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Modeling the Effects of Time Delay on HIV-1 in Vivo Dynamics in the Presence of ARVs

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Abstract: Mathematical models to describe in vivo and in vitro immunological response to infection in humans by HIV-1 have been of major concern due to the rich variety of parameters affecting its dynamics. In this paper, HIV-1 in vivo dynamics is studied to predict and describe its evolutions in presence of ARVs using delay differential equations. The delay is used to account for the latent period of time that elapsed between HIV – $CD4^+$ T cell binding (infection) and production of infectious virus from this host cell. The model uses four variables: healthy $CD4^+$T-cells (T), infected $CD4^+$T-cells (T^*), infectious virus (V_I) and noninfectious virus (V_N). Of importance is effect of time delay and drug efficacy on stability of disease free and endemic equilibrium points. Analytical results showed that DFE is stable for all $\tau > 0$. On the other hand, there is a critical value of delay $\tau_1 > 0$, such that for all $\tau > \tau_1$, the EEP is stable but unstable for $\tau < \tau_1$. The critical value of delay τ_1 is the bifurcation value where the HIV-1 in vivo dynamics undergoes a Hopf-bifurcation. This stability in both equilibria is achieved only if the drug efficacy $0 \leq \varepsilon \leq 1$ is above a threshold value of ε_c. Numerical simulations show that this stability is achieved at the drug efficacy of $\varepsilon_c = 0.59$ and time delay of $\tau_1 = 0.65$ days. This ratifies the fact that if $CD4^+$T cells remain inactive for long periods of time $\tau > \tau_1$ the HIV-1 viral materials will not be reproduced, and the immune system together with treatment will have enough time to clear the viral materials in the blood and thus the EEP is maintain.

Keywords: Equilibrium, Basic Reproductive Number, Delay, Stability, Bifurcation

1. Introduction

Understanding transmission characteristic of any infectious diseases in a community, leads to better approaches to its management and therefore reducing the negative impacts on time. HIV is currently threatening the future generation and immense research on the understanding of its dynamics is ongoing. The mathematical point of view is inclined to understanding the evolution at cellular level through the use of mathematical models.

The mathematical models seek to describe the evolution dynamics which help identify the drug targets, their optimal doses and modes of administration. [4].

The most virulent and most common HIV strain is HIV-1 which is under study. After exposure, the viral materials find its way to the $CD4^+$ T cells and gets entry into the cell where it gets both intracellular immunity and a mechanism for its replication. The infected cells are the same cells serving as a defense mechanism against pathogens. HIV-1 infection therefore disintegrates the immune system giving opportunity to other diseases.

HIV virus possesses a reverse transcriptase enzyme making it vulnerable to mutation. The mutants may be resistant to therapy and also invisible to the body defense mechanism. This has prolonged the discovery of an effective wholesome treatment regimen that completely solves the pandemic.

HIV-1 Infection and its Stages

The stages of HIV infection from exposure to replication of new HIV viral materials undergoes 5 distinct phases namely: Binding, reverse transcription, integration,

transcription and assembly. These stages are aided by the following receptors and enzymes; CD4, reverse transcriptase, integrase, polymerase and protease respectively. The transition from one stage to the other is characterized by the presence of the respective enzymes and a chemical reaction which is not instantaneous. Notable time delay is evident between stage three and stage four where the HIV DNA will remain integrated in the host cell until the cell receives a signal to be active. In this stage, the HIV DNA will use the host polymerase enzyme to create copies from the HIV mRNA as blueprint. The newly assembled viral materials are ready for budding and once out of the cell, the cycle begins again. If the host cell remains dormant, the HIV DNA will remain residing in the host nucleus for as long as the cell is inactive and thus no new HIV materials are produced. This implies that once a cell is infected, it will remain infected for its lifetime and new viruses are produced whenever the cell is activated [2].

Mathematical modeling of this scenario involves categorizing the stages into distinct compartments and representing the transition rates from one compartment to the other using differential equations. [4]. In this paper, host $CD4^+$T cells is put into two compartments; uninfected or naive cells referred to as susceptible (T) and infected cells referred to as Infectives (T^*). The viral population is also categorized into two compartments namely Infectious (V_I) and non-infectious viral materials (V_N). The two viral products are created during the transcription stage, where mRNA is coded to make copies of new infectious viral materials. If this stage is interrupted, poorly coded noninfectious HIV viral materials will be produced.

2. Literature Review

The use of differential equations to model biological systems dates to Malthus [11]. These models give rise to better understanding of phenomenal dynamics but limited due to a large number of parameters used and assumptions made. The effects of treatment on the dynamics of HIV have been studied by [5]. The various scenarios including the effects of AZT on HIV virus dynamics was considered. The most common assumption usually made is instantaneous effect to a cause, which in this paper is addressed by introducing a delay to gather for intracellular latency periods and other biological processes that take time between action and reaction.

Culshaw [7] studied a delay-differential equation model of HIV infection of $CD4^+$ T-cells using three compartments: the healthy $CD4^+$ T-cells infected $CD4^+$ T-cells and the free virus. The study examines the effects of time delay on the stability of endemically infected equilibrium. They found out that the infected steady state was stable for all $\tau \geq 0$. These results concur with the findings that ARV's reduce the amount of HIV type 1 in the blood plasma of infected patients to extremely low undetectable levels (see for instance [6] and [12]). However, a small percentage of infected patients experience viral rebound [13]. This could be associated with periodicity in viral load due to the time delay during interaction [14].

[10] studied a delay-differential equation model of HIV infection of $CD4^+$T-cells using a three compartment model: healthy $CD4^+$T-cells, infected $CD4^+$T-cells and the free virus. The study provided the restriction on the number of viral particles per infected cell in order for infection to be sustained. Under the restriction, the system has a positive equilibrium called the infected steady state. The study also provided the conditions on parameter values for the infected steady state to be stable together with the condition on delay for the stability of the steady states.

