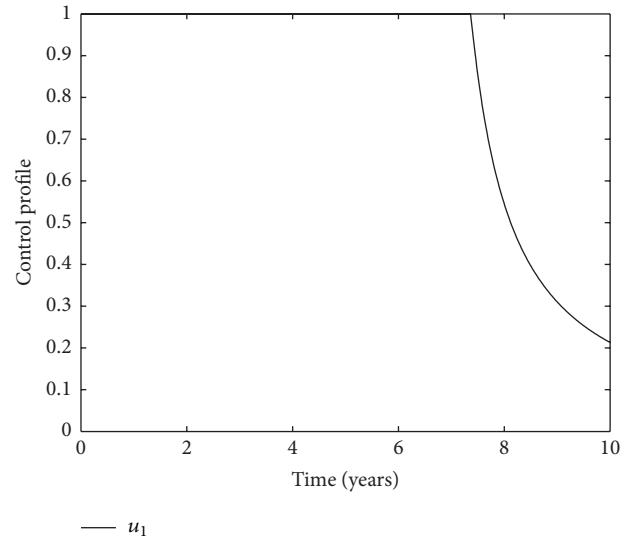

Figure 6: The profile of the optimal anti-TB control u_1^*.

5. Numerical Simulation

In this section, we investigate the numerical simulations of model (1) with and without optimal control. The optimal control strategy is obtained by the iterative method of Runge-Kutta method of order 4 [24]. We start to solve the state equations by the forward Runge-Kutta method of order 4. Then we use the backward Runge-Kutta method of order 4 to solve the costate equations with the terminal conditions. Then, the controls are updated by using a convex combination of the previous controls and the value from the characterizations of u_1^* and u_2^*. This process is repeated and iteration is stopped if the values of unknowns at the previous iteration are very close to the ones at the present iteration.

We consider three scenarios. In the first scenario, we consider only the anti-TB treatment control. In the second scenario, we consider only the ARV treatment control. In the last one, we use the optimal anti-TB and ARV treatment controls. Parameters used in these simulations are given in Table 1. In these simulations, we use initial condition $(S(0), I_t(0), I_h(0), I_{ht}(0), A_h(0), A_{ht}(0)) = (500, 50, 10, 5, 5, 5)$ and weighting constants $c_1 = 80$, $c_2 = 100$.

5.1. First Scenario. In this scenario, we set the ARV control u_2 to zero and activate only the anti-TB treatment control u_1. The profile of the optimal treatment control u_1^* for this scenario could be seen in Figure 6. To eliminate TB-HIV/AIDS coinfection in 10 years, the anti-TB treatment should be given intensively almost 7.5 years before decreasing to the lower bound in the end of 10th year.

The dynamics of the infected populations of this scenario are given in Figures 7 and 8. We observe in Figure 7 that this control strategy results in a significant decrease in the number of TB infected (I_t) and TB-HIV coinfection (I_{ht}) populations compared with the case without control. Specifically, using the control strategy, the TB-HIV coinfection population start to decrease from the third year. Also in the right of Figure 8, this control strategy results in a significant decrease in the number of TB-AIDS coinfections (A_{ht}) as against an increase in the uncontrolled case. On the contrary, the result in the left of Figure 8 shows that the number of AIDS infected (A_h) populations with and without the control does not differ significantly because there is no intervention against AIDS infection. Hence, the anti-TB treatment control gives a significant effect in controlling infected TB and also TB-HIV/AIDS coinfection.

5.2. Second Scenario. In the second scenario, we set the anti-TB treatment control u_1 to zero and activate only the ARV treatment control u_2. The control profile of ARV treatment is shown in Figure 9. We see that, to eliminate TB-HIV/AIDS

