DEVELOPMENT OF A MATHEMATICAL MODEL FOR OPTIMAL TREATMENT STRATEGIES TO CONTROL ACUTE HIV INFECTION

By

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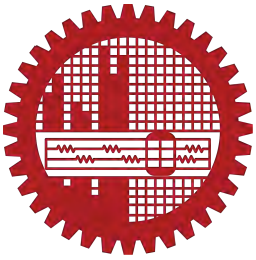
MASTER OF PHILOSOPHY
IN
MATHEMATICS



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Declaration of Authorship

I, Shohel Ahmed, declare that the work contained in this thesis entitled "DEVELOPMENT OF A MATHEMATICAL MODEL FOR OPTIMAL TREATMENT STRATEGIES TO CONTROL ACUTE HIV INFECTION" was done by me, under the supervision of Dr. Abdul Alim, Professor, Bangladesh University of Engineering and Technology (BUET), Dhaka-1000 for the award of the degree of Master of Philosophy and this work has not been submitted elsewhere for a degree.

Signed: 

Date: 26/06/2018

Dedication

This work is dedicated

to

My Family

Abstract

In this study, we seek to apply a system of nonlinear ordinary differential equations to analyze how the dynamics of primary infection affect the proliferation of Human Immunodeficiency Virus (HIV). We prove existence, uniqueness, positivity, and boundedness of the solution. Also investigate the qualitative behavior of the models, and find a threshold parameter that guarantee the asymptotic stability of the equilibrium points, this parameter is known as basic reproduction number. The terms in the equations introduce parameters which are determined by fitting the model to matching clinical data sets using nonlinear least-squares method. The aim of this work is to determine the optimal drug administration schemes useful in improving patient's health especially in poor resourced settings. The optimal treatments represent the efficacy of drug inhabiting viral production and preventing new infections with an objective functional which maximizes the T-cell (the white cells that coordinate activities of the immune system) and minimizes the systematic cost based on the percentage effect of the drug. The existence and the uniqueness of the optimal pair are discussed. A characterization of the optimal drug doses via adjoint variables is established. We obtain an optimality system that we solve numerically by a competitive Forward-Backward Sweep method.

Acknowledgements

First and foremost, I would like to express my cordial gratitude to my thesis supervisor Dr. Abdul Alim for his continuous support, motivation, and guidance through out my thesis work. I am really thankful to him and extremely fortunate to have studied mathematics under his supervision. I am very thankful to him for introducing me in this highly fascinating and applicable research area and finish this thesis successfully.

I would like to express my hearty gratitude to all of my teachers for their valuable suggestions. I express my gratitude to my teachers from Bangladesh University of Engineering and Technology.

I am grateful to Dr. Md. Mustafizur Rahman, Dr. Md. Abdul Hakim Khan and Dr. Md. Abdul Maleque for being on my defense committee, reading my thesis and suggesting improvements.

Specially, I am extremely thankful and highly indebted to Dr. Md. Kamrujjaman for his generous help, cooperation and valuable guidance during my research. I have learned a lot from him.

Finally, I wish to express my deep regards to my parents and all other family members and friends for their constant cooperation and motivations. Their sincerest wishes for me have played a very important role in the study.

(Shohel Ahmed)
Date: 26/06/2018

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Chapter 1

Introduction

1.1 Preamble

Human Immunodeficiency Virus (HIV), causing impairment of human immune system and inflicting the disease Acquired Immune Deficiency Syndrome (AIDS), is a grave problem that the human race encounters and needs immediate attention to formulate potential treatment strategy against the disease. Development of the medicines and vaccines will be required to control the high mutation rate of HIV. These facilities depend not only on knowledge of the complex life cycle of virus, but also on understanding of the difficulty in the management of immune system. Researchers have worked diligently and gained unprecedented knowledge of HIV and its interaction with the immune system. Yet, AIDS pandemic will continue for years to come. In recent years, the mathematically validated therapeutic approach is one of the most significant ways along with the biological, as well as clinical study to control the HIV for social realm of basic human rights. The dynamical behavior of the human immune system through drug ingestion will enable us to administer optimized level of therapies to AIDS patients.

We study the process of cell biology of disease progression in HIV infection and different drug dynamics. Also investigate how specific antiviral treatment can affect the immune response, that is, whether this treatment can predominantly reduce the viral load and in another sense, how it controls the disease progression in a long-term treatment of HIV infected patients. To avoid complications of the results, further analysis is performed to investigate the mathematical models with the help of optimal control theory.

1.2 Epidemiology of HIV virus

HIV is the etiological agent of AIDS and has become one of the major public health problems worldwide since its discoveries in the early 1980s. The most recent global health observatory (GHO, 2016) data of HIV/AIDS published by World Health Organization (WHO) [1] and proclaims that around 78 million people have been infected with the HIV virus and about 39 million people have died of HIV virus. In the current scenario, it is seen that globally around 35 million people are living with HIV. Nevertheless, the HIV burden may vary depending upon the geographical region, e.g. like Sub-Saharan Africa is the most affected region which contributes nearly 70% of the global HIV burden [1].

In Bangladesh, the first case of HIV was detected in 1989 and since then, it has been enhanced considerably. In 2016 (December 2015 to November 2016), the number of newly HIV infected people is 600 and the number of HIV/AIDS related death is 100. Till December 2016, there were 4595 reported cases of HIV and among them 758 died [2]. Although Bangladesh is still considered to be a low responded HIV infected country in the world, the present situation indicates that the influence of this pandemic disease is gradually increasing. However, obstacles to AIDS prevention and control lie not only in the nature of the HIV virus but also in the social realm of basic human rights. AIDS is having the greatest impact in poverty ridden countries, where public health infrastructure is already strained by other infectious diseases.

1.3 Biological Background of HIV virus

The human immunodeficiency virus (HIV) is a retrovirus that infects a white blood cell named $CD4^{+}T$ cells of the immune system. It deteriorates the person's immune system as infection progresses. The primary stage of infection takes around 10-15 years to develop into a full blown case of acquired immunodeficiency syndrome (AIDS). HIV is transmitted through various processes involving mixing of body fluids like transfusion of contaminated blood, sharing of contaminated needles, unprotected sexual intercourse, childbirth and breastfeeding. Being a retrovirus, HIV virus's genetic information is not encoded as DNA but instead as RNA. The HIV virus cannot reproduce on its own. The reproduction of the HIV

virus takes place in a cell of the infected host. Here the HIV virus inserts its RNA into the cell, and makes a DNA copy (called provirus) of its RNA by the process of reverse transcription. This proviral DNA integrates itself into the hosts DNA and is later transcribed and translated into viral proteins in non-latent cells. These viral proteins develop into the fully functional virus and are released by bursting open the cell. This process of replication of $CD4^{+}T$ cells is known as the HIV life cycle. The stages of HIV life cycle can be understood from Fig. 1.1.

