Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2026, 2026:73
https://doi.org/10.28919/cmbn/9983
ISSN: 2052-2541

ADAPTIVE IMMUNE RESPONSE IN HIV DYNAMICS: AN OPTIMAL CONTROL STUDY

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Abstract This research aims to optimize the control of an HIV infection model. The focus of this paper is on optimizing the control of an HIV infection model. Our mathematical model consists of six non-linear differential equations that illustrate what happens when uninfected cells, exposed cells, actively infected cells, free viruses, and the adaptive immune response interact. Furthermore, adaptive immunity will be characterized by cytotoxic T-lymphocytes (CTLs) and antibodies. The two treatments illustrate how drug therapy can stop the replication of viruses and reduce the risk of new infections. We demonstrate the existence of an optimal control pair and we apply Pontryagin's minimal approach to delineate these two optimum controls. In the end, numerical simulations are used to show how important effective treatment is for keeping the infection under control.

Keywords: adaptive immune response; HIV infection; optimal control; treatment; viral dynamics; numerical simulations.

2020 AMS Subject Classification: 92D30, 92C60, 49K15, 37N25, 65L06.

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Received May 15, 2026

1. INTRODUCTION

According to data from the World Health Organization, 36.7 million people are infected with the human immunodeficiency virus (HIV) [1], which is a virus that makes the body's defenses against infections weaker, what causes death after only years. The HIV life cycle begins when it attaches to the CD4 cell and transfers into its proteins and genetic material, then through specific enzymes the HIV Ribonucleic acid (RNA) converts into deoxyribonucleic acid (DNA) and integrates with the DNA of the CD4 cell hote to release new virus into the body [2]. Currently, the HIV virus cannot be completely eradicated by any treatment ; Nevertheless, medications such as protease inhibitors (PIs) and reverse transcriptase inhibitors (RTIs) can reduces replication of virus by interrupting stages of the HIV life cycle [3]. The challenge remains to determine the appropriate dosage of the drug that gives optimal results with a minimum of adverse effects. This paper is based on the work [4] where we will present therapies v_1 and v_2, which stand for the effectiveness of therapy in preventing viral generation and avoiding new infections. Our model is therefore as follows:

$$
\begin{cases}
\dfrac{dA(t)}{dt} = \delta - d_1 A(t) - \dfrac{(1-v_1(t))k_1 A(t)D(t)}{A(t)+D(t)}, \\
\dfrac{dB(t)}{dt} = \dfrac{(1-v_1(t))k_1 A(t)D(t)}{A(t)+D(t)} - d_2 B(t) - k_2 B(t), \\
\dfrac{dC(t)}{dt} = k_2 B(t) - d_3 C(t) - \rho C(t)F(t), \\
\dfrac{dD(t)}{dt} = (1-v_2(t))aC(t) - d_4 D(t) - \theta D(t)E(t), \\
\dfrac{dE(t)}{dt} = \psi D(t)E(t) - \omega E(t), \\
\dfrac{dF(t)}{dt} = cC(t)F(t) - bF(t).
\end{cases}
\tag{1.1}
$$

With the initial conditions $A(0) = A_0$, $B(0) = B_0$, $C(0) = C_0$, $D(0) = D_0$, $E(0) = E_0$ and $F(0) = F_0$. In this model, The letters A, B, C, D, E, and F stand for the concentrations of uninfected cells, exposed cells, infected cells, free viruses, antibodies, and CTL cells, respectively.

The production rate of susceptible host cells CD4+T cells is δ, their death rate is $d_1 A$, and their viral infection rate is $\dfrac{k_1 AD}{A+D}$.

Exposed cells are assumed to die at a rate proportional to $(d_2 + k_2)B$. The infected cells multiply at rate of k_2B, degrade at d_3C, get eliminated by the CTL response at ρCF.

Infected cells create free virus at a rate of aC, which decays at a rate of d_4D. Antibodies destroy the virus at a rate of θDE. The rate at which antibodies form in response to free viruses is ψDE, and their rate of decay is ωE. Ultimately, cytotoxic T lymphocytes proliferate in reaction to viral antigens originating from infected cells at a rate of cCF and diminish at a rate of bF when antigenic stimulus is not present. It should be noted that this model incorporates the saturated rate, also known as the saturated mass action [5], which more accurately depicts the viral infection rate. The rest of the document is structured as follows. In section 2 we present an examination of the model. In section 3 we provide numerical simulations to demonstrate the impact of optimal drug doses. We summarize our findings in the concluding section.

