Modelling the Effects of Immune Response and Time Delay on HIV-1 in Vivo Dynamics in the Presence of Chemotherapy

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Abstract: Numerous models of mathematics have existed to pronounce the immunological response to contagion by human immunodeficiency virus (HIV-1). The models have been used to envisage the regression of HIV-1 in vitro and in vivo dynamics. Ordinarily the studies have been on the interface of HIV virions, CD4+T-cells and Antiretroviral (ARV). In this study, time delay, chemotherapy and role of CD8+T-cells is considered in the HIV-1 in-vivo dynamics. The delay is used to account for the latent time that elapses between exposure of a host cell to HIV-1 and the production of contagious virus from the host cell. This is the period needed to cause HIV-1 to replicate within the host cell in adequate number to become transmittable. Chemotherapy is by use of combination of Reverse transcriptase inhibitor and Protease inhibitor. CD8+T-cells is innate immune response. The model has six variables: Healthy CD4+T-cells, Sick CD4+T-cells, Infectious virus, Non-infectious virus, used CD8+T-cells and unused CD8+T-cells. Positivity and boundedness of the solutions to the model equations is proved. In addition, Reproduction number (R_0) is derived from Next Generation Matrix approach. The stability of disease free equilibrium is checked by use of linearization of the model equation. We show that the Disease Free Equilibrium is locally stable if and only if $R_0 < 1$ and unstable otherwise. Of significance is the effect of CD8+ T- cells, time delay and drug efficacy on stability of Disease Free Equilibrium (DFE). From analytical results it is evident that for all $\tau > 0$, Disease Free Equilibrium is stable when $\tau = 0.67$. This stability is only achieved if drug efficacy is administered. The results show that when drug efficacy of $\alpha_1 = 0.723$ and $\alpha_2 = 0.723$ the DFE is achieved.

Keywords: HIV, Reproduction Number, Delay, Stability, Disease Free Equilibrium, Chemotherapy

1. Introduction

Human immunological disorder Virus (HIV) is one of the transmittable diseases thought to significantly cause death in developing countries like Kenya. HIV is categorized into two namely; HIV-1 and HIV-2. This paper will only focus on HIV-1 which is often chargeable for the bulk of HIV contagions worldwide. Radical point of HIV contagion is Acquired Immuno Deficiency virus (AIDs) which is contracted over direct contact with HIV-disease-ridden body fluids that include blood, semen, and reproductive organ secretions, or from HIV-infected mother to child through gestation, delivery or breastfeeding [10, 12]. T-helper is a type of the white blood cell that is targeted mainly by the HIV as soon as it enters the human body. Once it binds itself to this cell, the HIV life cycle immediately begins. HIV viral replication is rampant in the first stage of contagion [14]. Many scholars in the field of biological mathematics have designed models that explain the HIV-1 in vivo dynamics [1, 7, 11, 18]. A new HIV viral material submits to seven steps namely; binding, fusion, reverse transcription, integration, replication, assembly and budding [2-3, 8-10, 17]. The basic reproduction number R_0 is the most substantial measure in contagious disease epidemiology such as HIV. This parameter is one of the measures projected for emergent contagious diseases in outbreak state of affairs and its significance provide discernment when designing control

interventions for established contagions. R_0 is the typical amount of new cases of contagion caused by one distinctive disease-ridden person in a population comprising of vulnerable only. R_O, forms a threshold value for most models of infectious diseases since for $R_O < 1$, the disease-free equilibrium point is stable [5, 13, 15]. Various mathematical models have been developed to explain internal viral dynamics of HIV. In [6] intracellular delay in virus production at the side of the delay in immunologic response is studied where it is shown that the contagion free balanced state is steady when $R_o < 1$. This means that the contagion are often cleared if ARVs medical care is administered. In [4] a mathematical model that studies underlying transmission mechanisms of HIV infections is established and it is shown that when $R_0 > 1$ the disease free equilibrium state is asymptotically unstable and hence unwellness persist. In [7] a model that looks into the consequences of time delay on HIV undercurrents in the existence of ARVs ill-treatment delay differential equations is considered where it is shown that CD4+T-cells stay inactive for a short time and the HIV infective agent materials do not seem to be reproduced and that the system at the side of treatment gets enough time to clear the infective agent material within the blood hence maintaining the Endemic Equilibrium Point. However, in their study the used and unused CD8+T-cells were not considered. In [10] in-vivo dynamics of HIV subjected to the influence of CD8+T-cells is considered. It is proved that the virions free equilibrium state is domestically stable if Ro<1 and unstable otherwise. In their study however, they did not take into account effects of time delay on HIV-1 dynamics.