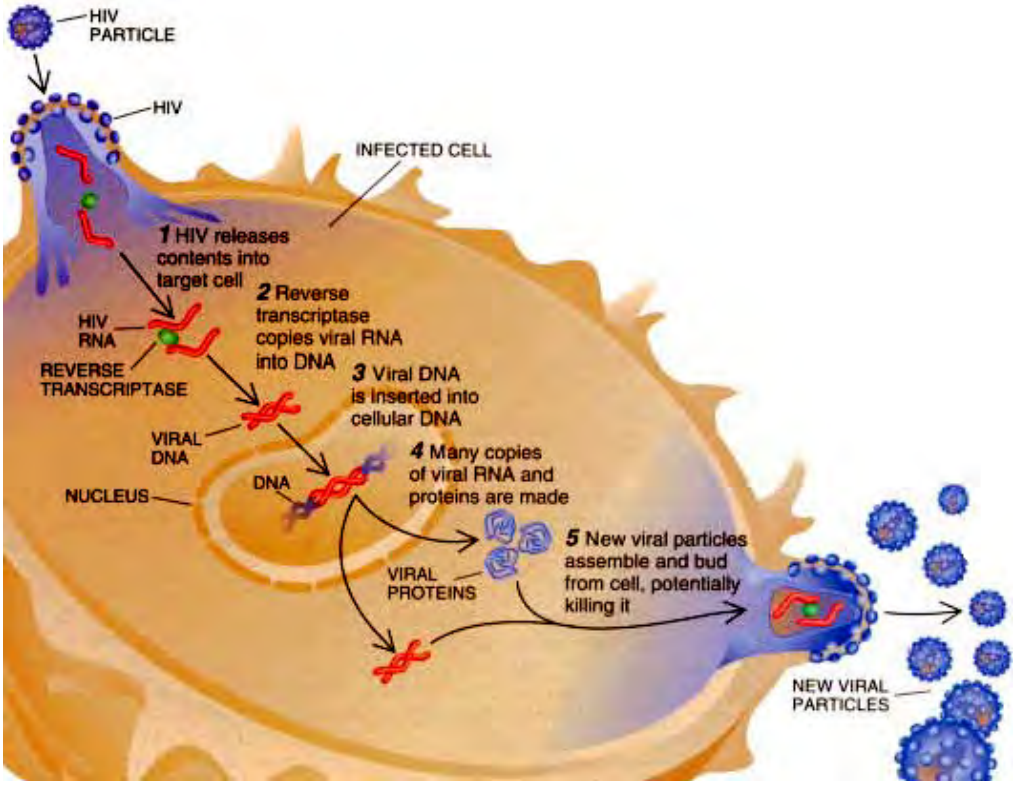

Figure. 1.1. The life cycle of the HIV in the host [3]

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Nowadays, there are some antiretroviral (ART) drugs available which help the immune system in preventing the infection due to HIV even though it is not possible to cure it. Reverse Transcriptase Inhibitors (RTIs), is one of the therapies which opposes the conversion of RNA of the virus to DNA (reverse transcription), so that the viral population will be minimum and on the other-hand the $CD4^{+}T$ count remains higher and the host can survive. Another one is the Protease Inhibitors (PIs) which prevents the production of viruses from the actively infected $CD4^{+}T$ cells.

1.4 Literature Review

In the literature, many mathematical models have been developed in order to understand the dynamics of HIV infection. In 1993, Perelson et al. [4] developed a model for the interaction between the human immune system and HIV during primary stage. Perelson [5] extended the model by considering uninfected, latently infected and actively infected T-cells. The growth of uninfected target cells has two origins: a constant supply of T-cells from the thymus and a logistic growth term that depends on the total amount of T-cells. Uninfected cells become latently infected T-cells upon infection with the virus and then proceed to the actively infected T-cell class. Only these active cells are able to produce new virus. This model fails to account for the initial peak of virus but it does capture the long term increase in viral load, the decrease in uninfected $CD4^+$T-cell density and the increase in the density of latently and actively infected cells. The interaction between $CD4^+$T cells and HIV virus was described by the simple system of differential equation proposed by Nowak et al. [6]. This system is the most simplified model relative to the standard form which exhibits different characteristics of the disease during acute infection. A possible extension of the Nowak's model is given in [7].

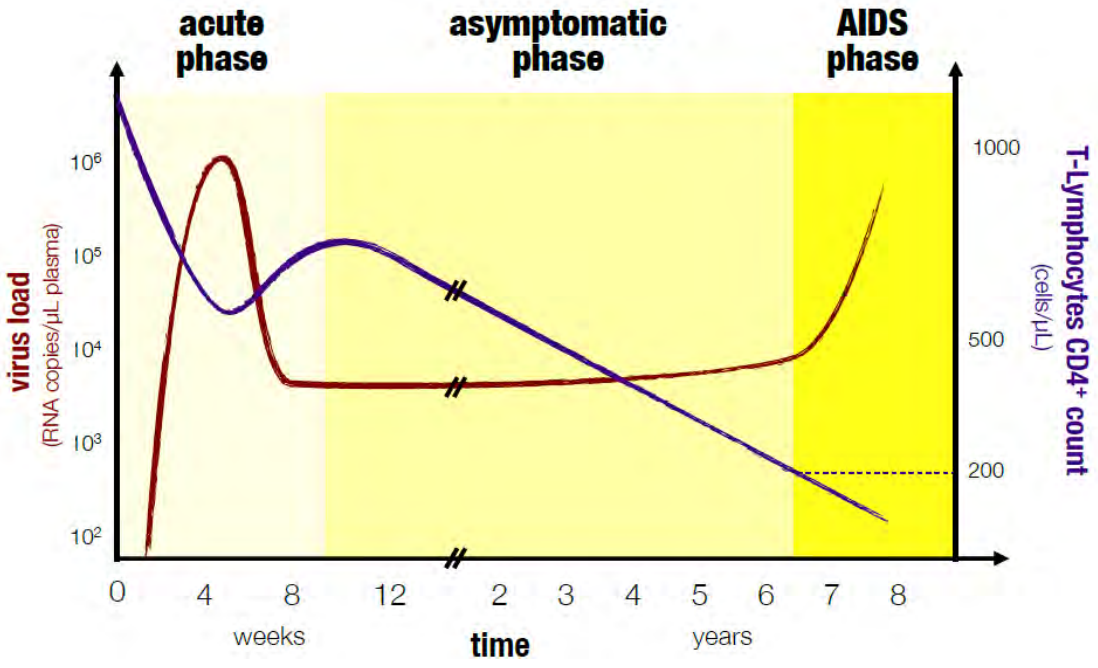


Figure. 1.2. Schematic time course of a typical HIV infection in an infected adult.