2. Exploration of the Model's Positivity and Boundedness

According to classical functional differential equations theory [6], we can confirm the existence of a unique local solution to system 1.1, in the interval $[0;t_m)$, for any time $t_m > 0$.
Due to biological considerations, the parameters A_0, B_0, C_0, D_0, E_0 and F_0 must be non-negative. Therefore, we have the theorem below:

Theorem 2.1. *The solution of model* (1.1) *is positive and bounded for all positive initial conditions.*

Proof. To show the positivity we consider

$$\begin{cases} \frac{dA(t)}{dt}|_{A=0} = \delta \geq 0, \\ \frac{dB(t)}{dt}|_{B=0} = \frac{(1-v_1(t))k_1A(t)D(t)}{A(t)+D(t)} \geq 0, \\ \frac{dC(t)}{dt}|_{C=0} = k_2B(t) \geq 0, \\ \frac{dD(t)}{dt}|_{D=0} = (1-v_2(t))aC(t) \geq 0, \\ \frac{dE(t)}{dt}|_{E=0} = 0 \geq 0, \\ \frac{dF(t)}{dt}|_{F=0} = 0 \geq 0. \end{cases} \tag{2.1}$$

Which proves that the solution is positive for $t \in [0, t_m)$. To examine the boundedness, let us consider:

$$M = A + B + C + \frac{\rho}{c}F$$

then, we have

$$\begin{aligned} \frac{dM}{dt} &= \delta - d_1 A - d_2 B - d_3 C - \frac{b\rho}{c}F \\ &\leq \delta - \zeta M. \end{aligned} \tag{2.2}$$

So that:

$$\begin{aligned} M(t) &\leq M(0)e^{-\zeta t} + \frac{\delta}{\zeta}(1 - e^{-\zeta t}) \\ &\leq M(0)e^{-\zeta t} + \frac{\delta}{\zeta}. \end{aligned}$$

Where $\zeta = min(d_1, d_2, d_3, b)$. Similarly, we consider

$$N = D + \frac{\theta}{\psi}E$$

therefore

$$\begin{aligned} \frac{dN}{dt} &= aC - d_4 D - \frac{\omega\theta}{\psi}E \\ &\leq (1 - v_2)aC - \beta N, \end{aligned}$$

where $\beta = min(d_4, \omega)$, then,

$$N(t) \leq N(0) + \frac{(1 - v_2)a}{\beta}\|C\|_\infty.$$

This demonstrates that the solutions $A(t)$, $B(t)$, $C(t)$, $D(t)$, $E(t)$ and $F(t)$ are bounded. Consequently, Every local solution has a global existence as it may be extended to any time $t_m > 0$.

3. THE OPTIMAL CONTROL SYSTEM

Our focus now is on exploring the situation when treatments are administered to infectious individuals. Our objective is to minimize both infection rates and the related treatment costs. The objective function we aim to minimize is:

$$J(v_1, v_2) = \frac{1}{2}\int_0^{t_f} (Q_1 B(t)^2 + Q_2 C(t)^2 + Q_3 D(t)^2 + A_1 v_1(t)^2 + A_2 v_2(t)^2)dt$$

Here, t_f denotes the duration of treatment, while A_1, A_2 represent the financial and physiological costs associated with administering the two treatments, respectively. The conditions $A_1 \geq 0, A_2 \geq 0$ indicate the level of toxicity of the drugs being used. It is assumed that the functions, $v_1(t)$ and $v_2(t)$, are Lebesgue integrable and bounded. The assumption that the pharmacological side effects have a nonlinear connection is represented by the quadratic variables $v_1^2(t)$ and $v_2^2(t)$ [7]. Our aim is to find the optimal control pair $(v_1^*; v_2^*)$ such that:

$$J(v_1^*, v_2^*) = min\{J(v_1, v_2) : (v_1, v_2) \in \mathbb{V}\}$$

where the set of admissible controls $\mathbb{V}$ is described as follows:

$$\mathbb{V} = \{((v_1, v_2) : v_i(t) measurable, a_i \leq v_i(t) \leq b_i, t \in [0, t_f], i = 1, 2\}$$

a_i and b_i ares the lower and the upper bounds on the therapeutic efficacy v_i $(i = 1; 2)$.

