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Comparison Of Different Control Strategies With Optimal Control Of Immunotherapeutic Treatment For HIV Infections*

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Abstract

The dynamics of CD4$^+$T cells and infected virus particles are described by a system of nonlinear ordinary differential equations and that mathematical model describes the behaviour of states for HIV infections in the presence of immune boosting nutrition and antiretroviral drugs. In this study, the constant control strategies are introduced for comparison with the optimal control strategy to minimize the treatment cost of HIV infections. The aim of this paper is to find the optimal immunotherapeutic treatment and compare them to various treatment strategies of HIV infections.

1 Introduction

The HIV response across Asia and the Pacific is not progressing as planned due to notable disparities and varying epidemic trajectories. The HIV pandemic in the area disproportionately impacts members of important demographics, particularly youth (15–24 years old) and their sexual partners [UNAIDS 2023]. Worldwide, HIV infection continues to be a serious public health concern. The human immunodeficiency virus (HIV) is responsible for causing acquired immunodeficiency syndrome (AIDS), which was first detected in the United States during the spring of 1981. AIDS is characterized by a severe reduction in CD4$^+$T cells, which means an infected person's immune system deteriorates and becomes vulnerable to contracting life-threatening infections. The presence of HIV in a person can be measured with the numbers of CD4$^+$T cells (i.e. white blood cells) and infected virus particles. The CD4$^+$T cell count is typically above 950 in a healthy individual. In 1995, a combination drug treatment known as the AIDS "Cocktail", referred to as highly active antiretroviral therapy (HAART), was introduced. HAART treatment helps maintain a low viral load and a normal CD4$^+$T cell count. However, this treatment does not cure the virus of an HIV-infected person. It can reduce the number of infected virus particles. Since it is a long-term treatment for HIV infections, the minimization of treatment cost and maximization of CD4$^+$T cells are necessitated. Now, mathematical modeling is a very useful tool to describe and analyze the dynamics of biomedical systems [6, 8, 15]. Joshi (2023) [10] conducted an initial study on immunological interactions between HIV and T-cells, determining the uniqueness of optimal control pairs and numerically solving the resulting optimality system with a fourth-order Runge-Kutta algorithm. Following that, Akudibillah et al. (2019) [1] proposed a mathematical model incorporating the WHO's 5-stage classification of HIV/AIDS disease progression to analyze the best treatment distribution and this study revealed that initiating treatment during Stages II and III is beneficial in reducing infection-years and new infections, whereas treatment during Stages III and IV is more effective in cost reduction and preventing deaths. A more effective approach to the challenges of HIV immunotherapy was proposed in a study by Biswas et al. (2019) [3] that implemented the Pontryagin maximum principle and a state constraint to develop an optimal treatment strategy for designing and implementing antiretroviral therapy for HIV infections aimed at maximizing CD4$^+$T cell count while reducing side effects and cost. Biswas et al. (2022) [4] investigated the transmission dynamics of HIV/AIDS, tuberculosis, and their co-infections, emphasizing the efficacy of optimal treatment-vaccination combinations. They stress the importance of counseling for HIV-TB co-infected individuals, early detection,

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treatment accessibility, and strategic plans to reduce transmission for effective disease management. After that, Mallick et al. (2023) [14] introduced a mathematical model for determining an optimal treatment approach applying target-oriented-treatment (TOT) for HIV infections. It is shown how the virus behaves when taking an antiretroviral medication and immune-boosting nutrition, and they observed that the number of infected particles can be reduced to almost nothing if the number of $CD4^+T$ cells does not decrease during treatment. Recently, some researchers used fractional calculus to model HIV infections, capturing the virus's intricate dynamics and its interaction with the immune system to better represent the infection process and demonstrate how chaotic parameters can control system chaos [9]. Besides, in order to study the system's behavior over the long term, Ahmad et al. (2023) [2] investigate both qualitative analysis and computer modeling, focusing on a fractional-order HIV model that uses the Caputo fractional differential operator. Here, a system of nonlinear ordinary differential equations describe the change of $CD4^+T$ cells count and the infected virus particles for HIV infections similar to the models of Kirschner [13], Webb [11], Serbin [12], Biswas [3, 5] and Perelson [20]. These models describe the interactions between $CD4^+T$ cells (i.e. white blood cells) and infected virus particles of a person. Let us consider $T(t)$ and $V(t)$ to represent the virus free $CD4^+T$ cells and infected virus particles respectively. Then, the present model is represented by a system of nonlinear ordinary differential equations below:

$$\frac{dT(t)}{dt} = s_1 - \frac{s_2 V(t)}{\beta_1 + V(t)} - \mu T(t) - kV(t)T(t), \tag{1}$$

$$\frac{dV(t)}{dt} = \frac{\gamma V(t)}{\beta_2 + V(t)} - \alpha V(t)T(t) \tag{2}$$

with the initial conditions

$$T(0) = T_0, \quad V(0) = V_0 \tag{3}$$

where $s_1 - \frac{s_2 V(t)}{\beta_1 + V(t)}$ represents the proliferation of virus free $CD4^+T$ cells and $\mu T(t)$ is the natural death of $CD4^+T$ cells, $kV(t)T(t)$ is the reduction of $CD4^+T$ cells by virus infections, $\frac{\gamma V(t)}{\beta_2 + V(t)}$ is the growth of infected virus particles and $\alpha V(t)T(t)$ is the depletion of virus by $CD4^+T$ cells and the descriptions of parameters were presented in Table 1 [4, 10]. Joshi [10] introduced the two control variables u_1 and u_2 which represent the control of immune boosting nutrition and antiretroviral drugs respectively in the following two compartmental dynamics of the optimal controlled model with the uniqueness of optimality system. The existence of the optimal control pair can be obtained by Fleming and Rishel [7].

$$\frac{dT(t)}{dt} = s_1 - \frac{s_2 V(t)}{\beta_1 + V(t)} - \mu T(t) - kV(t)T(t) + u_1(t)T(t), \tag{4}$$

$$\frac{dV(t)}{dt} = \frac{\gamma(1 - u_2(t))V(t)}{\beta_2 + V(t)} - \alpha V(t)T(t) \tag{5}$$

with the same initial conditions (3). Here, $u_1 = 0$ indicates no immune boosting nutrition, $u_2 = 0$ means no antiretroviral drugs and $u_1 = 0.02$ indicates maximum food for immune boosting nutrition, $u_2 = 0.9$ means the maximum doses of antiretroviral drugs. $0 \le u_1 \le 0.02$ and $0 \le u_2 \le 0.9$ means the optimal control for the following objective functional satisfying the state system (4)–(5) with the initial conditions (3).

$$\text{maximize } J(u_1(t), u_2(t)) = \int_0^{t_f} (T(t) - B_1 {u_1}^2(t) - B_2 {u_2}^2(t))dt \tag{6}$$

where B_1 and B_2 are the balancing parameters to find for an optimal solution. In this study, we analyze the model for different control strategies such as i) only immune boosting nutrition (no antiretroviral drugs), ii) only antiretroviral drugs (no immune boosting nutrition), iii) control of antiretroviral drugs with maximum food for immune boosting nutrition, iv) control of immune boosting nutrition with maximum doses of antiretroviral drugs, v) no control of immune boosting nutrition and antiretroviral drugs, vi) optimal control of immune boosting nutrition and antiretroviral drugs etc. We also observe the importance of immune boosting nutrition and antiretroviral drugs for HIV infections. We will find the answer of the question "what is better of immune boosting nutrition and antiretroviral drugs for HIV infections?".

