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THE BOUNDS OF TIME LAG AND CHEMOTHERAPEUTIC EFFICACY IN THE CONTROL OF HIV/AIDS

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ABSTRACT

The current use of Highly Active Anti-Retroviral Therapy (HAART) strategy to control Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) is inefficient in eradicating HIV/AIDS due to inadequate understanding of the dynamics relating to interaction between the immune system components and HIV. As a result, a pool of potential transmitters is continuously created and thus HIV has remained a pandemic. In this paper, we formulate a mathematical model using differential equations to study the effects of time lag $\tau > 0$ due to cellular latency and pharmacological delays and chemotherapy on the control strategy of AIDS epidemic. Equilibrium points of the model are computed and used to determine the reproductive ratio R_0. This important threshold parameter is then used to determine the critical bounds of time lag $\tau \in [\tau_{min}, \tau_{min}]$ and therapeutic window $C_p \in [MEC, MTC]$ that is, the bounds; above Minimum Effect Concentration (MEC) and below Minimum Toxic Concentration (MTC), where drug plasma concentration C_p should lie for effective maintenance of low levels of viral load and reduction of drug toxicity. The mathematical model gives qualitative understanding of HIV prognostic information which is a means of rejuvenating the existing Antiretroviral drugs (ARV's). Numerical simulations show that a stable and persistent endemic equilibrium state of low viral load is achieved when these thresholds $\tau \in [0, 25]$ and $C_p \in [0.79, 0.91]$ are satisfied. This persistent equilibrium state will lead to eventual eradication of HIV/AIDS.

Keywords: Equilibrium, Positivity, Boundedness, Basic reproductive number, Time lag, Therapeutic window, Toxicity, Stability.

JEL Subject Classification: C31, C53.

Contribution/ Originality

This paper contributes the first logical analysis on the effect of intracellular delay of HIV viral infection on drug efficacy. The study originates new formula for finding the optimal therapeutic window $[MEC, MTC] = [0.79, 0.91]$ of HAART necessary to control the reproductive ratio R_0 of HIV to less than one and evade the risk of drug toxicity.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) finds and destroys the immune cells called Thymus cells (briefly T cells) or $CD4^+ T$ cells (because of the presence of CD4+ proteins on its surface) that the immune system must have to fight disease. As the magnitude of infection increases, the immune system is depleted and the host becomes susceptible to opportunistic diseases and pathologies, therefore developing Acquired Immune Deficiency Syndrome (AIDS). AIDS is clinically diagnosed when the $CD4^+ T$ count is less than $200/mm^3$ out of the normal range of between $800/mm^3$ and $1200/mm^3$.

Immense research to curb the HIV/AIDS pandemic has been the concern of many scientific fields including mathematics and so far no effective one bullet solution to HIV/AIDS. This is sentinel in realizing that many pathogenic mechanisms leading to disease is unknown.

With the continued absence of cure, much research is deviating from the behavioural ways of controlling the disease into chemical methods which has led to the development of antiretroviral drugs (ARV). The success in using ARVs has been achieved with accompanying side effects including toxicity and mutation catalysis of HIV. This is associated with lack of understanding of the interaction dynamics between the immune system and the HIV, which provides guidelines on the composition of the drugs, levels of administration and timings.

1.1. HIV Infection and the Immune System

The process of viral infection begins with the interaction of viral products with $CD4^+T$ cells or $CD4^+$ macrophages. From the initial contact of HIV particle with the cell, the virus will roll over the surface of the cell until it comes in contact with $CD4^+T$ molecules. The high affinity of $CD4^+$ and gp120 will cause the binding which then undergoes complex conformational changes that causes fusion of viral and cell lipid bilayers, and the viral genome gains entry to the cell cytoplasm. This initiates intracellular infection [1].

Once the infection has taken place, the Cell Mediated Immunity (CMI) is aroused by the activation of antigen - specific B and T lymphocytes. On the surface of B and T cells are epitope-specific receptor proteins that bind to its cognate epitope. Activated T lymphocytes undergo a large number of divisions and form expanded clonal population of identical cells then differentiate into effector cells (e.g. helper $CD4^+T$ cells and cytotoxic $CD8^+T$ cells) which mount immune responses by lysing target cells bearing cognate foreign peptides. T and B effector cells are maintained as long as their cognate antigen is present to stimulate the production of new effector

cells and after the virus is vanquished, most of the effector cells will die and be cleared away by phagocytes, but a few of these cells will be retained as memory cells. Upon a later encounter, with the same antigen, these memory cells quickly differentiate into effector cells, dramatically shortening the time required to mount an effective response [2]. As the immune system attacks foreign particles, the virus will also activate its defense mechanisms which include intracellular immunity, down regulation of infection signal transmitted by infected cells and viral mutation.

Intracellular pathogens like HIV cannot be reached by specific antibodies and thus enjoy intracellular immunity. Cellular immune response is needed in order to suppress such infection. Infected cells signal their infection status and the Natural Killer cells (NK) kill the infected cells through the action of perforin and other molecules secreted by NK cells through the action of cytokines. This activation can also be limited by the viruses which are known to down regulate the expression of host proteins in signaling infection [3].

The other evasion mechanism of HIV is mutation. As the body prepares to fight the virus by developing specific responses, the virus changes some of its antigenic proteins, via mutation, so that it is no longer recognized. HIV have very high spontaneous rate of mutation because of the presence of Reverse Transcriptase (RT) that does not possess a repair domain which DNA polymerases usually have.

1.2. HIV and Mathematical Models

Mathematical epidemiology involves formulating mathematical models which yields mathematical results that can be applied to reduce number of laboratory experiments and testing which are comparatively expensive and detrimental in cases where the subjects of the experiment are humans. Models on interaction of viruses and $CD4^+ T$ cells helps in identifying essential characteristics of HIV pathogenesis and chemotherapy. This understanding will help in formulation of more effective control strategies.