In the control therapeutic approach a large number of mathematical models have been proposed by eminent researchers. Butler et al. [8] used a single control representing the percentage effect the therapy has on viral infectivity (this would simulate a drug like PIs). Fister et al. [9] used an optimal control represents the percentage effect the therapy has on the interaction of the $CD4^{+}T$ cells with the virus. In [10], Joshi considered two controls, one boosting the immune system and the other delaying HIV progression. Kirschner et al. [11] used a single control representing the percentage effect of the treatment has on viral production. Two controls, one simulating effect of RTIs and the other control simulating the effect of PIs, incorporating drug efficacy was considered by Garira et al. [12]. All these studies are based on HIV models which omitted the cure of infected cells. A part of these infected cells return to the uninfected state by loss of all covalently closed circular DNA (cccDNA) from their nucleus at a certain rate per infected cell [13]. In addition, PIs cause infected cells to produce noninfectious virions. However, virions that were created prior to the drug treatment remain infectious. Virus particles that are not being influenced by protease inhibitors and the other being influenced by protease inhibitors. Banks et al. [14] and David et al. [15] incorporated these types of virus particles and used the models which omitted the cure of infected cells. We have come to know about the structured treatment interruption (STI) from the paper of Admas et al. [16], where they showed that treatment reduced the pharmaceutical side effects in HIV treatment. An optimal control model of HIV treatment is established in [17] using a single drug by Culshaw et al. They showed that immune response may be rejuvenated by optimal treatment strategies.

1.5 Outline of the Thesis

By observing the previous studies in this thesis, we present and analyze the dynamics of the mathematical models for HIV infection in vivo. The organization of the thesis is as follows.

In Chapter 2, we provide some mathematical tools that are used throughout the thesis. We present some definitions and notation about dynamical systems and stability analysis, and theories that are required to analyze such systems. Theorems and lemmas from optimal control theory used in infectious diseases modeling are presented.

We examine a basic mathematical model for HIV infection in Chapter 3, , which incorporates the dynamics of target cells, infected cells and the virions. We analyze the stability of the uninfected and infected steady states and obtain the basic reproduction number R_0 in terms of the model parameters. If $R_0 \leq 1$ then the uninfected steady state is stable and the patient will be cleared of infection. On the other hand, if $R_0 > 1$ then the infected steady state is stable and the infection persists. Finally, the results obtained are numerically illustrated for various intial conditions.

In Chapter 4, we analyze the dynamics of modified HIV infection by taking into account two types of infected cells: active and latent along with the virions. We prove the conditions for local and global stability of both the uninfected and infected steady states in terms of the basic reproduction number. At the final stage, the models are illustrated numerically.

In Chapter 5, a model for combination therapy of Reverse Transcriptase Inhibitors and Protease Inhibitors is presented. A critical drug efficacy in terms of the parameters of the model comprising of coupled ordinary differential equations is obtained. The dynamics of model is greatly impacted by the relation of the efficacies of the individual drugs vis-a-vis the critical efficacy. A control problem is formulated and solved numerically to obtain the optimal therapeutic regimen keeping in mind both biomedical goals and cost constraints.

Finally, Chapter 6 concludes and outlines the future directions of the thesis. All the numerical simulations incorporated in this thesis were carried out using programming tools MatLab.

Chapter 2

Preliminaries

2.1 Introduction

In this chapter, we discuss some useful mathematical background material and well established theories that will aid our explanation in subsequent chapters. We define concepts such as existence and uniqueness of a solution, Routh-Hurwitz criteria, Hartman-Grobman theorem, Lyapunov functions, etc., and give some basic results on optimal control theory. In mathematics, in the study of dynamical systems, these theorems provides information on the local and global stability of dynamical systems in the neighbourhood of an equilibrium point.

2.2 Translating Biological Knowledge

To make Ordinary Differential Equation (ODE) from biological knowledge, first we need some syntax. For example, if we denote the count of uninfected and infected T-cells, with T and I, respectively, the syntax "$T \to 0$" can be used to present this biological descriptions: "Uninfected T-cells die" and the syntax "$T + I \to I + I$" can present: "The reaction between two infected and uninfected T-cells produces two infected T-cells". Now, for translating these syntaxes to the corresponding ODE's, we use "Mass action law". This law says: "The rate of change of products is proportional to the product of reactants concentration". So if the syntax "$a + b \to c$" is obtained, according to the mass action law, we can

write

$$\begin{aligned}\frac{dc}{dt} &= kab,\\ \frac{da}{dt} &= -kab,\\ \frac{db}{dt} &= -kab.\end{aligned}$$

for $k > 0$, Two other reactions in the previous syntax is dying a and b reactants, while producing c. Obviously, the rate of change of a product is the sum of changes from all reactions.

2.3 Fundamental Definitions

Consider autonomous differential equations as

$$\mathbf{x}' = \mathbf{f}(\mathbf{x}(t)), \quad \mathbf{x}(t_0) = \mathbf{x_0} \tag{2.1}$$

We recall that the word autonomous refers to the fact that $\mathbf{f}$ in (2.1) does not explicitly depend on time t with $\mathbf{x}(t) \in \mathbb{R}^n$. The initial value problem (IVP) (2.1) also known as Cauchy problem. In many problems it is important to emphasize the dependence of the solution on the initial conditions. Thus we introduce the notion of the flow of (2.1) as $\mathbf{x}(t) = \phi(t, \mathbf{x_0})$, which is the solution of the Cauchy problem.

Definition 2.1. (Equilibrium point). A point $\mathbf{x}^*(t) \in \mathbb{R}^n$ is said to be a steady state, stationary point, critical point or equilibrium point of the IVP (2.1) if

$$\mathbf{f}(\mathbf{x}^*(t)) = 0$$

Now differential equation (2.1) defines a well-posed IVP according to the the followings:

Definition 2.2. (Locally Lipschitz Functions). A function is locally Lipschitz if for each $\mathbf{x_0} \in \mathbb{R}^n$ there is a neighborhood of $\mathbf{x_0}$, $N_\epsilon(\mathbf{x_0}) \subset \mathbb{R}^n$, and a constant $k > 0$, such that for all $\mathbf{x}, \mathbf{y} \in N_\epsilon(\mathbf{x_0})$

$$|\mathbf{f}(\mathbf{x}) - \mathbf{f}(\mathbf{y})| < k|\mathbf{x} - \mathbf{y}|$$

Theorem 2.3. *(Fundamental Existence and Uniqueness Theorem). Suppose the function* $\mathbf{f} : \mathbb{R}^n \to \mathbb{R}^n$ *is continuously differentiable. Then* $\mathbf{x(t)}$ *is a solution of the differential equation* $\mathbf{x}' = \mathbf{f}(\mathbf{x}(t))$ *on an interval* I *if* $\mathbf{x(t)}$ *is differentiable on* I *and if for all* $t \in I, \mathbf{x(t)} \in \mathbb{R}^n$ *and* $\mathbf{x}' = \mathbf{f}(\mathbf{x}(t))$ *and given* $\mathbf{x_0} \in \mathbb{R}^n, \mathbf{x(t)}$ *is a solution of the initial value problem*

$$\mathbf{x}' = \mathbf{f}(\mathbf{x}(t)), \quad \mathbf{x}(t_0) = \mathbf{x_0}.$$

Remark 2.4. The above is a well known theorem and ensures that the solutions exists and is unique in the neighborhood of $\mathbf{x_0}$, i.e., the function is locally Lipschitz. The proof for this theorem can be found in [18].

Another well known theorem known as Comparison Theorem of functions, the proof to this theorem can be found in [19].