2 Mathematical Analysis

2.1 Existence and Uniqueness of the Model Solution

Theorem 1 (Existence and uniqueness of the model solution) *Let D be the domain defined in such a way that Lipschitz conditions are satisfied. Then, for all non-negative initial conditions, the solutions of the system exist and they are also unique at the same time for all time $T \geq 0$ in the domain D.*

Proof. It has come to light that the proposed theorem mentioned in [16, 22] needs to be followed, which suggests that the Lipschitz criterion for the existence and uniqueness of a solution must be followed in a region D. Let

$$f(T,V) = \frac{dT}{dt} = s_1 - \frac{s_2 V}{B_1 + V} - \mu T - KVT,$$

$$g(T,V) = \frac{dV}{dt} = \frac{\gamma V}{B_2 + V} - \alpha VT.$$

Using the above system's equation, the partial derivative of f, g, with respect to compartments T, V are obtained as:

$$\frac{\partial f}{\partial T} = -\mu - KV, \quad \therefore \left|\frac{\partial f}{\partial T}\right| = \mu + KV < \infty,$$

$$\frac{\partial f}{\partial V} = \frac{s_2 V}{(B_1+V)^2} - KT - \frac{s_2}{B_1+V}, \quad \therefore \left|\frac{\partial f}{\partial V}\right| = \left|\frac{s_2 V}{(B_1+V)^2} - KT - \frac{s_2}{B_1+V}\right| < \infty,$$

$$\frac{\partial g}{\partial T} = -\alpha V, \quad \therefore \left|\frac{\partial g}{\partial T}\right| = \alpha V < \infty,$$

$$\frac{\partial g}{\partial V} = \frac{\gamma}{B_2+V} - \alpha T - \frac{\gamma V}{(B_2+V)^2}, \quad \therefore \left|\frac{\partial g}{\partial V}\right| = \left|\frac{\gamma}{B_2+V} - \alpha T - \frac{\gamma V}{(B_2+V)^2}\right| < \infty.$$

Hence we have shown that all the partial derivatives are continuous and bounded. Therefore, Lipschitz's conditions are satisfied. Hence by theorem discussed in [22], there exists a unique solution of considering a system in the region D. ■

2.2 Equilibrium Analysis

To obtain the equilibrium point of the system, we have to solve the following algebraic equations

$$s_1 - \frac{s_2 V^*}{\beta_1 + V^*} - \mu T^* - kV^* T^* = 0, \tag{7}$$

$$\frac{\gamma V^*}{\beta_2 + V^*} - \alpha V^* T^* = 0. \tag{8}$$

Solving (7) and (8), we get the unique nonnegative equilibrium point $(T^*, V^*) = \left(\frac{s_1}{\mu}, 0\right)$. This nonnegative equilibrium point indicates the necessity of highly active antiretroviral therapy (HAART) to decrease the virus.

2.3 Local Stability

Finding equilibrium points (T^*, V^*), the characteristic equation of the system (4)–(5) around its equilibrium point is calculated as follows:

$$D_1 \lambda^2 + D_2 \lambda + D_3 = 0 \tag{9}$$

where

$$
\begin{aligned}
D_1 &= V^{*4}+2V^{*3}\beta_1+2V^{*3}\beta_2+V^{*2}\beta_1^2+4V^{*2}\beta_1\beta_2+V^{*2}\beta_2^2+2V^{*}\beta_1^2\beta_2+2V^{*}\beta_1\beta_2^2+\beta_1^2\beta_2^2,\\
D_2 &= V^{*5}k+V^{*4}\mu+V^{*3}\beta_1^2k+V^{*3}\beta_2^2k+V^{*2}\beta_1^2\mu+V^{*2}\beta_2^2\mu+\beta_1^2\beta_2^2\mu+T^{*}V^{*4}\alpha-V^{*2}\beta_2\gamma\\
&\quad+2V^{*4}\beta_1k+2V^{*4}\beta_2k+2V^{*3}\beta_1\mu+2V^{*3}\beta_2\mu-\beta_1^2\beta_2\gamma+2T^{*}V^{*3}\alpha\beta_1+2T^{*}V^{*3}\alpha\beta_2\\
&\quad+4V^{*3}\beta_1\beta_2k+2V^{*}\beta_1\beta_2^2\mu+2V^{*}\beta_1^2\beta_2\mu+4V^{2}\beta_1\beta_2\mu+T^{*}V^{*2}\alpha\beta1^2+T^{*}V^{*2}\alpha\beta_2^2\\
&\quad+T^{*}\alpha\beta_1^2\beta_2^2+V^{*}\beta_1^2\beta_2^2k+2V^{*2}\beta_1\beta_2^2k+2V^{*2}\beta_1^2\beta_2k-2V^{*}\beta_1\beta_2\gamma+2T^{*}V^{*}\alpha\beta_1\beta_2^2\\
&\quad+2T^{*}V^{*}\alpha\beta_1^2\beta_2+4T^{*}V^{*2}\alpha\beta_1\beta_2,\\
D_3 &= T^{*}V^{*4}\alpha\mu-V^{*3}\beta_2\gamma k-V^{*3}\alpha\beta_1s_2-V^{*2}\beta_2\gamma\mu-\beta_1^2\beta_2\gamma\mu+T^{*}\alpha\beta_1^2\beta_2^2\mu-2V^{*}\beta_1\beta_2\gamma\mu\\
&\quad+2T^{*}V^{*3}\alpha\beta_1\mu+2T^{*}V^{*3}\alpha\beta_2\mu-V^{*}\beta_1^2\beta_2\gamma k-2V^{*2}\beta_1\beta_2\gamma k-V\alpha\beta_1\beta_2^2s_2-2V^{*2}\alpha\beta_1\beta_2s_2\\
&\quad+T^{*}V^{*2}\alpha\beta_1^2\mu+T^{*}V^{*2}\alpha\beta_2^2\mu+2T^{*}V^{*}\alpha\beta_1\beta_2^2\mu+2T^{*}V^{*}\alpha\beta_1^2\beta_2\mu+4T^{*}V^{*2}\alpha\beta_1\beta_2\mu.
\end{aligned}
$$

Now we consider $\frac{D_2}{D_1}=N_1-N_2\gamma$ and $\frac{D_3}{D_1}=N_3-N_4\gamma$ with respect to the parameter γ, where,

$$
\begin{aligned}
N_1 &= (V^{*5}k+V^{*4}\mu+V^{*3}\beta_1^2k+V^{*3}\beta_2^2k+V^{*2}\beta_1^2\mu+V^{*2}\beta_2^2\mu+\beta_1^2\beta_2^2\mu+T^{*}V^{*4}\alpha+2V^{*4}\beta_1k\\
&\quad+2V^{*4}\beta_2k+2V^{*3}\beta_1\mu+2V^{*3}\beta_2\mu+2T^{*}V^{*3}\alpha\beta_1+2T^{*}V^{*3}\alpha\beta_2+4V^{*3}\beta_1\beta_2k+2V^{*}\beta_1\beta_2^2\mu\\
&\quad+2V^{*}\beta_1^2\beta_2\mu+4V^{2}\beta_1\beta_2\mu+T^{*}V^{*2}\alpha\beta1^2+T^{*}V^{*2}\alpha\beta_2^2+T^{*}\alpha\beta_1^2\beta_2^2+V^{*}\beta_1^2\beta_2^2k+2V^{*2}\beta_1\beta_2^2k\\
&\quad+2V^{*2}\beta_1^2\beta_2k+2T^{*}V^{*}\alpha\beta_1\beta_2^2+2T^{*}V^{*}\alpha\beta_1^2\beta_2+4T^{*}V^{*2}\alpha\beta_1\beta_2)/(V^{*4}+2V^{*3}\beta_1+2V^{*3}\beta_2\\
&\quad+V^{*2}\beta_1^2+4V^{*2}\beta_1\beta_2+V^{*2}\beta_2^2+2V^{*}\beta_1^2\beta_2+2V^{*}\beta_1\beta_2^2+\beta_1^2\beta_2^2),\\
N_2 &= (V^{*2}\beta_2+\beta_1^2\beta_2+2V^{*}\beta_1\beta_2)/(V^{*4}+2V^{*3}\beta_1+2V^{*3}\beta_2+V^{*2}\beta_1^2+4V^{*2}\beta_1\beta_2+V^{*2}\beta_2^2\\
&\quad+2V^{*}\beta_1^2\beta_2+2V^{*}\beta_1\beta_2^2+\beta_1^2\beta_2^2),\\
N_3 &= (T^{*}V^{*4}\alpha\mu-V^{*3}\alpha\beta_1s_2+T^{*}\alpha\beta_1^2\beta_2^2\mu+2T^{*}V^{*3}\alpha\beta_1\mu+2T^{*}V^{*3}\alpha\beta_2\mu-V\alpha\beta_1\beta_2^2s_2\\
&\quad-2V^{*2}\alpha\beta_1\beta_2s_2+T^{*}V^{*2}\alpha\beta_1^2\mu+T^{*}V^{*2}\alpha\beta_2^2\mu+2T^{*}V^{*}\alpha\beta_1\beta_2^2\mu+2T^{*}V^{*}\alpha\beta_1^2\beta_2\mu\\
&\quad+4T^{*}V^{*2}\alpha\beta_1\beta_2\mu)/(V^{*4}+2V^{*3}\beta_1+2V^{*3}\beta_2+V^{*2}\beta_1^2+4V^{*2}\beta_1\beta_2+V^{*2}\beta_2^2+2V^{*}\beta_1^2\beta_2\\
&\quad+2V^{*}\beta_1\beta_2^2+\beta_1^2\beta_2^2),\\
N_4 &= (V^{*3}\beta_2k+V^{*2}\beta_2\mu+\beta_1^2\beta_2\mu-2V^{*}\beta_1\beta_2\mu+V^{*}\beta_1^2\beta_2k+2V^{*2}\beta_1\beta_2k)/\\
&\quad(V^{*4}+2V^{*3}\beta_1+2V^{*3}\beta_2+V^{*2}\beta_1^2+4V^{*2}\beta_1\beta_2+V^{*2}\beta_2^2+2V^{*}\beta_1^2\beta_2+2V^{*}\beta_1\beta_2^2+\beta_1^2\beta_2^2).
\end{aligned}
$$

