Modelling Optimal control of in-host HIV Dynamics using different control strategies

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Abstract

HIV is a major cause of deaths especially in Sub-Sahara Africa. In this paper an in-vivo deterministic mode of differential equations is presented and analyzed for HIV dynamics. Optimal control theory is applied to investigate the key roles played by the various HIV treatment strategies. In particular, we wish to establish the optimal strategies for controlling the infection using three treatment regimes as the system control variables. We apply the Pontryagin's maximum principle in characterizing the optimality control, which is then solved numerically by applying the Runge-Kutta forth order scheme. The numerical results indicate that an optimal controlled treatment strategy would ensure significant reduction in viral load and also in HIV transmission. It is also evident from the results that protease inhibitor plays a key role in virus suppression; this is not to underscore the benefits accrued when all the three drugs regimes are used in combinations.

Keywords: HIV, Fusion inhibitors, Reverse transcriptase inhibitors, Protease inhibitors Runge-Kutta fourth order scheme, Pontryagin's maximum principle.

1 Introduction

The need for new and useful treatment regimes to provide assistance and relief in all aspects of the human condition is ever growing. Many researchers have embarked on the journey of analyzing the dynamics of various diseases affecting mankind with the aim of improving control, effect and finally eradicating the diseases from the population. Modeling and numerical simulations of the infectious diseases has been used as tools to optimize the disease control. This is due to the fact that medical community have insufficient animal models for testing efficacy of drug regimes used in controlling infections. Human immunodeficiency virus (HIV) is one of the major problem that researchers have been working on for over three decades. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS), there were 36.7 million people living with HIV/AIDS in 2016, where 1.6 million of which live in Kenya (World Health Organization, 2015). Nonetheless, many treatments regimes for HIV have been approved by the America food and drugs

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administration such as the highly active antiretroviral therapy (HAART) which is the latest combinations in use, in most countries. HAART has proved to be highly effective in viral suppression, prolongs life of the infected person and also reduce the rate of HIV transmission. However, even over three decades since the first HIV cases were reported, the virus has no cure and hence, various controls method for HIV/AIDS have been recommended. These controls range from preventive measures to treatment regimes. Preventive measures are mainly aimed at reducing the number of new HIV infections while treatment regimes targets the already infected persons aimed at increasing their life expectancy and reducing the rate of HIV transmission. Various treatment strategies are still the subject of many ongoing clinical trials that are investigating their benefits versus risks aimed at determining the most optimal treatment for HIV. Unfortunately, various host-pathogen interaction mechanisms during HIV infection and progression to AIDS are still unknown. Consequently, many questions like which is the best combination, when is the best time to start treatment and how the treatment should be administered, are yet to be answered fully.

Mathematical modelling is one of the many important tools used in understanding the dynamics of disease transmission. It is also used in developing guidelines important in disease control. In HIV, mathematical models have provided a framework for understanding the viral dynamics and have been used in the optimal allocation of the various interventions against the HIV virions (Mbogo et al., 2013; Nampala et al., 2014; Ogunlaran and Oukouomi Noutchie, 2016). A fundamental goal of developing and applying the aforementioned mathematical models of HIV is to influence treatment decisions and construct better treatment protocols for infected patients. 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 (Pontryagin, 1987). It has been applied by mathematicians to assist in the analysis of how to control the spread of infectious diseases. The results are used in making key decisions that involve complex biological mechanism. In particular, it is used to determine the best dosage for various available vaccines or treatment in use for controlling infection. For instance, Gaff and Schaefer (2009) applied optimal theory in evaluating mitigation strategy that would be highly effective in minimizing the number of people who get infected by an infection. The study applied both vaccinations and treatment as control variables for their various model. The results indicated that as much as treatment is paramount in controlling any infection, the most optimal method would be the combinations of the two interventions. Futhemore, Bakare et al. (2014) applied optimal control in an SIR model. The study illustrated the use of optimal control theory in establishing the optimal educational campaign and treatment strategies that would minimize the population of the infected persons as well cutting the cost of controlling the various diseases. The results indicated that for controlling infection it is important to target the uninfected populations and apply measures that will prevent them for getting the infection.

In the literature, optimal control theory has also been applied both in-host and population HIV dynamics model. For instance, Yusuf and Benyah (2012) applied optimal theory on HIV-population model. The study was aimed at determining the best method of control-

ling the spread of HIV/AIDS within a specified time frame. The study considered three control variables, that is, safe sex, education and ARTs. The numerical results of the objective function for the model indicated that safe sex practice as well as early initiation of ARTs are the most optimal ways of mitigating the spread of HIV/AIDS. The study established that if the aforementioned strategies are well implemented, would lead to a HIV free nation in 10 years. In addition, for in-host model, optimal control theory has been applied in the search of optimal therapies for HIV infection.

Drugs such as fusion inhibitors (FIs), reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) have been developed and applied in the various optimal control problems. Srivastava and Chandra (2009) analyzed an initial infection model with reverse transcriptase inhibitor (RTIs). The study argued that the use of RTIs reverts back an infected cell to susceptible. However, this is unlikely since once a $CD4^+$ T-cells is infected it cannot go back to susceptible. The only possible way is for it to remain latently infected but fail to produce infectious virus since RTIs inhibits the reverse transcription process. Hattaf and Yousfi (2012) analyzed a two optimal treatments of HIV infection model. The study was aimed at measuring the efficiency of RTIs and PIs. This was done by maximizing objective function aimed at increasing the number of the uninfected cells, decreasing the viral load and minimizing the treatment cost. The results indicated that use of therapy is important in HIV control. It is also important to note that the study included two types of viruses, that is the infectious virus and the non-infectious virus. Non-infectious virus is due to the use of PIs as a treatment regime.

Karrakchou et al. (2006) applied optimal control theory on HIV. Like Hattaf and Yousfi (2012) the study applied the two control strategies, that is, RTIs and the PIs. However, the study failed to put into account both the latently infected cells and the non-infectious virus that results due to the use of RTIs and PIs respectively. Failure to include such important variables in the model underscores the adequacy of the model in representing the actual HIV in-host mechanism. In addition, Arruda et al. (2015) applied optimal control theory in HIV immunology. The study used two control variables in fighting HIV with the inclusion of the $CD8^+$ T-cells. However, the study has some shortcomings, for instance the study suggested that activated $CD8^+$T-cells kill the HIV virions and also the infected cells. This is not the scenario since the activated $CD8^+$T-cells are only able to kill infected $CD4^+$T-cells which in turn reduces the population of the HIV virions. Unfortunately, even with the aforementioned work done on HIV the implementation of some of the recommendations has proved inefficient and in most cases not economically viable especially to the developing countries.

As per the literature cited it is clear that as much as ARTs have been used for viral suppression the optimal treatment schedule necessary to maintain low viral load is always an approximation. Until the time when HIV cure is found, physicians will try as much as possible apply the control strategy that will inhibit viral progression while simultaneously holding the side effects of treatment to a minimum. Most of the treatment regimes have many side effects that must be maintained at a low level. For example, long term use of protease inhibitors is associated with insulin intolerance, cholesterol elevation and the redistribution of body fat. Therefore, there is need to establish the optimal treatment

strategy, that is, the one which both maximizes the patient's uninfected $CD4^+$ T-cells and minimizes the harmful side-effects due to the drugs.

This study will address some of the shortcomings noted from the in-host HIV dynamics models. The study applies three control variables representing the three drug regimes on the market, that is, the fusion inhibitor, reverse transcriptase inhibitor and the protease inhibitor. In addition, the study will incorporate the $CD8^+$T-cells in the model. The study will apply optimal control theory together with the Pontryagins Maximum Principle in solving the objective function. The study is aimed at establishing the optimal treatment strategy.

2 Model formulation

2.1 Model Description

In order, for us to carry out optimal control processes it is paramount to formulate a model that describes the basic interaction between the HIV virions and the body immune system. We develop a mathematical model for HIV in-host infection with three combinations of drugs. We define eight variables for the model as follows. Susceptible $CD4^+$ T-cells (T), latently infected $CD4^+$ T-cells (I_l), infected $CD4^+$ T-cells (I), HIV infectious virions (V), non-infectious HIV virions (V_n) , $CD8^+$ T-cells (Z) and the activated $CD8^+$ T-cells (Z_a).

