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Optimal control of double delayed HIV-1 infection model of fighting a virus with another virus

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Abstract A double delayed- HIV-1 infection model with optimal controls is taken into account. The proposed model consists of double time delays and the following five compartments: uninfected cells CD4+ T cells, infected CD4+ T cells, double infected CD4+ T cells, human immunodeficiency virus and recombinant virus. Further, the optimal controls functions are introduced into the model. Objective functional is constituted which aims to (i) minimize the infected cells quantity; (ii) minimize free virus particles number; and (iii) maximize healthy cells density in blood Then, the existence and uniqueness results for the optimal control pair are established. The optimality system is derived and then solved numerically using an iterative method with Runge-Kutta fourth order scheme.

Keywords. HIV-1 model, Intracellular delay, Recombinant virus, Optimal control, Pontryagin Maximum Principle.

2010 Mathematics Subject Classification. 65L05, 34K06, 34K28.

1. Introduction

HIV-1 is the type of virus which stands for human immunodeficiency virus. HIV-1 attacks the bodys immune system, specifically the CD^{+4} T cell s which helps the immune system to fight off infections. If left untreated, HIV-1 reduce the density of CD^{+4} T cells in the body which causes the person more likely to get infections or infection-related cancers. These opportunistic infections make immune system very weak and this is the stag of AIDS (Acquired Immunodeficiency Syndrome). Currently, there is no cure for HIV-1 infection. But HIV/AIDS can be controlled with proper treatment and medical care. These medicines are called antiretroviral which can help in boosting the immune system against cell infections. These antiretroviral drugs consist of two groups which are reverse transcriptase inhibitors (RTIs) and protease

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inhibitors (PIs). RTIs break up the conversion of RNA of the virus to DNA so that new HIV-1 infection of cells is controlled. On the other hand, PIs block the production of the virus particles by the actively infected CD^{4+} T cells (see[7, 8, 15, 16, 17]).

In the literature, many mathematical models have been formulated in order to understand the dynamics of HIV-1 infection [1, 2, 6, 18, 20, 22]. Most of the modern mathematical models that have been developed apply the optimal control theory. Optimal control theory is a branch of mathematics developed to find optimal ways of controlling a dynamical system [11, 12, 13]. For instance, Yusuf and Benyah [5] applied optimal theory on HIV population model. The study aimed at determining the best method of controlling the spread of HIV/AIDS within a specified time frame. For the importance of optimization techniques and optimal control in the study of HIV, we refer the reader to [8] and references. Here we observe that, often, models introduce the effect of cellular immune response, also called the cytotoxic T-lymphocyte (CTL) response, which attacks and kills the infected cells [9]. It has been shown that this cellular immune response can control the load of HIV viruses [17]. In [7], it is assumed that CTL proliferation depends, besides infected cells, as usual, also on healthy cells. Moreover, an optimal control problem associated with the suggested model is studied [7]. therein

In this article, we formulate time delayed optimal control problem. We incorporate two controls functions u_1 and u_2. The control u_1 denotes the efficacy of drug therapy in blocking the infection of new cells, and the control u_2 denotes the efficacy of drug therapy in controlling the production of new viruses. These control functions are bounded, Lebesgue integrable and represent two different treatment strategies. As our control classes, we choose measurable functions which are defined on a fixed interval satisfying $0 \leq u_i(t) < 1$ for $i = 1, 2$. For most of HIV-1 chemotherapy drugs, the length of treatment is less then 500 days.

The paper is organized as follows. Section 3 is dedicated to the formulation of the proposed model and section 4 is devoted to the existence of the optimal control pair. Numerical simulation is introduced in section 5. In the last section, the conclusion is derived.

2. Formulation of the model

Hence, if we denote u_1 the RTI control variable and u_2 the PI control variable equations can be re-written, to accommodate control actions or chemotherapy treatment, as follows:

$$\begin{aligned}
\frac{dx(t)}{dt} &= \Lambda - dx(t) - (1 - u_1(t))\beta x(t)v(t), \\
\frac{dy(t)}{dt} &= (1 - u_1(t))\beta e^{-a_1\tau_1} x(t - \tau_1)v(t - \tau_1) - ay(t) - \alpha w(t)y(t),
\end{aligned}$$

$$\begin{aligned}
\frac{dz(t)}{dt} &= \alpha w(t)y(t) - bz(t), \\
\frac{dv(t)}{dt} &= ke^{-a_2\tau_2}(1-u_2(t))y(t-\tau_2) - pv(t), \\
\frac{dw(t)}{dt} &= cz(t) - qw(t),
\end{aligned} \tag{2.1}$$