In this paper, we have formulated deterministic mathematical Susceptible Infectious Recovered (SIR) models has described the HIV-1 in vivo dynamics in presence of chemotherapy using delay differential equations. The model has six variables: Healthy CD4+T-cells (u), Sick CD4+T-cells (v), Infectious virus (w), Non-infectious virus (x), used CD8+T-cells (y) and un-used CD8+T-cells (z).

2. Methods of Solution

The stability of the model has been approached from Jacobian matrix method of checking stability of Disease Free Equilibrium (DFE) and numerical simulations have been done using MATLAB to validate the analytic results.

2.1. Model Equations

The healthy CD4+T-cells (u) is produced at a rate ψ, die at a rate ε_u and become infected at a rate ω. Sick CD4+T-cells (v) die at a rate ε_v and are cured of virus due to chemotherapy at a rate α. Free virus is produced by infected cells at a rate p The control function α_1 represents the efficacy of Reverse Transcriptase Inhibitor (RTI) chemotherapy in blocking new infection, so that infection in the presence of chemotherapy is $(1 - \alpha_1)\omega$. The control function α_2 represents the efficacy of Protease Inhibitor (PI) chemotherapy to hinder viral production such that the viral production rate under chemotherapy is $(1 - \alpha_2)p$. The parameters and the model assumptions above together will lead to the following differential equations for chemotherapy.

$$\begin{cases} \frac{du}{dt} = \psi - \varepsilon_u u - (1 - \alpha_1)\omega w_\tau u + \alpha_1 v \\ \frac{dv}{dt} = (1 - \alpha_1)\omega w_\tau u - \varepsilon_v v - \alpha_1 v - \varphi v_\tau z \\ \frac{dw}{dt} = (1 - \alpha_1)(1 - \alpha_2)p v_\tau - \varepsilon_w w \\ \frac{dx}{dt} = (1 - \alpha_1)\alpha_2 p v_\tau - \varepsilon_x x \\ \frac{dy}{dt} = \varphi v_\tau z - \varepsilon_y y \\ \frac{dz}{dt} = \sigma - \varepsilon_z z \end{cases} \quad (1)$$

Here, $\tau > 0$ is the time lag required by the host cell to produce infectious virus. It will also represent the time needed for infected cells to be treated by chemotherapy.

Theorem

Let $C = (c[-\tau, 0], \mathbb{R}^6)$ be a Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^6$ with the topology of uniform convergence.

According to fundamental theory of differential equations it can be shown that there exists a unique solution $(u(t), v(t), w(t), x(t), y(t), z(t))$ of the system (1), with initial data

$$(u(0) > 0, v(0) > 0, w(0) > 0, x(0) > 0, y(0) > 0, z(0) > 0) \in C \ [7, 10] \tag{2}$$

In addition, we assume that the initial data for the system (1) satisfies

$$u_0(\psi) \geq 0, v_0(\psi) \geq 0, w_0(\psi) \geq 0, x_0(\psi) \geq 0, y_0(\psi) \geq 0, z_0(\psi) \geq 0, \psi \in [-\tau, 0] \tag{3}$$

The following theorem establishes the positivity and boundedness of solution with initial functions satisfying (2) and (3)

Theorem 2.1.2 let (u, v, w, x, y, z) be the solution of system (1) satisfying conditions (2) and (3) then u, v, w, x, y and z are all positive and bounded for all $t > 0$ at which the solutions exist

