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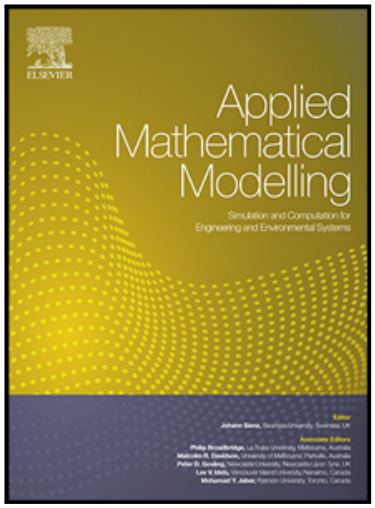

HIV drug resistance: insights from mathematical modelling

Purity Ngina, Rachel Waema Mbogo, Livingstone S. Luboobi

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Highlights

- For HIV in-vivo modelling inclusion of the different strain of HIV virus gives a better presentation of the HIV dynamics.
- ARTS plays a very important role as far as viral replication is concerned.
- Emergence drug resistant HIV strain is one of the major challenge facing HIV management process.
- Prevention of both development of HIV drug resistance and transmission of drug-resistant variants is vital.

HIV drug resistance: insights from mathematical modelling

Purity Ngina [†,*], Rachel Waema Mbogo [†] and Livingstone S. Luboobi [†]

[†] *Institute of Mathematical Sciences, Strathmore University, P.O Box 59857, Nairobi, 00200, Kenya.*

Abstract

In 2013 the World Health Organization recommended the initiation of antiretroviral therapy (ART) to any person who tests HIV positive irrespective of his/her $CD4^+$ count. However, implementation of the new guidelines poses a lot of challenges especially in Sub-Sahara Africa such as: drug side effects, drug resistance-mutations and significant financial burdens. Most importantly, it has been established that HIV resistance and subsequent virologic failure occur in a substantial proportion of HIV-infected patients receiving HAART. This study therefore, seeks to investigate the emergence of drug resistant HIV virus during treatment with the aim of determining the proper use of HIV therapy that would lessen drug resistance. To carry out the analysis a ten dimensional in-vivo mathematical model is proposed for HIV dynamics. The model is formulated in such away that it takes into account two virus strain, that is, the wild type as well as the naive type HIV virus. The in-vivo model is shown to be both biologically meaningful and mathematically well posed. The existence of unique infection-free equilibrium point is determined and both its local and global stability investigated. In addition, the basic reproduction number for each viral strain is computed using the next generation matrix method. An optimal control model is proposed and analysed by applying Pontryagin maximum principle, to obtain the optimal drug combination for HIV treatment. Here two drugs, that is, Reverse Transcriptase inhibitor and Protease inhibitor are used as the controls in the model. We provide an objective function for the minimization of the number of wild type HIV virus and the drug resistant virus as well as the costs associated with the use of Reverse Transcriptase inhibitor and protease inhibitor. The forward backward sweep method is applied to numerically solve the optimality system. From the numerical simulations, it is evident that protease inhibitor is the most effective drug in controlling HIV infection. The results suggest that prolonged use of HAART leads to development of drug resistant and that people with drug-resistant infection could play a core role in the epidemic of HIV.

Keywords: HIV, Wild type virus, drug resistant virus, virion free equilibrium, Reverse transcriptase inhibitor, protease inhibitor, optimal control.

*Corresponding author: Email: *pngina@strathmore.edu*

1 Introduction

HIV is a major problem for global public healthy. Currently, there are over 35 million infected by HIV in which 71% lives in the Sub-sahara Africa. Fortunately, much strides have been realised in terms of HIV treatment since its onset in early 1980 [1]. Twenty six drugs have been approved by the US food and drug administration (FDA). The introduction of these highly active antiretroviral therapy (HAART) in the management of HIV virus has led to a sustained suppression of viral replication, a partial restoration of the immune system, and a sharp decrease in the incidence of opportunistic complications and mortality. Unfortunately, long term use of HAART leads to various side effects and more so they lead to development of drug resistant virus. Other than long term use of HAART, new drugs such as pre-exposure prophylaxis(PrEp) which was introduced to assist in reducing the viral acquisition by the non-infected person have also been cited as a major contributor to the emergence HIV drug resistance virus [2]. Another process that leads to development of drug mutant HIV virions is the reverse transcription process. HIV is an RNA virus, unfortunately RNA virus polymerases have high error rates that are not subject to host cell proof reading mechanisms. According to [3] RNA viruses such as HIV leads to production of 1 mutation per genome per replication cycle. Hence, drug-resistant mutants are present in all infected patients before the initiation of therapy, and this fact underlies the basis of the need for combination therapy for HIV infection. HIV resistance is a complex issue and its existence especially in Sub-Sahara Africa where adherence to HIV therapy is poor need to be carefully analysed.

The problem of emergence of drug resistant during treatment has been of great interest to researchers on HIV modelling aimed at establishing the best way and optimal method of controlling it. Gene analysis has been done to determine the main phenotype of mutant HIV strains as compared to the non-mutant virus [4], unfortunately, not to any conclusive finding. Researches nonetheless, have deduced that drug resistant virus can be passed from one infected person to another. They have indicated that there is a relation between drug adherence and the development of drug mutant viral strain [5].

Mathematicians working on in-host HIV modelling on the other hand have also formulated and analysed models that address the question of drug resistant virus. These models have provided some mechanistic insights into HIV progression, drug efficacy, and the risk of drug resistance virus. For instance, [4] developed a five dimensional model with inclusion of two viral strains, that is, wild-type and drug-resistant, aimed at analysing the effect of non-adherence to HAART leading to drug mutant virus. This was advised by the fact that the reverse transcription process of the HIV RNA to DNA is error prone leading to mutation. However, the study did not include the $CD8^+$ T-cells which are an integral part of HIV dynamics. [6] used a six dimensional model that included both the drug-sensitive and drug-resistant viral strain. The model aimed at analysing the efficacy of different HIV treatment combinations with the evolution of the resistant strain in each case. The model also aimed at determining the correlation between drug efficacy, drug resistant and the adherence to the treatment. However, as much as this study gave very insightful recommendations it failed to put into account the non-infectious virus that results due to the use protease inhibitors. [7] used a six dimensional model to investigate

the effect of various HIV treatments. In this model, the study acknowledged the importance of including two type of the viral strain, that is the drug mutant and the drug sensitive. In addition, the model put into account the role played by the $CD8^+$ T-cells in viral suppression. From the results it was evident that health practitioners in the field of HIV should be concerned with ways of increasing the body immune mechanism. This is because it will help in reducing the mount of HIV treatment given to the infected person and in order to reduce the looming and evolving problem of drug resistance. [8] however, developed a seven dimensional in-vivo model. Here the study aimed at finding the most effective drug between the fusion inhibitor, reverse transcriptase inhibitor and protease inhibitor. However, as much as the study gave very insightful findings it failed to account for the resistance HIV virions which results either due to prolonged use of HAART or if the patient was infected by a resistant virus initially. Such consideration would be of importance in any in-vivo model.

This study is aimed at addressing the gaps so far identified in the in-vivo modelling by improving the in-vivo model proposed and anlysed by [9] which failed to account for the drug resistance virus. In particular, this study proposes and analyses a ten dimensional in-vivo HIV model with two treatment strategies. Optimal control theory, which is a branch of mathematics developed to find optimal ways of controlling an infection such as HIV [8, 10–12], is applied on the in-host HIV treatment model aimed at establishing the optimal drug combinations for HIV in relation to their per capita cost. There are few papers on in-vivo HIV modelling that apply optimal control theory to establish the best intervention practice for controlling the infection [13, 14]. Here we propose and analyse one such optimal control problem, where the control function represents the fraction of the two HIV types, that is, drug resistant and wild type virus, that will be subjected to treatment with Reverse transcriptase inhibitor and protease inhibitor. The objective is to find the optimal treatment strategy that minimizes the number of drug resistant and wild type HIV virions, as well as the cost of HIV treatment regime.

2 Model Formulation

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 [15]. We develop a mathematical model for HIV in-host infection with two treatment strategies combinations of drugs. We define ten variables for the model as follows. Population of the susceptible $CD4^+$ T-cells (T), population of the $CD4^+$ T-cells infected by the wild type HIV virion (I_w), population of the $CD4^+$ T-cells infected by the resistant type HIV virion (I_r), population of the latently infected $CD4^+$ T-cells resulting from the wild type HIV virion and in presence of Reverse Transcriptase inhibitor (I_{lw}), population of the latently infected $CD4^+$ T-cells resulting from resistant type HIV virion and use of reverse transcriptase inhibitor(I_{lr}), wild type infectious HIV virions (V_w), resistant type infectious HIV virions (V_r), non infectious HIV virions resulting after the use of protease inhibitors (V_n), $CD8^+$ T-cells (Z) and the activated $CD8^+$ T-cells (Z_a). Furthermore, two drug controls u_1 and u_2 are introduced to the model. Control u_1 represents RTIs that prevent the reverse transcription process from taking place. Control u_2 represents

PIs that inhibits the release of protease enzymes needed for the maturity of HIV virions hence it leads to the production of non-infectious and immature virions. This in turn reduces the amount of HIV virions in the body. Another control variable of interest is the control u_m which represents the degree of drug resistance mutation. The in-vivo dynamics under therapy is depicted by Figure 1 and the parameters used are as described in Table 1.