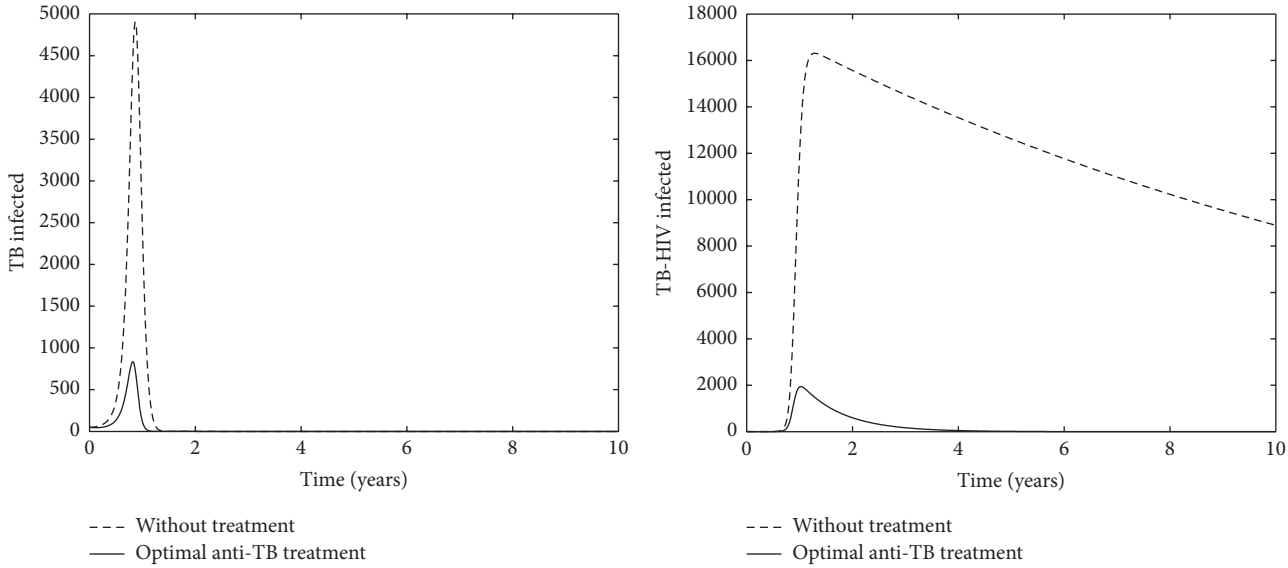

FIGURE 7: The dynamics of I_t and I_{ht} using control u_1^*.

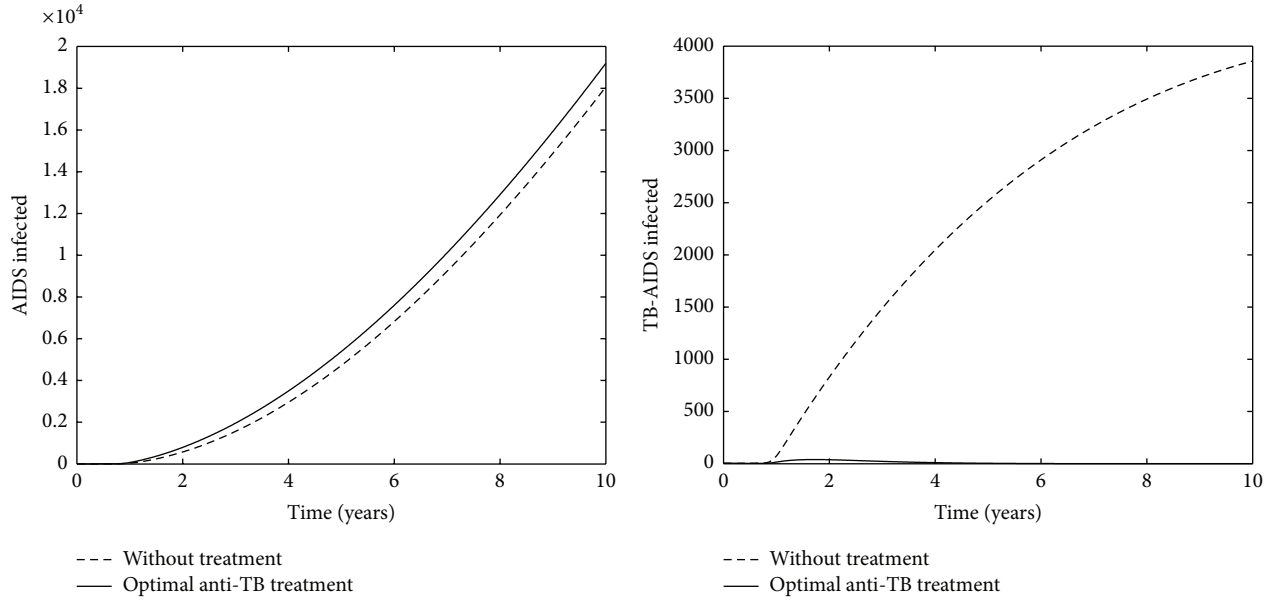

FIGURE 8: The dynamics of A_h and A_{ht} using control u_1^*.

coinfection in 10 years, the ARV treatment should be given intensively during 10 years.

