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Optimal control of combined antiretroviral therapies in an HIV infection model with cure rate and fusion effect

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This paper mainly targets to deduce an optimal treatment strategy for combined antiretroviral drugs, which can maximize healthy $CD4^+$ T cells level with minimum side effects and cost. For this purpose, we consider a within-host treatment model for the HIV infection with two controls incorporating full logistic proliferation of healthy $CD4^+$ T cells, cure rate and fusion effect. These two controls represent the effects of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), respectively. The model analysis begins with proving different basic properties like non-negativity, boundedness of the model solutions and calculation of the basic reproduction number of the model under consideration. Then, stability results are obtained for HIV infection-free equilibrium point and also, a critical efficacy for the combined therapies is calculated. After that, the optimal control problem is proposed and solved numerically using a forward–backward iterative method. Finally, we obtain an optimal treatment strategy that can maximize healthy $CD4^+$ T cells count and control the viral load, and HIV-infected

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$CD4^+$ T cells count to an undetectable level resulting in improved health conditions of infected individuals.

Keywords: HIV infection; antiretroviral drugs; critical efficacy; optimal control; Pontryagin's maximum principle.

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1. Introduction

Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), is still humankind's primary public health concern. As per the information shared by World Health Organization (WHO), approximately 36.3 million lives around the globe have been claimed by HIV so far, along with approximately 37.7 million active cases globally at the end of the year 2020 [1]. Different modes of HIV transmission include transmission via bodily fluids like vaginal fluid, semen, blood, breast milk, etc. [2]. Also, it can be transmitted from an infected mother to a newborn baby [3]. Due to HIV infection, the immune system of infected individuals deteriorates and fails to protect the body from other life-threatening opportunistic infections. Functioning of the immune system is measured by $CD4^+$ T cells count, which is the main target of HIV [4]. Based on $CD4^+$ T cells count, there are five stages of HIV infection: primary infection, clinical stage 1, clinical stage 2, clinical stage 3, and clinical stage 4 or AIDS. Out of these, the first two stages are asymptomatic, and the other three are symptomatic [5].

Although no anti-HIV vaccine has been developed to date, US Food and Drug Administration has approved different treatment regimes which can control infection in the human body. Among these, Highly Active Antiretroviral Therapy (HAART) has been used in different countries in which fusion inhibitors (FIs), reverse transcriptase inhibitors (RTIs), and protease inhibitors (PIs) are used in different proportions as combination therapy. Reverse transcriptase inhibitors (RTIs) is chemotherapy that helps to maintain healthy $CD4^+$ T cells count by opposing the conversion of RNA to viral DNA, while protease inhibitors (PIs) minimize the production of new HIV from actively infected $CD4^+$ T cells. Though combined antiretroviral therapy (ART) effectively suppresses viral load, there are different challenges associated with the use of this therapy. One of such challenges is their high cost due to the regular use of these drugs to suppress viral load. Also, daily use of these drugs leads to different side effects like fatigue, anemia, diarrhea, vivid dreams, various pain, and nerve-related problems [6]. These problems lead to discontinuation of treatments and non-adherence to ARTs in many infected individuals, which increases HIV load [7] as well as the emergence of drug-resistant mutations [8]. However, these challenges can be overcome by finding an optimal composition of these drugs capable of controlling HIV infection effectively.

Numerous mathematical models have been proposed and studied to understand the underlying dynamics of HIV in human body [9–21]. Moreover, optimal control theory has been applied to different within-host treatment models for finding

optimal combinations of available treatments. Kirschner *et al.* [22] considered an existing ordinary differential equation model for HIV infection and introduced a control representing the percentage effect of chemotherapy on viral production. They numerically solved an optimal control problem to find an optimal chemotherapy strategy to maximize T cells with minimum chemotherapy systemic cost. With the same objective, Butler *et al.* [23] solved another optimal control problem to find a treatment strategy of chemotherapy affecting viral infectivity simulating a drug like AZT. Fister *et al.*[24] implemented a control representing the percentage effect of chemotherapy on the interaction of healthy $CD4^+$ T cells with free HIV and found an optimal therapeutic strategy for 500 days to maximize the therapy benefits. Joshi [25] solved an optimization problem incorporating two controls for immune-boosting and viral suppressing and found an optimal combination of the drugs. Garira *et al.* [26] used two controls representing the effects of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) to a model describing the interactions among healthy $CD4^+$ T cells, HIV-infected $CD4^+$ T cells, free HIV and HIV-1 specific cytotoxic T lymphocytes (CTLs). Their studies suggest that implementing small drug dosages with drug holidays positively impacts the effectiveness and cost of the treatment for highly toxic drugs, while continuous therapy is beneficial for less toxic drugs. Similarly, these two controls, RTIs and PIs, have been taken into account in many other studies [27–30] with different within-host models for the HIV infection. Recently in 2018, Nagina *et al.* [45] considered the effect of fusion inhibitors (FIs) along with the effects of RTIs and PIs. Their study suggests that PIs are the best and FIs are the worst while used as a single drug to reduce infected cells count and viral load. As a combination, they suggest using RTIs as initial therapy, and then FIs should be introduced along with RTIs not alone. However, all these studies about optimal control of within-host HIV infection model were conducted without considering the proliferation of T cells, cure rate and fusion effect. Hattaf and Yousfi [29] considered cure rate, but the proliferation of T cells and fusion effect were not considered in their study. Ogunlaran and Noutchie [30] considered simple logistic proliferation of healthy $CD4^+$ T cells, but cure rate and fusion effect were ignored in their study. Moreover, other developments related to disease dynamics can be observed with the advancement of nonlinear dynamics [31]. Along with intrego-differential equations (IDE), researchers have been utilizing the concepts of fractional-order differential equations(FDE) [32] in the studies of both intra-host [34, 36] and inter-host models [33, 35, 37] of different diseases with greater precision. Also, deep learning (DL), a branch of machine learning and artificial intelligence, has been applied in this field for the detection and prevention of different diseases like HIV [38], cancer [39] etc. Moreover, along with the existing optimization techniques, different new optimization techniques have been developed [40], which can be used for solving optimal control problems related to disease dynamics.

Though different mechanisms have been proposed to support the gradual depletion of healthy $CD4^+$ T cells [41–43], it is still a controversial issue in the field of HIV research [44]. In 2019, Gupta and Dutta [18] proposed a within-host HIV

infection model with an assumption that few healthy $CD4^+$ T cells get infected to produce new virions while some die binding to HIV due to different effects of the fusion process. In their study, they also considered the cure rate for HIV-infected $CD4^+$ T cells. However, the proliferation of $CD4^+$ T cells was ignored in their study, which was later incorporated in the study of Nath and Sarmah [20]. Nevertheless, they observed that the proliferation of T cells plays an important role in describing the dynamics of the model. In this paper, we have explored the combined effects of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), considering the model studied in [20], which is the novelty of this study. Also, we have found an optimal treatment strategy for these drugs (RTIs and PIs) using optimal control theory to get maximum benefits with their minimum side effects and costs.

This paper is organized as follows. In Sec. 2, we describe the treatment model for HIV infection. Different qualitative behaviors of the model like non-negativity and boundedness of solutions, the existence of equilibrium points and stability criteria for HIV infection-free equilibrium point are discussed in Sec. 3. In Sec. 4, we propose and discuss an optimal control problem for the treatment model. Numerical simulations are done in Sec. 5 to verify the analytical results and to study the effects of the different treatment strategies. Also, the optimal problem is solved numerically. Finally, conclusions from the overall study are mentioned in Sec. 6.