Similar studies by [6] were able to predict an infected steady state, despite the choice of parameters which is highly individualized. An alternate strategy for the theoretical estimation of health and progression to AIDS in at-risk individuals was proposed, but the approach also has the problem that parameter estimation is highly individual. [7]. It does, however, address the problem of using viral load as a stand-in for patient health, and takes into account the particular type of decline in $CD4^+$ T-cells that is specific to AIDS patients.

In addition, the effect of time delay on the robustness of biological oscillators with respect to varying model parameters showed that time delay destabilize a stable steady state fixed point through Hopf Bifurcations implying oscillating behaviour [15]. This destabilization by Hopf Bifurcation creates a stable limit cycle. In turn, unstable fixed point cannot be stabilized by time delay. He found that time delays stabilize oscillations by enlarging the parameter space which correspond to periodic solutions.

Studies on CTL Response to HTLV-1 infection at cellular levels of the immune system versus viruses showed the existence of Multiple Stable Periodic Oscillations. [14]. This study was an extension of the work, on the investigation of the effect of time lag on temporal dynamics of their model using rigorous bifurcation analysis and numerical simulations. This showed that time delays can destabilize an otherwise stable positive steady state and lead to a phenomenon of stability switch.[9, 15]. As the delay increase, the positive steady state switches between being stable and unstable for a finite number of times that is; stability switches occur. Coexistence of multiple stable periodic solutions which differ in amplitude and period with their own basins of attraction, implying that the interaction of the immune system and the virus is that initial dosages of the viral infection may lead to quantitatively and qualitatively different outcomes.

The interaction between HIV-1, the human immune system and chemotherapy is a highly dynamic and multifactor process and as a result it is essential to base therapeutic interventions and preventions on more solid theoretical grounds. Kirschner and Webb [16] studied a model for treatment strategy in the chemotherapy of AIDS. The study looked at the interaction of HIV-1 and the immune system using a system of ODEs with the effect of chemotherapy modeled using a scalar function which was assumed to be on during treatment and off during off treatment. The results of the study were: One, periodicity of treatment during a given day does not reveal a significant difference in the overall effect, quantitatively or qualitatively. This means that

whether one receives a 500mg dose once a day or 100mg dose five times a day, the overall result is the same. This is because the treatment serves only to perturb the system of Aids into steady state. Two, chemotherapy should begin only after the second decline of $CD4^+$T-cells.

But according to Rotich [8], the control of HIV/AIDS depends not only on chemotherapy but also on the amount of time lag. In their analysis, they found that the higher the delay, the lesser the threshold drug efficacy required to lower reproductive ratio to less than one. Thus with a delay of 25 days, the minimum drug efficacy required was 79% of which any more than this will unnecessarily expose the user to risks of toxicity

Previous studies have considered different aspects on models of HIV-1 and examined local dynamics about the fixed points. Elaiw [3] studied a global dynamics of an HIV infection model with two classes of target cells and distributed delays. The study investigated the global dynamics of an HIV-1 infection with $CD4^+$ T-cells and macrophages. The incidence rate is modeled by a saturation functional response. Two types of distributed intracellular delays describing the time needed for infection of target cells and virus replication was been considered. Lyapunov functional was constructed to establish the global stability of infected and uninfected steady states of the model. In this study numerical investigation is not done nor the specific effect of time delay investigated.

In this paper, the effect of time delay on stability of $CD4^+$T-cells infection and production of HIV-1 infectious virus in presence of treatment was studied. The model is formulated using ODEs and the analysis of the effect of chemotherapy and time delay on stability of the system is considered and numerical solutions used to validate theoretical results.

3. Model Formulation

The mathematical model under study is formulated based on compartmental analysis of the rates of transitions between the compartments using differential equations. The equations are founded by the following assumptions.

3.1. Model Assumptions, Variables and Parameters

The analysis and results in this paper are obtained from the analysis of a model formulated using the following assumptions.

A1. The model used in this study assumes that there are only four interacting cell populations namely; Susceptible $CD4^+$ T cells ($\boldsymbol{T}$), Infected CD4+T cells ($\boldsymbol{T^*}$), Infectious HIV materials ($\boldsymbol{V_I}$) and Non-infectious HI materials ($\boldsymbol{V_N}$).

A2. The model assumes that the action of cell mediated immunity (CMI) response and humoral immune response are not significant to the intracellular viral dynamics.

A3. The model does not distinguish the existence and infection by different viral strains. It is only concerned with drug sensitive HIV-1 viral strain.

A4. Only $CD4^+\ T$ cells are infected and upon infection, cells become latent for some fixed time τ then during cell division, both infectious and noninfectious viral materials bud out.

A5. Infection of $CD4^+\ T$ cells is by mass action principle.

A6. Antiretroviral drugs acts in two stages, inhibition Reverse transcriptase and inhibition of Protease actions.

The model will be formulated using the above assumptions together with the following parameters that will be used in the model and their descriptions. K: Production rate of infectious and non-infectious free virus from infected $CD4^+$T cells, s: Production rate of uninfected $CD4^+$ T cells (T), β: Infection rate of uninfected $CD4^+$ T cells (T), $\mu_i: i = T,\ T^*, V_I,\ V_N$ Death rates of uninfected $CD4^+$T cells, Infected $CD4^+$ T cells, infectious virus and noninfectious virus, u_1: Efficiency of reverse transcriptase inhibition, u_2: Efficiency of protease inhibition, r: Rate of recovery of infected T cells due to treatment and τ: Time delay from infection of the cell to the time of production of new infectious viruses.

3.2. Modeling the Effects of Therapy on HIV Infection

As expected, drugs have a negative impact on the production of pathogens. In this case, the use of HAART has two effects, not directly on the pathogen, but on the enzymes that facilitate its replication. As discussed in section 1, under the HIV life cycle, HIV-1 requires two enzymes for its successful multiplication. One is the Reverse Transcriptase (RT) enzyme necessary to change viral RNA to viral DNA. It is at this point that reverse transcriptase inhibitor (RTI) works by inhibiting the process. If this inhibition is successful, the viral RNA materials will be cleared and the host cell is said to have recovered. Second is the Protease (P) necessary in assembling the viral protein so that new copies of HIV are formed. It is at this point that protease inhibitor (PI) works. If this process is successfully inhibited, noninfectious viruses will be produced. HAART drugs therefore have negative effects on the production rate of infectious HIV viral materials. The cell population dynamics is hereby studied with respect to the drug efficacy and the length of time delay.