The parameters for the model are as follows. The susceptible $CD4^+$ T-cells are produced from the thymus at a constant rate λ_T, die at a constant per capita rate μ_T and become infected by the HIV virions at the rate χTV. However, due to the use of fusion inhibitor (u_1) which prevents the entry of the HIV virions into the $CD4^+$ T-cells hence a fraction $u_1\chi VT$ reverts back to susceptible class. In addition, when the infected $CD4^+$ T-cells are exposed to the HIV virions in presence of reverse trascriptase inhibitor (u_2) the HIV virions RNA may not be reverse transcribed. This results to a proportion $u_2\chi VT$ of the infected cells becoming latently infected. The infected cells are killed by the $CD8^+$ T-cells at the rate α and they die naturally at the rate μ_I whereas latently infected cells die at the rate μ_{I_l}. This study assume that the latently infected cells will die naturally and has no possibility of producing infectious virions nor becoming activated to become infectious. However, if the protease inhibitor (u_3) is used as a treatment strategy, it inhibit the production of protease enzyme which is necessary for production of mature HIV virions. This therefore means that we have two kind of HIV virions produced from an infected $CD4^+$ T-cells; that is, the infectious HIV virions and the immature non-infectious virions. The infectious HIV virions are produced at the rate $(1-u_3)\epsilon_V$ and die at the rate μ_V while the non-infectious HIV virions are produced at the rate $u_3\epsilon_V$ and die at the rate μ_{V_n}. Furthermore, the $CD8^+$ T-cells are produced naturally from the thymus at the rate λ_Z, they die naturally at the rate μ_Z and can also be activated to kill the infected cells at the rate β. The activated $CD8^+$ T-cells die naturally at the rate μ_{Z_a}. It is very important to point out that the $CD8^+$ T-cells are activated to kill the infected $CD4^+$ T-cells and not the virus as suggested by Arruda et al. (2015).

The summary for the model description is given as follows. The variables, parameters and

the control variables for the in-host model are described in Tables 1, 2 and 3, respectively.

Table 1: Variables for HIV in-vivo model with therapy

Variable	Description
T(t)	The concentration of the non-infected $CD4^+$T-cells per cubic millimetre at any time t
I(t)	The concentration of the infected $CD4^+$T-cells per cubic millimetre at any time t
I_l	The concentration of latently infected $CD4^+$ T-cells per cubic millimetre at any time t
V(t)	The concentration of HIV virions $copies/mL$ at any time t
$V_n(t)$	The concentration of the immature non-infectious virions $copies/mL$ at any time t
Z(t)	The concentration of the $CD8^+$T-cells per cubic millimetre at any time t
Z_a(t)	The concentration of the activated $CD8^+$T-cells per cubic millimetre at any time t

Table 2: Parameters for HIV in-vivo with therapy model

Parameter	Description
λ_T	The rate at which the non-infected $CD4^+$ T-cells are produced per unit time.
μ_T	The rate at which the non-infected $CD4^+$T-cells decay.
χ	The rate at which the $CD4^+$T- cells are infected by the virus.
μ_I	The death rate of the infected $CD4^+$T-cells.
μ_{I_l}	The death rate of the latently infected $CD4^+$ T-cells.
ε_V	The rate in which HIV virions are generated from the infected $CD4^+$T-cells.
μ_V	The death rate of the infectious virus.
μ_{V_n}	The death rate of the non-infectious virions.
α	The rate at which the infected cells are eliminated by the activated $CD8^+$T-cells.
λ_Z	The rate at which the $CD8^+$ T-cells are produced per unit time.
μ_Z	The death rate of the $CD8^+$ T-cells.
β	The rate at which the $CD8^+$ T-cells are activated by the presence of the virus and the infected $CD4^+$ T-cells.
μ_{Z_a}	The rate at which the activated defense cells decay.

Table 3: Control Variables for HIV in-vivo model

Control Variable	Description	Purpose
$0 \leq u_1 \leq 1$	Fusion Inhibitors	are a class of antiretroviral drugs that work on the outside of the host CD4$^+$T-cell to prevent HIV from fusing with and infecting it.
$0 \leq u_2 \leq 1$	Reverse trancriptase inhibitors	are a class of antiretroviral drugs used to treat HIV infection by inhibiting the reverse transcription process.
$0 \leq u_3 \leq 1$	Protease inhibitors	are a class of antiviral drugs that are widely used to treat HIV/AIDS by inhibiting the production of protease enzyme necessary for the production of infectious viral particles.

The interactions aforementioned is represented in the compartmental diagram in Figure 1. From Figure 1 and the description above, we derive the following system of ordinary

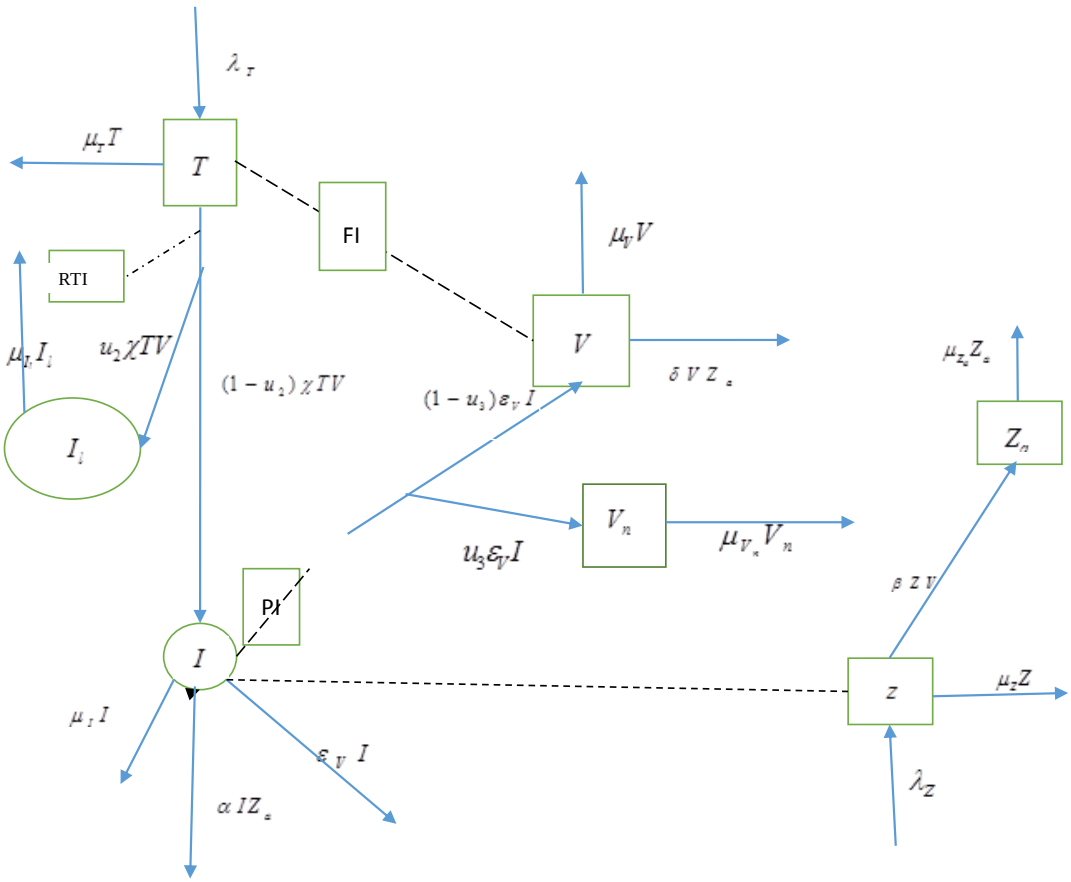


Figure 1: A compartmental representation of the in-vivo HIV Dynamics with therapy.

differential equations to describe the in-vivo dynamics of HIV.

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - (1-u_1(t))\chi TV, \\
\frac{dI}{dt} &= (1-u_2(t))\chi TV - \mu_I I - \alpha I Z_a, \\
\frac{dI_l}{dt} &= u_2(t)\chi TV - \mu_{I_l} I_l, \\
\frac{dV}{dt} &= (1-u_3(t))\epsilon_V \mu_I I - \mu_V V, \\
\frac{dV_n}{dt} &= u_3(t)\epsilon_V \mu_I I - \mu_{Vn} V_n, \\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I, \\
\frac{dZ_a}{dt} &= \beta Z I - \mu_{Z_a} Z_a
\end{aligned}\right\} \tag{1}$$

3 Optimization process

Control efforts are carried out to limit the spread of the disease, and in some cases, to prevent the emergence of drug resistance. Optimal control theory is a method that has been widely used to solve for an extremum value of an objective functional involving dynamic variables. In this section, we consider optimal control methods to derive optimal drug treatments as functions of time. The control variables as used in equations (1) are described as follows. The control u_1 represents the effect of fusion inhibitors, which are the drugs that protect the uninfected CD4$^+$ T-cells by preventing the entry of the virus into the CD4$^+$T-cells membrane. The control variable u_2 simulates the effect of reverse transcriptase inhibitors. These drugs hinders the reverse transcription process. The third control variable u_3 simulates the effect of protease inhibitors, which prevent the already infected cells from producing mature-infectious virions. The aforementioned controls represent effective chemotherapy dosage bounded between 0 and 1. The situation $u_1(t) = u_2(t) = u_3(t) = 1$ represents total efficacy of the Fusion inhibitors, Reverse transcriptase inhibitors and Protease inhibitors respectively and $u_1(t) = u_2(t) = u_3(t) = 0$ represents no treatment. It is worth noting that the control variables aforementioned are bounded Lebesques integrable functions. The study aims at maximizing the levels of the healthy CD4$^+$ T cells, as well as the levels of the CD8$^+$ T cells (Z) while minimizing the viral load (V) and at the same time keeping cost and side effects of treatment at a minimum. With the above description the following objective function (2) need to be maximized:

$$J(u_1(t), u_2(t), u_3(t)) = \frac{1}{2}\int_0^{T_f} (w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2)dt \tag{2}$$

subject to the equations given in model (1).