Proof

From system (1) we have;

$$u(t) = u(0)e^{-\int_0^t \varepsilon_u + (1-\alpha_1)\omega(\xi-\tau)d\xi} + \int_0^t [\alpha_1 v(\eta) + \psi]e^{-\int_\eta^t \varepsilon_u + (1-\alpha_1)\omega w(\xi-\tau)d\xi} d\eta \tag{4}$$

$$v(t) = v(0)e^{-\int_0^t (\varepsilon_v + \alpha_1 - \varphi v_\tau y)d\xi} + \int_0^t [(1-\alpha_1)\omega w(\eta-\tau)u(\eta)]e^{-\int_\eta^t \varepsilon_v + \alpha_1 - \varphi_1 v_\tau y))d\xi} d\eta \tag{5}$$

$$w(t) = w(0)e^{-\int_0^t \varepsilon_w d\xi} + \int_0^t [(1-\alpha_1)(1-\alpha_2)pv(\eta-\tau)]e^{-\int_\eta^t \varepsilon_w d\xi} d\eta \tag{6}$$

$$x(t) = x(0)e^{-\int_0^t \varepsilon_x d\xi} + \int_0^t [(1-\alpha_1)\alpha_2 pv(\eta-\tau)]e^{-\int_\eta^t \varepsilon_x d\xi} d\eta \tag{7}$$

$$y(t) = y(0)e^{-\int_0^t (\varphi v_\tau - \varepsilon_y)) d\xi} \tag{8}$$

$$z(t) = z(0)e^{-\int_0^t (-\varepsilon_z) d\xi} \tag{9}$$

Positivity immediately follows from (2) and (3)
For boundedness we define:

$$N(t) = u(t) + v(t) + w(t) - \frac{1-\alpha_2}{\alpha_2}x(t) + y(t) + z(t) \tag{10}$$

Let $\pi = \min(\varepsilon_u ; \varepsilon_{z} ; \varepsilon_y ; \varepsilon_v ; \varepsilon_w ; \varepsilon_x \left(\frac{1-\alpha_2}{\alpha_2}\right))$ then:

$$\frac{d}{dt}N(t) = \frac{d}{dt}u(t) + \frac{d}{dt}v(t) + \frac{d}{dt}w(t) - \frac{1-\alpha_2}{\alpha_2}\frac{d}{dt}x(t) + \frac{d}{dt}y(t) + \frac{d}{dt}z(t) \tag{11}$$

Thus:

$$\frac{d}{dt}N(t) \le \omega - \pi N(t) \text{where } \omega = \psi + \sigma$$

Implying that $N(t)$ is bounded, and so are $u(t), v(t), w(t), x(t), y(t), z(t)$. This completes the proof.

2.2. Computation of Basic Reproduction Number R_0

In this paper, we adopt next generation matrix approach in computation of R_0, such that $R_0 = \rho(FV^{-1})$ where ρ is the spectral radius of next generation matrix, while F is the matrix of the infection and V is the matrix of transfer of individuals out of the compartment by other means. To obtain R_0 the dominant eigenvalue of the NGM is considered [9, 16, 18]. In system (1), there are two infection classes, hence, at disease free equilibrium the matrix of new infection is given by; matrix F and V

Matrix F_i obtained by considering the rate of new infections entering compartment i,

$$F_i = \begin{bmatrix} 0 \\ (1-\alpha_1)\omega w_\tau u \\ (1-\alpha_1)(1-\alpha_2)pv_\tau \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{12}$$

The matrix that represents the rate of transfer into and out of compartment i by any other means at DFE is given by matrix V;

$$V_i = \begin{bmatrix} 0 \\ (\varepsilon_v + \gamma\alpha_1 + z)\varphi v \\ \varepsilon_w w \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{13}$$

Clearly,

$$F = \begin{bmatrix} 0 & (1-\alpha_1)e^{-\lambda\tau}\frac{\psi}{\varepsilon_u} \\ (1-\alpha_1)(1-\alpha_2)pe^{-\lambda\tau} & 0 \end{bmatrix} \tag{14}$$

$$V = \begin{bmatrix} (\varepsilon_v + \alpha_1 + \varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}) & 0 \\ 0 & \varepsilon_w \end{bmatrix} \tag{15}$$