2. The Treatment Model for HIV Infection

We incorporated the effects of combined antiretroviral treatments (RTIs and PIs) to the basic model for HIV infection discussed in [20] to obtain the following treatment model, which constitutes the system of three ordinary differential equations:

$$\begin{aligned}
\frac{dx}{dt} &= r - d_1 x + ax\left(1 - \frac{x+y}{x_{\max}}\right) - fzx - (1-\gamma_r)\beta zx + \rho y,\\
\frac{dy}{dt} &= (1-\gamma_r)\beta zx - d_2 y - \rho y,\\
\frac{dz}{dt} &= (1-\gamma_p)Nd_2 y - d_3 z - fzx,
\end{aligned} \tag{2.1}$$

with initial conditions

$$x(0) \geq 0, \quad y(0) \geq 0, \quad z(0) \geq 0, \tag{2.2}$$

where $x(t), y(t)$ and $z(t)$ denote the concentrations of healthy or HIV infection-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and free virus, respectively. The description of the parameters of the model (2.1) with their values is given in Table 1.

In the model (2.1), the first equation represents the dynamics of healthy $CD4^+$ T cells. It is assumed that healthy $CD4^+$ T cells are produced from their sources like precursors of bone marrow, thymus at constant rate r and the existing cells proliferates at rate a following the full logistic function $ax(1-\frac{x+y}{x_{\max}})$ to produce new cells [9, 12, 13, 16, 19]. They decline naturally at the rate d_1 and get infected by

Table 1. List of parameters with values for the model (2.1).

Parameters	Meaning	Values	Source
r	Healthy CD4$^+$ T cells production rate	10	[19, 20]
d_1	Normal death rate of healthy CD4$^+$ T cells	0.1	[19, 20]
a	Proliferation rate of healthy CD4$^+$ T cells	0.3	[19, 20]
$x_{\max}$	Maximum carrying capacity of healthy CD4$^+$ T cells	1500	[10, 19, 20]
β	Infection rate of healthy CD4$^+$ T cells	0.0027	[19, 20]
f	Fusion rate	0.00002	[17, 20]
ρ	Cure rate	0.2	[10, 20]
d_2	Death rate of HIV-infected CD4$^+$ T cells	0.2	[19, 20]
N	Virus produced per HIV-infected CD4$^+$ T cells	10	[19, 20]
d_3	Clearance rate of free virions	2.4	[19, 20]
γ_r	Efficacy of RTIs	0-1	Variable
γ_p	Efficacy of PIs	0-1	Variable

free HIV at rate β. In order to block new infections, reverse transcriptase inhibitors (RTIs) are administrated at rate γ_r and the term $(1-\gamma_r)$ is used in this equation to describe this activity. Also, some healthy CD4$^+$ T cells along with free HIV get lost at rate f due to the fusion effect [17, 18]. The dynamics of HIV-infected CD4$^+$ T cells is depicted by the second equation of the model (2.1). HIV-infected CD4$^+$ T cells decline naturally at rate d_2, and a portion returns to the healthy class at rate ρ, which is called cure rate [10]. In the third equation, the term $(1-\gamma_p)$ is used to represent the effect of protease inhibitors (PIs), which reduce the production rate of free HIV from actively infected CD4$^+$ T cells, and d_3 is used to define natural decay of free virions. In Fig. 1, the behaviors of the populations of the model (2.1) are represented with the help of a flowchart.

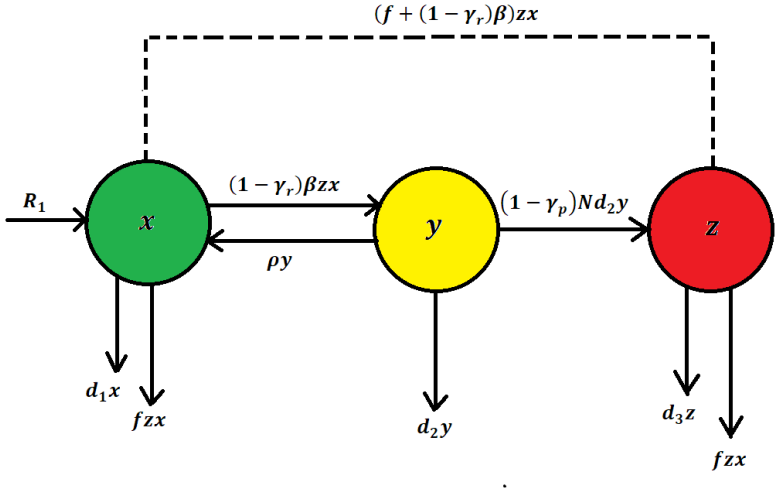

Fig. 1. Flowchart of the model (2.1), where $R_1 = r + ax(1 - \frac{x+y}{x_{\max}})$.

3. Qualitative Analysis of the Model

3.1. *Non-negativity and boundedness of solutions*

In this section, we will check different qualitative behaviors of the model (2.1) like non-negativity and boundedness of solutions.

Lemma 1. *All analytic solutions of the treatment model* (2.1) *associated with initial conditions* $x(0) \geq 0$, $y(0) \geq 0$, $z(0) \geq 0$ *exist in* $\mathbb{R}^3_+$, *more precisely* $x(t) \geq 0$, $y(t) \geq 0$, $z(t) \geq 0$ *for all* $t \geq 0$.

Proof. It is observed that uniform continuity and locally Lipschitzian conditions are satisfied for right-hand side of the treatment model (2.1) on its domain. So, there exists unique solution $(x(t), y(t), z(t))$ of the model (2.1). Now, rest part is to prove that the solutions $(x(t), y(t), z(t))$ along with initial conditions $x(0) \geq 0, y(0) \geq 0, z(0) \geq 0$ are non-negative for all $t \geq 0$.

Since all parameters are positive and $\gamma_r, \gamma_p \in [0, 1]$, we have the following from the model equations (2.1)

$$\begin{aligned} \frac{dx}{dt} &\geq -d_1 x + ax\left(1 - \frac{x+y}{x_{\max}}\right) - fzx - (1-\gamma_r)\beta zx, \\ \frac{dy}{dt} &\geq -d_2 y - \rho y, \\ \frac{dz}{dt} &\geq -d_3 z - fzx. \end{aligned} \tag{3.1}$$

Solving the above equations, we have

$$\begin{aligned} x(t) &\geq x(0) e^{\int_0^t \left\{-d_1 + a\left(1 - \frac{x(u)+y(u)}{x_{\max}}\right) - fz(u) - (1-\gamma_r)\beta z(u)\right\} du}, \\ y(t) &\geq y(0) e^{-(d_2+\rho)t}, \\ z(t) &\geq z(0) e^{\int_0^t (-d_3 - fx(u)) du}. \end{aligned}$$

Hence, the solution $(x(t), y(t), z(t))$ associated with initial conditions (2.2) is non-negative for all $t \geq 0$. □

Lemma 2. *All solutions of the treatment model* (2.1) *associated with initial conditions* $x(0) \geq 0, y(0) \geq 0, z(0) \geq 0$ *are bounded.*

Proof. In the absence of HIV, we can obtain T cell concentration as

$$x_0 = \frac{x_{\max}}{2a}\left[(a - d_1) + \sqrt{(a-d_1)^2 + \frac{4ra}{x_{\max}}}\right]. \tag{3.2}$$