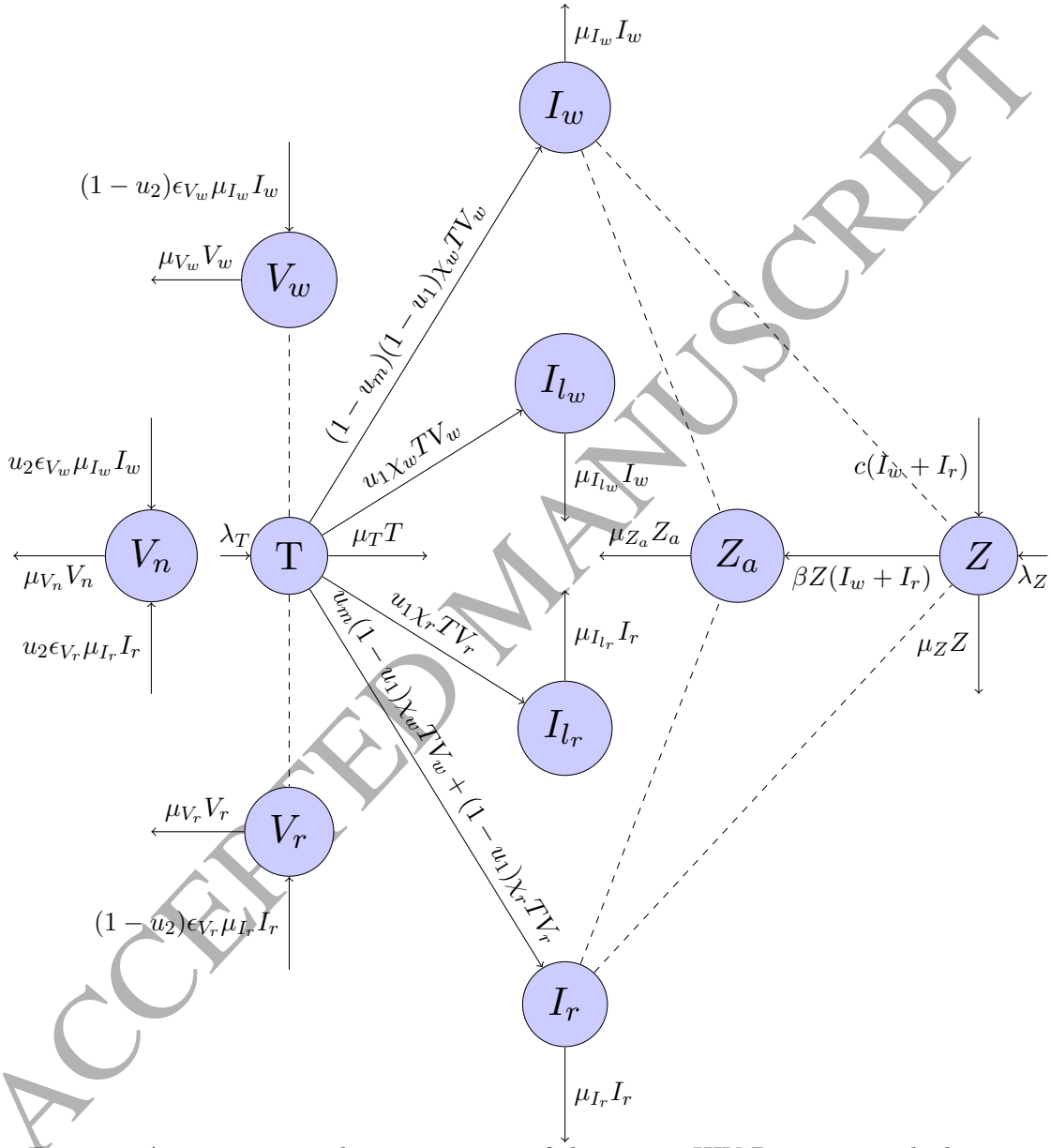

Figure 1: A compartmental representation of the in-vivo HIV Dynamics with therapy.

Table 1: 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 death rate of the the non-infected $CD4^+$T-cells.
χ_w	The rate at which the $CD4^+$T- cells susceptible to the wild type HIV virions are infected by the virus.
χ_r	The rate at which the $CD4^+$T- cells susceptible to the resistant type HIV virions are infected by the virus.
μ_{I_w}	The death rate of the wild type infected $CD4^+$T-cells.
μ_{I_r}	The death rate of the resistant type infected $CD4^+$T-cells.
$\mu_{I_{lw}}$	The death rate of the wild type latently infected $CD4^+$ T-cells.
$\mu_{I_{lr}}$	The death rate of the resistant type latently infected $CD4^+$ T-cells.
ε_{Vw}	Number of wild type HIV virions produced by a single wild type infected $CD4^+$T-cells.
ε_{Vr}	Number of resistant type HIV virions produced by a single resistant type infected $CD4^+$T-cells.
μ_{Vw}	The death rate of the wild type infectious virus.
μ_{Vr}	The death rate of the resistant type infectious virus.
μ_{V_n}	The death rate of the non-infectious viruss.
c	Proliferation rate of the $CD8^+$T-cells.
α	The rate at which the both the wild type and resistant type 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.

From Figure 1 we derive the following system of ordinary differential equations describing

the model dynamics.

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \chi_w T V_w - \chi_r T V_r \\
\frac{dI_w}{dt} &= (1-u_m)(1-u_1(t))\chi_w T V_w - \mu_{Iw} I_w - \alpha I_w Z_a, \\
\frac{dI_r}{dt} &= u_m(1-u_1(t)\chi_w T V_w + (1-u_1(t))\chi_r T_r V_r - \mu_{Ir} I_r - \alpha I_r Z_a, \\
\frac{dI_{lw}}{dt} &= u_1(t)\chi_w T V_w - \mu_{I_l w} I_{l_w}, \\
\frac{dI_{lr}}{dt} &= u_1(t)\chi_r T V_r - \mu_{I_l r} I_{l_r}, \\
\frac{dV_w}{dt} &= (1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vw} V_w, \\
\frac{dV_r}{dt} &= (1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vr} V_r, \\
\frac{dV_n}{dt} &= u_2(t)\epsilon_{Vr}\mu_{Ir} I_r + u_2(t)\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vn} V_n, \\
\frac{dZ}{dt} &= \lambda_Z + cZ(I_w + I_r) - \mu_Z Z - \beta Z(I_w + I_r), \\
\frac{dZ_a}{dt} &= \beta Z(I_w + I_r) - \mu_{Z_a} Z_a
\end{aligned}\right\} \tag{1}$$

3 Model analysis

3.1 Positivity of the Solutions

We assume that the initial values of the variables of the model are non-negative. We now show that also the solutions of the model (1) are also non-negative.

Theorem 1. *Let*

$$\begin{aligned}
\Phi(t) = \Big\{ &(T(t), I_w(t), I_r(t), I_{lw}(t), I_{lr}(t), V_w(t), V_r(t), V_n(t), Z(t), Z_a(t)) \in \mathbb{R}^{10^+} : \\
&T(0) \geq 0, I_w(0) \geq 0, I_r(0) \geq 0, I_{lw}(0) \geq 0, I_{lr}(0) \geq 0, V_w(0) \geq 0, V_r(0) \geq 0, \\
&V_n(0) \geq 0, Z(0) \geq 0, Z_a(0) \geq 0\}
\end{aligned}$$

then the solutions of $(T(t), I_w(t), I_r(t), I_{lw}(t), I_{lr}(t), V_w(t), V_r(t), V_n(t), Z(t), Z_a(t))$ *are non-negative for all* $t \geq 0$

Proof. From the first equation of system (1) the population of the $CD4^+$ T-cells is given by

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \chi_w T V_w - \chi_r T V_r \\
\frac{dT}{dt} &\geq -\mu_T T - \chi_w T V_w - \chi_r T V_r \\
\frac{dT}{dt} &\geq -T(\mu_T + \chi_w V_w + \chi_r V_r)
\end{aligned} \tag{2}$$

By separation of variable method, equation (2) reduces to

$$\begin{aligned} \frac{dT}{T} &\geq -\mu_T - \chi_w V_w - \chi_r V_r \\ T &\geq T_0 e^{-\int_0^t (\mu_T t + \chi_w V_w(s) + \chi_r V_r(s))ds} \end{aligned} \tag{3}$$

Hence,

$$T \geq 0 \tag{4}$$

From equation (4) is is evident that T is non-negative for all $t \geq 0$.
The same argument can be used to show that $I_w, I_r, I_{lw}, I_{lr}, V_w, V_r, V_n, Z$ and Z_a are also non-negative. □

3.2 Invariant Region

From (1) the total population of the $CD4^+$ T-cells satisfy

$$\frac{dN_4}{dt} = \lambda_T - \mu_T T - \mu_{Iw} I_w - \alpha Z_a (I_w + I_r)\mu_{Ir} - \mu_{I_l w} I_{l_w} - \mu_{I_l r} I_{l_r} \tag{5}$$

Thus, from equation (5) we have

$$\frac{dN_4}{dt} = \lambda_T - (\mu_T T + \mu_{Iw} I_w + \alpha Z_a (I_w + I_r)\mu_{Ir} + \mu_{I_l w} I_{l_w} + \mu_{I_l r} I_{l_r}) \tag{6}$$

Let $\Theta = \min\{\mu_T, \mu_{Iw}, \mu_{Ir}, \mu_{I_l w}, \mu_{I_l r}\}$, then from (6) we have

$$\begin{aligned} \frac{dN_4}{dt} &\leq \lambda_T - \Theta(T + I_w + I_r + I_{l_w} + I_{l_r}) \\ \frac{dN_4}{dt} &\leq \lambda_T - \Theta N_4 \end{aligned} \tag{7}$$

Using a suitable integrating factor, that is, I.f $= e^{\Theta t}$, the differential inequality (7) is solved to obtain

$$\begin{aligned} \frac{d}{dt}\left(N_4(t)e^{\Theta t}\right) &\leq \lambda_T e^{\Theta t} \\ N_4(t)e^{\Theta t} - T_0 &\leq \frac{\lambda_T}{\Theta} e^{\Theta t} - \frac{\lambda_T}{\Theta} \\ N_4(t) &\leq \left(T_0 - \frac{\lambda_T}{\Theta}\right) e^{-\Theta t} + \frac{\lambda_T}{\Theta} \end{aligned} \tag{8}$$

From equation (8) we have

$$N_4(t) \leq \max\left\{T_0, \frac{\lambda_T}{\Theta}\right\} \tag{9}$$

From equation (9) the total population of the $CD4^+$ T-cells is bounded. The same argument can be used to show that all the other state variables are bounded. Therefore, the basic model is well posed epidemiologically and mathematically.

