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Optimal control of HIV resistance and tuberculosis co-infection using treatment intervention

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4 ABSTRACT

In this paper we presented a mathematical model of the spread of HIV and tuberculosis (TB) co-infection considering the resistance of HIV to antiretroviral (ARV) drugs. The model also included anti-TB and ARV treatments as system control variables. For the model without controls, we investigated the existence and stability of equilibria based on three basic reproduction numbers corresponding to the TB and two strains HIV infection. We also performed sensitivity analysis to determine the dominant factor controlling the spread. Then, the optimal control condition was derived using Pontryagin Maximum Principle on the model to achieve the goal of minimizing the number of infected population. The numerical simulations of the optimal control were also performed to illustrate the results.

1. Introduction

HIV infection attacks human immune system. It could develop into AIDS if the infection is not treated properly. A weakened immune system of patients with HIV infection or AIDS will lead to a variety of bacteria/virus infections (opportunistic infections). Until now, there is still no effective cure or vaccine available for HIV infection or AIDS. However, antiretroviral (ARV) drugs could be used for treatment. ARV drugs could control the growth of HIV[1]. Currently, ARV drugs have been used widely in many countries. Without proper use of ARV drugs, HIV strains could be drug-resistant[2]. ARV drug resistance could cause failure of HIV treatment and spread of the infection among population.

Tuberculosis (TB) is usually transmitted through the air

contaminated with *Mycobacterium tuberculosis* that is released when patients with TB cough, talk or sneeze. TB can be prevented and cured with anti-TB drugs. Treatment of TB cases is one of the main strategies for TB control because it can break the chain of transmission. Despite the effective treatments that have been developed, TB remains one of the most destructive bacterial infections in humans. TB infection is a very common opportunistic infection that affects HIV patients. TB is one of the leading causes of death among HIV patients. In 2015, almost 35% of deaths among HIV patients are due to TB[3].

Mathematical models could be used for understanding the dynamic of the spread of HIV and TB co-infection. Many researchers have modeled the dynamics of HIV and TB co-infection[4-6]. For instance, Mallela *et al.*[4] developed a novel mathematical model that evaluates treatment strategies for HIV and TB co-infected individuals. A research[5] proposed a mathematical model to study the dynamic of TB for the spread of HIV in a logistically-growing population. Sharomi *et al.*[6] used a deterministic model to study the synergistic interaction between TB and HIV co-infection, with many of the essential biological and epidemiological characteristics of TB and HIV infection. Mathematical models with optimal

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control considering HIV and TB co-infection also have been established. Recently, Augusto and Adekunle[7] have used optimal control strategies associated with treating symptomatic individuals with TB using the two-strain TB-HIV/AIDS transmission model. A simple model to control the spread of HIV and TB co-infection was proposed[8]. In this paper, the model proposed previously[8] was developed by adding the factor of ARV drug resistance.

In the present paper, we constructed a model of HIV drug resistance and TB co-infection transmission with controls of anti-TB and ARV treatment. Then the model was analyzed, and some numerical simulations were performed to illustrate the effectiveness of the treatments.

2. Model formulation

We assumed that population is homogeneous and closed. We considered two strains of HIV, namely, the sensitive strain of HIV and the resistant strain of HIV which resists to ARV drugs.

The total population, denoted by N , was classified into seven disjoint subpopulations, namely, the susceptible subpopulation (S), the TB-infected subpopulation (I), the sensitive-HIV infected subpopulation (H_s), the resistant-HIV infected subpopulation (H_r), the TB and sensitive-HIV infected subpopulation (H_{st}), the TB and resistant-HIV infected subpopulation (H_{rt}) and the AIDS subpopulation (A).

We assumed that the susceptible subpopulation could not get TB and HIV infections simultaneously. The subpopulations A , H_{st} and H_{rt} were assumed to be isolated, so that they cannot infect anyone. The TB infected subpopulation (I) was assumed to be not susceptible to HIV.

We supposed the anti-TB treatment (u_1) and the ARV treatment (u_2) as the control efforts to reduce TB and HIV infections, respectively. The control functions u_1 and u_2 were defined on closed interval $[0, t_j]$, where $0 \leq u_i(t) \leq 1, t \in [0, t_j], i = 1, 2$ and t_j denotes the end time of the controls.

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

The model is as follows:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda + u_1\alpha_1 I - \beta_1 SI - (\beta_{hs}H_s + \beta_{hr}H_r)S - \delta S \\ \frac{dI}{dt} &= \beta_1 SI - u_1\alpha_1 I - (\delta + \mu_1)I \\ \frac{dH_s}{dt} &= \beta_{hs}SH_s - \sigma_s\beta_1 H_s I - (\delta + (1 - u_2)\gamma_1)H_s + u_2\alpha_2 H_{st} \\ \frac{dH_r}{dt} &= \beta_{hr}SH_r - \sigma_r\beta_1 H_r I - (\delta + (1 - u_2)\gamma_2)H_r + u_2\alpha_2 H_{rt} \\ \frac{dH_{st}}{dt} &= \sigma_s\beta_1 H_s I - u_2\alpha_2 H_{st} - (\delta + \mu_{st} + (1 - u_2)\gamma_3)H_{st} \\ \frac{dH_{rt}}{dt} &= \sigma_r\beta_1 H_r I - u_2\alpha_2 H_{rt} - (\delta + \mu_{rt} + (1 - u_2)\gamma_4)H_{rt} \\ \frac{dA}{dt} &= (1 - u_2)(\gamma_1 H_s + \gamma_2 H_r + \gamma_3 H_{st} + \gamma_4 H_{rt}) - (\delta + \mu_a)A. \end{aligned}$$

Model (1) has region of biological interest

$$\Omega = \{(S, I, H_s, H_r, H_{st}, H_{rt}, A) \in \mathbb{R}^7 : 0 \leq N \leq \frac{\Lambda}{\delta}\},$$

and the vector field of model (1) on the boundary does not point to the exterior, so model (1) is well-posed in the region Ω . All of the parameters used in the model (1) are non-negative and the description of the parameters is given in Table 1.