Also, $\lim_{t\to\infty} x(t) = x_0$. Adding the first and second equations of model (2.1), we get

$$x + y = r - d_1 x + ax\left(1 - \frac{x+y}{x_{\max}}\right) - fzx - d_2 y \leq r + ax_0 - d_1(x+y),$$

since $d_1 \leq d_2$. Thus, $\lim_{t\to\infty} \sup(x(t) + y(t)) \leq \frac{r+ax_0}{d_1}$. Therefore, we have $\lim_{t\to\infty} \sup y(t) \leq \frac{r+ax_0}{d_1}$ which implies $y(t) \leq \frac{r+ax_0}{d_1}$. Now, the third equation of the model (2.1) gives

$$\begin{aligned}
&\frac{dz}{dt} \leq \frac{(1-\gamma_p)(r+ax_0)Nd_2}{d_1} - d_3 z,\\
&\implies \lim_{t\to\infty} \sup z(t) \leq \frac{(1-\gamma_p)(r+ax_0)Nd_2}{d_1 d_3},\\
&\implies z(t) \leq \frac{(1-\gamma_p)(r+ax_0)Nd_2}{d_1 d_3}.
\end{aligned}$$

Hence, all three populations of the model (2.1) are bounded. □

Therefore, we have the following closed, bounded and positively invariant set

$$\Omega = \left\{(x,y,z) \in \mathbb{R}^3_+ : 0 \leq x \leq x_0, 0 \leq y \leq \frac{r+ax_0}{d_1}, \right.$$
$$\left. 0 \leq z \leq \frac{(1-\gamma_p)(r+ax_0)Nd_2}{d_1 d_3}\right\}, \tag{3.3}$$

with respect to the model (2.1), where $\mathbb{R}^3_+ = \{(x,y,z) : x,y,z \geq 0\}$.

3.2. *Equilibria of the treatment model* (2.1)

It is clear that the model (2.1) has an HIV infection-free equilibrium point $E_0(x_0,0,0)$ where $x_0 = \frac{x_{\max}}{2a}\left[(a-d_1) + \sqrt{(a-d_1)^2 + \frac{4ra}{x_{\max}}}\right]$. Now, we will calculate the basic reproduction number, which is a very important parameter in the study of virus dynamics. Biologically, it means that the number of new virions produced by an infected cell whenever almost all cells are healthy. We can find basic reproduction number of the treatment model (2.1) by means of the next generation matrix method [46].

Considering, $S = (y,z,x)$ we can represent our model (2.1) as follows:

$$\frac{dS}{dt} = E(S) - T(S), \tag{3.4}$$

where $E(S)$ is the appearance rate of new infections and $T(S)$ is the transfer rate of population to another compartment which are given by

$$E(S) = \begin{pmatrix} (1-\gamma_r)\beta zx \\ 0 \\ 0 \end{pmatrix},$$

$$T(S) = \begin{pmatrix} d_2 y + \rho y \\ d_3 z + fzx - (1-\gamma_p)Nd_2 y \\ d_1 x + fzx + (1-\gamma_r)\beta zx - r - ax\left(1 - \dfrac{x+y}{x_{\max}}\right) - \rho y \end{pmatrix}.$$

The Jacobian matrix of $E(S)$ and $T(S)$ at HIV infection free equilibrium point E_0 is as follows:

$$J_E(E_0) = \begin{pmatrix} e_{2\times 2} & 0_{2\times 1} \\ 0_{1\times 2} & 0 \end{pmatrix},$$

$$J_T(E_0) = \begin{pmatrix} & t_{2\times 2} & & 0_{2\times 1} \\ \dfrac{ax_0}{x_{\max}} - \rho & fx_0 + (1-\gamma_r)\beta x_0 & d_1 - a\left(1 - \dfrac{x_0}{x_{\max}}\right) + \dfrac{ax_0}{x_{\max}} \end{pmatrix},$$

with

$$e_{2\times 2} = \begin{pmatrix} 0 & (1-\gamma_r)\beta x_0 \\ 0 & 0 \end{pmatrix}, \quad t_{2\times 2} = \begin{pmatrix} d_2 + \rho & 0 \\ -(1-\gamma_p)Nd_2 & d_3 + fx_0 \end{pmatrix}.$$

Now

$$et^{-1} = \frac{1}{(d_2+\rho)(d_3+fx_0)} \begin{pmatrix} (1-\gamma_r)(1-\gamma_p)Nd_2\beta x_0 & (1-\gamma_r)\beta x_0(d_2+\rho) \\ 0 & 0 \end{pmatrix}.$$

Basic reproduction number (R_0) of the model (2.1) is given by the spectral radius of the matrix et^{-1} and hence

$$R_0 = \frac{(1-\gamma_r)(1-\gamma_p)Nd_2\beta x_0}{(d_2+\rho)(d_3+fx_0)}. \tag{3.5}$$

HIV infected equilibrium point $\overline{E}(\overline{x}, \overline{y}, \overline{z})$ can be obtained by solving the following system of equations:

$$\begin{aligned} &r - d_1\overline{x} + a\overline{x}\left(1 - \frac{\overline{x}+\overline{y}}{x_{\max}}\right) - f\overline{zx} - (1-\gamma_r)\beta\overline{zx} + \rho\overline{y} = 0, \\ &(1-\gamma_r)\beta\overline{zx} - d_2\overline{y} - \rho\overline{y} = 0, \\ &(1-\gamma_p)Nd_2\overline{y} - d_3\overline{z} - f\overline{zx} = 0. \end{aligned} \tag{3.6}$$

Solving second and third equations of the system (3.6), we obtain

$$\overline{x} = \frac{d_3(d_2+\rho)}{(1-\gamma_r)(1-\gamma_p)Nd_2\beta - f(d_2+\rho)}.$$

Putting the value of $\overline{x}$ in the second equation, we get $\overline{y} = \frac{(1-\gamma_r)\beta d_3\overline{z}}{(1-\gamma_r)(1-\gamma_p)Nd_2\beta - f(d_2+\rho)}$.

Considering $(1-\gamma_r)(1-\gamma_p)Nd_2\beta - f(d_2+\rho) = p$ and putting values of $\overline{x}$ and $\overline{y}$ in the first equation of system (3.6), we get

$$\overline{z} = \frac{rp^2 + (a-d_1)(d_2+\rho)d_3p + \frac{ad_3^2(d_2+\rho)^2}{x_{\max}}}{pfd_3(d_2+\rho) + (1-\gamma_r)\beta pd_3d_2 + \frac{(1-\gamma_r)(d_2+\rho)ad_3^2\beta}{x_{\max}}}.$$

It can be shown that $\overline{z}$ possesses positive value only when basic reproduction number R_0 is greater than one. Therefore, we have following proposition.

Proposition 1. *The treatment model* (2.1) *possesses only HIV infection-free equilibrium* $E_0(x_0, 0, 0)$ *in* Ω *for basic reproduction number* $R_0 \leq 1$ *but whenever* $R_0 > 1$, *the model possesses an HIV infected equilibrium point* $\overline{E}(\overline{x}, \overline{y}, \overline{z}) \in \text{int}(\Omega)$ *along with HIV infection-free equilibrium* E_0.

3.3. *Stability analysis of HIV infection-free equilibrium point*

In this section, we will study the stability of HIV infection-free equilibrium point E_0 of our treatment model (2.1). The following result for local stability of the HIV infection-free equilibrium point E_0 is obtained by analyzing the characteristic equations, which is also used in different earlier studies [10, 12, 18, 20, 21].

