HIV Viral Dynamics in the Presence of Antiretroviral Treatment

Simeon Mayala, and Nyimvua Shaban

***Abstract*—A mathematical model was used to investigate the effect of reverse transcriptase and protease inhibitor on cells and viruses populations. We identified that the suppression of the infectious viruses depend on the efficacy of the drugs as well as the time taken for the population of infectious viruses to be suppressed. It indicates that a small number of cells is infected because infectious viruses are continuously suppressed.**

***Index Terms*—T cells, Viral dynamic, Reverse transcriptase inhibitors, Protease inhibitor.**

I. Introduction

HUMAN Immunodeficiency Virus (HIV) is a retrovirus that infects the human cells dealing with the immune system. It causes infections and destroys the body's ability to fight infections [1]. Without treatment, HIV progresses to acquired immune deficiency syndrome (AIDS), which is a final stage [2]. Mainly, there are two types of HIV; namely, HIV-1 and HIV-2. HIV-1 is more common and can be easily transmitted. It is the kind of HIV referred to be the most prevalent throughout the world. HIV-2 is found in some places primarily in West Africa. It does not tend to progress to AIDS as quickly as HIV-1[3].

HIV transmission occurs through unprotected sexual contact, direct blood contact, such as blood transfusion and injection drug needles. Another way through which HIV transmission occurs is from the mother to the baby; it can be either through vertical transmission or through breastfeeding[4], [5]. Apart from the transmission factors that lead to HIV infections, some cofactors increase the risk of HIV transmissions such as gonorrhoea and syphilis [6].

In different studies, deterministic differential equations are used to describe the interaction between T cells and the viruses. They are also used to study the dynamics of their populations when there is an infection. In this study, we investigate the HIV dynamics by using the mathematical model within the host. HIV dynamics within a host depend on HIV replication resulting in the dynamics of infected and uninfected cells [7]. The model used in this study investigates the dynamics of the infected, uninfected, treated cells and infectious viruses in the presence of treatment.

There are different antiretroviral medications (ARV) that are used by patients with HIV. These are medications given to the people infected with HIV to extend their lifespan. They interfere with the life cycle of HIV to inhibit the replication of the viruses. These drugs do not cure the disease but rather prevent or suppress the progress of HIV, especially when taken in combination [8]. The drugs taken by the patients are categorized into different classes concerning the stages of the HIV life cycle.

In the process of treatment infectious viruses are inhibited from attaching themselves to the CD4 receptors [4]. The drugs classified for treating this stage are called entry inhibitors. They prevent HIV from entering healthy CD4 cells (T-cells) in the body [4]. In the next step, HIV uses reverse transcriptase enzyme to perform a reverse transcription of the HIV genetic material RNA to HIV DNA. It is this conversion that allows the virus to enter the cell's nucleus [4]. This step occurs within the CD4 cells and the treatment used at this step is reverse transcriptase inhibitor [9]. In the next step, the viral DNA is integrated into the host DNA by using the enzyme integrase and is treated as part of the host's DNA. The treatment used to interfere with this step is called integrase Inhibitor. The RNAs use the host cell machinery to produce long HIV protein chains [10]. The next step is translation. The step occurs after assembling the viral materials and then move to the surface of the CD4 cell. These are still immature and are not yet infectious. The newly formed immature HIV pushes itself out of the host CD4 cells. The treatment used to interfere with this step is called a protease inhibitor [11]. Generally, the use of a treatment can show its effect on suppressing infectious viruses, but it can vary from one patient to another.

The rapid increase in HIV infection is a result of high replication of the virus, the process that occurs in the host cells. However, treatments are needed to regulate the rate of HIV replication. Different studies are conducted to investigate and get control of the dynamics of HIV viral loads. The model used to investigate the dynamics of replication and T cells indicated a decay of the T cells by assuming total suppression of the viruses [12]. It is challenging to develop models that can suppress completely infectious viruses because of the genetic diversity of the viruses. In this paper, we analyse the model for the population dynamics of T cells and infectious viruses in the presence of treatment. It is important to know the variations for the populations of the T cells and infectious viruses.

Mathematical models have been applied in different studies to solve medical problems. There is a possibility of having a relatively small positive impact on medical applications if the models are not well-posed. In this paper, the model used by Ribeiro and Perelson in this paper [13] is extended by considering the population of the treated cells and use it to assess the dynamics of HIV, infected and uninfected T cells. In their model, they analysed the viral reservoirs, primary infection and immune responses. Different from the study by Ribeiro and Perelson in [13], this paper considers the population of the treated cells that result after reverse

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Simeon Mayala is an Assistant Lecturer of Biomedical engineering unit, Muhimbili University of Health and Allied Sciences, P.O. Box 65001, Dar es salaam, Tanzania, (email: mayalasimeon@gmail.com).

Nyimvua Shaban is a Senior Lecturer of Mathematics Department, College of Natural and Applied Sciences, University of Dar es salaam, P.O. Box 35065, Dar es salaam, Tanzania, (email: shabanmbare@gmail.com).

transcriptase inhibition and the inhibition in the translation stage. In this model, we assumed that no entry inhibitor was being used. That means all the inhibitors considered here are active against HIV after it has infected a CD4 cell. The rest of the paper is organised as follows: In section II, we describe the model to present the mechanism of HIV treatment by involving reverse transcriptase and protease inhibitors. Section III presents the model analysis including the local and global stability of the disease-free equilibrium point and then prove the local stability of the endemic equilibrium point. In section IV, we estimate parameters which will be used in the simulation. Section V presents numerical simulations which were done under different considerations but mainly to check the impact of treatment. Section VI gives a discussion of the results and conclusions.

II. Model Formulation

The model divides the cell population into susceptible cells (T_s), infected cells (T_i) and treated cells (T_t). The virus population is subdivided into two categories namely infectious viruses (V_i) and the non-infectious virus (V_{ni}). We create a base for the formulation of our model by getting the general understanding of the biological concepts of HIV viral dynamics, including infections, replications, and clearance of the viral population. The T cells are activated at the rate λ to enter the class of susceptible cells (T_s). They vary with respect to the time taken for the virus to infect the susceptible cells. Under normal circumstances, the production of T cells does decrease with the ageing of the human body [14], but in this model, it is assumed to be a constant process. The uninfected cells die at the rate of μ_1. Also, it is assumed that the CD4 cells become the susceptible class after being activated.

However, when a person is infected, the cells become susceptible to infection at a rate that is proportional to the number of uninfected cells and the infectious virus present at that time. Uninfected cells T_s are infected at the rate of κ after interacting with the infectious viruses and move to the class of infected cells T_i. After being infected, cells from the population T_i die at the rate of μ_2.

When a virus enters the cell, the reverse transcriptase enzyme performs reverse transcription of the HIV genetic material RNA single-stranded into HIV DNA double-stranded. It is this conversion that allows HIV to enter the cell's nucleus. So, the treatment used to interfere in this process is considered to be effective at the proportion of ν_{rt}. The proportion of infected cells which will not be treated at this stage will lead to the reduced mass action term $(1-\nu_{rt})\kappa T_s V_i$ that describes the removal from uninfected cells population and the addition of infected cells population.