3.1. Existence of an Optimal Pair of Controls. We require the upper bounds of the state variables in order to show that the optimum system has an optimal control pair [8]. Note that the super-solutions $A(t)$; $B(t)$; $C(t)$; $D(t)$; $E(t)$ and $F(t)$ are uniformly bounded. To establish the existence of an optimal control pair, we use Fleming and Rishel's result (see Theorem 4.1, pp 68–69 in [9]).

Theorem 3.1. *There exists a pair of controls* $(v_1^*, v_2^*) \in \mathbb{V}$ *such that*

$$J(v_1^*, v_2^*) = min\{J(v_1, v_2) : (v_1, v_2) \in \mathbb{V}\}$$

Proof. The existence result from [9] is applied by confirming the following properties:

(P_1) The set consisting of controls and their associated states is not empty.

(P_2) The set $\mathbb{V}$, representing the controls, is convex and closed.

(P_3) The right-hand side of every equation in 1.1 is continuous, has an upper bound given by the sum of the bounded control and the state, and is linear in the control pair $(v_1; v_2)$ with coeffecients depending on time and state.

(P_4) The function $L(\vec{X}; \vec{v}; t)$ which appears in the objective functional, is convex over the set $\mathbb{V}$.

(P_5) The integrand $L(\vec{X}; \vec{v}; t)$ of the objective functional satisfies an inequality of the form

$$L(\vec{X}, \vec{u}, t) \geq -c_1 + c_2(|v_1|^2 + |v_2|^2)$$

where $L(\vec{X};\vec{v};t) = Q_1B^2 + Q_2C^2 + Q_3D^2 + A_1v_1^2 + A_2v_2^2$, $\vec{X} = (A,B,C,D,E,t)$, $\vec{v} = (v_1,v_2)$ and $c_1 \geq 0, c_2 \geq 0$.

(P_1) Under the boundedness condition of the state system governed by the two controls in 1.1, the existence of a solution is ensured. So (P_1) is verified.

(P_2) By definition, the control set is both closed and convex.

(P_3) the right-hand side of the each equation of 1.1 is continuous and can be written as:

$$\vec{f}(t,\vec{X},\vec{v}) = \vec{\phi}(t,\vec{X}) + \vec{\psi}(t,\vec{X})\vec{v}$$

$$|\vec{f}(t,\vec{X},\vec{v})| \leq c_0(1 + |\vec{X}| + |\vec{v}|)$$

where c_0 depends on the coefficients of the state system 1.1.

(P_4) Let $\vec{X} = (A,B,C,D,E,t)$ be the state vector and $\vec{v} = (v_1,v_2)$, $\vec{w} = (w_1,w_2)$ be two control vectors, we have for $0 \leq \varepsilon \leq 1$

$$\begin{aligned}
&L(\vec{X},(1-\varepsilon)\vec{v}+\varepsilon\vec{w},t) - (1-\varepsilon)L(\vec{X},\vec{v},t) - \varepsilon L(\vec{X},\vec{v},t)\\
=&Q_1B^2(t) + Q_2C^2(t) + Q_3D^2(t) + \sum_{i=1}^{2} A_i((1-\varepsilon)v_i(t) + \varepsilon w_i(t))^2\\
&-\frac{1}{2}(Q_1B^2(t) + Q_2C^2(t) + Q_3D^2(t) - \sum_{i=1}^{2} A_i((1-\varepsilon)(v_i(t))^2 + \varepsilon(w_i(t))^2)\\
=&-\sum_{i=1}^{2} A_i(1-\varepsilon)\varepsilon(v_i(t) - w_i(t))^2 \leq 0.
\end{aligned}$$

So (P_4) is proven.

(P_5) We have

$$\begin{aligned}
L(\vec{X},\vec{v},t) =& Q_1B^2 + Q_2C^2 + Q_3D^2 + A_1v_1^2 + A_2v_2^2\\
&\geq A_1v_1^2(t) + A_2v_2^2(t)\\
&\geq -c_1 + c_2(|v_1|^2 + |v_2|^2)
\end{aligned}$$

where $c_2 = min(A_1,A_2)$ and c_1 is any non-negative real number. What ends the demonstration