3.3. Model Equations and Description

The model variables, parameters and the assumptions above will lead to the following delay differential equations.

$$T'(t) = s - (1-u_1)\beta T(t)V_I(t-\tau) - \mu_1 T(t) + ru_1 T^*(t) \quad (1)$$

$$T'^*(t) = (1-u_1)\beta T(t)V_I(t-\tau) - \mu_2 T^*(t) - ru_1 T^*(t) \quad (2)$$

$$V_I'(t) = (1-u_1)(1-u_2)KT^*(t-\tau) - \mu_3 V_I(t) \quad (3)$$

$$V_N'(t) = (1-u_1)u_2 KT^*(t-\tau) - \mu_4 V_N(t) \quad (4)$$

Define equation (1 – 4) as system (1), thus system (1) describes the dynamics of HIV-1 life cycle and its

interaction with treatment. Equation (1) represents the population of naive CD4$^+$ T cells. In absence of the disease, a constant recruitment rate of s and natural death rate of μ_1 affects their numbers. Equation (2) models infected CD4$^+$ T cells. Infection is said to have occurred if the viral material successfully gets entry into the CD4$^+$ T cell. Infected cells are recruited as follows: Probability of sufficient contact enough to cause attachment/binding β multiplied by the proportion of viruses that elude RTI treatment $(1-u_1)$ times the number of infective viruses produced τ units of time ago $V_I(t-\tau)$ multiplied by the number of naïve cells. These cells die at a rate of μ_2 and some recover at a rate of ru_2. Equation (3) represents infective viral materials which is the proportion that eludes the action of both RTI and PI $(1-u_1)(1-u_2)$ multiplied by the burst size K for every previously infected cell $T^*(t-\tau)$. The last equation (4) represents the proportion of poorly coded viral materials due to inhibition of PI by u_2 but eluded RTI $(1-u_1)$ multiplied by the burst size K per every previously infected cell $T^*(t-\tau)$. The classes of virus will be cleared at the rate of μ_3 and μ_4 respectively.

3.4. Model Preliminary Analysis

Since the model represents the dynamics of cell populations, it is required that the solutions are positive, bounded and feasible. This is confirmed from the following analysis.

3.4.1. Positivity

Define a positive quadrant space $C = C^1([-\tau,0];\mathbb{R}^4)$ equipped with the norm $\|\Phi\| = sup\Phi(t)_{t\in[-\tau,0]}$ as a Banach space of continuous functions $\Phi(t)$ mapping the interval $[-\tau,0]$ into $\mathbb{R}^4$ with the topology of uniform convergence. Let the positive initial conditions of system (1) at time $t = t_0$ to be $T(t_0) = T_0 \geq 0, T^*(t_0) = T_0^* \geq 0, V_I(t_0) = V_{I0} \geq 0, V_N(t_0) = V_{N0} \geq 0, t_0 \in [-\tau,0]$. In this case, we define a positive quadrant space of solutions as, $\mathbb{R}_{+0} = \{(T,T^*,V_I,V_N)|T \geq 0, T^* \geq 0, V_I \geq 0, V_N \geq 0\}$ and $\mathbb{R}_+ = \{\{T,T^*,V_I,V_N\}|T > 0, T^* > 0, V_I > 0, V_N > 0\}$. By the fundamental theory of differential equations, it is shown that there exists a unique solution $T(t), T^*(t), V_I(t), V_N(t)$ of system (1) with initial data in $\mathbb{R}_+$ as follows.

From system (1), by integration we have

$$T(t) = T(0)e^{-\int_0^t(\mu_1+(1-u_1)\beta V_1(\xi-\tau))d\xi} + \int_0^t[ru_1T^*(\eta)+s]e^{-\int_\eta^t(\mu_1+(1-u_1)\beta V_I(\xi-\tau))d\xi}d\eta, \quad (5)$$

$$T^*(t) = T^*(t)e^{-\int_0^t[\mu_2+ru_1]d\xi} + \int_0^t[(1-u_1)\beta V_I(\eta-\tau)T(\eta)]e^{-\int_\eta^t[\mu_2+ru_1]d\xi}d\eta, \quad (6)$$

$$V_I(t) = V_I(0)e^{-\int_0^t\mu_3 d\xi} + \int_0^t[(1-u_1)(1-u_2)KT^*(\eta-\tau)]\,e^{-\int_\eta^t\mu_3 d\xi}d\eta \quad (7)$$

and

$$V_N(t) = V_N(0)e^{-\int_0^t\mu_4 d\xi} + \int_0^t[(1-u_1)u_2KT^*(\eta-\tau)]\,e^{-\int_\eta^t\mu_4 d\xi}d\eta \quad (8)$$

Positivity immediately follows from the above integral forms and (5) to (8).

3.4.2. Boundedness

For boundedness, we define $N(t) = T(t) + T^*(t) + V_I(t) + \frac{1-u_2}{u_2}V_N(t)$ and define $\delta = \min(\mu_i), i = 1,2,3,4$ then $N'(t) \leq s - \delta N(t)$. Which implies that $N(t)$ is bounded, and so are $T(t), T^*(t), V_I(t)$ and $\frac{1-u_2}{u_2}V_N(t)$.

3.5. Equilibrium Points and Their Stability

We analyze system (3.6) by first finding the equilibrium points of the system and then study their stability. There are usually two important equilibrium points to consider in mathematical epidemiology. These equilibriums points are the Disease Free Equilibrium Point (DFE) and the Endemic Equilibrium Point (EEP).