Table 1
Parameters of model (1).

Description	Parameter	
Recruitment rate	Λ	
Natural death rate	δ	
Infection rate of TB	β_1	
Recovery rate of TB	α_1	
TB-induced death rate	μ_1	
AIDS-induced death rate	μ_a	
	Sensitive strain	Resistant strain
Infection rate for HIV	β_{hs}	β_{hr}
Recovery rate from TB of HIV-TB co-infection	α_s	α_r
Progression rate from HIV infection to HIV-TB co-infection	σ_s	σ_r
Disease HIV-TB induced death rate	μ_{st}	μ_{rt}
Progression rate from HIV infection to AIDS	γ_1	γ_2
Progression rate from HIV-TB co-infection to AIDS	γ_3	γ_4

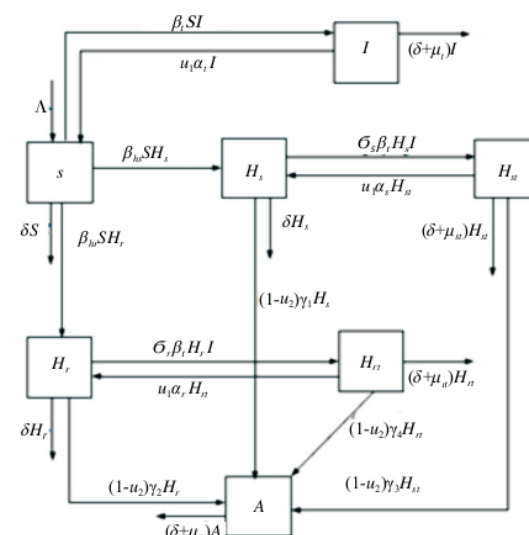


Figure 1. A two strain HIV and TB co-infection transmission diagram.

We want to minimize the number of HIV and TB co-infections while keeping the costs of applying anti-TB and ARV treatment controls as low as possible. The cost function is defined as

$$J(u_1, u_2) = \int_0^{t_f} \left(I + H_{st} + H_{rt} + A + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 \right) dt, \tag{2}$$

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[7,9,10]. The terms $c_1u_1^2$ and $c_2u_2^2$ represent the cost associated with anti-TB and ARV treatment controls respectively. Larger values of c_1 and c_2 will imply higher implementation cost for anti-TB and ARV treatment efforts.

Our aim is to find an optimal control pair u_1^* and u_2^* such that $J(u_1^*, u_2^*) = \min_{\Gamma} J(u_1, u_2)$, where, $\Gamma = \{(u_1, u_2) | 0 \leq u_i \leq 1, i=1,2\}$.

3. Model analysis

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

$$R_1 = \frac{\Lambda \beta_1}{\delta(\delta + \mu_1)}$$

$$R_2 = \frac{\Lambda \beta_{hs}}{\delta(\gamma_1 + \delta)}$$

$$R_3 = \frac{\Lambda \beta_{hr}}{\delta(\gamma_2 + \delta)}$$

Parameters R_1 , R_2 and R_3 are basic reproduction ratios corresponding to the TB infection, the sensitive-HIV and resistant-HIV infections, respectively. These ratios represent the number of secondary cases of primary case during the infectious period due to the type of infection [11,12].

By setting $u_1 = u_2 = 0$, model (1) has six equilibria [with respect to coordinate $(S, I, H_s, H_r, H_{ss}, H_{rs}, A)$], these are,

1. The disease-free equilibrium $E_0 = (\frac{\Lambda}{\delta}, 0, 0, 0, 0, 0, 0)$
2. The TB endemic equilibrium $E_1 = (\frac{\delta + \mu_1}{\beta_1}, \frac{\delta(R_1 - 1)}{\beta_1}, 0, 0, 0, 0, 0)$

which exists if $R_1 > 1$.

3. The sensitive-HIV endemic equilibrium

$$E_2 = (\frac{\delta + \gamma_1}{\beta_{hs}}, 0, \frac{\delta(R_2 - 1)}{\beta_{hs}}, 0, 0, 0, \frac{\gamma_1 \delta(R_2 - 1)}{\beta_{hs}(\delta + \mu_{1a})})$$

which exists if $R_2 > 1$.

4. The resistant-HIV endemic equilibrium

$$E_3 = (\frac{\delta + \gamma_2}{\beta_{hr}}, 0, 0, \frac{\delta(R_3 - 1)}{\beta_{hr}}, 0, 0, 0, \frac{\gamma_2 \delta(R_3 - 1)}{\beta_{hr}(\delta + \mu_{2a})})$$

which exists if $R_3 > 1$.