Then, the inverse of V is given by;

$$V^{-1} = \begin{bmatrix} \dfrac{1}{(\varepsilon_v + \alpha_1 + \varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})} & 0 \\ 0 & \dfrac{1}{\varepsilon_w} \end{bmatrix}$$

The next generation matrix FV^{-1} is given by:

$$FV^{-1} = \begin{bmatrix} 0 & \dfrac{(1-\alpha_1)e^{-\lambda\tau}\psi}{\varepsilon_u\varepsilon_w} \\ \dfrac{(1-\alpha_1)(1-\alpha_2)pe^{-\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})} & 0 \end{bmatrix} \tag{16}$$

The eigenvalues of the matrix (16) can be obtained as;

$$\begin{bmatrix} 0 - \lambda^* & \dfrac{(1-\alpha_1)e^{-\lambda\tau}\psi}{\varepsilon_u\varepsilon_w} \\ \dfrac{(1-\alpha_1)(1-\alpha_2)pe^{-\lambda\tau}}{(\varepsilon_v + \alpha_1 + \varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})} & 0 - \lambda^* \end{bmatrix}$$

Characteristic equation is of the above matrix is given by;

$$\lambda^{*2} - (\frac{(1-\alpha_1)(1-\alpha_2)pe^{-\lambda\tau}}{(\varepsilon_v + \alpha_1 + \varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})})(\frac{(1-\alpha_1)e^{-\lambda\tau}\psi}{\varepsilon_u\varepsilon_w}) = 0$$

whose roots are:

$$\lambda^*_{1,2} = \pm\sqrt{\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}(\frac{\psi}{\varepsilon_u\varepsilon_w})} \tag{17}$$

$$\lambda^*_1 = \sqrt{\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}(\frac{\psi}{\varepsilon_u\varepsilon_w})} \tag{18}$$

$$\lambda^*{}_2 = -\sqrt{\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}}\Big(\frac{\psi}{\varepsilon_u\varepsilon_w}\Big) \qquad (19)$$

Thus the R_0 which is given by the greatest eigenvalue is:

$$R_0 = \sqrt{\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}\Big(\frac{\psi}{\varepsilon_u\varepsilon_w}\Big)} \qquad (20)$$

Remark 2.1.3

Equilibrium Points and Their Stability

Here, we study the stability of model (1). In mathematical epidemiology we usually consider two equilibria points that is, Disease Free Equilibrium Point (DFE) and the Endemic Equilibrium Point (EEP). We analyze the stability of system (1) by estimating the R_0 using Next Generation Matrix approach and then check its stability using Jacobian matrix.

Remark 2.1.4

Disease Free Equilibrium

Disease free equilibrium point is a viable region in the solution set of system (1) in the absence of viral infections. For our model, the disease free equilibrium (DFE) is the set of points $(u^0, v^0, w^0, x^0, y^0, z^0) = (\frac{\psi}{\varepsilon_u}, 0, 0, 0, 0, \frac{\sigma}{\varepsilon_z})$, obtained by simple algebraic computation in the absence of the virus.

Remark 2.1.5

Stability of Disease Free Equilibrium

The disease free equilibrium is the state of variable of the model in the absence of disease. Its stability can be tested using the eigenvalues of the Jacobian matrix obtained at DFE, where at this point $R_o < 1$. The linearization matrix of system (1) at DFE is given by;

$$J = \begin{bmatrix} -\varepsilon_u & \alpha_1 & -(1-\alpha_1)\omega e^{-\lambda\tau}\frac{\psi}{\varepsilon_u} & 0 & 0 & 0 \\ 0 & -\varepsilon_v-\alpha_1-\varphi_1\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau} & (1-\alpha_1)\omega e^{-\lambda\tau}\frac{\psi}{\varepsilon_u} & (1-\alpha_1)\omega e^{-\lambda\tau}\frac{\psi}{\varepsilon_u} & 0 & 0 \\ 0 & (1-\alpha_1)(1-\alpha_2)pe^{-\lambda\tau} & -\varepsilon_w & 0 & 0 & 0 \\ 0 & (1-\alpha_1)\alpha_2 pe^{-\lambda\tau} & 0 & -\varepsilon_x & -\varepsilon_y & 0 \\ 0 & -\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau} & 0 & 0 & 0 & -\varepsilon_z \\ 0 & 0 & 0 & 0 & & \end{bmatrix} \qquad (21)$$

