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STABILITY ANALYSIS AND OPTIMAL CONTROL FOR HIV INFECTION WITHIN-HOST MODEL WITH IMMUNE RESPONSE AND ANTIRETROVIRAL TREATMENT

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ABSTRACT

In this study, we propose a within-host model for HIV infection of CD4+ T-cells. The model includes immune response, immune impairment, and antiretroviral treatment. Two types of antiretroviral drugs (reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs)) are used within the model. Positivity and boundedness of solutions are verified. We present two equilibrium points which are infection-free and infected one. The basic reproduction number is calculated, and it becomes the threshold indicating the stability of each equilibrium point. When it is less than a unity, an infection-free equilibrium point is locally stable, whereas when it is greater than one an infected equilibrium point exists. Global stability of infection-free equilibrium point is obtained with some conditions. Further, we extend the model by applying optimal control problem in which both antiretroviral drugs becomes control variables. This is to minimize the HIV infection of CD4+ T-cells. Our numerical results demonstrate that RTIs drug alone could slightly reduces an HIV infection whereas the PIs drug alone manages to reduce the infection largely. However, a combination of both types of drugs gives the best result for eliminating HIV infection of CD4+ T-cells.

KEYWORDS: HIV infection, immune response, immune impairment, antiretroviral treatment, optimal control

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that attacks immune cells causing an increase in the risk of other diseases and infections. It has been and continues to be a major global public health issue. According to World Health Organization (WHO), 650,000 people died from HIV-related causes and about 38.4 million people living with HIV at the end of 2021 (WHO, 2022). CD4+ T-cells are the majority host cells for HIV to attack. CD4+ T-cells can be infected via the contact from free virus and of cell-to-cell. When the CD4+ T-cells are being attacked, they will stimulate cytotoxic T lymphocyte cells (CTL) to control viral load, this is done by killing the infected CD4+ T-cells.

To the present time, there is no cure for HIV infection, however, it can be managed by treatment regimens which are combination of antiretroviral drugs. These drugs suppress viral replication, reduce the amount of HIV in patients' body and help patients to stay healthy. Antiretroviral drugs can be classified into six classes consisting of (i) nucleoside reverse transcriptase inhibitors (NRTIs), (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), (iv) integrase inhibitors, (v) fusion inhibitors, and (vi) post-attachment inhibitors (Karrakchou et al., 2006; Arts et al., 2012; Jones, 2021). Note that the first two classes ((i) and (ii)) are subclasses of RTIs. In this study, we mainly focus on two classes which are RTIs and PIs. RTIs treatment helps disrupting new infection, whereas PIs inhibits the activity for viral replication.

Mathematical models have been used as useful tool to study various infectious diseases including HIV infection. Several researchers give attention to HIV

infection in population level e.g., the work by Aldila, 2018, Omondi et al., 2019, Munawwaroh et al., 2020, Ayele et al., 2021, and Omondi et al., 2022, whereas some researchers focus on within-host model, e.g., the work by Ogunlaran and Noutchie, 2016, Ngina et al., 2017, Sutimin et al., 2018, Sutimin et al., 2019, Sutimin et al., 2020, and Arenas et al., 2021. In this study, we focus on a within-host model of HIV infection to better understand the processes regulating HIV load dynamics. For within-host HIV dynamics, some researchers proposed models involves immune response, e.g., the work by Sutimin et al., 2018, and Sutimin et al., 2019 where Bai and Xu, 2021 (Bai and Xu, 2021) included immune impairment in their model. Several researchers proposed a model with antiretroviral treatments, e.g., the work by Sutimin et al., 2018, Sutimin et al., 2019, Ouifki and Witten, 2007, and Srivastava et al., 2009. Further, optimal control problems were applied in some HIV infection studies, e.g., the work by Arruda et al., 2015, Ngina et al., 2018, Olabode et al., 2019, Tjahjana and Sutimin, 2020, and Nath et al., 2023.

In this study, we propose a deterministic model of within-host HIV infection of CD4+ T-cells involving immune response and antiretroviral treatment. This model extends the work of Sutimin et al., 2019 by adding the role of immune impairment. Further, we also apply optimal control problem by considering both drugs RTIs and PIs as control variables in the model, where Sutimin et al., (Sutimin et al., 2019) did not include in their study. The paper is organized as follows. The model description is presented in the next section. All model analysis including positivity and boundedness of solutions, equilibrium points and their stability and the basic reproduction number is presented in Section 3. Section 4 introduces the optimal control model, where its numerical results are presented in Section 5 with some discussion. Finally, we conclude this study in Section 6.

2. MODEL FORMULATION

A mathematical model of HIV infection of CD4+ T-cells is proposed. We modify the model of Sutimin et al., (Sutimin et al., 2019) by considering the importance of immune impairment and a reduction of free virus due to HIV infection of CD4+ T-cells by free virus itself. Later on in Section 4, we apply optimal control problem into our model which Sutimin et al., (Sutimin et al., 2019) did not study in their model. Our model therefore consists of five variables: the concentration of susceptible CD4+ T-cells (x), the concentration of exposed CD4+ T-cells (e), the concentration of infected CD4+ T-cells (y), the concentration of free virus (v), and the concentration of CTL cells (z). The definition of all parameters are shown in Table 1.

Our proposed model is as follows.

$$\begin{aligned}
\frac{dx}{dt} &= \Lambda - \beta xv - kxy + (u_1\alpha + \eta)e - \mu x,\\
\frac{de}{dt} &= \beta xv + kxy - \alpha e - \mu e - \eta e,\\
\frac{dy}{dt} &= (1-u_1)\alpha e - dy - qyz - \mu y, \qquad (1)\\
\frac{dv}{dt} &= (1-u_2)gdy - \varepsilon v - sv - \beta xv,\\
\frac{dz}{dt} &= byz - \delta z - myz.
\end{aligned}$$

The initial conditions are $x(0) \geq 0, e(0) \geq 0, y(0) \geq 0, v(0) \geq 0, z(0) \geq 0$.

Table 1 Definition of all parameters used in the model.

Parameter	Description	Parameter	Description
Λ	The constant production rate of CD4+ T-cells	g	The average number of virus particles produced by infected CD4+ T-cells
β	The infection rate of CD4+ T-cells by free virus	ε	The virus clearance rate
k	The infection rate of CD4+ T-cells by infected cells	s	The virus death rate
α	The increase rate of CD4+ T-cells due to RTIs drug	b	The proliferation rate of CTL cells
η	The reverting rate of infected cells to uninfected cells due to viral reverse transcription incompletion	δ	The decay rate of CTL cells

Table 1 Definition of all parameters used in the model (cont.).