Theorem 2.5. *(Gronwall's Inequality). Let* $[a, b]$ *be an interval and* f *and* g *be continuous functions on* $[a, b]$ *with* f *differentiable on* $[a, b]$*. If* f *satisfies the differential inequality:*

$$\frac{df}{dt} = f'(t) \leq f(t)g(t)$$

for every $t \in [a, b]$ *then*

$$f(t) \leq f(a)e^{\int_a^t g(s)ds}$$

for every $t \in [a, b]$.

2.3.1 The Basic Reproduction Number

The basic reproductive number is used to measure the ability of the disease to reproduce, and is denoted by R_0. This is defined as the expected number of secondary cases reproduced by one infected individual in his/her entire infectious period. When $R_0 < 1$, each infected individual can produce an average of less than one new infected individual during his entire period of infectiousness. In this case the disease will not persist in the population and may be eradicated. But in a situation where $R_0 > 1$ implies that each infected individuals during the entire period of infectiousness can produce more than one new infected individual. This is a strong indication that the disease can persist and invade the population.

The so-called next generation method introduced by Diekmann et al. [20] and Heffernan et al. [21] is a general method for deriving R_0 in cases where one or more classes of infectives are involved. Suppose we have n disease compartments and m non-disease compartments, and let $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ be the sizes of these compartments. Also, denote the rate of secondary infection increase of the i^{th} disease compartments by F_i. However V_i is the rate of disease progression, death and recovery decrease the i^{th} compartment, the compartmental model can then be written in the form:

$$\begin{cases} \dfrac{dx_i}{dt} = F_i(x,y) - V_i(x,y), & i = 1,2,...,n, \\ \dfrac{dy_i}{dt} = g_j(x,y) - V_i(x,y), & j = 1,2,...,m. \end{cases}$$

The calculation of the basic reproduction number is based on the linearization of the ordinary differential equations (ODE) model about a disease-free equilibrium, while the following assumptions ensure the existence and well-posedness of a model.

1. Assume $F_i(0,y) = 0$ and $V_i(0,y) = 0$ for all $y \geq 0$ and $i = 1,2,...,n$. All new infections are secondary arising from infected hosts.

2. $F_i(0,y) \geq 0$ for all non-negative x and y and $i = 1,2,...,n$. Then function F represent new infections and cannot be negative.

3. $V_i(0,y) \leq 0$ whenever $x_i = 0, i = 1,2,...,n$. Each component, V_i represents a net outflow from compartment i and must be negative (inflow only) whenever the compartment is non-empty.

4. Assume $\sum_{i=1}^{n} V_i(x,y) \geq 0$ for all non-negative x and y. The sum represents the total outflow from all infected compartments. Terms in the model leading to increases in $\sum_{i=1}^{n} x_i$ are assumed to represent secondary infections and therefore belong in F.

5. Assume the disease-free system $\dfrac{dy}{dt} = g(0,y)$ has a unique equilibrium that is asymptotically stable. That is, all solutions with initial conditions of the form $(0,y)$ approach a point $(0,y_0)$ as $t \to \infty$. This point is referred to as the disease-free equilibrium.

Assuming that F_i and V_i meet above conditions, we can form the next generation matrix (operator) FV^{-1} from matrices of partial derivatives of F_i and V_i particularly

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

where $i, j = 1, ..., m$ and where x_0 is the disease-free equilibrium. The R_0 is given by the spectral radius (dominant eigenvalue) of the matrix FV^{-1}.

2.4 Nonlinear Stability Analysis

In mathematical modeling systems it becomes apparent that nearly all systems are non-linear, including the simple model we are examining (2.1). However, most of the theory that has been developed by mathematicians governing the behavior of systems of differential equations, especially stability, is centered upon linear systems. Thus, in order to further understand the behavior of a non-linear system it is first crucial to linearize the system. Essentially, this process approximates a non-linear system in a linear manner. The linear approximation occurs at the critical points. Near the critical points we can make a linear approximation and so determine the local character of the paths. This technique allows the stability of the critical points to be determined and provides a starting point for global investigations of solutions. The goal of this stability analysis is to perturb the system from a critical point and examine if the system returns to the original critical point.

Let us first note the following result.

Lemma 2.6. *If* $\mathbf{f}$ *has continuous partial derivatives of the first order in some neighbourhood of* $\mathbf{x}^*$*, then*

$$\mathbf{f}(\mathbf{x} + \mathbf{x}^*) = \mathbf{f}(\mathbf{x}^*) + \mathcal{A}\mathbf{x} + \mathbf{g}(\mathbf{x})$$

where

$$\mathcal{A} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\mathbf{x}^*) & \cdots & \frac{\partial f_1}{\partial x_n}(\mathbf{x}^*) \\ \vdots & \ddots & \vdots \\ \frac{\partial f_1}{\partial x_n}(\mathbf{x}^*) & \cdots & \frac{\partial f_n}{\partial x_n}(\mathbf{x}^*) \end{pmatrix}$$

and $\mathbf{g}(\mathbf{x})/||\mathbf{x}||$ *is continuous in some neighbourhood of* $\mathbf{x}^*$ *and vanishes at* $\mathbf{x} = \mathbf{x}^*$.

Proof. The matrix $\mathcal{A}$ has constant entries so that $\mathbf{g}$ defined by

$$\mathbf{g}(\mathbf{x}) = \mathbf{f}(\mathbf{x} + \mathbf{x}^*) - \mathbf{f}(\mathbf{x}^*) - \mathcal{A}\mathbf{x}$$

is a continuous function of $\mathbf{x}$. Hence, $\mathbf{g}(\mathbf{x})/||\mathbf{x}||$ is also continuous for $\mathbf{x} \neq \mathbf{0}$. Using now Taylor's formula for each component of $\mathbf{f}$ we obtain

$$f_i(\mathbf{x} + \mathbf{x}^*) = f_i(\mathbf{x}^*) + \frac{\partial f_1}{\partial x_1}(\mathbf{x}^*)x_1 + \cdots + \frac{\partial f_i}{\partial x_n}(\mathbf{x}^*)x_n + R_i(\mathbf{x}), \quad i = 1, 2, ..., n,$$

where, for each i, the remainder R_i satisfies

$$|R_i(x) \leq M(||\mathbf{x}||)||\mathbf{x}||$$

and M tends to zero is $||\mathbf{x}|| \to 0$. Thus,

$$\mathbf{g}(\mathbf{x}) = (R_1(\mathbf{x}), \cdots, R_n(\mathbf{x}))$$

and

$$\frac{\mathbf{g}(\mathbf{x})}{||\mathbf{x}||} \leq M(||\mathbf{x}||) \to 0$$

as $||\mathbf{x}|| \to 0$ and, $\mathbf{f}(\mathbf{x}^*) = \mathbf{0}$, the lemma is proved. □

The linear system

$$\mathbf{x}' = \mathcal{A}\mathbf{x} \tag{2.2}$$

is called the linearization of (2.1) around the equilibrium point $\mathbf{x}^*$ and $\mathcal{A}$ is called the Jacobian matrix at $\mathbf{x}^*$.