The use of ordinary and partial differential equations to model biological systems has a long history, dating to Malthus [4]. Although these models give rise to better understanding of more complicated phenomena, it is becoming clear that simple models cannot capture the rich variety of dynamics observed in natural systems. In our study, we formulate a mathematical model using delay differential equations describing the interaction of these three components, namely; virus, immune and chemotherapy. The main objective of this study is to analyze the effects of time lag and therapeutic concentrations using the reproduction rate of HIV viral materials parameter. The results of this study will be used to acquire accurate prognostic information and use it to determine optimal drug administration procedures in order to overcome toxicity problems and reduce the occurrence of drug resistant mutants in chemotherapeutic intervention strategies.

This is how the paper is arranged. Section 2 is the literature review, in section 3 we develop a model, and carry out theoretical analysis including finding reproductive ratio parameter R_0 and demonstrate the effect of time delay and drug efficacy on R_0. We also determine the threshold

values for effective control of HIV progression to AIDS. Section 4 gives numerical simulations while conclusion and recommendation will follow in section 5.

2. LITERATURE REVIEW

Many mathematical models of HIV infection, have met with varying degrees of success, the ability to depict the real situation. One of the most widely cited is that of Perelson and Nelson [5], which studies the interactions between healthy T cells, actively infected T-cells, latently infected T-cells, and free virus in the bloodstream. This model was able to predict an infected steady state, despite the choice of parameters which is highly individualized. Culshaw [6] proposed an alternate strategy for the theoretical estimation of health and progression to AIDS in at-risk individuals. This addressed the problem of using viral load as a stand-in for patient health. It takes into account the particular type of decline in CD4+cells that is specific to AIDS patients.

Periodicity of the HIV/AIDS Epidemic in a Mathematical Model that incorporates Complacency was analyzed and simulations showed that complacency resulting from dependence of HIV transmission on the number of AIDS cases in a community leads to damped periodic oscillations in the number of infective with oscillations more marked at lower rates of progression to AIDS [7]. The implications of these results to public health with respect to monitoring the HIV/AIDS epidemic and widespread use of antiretroviral (ARV) drugs was discussed. 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 [8]. 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 oscillations at cellular levels of the immune system versus viruses were done by Li and Hongying [9], on Multiple Stable Periodic Oscillations in a Mathematical Model of CTL Response to HTLV-1 infection. This study was an extension of Radde [8] work, who showed that time delays can destabilize an otherwise stable positive steady state and lead to a phenomenon of stability switch.

The dynamic pattern of viral load in a patient's body critically depends on the hosts genes [10]. For this reason, the identification of those genes responsible for virus dynamics, although difficult, is of fundamental importance to design an optimal drug therapy based on patient's genetic makeup. With an increasing availability of genetic polymorphic data, the model will have great implications for probing the molecular genetic mechanism of virus dynamics and disease progression.

Various biological reasons lead to the introduction of time delays in models of infectious disease dynamics (see for instance [11] and [12]. Usually biological mechanisms includes; Delay due to temporary immunity, (see for instance [13]); Delay caused by the latency in a vector; and Delay caused by latent period in host, i.e. the time elapsed between exposure of a host to a

pathogenic organism, and the infectiousness of this host. A useful method to establish global stability is that of suitable Lyapunov functional [14]. Huang and Takeuchi [15] have considered two epidemiological models with the last two cases of delays and nonlinear incidence rate. Perelson and Nelson [5] 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 compared to the values estimated with a non-delay model. Kirschner and Webb [16] formulated a model to study treatment strategy in the chemotherapy of AIDS and analyzed three types of qualitative clinical behaviour: an uninfected steady state, an infected steady state (latency) and a progression to AIDS state. They simulated treatment schedules for the consideration of treatment regimes and suggested that 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. ARV's have been known to reduce the amount of HIV type 1 in the blood plasma of infected patients to extremely low undetectable levels (see for instance Gulick, et al. [17], Markowitz, et al. [18] and Perelson and Nelson [5]). However, a small percentage of infected patients experience viral rebound Gulick, et al. [17]. This could be associated with periodicity in viral load due to the time delay during interaction [9].

3. MODEL FORMULATION AND ANALYSIS

A compartmental model is formulated to describe the dynamics of T-cell populations in response to HIV viral particles and the immune system interactions. The model divides the cell population at any time t into five classes, namely; Susceptible $CD4^+ T$ cells (T), Exposed non infectious $CD4^+ T$ cells (T_1), Infectious $CD4^+ T$ cells (T_2), free virus articles (V) and Cytotoxic Thymus lymphocytes (CTL) responsible for the killing of infected cells. Parameters accounting for the rate of transfers from one compartment to another are also placed to describe the dynamics between the compartments. Before creating a mathematical model describing the interaction between the above said cells, the understanding of the effects of chemotherapy and the role of CTL is hereby described.

3.1. The Effects of HAART

There are several drugs employed to control HIV. They include: Transcriptase Inhibitors (RTI) (which interfere with the transcription of Ribonucleic Acid (RNA) to Deoxyribonucleic Acid (DNA) thus halting cellular infection) and Protease Inhibitors (PI) (which interfere with post-translation viral particle assembly). Highly Active Anti Retroviral Therapy (HAART) is combination therapy e.g. triple therapy which uses two nucleotide inhibitors and one protease inhibitor. This has an advantage of avoiding the occurrence of the resistant mutant which arises

during mono therapy and also has an advantage that the inhibitors are synergetic, meaning that the overall protection is greater than the sum afforded by the drugs individually. Thus the amount of each drug taken can be decreased, reducing the inevitable toxicity and high cost [3].