5. The sensitive-HIV and TB endemic equilibrium

$$E_{hs} = (\frac{\delta + \mu_1}{\beta_1}, I^s, H_s^s, 0, H_{ss}^s, 0, H_{rs}^s, 0, A^s)$$

where

$$I^s = \frac{(\delta + \gamma_1)(R_1 - 1)}{\beta_1 \beta_1}$$

$$H_s^s = \frac{\delta}{\beta_{hs}}(R_1 - 1) \frac{(\delta + \gamma_1)}{\beta_{hs} \beta_1} (R_1 - 1)$$

$$H_{ss}^s = \frac{\beta_1 \beta_{hs} I^s}{\delta + \mu_{1a} + \gamma_3}$$

$$A^s = \frac{\gamma_1 H_s^s + \gamma_3 H_{ss}^s}{\delta + \mu_a}$$

The equilibrium E_{hs} exists if $R_1 > R_2 > 1$ and $\delta \beta_1 R_1 (R_1 - 1) > (\delta + \gamma_1)(R_1 - R_2)$.

6. The resistant-HIV and TB endemic equilibrium

$$E_{hr} = (\frac{\delta + \mu_1}{\beta_1}, I^r, 0, H_r^r, 0, H_{rs}^r, A^r)$$

where

$$I^r = \frac{(\delta + \gamma_2)(R_3 - 1)}{\beta_1 \beta_1}$$

$$H_r^r = \frac{\delta}{\beta_{hr}}(R_3 - 1) \frac{(\delta + \gamma_2)}{\beta_{hr} \beta_1} (R_3 - 1)$$

$$H_{rs}^r = \frac{\beta_1 \beta_{hr} I^r}{\delta + \mu_{2a} + \gamma_4}$$

$$A^r = \frac{\gamma_2 H_r^r + \gamma_4 H_{rs}^r}{\delta + \mu_a}$$

The equilibrium E_{hr} exists if $R_3 > R_1 > 1$ and $\delta \beta_1 R_3 (R_3 - 1) > (\delta + \gamma_2)(R_3 - R_1)$.

The following theorems give the stability criteria of the equilibria.

Theorem 1. The disease-free equilibrium E_0 is locally asymptotically stable if $R_1, R_2, R_3 < 1$ and unstable if $R_1, R_2, R_3 > 1$.

Proof. Linearizing model (1) near the equilibrium E_0 gives eigenvalues $-\delta, -(\delta + \gamma_3 + \mu_1), -(\delta + \gamma_4 + \mu_2), -(\delta + \mu_a), (\delta + \mu_1)(R_1 - 1), (\delta + \gamma_1)(R_2 - 1)$ and $(\delta + \gamma_2)(R_3 - 1)$. It is clear that all of the eigenvalues are negative if $R_1, R_2, R_3 < 1$. So, if $R_1, R_2, R_3 < 1$, the equilibrium E_0 is locally asymptotically stable. Otherwise, it is unstable.

Theorem 2. Supposing the TB endemic equilibrium E_1 exists. It is locally asymptotically stable if $R_1 > 1, R_2 > R_1$ and $R_3 > R_1$, otherwise it is unstable.

Proof. Linearizing model (1) near the equilibrium E_1 gives eigenvalues $-(\delta + \mu_a), -(\delta + \mu_{1a} + \gamma_3), -(\delta + \mu_{1a} + \gamma_4), -\beta_1 \delta(R_1 - 1) \frac{\Lambda \beta_{hs}}{\delta R_1} (R_2 - R_1), -\beta_1 \delta(R_1 - 1) \frac{\Lambda \beta_{hr}}{\delta R_1} (R_3 - R_1)$, and the roots of quadratic equation $x^2 + \delta R_1 x + \delta(\delta + \mu_1)(R_1 - 1) = 0$. It is observed that all of the eigenvalues are negative if $R_1 > 1, R_2 > R_1$ and $R_3 > R_1$.

Theorem 3. Supposing the sensitive-HIV endemic equilibrium E_2 exists. It is locally asymptotically stable if $R_2 > 1, R_3 > R_2$ and $R_1 > R_2$, otherwise it is unstable.

Proof. Linearizing model (1) near the equilibrium E_2 gives eigenvalues $-(\delta + \mu_a), -(\delta + \mu_{2a} + \gamma_3), -(\delta + \mu_{2a} + \gamma_4), -(\delta + \gamma_2) \frac{(R_2 - R_1)}{R_2}, -(\delta + \mu_1) \frac{(R_2 - R_1)}{R_2}$, and the roots of quadratic equation $x^2 + \delta R_2 x + (\delta^2 + \delta \gamma_1)(R_2 - 1) = 0$. Clearly, all of the eigenvalues are negative if $R_2 > 1, R_3 > R_2$ and $R_1 > R_2$.

Theorem 4. Supposing the resistant-HIV endemic equilibrium E_3 exists. It is locally asymptotically stable if $R_3 > 1, R_1 > R_3$ and $R_2 > R_3$, otherwise it is unstable.

Proof. Linearizing model (1) near the equilibrium E_3 gives eigenvalues $-(\delta + \mu_a), -(\delta + \mu_{3a} + \gamma_3), -(\delta + \mu_{3a} + \gamma_4), -(\delta + \gamma_1) \frac{(R_3 - R_2)}{R_3}, -(\delta + \mu_1) \frac{(R_3 - R_2)}{R_3}$ and the roots of quadratic equation $x^2 + \delta R_3 x + (\delta^2 + \delta \gamma_2)(R_3 - 1) = 0$. It is observed that all of the eigenvalues are negative if $R_3 > 1, R_1 > R_3$ and $R_2 > R_3$.