To construct the population for the treated cells, we consider cells in which reverse transcriptase and protease inhibitors interfered with the infectious virus life cycle in the cell. The model does assume that no entry inhibitor was used, so there was no inhibition at the entry in the cell. The inhibitors considered in this model are active against the infectious virus after it has infected the cell. So, after treatment, infected cells from T_i move to the class T_t at the reverting rate ρ. We assume that after a certain period of treatment, the cells may absorb enough drugs and create immunity and these cells die at the rate of μ_3.

Also from the infected class, both the infectious viruses V_i and non-infectious viruses V_{ni} are replicated at the rate α and die at the rate β. There are two ways through which HIV can kill the cell, these include exhausting the cell's resources and then burst through the cell membrane. So, the death of infected cells release new viruses that go and affect the susceptible cells [15]. We assume that both infectious and non-infectious viruses are replicated due to the cells burst only. The efficacy of drugs ν_{pr} from the class of protease inhibitors (PRI) interferes with the maturation of new virions, which renders them non-infectious. The only proportion $(1-\nu_{pr})$ of new viruses will be infectious, and ν_{pr} proportion will be non-infectious. In our model, N will represent the total number of viral particles.
Based on the biological description and assumptions the following system of differential equations is obtained:

$$\begin{cases} \frac{dT_s}{dt} &= \lambda - \mu_1 T_s - (1-\nu_{rt})\kappa V_i T_s, \\ \frac{dT_i}{dt} &= (1-\nu_{rt})\kappa V_i T_s - \rho T_i - \mu_2 T_i - \alpha T_i, \\ \frac{dT_t}{dt} &= \rho T_i - \mu_3 T_t, \\ \frac{dV_i}{dt} &= (1-\nu_{pr})N\alpha T_i - \beta V_i, \\ \frac{dV_{ni}}{dt} &= \nu_{pr} N\alpha T_i - \beta V_{ni}. \end{cases} \tag{1}$$

The flow diagram of the model is presented in Figure 1 .

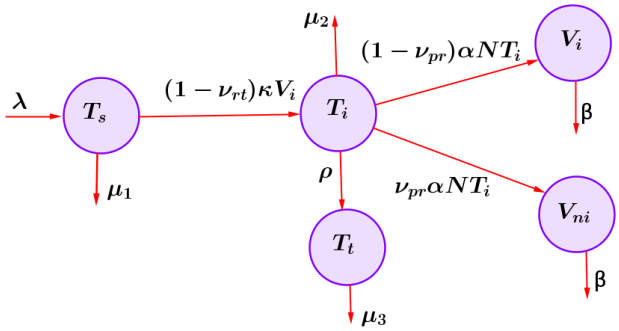

Fig. 1. The model is developed from the steps of the HIV life cycle presented in [4] though the figure presented here is mine. As described in the model formulation no entry inhibitor is considered when the virus is entering the cell. The population of the treated cells cannot proceed from the susceptible cells directly because we do not consider any entry inhibitor. So, the treated cells will proceed from the population of infected cells.

III. Model Analysis

In this model, the next-generation matrix method described in [16] was used to compute the basic reproduction number R_0. This method starts by distinguishing the new infections from all other changes in the population. The effective reproduction number R_e will be obtained from the spectral radius or greatest eigenvalue in the spectrum. The spectrum (the set of eigenvalues) obtained using the next-generation matrix is

$$\left\{ -\sqrt{\frac{(1-\nu_{rt})(1-\nu_{pr})\alpha N\kappa\lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}}, \sqrt{\frac{(1-\nu_{rt})(1-\nu_{pr})\alpha N\kappa\lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}} \right\}$$

Thus, dominant eigenvalue which is equivalent to R_e is $\sqrt{\frac{(1-\nu_{rt})(1-\nu_{pr})\alpha N\kappa\lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}}$. When there is no any treatment $(\nu_{rt} = \nu_{pr} = 0)$, the basic reproduction number R_0 is

deduced to be,

$$R_0 = \sqrt{\frac{\alpha N \kappa \lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}}$$

The infectious virus burst size gives the number of infectious virus particles produced by one infected cell over its lifespan. Therefore, R_1 gives the reproductive ratio of the viruses under the impact of drugs. Then, the reproductive ratio will be

$$R_1 = \left(\sqrt{(1-\nu_{rt})(1-\nu_{pr})}\right)\left(\sqrt{\frac{\alpha N \kappa \lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}}\right)$$

$$R_1 = \left[(1-\nu_{rt})(1-\nu_{pr})\right]^{\frac{1}{2}} R_0 = \mathcal{M} R_0,$$

where

$$\left[(1-\nu_{rt})(1-\nu_{pr})\right]^{\frac{1}{2}} \leq 1.$$

For the population which is no longer susceptible the reproductive ratio R_1 can be used to estimate the average number of secondary infectious resulting from each case as suggested by [17].

A. Stability Analysis

1) Local Stability of the Disease Free Equilibrium Point: We need to linearise the equations of the system and perform a stability analysis of the equilibrium points. The set of equations can be written in the following form,

$$\frac{d}{dt}\begin{pmatrix} T_s \\ T_i \\ T_t \\ V_i \\ V_{ni} \end{pmatrix} = \begin{pmatrix} \lambda - \mu_1 T_s - (1-\nu_{rt})\kappa V_i T_s \\ (1-\nu_{rt})\kappa V_i T_s - \rho T_i - \mu_2 T_i - \alpha T_i \\ \rho T_i - \mu_3 T_t \\ (1-\nu_{pr})N\alpha T_i - \beta V_i, \\ \nu_{pr} N \alpha T_i - \beta V_{ni}. \end{pmatrix}$$

Let,

$$\begin{aligned} f_1 &= \lambda - \mu_1 T_s - (1-\nu_{rt})\kappa V_i T_s, \\ f_2 &= (1-\nu_{rt})\kappa V_i T_s - \rho T_i - \mu_2 T_i - \alpha T_i, \\ f_3 &= \rho T_i - \mu_3 T_t, \\ f_4 &= (1-\nu_{pr})N\alpha T_i - \beta V_i, \\ f_5 &= \nu_{pr} N \alpha T_i - \beta V_{ni}. \end{aligned}$$

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial T_s} & \frac{\partial f_1}{\partial T_i} & \frac{\partial f_1}{\partial T_t} & \frac{\partial f_1}{\partial V_i} & \frac{\partial f_1}{\partial V_{ni}} \\ \frac{\partial f_2}{\partial T_s} & \frac{\partial f_2}{\partial T_i} & \frac{\partial f_2}{\partial T_t} & \frac{\partial f_2}{\partial V_i} & \frac{\partial f_2}{\partial V_{ni}} \\ \frac{\partial f_3}{\partial T_s} & \frac{\partial f_3}{\partial T_i} & \frac{\partial f_3}{\partial T_t} & \frac{\partial f_3}{\partial V_i} & \frac{\partial f_3}{\partial V_{ni}} \\ \frac{\partial f_4}{\partial T_s} & \frac{\partial f_4}{\partial T_i} & \frac{\partial f_4}{\partial T_t} & \frac{\partial f_4}{\partial V_i} & \frac{\partial f_4}{\partial V_{ni}} \\ \frac{\partial f_5}{\partial T_s} & \frac{\partial f_5}{\partial T_i} & \frac{\partial f_5}{\partial T_t} & \frac{\partial f_5}{\partial V_i} & \frac{\partial f_5}{\partial V_{ni}} \end{pmatrix}$$

$$J = \begin{pmatrix} -\mu_1 - (1-\nu_{rt})\kappa V_i & 0 & 0 & -(1-\nu_{rt})\kappa T_s & 0 \\ (1-\nu_{rt})\kappa V_i & -\rho-\mu_2-\alpha & 0 & (1-\nu_{rt})\kappa T_s & 0 \\ 0 & -\rho & -\mu_3 & 0 & 0 \\ 0 & (1-\nu_{pr})\alpha N & 0 & -\beta & 0 \\ 0 & \nu_{pr} N \alpha & 0 & 0 & -\beta \end{pmatrix}$$

