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# Modelling HIV *In-vivo* Cellular Dynamics in the Presence of Antiretroviral Therapy

**A. K. Omoyeni[1] and T. T. Yusuf[1*]**

*[1]Department of Mathematical Science, Federal University of Technology, Akure, Ondo State, Nigeria.*

***Authors' contributions***

*This work was carried out in collaboration between both authors. Author AKO managed the literature searches, developed the model, performed the qualitative analyses and wrote the first draft. Author TTY designed the study, numerically solved the model, carried out the model simulations and discussed findings from the simulations. Author TTY read and approved the final manuscript.*

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## Abstract

A treatment strategy for the total eradication of human immunodeficiency virus (HIV) in infected individuals is presently not feasible. However, the adoption of highly-active antiretroviral therapy (HAART) has been effective in managing HIV/AIDS infected patients in recent times. In this paper, a deterministic mathematical model is proposed and used to monitor the interactions between uninfected CD4+ T-cells, Infected CD4+ T-cells, CD8+ T-cells, infectious virus and immature non-infectious virus in the course of in-host HIV cellular dynamics. The goal is to find the adequate combination of the treatment regimens that will minimize the treatment systemic costs as well as deliver maximal health benefits to the HIV-positive patients. The model analyses show that the model disease-free equilibrium is locally and globally asymptotically stable if the basic reproduction number is less than unity. Thereafter, the proposed model is solved numerically and the result simulated for different combinations of the two common antiretroviral drugs effectiveness. Finding from the simulations show that treatment outcome would depend largely on patient's HIV/AIDS status indicators before initiating treatment and his/her antiretroviral therapy history.

*Keywords: Antiretroviral therapy; basic reproduction number; asymptotic stability; drug effectiveness; numerical simulation.*

**Corresponding author: E-mail: ttyusuf@yahoo.com;*

# 1 Introduction

Recently, there has been a rollout of antiretroviral (ARV) therapies in most developed countries around the world, but the availability of ARVs in poor resourced settings is still an issue of great concern. The cost of these drugs is beyond reach of many infected patients, thus there is the need to come up with a comprehensive drug administration scheme that would confer optimal clinical benefits on HIV/AIDS patients and ensures cost effectiveness. Clinical benefits of drug therapy for HIV infected individuals include restoration of CD4+ T cells levels, suppression of viral levels below detection limits and reduction of detrimental side effects such as risk of cardiovascular, acute retroviral syndrome, fat loss, lactic acidosis, abnormal fat distribution and mitochondrial damage [1,2,3,4].

Presently, there are more than twenty anti-HIV-1 drugs available and these are administered in many different combinations of three or four drugs cocktail. The drugs fall into four main categories: Reverse transcriptase inhibitors (RTIs) (nucleoside, nucleotide and non-nucleoside), Protease inhibitors (PIs), Integrase Inhibitors (IIs) and Fusion inhibitors (FIs) [3]. RTIs prevent new HIV-1 infections by disrupting the conversion of viral RNA into DNA that can be incorporated into the host cell's genome. PIs halt the assembling of key viral proteins after they have been produced by infected host cells. FIs prevent the fusion of the virus to the host cells while.

Integrase inhibitors block the integrase from inserting the viral genome into the DNA of the host T-cells. Thus, disrupting the completion of the virus infection of the host T-cells process [5,3].

HAART is usually a combination of drugs cocktail that includes two or three nucleoside agents alone or two nucleoside agents combined with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor [6]. Examples of such cocktail combinations include EFV (Efavirenz) + (3TC (Lamivudine))+ (AZT (Zidovudine)), a combination of a non-nucleoside reverse transcriptase inhibitor (EFV) and two nucleoside reverse transcriptase inhibitors (FTC and AZT) and LPV/r (Lopinavir) + (FTC) + AZT, a combination of a protease inhibitor (LPV/r) and two nucleoside reverse transcriptase inhibitors (FTC and AZT) and other options that are selected by government agencies, although these options are limited by generic formulations [1].

Over the years, there have been lots of research works on modelling HIV in-host cellular dynamics with or without the effect of antiretroviral therapy. Some of the recent works in this regards are [7,8,9,10,11,12]. For instance, Brown, Letham and Rudin (2016) modelled the dynamics of human immunodeficiency virus (HIV) and $CD4^+$ T-cells in the presence of interferon alpha. They found that interferon alpha inhibits the proliferation of HIV and this finding signals a new pathway in the design of ARV therapies [7]. Also, Xu, Geng, and Zhou (2017) considered an age-structured in-vivo HIV cellular dynamics in the presence of antiretroviral therapy. They showed that drug therapy which affects cell-cell infection would have critical influence on the proliferation of the virus and eventual viral load of patient undergoing ARV treatment [12]. In related study, Ngina, Mbogo, and Luboobi (2017) investigated the influence of $CD8^+$ T-cells on the in-host HIV cellular dynamics. The results from the analyses of their model established that $CD8^+$ T-cells play a key role in reducing HIV viral replication during acute HIV infection [11].