The use of HAART, reduce the severity of infection but do not completely eliminate the disease. This therapy makes the viruses non-infectious and non productive but remains integrated in the T cell's genome, thus continuously reproduced by infected cells. This increases the number of potential transmitters able to infect other individuals [1]. HAART drugs are available in the market with different brand names. The former is of a nucleoside class and examples include, deoxythymidine analog, AZT [ziduvudine], stavudine [d4T; deoxythymidine], lamivudine [3TC], zalcitabine [ddC; deoxycytidine] and didanosine [ddI; deoxyguanosine]. Their mechanism involves their incorporation into viral DNA, where they will block addition of further nucleotide causing DNA synthesis to cease. The later is tailored to inhibit the action of protease to cleave polyproteins which assemble to form the virions core proteins and enzymes. Examples of this drug include saquinavir, indinavir, ritonavir and nelfinafir (see for instance Dimmock, et al. [3]).

With this in mind, define the HAART drug efficacy against virus to be $\varepsilon = (1 - n_{rt})(1 - n_p)$ where $0 \leq (1 - n_{rt}) \leq 1$ accounts for the potential viral infections not blocked by the RTI and $0 \leq (1 - n_p) \leq 1$ the fraction not rendered non-infectious by the PI. Here $1 - \varepsilon$ is the fraction of potential infectious virus production that eludes the combination therapy. The efficacy of many drugs depends on their concentration in the blood plasma C_p. First-order kinetic input is the most common form of input where drugs is delivered at a rate proportional to the concentration gradient during the transfer of drug movement. The drug concentration profile due to multiple dosing is periodic [19], and the oscillations is required to lie between minimum effect concentration (MEC) and minimum toxic concentration (MTC). This range is called therapeutic window, defined by the interval and inequality;

$$\varepsilon(t) \leq \varepsilon^0 \pm |a_m| := [MEC, MTC] \equiv C_p \tag{1}$$

We consider the effect of multiple first-order input commonly used in HIV chemotherapy. If the drug is administered in equally sized doses at equal spaced time intervals, the accumulation of drug between the doses will produce at steady state an average profile shown by first-order input graph in Figure 1 below.
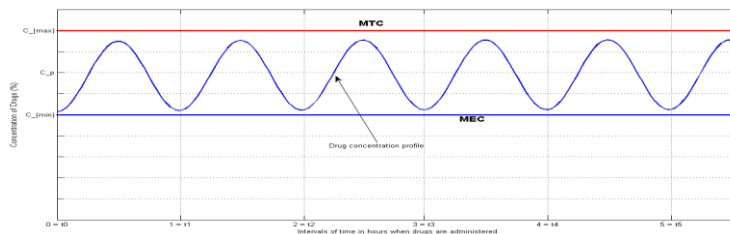
Figure-1. C versus time profile for zero order input and one compartment disposition together with multiple equalized first-order input into a one compartment disposition model

Source: Author

3.2. The Mechanism of the Immune System (CTL)

The immune system responds against every foreign particle introduced into the body. T cells carrying out the actual killing are known as cytotoxic T cells or activated cytotoxic T lymphocytes (CTLs). CTL kill infected cells by lysis, a process where Killer T-Cells or CTL releases perforin and granulysin cytotoxins which form pores in the target cells plasma membrane, allowing ions and water to flow into the infected cell and also release granzyme, a serine protease that enters the cell via pores to induce apoptosis causing the cell to burst and release its cytoplasmic contents which will be cleared by phagocytes. We account for the effects of CTL response using the parameters a and b together with the population of CTL denoted by $C(t)$ in modeling the effect of the immune system. The parameters a and b models the percentage effectiveness of CTL in reducing the viral infectivity of naïve $CD4^+T$ cells and percentage effectiveness of CTL in reducing the virus burst size respectively. The effect of CTL either by reducing the infectivity of virus or reducing the burst size is modeled by a non-increasing the exponential function $f(t) = e^{-aC(t)}$.

3.3. Model Variables and Definitions

The interacting classes of cells are described by the following variables:

(1) $T(t)$: Naive $CD4^+\,T$ cells containing cells produced and developed in the bone marrow (B cells) and the thymus (T cells) and through other proliferation terms;

(2) $T_1(t)$: Exposed and infected $CD4^+\,T$ cells which mature to become productive or remain unproductive and are retained by the system as memory cells for subsequent attack;

(3) $T_2(t)$: Population of infected $CD4^+\,T$ cells which produce viruses able to infect other naive T-cells;

(4) $V(t)$: Population of free infectious HIV virus in the blood plasma;

(5) C(t): The population of CTL that carry out the killing of infected cells and free viruses.

3.4. Model Parameters

The following definition of parameters is used to model the transfer terms of cells from one compartment to another due to their interactions.

(i) s represents the constant rate of production of uninfected $CD4^+\,T$ cells

(ii) r is the maximum rate of proliferation of $CD4^+\,T$ cells. T-cell population follows a logistic growth function with a carrying capacity of K/mm^3 of blood plasma.

(iii) μ_i is the natural death rates of the ith class with $i = T, T_1, T_2, V$.

(iv) ω is the constant time lag modeling the latency period of $CD4^+\,T$ cell from viral exposure up to the time infection develops to a level sufficient to produce viral particles.

(v) ι models the period during which the infected cell is productive.

(vi) $\tau := \omega + \iota$ models the total time that infected $CD4^+\,T$ cell survives.

(vii) β denote the probability of effective contact sufficient to result into infection.

(vii) N is the total number of virions produced by every infected cell.

(vii) s_1 , is a constant rate of production of new CTL-cells with δ as its death rate.

(viii) h is the CTL induced death rate of infected T_1 and T_2 cells.

(ix) $\varepsilon = (1 - n_{rt})(1 - n_p)$ measures the total HAART drug efficacy with $(1 - \varepsilon) \coloneqq \alpha$ the proportion of viruses that eludes the combination therapy.

(x) r_1 is the maximum differentiation rate of CTL from activated T-lymphocytes.