The local stability at the steady state is a situation that occur before therapy initiation. The equilibrium point E_0 at the steady state is

$$(T_s^*, T_i^*, T_t^*, V_i^*, V_{ni}^*) = \left(\frac{\lambda}{\mu_1}, 0, 0, 0, 0\right)$$

Now the Jacobian will be .

$$J_{E_0} = \begin{pmatrix} -\mu_1 & 0 & 0 & -(1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) & 0 \\ 0 & -\rho-\mu_2-\alpha & 0 & (1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) & 0 \\ 0 & -\rho & -\mu_3 & 0 & 0 \\ 0 & (1-\nu_{pr})N\alpha & 0 & -\beta & 0 \\ 0 & \nu_{pr}N\alpha & 0 & 0 & -\beta \end{pmatrix}$$

The eigenvalues of the Jacobian matrix at E_0 will be obtained by

$$det(J(E_0) - \sigma I) = P_n(\lambda) = 0$$

whereby I is an identity matrix, σ is an eigenvalue of the matrix $J(E_0)$

$$det\begin{pmatrix} -\mu_1-\sigma & 0 & 0 & -(1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) & 0 \\ 0 & -(\rho+\mu_2+\alpha)-\sigma & 0 & (1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) & 0 \\ 0 & -\rho & -\mu_3-\sigma & 0 & 0 \\ 0 & (1-\nu_{pr})N\alpha & 0 & -\beta-\sigma & 0 \\ 0 & \nu_{pr}N\alpha & 0 & 0 & -\beta-\sigma \end{pmatrix} = 0$$

We can obtain the first three eigenvalues from the following factors,

$$(-\mu_1-\sigma)(-(\rho+\mu_2+\alpha)-\sigma)(-\mu_3-\sigma) = 0$$

$$\Rightarrow \sigma_1 = -\mu_1, \quad \sigma_2 = -(\rho+\mu_2+\alpha), \quad \sigma_3 = -\mu_3$$

The other two eigenvalues can be obtained by finding the determinant of the sub matrix, this gives the equation,

$$(\sigma + (\rho+\mu_2+\alpha))(\sigma+\beta) - (1-\nu_{pr})(1-\nu_{rt})N\alpha\kappa\tfrac{\lambda}{\mu_1} = 0 \tag{2}$$

We can let $A = (\rho+\mu_2+\alpha)$ and $B = (1-\nu_{pr})(1-\nu_{rt})N\alpha\kappa\frac{\lambda}{\mu_1}$, in (2), so that after expansion the polynomial becomes

$$\sigma^2 + (A+\beta)\sigma + (A\beta - B) = 0,$$

whose solutions are

$$\sigma_4 = \frac{-(A+\beta) - \sqrt{(A+\beta)^2 - 4(A\beta - B)}}{2}$$

$$\sigma_5 = \frac{-(A+\beta) + \sqrt{(A+\beta)^2 - 4(A\beta - B)}}{2}.$$

If $(A+\beta)^2 - 4(A\beta - B) \geq 0$, then in this condition we are sure that σ_4 has a negative eigenvalue. Also σ_5 must have a negative value for the condition to be satisfied.
We can let,

$$\eta = (A+\beta)^2 - 4(A\beta - B)$$

$$\eta = (\rho+\mu_2+\alpha+\beta)^2 - 4\left\{(\rho+\mu_2+\alpha)\beta - (1-\nu_{pr})(1-\nu_{rt})N\alpha\kappa\tfrac{\lambda}{\mu_1}\right\}$$

$$\eta = (\rho+\mu_2+\alpha+\beta)^2 - 4(\rho+\mu_2+\alpha)\beta\left(1 - \tfrac{(1-\nu_{pr})(1-\nu_{rt})N\alpha\kappa\lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}\right)$$

In this case we ignore the effect of treatment because it is a disease free point. So we have, .

$$\eta - (\rho+\mu_2+\alpha+\beta)^2 = -4(\rho+\mu_2+\alpha)\beta\left(1 - \frac{N\alpha\kappa\lambda}{\beta(\rho+\mu_2+\alpha)\mu_1}\right)$$

$$\eta - (\rho+\mu_2+\alpha+\beta)^2 = -4(\rho+\mu_2+\alpha)\beta\left(1 - R_0^2\right) \tag{3}$$

From equation (3) we can establish the following theorem,
Theorem 3.1 If $R_0 < 1$, the disease free equilibrium is locally asymptotically stable in $\mathbb{R}_+^5$ otherwise it is unstable.

Proof:
The point $E_0 = \left(\frac{\lambda}{\mu_1}, 0, 0, 0, 0\right)$ is locally asymptotically stable if and only if $\sigma_5 < 0$. But this can be achieved when the value of $R_0 < 1$. Thus $\sigma_5 < 0$ if $R_0 < 1$. This shows that all the eigenvalues have negative real parts, thus the proof shows the establishment of the theorem.

The physiological implication:
If $R_0 < 1$, then there exist only one stable steady state that is the disease free state. Looking at the dynamics of the infected and uninfected cells; there will be a competition between the cells if and only if β, α, λ, ρ, and μ_1 are not the same.

2) Global Stability Analysis at the Disease Free equilibrium Point: The approach used in this research is to divide the population of uninfected and infected cells. Using the concept given by [18], the population is divided into the following way,

$$\frac{dX_1}{dt} = F(X_1, X_2), \text{ and}$$
$$\frac{dX_2}{dt} = G(X_1, X_2), \quad G(X_1, 0) = 0.$$

whereby $X_1 = (T_s, T_t, V_{ni})$, $X_2 = (T_i, V_i)$ and $X_1 \in \mathbb{R}^3_+$ represents the number of uninfected cells, treated cells and non-infectious Virus respectively. $X_2 \in \mathbb{R}^2_+$ represents the number of infected cells and infectious virus respectively. The disease free equilibrium is now denoted by $E_0 = (X_0, 0)$ We need to prove the following two conditions:

(H$_1$) For $\frac{dX_1}{dt} = F(X_1, 0), \quad X_0$ is globally asymptotically stable and

(H$_2$) $\hat{G}(X_1, X_2) = JX_2 - G(X_1, X_2), \quad \hat{G}(X_1, X_2) \geq 0.$