The system (1) is locally asymptotically stable if all the eigenvalues of linearization matrix of system (1) are negative. Clearly, the eigenvalues of (21) are:

$$\lambda^*{}_1 = -\varepsilon_u, \lambda^*{}_2 = -\varepsilon_x, \lambda^*{}_3 = -\varepsilon_y, \lambda^*{}_4 = -\varepsilon_z \qquad (22)$$

$$\lambda^*{}_{5,6} = \frac{-\varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}) \pm \sqrt{\Big(\varepsilon_w\Big(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}\Big)\Big)^2 - 4((\varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})) - (\frac{(1-\alpha_1)^2(1-\alpha_2)\omega pe^{-2\lambda\tau}\psi}{\varepsilon_u}))}}{2}$$

From (22) it is evident that $\lambda^*{}_1, \lambda^*{}_2, \lambda^*{}_3, \lambda^*{}_4, \lambda^*{}_5$ are all negative. The stability of our model will be determined by the sign of $\lambda^*{}_6$.

$$\lambda^*{}_6 = -\varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}) + \sqrt{\Big(\varepsilon_w\Big(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}\Big)\Big)^2 - 4((\varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})) - (\frac{(1-\alpha_1)^2(1-\alpha_2)\omega pe^{-2\lambda\tau}\psi}{\varepsilon_u}))} < 0 \quad (23)$$

$$\text{If} - \varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}) > \sqrt{\Big(\varepsilon_w\Big(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau}\Big)\Big)^2 - 4((\varepsilon_w(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})) - (\frac{(1-\alpha_1)^2(1-\alpha_2)\omega pe^{-2\lambda\tau}\psi}{\varepsilon_u}))}$$

then it follows that;

$$\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi_1\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}\Big(\frac{\psi}{\varepsilon_u\varepsilon_w}\Big) < 1 \text{ or } \sqrt{\frac{(1-\alpha_1)^2(1-\alpha_2)pe^{-2\lambda\tau}}{(\varepsilon_v+\alpha_1+\varphi\frac{\sigma}{\varepsilon_z}e^{-\lambda\tau})}\Big(\frac{\psi}{\varepsilon_u\varepsilon_w}\Big)} < 1 \qquad (24)$$

Therefore, $R_0 < 1$ is attained for DFE to be stable.

3. Main Results

Analytic solutions can be demonstrated using analytic results with specific numerical examples. The model equation (1) is considered. Numerical simulations of the model is calculated using list of parameters and their estimated values given in the table 1 & 2. The values have been obtained from [1, 7, 10]. In simulation of the model system (1), the following initial values in each compartment

at the onset of infection is assumed to apply; $u(0), v(0), w(0), x(0), y(0), z(0) = (1000, 0, 0.01, 0.01, 500, 30)$ on the interval $[-\tau, 0]$.

Table 1. *Table of Variable, Variable description and Value.*

Variables	Variable description	Value
u	Healthy CD4+ T- cells	1000
v	Sick CD4+ T- cells	0
w	Infectious virus	0.001
x	Non-infectious virus	0.001
y	CD8+ T-cells used	500
z	CD8+ T-cells un-used	30

Table 2. *Table of Parameters, Parameter description and Value.*

Parameters	Parameter description	Value
ψ	Production rate of healthy CD4$^+$T cells (u)	15 cells/mm^3/day
ε_u	Death rate of healthy CD4$^+$T cells (u)	0.06/day
α_1	Efficacy of RTI	$0 \leq \alpha_1 \leq 1$
α_2	Efficacy of PI	$0 \leq \alpha_2 \leq 1$
ω	Force of infection	0.53
p	Budding size of free virus from sick CD4$^+$T cells	13
ε_v	Death rate of sick CD4$^+$T cells	0.26
ε_w	Natural death rate of infectious virus from the body	2.4
ε_x	Natural death rate of non-infectious virus from the body	2.4
ε_y	Natural death rate of used CD8+ T-cells	0.06/day
ε_z	Natural death rate of un-used CD8+ T-cells	0.06/day
σ	Production rate of CD8+ T-cells	0.004/day
τ	Time delay	To be determined
φ	Rate at which CD8+ T-cells are used	20cell/mm^3/day