In this paper, we explore the treatment outcome of a combination of a protease inhibitor and a reverse transcriptase inhibitor, that is, we consider the outcome of two common types of drugs that are used in a HAART regimen. The ultimate goal is to prevent further immune deterioration of an HIV/AIDS infected patient. The controls in this paper represent the effectiveness of each of the drug on the interaction of the CD4+ T-cells with the virus (infection of CD4+ T-cells) and the virions produced by infected cells (burst size). Obviously the drugs used in the therapy have side effects if administered in high dosage or continuously, therefore adequate and timely administration of the treatment is central to a successful HAART treatment. Consequently, there is the need to evolve an HAART treatment in which the effectiveness of each of the class of drugs used in the therapy is such that it minimizes patient's viral load together with drug toxicity as well as enhances the immune system.

This paper is organized as follows: In section 2, we formulate a model of HIV in-vivo cellular dynamics and establish that the model is well-posed. In section 3, we carry out local and global stability analysis of the model virus-free equilibrium. In section 4, we numerically solve the model equations, simulate the result for different combinations of the ARV drugs, and discuss our findings.

## 2 Model Formulation

The model monitors temporal dynamics of five populations namely: $T(t)$, $T^*(t)$, $L(t)$, $V_I(t)$ and $V_{NI}(t)$ which represent the concentrations of uninfected $CD4^+$ T-cells, Infected $CD4^+$ T-cells, $CD8^+$ T-cells, infectious virus and immature non-infectious virus respectfully. The model is a system of non-linear ordinary differential equations given below:

$$\frac{dT}{dt} = \Lambda - \mu T + rT\left(1 - \frac{T}{T_{max}}\right) - (1 - u_1(t))\beta V_I T \tag{2.1}$$

$$\frac{dT^*}{dt} = (1 - u_1(t))\beta V_I T - \delta T^* - \theta \varrho T^* L \tag{2.2}$$

$$\frac{dL}{dt} = \alpha - \gamma L + \varphi L T^* \tag{2.3}$$

$$\frac{dV_I}{dt} = (1 - u_2(t))N\delta T^* - cV_I \tag{2.4}$$

$$\frac{dV_{NI}}{dt} = u_2(t)N\delta T^* - cV_{NI} \tag{2.5}$$

Equation (2.1) defines the dynamics of the uninfected CD4+ T cells ($T(t)$) which is produced at a constant rate $\Lambda$, die at rate $\mu$, and become infected at rate $\beta V_I T$ and the third term defines the proliferation of T cells at a rate $r$.

Equation (2.2) model the dynamics of Infected $CD4^+$ T-cells ($T^*(t)$) which is produced at rate $\beta V_I T$ and die at rate $\delta$ ($\delta > \mu$), the last term of the equation is due to loss of infected T-cell ($T^*$) based on the activities of the $CD8^+$ T-cells, where $\theta$ represent the effectiveness of CTL in killing $T^*$, $\varrho$ represents the proportion of CD8+ T cells that differentiate into HIV specific CTL.

In equation (2.3), $\alpha$ and $\gamma$ represent the production and death rates of CD8+ T-cells, respectfully, where $\varphi$ denote the rate of proliferation of $CD8^+$ T-cells due to the presence of infected T-cells.

Equation (2.4) denotes the dynamics of the Infectious virus $V_I(t)$ that is produced from infected T-cells at rate $N\delta T^*$ and dies at rate $cV_I$ while equation (2.5) stands for the dynamics of immature non-infectious virus $V_{NI}(t)$ produced from infected T-cells at rate $N\delta T^*$and dies at rate $cV_{NI}$. It is important to note that $u_1(t)$ is the effectiveness of RTI drugs and $u_2(t)$ is the effectiveness of the PI drugs.

It is imperative to mention here that series of models on HIV in-host cellular dynamics were reviewed before coming up with the modified model equations. Most of the models considered were single-drug therapy with/without $CD8^+$ T-cells dynamics or multidrug treatment without $CD8^+$ T-cells roles in the model

dynamics see [1,13,14,15,16,17,18]. Here, we presented a modified model for multidrug therapy with CD8+ T- cells inclusion in the in- host cellular dynamics, since current treatment is usually a multi-drug one while CD8+ T- cells play the remarkable role in the fight against infected CD4+ T- cells [19,10,11,12].

However, under the dynamics described by Equation (2.1 – 2.5), the region $\Omega$ defined by

$$\Omega = \left\{(T,\ T^*, L,\ V_I, V_{NI}) \in R_+^5 : 0 \le T + T^* \le \frac{\Lambda}{\mu - r},\ 0 \le L \le \frac{\alpha}{\gamma},\ 0 \le V_I + V_{NI} \le \frac{N\delta}{c}\right\}$$

is positively invariant.

***Lemma 1***: Given the feasible regions $\Omega$ defined by

$$\Omega = \left\{(T,\ T^*, L,\ V_I,\ V_{NI}) \in R_+^5 : 0 \le T + T^* \le \frac{\Lambda}{\mu - r},\ 0 \le L \le \frac{\alpha}{\gamma},\ 0 \le V_I + V_{NI} \le \frac{N\delta}{c}\right\},$$

then the solutions $\{T(t), T^*(t), L(t), V(t)_I, V_{NI}(t)\}$ of the system (2.1- 2.5) are positive invariant, $\forall\ t \ge 0$ and initial conditions $T(0) \ge 0,\ T^*(0) \ge 0, L(0) \ge 0,\ V_I(0) \ge 0,\ V_{NI}(0) \ge 0.$