3.5.1. Disease Free Equilibrium (DFE)

The disease free equilibrium point is the set of point(s) of system (1) obtained in absence of the virus. For our system, the disease free equilibrium (DFE) is the set of points $(T^0, T^{*0}, V_I^0, V_N^0) = (\frac{s}{\mu_1}, 0, 0, 0)$, corresponding to the maximal level of CD4$^+$ T -cells.

(i). Stability of DFE

Local asymptotic stability of nonlinear system about equilibrium points is governed by the stability matrix obtained from a linearized system about the equilibrium points. This stability is determined by the nature of eigenvalues of the linearization matrix. It is stable if all the eigenvalues are negative and unstable if at least one of the eigenvalues is positive. The linearization matrix J of system (1) about the DFE is given by;

$$J = \begin{pmatrix} -\mu_1 & ru_1 & -\bar{u}_1\beta T^0 e^{-\lambda\tau} & 0 \\ 0 & -(\mu_2+ru_1) & \bar{u}_1\beta T^0 e^{-\lambda\tau} & 0 \\ 0 & \bar{u}_1\bar{u}_2 K e^{-\lambda\tau} & -\mu_3 & 0 \\ 0 & \bar{u}_1 u_2 K e^{-\lambda\tau} & 0 & -\mu_4 \end{pmatrix} \quad (9)$$

where $\bar{u}_1$ and $\bar{u}_2$ are the complements of The characteristic roots of the equation $|J-\lambda I| = 0$ are all negative if the following condition is satisfied.

$$\frac{(1-u_1)^2(1-u_2)\beta K s e^{-2\lambda\tau}}{\mu_1\mu_3(\mu_2+ru_1)} < 1 \coloneqq R_0 e^{-2\lambda\tau} \quad (10)$$

For stability of DFE, we require that $R_0e^{-2\lambda\tau} < 1$. The

parameter defined in equation (10) is called basic reproductive ratio. It defines the ratio of new recruits into the infected $CD4^+$ T cells class versus clearance from the same class. This parameter determines whether the infection will grow to an epidemic or decay and become endemic.

(ii). Effects of Delay on the Stability of DFE

Our definition of reproductive ratio in equation (10) indicates that the parameter is a function of drug efficacy of both PI and RTI and delay τ. Fixing the value of drug efficacy $u_1 = u_2 = u$ (constant) in equation (10), the condition of stability $R_0 e^{-2\lambda\tau} < 1$ implies that;

$$\tau > \frac{1}{2\lambda}\log(R_0) \tag{11}$$

Since delay is always positive $\tau \geq 0$, stability of the system is guaranteed if the value of $R_0 e^{-2\lambda\tau}$ is less than unity.

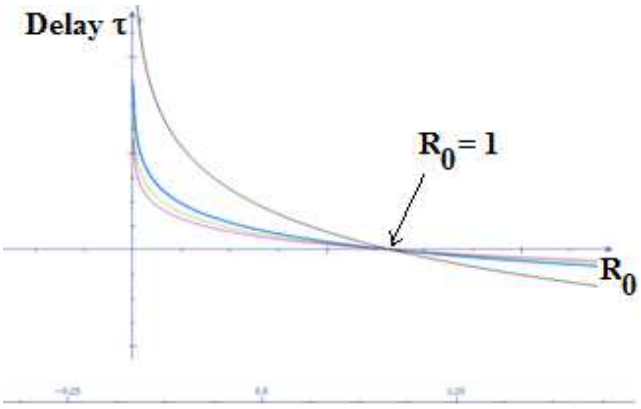


Figure 3.1. *Effects of Delay and R_0 on Stability of DFE.*

(iii). Effects of Drug Efficacy on the Stability of DFE

The graph of equation (10) is an exponential decay crossing the vertical axis at R_0 when $\lambda\tau = 0$. Since $\tau > 0$ for all time $t \geq 0$, the first quadrant of the graph in Figure 3.2 represents the region when $\lambda < 0$. This condition is achieved even at values of $R_0 > 1$. This implies that stability depends not only on delay but also on the value of drug efficacy u. The graph in Figure 3.2 shows that there is a critical value of drug efficacy $0 \leq u_c \leq 1$ such $R_0 e^{-2\lambda\tau} < 1$. At this point, DFE is stable and the disease will be eliminated. This assertion is confirmed by the following limit.

$$\lim_{\substack{u_1 \to 1 \\ u_2 \to 1}} \frac{(1-u_1)^2(1-u_2)\beta K s e^{-2\lambda\tau}}{\mu_1\mu_3(\mu_2 + ru_1)} = 0$$

The graph of reproductive ratio versus drug efficacy is illustrated in the figure below with a reference line of $R_0 e^{-2\lambda\tau} = 1$.

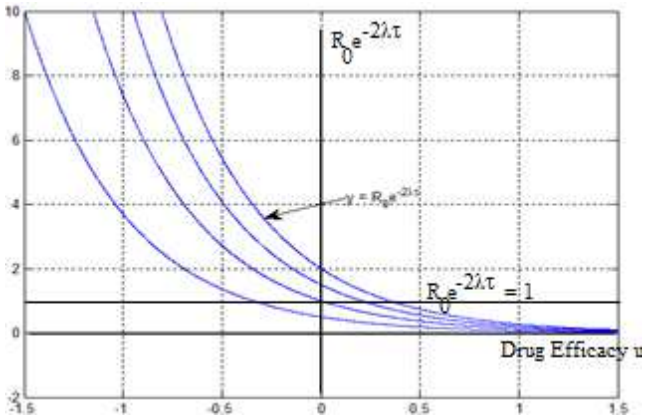


Figure 3.2. *Reproductive ratio R_0 versus $-\lambda$ eigenvalue.*

3.5.2. Endemic Equilibrium Point (EEP)

This is the critical point of system (1) which exists in presence of the disease, when $R_0 > 1$. Define the endemic equilibrium $\mathcal{E} := (T^e, T^{*e}, V_I^e, V_N^e)$. Computation from system (1) yields

$$\varepsilon := \left\{\frac{s}{\mu_1 R_0}, \frac{s(R_0-1)}{\mu_2 R_0}, \frac{\mu_1(\mu_2+ru_1)(R_0-1)}{\mu_2(1-u_1)\beta}, \frac{(1-u_1)\mu_2 K s(R_0-1)}{\mu_2\mu_4 R_0}\right\} \tag{12}$$

