Mathematical Theory and Modeling
ISSN 2224-5804 (Paper) ISSN 2225-0522 (Online)
Vol.3, No.7, 2013

Stability Criterion of Periodic Oscillations in a Mathematical Model of CTL Response to HIV Infection

Titus Rotich[*1], *Ronoh K. Nixon*[2], *Kandie K. Joseph*[2], *Mumo B. Nyamai*[2]

1. Center of Teacher Education, Mathematics Department, Moi University, Kenya,
P.O. Box 3900 - 30100, Eldoret, Kenya.

2. School of Biological and Physical Sciences, Mathematics Department, Moi University, Kenya,
P.O. Box 3900 - 30100, Eldoret, Kenya.

Abstract. With the continuing absence of HIV/AIDS cure, the current use of HAART (Highly Active Antiretroviral Therapy) has remained the only feasible control measure. Although it does not eradicate the disease completely, it maintains low viral load helping reduce infectivity of exposed individuals. The time lag between the cause (action of HIV virus) and the effect (reaction of the immune system) leads to periodic solutions representing oscillatory cell populations. In this paper we analyze a mathematical model that describes the dynamics of the immune system and a drug sensitive wild-type HIV variant. We study the transient and steady state behaviour of the model to assess the effects of time delay on the stability of periodic oscillations. The periodic solutions are stable if the value of time lag is within critical bounds, say $\tau \in [\tau_{min}, \tau_{max}]$. Using τ as a bifurcation parameter, the solutions become unstable when $\tau > \tau_{min}$. Drug efficacy is achieved at a critical value of time delay which leads to oscillator death of periodic solutions. The value of this parameter once determined, help in the management and control of the HIV pandemic through therapeutic intervention. Although parameter estimation which depends on the dynamics of viral and immune system interaction is highly individualistic, the bounds of time delay and minimum efficacy of the concoction will capture diverse reaction of many patients.

Keywords: Equilibrium, Basic reproductive number, Stability.

1. Introduction

Since HIV pandemic first became visible, enormous research on how to control the epidemic in terms of prevention of transmission and treatment has been conducted. Mathematical modeling helps in understanding the dynamics of infectious diseases. The use of mathematical model results, lesser clinical experiments is required in research and valuable information on the dynamics of pathogens is obtained helping in designing a more effective regimen. With the continued absence of HIV/AIDS cure, the use of the current combination of ARV's and vaccines have not been effective because of inadequate understanding of the basic principles underlying the interaction of the immune system in response to diverse set of pathogens.

Many mathematical models of HIV infection, notable among them is that of Perelson [2], Kirschner [3], and DeBoer, [14] studies the interactions between healthy T cells, actively infected T-cells, latently infected T-cells and free virus in the bloodstream. Their utility lies in the ability to predict an infected steady state. The models are used in examining the effects

E-mail: tisesko@yahoo.com*, nixonronoh@gmail.com, kandiekipchirchir@gmail.com, nyamaib@ymail.com.

that changes in parameters have on the outcome of the system over time, to determine which parameters are most important in disease progression, and further determine critical threshold values for these parameters. Second, treatment strategies can theoretically be simulated, allowing the design of clinical trials to be streamlined. This paper shows how parameter estimation and drug toxicity affects the efficiency of the mathematical model.

This is how the paper is arranged. Section 2 is the literature review, in section 3 we develop a model, and examine equilibrium points and the effect of delay τ on their stabilities and CTL response in presence of treatment. We obtain theoretical results showing minimum bounds of periodic drug supply and bounds of time lag required for effective control of HIV. In the last section we show numerical results, give a summary and a conclusion.

2. Literature Review

Various biological reasons lead to the introduction of time delays in models of disease transmission. Time delays are used to model the mechanisms in the disease dynamics (see for instance [12], [10]). The following several different biological mechanisms have been modeled by the introduction of time delays in epidemiological models: (i) Delay due to temporary immunity; which can be attained through immunization; naturally or in some cases maternal antibodies can be transmitted to a new born providing a certain level of immunity. In each case, the immunity period will vary, as some diseases provide almost life-long immunity while others give only a very short-lived non-susceptibility. Kyrychko and Blyuss (2005) [7] and Blyuss and Kyrychko (2010) [8] considered delay models with fixed immune period and varying immune period. It was proved that the disease-free equilibrium is locally stable and under some conditions, the endemic equilibrium is globally asymptotically stable. (ii) Delay caused by the latency in a vector; e.g. in the case of diseases like Malaria, Dengue fever and yellow fever, Trypanosomiasis and Bubonic plague, just to mention by a few, and (iii) Delay caused by latent period in host; The latent period is the time elapsed between exposure of a host to a pathogens, and the time of infectiousness of this host. Inclusion of time delay means that the models can be formulated as functional differential equations. One important aim is to investigate the effect of time delays on global properties of models. Lyapunov-LaSalle type theorem for delay differential equations Kuang [15] (1993) provides a useful method to establish global stability by suitable Lyapunov functional. Huang et al. [5] (2010) have considered two epidemiological models with the last two case delays and nonlinear incidence rate. A. S. Perelson et al [2], modeled HIV-1 infection that include intracellular delays and analyzed the effects of delays, combination antiretroviral therapy, and the dynamics of both infected and uninfected T cells. They showed that when the drug efficacy is less than perfect the estimated value of the loss rate of productively infected T cells is increased when data is fit with delay models, as compared to the values estimated with a non-delay model. D. Krischner and G. F. Webb [4] formulated a model to study treatment strategy in the chemotherapy of AIDS using AZT. They studied the role of treatment to perturb the system from progression to AIDS back to latency. They simulated treatment schedules for the consideration of treatment regimes. The following issues of chemotherapy were addressed; (i) daily frequency of treatment, (ii) early verses late initiation of treatment and (iii) intermittent treatment. The simulation suggested that (i) the daily period of treatment does not affect the outcome of the treatment, (ii) treatment should not begin until after the final decline of T cells begins and (iii) a possible strategy for treatment which may cope with side effects and/or resistance is to treat intermittently with chemotherapy followed by interruptions in the treatment during which a different drug or no treatment is administered.