Next, we investigated the sensitivity of the basic reproduction ratios R_1, R_2 and R_3 to the parameters in the model. The aim of this analysis is to determine the parameters that have a high impact on the basic reproduction ratios. Using the reported approach [13], we derived the sensitivity indices of R_1, R_2 and R_3 to each parameter.

The normalized forward sensitivity index of variable which depends differentially on parameter l is defined as

$$\gamma_l^R := \frac{\partial R_0}{\partial l} \times \frac{l}{R_0}$$

For example, the sensitivity index of R_1 with respect to β_1 is

$$\gamma_{\beta_1}^{R_1} := \frac{\partial R_1}{\partial \beta_1} \times \frac{\beta_1}{R_1} = 1$$

By using the parameter values in Table 2, the sensitivity indices of R_1, R_2 and R_3 with respect to parameters $\Lambda, \delta, \mu_1, \beta_{hs}, \gamma_1, \beta_{hr}$ and γ_2

50 are listed in Table 3.

Table 2
Parameter values.

Parameter	Value	Reference	Parameter	Value	Reference
Λ	50000/year	[7]	α_r	1/year	Assumed
δ	0.02/year	[7]	μ_i	0.02/year	[6]
β_i	0.00031/year	Assumed	μ_{sr}	0.03/year	[6]
β_{hs}	0.00045/year	Assumed	μ_{sr}	0.03/year	Assumed
β_{nr}	0.00035/year	Assumed	μ_{sr}	0.03/year	Assumed
σ_s	1.2/year	[6]	γ_1	0.01/year	Assumed
σ_r	1.2/year	[6]	γ_2	0.05/year	Assumed
α_r	1.4/year	Assumed	γ_3	0.08/year	Assumed
α_s	1/year	Assumed	γ_4	0.08/year	Assumed

Table 3
Sensitivity indices to some parameters of model (1).

Parameter (o)	Sensitivity index γ_o^R	Parameter (o)	Sensitivity index γ_o^R	Parameter (o)	Sensitivity index γ_o^R
Λ	1	Λ	1	Λ	1
β_i	1	β_{hs}	1	β_{nr}	1
δ	-1.5	δ	-1.667	δ	-1.286
μ_i	-0.5	γ_1	-0.333	γ_2	-0.714

The interpretation of the sensitivity index $\gamma_{\beta_i}^R = 1$ is as follow. If there is an increment (decrement) in infection rate of TB β_i by 10%, then there will be an increment (decrement) of the basic reproduction number R_i by 10%. For $\gamma_{\delta}^R = -1.5$, if there is an increment (decrement) in natural death rate δ by 10%, then there will be a decrement (increment) of basic reproduction ratio R_i by 15%.

11 **4. Analysis of optimal control**

In this section, we analyzed model (1) with its control functions u_1 and u_2 and the cost function (2). We used the Pontryagin Maximum Principle to obtain the optimal controls u_1^* and u_2^* such that condition (3) with constraint model (1) holds [14]. The Pontryagin Maximum Principle converts equations (1-3) into a minimizing Hamiltonian function problem with respect to (u_1, u_2) . The Hamiltonian function H is as follow.

$$H(S, I, H_s, H_r, H_{sr}, A, u_1, u_2, \lambda_1, \lambda_2, \dots, \lambda_7) = I + H_s + H_r + A + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2 + \sum_{i=1}^7 \lambda_i g_i$$

where g_i denotes the right hand side of model (1) which is the i -th state variable equation. The variables $\lambda_i, i=1,2,\dots,7$, are called adjoint variables satisfying the following co-state equations

$$\begin{aligned} \frac{d\lambda_1}{dt} &= (\lambda_1 - \lambda_2) \beta_i I + (\lambda_1 - \lambda_3) \beta_{hs} H_s + (\lambda_1 - \lambda_4) \beta_{nr} H_r + \lambda_1 \delta \\ \frac{d\lambda_2}{dt} &= -1 + (\lambda_1 - \lambda_2) \beta_i S + (\lambda_2 - \lambda_3) u_1 \alpha + (\lambda_2 - \lambda_4) \sigma_s \beta_i H_s + (\lambda_2 - \lambda_5) \sigma_r \beta_i H_r + \lambda_2 (\delta + u_1) \\ \frac{d\lambda_3}{dt} &= (\lambda_1 - \lambda_3) \beta_{hs} S + (\lambda_3 - \lambda_4) \sigma_s \beta_i I + (\lambda_3 - \lambda_5) (1 - u_2) \gamma_1 + \lambda_3 \delta \\ \frac{d\lambda_4}{dt} &= (\lambda_1 - \lambda_4) \beta_{nr} S + (\lambda_4 - \lambda_5) \sigma_r \beta_i I + (\lambda_4 - \lambda_6) (1 - u_2) \gamma_2 + \lambda_4 \delta \\ \frac{d\lambda_5}{dt} &= -1 + (\lambda_2 - \lambda_5) u_1 \alpha + (\lambda_5 - \lambda_6) (1 - u_2) \gamma_3 + \lambda_5 (\delta + u_2) \\ \frac{d\lambda_6}{dt} &= -1 + (\lambda_5 - \lambda_6) u_1 \alpha + (\lambda_6 - \lambda_7) (1 - u_2) \gamma_4 + \lambda_6 (\delta + u_2) \\ \frac{d\lambda_7}{dt} &= -1 + \lambda_7 (\delta + u_2) \end{aligned} \tag{6}$$

where the transversality conditions $\lambda_i(t_f) = 0, i = 1, \dots, 7$.

