Optimal control strategy of HIV-1 epidemic model for recombinant virus

Nigar Ali*, Gul Zaman1 and Ali Saleh Alshomrani2

Abstract: In this work, an optimal control strategy is developed to eliminate the spread of HIV-1. To do this, two control variables are used such as the efficaciousness of drug therapy in reducing the infection of new cells and decreasing the production of new viruses. Existence for the optimal control pair is accomplished and the Pontryagins Maximum Principle is used to characterize these optimal controls. Objective functional is constituted to minimize the densities of infected cells and free virus and to maximize the density of healthy cells. The optimality system is derived and solved numerically.

Subjects: Science; Bioscience; Mathematics & Statistics; Physical Sciences

Keywords: HIV-1 infection model; recombinant virus; optimal control; numerical simulation

1. Introduction

Human immuno deficiency virus (HIV-1) is a lentivirus that causes acquired immuno deficiency syndrome (AIDS), a condition in humans in which the immune system gets to fail, leading to life-threatening opportunistic infections. Infection with HIV-1 occurs by the transfer of blood, semen, vaginal fluid, or breast milk. Within these bodily fluids, HIV-1 is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (vertical transmission). Screening of blood products for HIV has largely eliminated transmission through blood
transfusions or infected blood products in the built-up world. There are some antiretroviral (ARV) drugs available nowadays which help the immune system in preventing the infection due to HIV even though it is not possible to cure it. Reverse Transcriptase Inhibitors (RTIs) are one of the chemotherapies which balances the conversion of RNA of the virus to DNA (reverse transcription), so that the viral population will be minimum and on the other hand the CD4 T cells count remains higher and the host can live.

Once HIV enters the body, the human immune system tries to get free of it. The invasion is reported to CD4 T cells. The CD4 T cell is a protein marker in the surface of the T cell, where letter T refers to thymus, the organ responsible for maturing these cells after they migrate from the bone marrow (where they are manufactured). The surface of CD4 T cell has a protein that can bind to foreign substances such as HIV. The HIV needs a host in order to reproduce and the above-mentioned protein provides shelter. The HIV virus is a retrovirus, the RNA of virus is converted into DNA inside the CD4 T cell. Thus, when infected the CD4 T cells begin to multiply to fight this pathogen, they produce more virus. See Fister, Lenhart, and McNally (1998) and Kirschner, Lenhart, and Serbin (1997) for more details on disease progression.

Although global allegiance to control the HIV/AIDS endemic has increased importantly in recent years, but the virus are spreading continuously. Sub-Saharan Africa remains the region most affected by HIV/AIDS, however, the virus is now circulating rapidly in Asia and parts of eastern Europe. In spite of the rapid spread of HIV, several countries have achieved important success in controlling its transmission. ARV therapy is effective in reducing viral load and partially enabling immune restoration, thereby preventing the oncoming and recurrence of opportunistic infections. The effectuality of ARV therapy is determined by its ability to rapidly reduce viral load and to corroborate low levels of viral activity.

2. Background

In the literary study, many mathematical models have been formulated in order to understand the dynamics of HIV infection (Ali & Zaman, 2016; Ali, Zaman, & Algahtani, 2016; Perelson & Nelson, 1999) and optimal control methods have been applied to the derivation of optimal therapies for this HIV infection. But Butler, Kirschner, and Lenhart (1997) used a single control representing the percentage effect the chemotherapy has on viral infectivity (this would simulate a drug such as AZT). Fister, Lenhart, and McNally (1998) used an optimal control which represents the percentage effect the chemotherapy has on the fundamental interaction of the CD4 T cells with the virus. Joshi (2002) considered two controls, boosting the immune system and retarding HIV advancement. Kirschner, Lenhart, and Serbin (1997) used a single control comprising the percentage effect the chemotherapy has on viral production. Garira, Musekwa, and Shiri (2005) used two controls, one simulating effect of RTIs and the other control simulating the effect of PIs, integrating drug efficacy. We propose the mathematical model which is different from the mathematical models in the existing literature in the sense that it describes two types of control strategies for reducing this infection. One is the recombinant virus and the other is the proposed control variables. Therefore, our proposed model predicts two types of treatments. In this article, we apply optimal control to the HIV-1 recombinant model presented in Revilla and Garca-Ramos (2003). We incorporate two control functions \( u_1 \) and \( u_2 \). The control \( u_1 \) denotes the efficaciousness of drug therapy in blocking off the infection of new cells, and the control \( u_2 \) denotes the efficacy of drug therapy in decreasing the production of virus. If, for instance, \( u_1 = 1 \), the obstruction is 100 percent efficient. On the other hand, if \( u_2 = 0 \), there is no blockage. Our control functions are bounded and Lebesgue integrable. As our control variables, we choose measurable functions which are defined on a fixed interval (as treatments cannot be continued for infinite time period due to risky side effects and more cost) satisfying \( 0 \leq u_i(t) < 1 \) for \( i = 1, 2 \). For most of HIV chemotherapy drugs, the length of treatment is less than 500 days. The physical meaning of our control problem is to minimize the infected cells measure and free virus particles amount and maximize the healthy cells density in blood by implementing the two control variables.
The paper is organized as follows. Section 3 is devoted to the formulation of the proposed model. Section 4 is dedicated to the existence of optimal control pair. The analysis of optimization problems is acquainted in Section 5. In Section 6, numerical appropriate method and the simulation corresponding results are discussed in detail.