Figure 3. *Figure showing R_0 with respect to Drug Efficacy.*

Figure 1 A figure showing Reproduction number with respect to time delay. It is evident that if time delay is large viral replication is high. It is clear that $R_0 < 1$ for $0 < \tau < 1$. Therefore Disease Free Equilibrium is stable for $\tau < 1$.

Figure 2 A figure showing Reproduction number with respect to bursting size. It is evident that R_0 is directly proportional to the bursting size. It is clear that $R_0 < 1$ if $0 < p < 200$. For DFE to be stable $p < 200$.

Figure 3 A figure showing Reproduction number with respect to drug efficacy at 80% efficacy. It is evident that DFE is achieved when drug efficacy is at 80%. Therefore, chemotherapy played a major role in reducing the viral replication for stability to be achieved at $R_0 < 1$.

Figure 4 A figure showing Reproduction number with respect to immune response (CD8+T-cells). It is evident that immune response plays a role in reducing viral replication. Clearly, for $R_0 \leq 1$ for CD8+ T cells ≤ 30. Stability of Disease Free Equilibrium is achievable in the presence of CD8+ T cells.
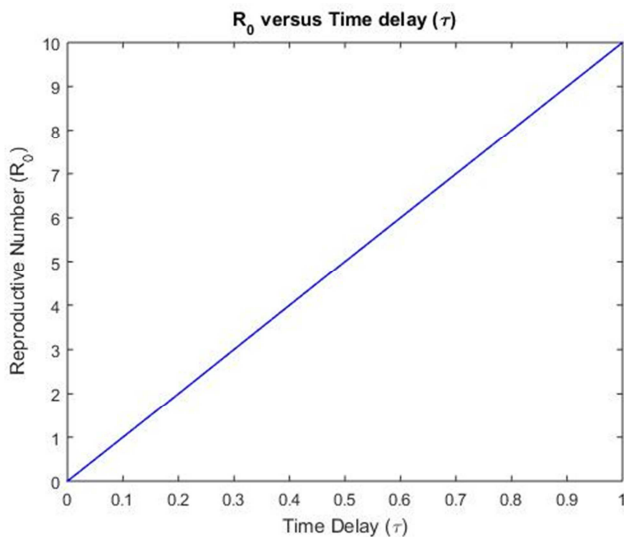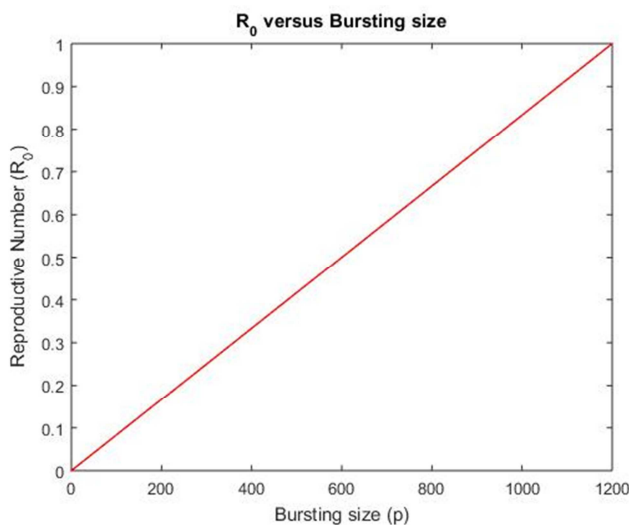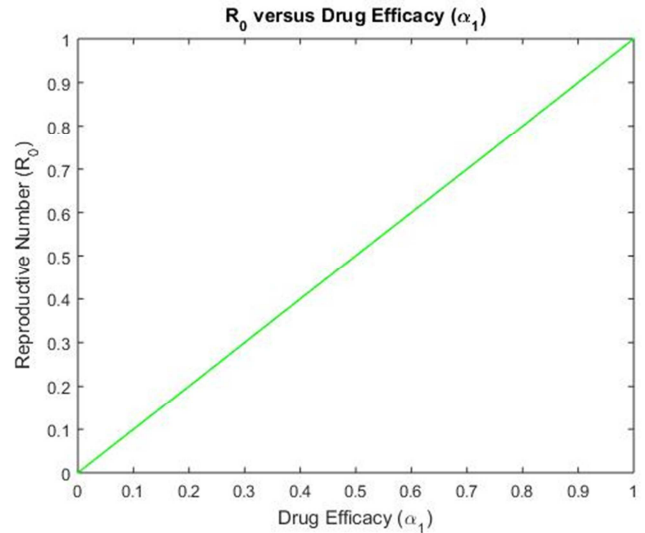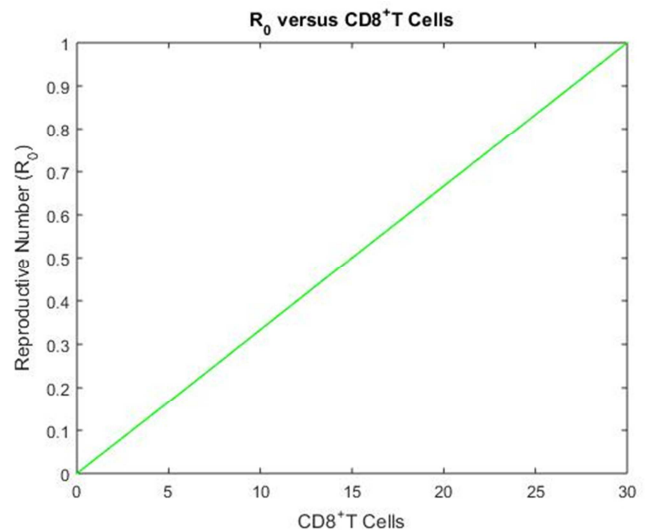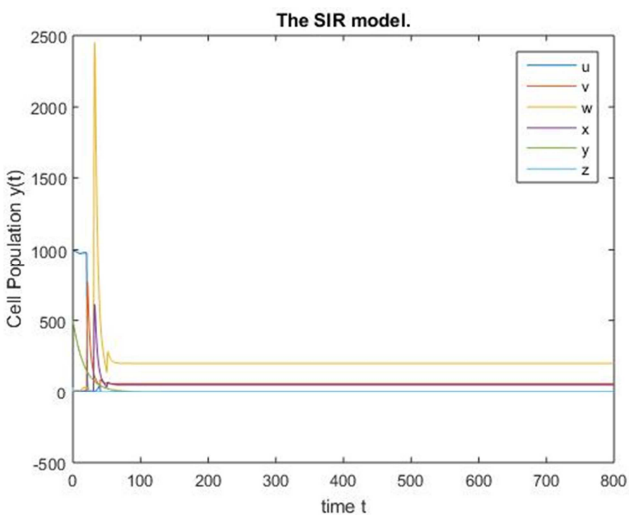

Figure 1. *Figure showing R_0 with respect to Time Delay.*

Figure 2. *A figure showing R_0 with respect to bursting size.*

Figure 4. *Figure showing R_0 with respect to CD8+T-cells.*

Figure 5 A figure showing the dynamics population of CD4+T-cells and contagious viral cells with neither treatment nor immune response. It is evident that initially the contagious virus was at zero and immediately its number shots to 4000/mm^3 due to rapid viral replication. As a result CD4+T-cells count goes down.
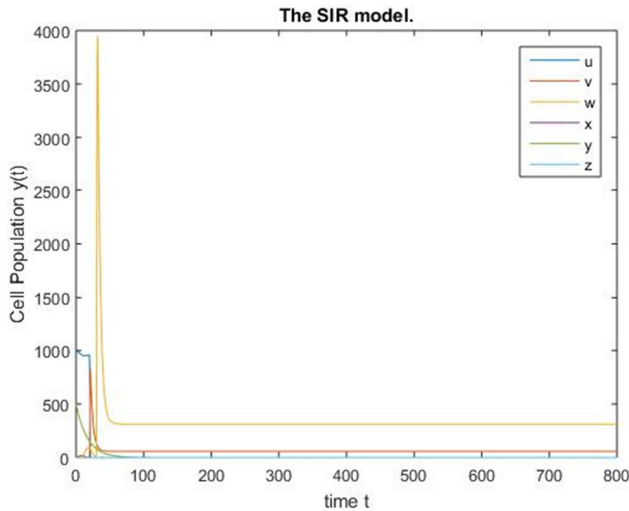
Figure 5. *Dynamics population of CD4+T-cells and contagious cells with neither treatment nor immune response.*