Jonathan Erwin Forde [6] studied Delay Differential Equation Models in Mathematical Biology and showed that varying the delay length can change the stability characteristics of a steady state. So, the length of the delay acts as a bifurcation parameter. Anti Retrovirals (ARV's) have been known to reduce the amount of human immunodeficiency virus type 1 in

the blood plasma of infected patients to extremely low undetectable levels (see for instance [13], [9], and [1]). 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 [16] and in an attempt to maintain a low viral load of HIV virus, in this paper we study the periodicity of viral levels and determine the parameters necessary to control the periodic behaviour of the cells.

A biological model is formulated to describe the interaction of HIV retro viruses, the immune system and concentrations of therapeutic drugs in the human body. The model is used to analyze the virologic effect of drugs on HIV viral load and to establish immunologic effects of periodic supply of therapeutic drugs on CD4+ T cells. This involves the interaction of three groups of cells; CD4+T cells, virions and CTL cells in presence of antiretroviral drugs. Here, multiple delays ω are used to account for the time between viral entry into the target cell and the production of new virus particles and $\tilde{\tau}$ is used to model the time during which the target cell continue being productive, with $\tau = \tilde{\tau} + \omega$.

3 Theoretical Analysis

3.1 Treatment and CTL Model

In order to assess the dynamics of the viral and immune system interactions in an ideal situation, the effect of drugs and CTL response is incorporated onto the viral interaction with the CD4+T-cells. The HAART drug efficacy of the combination therapy against virus is defined to be $\epsilon(t)$. $\epsilon(t)$ is allowed to be a function of time for the sake of assessing periodic supply of chemotherapy. In order to mimic the effect of drugs and the immune system response on the dynamics of HIV virus, parameters measuring drug efficacy and CTL action are incorporated. The following variables and parameters are defined, to be used in the next model.

Definition of Variables:

T(t) the sum total of Naive T cells, $T_1(t)$ Infected and unproductive non-infectious CD4+T cells, $T_2(t)$ Population of productive CD4+T cells infected by virus type 1 and V(t) Population of infectious HIV-1 virus;

Definition of Parameters:

(i) *s* represents the constant rate of production of uninfected CD4+T-cells.

(ii) *r* is the maximum rate of proliferation of CD4T-Cells due to the presence of antigen, with a maximum uninfected CD4+T-cell concentration of T_{max}.

(iii) β is the rate at which CD4+T cells are infected by the virus.

(iv) *N* is the constant rate at which new virions are produced during cell burst.

(v) $(1-\gamma)$ is the proportion of virus which remain faithful during transcription to the original wild strain and is the complimentary proportion of virus which significantly mutate.

(vi) μ is the natural death rates of the i[th] class, i = $T(t), T_1(t), T_2(t)$ and $V(t)$.

(vii) ω and $\tilde{\tau}$ is the constant time lag modeling latent period and infective period respectively.

(viii) *h* is the CTL induced death rate of infected T cells.

(ix) $\grave{o}(t)$ time dependent periodic drug efficacy.

(x) *a* models the effectiveness of CTL in reducing the viral infectivity of naive CD4+T cells.

(xi) *b* is the effectiveness of CTL in reducing the virus burst size.

Model assumptions

In order to have explicit dynamical relations we make the following model assumptions:

A1 The model assumes that there is cell mediated response and no hormonal immune response.

A2 The model does not distinguish infection by different viral strains.

A3 Any uninfected cell once infected will remain infected forever.

A4 Only CD4+T cells are infected and up on infection, cells become latent for some fixed time then become productive for time $\tau = \omega + \tilde{\tau}$ units.

A5 There are only four interacting cell species $T(t), T_1(t), T_2(t)$ and $V(t)$.

A6 Mass action principle, where interaction is assumed to be a function of interacting populations is employed or in proportion to the product of abundances of T cells and viral load.

3.2. Model Equations

The definition of parameters result in the following Model Equations,

$$\frac{dT}{dt} = s + rT(1-\frac{T}{K}) - (1-\gamma)(1-\grave{o}(t))\beta e^{-a}TV - \mu_T T$$

$$\frac{dT_1}{dt} = (1-\gamma)(1-\grave{o}(t))\beta e^{-a}TV - (1-\gamma)(1-\grave{o}(t))\beta e^{-a}T(t-\omega)V(t-\omega)e^{-\mu_T\omega} - (\mu_1 + h)T \qquad (1)$$

$$\frac{dT_2}{dt} = (1-\gamma)(1-\grave{o}(t))\beta e^{-a}T(t-\omega)V(t-\omega)e^{-\mu_T\omega} - (1-\gamma)(1-\grave{o}(t))\beta e^{-a}T(t-\tau)V(t-\tau)e^{-\mu_T\tau} - (\mu_2 + h)T_2$$

$$\frac{dV}{dt} = (1-\gamma)(1-\grave{o}(t))N\beta T(t-\tau)V(t-\tau)V(t-\tau)e^{-(\mu_1\tau+b)} - \mu_v V$$