3. Optimal strategy
In this section, we consider the HIV-1 epidemic model to develop our control strategy. By implementing two control variables such as the efficaciously of drug therapy in blocking off the infection of new cells and the efficacy of drug therapy in decreasing the production of virus. Then the proposed model becomes

\begin{align}
\frac{dx(t)}{dt} &= \lambda - dx(t) - \beta x(t)v(t) + u_1(t)x(t), \\
\frac{dy(t)}{dt} &= \beta x(t)v(t) - ay(t) - aw(t)y(t), \\
\frac{dz(t)}{dt} &= aw(t)y(t) - bz(t), \\
\frac{dv(t)}{dt} &= ku_2(t)y(t) - pv(t), \\
\frac{dw(t)}{dt} &= cz(t) - qw(t),
\end{align}

(3.1)

with initial conditions \(x(0) \geq 0, y(0) \geq 0, z(0) \geq 0, v(0) \geq 0\) and \(w(0) \geq 0\).

Here \(x(t)\) stands for uninfected target cells and \(y(t)\) denotes the density of infected cells, \(v(t)\) is the density of virus, \(w(t)\) is the density of recombinant virus and the density of the double-infected cells is represented by \(z(t)\) at time \(t\). \(\beta\) is infection rate of infected cells and the healthy cells are assumed to be produced at a constant rate \(\lambda\). \(a\) is the death rate of infected cells either due to the action of the virus or the immune system and in the mean time each produces HIV-1 virus particles at a rate \(k\) during their life with an average length \(1/\alpha\).

Let the objective functional be defined by

\[J(u_1(t), u_2(t)) = \int_0^T \left[ Bx(t) - (S_1u_1^2(t) + S_2u_2^2(t)) \right] dt \]

(3.2)

Then, we have to maximize this objective functional. Here, \(Bx(t)\) represents the benefits of T cells and the other terms \(S_1u_1^2(t) + S_2u_2^2(t)\) are systemic costs of the drug treatments. The positive constants \(S_1\) and \(S_2\) are representing the relative weights attached to the drug therapies. These constants balance the size of the cell used in the control model. \(u_1(t)\) and \(u_2(t)\) are the control variables as defined above. The quadratic terms in the functional justify that when drugs such as interleukin are administered in high dose, they are cyanogenetic to the human body. Our goal is to increase the number of the uninfected CD4T cells, reducing the viral load (the number of freevirions), and minimizing the cost of treatment. We are looking to find an optimal control pair \(\bar{u}_1(t)\) and \(\bar{u}_2(t)\) such that

\[J(\bar{u}_1(t), \bar{u}_2(t)) = \max \{J(u_1(t), u_2(t))/u_1(t), u_2(t) \in U\},\]

(3.3)

where \(U = \{(u_1(t), u_2(t))/u_i(t)\) is Lebesgue measurable on \([0, 1], 0 \leq u_i(t) \leq 1, i = 1, 2\) is the control set.
4. Existence of control problem

In this section, we prove the existence of control problem. For the existence of the optimal pair, we use the idea presented in Fleming and Rishel (1975), Lukes (1982), Pontryagin, Boltyanskii, Gamkrelidze, and Mishchenko (1986) and Khan, Zaman, and Chohan (2016).