4 Infection-free equilibrium

Model (1) has a infection-free equilibrium (IFE) which occurs when $I_w = I_r = I_{lw} = I_{lr} = V_w = V_r = V_n = Z_a = 0$) given by:

$$E_0(T_0, I_{w_0}, I_{r_0}, I_{lw_0}, I_{lr_0}, V_{w_0}, V_{r_0}, V_{n_0}, Z_0, Z_{a_0}) = \left(\frac{\lambda_T}{\mu_T}, 0, 0, 0, 0, 0, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0\right) \tag{10}$$

4.1 The basic reproductive number

In this section, we apply the next generation matrix in determining the threshold parameter that governs the spread of a disease which is called the basic reproduction number [16]. According to [17] basic reproductive number, R_0, measures the average number of secondary infection cases generated by a primary case in a pool of mostly susceptible individuals. For HIV in-vivo modelling R_0 represents the number of $CD4^+$ T-cells that results from a single infected $CD4^+$ T-cell throughout its life time. R_0 answers very important questions regarding the infection. For instance, having $R_0 < 1$ implies that the disease is likely to be eliminated from the body, this can be done through introduction of various HIV therapy that targets parameters sensitive to R_0.

4.2 Computation of the basic reproductive number

By use of the next generation method R_0 is the dominant eigenvalue of the matrix $G = FV^{-1}$. Here F is the matrix that represents the appearance of new infections and V is the matrix representing transfer of infections from one compartment to another, both evaluated at the infection-free equilibrium state. R_0 is therefore derived as follows:
From system (1) the infective compartments are

$$\begin{aligned}
\frac{dI_w}{dt} &= (1-u_m)(1-u_1(t))\chi_w T V_w - \mu_{Iw} I_w - \alpha I_w Z_a,\\
\frac{dI_r}{dt} &= u_m(1-u_1(t))\chi_w T V_w + (1-u_1(t))\chi_r T_r V_r - \mu_{Ir} I_r - \alpha I_r Z_a,\\
\frac{dI_{lw}}{dt} &= u_1(t)\chi_w T V_w - \mu_{I_l w} I_{l_w},\\
\frac{dI_{lr}}{dt} &= u_1(t)\chi_r T V_r - \mu_{I_l r} I_{l_r},\\
\frac{dV_w}{dt} &= (1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vw} V_w,\\
\frac{dV_r}{dt} &= (1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vr} V_r,\\
\frac{dZ}{dt} &= \lambda_Z + cZ(I_w + I_r) - \mu_Z Z - \beta Z(I_w + I_r),\\
\frac{dZ_a}{dt} &= \beta Z(I_w + I_r) - \mu_{Z_a} Z_a
\end{aligned} \tag{11}$$

The matrix of new infections at infection-free equilibrium is given by

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & (1-u_m)(1-u_1)\chi_w\frac{\lambda_T}{\mu_T} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & u_m(1-u_1)\chi_w\frac{\lambda_T}{\mu_T} & (1-u_1)\chi_r\frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & 0 & 0 & 0 & u_1\chi_w\frac{\lambda_T}{\mu_T} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & u_1\chi_r\frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ c\frac{\lambda_Z}{\mu_Z} & c\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & 0 & 0 \\ c\frac{\lambda_Z}{\mu_Z} & c\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{12}$$

The matrix of transfer of infections from one compartment to another at the infection-free equilibrium is given by;

$$V = \begin{bmatrix} \mu_{Iw} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mu_{Ir} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mu_{I_lw} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu_{I_lr} & 0 & 0 & 0 & 0 \\ -(1-u_2(t))\epsilon_{Vw}\mu_{Iw} & 0 & 0 & 0 & \mu_{Vw} & 0 & 0 & 0 \\ 0 & -(1-u_2(t))\epsilon_{Vr}\mu_{Iw} & 0 & 0 & 0 & \mu_{Vr} & 0 & 0 \\ \beta\frac{\lambda_Z}{\mu_Z} & \beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & \mu_Z & 0 \\ \beta\frac{\lambda_Z}{\mu_Z} & \beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & 0 & \mu_{Z_a} \end{bmatrix} \tag{13}$$

The inverse of V from (13) is given by

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_{Iw}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\mu_{Ir}} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\mu_{I_lw}} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\mu_{I_lr}} & 0 & 0 & 0 & 0 \\ \frac{(1-u_2(t))\epsilon_{Vw}\mu_{Iw}}{\mu_{Vw}} & 0 & 0 & 0 & \frac{1}{\mu_{Vw}} & 0 & 0 & 0 \\ 0 & \frac{(1-u_2(t))\epsilon_{Vr}\mu_{Iw}}{\mu_{Vr}} & 0 & 0 & 0 & \frac{1}{\mu_{Vr}} & 0 & 0 \\ -\beta\frac{\lambda_Z}{{\mu_Z}^2\mu_{Iw}} & -\beta\frac{\lambda_Z}{{\mu_Z}^2\mu_{Iw}} & 0 & 0 & 0 & 0 & \frac{1}{\mu_Z} & 0 \\ -\beta\frac{\lambda_Z}{\mu_Z\mu_{Iw}\mu_{Z_a}} & -\beta\frac{\lambda_Z}{\mu_Z\mu_{Ir}\mu_{Z_a}} & 0 & 0 & 0 & 0 & 0 & \frac{1}{\mu_{Z_a}} \end{bmatrix} \tag{14}$$

Multiplying equation (12) and (14) we have

$$FV^{-1} = \begin{bmatrix} \frac{(1-u_m)(1-u_1)(1-u_2)\chi_w\lambda_T\epsilon_{vw}}{\mu_T\mu_{Vw}} & 0 & 0 & 0 & \frac{(1-u_m)(1-u_1)\chi_w\lambda_T}{\mu_T\mu_{Vw}} & 0 & 0 & 0 \\ \frac{(1-u_m)(1-u_1)(1-u_2)\chi_w\lambda_T\epsilon_{vw}}{\mu_T\mu_{Vw}} & \frac{(1-u_1)(1-u_2)\chi_r\lambda_T\epsilon_{vr}}{\mu_T\mu_{Vr}} & 0 & 0 & \frac{u_m(1-u_1)\chi_w\lambda_T\epsilon_{vw}}{\mu_T\mu_{Vw}} & \frac{(1-u_1)\chi_r\lambda_T}{\mu_T\mu_{Vr}} & 0 & 0 \\ \frac{u_1(1-u_2)\chi_w\lambda_T\epsilon_{vw}}{\mu_T\mu_{Vw}} & 0 & 0 & 0 & \frac{u_1\chi_w\lambda_T}{\mu_T\mu_{Vw}} & 0 & 0 & 0 \\ 0 & \frac{u_1(1-u_2)\chi_w\lambda_T\epsilon_{vw}}{\mu_T\mu_{Vw}} & 0 & 0 & 0 & \frac{u_1\chi_r\lambda_T}{\mu_T\mu_{Vr}} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ c\frac{\lambda_Z}{\mu_Z\mu_{Iw}} & c\frac{\lambda_Z}{\mu_Z\mu_{Iw}} & 0 & 0 & 0 & 0 & 0 & 0 \\ c\frac{\lambda_Z}{\mu_Z\mu_{Iw}} & c\frac{\lambda_Z}{\mu_Z\mu_{Iw}} & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{15}$$

The eigenvalues of (15) are given by

$$\Lambda = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ (1-u_m)(1-u_1)(1-u_2)\chi_w\frac{\lambda_T}{\mu_T}\frac{\epsilon_{vw}}{\mu_{Vw}} \\ (1-u_1)(1-u_2)\chi_r\frac{\lambda_T}{\mu_T}\frac{\epsilon_{vr}}{\mu_{Vr}} \end{bmatrix} \tag{16}$$

From the eigenvalues obtained in equation (16) it is evident that the basic reproductive number is given by

$$R_0 = max\left\{R_{0_w}, R_{0_r}\right\} \tag{17}$$

where

$$R_{0_w} = (1-u_m)(1-u_1)(1-u_2)\chi_w\frac{\lambda_T}{\mu_T}\frac{\epsilon_{vw}}{\mu_{Vw}} \tag{18}$$

and

$$R_{0_r} = (1-u_1)(1-u_2)\chi_r\frac{\lambda_T}{\mu_T}\frac{\epsilon_{vr}}{\mu_{Vr}} \tag{19}$$

If $R_0 < 1$ in equation (17), then the HIV virions cannot invade the body and the disease will die out over time. However, as much as the time before the virions goes to non-detectable level depends on how small R_0 is, the HIV patients must continue taking HAART to avoid the recurrence of the disease. It can be seen from equation (18) that if both the Reverse Transcriptase inhibitor and the Protease inhibitor are 100% effective, that is $u_1 = u_2 = 1$, then there is no secondary infections in the cells.

To determine the best ways of reducing mortality due to HIV/AIDS related illness the importance of each parameter in relation to R_0 is evaluated as shown in the next section.

4.3 Analysis of the Basic Reproductive number

This section is aimed at determining the relative importance of different parameters responsible for the viral replication related to the basic reproduction number, obtained in equation (17). This is because the basic reproduction number, R_0, is a measure of the potential for infection to spread in a population, and is one of the foremost and most valuable ideas that mathematicians have brought to epidemic theory [18]. To date, there are many ways of conducting Sensitivity Analysis, all resulting in a slightly different sensitivity ranking. In this study, we use the normalized forward index.

The normalized forward sensitivity index of R_0 with respect to the parameter P is given by:

$$\gamma_P^{R_0} = \left(\frac{\partial R_0}{\partial P}\right) * \left(\frac{P}{R_0}\right) \tag{20}$$

where P represents a parameter in the expression of the basic reproductive number. From the basic reproductive number given by equation (17) the sensitivity indices of R_0 with respect to the parameters $\chi_i, \epsilon_{V_i}, \lambda_T, \mu_{V_i}, \mu_T$ (where $i = w, r$) are respectively given as:

$$\frac{\partial R_0}{\partial \chi_i}\frac{\chi_i}{R_0} = 1 \tag{21}$$

$$\frac{\partial R_0}{\partial \epsilon_{V_i}}\frac{\epsilon_{V_i}}{R_0} = 1 \tag{22}$$

$$\frac{\partial R_0}{\partial \lambda_T}\frac{\lambda_T}{R_0} = 1 \tag{23}$$

$$\frac{\partial R_0}{\partial \mu_{V_i}}\frac{\mu_{V_i}}{R_0} = -1 \tag{24}$$

$$\frac{\partial R_0}{\partial \mu_T}\frac{\mu_T}{R_0} = -1 \tag{25}$$

From the sensitivity indices, it is evident that μ_T, χ_i and λ_T are the most positively sensitive parameters. Thus increasing any of these parameters will lead to an increase in the value of R_0 whereas μ_{V_i} and μ_T are the most negatively sensitive parameters in that increasing any of these parameters will decrease the value of R_0. In particular, a 1% increase in any of μ_{V_i} and μ_T results to a 1% decrease in R_0. Hence, health practitioners should use controls that targets the most positively sensitive parameters; this in turn will lead to the reduction in the number of HIV virions.