3.5. Model Assumptions

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

A_1 The model assumes that there is cell mediated immunity (CMI) response and no humoral immune response

A_2 The model does not distinguish the existence and infection by different viral strains.

A_3 Any uninfected cell once infected, will remain infected until its death.

A_4 Only $CD4^+ T$ cells are infected and upon infection, cells become latent for some fixed time ω then a bigger proportion become productive for an additional time ι while a small negligible proportion remain latent as memory cells.

A_5 There are only five interacting cell species T, T_1, T_2, V and C.

A_6 Infection of $CD4^+ T$ cells is by mass action principle.

A_7 $CD4^+T$ cells are depleted by lysis and apoptosis.

A_8 The action of antiretroviral involves prevention of infection and inhibition of viral replication.

A_9 There is a limited genetic mutation in viral genes which would result in viral variants.

3.6. Model Equations

With the above assumptions and parameters, we formulate the following model to describe the dynamics of immune response to HIV infection in presence of treatment and the action of the immune system.

$$T'(t) = s + rT(t)\left(1 - \frac{T(t)}{K}\right) - \alpha\beta e^{-aC}T(t)V(t) - \mu_T T(t)$$

$$T_1'(t) = \alpha\beta e^{-aC}T(t)V(t) - \alpha\beta T(t-\omega)V(t-\omega)e^{-(aC+\mu_1\omega)} - \mu_1 T_1(t) \qquad (2)$$

$$T_2'(t) = \alpha\beta T(t-\omega)V(t-\omega)e^{-(aC+\mu_1\omega)} - \alpha\beta T(t-\tau)V(t-\tau)e^{-(aC+\mu_2\tau)} - \left(\mu_2 + hC(t)\right)T_2(t)$$

$$V'(t) = N\alpha\beta T(t-\tau)V(t-\tau)e^{-((a+b)C+\mu_2\tau)} - \mu_v V(t)$$

$$C'(t) = s_1 + r_1 T(t)V(t) - \delta C(t)$$

3.6.1 Model Description

The model is briefly explained as follows. The first equation models the population of naive $CD4^+T$ cells. Note that in absence of infection, the $CD4^+T$ cell population grows logistically with a carrying capacity of $K = T + T_1 + T_2$. The infection of $CD4^+T$ cells by the virus is determined by the rate of encounters of $CD4^+T$ cells by the virus. This is based on law of mass action

with β as the probability of infection and $(1 - \varepsilon) := \alpha$ measures the percentage preventability of infection by HAART. The function $e^{-aC(t)}$, representing the effectiveness of CTL to cause exponential decrease of infectivity at a constant rate a and 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 cells survive until it becomes active and produce viruses after incubation period is given by $e^{-\mu_1\omega}$. The third equation of system (2) models the rate of change of actively infected $CD4^+T$ cells with the probability $e^{-\mu_2\tau}$ that they continue surviving in the class and actively producing viruses for time ι. The last term also represents the death rate, with $\mu_2 > \mu_1$ due to infection and augmented by the accelerated death rate caused by the action of CTL given by $hC(t)$. The fourth equation of system (2) models the population of free virus in the blood plasma. It is assumed that only actively infected $CD4^+T$ cells produce viruses at a constant rate N per cell before they die. This includes viruses which bud out of an infected and active $CD4^+T$ cell before they die, with $\tau = \omega + \iota$ representing the total time of latency and infectivity. The last equation represents the rate of change of HIV specific CTL population with δ as CTL mortality rate.

3.7. Model Preliminary Analysis

We begin by establishing some basic properties of solutions to the system (2). These properties are, positivity, Boundedness, steady states and their stabilities. In order to do the analysis stated above, we begin by defining the initial conditions and the space we operate in.

3.7.1. Initial Conditions

The initial conditions for the system (2) at time $t = 0$ are $T(0) = T_0 \geq 0$, $T_1(0) = T_{10} \geq 0$, $T_2(0) = T_{20} \geq 0$, $V(0) = V_0 \geq 0$, $C(0) = C_0 \geq 0$. In the following we define a positive pentagonal cone as,

$$R_{+0} = \{(T, T_1, T_2, V, C) \mid (T \geq 0, T_1 \geq 0, T_2 \geq 0, V \geq 0, C \geq 0\}$$
$$R_{+} = \{(T, T_1, T_2, V) \mid (T > 0, T_1 > 0, T_2 > 0, V > 0, C > 0\}$$

3.7.2. Positivity and Boundedness of Solutions

System (2) describes human cell population and therefore it is very important to prove that all the state variables $T(t)$, $T_1(t)$, $T_2(t)$, $V(t)$ and $C(t)$ is non-negative for all time t.

Positivity

We prove that all solutions of system (2) 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

$$T(s) = T_0(s) \geq 0, T_1(s) = T_{10}(s) \geq 0, T_2(s) = T_{20}(s) \geq 0, V(s) = V_0(s) \geq 0, C(s) = C_0(s) \geq 0$$

with $s \in [-\omega, 0)$ and $T(0) \geq 0$, $T_1(0) \geq 0$, $T_2(0) \geq 0$, $V(0) \geq 0$ and $C(0) \geq 0$. Then the solutions $T(t)$, $T_1(t)$, $T_2(t)$, $V(t)$ and $C(t)$ of system (2) are positive for all $t > 0$. The region R for system (2) is positively invariant and all solutions starting in R_{+0} or R_+ approach, enter or stay in R. For the proof, see [20].

3.7.3. Equilibrium Points and their Stability

We analyze the stability of system (2) by first finding its equilibria and then study their linear stability at the obtained equilibrium points.