**Proof:** To prove the lemma, we will use differential equations of the system (2.1)- (2.5).

Using the equation (2.1), we have

$$\frac{dT}{dt} = \Lambda - \mu T + rT\left(1 - \frac{T}{T_{max}}\right) - (1 - u_1(t))\beta V_I T$$

To determine positivity of $T$, we consider

$$\frac{dT}{dt} \le \Lambda - \mu T + rT$$

$$\frac{dT}{dt} \le \Lambda - (\mu - r)T$$

It follows that $\frac{dT}{dt} + (\mu - r)T \le \Lambda$

Which is a first order linear differential equation that can be simplified to?

$$e^{(\mu - r)t}\frac{dT}{dt} + (\mu - r)Te^{(\mu - r)t} \le \Lambda e^{(\mu - r)t}$$

$$\Rightarrow \frac{d(Te^{(\mu - r)t})}{dt} \le \Lambda e^{(\mu - r)t}.$$

Therefore,

$$d(Te^{(\mu - r)t}) \le (\Lambda e^{(\mu - r)t})dt$$

Integrating both sides of the preceding equation yields

$$Te^{(\mu - r)t} \leq \frac{\Lambda e^{(\mu - r)t}}{\mu - r} + c$$

where c is the constant of integration, it then follows that,

$$T(t) \leq \frac{\Lambda}{\mu - r} + ce^{(r - \mu)t}$$

Evaluating the value $T(0)$ at time, we have

$$T(0) \leq \frac{\Lambda}{\mu - r} + c$$

Therefore,

$$T(0) - \frac{\Lambda}{\mu - r} \leq c.$$

$$T(t) \leq \frac{\Lambda}{\mu - r} + \left(T(0) - \frac{\Lambda}{\mu - r}\right)e^{(r - \mu)t}$$

Since $T(0) \geq 0, r - \mu < 0$, it follows that $T(t) \geq 0$ if $t = 0$ *and* $T(t) \leq \frac{\Lambda}{\mu - r}$ *as* $t \to \infty$.

Therefore, $T(t)$ *is positive invariant for all time* $t \geq 0$.

Similarly, the positivity of $T^*(t)$, $L(t)$, $V_I(t)$ *and* $V_{NI}(t)$ can be proved using the same procedure for $T$ as done above.

## 3 Stability Analysis

The model equations (2.1 – 2.5) has a virus-free steady state

$$E_0 = \left(T_0, 0, \frac{\alpha}{\gamma}, 0, 0\right) = \left(\frac{T_{max}}{2r}\left[(r - \mu) + \sqrt{(r - \mu)^2 + \frac{4r\Lambda}{T_{max}}}\right], 0, \frac{\alpha}{\gamma}, 0, 0\right),$$

and the model basic reproduction number $(R_0)$, is as given below:

$$R_0 = \frac{(1 - u_1)(1 - u_2)\gamma\beta N\delta T_{max}\left[(r - \mu) + \left((r - \mu)^2 + \frac{4r\Lambda}{T_{max}}\right)^{1/2}\right]}{2cr(\delta\gamma + \theta\varrho\alpha)}$$

Note that, in this paper, we interpret $R_0$ as the average number of new virus produced as a result of infection of the CD4+ T-cell of an HIV- negative individual by an infectious virus before its eradication. Thus, the

virus is expected to eventually die out in the entire cells when $R_0 < 1$ while the virus will invade the entire cells when $R_0 > 1$. $R_0$ is obtained using the next- generation matrix approach as described by *Diekmann and Heesterbeek (1990)*.

**Theorem 1.** *The disease free equilibrium of the system is locally asymptotically stable if* $R_0 < 1$.

**Proof:**

We linearize the model system of equations using the Jacobian matrix approach and we evaluated the resulting matrix at the disease-free equilibrium to obtain:

$$J_{E_0} = \begin{bmatrix} -\left(\mu - r + \frac{2rT_0}{T_{max}}\right) & 0 & 0 & -(1-u_1)\beta T_0 & 0 \\ 0 & -(\delta + \theta\varrho L_0) & 0 & (1-u_1)\beta T_0 & 0 \\ 0 & \varphi L_0 & -\gamma & 0 & 0 \\ 0 & (1-u_2)N\delta & 0 & -c & 0 \\ 0 & u_2 N\delta & 0 & 0 & -c \end{bmatrix}$$

We represent, $k_1 = \mu - r + \frac{2rT_0}{T_{max}}$ *and* $k_2 = \delta + \theta\varrho L_0$ to get

$$J_{E_0} = \begin{bmatrix} -k_1 & 0 & 0 & -(1-u_1)\beta T_0 & 0 \\ 0 & -k_2 & 0 & (1-u_1)\beta T_0 & 0 \\ 0 & \varphi L_0 & -\gamma & 0 & 0 \\ 0 & (1-u_2)N\delta & 0 & -c & 0 \\ 0 & u_2 N\delta & 0 & 0 & -c \end{bmatrix}.$$

Now, we obtain the above matrix eigenvalues as below;

$$|\lambda I - J_{E_0}| = \begin{vmatrix} k_1+\lambda & 0 & 0 & (1-u_1)\beta T_0 & 0 \\ 0 & k_2+\lambda & 0 & -(1-u_1)\beta T_0 & 0 \\ 0 & \varphi L_0 & \gamma+\lambda & 0 & 0 \\ 0 & -(1-u_2)N\delta & 0 & c+\lambda & 0 \\ 0 & -u_2 N\delta & 0 & 0 & c+\lambda \end{vmatrix} = 0 \qquad (3.1)$$

The virus-free steady state is asymptotically stable if and only if each of all the eigenvalues of the matrix in equation (3.1) have negative real parts.

