DELAY DIFFERENTIAL EQUATION MODEL OF HIV-1 IN VIVO DYNAMICS IN THE PRESENCE OF ARV TREATMENT

BY

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DECLARATION

Declaration by Candidate

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DEDICATION

This thesis is dedicated to my parents, who showed the way, my family who held me on the way and my friends and relatives who encouraged me and facilitated the success of my journey

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ABSTRACT

Many mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV-1). The models have been used to predict the evolutions of HIV-1 in vivo and in- vitro dynamics. This study looked into an HIV-1 *in-vivo* dynamics in the presences of antiretroviral (ARVs) using delay differential equations. The delay is used to account for latent period of time that elapsed between exposure of a host cell to HIV-1 and the production of infectious virus from this host cell. This is the time needed to enable HIV-1 to reproduce within the host cell in sufficient number to become infectious. The model has four variables: healthy $CD4^+$T-cells (T), infected $CD4^+$T-cells (T^*), infectious virus (virus not affected by treatment with ARV) (V_I) and finally noninfectious virus (virus affected by treatment with ARV) (V_{NI}). Stability analysis of disease free equilibrium (DFE) of the model and endemic equilibrium point (EEP) of the model were studied. The effects of time delay on the stability of equilibrium points were also considered. The study revealed that the stability of equilibrium points are affected by delay and efficacy of the drug. Analytical results showed that DFE is stable for all $\tau > 0$. Similarly, there is a critical value of delay $\tau_1 > 0$, such that for all $\tau > \tau_1$, the EEP is stable and unstable for $\tau < \tau_1$. When the value of delay(τ) is equal to the critical valueτ_1, the HIV-1 in vivo dynamics undergoes a Hopf bifurcation and remains stable for all values $\tau > \tau_1$ as confirmed by the transversality condition. Numerical simulations show that this stability is achieved at the drug efficacy of 0.79 and $\tau_1 = 0.65$ days, or approximately 16 hours. This verifies the fact that if $CD4^+$T cells remain inactive for long periods $\tau > \tau_1$ 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 maintained.

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ABBREVIATIONS, ACRONYMS AND SYMBOLS

T: Uninfected $CD4^+$T cells

T^*: Infected $CD4^+$T cells

V_I: Infectious virus

V_{NI}: Noninfectious virus.

s: Production rate of uninfected $CD4^+$T cells (T)

μ_T : Death rate of uninfected $CD4^+$T cells (T)

β : Infection rate of uninfected $CD4^+$T cells (T)

μ_{T^*} : Death rate of Infected $CD4^+$T cells (T^*)

k : Production rate of free virus from infected cells

$\mu_i\ i = V_{NI}, V_I$: Clearance rate of free virus from the body

u_1 : Efficiency of reverse transcriptase inhibition

u_2 : Efficiency of protease inhibition

r : Rate of recovery of infected T cells.

$\Re^n$: Real n −dimensional vector space

R_0: Basic reproduction number.

τ : Time delay

ρ : Spectral radius/Dominant eigen-value.

C: Continuous.

ARV: Antiretroviral

$CD4^{+}T$: T Helper cells bearing CD4 receptor cells on its surface.

CDC: Centre for disease control.

cccDNA: covalently closed circular DNA.

DDE: Delay Differential Equation

DFE: Disease Free Equilibrium

DNA: Deoxyribonucleic Acid

EE: Endemic Equilibrium

EEP: Endemic Equilibrium Point(s)

HIV: Human Immune Deficiency Virus

MATLAB: Mathematical Laboratory program for solving mathematical problems

ODE: Ordinary Differential Equations

PI: Protease Enzyme Inhibitor

RNA: Ribonucleic Acid

RTI: Reverse Transcriptase Inhibitor

SARS: Severe Acute Respiratory Syndrome.

STI: Structural treatment interferences.

WHO: World Health Organizations.

CHAPTER ONE

INTRODUCTION

1.0 Background Information

Mathematical modeling has proven to be valuable in understanding the dynamics of HIV-1 infections. (Xinyu and Shuhan 2005).Such models provide an understanding of the underlying mechanism that influence the spread and control of HIV-1 infection. The model formulation process clarifies assumptions, variables and parameters of the models to be formulated. Mathematical analysis of such model provides conceptual results on thresholds like reproductive number of HIV-1 infection.

Computer simulations of mathematical models are useful experimental tools for building and testing theories, assessing qualitative conjectures, answering specific questions on the disease dynamics, determining sensitivities to changes in parameter values and estimating key parameter(s) from data.

Understanding transmission characteristic of any infectious diseases in a community, region or county can lead to better approaches to decreasing the transmission of these infectious diseases in the community, region or county, thus reducing or eliminating the burden of these diseases.

Mathematical models can be discrete or continuous, depending on whether you want to examine theoretical changes in a population as a smooth continuous process or in chunks of discrete steps. It can be deterministic if it is not subject to chances or stochastic if it incorporates randomness into the equations.

This study confines itself to deterministic models and considers the delay and chemotherapy as variable parameters of the model under study, since their effects on

DFE (Disease Free Equilibrium) and EEP (Endemic Equilibrium Point) stabilities were investigated.

In applications, the future behavior of many phenomena is assumed to be described by the solutions of an ordinary differential equation. Implicit in this assumption is that the future behavior is uniquely determined by the present and is independent of the past. In differential difference equations, or more generally functional differential equations, the past exert its influences in a significant manner upon the future and cannot be ignored. With this in mind the study uses functional differential equations to model HIV-1*in vivo* dynamics. The major reason is that HIV-1*in vivo* dynamics have the so called latent period. The latent period being the time elapsed between exposure of a host cell to HIV-1 and the infectiousness of this host cell. This is the time needed for HIV-1 to reproduce within the infected host cell in significant number to become infectious to other cells.

1.1 Mathematical Background on Infectious Diseases

The confidence that the infectious diseases would soon be eliminated was created by improved sanitations, effective antibiotics and vaccinations programs in the 1960s (Peilin and Lingzhen 2012), but this confidence is no longer there. Human and animal invasions of new ecosystems, global warming, environmental degradations, and increased international travels are some of the factors that have fueled the spread and eruptions of infectious diseases. In the recent past, new infectious diseases have emerged for example Human Immunodeficiency Virus (HIV), Severe Acute Respiratory Syndrome (SARS), EBOLA and many more have caused terrible suffering and mortality to the infected persons, and suffering to human populations at large. Some eliminated diseases are reemerging since the infectious agents have

evolved and adapted to the environment. Consequently infectious diseases are receiving more and more attentions in both developed and developing nations.

Emerging and reemerging infectious diseases have been studied by many researchers in different science disciplines. Mathematicians have studied infectious diseases by developing and analyzing mathematical epidemiological models. Mathematical models of infectious diseases are important tools to analyze the spread and control of infectious diseases. Hethcotes (2000) gives a review on the mathematics of infectious diseases.

Most models that have been developed and studied by mathematicians are based on the pioneering work of Kermark and Mckerdrick (1927) model on Susceptible-Infectious-Removed (SIR) model, in which vital dynamics due to demographic factors (birth and death) are negligible for infectious diseases having a short incubation period.

For any mathematical model of an infectious disease, thresholds are obtained which determine whether the disease die out or break out. The existence and stability of equilibrium points are usually investigated for each model. Two equilibrium points: diseases free equilibrium (DFE) and endemic equilibrium points (EEP) are considered in any model.

1.1.1 Deterministic SIR Epidemic Model

The simplest general mathematical model for the dynamical processes of epidemics is the SIR model developed by Kermack and Mckendrick. This model divides a population under study into three classes: susceptible, infected (assumed to be infective) and recovered (assumed to be immune) or removed (those who die through infection) with numbers or densities represented at time t by continuous variables $S(t)$, $I(t)$ and $R(t)$ respectively.

At the heart of the original Kermack-Mckendrick model is the transmission function βSI, with transmission parameter $\beta > 0$, which arises from the assumption that the rate at which susceptible become infected is proportional to the densities or numbers of susceptible and infected population, that is transmission is a mass action process.

The assumptions made on Kermack and Mckendrick model are

1) Individual are infectious immediately they become infected, that is there is no latent period.

2) Infectious individuals are removed from the population at a rate α to enter the removed class of size $R(t)$ (those recovered or dead).

With these two assumptions, the model equations have the following form:

$$\frac{dS(t)}{dt} = -\beta SI$$

$$\frac{dI(t)}{dt} = \beta SI - \alpha I$$

$$\frac{dR(t)}{dt} = \alpha I$$

Ambiguity however arises from the above model in that, in the $R(t)$ class, the number of individual recovered and those who are dead are not explicitly known. To avoid this ambiguity, the $R(t)$ class is further split into two subclasses: $V(t)$ and $D(t)$ subclasses, where $V(t)$ subclass comprises of the entire individual who are recovered and immune (naturally vaccinated) and $D(t)$ subclass consists of individual who are dead. The flow from the I(t) class is α_V and α_D for the $V(t)$ and $D(t)$ subclasses respectively (Wayne and Lioyd-Smith, 2005). Immunity is life-long for small subclasses of diseases such as measles or chickenpox. Thus for generality, it is further assumed that the individual in the $V(t)$ subclass loss their immunity at a rate $\rho > 0$ (also known as relapse rate) to return to the $S(t)$ class. Under the modified assumption the model equations takes the following form;

$$\frac{dS(t)}{dt} = -\beta SI + \rho V$$

$$\frac{dI(t)}{dt} = \beta SI - (\alpha_V + \alpha_D)I$$

$$\frac{dV(t)}{dt} = \alpha_V I - \rho V$$

$$\frac{dD(t)}{dt} = \alpha_D I$$

In the above model, it can be noted that the total density of the individual who are alive at time t is given by $N(t) = S(t) + I(t) + V(t)$. The sum $N(t) + D(t) = S_0 + I_0 + V_0$ throughout the epidemic since the model above does not include demographic

processes, assumed to be operating at larger time scales than the epidemic itself. An epidemic occurs if the number of infected individuals increases with time, that is $\frac{dI}{dt} > 0$.

From the model above it can easily be shown that $S_T > \frac{\alpha}{\beta}$ where $(\alpha = \alpha_V + \alpha_D)$ is threshold population density needed for the disease to invade the susceptible population for a disease with a mass-action transmission term. This threshold population is often expressed in a more general threshold criterion $R_0 > 1$, where R_0 is the basic reproduction number defined in section 1.5 in this thesis.

For the SIR model above $R_0 = \frac{\beta S_T}{\alpha}$, and it is clear that $R_0 > 1$ for the disease to invade the susceptible population.

1.2 Pathogen Transmission Process

At the core of any mathematical model formulation, is the pathogen transmission process which in the above SIR model, it is assumed to be a mass-action process. This assumption ignores certain aspect of the pathogen transmission process. In more refined models, the transmission process considers two important aspects: transmission probability and contact process. Contact process considers the rate at which susceptible individual encounter infected individuals. While the transmissions probability is the probability a susceptible individual will become infected per susceptible-infected contact.

1.3 Basic Facts and Concepts

In this section, we introduce basic facts and concepts that the study used. The basic concepts like reproduction number and its computation, equilibrium points and their stability for the HIV-1 in-vivo mathematical model.

1.3.1 Facts on HIV-1 Infections

HIV-1 is a type of HIV which is virulent and more widely spread in the world than HIV-2 (WHO). Since it is virulent and more widely spread we choose to study it. HIV-1 affects the immune system which would normally fight it. The major targets of HIV-1 infection are a class of lymphocytes or white blood cells known as $CD4^+$T-cells, which are the most abundant white blood cells of the immune system. It is thought that HIV-1, although attacking many different cells, wreak the most havoc on the $CD4^+$ T-cells by causing their destruction and decline thus decreasing the body's ability to fight infection. HIV-1 is an RNA virus. However when it infects a cell, the enzyme reverse transcriptase which it carries, makes a DNA copy of its RNA genome. The DNA copy is then integrated into DNA of the infected cell. The viral DNA, call the provirus is then duplicated with the infected cell every time the cell divides. Thus once infected, the cell remains infected for life. Inside an infected cell, the provirus can remain latent giving no sign of its presences for months or years.

1.4 Delay Differential Equation

Delay differential equations (DDEs) are a class of differential equations in which some unknown functions at the present time are dependent on the values of the functions at previous times. Mathematically, a general delay differential equation for $x(t) \in R^n$ takes the form:

$$\frac{dx(t)}{dt} = f(t, x_t), \text{ where } x_t = x_t(\theta) \text{ and } -\tau \le \theta \le 0.$$

It is noted that $x_t(\theta)$ with $-\tau \le \theta \le 0$ represents a portion of the solution trajectory in a recent past. Here f is a functional operator that takes the inputs of time and a

continuous function $x_t(\theta)$ with $-\tau \le \theta \le 0$ and generates a real number $\left(\frac{dx(t)}{dt}\right)$ as its output. A well known example of delay differential equation is the Hutchinson equation,

$$x' = rx\left(1 - \frac{x(t-\tau)}{k}\right), \tag{1.1}$$

which can be put in the form:

$$\left(\ln x\right)' = r\left(1 - \frac{x(t-\tau)}{k}\right). \tag{1.2}$$

This equation can be solved using the method of step for x in the interval $-\tau \le \theta \le 0$

DDEs such as: $x'(t) = rx(t)\left[1 - a\int_{-\infty}^{0} e^{as}x(t+s)ds \,/\, k\right]$ (1.3)

are in fact systems of ordinary differential equations (ODE's) in disguise. This can be seen by letting

$y(t) = \int_{-\infty}^{0} e^{as}x(t+s)ds$ And noting that $y'(t) = a\left(x(t) - y(t)\right)$ which yield a system of

ODEs: $x'(t) = rx(t)\left(1 - \frac{y(t)}{k}\right)$; (1.4)

$$y'(t) = a\left(x(t) - y(t)\right). \tag{1.5}$$

In fact, an integral-differential equation of the form

$$x'(t) = f(t, x(t)) + \int_{-\infty}^{0} k(s)g(x(t)+s)ds \tag{1.6}$$

with initial condition $x_t(\theta)$ with $-\infty \leq \theta \leq 0$ is equivalent to a system of ODEs with initial condition if k is a linear combination of the functions $e^{at}, te^{at}, t^2e^{at}, \ldots, t^me^{at}$ where a is a real number and m is a positive integer.

Numerically solving most delay differential equations or systems is almost as similar as solving ODEs. The popular MATLAB based DDE23 solver developed by Shampine and Thompson for DDE is well tested and user-friendly.

1.5 Basic Reproduction Number R_0

Basic reproduction number is the number of newly infected cells produced by one infected cell during its life time, assuming all other cells are susceptible (Heffernan *et.al.,* 2005). From this definition, it is immediately clear that when $R_0 < 1$ each infected individual cell produces, on average less than one new infected cell, and therefore we predict that the infection will be cleared from the population, or the micro parasites will clear from the infected individual.

If $R_0 > 1$, the pathogen is able to invade the susceptible population. This threshold behavior is the most important aspect of R_0 concept. In endemic infection, we can determine which control measures and at what magnitude would be most effective in reducing R_0 below one, thus providing guidance for public health initiatives.

1.5.1 Computation of Basic Reproduction Number

We computer basic reproduction number R_0 following the next generation matrix operator approach by Dickmann *et.al.,* (1990), Van den Dreische and Watmough (2002).