Parameter	Description	Parameter	Description
μ	The natural death rate of CD4+ T-cells	m	The rate of immune impairment
d	The viral lysis rate of infected CD4+T-cells	u_1	The efficacy of RTIs drugs
q	The rate at which the infected CD4+ T-cells are eliminated by the CTL cells	u_2	The efficacy of PIs drugs

Here we assume that $0<u_1<1$ and $0<u_2<1$, and $b>m$.

3. MODEL ANALYSIS

3.1 Positivity of the solutions

Theorem 1. With nonnegative initial conditions, all solutions of equation (1) remain nonnegative for all $t>0$.

Proof. For $t\geq 0$, we consider the five cases where each variable is the first variable to become zero and the other four variables remain nonnegative.

1. If $x(t)$ is the first variable to become zero at $t=t_x$, then at t_x, we have from equation (1) that

$$\frac{dx}{dt}(t_x)=\Lambda+(u_\alpha+\eta)e(t_x)\geq 0,$$

since $e(t_x)\geq 0$ and $\beta x(t_x)v(t_x)+kx(t_x)y(t_x)+\mu(t_x)=0.$ Therefore, $x(t)\geq 0$ in the positive neighbourhood of $t=t_x$.

2. If $e(t)$ is the first variable to become zero at $t=t_e$, then at t_e, we have from equation (1) that

$$\frac{de}{dt}(t_e)=\beta x(t_e)v(t_e)+kx(t_e)y(t_e)\geq 0,$$

since $x(t_e)\geq 0$ and $v(t_e)\geq 0$, $y(t_e)\geq 0$ and $\alpha e(t_e)+\mu e(t_e)+\eta(t_e)=0$. Therefore, $e(t)\geq 0$ in the positive neighbourhood of $t=t_e$.

3. If $y(t)$ is the first variable to become zero at $t=t_y$, then at t_y, we have from equation (1) that

$$\frac{dy}{dt}(t_y)=(1-u_1)\alpha e(t_y)\geq 0,$$

since $e(t_y)\geq 0$ and $dy(t_y)+qy(t_y)z(t_y)+\mu y(t_y)=0.$ Therefore, $y(t)\geq 0$ in the positive neighbourhood of $t=t_y$.

4. If $v(t)$ is the first variable to become zero at $t=t_v$, then at t_v, we have from equation (1) that

$$\frac{dv}{dt}(t_v)=(1-u_2)gdy(t_v)\geq 0,$$

since $y(t_v)\geq 0$ and $\varepsilon v(t_v)+sv(t_v)+\beta x(t_v)v(t_v)=0.$ Therefore, $v(t)\geq 0$ in the positive neighbourhood of $t=t_v$.

5. If $z(t)$ is the first variable to become zero at $t=t_z$, then at t_z, we have from equation (1) that

$$\frac{dz}{dt}(t_z)=0,$$

since $by(t_z)z(t_z)+\delta z(t_z)+my(t_z)z(t_z)=0.$ Therefore, $z(t)\geq 0$ in the positive neighbourhood of $t=t_z$.

Therefore, the positivity of all solutions of system (1) is guaranteed for all $t>0$. This completes the proof.

3.2 Invariant region

Theorem 2. Given all initial values are nonnegative and lie in the biologically feasible region Ω for system (1) defined by

$$\Omega=\left\{(x,e,y,v,z)\in\mathbb{R}_+^5 : x+e+y+\frac{q}{b}z\leq\frac{\Lambda}{\phi}, v\leq\frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\phi}\right\},$$

then all solutions of system (1) are nonnegative and remain inside the region Ω for all $t\geq 0$.

Proof. We first let $N(t)=x(t)+e(t)+y(t)+\frac{q}{b}z(t),$ then

$$\begin{aligned}\frac{dN_1}{dt}&=\Lambda-\mu x-\mu e-dy-\mu y-\frac{q}{b}\delta z-\frac{q}{b}myz\\&\leq\Lambda-\mu x-\mu e-\mu y-\frac{q}{b}\delta z\\&\leq\Lambda-\phi N,\text{where},\phi=\min(\mu,\delta).\end{aligned}\qquad(2)$$

By solving (2), we obtain

$$N(t)\leq\frac{\Lambda}{\phi}-\left(\frac{\Lambda}{\phi}-N(0)\right)e^{-\phi t}.\qquad(3)$$

Hence, $N(t)$ is bounded above by $\frac{\Lambda}{\phi}$ for all initial data in Ω.. We next consider

$$\begin{aligned}\frac{dv}{dt}&=(1-u_2)gdy-\varepsilon v-sv-\beta xv\\&\leq(1-u_2)gdy-sv-\varepsilon v\end{aligned}\qquad(4)$$

$$\leq (1-u_2)gd\frac{\Lambda}{\phi}-(s+\varepsilon)v. \qquad (5)$$

Similarly, we have

$$v(t)\leq \frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\phi}-\left(\frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\phi}-v(t)\right)e^{(s+\varepsilon)t}.$$

Thus, $v(t)$ is bounded above by $\frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\phi}$ for all initial data in Ω..

Hence, the biologically feasible region Ω for system (1) is defined by

$$\Omega=\left\{(x,e,y,v,z)\in\mathbb{R}_+^5 : x+e+y+\frac{q}{b}z\leq\frac{\Lambda}{\phi}, v\leq\frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\phi}\right\}.$$

This completes the proof.