These eigenvalues are obtained by solving for the roots of the characteristic polynomial resulting from equation (3.1)

The characteristic polynomial equation is given by,

$$f(\lambda) = (k_1+\lambda)(c+\lambda)(\gamma+\lambda)(\lambda^2 + A\lambda + B) = 0 \qquad (3.2)$$

*Where* $(\lambda^2 + A\lambda + B) = (k_2+\lambda)(c+\lambda) - (1-u_2)(1-u_1)N\delta\beta T_0 = 0$

Equation (3.2) has roots $\lambda_1 = -k_1 < 0$, $\lambda_2 = -c < 0$ *and* $\lambda_3 = -\gamma < 0$. The other two roots are obtained from

$$\lambda^2 + (k_2 + c)\lambda + [ck_2 - (1 - u_2)(1 - u_1)N\delta\beta T_0] = 0 \tag{3.3}$$

These two roots both have negative real parts provided the model basic reproduction number is less than unity ( $R_0 < 1$ ). This is established using the Routh-Hurwitz criteria.

Hence, the virus-free equilibrium is locally asymptotically stable if $R_0 < 1$ .

**Theorem 2:** *The virus-free equilibrium of the system ($E_0$) is globally asymptotically stable if $R_0 < 1$.*

**Proof:**

Suppose our Lyapunov function takes the form

$$y(t) = T^* + \omega V_I \tag{3.4}$$

This implies that

$$\frac{dy}{dt} = \frac{dT^*}{dt} + \omega\frac{dV_I}{dt} \tag{3.5}$$

Substituting our model equations (2.2) and (2.4) into (3.5) gives

$$\frac{dy}{dt} = [(1 - u_1)\beta V_I T - \delta T^* - \theta\rho T^* L] + \omega[(1 - u_2)N\delta T^* - cV_I] \tag{3.6}$$

With $T = T_0$ and $L = L_0$, we have

$$\frac{dy}{dt} \leq [(1 - u_1)\beta V_I T_0 - \delta T^* - \theta\rho T^* L_0] + \omega[(1 - u_2)N\delta T^* - cV_I] \tag{3.7}$$

On expansion and factorisation, we obtain

$$\frac{dy}{dt} \leq [(1 - u_1)\beta T_0 - \omega c]V_I + [\omega(1 - u_2)N\delta - (\delta + \theta\rho L_0)]T^* \tag{3.8}$$

Taking $\omega = \dfrac{(1 - u_1)\beta T_0}{c}$, the preceding equation simplifies to

$$\frac{dy}{dt} \leq [\omega(1 - u_2)N\delta - (\delta + \theta\rho L_0)]T^* \tag{3.9}$$

$$\frac{dy}{dt} \leq (\delta + \theta\rho L_0)\left(\frac{\omega(1-u_2)N\delta}{\delta + \theta\rho L_0} - 1\right)T^* \tag{3.10}$$

Substituting $L_0 = \dfrac{\alpha}{\gamma}$, we have,

$$\begin{aligned}\frac{dy}{dt} &\leq \left(\frac{\delta\gamma+\theta\rho\alpha}{\gamma}\right)\left(\frac{(1-u_1)(1-u_2)N\delta\beta\gamma T_0}{c(\delta+\theta\rho\alpha)}-1\right)T^* \\ &\leq \left(\frac{\delta\gamma+\theta\rho\alpha}{\gamma}\right)(R_0-1)T^* \\ &\leq 0 \quad \text{if } R_0<1.\end{aligned} \tag{3.11}$$

It is important to note that $y' = 0$ only when $T^* = V_I = 0$. Moreover, setting $T^* = 0$ and $V_I = 0$ in our model equations implies that

$T \to \frac{\Lambda}{\mu - r}$, $L \to \frac{\alpha}{\gamma}$, $V_{NI} \to 0$ as $t \to \infty$. In view of the foregoing, we can therefore apply the Lasalle's invariance principle to conclude that every solution of our model equations, with initial conditions in Ω converges to the virus-free equilibrium $(E_0)$. Consequently, the virus-free equilibrium is globally asymptotically stable in $\Omega$ if $R_0 < 1$.

At this jucture, it is important to know that the implication of the stability of virus-free equilibrium (i.e. virus free situation) is that it shows that if we could find a multi-drugs HIV therapy that drives the viral-load of an HIV patient sufficiently close to the viral-free state, then the viral-free situation can eventually be attained.

## 4 Numerical Simulation Results and Discussion

The model system of ordinary differential equations is solved numerically using Runge-Kunta of order 4 scheme executed with MATLAB software. We carry out the numerical simulations of the model for different combinations of the two common classes of ARV drugs.