Now using Routh-Hurwitz criterion around equilibrium point, we can state and prove the following theorem for local asymptotical stability of the system (4)–(5).

Theorem 2 *The system will be locally asymptotically stable around the equilibrium point* (T^*,V^*) *if*

$$\min\left\{\frac{N_1}{N_2},\frac{N_3}{N_4}\right\}>\gamma.$$

Proof. Using Routh-Hurwitz criterion, all eigenvalues of the system (4)–(5) contain the negative real part at the equilibrium point (T^*,V^*) if $\frac{D_2}{D_1}>0$ and $\frac{D_3}{D_1}>0$. So, $\frac{N_1}{N_2}>\gamma$ and $\frac{N_3}{N_4}>\gamma$. We can write $\min\left\{\frac{N_1}{N_2},\frac{N_3}{N_4}\right\}>\gamma$. Therefore, the system is locally asymptotically stable around the equilibrium point. ■

2.4 Characteristics of States for Equilibrium Values with Respect to μ

We will discuss the characterization of the equilibrium values of $CD8+T$ cells and infected virus $V(t)$ with respect to μ. From the equations (4)–(6) we can obtain two functions of T^*,V^*,μ as follows:

$$f(T^*,V^*,\mu)=s_1-\frac{s_2V^*}{\beta_1+V^*}-\mu T^*-kV^*T^*, \tag{10}$$

$$g(T^*, V^*, \mu) = \frac{\gamma V^*}{\beta_2 + V^*} - \alpha V^* T^*, \tag{11}$$

$$\frac{dT^*}{d\mu} = \frac{\begin{vmatrix} \frac{\partial f}{\partial V^*} & \frac{\partial f}{\partial \mu} \\ \frac{\partial g}{\partial V^*} & \frac{\partial g}{\partial \mu} \end{vmatrix}}{\begin{vmatrix} \frac{\partial f}{\partial T^*} & \frac{\partial f}{\partial V^*} \\ \frac{\partial g}{\partial T^*} & \frac{\partial g}{\partial V^*} \end{vmatrix}} = \frac{\frac{\partial f}{\partial V^*}\frac{\partial g}{\partial \mu} - \frac{\partial f}{\partial \mu}\frac{\partial g}{\partial V^*}}{\frac{\partial f}{\partial T^*}\frac{\partial g}{\partial V^*} - \frac{\partial f}{\partial V^*}\frac{\partial g}{\partial T^*}}.$$

Then

$$\begin{vmatrix} \frac{\partial f}{\partial V^*} & \frac{\partial f}{\partial \mu} \\ \frac{\partial g}{\partial V^*} & \frac{\partial g}{\partial \mu} \end{vmatrix} = \begin{vmatrix} -kT^* - \frac{\beta_1 s_2}{(\beta_1+V^*)^2} & -T^* \\ \frac{\gamma\beta_2}{(\beta_2+V^*)^2} - \alpha T^* & 0 \end{vmatrix} = T^* \left(\frac{\gamma\beta_2}{(\beta_2+V^*)^2} - \alpha T^* \right),$$

and

$$\begin{aligned} \begin{vmatrix} \frac{\partial f}{\partial T^*} & \frac{\partial f}{\partial V^*} \\ \frac{\partial g}{\partial T^*} & \frac{\partial g}{\partial V^*} \end{vmatrix} &= \begin{vmatrix} -\mu - kV^* & -kT^* - \frac{\beta_1 s_2}{(\beta_1+V^*)^2} \\ -\alpha V^* & \frac{\gamma\beta_2}{(\beta_2+V^*)^2} - \alpha T^* \end{vmatrix} \\ &= -\frac{\gamma\beta_2(\mu + V^*k)}{(\beta_2+V^*)^2} - \frac{\alpha\beta_1 s_2 V^*}{(\beta_1+V^*)^2} + \alpha\mu T^*. \end{aligned}$$

If $\frac{\gamma\beta_2}{(\beta_2+V^*)^2} < \alpha T^*$, then

$$-\frac{\gamma\beta_2(\mu + V^*k)}{(\beta_2+V^*)^2} - \frac{\alpha\beta_1 s_2 V^*}{(\beta_1+V^*)^2} + \alpha\mu T^* < -\alpha T^*(\mu + V^*k) - \frac{\alpha\beta_1 s_2 V^*}{(\beta_1+V^*)^2} + \alpha\mu T^* < -\alpha V^* k - \frac{\alpha\beta_1 s_2 V^*}{(\beta_1+V^*)^2}.$$

Therefore, the both denominator and numerator are negative when $\gamma\mu < \alpha s_1\beta_2$. So, the number of CD4$^+$T cells will be increased when μ increases, satisfying the condition $\gamma\mu < \alpha s_1\beta_2$. From the equation (11), it is seen that the relation between CD4$^+$T cells and virus particles is inversely proportional. Thus, it can be concluded that the viral load decreases when CD4$^+$T cells increase.

2.5 Convergence of CD4$^+$T Cells for Constant Level of Virus Particles

If possible, the virus particles are constant [18] using antiretroviral drugs as well as uptaking immune boosting nutrition. In this situation, we analyze the mathematical model of nonlinear differential equations for HIV patients where the number of virus particles V_c for the above system is constant. From the first equation of the model, we get,

$$\frac{dT}{dt} = s_1 - \frac{s_2 V_c}{B_1 + V_c} - \mu T - K V_c T. \tag{12}$$

Taking limit $t \to \infty$ in the solution of the equation (12) for the initial condition $T(0) = T_0$, then we get

$$\limsup_{t\to\infty} T(t) = \frac{s_1 - \frac{s_2 V_c}{B_1+V_c}}{\mu + KV_c}.$$

Therefore, the sequence of the number of CD4$^+$T cells $\{T_n(t)\}$ converges to $\frac{s_1 - \frac{s_2 V_c}{B_1+V_c}}{\mu+KV_c}$.