3.3 Equilibrium points

Two equilibrium points are calculated for this model. They are

i) the infection-free equilibrium point:

$$E_0=(x_0,e_0,y_0,v_0,z_0)=\left(\frac{\Lambda}{d},0,0,0,0\right). \qquad (6)$$

ii) the infected equilibrium point:

$E_1=(x^*,e^*,y^*,v^*,z^*)$ where

$$e^*=\frac{(d+\mu)\delta+q\delta z^*}{(b-m)(1-u_1)\alpha},\ y^*=\frac{\delta}{b-m},$$

$$v^*=\frac{(1-u_2)gd\delta}{(b-m)(\varepsilon+s+\beta x^*)},$$

$$z^*=\frac{(1-u_1)(1-u_2)\alpha\beta gdx^*}{(\varepsilon+s+\beta x^*)(\alpha+\mu+\eta)q}+\frac{(1-u_1)\alpha kx^*}{(\alpha+\mu+\eta)q}-\frac{(d+\mu)}{q}.$$

x^* is a positive solution of equation

$A_1x^2+A_2x+A_3=0$, where

$$A_1=(b-m)(1-u_1)(\alpha+\mu+\eta)\alpha\beta\mu$$
$$+(1-u_1)(\alpha+\mu+\eta)\alpha\beta k\delta$$
$$-(1-u_1)(u_1\alpha+\eta)\alpha\beta k\delta>0,$$

since $(1-u_1)(\alpha+\mu+\eta)\alpha\beta k\delta$
$$>(1-u_1)(u_1\alpha+\eta)\alpha\beta k\delta,$$

$$A_2=(b-m)(1-u_1)(\varepsilon+s)(\alpha+\mu+\eta)\alpha\mu$$
$$+(1-u_1)(\varepsilon+s)(\alpha+\mu+\eta)\alpha k\delta$$
$$+(1-u_1)(1-u_2)(\alpha+\mu+\eta)\alpha\beta gd\delta$$
$$-(1-u_1)(\varepsilon+s)(u_1\alpha+\eta)\alpha k\delta$$
$$-(b-m)(1-u_1)(\alpha+\mu+\eta)\alpha\beta\Lambda$$
$$-(1-u_1)(1-u_2)(u_1\alpha+\eta)\alpha\beta gd\delta,$$

$$A_3=-(b-m)(1-u_2)(\varepsilon+s)(\alpha+\mu+\eta)\alpha\Lambda<0.$$

Since $A_1>0$ and $A_3<0$, either the value of A_2 is positive or negative, there is only one time change of sign. By Descartes' rule of sign, this ensures that there is one positive solution of x^*. Thus, E_1 exists when

$$\frac{(1-u_1)(1-u_2)\alpha\beta gdx^*}{(\varepsilon+s+\beta x^*)(\alpha+\mu+\eta)q}+\frac{(1-u_1)\alpha kx^*}{(\alpha+\mu+\eta)q}>\frac{d+\mu}{q}.$$

3.4 The basic reproduction number (R_0)

The basic reproduction number (R_0) is the expected number of secondary cases of HIV infection caused by a typical case of infected CD4+ T-cells. The next-generation matrix method by van den Drissche and Watmough (2002) is used to calculate R_0. We first write matrix $\mathcal{F}$ which is the matrix of the rate of appearance of new infections and then write matrix $\mathcal{V}$ which is the matrix of the transfer rate of individual infections. $\mathcal{F}$ and $\mathcal{V}$ of our model are shown below.

$$\mathcal{F}=\begin{bmatrix}\beta xv+kxy\\0\\0\end{bmatrix} \text{ and } \mathcal{V}=\begin{bmatrix}\alpha e+\mu e+\eta e\\dy+\mu y+qyz-(1-u_1)\alpha e\\\varepsilon v+sv+\beta xv-(1-u_2)gdy\end{bmatrix}.$$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ are

$$F=\begin{bmatrix}0&kx&\beta x\\0&0&0\\0&0&0\end{bmatrix} \text{ and}$$

$$V=\begin{bmatrix}\alpha+\mu+\eta&0&0\\-(1-u_1)\alpha&d+\mu+qz&0\\0&-(1-u_2)gd&\varepsilon+s+\beta x\end{bmatrix}.$$

We next calculate the next generation matrix as follows:

$$F(E_0)V^{-1}(E_0)$$

$$=\begin{bmatrix}\frac{(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\frac{\alpha k\Lambda}{\mu}+(1-u_1)(1-u_2)\frac{\alpha gd\beta\Lambda}{\mu}}{(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)} & \frac{\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\frac{k\Lambda}{\mu}+(1-u_2)\frac{gd\beta\Lambda}{\mu}}{(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)} & \frac{\frac{\beta\Lambda}{\mu}}{\varepsilon+s+\frac{\beta\Lambda}{\mu}}\\0&0&0\\0&0&0\end{bmatrix}$$

The spectral radius of the matrix FV^{-1} is the basic reproduction number, thus

$$R_0=\frac{(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\alpha k\Lambda+(1-u_1)(1-u_2)\alpha gd\beta\Lambda}{\mu(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)}. \qquad (7)$$

3.5 Stability of infection-free equilibrium point

- **Local stability of infection-free equilibrium point**

Theorem 3. The infection-free equilibrium point (E_0) is locally asymptotically stable if $R_0<1$, otherwise it is unstable.

Proof. The Jacobian matrix at the infection-free equilibrium point is

$$J(x_0,e_0,y_0,v_0,z_0)=\begin{bmatrix} -\mu & u_1\alpha+\eta & -\frac{k\Lambda}{\mu} & -\frac{\beta\Lambda}{\mu} & 0 \\ 0 & -\alpha-\mu-\eta & \frac{k\Lambda}{\mu} & \frac{\beta\Lambda}{\mu} & 0 \\ 0 & (1-u_1)\alpha & -d-\mu & 0 & 0 \\ 0 & 0 & (1-u_2)gd & -\varepsilon-s-\frac{\beta\Lambda}{\mu} & 0 \\ 0 & 0 & 0 & 0 & -\delta \end{bmatrix}. \tag{8}$$

Its first two eigenvalues are $\lambda_1=-\mu<0,\ \lambda_2=-\delta<0.$ And the characteristic equation for the remaining 3×3 matrix is $\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0$, where

$$a_1=\varepsilon+s+\frac{\beta\Lambda}{\mu}+d+2\mu+\alpha+\eta,$$

$$a_2=(d+2\mu+\alpha+\eta)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)+(\alpha+\mu+\eta)(d+\mu)-(1-u_1)\frac{\alpha k\Lambda}{\mu},$$

$$\begin{aligned} a_3&=(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right) \\ &\quad-\left[(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\frac{\alpha k\Lambda}{\mu}+(1-u_1)(1-u_2)\frac{\alpha gd\beta\Lambda}{\mu}\right] \\ &=(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)(1-R_0). \end{aligned}$$

When $R_0<1$, we obtain $a_1>0,\ a_3>0$ and $a_1a_2-a_3>0.$ Thus, with Routh-Hurwitz Criterion, the infection-free equilibrium point is locally asymptotically stable if $R_0<1.$ It is unstable when $R_0>1.$ This completes the proof.