$T(t)$, $Z(t)$ and $V(t)$ are the solutions of the ODEs (1). The quantities w_1 and w_2 represent the cost associated with maximizing the number of CD4$^+$ T-cells and the CD8$^+$ T-cells

respectively, while w_3 represents the cost associated with minimizing the viral load. In addition, A_1, A_2 and A_3 are non-negative constants representing the relative weights attached to the current cost of each treatment regime and T_f is a fixed terminal time of the treatment program subject to the ordinary differential equations described in model (1). This study assumes that the cost of controls are of quadratic form. Furthermore, it is also based on the fact that there is no linear relationship between the effect of treatment on $CD4^+$ T-cells, $CD8^+$ T-cells or the HIV virions. Consequently, u_1, u_2 and u_3 are Lebesgue integrable; that is, they are piecewise continuous and integrable. The fundamental aim of this therapeutic strategy is to maximize the objective functional defined in equation (2) by increasing the number of the uninfected $CD4^+$ T-cells and the $CD8^+$T-cells, decreasing the viral load (V) and minimizing the harmful side effects and cost of treatment over the given time interval $[0, T_f]$. Therefore, we aim at determining the optimal control $u_1{}^*$,$u_2{}^*$ and $u_3{}^*$ such that;

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = max\left\{J(u_1(t), u_2(t), u_3(t)) : (u_1, u_2, u_3) \in U\right\} \tag{3}$$

where U is a set of all measurable controls defined by:

$$U = \{u = (u_1, u_2, u_3) : u_i \text{ measurable }, 0 \leq u_i(t) \leq 1, t \in [0, T_f]\} \tag{4}$$

In the next section we show the existence of an optimal control for the system (1) and later derive the optimality system. This study will employ the Pontryagins Maximum Principle .

4 Characterization of the Optimal control

The necessary conditions that an optimal control must satisfy come from the Pontryagins Maximum Principle Pontryagin (1987).

Theorem 1. *Suppose the objective function*

$$J(u_1(t), u_2(t), u_3(t)) = \frac{1}{2}\int_0^{T_f} (w_1T(t) + w_2Z(t) - w_3V(t) - A_1u_1^2 - A_2u_2^2 - A_3u_3^2)dt$$

is maximized subject to the controls and state variables given in model (1) with

$$T(0) = T_0, \quad I(0) = I_0, \quad I_l(0) = I_{l0}, \quad V(0) = V_0, \quad V_n(0) = V_{n0}, \quad Z(0) = Z_0 \text{ and } Z_a(0) = Z_{a0}$$

Then there exists optimal controls $(u_1^*, u_2^*, u_3^* \in U)$ such that;

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = max\left\{J(u_1(t), u_2(t), u_3(t)) : (u_1, u_2, u_3) \in U\right\}$$

Proof. The existence of the solution can be shown using the results obtained in Fleming and Rishel (2012), since:

1. The class of all initial conditions with controls u_1, u_2 and u_3 in the control set U are non-negative values and are non-empty where $u_i, i = 1, 2, 3$ is a Lebesgue-integrable

function on $[0, T_f]$

2. The right hand side of system (1) is bounded by a linear function of the state and control variables.

   By definition, each right hand side of system (1) is continuous and can be written as a linear function of U with coefficients depending on time and state. Furthermore, all the state and control variables $T, I, I_l, V, V_n, Z, Z_a, u_1, u_2,$ and u_3 are bounded on $[0, T_f]$.

3. By definition the control set U is convex and closed.
   A set $K \in \mathbb{R}^{\kappa}$ is said to be a convex set if and only if

   $$\lambda x + (1 - \lambda)y \in K$$

   for all $x, y \in K$, and all $\lambda \in [0, 1]$.

   This condition is satisfied by the control set U.

4. The integrand which is, $\frac{1}{2}\left(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2\right)$, of the objective functional is concave on U.

5. There exist constants $b_1 > 0$, $b_2 > 0$ and $\beta > 1$ such that the integrand of the objective function $J(U, t)$ is bounded by $L(t, T, V, V_n, I, I_l, Z, Z_a, u_1, u_2, u_3) \leq b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\beta}{2}}$
   This implies that,

   $$w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2 \leq b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_3|^2)$$

   where b_1 depends on the upper bound on T, $\quad Z$and $\quad V$ and $b_1 > 0$ since $A_1, A_2, A_3 > 0$ according to the definition.

Since all the above conditions are satisfied then we conclude that there exist optimal controls ${u_1}^*, {u_2}^*,$ and ${u_3}^*$. □

5 Necessary conditions of the control

We now proceed by applying the Pontragin's maximum principle (Pontryagin, 1987). We begin by defining Lagrangian (Hamiltonian augmented):

$$\begin{aligned} &L(T, I, I_l, V, V_n, Z, Z_a, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, u_1, u_2, u_3) \\ &\quad = w_1 T + w_2 Z - w_3 V - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2 + \lambda_1(\lambda_T - \mu_T T - (1 - u_1(t))\chi T V) \\ &+\lambda_2((1 - u_2(t))\chi T V - \mu_I I - \alpha I Z_a) + \lambda_3(u_2(t)\chi T V - \mu_{I_l} I_l) + \lambda_4((1 - u_3(t))\epsilon_V \mu_I I - \mu_V V) \\ &\quad + \lambda_5(u_3(t)\epsilon_V \mu_I I - \mu_{V_n} V_n) + \lambda_6(\lambda_Z - \mu_Z Z - \beta Z I) + \lambda_7(\beta Z I - \mu_{Z_a} Z_a) \\ &\quad + w_{11} u_1 + w_{12}(1 - u_1) + w_{21} u_2 + w_{22}(1 - u_2) + w_{31} u_3 + w_{32}(1 - u_3) \end{aligned} \tag{5}$$

where $w_{ij}(t) \leq 0$ are the penalty multipliers which ensure the boundedness of the control variables $u_1(t)$, $u_2(t)$ and $u_3(t)$ and satisfying the following conditions.

$$\begin{aligned} w_{11}u_1 = w_{12}(1-u_1) = 0 \text{ at } u_1^* \\ w_{21}u_2 = w_{22}(1-u_2) = 0 \text{ at } u_2^* \\ w_{31}u_3 = w_{32}(1-u_3) = 0 \text{ at } u_3^* \end{aligned} \tag{6}$$

where, u_1^*, u_2^*, u_3^* represent the optimal controls.

Therefore, the Pontragin's maximum principle gives the existence of adjoint variables which are obtained by differentiating the Lagrangian given by equation (5), with respect to the state variables T, V, I, I_l, Z and Z_a.

The adjoint variables are given by:

$$\begin{aligned} \dot{\lambda}_1 &= -\frac{\partial L}{\partial T} = -w_1 + \lambda_1(\mu_T + (1-u_1)\chi V) - \lambda_2\chi V(1-u_2) - \lambda_3 u_2 \chi V, \\ \dot{\lambda}_2 &= -\frac{\partial L}{\partial I} = \lambda_2(\mu_I + \alpha Z_a) - \lambda_4 \varepsilon_V \mu_I (1-u_3) - \lambda_5 u_3 \epsilon_V \mu_I + \lambda_6 \beta Z - \lambda_7 \beta Z, \\ \dot{\lambda}_3 &= -\frac{\partial L}{\partial I_l} = \lambda_3 \mu_{I_l}, \\ \dot{\lambda}_4 &= -\frac{\partial L}{\partial V} = w_3 + \lambda_1 \chi T(1-u_1) - \lambda_2 \chi T(1-u_2) - \lambda_3 \chi T u_2 + \lambda_4 \mu_V, \\ \dot{\lambda}_5 &= -\frac{\partial L}{\partial V_n} = \lambda_5 \mu_{V_n}, \\ \dot{\lambda}_6 &= -\frac{\partial L}{\partial Z} = -w_2 + \lambda_6(\mu_Z + \beta I) - \lambda_7 \beta I, \\ \dot{\lambda}_7 &= -\frac{\partial L}{\partial Z_a} = \lambda_2 \alpha I + \lambda_7 \mu_{Z_a} \end{aligned} \tag{7}$$

where,

$$\lambda_i(T_f) = 0, i = 1, ..., 7 \tag{8}$$

are the transversality conditions.