3 Characterization of Optimal Control Problem

The model with the objective functional (6) and the states (4)–(5) can be written as an optimal control problem as follows:

$$\text{maximize } J(u_1(t), u_2(t)) = \int_0^{t_f} (T(t) - B_1 {u_1}^2(t) - B_2 {u_2}^2(t))dt, \tag{13}$$

$$\text{subject to } \frac{dT(t)}{dt} = s_1 - \frac{s_2 V(t)}{\beta_1 + V(t)} - \mu T(t) - kV(t)T(t) + u_1(t)T(t), T(0) = T_0, \tag{14}$$

$$\frac{dV(t)}{dt} = \frac{\gamma(1-u_2(t))V(t)}{\beta_2 + V(t)} - \alpha V(t)T(t), V(0) = V_0, \tag{15}$$

with $0 \le u_1(t) \le 0.02$ and $0 \le u_2(t) \le 0.9$. Let us consider the optimal controls $u_1^*(t)$, $u_2^*(t)$ and the corresponding states $T^*(t)$, $V^*(t)$ of the model, using Pontryagin's maximum principle [21, 23], there exist adjoint states $\lambda_1(t)$, $\lambda_2(t)$ satisfying

$$\frac{d\lambda_1(t)}{dt} = -1 + \lambda_1(t)(\mu + kV^*(t) - u_1^*(t)) + \lambda_2(t)\alpha V^*(t), \lambda_1(t_f) = 0, \tag{16}$$

$$\frac{d\lambda_2(t)}{dt} = \lambda_1(t)\left\{\frac{\beta_1 s_2}{(\beta_1 + V^*(t))^2} + kT^*(t)\right\} - \lambda_2(t)\left\{\frac{\beta_2\gamma(1-u_2^*(t))}{(\beta_2 + V^*(t))^2} - \alpha T^*(t)\right\},$$

$$\lambda_2(t_f) = 0, \tag{17}$$

$$u_1^*(t) = \max\left\{0,\ \min\left\{\frac{\lambda_1 T^*(t)}{2\beta_1},\ 0.02\right\}\right\}, \tag{18}$$

and

$$u_2^*(t) = \max\left\{0,\ \min\left\{\frac{-\lambda_2\gamma V^*(t)}{2\beta_2(\beta_2 + V^*(t))},\ 0.9\right\}\right\}. \tag{19}$$

These above optimal controls present an optimal treatment strategy for HIV infections with immune boosting nutrition and antiretroviral drugs.

4 Numerical Simulations

The system of nonlinear ordinary differential equations with control functions and objective functional has been solved using the forward-backward sweep method [17, 19]. The fourth order Runge-Kutta method in forward is used to solve the states and backward is used to solve the adjoints considering the controls are zero. After each iteration, the controls are updated from the conditions (18)–(19). For the iterative process, 1152 time-grid for 50 days treatment schedule is considered and the increment of time $\Delta t = 50/1152 = 0.0434$ is used. Since the optimal control problem is solved by indirect method, the convergence tolerance of cost function at 10^{-8} is acceptable. MATLAB(R2014a) is used to run the program using the value of parameters from Table 1 with the balancing parameters $B_1 = 250000$, $B_2 = 75$ and initial conditions $T(0) = 400$, $V(0) = 2$. In this section, this optimal controlled problem is solved in the absence of controls (i.e. $u_1(t) = 0$, $u_2(t) = 0$), with no control (maximum doses) of immune boosting nutrition and antiretroviral drugs (i.e. $u_1(t) = 0.02$, $u_2(t) = 0.9$) and for optimal immunotherapeutic treatment (i.e. $0 \le u_1(t) \le 0.02$, $0 \le u_2(t) \le 0.9$). Using these different control strategies, the value of objective functional, infected virus particles and $CD4^+T$ cells are calculated and shown in Table 2 which is sorted by the value of objective functional. In Table 2, $u_1(t) = 0$ and $u_2(t) = 0.9$ represent the maximum doses of antiretroviral drugs are recommended in the absence of immune boosting nutrition. Without immune boosting nutrition, the number of $CD4^+T$ cells is insufficient (4.565×10^2) in Figure 3 and the number of infected virus particles is very low (1.100×10^{-3}) in Figure 4. We know that the HAART treatment does not cure the infected virus particles but it can reduce the amount of infected virus particles of HIV infections. We see also that the value of objective functional for that treatment is 1.8386×10^4 (see Table 2). So, without immune boosting nutrition, only antiretroviral drugs are not good treatment for HIV infections. Similarly, $u_1(t) = 0$ and $u_2(t) = 0$ mean without immune boosting nutrition and no antiretroviral drugs. In this situation, the number of $CD4^+T$ cells is very low (3.815×10^2) in Table 2 and Figure 1 and the infected virus particles are 10.22 in Table 2 and Figure 2. Since the value of objective functional is 1.9548×10^4. So, without immune boosting nutrition and no antiretroviral drugs, it is very bad for HIV infections. Now, $u_1(t) = 0$ and $0 \le u_2(t) \le 0.9$ mean optimal control of antiretroviral drugs in the absence of immune boosting nutrition. Figures 9 and 10 show

Table 1: Value and Description of the parameters and constants

Sl. no.	Parameters and constants	Description of Parameters and Constants	Values
1	s_1	Source coefficient of CD4$^+$T Cells	2.0
2	s_2	Source coefficient of infected virus particles	1.5
3	μ	Rate of natural death of CD4$^+$T Cells	0.002
4	λ	Rate of infected CD4$^+$T Cells	0.00025
5	γ	Source coefficient of external virus particles	30
6	α	Death rate of infected virus particles for immune system	0.007
7	β_1	First half-satuaration constant	14
8	β_2	Second half-satuaration constant	1
9	T	Days of drug doses for HAART	50
10	T_0	CD4$^+$T Cells before HAART	400
11	V_0	Infected virus particles before HAART	2

Table 2: Summary of objective functional and states at final time

Sl. no.	Status of Controls	Objective functional	Virus Concentrations	T Cells Count
1	$u_1(t)=0, u_2(t)=0.9$	1.8386×10^4	1.100×10^{-3}	4.565×10^2
2	$u_1(t)=0, u_2(t)=0$	1.9548×10^4	1.022×10^{1}	3.815×10^2
3	$u_1(t)=0$ & $0\le u_2(t)\le 0.9$	1.9869×10^4	9.642×10^{0}	4.018×10^2
4	$u_1(t)=0.02, u_2(t)=0.9$	2.7820×10^4	5.134×10^{-46}	1.145×10^3
5	$0\le u_1(t)\le 0.02$ & $u_2(t)=0.9$	2.8136×10^4	5.718×10^{-45}	1.038×10^3
6	$u_1(t)=0.02, u_2(t)=0$	2.8434×10^4	3.155×10^{0}	1.035×10^3
7	$0\le u_1(t)\le 0.02$ & $u_2(t)=0$	2.8784×10^4	3.619×10^{0}	9.277×10^2
8	$u_1(t)=0.02$ & $0\le u_2(t)\le 0.9$	2.9193×10^4	2.920×10^{0}	1.096×10^3
9	$0\le u_1(t)\le 0.02$ & $0\le u_2(t)\le 0.9$	2.9522×10^4	3.331×10^{0}	9.886×10^2

the states trajectories for the above control strategy. It is interesting that the value of objective functional 1.9869×10^4 for the optimal strategy (see Figures 13 and 14) is greater than the value of objective functional 1.8386×10^4 for the control strategy $u_1(t)=0$, $u_2(t)=0.9$. According to the transversality condition of the optimal controlled problem, the adjoints of states are zero at final time. So, Figures 11 and 12 satisfy the completeness of the optimal controlled problem. But the number of CD4$^+$T cells is very low. So, it is not an appropriate treatment for HIV infections.

Now we will see that the treatment strategy $u_1(t)=0.02$ and $u_2(t)=0.9$ means the maximum doses of antiretroviral drugs and immune boosting nutrition plays a vital role to reduce the infected virus particles (5.134×10^{-46} are close to zero in Table 2 and Figure 8) and build up the CD4$^+$T cells (1.145×10^3 in Table 2 and Figure 7). So, there is no doubt about doses of antiretroviral drugs and immune boosting nutrition. But the value of objective functional is 2.7820×10^4 which is not maximum. Therefore, it is clinically favorable for HIV infection but not optimal. If we control only immune boosting nutrition with maximum doses of antiretroviral drugs (i.e. $0\le u_1(t)\le 0.02$ and $u_2(t)=0.9$), then we get the value of objective functional 2.8136×10^4 which is greater than before. But the number of CD4$^+$T cells (see Figure 27) is less than before and the number of virus particles (see Figure 28) is near to zero. We know that a normal CD4$^+$T cells count is between 800 and 1500 cells per mm^3 for a healthy person. So, we consider CD4$^+$T Cells above 950 cells per mm^3 for a better healthy person. For the treatment strategy, controls are shown in Figures 31–32 and for completeness of optimal solution, the adjoint states are shown in Figures 29–30. So, it is a better treatment than the previous. Now we see an interesting strategy $u_1(t)=0.02$ and $u_2(t)=0$ means only immune

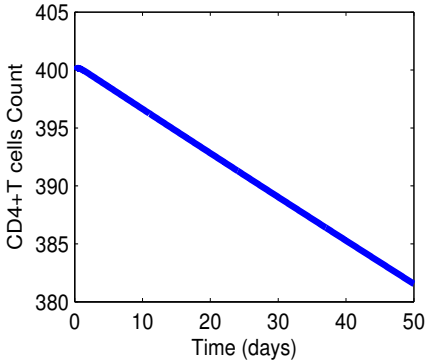

Figure 1: $CD4^+T$ Cells are reducing rapidly when no drugs are recommended for treatment of HIV in absence of immune-boosting nutrition.