In order to carry out the model numerical simulations, we use the parameters values in Table 1 and the initial variables conditions below: $T(0) = 800,\ T^*(0) = 50,\ L(0) = 10,\ V_I(0) = 50,\ and\ V_{NI} = 50$

**Table 1. Description of the model parameters and their respective values**

| Parameter | Description | Values | Unit | Source |
|---|---|---|---|---|
| $\Lambda$ | Rate of supply of uninfected CD4+ T cells from source | 10 | $\frac{cells/\mu l}{day}$ | [3] |
| $\mu$ | The death rate of uninfected CD4+ T-cells | 0.02 | $day^{-1}$ | [3] |
| $r$ | The proliferation rate of the uninfected CD4+ T-cell population | 0.03 | $day^{-1}$ | [3] |
| $T_{max}$ | Maximum CD4+ T-cell population level | $1.5 \times 10^3$ | $cells/\mu l$ | [3] |
| $\beta$ | The rate constant for CD4+ cells becoming infected by a free virus | $2.4 \times 10^{-3}$ | $\frac{day^{-1}}{cells/\mu l}$ | Estimate |
| $\delta$ | The death rate of actively infected CD4+ T-cell population | 0.5 | $day^{-1}$ | [14] |
| $\theta$ | The effectiveness of CTL in killing infected CD4+ T-cell | 0.8 | $\frac{day^{-1}}{cells/\mu l}$ | [4] |

| Parameter | Description | Values | Unit | Source |
|---|---|---|---|---|
| $\varrho$ | The proportion of CD8+ T cells that differentiate into HIV | 0.01 | - | [4] |
| $\alpha$ | The rate of production of CD8+ T-cells | 2.0 | $\frac{cells/\mu l}{day}$ | Estimate |
| $\gamma$ | The death rate of CD8+ T-cells | 0.01 | $day^{-1}$ | [3] |
| $\varphi$ | The rate of the proliferation of CD8+ T-cells with the help of CD4+ T-cells | 0.4 | $\frac{day^{-1}}{cells/\mu l}$ | [20] and Estimate |
| $c$ | The death rate of infectious and non-contagious virus | 0.4 | $day^{-1}$ | [14] and Estimate |
| $N$ | Number of free virus produced | 100 | $\frac{count}{cells/\mu l}$ | [14] and Estimate |

Results from the simulations are displayed in the graphs that follow. Figs. 1–10 are the simulation results from which conclusions could be drawn on the effectiveness of the antiretroviral therapy based on the prevailing concentrations of uninfected $CD4^+$ T-cells (T), uninfected $CD4^+$ T-infected cells (T*), $CD8^+$T-cells (L), Infectious Virus ($V_I$) and Non-infectious Virus ($V_{NI}$) of an infected HIV/AIDS patient while undergoing ARV treatment.

In the first instance, we consider four different HIV/AIDS patients' treatment scenarios:

(i) A case of an HIV/AIDS patient not undergoing ARV treatment (i.e. $u_1$=0.0, $u_2$=0.0);
(ii) A case of an HIV/AIDS patient undergoing ARV treatment involving only mild RTI drugs (i.e. $u_1$=0.5, $u_2$=0.0);
(iii) A case of an HIV/AIDS patient undergoing ARV treatment involving only mild PI drugs (i.e. $u_1$=0.0, $u_2$=0.5) and
(iv) A case of an HIV/AIDS patient undergoing ARV treatment involving both mild RTI and PI drugs (i.e. $u_1$=0.5, $u_2$=0.5).