- **Global stability of the infection-free equilibrium point**

We use Lyapunov method (see, e.g., Luenberger, 1979) and the concept is as follows.

Let E be an open subset of $\mathbb{R}^n$ containing equilibrium point x_0. Suppose $f\in C^1(E)$ and that $f(x_0)=0.$ Suppose further that there exists a real valued function $L\in C^1(E)$ satisfying $L(x_0)=0$ and $L(x)>0$ if $x\neq x_0$. If

1. $L(x)<0$ for all $E\setminus x_0$, x_0 is asymptotically stable.

2. $L(x)>0$ for all $x\in E$, x_0 is unstable.

Theorem 4. If $R_0<1$ and $1-\frac{(\alpha+\mu+\eta)(\varepsilon+s)q\mu^2}{(1-u_2)\alpha gd\beta\Lambda^2}<u_1<1$, then the infection-free equilibrium point E_0 is globally asymptotically stable.

Proof. We use Lyapunov method in this proof and it is defined as

$$L=(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\alpha e+(\alpha+\mu+\eta)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)y+(1-u_1)\frac{\alpha\beta\Lambda}{\mu}v.$$

Here, L is positive definite. We next calculate the derivative of L with respect to time,

$$\begin{aligned} L'&=\frac{\partial L}{\partial e}\cdot\frac{de}{dt}+\frac{\partial L}{\partial y}\cdot\frac{dy}{dt}+\frac{\partial L}{\partial v}\cdot\frac{dv}{dt} \\ &=(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\alpha\left[\beta xv+kxy-\alpha e-\mu e-\eta e\right] \\ &\quad+(\alpha+\mu+\eta)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\left[(1-u_1)\alpha e-dy-qyz-\mu y\right] \\ &\quad+(1-u_1)\frac{\alpha\beta\Lambda}{\mu}\left[(1-u_2)gdy-\varepsilon v-sv-\beta xv\right] \\ &\le(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\frac{\alpha k\Lambda}{\mu}y+(1-u_1)(1-u_2)\frac{\alpha gd\beta\Lambda}{\mu}y \\ &\quad-(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)y \\ &\quad+(1-u_1)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\frac{\alpha\beta\Lambda}{\mu}\frac{(1-u_2)gd\Lambda}{(s+\varepsilon)\mu} \\ &\quad-(\alpha+\mu+\eta)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\ge q \\ &=(\alpha+\mu+\eta)(d+\mu)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)y\ (R_0-1) \\ &\quad+\frac{(1-u_1)(1-u_2)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)\alpha gd\beta\Lambda^2}{(\varepsilon+s)\mu^2} \\ &\quad-(\alpha+\mu+\eta)\left(\varepsilon+s+\frac{\beta\Lambda}{\mu}\right)q. \end{aligned}$$

We obtain that $L'<0$ when $R_0<1$ and

$$1-\frac{(\alpha+\mu+\eta)(\varepsilon+s)q\mu^2}{(1-u_2)\alpha gd\beta\Lambda^2}<u_1<1.$$

Therefore, E_0 is globally asymptotically stable if

$$R_0 < 1 \text{ and } 1-\frac{(\alpha+\mu+\eta)(\varepsilon+s)q\mu^2}{(1-u_2)\alpha g d\beta\Lambda^2} < u_1 < 1.$$

This completes the proof.

4. Optimal control model

We apply two optimal control variables in the model of equation (1). This is to look for the best strategy in controlling the HIV infection of CD4+ T-cells. The controls variables are

i) $u_1(t)$ is the treatment effort by RTIs drugs.

ii) $u_2(t)$ is the treatment effort by PIs drugs.

The optimal control is for $R_0 > 1$, and this model can be written as

$$\begin{aligned}
\frac{dx}{dt} &= \Lambda - \beta xv - kxy + (u_1(t)\alpha + \eta)e - \mu x,\\
\frac{de}{dt} &= \beta xv + kxy - \alpha e - \mu e - \eta e,\\
\frac{dy}{dt} &= (1-u_1(t))\alpha e - dy - qyz - \mu y, \qquad (9)\\
\frac{dv}{dt} &= (1-u_2(t))gdy - \varepsilon v - sv - \beta xv,\\
\frac{dz}{dt} &= byz - \delta z - myz.
\end{aligned}$$

We would like to minimize the concentration of exposed CD4+ T-cells, the concentration of infected CD4+ T-cells and the concentration of free virus at a minimal cost of control over the time interval $[0,T]$. The objective function is defined by

$$J(u_1,u_2) = \min \int_0^T \Big[W_1 e(t) + W_2 y(t) + W_3 v(t) + \frac{1}{2}(W_4 u_1^2(t) + W_5 u_2^2(t))\Big] dt .$$

The initial conditions are $x(0) \geqslant 0$, $e(0) \geqslant 0$, $y(0) \geqslant 0$, $v(0) \geqslant 0$ and $z(0) \geqslant 0$.

The notations W_1, W_2 and W_3 are the weight constants and $W_4 u_1^2(t)$ and $W_5 u_2^2(t)$ represent the costs associated with antiretroviral drugs used to treat HIV infection by disrupting new infection with RTIs drug, and antiretroviral drugs used to treat HIV infection by blocking protease and preventing new virus from becoming a mature virus that can infect other CD4+ T-cells with PIs drug. The following function is the Lagrangian of the optimal control problem:

$$f(e,y,v,u_1,u_2) = W_1 e(t) + W_2 y(t) + W_3 v(t) + \frac{1}{2}\left(W_4 u_1^2(t) + W_5 u_2^2(t)\right).$$

Following the Pontryagin's Minimum Principle (PMP) (Pontryagin et al., 1986), the Hamiltonian for the optimal control problem is defined as

$$\begin{aligned}
H &= W_1 e(t) + W_2 y(t) + W_3 v(t)\\
&\quad + \frac{1}{2}\left(W_4 u_1^2(t) + W_5 u_2^2(t)\right)\\
&\quad + \lambda_x[\Lambda - \beta xv - kxy + (u_1(t)\alpha + \eta)e - \mu x]\\
&\quad + \lambda_e[\beta xv + kxy - \alpha e - \mu e - \eta e]\\
&\quad + \lambda_y[(1-u_1(t))\alpha e - dy - qyz - \mu y]\\
&\quad + \lambda_v[(1-u_2(t))gdy - \varepsilon v - sv - \beta xv]\\
&\quad + \lambda_z[byz - \delta z - myz], \qquad (10)
\end{aligned}$$

where the adjoint functions associated with the state equations for x, e, y, v and z are $\lambda_x, \lambda_e, \lambda_y, \lambda_v$ and λ_z, respectively.