By maximization of the Lagrangian with respect to the control variables u_1, u_2, u_3 at the optimal controls (u_1^*, u_2^*, u_3^*) then we have

$$\begin{aligned} \frac{\partial L}{\partial u_1} = 0, \\ \frac{\partial L}{\partial u_2} = 0, \\ \frac{\partial L}{\partial u_3} = 0 \end{aligned} \tag{9}$$

Therefore, differentiating the Lagrangian L given in equation (5) with respect to u_1 on

the set $U : t|0 \leq u_1(t) \leq 1$, we get the following optimality equation;

$$\frac{\partial L}{\partial u_1} = -2A_1 u_I + \chi TV\lambda_1 + w_{11} - w_{12} = 0 \tag{10}$$

Let $u_1 = u_1^*$ in equation (10). Then, solving equation (10) we obtain the optimal control u_1^* as

$$u_1^* = \frac{\chi TV\lambda_1 + w_{11} - w_{12}}{2A_1} \tag{11}$$

To determine an explicit expression for an optimal control u_1^* without w_{11} and w_{12}, we consider the following three cases:

1. On the set $(t|0 < u_1^* < 1)$, suppose we set $w_{11} = w_{12} = 0$ in equation (11). Then the optimal u_1^* control is given by

$$u_1^* = \frac{\chi TV\lambda_1}{2A_1} \tag{12}$$

2. Similarly, on the set $(t|u_1^* = 1)$ we have $w_{11} = 0$ and $w_{12} \geq 0$ then from equation (11) we have

$$u_1^* = 1 = \frac{\chi TV\lambda_1 - w_{12}}{2A_1} \tag{13}$$

Equation (13) can be reduced to;

$$\frac{\chi TV\lambda_1}{2A_1} \geq 1 = u_1^* \tag{14}$$

Therefore, for this set we have

$$u_1^* = min\left(1, \frac{\chi TV\lambda_1}{2A_1}\right) \tag{15}$$

3. Finally, on the set $(t|u_1^* = 0)$, we have $w_{12} = 0$ and $w_{11} \geq 0$ then from equation (11) we have

$$u_1^* = 0 = \frac{\chi TV\lambda_1 + w_{11}}{2A_1} \tag{16}$$

which implies that

$$\frac{\chi TV\lambda_1}{2A_1} \leq 0 \tag{17}$$

Consequently, combining all the three cases given by equations (12), (15), and (17) we obtain the optimal control, u_1^*, as

$$u_1^*(t) = \begin{cases} \frac{\chi TV\lambda_1}{2A_1} & \text{if} \quad 0 < \frac{\chi TV\lambda_1}{2A_1} < 1 \\ 0 & \text{if} \quad \frac{\chi TV\lambda_1}{2A_1} \leq 0 \\ 1 & \text{if} \quad \frac{\chi TV\lambda_1}{2A_1} \geq 1 \end{cases} \tag{18}$$

This implies that the control $u_1^*(t)$ is formulated as follows:

$$u_1^* = max\left(0, min\left(1, \frac{\chi TV\lambda_1}{2A_1}\right)\right) \tag{19}$$

We use the same argument to obtain an explicit expression for an optimal control u_2^* without w_{21} and w_{22}. We differentiate the Lagrangian L given in equation (5) with respect to u_2 on the set $U : t|0 \leq u_2(t) \leq 1$. We therefore, obtain the optimality equation as

$$\frac{\partial L}{\partial u_2} = -2A_2u_2 + \chi TV(\lambda_3 - \lambda_2) + w_{21} - w_{22} = 0 \text{ at } u_2 = u_2^* \tag{20}$$

Therefore, solving equation (20) we obtain the optimal control u_2^* as

$$u_2^* = \frac{\chi TV(\lambda_3 - \lambda_2) + w_{21} - w_{22}}{2A_2} \tag{21}$$

According to the conditions given by equation (6) we derive the following distinct three cases;

1. On the set $(t|0 < u_2^* < 1)$, we have $w_{21} = w_{22} = 0$ in equation (21). Then the optimal u_2^* control is given by

$$u_2^* = \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \tag{22}$$

2. On the set $(t|u_2^* = 1)$, we have $w_{21} = 0$ and $w_{22} \geq 0$ then from equation (21) we have

$$u_2^* = 1 = \frac{\chi TV(\lambda_3 - \lambda_2) + w_{22}}{2A_2} \tag{23}$$

   Rearranging equation (23) we have,

$$\frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \geq 1 = u_2^* \tag{24}$$

   Thus, for the this set we have

$$u_2^* = min\left(1, \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}\right) \tag{25}$$

3. Finally, on the set $(t|u_2^* = 0)$ we have $w_{22} = 0$ and $w_{21} \geq 0$ then from equation (21) we have

$$u_2^* = 0 = \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \tag{26}$$

   which implies that

$$\frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \leq 0 \tag{27}$$

Consequently, combining all the three cases given by equations (22), (25) and (27) we obtain the optimal control u_2^* as

$$u_2^*(t) = \begin{cases} \frac{\chi TV(\lambda_3-\lambda_2)}{2A_2} & \text{if} \quad 0 < \frac{\chi TV(\lambda_3-\lambda_2)}{2A_2} < 1 \\ 0 & \text{if} \quad \frac{\chi TV(\lambda_3-\lambda_2)}{2A_2} \leq 0 \\ 1 & \text{if} \quad \frac{\chi TV(\lambda_3-\lambda_2)}{2A_2} \geq 1 \end{cases} \tag{28}$$

Hence, the optimal control $u_2{}^*(t)$ is formulated as follows:

$$u_2^* = max\left(0, min\left(1, \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}\right)\right) \tag{29}$$

To obtain the expression for optimal control u_3^* we differentiate equation (5) with respect to u_3 on the set $U : t|0 \leq u_3(t) \leq 1$ to get the following optimality equation

$$\frac{\partial L}{\partial u_3} = -2A_3u_3 - \varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32} = 0 \tag{30}$$

Let $u_3 = u_3^*$ in equation (30) then we obtain the optimal control u_3^*

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32}}{2A_3} \tag{31}$$

1. On the set $(t|0 < u_3^* < 1)$, we have $w_{31} = w_{32} = 0$ in equation (31). Then the optimal control u_3^* is given by

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \tag{32}$$

2. On the set $(t|u_3^* = 1)$, we have $w_{31} = 0$ and $w_{32} \geq 0$ then from equation (31) we have

$$u_3^* = 1 = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{32}}{2A_3} \tag{33}$$

   Equation (33) can be reduced to

$$\frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \geq 1 = u_3^* \tag{34}$$

   Hence, for this set we have

$$u_3^* = min\left(1, \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}\right) \tag{35}$$

3. Finally, on the set $(t|u_3^* = 0)$, we have $w_{32} = 0$ and $w_{31} \geq 0$ then from equation (31) we have

$$u_3^* = 0 = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{31}}{2A_3} \tag{36}$$

which implies that

$$\frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \leq 0 \tag{37}$$

Consequently, combining all the three cases given by equations (32), (35) and (37) the optimal control, u_3^*, is characterized as;

$$u_3^*(t) = \begin{cases} \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} & \text{if} \quad 0 < \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} < 1 \\ 0 & \text{if} \quad \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \leq 0 \\ 1 & \text{if} \quad \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \geq 1 \end{cases} \tag{38}$$

Therefore, the optimal control, $u_3^*(t)$, is formulated as:

$$u_3^* = max\left(0, min\left(1, \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3}\right)\right) \tag{39}$$

It is worth noting that the optimal controls depend on the adjoint $\lambda_1, \lambda_2, \lambda_3,$ and λ_4 since the adjoint corresponds to the state variables, T, I, I_l, V and the first four equations on equation (1) contain the control terms.

6 Numerical simulation

In this section, we investigate the effect of optimal strategy on HIV by applying Runge-Kutta forth order scheme on the optimality system. The Optimality system is obtained by taking the state system together with the adjoint system, the optimal control, and the transversality conditions. The dynamical behavior of the models in relation to various control are also studied. The optimal strategy is achieved by obtaining a solution for the state system (1) and co-state system (7). An iterative scheme is explored and used to determine the solution for the optimality system. The numerical method utilized is the forward-backward sweep method which incorporates iterative Runge-Kutta fourth order progressive-regressive schemes. The progressive scheme is used in obtaining the solutions of the state ODEs given in equation (1) with the initial conditions while the regressive scheme is applied in obtaining the solutions of the adjoint system given by equation (7) with transversality conditions given in equation (8). The controls are updated at the end of each iteration using the formula for optimal controls. We continue with the iterations until convergence is achieved. This is a two-point boundary-value problem, with separated boundary conditions at times $t_0 = 0$ and $t = T_f$. This explains our choice in using the fourth-order Runge-Kutta scheme. For the numerical simulation we take $T = 350$ days . This value represent the time in which treatment is stopped. Furthermore, the values of the weight function are taken as: $A_1 = A_2 = A_3 = 0.01$. Table 4 consists of the parameter values that are used in the numerical simulations of the in-vivo model while Table 5 consists of the proposed initial values of the state variables.