The procedure to obtain the optimal controls $u = (u_1^*, u_2^*)$ are as follows [15,16].

1. Minimize the Hamilton function H with respect to u , that is $\frac{\partial H}{\partial u} = 0$. The stationary condition gives

$$u_1^* = \begin{cases} 0 & \text{for } u_1 \leq 0 \\ \frac{(\lambda_1 - \lambda_2) \alpha_i H_s + (\lambda_2 - \lambda_3) \alpha_i I + (\lambda_3 - \lambda_4) \alpha_i H_r}{c_1} & \text{for } 0 < u_1 < 1 \\ 1 & \text{for } u_1 \geq 1 \end{cases}$$

$$u_2^* = \begin{cases} 0 & \text{for } u_2 \leq 0 \\ \frac{(\lambda_2 - \lambda_5) \gamma_1 H_s + (\lambda_2 - \lambda_6) \gamma_2 H_r + (\lambda_2 - \lambda_7) \gamma_3 H_{sr} + (\lambda_2 - \lambda_8) \gamma_4 H_n}{c_2} & \text{for } 0 < u_2 < 1 \\ 1 & \text{for } u_2 \geq 1 \end{cases}$$

2. Solve the state system $\dot{x}(t) = \frac{\partial H}{\partial x}$ where $x = (S, I, H_s, H_r, H_{sr}, H_n, H_{nr})$.

A), $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_7)$ and the initial condition $x(0)$.

3. Solve the co-state system $\dot{\lambda}(t) = -\frac{\partial H}{\partial x}$ with the end condition

$\lambda_i(t_f) = 0, i = 1, \dots, 7$.

Applying the procedure, we obtained the optimal controls as follows.

Theorem 5. The optimal controls (u_1^*, u_2^*) that minimize the objective function $J(u_1, u_2)$ on Γ is given by

$$u_1^* = \max \left\{ 0, \min \left(1, \frac{(\lambda_1 - \lambda_2) \alpha_i H_s + (\lambda_2 - \lambda_3) \alpha_i I + (\lambda_3 - \lambda_4) \alpha_i H_r}{c_1} \right) \right\}$$

$$u_2^* = \max \left\{ 0, \min \left(1, \frac{(\lambda_2 - \lambda_5) \gamma_1 H_s + (\lambda_2 - \lambda_6) \gamma_2 H_r + (\lambda_2 - \lambda_7) \gamma_3 H_{sr} + (\lambda_2 - \lambda_8) \gamma_4 H_n}{c_2} \right) \right\}$$

where $\lambda_i, i = 1, \dots, 7$ is the solution of the co-state equation (6) with the transversality conditions $\lambda_i(t_f) = 0, i = 1, \dots, 7$.

The optimal system is obtained by substituting the optimal control (u_1^*, u_2^*) . The solutions of the optimality system will be solved numerically for some parameter choices. Most of the parameter values are assumed within realistic ranges due to lack of data.

35 **5. Numerical simulation**

In this section, we investigated the dynamic of model (1) with and without the optimal controls. We used iteration of 4-order Runge-Kutta method to obtain the optimal controls [17]. First, we solved the state equations using the forward 4-order Runge-Kutta method. Then we solved the co-state equations with the terminal conditions using the backward 4-order Runge-Kutta method. After that, we updated the controls using a convex combination of the previous controls and the value from the characterizations of u_1^* and u_2^* . This procedure was iterated. The iteration was stopped if the values of unknowns at the previous iteration are very close to the ones at the current iteration.

We considered three scenarios to explore the dynamics of TB-HIV co-infection. We considered the anti-TB treatment control u_1 in the

first scenario. In the second one, we considered the ARV treatment control u_2 . In the third scenario, we used the optimal anti-TB and ARV treatment controls u_1 and u_2 .

For these numerical simulations, we used parameters' values as in Table 2. Moreover, we used initial condition $[S(0), I(0), H_s(0), H_r(0), H_w(0), H_n(0), A(0)] = (5000, 100, 50, 30, 10, 10, 10)$, and weighting constants $c_1 = 80, c_2 = 100$.

5.1. First scenario

We deployed the anti-TB treatment control u_1 and set the ARV control u_2 to zero. The profile of the optimal control u_1^* is depicted in Figure 2. To reduce HIV resistance and TB co-infection in 10 years, the anti-TB treatment should be given intensively in the first nine years before decreasing to the lower bound in the end of the 10th year.