**Theorem 4.1** For the control problem (3.1) there exists \( \tilde{u}(t) = (\tilde{u}_1(t), \tilde{u}_2(t)) \in U \) such that

\[
\max_{(u_1(t), u_2(t)) \in U} J(u_1(t), u_2(t)) = J(\tilde{u}_1(t), \tilde{u}_2(t)).
\]

**Proof** To prove the existence of optimal control, we follow the same techniques as in Pontryagin et al. (1986). We see that the set of controls and comparable state variables are nonempty (Lukes, 1982). We also note, that the solutions are bounded. Therefore, the control set \( U \) is convex and closed. Using the boundedness of the solution, we see that right-hand sides of the state system is bounded by a linear function in the state and control variables because our state system is bilinear in \( u_1(t) \) and \( u_2(t) \). Moreover, the integrand of the objective functional is concave on \( U \). Finally, we can prove that there exists constants \( h_1, h_2 > 0, \) and \( \rho > 1 \) such that the integrand \( L(x(t), u_1(t), u_2(t)) \) of the objective functional satisfies

\[
L(x(t), u_1(t), u_2(t)) = h_2 - h_1(|u_1(t)|^2 + |u_2(t)|^2)^{\rho/2}.
\]

Pontryagins Maximum Principle given in Pontryagin et al. (1986) provides necessary conditions for an optimal control problem. This principle changes the Equations (3.1)–(3.3) into a problem of maximizing an Hamiltonian, \( H \), point wisely with respect to \( u_1 \) and \( u_2 \):

\[
H = Bx(t) - \frac{1}{2} \left( S_1 u_1^2(t) + S_2 u_2^2(t) \right) + \sum_{m=1}^{5} \lambda_m(t) g_m(x, y, z, v, w)
\]

where \( g_m(x, y, z, v, w) \) is the right-hand side of the differential equation of state variables \( x, y, z, v, w \). By applying Pontryagins Maximum Principle (Pontryagin et al., 1986), we state and prove the following results.

**Theorem 4.2** Given optimal controls \( Q_1(t), Q_2(t) \) and solutions \( x(t), \tilde{y}(t), \tilde{z}(t), \varphi(t), \tilde{w}(t) \) of the corresponding state system (3.1), there exists adjoint variables \( \lambda_m(t), m = 1, \ldots, 5 \)

\[
\begin{align*}
\lambda_1(t) &= (\lambda_1(t) - \lambda_2(t))\tilde{v}(t) - B + \lambda_1(t)d - \lambda_1(t)\tilde{u}_1(t), \\
\lambda_2(t) &= a\lambda_1(t) + (\lambda_2(t) - \lambda_3(t))a\tilde{w}(t) - \lambda_2(t)k\tilde{u}_2(t), \\
\lambda_3(t) &= b\lambda_1(t) - c\lambda_5(t), \\
\lambda_4(t) &= (\lambda_1(t) - \lambda_4(t))\tilde{p}(t) + \lambda_4(t)p, \\
\lambda_5(t) &= (\lambda_2(t) - \lambda_5(t))a\tilde{y}(t) + \lambda_5(t)q,
\end{align*}
\]

with transversality conditions \( \lambda_m(t) = 0, m = 1, 2, \ldots, 5 \).

**Proof** By setting \( x = \tilde{x}, y = \tilde{y}, z = \tilde{z}, v = \tilde{v} \) and \( w = \tilde{w} \) and differentiating the Hamiltonian with respect to states variable \( x(t), y(t), z(t), v(t) \) and \( w(t) \), respectively, we obtain the following adjoint system

\[
\begin{align*}
\lambda_1(t) &= (\lambda_1(t) - \lambda_2(t))\tilde{v}(t) - B + \lambda_1(t)d - \lambda_1(t)\tilde{u}_1(t), \\
\lambda_2(t) &= a\lambda_1(t) + (\lambda_2(t) - \lambda_3(t))a\tilde{w}(t) - \lambda_2(t)k\tilde{u}_2(t), \\
\lambda_3(t) &= b\lambda_1(t) - c\lambda_5(t), \\
\lambda_4(t) &= (\lambda_1(t) - \lambda_4(t))\tilde{p}(t) + \lambda_4(t)p, \\
\lambda_5(t) &= (\lambda_2(t) - \lambda_5(t))a\tilde{y}(t) + \lambda_5(t)q,
\end{align*}
\]
\[ \dot{\lambda}_1(t) = (\lambda_2(t) - \lambda_3(t))\dot{x}(t) + \lambda_5(t)q, \] (4.6)

satisfying transversality conditions \( \lambda_m = 0, \ m = 1, 2, \ldots, 5. \)