Table 4: Parameters and controls for HIV in-vivo with therapy model

Parameters	Value	Source
λ_T	10 cell/mm^3/day	Nowak et al. (1996)
μ_T	0.01 day^{-1}	Srivastava and Chandra (2010)
χ	0.000024 mm^3 vir$^-$1 day$^-$1	Alizon and Magnus (2012)
μ_I	0.5 day$^-$1	Wodarz and Nowak (2000)
μ_{I_l}	0.5 day$^-$1	Wodarz and Nowak (2000).
ε_V	100 vir. cell$^-$1 day$^-$1	Estimate
μ_V	3 day$^-$1	Mbogo et al. (2013).
μ_{V_n}	0.06 day$^-$1	Estimate
α	0.02 day^{-1}	Arruda et al. (2015)
λ_Z	20 cell/ mm^3/day	Arruda et al. (2015).
μ_Z	0.06 day^{-1}	Arruda et al. (2015)
β	0.004 day^{-1}	Arruda et al. (2015)
μ_{Z_a}	0.004 day^{-1}	Arruda et al. (2015)
u_1	$0-1$ variable	Estimate.
u_2	$0-1$ variable	Estimate.
u_3	$0-1$ variable	Estimate

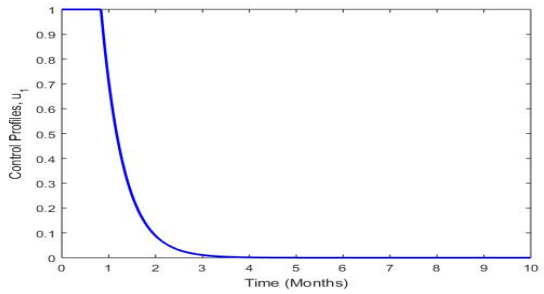
Table 5: The initial values for the variables for HIV in-vivo model

Variable	Values
T(t)	$T(0) = 500$ cell/mm^3
I(t)	$I(0) = 100$ cell/mm^3
I_l	$I_l(0) = 0$ cell/mm^3
V(t)	$V(0) = 100$ virion/mm^3
$V_n(t)$	$V_n(0) = 0$ virion/mm^3
Z(t)	$Z(0) = 100$ cell/mm^3
Z_a(t)	$Z_a(0) = 10$ cell/mm^3

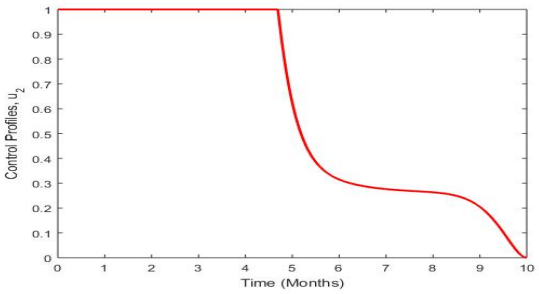
The initial values given in Table 5 are chosen in such away that they reflect a patient during acute infection. This is in line with the WHO recommendations which stipulate that all people living with the HIV be put on ARTs irrespective of their CD4$^+$ counts unlike in the past where the CD4$^+$ count had to be below 500 cell/mm^3 (World Health Organization and others, 2014).

6.1 Results and discussion

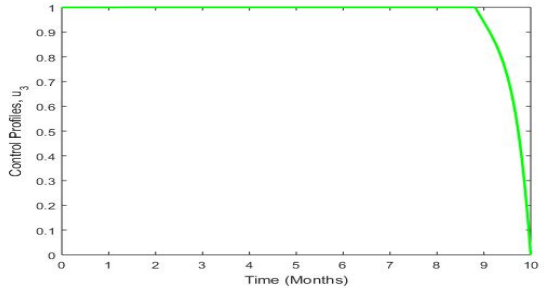
Figure 2 represents the various control strategies. It is evident that the control u_1 remains at the maximum for the first two months and drop to zero onward while control u_2 remains at maximum for the first four and a half months then drops to 30% the sixth and the ninth month, the drop to the minimum after the 10th month. In addition, the



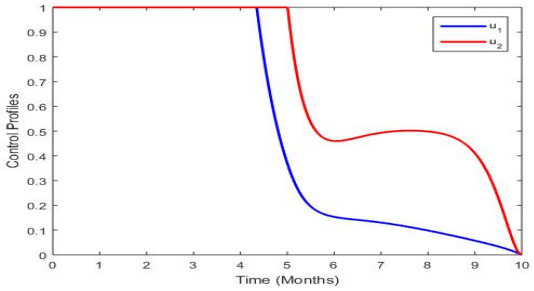
Control u_1



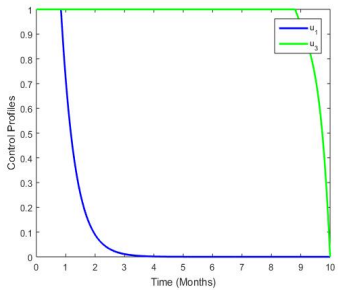
Control u_2



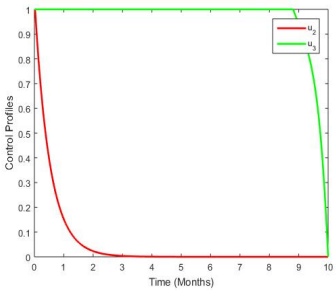
Control u_3



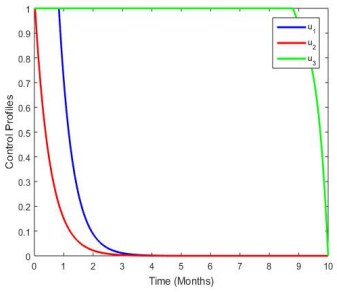
Controls u_1 and u_2



Controls u_1 and u_3



Controls u_2 and u_3

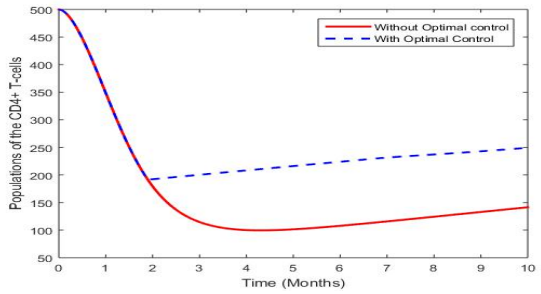


Controls u_1, u_2 and u_3

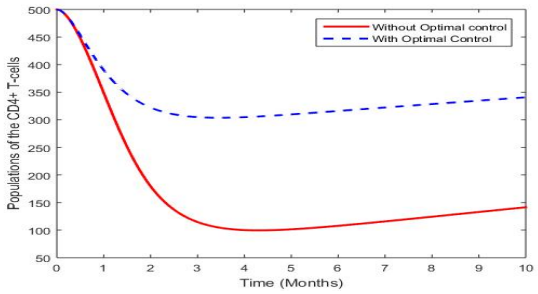
Figure 2: Simulated control strategies

control strategy u_3 remains at a maximum for the first ninth month only dropping to a minimum at the tenth month. From these results we can see that protease inhibitor can be administered for a longer period of time.

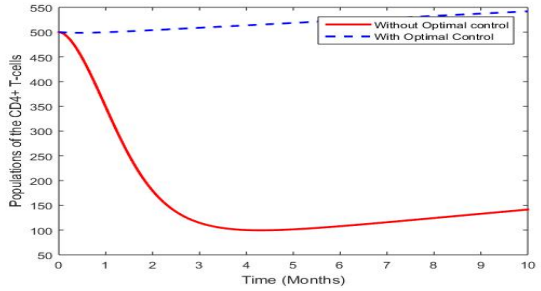
Figure 3 shows the population of the CD4$^+$ T-cells in different treatment strategy. In all the cases it is evident that the introduction of the ARTs plays a significant role as far as controlling HIV is concerned. Nonetheless it is clear that when Fusion inhibitor (u_1) is used without other controls the numbers of CD4$^+$ T-cells reduces significantly and takes a longer time before the number increases. In particular, the drug effectiveness seems to be felt after the first two months. We interpret the results to mean that it is difficult to control the HIV virions by targeting its cell-entry mechanism. The use of Protease inhibitor however, leads to an increase in the number of the CD4$^+$ T-cells. In addition, it is evident that a combination of the three drugs evoke a more pronounced CD4$^+$ T-cells



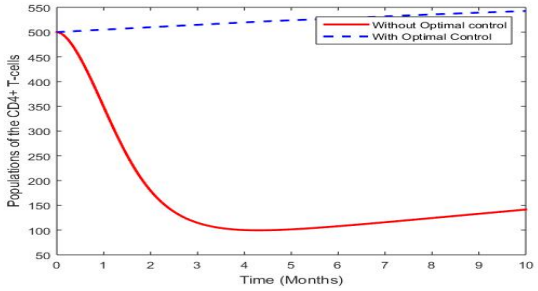
With control u_1



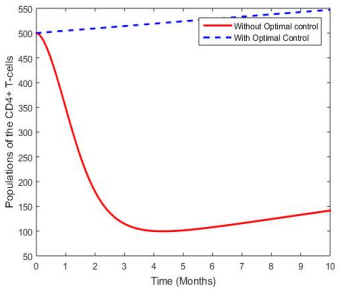
With control u_2



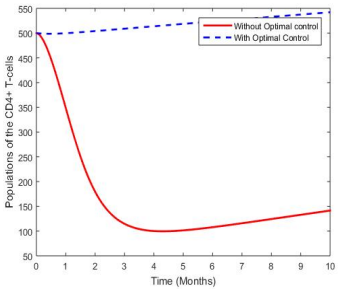
With control u_3



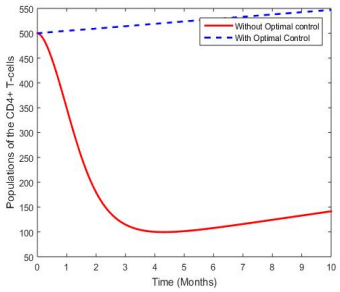
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3