Another important observation from the basic reproductive number (17) is that if $u_1 = u_2 = u_m = 1$ then the $R_0 = 0$ and hence the disease will die out.

4.4 Local stability of the infection-free equilibrium

Theorem 2. *The infection-free equilibrium, E_0, is locally asymptotically stable when $R_0 < 1$ and unstable otherwise.*

Proof. We apply the linearisation method to determine the local stability of the infection-free equilibrium. The Jacobian matrix of the system (1) at the infection-free equilibrium is given by;

$$J = \begin{bmatrix}
-\mu_T & 0 & 0 & 0 & 0 & \frac{\chi_w\lambda_T}{\mu_T} & \frac{\chi_r\lambda_T}{\mu_T} & 0 & 0 & 0 \\
0 & -\mu_{Iw} & 0 & 0 & 0 & \frac{(1-u_m)(1-u_1)\chi_w\lambda_T}{\mu_T} & 0 & 0 & 0 & 0 \\
0 & 0 & -\mu_{Ir} & 0 & 0 & 0 & \frac{u_m(1-u_1)\chi_w\lambda_T}{\mu_T} & \frac{(1-u_1)\chi_r\lambda_T}{\mu_T} & 0 & 0 \\
0 & 0 & 0 & -\mu_{I_{lw}} & 0 & \frac{u_1\chi_w\lambda_T}{\mu_T} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\mu_{I_{lr}} & 0 & 0 & \frac{u_1\chi_r\lambda_T}{\mu_T} & 0 & 0 \\
0 & (1-u_2)\epsilon_{Vw}\mu_{Iw} & 0 & 0 & 0 & -\mu_{Vw} & 0 & 0 & 0 & 0 \\
0 & 0 & (1-u_2)\epsilon_{Vr}\mu_{Ir} & 0 & 0 & 0 & -\mu_{Vr} & 0 & 0 & 0 \\
0 & u_2\epsilon_{Vw}\mu_{Iw} & u_2\epsilon_{Vr}\mu_{Ir} & 0 & 0 & 0 & 0 & -\mu_{Vn} & 0 & 0 \\
0 & c\frac{\lambda_Z}{\mu_Z} & c\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & 0 & -\mu_Z & 0 \\
0 & \beta\frac{\lambda_Z}{\mu_Z} & \beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{Z_a}
\end{bmatrix} \tag{26}$$

The eigenvalues of J in (26) are the solutions of the tenth-order polynomial equation and they are given by

$$\Lambda_1 = -\mu_Z \tag{27}$$

$$\Lambda_2 = -\mu_{Vn} \tag{28}$$

$$\Lambda_3 = -\mu_{I_{lr}} \tag{29}$$

$$\Lambda_4 = -\mu_{I_{lw}} \tag{30}$$

$$\Lambda_5 = -\mu_T \tag{31}$$

$$\Lambda_6 = \frac{-\mu_T(\mu_{Ir}+\mu_{Vr}) + \sqrt{4(1-u_1)(1-u_2)\lambda_T\mu_T\mu_{Ir}\epsilon_{Vr}\chi_r + \mu_T^2\mu_{Ir}^2 - 2\mu_T^2\mu_{Ir}\mu_{Vr} + \mu_T^2\mu_{Vr}^2}}{2\mu_T} \tag{32}$$

$$\Lambda_7 = -\frac{\mu_T(\mu_{Ir}+\mu_{Vr}) + \sqrt{4(1-u_1)(1-u_2)\lambda_T\mu_T\mu_{Ir}\epsilon_{Vr}\chi_r + \mu_T^2\mu_{Ir}^2 - 2\mu_T^2\mu_{Ir}\mu_{Vr} + \mu_T^2\mu_{Vr}^2}}{2\mu_T} \tag{33}$$

$$\Lambda_8 = \frac{-\mu_T(\mu_{Iw}+\mu_{Vw})}{2\mu_T} + \frac{\sqrt{4(1-u_m)(1-u_1)(1-u_2)\lambda_T\mu_T\mu_{Iw}\epsilon_{Vw}\chi_w + \mu_T^2\mu_{Iw}^2 - 2\mu_T^2\mu_{Iw}\mu_{Vw} + \mu_T^2\mu_{Vw}^2}}{2\mu_T} \tag{34}$$

$$\Lambda_9 = -\frac{\mu_T(\mu_{Iw}+\mu_{Vw})}{2\mu_T} + \frac{\sqrt{4(1-u_m)(1-u_1)(1-u_2)\lambda_T\mu_T\mu_{Iw}\epsilon_{Vw}\chi_w + \mu_T^2\mu_{Iw}^2 - 2\mu_T^2\mu_{Iw}\mu_{Vw} + \mu_T^2\mu_{Vw}^2}}{2\mu_T} \tag{35}$$

$$\Lambda_{10} = -\mu_{Z_a} \tag{36}$$

Using Routh-Hurwitz criterion, we deduce that all the eigenvalues of Jacobian matrix J in (26) have negative real part, hence the infection-free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. □

4.5 Global stability of the infection-free equilibrium point

[19] stipulated the conditions that must be satisfied for the global stability.

Theorem 3. *For system (1), the infection-free equilibrium E_0 is globally asymptotically stable if $R_0 \leq 0$*

Proof. We transform model (1) by re-writing it in the form given by equations (37);

$$\begin{aligned} \frac{dX}{dt} &= H(X,W) \\ \frac{dZ}{dt} &= G(X,W) \quad G(X;0) = 0 \end{aligned} \tag{37}$$

where $X = (T, V_n, Z, Za)$ and $W = (I_w, I_r, I_{lw}, I_{wr}, V_w, V_r)$. Here, $X \in \mathbb{R}^4$ denotes the non-infected compartments while $W \in \mathbb{R}^6$ denotes the HIV infected compartments. Hence

$$H(X,W) = \begin{pmatrix} \lambda_T - \mu_T T - \chi_w T V_w - \chi_r T V_r \\ \lambda_Z + cZ(I_w + I_r) - \mu_Z Z - \beta Z(I_w + I_r) \\ \beta Z(I_w + I_r) - \mu_{Z_a} Z_a \end{pmatrix} \tag{38}$$

$$G(X,W) = \begin{pmatrix} (1-u_m)(1-u_1(t))\chi_w T V_w - \mu_{Iw} I_w - \alpha I_w Z_a \\ u_m(1-u_1(t))\chi_w T V_w (1-u_1(t))\chi_r T_r V_r - \mu_{Ir} I_r - \alpha I_r Z_a \\ u_1(t)\chi_w T V_w - \mu_{I_l w} I_{l_w} \\ u_1(t)\chi_r T V_r - \mu_{I_l r} I_{l_r} \\ (1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vw} V_w \\ (1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vr} V_r \\ u_2(t)\epsilon_{Vr}\mu_{Ir} I_r + u_2(t)\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vn} V_n \end{pmatrix} \tag{39}$$

At the infection-free equilibrium we have

$$H(X,0) = \begin{pmatrix} \lambda_T - \mu_T T \\ \lambda_Z - \mu_Z Z \\ -\mu_{Z_a} Z_a \end{pmatrix} \tag{40}$$

The infection-free equilibrium point for system (40) is given by, $E_{0v} = \frac{\lambda_T}{\mu_T}, \frac{\lambda_Z}{\mu_Z}, 0$. We first determine the existence of a biologically feasible region Ω_H.

Lemma 1. *The biologically feasible region Ω_H; defined by the compact set;*

$$\Omega_H = \left\{ (T, Z, Z_a) \in \mathbb{R}^3 : T \leq \ max \left\{ T_0, \frac{\lambda_T}{\mu_T} \right\}, Z \leq \ max \left\{ Z_0, \frac{\lambda_Z}{\mu_Z} \right\}, Z_a = 0 \right\} \tag{41}$$

with initial conditions $T(0), Z(0), Z_a(0) > 0$ is positively invariant for all $t > 0$.

Proof. We now show that Ω_H is the invariant region for the model (40). Taking the first equation of the system given by equation (40) the population of the susceptible $CD4^+$

T-cells satisfy

$$\begin{aligned} \frac{dT}{dt} &= \lambda_T - \mu_T T \\ \frac{dT}{dt} &+ \mu_T T = \lambda_T \end{aligned} \tag{42}$$

Thus equation (42) becomes

$$\begin{aligned} \frac{d(Te^{\mu_T t})}{dt} &= \int \lambda_T e^{\mu_T t} \\ T &= \frac{\lambda_T}{\mu_T} + Ce^{-\mu_T t} \end{aligned} \tag{43}$$

Applying the initial condition, at $t = 0$, and denoting $T(0) = T_0$, equation (43) gives

$$C = T_0 - \frac{\lambda_T}{\mu_T} \tag{44}$$

Substituting (44) in (43) the inequality for the susceptible CD4$^+$ T-cells is given by;

$$T = \frac{\lambda_T}{\mu_T} + \left(T_0 - \frac{\lambda_T}{\mu_T}\right) e^{-\mu_T t} \tag{45}$$

Hence at any time $t > 0$

$$T \leq \max\left\{T_0, \frac{\lambda_T}{\mu_T}\right\} \tag{46}$$

This argument can be used to show that the other state variables are bounded. This implies that any solution $(T(t), Z(t), Z_a(t))$, at $t \geq 0$, in $\mathbb{R}^3$ will always remain confined in Ω_H. Hence, the region Ω_H is positively invariant for the model system (40). □

From equation (37) we compute $G(X, W) = PG - \hat{G}(X, W), \hat{G}(X, W) \geq 0$ for $(X, W) \in \Omega_H$

$$G(X,W) = \begin{pmatrix} (1-u_m)(1-u_1(t))\chi_w T V_w - \mu_{Iw} I_w - \alpha I_w Z_a \\ u_m(1-u_1(t))\chi_w T V_w (1-u_1(t))\chi_r T_r V_r - \mu_{Ir} I_r - \alpha I_r Z_a \\ u_1(t)\chi_w T V_w - \mu_{I_l w} I_{l_w} \\ u_1(t)\chi_r T V_r - \mu_{I_l r} I_{l_r} \\ (1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vw} V_w \\ (1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vr} V_r \\ u_2(t)\epsilon_{Vr}\mu_{Ir} I_r + u_2(t)\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vn} V_n \end{pmatrix} \tag{47}$$