Where J is a Jacobian matrix with respect to the infected compartment. The Jacobian is obtained by using

$$J = \frac{\partial G(X_2, 0)}{\partial X_2}.$$

We start the proof of H$_1$ as follows. From our model

$$X_1 = (T_s, T_t, V_{ni}) \quad \text{and}$$
$$X_2 = (T_i, V_i).$$

The system for uninfected class is given by

$$X_1^{'}(t) = \frac{d}{dt}\begin{pmatrix} T_s \\ T_t \\ V_{ni} \end{pmatrix} = \begin{pmatrix} \lambda - \mu_1 T_s - (1-\nu_{rt})\kappa V_i T_s \\ \rho T_i - \mu_3 T_t \\ \nu_{pr} N\alpha T_i - \beta V_{ni}. \end{pmatrix} \tag{4}$$

For the infected classes the subsystem will be

$$X_2^{'}(t) = \frac{d}{dt}\begin{pmatrix} T_i \\ V_i \end{pmatrix} = \begin{pmatrix} (1-\nu_{rt})\kappa V_i T_s - (\rho + \mu_2 + \alpha)T_i \\ (1-\nu_{pr})N\alpha T_i - \beta V_i \end{pmatrix}.$$

When $T_i = V_i = 0$ the uninfected subsystem will be,

$$\frac{d}{dt}\begin{pmatrix} T_s \\ T_t \\ V_{ni} \end{pmatrix} = \begin{pmatrix} \lambda - \mu_1 T_s \\ -\mu_3 T_t \\ -\beta V_{ni}. \end{pmatrix} \tag{5}$$

Solving the system (5) we have

$$T_s(t) = \frac{\lambda}{\mu_1} + (T_s(0) - \frac{\lambda}{\mu_1})e^{-\mu_1 t}, \quad T_t(t) = T_t(0)e^{-\mu_3 t},$$
$$V_{ni}(t) = V_{ni}(0)e^{-\beta t}$$

$$\text{as } t \to \infty, \quad T_s(t) \to \frac{\lambda}{\mu_1}, \quad T_t(t) \to 0, \quad V_{ni}(t) \to 0.$$

Without regard to the values of $T_s(0), T_t(0)$ and $V_{ni}(0)$, $X_0 = (\frac{\lambda}{\mu_1}, 0, 0)$ is globally asymptotically stable. This implies that the solution of (4) exist for large t and $X_1^{'}(t) \to 0$ as $t \to \infty$.
Also we need to prove (H$_2$)

$$\hat{G}(X_1, X_2) = JX_2 - G(X_1, X_2), \quad \hat{G}(X_1, X_2) \geq 0,$$

by computing the Jacobian matrix J as follows: From

$$X_2^{'}(t) = \frac{d}{dt}\begin{pmatrix} T_i \\ V_i \end{pmatrix} = \begin{pmatrix} (1-\nu_{rt})\kappa V_i T_s - (\rho + \mu_2 + \alpha)T_i \\ (1-\nu_{pr})N\alpha T_i - \beta V_i \end{pmatrix}$$

the Jacobian matrix will be

$$J(X_2) = \begin{pmatrix} -(\rho + \mu_2 + \alpha) & (1-\nu_{rt})\kappa T_s \\ (1-\nu_{pr})N\alpha & -\beta \end{pmatrix}$$

At the DFE the Jacobian matrix $J(X_2)$ becomes

$$J(X_2) = \begin{pmatrix} -(\rho + \mu_2 + \alpha) & (1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) \\ (1-\nu_{pr})N\alpha & -\beta \end{pmatrix}.$$

But $\hat{G}(X_1, X_2) = JX_2 - G(X_1, X_2)$

$$JX_2 = \begin{pmatrix} -(\rho + \mu_2 + \alpha) & (1-\nu_{rt})\kappa(\frac{\lambda}{\mu_1}) \\ (1-\nu_{pr})N\alpha & -\beta \end{pmatrix}\begin{pmatrix} T_i \\ V_i \end{pmatrix}$$

$$JX_2 = \begin{pmatrix} (1-\nu_{rt})\kappa V_i(\frac{\lambda}{\mu_1}) - (\rho + \mu_2 + \alpha)T_i \\ (1-\nu_{pr})N\alpha T_i - \beta V_i \end{pmatrix}$$

$$G(X_1, X_2) = \begin{pmatrix} (1-\nu_{rt})\kappa V_i T_s - (\rho + \mu_2 + \alpha)T_i \\ (1-\nu_{pr})N\alpha T_i - \beta V_i \end{pmatrix}$$

$$\hat{G}(X_1, X_2) = \begin{pmatrix} \hat{G}_1(X_1, X_2) \\ \hat{G}_2(X_1, X_2) \end{pmatrix} = \begin{pmatrix} (1-\nu_{rt})\kappa V_i(\frac{\lambda}{\mu_1} - T_s) \\ 0 \end{pmatrix}$$

It is clearly seen that $\hat{G}_1 = (1-\nu_{rt})\kappa V_i(\frac{\lambda}{\mu_1} - T_s) = 0 \quad$ and $\hat{G}_2 = 0$.
Since $\hat{G}_1 = \hat{G}_2 = 0$, the disease free equilibrium point E_0 is globally asymptotically stable.

3) Local Stability Analysis at the Endemic Equilibrium Point: The endemic equilibrium point $E_1(T_s^*, T_i^*, T_t^*, V_i^*, V_{ni}^*)$ for the disease to persist in the population of cells, this occurs when the state variables assume the following form:

$$T_s^* = \frac{\lambda\beta(\rho + \mu_2 + \alpha)}{N\alpha\kappa\lambda(1-\nu_{rt})(1-\nu_{pr})},$$
$$T_i^* = \frac{\beta\left[N\alpha\kappa\lambda(1-\nu_{rt})(1-\nu_{pr}) + \beta\mu_1(\rho + \mu_2 + \alpha)\right]}{(1-\nu_{pr})N\alpha\beta(\rho + \mu_2 + \alpha)(1-\nu_{rt})\kappa},$$
$$T_t^* = \frac{\rho\left[N\alpha\kappa\lambda(1-\nu_{rt})(1-\nu_{pr}) + \beta\mu_1(\rho + \mu_2 + \alpha)\right]}{\mu_3\beta(\rho + \mu_2 + \alpha)(1-\nu_{rt})\kappa},$$
$$V_i^* = -\frac{N\alpha\kappa\lambda(1-\nu_{rt})(1-\nu_{pr}) + \beta\mu_1(\rho + \mu_2 + \alpha)}{\beta(\rho + \mu_2 + \alpha)(1-\nu_{rt})\kappa},$$
$$V_{ni}^* = \frac{N\alpha\kappa\lambda(1-\nu_{rt})(1-\nu_{pr}) + \beta\mu_1(\rho + \mu_2 + \alpha)}{N\alpha(1-\nu_{pr})(\rho + \mu_2 + \alpha)(1-\nu_{rt})\kappa}.$$

The local stability analysis at the endemic equilibrium will be performed by using the Jacobian matrix of the System (1).

Routh-Hurwitz criteria will be used to determine the stability.

Theorem 3.2 The endemic equilibrium point E_1 is said to be locally asymptotically stable, if $R_0 > 1$.