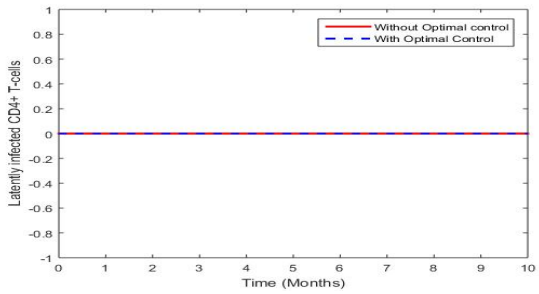
With all the three controls

Figure 3: The population of the $CD4^+$ T-cells in various control strategies

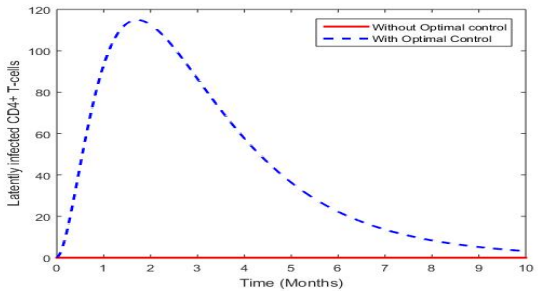
increase than in monotherapy or two drugs combination.

It is important to point out that $CD4^+$ T-cell responses in number of cells gained, were similar for patients treated with two drug combination therapies and patients treated with three drug combination therapies.

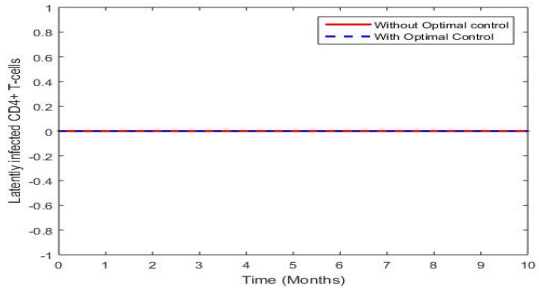
Figure 4 presents the dynamics of the latently infected cells after the introduction of



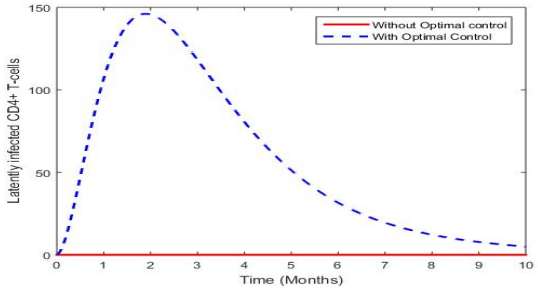
With control u_1



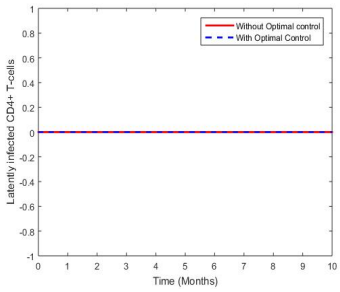
With control u_2



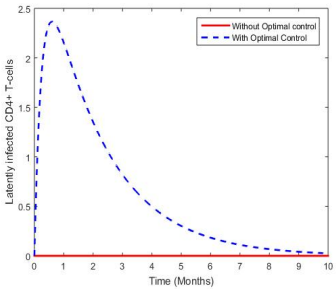
With control u_3



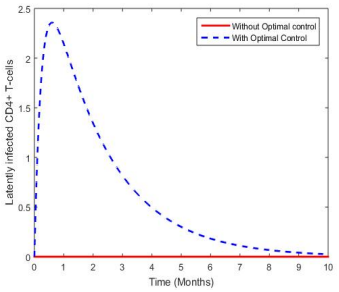
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3

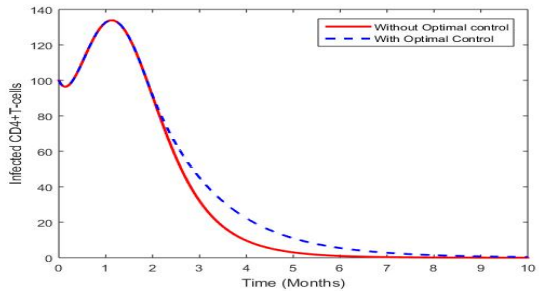


With all the three controls

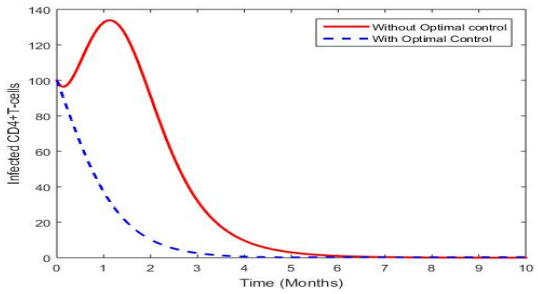
Figure 4: The population of the latently infected CD4$^+$ T-cells in various control strategies

the various control strategies. It is evident that the latently infected cells are produced after the introduction of reverse Transcriptase inhibitor to an HIV infected cell. Since the latently infected cells do not produce infectious virions then it is important to administer RTIs to an infected person. This will reduce the number of virions producing cells.

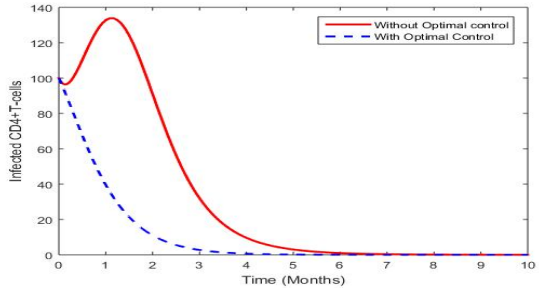
Figure 5 shows the change in the population of the infected CD4$^+$ T-cells with time



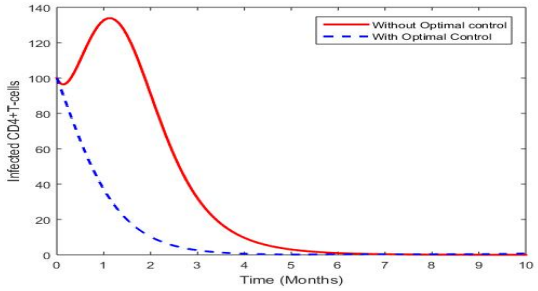
With control u_1



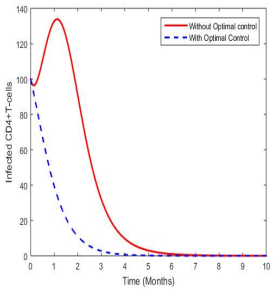
With control u_2



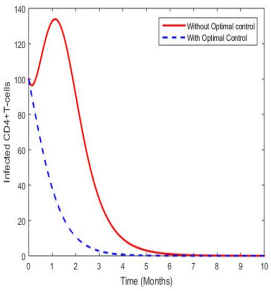
With control u_3



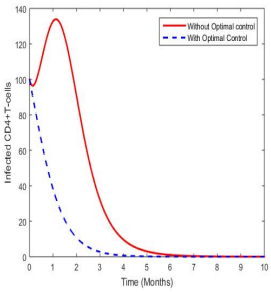
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_1 and u_2



With all the three controls

Figure 5: The population of the infected CD4$^+$ T-cells in various control strategies

in different control strategies. From the simulated results we see that use of ARTs plays a fundamental role especially in controlling the rate of infection. Nonetheless, when the fusion inhibitors are introduced in the body the number of the infected cells still increases for the first few months. This clearly shows that it is very difficult to control the HIV virions at the entry level. The reason would probably be based on the fact HIV uses a complex series of steps to deliver its genome into the host cell cytoplasm while simultaneously evading the host immune response as shown in Figure 6.