The approach involves the use of infective classes of the model system. Define F as the matrix whose elements represents the rate of change of new infections, or the rate of appearance of new infections but not including the terms that describe the transfer of infective from one compartment to another. Also let the matrix V denote the rate of change of cell populations through other means, that is the elements of V denotes the rate of transfer of individuals by other means. Then the difference $F - V$ gives the total rate of change of individual populations in all the four compartments.

The next generation matrix FV^{-1} is formed by evaluating the partial derivatives of F and V at the fixed points, that is

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right], \quad V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right] \tag{1.7}$$

Given $i = 1, 2, 3, \ldots, n$, where n is the dimension of the matrix and x_0 is the fixed point(s) of model system and $x_{j,}$ are the variables of system model.

The entries of the matrix FV^{-1} gives the rate at which infected cells produces new infective. R_0 is the dominant eigenvalue (the spectral radius) of the matrix FV^{-1}. Using this approach, we compute the basic reproduction ratio as,

$$R_0 = \rho(FV^{-1}) \tag{1.8}$$

1.6 HOPF Bifurcation

Most differential equations depend on parameters. Depending on the values of these parameters, the qualitative behavior of the systems solutions can be quite different. The change in the stability of a system of equations as the parameters of the systems are changed is called bifurcation. The parameter that brings about this change is call bifurcation parameter(s).

Hopf bifurcation (also called Poincare-Andronov-Hopf bifurcation) is a type of bifurcations in which the characteristics equations of Jacobian matrix of the system equation has a complex eigen-value and cross the imaginary axis as the bifurcation parameter is changed with nonzero speed.

1.7 Statement of the Problem

The interaction between HIV-1, the human immune system and chemotherapy is a highly dynamical and multifactor process and as a result it is essential to base therapeutic interventions and preventions on more solid theoretical grounds than it has been the case until now. Previous studies have considered different aspects on models of HIV-1, namely: effects of mutations, cellular HIV-1 infection, intra-cellular time delays due to incubation period, just to mention but a few. For HIV-1 *in vivo* dynamic models to be more realistic effect of time delay on $CD4^+$T-cells infection and production of HIV-1 infectious virus together with treatment on the infection of T-cells should be incorporated. Actually, there is time delay between infection of a cell and its infectiousness. This time delay is called latency period. Antiretroviral (ARVs) treatment also causes a change in the population of $CD4^+$ T-cells due to the recovery of these cells as a result of treatment. The treatment also causes production of virus cells that are non- infectious.

The effects of these time delays and chemotherapy are therefore important factors in the HIV-1in vivo dynamics. It is for this reason that this study sought to formulate a mathematical model with delay to study the effects of time delay on the dynamics of HIV-1 infections.

1.8 Objective of the Study

1.8.1 General Objectives of the Study

The main objective of this work was to formulate a mathematical model of HIV-1 in vivo dynamics using delay differential equations and then examine the effects of time delays and drug therapy on the stability of Disease Free Equilibrium (DFE) point and Endemic equilibrium point (EEP) of the model formulated.

1.8.2 Specific Objectives of the Study

i. To formulate a well posed mathematical model with delay for the HIV-1 infection with chemotherapy.

ii. To compute the DFE and investigate the effects of drug efficacy and delay on the model stability.

iii. To compute the EEP and examine the effects of drug efficacy and delay on the model stability.

iv. To perform numerical simulations of the model to justify analytic results and determine the threshold values that leads to the control of HIV-1 pandemic.

1.9 Significance of the Study

The results of this study is useful to the following parties

1) Drug manufacturers: manufacture of ARVs by different pharmaceutical companies will benefit from the results of this study in two ways; cost saving and manufacture of effective drugs. The optimal efficacy levels of the ARVs has been provided by this study for combinational ARVs therapy of persons infected by HIV-1, the drugs company can therefore concentrate on drugs of this efficacy levels thus reducing cost on trials and making effective drugs for HIV-1 treatment.
2) The government: HIV-1 infection has been a major concern to government agencies due to its detrimental effects on productivity of persons infected with the virus. The government work tirelessly to find lasting solutions to HIV-1 infections and its effects among its citizens. The result of this study has provided insight of HIV-1 in vivo dynamics in the presences of treatment. The government can therefore design cost effective treatment strategies like STI which are more cost effectives; thus saving cost of treatment and increasing productive of persons living with HIV-1 infections which is a double gain to the government in its economic development agenda. The results from this study can also be used in the development of better intervention and prevention strategies using DFE stability analysis.
3) Medics: medics can use results from stability analysis of EEP to design clinical trial that are more efficient in the evaluation of STI treatment strategy thus providing a more reliable ARV treatment of persons infected by HIV-1 which will save the cost of treatment and lower the toxicity of the treatment of

persons infected by HIV-1 virus since ARV treatment is live long. The medics can also better provide prevention of infection on persons exposed to HIV-1 by providing post exposure prophylaxis within the save widow period as provided by the DFE stability analysis.

4) Infected persons: since HIV-1 infection has no cure at the moment and also because it has proved difficult to tackle, the result of this study can be used meanwhile to control the adverse effects of the virus to the immune system thus helping to prolong the life of persons infected by the virus while research on treatment and other higher levels of eradications of the infections is carried out.
5) The public: the results of this study provides information to pharmaceutical companies on efficacy of ARV combinational treatment therapy, this provides guidelines to administration of drugs to HIV-1 infected persons in a manner to produce better results. The public thus get better services from public officers infected by HIV-1.

CHAPTER TWO

LITERATURE REVIEW

Culshaw *et.al.,* (2000) 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. Numerical simulation to illustrate the effects of time delay is presented by the study.

They found out that the infected steady state was stable for all $\tau \geq 0$ .They also found out that under certain assumption for large values of N, the effect of delay is not strong as for small N.

This work has not considered effects of chemotherapy on the in vivo dynamics of HIV nor does it examine the effect of time delay on the disease free equilibrium.

Perelson *et.al.,* (1992) studied the dynamics of HIV infection of $CD4^{+}$T cells, using ODE model with four compartments: uninfected $CD4^{+}$T cells, latently infected $CD4^{+}$T cells , actively infected $CD4^{+}$T cells and the free infectious virus. Their study reveals that, there is a critical number of virus released from infected cells for stability of DFE. Numerical simulations of the model reveals the number as 774. DFE is stable for $N < 774$ and unstable for $N > 774$. At $N = 774$, Hopf Bifurcation occurred via oscillations of solution. The study gives the conditions for the stability of DFE. The study gives the parameters which affects the EEP, which depends on uninfected cells and the number of free virus. Though the study discussed various scenarios including

the effects of AZT on HIV virus dynamics, effects of time delay on chemotherapy or on infection of $CD4^+$ T cells is not considered.

Nelson and Perelson, (2002) developed a mathematical analysis of delay differential equation model of HIV-1 infection. This study considered delay in reference to protease inhibitor only. The study therefore has not considered time delay on HIV-1*in vivo* dynamics in the present of both protease and reverse transcriptase inhibitors or in absent of treatment.

Khalid and Noura, (2011) examined a delay differential equation model of HIV with therapy and cure rate. In their study, it was shown that the basic reproduction number at disease free and endemic equilibriums, depends on efficacy, cure and delay. In this study, the numerical value for efficacy of the therapy is not given. The study has also not explicitly shown the bound of delay for stability of the equilibrium points. Issues like bifurcations is not study in this paper.

Xinyu and Shuhan, (2005) examined 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 work provided 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 using numerical analysis. The study further established the condition on delay for the stability of the steady states.

This work did not considered effects of chemotherapy on the in vivo dynamics of HIV. The noninfectious virus that could result from incomplete protease action on the provirus has not also been considered in this study.

Kirschner and Webb, (1996) worked on 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. A mechanistic description of chemotherapy was studied by age structuring of $CD4^+$T-cells. The effects of chemotherapy in this study was modeled using a scalar function which was assumed to be on during treatment and of during off treatment. Two types of models were considered: age structured model and the other without age structure.

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. Although this study looked at various aspects in chemotherapy of AIDs, effects of time delay is not considered in the HIV-1 in vivo dynamics.

Kouche *et.al.,* (2010) developed a mathematical model of HIV-1 infection including the saturation effect of healthy cell proliferation. The study assumed that the infection rate between healthy and infected cell is a saturating function of cell concentration. Numerical simulation and stability analysis of the model was carried. The study revealed through simulation that, if less than 7.7% of infected cells survive the incubation period, the system converges to its healthy equilibrium. If between 7.7% and 30% of infected cells survive the incubation period, then system stabilize at infected equilibrium, and if more than 30% of infected cells survive the incubation period, periodic oscillation of cell concentration was observed. Qualitatively under realistic parameter regimes, the model exhibits two Hopf bifurcation and the infected

steady state is locally asymptotically stable either when the average delay is high or small. The study has also reported that for other delays the model exhibited stable periodic solutions due latently infected cells. Though the study looked at various scenarios on delay effects, effects of chemotherapy is not mention in the study.

Elaiw (2012) worked on 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-1infection with $CD4^{+}$T-cells and macrophages. The incidence rate is modeled by a saturation functional response. Two types of distributed delays describing the time needed for infection of target cells and virus replication has 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.

Elaiw *et.al.,* (2012) examined a global dynamics of an HIV infection model with two classes of target cells and distributed delay . In the first of the model, delay ODEs are used to describe the dynamics of the interaction of HIV with two classes of target cells, $CD4^{+}$T-cells and macrophages taking into account the saturation infection rates. The second model is a generalization of the first one by assuming that the infection rate is given by Bennington-DeAngelis functional response. Two time delays are used in each of the models to describe the time periods between viral entry into the two classes of target cells and the production of new virus particles. The study used Lyapunov functional and Lasalle-type theorem for DDEs to establish the global asymptotic stability of the uninfected and infected steady states of the HIV infection models. A deep study of the effects of the time delays nor the effects of chemotherapy has not been considered by this study.

2.1 HIV-1 in Vivo Model with Delay

We modify HIV-1 in vivo chemotherapy model without delay used by Khalid Hattaf *et.al.,* (2012) which has the following variables: uninfected $CD4^+$T cells (T), infected $CD4^+$T cells (T^*), infectious virus V_I and noninfectious virus V_{NI}.

2.1.1 Assumptions of the Model

The uninfected $CD4^+$T cells (T) is produced at a rate s, die at a rate d and become infected at a rate β. Infected $CD4^+$T cells (T^*), die at a rate a and are cured of virus due to therapy at a rate r. Free virus is produced by infected cells at a rate k and cleared at a rate μ. The control function u_1 represents the efficiency of drug therapy in blocking new infection, so that infection in the presence of drug is $(1-u_1)\beta$. The control function u_2 represents the efficiency of drug therapy to inhibit viral production such that the viral production rate under therapy is $(1-u_2)k$. With these parameters and variables, the delay differential equation model we propose will take the following form:

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - dT(t) - (1-u_1)\beta V_I(t-\tau)T(t) + rT^*(t-\tau) \\
\frac{dT^*(t)}{dt} &= (1-u_1)\beta V_I(t-\tau)T(t) - aT^*(t) - rT^*(t-\tau) \\
\frac{dV_I(t)}{dt} &= (1-u_1)(1-u_2)kT^*(t-\tau) - \mu V_I(t) \\
\frac{dV_{NI}(t)}{dt} &= (1-u_1)u_2kT^*(t-\tau) - \mu V_{NI}(t)
\end{aligned} \tag{2.1}$$

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

CHAPTER THREE

METHODOLOGY

This chapter is divided into three sections: introduction (background information of HIV-1 infection, HIV-1 drug therapy and HIV-1 life cycle), model assumption and formulation, and finally model analytical analysis.

3.1 Introduction

In this section we provide a short overview of what is known about HIV-1 infection and HIV-1 drug therapy. In addition we describe how HIV-1 behaves at cellular level. This basic background information is essential in order to understand how to construct the phenomenological models governed by delay differential equations. The information helps place the mathematical model in a biological context. Since the models are described by delay differential equations, we also provide a brief background on solution of delay differential equations.

3.1.1 HIV-1 Infection

Infection by human immunodeficiency virus-type-1 (HIV-1) has many puzzling quantitative features. One of these features is an average lag of nearly 10 years between infection and the onset of AIDS in adults. The reason for this time lag remains largely unknown, although it seems tied to changes in the $CD4^{+}$T-cells

Immediately after infection by HIV-1, the amount of virus detected in the blood rises dramatically. Along with the rise in the virus, flu-like symptoms tend to appear. After a few weeks to months, the symptoms disappear and the virus concentration falls to a lower level. An immune response to the virus occurs and antibodies against the virus

are detectable in the blood. A test to detect the antibodies in the blood is used to determine if one has been exposed to HIV-1 or not. If the antibodies are detected, the person is said to be HIV-1 positive otherwise the person is HIV-1 negative.

The viral levels "primary infection" falls to a set-point. The viral concentration deviates little from this set-point level for many years; however, the concentration of $CD4^{+}$T cells measured in blood slowly declines. This period in which the virus concentration stays relatively constant but in which the $CD4^{+}$T cells count slowly falls is typically a period in which the infected person has no symptoms. The asymptomatic period (window period) can last as long as 10 years.

HIV infects cells that carry the CD4 cell proteins on the surface as well as other receptors called co- receptors. Cells that are susceptible to HIV infections are called target cells. After infection such cells can produce new HIV particles.

The major target of HIV-1 infection is a class of lymphocytes or white blood cell called $CD4^{+}$T cells. These cells secrete growth and differential factors that are required by other cell populations in the immune system, and hence these cells are also called helper T cells. Because of the central role of $CD4^{+}$T cells in the immune regulation; their depletion has widespread deleterious effects on the function of the immune system as a whole and leads to immunodeficiency that characterizes HIV-1 infection.

3.1.2 HIV-1 Live Cycle

HIV-1 belongs to the class of viruses called retroviruses, which carry their genetic information in the form of RNA. HIV-1 infects T cells that carry the CD4 antigen on their surface. The infection of the virus requires fusion of the viral and cellular

membranes, a process that is mediated by the viral envelope glycoprotein (gp120, gp41) and the CD4 receptor on $CD4^{+}$T target cell. As virus enters the target cell, its RNA is reverse-transcribed to DNA by virally encoded enzyme the reverse-transcriptase (RT). The viral DNA is transported into the cell nucleus, where it is integrated into the genetic material of the cell by a second virally encoded enzyme, the integrase enzyme and stays latent. Activation of the host cell results in the transcriptions of viral DNA into messenger RNA, which is then translated into viral proteins.HIV protease, the third virally encoded enzyme, is required in this step to cleave a viral poly-proteins precursor into individual mature proteins. The viral RNA and the viral proteins assemble at the cell surface into new virions which then bud from the cell and are released to infect another cell. The extensive cell damage from the destruction of the host genetic system to budding and release of virions leads to the death of the infected cell.

3.1.2.1 HIV Structure

An HIV virus particle is spherical and has a diameter of about 1/10,000 mm. Like other viruses, HIV does not have a cell wall or a nucleus. See Figure 3.1 below.