Since every element of the matrix $G(X; W)$ contains virions or infected component then $G(X; 0) = 0$. The M-matrix P can be constructed as:

$$P = D_W G(X^*, 0)$$

$$= \begin{bmatrix} -\mu_{Iw} & 0 & 0 & 0 & (1-u_m)(1-u_1)\chi_w \frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & -\mu_{Ir} & 0 & 0 & u_m(1-u_1)\chi_w \frac{\lambda_T}{\mu_T} & (1-u_1)\chi_r \frac{\lambda_T}{\mu_T} & 0 \\ 0 & 0 & -\mu_{I_{lr}} & 0 & u_1\chi_w \frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & 0 & 0 & -\mu_{I_{lr}} & 0 & u_1\chi_r \frac{\lambda_T}{\mu_T} & 0 \\ (1-u_2)\epsilon_{Vw}\mu_{Iw} & 0 & 0 & 0 & -\mu_{Vw} & 0 & 0 \\ 0 & (1-u_2)\epsilon_{Vr}\mu_{Ir} & 0 & 0 & 0 & -\mu_{Vr} & 0 \\ u_2\epsilon_{Vw}\mu_{Iw} & u_2\epsilon_{Vw}\mu_{Iw} & 0 & 0 & 0 & 0 & -\mu_{Vn} \end{bmatrix} \tag{48}$$

By definition of $G(X,W) = PG - \hat{G}(X,W)$ hence $\hat{G}(X,W)$ is given as

$$\hat{G}(X,W) = \begin{pmatrix} \hat{G}_1(X,W) \\ \hat{G}_2(X,W) \\ \hat{G}_3(X,W) \\ \hat{G}_4(X,W) \\ \hat{G}_5(X,W) \\ \hat{G}_6(X,W) \end{pmatrix} = \begin{pmatrix} \alpha Z_a I_w \\ \alpha Z_a I_r \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{49}$$

Since $\alpha Z_a I_w \geq 0$ and $\alpha Z_a I_r \geq 0$, then, $\hat{G}(X,W) \geq 0$ for $(X,W) \in \Omega_H$. Hence the infection-free equilibrium (E_0) is globally stable. □

In the next section we carry out optimal control analysis for the model (1).

5 Optimization process

One of the main objectives for studying HIV infection dynamics is to improve the control strategy so as to suppress the viral load to non-detectable level and 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, optimal control theory is applied in deriving the 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 Reverse Transcriptase inhibitors. These drugs hinder the reverse transcription process. The second control variable u_2 simulates the effect of Protease inhibitors, which prevents the already infected cells from producing mature-infectious virions.

The aforementioned controls represent effective chemotherapy dosage bounded between 0 and 1. The situation $u_1(t) = u_2(t) = 1$ represents 100% efficacy of the Reverse Transcriptase inhibitors and Protease inhibitors respectively and $u_1(t) = u_2(t) = 0$ represents 0% efficacy and $u_m = 1$ represents high rate of drug resistance mutation and $u_m = 0$ represent the situation where no drug resistance mutation present. The study aims at minimising the viral load, drug resistance mutation and at the same time reducing the cost of HIV treatment. With the above description we construct the objective functional to be optimized as follows:

$$J(u_1(t), u_2(t), u_m(t)) = \frac{1}{2}\int_0^{T_f} (w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2)dt \tag{50}$$

subject to the equations given in model (1).

$V_w(t)$, and $V_r(t)$ are the solutions of the model (1). The quantities w_1 and w_2 represent the cost associated with minimising the wild type HIV virions and the resistant type HIV virions respectively. In addition, A_1 and A_2 are non-negative constants representing the relative weights attached to the current cost of each treatment regime, A_3 represents the cost associated to emergence of drug resistant mutant and T_f is a fixed terminal time of

the treatment program subject to the ordinary differential equations described in model (1). We consider a quadratic expression of the control in order to indicate non-linear costs potentially arising at high treatment levels, as proposed in [20]. Consequently, u_1, u_2 and u_m are Lebesgue integrable; that is, they are piecewise continuous and integrable. The fundamental aim of this therapeutic strategy is to minimise the objective functional defined in equation (50) by decreasing the viral load both the V_r and V_w and the cost of treatment over the given time interval $[0, T_f]$. Therefore, the study aims at determining the optimal control ${u_1}^*$, ${u_2}^*$ and ${u_m}^*$ such that:

$$J(u_1^*(t), u_2^*(t), u_m^*(t)) = min\{J(u_1(t), u_2(t), u_m(t)) : (u_1, u_2, u_m) \in U\} \tag{51}$$

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

$$U = \{u = (u_1, u_2, u_m) : u_{i=1,2,m} \text{ measurable }, 0 \leq u_{i=1,2,m}(t) \leq 1, t \in [0, T_f]\} \tag{52}$$

In the next section we determine the existence of an optimal control for the system (1) and derive the optimality system.

5.1 Characterization of the Optimal control

The necessary conditions that an optimal control must satisfy come from the Pontryagins Maximum Principle [21].

Theorem 4. *Suppose the objective function*

$$J(u_1(t), u_2(t), u_m(t)) = \frac{1}{2}\int_0^{T_f} (w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2)dt \tag{53}$$

is minimised subject to the controls and state variables given in model (1) with $T(0) = T_0$, $I_w(0) = I_{w_0}$, $I_r(0) = I_{r_0}$, $I_{lw}(0) = I_{lw_0}$, $I_{lr}(0) = I_{lr_0}$, $V_w(0) = V_{w_0}$, $V_r(0) = V_{r_0}$ $V_n(0) = V_{n_0}$, $Z(0) = Z_0$ *and* $Z_a(0) = Z_{a0}$ *as the initial conditions. Then there exists optimal controls* $(u_1^*, u_2^*, u_m^* \in U)$ *such that;*

$$J(u_1^*(t), u_2^*(t), u_m^*(t)) = min\{J(u_1(t), u_2(t), u_m(t) : (u_1, u_2, u_m(t)) \in U\}$$

Proof. The existence of the solution can be shown using the results obtained in [22], since:

1. The class of all initial conditions with controls u_1, u_2 and u_m in the control set U are non-negative values and are non-empty where $u_i, i = 1, 2, m$ 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 and the solutions exist.

   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 $T, I_w, I_r, I_{lw}, I_{lr}, V_w, V_r, V_n, Z, Z_a, u_1, u_2$ and u_m are bounded on $[0, T_f]$. In particular considering the control system (1) with initial

conditions $T_0, T_{r_0}, I_{w_0}, I_{r_0}, I_{lw_0}, I_{lr_0}, V_{w_0}, V_{r_0}, V_{n_0}, Z_0, Z_{a_0}$, of the respective variables it can be written in form:

$$\dot{Y} = AY + F(Y) \tag{54}$$

where

$$Y = \begin{bmatrix} T \\ I_w \\ I_r \\ I_{lw} \\ I_{lr} \\ V_w \\ V_r \\ V_n \\ Z \\ Z_a \end{bmatrix} \tag{55}$$

is the vector of the state variables and A and $F(Y)$ are defined as in equations (56) and (57) respectively:

$$A = \begin{bmatrix} -\mu_T & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_{Iw} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_{Ir} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_{I_{lw}} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{I_{lr}} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_{Vw} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{Vr} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{V_n} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_Z & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{Z_a} \end{bmatrix} \tag{56}$$

$$F(Y) = \begin{bmatrix} \lambda_T - \chi_w T V_w + \chi_r T V_r \\ (1-u_m)(1-u_1(t))\chi_w T V_w - \alpha I_w Z_a \\ u_m(1-u_1(t))\chi_w T V_w + (1-u_1(t))\chi_r T V_r - \alpha I_r Z_a \\ u_1(t)\chi_w T_w V_w \\ u_1(t)\chi_r T_r V_r \\ (1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w \\ (1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r \\ u_2(t)\epsilon_{Vw}\mu_{Iw} I_w + u_2(t)\epsilon_{Vr}\mu_{Ir} I_r \\ \lambda_Z - \beta Z(I_w + I_r), \\ \beta Z(I_w + I_r) \end{bmatrix} \tag{57}$$

The system (54) is a non-linear system with a bounded coefficient. Let

$$B(Y) = R(Y) + F(Y) \tag{58}$$

then, the second term on the right-hand side of (58) satisfies

$$\begin{aligned}|F(Y_1) - F(Y_2)| \leq\ & K_1\,|T_1(t) - T_2(t)| + K_2\,|I_{w_1}(t) - I_{w_2}(t)| + \\ & K_3\,|I_{r_1}(t) - I_{r_2}(t)| + K_4\,|I_{lw_1}(t) - I_{lw_2}(t)| + K_5\,|I_{lr_1}(t) - I_{lr_2}(t)| + \\ & K_6\,|V_{w_1}(t) - V_{w_2}(t)| + K_7\,|V_{r_1}(t) - V_{r_2}(t)| + K_8\,|V_{n_1}(t) - V_{n_2}(t)| + \\ & K_9\,|Z_1(t) - Z_2(t)| + K_{10}\,|Z_{a_1}(t) - Z_{a_2}(t)| \\ \leq\ & K\Big[\,|T_1(t) - T_{w2}(t)| + |I_{w_1}(t) - I_{w_2}(t)| + |I_{r_1}(t) - I_{r_2}(t)| + \\ & |I_{lw_1}(t) - I_{lw_2}(t)| + |I_{lr_1}(t) - I_{lr_2}(t)| + |V_{w_1}(t) - V_{w_2}(t)| + \\ & |V_{r_1}(t) - V_{r_2}(t)| + |V_{n_1}(t) - V_{n_2}(t)| + |Z_1(t) - Z_2(t)| + |Z_{a_1}(t) - Z_{a_2}(t)|\,\Big]\end{aligned} \tag{59}$$

where the positive constant $K = \max\ (K_i, i = 1, 2, 3..., 10)$ is independent of the state variables. In addition, $B(Y_1) - B(Y_2) \leq K\,|Y_1 - Y_2|$, where $K = \sum_{i=1}^{10} K_i + ||M||\, < \infty$. So, it follows that the function $B(Y)$ is uniformly Lipschitz continuous. From the definition of the controls u_1, u_2 and u_m and the restrictions on the non-negativeness of the state variables then the solutions of the system (54) exists.