with initial conditions

$$x(0) = x_0, y(0) = y_0, z(0) = z_0, v(0) = v_0, w(0) = w_0. \tag{2.2}$$

Here $x(t), y(t), z(t), v(t)$ and $w(t)$ denote the densities of uninfected target cells, infected cells, double infected cells, free virus and recombinant virus at time t, respectively. The parameters in the proposed model can be explain as follows: d is the natural death rate of uninfected cells and β is infection rate of infected cells. The healthy cells are assumed to be produced at a constant rate Λ. 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 which on average has length $1/a$. α is the infection rate of double infected cells. b, p and q are deaths rates of double infected cells, pathogen viruses and recombinant virus respectively. k and c are rates of production of free viruses and double infected cells respectively.

To proceed further, let the objective functional be defined by

$$J(u_1, u_2) = \int_0^{t_f} \Big[Ax(t) - (\nu_1 u_1^2 + \nu_2 u_2^2) \Big]. \tag{2.3}$$

We have to maximized the above objective functional. Here, $Ax(t)$ represents the benefits of T cells and the other terms $\nu_1 u_1^2 + \nu_2 u_2^2$ are systemic costs of the drug treatments, where ν_1 and ν_2 are positive constants representing the relative weights attached to the drug therapies which balance the size of the terms u_1 and u_2. The quadratic terms in the functional shows that When drugs such as interleukin are administered in high dose, they are toxic to the human body. Our aim is to increase the density of the uninfected CD^{4+} T cells, reducing the viral load (the number of free virion) and minimizing the cost of treatment.

Next, we find optimal controls functions $u_1^\star(t)$ and $u_2^\star(t)$ such that

$$J(u_1^\star(t), u_2^\star(t)) = \max\{J(u_1(t), u_2(t)) \setminus (u_1(t), u_2(t)) \in U\}, \tag{2.4}$$

where $U = \{(u_1(t), u_2(t)) \setminus u_i\}$ is the control set which is Lebesgue measurable on $[0, 1], 0 \le u_i(t) \le 1, i = 1, 2$. In our research work, the optimality conditions given by the Pontryagin Maximum Principle for multiple delayed optimal control problems of Gaollmann and Maurer [19], is considered. The extremal control for the proposed probelm, with the same values for the parameters as those of [5], is bangbang, that is, it attains alternately the boundary values 0 and 1. This type of control is easier to implement, from a medical point of view, and leads to better results than the ones previously obtained in [5] for a non-delayed problem with a L^2 functional. In [5], the authors considered a different L^2 cost functional for a non-delayed control system.

Therefore, we claim that our proposed delayed control system describes better the reality.

3. Optimal Control Existence

Lets define the lagrangian for the optimal control problem as

$$L(t) = Ax(t) - \frac{1}{2}(\xi_1 u_1^2(t) + \xi_2 u_2^2(t)). \tag{3.1}$$

Then, the corresponding Hamiltonian becomes

$$\begin{aligned} &H\big(x, y, z, v, w, x_{\tau_1}, v_{\tau_1}, y_{\tau_2}, u_1, u_2, \lambda(t)\big) \\ &= \frac{1}{2}\big(\nu_1 u_1^2 + \nu_2 u_2^2\big) - Ax(t) \\ &+ \lambda_1(t)\big(\Lambda - dx(t) - (1-u_1(t))\beta x(t)v(t)\big) \\ &+ \lambda_2(t)\big((1-u_1(t))\beta e^{-a_1\tau_1} x_{\tau_1} v_{\tau_1} - ay(t) - \alpha w(t)y(t)\big) \\ &+ \lambda_3(t)\big(\alpha w(t)y(t) - bz(t)\big) + \lambda_4(t)\big(ke^{-a_2\tau_2}(1-u_2(t))y_{\tau_2} \\ &- pv(t)\big) + \lambda_5(t)\big(cz(t) - qw(t)\big), \end{aligned} \tag{3.2}$$

where $x_{\tau_1} := x(t-\tau_1)$, $y_{\tau_1} := y(t-\tau_1)$ and $v_{\tau_2} := v(t-\tau_2)$. This Hamiltonian is used to find the control functions for the proposed optimal control problem. To check the existence of optimal pair, we use Fleming and Rishel [9].