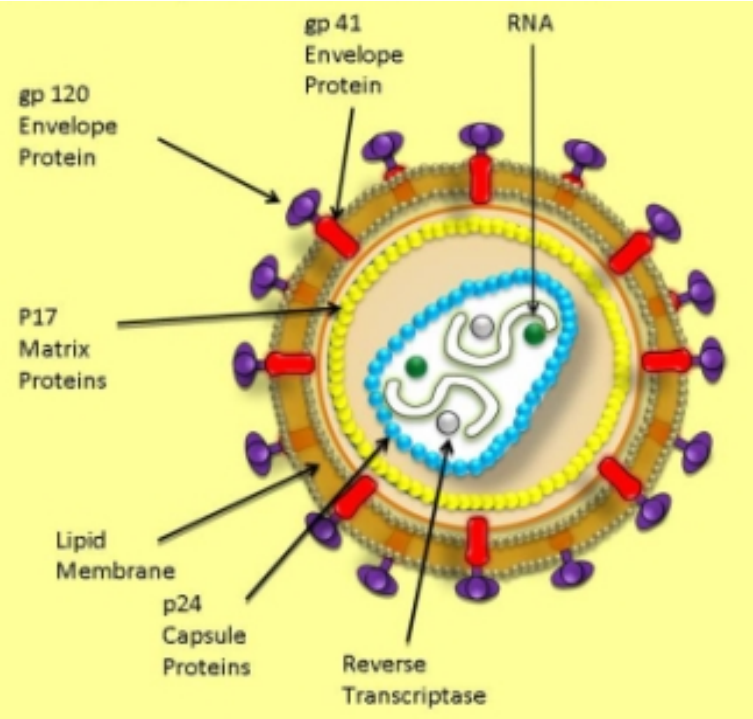


Figure 3.1 Anatomy of Aids virus

Source: http://www.itg.be/internet/e-learning/written_lecture_eng/1_hiv_structure.html

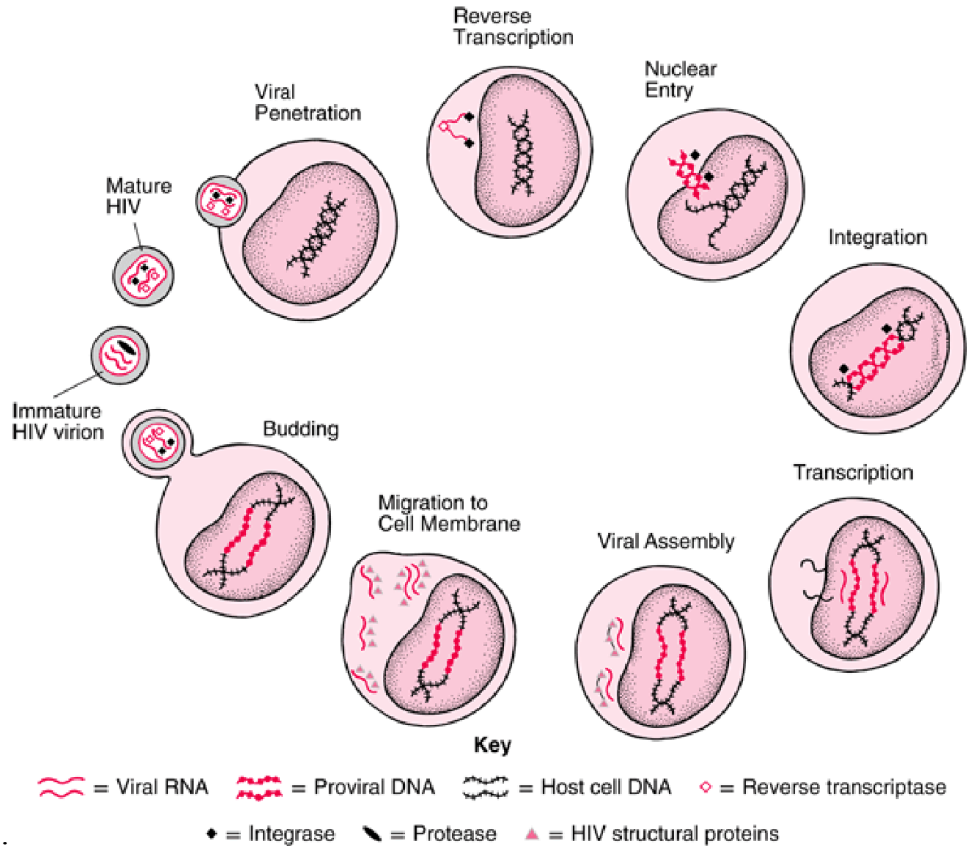


Figure 3.2 Infection Life cycle of HIV-1 Virus

Source: http://www.itg.be/internet/e-learning/written_lecture eng/1_hiv structure.html

HIV attaches to and penetrates host T cells, then releases HIV RNA and enzymes into the host cell. HIV reverse transcriptase copies viral RNA as proviral DNA. Proviral DNA enters the host cell's nucleus, and HIV integrase facilitates the proviral DNA's integration into the host's DNA.

The host cell then produces HIV RNA and HIV proteins. HIV proteins are assembled into HIV virions and budded from the cell surface. HIV protease cleaves viral proteins, converting the immature virion to a mature, infectious virus.

It takes around 1.5 days for an HIV virus to complete its life-cycle. The life-cycle can be summarized into the following 6 stages with the responsible enzyme given in brackets;

Stage1: Binding and fusion a protein, glycoprotein120 (gp120).

Stage2: Conversion of single stranded RNA to a double strand DNA. The enzyme required for this stage is the Reverse transcriptase (RT).

Stage3: Integration of HIV DNA to host cell DNA.

Stage4: Transcription after a signal activates the host cell.

Stage5: Assembling of HIV mRNA chain proteins to form a new virus the enzyme responsible for this stage is called Protease (P).

Stage6: Budding.

3.1.2.2 Other Cells Affected by Virus

HIV also infects nonlymphoidmonocytic cells (e.g., dendritic cells in the skin, macrophages, brain microglia) and cells of the heart and kidneys, causing disease in the corresponding organ systems. HIV strains in several compartments, such as the central nervous system (CNS) and genital tract fluid (e.g. semen), can be genetically distinct from those in plasma. Thus, HIV levels and resistance patterns in these compartments may differ from those in plasma.

Disease progression: Antibodies to HIV are measurable usually within a few weeks after primary infection; however, antibodies cannot fully control HIV infection

because mutated forms of HIV that are not controlled by the patient's current antibodies are generated.

3.1.3 HIV-1 Drug Therapy

Antiretrovirals (ARVs) are powerful life saving drugs that control the spread of HIV in vivo in those who are HIV positive. ARVs are not a cure, but they can add many years to the life of those who take them ones infected by HIV. The goal of HIV-1 drug therapy is to reduce the amount of virus in a person's body and prevent destructions of the immune system. ARVs can also allow the immune system to recover thus reducing incidence of opportunist infections. This will then reduce morbidity and mortality of infected persons.

As mentioned before, HIV attaches itself to the cells in the body using special chemicals that are found in CD4 receptors. Once inside the $CD4^{+}$T cell, HIV use a special enzyme called reverse transcriptase to change itself from viral RNA to viral DNA. It is at this point that reverse transcriptase inhibitor (RTI) works. It works by blocking the process whereby viral RNA is converted to viral DNA. By blocking this process, the HIV is unable to transform from RNA to DNA and it dies.

If the HIV is successfully converted from RNA to DNA, HIV needs another special protein called protease (P) that assembles the viral protein so that new copies of HIV are formed and can bud out of the cell. It is at this point that protease inhibitor **(**PI) works. It works by blocking the protease enzyme thus the newly formed HIV cannot bud out of the cell and so they die. In other words protease inhibitors cause infected cells to produce noninfectious virus. Thus in the presence of protease inhibitors, we have two types of virus: Infectious virus produce by cells not affected by therapy and noninfectious virus produced by cells affected by protease inhibitor. It is also

important to note that PI acts on infected active cells, which in our model was infected at an earlier time $t-\tau$.

In summary, current drug therapies for patients infected with HIV involves inhibiting either Reverse Transcriptase Enzyme (RTE) or HIV protease enzyme. If RTE is inhibited, HIV can enter a cell but will not successfully infect it, a DNA copy of the viral genome will not be made and the cell will not make viral proteins or virus particles. The virus RNA that enters the cell is not stable and will degrade. If on the other hand HIV protease enzyme is inhibited, cleavage of the viral polyprotein will not occur, and the viral particles will be made that lack functional reverse transcriptase, protease and Integrase enzymes. The net effects of blocking HIV protease enzyme is that defective or noninfectious viral particles are made.

The third viral enzyme Integrase is also another potential target of drug therapy, and many pharmaceutical companies are trying to develop Integrase inhibitors

3.1.4 Method of Steps for Delay Differential Equations

Discussing properties of solutions to our model requires an understanding of the method of steps.

The method of steps for solving a DDE involves converting the DDE into an ODE on a given interval using the history of the function on this interval. The resulting equation is then solved and the process of converting a DDE to an ODE is repeated for the next interval with the newly found solution serving as the history function for the next interval.

Let us illustrate this method with a simple DDE;

$$y'(t) = a_1(t) + a_2(t)y(t-\tau) \text{ for } t \in [0,\tau] \tag{3.1}$$

$$y(t) = p(t) \text{ for } t \in [-\tau,0] \tag{3.2}$$

We solve this system of equations in the following steps:

Step 1: On the interval $[-\tau,0]$, the function $y(t)$ is known there, it is the given function $p(t)$. Thus the system is solved for the interval $[-\tau,0]$ call the solution in this interval $y_0(t)$.

Note that when $t \in [0,\ \tau]$, $t-\tau \in [-\tau,\ 0]$ and so $y(t-\tau)$ becomes $y_0(t-\tau)$ on $[0,\ \tau]$.

Step 2: In the interval $[0,\ \tau]$, the system (3.1) and (3.2) becomes:

$$y'(t) = a_1(t)y(t) + a_2(t)y_0(t-\tau) \quad \text{On} \quad t \in [0,\tau]$$

$$y(o) = p(o) \tag{3.3}$$

Equation (3.3) is an ODE and not a DDE because $y_0(t-\tau)$ is know; it is simply $p(t-\tau)$. Thus we solve this ODE on $[0,\tau]$ using $y(o)=p(o)$ as our initial condition. Denote by $y_1(t)$ this solution on the interval $[0,\tau]$.

Note 1: solving (3.3) may be accomplished by treating it as a non homogeneous equation,

$$y'(t)=a_1(t)y(t)+a_2(t)y_0(t-\tau) \quad \text{On} \quad t\in[0,\tau]$$

$$y(o)=p(o) \tag{3.4}$$

System (3.4) will then be solved for a closed form solution using an integrating factor $e^{\int -a_1(t)dt}$.

Step 3: on the interval $[\tau,\ 2\tau]$ the system becomes

$$y'(t)=a_1(t)y(t)+a_2(t)y_1(t-\tau) \quad \text{On} \quad t\in[\tau,\ 2\tau]$$

$$y(\tau)=y_1(\tau) \tag{3.5}$$

This is again an ODE. We solve this system using the initial condition at τ and get a solution $y_2(t)$ for system on $[\tau,\ 2\tau]$. These steps may be repeated for subsequent interval. This scheme is what is applied in MATLAB DDE23 solver.

3.2 Model Assumption and Formulation

We begin by stating the assumptions of our models then formulate the models which describes the dynamics of T-cells populations in response to HIV-1 infections. The model has four state variables namely: uninfected $CD4^+$T-cells (T), productively infected $CD4^+$T- cells (T^*), infectious virus (V_I) and noninfectious virus (V_{NI}).

In order to formulate our model, the following assumptions are made:

1) $CD4^+T$ cells are depleted by lyses' and natural death. Lyses leads to production of HIV-1 viral materials but natural death does not produce HIV-1 viral materials.
2) An antiretroviral effect involves preventions of infections and inhibitions of viral replications through inhibition of the functions of reverse transcriptase and protease enzymes which are virally encoded.
3) There are limited mutations of viral genes which would lead to production of drug resistant strain of the virus.
4) There is no cell-to-cell infections of $CD4^+T$ cells, infections are only by free virus.
5) There is no proliferation of existing $CD4^+T$ cells, $CD4^+T$ cells are only from source (thymus).
6) Some $CD4^+T$ cells recover on drug therapy.

3.2.1 Model Parameters

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 $CD4^+$ cells.

s: Production rate of uninfected $CD4^+T$ cells (T).

β : Infection rate of uninfected $CD4^+T$ cells (T).

μ_i : $i = T, T^*, V_I, V_{NI}$ Death rate of uninfected $CD4^+$T cells, Infected $CD4^+$T cells, free infectious virus and free 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.

τ : Time delay from infection of the cell to production of new infectious viruses

3.2.2 Model Flow Chart

Using compartmental model, the parameters described above represents the dynamics of populations from one compartment to another as shown in the flow chart in Figure 3.3 and Figure 3.4 below.