Theorem 6. Let optimal state solutions with associated optimal control variables $u_1^*(t)$, and $u_2^*(t)$ be $\tilde{x}, \tilde{e}, \tilde{y}, \tilde{v}$ and $\tilde{z}$. Then, there exists adjoint variables $\lambda_x, \lambda_e, \lambda_y, \lambda_v$ and λ_z satisfying:

$$\begin{aligned}
\lambda_x' &= -\Big[-(\beta\tilde{v} + k\tilde{y} + \mu)\lambda_x + (\beta\tilde{v} + k\tilde{y})\lambda_e - (\beta\tilde{v})\lambda_v\Big]\\
\lambda_e' &= -\Big[W_1 + (u_1(t)\alpha + \eta)\lambda_x - (\alpha + \mu + \eta)\lambda_e + (1-u_1(t))\alpha\lambda_y\Big]\\
\lambda_y' &= -\Big[W_2 - k\tilde{x}\lambda_x + k\tilde{x}\lambda_e - (d + q\tilde{z} + \mu)\lambda_y\\
&\qquad + (1-u_2(t))gd\lambda_v + (b\tilde{z} - m\tilde{z})\lambda_z\Big]\\
\lambda_v' &= -\Big[W_3 - \beta\tilde{x}\lambda_x + \beta\tilde{x}\lambda_e - (\varepsilon + s + \beta\tilde{x})\lambda_v\Big]\\
\lambda_z' &= -\Big[-q\tilde{y}\lambda_y + (b\tilde{y} - \delta - m\tilde{y})\lambda_z\Big].
\end{aligned}$$

Its transversality conditions are

$$\lambda_x(T) = 0, \lambda_e(T) = 0, \lambda_y(T) = 0, \lambda_v(T) = 0, \lambda_z(T) = 0$$

with characterization of the optimal control

$$u_1^*(t) = \max\left\{0, \min\left\{\frac{\alpha\tilde{e}(\lambda_y - \lambda_x)}{W_4}, u_{1\max}\right\}\right\},$$

$$u_2^*(t) = \max\left\{0, \min\left\{\frac{gd\tilde{y}\lambda_v}{W_5}, u_{2\max}\right\}\right\}.$$

Proof. By using the Pontryagin's Minimum Principle, we determine the adjoint equations. We differentiate the

Hamiltonian with respect to x, e, y, v and z, respectively. The adjoint system is therefore as follows:

$$\begin{aligned}
\lambda_x' &= -\frac{\partial H}{\partial x} = -\left[-(\beta\tilde{v}+k\tilde{y}+\mu)\lambda_x + (\beta\tilde{v}+k\tilde{y})\lambda_e - (\beta\tilde{v})\lambda_v\right] \\
\lambda_e' &= -\frac{\partial H}{\partial e} = -\left[W_1 + (u_1(t)\alpha+\eta)\lambda_x - (\alpha+\mu+\eta)\lambda_e \right. \\
&\qquad \left. +(1-u_1(t))\alpha\lambda_y\right] \\
\lambda_y' &= -\frac{\partial H}{\partial y} = -\left[W_2 - k\tilde{x}\lambda_x + k\tilde{x}\lambda_e - (d+q\tilde{z}+\mu)\lambda_y \right. \\
&\qquad \left. +(1-u_2(t))gd\lambda_v + (b\tilde{z}-m\tilde{z})\lambda_z\right] \qquad (11) \\
\lambda_v' &= -\frac{\partial H}{\partial v} = -\left[W_3 - \beta\tilde{x}\lambda_x + \beta\tilde{x}\lambda_e - (\varepsilon+s+\beta\tilde{x})\lambda_v\right] \\
\lambda_z' &= -\frac{\partial H}{\partial z} = -\left[-q\tilde{y}\lambda_y + (b\tilde{y}-\delta-m\tilde{y})\lambda_z\right].
\end{aligned}$$

Next, we determine $\frac{\partial H}{\partial u_i} = 0$ at u_i^*, for $i = 1, 2$ and we obtain

$$\frac{\partial H}{\partial u_1} = W_4 u_1(t) + \alpha\tilde{e}\lambda_x - \alpha\tilde{e}\lambda_y = 0$$

$$u_1 = \frac{\alpha\tilde{e}(\lambda_y - \lambda_x)}{W_4}. \qquad (12)$$

$$\frac{\partial H}{\partial u_2} = W_5 u_2(t) - gd\tilde{y}\lambda_v = 0$$

$$u_2 = \frac{gd\tilde{y}\lambda_v}{W_5}. \qquad (13)$$

Then, we have optimal control variables as

$$u_1^*(t) = \max\left\{0, \min\left\{\frac{\alpha\tilde{e}(\lambda_y - \lambda_x)}{W_4}, u_{1\max}\right\}\right\}, \qquad (14)$$

$$u_2^*(t) = \max\left\{0, \min\left\{\frac{gd\tilde{y}\lambda_v}{W_5}, u_{2\max}\right\}\right\}. \qquad (15)$$

This completes the proof.

5. Numerical simulation of optimal control model

Numerical simulation of the dynamics of the equation (9) is performed. We use the forward-backward sweep method to solve the optimality system numerically. The optimal control is applied continuously for 300 days. All parameter values used in this study is shown in Table 2. Some parameters used are from previous research as indicated in Table 2 and they are based on existing experiment data or data collected from clinical experiments and some are assumed. The numerical results are shown in Figure 1- Figure 3. We divide our results into three strategies as shown below.

Table 2. Parameter values of the model used in numerical study.