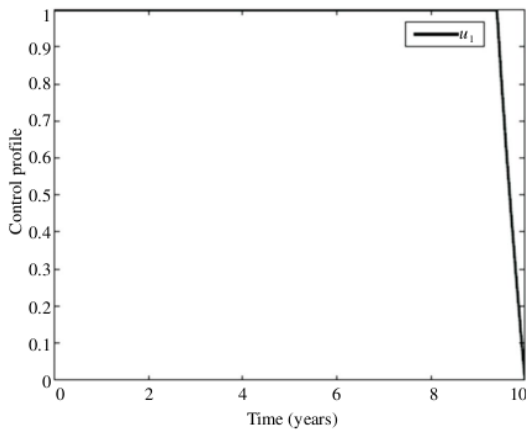
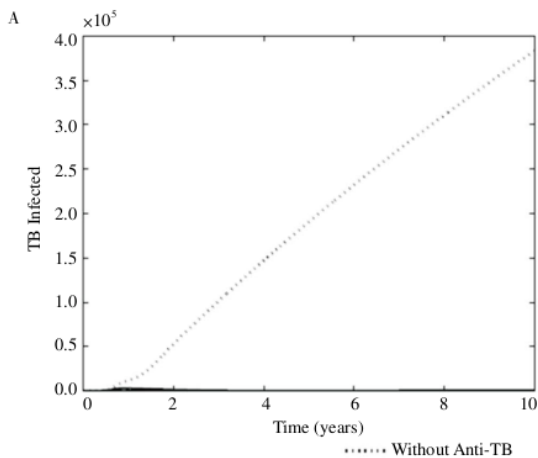


Figure 2. The profile of the optimal anti-TB control u_1^* .

From Figure 3A, we observed that the TB-infected subpopulation I decreased to zero by deploying the optimal control u_1^* and it increased without deploying u_1^* . Contrary, the result in Figure 3B shows that the AIDS subpopulation A tends to increase by deploying



the optimal control u_1^* compared with the case without control because there is no intervention against AIDS. For the sensitive-HIV-TB co-infection subpopulation H_{sp} , a decrease in the number of infected hosts is observed in Figure 4A in the presence of the optimal control u_1^* compared to an increase in the number of infected hosts in the absence of the control u_1^* . Similarly, in Figure 4B, this control strategy results in a significant decrease in the number of resistant-HIV and TB co-infection subpopulation H_r as against an increase in the uncontrolled case. Hence, the anti-TB treatment control u_1^* gives a significant effect in controlling the TB-infected, sensitive-HIV and TB co-infection subpopulations.

5.2. Second scenario

Here, we deployed the ARV treatment control u_2 and set the anti-TB treatment control u_1 to zero. The optimal control profile of ARV treatment u_2^* is shown in Figure 5. We can see that to eliminate resistant-HIV and TB co-infection in 10 years, the ARV treatment should be given intensively during the first year before it drops gradually and vanishes at the end of second year.

With this strategy, we observed in Figures 6 and 7 that there is not a significant difference in the number of TB infection, AIDS infection, HIV-TB co-infection with and without the ARV control treatment only. The result in Figures 6 and 7 clearly suggests that this strategy is not very effective in the control of the number of the infected cases.

5.3. Third scenario

In the third scenario, the anti-TB and ARV treatment controls u_1 and u_2 are used simultaneously. The profile of the optimal anti-TB treatment control u_1^* and ARV control u_2^* of this scenario is given in Figure 8. To reduce resistant-HIV and TB co-infection in 10 years, the anti-TB and ARV treatment should be given intensively during the first nine years

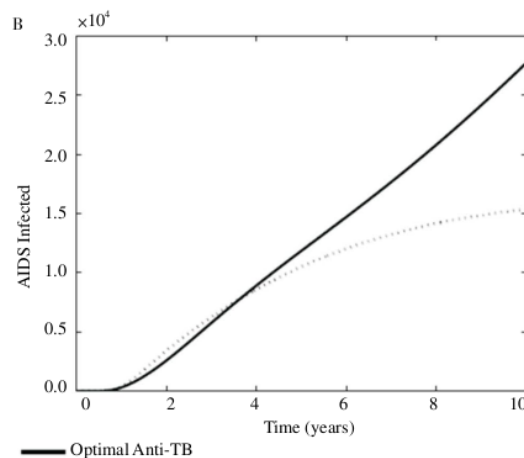


Figure 3. The dynamics of I (A) and A (B) using the optimal control u_1^* .

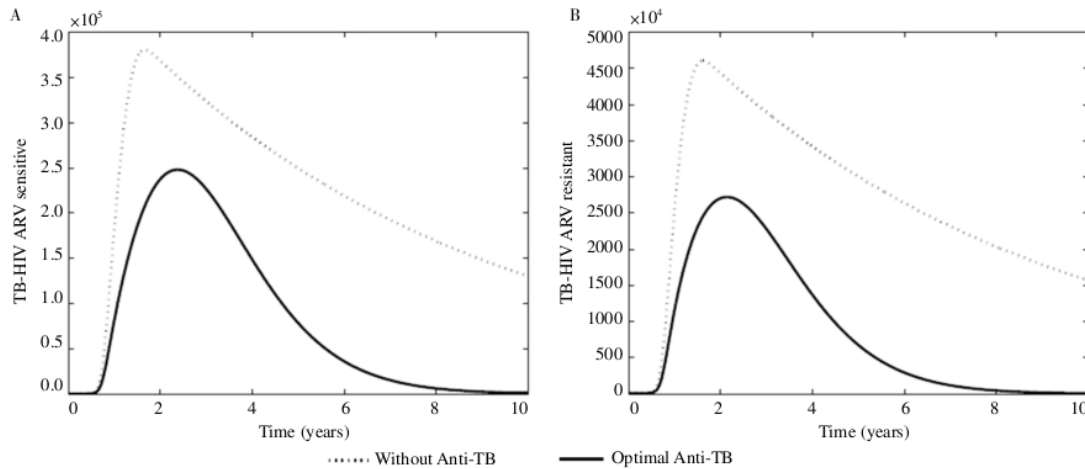


Figure 4. The dynamics of H_{si} (A) and H_{ri} (B) using the optimal control u_1^* .

and it drops gradually and vanishes at the end of the 10th year.