□

3.2. Necessary condition of optimality. The Lagrangian of our problem is defined as follows:

$$\begin{aligned}\mathscr{L}(t,A,B,C,D,E,F,v_1,v_2) =& \frac{1}{2}(Q_1B^2+Q_2C^2+Q_3D^2+A_1v_1^2+A_2v_2^2)+R^T.P\\ &-x_{11}(t)(b_1-v_1)-x_{12}(t)(v_1-a_1)\\ &-x_{21}(t)(b_2-v_2)-x_{22}(t)(v_2-a_2).\end{aligned}$$

With $R=\begin{pmatrix}\frac{dA(t)}{dt}\\ \frac{dB(t)}{dt}\\ \frac{dC(t)}{dt}\\ \frac{dD(t)}{dt}\\ \frac{dE(t)}{dt}\\ \frac{dF(t)}{dt}\end{pmatrix}$, $P=\begin{pmatrix}p_1\\ p_2\\ p_3\\ p_4\\ p_5\\ p_6\end{pmatrix}\in\mathbb{R}^6$.

And $x_{11}(t)$, $x_{12}(t)$, $x_{21}(t)$, $x_{22}(t)\geq 0$ are penalty multipliers satisfying $x_{11}(t)(b_1-v_1^*)=0$, $x_{12}(t)(v_1^*-a_1)=0$, $x_{21}(t)(b_2-v_2^*)=0$ *and* $x_{22}(t)(v_2^*-a_2)=0$. The following theorem is obtained by applying Pontryagin's minimum principle in state.

Theorem 3.2. *Given any optimal control pair v_1^*, v_2^* and the associated solutions A^*, B^*, C^*, D^*,E^*, F^* of the state system (1.1), there are adjoint variables p_1, p_2, p_3, p_4, p_5 and p_6 satisfying the system of equations below*

$$\begin{cases}\dot{p_1}(t)=p_1[d_1+(1-v_1^*(t))k_1\dfrac{D^{*2}}{(A^*+D^*)^2}]-p_2(1-v_1^*(t))k_1\dfrac{D^{*2}}{(A^*+D^*)^2},\\ \dot{p_2}(t)=-Q_1B^*+p_2(d_2+k_2)-p_3k_2,\\ \dot{p_3}(t)=-Q_2C^*+p_3(d_3+pF^*)-p_4(1-v_2^*)a-p_6cF^*,\\ \dot{p_4}(t)=-Q_3D^*+p_1(1-v_1^*(t))k_1\dfrac{A^{*2}}{(A^*+D^*)^2}-p_2(1-v_1^*(t))k_1\dfrac{A^*}{(A^*+D^*)^2}\\ \qquad\quad +p_4(d_4+\theta E^*)-p_5\psi E^*,\\ \dot{p_5}(t)=p_4\theta D^*+p_5(\omega-\theta D^*),\\ \dot{p_6}(t)=p_3\rho C^*+p_6(b-cC^*).\end{cases}\tag{3.1}$$

With the transversality conditions $p_i(t_f) = 0$ *for* $i = 0, ..., 6$

Additionally, the optimal control can be given by

$$v_1^* = \min(b_1, \max(a_1, \frac{1}{A_1}(p_2 - p_1)\frac{k_1 A^* D^*}{A^* + D^*}))$$

$$v_2^* = \min(b_2, \max(a_2, \frac{1}{A_2} p_3 a C^*))$$

Proof. Pontryagin's minimal principle [10] can be used to get the adjoint equations and transversality requirements, so that

$$\begin{cases} \dot{p_1}(t) = -\dfrac{\partial \mathscr{L}}{\partial A}(t), \\ \dot{p_2}(t) = -\dfrac{\partial \mathscr{L}}{\partial B}(t), \\ \dot{p_3}(t) = -\dfrac{\partial \mathscr{L}}{\partial C}(t), \\ \dot{p_4}(t) = -\dfrac{\partial \mathscr{L}}{\partial D}(t), \\ \dot{p_5}(t) = -\dfrac{\partial \mathscr{L}}{\partial E}(t), \\ \dot{p_6}(t) = -\dfrac{\partial \mathscr{L}}{\partial F}(t). \end{cases} \tag{3.2}$$

The optimal control v_1^* and v_2^* can be solved using optimality conditions,

$$\frac{\partial \mathscr{L}}{\partial v_1}(t) = 0 \quad and \quad \frac{\partial \mathscr{L}}{\partial v_2}(t) = 0$$

□

4. Numerical Analysis and Simulations

Numerical resolution of the optimization system is achieved using an explicit Euler scheme. We will base our simulations on the values indicated on table 1 inspired from [11, 12].