3.7.4. Disease Free Equilibrium (DFE)

The disease-free equilibrium, is the set of points of the system (2) in absence of infection. This points is given by $E^0 = (T^0(t), T_1^0(t), T_2^0(t), V^0(t), C^0(t)) = \left(T^0, 0, 0, 0, C^0\right)$, where;

$$T_0 = \frac{K}{2r}\left\{r - \mu_T + \left[(r - \mu_T)^2 + \frac{4rs}{K}\right]^{\frac{1}{2}}\right\} \text{ and } C^0 = \frac{s_1}{\delta}.$$

3.7.5. Stability of DFE and R_0

Local asymptotic stability at equilibrium is governed by linearization of the model equations about this equilibrium. The computation of eigenvalues of this linearization leads to a characteristic equation whose roots determine its stability. The system is stable if all the roots are negative and unstable if any one or all of the characteristic roots are positive. The condition on one of the characteristic roots yields a dimensionless parameter denoted by R_0.

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 susceptible (see for instance Dickmann, et al. [21] and Van Den Driessche and Watmough [12]). The use of R_0 is fundamental to the study of epidemiological dynamics since it serves as a threshold parameter that predicts whether an infection will spread or die off. If $R_0 < 1$, the viral materials will be cleared from the individual. On the other hand, if $R_0 > 1$, then the number of infected individuals will increase with each generation and the disease will spread. In an endemic infection, we can determine which control measures, and at what magnitude, would be most effective in reducing R_0 below one, providing important guidance for public health initiatives [12].

3.7.6. Computation of R_0

We compute the basic reproductive number, R_0 following the next-generation operator approach by Dickmann, et al. [21] and Van Den Driessche and Watmough [12].

In our case, the basic reproductive number R_0 is obtained using equation (ii), (iii) and (iv) of system (2) and the basic reproductive number is

$$R_0 = \rho(FV^{-1}) := \frac{(1-\varepsilon)N\beta T^0 e^{-\left((a+b)C^0+\mu_2\tau\right)}}{\mu_v} \qquad (3)$$

The stability of system (2) can be summarized in the following lemma.

Lemma 3.2. The disease free equilibrium E^0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof. The matrix of linearization of system (2) yields the matrix

$$A := \begin{bmatrix} r - \frac{2r}{K}T - \chi V - \mu_T & 0 & 0 & -\chi T & \frac{1}{a}\chi TV \\ \xi V & -\mu_1 & 0 & \xi T & -\frac{1}{a}\xi TV \\ \eta V & 0 & -\mu_2 - hC & \eta T & -\frac{1}{a}\eta TV - hT_2 \\ \zeta NV & 0 & 0 & \zeta NT - \mu_v & -\frac{1}{(a+b)}\zeta NTV \\ r_1 V & 0 & 0 & r_1 T & -\delta \end{bmatrix} \qquad (4)$$

where $\chi := \alpha\beta e^{-aC}$, $\xi := \alpha\beta e^{-aC}[1 - e^{-\mu_1\omega}]$, $\eta := \alpha\beta e^{-aC}[e^{-\mu_1\omega} - e^{-\mu_2\tau}]$ and $\zeta := \alpha\beta e^{-[(a+b)C+\mu_2\tau]}$. Evaluating the eigenvalues of this matrix at DFE when $V = 0$ and $T = K$ yields the characteristic roots, $\lambda_1 = -r - \mu_T$, $\lambda_2 = -\mu_1$, $\lambda_3 = -\mu_2 - hC^0$, $\lambda_5 = -\delta$ and $\lambda_4 = N\alpha\beta T^0 e^{-\left((a+b)C^0+\mu_2\tau\right)} - \mu_v$. The stability of system (2) depends on the sign of λ_4 which is

expressed in terms of equation (3) as; $\frac{N\alpha\beta T^0 e^{-\left((a+b)C^0+\mu_2\tau\right)}}{\mu_v} - 1 := R_0 - 1$. System (2) is stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.8. Effects of τ and ε on R_0

We are interested in any critical values of τ at which the reproductive ratio R_0 transitions from being less than one to being greater than one.

Denote the value of R_0 in absence of treatment $(\varepsilon = 0)$ by $R_T = \frac{N\beta T^0 e^{-\left((a+b)C^0+\mu_2\tau\right)}}{\mu_v}$ and denote the reproductive number in absence of both treatment and immune response (i.e. $\varepsilon = a = b = 0$) by $R_C = \frac{N\beta T^0 e^{-\mu_2\tau}}{\mu_v}$, we clearly note that the following inequality holds; $R_C \geq R_T \geq R_0$.

This shows the contribution of the immune response and chemotherapy in the reduction of the production of infectious virus from infected T-cells. The parameters that determine the value

of R_0 include the value of $\varepsilon, a, b, s_1, \delta, T^0, \tau$ among others. Our interest is the investigation of the effect of delay τ, immune response a, b, and the drug efficacy ε on R_0.

The simulation of time delay τ against reproductive number R_0 at different values of drug
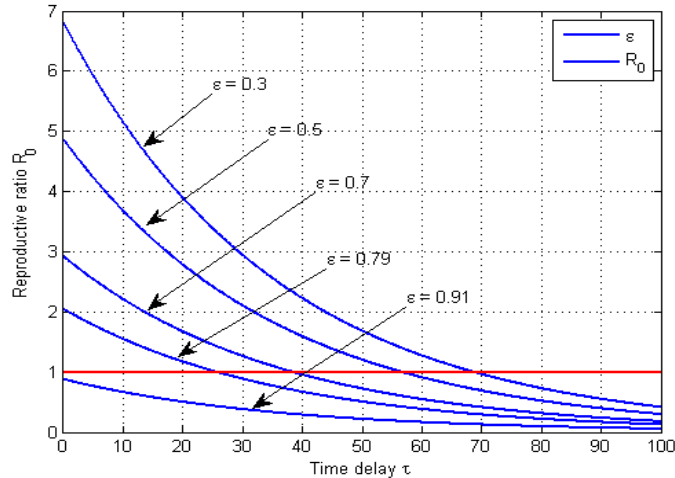
efficacy ε as shown in Figure 2.