Proof:

The Jacobian J at E_1 yields

$$J(E_1) = \begin{pmatrix} A_1 & 0 & 0 & -A_4 & 0 \\ A_2 & A_3 & 0 & A_4 & 0 \\ 0 & -\rho & -\mu_3 & 0 & 0 \\ 0 & (1-\nu_{pr})\alpha N & 0 & -\beta & 0 \\ 0 & \nu_{pr} N\alpha & 0 & 0 & -\beta \end{pmatrix}$$

where

$$\begin{aligned} A_1 &= -\mu_1 - (1-\nu_{rt})\kappa V_i \\ A_2 &= (1-\nu_{rt})\kappa V_i \\ A_3 &= -\rho - \mu_2 - \alpha \\ A_4 &= (1-\nu_{rt})\kappa \frac{\lambda}{\mu_1} \end{aligned}$$

The characteristic polynomial corresponding to the matrix $J(E_1)$ is

$$P_5(\sigma) = \sigma^5 + a_1\sigma^4 + a_2\sigma^3 + a_3\sigma^2 + a_4\sigma + a_5 = 0$$

whereby,

$$\begin{aligned} a_1 &= 2\beta + \mu_3 - A_3 - A_1 \\ a_2 &= N\alpha A_4(\nu_{pr} - 1) + \beta^2 - 2\beta(A_1 + A_3 - \mu_3) + \\ &\quad A_1A_3 - A_1\mu_3 - A_3\mu_3 \\ a_3 &= N\alpha A_4(\beta - A_1 - A_2 + \mu_3)(\nu_{pr} - 1) - \beta^2(A_1 \\ &\quad + A_3 - \mu_3) + 2\beta(A_1A_3 - A_1\mu_3 - A_3\mu_3) + A_1A_3\mu_3 \\ a_4 &= N\alpha A_4(1-\nu_{pr})\left[\beta(A_1 + A_2 - \mu_3) + \mu_3(A_1 + A_2)\right] \\ &\quad + \beta^2(A_1A_3 - A_1\mu_3 - A_3\mu_3) + 2\beta A_1A_3\mu_3 \\ a_5 &= -\beta\mu_3 N\alpha A_4(A_1 + A_2)(\nu_{pr} - 1) + \beta^2\mu_3 A_1A_3 \end{aligned}$$

Using Routh-Hurwitz criteria $J(E_1)$ is asymptotically stable if

(i) $a_1 > 0$
(ii) $a_1a_2 - a_3 > 0$
(iii) $a_1a_2a_3 + a_1a_5 - a_1^2a_4 - a_3^2 > 0$
(iv) $(a_3a_4 - a_2a_5)(a_1a_2 - a_3) - (a_1a_4 - a_5)^2 > 0$
(v) $a_4\left[(a_3a_4 - a_2a_5)(a_1a_2 - a_3) - (a_1a_4 - a_5)^2\right] > 0$

otherwise $J(E_1)$ will be unstable.

The physiological implication:

If $R_0 > 1$, this implies that the production of the infected and uninfected cells is greater than the number of the cells dying. So, we expect the competition between the infected and uninfected cells to exist. Thus, the time for clearing the virus will depend on the initial values of the infected cells, infectious virus, and the efficacy of the therapy used.

IV. Parameters Estimation

We use the uncertainty technique related to the reproductive number R_1, which is performed by using Adaptive Metropolis technique to describe the effect of the parameters in our dynamic system model. We obtained the initial parameters and states from different literature reviews. We use the Adaptive Metropolis technique to obtain the values that will give us good estimates to be used for simulation. The estimates were obtained under the conditions (*Iterations* = 200000-400000, *burn* = 100000-200000, *thin* = 20, *verbose* = 1). Below are the graphs indicating the behaviour for some parameters.

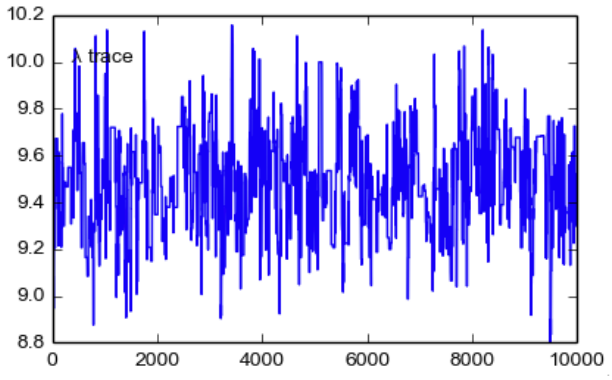

Fig. 2. Trace plot (x-axis = number of iterations, y-axis = samples) shows that the values of λ converge to 9.5327.

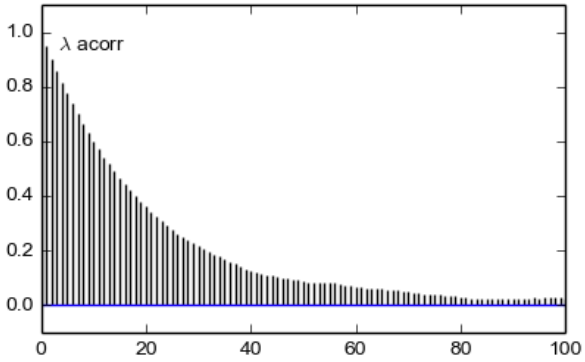

Fig. 3. The autocorrelation plot (x-axis = Number of lags, y-axis = autocorrelation coefficients), the autocorrelation coefficients decay and stabilize around zero as the number of lags increase.

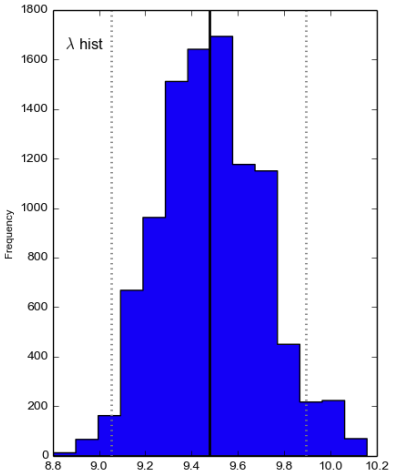

Fig. 4. The figure shows the values of λ converging to 9.5327 and the posterior is distributed normally.

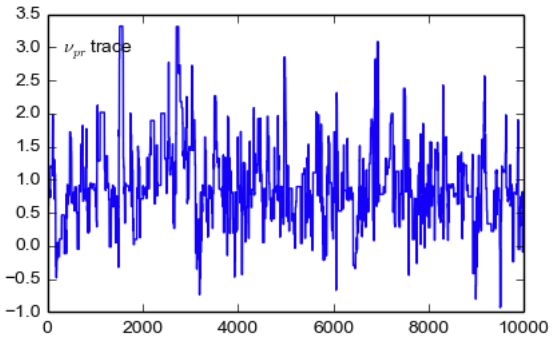

Fig. 5. Trace plot (x-axis = number of iterations, y-axis = samples) shows the values of ν_{pr} converging to 0.8767.

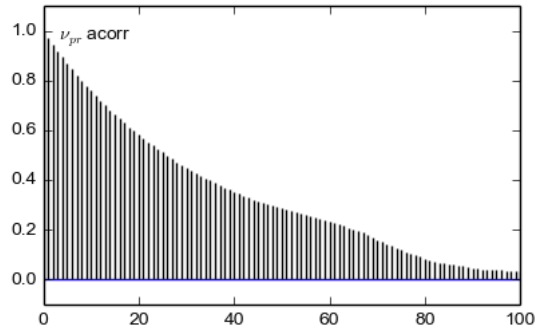

Fig. 6. The autocorrelation plot (x-axis = Number of lags, y-axis = autocorrelation coefficients), the autocorrelation coefficients decay and stabilize around zero as the number of lags increases.