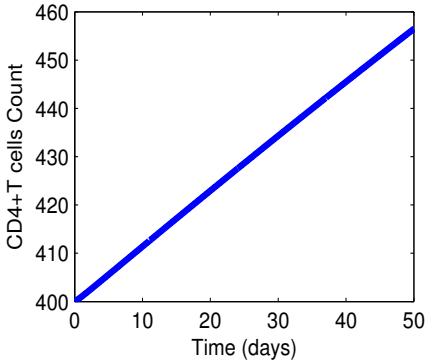

Figure 3: $CD4^+T$ Cells are rapidly grown when no control of antiretroviral drugs (i.e. maximum doses) in absence of immune-boosting nutrition.

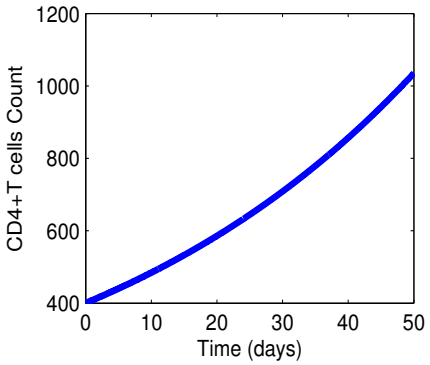

Figure 5: $CD4^+T$ Cells are grown up quickly when no control of immune-boosting nutrition in absence of antiretroviral drugs.

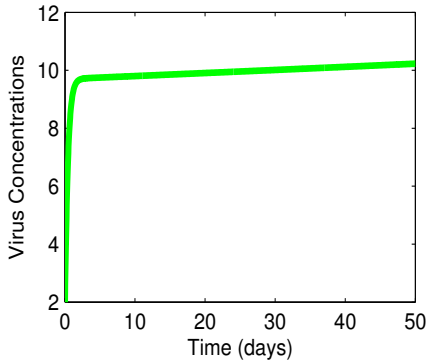

Figure 2: Infectious virus particles expand quickly when no drugs are recommended for treatment of HIV in absence of immune-boosting nutrition.

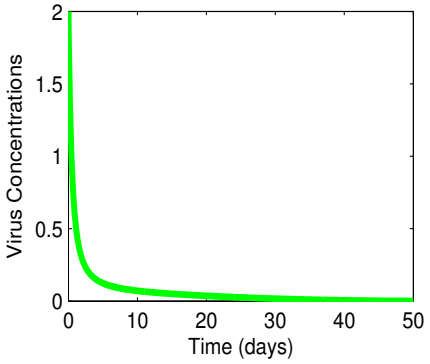

Figure 4: Infectious virus particles are reduced (tends to zero) when no control of antiretroviral drugs (i.e. maximum doses) in absence of immune-boosting nutrition.

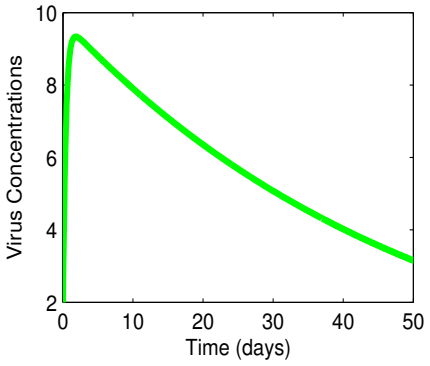

Figure 6: Infectious virus particles increase rapidly to 2 days but decrease after the time when no control of immune-boosting nutrition in absence of antiretroviral drugs.

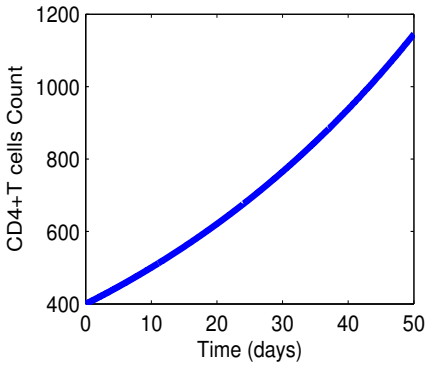

Figure 7: CD4$^+$T Cells are increased quickly when no control of immune-boosting nutrition and antiretroviral drugs.

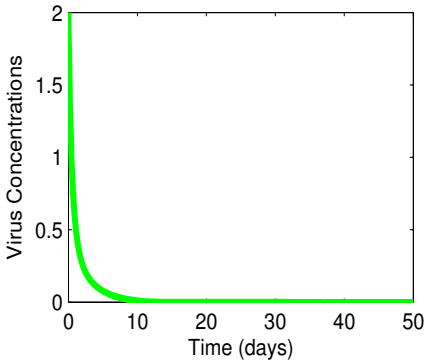

Figure 8: Infectious virus particles are reduced (tends to zero) when no control of immune-boosting nutrition and antiretroviral drugs are used.

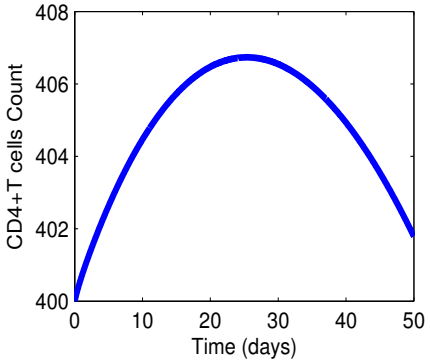

Figure 9: CD4$^+$T Cells increase to 27 days but are depleted finally when optimal control of antiretroviral drugs applied in absence of immune-boosting nutrition.

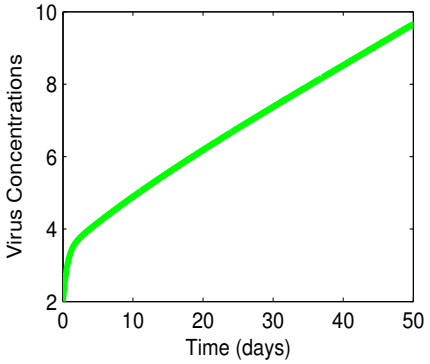

Figure 10: Infectious virus particles increase quickly to 1 day and linearly increase after the time when optimal control of antiretroviral drugs are applied in absence of immune-boosting nutrition.

boosting nutrition without any antiretroviral drugs. Here, the value of the objective functional proves that this strategy is better than $u_1(t) = 0$ and $u_2(t) = 0.9$. The state trajectories are shown in Figures 5–6 and the value of states at final time is presented in Table 2. So, we decide that immune boosting nutrition is better than antiretroviral drugs of HIV infections.

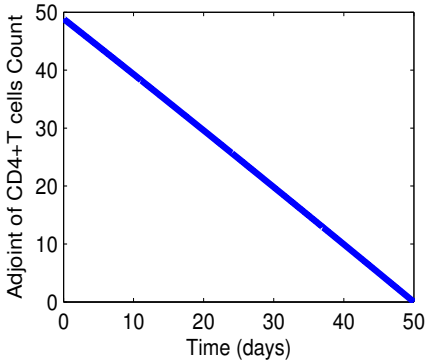

Figure 11: Adjoint of $CD4^+$ T Cells is zero at final time when optimal control of antiretroviral drugs are applied in absence of immune boosting nutrition.