3.3. Model Description

The model is briefly explained as follows. The first term of the first equation of system (1) represents a constant source of new uninfected CD4+ T-cells from the Thymus. The next term represents a logistic growth rate of CD4 cells with a carrying capacity of $K = T_{max}$, this is then followed by a term which represents the infection of CD4+ T-cells by the virus and is determined by the rate of encounters of CD4+ cells by the virus. This is based on the law of mass action with β as the probability of infection and $(1-\grave{o}(t))$ measuring the proportion of infectious viruses that eludes the effect of combination therapy and γ the proportion of HIV mutant strain that cannot be prevented by HAART. The term e^{-a} represents the effectiveness of CTL to prevent infectivity. The last term μ_T is the natural death rate. The second equation models the population of latently infected unproductive CD4+ T-cells with an exposure latent period of $\omega > 0$ before they become productive. The probability that the infected cell survive until it becomes active and produce viruses after time $\omega > 0$ (incubation period) is given by $e^{-\mu_T\omega}$. The last term μ_1 represents the natural death rate augmented by the accelerated death rate due to the action of CTL given by *h*. The third equation of system (1) models the rate of change of actively infected CD4+ cells with the probability $e^{-\mu_T\tau}$ that they continue surviving and actively producing viruses for time $\tau > 0$. The last term also represents augmented natural death rate due to the action of CTL. The last equation of (1) models the population of free virus in the blood plasma. It is assumed that only actively infected CD4 cells produce viruses

at a rate *N* per cell over the entire life time of the cell $\frac{1}{\tau}$ with $\tau > \omega$ representing the total time of latency and infectivity (production of virus). The equation monitoring the rate of change of HIV specific CTL population is not included. Here it is assumed that the first equation captures the total T-helper cells which later differentiate into CD4+T-cells, HIV specific CD8+T-cells and memory cells.

3.4 Model Preliminary Analysis

Some basic properties of solutions to the system (1) are first established. These include positivity, boundedness of solutions and stability of steady states.

Initial Conditions

The initial conditions for the system (1) at time t= 0 are

$$T(0) = T_0 \geq 0,\ T_1(0) = T_{10} \geq 0,\ T_2(0) = T_{20} \geq 0,\ V(0) = V_0 \geq 0 \qquad (2)$$

A positive quadrant is defined in the following as,

$$R_{+0} = \{(T, T_1, T_2, V) \mid T \geq 0, T_1 \geq 0, T_2 \geq 0, V \geq 0\} \text{ and}$$
$$R_{+} = \{(T, T_1, T_2, V) \mid T > 0, T_1 > 0, T_2 > 0, V > 0\} \qquad (3)$$

It is then shown that the variables in model (1) are non negative for all time t > 0 and proven that all solutions with positive initial data as defined in (2) will remain positive for all time t > 0 and are bounded.

3.5 Positivity and Boundedness of Solutions

Model (1) describes human cell population and therefore it is very important to prove that all the state variables $T(t), T_1(t), T_2(t)$ and $V(t)$ are non-negative for all time t. It is proven that all solutions of system (1) with positive initial data will remain positive for all time $t > 0$ and are bounded in $R = R_{+0} + R_{+}$.

Theorem 3.1 *Let the initial data be* $T(s) = T_0(s) \geq 0, T_1(s) = T_{10}(s) \geq 0, T_2(s) = T_{20}(s) \geq 0, V(s) = V_0(s) \geq 0$ *with* $T_0(s) \geq 0, T_{10}(s) \geq 0, T_{20}(s) \geq 0$ *and* $V_{10}(s) \geq 0,\ s \in [-\omega, 0)$ *with* $T_0(0) > 0, T_{10}(0) > 0, T_{20}(0) > 0$ *and* $V_0(0) > 0$. *Then the solutions* $T(t), T_1(t), T_2(t)$ *and* $V(t)$ *of system (1) are positive for all* $t > 0$. *For the model system (1), the region* R *is positively invariant and all solutions starting in* R_{+0} *approach enter or stay in* R.

Proof. First, it is proven that T(t) is positive for $t \geq 0$. Assuming the contrary and letting $t_1 > 0$ be the first time such that $T(t_1) = 0$, by the first equation of system (1), we have $T'(t_1) = s > 0$, and hence T(t) < 0 for $t \in (t_1 - \varepsilon, t_1)$ and sufficiently small $\varepsilon > 0$. This contradicts the assumption that T(t) > 0 for all $t \in [0, t_1)$. It follows that T(t) > 0 for all t > 0 as long as T(t) exists. Secondly, from equation (2) of system (1), $(\mu_1 + h) > 0$

and thus; $\frac{dT_1(t)}{dt} + (\mu_1 + h)T_1(t) = (1-\gamma)(1-\text{ò})\beta e^{-a}T(t)V(t) - (1-\gamma)(1-\text{ò})\beta e^{-a}T(t-\omega)V(t-\omega)e^{-\mu_T\omega}$,

and given a bounded positive initial history on an interval $[a-\omega,\ a]$,

$$T_1(a+\omega) = e^{(\mu_1+hC)a}T_1(a) + \int_a^{a+\text{ò}} (\gamma(1-n_{rt})\beta e^{-aC}TV - \gamma(1-n_{rt})\beta e^{-aC}T_\omega V_\omega e^{-\mu_T\omega})e^{-(\mu_1+hC)(a+\text{ò}-s)}ds.$$

The right hand side of the last expression is positive and definite for $\grave{o} \in [0, \omega]$, since the integrand is also bounded. This result can be iterated to show that $T_1(t)$ is positive and finite for $t \geq a - \omega$. Using the same argument, it can be shown that the third and fourth equation of (1) is positive and finite.

Boundedness

Its next shown that positive solutions of (1) are ultimately uniformly bounded for $t \geq 0$. From the first equation of system (1), the following is obtained;

$T^{'}(t) \leq s + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \mu_T T(t)$ and $\limsup_{t\to\infty} T(t) \leq \frac{s}{\mu_T}$.