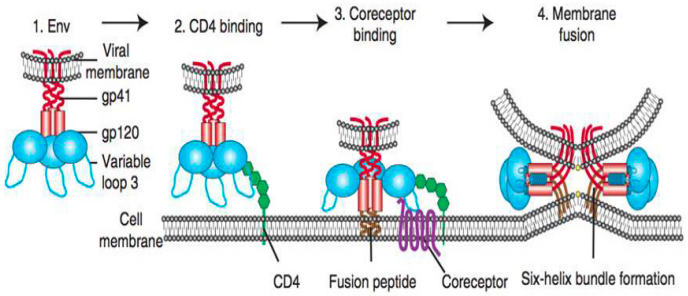
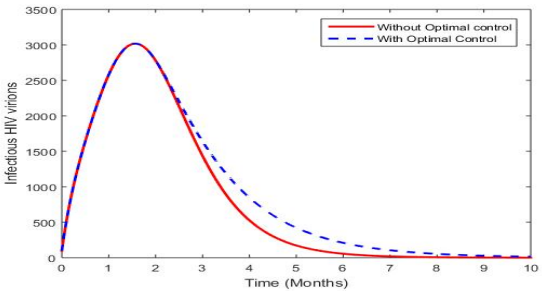


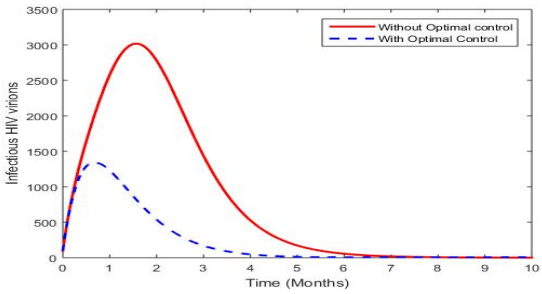
Figure 6: HIV entry mechanism
Wilen, C. B, Tilton, J. C, & Doms, R. W. (2012)

Figure 7 shows the change in the population of the HIV virions in different drug combination(s). It is evident that control u_1 and u_2 are not very as effective as PIs in controlling viral progression. In particular, there is no significant difference when both the the control u_1 is used and when no control is used at all. Researchers such as (Kramer et al., 2012) suggest that viruses blocked by entry inhibitors such the fusion inhibitors are likely redistributed to plasma, where they artificially increases the number of HIV virions. This may probably be the reason why there is an indication of having high number of viral load even when control u_1 is applied. In addition, the fusion inhibitor prevents the entry of the virions unlike the other two drugs which allow the entry of the HIV virions into the cells, confirming the absorption effect. Simulated results shows that Protease Inhibitor plays a significant role in reducing viral progression and it is the best single drug in use for viral suppression. This is in agreement with some of the work done in the field of in-vivo HIV dynamics which have concluded that protease inhibitors are more effective than reverse transcriptase inhibitors and fusion inhibitors in terms of viral load reduction in HIV infected patient (Allers and Schneider, 2015; Shen et al., 2011; Shi et al., 2016). The simulated results also emphasizes the importance of using a combination of the various ARTS when treating HIV.

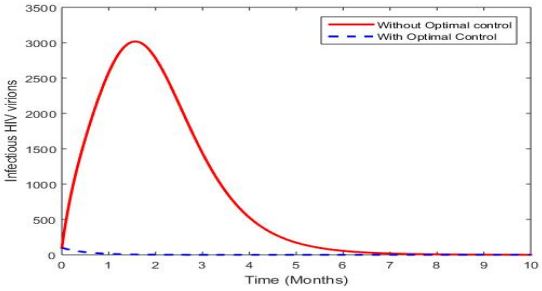
From Figure 8 it is evident that non-infectious virus are produced after the introduction



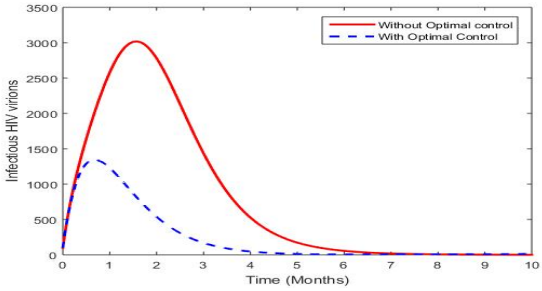
With control u_1



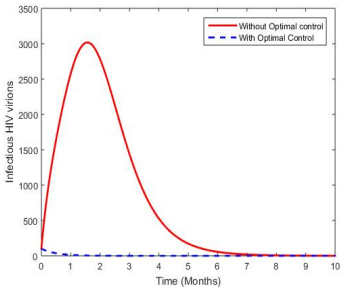
With control u_2



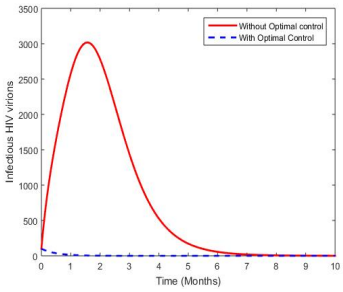
With control u_3



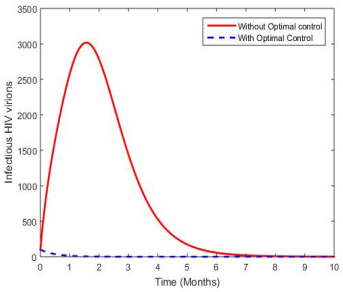
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3

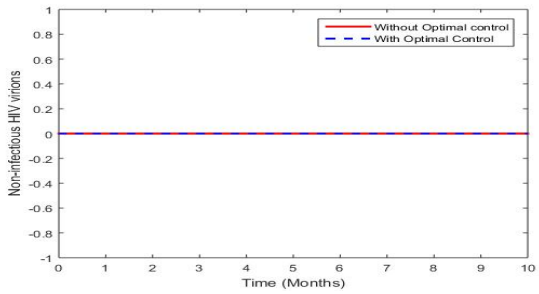


With all the three controls

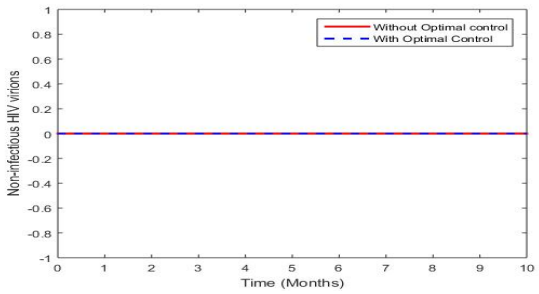
Figure 7: The population of the HIV-virions in various control strategies

of the Protease inhibitor in the body. Introduction of PIs to a HIV infected cells generates a pool of immature HIV virions, this leads to the transfer of non-infectious virus across the virological synapse. This therefore implies that the virus produced will not infect more susceptible $CD4^+$ T-cells.

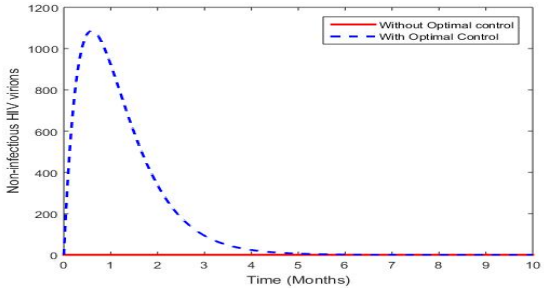
Figure 9 shows the population of the $CD8^+$ T-cells in different treatment strategy. Both



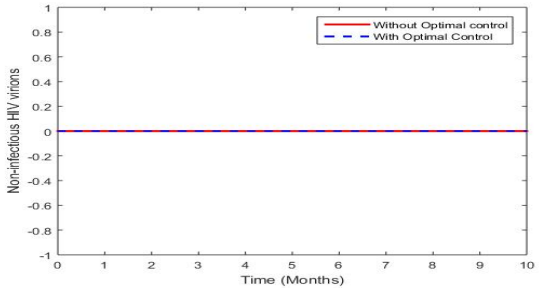
With control u_1



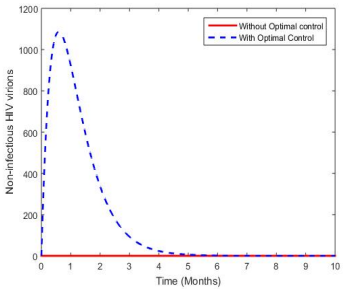
With control u_2



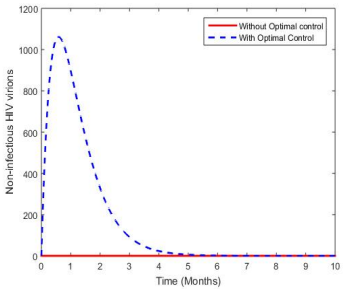
With control u_3



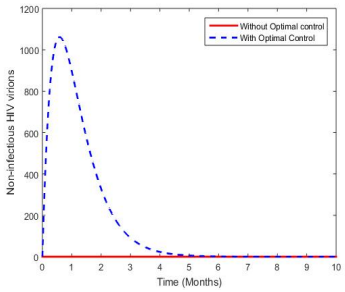
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3

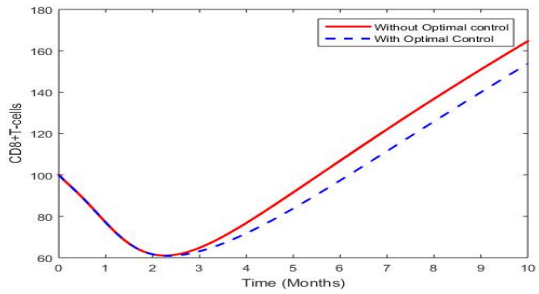


With all the three controls

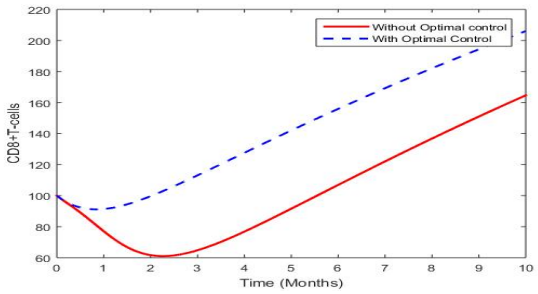
Figure 8: The population of the non-infectious HIV-virions in various control strategies

the RTIs and PIs cause a substantial increases in the population of the CD8$^+$ T-cell in HIV-infected patients. However, it is evident that as much as these two drugs plays a major role, the combination of all the three controls produces a higher immune system reconstitution with sustained increases in circulating number of CD8$^+$T cells.

