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Analysis of optimal control problem of HIV-1 model of engineered virus

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ABSTRACT

In this article, an optimal control problem of HIV-1 infection model consists of pathogen virus and engineered virus is taken into account. The purpose of this work is to investigate an optimal control model of drug treatment of HIV infection of genetically modified virus and CD4+T-cells. The optimal control problem is to design an effective drug plan in order to reduce the number of infected cells and free virions for patients infected by HIV. Two kinds of treatments are used, and existence and uniqueness results for the optimal control pair are established. Pontryagins maximum principle is used to characterize the optimal levels of the controls. The results of optimality are solved numerically using MATLAB software. In the last few decades, the researchers have focused on controlling problems on similar models of HIV infection in different types of models using treatment with a single drug and similar objective functional. Many researchers have studied the HIV models consisting of the only class of pathogen virus and class of single infected cells. Here we consider the HIV-1 optimal control problem consisting of a genetically modified virus and double infected cells.

1. Introduction

HIV stands for a human immunodeficiency virus which is lentivirus that causes AIDS (acquired immunodeficiency syndrome). In this stage, the immune system is badly damaged, which can cause the life-threatening opportunistic infections. AIDS emerged in 1981 which is sexuality transmitted disease throughout the world. More than 30 million people have been killed in the last 30 years (Jordan et al., 2012). It is approximated that HIV spreads at the rate of 7, 000 people per day (Jordan et al., 2012). Nowadays, several antiretroviral drugs are available which can help the immune system in reducing the HIV-1 infection. Although it is not possible to cure it. RTIs which stands for Reverse Transcriptase Inhibitors are the type of chemotherapies which can oppose the conversion of RNA of the virus to DNA. Thus, the viral population will be minimum and the CD4+ count remains higher and due to this the host can survive. The other types are protease inhibitors (PIs) which keep the density of new viruses minimum. In the literature, optimal control theory has been applied in the analysis of in-host HIV dynamics as well as in population-based HIV models. Consequently, researchers have formulated and analyzed mathematical models in order to understand the dynamics of HIV-1 infection (Fister et al., 1998; Adams et al., 2005; Kirschner et al., 1997; Ali and Zaman, 2016; Richter et al., 1999; Zhou et al., 2008; Cohen et al., 2011; Boltyanskii et al., 1960; Joshi, 2002; Garira et al., 2005; Revilla and García-Ramos, 2003; Ali et al., 2017). From another point of view, optimal control theory has been applied to biological or medical models to draw conclusions about the control of infections (Kirschner et al., 1997; Garira et al., 2005; Ali et al., 2017). The desired goals, performance and outcomes of control actions depend on specific situations. The foundation of theoretical approach of optimal control was developed by Pontryagin et al. (1962). They applied this theory to ordinary differential equations. After that, the applications of this theory and corresponding numerical simulations are progressing continuously. One can find an interesting work on control of epidemics in Joshi (2002) and a survey on the control of pests and infectious diseases in Joshi (2002). For this purpose, an optimal control model of HIV therapy was considered by Fister et al. (1998). This model represents the effects of the treatment on the interaction of the healthy T cells with the pathogen virus. Joshi (2002) examined an optimal control HIV-

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1 infection model which was consists of two optimal controls. One for strengthening the immune system and the other for delaying HIV-1 progression. Further, a single control variable was taken into account in Garira et al. (2005) which represents the percentage effect of the chemotherapy and viral production. Then, Garira et al. (2005) considered two controls variables which simulate the effects of RTIs and PIs. These models are used to investigate an optimal chemotherapy treatment to avoid drugs beyond normal limits. Therefore, we chose an HIV-1 infection within-host model which is focusing on mathematical study supporting the previous HIV-1 models. Our proposed model of genetically modified virus is consists of system of ordinary differential equations which was considered in Fleming and Rishel (1975).

In the literature cited above, one can observe that as much as ARTs have been used for the suppression of virus, the optimal control treatment is necessary to keep low viral load is an approximation. At the time, when HIV cure is found, physicians will try their best to apply the control strategy that can inhibit viral progression while keeping the side effects to a minimum. Most of the drugs have side effects that should be maintained at a very low level. As, long-term use of protease inhibitors cause insulin intolerance, cholesterol elevation, and the redistribution of body fat. Therefore, there is a need to establish the optimal treatment strategy. hus, we formulate a (new) model by introducing optimal controls, representing the regular use of microbicide gel and treatment by HAART. Thus, by adopting this policy, the following three objectives will be obtained: (a) maximizing the healthy T cells populations, (b) minimizing virus population and (c) minimizing the infected T cells population.