Parameters	Value	Units
δ	10	cells $\mu l^{-1}\ Day^{-1}$
k_1	0,04	$\mu l\ virion^{-1}\ Day^{-1}$
k_2	1,1	Day^{-1}
d_1	0.0139	Day^{-1}
d_2	0,0495	Day^{-1}
d_3	0,5796	Day^{-1}
d_4	0,6	Day^{-1}
a	40	Day^{-1}
b	0,5	Day^{-1}
c	0,15	cells $cell^{-1}\ Day^{-1}$
ρ	0,0024	$\mu l\ cell^{-1}\ Day^{-1}$
θ	0,5	$\mu l\ virion^{-1}\ Day^{-1}$
ψ	0,001	$\mu l\ virion^{-1}\ Day^{-1}$
ω	0,1	Day^{-1}

TABLE 1. The used parameters.

Moreover, we define the lower and upper bounds of the control functions as $a_i = 0,01$ and $b_i = 0,99$, for $i = 1;2$. The optimal control pair (v_1^*, v_2^*) is determined over an observation period of 100 days. The cost coefficients introduced in the definition of the objective function are $Q_1 = Q_2 = Q_3 = 10^{-5}$ and $A_1 = A_2 = 5000$ [13].

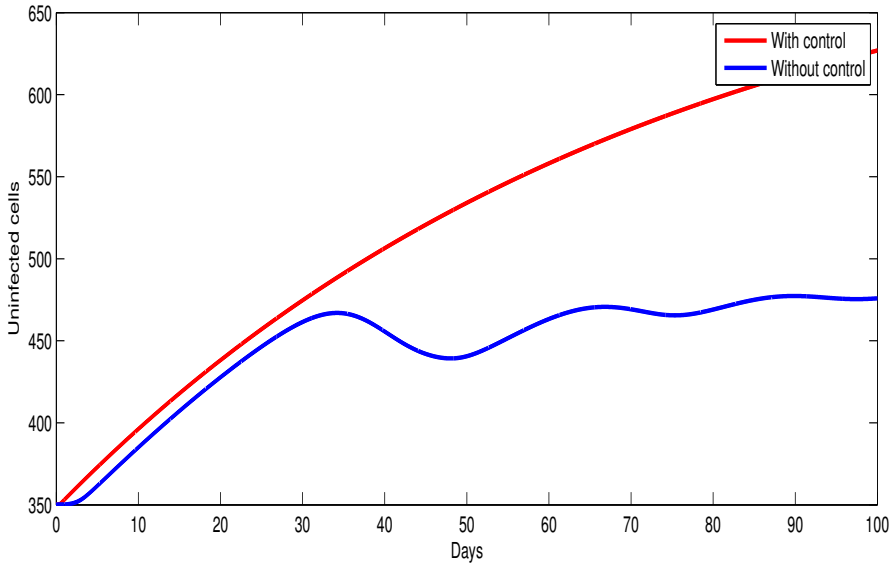

FIGURE 1. The total number of cells that are not infected throughout time.

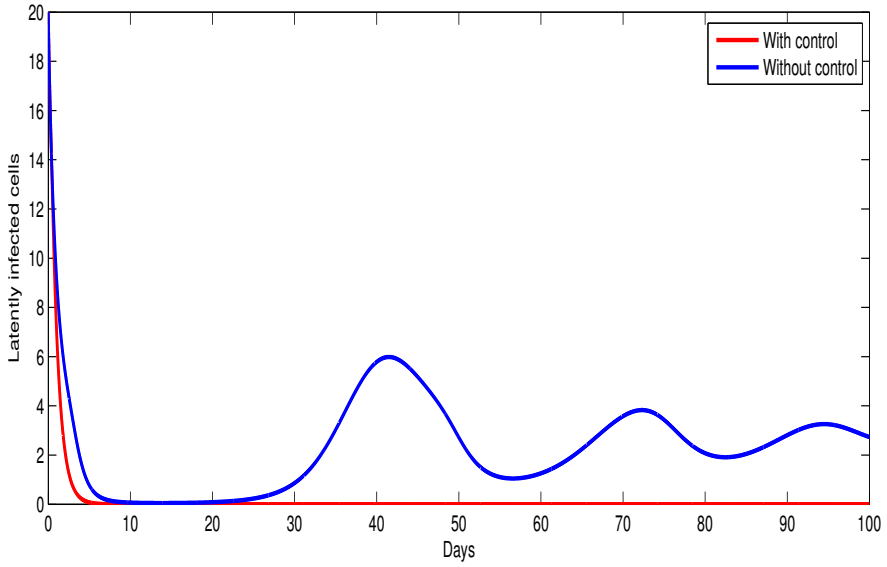

FIGURE 2. The total number of cells that are latently infected throughout time.