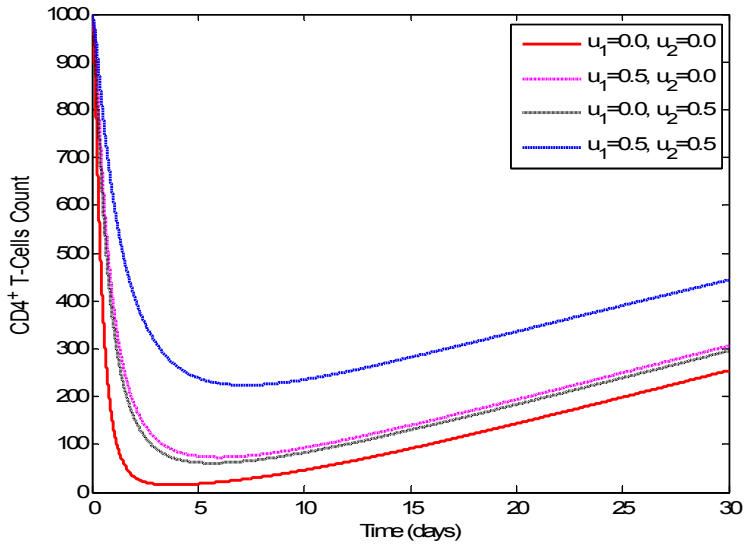


**Fig. 1. $CD4^+$ T-cells concentration profile for different ART scenarios**

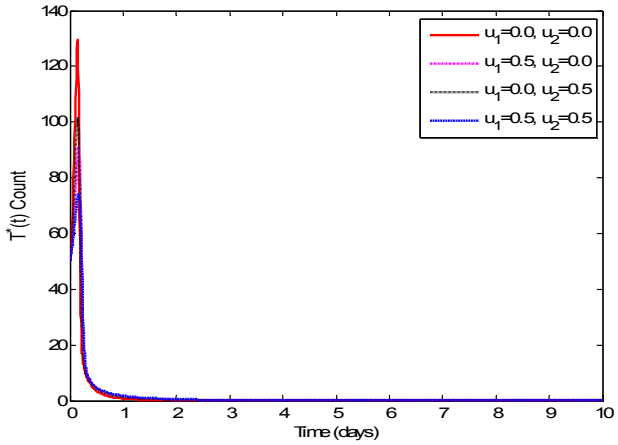


**Fig. 2. Infected $CD4^+$ T-cells concentration profile for different ART scenarios**

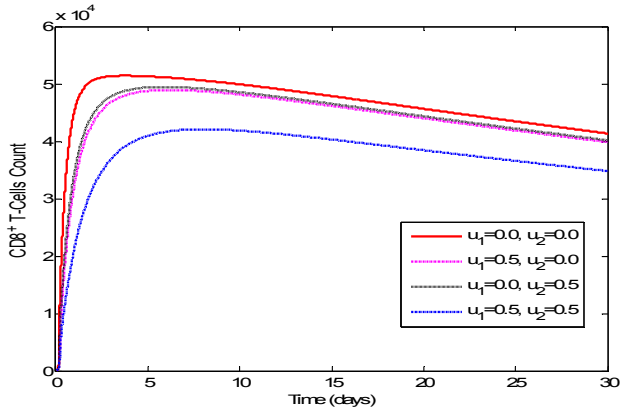


**Fig. 3. $CD8^+$ T-cells concentration profile for different ART scenarios**

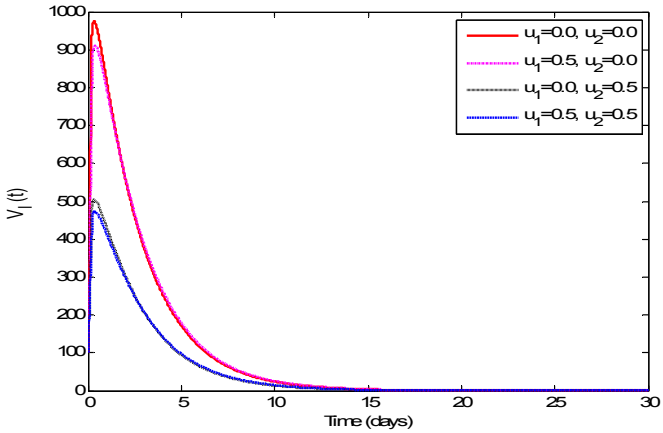


**Fig. 4. Infectious virus population profile for different ART scenarios**

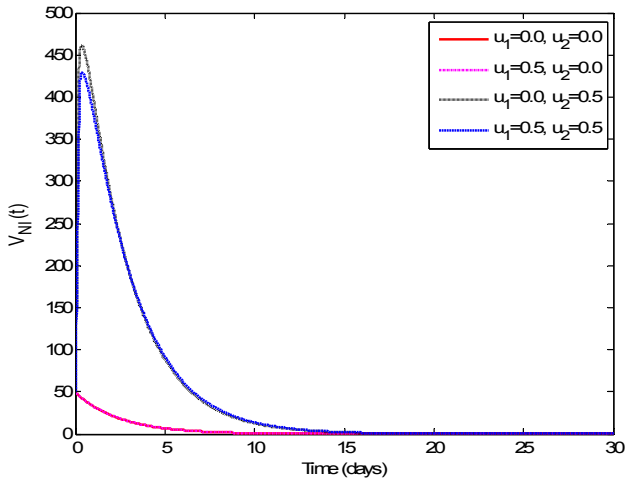


**Fig. 5. Non-infectious virus population profile for different ART scenarios**

Fig. 1 describes the dynamics of the uninfected CD4+T cells concentration over time with respect to different treatment scenarios. The graphs show that the patient's CD4+ T-cells count profile is worst for the situation without ARV treatment while CD4+ T-cells count profile is best for the scenario involving patient's therapy with both RTI and PI. However, the scenes involving therapy with only one of the two classes of drugs (RTI or PI ) are not significantly better than one another while either of these two scenarios is not as good as the case of treatment involving both classes of ARV drugs. This, possibly, justifies why multidrug therapy is the trend in the administration of ARV treatment.

Similarly, Figs. 2-5 describes the dynamics of the infected $CD4^+$ T-cells concentration, $CD8^+$ T-cells concentration, Infectious virus population, and Non-infectious virus population respectively as regards the different treatment scenarios. In general, the profile in each of the figures is best for the situation involving the two classes of the ARV drugs, and it is worst for the scenarios without ARV drugs. Moreover, the two categories ARV drugs used in these simulations were the moderately effective ones. Based on the observations from these initial simulations, we were motivated to consider combinations of the two classes of ARV drugs with varying level of effectiveness. Thus, we investigated the possible outcome of a treatment regimen involving a mild RTI and mild PI, strong RTI and mild PI, mild RTI and strong PI, and strong RTI and strong PI respectively. The results of the investigation are displayed in Figs. 6-10.