Theorem 3.1. *There exists $u^\star = (u_1^\star, u_2^\star) \in U$ for the control problem with model (2.1), such that*

$$\max_{(u_1(t),u_2(t))\in U} J(u_1(t), u_2(t)) = J(u_1^\star(t), u_2^\star(t)).$$

Proof. To use an existence result [17], the following properties must be checked.

(H_1) The controls pair and the corresponding state variables is nonempty.

(H_2) The control set U is closed and convex.

(H_3) The Right Hand Side of the state system is bounded by a linear function in the state and control variables

(H_4) Finally, we can prove that there exist constants $h_1, h_2 > 0$, and κ_1 such that the integrand $L(x(t), u_1(t), u_2(t))$ of the objective functional satisfies

$$L\big(x(t), u_1(t), u_2(t)\big) = h_2 - h_1(|u_1|^2 + |u_2|^2)^{\kappa_1/2}.$$

□

Next, we use Pontryagins Maximum Principle for multiple delays [10]to discuss the following theorem.

Theorem 3.2. *Given optimal controls $u_1^\star(t), u_2^\star(t)$ and solutions $x^\star(t), y^\star(t), z^\star(t), v^\star(t)$, and $w^\star(t)$ of the corresponding state system (2.1), there exists adjoint variables $\lambda_i(t), i = 1, 2, ..., 5$, satisfying*

$$\begin{aligned} \frac{d\lambda_1}{dt} &= A + \lambda_1(t)\big(d + (1-u_1^\star(t))\beta v^\star(t)\big) + \lambda_1(t+\tau_1)\lambda_2(t)\beta e^{-a_1\tau_1} \\ &\quad v^\star(t-\tau)(u_1^\star(t) - 1), \end{aligned}$$

$$\frac{d\lambda_2}{dt} = a\lambda_2(t) + (\lambda_2(t) - \lambda_3(t))\alpha w^\star(t) - \lambda_2(t+\tau_2)\lambda_4(t)e^{-a_2\tau_2} k(1-u_2^*(t)),$$

$$\begin{aligned}
\frac{d\lambda_3}{dt} &= b\lambda_3(t) - c\lambda_5(t), \\
\frac{d\lambda_4}{dt} &= \lambda_1(t)(1-u_1^\star(t))\beta x^\star(t) + \lambda_4(t+\tau_1)\lambda_2(t)\beta e^{-a_1\tau_1} \\
& x^\star(t-\tau_1)(u_1^\star(t)-1) + \lambda_4(t)p, \\
\frac{d\lambda_5}{dt} &= (\lambda_2(t) - \lambda_3(t))\alpha y^\star(t) + \lambda_5(t)q,
\end{aligned} \tag{3.3}$$

with transversality conditions

$$\lambda_j(t_f) = 0, j = 1, 2, ..., 5. \tag{3.4}$$

Proof. Using Pontryagins Maximum Principle [10] , we get the following system of equations of adjoint variables,

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial H(t)}{\partial x} - \lambda_1(t+\tau_1)\frac{\partial H(t)}{\partial x_{\tau_1}}, \lambda_1(t_f) = 0, \\
\frac{d\lambda_2}{dt} &= -\frac{\partial H(t)}{\partial y} - \lambda(t+\tau_2)\frac{\partial H(t)}{\partial y_{\tau_2}}, \lambda_2(t_f) = 0, \\
\frac{d\lambda_3}{dt} &= -\frac{\partial H(t)}{\partial z}, \lambda_3(t_f) = 0, \\
\frac{d\lambda_4}{dt} &= -\frac{\partial H(t)}{\partial v}(t) - \lambda_4(t+\tau_1)\frac{\partial H(t)}{\partial v_{\tau_1}}, \lambda_4(t_f) = 0, \\
\frac{d\lambda_5}{dt} &= -\frac{\partial H(t)}{\partial w}, \lambda_5(t_f) = 0.
\end{aligned}$$

Further, adjusting $x(t) = x^\star(t), y(t) = y^\star(t), z(t) = z^\star(t), v(t) = v^\star(t)$ and $w(t) = w^\star(t)$, we get the adjoint system (3.3) satisfying tranversality conditions $\lambda_j(t_f) = 0, j = 1, 2, ..., 5$. □

Theorem 3.3. *The control pair $(u_1^\star(t), u_2^\star(t))$, which maximizes the objective functional J over the region U, can be written as*

$$\begin{aligned}
u_1^\star(t) &= \max\left\{\min\left\{\frac{\beta}{\nu_1}\left(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)\right)\right.\right. \\
&- \left.\left.\lambda_1(t)x^\star(t)v^\star(t), 1\right\}, 0\right\}, \\
u_2^\star(t) &= \max\left\{\min\left\{\frac{\lambda_4(t)e^{-a_2\tau_2}ky^\star(t-\tau_2)}{\nu_2}, 1\right\}, 0\right\}.
\end{aligned}$$