Parameter	Value	Unit	Ref
Λ	23	day^{-1}	Arenas et al., 2021
β	0.0005	mm^3 / day	Sutimin et al., 2019
k	0.0008	mm^3 / day	Sutimin et al., 2019
α	0.1	1/ day	Sutimin et al., 2019
η	0.01	1/ day	Assume
μ	0.02	1/ day	Sutimin et al., 2019
d	0.24	1/ day	Sutimin et al., 2019
q	0.01	1/ day	Sutimin et al., 2019
g	100	$cell$ / day	Sutimin et al., 2019
ε	2.4	1/ day	Arenas et al., 2021
s	2.4	1/ day	Sutimin et al., 2019
b	0.01	1/ day	Sutimin et al., 2019
δ	0.05	1/ day	Sutimin et al., 2019
m	0.005	$cells^{-1}$ / day^{-1}	Bai and Xu, 2021

5.1 Strategy A : Control with treatment effort by using RTIs drug only

We use control u_1 to optimize the objective function while we set u_2 to be zero. Figure 1(a) shows that the concentration of susceptible CD4+ T-cells (x) in control case is equal to those in non-control case for the first few days and after that it largely increases and reaches higher equilibrium value than non-control case. Figure 1(b) shows that the concentration of exposed CD4+ T-cells (e) in control condition rarely changes in the first 50 days comparing to non-control one, whereas after that it drops to zero on 60^{th} day which is lower equilibrium value than non-control case. Similarly, Figure 1(c) and (d) show that the concentration of infected CD4+ T-cells (y) and the concentration of free virus (v) have the same pattern as of Figure 1(b). Figure 1(f) shows that the concentration of CTL cells (z) is largely lower in control case than non-control one and drops to zero as equilibrium value towards 125^{th} day. Figure 1(g) shows the strategy of u_1 that we have to start controlling with u_1 at around 7%. After that it has to go up to 90% on 30^{th} day until 300^{th} day, then it can be dropped down to zero.

5.2 Strategy B : Control with treatment effort by using PIs drug only

Here, we set the control u_1 to be zero and use control u_2 to optimize the objective function. Figure 2(a) shows that the concentration of susceptible CD4+ T-cells (x) in control case decreases much less than in non-control one and it fluctuates around 760-960 $cell/mm^3$ until the end of 300 days which reaches higher equilibrium value. Figure 2(b) shows that the concentration of exposed CD4+ T-cells (e) is significantly lower in control case for the first peak and slightly lower in the second peak than without control case. Further, it reaches lower equilibrium value in control one comparing to without control condition. Figure 2(c) shows that the concentration of infected CD4+ T-cells (y) is also significantly lower in control case, and time for the peak to occur is slightly slower than non-control one. However, it can be seen that the concentration of infected CD4+ T-cells (y) is slightly higher in the second peak in control case, whereas it reduces to the same equilibrium value towards the end. Figure 2(d) shows that the concentration of free virus (v) is dramatically lower in control case with the peak of about 25 $cell/mm^3$, whereas it reaches the peak to more than 600 $cell/mm^3$ in no control one. After that it decreases to reach lower equilibrium value than without control one. Figure 2(f) shows that in control condition, the concentration of CTL cells (z) is largely lower than without control case and is lower all along towards 300^{th} day. Figure 2(g) shows that in this strategy we have to start controlling u_2 at the maximum rate of 90% for all 300 days and finally it can be dropped down to 0% at the end. From results above, this strategy demonstrates that u_2 could have a bigger impact in reducing the concentration of e, y, v and z.

5.3 Strategy C : Combination of all controls

A combination of both controls is applied to optimize the objective function. Figure 3(a) shows that the concentration of susceptible CD4+ T-cells (x) reduces much slower in control case than without control one and after 30 days it gradually increases to almost 1,148 $cell/mm^3$ at the end. Figure 3(b) shows a dramatic decrease in the concentration of exposed CD4+ T-cells (e) in control case with the peak of about 417 $cell/mm^3$, whereas it increases and reaches the peak of more than 1,077 $cell/mm^3$ in non-control case. After that it drops to zero on the 75^{th} day in control case, which gives better result than Strategy A and B. Similarly, Figure 3(c) shows a dramatic reduction in the concentration of infected CD4+ T-cells (y) in control case with the peak of about 58 $cell/mm^3$,

whereas it increases and reaches the peak of more than $125\ cell/mm^3$ in non-control one. Then, it drops to zero on the 75^{th} day in control condition, which again gives better result than Strategy A and B. In the control condition, Figure 3(d) shows a significant decrease in the concentration of free virus (v) with the peak of about $25\ cell/mm^3$, whereas it increases and reaches the peak of more than $600\ cell/mm^3$ in without control one, and it reaches zero on the 25^{th} day. Finally, Figure 3(e) shows that the concentration of CTL cells (z) reduces largely in control case and it reduces to reach zero on 125^{th} day. Hence, we can see that the results in this strategy gives better control in reducing the HIV infection than previous two strategies. Figure 3(f) shows that in this strategy we need to start controlling u_1 from 0% for about 15 days and increases u_1 gradually to 90% on 105^{th} day, then remains at 90% until 290^{th} day. After that we can gradually drop u_1 to zero towards the 300^{th} day. Further, Figure 3(g) shows that we need to start controlling u_2 at the maximum rate of 90% for all 300 days and can drop it to zero on 300^{th} day.

Overall, our results demonstrate that with the treatment effort, i.e., the use of RTIs drug (u_1) alone in Strategy A can slightly reduce the concentration of $e,\ y,\ v$ and z, although the equilibrium value of $e,\ y$ and v reach zero. The use of PIs drug (u_2) alone gives a better result in reducing $e,\ y,\ v$ and z than a control with u_1 alone, although the equilibrium value of e and y do not seem to reach zero. Further, Strategy C shows that when using both drugs, the concentration of $e,\ y,\ v$ and z not only reduce largely as Strategy B, but also reach zero as Strategy A. Moreover, time for the peak to occur of $e,\ y,\ v$ and z in control case is slightly later than those of non-control case. Hence, Strategy C gives the best result.