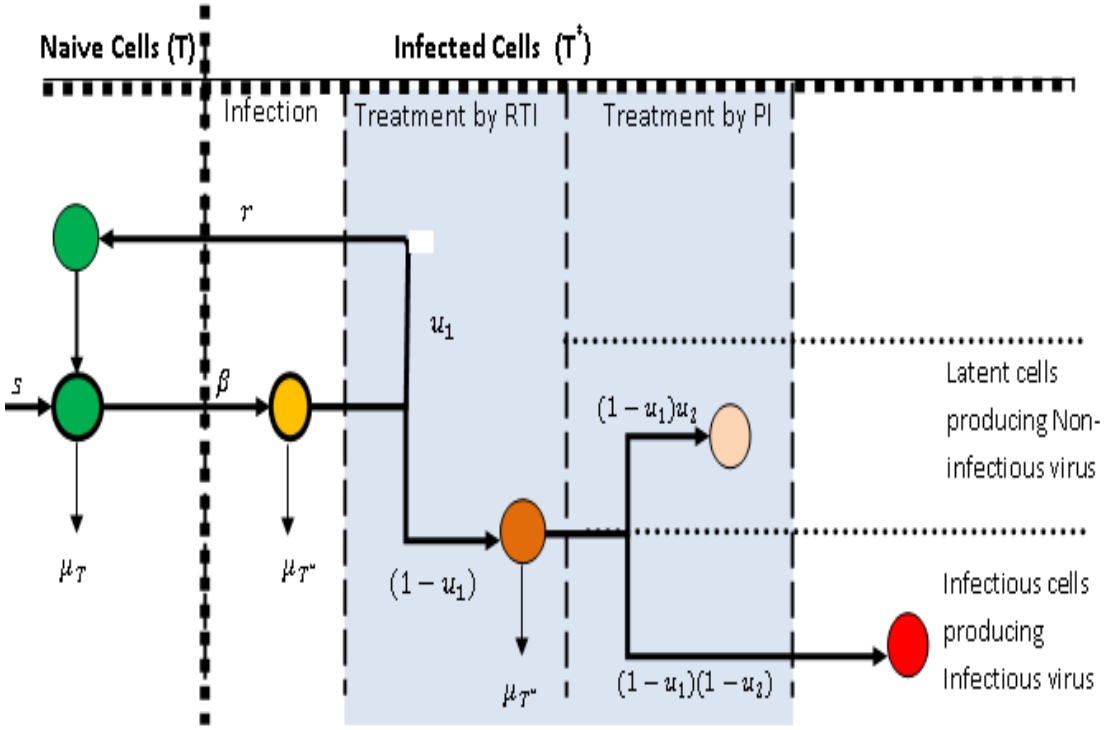


Figure 3.3 Flow-Chart showing progression of infection and viral production

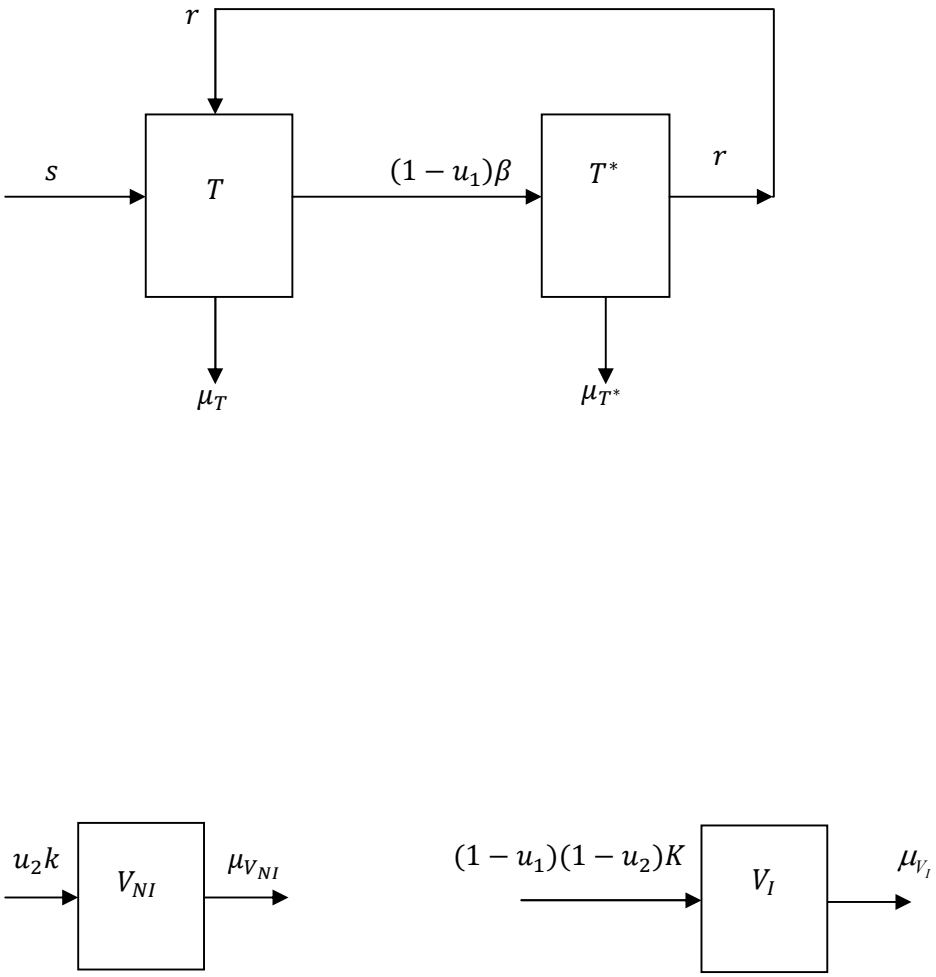


Figure 3.4 Flow chart showing T-cell compartments and viral compartments

3.2.3 Model Equations

The model parameters and the model assumptions above, together with the flow charts in Figure 3.3 and Figure 3.4 will lead to the following system of delay differential equations for the combinational therapy.

$$\begin{cases} \dfrac{dT(t)}{dt} = s - \mu_T T(t) - (1-u_1)\beta V_I(t-\tau)T(t) + ru_1 T^*(t) \\ \dfrac{dT^*(t)}{dt} = (1-u_1)\beta V_I(t-\tau)T(t) - \mu_{T^*} T^*(t) - ru_1 T^*(t) \\ \dfrac{dV_I(t)}{dt} = (1-u_1)(1-u_2)kT^*(t-\tau) - \mu_{V_I} V_I(t) \\ \dfrac{dV_{NI}(t)}{dt} = (1-u_1)u_2 kT^*(t-\tau) - \mu_{V_{NI}} V_{NI}(t) \end{cases} \tag{3.6}$$

In this model, time delay has been incorporated to describe the time between infection of a $CD4^+$T-cell and the emission of viral particles on cellular level. We do not consider the proliferation of target cells since our goal is to simplify the model to get more insight about the effects of intracellular delays and chemotherapy on HIV-1 in vivo dynamics. The model includes the completely recovered cells when they loss all covalently closed circular DNA (cccDNA) from their nucleus at a rate r, (a recovery rate of those responding to treatmentu_1) as a result of chemotherapy.

3.3 Model Preliminary Analysis

3.3.1 Properties of Solutions of the Model

Before we can do analysis of our model, we need to look at the positivity and boundedness of solutions of our model. Because this model describes the evolution of a cell population, the cell numbers should remain non-negative and bounded. These properties imply global existence of the solutions.

Let $C=C\left([-\tau,0],\ R^4\right)$ be a Banach space of continuous functions mapping the interval $[-\tau,0]$ into R^4 with the topology of uniform convergence.

By the fundamental theory of differential equations, it can be shown that there exists a unique solution $(T(t),T^*(t),V_I(t),V_{NI}(t))$, of system (3.6) with initial data

$$\left(T(0)>0,\ T^*(0)>0,\ V_I(0)>0,\ V_{NI}(0)>0\right)\in C. \tag{3.7}$$

In addition, for biological reasons, we assume that the initial data for system (3.6) satisfies:

$$T_0(s)\geq 0,\ T_0^*(s)\geq 0,\ V_{I_0}(s)\geq 0,\ V_{NI_0}(s)\geq 0,\quad s\in[-\tau,0] \tag{3.8}$$

The following theorem establishes the positivity and boundedness of solutions of equation (3.6) with initial functions satisfying (3.7) and (3.8).

Proposition 3.1 Let $\left(T(t),\, T^{*}(t),\, V_I(t),\, V_{IN}(t)\right)$ be the solutions of system (3.6) satisfying conditions (3.7) and (3.8). Then $T(t),\ T^{*}(t),\ V_I(t),$ and $V_{IN}(t)$ are all non-negative and bounded for all $t > 0$ at which the solutions exists.

Proof

Note that from (3.6) we have

$$T(t) = T(0)e^{-\int_0^t (\mu_T + (1-u_1)\beta V_1(\xi-\tau))d\xi} + \int_0^t [ru_1 T^*(\eta) + s]e^{-\int_\eta^t (\mu_T + (1-u_1)\beta V_1(\xi-\tau))d\xi} d\eta,$$

$$T^*(t) = T^*(t)e^{-\int_0^t [\mu_{T^*} + ru_1]d\xi} + \int_0^t [(1-u_1)\beta V_1(\eta-\tau)T(\eta)]e^{-\int_\eta^t [\mu_{T^*} + ru_1]d\xi} d\eta,$$

$$V_1(t) = V_1(0)e^{-\int_0^t \mu_{V_I} d\xi} + \int_0^t [(1-u_1)(1-u_2)kT^*(\eta-\tau)]\, e^{-\int_\eta^t \mu_{V_I} d\xi} d\eta$$

and

$$V_{NI}(t) = V_{NI}(0)e^{-\int_0^t \mu_{V_{NI}} d\xi} + \int_0^t [(1-u_1)u_2 kT^*(\eta-\tau)]\, e^{-\int_\eta^t \mu_{V_{NI}} d\xi} d\eta$$

Positivity immediately follows from the above integral forms and (3.7) and (3.8).

For boundedness, we define $N(t) = T(t) + T^*(t) + V_I(t) - \dfrac{(1-u_2)}{u_2} V_{NI}(t)$ and

$\delta = \min\left(\mu_T, \mu_{T^*}, \mu_{V_I}, \mu_{NI}\left(\dfrac{1-u_2}{u_2}\right)\right)$ then

$\dfrac{d}{dt}N(t) = \dfrac{d}{dt}T(t) + \dfrac{d}{dt}T^*(t) + \dfrac{d}{dt}V_I(t) - \dfrac{(1-u_2)}{u_2}\dfrac{d}{dt}V_{NI}(t)$. Thus

$\dfrac{d}{dt}N(t) \le s - \delta N(t).$

Which implies that $N(t)$ is bounded, and so are $T(t), T^*(t), V_I(t), V_{NI}(t)$ this completes the proof of proposition 3.1**.**

3.4 Equilibrium Points and their Stability

We analyze equation (3.6) by first finding the equilibrium points of the system and then studying their stability. An equilibrium point is obtained by setting the right hand side of each equation of system (3.6) to zero, then solving each equation algebraically for the constant solutions.

There are usually two important equilibrium points to consider in mathematics of infectious diseases. These equilibriums points are the Disease Free Equilibrium Point(s) (DFE) and the Endemic Equilibrium Point(s) (EEP).

3.4.1 Disease Free Equilibrium Point(S) (DFE)

The disease free equilibrium point(s) is the set of point(s) of system (3.6) in the absence of the virus. For our system, the disease free equilibrium (DFE) is the set of points $\left(T^0, T^{*0}, V_I^0, V_{NI}^0\right) = \left(\frac{s}{\mu_T},\ 0,\ 0,\ 0\right)$, corresponding to the maximal level of $CD4^+$T-cells.

3.4.1.1 Stability of Disease Free Equilibrium

Local asymptotic stability of nonlinear system about equilibrium is governed by the stability of the linearized system about the equilibrium. The zero solution of the nonlinear system is asymptotically stable if and only if the zero solution of the linear system is asymptotically stable. The eigen-values of the linearization matrix, is used in determining the stability of the linear system obtained from the nonlinear system. If all the eigen-values of the linearization matrix have negative real parts, then the system is stable. If any one of these eigen-values is having a positive real part, the system will be unstable.

Letting $f_i, i = 1, 2, 3, 4$ be the sub-equations 1, 2, 3 and 4 of model equation (3.6), we can obtain the linearization matrix M of our model at DFE as,

$$M = \frac{\partial(f_1, f_2, f_3, f_4)}{\partial(T, T^*, V_I, V_{NI})}\Big|_{DFE} \tag{3.9}$$

Which simplify to the following for our model at DFE without delay,

$$M = \begin{pmatrix} -\mu_T & ru_1 & \frac{-(1-u_1)\beta s}{\mu_T} & 0 \\ 0 & -\mu_{T^*} - ru_1 & \frac{(1-u_1)\beta s}{\mu_T} & 0 \\ 0 & (1-u_1)(1-\mu_2)k & -\mu_{V_I} & 0 \\ 0 & (1-u_1)u_2 k & 0 & -\mu_{V_{NI}} \end{pmatrix} \tag{3.10}$$

The two eigen-values associated with the above matrix can easily be computed to obtain, $\lambda_1 = -\mu_T$, and $\lambda_4 = -\mu_{NI}$ both of which are negative since the death rate are positive quantities. The other two remaining eigen-values are computed from the following 2x2 matrix;

$$M_1 = \begin{pmatrix} -\mu_{T^*} - ru_1 & \frac{(1-u_1)\beta s}{\mu_T} \\ (1-u_1)(1-u_2)k & -\mu_{V_I} \end{pmatrix}$$

The characteristics polynomial associated with matrix M_1 is

$$\lambda^2 + (\mu_{V_I} + \mu_T + ru_1)\lambda + \mu_{V_I}(\mu_T + ru_1) - \frac{(1-u_1)^2(1-u_2)\beta ks}{\mu_T} = 0$$

This characteristics polynomial can be solved to obtain

$$\lambda_{2,3} = \frac{1}{2}\left(-(\mu_{V_I} + \mu_T + ru_1) \pm \sqrt{(\mu_{V_I} + \mu_T + ru_1)^2 - 4\left(\mu_{V_I}(\mu_T + ru_1) - \frac{(1-u_1)^2(1-u_2)\beta ks}{\mu_T} \right)} \right)$$

For both roots of the above equations to be negative, we have that

$$\mu_{V_I}(\mu_T + ru_1) - \left(\frac{(1-u_1)^2(1-u_2)\beta ks}{\mu_T}\right) > 0 \text{ or } \left(\frac{(1-u_1)^2(1-u_2)\beta ks}{\mu_T \mu_{V_I}(\mu_{T^*} + ru_1)}\right) < 1$$

This condition can be written as $R_0 < 1$ where R_0 is defined as

$$R_0 = \frac{(1-u_1)^2(1-u_2)\beta ks}{\mu_T \mu_{V_I}(\mu_{T^*} + ru_1)} \tag{3.11}$$

Clearly the condition $R_0 < 1$ must be satisfied for DFE to be stable in absence of delay.

3.4.1.2 Effects of Delay on Stability of DFE

We can check the effect of delay on DFE by considering the Jacobian (linearization) matrix of model equation (3.6) at DFE with delay. This would lead us to the following linearization matrix at DFE with delay,

$$\begin{pmatrix} -\mu_T & ru_1 & -\frac{(1-u_1)\beta s e^{-\lambda\tau}}{\mu_T} & 0 \\ 0 & -\mu_{T^*} - ru_1 & \frac{(1-u_1)\beta s e^{-\lambda\tau}}{\mu_T} & 0 \\ 0 & (1-u_1)(1-u_2)ke^{-\lambda\tau} & -\mu_{V_I} & 0 \\ 0 & (1-u_1)u_2 ke^{-\lambda\tau} & 0 & -\mu_{NI} \end{pmatrix} \tag{3.12}$$

The eigen-values of matrix (3.12) can easily be found as $\lambda_1 = -\mu_T$ and $\lambda_4 = -\mu_{V_{NI}}$ with the remaining two eigen-values obtain from the following transcendental equation,

$$\lambda^2 + (\mu_{T^*} + ru_1 + \mu_{V_I})\lambda + \mu_{V_I}(\mu_{T^*} + ru_1) - \frac{(1-u_1)^2(1-u_2)\beta ks e^{-2\lambda\tau}}{\mu_T} = 0 \tag{3.13}$$

$$\lambda^2 + (\mu_{T^*} + ru_1 + \mu_{V_I})\lambda + \mu_{V_I}(\mu_{T^*} + ru_1)\left[1 - \frac{(1-u_1)^2(1-u_2)\beta k s e^{-2\lambda\tau}}{\mu_T \mu_{V_I}(\mu_{T^*} + ru_1)}\right] = 0$$

$$\lambda^2 + (\mu_{T^*} + \mu_{V_I})\lambda + \mu_{V_I}\mu_{T^*} + \left\{\lambda r u_1 + \mu_{V_I} r u_1\left[1 - \frac{(1-u_1)^2(1-u_2)\beta k s e^{-\lambda\tau}}{\mu_T \mu_{V_I}(\mu_{T^*} + ru_1)}\right]\right\} e^{-\lambda\tau} = 0$$

$$\lambda^2 + (\mu_{T^*} + \mu_{V_I})\lambda + \mu_{V_I}\mu_{T^*} + \{\lambda r u_1 + \mu_{V_I} r u_1[1 - R_0 e^{-\lambda\tau}]\}e^{-\lambda\tau} = 0$$

or

$$\lambda^2 + a\lambda + b + (\lambda c + d)e^{-\lambda\tau} + he^{-2\lambda\tau} = 0 \qquad (3.14)$$

where $a = (\mu_{T^*} + \mu_{V_I}),\ b = \mu_{V_I}\mu_{T^*},\ c = ru_1,\ d = \mu_{V_I} r u_1, h = \mu_{V_I} r u_1 R_0$

We seek the distribution of the roots of the second order transcendental polynomial equation (3.14) where the parameters $a,\ b, c, d, h$ and τ are real numbers and d and $h$satisfy the following two assumptions (ShanShan *et. al.*, 2013)

A_1: c cannot be zero

A_2: h cannot be zero.