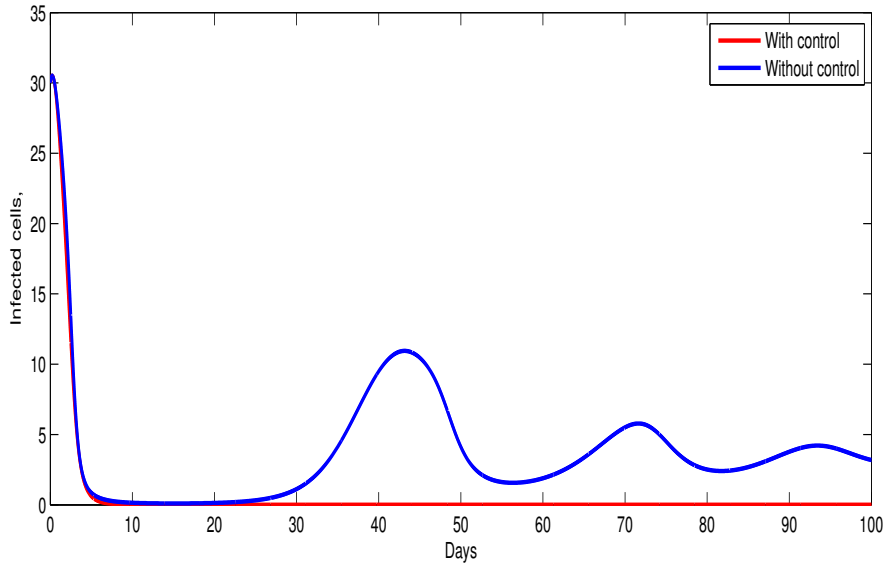

FIGURE 3. The total number of infected cells over time.

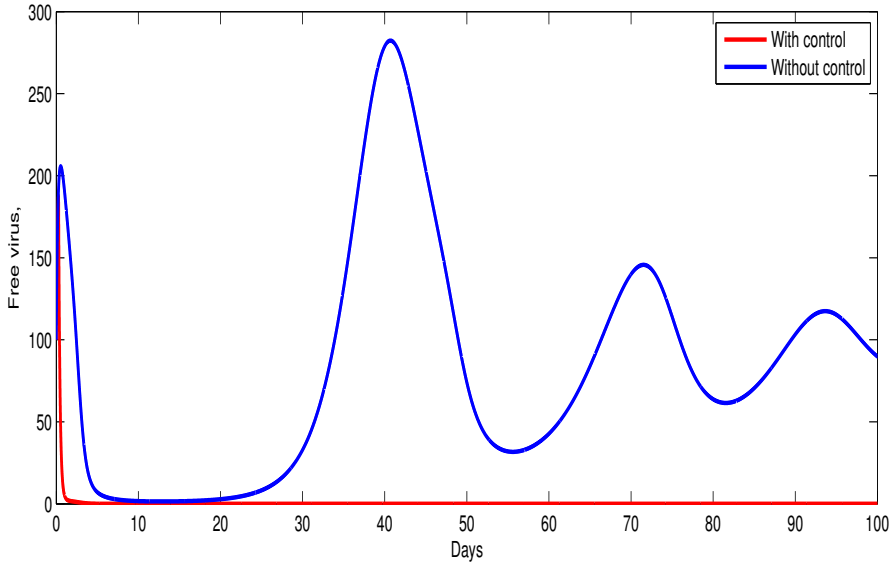

FIGURE 4. The total number of free virus, over time.