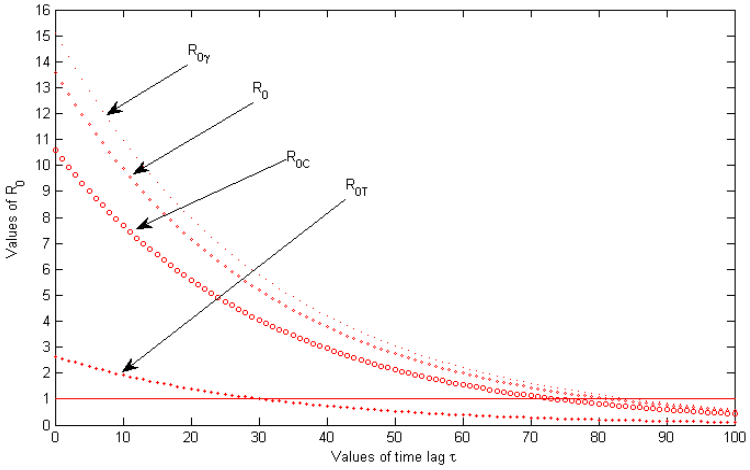
Define X(t):=T(t)+T_1(t) then $X^{'}(t) \leq s + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \tilde{\mu} X(t)$ where $\tilde{\mu} = min\{\mu_T, \mu_1 + h\}$, thus $\limsup_{t\to\infty} X(t) \leq \frac{s}{\tilde{\mu}}$. Also let Y(t):=T(t)+T_1(t)+T_2(t), then $Y^{'}(t) \leq s + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \hat{\mu} Y(t)$ with $\hat{\mu} = min\{\mu_T, \mu_1 + h, \mu_2 + h\}$. Therefore, $\limsup_{t\to\infty} Y(t) \leq \frac{s}{\hat{\mu}}$.

Similarly, adding all equations of system (1), the following is obtained;

$Z^{'}(t) \leq s + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \breve{\mu} Z(t)$, where $Z(t) := T(t) + T_1(t) + T_2(t) + \frac{V(t)e^{(b-a)}}{N}$ and $\breve{\mu} = min\{\mu_T, \mu_1 + h, \mu_2 + h, \mu_v\}$ and $\limsup_{t\to\infty} Z(t) \leq \frac{s}{\breve{\mu}}$. Therefore, T(t),$T_1$(t), T_2(t) and V(t) are ultimately uniformly bounded in R.

3.6 Basic Reproductive Number

The Basic Reproductive Number R_0 is defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period, in a population of purely susceptible individuals. In our context, R_0 is defined as the number of secondary infectious HIV viral particles produced by one virus introduced into the blood system of uninfected individual with purely naive and susceptible population of CD4+T cells. This number is a measure of the potential for disease spread within a population. This concept is fundamental to the study of epidemiology and within-host pathogen dynamics since it serves as a threshold parameter that predicts whether an infection will spread or not. From this definition, it is immediately clear that when $R_0 < 1$, each infected cell produces, on average, less than one new infected cell failing to replace themselves, and we therefore interpret to mean that the infection will be cleared from the population. If, on the other hand, $R_0 > 1$, the number of infected cells will increase with each generation and the pathogen is able to invade the susceptible cell population. In the study of R_0, we can determine which parameters and at what magnitude that they contribute in reducing R_0 below one, providing important guidance for public health initiatives [12]. We compute the basic reproductive number, R_0 following the next-generation operator approach by Dickmann et al., 1990 [11], Van den Driesche and Watmough, 2002 [12]. Using this approach, R_0 is obtained as



$$R_0 = \rho(FV^{-1}) \tag{4}$$

where the matrix FV^{-1} is referred to as the next generation matrix for the system at the disease-free equilibrium and $\rho(A)$ denotes the spectral radius of a matrix A computed using the Euclidian norm.

3.6.1 Disease Free Equilibrium (DFE)

The DFE of system (1) is given by $E^0 = \{(T^0, T_1^0, T_2^0, V^0) \mid (T^0, 0, 0, 0\}$ where

$$T^0 := \frac{1}{2}\left\{\frac{K(r-\mu_T)}{r} \pm \sqrt{\frac{K^2(r-\mu_T)^2}{r^2} + \frac{4sK}{r}}\right\}$$

The reproductive number R_{0TC} is computed as defined in (4) and the following is obtained;

$$R_{0TC} = \frac{(1-\gamma)(1-\grave{o}(t))N\beta T^0 e^{-(\mu_1\tau+b)}}{\mu_v}. \tag{5}$$

Note that in absence of treatment that is $\grave{o}(t) = 0,$ the basic reproductive number in (5) reduces

Figure 3.1 Comparison of values of Reproductive numbers

Source: Author

to $$R_{0C} = \frac{(1-\gamma)N\beta T^0 e^{-(\mu_1\tau+b)}}{\mu_v} \tag{6}$$

and in absence of CTL response $\mathrm{b} = \mathrm{a} = 0$, the basic reproductive number reduces to

$$R_0 = \frac{(1-\gamma)N\beta T^0 e^{-\mu_1\tau}}{\mu_v} \tag{7}$$

The basic reproductive number R_{0C} in (6) incorporate the effect of HIV specific CTL response to the infection and R_0 in (7), it measures the reproductive number without any intervention of viral reproduction. By comparison the three reproductive ratios satisfy the inequality $R_{0T} \le R_{0C} \le R_0$. This clearly shows that therapy and presence of HIV suppressive factors produced by CTL control the viral load during HIV infection. Other factors like the presence of HIV drug resistant mutant strain γ is mathematically seen to increase the value of R_0 . Define $R_{0\gamma} := \frac{N\beta T^0 e^{-\mu_1\tau}}{\mu_v}$, then it is clear that $R_0 \le R_{0\gamma}$ for all $\gamma \in (0,1)$. Therefore, the inequality $R_{0T} \le R_{0C} \le R_0 \le R_{0\gamma}$ is satisfied.