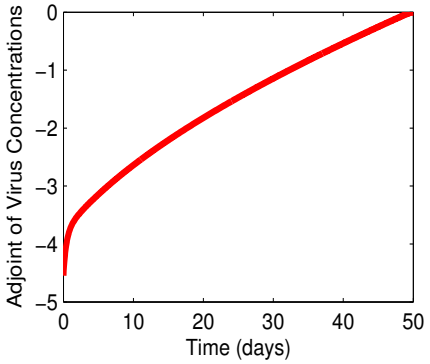

Figure 12: Adjoint of infected virus particles is zero at final time for optimal control of antiretroviral drugs in absence of immune boosting nutrition.

Now, we should check the situation for optimal control of immune boosting in the absence of any antiretroviral drugs (i.e. $0 \leq u_1(t) \leq 0.02$ and $u_2(t) = 0$). Here, the number of $CD4^+$T cells is 9.277×10^2 at final time in Figure 21 and the infected virus particles are 3.619 at final time in Figure 22. But the value of objective functional 2.8784×10^4 confirm that the optimization is necessary. The optimal control strategies are shown in Figures 25–26 and the adjoint states are zero at final time (Figures 23 and 24) that prove the completeness of optimal solution. Since the $CD4^+$T cells are above 950 for a good healthy person. So, the solution is an optimum but not a good treatment. If we use the maximum immune boosting nutrition and control on the antiretroviral drugs (i.e. $u_1(t) = 0.02$ and $0 \leq u_2(t) \leq 0.9$), we get better $CD4^+$T cells (1.096×10^3 in Figure 15) and low infected virus particles (2.920 in Figure 16). That control strategies are shown in Figures 19–20 and adjoint of states are shown in Figures 17–18. If we observe the value of objective functional for the treatment strategy, then it is clear that this control strategy outperforms the previously considered strategies. We now examine the control strategy defined by $0 \leq u_1(t) \leq 0.02$ and $0 \leq u_2(t) \leq 0.9$,

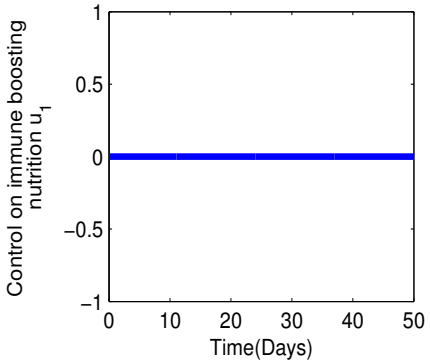

Figure 13: No immune boosting nutrition is applied.

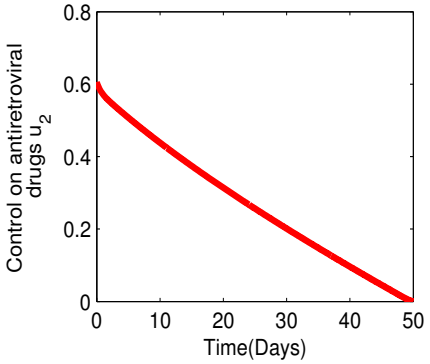

Figure 14: Optimal control of antiretroviral drugs is applied.

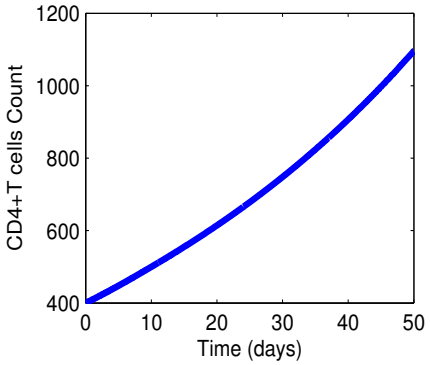

Figure 15: $CD4^+T$ Cells are increased quickly for optimal control of antiretroviral drugs with no control of immune boosting nutrition.

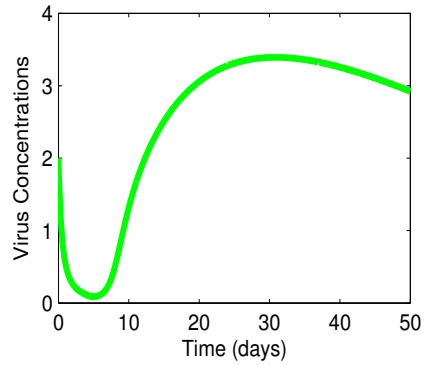

Figure 16: Infected virus particles down but up finally for optimal control of antiretroviral drugs with no control of immune boosting nutrition.

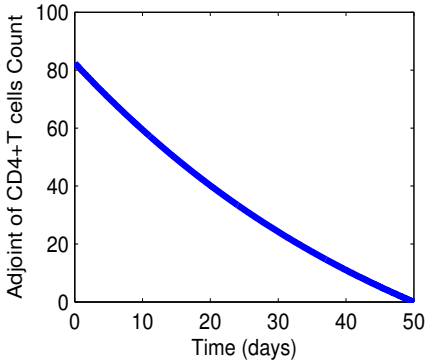

Figure 17: Adjoint of $CD4^+T$ Cells is zero at final time for optimal control of antiretroviral drugs with no control of immune boosting nutrition.

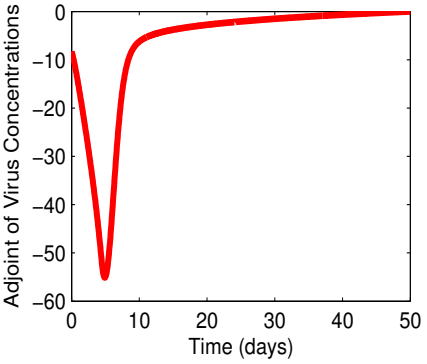

Figure 18: Adjoint of infected virus particles is zero at final time for optimal control of antiretroviral drugs with no control of immune boosting nutrition.

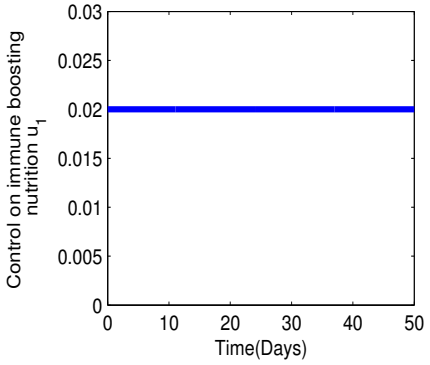

Figure 19: Maximum food of immune boosting nutrition is uptaken.

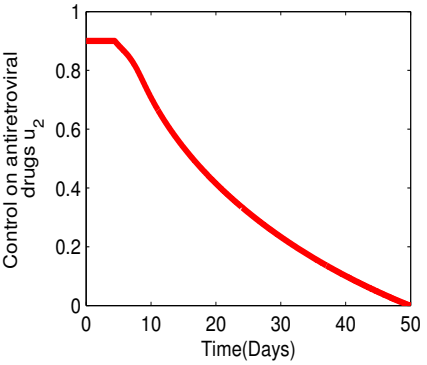

Figure 20: Optimal control of antiretroviral drugs is taken.

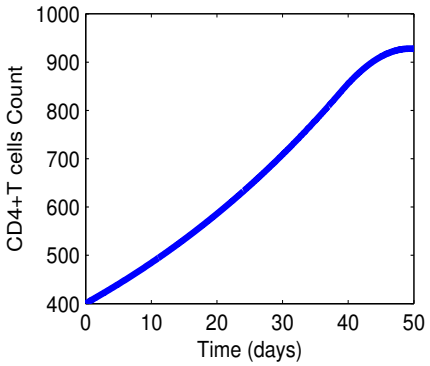

Figure 21: $CD4^+T$ Cells are increased and finally behaved asymptotically for optimal control of immune boosting nutrition in absence of antiretroviral drugs.

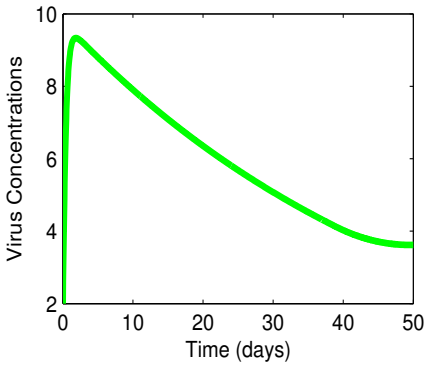

Figure 22: Infectious virus particles are increased rapidly in two days but are decreased quickly for optimal control of immune boosting nutrition in absence of antiretroviral drugs.