Theorem 1. *The HIV infection-free equilibrium point* E_0 *of the treatment model* (2.1) *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. We have linearized our model (2.1) around HIV infection-free equilibrium E_0 and found the Jacobian matrix J_0 as follows

$$J_0 = \begin{pmatrix} -d_1 + a - \dfrac{2ax_0}{x_{\max}} & \rho - \dfrac{ax_0}{x_{\max}} & -fx_0 - (1-\gamma_r)\beta x_0 \\ 0 & -d_2 - \rho & (1-\gamma_r)\beta x_0 \\ 0 & (1-\gamma_p)Nd_2 & -d_3 - fx_0 \end{pmatrix}. \tag{3.7}$$

One of the eigenvalues of the Jacobian matrix J_0 is

$$\lambda_1 = -d_1 + a - \frac{2ax_0}{x_{\max}} = -\frac{r}{x_0} - \frac{ax_0}{x_{\max}} < 0.$$

Other two eigenvalues are given by the equation

$$\lambda^2 + A_1\lambda + A_2 = 0, \tag{3.8}$$

where

$$\begin{aligned} A_1 &= d_2 + d_3 + \rho + fx_0 > 0, \\ A_2 &= (d_2 + \rho)(d_3 + fx_0) - (1-\gamma_r)(1-\gamma_p)Nd_2\beta x_0 \\ &= (d_2 + \rho)(d_3 + fx_0)(1 - R_0). \end{aligned}$$

It is observed that sum of the roots of Eq. (3.8) is negative. Also, product of the roots (A_2) is positive whenever $R_0 < 1$. So, the roots of Eq. (3.8) are negative for $R_0 < 1$. Already, it is shown that one characteristic root (λ_1) of the Jacobian matrix J_0 is negative. Hence, all characteristic roots of J_0 are negative if $R_0 < 1$, implying that E_0 is locally asymptotically stable for $R_0 < 1$. Clearly, the Jacobian matrix J_0 has a positive characteristic root for $R_0 > 1$ which implies that E_0 is unstable for $R_0 > 1$. This completes the proof. □

Following some earlier works [10, 12, 18], we have used Lyapunov functionals and LaSalle's invariance principle [47] to obtain the below mentioned result for global stability of HIV infection-free equilibrium point E_0.

Theorem 2. *The HIV infection-free equilibrium point E_0 is globally asymptotically stable for $R_0 \leq 1$ and unstable for $R_0 > 1$.*

Proof. Define Lyapunov's functional as

$$\bar{L} = \frac{(1-\gamma_p)Nd_2}{d_2+\rho}y + z. \tag{3.9}$$

Differentiating (3.9) with respect to t, we obtain

$$\frac{d\bar{L}}{dt} = \frac{(1-\gamma_p)Nd_2}{d_2+\rho}\frac{dy}{dt} + \frac{dz}{dt}. \tag{3.10}$$

Now, by substituting the values of $\frac{dy}{dt}$ and $\frac{dz}{dt}$ from system (2.1), we obtain

$$\frac{d\bar{L}}{dt} = z(d_3+fx)\left[\frac{(1-\gamma_r)(1-\gamma_p)Nd_2\beta x}{(d_2+\rho)(d_3+fx)} - 1\right] \leq z(d_3+fx_0)(R_0-1). \tag{3.11}$$

From Eq. (3.11), it is clear that $\frac{d\bar{L}}{dt} \leq 0$ for $R_0 \leq 1$. By defining the set

$$S = \left\{(x,y,z) \in \Omega : \frac{d\bar{L}}{dt} = 0\right\},$$

we can use Lyapunov–Lassale's invariance principle [47], which indicates that all curves in Ω approach toward the maximum invariance subset of S while t approaches to ∞. The only two cases which satisfy the condition $\frac{d\bar{L}}{dt} = 0$ are $z = 0$ or $R_0 = 1$ and $x = x_0$ and the maximum invariant subset of S in both cases is $\{E_0\}$. Hence, the HIV infection-free equilibrium point E_0 is globally asymptotically stable for $R_0 \leq 1$.

It is already observed that the Jacobian matrix J_0 has a positive eigenvalue for $R_0 > 1$ which implies the instability of E_0 in this case. □

3.4. *Critical efficacy for the combined antiretroviral therapies*

In the model (2.1), we introduced the terms $(1-\gamma_r)$ and $(1-\gamma_p)$ with $\gamma_r, \gamma_p \in [0,1]$ in order to incorporate the efficacies of the antiretroviral therapies or treatments namely RTIs and PIs, respectively. The situation $\gamma_r = \gamma_p = 0$ represents no antiretroviral therapies and the situation $\gamma_r = \gamma_p = 1$ represents complete effective antiretroviral therapies. The efficacy of overall treatment [48] while both RTIs and PIs are administrated together is given by

$$\gamma = 1 - (1-\gamma_r)(1-\gamma_p). \tag{3.12}$$

From stability criterion of the HIV infection-free equilibrium point E_0, we obtain that HIV is completely cured for $R_0 < 1$, which is equivalent to

$$(1-\gamma_r)(1-\gamma_p) < \frac{(d_2+\rho)(d_3+fx_0)}{Nd_2\beta x_0}$$

$$\implies \gamma > 1 - \frac{(d_2+\rho)(d_3+fx_0)}{Nd_2\beta x_0}.$$

Similarly, the condition $R_0 > 1$ for existence of HIV-infected equilibrium point is equivalent to

$$\gamma < 1 - \frac{(d_2+\rho)(d_3+fx_0)}{Nd_2\beta x_0}.$$

Therefore, we obtain a transcendental bifurcation point at $\gamma = 1 - \frac{(d_2+\rho)(d_3+fx_0)}{Nd_2\beta x_0}$ and define it as critical efficacy for combined antiretroviral therapies

$$\gamma_{\text{crit}} = 1 - \frac{(d_2+\rho)(d_3+fx_0)}{Nd_2\beta x_0}.$$

Thus, HIV can be eliminated for combined antiretroviral therapies with efficacy $\gamma > \gamma_{\text{crit}}$ and HIV-infected equilibrium point exists for $\gamma < \gamma_{\text{crit}}$. Therefore, our main objective is to choose RTIs, and PIs efficacies γ_r and γ_p such that the overall treatment efficacy γ must satisfy the condition $\gamma > \gamma_{\text{crit}}$. But it is also important to avoid excessive use of drugs due to their different side effects and costs. So, we have formulated an optimal control problem in the next section to control HIV infection by using minimum doses of antiretroviral drugs.

4. The Optimal Control Problem

Generally, an optimal control problem for a treatment model has three main parts: an objective function, a set of state variables and a set of treatments or drugs. When solving an optimal control problem, the objective function has to be optimized using optimal combinations of therapies in time t, $0 \le t \le t_f$ where t_f is the time for which treatment is being administrated.

In our study, we have considered the following objective functional:

$$J(x, \gamma_r, \gamma_p) = \int_0^{t_f} \left\{ x(t) - \left(\frac{A_1}{2}\gamma_r^2 + \frac{A_2}{2}\gamma_p^2 \right) \right\} dt, \tag{4.1}$$

which have to maximize by increasing the concentration of healthy $CD4^+$ T cells, reducing the number of free HIV and minimizing the side effects and costs of the treatments. In Eq. (4.1), the positive constants A_1 and A_2 represent the relative weights attached to benefits and costs of the treatments and t_f is the time period for which the treatment is administrated. Thus, our main objective is to find an optimal control pair (γ_r^*, γ_p^*) for our problem such that

$$J(\gamma_r^*(t), \gamma_p^*(t)) = \max_{(\gamma_r^*(t), \gamma_p^*(t)) \in \Gamma} J(\gamma_r(t), \gamma_p(t)), \tag{4.2}$$

subject to the state constraints (2.1) and initial conditions (2.2). Here, Γ is the control set defined by

$$\Gamma = \{\gamma = (\gamma_r, \gamma_p) : \gamma_r, \gamma_p \text{ are measurable}, 0 \leq \gamma_r, \gamma_p \leq 1, 0 \leq t \leq t_f\}. \quad (4.3)$$

4.1. *Existence of optimal control pair*

Now, our first target is to show the existence of optimal control, which can maximize the objective function (4.1) and then we will find the pair of optimal control. In order to show the existence of optimal control pair, we have used the methods from different earlier studies [29, 49–51] and present the following theorem.