3.7 Stability

Stability of this system is determined by examining the sign of the dominant eigenvalue of the linearization of the model equations about the equilibrium point and since $R_0 - 1$ is the dominant eigen-value, we summarize stability with the following Theorem whose proof can be easily provided.

Theorem 3.2 *If* $R_0 \leq 1$, *then* E^0 *is the only equilibrium in* R *and it is globally asymptotically stable. Here the Viral clearance is achieved. If* $R_0 > 1$, *then* E^0 *is unstable and there exist an endemic equilibrium, say* E^e *where the patient remains as an asymptotic carrier.*

Following this theorem, the attention focuses on to the stability parameter R_0 and the parameters that affect its value are established. Notable among them is the drug efficacy and time delay. Time delay is known to destabilize once stable equilibrium [16] and since time delays are inevitable in life, the delay $\tau > 0$ is used as a bifurcation parameter and the stability of the Disease Free Equilibrium Point (DFE) $\boldsymbol{E^0}$ investigated when $\tau > 0$ is varied. Of importance is any critical values of $\tau > 0$ at which the basic reproductive number of equation (1) transitions from being less than one to being greater than one. If this is to occur, there must be a critical value of $\tau > 0$, such that the Reproductive number R_0 is less than unity. At the onset of infection, the virus population shoots to a very high value then drops. Meanwhile, the CD4+T-cells drops then begin to increase as illustrated in Figure 3.2 (a) below. With a small delay, the course become periodic as depicted in Figure 3.2 (b).

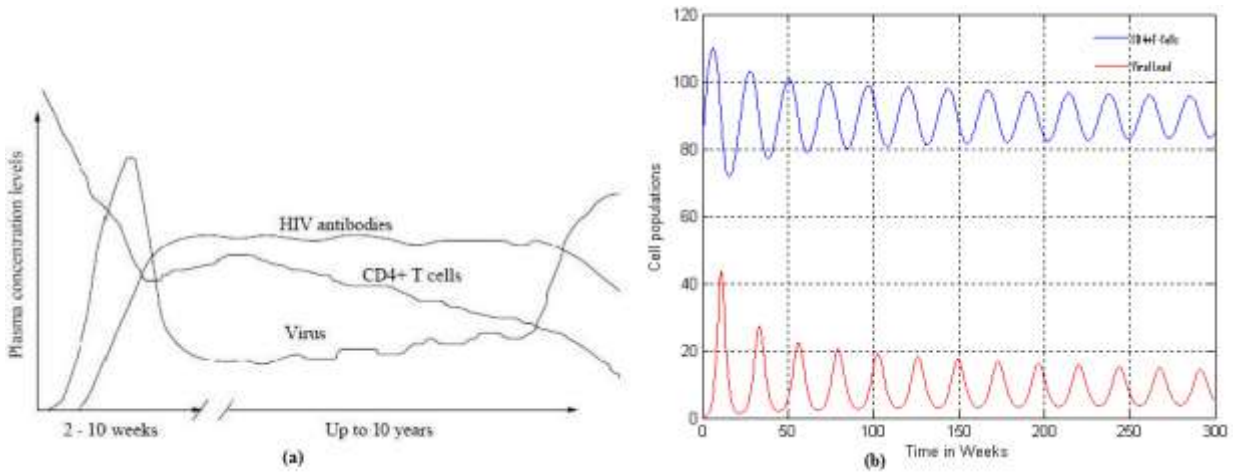


Fig. 3.2(a) Plasma concentration of CD4+ T cells, CTL and HIV Virus and Fig. 3.1(b) Cell population in the Blood Plasma showing periodic oscillations in the course of time.

Source: Fig 3.1(a). Z. H. Zhou, B.V.V Prasad, J. Jakana, F.R. Rixon, W. Chiu Baylor College of Medicine, Journal of Molecular Biology

The analysis of the value of R_0 for various values of $\tau > 0$ and drug efficacy ε > 0 is given in Figure 3.3. We can clearly see that the determination of critical delay depends on the value of drug efficacy. For example, at

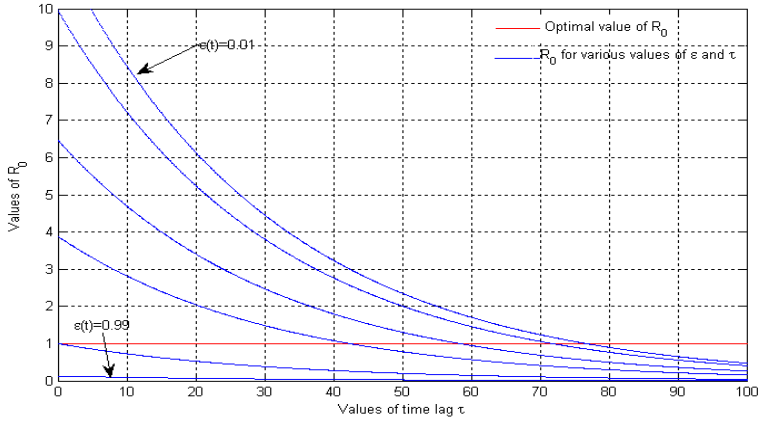


Fig. 3.3 Values of R_0 for various values of drug efficacy ò and delay τ .

Source: Author

$ò = 0.75$, the time delay must be greater than 30 hours for the reproductive number to be less than one.

3.8 Periodic Supply of Therapeutic drugs

As stated earlier, drug efficacy $ò(t) \in [0\ 1]$ is periodic rendering the basic reproductive number to be periodic as well. Of interest is the bound of the parameter $ò(t)$ which guarantees stability.