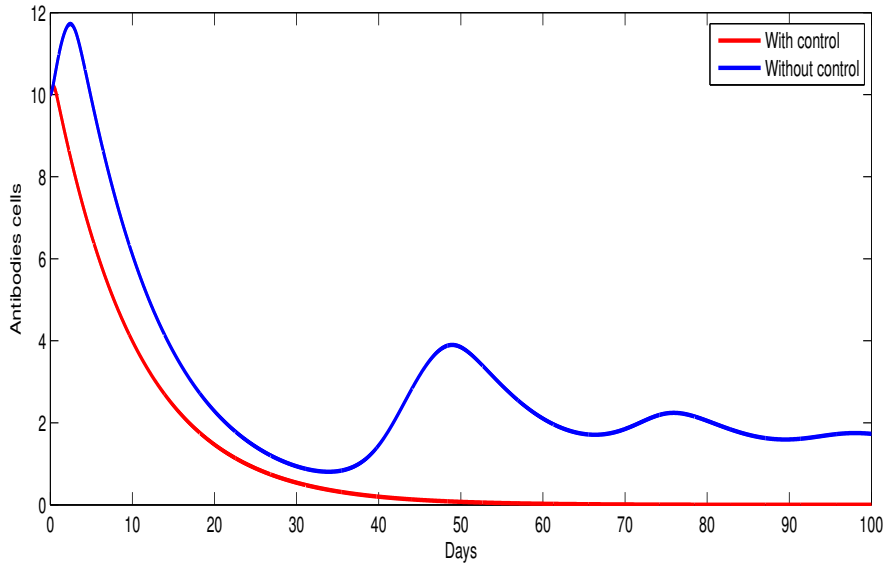

FIGURE 5. The total number of antibodies cells over time.

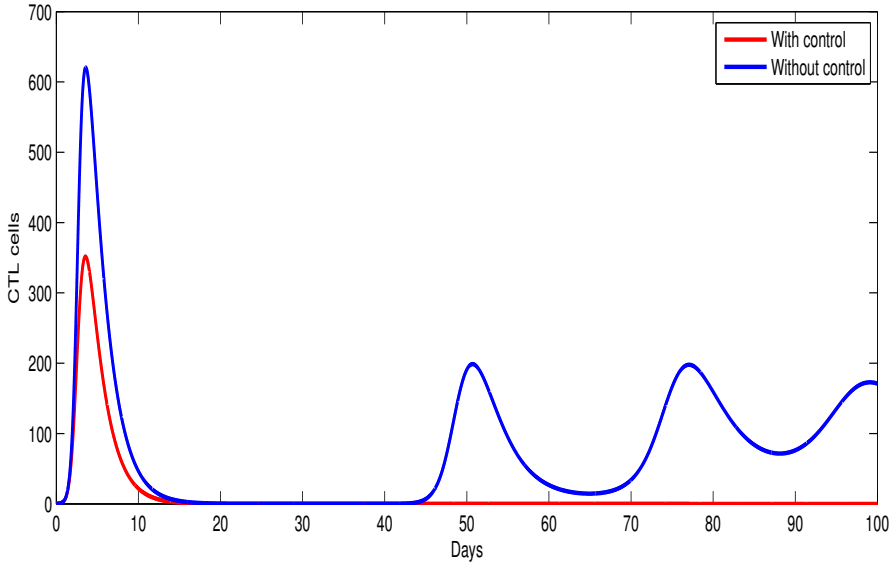

FIGURE 6. The total number of CTL cells throughout time.

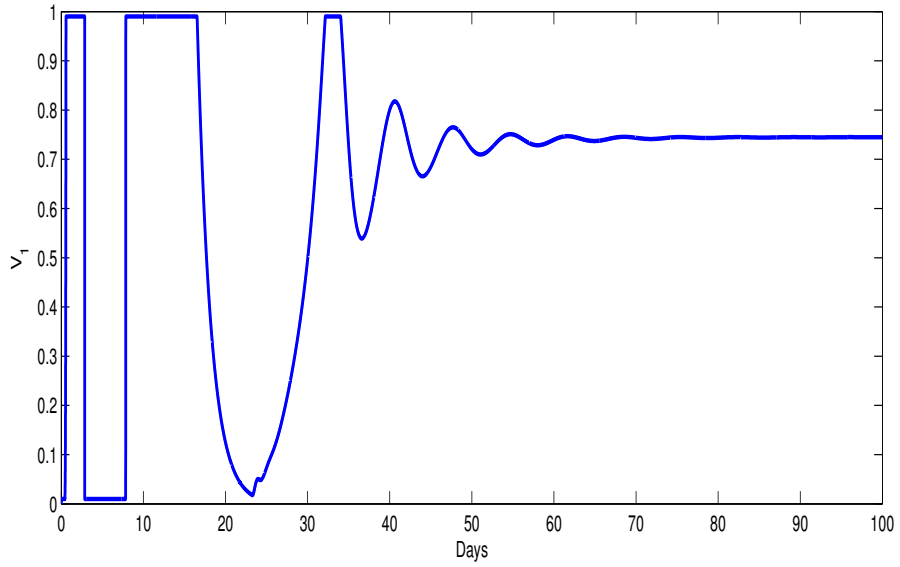

FIGURE 7. The optimal control v_1 as function of time.