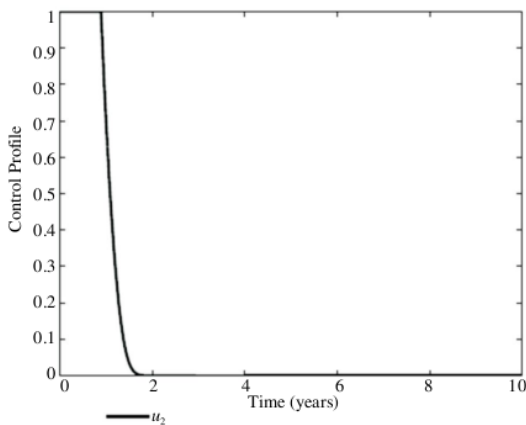


Figure 5. The profile of the optimal ARV control u_2^* .

Using the optimal controls in Figure 8, the dynamics of the TB, AIDS, HIV-TB co-infection subpopulations are given in Figures 9 and 10. For this strategy, we observed in Figure 9 that the control strategies resulted in a decrease in the number of TB infected and AIDS infected subpopulations compared to the number without control. A similar decrease is observed in Figure 10 for HIV-TB co-infection with drug-sensitivity and drug-resistance to ARV in the control strategy, while an increased number for the uncontrolled case was observed.

Our numerical results suggest that the combination of anti-TB treatment and ARV treatment is the most effective to eliminate the number of TB infection, AIDS infection and HIV-TB co-infection with drug-sensitivity and drug-resistance. Thus, if we can employ one treatment only, then anti-TB treatment is better than ARV treatment to reduce the number of TB infected and two strains HIV-TB co-infected populations.

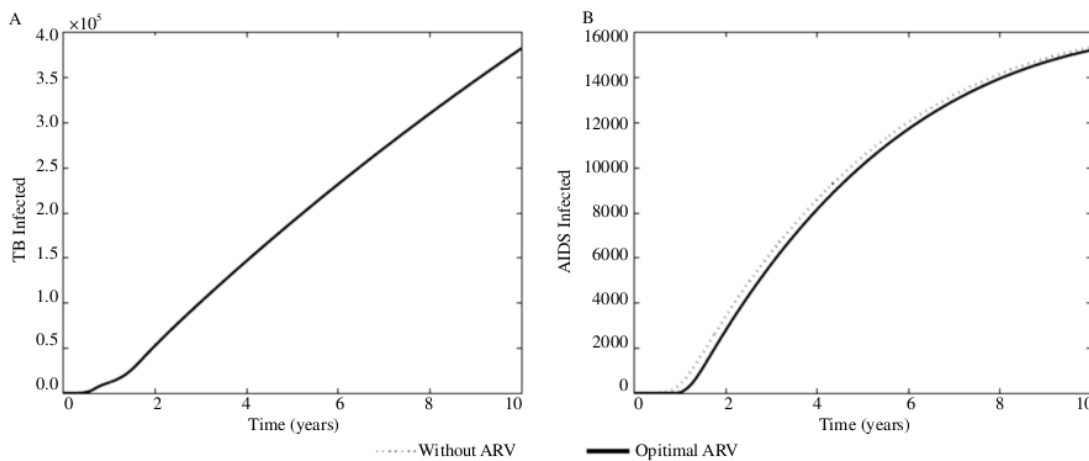


Figure 6. The dynamics of I (A) and A (B) using the optimal control u_2^* .

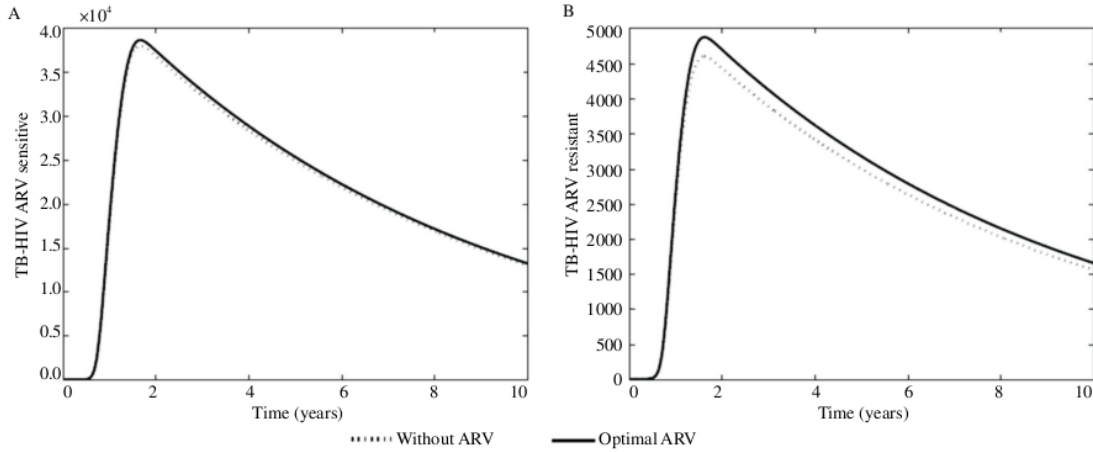


Figure 7. The dynamics of H_s (A) and H_r (B) using the optimal control u_2^* .