3. The control set U is convex and closed.
We denote the elements of the control set U as vectors

$$\hat{U} = (u_1, u_2, u_m) \text{ where } 0 \leq u_1, u_2 \leq 1 \text{ and } u_m \geq 0. \tag{60}$$

Now we show that U is convex.
Let $w = (w_1, w_2, w_m)$ be another element in U, that is, $0 \leq w_1, w_2 \leq 1$ and $w_m \geq 0$.
Next we prove that

$$x = \lambda u + (1 - \lambda)w \quad \text{for } 0 \leq \lambda \leq 1$$

is a number contained in U.

$$\begin{aligned} x &= \lambda(u_1, u_2, u_m) + (1 - \lambda)(w_1, w_2, w_m) \\ &= (\lambda u_1 + (1 - \lambda)w_1, \lambda u_2 + (1 - \lambda)w_2, \lambda u_m + (1 - \lambda)w_m) \\ &= (x_1, x_2, x_m) \end{aligned} \tag{61}$$

Then $x_1 = \lambda u_1 + (1 - \lambda)u_2$ which is in the interval $[0, 1]$. Thus, $0 \leq x_1 \leq 1$ and $0 \leq x_2 \leq 1$.
Next we consider

$$x_m = \lambda u_m + (1 - \lambda)w_m \tag{62}$$

which is non-negative for $u_m, w_m \geq 0$. Hence $x_m \geq 0$.
Thus $x = (x_1, x_2, x_m)$ satisfies the conditions (60) for convexity.
Therefore, the control set U is convex, and bounded and condition 3 is satisfied.

4. The integrand, $\frac{1}{2}\,(w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2)$, of the objective functional is convex on U. We now apply the Hessian matrix method to prove that the integrand is convex. A function of many variables, $g(x_1, x_2, ..., x_n)$ is a concave function if and only if the Hessian matrix,

$$H(x) = \left[\frac{\partial^2 g}{\partial x_i \partial x_j}\right] \leq 0 \quad \forall \quad x \neq 0 \tag{63}$$

Let $L_i = \frac{1}{2}\left(A_1 u_1^2 + A_2 u_2^2 + A_m u_m^2\right)$ where $L_i \in L$ then the Hessian matrix H of L_i is given as;

$$H = \begin{bmatrix} \frac{\partial^2 L}{\partial {u_1}^2} & \frac{\partial^2 L}{\partial u_1 \partial u_2} & \frac{\partial^2 L}{\partial u_1 \partial u_m} \\ \frac{\partial^2 L}{\partial u_2 \partial u_1} & \frac{\partial^2 L}{\partial {u_2}^2} & \frac{\partial^2 L}{\partial u_2 \partial u_m} \\ \frac{\partial^2 L}{\partial u_m \partial u_1} & \frac{\partial^2 L}{\partial u_m \partial u_2} & \frac{\partial^2 L}{\partial {u_m}^2} \end{bmatrix} = \begin{bmatrix} A_1 & 0 & 0 \\ 0 & A_2 & 0 \\ 0 & 0 & A_m \end{bmatrix} \geq 0 \tag{64}$$

Since $L_i \in L$ then, the integrand L is convex on U.

5. There exist constants; $b_1 > 0$, $b_2 > 0$ and $\beta > 1$ such that the integrand of the objective function equation (53), $J(U,t)$ is bounded by
$L(t, T, I_w, I_r, I_{lw}, I_{lr}, V_w, V_r, V_n, Z, Z_a, u_1, u_2, u_m) \leq b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_m|^2)^{\frac{\beta}{2}}$
From the objective function (53) then,

$$J(u_1, u_2, u_m) = \frac{1}{2}\left(w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2\right) \tag{65}$$

Thus,

$$J(u_1, u_2, u_m) \leq w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2 \tag{66}$$

Suppose, $A_1 = A_2 = A_3 = A$ in equation (66) then,

$$J(u_1, u_2, u_m \leq w_1 V_w(t) + w_2 V_r(t) + A\left(u_1^2 + u_2^2 + u_m^2\right) \tag{67}$$

This implies that,

$$w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_3 u_m^2 \leq b_2 + b_1(|u_1|^2 + |u_2|^2 + |u_m|^2) \tag{68}$$

where b_1 depends on the upper bound on V_n and V_r and $b_1 > 0$ since $A_1, A_2, A_3 > 0$ according to the definition. Equation (67) can be written as,

$$J(u_1, u_2, u_m) \leq b_2 + b_1(u_1, u_2, u_m)^2 \tag{69}$$

It is evident from equation (69) that $\beta = 2 > 1$, and $b_1, b_2 > 0$ thus condition (5) is satisfied.

Since all the above conditions are satisfied then there exist optimal control pair, ${u_1}^*, {u_2}^*$ and ${u_m}^*$. □

5.2 Necessary conditions of the optimal control

According to the Pontryagin Maximum Principle if $u_i^* \in U$ is optimal for problem (53) with fixed final time T_f, then there exists a nontrivial absolutely continuous mapping

$$\lambda(t) : [0, T_f] \to \mathbb{R}^{10}, \text{ that is,}$$
$$\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t), \lambda_7(t), \lambda_8(t), \lambda_9(t), \lambda_{10}(t)),$$

called the adjoint vector, such that the conditions outlined below hold for all $t \in [0, T_f]$,

1. The state variables:

$$\begin{aligned}
&\frac{dT}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_1}, \quad \frac{dI_w}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_2}, \\
&\frac{dI_r}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_3}, \quad \frac{dI_{lw}}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_4}, \\
&\frac{dI_{lr}}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_5}, \quad \frac{dV_w}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_6}, \\
&\frac{dV_r}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_7}, \quad \frac{dV_n}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_8}, \\
&\frac{dZ}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_9}, \quad \frac{dZ_a}{dt} = \frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial \lambda_{10}}
\end{aligned} \tag{70}$$

2. The optimality conditions:

$$\frac{\partial L(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial u_1} = 0 \quad \frac{\partial L(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial u_2} = 0 \tag{71}$$

3. The adjoint equations:

$$\begin{aligned}
&\frac{d\lambda_1}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial T}, \quad \frac{d\lambda_2}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial I_w}, \\
&\frac{d\lambda_3}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial I_r}, \quad \frac{d\lambda_4}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial I_{lw}}, \\
&\frac{d\lambda_5}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial I_{lr}}, \quad \frac{d\lambda_6}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial V_w}, \\
&\frac{d\lambda_7}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial V_r}, \quad \frac{d\lambda_8}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial V_n}, \\
&\frac{d\lambda_9}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial Z}, \quad \frac{d\lambda_{10}}{dt} = -\frac{\partial H(t, u_1^*, u_2^*, u_m^*, \lambda(t))}{\partial Z_a}
\end{aligned} \tag{72}$$

We now state the Lagrangian (Hamiltonian augmented) as

$$\begin{aligned}
&L(T, I_w, I_r, I_{lw}, I_{lr}, V_w, V_r, V_n, Z, Z_a, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8, \lambda_9, \lambda_{10}, u_1, u_2, u_m) \\
&= \left(w_1 V_w(t) + w_2 V_r(t) + A_1 u_1^2 + A_2 u_2^2 + A_2 u_m^2\right) + \lambda_1(\lambda_T - \mu_T T - \chi_w T V_w - \chi_r T V_r) \\
&+ \lambda_2((1-u_m)(1-u_1(t))\chi_w T V_w - \mu_{Iw} I_w - \alpha I_w Z_a) + \lambda_3(u_m(1-u_1(t))\chi_w T V_w + \\
&(1-u_1(t))\chi_r T V_r - \mu_{Ir} I_r - \alpha I_r Z_a) + \lambda_4(u_1(t)\chi_w T V_w - \mu_{l_w} I_{l_w}) + \lambda_5(u_1(t)\chi_r T V_r - \\
&\mu_{I_{lr}} I_{l_r}) + \lambda_6((1-u_2(t))\epsilon_{Vw}\mu_{Iw} I_w - \mu_{Vw} V_w) + \lambda_7((1-u_2(t))\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vr} V_r) + \\
&\lambda_8(u_2(t)\epsilon_{Vw}\mu_{Iw} I_w + u_2(t)\epsilon_{Vr}\mu_{Ir} I_r - \mu_{Vn} V_n) + \lambda_9(\lambda_Z + cZ(I_w + I_r) - \mu_Z Z - \\
&\beta Z(I_w + I_r)) + \lambda_{10}(\beta Z(I_w + I_r) - \mu_{Z_a} Z_a) + w_{11} u_1 + w_{12}(1-u_1) + w_{21} u_2 + \\
&w_{22}(1-u_2) + w_{31} u_m + w_{32}(1-u_m)
\end{aligned} \tag{73}$$

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

$$\begin{aligned}
w_{11} u_1 = w_{12}(1-u_1) = 0 \text{ at } u_1^* \\
w_{21} u_2 = w_{22}(1-u_2) = 0 \text{ at } u_2^* \\
w_{31} u_m = w_{32}(1-u_m) = 0 \text{ at } u_m^*
\end{aligned} \tag{74}$$

where, u_1^*, u_2^* represent the optimal controls and u_m^* represents the rate of emergence of drug resistance mutation.

Therefore, the Pontryagin's maximum principle gives the existence of adjoint variables which are obtained by differentiating the Lagrangian given by equation (73), with respect to the state variables $T, I_w, I_r, I_{lw}, I_{lr}, V_w, V_r, V_n, Z$ and Z_a.