Theorem 3. *Consider the treatment model* (2.1) *with a pair of controls* γ_r *and* γ_p. *Then, there exists an optimal control pair* $(\gamma_r^*, \gamma_p^*) \in \Gamma$ *such that*

$$J(\gamma_r^*, \gamma_p^*) = \max_{(\gamma_r^*(t), \gamma_p^*(t)) \in \Gamma} J(\gamma_r(t), \gamma_p(t)).$$

Proof. In order to use the results of Fleming and Rishel [50], we need to check the following properties:

(P1) The set of controls and corresponding state variables are non-empty.
(P2) The control set Γ is convex and closed.
(P3) The right-hand side of the state system is bounded by a linear function in the state and control variables.
(P4) The integral of the objective function is concave on Γ.
(P5) There exist constants c_1 and $c_2 > 0$ and $k > 0$ such that the integrand $L(x, \gamma_r, \gamma_p)$ of the objective functional satisfies

$$L(x, \gamma_r, \gamma_p) \leq c_2 - c_1(|\gamma_r|^2 + |\gamma_p|^2)^{\frac{k}{2}},$$

where

$$L(x, \gamma_r, \gamma_p) = x(t) - \left\{ \frac{A_1}{2}\gamma_r^2(t) + \frac{A_2}{2}\gamma_p^2(t) \right\}.$$

The condition (P1) can be verified using Lemmas 1 and 2. For all admissible controls in the set Γ, Lemma 2 indicates the continuity and boundedness of the solutions of the model (2.1), whereas the existence of a unique non-negative solution for the system (2.1) is implied by Lemma 1. Therefore, the system (2.1) with the initial conditions (2.2) has a unique solution for corresponding control function $\gamma \in \Gamma$ which verifies the condition (P1). From the definition, it is clear that the control set Γ is convex and closed. So, (P2) is satisfied. Using boundedness of the solution, we can state the right-hand side of the system (2.1) satisfies condition (P3) as the system is bilinear in the controls γ_r and γ_p.

Now, the concavity of the integrand function $L(x, \gamma_r, \gamma_p)$ can be tested by determining the Hessian matrix. The Hessian matrix H_L for the integrand $L(x, \gamma_r, \gamma_p)$

is given by

$$H_L = \begin{bmatrix} L_{\gamma_r\gamma_r} & L_{\gamma_r\gamma_p} \\ L_{\gamma_p\gamma_r} & L_{\gamma_p\gamma_p} \end{bmatrix} = \begin{bmatrix} -A_1 & 0 \\ 0 & -A_2 \end{bmatrix}.$$

$\mathrm{Det}(H_L) = A_1A_2 > 0$ for all $(\gamma_r, \gamma_p) \in \Gamma$. Therefore, D-test implies that the integrand L is concave for all $\gamma_r, \gamma_p \in \Gamma$ i.e. the integrand L is concave in Γ. Therefore, the condition (P4) is satisfied.

From the expression of the integrand L, we have

$$L(x, \gamma_r, \gamma_p) \leq c_2 - c_1(|\gamma_r|^2 + |\gamma_p|^2),$$

where c_2 depends on upper bound of x and $c_1 = \min\{\frac{A_1}{2}, \frac{A_2}{2}\} > 0$. So, the condition (P5) is satisfied with $k = 2$. Therefore, we can conclude that there exists an optimal control pair $(\gamma_r^*, \gamma_p^*) \in \Gamma$ such that

$$J(\gamma_r^*, \gamma_p^*) = \max_{(\gamma_r^*(t), \gamma_p^*(t)) \in \Gamma} J(\gamma_r(t), \gamma_p(t)).$$

□

4.2. *Optimality conditions*

Now, we will apply Pontryagin's maximum principle [52] in order to find the necessary conditions for optimal control problem. In order to apply this principle, the Hamiltonian H associated with the system (2.1) which has to be maximized pointwisely with respect to γ_r and γ_p, is defined as

$$H(t, \gamma_r, \gamma_p, x, y, z, \theta_1, \theta_2, \theta_3) = L(x, \gamma_r, \gamma_p) + \theta_1 \frac{dx(t)}{dt} + \theta_2 \frac{dy(t)}{dt} + \theta_3 \frac{dz(t)}{dt}, \tag{4.4}$$

where $\frac{dx(t)}{dt}$, $\frac{dy(t)}{dt}$, $\frac{dz(t)}{dt}$ can be obtained from the model equations (2.1) and θ_1, θ_2, θ_3 are adjoint functions to be determined. Application of Pontryagin's Maximum principle [52] gives rise to the following theorem.

Theorem 4. *For a given pair of optimal controls (γ_r^*, γ_p^*) with associated optimal solutions x^*, y^*, and z^* to the model* (2.1)*, there exist adjoint variables θ_1, θ_2, and θ_3 which satisfy the conditions*

$$\begin{aligned}
\frac{d\theta_1}{dt} &= -1 + \theta_1 d_1 - a\theta_1 \left(1 - \frac{2x^* + y^*}{x_{\max}}\right) + (\theta_1 + \theta_3) f z^* + (\theta_1 - \theta_2)(1 - \gamma_r^*)\beta z^*, \\
\frac{d\theta_2}{dt} &= -\rho\theta_1 + \frac{ax^*}{x_{\max}}\theta_1 + (d_2 + \rho)\theta_2 - (1 - \gamma_p^*) N d_2 \theta_3, \\
\frac{d\theta_3}{dt} &= f x^* \theta_1 + (\theta_1 - \theta_2)(1 - \gamma_r^*)\beta x^* + \theta_3(d_3 + f x^*),
\end{aligned} \tag{4.5}$$

with transversality conditions

$$\theta_1(t_f) = \theta_2(t_f) = \theta_3(t_f) = 0. \tag{4.6}$$

Moreover, the optimal controls are given by

$$\gamma_r^* = \min\left\{\max\left\{0, \frac{(\theta_1-\theta_2)\beta z^* x^*}{A_1}\right\}, 1\right\}, \tag{4.7}$$

$$\gamma_p^* = \min\left\{\max\left\{0, \frac{-\theta_3 N d_2 y^*}{A_2}\right\}, 1\right\}. \tag{4.8}$$

Proof. We can obtain adjoint equations and transversality conditions using Pontryagin's maximum principle [52] such that

$$\begin{aligned}
\frac{d\theta_1}{dt} &= -\frac{\partial H}{\partial x} = -1 + \theta_1 d_1 - a\theta_1\left(1 - \frac{2x+y}{x_{\max}}\right) + (\theta_1+\theta_3) fz \\
&\quad + (\theta_1-\theta_2)(1-\gamma_r)\beta z, \\
\frac{d\theta_2}{dt} &= -\frac{\partial H}{\partial y} = -\rho\theta_1 + \frac{ax}{x_{\max}}\theta_1 + (d_2+\rho)\theta_2 - (1-\gamma_p) N d_2 \theta_3, \\
\frac{d\theta_3}{dt} &= -\frac{\partial H}{\partial z} = fx\theta_1 + (\theta_1-\theta_2)(1-\gamma_r)\beta x + \theta_3(d_3+fx).
\end{aligned}$$