The dynamics of the TB-HIV/AIDS coinfection of this scenario are given in Figures 10 and 11. We observe in Figure 10 that there is no significant difference in the number of TB infected populations with and without the ARV control treatment only. This may be due to the absence of the treatment against TB infection. It was also observed that the number of TB-HIV coinfection populations increases with this control strategy compared to the number without control. The positive impact of this strategy is shown in Figure 11, where the number of the AIDS infected and the TB-AIDS coinfection populations decreases significantly at the end of the intervention period.

5.3. Third Scenario. In this scenario, we consider the anti-TB and ARV treatment controls simultaneously. The profile of the optimal anti-TB treatment control u_1^* and ARV control u_2^* of this scenario is in Figure 12. To eliminate TB-HIV/AIDS coinfection in 10 years, the anti-TB treatment should be given

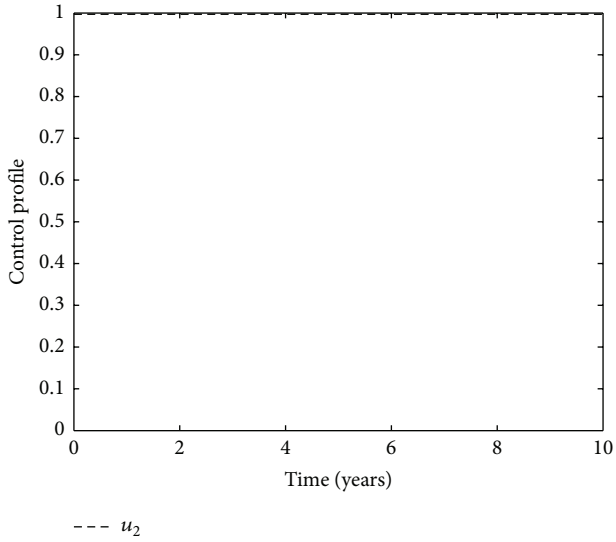

Figure 9: The profile of the optimal ARV control u_2^*.