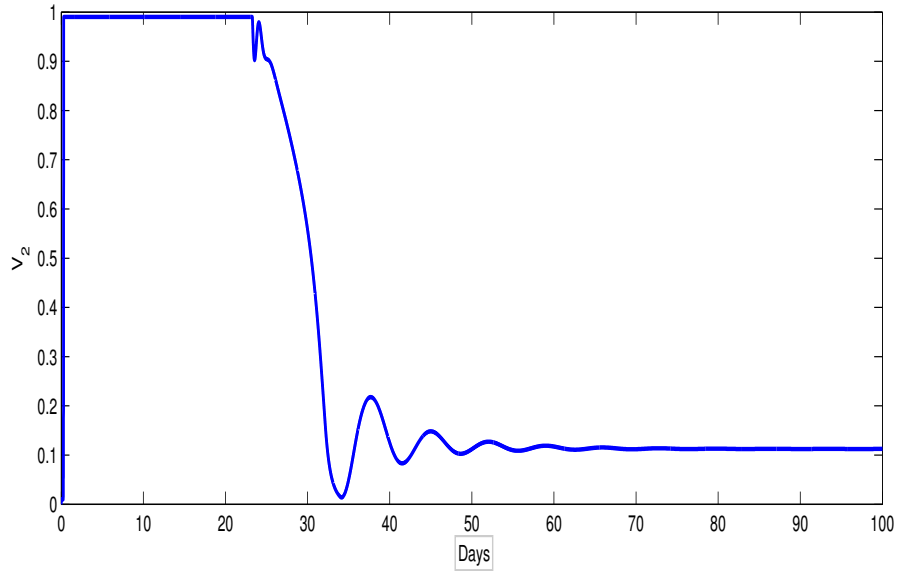

FIGURE 8. The optimal control v_2 as function of time.

Figure 1 illustrates that the number of uninfected cells is greater when control measures are applied compared to when no control is implemented.

Figure 2 shows that the concentration of latently infected cells decreases towards zero when control is applied, while in the absence of control, it stabilizes around 2.73.

Figure 3 shows how the total number of infected cells diminishes under control to zero shortly after the first few days of therapy. In contrast, without control, this number stays at a positive level, around 3.18.

Figure 4 shows that the number of HIV viruses significantly decreases after the initial days of therapy when control is applied, while it remains at 89.82 without control. This highlights the effectiveness of the administered therapy in suppressing viral replication.

Figure 5 Shows the number of antibodies cells converges towards zero following the initial days of treatment under control, However, in the absence of control, it stays at 2.22.

Figure 6 shows that the number of CTL cells converges to zero under control, and converges towards 171.05 without any control. This underscores the crucial role of the CTL (Cytotoxic T Lymphocyte) component in the dynamics of HIV viral replication.

Figures 7 and 8 display the two ideal controls, V_1 and V_2, which stand for preventing new infections and preventing the creation of viruses, respectively. The ideal medication administration regimen for the duration of the treatment is shown by these graphs.

5. Conclusion

In this paper, we present a mathematical model that describes HIV viral infection with a saturated rate in the presence of the adaptive immune response, where the patient is being treated with a combination of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). First we have proved the well posedness of the model. Then we have developed a problem for optimum control in order to reduce the proportion of HIV free virus, latently infected cells, and infected cells while simultaneously reducing the therapeutic cost of the the combined treatment. We demonstrate the existence of an optimal control pair and we apply Pontryagin's minimum principle to define and describe each of these two optimal controls. Finally, numerical results indicated that using of the two optimal treatments implies an increase in the number of healthy CD4+ T cells, whereas the numbers of both latently infected and infected CD4+ T cells decline.

Additionally, there was a reduction in the viral load significantly under the control strategy when compared to the model without control.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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