**Theorem 4.3** The control pair \((\bar{u}_1(t), \bar{u}_2(t))\), which maximizes the objective functional \( J \) over the region \( U \) are given by

\[ \ddot{u}_1(t) = \max \left\{ \min \left\{ \frac{\lambda_1(t)\dot{x}(t)}{s_1}, 1 \right\}, 0 \right\}, \]
\[ \ddot{u}_2(t) = \max \left\{ \min \left\{ \frac{\lambda_4(t)\dot{y}(t)}{s_2}, 1 \right\}, 0 \right\}. \]

**Proof** The optimality condition yields the following

\[ \frac{\partial H}{\partial \ddot{u}_1} = \lambda_1(t)\dot{x}(t) - S_1\ddot{u}_1(t), \] (4.7)

and

\[ \frac{\partial H}{\partial \ddot{u}_2} = \lambda_4(t)\dot{y}(t) - S_2\ddot{u}_2(t). \] (4.8)

Solving Equations (4.7) and (4.8) simultaneously for the optimal control variables \( \ddot{u}_1 \) and \( \ddot{u}_2 \), we get

\[ \ddot{u}_1(t) = \frac{\dot{x}(t)\lambda_1(t)}{s_1}, \] (4.9)
\[ \ddot{u}_2(t) = \frac{k\dot{y}(t)\lambda_4(t)}{s_2}. \] (4.10)

Using the property of control space, Equations (4.9) and (4.10) can be written as

\[ \ddot{u}_1 = \begin{cases} 0 & \text{if } \frac{\dot{x}(t)\lambda_1(t)}{s_1} \leq 0, \\ \frac{\dot{x}(t)\lambda_1(t)}{s_1} & \text{if } 0 < \frac{\dot{x}(t)\lambda_1(t)}{s_1} < 1, \\ 1 & \text{if } \frac{\dot{x}(t)\lambda_1(t)}{s_1} \geq 1. \end{cases} \]
\[ \ddot{u}_2 = \begin{cases} 0 & \text{if } \frac{k\dot{y}(t)\lambda_4(t)}{s_2} \leq 0, \\ \frac{k\dot{y}(t)\lambda_4(t)}{s_2} & \text{if } 0 < \frac{k\dot{y}(t)\lambda_4(t)}{s_2} < 1, \\ 1 & \text{if } \frac{k\dot{y}(t)\lambda_4(t)}{s_2} \geq 1. \end{cases} \]

The above two equations for \( \ddot{u}_1(t) \) and \( \ddot{u}_2(t) \) can be written as (using compact notation)

\[ \ddot{u}_1(t) = \max \left\{ \min \left\{ \frac{\lambda_1(t)\dot{x}(t)}{s_1}, 1 \right\}, 0 \right\}, \] (4.11)
\[ \ddot{u}_2(t) = \max \left\{ \min \left\{ \frac{k\lambda_4(t)\dot{y}(t)}{s_2}, 1 \right\}, 0 \right\}. \] (4.12)

Using Equations (4.11) and (4.12), we can write the following optimality system
The optimal control variables and state variables are found by solving the optimality system (4.14), the adjoint system
\[
\frac{d\tilde{y}(t)}{dt} = \beta \tilde{x}(t)\tilde{v}(t) - a\tilde{w}(t)\tilde{y}(t),
\]
\[
\frac{d\tilde{z}(t)}{dt} = a\tilde{w}(t)\tilde{y}(t) - b\tilde{z}(t),
\]
\[
\frac{d\tilde{v}(t)}{dt} = k\left(1 - \max\left\{\min\left\{\frac{\lambda_1(t)\tilde{x}(t)}{S_1}, 1\right\}, 0\right\}\right)\tilde{y}(t) - \rho\tilde{v}(t),
\]
\[
\frac{d\tilde{w}(t)}{dt} = c\tilde{z}(t) - q\tilde{w}(t).
\] (4.13)

The optimal control variables and state variables are found by solving the optimality system (4.14), the adjoint system \(\frac{d\tilde{y}(t)}{dt}\) with initial and boundary conditions and the equations of the optimal control (4.11) and (4.12). Since the second derivatives of the Lagrangian with respect to \(u_1^*\) and \(u_2^*\) are positive, so optimal problem is minimum at controls \(u_1^*\) and \(u_2^*\). Once we obtain the optimal control problem, our Hamiltonian becomes
\[
H^* = Bx^*(t) - \frac{1}{2}\left(S_1u_1^2(t) + S_2u_2^2(t)\right) + \sum_{m=1}^{s}\lambda_m(t)g_m(x^*, y^*, z^*, v^*, w^*). \tag{4.14}
\]