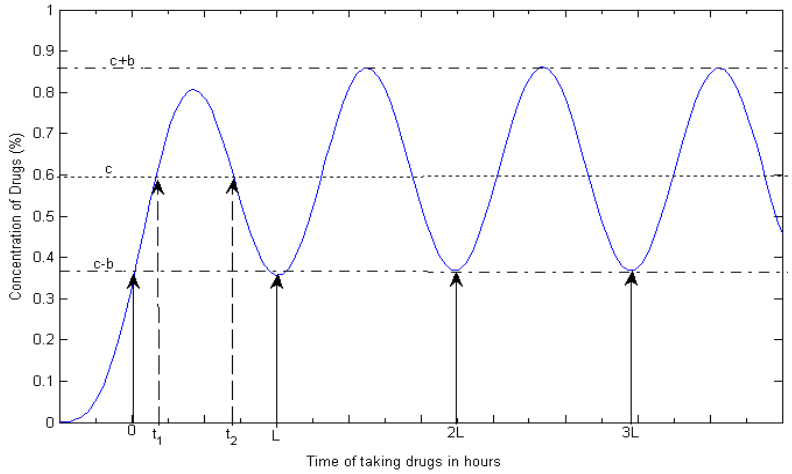


Fig.3.4 Drug Concentration in Blood Plasma C showing periodic intake at multiples of time.

Source: Author

With periodic intake of drugs and the effect of decay, the concentration of drugs in the blood plasma is periodic as depicted in Figure 3.4. where it is assumed that the drugs are taken after every *L* time units and the concentration fluctuates with amplitude of b from an average concentration which stabilizes at *c*.

If one lets $D(t)$ represent the periodic input concentration, then;

$$\grave{o}(t)=\begin{cases} c-b, & if \;\; 0\le t\le t1 \\ c+b, & if \;\; t1\le t\le t2 \\ c-b, & if \;\; t2\le t\le L \end{cases} \tag{8}$$

The period L is in hours. The concentration $\epsilon(t)$ can be represented in Fourier series of the form,

$$\grave{o}(t)= a_0+\sum_{n=1}^{\infty}\left(a_n\cos\frac{2n\pi t}{L}+b_n\sin\frac{2n\pi t}{L}\right), \tag{9}$$

Where a_n and b_n are the Fourier coefficients and a_0 is a constant term. Since $\grave{o}(t)$ depends on bioavailability of drugs and concentration in the required site, the graph of drug efficacy corresponds to the sketch in Figure 3.4. Since the graph is even, $b_n=0$ while

$$a_0=\frac{1}{L}\int_0^L \grave{o}(t)dt \;=c+b+2b\left(\frac{(t1-t2)}{L}\right). \tag{10}$$

and

$$a_n=\;\frac{1}{L}\int_0^L \grave{o}(t)\cos\frac{2n\pi t}{L}dt\;=\frac{4b}{n\pi}\cos\left(\frac{n\pi}{L}(t1+t2)\right)\sin\left(\frac{n\pi}{L}(t1-t2)\right). \tag{11}$$

Hence Equation (9) reduces to,

$$\grave{o}(t)= c+b\left(1+\frac{2t1}{L}-\frac{2t2}{L}\right)+\sum_{n=1}^{\infty}a_n\cos\frac{2n\pi t}{L}dt \tag{12}$$

Let $\grave{o}^0:=c+b\left(1+\frac{2t1}{L}-\frac{2t2}{L}\right)$ and

$$\alpha(t):=\sum_{n=1}^{\infty}a_n\cos\frac{2n\pi t}{L}dt\;\;=\frac{4b}{n\pi}\sum_{n=1}^{\infty}\frac{1}{n}\cos\left(\frac{n\pi}{L}(t1+t2)\right)\sin\left(\frac{n\pi}{L}(t1-t2)\right)\cos\left(\frac{2n\pi t}{L}\right) \tag{13}$$

then $\grave{o}(t)=\grave{o}^0+\alpha(t)$. From Equation (13) we observe that $|\alpha(t)|\le\frac{4b}{\pi}$. The drug supply at any instant satisfy the inequality,

$$\grave{o}^0-|\alpha(t)|\le\grave{o}(t)\le\grave{o}^0+|\alpha(t)|. \tag{14}$$

It is known practically that $\grave{o}(t)>0$. Therefore inequality (14) means that $\grave{o}^0-|\alpha(t)|>0$. That is,

the amplitude of the drug concentration graph fluctuation about *c* must be small in comparison to $\grave{o}^0$. From Equation (5) it is seen that viral eradication is only possible if

$$\grave{o}(t)\ge 1-\frac{\mu_v e^{(\mu_1\tau+b)}}{(1-\gamma)N\beta\tilde{T}^0} \tag{15}$$

Comparing with inequality (14), the bounds are obtained that the amplitude of drug concentration

must be within for the reproductive ratio $R_0<1$, a necessary condition for eradication of viral infection. The following proposition is thus made.

Proposition 2 *Viral Eradication is possible with the use of ARV's if the drug efficacy* $\grave{o}(t)>0$ *satisfies the inequality*

$$\dot{o}^0 - |\alpha(t)| \le 1 - \frac{\mu_v e^{(\mu_1 \tau + b)}}{(1-\gamma) N \beta \tilde{T}^0} \le \dot{o}^0 + |\alpha(t)|. \quad (16)$$

4. Numerical simulations

In the simulation of the model system (1), the parameters in Table 1 below, will be used. Assumed are the following initial proportions of cell populations of each compartment when the epidemic is first tested in a person. $T(0) = 100,\ T_1(0) = 0.01,\ T_2(0) = 0.01,\ V(0) = 0.001$.