Proof. By using the optimality conditions, we get the following values

$$\frac{\partial H}{\partial u_1} = \nu_1 u_1^\star(t) + \lambda_1(t)\beta x^\star(t)v^\star(t) - \lambda_2(t)\beta x^\star(t-\tau)v^\star(t-\tau), \tag{3.5}$$

and

$$\frac{\partial H}{\partial u_2} = \nu_2 u_2^\star(t) - \lambda_4(t)e^{-a_2\tau_2}ky^\star(t-\tau_2). \tag{3.6}$$

Solving equations (3.5) and (3.6) simultaneously for the optimal control variables $u_1^\star(t)$ and $u_2^\star(t)$, we get

$$u_1^\star(t) = \frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)) - \lambda_1(t)x^\star(t)v^\star(t)\big), \tag{3.7}$$

$$u_2^\star(t) = \frac{\lambda_4(t)e^{-a_2\tau_2}ky^\star(t-\tau_2)}{\nu_2}. \tag{3.8}$$

By using the property of control space, equations (3.7) and (3.8) can be written as

$$u_1^\star(t) = \begin{cases} 0 \text{ if } \frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau_1)v^\star(t-\tau_1)) \\ -\lambda_1(t)x^\star(t)v^\star(t)\big) \le 0, \\ \frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)) - \lambda_1(t)x^\star(t)v^\star(t)\big), \text{ if} \\ 0 < \frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a\tau}x^\star(t-\tau)v^\star(t-\tau)) \\ -\lambda_1(t)x^\star(t)v^\star(t)\big) < 1, \\ 1 \text{ if } \frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)) \\ -\lambda_1(t)x^\star(t)v^\star(t)\big) \ge 1. \end{cases}$$

$$u_2^\star(t) = \begin{cases} 0 \text{ if } \frac{e^{-a_2\tau_2}\lambda_4(t)ky^\star(t-\tau_2)}{\xi_2} & \le 0, \\ \frac{e^{-a_2\tau_2}\lambda_4(t)ky^\star}{\nu_2} \text{ if} & 0 < \frac{\lambda_4(t)ky^\star(t)}{\xi_2} < 1, \\ 1 \text{ if } \frac{e^{-a_2\tau_2}\lambda_4(t)ky^\star(t)}{\nu_2} & \ge 1. \end{cases}$$

The above two equations for $u_1^\star(t)$ and $u_2^\star(t)$ can be written as (using compact notation)

$$\begin{aligned} u_1^\star(t) = \max\{\min\{&\frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)) \\ &- \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\}, \end{aligned} \tag{3.9}$$

and

$$u_2^\star(t) = \max\{\min\{\frac{\lambda_4(t)e^{-a_2\tau_2}ky^\star(t-\tau_2)}{\nu_2}, 1\}, 0\}. \tag{3.10}$$

Here, we call formula (3.9) and (3.10) for $u_1^\star(t)$ and $u_2^\star(t)$ the characterization of the optimal control.

Therefore, we get the following optimality system.

$$\begin{aligned}
&\frac{dx^\star(t)}{dt} = \Lambda - dx^\star(t) - \beta x^\star(t)v^\star(t)\Big(1 - \max\{\min\{\frac{\beta}{\nu_1}\\
&\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau)) - \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\}\Big),\\
&\frac{dy^\star(t)}{dt} = \Big(1 - \max\{\min\{\frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau)v^\star(t-\tau))\\
&- \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\}\Big)\beta x^\star(t-\tau)v^\star(t-\tau)\\
&- ay^\star(t) - \alpha w^\star(t)y^\star(t),\\
&\frac{dz^\star(t)}{dt} = \alpha y^\star(t)w^\star(t) - bz^\star(t),\\
&\frac{dv^\star(t)}{dt} = k\Big(1 - \max\{\min\{\frac{\lambda_4 e^{-a_2\tau_2}y^\star(t-\tau_2)}{\nu_2}, 1\}, 0\}\Big)y^\star(t)\\
&- pv^\star(t),\\
&\frac{dw^\star(t)}{dt} = cz^\star(t) - qw^\star(t)\rho_2 + (\lambda_2(t) - \lambda_3(t))\alpha y^\star(t) + \lambda_5(t)q,
\end{aligned} \tag{3.11}$$