3.5.3. Stability of EEP

Like for the DFE, system (1) is stable if all the eigenvalues of linearization matrix about EEP are negative, and otherwise unstable. Analysis of stability is simplified by transforming the equilibrium point to the origin. This is facilitated by the transformation

$$W_1 = T - T^e, W_2 = T^* - T^{*e}, W_3 = V_I - V_I^e, W_4 = V_N - V_N^e \tag{13}$$

which transforms system (1) into;

$$\dot{W}_1(t) = -\mu_1 W_1 - (1-u_1)\beta[W_1(t)V_I^e + W_3(t-\tau)T^e] + ru_1 W_2 \tag{14}$$

$$\dot{W}_2(t) = (1-u_1)\beta[W_1(t)V_I^e + W_3(t-\tau)T^e] - (\mu_2 + ru_1)W_2(t)) \tag{15}$$

$$\dot{W}_3(t) = (1-u_1)(1-u_2)KW_2(t-\tau) - \mu_3 W_3(t) \tag{16}$$

$$\dot{W}_4(t) = (1-u_1)u_2 KW_2(t-\tau) - \mu_4 W_4(t) \tag{17}$$

Denote equations (14 – 17) as system (2). Assume a solution of the form $W(t) = W_0 e^{-\lambda t}$ and linearize system (2) about the equilibrium $(W_1, W_2, W_3, W_4) = (T^e, T^{*e}, V_I^e, V_N^e)$ to obtain,

$$\dot{\widehat{W}}(t) = A\widehat{W}(t) \tag{18}$$

where $= \begin{pmatrix} -(\mu_1 + aV_1^e) & ru_1 & -aT^e e^{-\lambda\tau} & 0 \\ aV_1^e & -b & aT^e e^{-\lambda\tau} & 0 \\ 0 & ce^{-\lambda\tau} & -\mu_3 & 0 \\ 0 & de^{-\lambda\tau} & 0 & -\mu_4 \end{pmatrix} \widehat{W} =$ $\left(W_1(t), W_2(t), W_3(t), W_4(t)\right)^{\mathrm{T}}, a = (1-u_1)\beta, b = (\mu_2 + ru_1), c = (1-u_1)(1-u_2)K, d = (1-u_1)u_2 K$

(i). Stability of EEP in Absence of Delay $(\boldsymbol{\tau = 0})$

In order to determine stability, we find the condition for which all the eigenvalues of the linearization matrix in system (18) are negative. The characteristic equation of the linearization matrix is

$$(\lambda + \mu_4)(\lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3) = 0 \qquad (19)$$

where; $a_1 = b + \mu_3 + \mu_1 + \frac{\mu_1 b(R_0-1)}{\mu_2}$, $a_2 = b(\mu_2 + 2\mu_3) + \mu_1\mu_3 + \frac{\mu_1(\mu_2+\mu_3)b(R_0-1)}{\mu_2}$ and $a_3 = \mu_1\mu_3 b(R_0 - 1)$. Clearly, one of the factors $\lambda_4 = -\mu_4$ in (19) gives a negative eigenvalue, and using Routh - Hurwitz condition, the other three eigenvalues are negative if the following condition is satisfied. For a polynomial of degree three, we require that, $a_1 > 0$, $a_1 a_2 - a_3 > 0$ and $a_3 > 0$. In this case all the conditions for stability are satisfied as required, hence we conclude that;

In absence of delay $\tau = 0$ and for $R_0 > 1$, the EEP is stable. This equilibrium creates people living with HIV/AIDS.

(ii). Stability of EEP with Delay

In presence of delay, the eigenvalues of matrix (19) are obtained from the following transcendental equation

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3\lambda e^{-2\lambda\tau} + b_4 e^{-2\lambda\tau} + b_5 = 0 \qquad (20)$$

where: $b_1 = a_1, b_2 = a_2 + b\mu_3, b_3 = -b\mu_3, b_4 = -b_3\left[\mu_1 + \frac{\mu_1 b(R_0-1)}{\mu_2} + \frac{(1-u_1)\beta s}{\mu_1 R_0}\right]$ and $b_5 = a_3 - b_4$.

The characteristics equation (20) compares to the one analyzed by Rebecca and Shigui, (2000) and we use the same approach to locate the roots of this equation analytically. Let $\lambda = \eta(\tau) + i\omega(\tau)$ be the eigenvalue of the characteristic equation (20). Since EEP of system (2) is stable in absence of delay, it implies that $Re(\lambda) = \eta(0) < 0$. As τ increases from zero, there is a value $\tau_0 > 0$ such that the EEP is stable for $\tau = [0, \tau_0)$ and unstable for $\tau > \tau_0$. At this threshold value, EEP loses stability and undergo Hopf bifurcation. The bifurcation value of $\tau_0 > 0$ occurs when $\lambda = \eta(\tau_0) + i\omega(\tau_0)$ is purely imaginary, that is $\eta(\tau_0) = 0$. Define this eigenvalue as, $\lambda = \pm i\omega_0$. Substituting this in to equation (20) and writing the exponential in terms of trigonometric ratios, we obtain the following equations,

$$Im: \omega_0^3 - b_2\omega_0 = b_3 \cos 2\omega_0\tau - b_4 \sin 2\omega_0\tau \qquad (21)$$

$$Re: b_1\omega_0^2 - b_5 = b_3 \sin 2\omega_0\tau + b_4 \cos 2\omega_0\tau \qquad (22)$$

Squaring each side of equations (21) and (22) and adding yields

$$\omega_0^6 + (b_1^2 - 2b_2)\omega_0^4 + (b_2^2 - 2b_1b_5)\omega_0^2 + b_5^2 - b_3^2 - b_4^2 = 0 \qquad (23)$$

Let $\alpha_1 = b_1^2 - 2b_2$, $\alpha_2 = b_2^2 - 2b_1b_5, \alpha_3 = b_5^2 - b_3^2 - b_4^2$ and let $v = \omega_0^2$. Substituting these in to Equation (23) reduces to;

$$v^3 + \alpha_1 v^2 + \alpha_2 v + \alpha_3 = 0 \qquad (24)$$

The following two propositions are made about stability and critical delay.