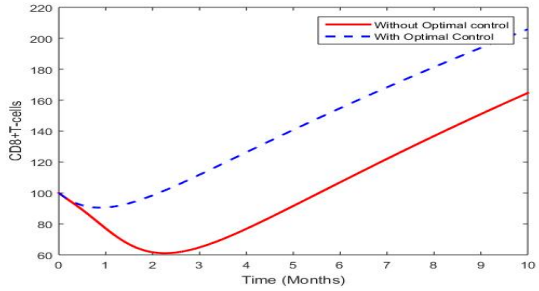
Figure 10 shows the population of the activated CD8$^+$ T-cells. The activation process



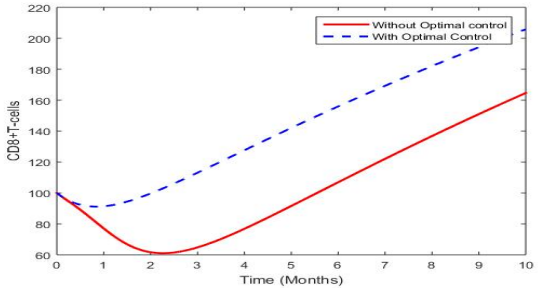
With control u_1



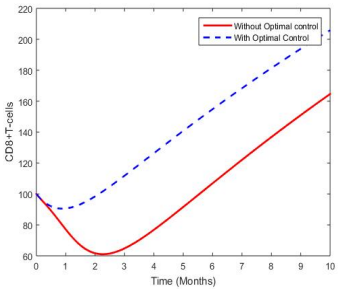
With control u_2



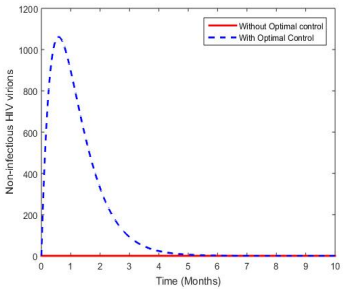
With control u_3



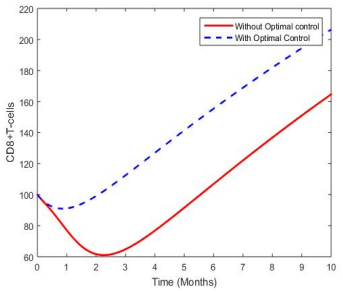
With controls u_1 and u_2



With controls u_1 and u_3



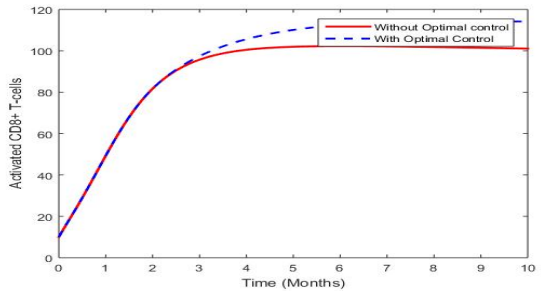
With controls u_2 and u_3



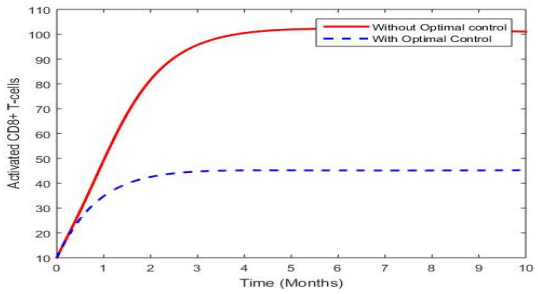
With all the three controls

Figure 9: The population of the CD8$^+$ T-cells in various control strategies

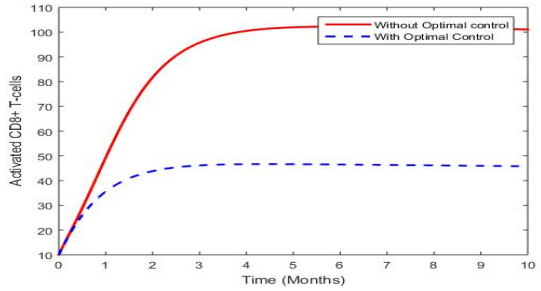
plays a major role in controlling the HIV virus particles. This is because the cells fight, destroy and kill the infected CD4$^+$ T-cells. This in turn reduces the number of HIV virions produced. From the simulated results it is evident that after the introduction of the ARTs the number of activated CD8$^+$ reduced significantly. The reduction may be attributed to the reconstituted immune system or due to the reduction of the retroviral activity on the cells (Autran et al., 1997). However, the question we need to ask ourselves is whether this reduction has any clinical benefit. In future it is important to analyze the clinical benefit that accrual from the reduction of the CD8$^+$ T-cells activation process.



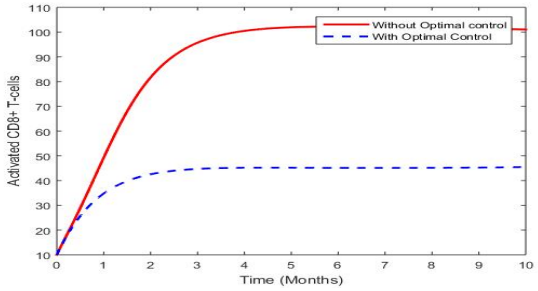
With control u_1



With control u_2



With control u_3



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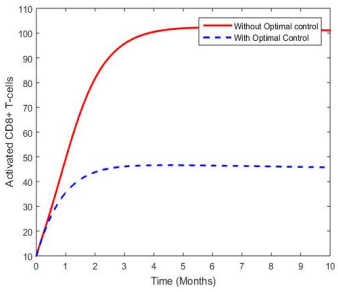

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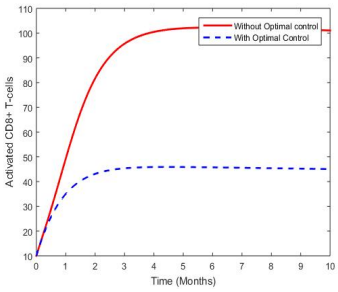
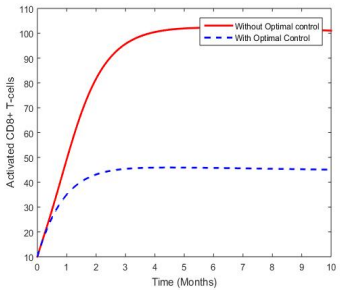


With controls u_2 and u_3



With all the three controls

Figure 10: The population of the Activated CD8$^+$ T-cells in various control strategies

7 Conclusion

In this paper we have analysed a seven-dimension in-vivo HIV model with inclusion of three drug combinations, that is, FIs, RTIs and PIs . Optimal control theory is applied to determine the optimal treatment regime. The study applied the Pontryagin maximum principle in deriving the conditions for optimal control which maximizing the objective function. The systems of ODE's, the state system and the adjoint system were solved numerically by both forward and backward Runge-Kutta forth order scheme. Results from the numerical simulations show that FIs and RTIs should be used within the four months and later the doctors should change the drugs and introduce another type whereas the PIs can be used for a longer period of time without necessarily leading to major side effect. However, the inferiority of monotherapy compared with combination therapies has been

observed in the simulated result especially in suppression of viral replication, $CD4^+$ and $CD8^+$ T-cells reconstitution, and in controlling disease progression.

ARTs have been seen to play a significant role as far as viral suppression is concerned. Therefore, they should be recommended for all patients immediately after one is diagnosed HIV positive regardless of the $CD4^+$ count. This supports the guidelines by the WHO. However, the simulated results suggest that PIs is possibly the best single drug and fusion inhibitor the worst drug in terms of viral load and infected cells reduction. From the results we recommend that RTIs to be used as initial therapy for HIV. FI should be introduced to the patient after the RTIs but should never be used alone.

In future it is important to develop the model in such away that it brings out the relationship between the number of the number of the $CD8^+$ T-cells and the $CD4^+$ T-cells produced in the thymus.

Acknowledgment

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