The transversality conditions are

$$\theta_1(t_f) = 0, \quad \theta_2(t_f) = 0, \quad \theta_3(t_f) = 0.$$

To obtain the optimal control pair γ_r^* and γ_p^*, we have to solve the following equations:

$$\frac{\partial H}{\partial \gamma_r} = -A_1\gamma_r + (\theta_1-\theta_2)\beta z x = 0, \quad \frac{\partial H}{\partial \gamma_p} = -A_2\gamma_p - \theta_3 N d_2 y = 0.$$

Using the bounds of the controls γ_r and γ_p, we get the optimal controls γ_r^* and γ_p^* as follows:

$$\gamma_r^* = \begin{cases} 0, & \text{if } \dfrac{(\theta_1-\theta_2)\beta z^* x^*}{A_1} \le 0 \\ \dfrac{(\theta_1-\theta_2)\beta z^* x^*}{A_1}, & \text{if } 0 < \dfrac{(\theta_1-\theta_2)\beta z^* x^*}{A_1} < 1 \\ 1, & \text{if } \dfrac{(\theta_1-\theta_2)\beta z^* x^*}{A_1} \ge 1 \end{cases} \tag{4.9}$$

and

$$\gamma_p^* = \begin{cases} 0, & \text{if } \dfrac{-\theta_3 N d_2 y^*}{A_2} \le 0 \\ \dfrac{-\theta_3 N d_2 y^*}{A_2}, & \text{if } 0 < \dfrac{-\theta_3 N d_2 y^*}{A_2} < 1 \\ 1, & \text{if } \dfrac{-\theta_3 N d_2 y^*}{A_2} \ge 1 \end{cases} \tag{4.10}$$

which can be also written in the form as given in (4.7) and (4.8). □

5. Numerical Simulations

In this section, we numerically verified the results of the HIV treatment model (2.1) and also discussed the consequences of the implementation of combined antiretroviral therapies in the form of RTIs and PIs. Also, we numerically solved the optimal control problem defined in the earlier section. For the simulations, we considered the parameter values given in Table 1 and the initial values as $x_0 = 1000$ cells/mm^3, $y_0 = 10$ cells/mm^3, and $z_0 = 100$ virions/mm^3. These initial values are consistent with the data of HIV-infected individuals at clinical stage 1.

Consider the treatments parameters as $\gamma_r = 0.55$, $\gamma_p = 0.65$, and the values of other parameters from Table 1. Using the expression in Eq. (3.5), we have $R_0 = 0.920183 < 1$ and the overall efficacy for combined treatments $\gamma = 0.8425 > \gamma_{\text{crit}} = 0.828838$ for this parameter set in Table 1. So, Theorem 2 indicates global stability of the HIV infection-free equilibrium point $E_0(1047.72, 0, 0)$. For this, time series diagrams of the different populations of the model (2.1) are shown in Figs. 2(a)–2(c) which verify the above result numerically.

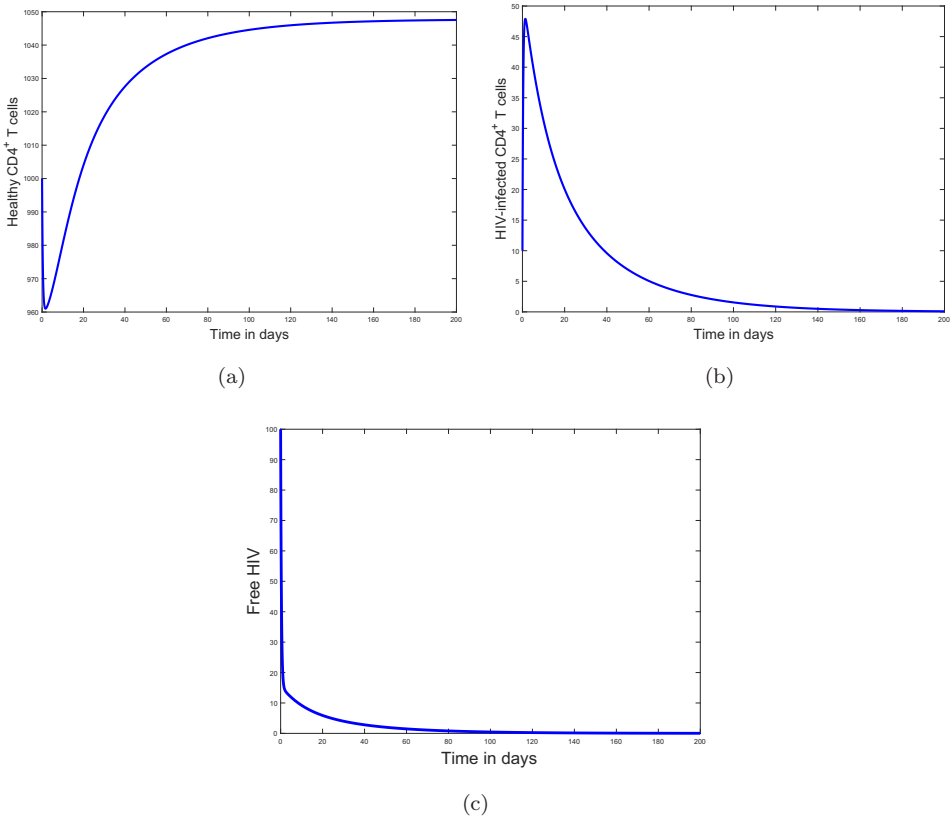

Fig. 2. Time series diagrams of the different populations of the model (2.1) for $R_0 = 0.920183 < 1$.

Now, we simulate the system using the same parameter set from Table 1 to understand the dynamics of the model due to the administration of combined antiretroviral therapies. Without therapies ($\gamma_r = \gamma_p = 0$), basic reproduction number is $R_0 = 5.84243 > 1$ for these parameter values. Now, we consider four different combined treatment scenarios with overall treatment efficacy γ =0.51, 0.75, 0.91, and 0.99 and compare the corresponding dynamics of the model populations. Incorporating RTIs and PIs in the equal proportion, we have $\gamma_r = \gamma_p$ =0.3, 0.5, 0.7, and 0.9, respectively, for these four combined treatment scenarios. Time series curves of healthy and HIV-infected CD4$^+$ T cells along with free virions without any treatment and with treatments for these four different overall efficacies are shown in Figs. 3(a)–3(c). From Fig. 3(a), we observe that in the absence of any treatment, healthy CD4$^+$ T cells count decreases drastically during the first 10 days, and after approximately 60 days, it goes to the equilibrium state, which is less than 200 cells per mm^3. Healthy CD4$^+$ T cells count can be improved by increasing overall treatment efficacy. Figures 3(b) and 3(c) depict that without any treatment, HIV-infected CD4$^+$ T cells along with free HIV count increase rapidly during the first