2. The mathematical model

The following HIV-1 model was considered by Revilla and García-Ramos (2003) which discusses the approach of fighting HIV with a recombinant virus and capable of controlling the infections of HIV-1:

$$\left.\begin{aligned} \frac{dI_1(t)}{dt} &= \lambda - dI_1(t) - \beta I_1(t)P_v(t), \\ &\text{and} \\ \frac{dI_2(t)}{dt} &= \beta I_1(t)P_v(t) - aI_2(t) - \alpha R_v(t)I_2(t), \\ &\text{and} \\ \frac{dI_3(t)}{dt} &= \alpha R_v(t)I_2(t) - bI_3(t), \\ &\text{and} \\ \frac{dP_v(t)}{dt} &= kI_2(t) - pP_v(t), \\ &\text{and} \\ \frac{dR_v(t)}{dt} &= cI_3(t) - qR_v(t). \end{aligned}\right\} \quad (1)$$

with initial conditions

$$T(t_0) = T^0,\ I(t_0) = I^0,\ D(t_0) = D^0,\ V_p(t_0) = V_p^0,\ V_r(t_0) = V_r^0 \quad (2)$$

Here $I_1(t)$, $I_2(t)$, $I_3(t)$, $P_v(t)$ and $R_v(t)$ stand for the concentrations of uninfected T cells, single infected T cells, double infected T cells, pathogen virus, and recombinant virus respectively at any time t. The parameters of the model can be defined as follows: uninfected T cells are produced at rate λ and die at rate a. The rate of infection of healthy cells is denoted by β and d is the death rate of infected cells. The new viruses are produced at rate k. p is the death rate of pathogen virus. q is the death rate of recombinant virus. c is the rate of production of double infected cells. The rate of infection of infected T cells is denoted by α and b is the death rate of double infected T cells.

The rest of the paper is divided as follows: next section is the formulation of the optimal control model. Section 4 is devoted to examine the existence of the optimal control. In section 5, we will study the theatrical derivations of the optimal controls. Numerical simulations will be carried out in section 6 and conclusions will be drawn in Section 7 respectively.

3. The policy of optimal control

We incorporate the following two control variables in the system (1): the first control $K_1(t)$ is applied to the first step of infection, which compromise the entry of virus into the host cell. Therefore, it is brought into the infection term $\beta I_1 P_v$ to reduce parameter β. It could be an entry inhibitor, or treatments of other types which can block infection caused by pathogen virus (Revilla and García-Ramos, 2003). The second control $K_2(t)$ represents HAART treatment which is highly active antiretroviral therapy. The effect of HAART is to produce viruses which are non-infectious. Therefore, it is introduced into the term kI_2 to reduce the value of the parameter k. The following controlled system can be obtained by using the above assumptions:

$$\left.\begin{aligned} \frac{dI_1(t)}{dt} &= \lambda - dI_1(t) - (1-K_1(t))\beta I_1(t)P_v(t), \\ &\text{and} \\ \frac{dI_2(t)}{dt} &= (1-K_1(t))\beta I_1(t)P_v(t) - aI_2(t) - \alpha R_v(t)I_2(t), \\ &\text{and} \\ \frac{dI_3(t)}{dt} &= \alpha R_v(t)I_2(t) - bI_3(t), \\ &\text{and} \\ \frac{dP_v(t)}{dt} &= k(1-K_2(t))I_2(t) - pP_v(t), \\ &\text{and} \\ \frac{dR_v(t)}{dt} &= cI_3(t) - qR_v(t). \end{aligned}\right\} \quad (3)$$

The biological interpretation of the proposed model is to maximize the density of uninfected healthy T cells and minimize the viral load.