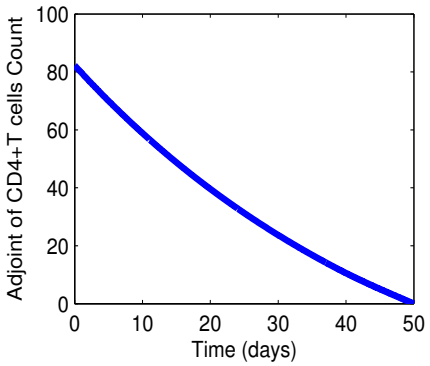

Figure 23: Adjoint of $CD4^+T$ Cells is zero at final time for optimal control of immune boosting nutrition in absence of antiretroviral drugs.

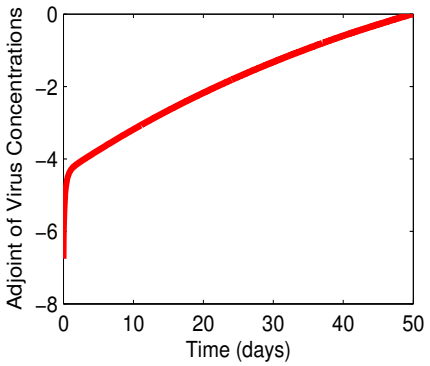

Figure 24: Adjoint of infected virus particles is zero at final time for optimal control of immune boosting nutrition in absence of antiretroviral drugs.

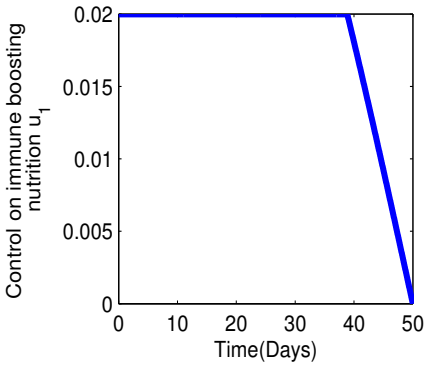

Figure 25: Optimal control of immune boosting nutrition is applied.

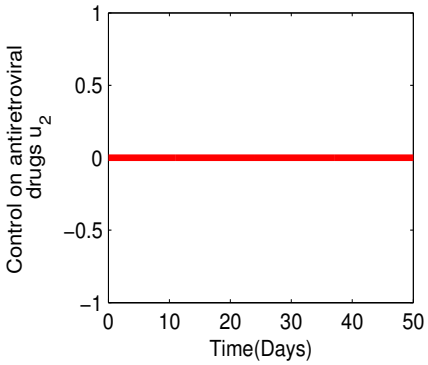

Figure 26: No antiretroviral drugs is taken.

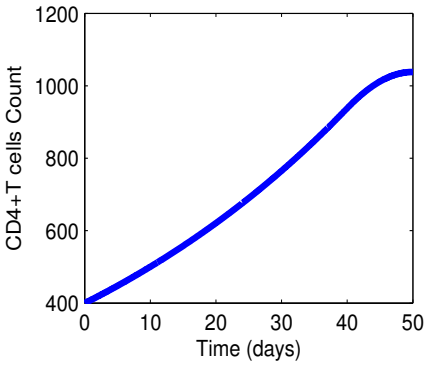

Figure 27: $CD4^+T$ Cells are increased and finally behaved asymptotically for optimal control of immune boosting nutrition with no control of antiretroviral drugs.

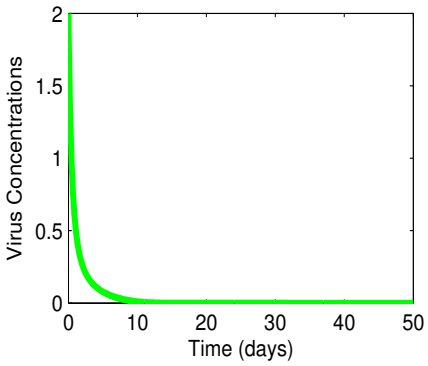

Figure 28: Infectious virus particles are reduced (tends to zero) for optimal control of immune boosting nutrition with no control of antiretroviral drugs.

which corresponds to the optimal control of immune boosting nutrition and antiretroviral drugs. Under this strategy, the objective functional attains its maximum value 2.9522×10^4 (see Table 2) and the number of $CD4^+T$ cells reaches 9.886×10^2 (see Table 2 and Figure 33). According to the number of $CD4^+T$ cells, the patient exhibits improved health, while the number of infected virus particles remains low (see Figure 34). These results support the conclusion that the proposed optimal control strategies (see Figures 37–38) provide the optimal treatment for HIV infection. We observe that the adjoints of states are zero at final time in Figures 35–36. Hence, the optimal immunotherapeutic treatment (see Figures 37–38) does better health but no cure for HIV infections.

5 Conclusions

Immune boosting nutrition is more effective than the antiretroviral drugs for HIV infections. It is also an interesting factor that no treatment of HIV infections is better than the treatment with antiretroviral drugs in absence of immune boosting nutrition based on the value of objective functional. Therefore, people should know the knowledge of food and nutrition to control the disease. In this study, the two applied two optimal control strategies are most useful to control virus in human body based HIV model. So, the numerically analyzed treatment strategies for HIV infections will be recommended in the world.

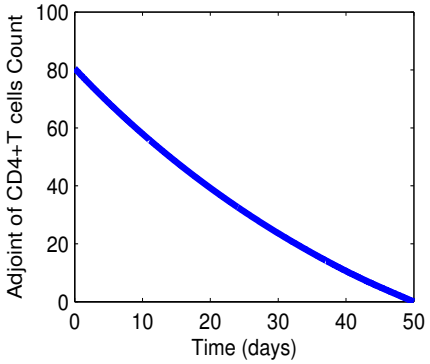

Figure 29: Adjoint of CD4$^+$T Cells is zero at final time for optimal control of immune boosting nutrition with no control of antiretroviral drugs.

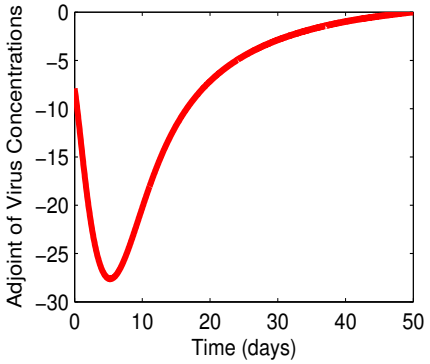

Figure 30: Adjoint of infected virus particles is zero at final time for optimal control of immune boosting nutrition with no control of antiretroviral drugs.

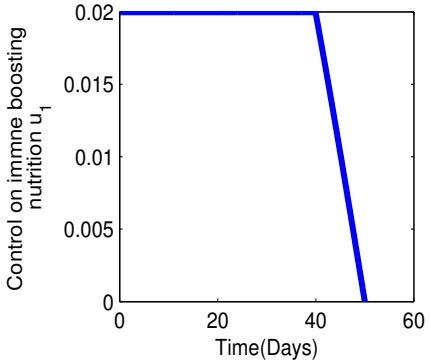

Figure 31: Optimal control of immune-boosting nutrition is applied.

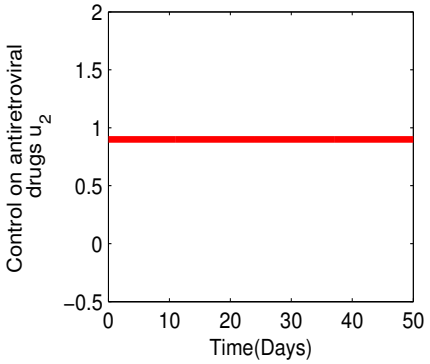

Figure 32: Maximum doses of antiretroviral drugs is taken.