The two assumptions above ensures that we always have a second order transcendental polynomial equation to deal with it also mean that recovery rate cannot be zero in a chemotherapy model of HIV-1 in vivo dynamics. We also fix the parameters $a,\ b, c, d$ and h and vary τ since we are interested on the effect of τ on the stability of diseases free equilibrium.

By linearization theorem, DFE is asymptotically stable if all the eigen-values of (3.14) have negative real part.

Using the approach described by (Chen *et.al.,* 2013) set $\lambda = \alpha + i\omega$. We then seek conditions on τ such that $\mathrm{Re}(\lambda)$ changes from a negative number to a positive number.

By continuity, if $\mathrm{Re}(\lambda) = \alpha$ changes from $\mathrm{Re}(\lambda) = \alpha < 0$ to a value such that $\mathrm{Re}(\lambda) = a > 0$, as τ increases from zero, there must be some value of τ say τ_0 at which $\mathrm{Re}\,\lambda(\tau_0) = \alpha(\tau_0) = 0$. In other words, the characteristics equation (3.14) must have a pair of purely imaginary roots $\pm i\omega_0$. If that be the case then equation (3.14) becomes

$$\omega^2 + ai\omega + b + (ci\omega + d)e^{-i\omega\tau} + he^{-2i\omega\tau} = 0 \tag{3.15}$$

If $\frac{\omega\tau}{2} \neq \frac{\pi}{2} + j\pi, j \in Z$ and $\theta = \tan\frac{\omega\tau}{2}$ then $e^{-i\omega\tau} = \frac{1 - i\theta}{1 + i\theta}$.

Separating the real and imaginary parts, then θ satisfies the following two equations

$$(\omega^2 - b + d - h)\theta^2 - 2a\omega\theta = \omega^2 - b - d - h$$

$$(c\omega - a\omega)\theta^2 + (-2\omega^2 + 2b - 2h)\theta = -(a\omega + c\omega) \tag{3.16}$$

Denote

$$M = \begin{pmatrix} \omega^2 - b + d - h & -2a\omega & \omega^2 - b - d - h \\ (c-a)\omega & -2\omega^2 + 2b - 2h & -(c+a)\omega \end{pmatrix}$$

$$M_2 = \begin{pmatrix} \omega^2 - b + d - h & -2a\omega \\ (c-a)\omega & -2\omega^2 + 2b - 2h \end{pmatrix}$$

$$M_3 = \begin{pmatrix} \omega^2 - b - d - h & -2a\omega \\ -(c-a)\omega & -2\omega^2 + 2b - 2h \end{pmatrix} \text{ and}$$

$$M_4 = \begin{pmatrix} \omega^2 - b - d - h & -2a\omega \\ (c-a)\omega & -2\omega^2 - 2b - 2h \end{pmatrix}$$

and define

$$D(\omega) = D\text{et}(M_1)\,, E(\omega) = D\text{et}(M_3)\,, F(\omega) = D\text{et}(M_4)\,.$$

If, $D(\omega) \neq 0$ then (3.16) can be solved to get:

$$\theta^2 = \frac{E(\omega)}{D(\omega)}, \qquad \theta = \frac{F(\omega)}{D(\omega)}\ .$$

From which we get that $D(\omega)E(\omega) - F(\omega)^2 = 0$ .Therefore by simple algebraic manipulations we see that ω satisfies the following 8th order polynomial equation for $D(\omega) \neq 0$.

$$\omega^8 + s_1\omega^6 + s_2\omega^4 + s_3\omega^2 + s_4 \tag{3.17}$$

Where

$$s_1 = 2a^2 - 4b - c^2$$

$$s_2 = 6b^2 - 2h^2 - 4ba^2 - d^2 + a^4 - a^2c^2 + 2c^2b + 2hc^2$$

$$s_3 = 2d^2b - a^2d^2 - 4b^3 + 2b^2a^2 - c^2b^2 - 2bc^2h + 4acdh - 2d^2h + 4bh^2 - 2h^2a^2 - c^2h^2$$

$$s_4 = b^4 - d^2b^2 - 2b^2h^2 + 2bd^2h - d^2h^2 + h^4 = (b-h)^2\left[-d^2 + (b+h)^2\right] \tag{3.18}$$

and ω^2 is a positive root of

$$z^4 + s_1z^3 + s_2z^2 + s_3z + s_4 \tag{3.19}$$

If $\omega\tau = \frac{\omega}{2} + j\omega,\ j \in Z$then $a = c$ and $\omega = b + h - d$, hence $D(\omega) = F(\omega) = 0$. So ω^2 is still a positive root of equation (3.19).From this analysis the following lemma can be stated.

Lemma 3.1

If $\pm i\omega$ $(\omega > 0)$ is a pair of purely imaginary roots of equation (3.14) then ω^2 is a positive root of Equation (3.19) for s_i for $1 \leq i \leq 4$ are given in equation (3.18).

The converse of Lemma 3.1 does not always hold. The conditions for which the converse of this lemma holds has been very well established in (ShanShan *et.al.*, 2013) .

Lemma 3.2

If equation (3.19) has a positive root ω_N^2 $(\omega_N > 0)$ and $D(\omega_N) \neq 0$, then equation (3.15) has a unique root

$\theta_N = \dfrac{F(\omega_N)}{D(\omega_N)}$ when $\omega = \omega_N$. Hence (3.14) has a pair of purely imaginary roots $\pm i\omega_N$ when

$$\tau = \tau_N^j = \frac{2\arctan\theta_N + 2j\pi}{\omega_N}, j \in \mathbf{Z} \tag{3.20}$$

Proof

If $D(\omega_N) \neq 0$ then $\dfrac{E(\omega_N)}{D(\omega_N)} = \left(\dfrac{F(\omega_N)}{D(\omega_N)}\right)^2$. Consequently (3.15) has a real root $\omega_N = \omega$ and hence (3.14) has a pair of purely imaginary roots $\pm i\omega_N$ when $\tau = \tau_N^j$ has define in (3.20)

If the root ω^2 of equation (3.19) and the root θ of equation (3.15) are solved, then the corresponding τ −value is always solved from the relation

$$\tau = \tau^j = \frac{2\arctan\theta + 2j\pi}{\omega}, j \in \mathbf{Z} \quad (3.21)$$

Since $\theta = \tan\frac{\omega\tau}{2}$, if τ is restricted to be positive, then $j \in \mathbb{N}$ or $j \in \mathbb{N}\cup\{0\}$ depending on θ

There is one except to this statement, which is a limit case in the sense that $\theta = \infty$, $\omega\tau = \pi$ and $\arctan\theta = \frac{\pi}{2}$.

3.4.1.3 Transversality Condition

Suppose that (3.19) has a positive root $\omega^2(\omega > 0)$, (3.15) has a real root θ with this ω and $\tau = \tau^j$ $(j \in \mathbb{Z})$.

For $\theta \in (-\infty, +\infty)$ define the following function;

$$G(\omega,\theta) = \left[d(1+\theta^2) + 2h(1-\theta^2)\right].\left[2\omega(1-\theta^2) + 2a\theta\right]$$

$$-\left[c\omega(1+\theta^2) - 4h\theta\right].\left[a(1-\theta^2) - 4\omega\theta + c(1+\theta^2)\right]. \quad (3.22)$$

If $G(\omega,\theta) \neq 0$, then $i\omega$ is a simple root (3.14) for $\tau = \tau^j$ and there exists

$\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ which is the unique root of (3.14) for $\tau \in (\tau^j - \varepsilon, \tau^j + \varepsilon)$ for some small $\varepsilon > 0$ satisfying $\alpha(\tau^j) = 0$ and $\omega(\tau^j) = \omega$. Moreover, $\frac{dRe\{\lambda(\tau)\}}{d\tau}|_{\tau=\tau^j} = \frac{d\alpha(\tau)}{d\tau}|_{\tau=\tau^j} > 0,\ j \in \mathbb{Z}$ when $G(\omega,\theta) > 0$

$$\frac{dRe\{\lambda(\tau)\}}{d\tau}|_{\tau=\tau^j} = \frac{d\alpha(\tau)}{d\tau}|_{\tau=\tau^j} < 0,\ j \in \mathbb{Z} \text{ when } G(\omega,\theta) < 0 \quad (3.23)$$

For $\theta = \infty$ (in the sense that $\arctan\theta = \frac{\pi}{2}$) if $2h - d \neq 0$, then the conclusion in lemma 3.1 holds

Proof

$Denote\ M(\lambda,\tau) = \lambda^2 + a\lambda + b + (c\lambda + d)e^{-\lambda\tau} + he^{-2\lambda\tau}$

Then $\frac{\partial M}{\partial \lambda}(\lambda,\tau) = e^{-\lambda\tau}P(\lambda,\tau)$ and

$$\frac{\partial M}{\partial \tau}(\lambda,\tau) = -\lambda e^{-\lambda\tau}Q(\lambda,\tau)$$

where

$$P(\lambda,\tau) = (2\lambda + a)e^{\lambda\tau} + c + (c\lambda + d)\tau - 2h\tau e^{-2\lambda\tau},$$

and

$$Q(\lambda,\tau) = c\lambda + d + 2h\tau e^{-2\lambda\tau}.$$

For $\theta \in (-\infty, +\infty)$, substituting $\lambda = i\omega,\ \tau = \tau^j$ and $\theta = \tan\frac{\omega\tau^j}{2}$ $P(\lambda,\tau)$ and $Q(\lambda,\tau)$,

leads to $(1+\theta^2)P(i\omega,\tau^j) = a(1-\theta^2) - 4\omega\theta + c(1+\theta^2) - \tau^j d(1+\theta^2) - 2h\tau^j(1-\theta^2)$

$$+i\left[2\omega(1-\theta^2) + 2a\theta - c\omega\tau^j(1+\theta^2) + 4h\tau^j\theta\right],$$

and

$$(1+\theta^2)Q(i\omega,\tau^j) = d(1+\theta^2) + 2h(1-\theta^2) + i(c\omega(1+\theta^2)) - 4h\theta).$$

Hence

$$IM\left\{(1+\theta^2)^2 P(i\omega,\ \tau^j)\overline{Q(i\omega,\ \tau^j)}\right\}$$

$$= \left[d(1+\theta^2) + 2h(1-\theta^2)\right].\left[2\omega(1-\theta^2) + 2a\theta - c\omega\tau^j(1+\theta^2) + 4h\tau^j\theta\right]$$

$$-\left[c\omega(1+\theta^2))-4h\theta\right].\left[a(1-\theta^2)-4\omega\theta+c(1+\theta^2)\right]$$

$$-\left[c\omega(1+\theta^2))-4h\theta\right].\left[-\tau^j d(1+\theta^2)-2h\tau^j(1-\theta^2)\right]$$

$$=\left[d(1+\theta^2)+2h(1-\theta^2)\right].\left[2\omega(1-\theta^2)+2a\theta\right]$$

$$-\left[c\omega(1+\theta^2))-4h\theta\right].\left[a(1-\theta^2)-4\omega\theta+c(1+\theta^2)\right]$$

$$=G(\omega,\theta).$$

Since

$$\frac{\partial M}{\partial \lambda}(i\omega,\tau^j)=P(i\omega,\tau^j)e^{-i\omega\tau^j},$$

when $G(\omega,\theta)\neq 0,$ implying that $\frac{\partial M}{\partial \lambda}(i\omega,\tau^j)\neq 0.$ From implicit function theorem, it will implies that $i\omega$ is simple and there exist $\lambda(\tau)=\alpha(\tau)+i\omega(\tau)$ which is the unique root of equation (3.14) for $\tau\in(\tau^j-\varepsilon,\tau^j+\varepsilon)$ .for some small $\varepsilon>0$ satisfying $\alpha(\tau^j)=0$ and $i\omega(\tau)=\omega$. Substituting $\lambda(\tau)$ into (3.14) and taking derivatives with respect to τ gives

$$P(\lambda,\tau)\frac{d\lambda}{d\tau}=\lambda Q(\lambda,\tau),$$

and

$$\frac{d\,\mathrm{Re}\{\lambda(\tau)\}}{d\tau}\Big|_{\tau=\tau^j}>0, j\in\mathbf{Z}\ \text{when}\ G(\omega,\theta)>0\,.$$

$$\frac{d\,\mathrm{Re}\{\lambda(\tau)\}}{d\tau}\Big|_{\tau=\tau^j}<0, j\in\mathbf{Z}\ \text{when}\ G(\omega,\theta)<0\,.$$

Hence the case when $\theta \neq \infty$ is obtained.

When $\theta = \infty$, then $a = c$ and $b + h - d > 0$, and equation (3.14) has a pair of purely imaginary roots $\pm i\omega = \pm\sqrt{b + h - d}$ when $\tau^j = \frac{\pi + 2j\pi}{\omega}$. In this case,

$$\operatorname{Im}\left\{P(i\omega,\tau^j)\overline{Q(i\omega,\tau^j)}\right\} = 2\omega(2h - d),.$$

This completes the verification of the transversality condition.

Equation (3.20) implies that

$\tau = \tau^0 = \frac{2\arctan\theta}{\omega}$ Is the critical value of delay for stability of endemic equilibrium and $\theta = \frac{F(\omega)}{D(\omega)}$

From the above analysis, the following proposition can be stated

Proposition 3.2:

(i) If $0 < \tau < \tau^0$, then the DFE of our model is asymptotically stable.

(ii) If $\tau > \tau^0$, then the DFE of our model is unstable.

(iii) If $\tau = \tau^0$, then the DFE of our model will undergo a Hopf bifurcation, that is a periodic solution bifurcate from $\tau = \tau^0$. The periodic solution exists for $\tau < \tau^0$ and is stable.

3.4.2 Stability of Endemic Equilibrium in Absence of Delay

Stability of system equation (3.6) at EEP is determined by the signs of the Eigen-values of linearization matrix of the system evaluated at EEP.

The zero solutions of the nonlinear system equation (3.6) at EEP is asymptotically stable if and only if the zero solutions of the linear system obtain from equation (3.6) is asymptotically stable. Therefore asymptotic stability of equation (3.6) at EEP is established by examining the signs of the Eigen-values of the zero solutions of the linearized system.