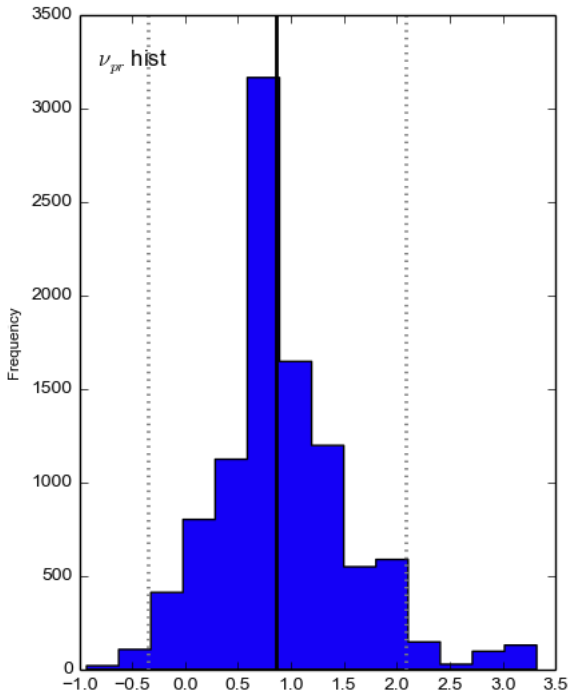

Fig. 7. The figure shows the values of ν_{pr} converges to 0.8767 and the posterior is distributed normally.

Figures 2 and 5 show trace plots. Figures 3 and 6 show autocorrelation plots and figures 4 and 7 show the histogram. The parameters show lower autocorrelation, including the other parameters whose figures are not indicated here. This implies that the samples which were drawn, accurately represent the posterior distribution. Moreover, the lower autocorrelation observed in these Figures show higher efficiency in the chains which leads to better estimates.

TABLE I
PARAMETERS AND THE ESTIMATED VALUES.

Parameter	Descriptions	Interval	Estimated Value	Source
λ	Activation rate of the T cells to enter uninfected cells population.	10	9.53273 $mm^{-3}day^{-1}$	[19]
α	The rate at which the viruses are replicated.	0.1 - 0.8	$0.1554day^{-1}$	[20]
μ_1	Death rate of uninfected T Cells	0.004 - 0.02	0.0101 day^{-1}	[20]
μ_2	Death rate of the infected T Cells from infected class.	0.015	0.0150 day^{-1}	[19]
μ_3	Death rate of the cells in the class of treated T Cells.	0.015	$0.0100day^{-1}$	estimated
κ	Infection rate of the susceptible cells	0.000024	$\frac{2356}{100000000}$ $mm^{-3}day^{-1}$	[19]
ν_{rt}	Drug efficacy due to RTI treatment.	0.6 - 0.9	0.7545 (ratio)	[21], [19]
ν_{pr}	Drug efficacy due to PRI treatment.	0.6 - 0.9	0.8767 (ratio)	[19]
ρ	The reverting rate (the incompletion of the reverse transcription process).	0.26	0.2573 day^{-1}	[19]
β	Death rate of the infectious and non infectious viruses.	2.4 - 3.0	2.40000 day^{-1}	[20]

V. NUMERICAL SIMULATION

In this subsection, we present some of the simulated results from the model and visualise the population dynamics of uninfected, infected, treated cells, infectious and non-infectious viruses.

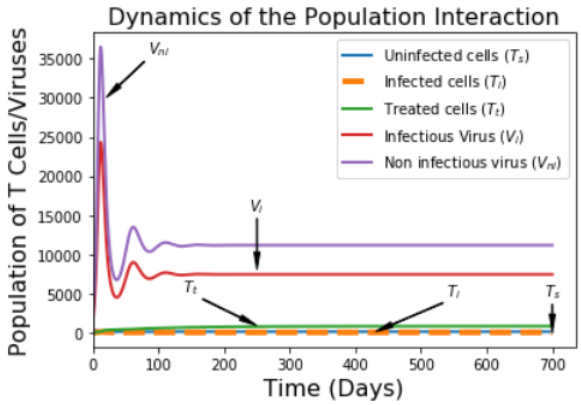

Fig. 8. The Dynamics of the populations which were obtained after simulation of the system at $\nu_{pr} = \nu_{rt} = 0.6$ keeping constant the other conditions. The population of the infectious viruses is still high.

Figure 8 shows the variation of cells and viruses populations that are involved in the system. The populations for infectious and non infectious viruses are much higher compared to the populations of the cells.

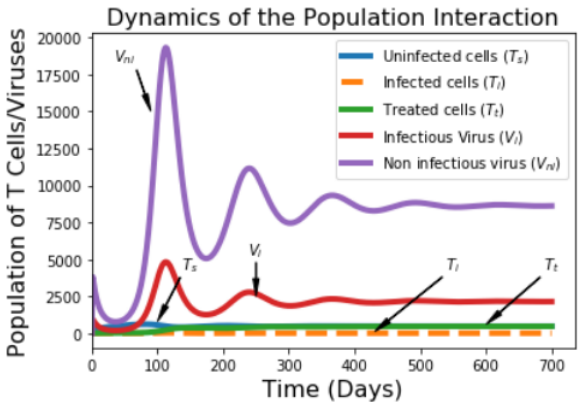

Fig. 9. The Dynamics of the populations which were obtained after simulation of the system at $\nu_{pr} = \nu_{rt} = 0.8$ keeping constant the other conditions. The increase of treatment efficacy leads to the suppression of infectious viruses. Therefore, low number of infected cells.

Figure 9 shows the dynamics for Cells and viruses population after increasing the efficacy $\nu_{pr} = \nu_{rt} = 0.8$. We note the suppression of the infectious viruses compared to figure 8 when the efficacy was $\nu_{pr} = \nu_{rt} = 0.6$. We also note the increase in the gap between the number of non-infectious and infectious viruses. This indicates that the number of infectious viruses is decreasing due to the increased treatment effect. It has been observed that the increase of drug efficacy will suppress the population of infectious virus to an undetectable level.

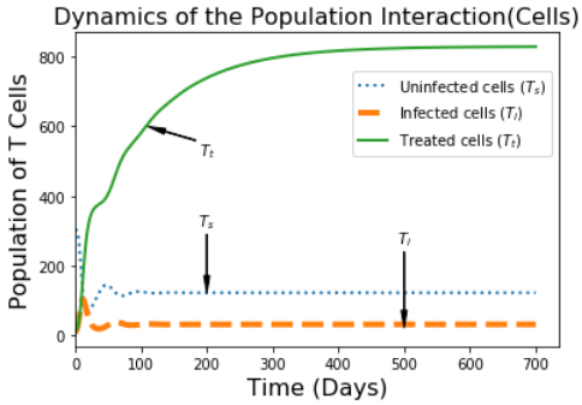

Fig. 10. The Dynamics of T_s, T_i and T_t populations obtained after simulation of the system at $\nu_{pr} = \nu_{rt} = 0.6$ keeping constant the other conditions. The high number of treated cells shows tha many cells are treated after being infected.