Figure-2. The profile of R_0 for various values of τ and ε.

Source: Author

Time delay τ here, refers to the total time that the infected T-cell survives before it dies. We note from Figure 3 that the longer the delay, the lesser the value of R_0, regardless of the value of ε, but the lifespan of naive $CD4^+T$ cell is between 20 - 30 days and the lifespan of a productively infected T-cell is between 3 - 4 days (see for instance [22]). To the left of $\tau = 30$, the minimum drug efficacy which yields $R_0 < 1$ is 0.792. This implies that we can only control the production of infectious viruses by increasing the drug efficacy above 79% concentration or a $C_p = 0.79 amnt/vol$. We therefore take the minimum effective concentration (MEC) to be $0.79\ amnt/vol$. We also note that even at instantaneous death of infected T-cell, the value of drug efficacy ε need not to be more than $0.91 amnt/vol$. This is evidenced by the value of $R_0 < 1$ at values greater than $\varepsilon = 0.91$.

3.8.1. R_0 and Drug Efficacy ε

From the expression of R_0 in Equation (3) we see that viral eradication is only possible if the drug efficacy $\varepsilon(t)$ at any time t satisfies,

$$\varepsilon(t) > 1 - \frac{\mu_v e^{[(a+b)C^0 + \mu_2\tau]}}{N\beta T^0} \tag{5}$$

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Comparing (5) with inequality in equation (1), we obtain the bounds of therapeutic window [MEC, MTC] for the reproductive ratio $R_0 < 1$. This is a necessary condition for eradication of viral infection and reduction of toxicity with the use of ARV's. Figure 4 illustrates therapeutic window described above.
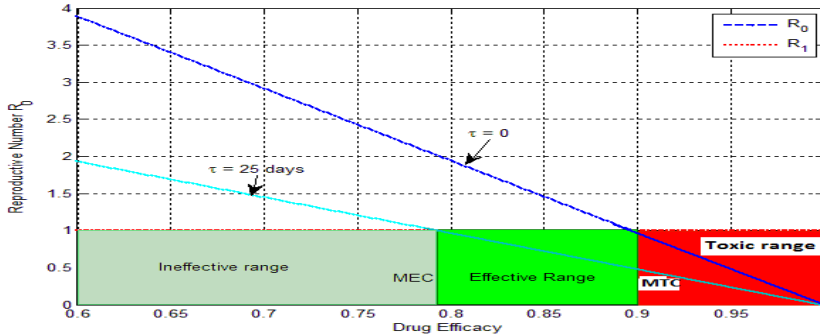

Figure-3. Recommended therapeutic window for $\tau \in [0, 25]$.

We thus make the following proposition.

Proposition 1. Viral Eradication is achieved and the gravity of toxicity is reduced with the use of ARV's in controlling HIV scourge, if the drug efficacy $\varepsilon(t)$ satisfies the inequality

$$\varepsilon^0 - |a_m| \leq \frac{\mu_v e^{\wedge}[(a+b)C^0 + \mu_2\tau]}{N\beta T^0} \leq \varepsilon^0 + |a_m| \qquad (6)$$

4. NUMERICAL RESULTS

To bring out the analytic solutions in the previous section clear, we wish to illustrate the analytic results with specific numerical examples. We will consider using the model system 2. A complete list of parameters and their estimated values that we use for numerical simulations of the model are given in Table 1. Much of these parameters were adopted from Perelson, et al. [22], and a complete discussion of their estimation can be found therein.

The simulation of the model (2), uses the values of the parameters presented in Table 1, and the following initial values for each variable in each compartment at the onset of infection to apply. $T(0)$, $T_1(0)$, $T_2(0)$, $V(0)$, $C(0) = (1000, 0, 0, 1, 0)$ on the interval $[-\tau, 0]$, with $CD4^+T$ cell carrying capacity of $1300 mm^{-3}$. At the onset of infection, the initial viral population is zero but for simulation purposes, we use $V_0 = 0.01$ since at $V_0 = 0$, is a stable equilibrium.

Table-1. Data for the Simulation of the Immune response to HIV infection model.

No	Parameter Description	Symbol	Value
1	Constant recruitment rate of naive CD4+ T-cells	s	15
2	Constant recruitment rate of CTL cells	s_1	0.01
3	CTL accelerated death rate of infected CD4+ T cells	h	0.005
4	Effect of CTL on reducing infectivity of CD4+ T cells	a	0.05
5	Effect of CTL on reducing the viral burst size	b	0.05
6	Viruses produced by each infected CD4+ cell through budding and during lysis	N	35
8	Time lag during latency of exposed CD4+ T-cell	ω	3 days
9	Time lag representing infectious period of CD4+ T-cell	ι	0.5 days
10	CD4+ T-cell survival time from viral exposure to cell death	τ	3.5 days
11	Maximum growth rate of CD4+ T-cells	r	0.035
12	Maximum proliferation rate of CTL	r_1	0.00000019
13	Infection rate of CD4+ T-cells by viral materials	β	0.33×10^{-3}
14	Death rates of naive CD4+ T-cells	μ_T	0.022
15	Death rates of latently infected CD4+ T-cells	μ_1	0.026
16	Death rates of infectious CD4+ T-cells	μ_2	0.028
17	Death rate of HIV virus outside the CD4+ T-cells	μ_v	1.25
18	Variable HAART drug efficacy or concentration	ε	(0, 1)
19	Natural death rate of CTL	δ	0.0012

We begin by illustrating the general dynamics of the model (2) in absence of any external intervention. In this case, we treat the value of $\varepsilon = 0$. We also assume that the effect of CTL on reducing the infectivity of virus and reducing the burst size is constant. In an ideal situation, the use of drugs should improve the effectiveness of these parameters.