The Hartman-Grobman theorem is essential for showing how our analysis of the linearized system relates to the non-linear system. The Hartman-Grobman Theorem shows that near a critical point for a nonlinear system (2.1) exhibits the same qualitative structure as the linear system (2.2).

Definition 2.7. Two autonomous systems of differential equations are said to be topologically equivalent in a neighborhood of the origin or to have the same qualitative structure near the origin if there is a homeomorphism H mapping an open set U containing the origin onto an open set V containing the origin which maps trajectories of (2.1) in U onto trajectories of (2.2) in V and preserves their orientation by time in the sense that if a trajectory is directed from x_1 to x_2 in U,

then its image is directed from $H(x_1)$ to $H(x_2)$ in V. If the homeomorphism H preserves the parameterization by time, then the systems (2.1) and (2.2) are said to be topologically conjugate in a neighborhood of the origin [22].

Theorem 2.8. *(The Hartman-Grobman Theorem). Let E be an open subset of $\mathbb{R}^n$ containing the origin, let $\mathbf{f} \in C^2(E)$ and let ϕ_t be the flow of the nonlinear system (2.1). Suppose that $\mathbf{f}(\mathbf{0}) = \mathbf{0}$ and that the matrix $\mathcal{A}(0)$ has no eigenvalue with zero real part. Then there exists a homeomorphism H of an open set U containing the origin onto an open set V containing the origin such that for each $\mathbf{x_0} \in U$ there is an open interval $I_0 \subset \mathbb{R}$ containing zero such that for all $\mathbf{x_0} \in U$ and $t \in I_0$*

$$H \circ \phi_t(\mathbf{x_0}) = e^{\mathcal{A}t} H(\mathbf{x_0})$$

It is noted that the proof for the Hartman Grobman Theorem are well known and can be found in [22].

This theorem essentially states that H maps the trajectories of the nonlinear system near the critical points onto the trajectories of the linear system near the critical points and preserves the parameterization of time [22]. In other words, if the Jacobian matrix has no zero or purely imaginary eigenvalues, the stability properties of the system of nonlinear equations is the same as those for the system of linear equations at the critical points.

2.4.1 Local Stability Analysis

To analyze the eigenvalues of the Jacobian matrix $\mathcal{A}$ evaluated at the critical points gives insights into the stability properties at that critical point. There are three possible values for an eigenvalue: positive, negative, and imaginary. In more complex systems, combinations of all three types of values are possible and lead to different interpretations of the stability at the point. For analysis of a non-linear system, it is necessary to use:

Theorem 2.9. *(Poincare-Perron). Let A be a constant matrix in the system $\mathbf{x}' = \mathcal{A}\mathbf{x}$ with eigenvalues $\lambda_i, i = 1, 2, ..., n$.*

(i) If the system is stable, then $Re\{\lambda_i\} \leq 0, i = 1, 2, ..., n$.

(ii) *If either* $Re\{\lambda_i\} < 0, i = 1, 2, ..., n$; *or if* $Re\{\lambda_i\} \leq 0, i = 1, 2, ..., n$ *and there is no zero repeated eigenvalue; then the system is uniformly stable.*

(iii) *The system is asymptotically stable if and only if* $Re\{\lambda_i\} < 0, i = 1, 2, ..., n$; *note that it is also uniformly stable by (ii).*

(iv) *If* $Re\{\lambda_i\} > 0$, *for any* $i = 1, 2, ..., n$ *the solution is unstable.*

This theorem was adopted from [23].

Remark 2.10. If any of the eigenvalues have a positive real part, we define the critical point to be a source, and thus, unstable. If all of the real parts of the eigenvalues are negative real numbers, we define the critical point to be a sink, and thus, stable.

One way to find the sign of the eigenvalue is to solve for the eigenvalue explicitly. However, for more complex systems the eigenvalues can be incredibly complex and difficult to work with. Thus, in order to determine the sign of the eigenvalue we can use the Routh-Hurwitz Criteria.

Theorem 2.11. *(Routh-Hurwitz Criteria). Given the polynomial*

$$P(x) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n$$

where the coefficients a_i *are real constants,* $i = 1, 2, ..., n$, *define the* $n \times n$ *Hurwitz matrix using the coefficients* a_i *of the characteristic polynomial:*

$$H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{bmatrix}$$

where $a_i = 0$ *if* $j > n$. *All of the roots of the polynomial* $P(x)$ *are negative or have negative real parts iff the determinants of all Hurwitz matrices are positive:*

$$\det(H_j) > 0, j = 1, 2, ..., n.$$

Considering n=4 and n=5, the theorem simplifies and we are able to apply the theorem to the analysis of our system.

For n=3, the following conditions must be met:

(i) $a_1, a_2, a_3 > 0$

(ii) $a_1 a_2 > a_3$

For n=4, the following conditions must be satisfied:

(i) $a_1, a_2, a_3, a_4 > 0$,

(ii) $a_1 a_2 > a_3$,

(iii) $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$.

For n=5, the following conditions must be met:

(i) $a_1, a_2, a_3, a_4, a_5 > 0$,

(ii) $a_1 a_2 > a_3$,

(iii) $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$,

(iv) $(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2$.

The proof of the Routh Hurwitz Criteria is well known and can be found in [24].

The signs of the roots of the polynomials will tend to depend on several parameters known as threshold parameters. Later we will show that this values of these parameters, sometimes called, the reproductive constants influence and determine the stability of the system. An important part of our analysis will be deducing and applying these quantities effectively.

2.4.2 Global Stability Analysis

Consider again the system (2.1) in $\mathbb{R}^n$. Suppose that it has an equilibrium at $\mathbf{x^0}$. Then, by writing $\mathbb{R}^n$ as

$$\mathbf{y}' = (\mathbf{y} - \mathbf{x_0})' = \mathbf{x}' = \mathbf{f}(\mathbf{x} + \mathbf{x_0}) = \hat{\mathbf{f}}(\mathbf{x})$$

we obtain an equivalent system for which $\mathbf{x} = \mathbf{0}$ becomes an isolated equilibrium. Thus there is no loss of generality to consider (2.1) with $\mathbf{x} = \mathbf{0}$ as its equilibrium.

Let Ω be an open neighbourhood of 0 and let $V : \Omega \to \mathbb{R}$ be a continuously differentiable function. We define the derivative of V along trajectories of (2.1) by the chain rule

$$V' = \frac{dV}{dt} = \mathbf{x}'.\nabla V = \mathbf{f}.\nabla V = \sum_{i=1}^{n} f_i \frac{\partial V}{\partial x_i}$$

In general, $\mathbf{f}$ being a potential field, then there is a scalar function V satisfying

$$\mathbf{f}(\mathbf{x}) = -\text{grad } V(\mathbf{x}),$$

That implies

$$V' \leq 0.$$

Definition 2.12. A continuously differentiable function V on $0 \in \Omega$ is called a Lyapunov function for (2.1) if

(i) $V(0) = 0$ and $V(\mathbf{x}) > 0$ on Ω;

(ii) $V' \leq 0$ on Ω.

Now we seek for the gobal stability of system (2.1) based on the following theorems and proof can be found in [25].