We define the objective functional T (to be maximized over all $K_1(t), K_2(t) \in U$)

$$J(K_1(t), K_1(t)) = \int_0^T [\rho I_1(t) - (W_1K_1^2(t) + W_2K_2^2(t)] \quad (4)$$

The proposed objective functional focuses on the maximization of heathy T cells over the time period $[0,T]$ by means of the first term in the integrand. Here, $\rho I_1(t)$ shows the benefits of T cells. Moreover, the systemic costs of the drug therapy are represented by $W_1K_1^2(t)+W_2K_2^2(t)$. The coefficients W_1 and W_2 stand for weight constants. Also, it expected that the effects of drugs are nonlinear and we choose the terms $K_1^2(t)$ and $K_2^2(t)$ which are quadratic cost terms and reflect the side effects of drugs. Our aim is to investigate optimal control pair (K_1,K_2), which satisfies

$$J(\tilde{K}_1(t),\tilde{K}_2(t))=max\{J(K_1(t),K_2(t))\backslash K_1(t),K_2(t)\in U\}, \quad (5)$$

so that the density of the uninfected T cells is increased, and viral load and cost of treatment is reduced, where $U=\{(K_1(t),K_2(t))\backslash K_i(t)$ is Lebesgue measurable on $[0,1],0\le K_i(t)\le 1,i=1,2\}$ is the control set. Next, we discuss the existence of the optimal control pair.

3.1. Existence of control problem

The existence of an optimal control is accomplished by the assumptions of compactness on control and state spaces. Moreover, it can be proved by the structure of convexity of the optimal problem and boundedness of the solutions, and smoothness of the right-hand side of system (1) (Joshi, 2002).

3.2. Conclusions about optimal control pair

The Hamiltonian related to the control system (3) is defined as follows:

$$H=\rho I_1(t)-\frac{1}{2}(W_1K_1^2(t)+W_2K_2^2(t))+\gamma_1(\lambda-dI_1(t)-(1-K_1(t))\beta I_1(t)P_v(t)+\gamma_2(\lambda-K_1(t))-\beta I_1(t)P_v(t)-aI_2(t)-\alpha R_v(t)I_2(t)+\gamma_3(R_v(t)I_2(t)-bI_3(t)+\gamma_4(k(1-K_2(t)I_2(t)-pP_v(t))+\gamma_5(cI_3(t)-qR_v(t)). \quad (6)$$

Further, we derive the necessary conditions for the proposed study by using the Pontryagins Maximum Principle (Boltyanskii et al., 1960). The following three conditions are satisfied for continuous function $\gamma(t)$ on $[0,T]$:

$$x(t)=H_\gamma(x,R_1,R_2,\gamma)(t), \quad (7)$$

which represents the state equation

$$0=H_U(x,R_1,R_2,\gamma)(t), \quad (8)$$

which shows optimality conditions and the adjoint equation is represented by

$$\frac{-d\gamma(t)}{dt}=H_x(x,R_1,R_2,\gamma)(t) \quad (9)$$

here, H_γ, H_U and H_x represent derivatives with respect to $\gamma,R_1,R_2,x(t)$ respectively, where, $x(t)=(I_1(t),I_2(t),I_3(t),P_v(t),R_\gamma(t))$. Next, this Hamiltonian will be used to determine the adjoint system by Pontryagin Maximum Principle (Cohen et al., 2011).

Theorem 3.1: There exist the following adjoint variables $\gamma_n(t),n=1,\ldots,5$, for the given control variables $\tilde{K}_1(t),\tilde{K}_2(t)$ and solutions $\tilde{I}_1(t),\tilde{I}_2(t),\tilde{I}_3(t),\tilde{P}_v(t),\tilde{R}_v(t)$ of the corresponding state system (1).

$$\left.\begin{aligned}\frac{d\gamma_1}{dt}&=[\gamma_1(t)(\rho-\tilde{K}_1(t)-\gamma_2(t)]\beta\tilde{P}_v(t)-\rho+\gamma_1(t)d,\\ &\text{and}\\ \frac{d\gamma_2}{dt}&=a\gamma_2(t)+(\gamma_2(t)-\gamma_3(t))\alpha\tilde{R}_v(t)-\gamma_4(t)k(1-\tilde{K}_2(t)),\\ &\text{and}\\ \frac{d\gamma_3}{dt}&=b\gamma_3(t)-c\gamma_5(t),\\ &\text{and}\\ \frac{d\gamma_4}{dt}&=((\gamma_1(t)(\rho\tilde{K}_1(t))-\gamma_2(t)))\beta\tilde{I}_1(t)+\gamma_4(t)p,\\ &\text{and}\\ \frac{d\gamma_5}{dt}&=(\gamma_2(t)-\gamma_3(t))\alpha\tilde{I}_2(t)+\gamma_5(t)q.\end{aligned}\right\} \quad (10)$$

along with $\gamma_n(T)=0,n=1,2,\ldots,5$, which are transversality conditions.