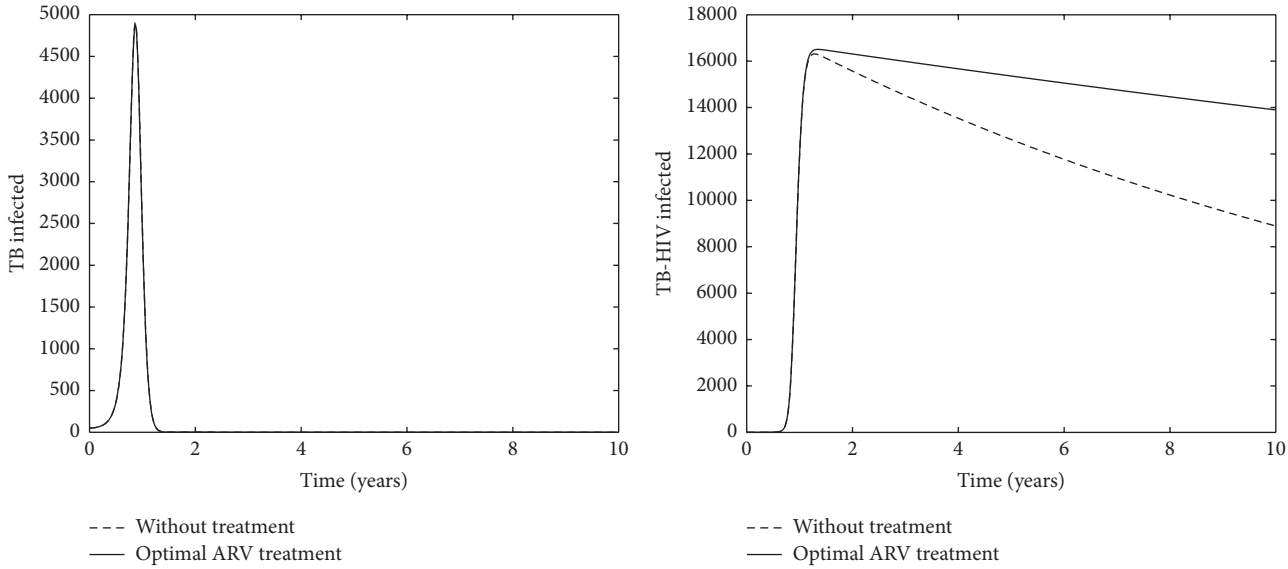

Figure 10: The dynamics of I_t and I_{ht} using control u_2^*.

intensively almost 8 years before dropping gradually until reaching the lower bound in the end of 10th year, and the ARV treatment is also given similar to anti-TB treatment, except at the beginning of the treatment.

Using the optimal controls in Figure 12, the dynamics of the TB-HIV/AIDS coinfection populations are given in Figures 13 and 14, respectively. For this strategy, we observed in Figure 13 that the control strategies resulted in a decrease in the number of TB infected and TB-HIV coinfection populations compared to the number without control. A similar decrease is observed in Figure 14 for AIDS infected and TB-AIDS coinfection populations in the control strategy, while an increased number for the uncontrolled case resulted.

Our numerical results show that the combination of anti-TB treatment and ARV treatment has the highest impact to diminish the size of TB-HIV/AIDS coinfection. When using only one control, the anti-TB treatment is more effective than ARV treatment to reduce the number of TB-HIV/AIDS coinfection populations.

6. Conclusion

In this paper, we have studied a deterministic model for the transmission of TB-HIV coinfection that includes use of anti-TB and ARV treatment as optimal control strategies. The model without controls exhibits four equilibria, namely, the

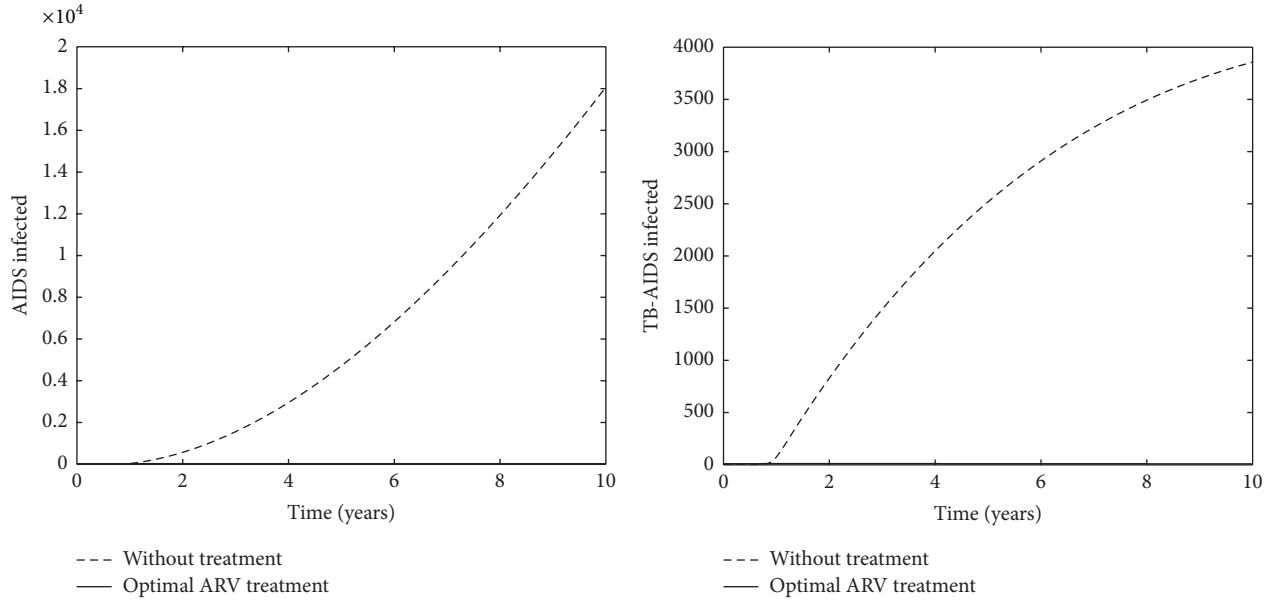

Figure 11: The dynamics of A_h and A_{ht} using control u_2^*.