Theorem 2.13. *(Lyapunov Stability). Assume that there exists a Lyapunov function defined on a neighbourhood Ω of an equilibrium $\mathbf{x} = \mathbf{0}$ of system (2.1). Then the solutions originating from Ω are globally defined (for all $t \geq 0$) and the equilibrium $\mathbf{x} = \mathbf{0}$ is stable.*

Theorem 2.14. *(Lyapunov Asymptotic Stability). Assume that there exists a Lyapunov function defined on a neighbourhood Ω of an equilibrium $\mathbf{x} = \mathbf{0}$ of system (2.1), which additionally satisfies $V' < 0$ in $\Omega \backslash \{0\}$, then $\mathbf{x} = \mathbf{0}$ is asymptotically stable.*

Definition 2.15. The set

$$\Gamma_{\mathbf{x_0}} = \{\mathbf{x} \in \mathbb{R}^n : \mathbf{x}(t) = \phi(t, \mathbf{x_0}), t \in \mathbb{R}\}$$

is called the trajectory, or orbit, of the flow through $\mathbf{x_0}$.

Theorem 2.16. *(LaSalle's Invariance Principle). Let* $\mathbf{x} = \mathbf{0}$ *be a stationary point of (2.1) and let* V *be a Lyapunov function on some neighbourhood* $0 \in \Omega$*. If, for* $\mathbf{x} \in \Omega$, $\Gamma_{\mathbf{x}}^{+}$ *is bounded with limit points in* Ω *and* M *is the largest invariant set of*

$$E = \{\mathbf{x} \in \Omega : V'(\mathbf{x}) = \mathbf{0}\},$$

then

$$\phi(t, \mathbf{x}) \to M, \quad t \to \infty.$$

2.5 Optimal Control Method

In an optimal control problem for ordinary differential equations, we use $u(t)$ for the control and $x(t)$ for the state variables. The state variable satisfies a differential equation which depends on the control variable:

$$x'(t) = g(t, x(t), u(t))$$

where x' denote the derivative with respect to time t. Both $u(t)$ and $x(t)$ affect the goal, as the control function changes, the solution to the differential equation will also change. The basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and the associated state variable $x(t)$ to maximize or minimize the given objective functional depending on the situation. Let us consider the former for this case, i.e.,

$$\text{Maximize } J(u) = \int_0^T f(t, x(t), u(t))$$

subject to

$$x'(t) = g(t, x(t), u(t)) \tag{2.3}$$

where $x(0) = x_0$ and $x(T)$ is free.

We assume that the controls are piecewise continuous functions with values in a set. The principal technique for such an optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy. Next we presented a brief derivation of the necessary conditions. That is, if $u(t)$, $x(t)$ is an optimal pair, then these conditions will hold. These necessary

conditions for optimal control theory for ODEs was developed by Pontryagin and his collaborators around 1950. They developed the key idea of introducing the adjoint function to attach the differential equation to the objective functional. This idea is similar to Lagrange multipliers that attach the constraints when finding the maximum of a function in multi-dimensional calculus subject to some equation constraints. The following theorem (known as Pontryagin's Maximum Principle), provide necessary conditions for the optimal control using the Hamiltonian [26].

Theorem 2.17. *(Pontryagin's Maximum Principle). If u^* and x^* are optimal for equation (2.3), subject to the ODEs defining the given dynamical system, then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

$$H(t, x^*, u(t), \lambda(t)) \leq H(t, x^*, u^*(t), \lambda(t))$$

for each control u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t))$$

and

$$\begin{aligned} \lambda'(t) &= -\frac{\partial H(t, x^*, u^*(t), \lambda(t)}{\partial x}, \\ \lambda(T) &= 0. \end{aligned}$$

where f is the integrand of the objective functional and g, the right hand side of the given dynamical system. The optimal control u^* must maximize the Hamiltonian.

Chapter 3

The HIV Infection Model

3.1 Introduction

In this chapter, we analyze a HIV infection model proposed by Nowak et al. [6], which is known as basic HIV model. We show the existence of the steady states and obtain the conditions for the local and global stability in terms of the basic reproduction number. Further, by using clinical data from HIV infected individuals, we determine the model parameters which best fit the data. Finally, numerical simulations are presented to support the theoretical results.

3.2 Mathematical Model

The basic model of HIV infection which was developed in [6], has been widely studied in an effort to describe the viral dynamics of primary infection. The model takes into account three types of population, the number of target $CD4^+T$ cells $T(t)$, the number of infected $CD4^+T$ cells $I(t)$ and the number of virions $V(t)$ in plasma all at time t. The model is described by three coupled ordinary differential equations (ODEs) as follows:

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - kT(t)V(t) - d_T T(t), \quad T(0) = T_0, \\ \dfrac{dI(t)}{dt} = kT(t)V(t) - d_I I(t), \quad I(0) = I_0, \\ \dfrac{dV(t)}{dt} = N d_I I(t) - d_V V(t), \quad V(0) = V_0. \end{cases} \tag{3.1}$$

Here λ is positive and represents the creation rate of the Target T-cells. This cells can be eliminated by becoming infected by the virus at rate k, which is directly proportional to the product of the participating populations. The death rate, d_T, can be assumed to be proportional to the target cell population. The only way that infected cells can be created is by infecting previously uninfected target cells. Thus, the term kVT is the same as the infection rate term in the target cell differential equation with a reversal in sign. Similar to target cell death, infected cells are cleared by the immune system at a rate, d_I, proportional to the infected cell population. The free virus population is described by our final ODE of the system. We assume that each infected cell produces N viral particles before it dies and the virus is then killed off at a clearance rate, d_V, proportional to the virus population. In some literature [6], Nd_I is called the virus proliferation rate p. Based on biological considerations we assume that these model parameters are positive. In addition, there are two biologically reasonable assumptions we are able to make with regard to the values of parameters in relation to one another. Notably, it is biologically reasonable to assume that infected cells have a higher death rate than target cells, namely $d_I > d_T$. Furthermore, in early HIV infection, before the peak in viral load, we assume that the total number of target cells remains approximately constant, to make each T-cell is susceptible only to virus. A schematic representation of the model (3.1) is given in Figure 3.1.

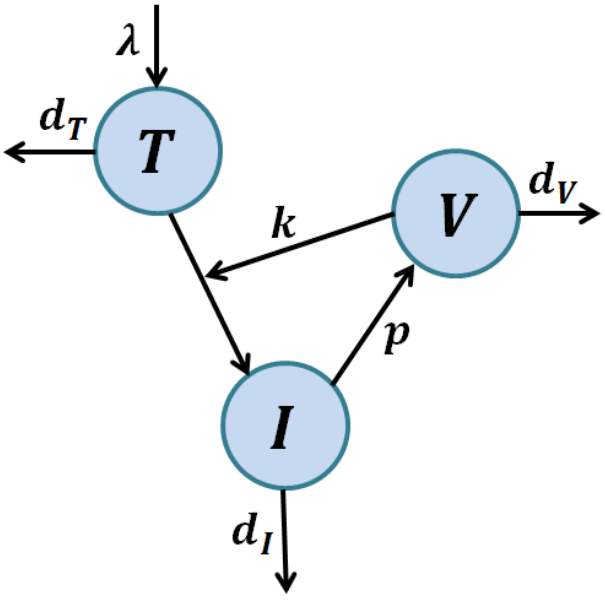


Figure. 3.1. Schematic representation of the HIV model. Here $p(= Nd_I)$ is the virus proliferation rate.