along with equations (3.3) and initial conditions (2.3), and (3.4). And the Hamiltonian $H^\star$ at $\big(x^\star, y^\star, z^\star, v^\star, w^\star, x^\star_{\tau_1}, y^\star_{\tau_2}, v^\star_{\tau_1}, u_1^\star, u_2^\star, \lambda_1, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5\big)$, is given by

$$\begin{aligned}
&H^\star(t) = \frac{1}{2}\Big(\nu_1(\max\{\min\{\frac{\beta}{\xi_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau_1)v^\star(t-\tau_1))\\
&- \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\})^2\\
&+ \nu_2(\max\{\min\{\frac{\lambda_4(t)ky^\star(t-\tau_2)}{\nu_2}, 1\}, 0\})^2\Big) - Ax^\star(t)\\
&+ \lambda_1\Big[\Lambda - dx^\star(t) - \big(1 - \max\{\min\{\frac{\beta}{\xi_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau_1)\\
&v^\star(t-\tau_1)) - \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\}\big)\beta x^\star(t)v^\star(t)\Big]\\
&+ \lambda_2\Big[\big(1 - \max\{\min\{\frac{\beta}{\nu_1}\big(\lambda_2(t)e^{-a_1\tau_1}x^\star(t-\tau_1)v^\star(t-\tau_1))\\
&- \lambda_1(t)x^\star(t)v^\star(t)\big), 1\}, 0\}\big)\beta e^{-a_1\tau_1}x^\star(t-\tau_1)v^\star(t-\tau_1)\\
&- ay^\star(t) - \alpha w^\star(t)y^\star(t)\Big] + \lambda_3\Big[\alpha w^\star(t)y^\star(t) - bz^\star(t)\Big]\\
&+ \lambda_4\Big[k\big(1 - \max\{\min\{\frac{\lambda_4(t)ke^{-a_2\tau_2}y^\star(t-\tau_2)}{\nu_2}, 1\}, 0\}\big)\\
&y^\star(t-\tau_2) - pv^\star(t)\Big] + \lambda_5\Big[cz^\star(t) - qw^\star(t)\Big].
\end{aligned} \tag{3.12}$$

□

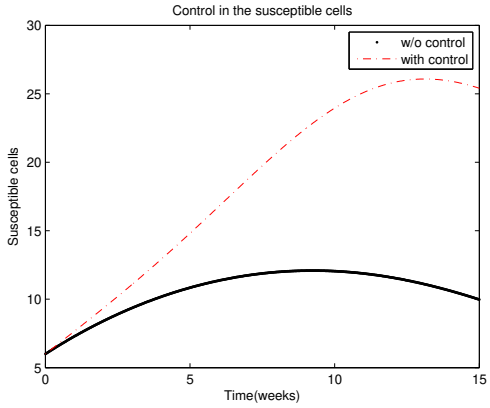

FIGURE 1. The graph represents the density of uninfected cells verses time t in weeks.

To find out the optimal control and state variable we will numerically solve the above system (3.11) and(3.12).

4. Numerical Simulation

Figures 15 are the simulation results from which we can conclude the effectiveness of drug therapies based on the densities of uninfected cells, infected cells,free virus, double infected cells and recombinant virus. Fig 1 shows the density of uninfected target cells with and without control. We see that without treatment, the density of uninfected cells decreases drastically. But after treatment the number of these cells increases. Fig (2) represents the concentration of infected CD^{4+} T cells with and without control. The density of infected cells decreases rapidly from the very beginning of treatment and increases throughout the period of treatment but without treatment the concentration of infected cells increases. Similarly, Fig (3) shows the concentration of double infected cells with treatment and without treatment. Moreover, There no direct effect of (RTIs) and (PIs) on the density of double infected cells. From fig (4), we see that the viral load increases drastically without treatments but with treatments there is no increase in the concentration of free virus. In fact, instead of the density to increase it reduces. Fig (5) represents that there in no effect of our optimal control strategies on the density of recombinant virus as our focus is only to use the drugs which have the effect only on the reducing the number of pathogen virus. Fig (6) is the representation of optimal treatments u_1 and u_2. One can see that control u_1 is on its maximal value all the time and boosts healthy cells efficiently.