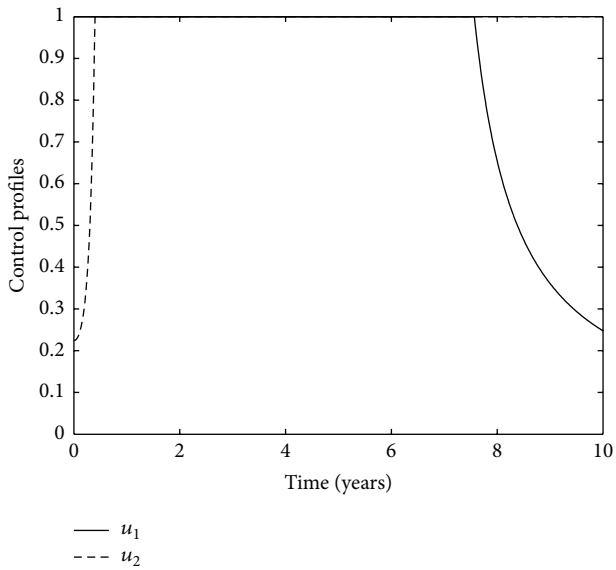

Figure 12: The profile of the optimal controls u_1^* and u_2^*.

disease-free equilibrium, the HIV-free equilibrium, the TB-free equilibrium, and the endemic equilibrium. We further obtain two thresholds, R_t and R_h, which are basic reproduction ratios for TB and HIV infections, respectively. These ratios determine the existence and stability of the equilibria of the model. The existence of the equilibria with respect to the thresholds R_t and R_h is summarized in Figure 2. If both the thresholds are less than unity then the diseases-free equilibrium is locally asymptotically stable. But if R_t is greater than unity with the condition $R_t > R_h$ and R_h is greater than unity with the condition $R_h > R_t$, then the HIV-free and TB-free equilibriums are locally asymptotically stable, respectively. Finally, the optimal control theory for TB-HIV coinfection model is derived analytically by applying the Pontryagin Maximum Principle. The numerical simulations were carried out to perform the optimal anti-TB and ARV treatment controls. From our analysis and numerical results, we conclude that the combination of anti-TB and ARV treatments is the most effective to reduce the TB-HIV coinfection. However, if we have to use only one control, then the anti-TB treatment