In figure 10 and 11, we only compare the dynamics for cells populations in their respective groups. We note a small number of infected T cells compared to the uninfected and treated T cells. Figure 8 and 9 show that the increase in the treatment effect causes the suppression of the infectious viruses and in turn we experience much increase in the uninfected cells than the treated cells in figures 10 and 11. The number of infected cells will continue decreasing as well as the number of treated cells as seen from 11.

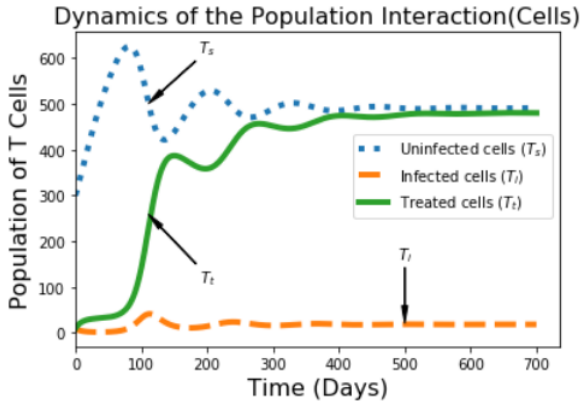

Fig. 11. The Dynamics of T_s, T_i and T_t populations obtained after simulation of the system at $\nu_{pr} = \nu_{rt} = 0.8$ keeping constant the other conditions. The increase of treatment efficacy leads to the suppression of infectious viruses. Hence, low number of infected cells and high number of uninfected cells.

Looking at figures 8, 9, 10 and 11 together the results show the continuous suppression of the infectious viruses due to the increased treatment effect. The number of infected cells continues to decrease, the factor that decreases the number of treated cells. We note that when the efficacy of the treatment effect increases, non-infectious viruses increase and the number of infectious viruses decreases, causing a continuous decrease of the infected cells.
Figures 12, 13 and 14 indicate the dynamics of uninfected, infected and treated cells, respectively. The simulation is performed to check the dynamics of the cells populations and study the impact of the two treatments used to limit the rate of producing the infectious viruses.

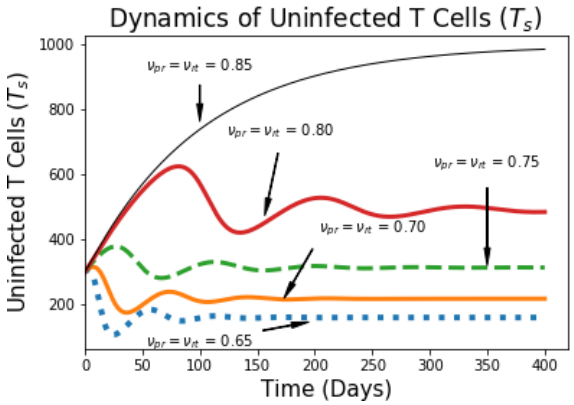

Fig. 12. The dynamics of Uninfected Cells at different levels of combined treatment efficacy. The increase of the treatment efficacy leads to increase of uninfected cells.

The graph in Figure 12 shows the dynamics of uninfected cells. The continuous increase in the efficacy of both treatments leads to the continuous increase of uninfected cells. The efficacy of the treatments varying from (0.65 to 0.85), while other parameters are kept constant shows the impact of treatment in cells and viruses population.When the number of infectious viruses decreases, we expect a continuous increase in the number of uninfected cells.

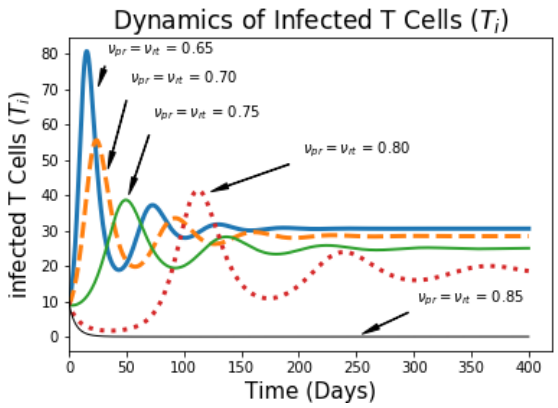

Fig. 13. The dynamics of infected Cells at different levels of treatment efficacy. The increase of the treatment efficacy leads to decrease of infected cells.

Figure 13 indicates that the number of infected cells varies with the damped oscillations while indicating a continuous decrease in the number of infected cells. The graph indicates the stability after some days of applying treatment. Also, figure 13 indicates a decrease in the infected cells when the efficacy of both treatments vary in the interval of (0.65 - 0.85). In some levels of treatment, the population of uninfected cells shows a continuous variation of the population, but as the efficacy of the drugs increases, the population of infected cells decreases and becomes stable. The population of infected cells obtained at 0.85 efficacy in figure 13 indicates that the population of uninfected cells in figure 12 continues increasing and become stable after a certain number of days.

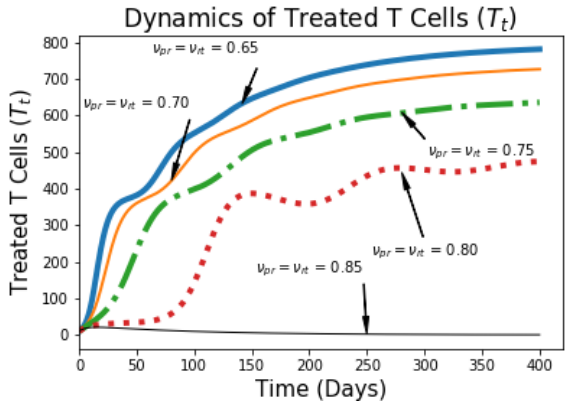

Fig. 14. The dynamics of treated Cells at different levels of treatment efficacy show that the increase of treatment efficacy leads to decrease in the number of treated cells.

Figure 14, indicates the variation of the treated cells when the two treatments are applied. The graph shows the decrease in the number of treated cells as the efficacy of the treatments increases. The dynamics of the treated cells depend much on the number of cells that are infected and the efficacy of the treatment applied. Because of treatment, the number of treated cells decreases continuously as the number of infectious viruses decreases. The big efficacy of treatment reduces the chance of escape of infectious viruses, which decreases infected cells and hence low number of treated cells. When both treatment efficacy increases to 0.85 the number of treated cells approaches to zero.

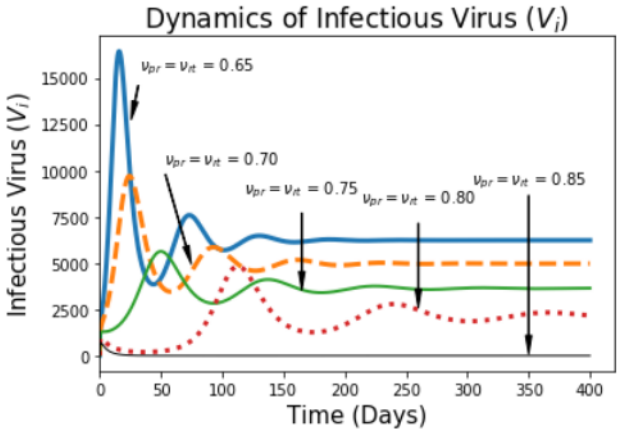

Fig. 15. The dynamics of infectious viruses at different levels of treatment efficacy show that the increase of the treatment efficacy leads to decrease of infectious viruses.