P_1: If in equation (24), $\alpha_1 > 0, \alpha_1\alpha_2 - \alpha_3 > 0$ and $\alpha_3 \geq 0$, then all the eigenvalues of equation (23) have negative real parts for all delay $\tau \geq 0$ and therefore the infected steady state ε for system (1) is stable for all $\tau \geq 0$.

The eigenvalue of equation (20) with $\eta(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$, is obtained from equations (21) and (22) as;

$$\tau_j = \frac{1}{\omega_0}\arccos\left(\frac{b_3\omega_0^4 + (b_1b_4 - b_2b_3)\omega_0^2 - b_4b_5}{b_4^2 + b_3^2\omega_0^2}\right) + \frac{2\pi j}{\omega_0} \quad j = 0, 1, 2, \ldots \qquad (25)$$

with the Hopf-Bifurcation critical value τ_0 as;

$$\tau_0 = \frac{1}{\omega_0}\arccos\left(\frac{b_3\omega_0^4 + (b_1b_4 - b_2b_3)\omega_0^2 - b_4b_5}{b_4^2 + b_3^2\omega_0^2}\right) \qquad (26)$$

P_2: Also if in equation (24) either $\alpha_3 < 0$ or $\alpha_3 \geq 0$ and $\alpha_2 < 0$, then ε is stable when $\tau < \tau_0$ and unstable when $\tau > \tau_0$ where the bifurcation value τ_0 is defined in equation (26).

4. Numerical Simulations and Results

The analytic solutions in section three are illustrated by numerical simulation of system (1) using a list of parameters and their estimated values given in Table 4.1. Much of these parameters were adopted from [6].

In the simulation of the system (1), the following initial values in each compartment at the onset of infection are assumed to apply, $\big(T(0), T^*(0), V_I(0), V_N(0)\big) = (1200, 0, 0.01, 0.01)$. Values of other parameters are provided in Table 4.1 below.

Table 4.1. *Table of Simulation Parameters and their Values.*

No	Parameter description	Symbol	Value
1	Production rate of uninfected $CD4^+$T cells (T)	s	10
2	Death rate of uninfected $CD4^+$T cells (T)	μ_1	0.02
3	Infection rate of uninfected $CD4^+$T cells (T)	β	0.00024
4	Death rate of Infected $CD4^+$T cells (T^*)	μ_2	0.26
5	Burst size of free virus from infected $CD4^+$ T cells.	N	13
6	Clearance rate of free infectious virus from the body	μ_3	2.4
7	Clearance rate of free noninfectious virus from the body	μ_4	2.4

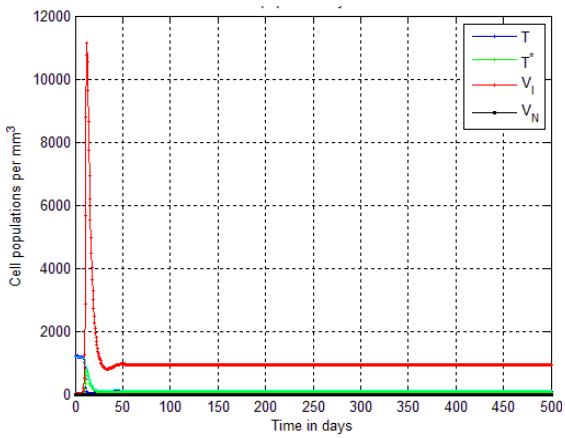
No	Parameter description	Symbol	Value
8	Efficiency of reverse transcriptase inhibition	u_1	$0 \leq u_1 \leq 1$
9	Efficiency of protease inhibition	u_2	$0 \leq u_2 \leq 1$
10	Rate of recovery of infected T cells due to treatment.	r	0.53
11	Time delay from infection to production of new viruses	τ	To be determined

Numerical and graphical representations of simulated results using MATLAB dde23 function are provided to validate the analytic theoretical solutions presented in the previous sections. The parameters given in Table 4.1 above are used in the simulation. Graphs presented begin with population dynamics of $CD4^+$ T cells and viral cells without treatment and with different levels of treatment beginning with 20%, 50% and the minimum threshold of 79% drug efficacy. Also, stability threshold values of drug efficacy and delay are simulated.

4.1. Cell Population Dynamics

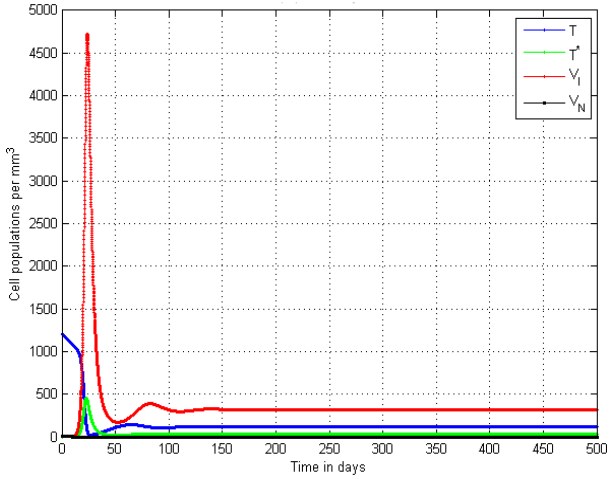
The population dynamics of the $CD4^+$ T cells and the viral cells are illustrated in Figure 4.1 and 4.2. The population of $CD4^+$ T cells is expected to fall while that of HIV is expected to increase due to its multiplicative burst size. The use of drugs is expected to reverse the scenario, depending on the efficacy of the drug. The HIV viral cells are elimination target. This is achieved through two ways, namely; use of highly effective drugs and use of time delay from infection (viral entry into the cell) to budding of infectious virus. If this time is prolonged, the drop in $CD4^+$ T cell population will not be depleted within a short time.