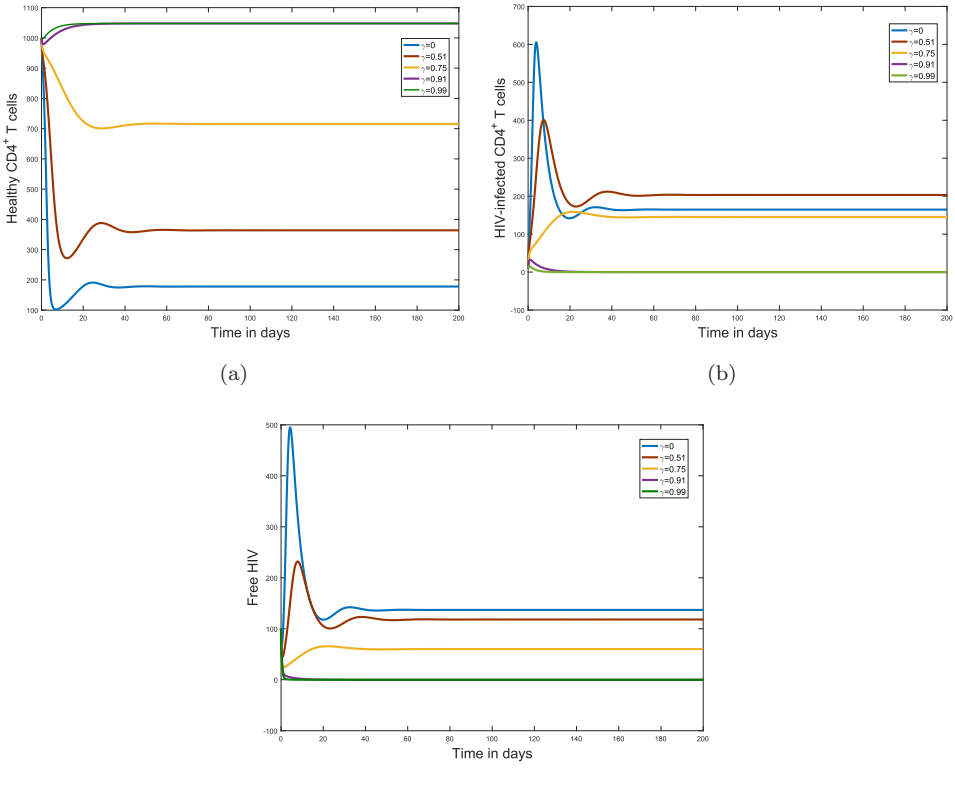

Fig. 3. Dynamics of (a) HIV infection-free CD4$^+$ T cells, (b) HIV-infected CD4$^+$ T cells and (c) Free HIV versus time for different overall treatment efficacies (γ).

10 days and then approach the equilibrium states indicating the symptomatic stage of HIV infection. But we can control the production of HIV-infected CD4$^+$ T cells and free HIV by increasing overall treatment efficacy and HIV is eliminated if the overall treatment efficacy (γ) satisfies the condition $\gamma > \gamma_{\text{crit}}$.

In order to investigate the effectiveness of different combinations of RTIs and PIs, we fix $\gamma_r = 0.5$ and consider four different PIs efficacies $\gamma_p = 0.3$, 0.5, 0.7 and 0.9. We have overall treatment efficacy $\gamma = 0.65, 0.75, 0.85$ and 0.95, respectively, for these four treatment combinations. For the first two treatment combinations, overall efficacies are less than critical treatment efficacy $\gamma_{\text{crit}} = 0.828838$, and the overall efficacies exceed the critical efficacy $\gamma_{\text{crit}} = 0.828838$ in the latter two combinations. The dynamics of the model populations for the first 200 days of treatment are shown in Figs. 4(a)–4(c), considering all these combinations. From Fig. 4(a), it is observed that healthy CD4$^+$ T cells level decreases during the initial days of treatment and then goes to the equilibrium state if the overall treatment efficacy is less than critical efficacy. The number of initial days while the healthy CD4$^+$ T cells count

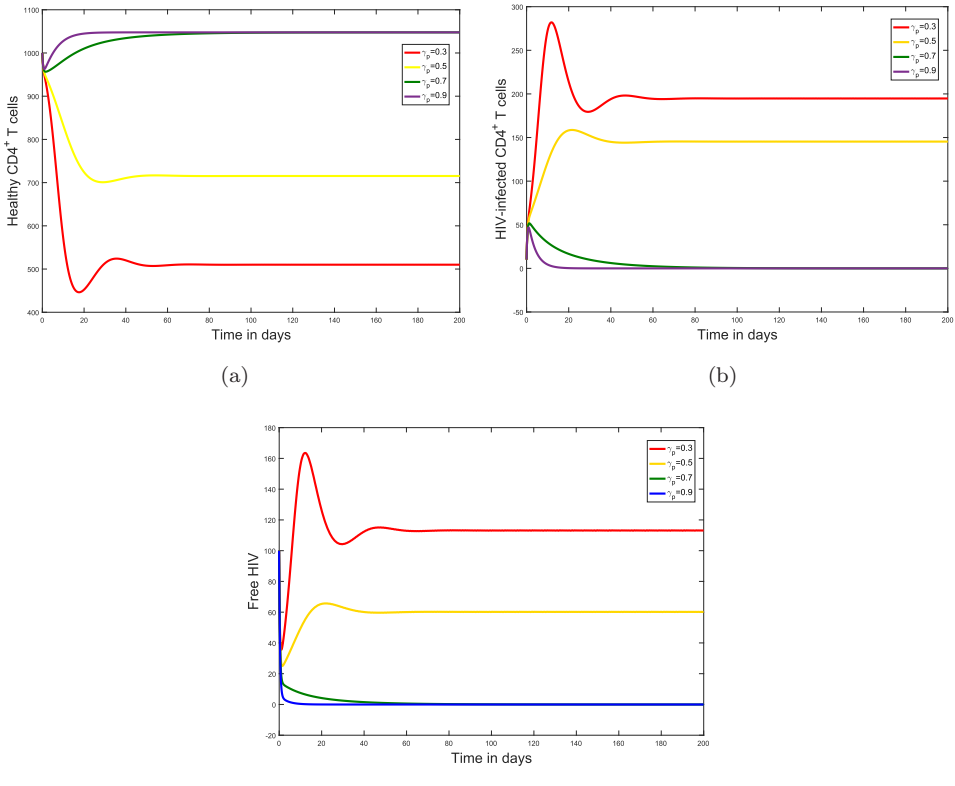

Fig. 4. Dynamics of (a) HIV infection-free CD4$^+$ T cells, (b) HIV-infected CD4$^+$ T cells and (c) Free HIV versus time for different values of γ_p with $\gamma_r = 0.5$.

decreases can be minimized, and the steady-state level of healthy CD4$^+$T cells can be improved by increasing the efficacy of PIs while RTIs efficacy is constant. Similarly, Figs. 4(b) and 4(c) describe that both HIV-infected CD4$^+$ T cells and free HIV increases during the first days of treatment and then goes to steady states if overall treatment efficacy is less than critical efficacy. But HIV-infected cells and free HIV can be eliminated after some days of treatment by increasing PIs efficacy so that the overall efficacy exceeds the critical efficacy. Similar behavior of the model populations can be observed if we fix $\gamma_p = 0.5$ and vary RTIs efficacies $\gamma_r = 0.3$, 0.5, 0.7, and 0.9. We presented these results in Figs. 5(a)–5(c). Also, we observe that the behavior of healthy and HIV-infected CD4$^+$ T cells is almost the same for a fixed overall efficacy with different composition (γ_r, γ_p) of RTIs and PIs. But in the case of overall efficacy $\gamma = 0.51$, free HIV is controlled more effectively by the composition $(0.3, 0.5)$ as compared to $(0.5, 0.3)$. Thus, PIs are more effective as compared to RTIs in combined treatment strategy.