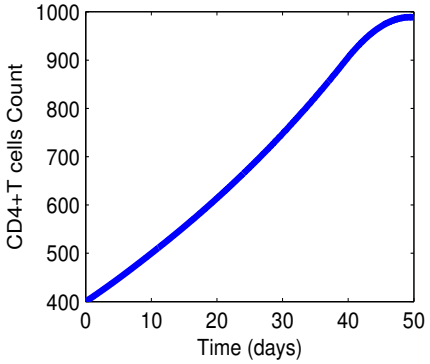

Figure 33: CD4$^+$T Cells are increased and finally behaved asymptotically for optimal control of immune boosting nutrition and antiretroviral drugs.

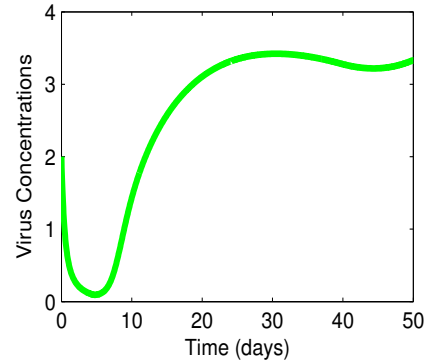

Figure 34: Infectious virus particles are decreased but increased with stability for optimal control of immune boosting nutrition and antiretroviral drugs.

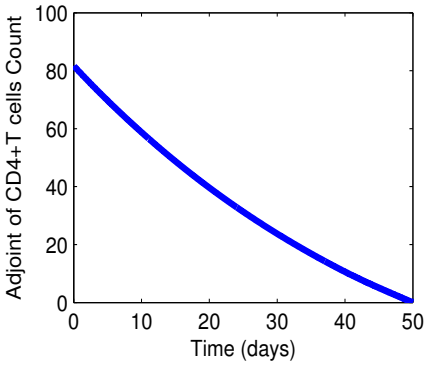

Figure 35: Adjoint of $CD4^{+}T$ Cells is zero at final time for optimal control of immune boosting nutrition and antiretroviral drugs.

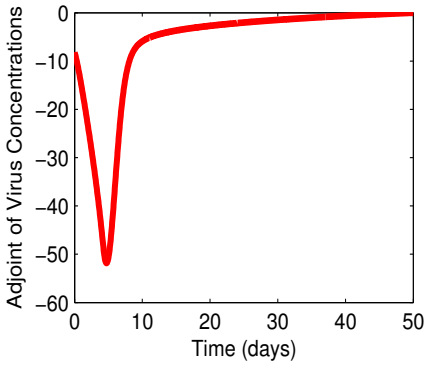

Figure 36: Adjoint of infected virus particles is zero at final time for optimal control of immune boosting nutrition and antiretroviral drugs.

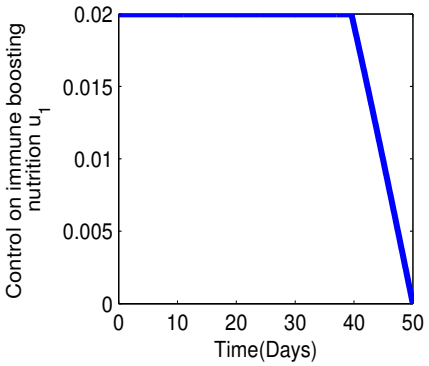

Figure 37: Optimal control of immune boosting nutrition is applied.

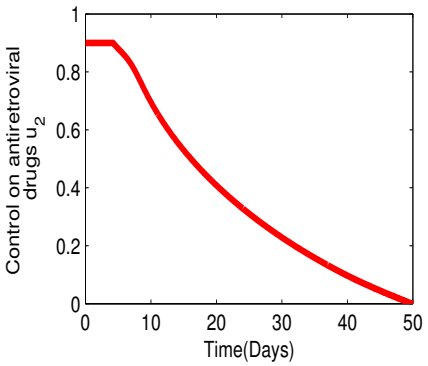

Figure 38: Optimal control of antiretroviral drugs is taken.

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References

[1] G. Akudibillah, A. Pandey and J. Medlock, Optimal control for HIV treatment, Math. Biosci. Eng., 16(2019), 373–396.

[2] A. Ahmad, R. Ali, I. Ahmad, F. Awwad and E. Ismail, Global stability of fractional order HIV/AIDS epidemic model under Caputo operator and its computational modeling, Fractal and Fractional, 7(2023), 643.

[3] M. H. A. Biswas, S. Samad, T. Parvin, M. Tanvir and A. Supriatna, Optimal control strategy to reduce the infection of pandemic HIV associated with tuberculosis, Communication in Biomathematical Sciences, 5(2022), 20–39.

[4] M. H. A. Biswas, M. M. Haque and U. K. Mallick, Optimal control strategy for the Immunotherapeutic treatment of HIV infection with state constraint, Optimal Control Applications and Methods, 40(2019), 807–818.

[5] M. H. A. Biswas, On the evolution of AIDS/HIV treatment: An optimal control approach, Current HIV Research, 12(2014), 1–12.

[6] K. R. Fister, S. Lenhart and J. S. McNally, Optimizing chemotherapy in an HIV model, Electron. J. Differential Equations, 32(1998), 1–12.

[7] W. H. Fleming and R. W. Rishel, Deterministic and Stochastic Optimal Control, Applications of Mathematics, Springer Verlag, New York, 1975.

[8] F. Garcia, Functional cure of HIV infection: The role of Immunotherapy, Immunotherapy, 4(2012), 245–248.

[9] A. Jan, H. Srivastava, A. Khan, P. Mohammed, R. Jan and Y. Hamed, In vivo HIV dynamics, Modeling the Interaction of HIV and Immune System via Non-Integer Derivatives, Fractal and Fractional, 7(2023), 361.

[10] H. R. Joshi, Optimal control of an HIV immunology model, Optimal Control Applications and Methods, 23(2002), 199–213.

[11] D. Kirschner and G. F. Webb, Immunotherapy of HIV-1 infection, J. Biol. Systems, 6(1998), 71–83.

[12] D. Kirschner, S. Lenhart and S. Serbin, Optimal control of the chemotherapy of HIV, J. Math. Biol., 35(1997), 775–792.

[13] D. Kirschner, A. Perelson and R. D. Boer, The dynamics of HIV infection of $CD4^+$T cells, Math. Biosci., 114(1993), 81–125.

[14] U. K. Mallick, A. Rahman, M. H. A. Biswas, M. Samsuzzoha and S. Roy, An optimal immunotherapeutic treatment of HIV infections to regain the targeted $CD4^+$T cell count: a boundary value problem approach, J. Appl. Nonlinear Dyn., 12(2023), 39–51.

[15] S. Karmaker, F. Y. Ruhi and U. K. Mallick, Mathematical analysis of a model on guava for biological pest control mathematical analysis of a model on guava for biological pest control, Mathematical Modelling of Engineering Problems, 5(2018), 427–440.

[16] P. Kundu and U. K. Mallick, Modeling the impact of natural pesticides on optimize guava nutrients in an integrated cultivation, Modeling Earth System and Environment, 10(2024), 2329–2348.

[17] S. Lenhart and J. T. Workman, Optimal Control Applied to Biological Models, CRC Press, Taylor and Francis Group, London, UK, 2007.

[18] U. K. Mallick and M. H. A. Biswas, Mathematical approach with optimal control: Reduction of unemployment problem in Bangladesh, J. Appl. Nonlinear Dyn., 9(2020), 231–246.

[19] R. M. Neilan and S. Lenhart, An Introduction to optimal control with an application in disease modeling, DIMACS Series in Discrete Mathematics, 75(2010), 67–81.

[20] A. S. Perelson, D. E. Kirschner and R. D. Boer, Dynamics of HIV infection of $CD4^+$T cells, Math. Biosci., 114(1993), 81–125.

[21] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze and E. F. Mischenko, The Mathematical Theory of Optimal Processes, John Wiley, New York, 1962.

[22] S. O. Sowole, D. Sangare, A. Ibrahim and I. A. Paul, On the existence, uniqueness, stability of solution and numerical simulations of a mathematical model for measles disease, Int. J. Adv. Appl. Math. Mech., 2019(2019), 84–111.

[23] R. B. Vinter, Optimal Control, Birkhauser, Boston, 2000.