From Figure 4.1 (a), immediately after infection, the viral levels shoot to over $sN \approx 130$ times the level of $CD4^+$ T cells, where N is the burst size. Since the $CD4^+$ T cells die as a result, this trend will be reversed so that within in 40 days, the victim will succumb to death due to very low levels of $CD4^+$ T cells of below$200mm^{-3}$. In the second figure 4.1 (b), a treatment level of 20% efficacy improves the situation but because of continued presence of $CD4^+$ T cells, the HIV viral cells will also be maintained at about $400mm^{-3}$ while $CD4^+$ T cells remain stable at about $200mm^{-3}$.



Source: Author's Simulation Results.

Figure 4.1.(a). *Population Dynamics of T cells and Viral cells in absence of Treatment and no Immune Response.*

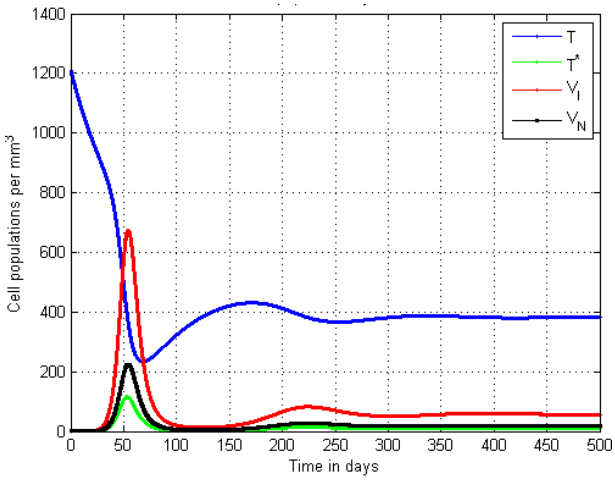


Source: Author's Simulation Results.

Figure 4.1.(b). *Population Dynamics of T cells and Viral cells with 20% Treatment Efficacy and in no Immune Response.*

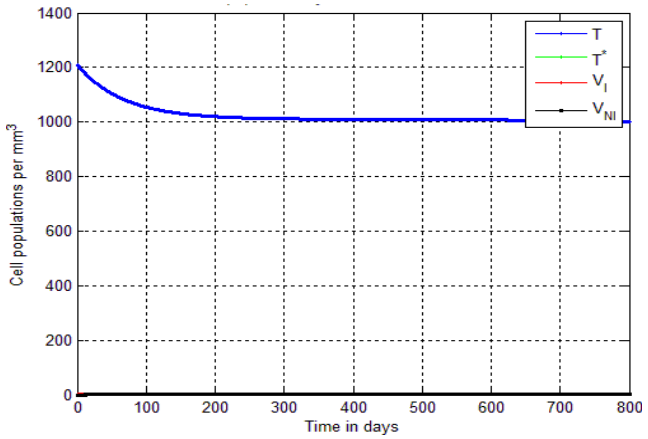
If drug efficacy is increased to 50%, the $CD4^+$ T cells levels increase to 400/mm^3 while viral cells drop to below 70/mm^3 as shown in Figure 4.2 (a) below. Here, the victim will live with HIV and remain sick ling due to opportunistic diseases.

Increasing drug efficacy to above minimum threshold value of 79%, the $CD4^+$ T cells rise to above 1000/mm^3. The original $CD4^+$ T cell level of 1200/mm^3 cannot be restored due to permanent infection of cells, that is, once a cell is infected, the viral material will remain integrated in the cell nucleus forever. However, the viral materials remain at very low undetectable levels in the blood stream as seen in Figure 4.2 (b) below.



Source: Author's Simulation.

Figure 4.2.(a). *Cell Population Dynamics at 50% Level of Drug Efficacy.*

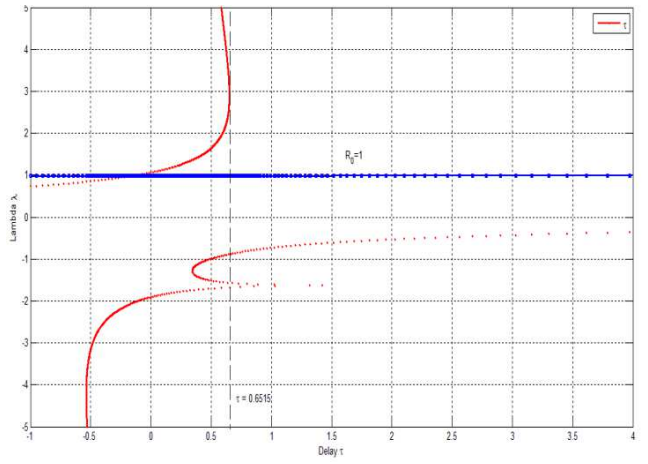


Source: Author's Simulation.

Figure 4.2.(b). *Cell Population Dynamics at 79% Level of Drug Efficacy.*

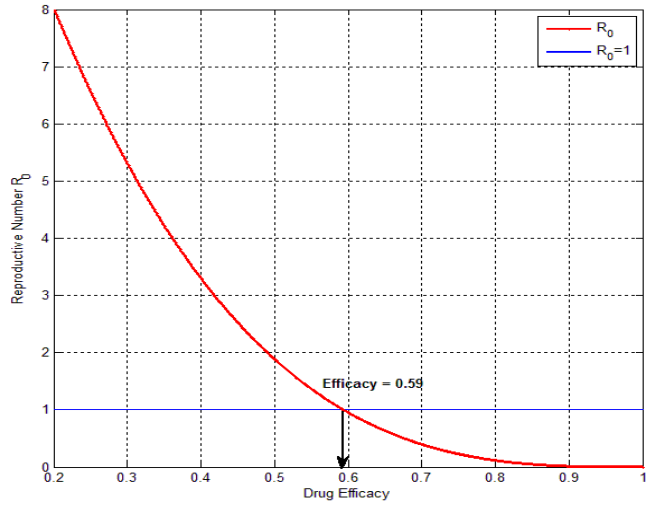
4.2. Drug Efficacy and Time Delay Stability Threshold Values