Figure 6 A figure showing the dynamics population of CD4+T-cells with 20% drug efficacy and immune response. It is evident that CD4+ T-cells count is at 2500/mm^3 after some time which is a value lower than 4000/mm^3 that was evident when there were no treatment and immune response. This implies that chemotherapy and immune response played a major role in reducing the replication of the contagious virus and delaying it to happen.

Figure 6. *Dynamics population of CD4+T-cells and contagious cells with 20% drug efficacy and immune response with respect to time.*

Figure 7 A figure showing dynamic population of CD4+T-cells and contagious viral cells with 80% drug efficacy and immune response. It is evident that contagious viral replication rises slowly to a value slightly above 200/mm^3.

The CD4+T-cells are maintained at a value above 200cell/mm^3.
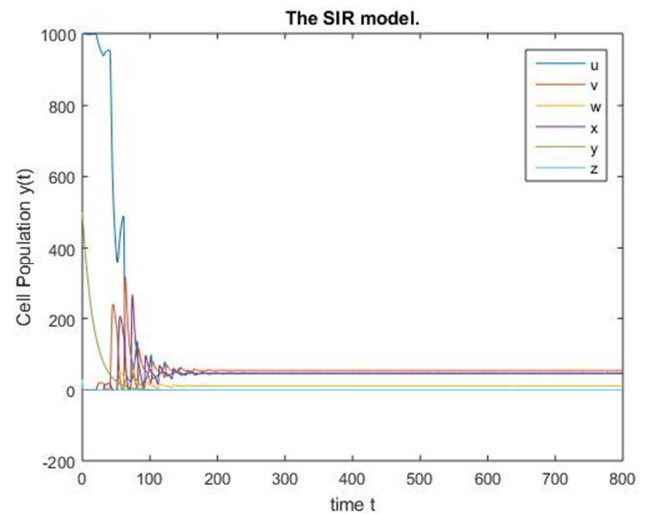
Figure 7. *Dynamics population of CD4+T-cells and contagious cells with 80% drug efficacy and immune response with respect to time.*

4. Conclusion

In this paper, the main objective is to study the dynamics of HIV-1 in-vivo in the presence of time delay, chemotherapy and role of CD8+ T-cells. Disease Free Equilibrium is attained when $R_0 < 1$. This reproduction number has been obtained using NGM and Jacobian matrix and it is clearly seen that R_0 is affected by delay, immune response and chemotherapy of both RTI and PI. The study found out that if all other factors are kept constant then DFE is achieved when drug efficacies for RTI and PI are at 0.723. Any values of efficacies above this value has no change in dynamics whereas any value below this may be as good in decreasing the reproduction number. It is also clear that for $\tau > 0$ DFE is stable and unstable otherwise. Time delay, immune response and chemotherapy plays an important role in reducing the replication of HIV virus and stability at DFE. Thus elimination of HIV contagious virus are achieved through use of chemotherapy, time delay and CD8+T-cells from the contagion (entering of virus into the cell) to bursting of the contagious virus. Prolonging this time, then the drop in CD4+T-cells count will not deplete within a shorter period.

5. Suggestions for Further Research

This study has not explored all about HIV-1 In vivo dynamics. Sensitivity analysis and Hopf bifurcation is not captured in the study. Also, Studies on chemotherapy using Structured Treatment Interference (STI) regime by narrowing to the delay for stabilities at EEP is not captured.

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