3.3 Basic Properties of the Model

In order to retain the biological validity of the model, we must prove that solutions to the system of differential equations exist and they are positive and bounded for all values of time.

Theorem 3.1. *(Existence of Solution). Let $T_0, I_0, V_0 \in \mathbb{R}$ be given. There exists $t_0 > 0$ and continuously differentiable functions $\{T, I, V : [0, t_0) \to \mathbb{R}\}$ such that the ordered triple (T, I, V) satisfies (3.1) and $(T, I, V)(0) = (T_0, I_0, V_0)$.*

Proof of Theorem 3.1. The Picard-Lindelöf Theorem states that for the initial value problem $y'(t) = f(y(t)),\ y(t_0) = y_0, t \in [t_0 - \epsilon, t_0 + \epsilon]$, if f is locally Lipschitz in y and continuous in t, then for some value $\epsilon > 0$, there exists a unique solution $y(t)$ to the initial value problem within the range $[t_0 - \epsilon, t_0 + \epsilon]$. Since the system of ODEs is autonomous, it suffices to show that the function $\mathbf{f} : \mathbb{R}^3 \to \mathbb{R}^3$ defined by

$$\mathbf{f}(\mathbf{y}) = \begin{pmatrix} \lambda - kTV - d_T T \\ kTV - d_I I \\ N d_I I - d_V V \end{pmatrix}$$

is locally Lipschitz in its $\mathbf{y}$ argument. Note that the Jacobian matrix

$$\nabla \mathbf{f}(\mathbf{y}) = \begin{pmatrix} -kV - d_T & 0 & -kT \\ kV & -d_I & kT \\ 0 & N d_I & -d_V \end{pmatrix}$$

is linear in $\mathbf{y} \in \mathbb{R}^3$. Thus, $\nabla \mathbf{f}(\mathbf{y})$ is continuous on a closed interval and differentiable on an open interval $I \in \mathbb{R}^3$. By the Mean Value Theorem, we know

$$\frac{|\mathbf{f}(\mathbf{y_1}) - \mathbf{f}(\mathbf{y_2})|}{|\mathbf{y_1} - \mathbf{y_2}|} \leq |\nabla \mathbf{f}(\mathbf{y}^*)|$$

for some $\mathbf{y}^* \in I$. By letting $|\nabla \mathbf{f}(\mathbf{y}^*)| = K$, we obtain $|\mathbf{f}(\mathbf{y_1}) - \mathbf{f}(\mathbf{y_2})| \leq K|\mathbf{y_1} - \mathbf{y_2}|$ for all $\mathbf{y_1}, \mathbf{y_2} \in I$ and therefore $\mathbf{f}(\mathbf{y})$ is locally bounded for every $\mathbf{y} \in \mathbb{R}^3$. Hence, $\mathbf{f}$ has a continuous, bounded derivative on any compact subset of $\mathbb{R}^3$ and so $\mathbf{f}$ is locally Lipschitz in $\mathbf{y}$. By the Picard-Lindelöf Theorem, there exists a unique solution, $y(t)$, to the ordinary differential equation $y'(t) = f(y(t))$ with initial value $y(0) = y_0$ on $[0, t_0]$ for some time $t_0 > 0$. □

Additionally, we may show that for positive initial data, solutions remain positive as long as they exist. A fortunate byproduct of this result is that the solutions are also bounded.

Theorem 3.2. *(Positivity and Boundedness). Assume the initial conditions of (3.1) satisfy* $T_0 > 0, I_0 > 0$, *and* $V_0 > 0$. *If the unique solution provided by Theorem 3.1 exists on the interval* $[0, t_0]$ *for some* $t_0 > 0$, *then the functions* $T(t), I(t)$ *and* $V(t)$ *will be bounded and remain positive for all* $t \in [0, t_0]$.

Proof of Theorem 3.2. We assume that $T(t), I(t)$ and $V(t)$ initially have positive values. From the previous theorem, there exists a $t > 0$ such that the solution exists on $[0, t]$. Let us denote by T^* the largest time for which all populations remain positive, or more precisely

$$T^* = \sup\{t > 0 : T(s), I(s), V(s) > 0, \ \forall s \in [0, t]\}.$$

Since each initial condition is nonnegative and the solution is continuous, there must be an interval on which the solution remains positive, and we see that $T^* > 0$. Then on the interval $[0, T^*]$ we estimate each term.

We can place lower bounds on I, and V instantly

$$\frac{dI(t)}{dt} = kT(t)V(t) - d_I I(t) \geq -d_I I(t),$$

since the decay terms are linear, that concludes

$$I(t) \geq I(0)e^{-d_I t} > 0,$$

for $t \in [0, T^*]$. Again

$$\frac{dV(t)}{dt} = Nd_I I(t) - d_V V(t) \geq -d_V V(t),$$
$$\text{i.e. } V(t) \geq V(0)e^{-d_V t} > 0$$

for $t \in [0, T^*]$. Similarly, we can place an upper bound on $\dfrac{dT}{dt}$ so that

$$\frac{dT(t)}{dt} = \lambda - kT(t)V(t) - d_T T(t) \leq \lambda,$$
$$\text{i.e. } T(t) \leq T(0) + \lambda t \leq C(1 + t),$$

where the constant C depends on the upper bound of λ and $T(0)$. Next, we sum the equations for I, and V, and by positivity of these functions and place bounds on this sum. Using the upper bound on $T(t)$, we find

$$\begin{aligned}
\frac{d}{dt}(I+V) &= kT(t)V(t) + (N-1)d_I I(t) - d_V V(t), \\
&\leq kC(1+t)V + Nd_I I(t) + d_V V(t), \\
&\leq C_2(1+t)(I+V), \qquad \text{where } C_2 \geq \max\{kC, Nd_I, d_V\}, \\
\text{i.e. } (I+V)(t) &\leq C_3 e^{t^2}
\end{aligned}$$

for $t \in [0, T^*]$, where $C_3 > 0$ depends upon $C_2, I(0)$, and $V(0)$ only. Since $I(t)$ and $V(t)$ are positive, we can place an upper bound on both I and V by

$$C_3 e^{t^2} \geq (I+V)(t) \geq I(t),$$

and

$$C_3 e^{t^2} \geq (I+V)(t) \geq V(t).$$

With these bounds in place, we can now examine $T(t)$ and bound it from below using

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - kTV - d_T T \geq -kTV - d_T T \geq -d_T T - kC_3 e^{t^2} T, \\
&\geq -C_4(1+e^{t^2})T, \qquad \text{where } C_4 \geq \max\{kC_3, d_T\}, \\
\Rightarrow \frac{dT}{dt} &+ C_4(1+e^{t^2})T \geq 0, \\
\text{i.e. } T(t) &\geq T(0)e^{-C_4 \int_0^t (1+e^{\tau^2} d\tau)} > 0
\end{aligned}$$

for $t \in [0, T^*]$. Thus, the values of T, I and V stay strictly positive for all of $[0, T^*]$, including at time T^*. By continuity, there must exist a $t > T^*$ such that $T(t), I(t)$, and $V(t)$ are still positive. This contradicts the definition of T^*, and shows that $T(t), I(t), L(t)$ and $V(t)$ are strictly positive on the entire interval $[0, t]$. Additionally, on this same interval, all of the functions remain bounded, so the interval of existence can be extended further. In fact, the bounds on T, I, and V derived above hold on any compact time interval. Thus, we may extend the time interval on which the solution exists to $[0, t]$ for any $t > 0$ and from the above argument, the solutions remain both bounded and positive on $[0, t]$. □

3.3.1 Equilibria of the System

In order to fully understand the dynamics of the basic model, it is necessary to study the equilibrium points.