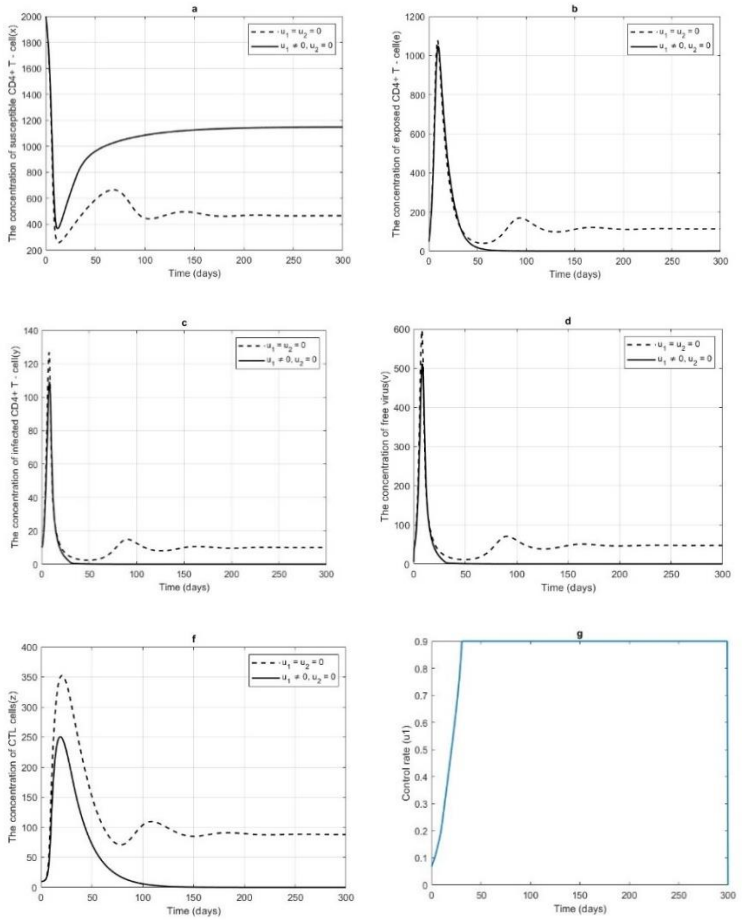


Figure 1 Numerical simulation of the optimal control model (9) with treatment effort by using RTIs drug of u_1 alone when $u_{1\max} = 0.9$.

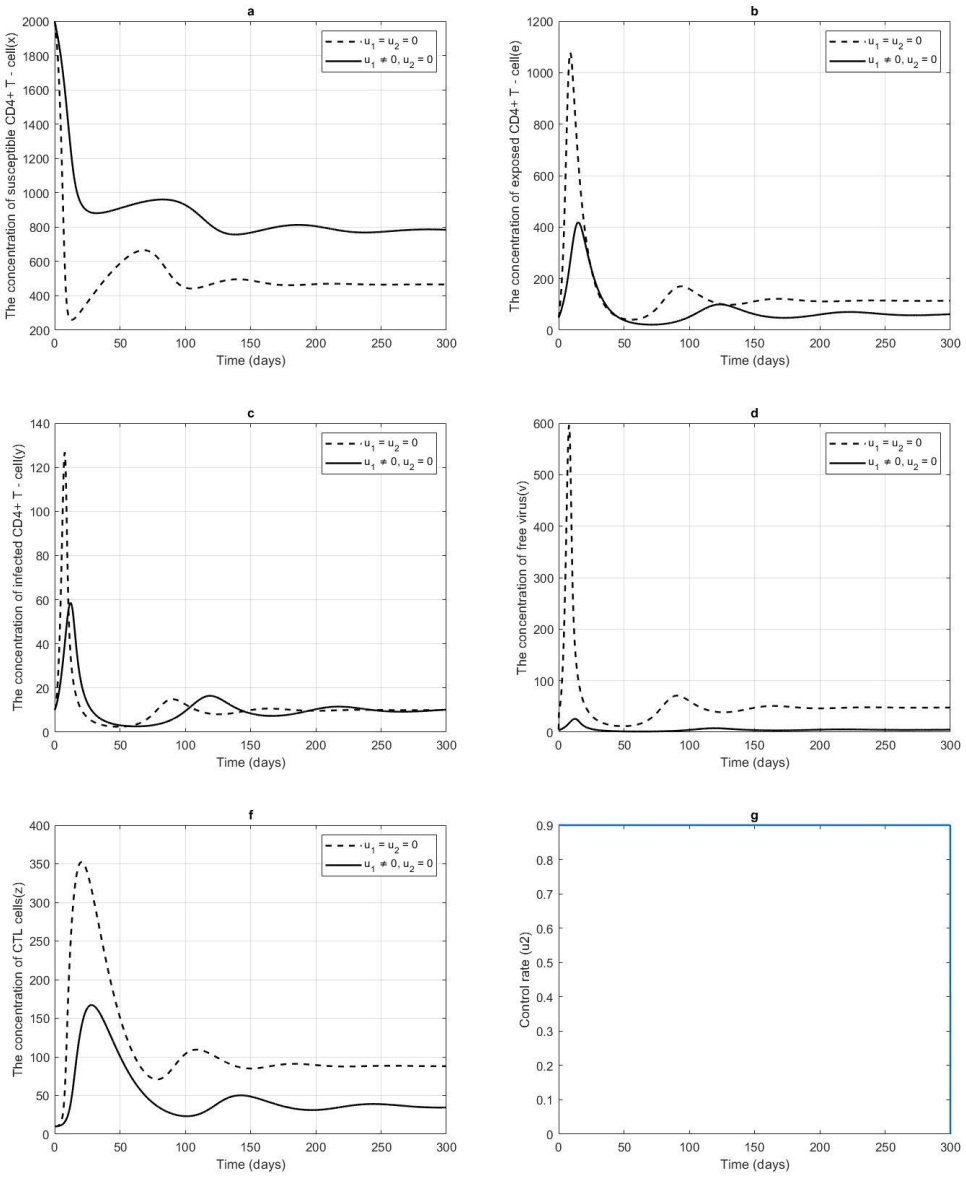
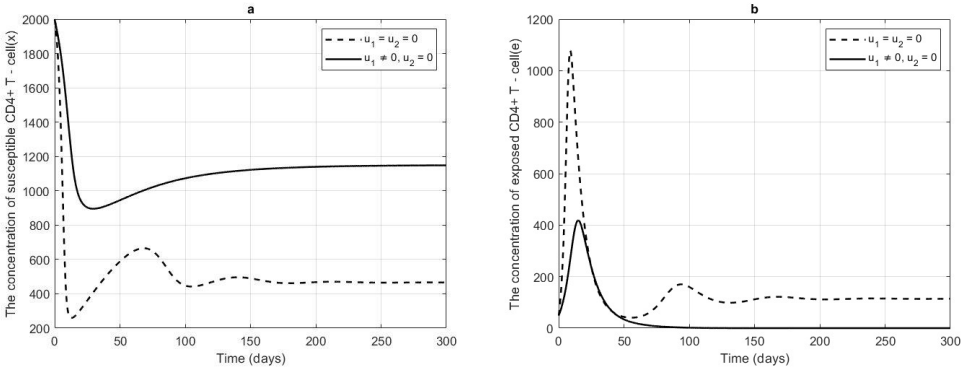


Figure 2 Numerical simulation of the optimal control model (9) with optimal control of treatment effort by using PIs drug of u_2 alone when $u_{2\max} = 0.9$.