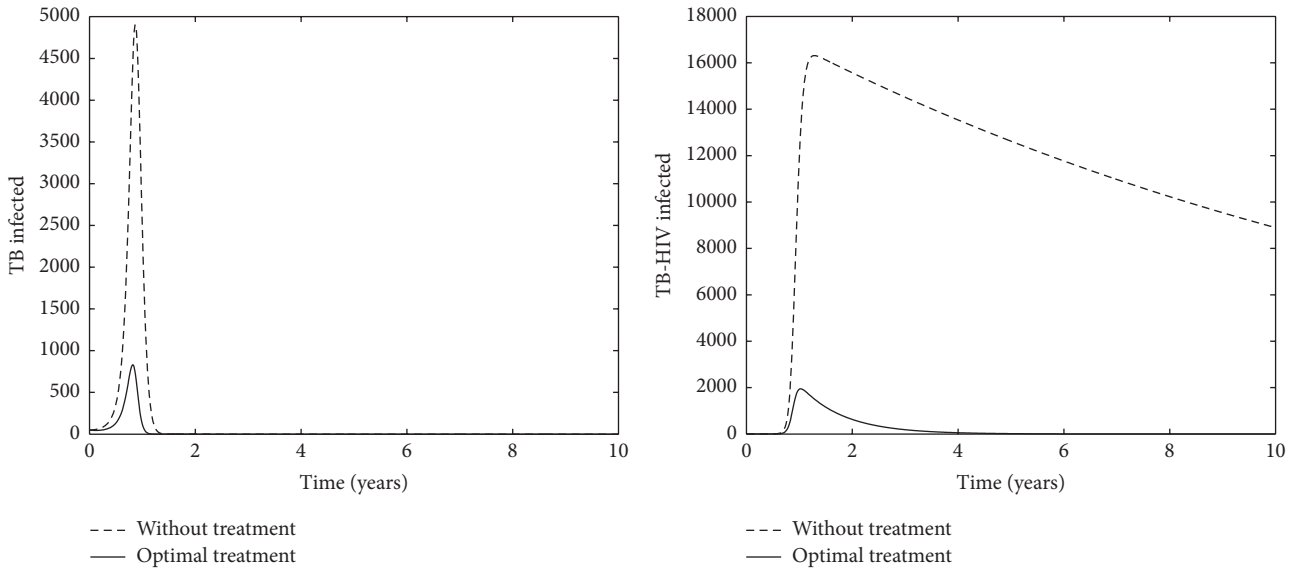

Figure 13: The dynamics of I_t and I_{ht} using controls u_1^* and u_2^*.

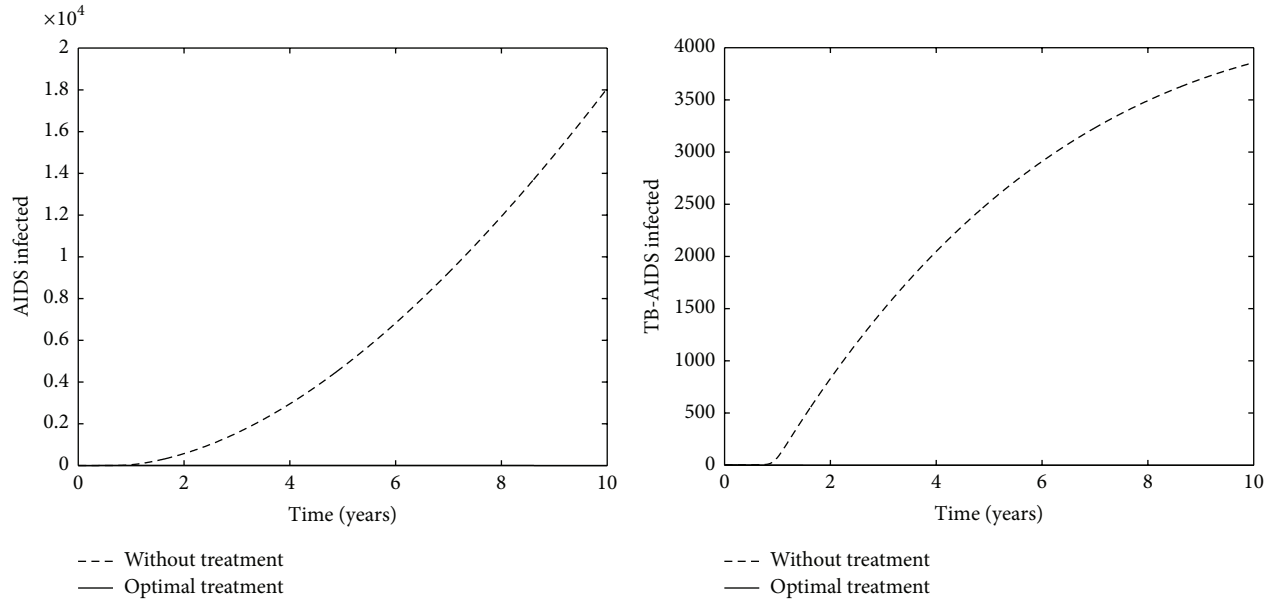

Figure 14: The dynamics of A_h and A_{ht} using controls u_1^* and u_2^*.

is better than ARV treatment to eliminate the number of TB-HIV/AIDS coinfection populations.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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References

[1] WHO, *Factsheet on the World Tuberculosis Report 2013*, WHO, Geneva, Switzerland, 2013.

[2] http://www.cdc.gov/tb/statistics.

[3] http://www.who.int/mediacentre.