Proof: Pontryagins Maximum Principle (Cohen et al., 2011) and the substitutions $I_1=\tilde{I}_1,I_2=\tilde{I}_2,I_3=\tilde{I}_3,P_v=\tilde{P}_v,R_v=\tilde{R}_v,K_1=\tilde{K}_1,K_2=\tilde{K}_2$ give the adjoint system (10), after determining the following differentiations:

$$\frac{d\gamma_1}{dt}=-\frac{\partial H}{\partial I_1},\frac{d\gamma_2}{dt}=-\frac{\partial H}{\partial I_2},\frac{d\gamma_3}{dt}=-\frac{\partial H}{\partial I_3},\frac{d\gamma_4}{dt}=-\frac{\partial H}{\partial P_v},\frac{d\gamma_5}{dt}=-\frac{\partial H}{\partial R_v},$$

which satisfy the transversality conditions $\gamma_n(T)=0,n=1,2,\ldots,5$.

Theorem 3.2: The optimal control pair $(\tilde{K}_1(t),\tilde{K}_2(t))$, which maximizes J over U is given by

$$\tilde{K}_1(t)=max\{min\{K_1(t),1\},0\} \quad (11)$$
$$\tilde{K}_2(t)=max\{min\{K_2(t),1\},0\} \quad (12)$$

where, $K_1(t)=\frac{\tilde{I}_1(t)\lambda_1}{2W_1}$, $K_2(t)=-\frac{k\tilde{I}_2(t)\gamma_4(t)}{2W_2}$.

Proof: The optimality conditions are used to find the following:

$$\frac{\partial H}{\partial K_1}=\gamma_1(t)\tilde{I}_1(t)\beta P_v(t)-2W_1(t)\tilde{K}_1(t),\text{ at } K_1=\tilde{K}_1 \quad (13)$$

and

$$\frac{\partial H}{\partial K_2}=-2W_2\tilde{K}_2(t)-\gamma_4(t)kI_2(t),\text{ at } K_2=\tilde{K}_2 \quad (14)$$

The following equations can be obtained after solving for $\tilde{K}_1(t),\tilde{K}_2(t)$:

$$K_1(t)=\frac{\beta\gamma_1(t)\tilde{I}_1(t)P_v(t)}{2W_1} \quad (15)$$
$$K_2(t)=-\frac{k\tilde{I}_2(t)\gamma_4(t)}{2W_2} \quad (16)$$

By using the bounds $0 \le K_1 \le 1$ and $0 \le K_2 \le 1$, after letting $K_1(t) = \frac{\tilde{I}_1(t)\lambda_1}{2W_1}$, $K_2(t) = -\frac{k\tilde{I}_2(t)\gamma_4(t)}{2W_2}$, we get Equations (11) and (12).

Thus, we get the following optimality system (Boltyanskii et al., 1960; Joshi, 2002; Kirschner et al., 1997; Garira et al., 2005; Revilla and García-Ramos, 2003; Ali et al., 2017; Fleming and Rishel, 1975):