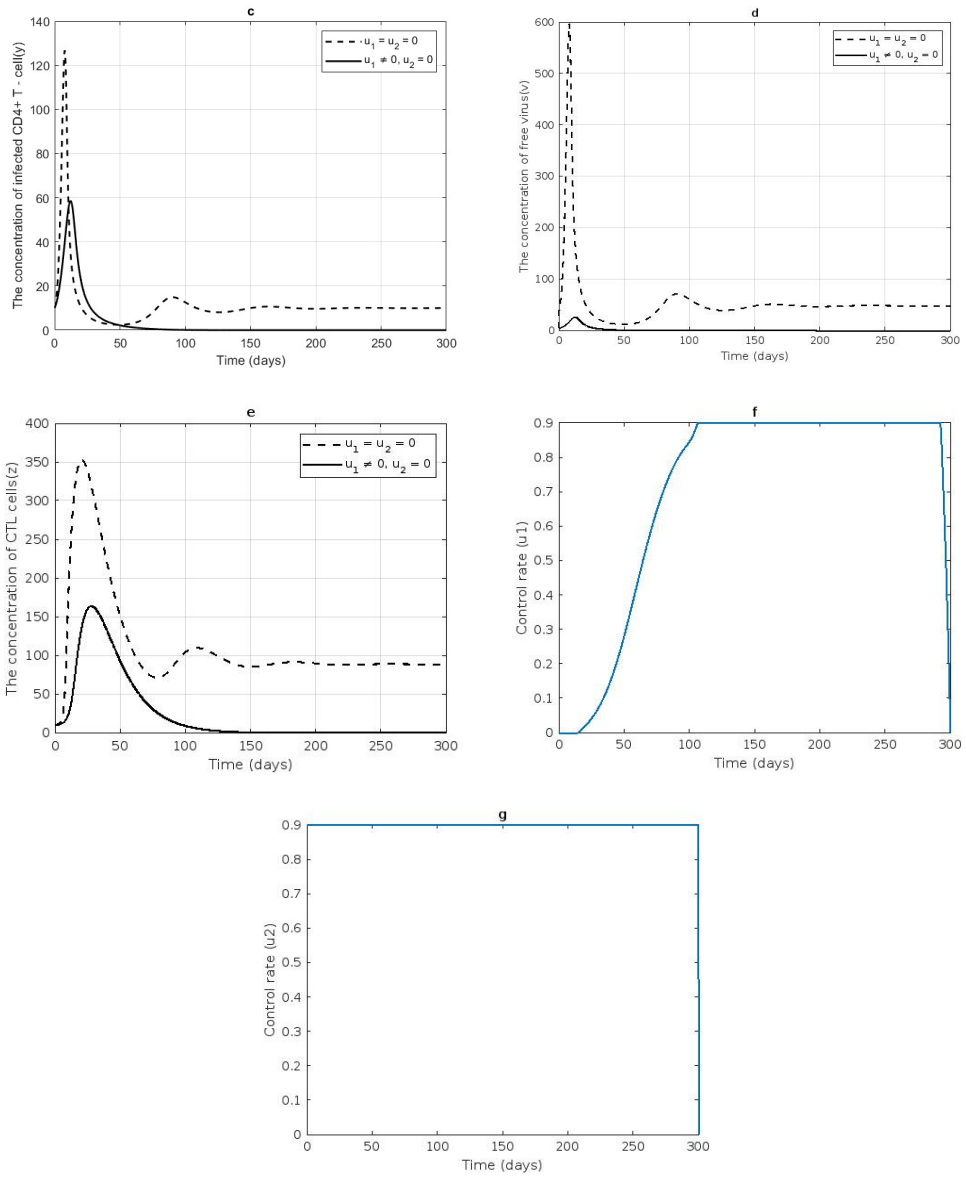


Figure 3 Numerical simulation of the optimal control model (9) with all optimal controls u_1 and u_2 when $u_{1\max} = u_{2\max} = 0.9$.

6. Conclusions

Even with great attempt of various organization trying to eliminate HIV infection, there are still a high number of HIV infected patients globally every year. A better understanding of virus kinetic of HIV infection therefore remains essential. In this study, we propose a within-host model of HIV infection of CD4+ T-cells. The model is modified from the work of Sutimin et al., (Sutimin et al., 2019) by including the immune impairment and a fact that free viruses are reduced due to an HIV infection by free virus itself. The model consists of five variables: the concentration of susceptible CD4+ T-cells (x), the concentration of exposed CD4+ T-cells (e), the concentration of infected CD4+ T-cells (y), the concentration of free virus (v), and the concentration of CTL cells (z). The positivity and boundedness of model solutions are verified. Two equilibrium points are obtained and they are infection-free and infected steady state. The basic reproduction number is calculated and when it is less than a unity, an infection-free equilibrium point is locally stable. When it is greater than one, an infected equilibrium point exists. Infection-free equilibrium point is globally stable when they meet some required conditions. In addition, optimal control problem is applied into the model by considering both type of

antiretroviral drugs, which are RTIs and PIs drugs as control variables. We performed some numerical simulations of optimal control model. The results demonstrate that RTIs drug alone could slightly reduce an HIV infection whereas the PIs drug alone gives better result in reducing the infection than RTIs drug. Nevertheless, for eliminating an HIV infection of CD4+ T-cells, a combination of both types of drugs gives the best result. Our study therefore encourages a mixed use of antiretroviral drugs, RTIs and PIs, however, an amount of each type of drugs are to be decided by the medical doctors. Further, we like to point out that our numerical results of optimal control model show that with optimal control, it can reduce an infection to zero. However, if the controls are omitted, an infection could occur and increase again. Hence, antiretroviral drugs are required to make $R_0 < 1$ in order to let the infection-free equilibrium point stable all the time.

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