Thus the adjoint variables are given by:

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial L}{\partial T} = \lambda_1(\mu_T + \chi_w V_w + \chi_r V_r) - \lambda_2 \chi_w V_w (1-u_m)(1-u_1) - \\
&\quad \lambda_3(\chi_w V_w u_m (1-u_1) + \chi_r V_r (1-u_1)) - \lambda_4 u_1 \chi_w V_w - \lambda_5 u_1 \chi_r V_r, \\
\dot{\lambda}_2 &= -\frac{\partial L}{\partial I_w} = \lambda_2(\mu_{Iw} + \alpha Z_a) - \lambda_6 \varepsilon_{V_w} \mu_{Iw}(1-u_2) - \lambda_8 u_2 \epsilon_{Vw} \mu_{Iw} + \lambda_9(\beta Z - cZ) - \\
&\quad \lambda_{10} \beta Z, \\
\dot{\lambda}_3 &= -\frac{\partial L}{\partial I_r} = \lambda_3(\mu_{Ir} + \alpha Z_a) - \lambda_7 \varepsilon_{V_r} \mu_{Ir}(1-u_2) - \lambda_8 u_2 \epsilon_{Vr} \mu_{Ir} + \lambda_9(\beta Z - cZ) - \lambda_{10} \beta Z, \\
\dot{\lambda}_4 &= -\frac{\partial L}{\partial I_{lw}} = \lambda_4 \mu_{I_{lw}}, \\
\dot{\lambda}_5 &= -\frac{\partial L}{\partial I_{lr}} = \lambda_5 \mu_{I_{lr}}
\end{aligned} \tag{75}$$

$$\dot{\lambda}_6 = -\frac{\partial L}{\partial V_w} = -w_1 + \lambda_1\chi_w T - \lambda_2\chi_w T(1-u_m)(1-u_1) - \lambda_3\chi_w T u_m(1-u_1) - \lambda_4\chi_w T u_1 + \lambda_6\mu_{Vw},$$

$$\dot{\lambda}_7 = -\frac{\partial L}{\partial V_r} = -w_2 + \lambda_1\chi_r T - \lambda_2\chi_r T(1-u_1) - \lambda_3\chi_r T(1-u_1) - \lambda_4\chi_r T u_1 + \lambda_7\mu_{Vr},$$

$$\dot{\lambda}_8 = -\frac{\partial L}{\partial V_n} = \lambda_8\mu_{V_n},$$

$$\dot{\lambda}_9 = -\frac{\partial L}{\partial Z} = \lambda_9\Big(\mu_Z + \beta(I_w + I_r) - c(I_w + I_r)\Big) - \lambda_{10}\beta(I_w + I_r)$$

$$\dot{\lambda}_{10} = -\frac{\partial L}{\partial Z_a} = \lambda_2\alpha I_w + \lambda_3\alpha I_r + \lambda_{10}\mu_{Z_a}$$

where,

$$\lambda_i(T_f) = 0, i = 1, ..., 10 \tag{76}$$

are the transversality conditions.

Theorem 5. *The optimal controls (u_1^*, u_2^*, u_m^*) which minimizes the objective function given by equation (53) over the invariant region are given by:*

$$\begin{aligned} u_1^* &= \min_{[0,T_f]}\left(max\Big(0, \frac{(\lambda_2-\lambda_4)\chi_w T V_w + (\lambda_3-\lambda_4)\chi_r T V_r}{2A_1}\Big), 1\right) \\ u_2^* &= \min_{[0,T_f]}\left(max\left(0, \frac{(\lambda_6-\lambda_8)\epsilon_{Vw}\mu_{Iw} I_w + (\lambda_7-\lambda_8)\epsilon_{Vr}\mu_{Ir} I_r}{2A_2}\right), 1\right) \\ u_m^* &= \min_{[0,T_f]}\left(max\left(0, \frac{(\lambda_2-\lambda_3)(1-u_1)\chi_w T V_w}{2A_3}\right), 1\right) \end{aligned} \tag{77}$$

Proof. At the optimal controls u_1^*, u_2^*, u_m^* the following condition hold:

$$\begin{aligned} \frac{\partial L}{\partial u_1} &= 0, \\ \frac{\partial L}{\partial u_2} &= 0, \\ \frac{\partial L}{\partial u_m} &= 0 \end{aligned} \tag{78}$$

Therefore, differentiating the Lagrangian, L, given in equation (73) with respect to u_1 on the set $U : t|0 \le u_1(t) \le 1$, the following optimality equation is obtained;

$$\frac{\partial L}{\partial u_1} = 2A_1u_1 - (1-u_m)\chi_w T V_w\lambda_2 - (u_m\chi_w T V_w + \chi_r T V_r)\lambda_3 + \chi_w T V_w\lambda_4 + \chi_r T V_r\lambda_5 + w_{11} - w_{12} = 0 \tag{79}$$

Let $u_1 = u_1^*$ in equation (79). Then, solving equation (79) the optimal control u_1^* becomes

$$u_1^* = \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w T V_w + (\lambda_3-\lambda_5)\chi_r T V_r + w_{12} - w_{11}}{2A_1} \tag{80}$$

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 $w_{11} = w_{12} = 0$ in equation (80). Then the optimal control u_1^* is given by

$$u_1^* = \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r}{2A_1} \tag{81}$$

2. Similarly, on the set $(t|u_1^* = 1)$ let $w_{11} = 0$ and $w_{12} \geq 0$ then equation (80) gives

$$u_1^* = 1 = \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r + w_{12}}{2A_1} \tag{82}$$

   Equation (82) reduces to

$$\frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r}{2A_1} \leq 1 = u_1^* \tag{83}$$

3. Finally, on the set $(t|u_1^* = 0)$, let $w_{12} = 0$ and $w_{11} \geq 0$ then equation (80) gives

$$u_1^* = 0 = \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r - w_{11}}{2A_1} \tag{84}$$

   which implies that

$$\frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r}{2A_1} \geq 0 \tag{85}$$

   Thus, for the this set the control ${u_1}^*$ is given as

$${u_1}^* = max\left(0, \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r}{2A_1}\right) \tag{86}$$

Combining the three cases, the control $u_1^*(t)$ reduces to, formulated as:

$$u_1^* = min\left(max\left(0, \frac{((1-u_m)\lambda_2 + u_m\lambda_3 - \lambda_4)\chi_w TV_w + (\lambda_3 - \lambda_5)\chi_r TV_r}{2A_1}\right), 1\right) \tag{87}$$

The same argument is used in obtaining an explicit expression for an optimal control u_2^* without w_{21} and w_{22}. This is done by differentiating the Lagrangian L given in equation (73) with respect to u_2 on the set $U : t|0 \leq u_2(t) \leq 1$. Thus the optimality equation as was obtained as

$$\frac{\partial L}{\partial u_2} = 2A_2u_2 + (\lambda_9 - \lambda_7)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_{10} - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r - w_{22} + w_{21} = 0 \text{ at } u_2 = u_2^* \tag{88}$$

Therefore, solving equation (88) the optimal control u_2^* is given as

$$u_2^* = \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r + w_{22} - w_{21}}{2A_2} \tag{89}$$

According to the conditions given by equation (74) the following distinct three cases are derived;

1. On the set $(t|0 < u_2^* < 1)$, let $w_{21} = w_{22} = 0$ in equation (98). Then the optimal u_2^* control is given by

$$u_2^* = \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r}{2A_2} \tag{90}$$

2. On the set $(t|u_2^* = 1)$, let $w_{21} = 0$ and $w_{22} \geq 0$ then from equation (98) the control u_2^* becomes

$$u_2^* = 1 = \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r + w_{22}}{2A_2} \tag{91}$$

   Rearranging equation (100) reduces to,

$$\frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r}{2A_2} \leq 1 = u_2^* \tag{92}$$

3. Finally, on the set $(t|u_2^* = 0)$. let $w_{22} = 0$ and $w_{21} \geq 0$ then from equation (98) the control u_2^* becomes

$$u_2^* = 0 = \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r - w_{21}}{2A_2} \tag{93}$$

   which implies that

$$\frac{((\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r}{2A_2} \geq 0 \tag{94}$$

   Thus, for the this set the control u_2^* is given as

$$u_2^* = max\left(0, \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r}{2A_2}\right) \tag{95}$$

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

$$u_2^* = min\left(max\left(0, \frac{(\lambda_6 - \lambda_8)\epsilon_{Vw}\mu_{Iw}I_w + (\lambda_7 - \lambda_8)\epsilon_{Vr}\mu_{Ir}I_r}{2A_2}\right), 1\right) \tag{96}$$

The same argument is used in obtaining an explicit expression for an optimal control u_m^*

without w_{31} and w_{32}. This is done by differentiating the Lagrangian L given in equation (73) with respect to u_m on the set $U : t|0 \leq u_m(t) \leq 1$. Thus the optimality equation as was obtained as

$$\frac{\partial L}{\partial u_m} = 2A_3 u_m + (\lambda_3 - \lambda_2)(1 - u_1)\chi_w T V_w + w_{31} - w_{32} = 0 \text{ at } u_m = u_m^* \tag{97}$$

Therefore, solving equation (97) the optimal control u_m^* is given as

$$u_m^* = \frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w - w_{31} + w_{32}}{2A_3} \tag{98}$$

According to the conditions given by equation (74) the following distinct three cases are derived;

1. On the set $(t|0 < u_m^* < 1)$, let $w_{31} = w_{32} = 0$ in equation (98). Then the optimal u_m^* control is given by

$$u_m^* = \frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w}{2A_3} \tag{99}$$

2. On the set $(t|u_m^* = 1)$, let $w_{31} = 0$ and $w_{32} \geq 0$ then from equation (98) the control u_m^* becomes

$$u_m^* = 1 = \frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w + w_{32}}{2A_3} \tag{100}$$

   Rearranging equation (100) reduces to,

$$\frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w + w_{32}}{2A_3} \leq 1 = u_m^* \tag{101}$$

3. Finally, on the set $(t|u_m^* = 0)$. let $w_{32} = 0$ and $w_{31} \geq 0$ then from equation (98) the control u_m^* becomes

$$u_m^* = 0 = \frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w - w_{31}}{2A_3} \tag{102}$$

   which implies that

$$\frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w}{2A_3} \geq 0 \tag{103}$$

   Thus, for the this set the control u_m^* is given as

$$u_m^* = max\left(0, \frac{(\lambda_2 - \lambda_3)(1 - u_1)\chi_w T V_w}{2A_3}\right) \tag{104}$$

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

$$u_m^* = min\left(max\left(0, \frac{(\lambda_2 - \lambda_3)(1-u_1)\chi_w T V_w}{2A_3}\right), 1\right) \tag{105}$$

□

6 Numerical analysis

In this section, we investigate the numerical simulations of model (1) with and without controls. Here we apply the forward-backward sweep method (FBSM) which uses the Runge-Kutta fourth order scheme. We start the process with an initial guess of the control variables, that is, u_1, u_2 and u_m. Then the state equations are solved forward in time and the adjoint equations are solved backward in time. Moreover, the controls are updated by using a convex combination of the previous controls and the value from the characterizations of u_1, u_2 and u_m. The process is repeated until convergence is achieved. For numerical analysis this study adopted the values as given and justified in Tables 2 and 3.