$$\left.\begin{aligned}
\frac{dI_1(t)}{dt} &= \lambda - dI_1(t) - (1 - max\{min\{K_1(t),1\},0\})\beta I_1(t)P_v(t),\\
\frac{dI_2(t)}{dt} &= (1 - max\{min\{K_1(t),1\},0\})\beta I_1(t)P_v(t) - aI_2(t) - \alpha R_v(t)I_2(t),\\
\frac{dI_3(t)}{dt} &= \alpha R_v(t)I_2(t) - bI_3(t),\\
\frac{dP_v(t)}{dt} &= k(1 - max\{min\{K_2(t),1\},0\})I_2(t) - pP_v(t),\\
\frac{dR_v(t)}{dt} &= cI_3(t) - qR_v(t).\\
\frac{d\gamma_1}{dt} &= [\gamma_1(t)(\rho - \tilde{K}_1(t) - \gamma_2(t)]\beta\tilde{P}_v(t) - \rho + \gamma_1(t)d,\\
\frac{d\gamma_2}{dt} &= a\gamma_2(t) + (\gamma_2(t) - \gamma_3(t))\alpha\tilde{R}_v(t) - \gamma_4(t)k(1 - \tilde{K}_2(t)),\\
\frac{d\gamma_3}{dt} &= b\gamma_3(t) - c\gamma_5(t),\\
\frac{d\gamma_4}{dt} &= ((\gamma_1(t)(\rho\tilde{K}_1(t)) - \gamma_2(t)))\beta\tilde{I}_1(t) + \gamma_4(t)p,\\
\frac{d\gamma_5}{dt} &= (\gamma_2(t) - \gamma_3(t))\alpha\tilde{I}_2(t) + \gamma_5(t)q.\\
\tilde{K}_1(t) &= max\{min\{K_1(t),1\},0\\
\tilde{K}_2(t) &= max\{min\{K_2(t),1\},0\}
\end{aligned}\right\} \quad (17)$$

along with initial conditions $T(t_0) = T^0$, $I(t_0) = I^0$, $D(t_0) = D^0$, $V_p(t_0) = V_p^0$, $V_r(t_0) = V_r^0$ transversility conditions $\gamma_n(T) = 0, n = 1,2,\ldots,5$.

4. Numerical simulation

We introduce in this part the comparison of the progression of HIV-1 infection before and after the control treatment chemotherapy. Therefore, for the following parameters and initial values, we use some of the values from the exiting literature and some are estimated: $\lambda = 2$ (Joshi, 2002), $\alpha = 0.0004$ (Ali et al., 2017), $d = 0.01$ (Fleming and Rishel, 1975), $\beta = 0.004$ (Fleming and Rishel, 1975; Ali et al., 2016), $c = 20$ (estimated), $b = 0.5$ (estimated), $k = 0.1$ (estimated), $p = 0.21$ (estimated), $a = 0.5$ (Kirschner et al., 1997), $q = 3$ (Garira et al., 2005), $I_1^0 = 4$, $I_2^0 = 2$, $I_3^0 = 2$, $P_v^0 = 3$, $R_v^0 = 2$. For this purpose, Runge-Kutta method of order fourth is used. The following figures can justify our proposed strategy.

Figs. 1-6 represent optimal controls plots. When the virus inters in the human body, it destroys and kills the CD4+ cells and due to this reason, the concentration of healthy T cells reduces (Fig. 1). Consequently, the virus P_v spreads more rapidly and so its concentration increases (Fig. 4). But after using the optimal treatment, this situation is controlled. The effects of chemotherapy can be observed after few days. These effects appear in the form of growth of healthy T cells and decrease of virus P_v (Figs. 1 and 4). Moreover, the density of infected cells I_2 decreases after treatment as shown in (Fig. 2). The concentration of double infected cells $I_3(t)$, shown in (Fig. 3), decreases after treatment. Fig. 6 shows the optimal controls treatment for drug administration.

5. Discussion

In this work, optimal control strategies were developed for reducing the infection of HIV-1. Two optimal control treatments were introduced which are enough for reducing the density of infected cells and the population of free viruses. These variables produce very fruitful results. They produce a large amount of healthy cells and bring it to a level which is convenient. Further, the densities of free viruses and infected cells could reach to the low level.

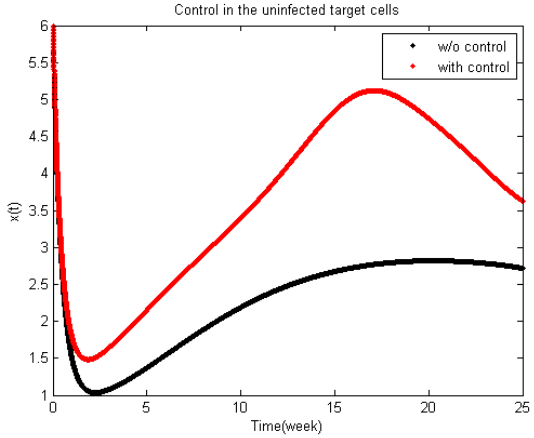

Fig. 1: The difference between the concentration the heathy target cells $I_1(t)$ with and without control