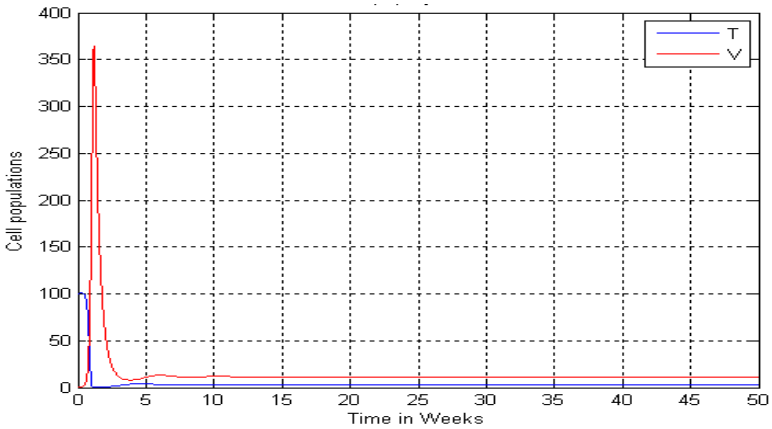
Table 1. Data for the CD4, CTL and Viral cell Interaction with Therapy model

ıeter definition		ol	
ant recruitment rate of naive CD4	s		3
ant recruitment rate of CTL clone	s_1		-3
num growth rate of CD4	r		$mm^{-3}day^{-1}$
ion rates of CD4 by V	β		$nm^{-3}day^{-1}$
tion of viral infectivity by CTL	a		$nm^{-3}day^{-1}$
al death rate of naive CD4+T-cells	μ_T		$nm^{-3}day^{-1}$
al death rates of T_1, T_2, V	μ_1, μ_2, μ_v		2, 0.028, 2.64) $mm^{-3}day^{-1}$
RT or ARVs' drug efficacies (Variable)	$\epsilon(t)$		0.99] $mm^{-3}day^{-1}$
rtion of mutation during viral transcription (Variable)	γ		0.99] $mm^{-3}day^{-1}$
burst size	N		$m^{-3}day^{-1}$
iveness of CTL in reducing viral burst size	b		$nm^{-3}day^{-1}$
nduced death rates of infected CD4+T-cells	h		02 $mm^{-3}day^{-1}$
al growth rate of CTL	r_1		$mm^{-3}day^{-1}$
rate of CT L	δ		$mm^{-3}day^{-1}$
delay during exposure and infectiousness of CD4	$(\omega, \tilde{\tau})$		2) day^{-1}

Using the parameters and variables defined in Table 1, the general dynamics of HIV virus and CD4+T- cells for model (1) during infection is illustrated in Figure 4.1. In absence of reatment and CTL action $a \ll 1$ and $b \ll 1$, the cell interaction is oscillatory but eventually CD4+ T-cells drop much below the levels of virus cells as shown in Figure 4.2.

Figure 4.1 Dynamics of cell populations without therapy.

Source: Author



Under treatment, with minimum amplitude of drug supply as low as 40%, the virus stabilizes and coexist within the host as illustrated in Figure 4.2.(b). Increasing drug efficacy above 60%, with the action of CTL as low as a = 0.02 and b= 0.05, the

viral population levels drop drastically but still exist as depicted in Figure 4.3.(a). Drug efficacy above 85% with little increase in CTL response, the viral levels is encouraging even with lower drug efficacy. See Figure 4.3.(b). The desired results is obtained.

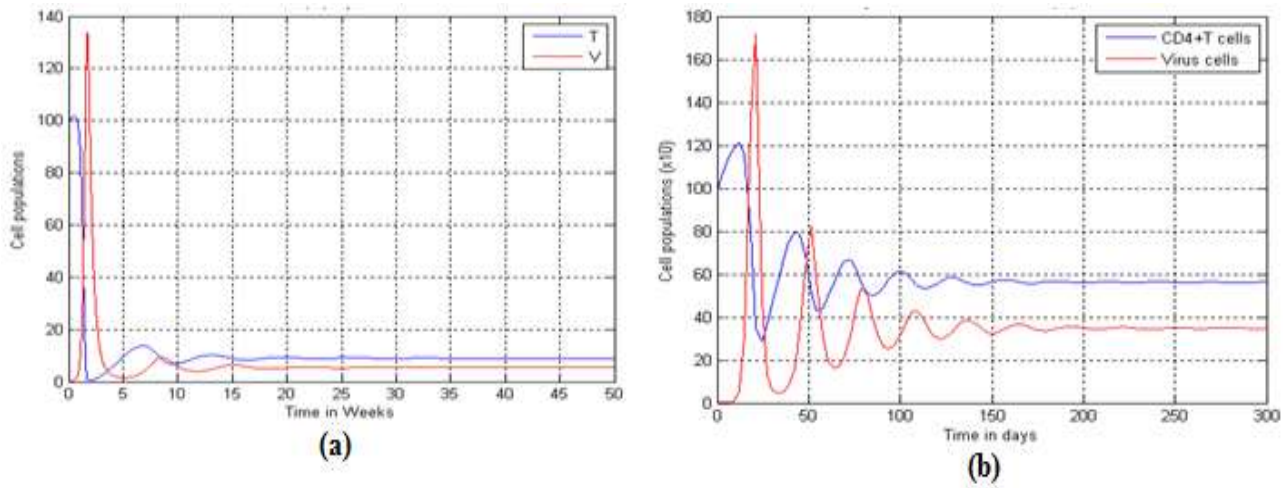


Figure 4.2. (a) Coexistence of HIV within host at less than 40% drug efficacy. (b) Coexistence of HIV within host at less than 60% drug efficacy.