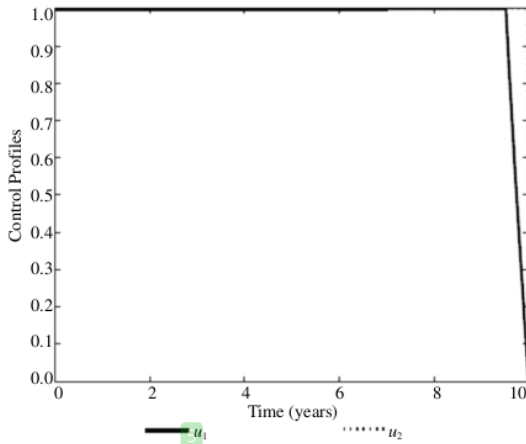


Figure 8. The profile of the optimal controls u_1^* and u_2^* .

6. Conclusion

In this paper, we have developed a deterministic mathematical model for the spread of two strains HIV and TB co-infection that incorporates anti-TB and ARV treatment as optimal control strategies. For the model without controls, we obtained three thresholds R_n , R_s and R_r , which are the basic reproduction ratios for the TB and two strains of HIV infections respectively. These ratios determine the existence and stability of the equilibria of the model. If the thresholds are less than unity, the diseases-free equilibrium is locally asymptotically stable. Finally, the conditions for existence of optimal control were studied analytically using the Pontryagin Maximum Principle. Our numerical simulation of the optimal control indicates that the best strategy is to combine the anti-TB and ARV treatments in order to reduce the two strains HIV and TB co-infection. However, if we have to use only one control, the anti-TB

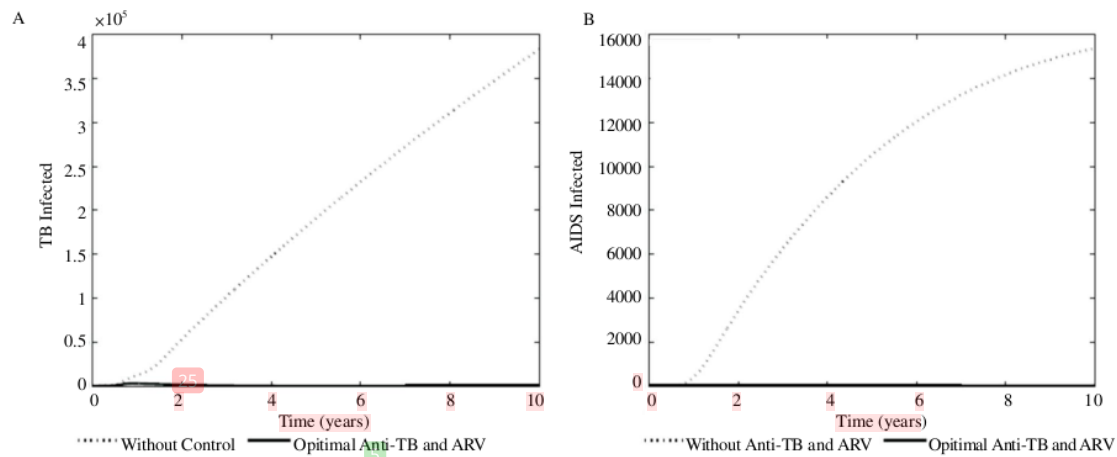


Figure 9. The dynamics of I (A) and A (B) using the optimal controls u_1^* and u_2^* .

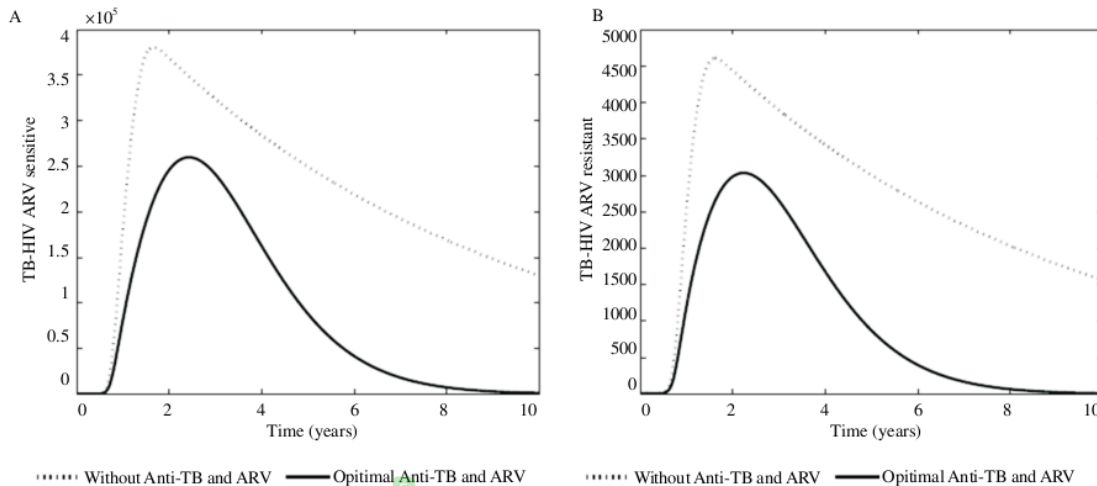


Figure 10. The dynamics of H_{1t} (A) and H_{2t} (B) using the optimal controls u_1^* and u_2^* .

treatment is more effective than ARV treatment to eliminate the number of two strains HIV and TB co-infected subpopulations.

Conflict of interest statement

We declare that we have no conflict of interest.

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