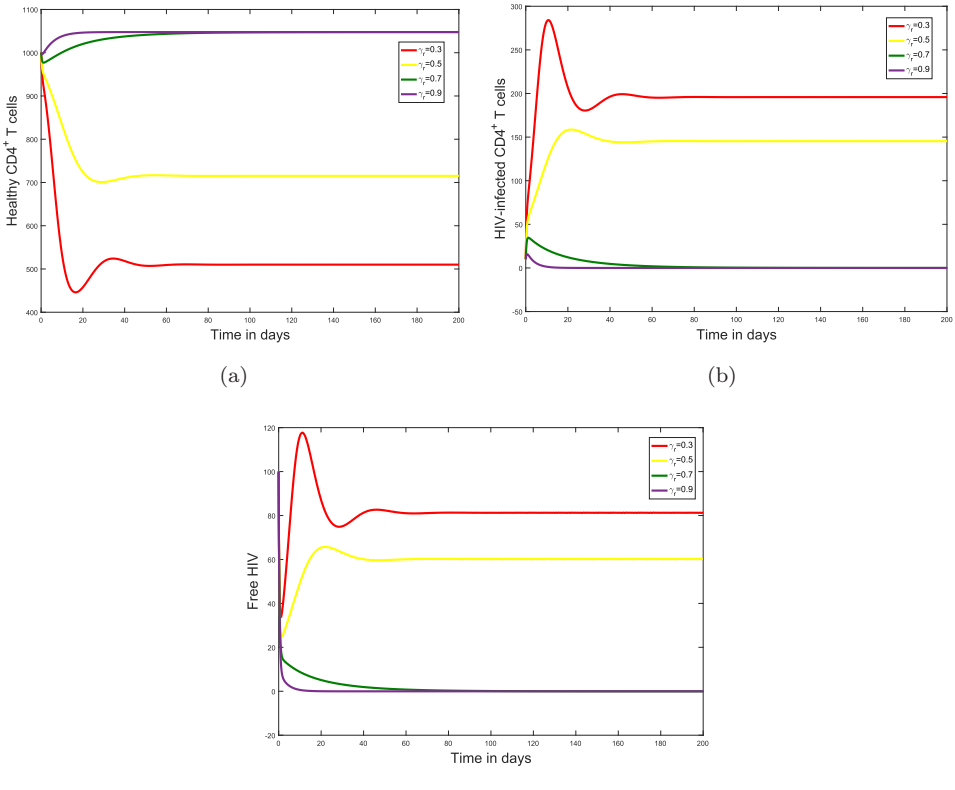

Fig. 5. Dynamics of (a) HIV infection-free CD4$^+$ T cells, (b) HIV-infected CD4$^+$ T cells and (c) Free HIV versus time for different values of γ_r with $\gamma_p = 0.5$.

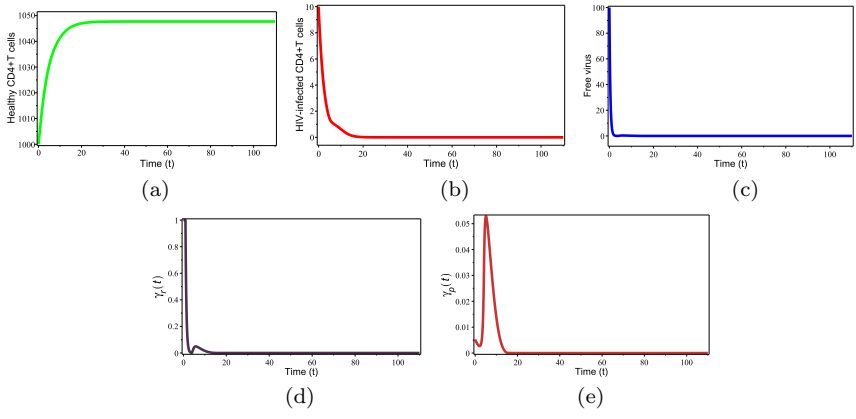

Fig. 6. Dynamics of (a) HIV infection-free CD4$^+$ T cells; (b) HIV-infected CD4$^+$ T cells; (c) Free HIV during treatment; (d) The optimal control γ_r^*; (e) The control γ_p^* for a treatment period of 100 days.

The above discussion shows that HIV can be eliminated by implementing combined antiretroviral therapies with overall efficacy greater than the critical efficacy. In order to find an optimal combination of therapies that can eliminate HIV effectively with fewer side effects, we proposed an optimal control problem and obtained the conditions for the existence of optimal pair of therapies in Sec. 4. We solved the problem numerically using a forward–backward iterative method to find the optimal combination of therapies. We considered the values of weight functions as $A_1 = A_2 = 150$ with all other parameters from Table 1 and performed numerical simulations to observe the dynamics of model populations after introducing the combined antiretroviral therapies for 100 days. Figures 6(a)–6(e) describe the dynamics of healthy CD4$^+$ T cells (x), HIV-infected CD4$^+$ T cells (y), and free HIV (z) after initiating optimal combined antiretroviral therapies along with the change of optimal treatments γ_r and γ_p with time for blocking new infections.

We already observed in Fig. 3 that without any treatment, healthy CD4$^+$ T cells count decreases during initial days of infection and approaches to a steady-state with count < 200 cells/mm^3. Similarly, HIV-infected CD4$^+$ T cells count and free HIV load increase without treatment and hence the infection lead to clinical stage 4 or AIDS, which is symptomatic and the most advanced stage of HIV infection. But Fig. 6(a) shows that healthy CD4$^+$ T cells count increases from the initial day of treatment and goes to a steady state after almost 30 days of treatment with optimal doses of antiretroviral drugs. Figure 6(b) depicts that HIV-infected CD4$^+$ T cells' count decreases and goes to zero level after almost 20 days of treatment. From Fig. 6(c), it is observed that HIV load declines drastically and goes to zero level after 4–5 days of treatment due to the administration of optimal treatments. The optimal controls $\gamma_r^*(t)$ and $\gamma_p^*(t)$ for the treatment period are shown in Figs. 6(d)–6(e).

6. Conclusion

This paper has incorporated the effects of combined antiretroviral therapies (RTIs and PIs) to a within-host mathematical model for HIV infection with cure rate and fusion effect. The basic properties of the model, like non-negativity and boundedness of the solutions, are verified to check the biological feasibility of the model. Also, the basic reproduction number of the model is calculated using the next-generation matrix method. For our model, we found two biologically feasible equilibrium points: HIV infection-free and HIV-infected equilibrium points. We then obtained sufficient conditions for the stability of HIV infection-free equilibrium point. The stability results imply that HIV is eradicated for $R_0 < 1$. Also, we found a critical efficacy γ_{crit} for combined therapies such that HIV is eradicated from the body of infected individuals for overall treatment efficacy $\gamma > \gamma_{\text{crit}}$. From numerical simulations, we observed that HIV-infected $CD4^+$ T cells count and viral load can be controlled by increasing the overall treatment efficacy, which can be executed either by increasing the efficacies of both antiretroviral drugs or by increasing the efficacy of only one therapy and keeping the other constant. Moreover, it is verified that PIs are more effective than RTIs by means of simulations of the model under consideration. Further, we proposed an optimal control problem to find an optimal combination of antiretroviral therapies which can block new infection and maximize healthy $CD4^+$ T cells count with minimum cost and side effects of these antiretroviral therapies. We proved the existence of optimal control pair and found the optimality conditions using Pontryagin's maximum principle. Then, the problem is solved numerically using a forward-backward iterative method and found an optimal combination of RTIs and PIs that can eliminate HIV after a treatment period. Overall, this study facilitates a critical efficacy γ_{crit} and an optimal combination of the antiretroviral therapies in the presence of both fusion effects and cure rate, which would be useful for the clinicians in developing improved protocols to control HIV infection in the human body.

We incorporated the cure rate and fusion effect along with the effects of antiretroviral drugs (RTIs and PIs) in this paper to improve HIV infection. However, the effect of HIV-specific cytotoxic T lymphocyte cells is not considered here. Thus, the dynamics of the model (2.1) with the effect of cytotoxic T lymphocyte cells can be studied in future to get insight into the immune system's responses against HIV infection. Moreover, the effects of multiple delays like intracellular, pharmacological delays can be incorporated into the model (2.1) to study their effects on the dynamics of the model.

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