In figure 15, we note a high suppression of the infectious virus after using two treatments. The population of the infectious virus indicates big variation at the beginning, followed by the stabilisation, however a step-by-step decrease in the population of the infectious viruses as the efficacy of the treatments increases is noted. Figure 15 indicates that the increase of ν_{rt} and ν_{pr} between 0.6 and 0.9 decreases infectious viruses and infected cells in figure 13.
Also, we note that as ν_{rt} and ν_{pr} approaches 0.85 the graph indicates that the suppression of the infectious viruses goes to zero after a certain number of days of treatment. The biological implication of this follow-up in clinical care would be; the suppression of the viruses to the extent that it cannot be detected does not mean the total extinction of the infectious viruses.

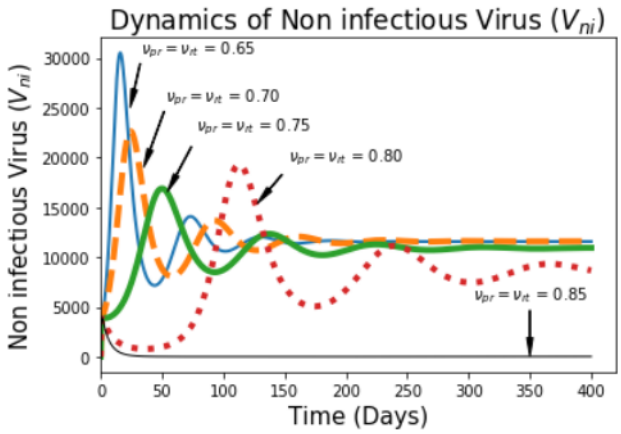

Fig. 16. The dynamics of non infectious viruses at different levels of treatment efficacy. The graph shows that the increase of the treatment efficacy leads to decrease of non infectious viruses.

Looking at figure 16 the population of the non-infectious viruses varies similarly to the population of the infectious viruses. More important is that the non-infectious viruses have no effect on the HIV infections caused in the body.

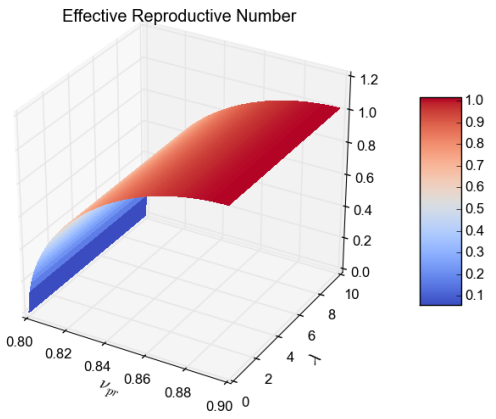

Fig. 17. Three Dimensional figure showing the variation of the effective reproductive number. $\nu_{pr} \in (0.8, 0.9)$ and $\lambda \in (0, 10)$, the variation of the effective reproductive number is between 0.1-1.0

Biologically, the relation between the T cells activation rate λ and the treatment effect ν_{pr} is shown in Figure 17. In the paper [22], they investigated the relationship between T cells activation and the CD4+ T cell counts and confirmed that lower the CD4+ T cells counts were associated with a higher level of activated CD4+ cells. [22] also confirmed that an indirect mechanism of HIV can cause the T cells activation rate even if there is a viral suppression. Thus, the relationship between the treatment effect and the activation rate is not a proper way of confirming the clearance of the disease.

VI. Discussions and Conclusion

A. Discussions

In this study, we investigated the dynamics of the viruses and T cells in the presence of treatment to understand the impact of the drugs administered to the patients. ARV therapy comes as a means to control the rapid replication of virus of which some have no clear descriptions of their replication rates. This study intended to identify the conditions under which the therapy applied has a positive impact on HIV treatment.

We analysed a mathematical model of five compartments which includes uninfected, infected, treated cells, infectious and non-infectious viruses. Between these, the population of infectious viruses appear to have more effect on the increase and decrease of the uninfected cells.

In the model analysis, we considered two treatments, that is reverse transcriptase inhibitors and protease inhibitors which were incorporated in the model. Different from the existing models from the literature, the proposed model accounts for the treated cells population which is considered during the therapy. We added a compartment that develops from the treated cells. Stability analysis for the possible equilibrium points was performed and found to be stable under certain conditions which clear the infections.

The model simulated at different efficacy values of the drugs indicated that the dynamics of the population depends on the effects of the drug. The treatment effect leads to the increase of the treated cells which were infected. The variation of the drug efficacy from 0.6 to 0.8 leads to the suppression of the infectious virus. It implies that a small number of T cells is infected leading to the decrease of the treated cells and the infected cells, in turn, there is an increase of uninfected cells, the result which matches the findings of [19].

Focusing on the dynamics of the treated cells; the simulation at $\nu_{pr} = \nu_{rt} = 0.6$ indicated that the population of the treated cells was higher than that of other T cells. It implies that a higher number of treated cells was caused by a higher number of infected cells which were moving to treated compartment after treatment. When we increased the drug efficacy to 0.8 we noted the decrease in the population of treated cells and the increase of uninfected cells. It implies that there was a high suppression of infectious viruses. Only a few cells were infected and hence increased the number of uninfected cells and decreased the number of infected cells.

The results suggest that the treatment (PRI) that interferes the stage of producing the infectious viruses has more impact on the population dynamics even though the effect of other drugs can not be left out. Other studies suggest that an optimal adherence to RT suppresses the viral replication [23]. Results on the study of Rapid turnover of plasma virions and CD4+ lymphocytes in HIV-I infection [24] states about an exponential decrease of viruses when Protease inhibitor is administered. Suppressed number of infectious viruses will lead to the decrease of infected cells and increase of uninfected cells, but this depends on the time since the initiation of treatment; the fact which is also confirmed by [13].

The results suggest that the use of two treatments with the maintained drug efficacy suppress the rapid increase of the viruses replication in the body of the infected person, but this depends on the initial populations of the cells infected and the infectious viruses. Even though our result is simulation-based, the study on the Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time based on real data which performed in the paper [25] similarly suggests that the multiple combinations are effective treatment on the viral suppression.

B. Conclusion

We aimed at modelling the population dynamics when the treatment parameters are included in the model. It has pointed out that the variation of different viral and cells populations depends on the drug effects and the time taken to clear the population of the infectious viruses. The model has shown the drug effects on the populations involved in the model.

Different from the previous models used to investigate the population dynamics of HIV models, it has visualised the dynamics of the treated T cells in the infected and uninfected cells populations. The model has pointed out that the population of the treated cells can increase and attain a maximum point during the continuous suppression of infectious viruses.

The simulations of the within-host viral dynamics model can be implemented by sampling from distributions that describe the variation of parameters amongst populations involved in the model. We simulate using the parameters which were estimated using sampling and they give good results of the dynamics that take place in the system.

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