4.1. Dynamics of $CD4^+T$-Cells and Free Virions

The simulation results for model system (2) for various values of drug concentration are discussed in this section. The illustrations shows the simulation of the general dynamics of the naive $CD4^+T$ cells $T(t)$, exposed $CD4^+T$ -cells ($T_1(t)$, Infective $CD4^+T$ cells $T_2(t)$, Free Virus in the blood plasma $V(t)$ and the population of CTL cells $C(t)$ in every mm^3 of blood plasma.
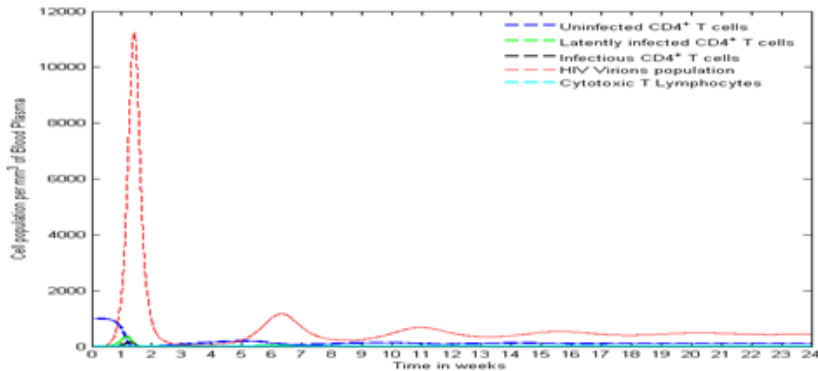

Figure-4. The profile of $CD4^+T$ cells and Virus population in Absence of Therapeutic Treatment.

Source: Author

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4.1.1. Effects of Drug Efficacy on T-cell and Virions Cell Population

In absence of treatment, or with drug concentrations less than MEC, we note from the simulations in Figures 5, 6, 7 and 8 that the level of viral population is higher than that of T-cells. Also we note that the level of $CD4^+T$ cells are below $200mm^{-3}$ which is the sentinel of the onset of AIDS and eventually death of the victim.

Figure 5 show the levels of cell populations at zero treatment. We note that after initial infection, the virus population aggressively increases before the adaptive immunity is triggered. This sharp increase is brought under control within two week after infection.

After the T-cells have been activated, clonal differentiation and mass production of CTL ensues and this will reduce the free virus population in blood plasma to levels below $100mm^{-3}$. This level is maintained shortly, and then the immune system wanes allowing the viral population to rise again in an oscillating manner due to action and reaction of the immune system. Introduction of treatment will increase the $CD4^+T$ cells population while the viral population is decreased. Figure 6 shows the dynamics at 55% drug treatment. In this case, the T-cell population has increased but still low, the patient will be symptomatic but able to fight opportunistic diseases.
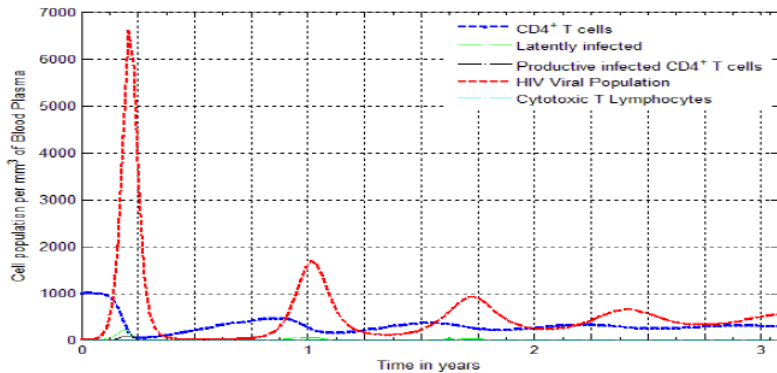

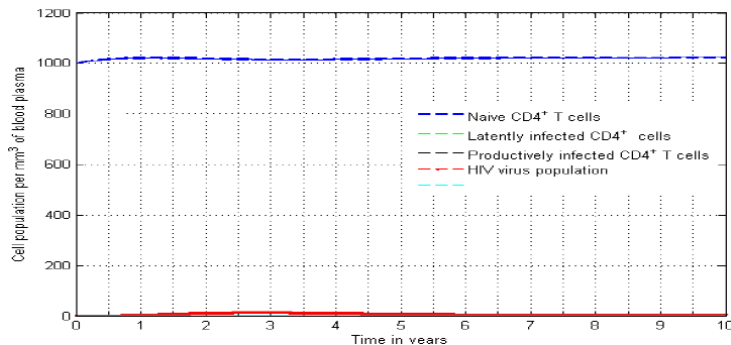**Figure-5.** The profile of $CD4^+T$ cells and Virus population at Treatment below MEC.

Source: Author

Figure-6. $CD4^+T$ cells and Virus Population at MEC Therapy, $\varepsilon = C_{p,min}$.

Source: Author

Increasing drug concentration to 80% (see figure 7), $CD4^+T$ cells are increased significantly to a stable value greater than $700mm^{-3}$ copies while the virus population is reduced to below $300mm^{-3}$ copies of blood plasma. This shows that each infected T-cell produces less than one virus in lifetime. At this level, eventually, the virus population will be wiped. This can be taken as the Minimum Effective Concentration (MEC) of the drug. At 90% drug efficacy, the $CD4^+T$ cell population is normal, i.e. the initial value of $1000mm^{-3}$ copies is maintained though slightly increased due to increased proliferation by the presence of viral infection (see figure 6). At this level, we achieve the reduction of virions to undetectable levels. We therefore need not to increase the drug efficacy beyond this level. We take 91% as the maximum toxic concentration (MTC). This graphical analysis determines the therapeutic window as $(MEC, \ MTC) = (0.79, \ 0.91)$.
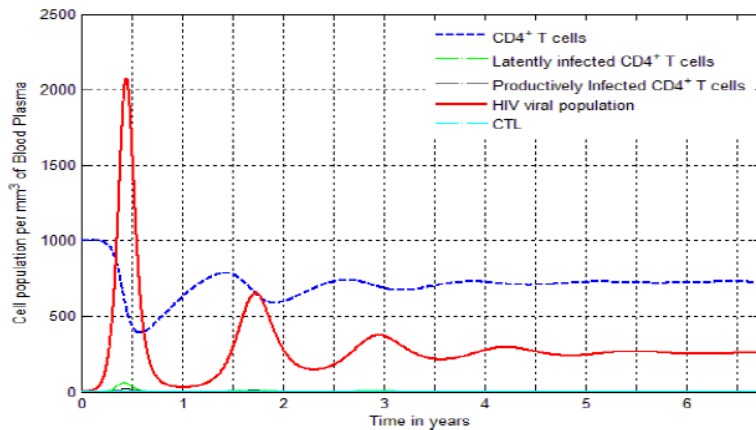