[4] S. Gakkhar and N. Chavda, "A dynamical model for HIV-TB co-infection," *Applied Mathematics and Computation*, vol. 218, no. 18, pp. 9261–9270, 2012.

[5] R. Naresh, D. Sharma, and A. Tripathi, "Modelling the effect of tuberculosis on the spread of HIV infection in a population with density-dependent birth and death rate," *Mathematical and Computer Modelling*, vol. 50, no. 7-8, pp. 1154–1166, 2009.

[6] L. W. Roeger, Z. Feng, and C. Castillo-Chavez, "Modeling TB and HIV co-infections," *Mathematical Biosciences and Engineering*, vol. 6, no. 4, pp. 815–837, 2009.

[7] O. Sharomi, C. N. Podder, A. B. Gumel, and B. Song, "Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment," *Mathematical Biosciences and Engineering*, vol. 5, no. 1, pp. 145–174, 2008.

[8] Ahmadin and Fatmawati, "Mathematical modeling of drug resistance in tuberculosis transmission and optimal control treatment," *Applied Mathematical Sciences*, vol. 8, no. 92, pp. 4547–4559, 2014.

[9] F. B. Agusto, "Optimal chemoprophylaxis and treatment control strategies of a tuberculosis transmission model," *World Journal of Modelling and Simulation*, vol. 5, no. 3, pp. 163–173, 2009.

[10] S. Bowong and A. M. A. Alaoui, "Optimal intervention strategies for tuberculosis," *Communications in Nonlinear Science and Numerical Simulation*, vol. 18, no. 6, pp. 1441–1453, 2013.

[11] Fatmawati and H. Tasman, "An optimal control strategy to reduce the spread of malaria resistance," *Mathematical Biosciences*, vol. 262, pp. 73–79, 2015.

[12] O. D. Makinde and K. O. Okosun, "Impact of chemo-therapy on optimal control of malaria disease with infected immigrants," *Biosystems*, vol. 104, no. 1, pp. 32–41, 2011.

[13] K. O. Okosun, O. D. Makinde, and I. Takaidza, "Impact of optimal control on the treatment of HIV/AIDS and screening of unaware infectives," *Applied Mathematical Modelling*, vol. 37, no. 6, pp. 3802–3820, 2013.

[14] K. O. Okosun and O. D. Makinde, "A co-infection model of malaria and cholera diseases with optimal control," *Mathematical Biosciences*, vol. 258, pp. 19–32, 2014.

[15] K. O. Okosun and O. D. Makinde, "Optimal control analysis of hepatitis C virus with acute and chronic stages in the presence of treatment and infected immigrants," *International Journal of Biomathematics*, vol. 7, no. 2, Article ID 1450019, 1450019, 23 pages, 2014.

[16] B. Seidu, O. D. Makinde, and I. Y. Seini, "Mathematical analysis of the effects of HIV-Malaria co-infection on workplace productivity," *Acta Biotheoretica*, vol. 63, no. 2, pp. 151–182, 2015.

[17] F. B. Agusto and A. I. Adekunle, "Optimal control of a two-strain tuberculosis-HIV/AIDS co-infection model," *BioSystems*, vol. 119, no. 1, pp. 20–44, 2014.

[18] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, "On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogenous populations," *Journal of Mathematical Biology*, vol. 28, no. 4, pp. 362–382, 1990.

[19] O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases, Model Building, Analysis and Interpretation*, John Wiley & Sons, 2000.

[20] N. Chitnis, J. M. Hyman, and J. M. Cushing, "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model," *Bulletin of Mathematical Biology*, vol. 70, no. 5, pp. 1272–1296, 2008.

[21] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze, and E. F. Mishchenko, *The Mathematical Theory of Optimal Processes*, John Wiley & Sons, New York, NY, USA, 1962.

[22] F. L. Lewis and V. L. Syrmos, *Optimal Control*, John Wiley & Sons, New York, NY, USA, 1995.

[23] D. S. Naidu, *Optimal Control Systems*, CRC Press, New York, NY, USA, 2002.

[24] S. Lenhart and J. T. Workman, *Optimal Control Applied to Biological Models*, Chapman & Hall, New York, NY, USA, 2007.