Table 2: The initial values for the variables for HIV in-vivo model

Variable	Initial Values
T(t)	$T(0) = 500$ cell/mm^3
$I_i(t)$	$I_i(0) = 100$ cell/mm^3
I_{l_i}	$I_{l_i}(0) = 0$ cell/mm^3
V_i(t)	$V_i(0) = 100$ 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

Table 3: Parameters for HIV in-vivo with therapy model

Parameters	Value	Source
λ_T	10 cell/mm^3/day	[23]
μ_T	0.01 day^{-1}	[24]
χ_i	0.000024 mm^3 vir$^-$1 day$^-$1	[25]
μ_{I_i}	0.5 day$^-$1	[26]
$\mu_{I_{l_i}}$	0.5 day$^-$1	[26].
ε_{V_i}	100 vir. cell$^-$1 day$^-$1	Estimate
μ_{V_i}	2.4 day$^-$1	[27].
μ_{V_n}	0.06 day$^-$1	Estimate
α	0.02 day^{-1}	[9]
c	0.0000005 cell/ mm^3/day	[28].
λ_Z	20 cell/ mm^3/day	[29].
μ_Z	0.06 day^{-1}	[30]
β	0.004 day^{-1}	[9]
μ_{Z_a}	0.004 day^{-1}	[15]

6.1 Relationship between controls and drug resistance mutation

From Figures 2 it is evident that when the efficacy of Protease inhibitor is at the maximum, the level of drug resistance mutation is at a minimum. However, after four months of using the drug, the level of drug resistance mutation increases with prolonged treatment. This is a very important observation since it gives insight on why the health practitioners should change the treatment regime and give a different one to avoid resistance. It is also evident that use of protease inhibitor remains at a maximum for the first five months and then reduces to a minimum.

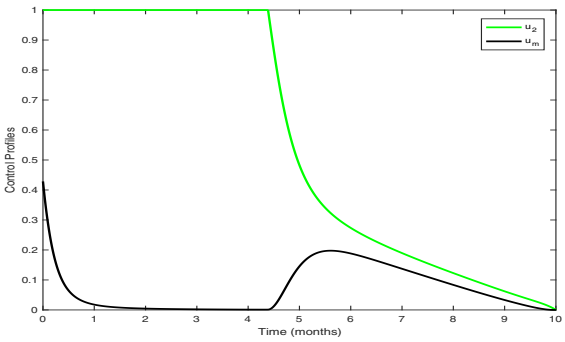

Figure 2
Drug resistant due to Protease inhibitor

Figure 3 represents a very important phenomena. From the figure we see that even when the use of Reverse Transcriptase inhibitor is at the maximum the level of drug resistance mutation is very high. The only feasible explanation would be due to the dead time the reverse inhibitor takes before getting to a maximum. The patient had a drug resistant

virus which with time before the control took into effects continued to multiply.

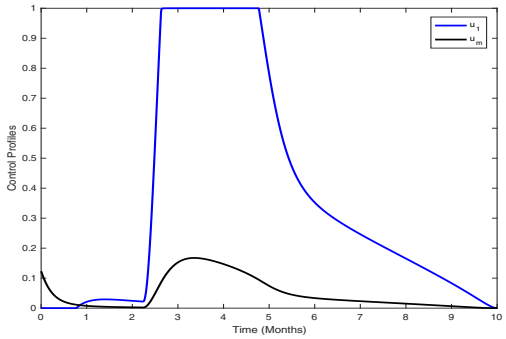

Figure 3
Drug resistant due to Reverse Transcriptase inhibitor

From Figure 4 we observe that the Reverse Transcriptase inhibitor behaves like a bang bang control. This means that it is very important for us to apply Bang-Bang Control on this in-vivo HIV Model and compare the results. However, no much effect on the mutation of the virus can be deduced from Figure 4. In addition, the results indicate that protease inhibitor should be administered for the first five months and the reverse transcriptase inhibitor should be introduced.

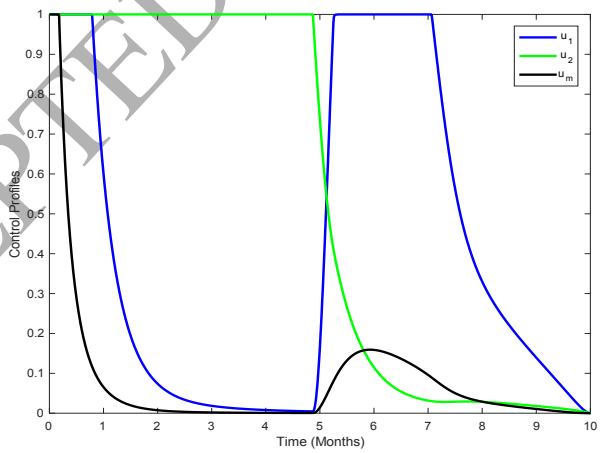

Figure 4
Drug resistant due to Reverse Transcriptase and Protease inhibitors

In Figure 5 we assumed that there is no drug resistance mutation, that is, $u_m = 0$ it is evident that protease inhibitor is more effective and remains at a maximum for a very long period of time unlike the Reverse Transcriptase inhibitor.

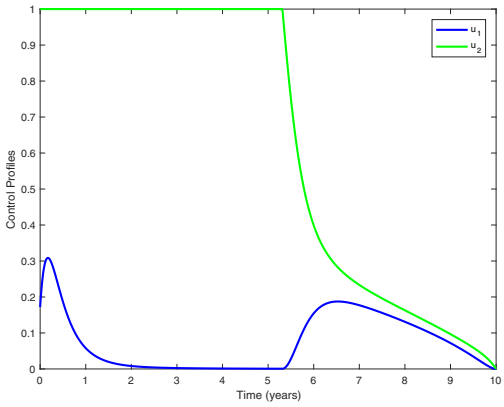

Figure 5
Drug resistant due to protease inhibitor

6.2 Restoration of the Immune system by HAART

In this section we use the number of the CD4$^+$ T-cells to analyse how effective the HAART are as far as restoration of the immune system is concerned.

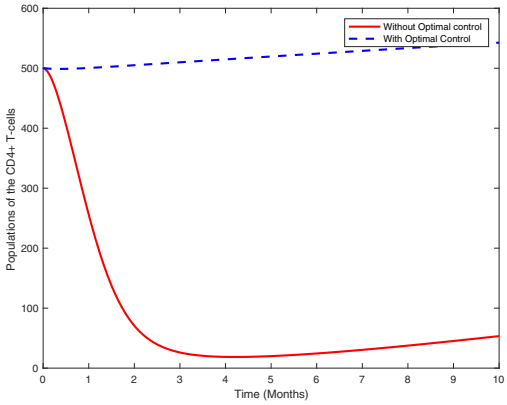

Figure 6
Susceptible CD4$^+$ T-cells

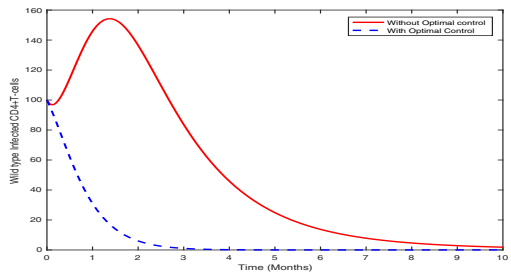

Figure 7
Wild type Infected $CD4^+$ T-cells

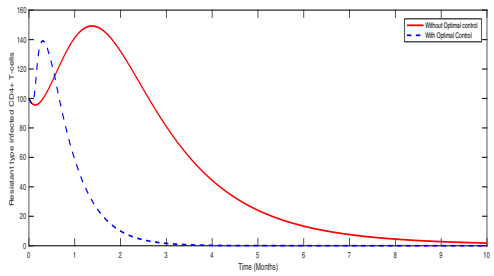

Figure 8
Resistant type Infected $CD4^+$ T-cells

From Figures 6 to 8 it is evident that use of HAART plays a paramount role in HIV suppression. This is so since we see the number of the infected $CD4^+$ T-cells reducing significantly while the number of the susceptible $CD4^+$ T-cells increase in presence of the HIV controls. This shows how use of antiretroviral therapy is remarkably effective in controlling the progression of human immunodeficiency virus (HIV) infection and prolonging patients survival. Nonetheless, in Figure 8 we observe that even with the introduction of the HAART the there is an increase in the number of the cells infected by the resistant type virus, this is because the drugs takes time before it manages to penetrate and destroy the cells infected by the resistant virus.

7 Conclusion

In this study, a deterministic model for the in-vivo dynamics of HIV is formulated and analysed. The qualitative analysis of the model shows that the solutions of the model are bounded and positive. The infection-free equilibrium point of the model is obtained and its local as well as global stability condition investigated in reference to the basic reproduction number, in which the results indicate that the infection-free equilibrium of the model is both locally and globally stable.

The Pontryagins maximum principle is used in the formulation of the optimal control problem. The conditions for optimal control of the HIV are analyzed with respect to two treatment regimes. Existence conditions for optimal control are established and the optimality system is developed. The proposed strategies are investigated numerically by use of forward-backward sweep method and their results are displayed graphically. The findings indicate that protease inhibitor is the most effective drug for HIV treatment if well implemented.

Use of antiretroviral therapy has proven to be remarkably effective in controlling the progression of human immunodeficiency virus (HIV) infection and prolonging patients survival. However, the results indicate that prolonged use of antiretroviral therapy could be very catastrophic since it leads to emergence of drug resistant mutation. It is therefore paramount for all stake holders in the field of HIV to deduce ways of preventing cases of

acquired drug resistance developing during treatment, because they can lead to cases of transmitted resistance and may significantly contribute to the HIV epidemic.

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