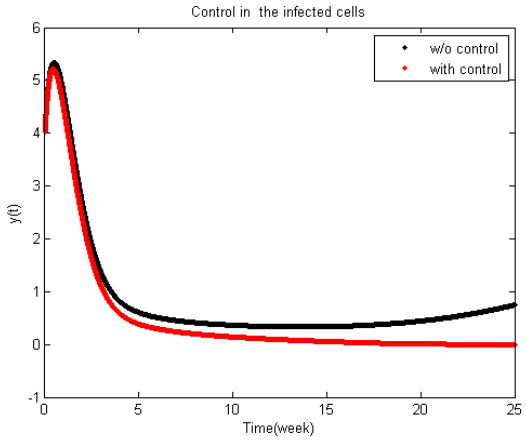

Fig. 2: The difference between the concentration of the infected cells $I_2(t)$ before and after control treatment

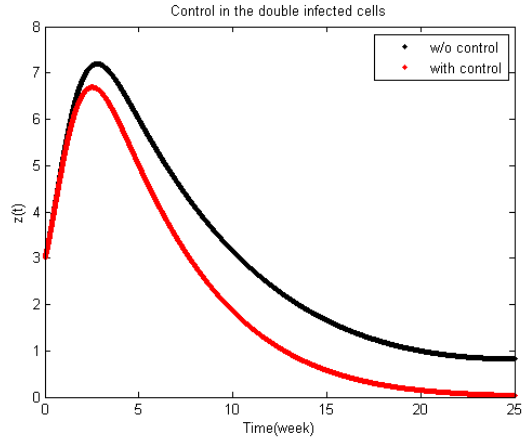

Fig. 3: The difference between the concentration the double infected cells $I_3(t)$ before and after control treatment

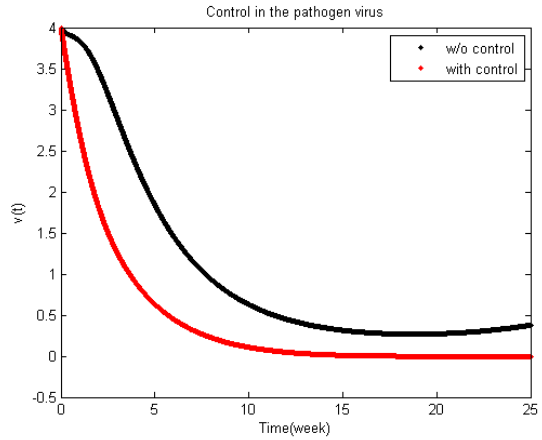

Fig. 4: The difference between the viral load $P_v(t)$ before and after control treatment

One can also observed that during the whole time period for drug administration, K_1 and K_2 stay on value which is maximal. Moreover, an efficient numerical method was presented in order to reduce the infection rate and viral production. The derived results show the growth of healthy T cells, and decrease of infected cells and viral load by using inhibitors and HAART.

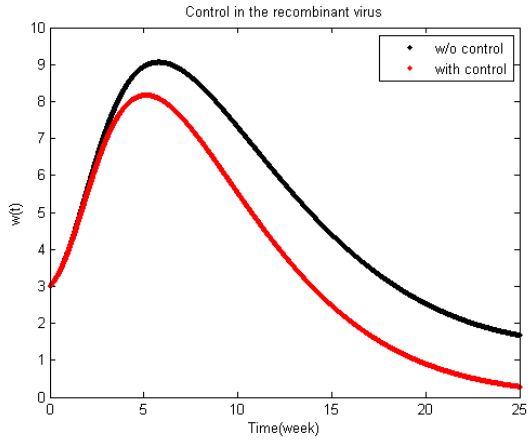

Fig. 5: The difference between the viral load $R_v(t)$ before and after control treatment