### 5. Numerical simulation

In this section, we show the numerical simulation of the proposed optimal control problem. To do this, we use Runge–Kutta four-order scheme forward in time for the state system and backward in time for the adjoint system. For numerical simulation we use the parameter values. Our numerical results are given in Figures 1–5 which show potency of drug therapies based on the densities of uninfected cells, infected cells, free viruses, and recombinant viruses with and without control. Figure 1 shows that without treatments, the number of uninfected \(x(t)\) cells decreases drastically. But after treatments, the concentration of CD4T cells are increasing up to some time. Figure 2 shows the density of infected cells with and without control. It shows that applying optimal control the density of infected cells decreases but without control the density of infected cells increases. Figure 3 represents the difference between the densities of the double infected cells before and after treatment. It shows that without treatment the density of double infected cells increases continuously but
Figure 2. The graph represents the density of infected cells $y(t)$ with and without control.  

Note: The number of infected cells approach to a small number due to optimal control.

Figure 3. The graph represents the density of double-infected cells $z(t)$ with and without control.  

Note: The density of double infected cells approaches to a small quantity after optimal control.
after treatment the concentration of these cells decreases. Figure 4 shows that density of pathogen viruses before and after optimal control. It represents that after treatment the density of pathogen viruses decreases rapidly. Moreover, the intensity of recombinant viruses \(w(t)\) decrease with the passage of time after therapy as these viruses are used to infect the cells, which is given in Figure 4. Moreover, we see that optimal treatments \(u_1\) and \(u_2\) are used to block new infection of cells and prevent viral production with minimum side effects. For numerical simulation we use the following data (Table 1).
6. Concluding remarks

In this work, we developed an optimal control strategy which described HIV-1 infection of CD$_4$ T cells during therapy by applying two controls variables. Presently, there is no effective therapy for HIV-1 infection in order to cure this infection. Different treatments are used to block the evolution of the viruses in the body. Moreover, the cost of treatment is beyond the reach of many infected patients. Hence, we introduced an optimal therapy in order to minimize the cost of treatment, reduce the viral load and boost the immune response. We used two controls which measure the efficacy of reverse transcriptase and protease inhibitors, respectively. In addition, we discussed an efficient numerical method based on optimal control to identify the best treatment strategy of HIV infection in order to block new infection and prevent viral production using drug therapy with minimum side effects. Our numerical results shown that the viral load reducing after treatment and the CD$_4$ T population increases. The results show the enhance of healthy cells, and drop-off infected cells and viral load. In fact, these consequences could be useful in arising bettered treatment regimen toward directing the challenge of HIV/AIDS.

Table 1. Parameters values used for numerical simulation

| Parameters | Definition | Values with sources |
|------------|------------|---------------------|
| A          | Production rate of host cell | 2 cell/mm$^3$ (Revilla & Garca-Ramos, 2003) |
| d          | Death rate of host cell      | 0.6 Assumed          |
| $\beta$    | Infection rate of host cell by virus | 0.04 mm$^3$/vir (Revilla & Garca-Ramos, 2003) |
| a          | Death rate of HIV-1-infected cell | 0.1 (Revilla & Garca-Ramos, 2003) |
| $\alpha$   | Infection rate by recombinant | 0.2 assumed         |
| b          | Death rate of double-infected cell | 0.3 assumed       |
| k          | HIV-1 production rate by a cell | 0.2 vir/cell assumed |
| p          | Removal rate of HIV-1         | 0.3 assumed          |
| c          | Production rate of recombinant by a double-infected cell | 0.5 vir/cell assumed |
| q          | Removal rate of recombinant   | 0.3 assumed          |
| $S_1$      | Weight constant               | 40 days assumed      |
| $S_2$      | Weight constant               | 20 assumed           |
| B          | Constant                       | 1 (Joshi, 2002)      |

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6. Author details

Nigar Ali
E-mail: nigaruom@gmail.com
Gul Zaman
E-mail: gzaman@uom.edu.pk
Ali Saleh Alshomrani
E-mail: asalshomrani@kau.edu.sa

1 Department of Mathematics, University of Malakand, Chakdara Dir (Lower), Khyber Pakhtunkhawa, Pakistan.
2 Faculty of Science, Department of Mathematics, King Abdul Aziz University, Jeddah, Saudi Arabia.

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