The desired threshold drug efficacy level is determined as the minimum required to reduce the reproductive ratio to less than one. Using the parameters in Table 4.1 above, this threshold value was found to be 59%. This threshold value is easily achieved when the delay is long. The minimum delay for stability of the system is 0.65 days or equivalent to about 16 hours. This is the desired time enough for the drug to be effective before the viral materials are replicated. The Figure below illustrates this. For values of delay less than 16 hours, the system is unstable. The value of delay $\tau = 0.65$ is the Hopf bifurcation value, where the system changes stability. The threshold value of delay and the corresponding threshold drug efficacy is illustrated in Figure 4.3 (a) and Figure 4.3 (b) below.



Source: Author's Simulation.

Figure 4.3.(a). *Threshold Value of Delay that Guarantee Stability of the System.*



Source: Author's Simulation.

Figure 4.3.(b). *Threshold Value of Drug Efficacy Corresponding to Minimum Delay of 0.65days.*

5. Summary of the Main Findings and Recommendations

The main objective of the study was to formulate an HIV-1 in vivo dynamics using delay differential equations and then study the effects of delay and efficacy on the stabilities of EEP and DFE. The effects of these two are analyzed analytical and numerical using MATLAB and parameter values from literature.

The disease free equilibrium in the absence of delay is affected by efficacy of both drugs used in our model: protease inhibitor and reverse transcriptase inhibitor since reproduction number which determine stability depend on their efficacy. The study reveals that a higher efficacy of RTI and a moderate efficacy of PI could easily lower reproduction number below one if other factors like death rates are kept constant. Numerical simulations using data from literature in the absent of delay puts PI and RTI efficacies at 0.59 and 0.59 respectively for reproduction number to go below one as earlier as possible. Any values of efficiency above this value for RTI may result in no change in the dynamics of DFE, and any value of PI below this value may not be as good in reducing reproduction number.

The delay on the onset of infectious virus production as an effect on DFE in that its stability depends on it. The study reveals that there is a critical value τ_0 of delay for which the DFE is stable. The value of this delay depends on θ and ω as define in the analysis of DFE in section three.

In fact for $\tau > 0$ the DFE is stable. Numerical solution of the model with delay using MATLAB DDE23 solver.

The characteristics equations of the linearization matrix of our model at EEP has both delay and recovery rate. The solution of this equation determines the stability of the EEP, therefore this two parameters affects EEP stability. The fact that this stability is affected by recovery rates implies that chemotherapy affect stability of EEP. The variable R_1 defined in the analysis of EEP is a function of drug efficacy

of both PI and RTI and the signs of the eigen-values is determined using the Routh Hurwitz condition for stability.

In presence of delay, the EEP stability changes with the change in the value of the delay. The analysis reveals that there is a critical value of delay $\tau > \tau_1 = 0.65$ days. This threshold value acts as a stability switch of the Hopf type as revealed by the transversality analysis similar to that in [10].

5.1. Discussions and Conclusions

The efficacy threshold on the two drugs in the study is established numerically to be 0.59 in order for the stability of the DFE. Biologically, stability of DFE means being free of infection after a small dose of the virus that comes into the body is cleared by chemotherapy. The finding agrees with the current practice in which prophylaxis is administered on suspecting exposure to HIV-1 virus within a small duration after exposure. However the efficacy of the drugs is still a moving target for researchers. These findings form a stronger theoretical foundation and therefore provide a basis for clinical trials. The current duration allowable after exposure is 24 hours or less (see for instance CDC and WHO website). This is the period that HIV-1 is thought to require before it can multiply to a number able to overcome the body immune system. The finding of this research suggest the time as 15hours on the onset of exposure, which is again within the allowable time for the administrations of prophylaxis. The model therefore can be used in the predictions of hiv-1 in vivo dynamics. In conjunctions with clinical trial, the model can be used in determinations of HIV-1 infection parameters like viral death rates, $CD4^+$T-cell turnover rates, viral clearance rate to mention a few.

Biologically, the stability of endemic equilibrium implies the co-existence of hiv-1 and the $CD4^+$T-cells in the plasma fluids of a person without the virus affecting the functioning of the $CD4^+$T-cells. This implies that the person will have HIV-1 and don't become sick due to this presence, very good news for the human populations because of the negative impact that HIV-1 sickness has on economic, social and political development. The study reveals that drug efficacy and time delays play an important role in the stability of EEP. That can also be seen in the analysis of EEP that drug potency play a role in lowering Reproduction number and therefore it is not only efficacy of a drug but it potency matters. The model finding again agrees with the current practice where post-exposure prophylaxis is administered to perturb HIV-1 progression in vivo.

The facts that delay has an effect on stability of EEP provide a strong theoretical foundation of the new practice of ARV treatment called STI (structural treatment interference). This treatment strategy involves a deliberate stopping of ARV treatment for sometime then recovering the treatment again. The strategy has many advantages for instance reduction in cost of treatment and toxicity to mention a few. The duration (delay) between treatments is what is important for effective ARV treatment of persons infected by HIV-1.

5.2. Suggestions for Further Research

This study has not exhausted all about HIV-1 in vivo dynamics. The effect of an individual's immune response is not captured. The carrying capacity of $CD4^+$T-cells and their proliferations is also a possible factor in another research on in vivo dynamics of HIV-1.

Clinical trials on efficacies of ARV treatment can now be carried around the threshold suggest by this study. Studies on ARV using STI regime can now be narrowed to the value of delays for stabilities of EEP.

Emphasis is hereby given that the above model results contains numerical simulation but still theoretical and it is recommended, that infectious disease models, which are to be used in control programmes, must have a realistic validation, which can only come from a comparison of their solutions and predictions with actual data collected from the field. This should, of course, apply to all disease control models.

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