From simple algebraic calculations we obtain the values of the endemic equilibrium points as;

$$T^e = \frac{sR_0}{\mu_T}, \quad T^{*e} = \frac{\mu_T \mu_{V_I}(R_0 - 1)}{r\mu_T^2 \mu_{V_I} - (1-u_1)\beta s R_0},$$

$$V_I^e = \frac{\mu_T(1-u_1)(1-u_2)ks(R_0-1)}{r\mu_T^2\mu_{V_I} - (1-u_1)\beta s R_0}$$

and $$V_{NI}^e = \frac{\mu_T \mu_{T^*} \mu_{V_I}(1-u_1)ks(R_0-1)}{\mu_{V_{NI}}(r\mu_T^2\mu_{V_I} - (1-u_1)\beta s R_0)} \tag{3.21}$$

We start by centering the model equation (3.6) at endemic equilibrium $E^e(T^e, T^{*e}, V_I^e, V_{NI}^e)$ by introducing new variables

$$W_1 = T - T^e, \quad W_2 = T^* - T^{*e}, \quad W_3 = V_I - V_I^e, \quad W_4 = V_{NI} - V_{NI}^e$$

We then rewrite the model equations of system (3.6) in term of the new variables, and because $E^e(T^e, T^{*e}, V_I^e, V_{NI}^e)$ is an equilibrium point, the constant term cancel. We also discard the quadratic terms because their partial derivatives at the origin are zero.

The system (3.6) with the new variables becomes

$$\dot{W}_1(t) = \mu_W W_1(t) - (1-u_1)\beta(W_1(t)V_1^e + W_3(t-\tau)T^e)$$

$$\dot{W}_2(t) = (1-u_1)\beta(W_1(t)V_1^e + W_3(t-\tau)T^e) - (\mu_{W_2} + ru_1)W_2(t)$$

$$\dot{W}_3(t) = (1-u_1)(1-u_2)kW_2(t-\tau) - \mu_{W_3}W_3(t) \tag{3.22}$$

$$\dot{W}_4(t) = (1-u_1)u_2kW_2(t-\tau) - \mu_{W_4}W_4(t)$$

System (3.22) in matrix form is given by

$$\begin{pmatrix} \dot{W}_1(t) \\ \dot{W}_2(t) \\ \dot{W}_3(t) \\ \dot{W}_4(t) \end{pmatrix} = \begin{pmatrix} -\mu_{W_1} - aV_I^e & ru_1 & -aT^e e^{-\lambda\tau} & 0 \\ aV_I^e & -b & aT^e e^{-\lambda\tau} & 0 \\ 0 & ce^{-\lambda\tau} & \mu_{w_3} & 0 \\ 0 & de^{-\lambda\tau} & 0 & \mu_{W_4} \end{pmatrix} \begin{pmatrix} W_1(t) \\ W_2(t) \\ W_3(t) \\ W_4(t) \end{pmatrix}$$

where $a = (1-u_1)\beta$, $b = (\mu_{W_2} + ru_1)\beta$, $c = (1-u_1)(1-u_2)k$, $d = (1-u_1)u_2k$.

The eigen-values of the above matrix are obtained from evaluating and solving the following determinant for λ .

$$\begin{vmatrix} -\mu_T - (1-u_1)\beta V_I^e - \lambda & ru_1 & -(1-u_1)\beta T^e e^{-\lambda\tau} & 0 \\ (1-u_1)\beta V_I^e & -(\mu_{T^*} + r)e^{-\lambda\tau} - \lambda & (1-u_1)\beta T^e e^{-\lambda\tau} & 0 \\ 0 & (1-u_1)(1-u_2)ke^{-\lambda\tau} & -\mu_{V_I} - \lambda & 0 \\ 0 & (1-u_2)u_2ke^{-\lambda\tau} & 0 & -\mu_{V_{IN}} - \lambda \end{vmatrix} = 0 \tag{3.23}$$

Matrix (3.23) without delay becomes,

$$\begin{vmatrix} -\mu_T - (1-u_1)\beta V_I^e - \lambda & ru_1 & -(1-u_1)\beta T^e & 0 \\ (1-u_1)\beta V_I^e & -(\mu_{T^*} + r) - \lambda & (1-u_1)\beta T^e & 0 \\ 0 & (1-u_1)(1-u_2)k & -\mu_{V_I} - \lambda & 0 \\ 0 & (1-u_2)u_2k & 0 & -\mu_{V_{IN}} - \lambda \end{vmatrix} = 0 \tag{3.24}$$

In order to determine stability, we linearize the system equation (3.22) about the equilibrium point in equation (3.21) and find the condition for which all the eigenvalues of the coefficient matrix are negative.

Assume a solution of the form $w(t) = w_0 e^{-\lambda t}$, then linearizing about the origin $(W_1, W_2, W_3, W_4) = (0, 0, 0, 0)$ yields the system

$$\begin{pmatrix} W_1' \\ W_2' \\ W_3' \\ W_4' \end{pmatrix} = \begin{pmatrix} -\mu_T - (1-u_1)\beta V^e - \lambda & ru_1 & -(1-u_1)\beta T^e e^{-\lambda\tau} & 0 \\ (1-u_1)\beta V^e & -(\mu_{T^*} + ru_1) - \lambda & (1-u_1)\beta T^e e^{-\lambda\tau} & 0 \\ 0 & (1-u_1)(1-u_2)ke^{-\lambda\tau} & -\mu_{V_I} - \lambda & 0 \\ 0 & (1-u_1)ke^{-\lambda\tau} & 0 & -\mu_{V_{NI}} - \lambda \end{pmatrix} \begin{pmatrix} W_1 \\ W_2 \\ W_3 \\ W_4 \end{pmatrix} \tag{3.25}$$

Clearly, the fourth eigen-value is negative, that is, $\lambda_4 = -\mu_{V_{NI}}$and the sign of the other three can be determined using Routh Hurwitz criteria.

The characteristic equation of the reduced 3×3 matrix from equation (3.25) is given by

$$\lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3 = 0 \tag{3.26}$$

where;

$$a_1 = \mu_{T^*} + ru_1 + \mu_{V_I} + \mu_T + (1-u_1)\beta V^e$$

$$a_2 = (\mu_{T^*} + ru_1)\mu_{V_I} + (1-u_1)(1-u_1)k\beta T^e e^{-2\lambda\tau} + \left[(\mu_{T^*} + ru_1) + \mu_{V_I}\right][-\mu_T - (1-u_1)\beta V^e] - ru_1(1-u_1)\beta V^e$$

and

$$a_3 = \left[(\mu_{T^*} + ru_1)\mu_{V_I} - (1-u_1)u_2 k\beta T^e e^{-2\lambda\tau}\right][-\mu_T - (1-u_1)\beta V^e] - ru_1\mu_{V_I}(1-u_1)\beta V^e$$
$$+ (1-u_1)(1-u_1)(1-u_2)k\beta^2 V^e T^e e^{-2\lambda\tau}$$

Routh Hurwitz condition requires that for all eigenvalues to be negative, the conditions below must be satisfied.

$H_1 = a_1 > 0,\ H_2 = a_1 a_2 - a_3 > 0$ and $H_3 = a_3 > 0$.

In the absent of delay we clearly see that, $a_1 > 0$ and $a_3 > 0$ if the following condition is satisfied;

Defining $R_1 = \frac{(1-u_1)^2(1-u_2)\beta k T^e}{\mu_T \mu_{V_I}(\mu_T^* + ru_1)}$, then all eigenvalues are negative if $R_1 > 0$ or $R_0^2 > 0$.

3.4.3 Stability of Endemic Equilibrium with Delay

In the presences of delay, the remaining eigen-values are obtained from the following 3X3 determinant

$$\begin{vmatrix} -a-\lambda & b & -ce^{-\lambda\tau} \\ d & -f-\lambda & ce^{-\lambda\tau} \\ 0 & ge^{-\lambda\tau} & -h-\lambda \end{vmatrix} = 0$$

where: $a = \mu_{w1} + (1-u_1)\beta v^e$, $b = ru_1, c = (1-u_1)\beta T^e$.

$d = (1-u_1)\beta v^e, f = \mu_{w2} + ru_1,\ g = (1-u_1)(1-u_2)k,\ h = \mu_{w_3}$.

Which simply to the following transcendental equation

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3\lambda e^{-2\lambda\tau} + b_4 e^{-2\lambda\tau} + b_5 = 0 \qquad (3.27)$$

where:

$$b_1 = a + f + h$$

$$b_2 = af + ah - fh - bd$$

$$b_3 = -cg$$

$$b_4 = cbg - acg = cg(b - a)$$

$$b_5 = afh - bdh = h(af - bd)$$

The characteristics equation (3.27) compares to the one analysized by Rebecca and Shigui, (2000) and we use the approach used in their paper to locate the roots of this equation analytically.

Let $\lambda = \alpha \pm i\omega$, substituting into equation (3.27) and assuming purely imaginary $\alpha = 0$, we clearly see that $\lambda = \pm i\omega \ (\omega > 0)$ is the root of equation (3.26) if and only if

$$-i\omega^3 - b_1\omega^2 + b_2 i\omega + b_3 i\omega(\cos 2\omega\tau - i\sin 2\omega\tau) + b_4(\cos 2\omega\tau - i\sin 2\omega\tau) + b_5 = 0 \tag{3.28}$$

Separating the real and imaginary parts, we have that:

$$b_1\omega^2 - b_5 = b_4 \cos 2\omega\tau + b_3\omega \sin 2\omega\tau \tag{3.29}$$

$$\omega^3 - b_2\omega = -b_4 \sin 2\omega\tau + b_3\omega \cos 2\omega\tau \tag{3.30}$$

Adding the squares of both sides of these two equations and collecting like terms, one gets that:

$$\omega^6 + (b_1^2 - 2b_2)\omega^4 + (b_2^2 + 2b_1b_5 - b_3^2)\omega^2 + b_5^2 - b_4^2 = 0 \tag{3.31}$$

Let $z = \omega^2$, $\alpha = b_1^2 - 2b_2$, $\beta = b_2^2 + 2b_1b_5 - b_3^2$ and $\gamma = b_5^2 - b_4^2$ then equation (3.31) becomes:

$$h(z) = z^3 + \alpha z^2 + \beta z + \gamma = 0 \tag{3.32}$$

Let $\frac{dh(z)}{dz} = 3z^2 + 2\alpha z + \beta = 0$ (3.33)

If $\gamma \geq 0$, and $\beta \geq 0$ then equation (3.32) has no positive real roots.

In fact we have that

$\frac{dh(z)}{dz} = 3z^2 + 2\alpha z + \beta.$ Setting $3z^2 + 2\alpha z + \beta = 0$ (3.34) then the roots of this equation can be expressed as $z_{1,2} = \frac{-\alpha \pm \sqrt{\alpha^2 - 3\beta}}{3}$.

If $\beta > 0$,then $\alpha^2 - 3\beta < \alpha^2$, that is $\sqrt{\alpha^2 - 3\beta} < \alpha$. Hence both roots of equation (3.34) are negative. Since $h(0) = \gamma \geq 0$ equation (3.32) has no positive roots.

Proposition 3.3

Suppose that

(i) $b_1 > 0, b_3 + b_5 > 0, b_1(b_2 + b_4) - (b_3 + b_5) > 0;$

(ii) $\gamma \geq 0$ and $\beta > 0$

Then the EEP is asymptotically stable for $\tau \geq 0$.

Proposition 3.3 implies that if the parameters satisfy the conditions (i) and (ii), then the EEP of our model is asymptotically stable. However if (ii) is not satisfied, then the stability of EEP will depend on the delay value and the delay can induce bifurcations. As an example consider the following two cases:

(a) $\gamma < 0$ in which case from (3.32) $h(0) < 0$ and $\lim_{z\to\infty} h(z) = \infty$. Thus equation (3.32) has at least one positive root say z_0. Consequently equation (3.31) has at least one positive root, denoted by ω_0.

(b) If $\beta < 0$ then $\sqrt{\alpha^2 - 3\beta} > \alpha$ and hence one of the roots of equation (3.34) is positive and hence equation (3.31) has at least one positive root. This implies that the Characteristics equation (3.26) has a pair of purely imaginary roots $\pm i\omega$ has τ is varied.

Let $\lambda(\tau) = \eta(\tau) + i\omega(\tau)$ be the eigen-value of the characteristic equation (3.26) such that $\eta(\tau_0) = 0$, $\omega(\tau_0) = \omega_0$, then we have from (3.29) and (3.30)that

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

We can also verify that the transversality conditions

$\frac{d}{d\tau} Re\lambda(\tau)\Big|_{\tau=\tau_1} = \frac{d}{d\tau}\eta(\tau)\Big|_{\tau=\tau_1} > 0$ holds, where τ_1 is the critical value of delay for stability of endemic equilibrium.

Differentiating equation (3.26) with respect to τ we get that

$$(3\lambda^2 + 2b_1\lambda + b_2 + b_3e^{-2\lambda\tau} - 2b_3\tau e^{-2\lambda\tau} - 2b_4\tau e^{-2\lambda\tau})\frac{d\lambda}{d\tau} = 2\lambda e^{-2\lambda\tau}(\lambda b_3 + b_4)$$

and therefore

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2b_1\lambda + b_2 + b_3e^{-2\lambda\tau} - 2\lambda b_3\tau e^{-2\lambda\tau} - 2b_4\tau e^{-2\lambda\tau}}{2\lambda e^{-2\lambda\tau}(\lambda b_3 + b_4)}$$

or

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2b_1\lambda + b_2}{-2\lambda(\lambda^3 + b_1\lambda^2 + b_2\lambda + b_5)} + \frac{b_3}{2\lambda(b_3\lambda + b_4)} - \frac{\tau}{\lambda}$$

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2b_1\lambda + b_2}{-2\lambda(\lambda^3 + b_1\lambda^2 + b_2\lambda + b_5)} + \frac{b_3}{2b_4\lambda} - \frac{b_3^2}{2b_4(b_3\lambda + b_4)} - \frac{\tau}{\lambda} \quad (3.33)$$

Thus, evaluating equation (3.34) at $\lambda = i\omega_0$ and examining the sign of the real part, we have,

$$sign\left\{\frac{d(Re\lambda)}{d\tau}\right\} = sign\left\{Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\}$$

$$= sign\left\{Re\left[\frac{3\lambda^2 + 2b_1\lambda + b_2}{-2\lambda(\lambda^3 + b_1\lambda^2 + b_2\lambda + b_5)}\right] + Re\left[-\frac{b_3^2}{2b_4(b_3\lambda + b_4)}\right]\right\}$$

$$= sign\frac{1}{2}\left[\frac{(b_2 - 3\omega_0^2)(b_2 - \omega_0^2) + 2b_1(b_1\omega_0^2 - b_5)}{(b_2\omega_0 - \omega_0^3)^2 + (b_1\omega_0^2 - b_5)^2} - \frac{b_4^2}{b_3^2 + b_4^2\omega_0^2}\right]$$

$$= sign\left[\frac{P}{Q}\right],$$

where, $P = (b_3^2 + b_4^2\omega_0^2)[(b_2 - 3\omega_0^2)(b_2 - \omega_0^2) + 2b_1(b_1\omega_0^2 - b_5)] - b_4^2[(b_2\omega_0 - \omega_0^3)^2 + (b_1\omega_0^2 - b_5)^2]$

$$Q = (b_3^2 + b_4^2\omega_0^2)[(b_2\omega_0 - \omega_0^3)^2 + (b_1\omega_0^2 - b_5)^2]$$

Since $b_1^2 - 2b_2 > 0,\ b_3^2(b_2^2 - 2b_1b_5) - b_4^2b_5^2 > b_5^2(b_2^2 - 2b_1b_5 - b_4^2) > 0$

this implies that

$$\left.\frac{d(Re\lambda)}{d\tau}\right|_{\tau=\tau_1,\ \omega=\omega_0} > 0.$$

and thus the transversality condition holds and hence Hopf bifurcation occurs at $\tau = \tau_1, \omega = \omega_0$. This completes the verification of the transversality condition.