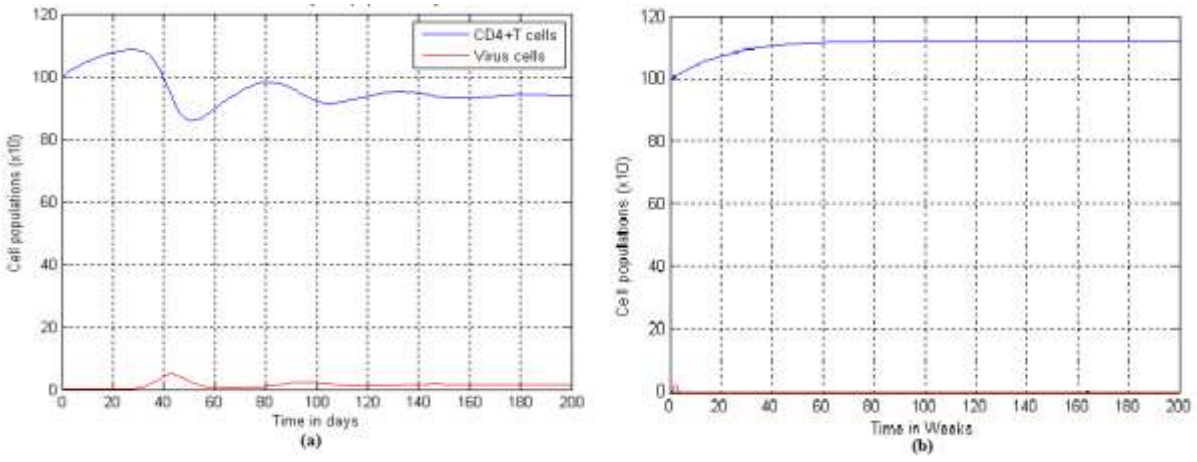


Figure 4.3 (a) Coexistence of HIV within host at less than 70% drug efficacy. (b) Treatment at 70% drug efficacy and time delay greater than 30 hours with as low effect of CTL as a =0.07 and b =0.05 and induced death rate as low as h =0.00002.

5. Conclusion and Recommendation

From the analysis given it is noted that among the parameters which affect the management of HIV virus at very low levels, time delay and drug efficacy are the major contributors of stability condition. Since the lifespan of infected cell cannot be stretched beyond a certain limit, the minimum time delay before the infected cell become productive is given as τ_{min} and the maximum lifespan of the cell will be our τ_{max}. Also at this range of time delay, the value of drug efficacy which is effective within an interval [50%, 70%]. Thus the administration dosages of treatment drugs must observe these critical levels. It is at this levels that the drug manufacturers must ensure that the concoction must contain ingredients necessary to cause the desired effects of prolonging the lifespan of infected cell to above τ_{min} and the ability of the drug to prevent infection and reduce burst size must be within the stated range. Although these measures are highly individualized, the guidelines can

apply to most affected individuals and we recommend that further research on the same be done to include other necessary and significantly important parameters.

In this work, other parameters which contribute to the dynamics of HIV virus were not considered and such extensions are recommended to suit the ideal situation. The dynamics of mutant virus were also ignored since they are drug resistant and cannot be affected by both time delay and drug efficacy which were fundamental to this study.

References

[1] A. S. Perelson, P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41 (1999) 3.

[2] A. S. Perelson, D.E. Kirschner, R. De Boer, Dynamics of HIV Infection of CD4. T-cells, Math. Biosci. 114 (1993) 81.

[3] D. E. Kirschner, (1996). Using mathematics to understand HIV immune dynamics, Notices Am. Math. Soc. Vol.43. 191.

[4] D. E. Kirschner, and G. F. Webb,(1996). A Model for Treatment Strategy in the Chemotherapy of AIDS., Bulletin of Mathematical Biology, Elsevier Science Inc. Vol. 58, No. 2, pp. 367 -390.

[5] G. Huang, Y. Takeuchi, Ma W (2010) Lyapunov functional for delay differential equations model for viral infections. SIAM J Appl. Math 70:26932708.16

[6] J. E. Forde., Delay Differential Equation Models in Mathematical Biology., A Doctor of Philosophy dissertation. The University of Michigan. (2005).

[7] K. B. Blyuss , Kyrychko Y. N. (2005) Global properties of a delay SIR model with temporary immunity and nonlinear incidence rate. Nonlinear Anal RWA 6:495507

[8] K. B. Blyuss , Kyrychko Y. N. (2010) Stability and bifurcations in an epidemic model with varying immunity period. Bull Math Biol. 72:490505

[9] M. Markowitz, Y. Cao, A. Hurley et al. (1996). Triple Therapy with AZT, 3TC and Ritonavir in 12 subjects newly infected with HIV-1. XI International Conference on AIDS, Vancouver, 11 July 1996, Abstr. Th.B.933.

[10] O. Arino, M. L. Hbid, E. Ait Dads., Delay Differential Equations and Applications. Springer, Series II: Mathematics, Physics and Chemistry - Vol. 205, (2006).

[11] O. Diekmann, J. A. P. Heesterbeek, and Metz, J. A. J. (1990) On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases. J. Math. Biol. 35, 503522.

[12] P. Van-den Driessche, and J. Watmough, (2002) Reproduction numbers and sub-threshold
endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 2948.

[13] R. M. Gulick., J. Mellors., D. Havlir et al.,(1996). Potent and Sustainable Antiretroviral activity of Indinavir (IDV), Zidovudine (ZDV) and Lamiduvive (3TC). XI International Conference on AIDS, Vancouver, 11 July 1996, Abstr. Th.B.931.

[14] R. V. Culshaw, S. Ruan., A delay-differential equation model of HIV infection of CD4+ T-cells, Mathematical Biosciences 165 (2000) 27-39

[15] Y. Kuang (1993) Delay differential equations with applications in population dynamics. Academics Press, Boston.

[16] Y. M. Li, H. Shu., Multiple Stable Periodic Oscillations in a Mathematical Model of CTL
Response to HTLV-I Infection. Bull Math Biol. DOI 10.1007/s11538-010-9591-7, (2010) 17