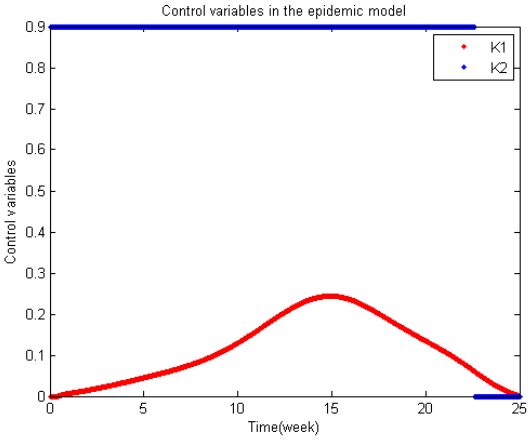

Fig. 6: The graph shows the effect of control variables

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

References

Adams BM, Banks HT, Davidian M, Kwon HD, Tran HT, Wynne SN, and Rosenberg ES (2005). HIV dynamics: Modeling, data analysis, and optimal treatment protocols. Journal of Computational and Applied Mathematics, 184(1): 10-49. https://doi.org/10.1016/j.cam.2005.02.004

Ali N and Zaman G (2016). Asymptotic behavior of HIV-1 epidemic model with infinite distributed intracellular delays. SpringerPlus, 5(1): 324-337. https://doi.org/10.1186/s40064-016-1951-9 **PMid:27066352 PMCid:PMC4789014**

Ali N, Zaman G, and Algahtani O (2016). Stability analysis of HIV-1 model with multiple delays. Advances in Difference Equations, 2016: 88. https://doi.org/10.1186/s13662-016-0808-4

Ali N, Zaman G, and Alshomrani AS (2017). Optimal control strategy of HIV-1 epidemic model for recombinant virus. Cogent Mathematics, 4(1): 1293468. https://doi.org/10.1080/23311835.2017.1293468

Boltyanskii VGE, Gamkrelidze RVY, and Pontryagin LS (1960). The theory of optimal processes. I. The maximum principle. Izvestiya Rossiiskoi Akademii Nauk. Seriya Matematicheskaya, 24(1): 3-42.

Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, and Godbole SV (2011). Prevention of HIV-1 infection with early antiretroviral therapy. New England Journal of Medicine, 365(6): 493-505. https://doi.org/10.1056/NEJMoa1105243 **PMid:21767103 PMCid:PMC3200068**

Fister KR, Lenhart S, and McNally JS (1998). Optimizing chemotherapy in an HIV model. Electronic Journal of Differential Equations, 1998(32): 1-12.

Fleming WH and Rishel RW (1975). Deterministic and stochastic optimal control. Springer Verlag, New York, USA. https://doi.org/10.1007/978-1-4612-6380-7

Garira W, Musekwa SD, and Shiri T (2005). Optimal control of combined therapy in a single strain HIV-1 model. Electronic Journal of Differential Equations, 2005(52): 1-22.

Jordan MR, Bennett DE, Wainberg MA, Havlir D, Hammer S, Yang C, and Nachega JB (2012). Update on world health organization HIV drug resistance prevention and assessment strategy: 2004–2011. Clinical Infectious Diseases, 54(suppl_4): S245-S249. https://doi.org/10.1093/cid/cis206

Joshi HR (2002). Optimal control of an HIV immunology model. Optimal Control Applications and Methods, 23(4): 199-213. https://doi.org/10.1002/oca.710

Kirschner D, Lenhart S, and Serbin S (1997). Optimal control of the chemotherapy of HIV. Journal of Mathematical Biology, 35(7): 775-792. https://doi.org/10.1007/s002850050076 **PMid:9269736**

Pontryagin LS, Boltyanskii VG, Gamkredligze RW, and Mishchenko EF (1962). The mathematical theory of optimal processes. Wiley, New York, USA.

Revilla T and García-Ramos G (2003). Fighting a virus with a virus: A dynamic model for HIV-1 therapy. Mathematical Biosciences, 185(2): 191-203. https://doi.org/10.1016/S0025-5564(03)00091-9

Richter A, Brandeau ML, and Owens DK (1999). An analysis of optimal resource allocation for prevention of infection with human immunodeficiency virus (HIV) in injection drug users and non-users. Medical Decision Making, 19(2): 167-179. https://doi.org/10.1177/0272989X9901900207 **PMid:10231079**

Zhou X, Song X, and Shi X (2008). A differential equation model of HIV infection of CD4+ T-cells with cure rate. Journal of Mathematical Analysis and Applications, 342(2): 1342-1355. https://doi.org/10.1016/j.jmaa.2008.01.008