Figure-7. $CD4^+T$ cells and Virus Population at MTC Therapy, $\varepsilon = C_{p,max}$.

Source: Author

4.2. Therapeutic Window

Therapeutic window refers to the bounds of therapeutic concentrations desired for effective and non-toxic treatment. The minimum concentration is denoted by MEC and the maximum is denoted by MTC. This bound depends on individual metabolic rates but generally, the limits can be computed from Equation (16) in Proposition 1, where MEC and MTC are defined as $[\varepsilon^0 - |\alpha(t)|, \ \varepsilon^0 + |\alpha(t)|]$. Consider the graph showing the relation between ε, τ and R_0 below. Assuming a maximum lifespan of infected T-cell as 25 days, the condition for reducing R_0 to less than one is a drug efficacy of $\varepsilon = 0.79$ as depicted in Figure 9.

With $[MEC, MTC] = [0.79, 0.91]$, we obtain $b = 0.06$, and $\varepsilon^0 = 0.85$. Viral Eradication is achieved and the gravity of toxicity is reduced with the use of ARV's in controlling HIV scourge, if the drug efficacy $\varepsilon(t)$ satisfies the inequality;

$$1 - \frac{\mu_v e^{\wedge [(a+b)C^0 + \mu_2 \tau]}}{N\beta T^0} \in [\varepsilon^0 - |\alpha(t)|, \ \varepsilon^0 + |\alpha(t)|] = [0.79, 0.91].$$
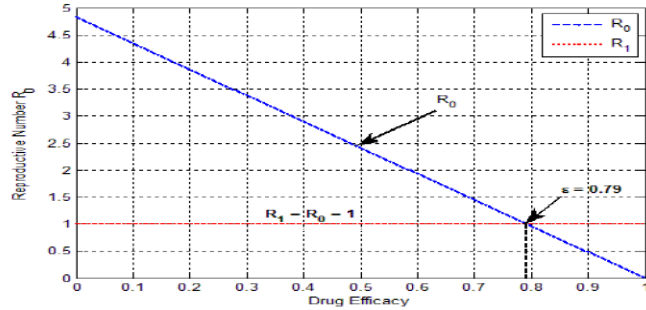
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Figure-8. The Minimum Drug Efficacy necessary to lower $R_0 < 1$ at $\tau_{\max} = 25$ time units.

Source: Author

5. DISCUSSION AND CONCLUSION

5.1. Introduction

The AIDS epidemic and outbursts of diseases such as the Ebola virus are events of concern and interest to many people. Epidemics, have been experienced since human beings began to form communities and they were well known as plagues. As biologists turn to mathematical epidemiology to provide a framework for understanding complicated phenomena, it is important to use as practical modeling techniques as possible.

5.2. Discussion

In our results, the dimensionless quantity R_0 obtained and its value analyzed with respect to time delay τ and drug efficacy ε parameters. It is seen that for any value of drug efficacy, there exist a minimum value of time delay τ_{min} necessary for $R_0 < 1$, however, since the time delay depends on the lifespan of a T-cell, we use the maximum length of time that the cell survives after infection as τ_{max} to determine the minimum drug efficacy $\varepsilon_{min} = C_{p,min}$ required for desired results to be obtained; namely, to eradicate the virus completely or to control it at low undetectable levels. Any drug efficacy levels above $C_{p,min}$ can control the virus but increases the chances of being toxic. From the analytic results we found that the minimum drug efficacy to reduce $R_0 < 1$ to less than one is $C_{p,max}$ This is taken as the optimum drug concentration such that any further concentration makes no difference any and more addition will not yield extra benefit but may cause toxicity. We therefore find that the interval $[C_{P,min}, C_{p,max}]$ forms our recommended therapeutic window [MEC,MTC] which is obtained from the numerical results evaluated in section four as [0.79, 0.91].

5.3. Conclusion

The results obtained are used to propose a treatment strategy which begins immediately at the onset of the infection or at the time the individual tests positive, and the treatment efficacy should be maintained within this therapeutic window.

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The results obtained show that maintenance of low viral load and eventual eradication of the disease does not only depend on the drug efficacy but also on the value of time lag $\tau > 0$ due to intracellular latency. Critical bounds of this time lag is used to determine the minimum drug efficacy levels required for effective control and management of HIV/AIDS and thus propose a more realistic treatment strategy which will cope up with the problems of drug toxicity, side effects and HIV resistance or viral mutation.

5.4. Recommendation

The immune system complexity and balancing of the humoral immune response and CMI is not considered although they happen simultaneously. The consideration of the two may affect the value of time delay τ used in our analysis. Similarly, the assumption of having one viral strain is unrealistic given the high rate of HIV mutation. Finally, the ability of the HIV virus to infect other cells such as the macrophages affects the dynamics of the infection. In this paper, the simulation results is robust and persistent to small perturbation which may be caused by such assumptions made but it is recommended that such scenarios are considered in the analysis to make the model closer to the reality.

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