CHAPTER FOUR

RESULTS AND DISCUSSIONS

To bring out the analytic solutions in the previous Chapter clear, we illustrate the analytic results with specific numerical examples. We will consider simulation of model equation (3.6) and parameters from literature. A complete list of parameters and their estimated values that can be used for numerical simulations of the model are given in Table 1. The majority of the values have been taken from the data found in scholarly articles published in various journals. Much of these parameters were adopted from Perelson *et.al.,* (1993), and a complete discussion of their estimation is found therein. These data do not depict a strict situation but the parameter range is within the plausible and realistic values.

In the simulation of the model (3.6), the following initial values in each compartment at the onset of infection are assumed to apply.

$\big(T(0), T^*(0),\ V_I(0), V_{NI}(0)\big) = (1000,\ 0,\ 0.01,\ 0.01)$ On the interval $[-\tau\ 0]$. at the onset of infection the initial viral population is zero but for simulation purpose, we use $V_I(0) = 0.01$ and $V_{NI}(0) = 0$ since if $V_I(0) = 0$ and $V_{NI}(0) = 0$, the graph will remain at zero throughout as time grows.

Table 1: Table of Parameters and their Values

Item	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_T	0.02
3	Infection rate of uninfected $CD4^+$T cells (T)	β	0.00024
4	Death rate of Infected $CD4^+$T cells (T^*)	μ_{T^*}	0.26
5	Production rate of infectious and non-infectious free virus from infected $CD4^+$ cells.	k	1000
6	Clearance rate of free infectious virus from the body	μ_{V_I}	2.4
7	Clearance rate of free noninfectious virus from the body	$\mu_{V_{NI}}$	0.3
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 of the cell to production of new infectious viruses	τ	To be determined

Source: Perelson *et.al.,* (1993)

4.1 Dynamics of CD4+T-Cells and Free Virus Populations for Various Efficacies

The simulation results for model equation (3.6) for various efficacies of the combination chemotherapy are discussed in this section. The illustrations shows the simulations of the general dynamics of uninfected $CD4^+$T-cells $(T(t))$, infected $CD4^+$T-cells $(T^*(t))$, infectious virus$(V_I(t))$, and noninfectious virus $(V_{NI}(t))$

4.1.1 Effects of Efficacy on T-Cells and Free Virus Populations

In the absence of treatment or with combined chemotherapy of up to 20%, we note from the simulations in Figure 4.1 and Figure 4.2 that the level of infectious free virus is higher than that of T-cells and noninfectious virus. The two graph shows that uninfected $CD4^+$T-cells are below $200mm^{-3}$. This value is not good for immune system to fight any subsequent infections (see for instance WHO, for the requirement of $CD4^+$T-cell level for a strong immune system).

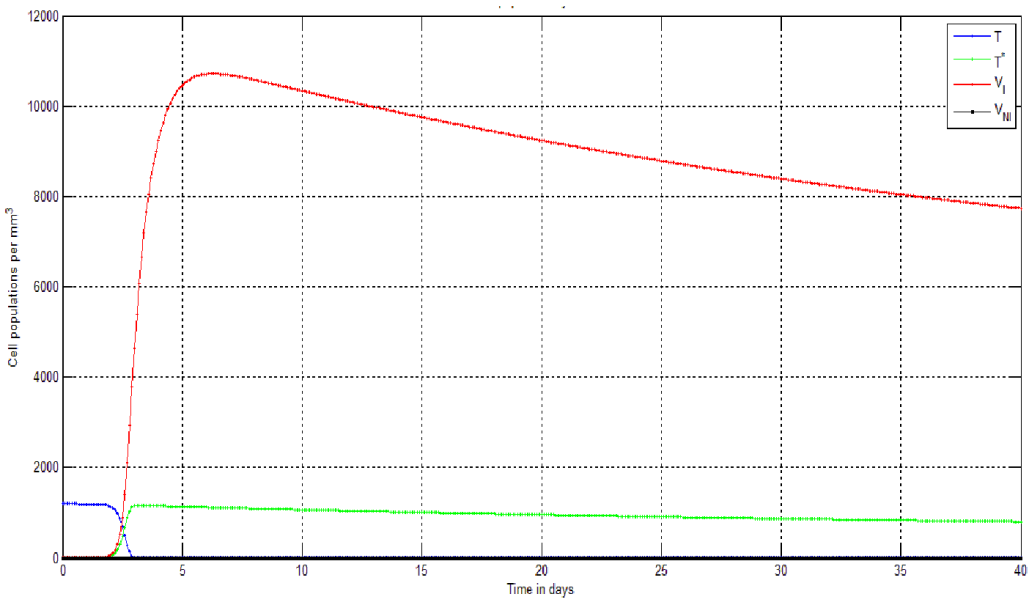


Figure 4.1 Graph of HIV-1 in vivo dynamics in the absence of treatment.

In Figure 4.1 above, the illustrations shows that the level of infectious virus rise sharply and falls to a stable value as time increases. This can be due to reduction in uninfected $CD4^+$T-cell which make the contact rate of uninfected $CD4^+$T-cell and infectious virus to be low. A lower contact rate results in a fewer infected $CD4^+$T-cell hence a lower number of infections virus since they are determine by the number of infected $CD4^+$T-cell. The level of infected $CD4^+$T-cells initially increases because of a higher contact rate of uninfected $CD4^+$T-cell and infectious virus which would produce a higher number of infected $CD4^+$T-cell. In the absence of treatment simulation of system (3.6) predicts a collapse of the immune system, a bad scenario for the infected individual.

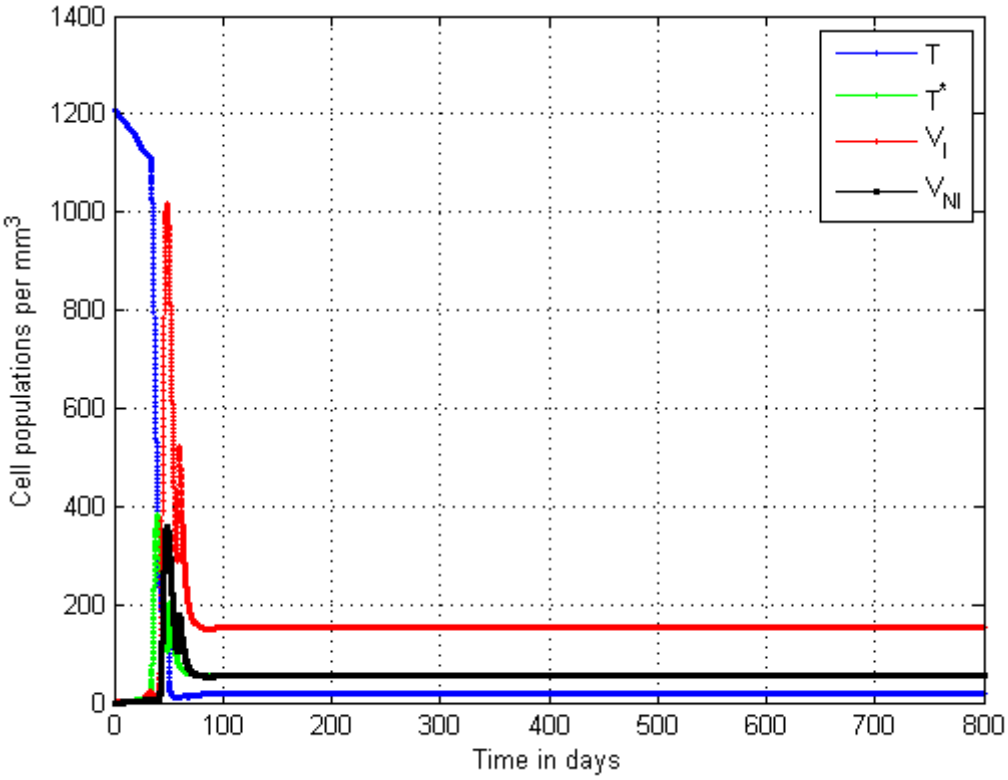


Figure 4.2 Graph of HIV-1 in vivo dynamics at 20% Drug Efficacy.

In Figure 4.2 the level of uninfected $CD4^{+}$T-cell is initially higher but falls sharply and stabilize at a value below $200mm^{-3}$ of plasma, which again is not good for the immune system for it to fight secondary infectious. This implies that at efficacy levels of up to 20%, the chemotherapy has no benefit to the immune system.

The same graph gives an interesting dynamics of infected $CD4^{+}$T-cell, it falls first then oscillate and falls to a steady value. This can be attributed to two processes apart from death:

1) Reduced number of uninfected T- cells which would lower the contact rate of uninfected $CD4^{+}$T-cell and infectious virus leading to lower infected T-cells.

2) Some infected $CD4^{+}$T-cell are treated by combined chemotherapy thus reducing its numbers.

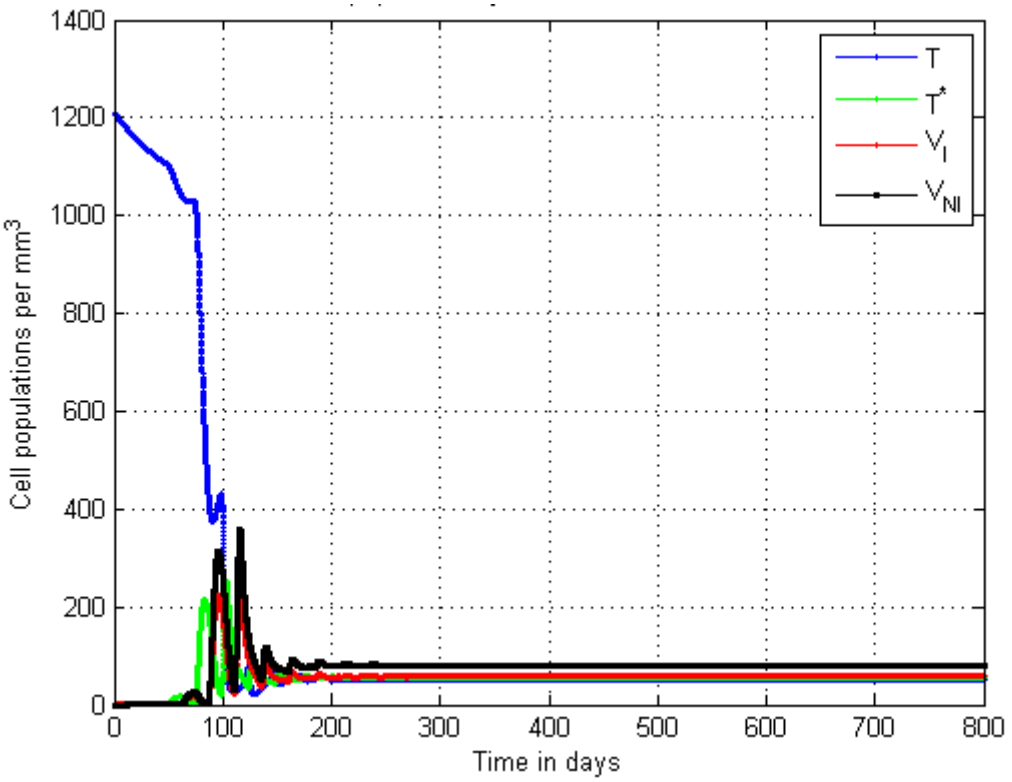


Figure 4.3 Graph of HIV-1 in vivo dynamics at 50% Drug Efficacy.

At efficacy of 50%, a simulation of systems (3.6) shows that the cells populations almost come to the same levels after around 200 days (Figure 4.3). The level of uninfected $CD4^{+}$T-cells is however still lower, which implies that chemotherapy at 50%, is still not benefiting the immune system.

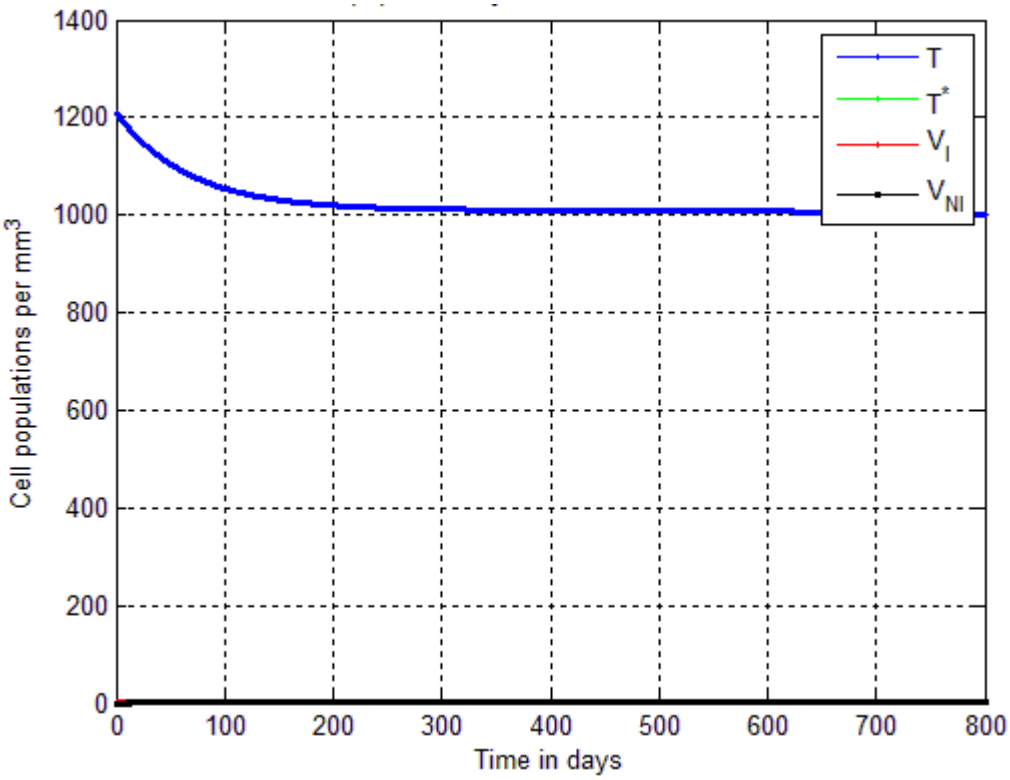


Figure 4.4 Graph of HIV-1 in vivo dynamics at 80% Drug Efficacy.

At efficacy of 80% and above the combined chemotherapy lowers the free virus to very negligible levels (figure 4.4). This is good news for the immune system.