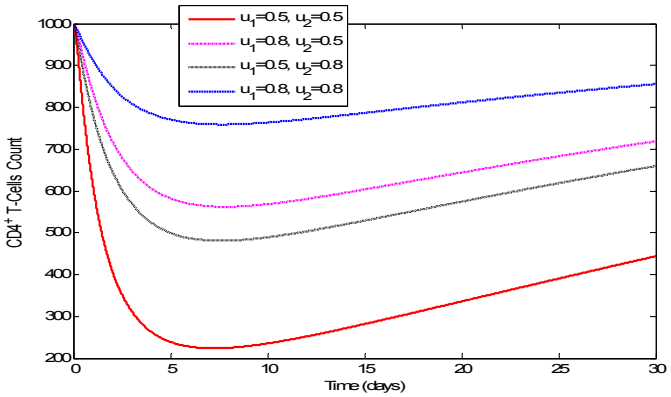


**Fig. 6. $CD4^+$ T-cells concentration profile with different effectiveness of the combined ART drugs**

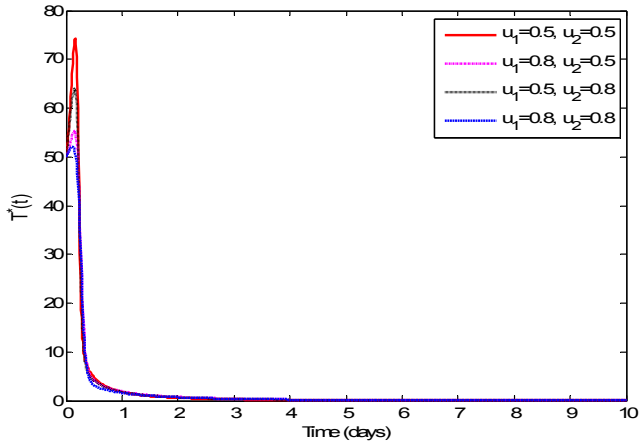


**Fig. 7. Infected CD4$^+$ T-cells concentration profile with different effectiveness of the combined ART drugs**

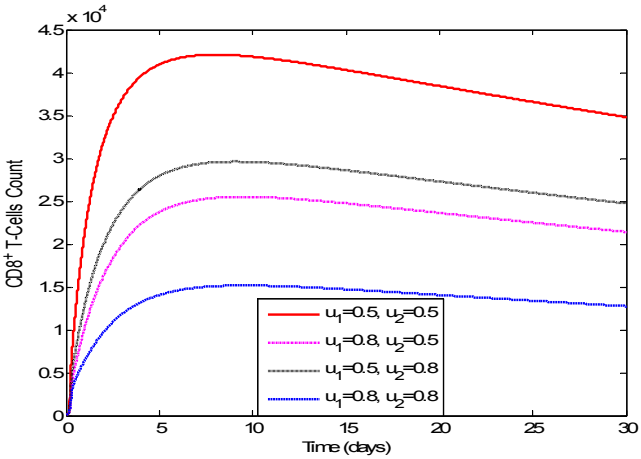


**Fig. 8. CD8$^+$ T-cells concentration profile with different effectiveness of the combined ART drugs**

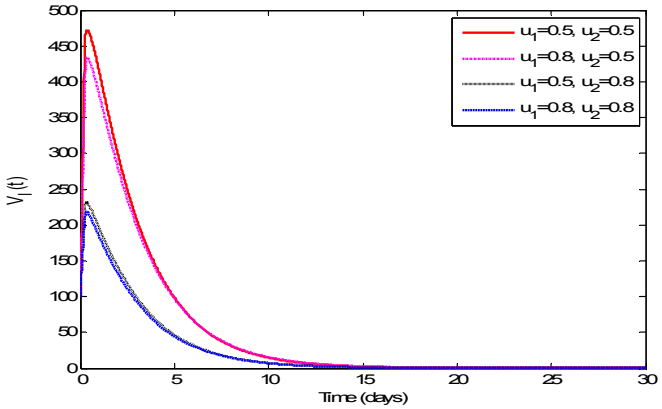


**Fig. 9. Infectious virus population profile with different effectiveness of the combined ART drugs**

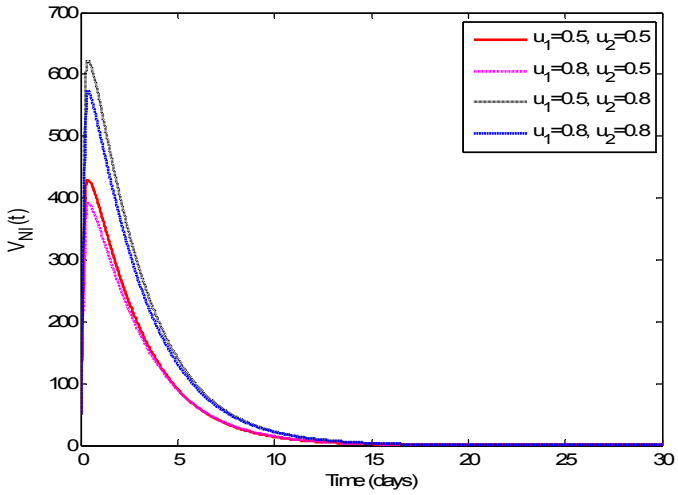


**Fig. 10. Non-infectious virus population profile with different effectiveness of the combined ART drugs**

The results from our simulations in this latter instance showed that the profile for each of uninfected $CD4^+$ T-cells (T), uninfected $CD4^+$ T-infected cells (T*), $CD8^+$T-cells (L), Infectious Virus ($V_I$) and Non-infectious virus ($V_{NI}$) gets better as we substitute a strong RTI or PI for a mild one. Thus, the best profile was obtained when a strong RTI and PI were used while the worst pattern was obtained when a mild RTI and PI classes of ARV drugs were used. However, the scenario with strong RTI drugs and mild PI drugs had better profiles regarding the uninfected $CD4^+$ T-cells (T), infected $CD4^+$ T-infected cells (T*), and $CD8^+$T-cells (L) concentration when compared with the scenario with mild RTI drugs and strong PI drugs (see Figs. 6-8). On the contrary, this latter scenario had better profiles in terms of the Infectious Virus ($V_I$) and Non-infectious virus ($V_{NI}$) when compared with the former situation (see Figs. 9-10).