5. Conclusion

In this work, we have presented double delayed HIV-1 infection model with two controls variables. Although, there is no effective therapy for HIV infection but different treatments have a role to block the virus production in the body and maintain

TABLE 1. The values of parameters used for numerical simulation

Parameters	Definition	Values with sources
λ	Production rate of host cell	4 cell/mm^3 [3]
d	Death rate of host cell	0.01 [16]
β	Infection rate of host cell by virus	0.004 mm^3/vir [9]
a	Death rate of HIV-1 infected cell	0.09[14]
α	Infection rate by recombinant	0.004 [9]
b	Death rate of double-infected cell	1 (assumed)
k	HIV-1 production rate by a cell	0.02 vir/cell [3]
p	Removal rate of HIV-1	0.004 (assumed)
c	Production rate of recombinant by a double-infected cell	0.05 vir/cell (assumed)
q	Removal rate of recombinant	1 (assumed)
a_1	rate of death of cells before infection	0.05 [3]
a_2	rate of clearness of virus before attachment to cells	0.01 [9]
τ_1	latent period	1 [3]
τ_2	virus production period	1 [3]
ξ_1	Weight Constant	9000 (assumed)
ξ_2	Weight Constant	770 (assumed)
A	Constant	100 (assumed)

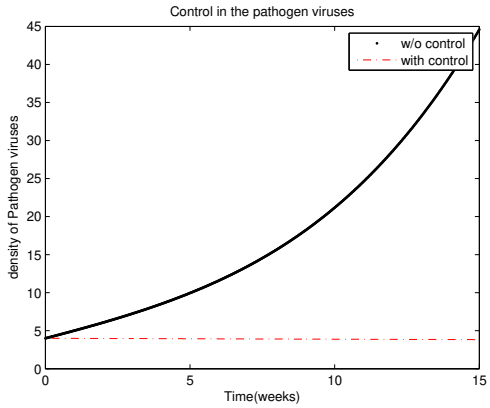

FIGURE 2. The graph represents the density of infected cells verses time t in weeks.

balance between the virus and the defense system. The mathematical analysis of the proposed model shows the effectiveness of the model in increasing the density of uninfected CD^{4+} T cells, reducing the concentrations of infected cells and free virions in the body with a minimum side effects and also indirectly minimizing the cost of

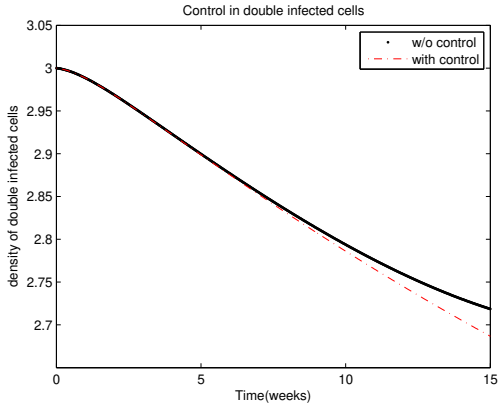

FIGURE 3. The graph represents the density of double infected cells verses time t in weeks.

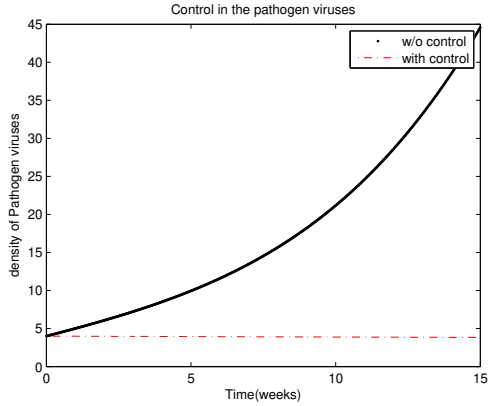

FIGURE 4. The graph represents the density of pathogen virus verses time t in weeks.

treatment. Certainly, these results could be useful in developing improved treatment regimen for addressing the challenge of HIV/AIDS.

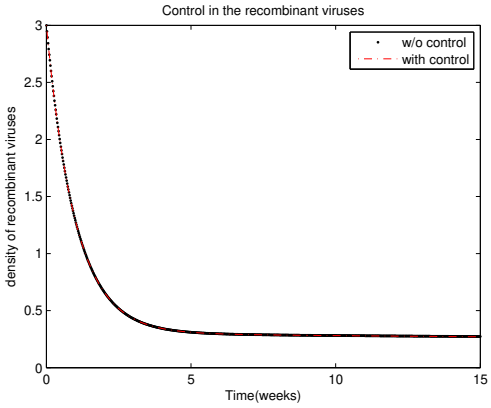

FIGURE 5. The graph represents the density of recombinant virus verses time t in weeks.

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