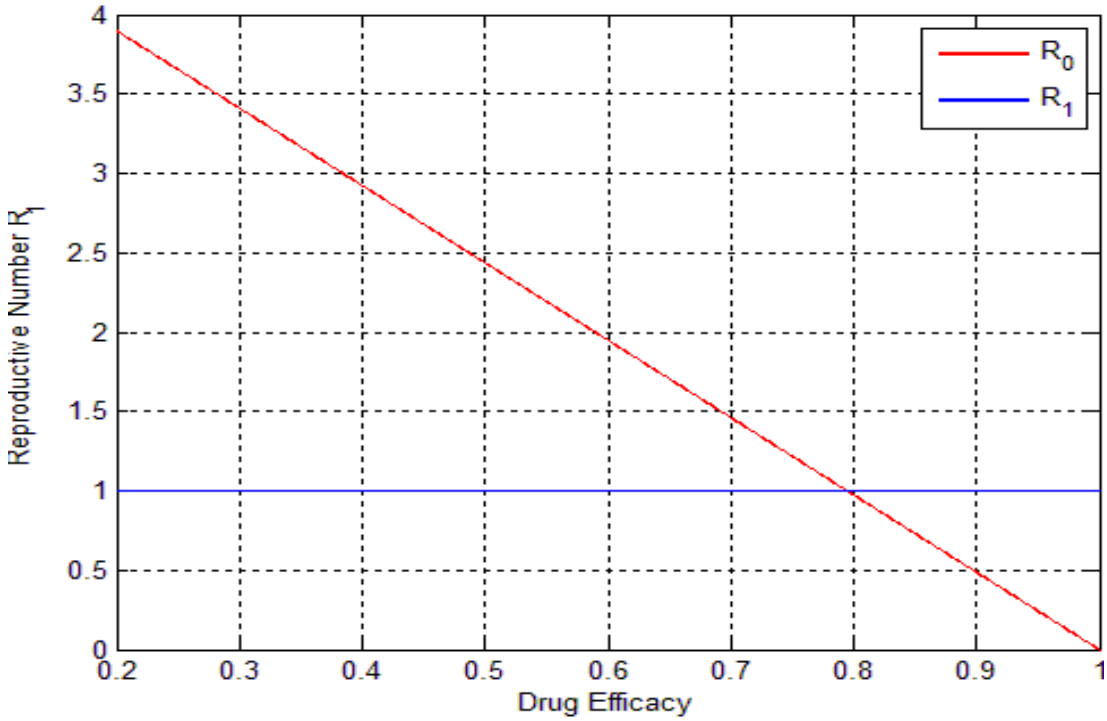
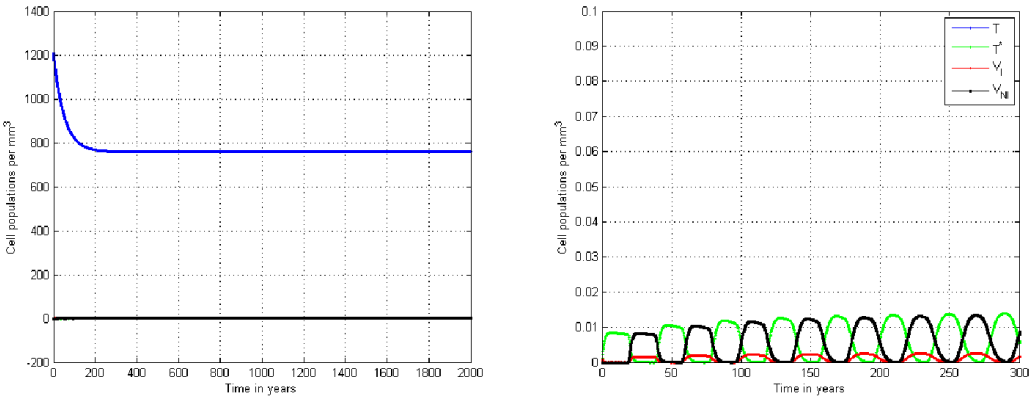


Figure 4.5 Graph of R_1 against Drug Efficacy showing Efficacy threshold value.

In Figure 4.5 the threshold efficacy is about 79%. We however need to be careful since there are other cells infected by HIV-1 virus which would act as a reservoir for another round of infection. This therefore calls for a more structured chemotherapy after lowering the plasma virus to negligible levels.



(a) (b)

Figure 4.6 Graph of HIV-1 in vivo dynamics at 79% Drug Efficacy.

In Figure 4.6 we see that a magnification of the lower line in Figure 4.6 (a) shows oscillations of the virus populations and infected $CD4^{+}$T-cells Figure 4.6 (b). The oscillation can be attributed to drug concentrations at plasma levels.

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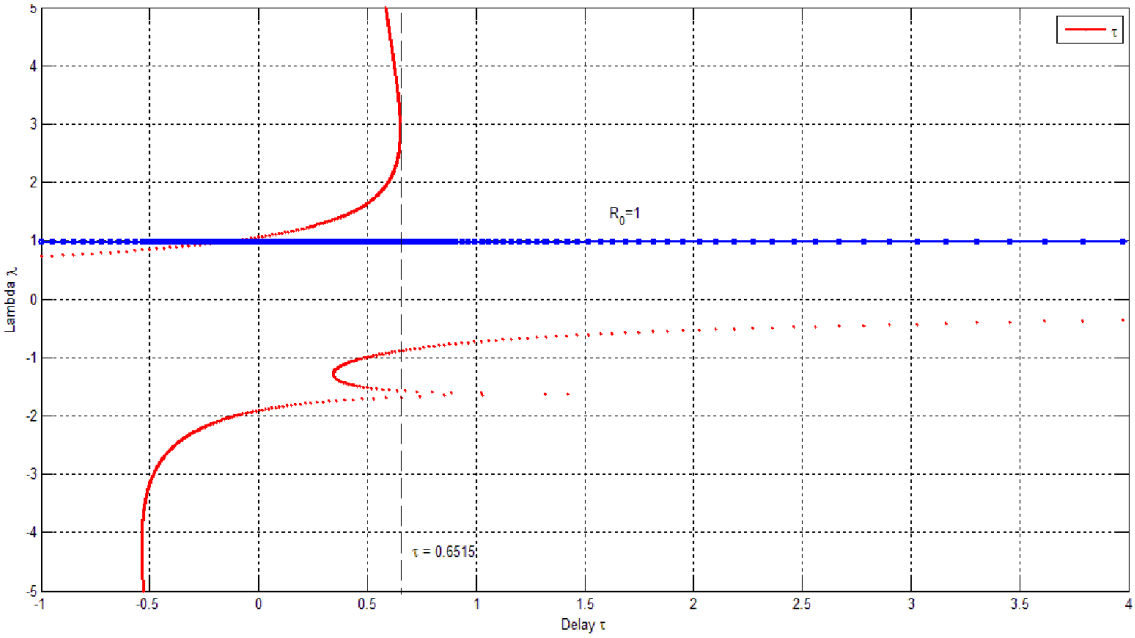

Figure 4.7 Graph of λ against τ.

In the Figure 4.7 above, the simulation of eigenvalues of linearization matrix of system (3.6) at EEP against the length of time lag (τ) is illustrated. Clearly, the time delay must be positive, and from the graph, we note that for $0 \leq \tau \leq 0.6515$ the system is orderly chaotic, starting from two eigenvalues (one positive and the other negative) then increase to three, then four (one positive and the other negative). After the critical value of delay $\tau_c = 0.6515$, the system undergoes Hopf Bifurcation and remain stable for all $t > \tau_c$. This agrees with the transversality condition obtained in the analytic results

CHAPTER FIVE

CONCLUSION

This chapter will revisit the objective of this research outlined in chapter one, discuss each of them and draw conclusions. 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.

5.1 Effects of Delay and Efficacy on Disease Free Equilibrium

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 absence of delay puts PI and RTI efficacies at 0.79 and 0.79 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 chapter three.

In fact for $\tau < \tau_0$ the DFE is stable and for $\tau > \tau_0$ the DFE is unstable but for $\tau = \tau_0$ there will be stability switch of the Hopf type as reveal by the transversality analysis. Numerical solution of the model with delay using MAT LAB DDE23 solver reveals that the value of τ_0 is 0.65 days or 15 hours for EEP to be stable.

Reproduction number can also be affected by the cure rate of $CD4^+$T-cells, which implies that drugs of higher potency are the best in the stability of DFE equilibrium.

5.2 Effects of Delay and Efficacy on Endermic Equilibrium

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 EEP stability is affected by recovery rate implies that chemotherapy affect stability of EEP. The variable R_1 define in the analysis of EEP stability in fact has efficacy of both the drug used in the model under study and determines the signs of the eigen-values has per the Routh Hurwitz condition for stability.

In the presences 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 denoted by τ_1 so that stability of EEP is achieved .This critical value depends on $b_i (1 \le i \le 5)$ and ω_0 as define in the text. In fact for $\tau < \tau_1$ the EEP is stable and for $\tau > \tau_1$ the DFE is unstable but for $\tau = \tau_1$ there will be stability switch of the Hopf type as reveal by the transversality analysis.

The efficacy threshold on the two drugs in the study is established numerically to be 0.79 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. This finding can therefore provide a basis for clinical trials from a stronger theoretical foundation. The current duration allowable after exposure is 72 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 some time 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. This study is a stronger theoretical foundation on clinical trial in this treatment regime. The study suggests a delay of 0.65 days or approximately 6 hours for stability of EEP.

5.3 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 suggested by this study. Studies on ARV using STI regime can now be narrowed to the value of delays for stabilities of EEP

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APPENDICES

MATLAB CODE

APPENDIX I DYNAMICS OF HIV/AIDS WITH VARIOUS DRUG EFFICACIES

```
function Dynamics of HIV/AIDS with various drug efficacies
global tau;
global u1;
global u2;
for u2 = 0.8; %RTI drug efficacy
for u1 = 0.8; %PI drug efficacy
lag=tau;
for tau=[12];
tspan = [0, 800];
sol = dde23(@relag2,lag,@hist2,tspan);
figure;
t = linspace(0,800, 10000);
x = deval(sol,t,1);
y = deval(sol,t,2);
z = deval(sol,t,3);
p = deval(sol,t,4);
tot=x+y;
%-----------------------------------------------------------
%subplot(1,2,1);
plot(t,x+10,'-b*',t,y,'-g+',t,z,'-rd',t,p,'-ks','LineWidth',1,'MarkerSize',2)
%subplot(1,2,2);
%plot(x(:),p(:))
%subplot(2,2,3);plot(t,y,t,z)
%subplot(2,2,4);
%%plot(x,p,'r','LineWidth',1,'MarkerSize',1)
%plot(t,x+10,'-b*',t,y,'-g+',t,z,'-rd',t,p,'-ks','LineWidth',1,'MarkerSize',2)
axis([0 800 0 1400]);

%-----------------------------------------------------------
title('Cell population dynamics at 80% treatment');
xlabel('Time in days')
ylabel('Cell populations per mm^3')
legend('T','T^*','V_I','V_{NI}');grid,%hold on;
end
end
end
%-------------------------------------------------------------------------
function IC = hist2(t)
% Constant history function for DDEX1.
IC = [1200; 0; 0.001; 0];
```

```
%s = [T;  T1;  VI;   VN];
% ------------------------------------------------------------------------
functiondydt = relag2(t,v,Z)
% Differential equations function for DDE.
%Parameters.....................................................
s=15; % recruitment rate of naive CD4, CTL1 and CTL2
r=0.53; % max recovery rate of treated CD4
be1=0.024;%infection rate of cd4 by virus 1 and virus 2
d1=0.015;  %death rates of T
d2=0.26;% death rates of T and T*
d3=2.4;  %death rate of infectious virus
d4=1.7; % death rates of Non-infectious virus
k = 10; %Burst size Infectious

global u1;
global u2;
%.............................................................
% Model Equations
vlag1 = Z(:,1);% Delay on exposure of latently infected cells
dydt = [ s-(1-u1)*be1*v(1)*vlag1(3)-d1*v(1)+r*u1*v(2)
   (1-u1)*be1*v(1)*vlag1(3)-d2*v(2)-r*u1*v(2)
   (1-u1)*(1-u2)*k*vlag1(2)-d3*v(3)
   (1-u1)*u2*k*vlag1(2)-d4*v(4)];
%.............................................................
```

APPENDIX II DRUG EFFICACY VERSUS REPRODUCTIVE RATIO R_0

```
function Drug Efficacy Versus Reproductive Ratio R_0
%Parameters.....
s=15; % recruitment rate of naive CD4, CTL1 and CTL2
r=0.53; % max recovery rate of treated CD4
be1=0.024;%infection rate of cd4 by virus 1 and virus 2
d1=0.015;  %death rates of T
d2=0.26;% death rates of T and T*
d3=2.4;  %death rate of infectious virus
d4=1.7; % death rates of Non-infectious virus
k = 10; %Burst size Infectious
%.....
%Equations
for u1 = 0:0.001:1 % RTI
for u2 = [0.2 0.5 0.7 0.79 0.85]; % PI
    R0 = ((1-u1)^2*(1-u2)*be1*k*s)/(d1*d3*(d2+r*u1));
   %plot(u1,R0,'-ro',u1,1,'-b*','LineWidth',2,'MarkerSize',2),hold on  grid
plot(u1,R0,'-ro',u1,1,'-b*','LineWidth',2,'MarkerSize',2),hold on  grid
axis([0 1 0 50])
   %plot(tau(:),R0(:),'b-*',tau,R1,'r-d','LineWidth',2,'MarkerSize',1),hol
   %d on  grid
end
end
title('R_0 versus Drug efficacy profile');
xlabel('Drug Efficacy')
ylabel('Reproductive Number R_0')
legend('R_0','R_1');grid,%hold on;
```

APPENDIX III BOUNDS OF DELAY τ FOR STABILITY AND BIFURCATION

```
function Bounds of Delay τ for Stability and Bifurcation
for la=-5:0.01:5; % lambda eigenvalue
%Parameters.....
s=10; % recruitment rate of naive CD4, CTL1 and CTL2
r=0.53; % max recovery rate of treated CD4
%be1=0.0062;%infection rate of cd4 by virus 1 and virus 2
be1=0.0062;%infection rate of cd4 by virus 1 and virus 2
d1=0.0152;  %death rates of T
d2=0.034;% death rates of T and T*
d3=0.074;  %death rate of infectious virus
d4=2.8; % death rates of Non-infectious virus
k = 5; %Burst size Infectious
for u1 = 0.69;
u2 = u1;
R0 = ((1-u1)^2*(1-u2)*be1*k*s)/(d1*d3*(d2+r*u1));
Ve = (d1*(1-u1)*(1-u2)*k*s*(R0-1))/(d1^2*d3-(1-u1)*be1*s*R0);
Te=(s*R0)/d1;
a = d1+(1-u1)*be1*Ve;
b = r*u1;
c = (1-u1)*be1*Te;
d = (1-u1)*be1*Ve;
f = d2+r*u1;
g = (1-u1)*(1-u2)*k;
h = d3;
b1 = a+f+h;
b2 = a*f+a*h-f*h-b*d;
b3 = -c*g;
b4 = c*g*(b-a);
b5 = h*(a*f-b*d);
tau = (1/(2*la))*log((la^3+b1*la^2+b2*la*b5)*(la*b3+b4));
if tau > 0
Delay_Lambda = [tau, la]
elsedisp('Error')
end
%delay = tau
%plot(tau,la,'-r*',tau,R0,'-bo','LineWidth',2,'MarkerSize',2), hold on, grid on
title('Value of \tau which gives \lambda<0');
ylabel('Lambda \lambda')
xlabel('Delay \tau')
legend('\tau'),grid on, hold on;
end
end
```