# 5 Conclusion

In this paper, we considered a deterministic mathematical model for HIV in-vivo cellular dynamics in the presence of antiretroviral therapy, and we showed that the model is mathematically well-posed. We obtained the model primary reproduction number and determined the model virus-free equilibrium. We established that this equilibrium is locally and globally asymptotically stable whenever necessary reproduction number is less than unity. After that, we solved the model numerically and simulate the model for a different scenario of an HIV infected patient undergoing ARV treatment. Findings from our simulations show that ARV treatment involving the two common classes of ARV drug (RTI and PI) would give better ARV treatment outcome to patients as compared to the treatment scenarios involving only one type of ARV drugs or plot without ARV treatment. Also, it was observed that the effectiveness of each of the classes of drugs involved in the multidrug ARV treatment would dictate the outcome of the procedure. Since the human immunodeficiency virus often develops resistance to ARV drugs, it is intuitive to allow the patient's CD4+ T-cells counts and viral load together with ARV drugs treatment history serve as a guide in the administration of ARV drugs for an improved treatment outcome.

# Competing Interests

Authors have declared that no competing interests exist.

## References


[1] Culshaw R. Review of HIV models: the role of the natural immune response and implications for treatment. Journal of Biological Systems. 2004;12:123-135.

[2] Orellana J. Optimal control for HIV multitherapy enhancement. Comptes Rendus Mathematique. 2011;348.

[3] Perelson S, Nelson P. Mathematical analysis of HIV-1 dynamics *in-vivo*. SIAM Review. 1999;41(1): 3-44.

[4] Walensky R, Paltiel A, Losina E, Al E. The survival benefits of AIDS treatment in the United States. The Journal of Infectious Diseases. 2006;194(1):11-19.

[5] Cai L, Li X, Ghosh M, Guo B. Stability analysis of an HIV/AIDS epidemic model with treatment. Journal of Computational and Applied Mathematics. 2009;229(1):313–323.

[6] Li D, Ma W. Asymptotic properties of a HIV-1 infection model with time delay. Journal of Mathematical Analysis and Applications. 2007;335(1):683–691.

[7] Alshorman A, Wang X, Meyer M, Rong L. Analysis of HIV models with two time delays. Journal of Biological Dynamics; 2016.

[8] Browne E, Letham B, Rudin C. A computational model of inhibition of HIV-1 by interferon-alpha. Plos One. 2016;11(3):e0152316.

[9] Luo J, Wang WC, Fu R. Bifurcations of a mathematical model for HIV dynamics. Journal of Mathematical Analysis and Applications. 2016;434(1):837-854.

[10] Lythgoe K, Blanquart F, Pellis L, Fraser C. Large variations in HIV-1 viral load explained by shifting-mosaic metapopulation dynamics. Plos Biology. 2016;14(10):e1002567.

[11] Ngina P, Mbogo R, Luboobi L. Mathematical modelling of *in-vivo* dynamics of HIV subject to the influence of the CD8+ T-cells. Applied Mathematics. 2017;08(08).

[12] Xu J, Geng Y, Zhou Y. Global dynamics for an age-structured HIV virus infection model with cellular infection and antiretroviral therapy. Applied Mathematics and Computation. 2017;305:62-83.

[13] Jiang X, Zhou X, Shi X, Song X. Analysis of stability and Hopf bifurcation for a delay-differential equation model of HIV infection of CD4+ T cells. Chaos. Chaos, Solitons and Fractals. 2008;38:447-460.

[14] Perelson A, Neumann A, Markowitz M, Leonard J, Ho D. HIV-1 dynamics in-vivo—virion clearance rate, infected cell life-span, and viral generation time. Science. 1996;271:1582–1586.

[15] Ribeiro R, Perelson A. The analysis of HIV dynamics using mathematical models. In Wormser G, Wormser G. (Ed.). AIDS and other manifestations of HIV infection san diego: Elsevier. 2004;905-912.

[16] Strivastava P, Chandra P. Modeling the dynamics of HIV and CD4+ T cells during primary infection. Nonlinear Analysis: Real World Applications. 2010;11:612-618.

[17] Wang X, Song X. Global stability and periodic solution of a model for HIV infection of CD4+ T cells. Applied Mathematics and Computation. 2007;189:1331-1340.

[18] Zhou Y, Liang Y, Wu J. An optimal strategy for HIV multitherapy. Journal of Computational and Applied Mathematics. 2014;263:326–337.

[19] Lieberman J, Shankar P, Manjunath N, Anderson J. Dressed to kill? A review of why antiviral CD8 T lymphocytes fail to prevent Progressive immunodeficiency in HIV-1 infection. Blood. 2001;98(6): 1667-1677.

[20] Ren C, Li Y, Ling H. Neutralizing anti bodies responses during natural HIV-1 infection. International Journal of Immunology. 2012;3(35):176–179.



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