Definition 3.3. Consider the differential equation $y'(t) = f(y(t), t)$, a point $y(t)$ is an equilibrium point if $y'(t) = f(y(t), t) = 0$ for all $t \in \mathbb{R}$.

In our case, an equilibrium point is the constant solution of (3.1) so that if the system begins at such a value, it will remain there for all time. In other words, the cell numbers are unchanging; so, the rate of change for each compartment is zero. By setting the right-hand side of (3.1) to zero, we get

$$\lambda - kTV - d_T T = 0, \tag{3.2}$$

$$kTV - d_I I = 0, \tag{3.3}$$

$$Nd_I I - d_V V = 0, \tag{3.4}$$

and solving the resulting equations for T, I, and V, we find that there exist exactly two equilibria which are biologically meaningful. We can categorize these points to be when the HIV virus is either extinct from the body, i.e., $I = V = 0$, or when the virus persists within the body ($I \neq 0, V \neq 0$) as t grows large.

We begin by solving for the nonlinear interaction term in the equations (3.3) and (3.4), that gives

$$kTV = d_I I,$$
$$Nd_I I = d_V V,$$

which implies

$$V\left(kT - \frac{d_V}{N}\right) = 0.$$

Thus, either $V = 0$ or $T = \dfrac{d_V}{kN}$. Using $V = 0$, in the equations (3.2) and (3.4) gives $I = 0$ and $T = \dfrac{\lambda}{d_T}$. Hence, the ordered triplet

$$(T, I, V) = \left(\frac{\lambda}{d_T}, 0, 0\right).$$

This particular equilibrium point is also known as viral extinction, since there are no virus particles or infected cells. We will refer to this point as $E^0 = (T^0, I^0, V^0)$.

In the latter case, $T = \dfrac{d_V}{kN}$ and substituting this value of T into equation (3.2) yields $V = \dfrac{\lambda N}{d_V} - \dfrac{d_T}{k}$ and further substitution shows $I = \dfrac{\lambda}{d_I} - \dfrac{d_V d_T}{N k d_I}$. Thus, a second equilibrium exists at the point

$$(T, I, V) = \left(\frac{d_V}{kN}, \ \frac{\lambda}{d_I} - \frac{d_V d_T}{N k d_I}, \ \frac{\lambda N}{d_V} - \frac{d_T}{k} \right).$$

Since there are distinct presences of virus particles and infected cells, we refer to this point as viral persistence and abbreviate the point as $E^* = (T^*, I^*, V^*)$.

In terms of biology, we can say E^0 is the case in which an infection exists for a short period of time, then is removed from the body by natural means. The virus does not persist. The second case, where the system of equations tends to E^*, denotes that situation where the body is unable to clear the infection by itself. If this ends up being the case, than after a certain period of time, the HIV infection model loses its applicability as the infection takes a deeper hold on the body. More complex models, which consider latent infection, effects of macrophages, cytotoxic immune response (CLT), or spatial dependence are then required to describe the spread of HIV within the body and its development towards AIDS.

If the system (3.1) takes on the value of a equilibrium point at any time, it will remain at the point for all remaining time, otherwise the system need not necessarily obtain these values. However, the system may approach the equilibrium point, move away from the equilibrium point, or cycle between specific values. In order to accurately determine the behavior and thus how the system will interact with the equilibrium we must undergo a stability analysis for the system.

3.3.2 Basic Reproduction Number

The basic reproduction number, sometimes called basic reproductive rate or basic reproductive ratio, is an important threshold quantity that developed for the field of epidemiology in order to mathematically characterize the volatility of an infectious disease. This formula is very helpful to find the average number of infected cells generated by a single virus particle introduced into a site with completely uninfected target cells. For computing the basic reproduction ratio R_0, we apply

the next generation method [20, 21]. Assume that there are n infective cells in the model and define the vector $\bar{x} = x_i$, where x_i, $i = 1, 2, ..., n$, denotes the number or the proportion of compartments in the ith infective cell. Let $F_i(\bar{x})$ be the rate of appearance of new infections in the ith cell and let $V_i(\bar{x}) = V_i^-(\bar{x}) - V_i^+(\bar{x})$, where V_i^+ consists of transfer of individuals into cell i and V_i^- consists of transfer of individuals out of cell i. The difference $F_i(\bar{x}) - V_i(\bar{x})$ gives the rate of change of x_i. Notice that F_i consists of new infections from target cell, whereas V_i includes the transfer of infected components from one infected cell to another [21]. We can then form the next generation matrix from the partial derivatives of F_i and V_i:

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

where $i, j = 1, 2, ..., n$ and x_0 is the initial diseses free condition of the epidemic. The basic reproduction ratio R_0 is given by the dominant eigenvalue of the matrix FV^{-1} [21].

Applying the next generation method to the model (3.1), and since we are only concerned with cells that spread the infection, we only need to model the infected cells, I, and virions, V, compartments. Let us define the model dynamics using the equations

$$\begin{cases} \dfrac{dI(t)}{dt} = kT(t)V(t) - d_I I(t), \\ \dfrac{dV(t)}{dt} = Nd_I I(t) - d_V V(t). \end{cases}$$

For this system, at the disease free equilibrium point

$$F = \begin{pmatrix} 0 & k\dfrac{\lambda}{d_T} \\ 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} d_I & 0 \\ -Nd_I & d_V \end{pmatrix}$$

Then, for the system (3.1), the next generation matrix is

$$FV^{-1} = \begin{pmatrix} \frac{kN\lambda}{d_T d_V} & \frac{k\lambda}{d_T d_V} \\ 0 & 0 \end{pmatrix}$$

The dominant eigenvalue of FV^{-1} is given by expression

$$R_0 = \rho\left[FV^{-1}\right] = \frac{k\lambda N}{d_T d_V} \tag{3.5}$$

and it is basic reproduction number for the system (3.1).

The basic reproduction number R_0 is the average number of secondary infections produced when one single virus cell is introduced into a host where every T-cell is susceptible [21]. Note that our model R_0 above is a product of the average number of target cell per unit time (in the presence of natural death) and the rate of the disease transmission by an infective cell. It is indeed a threshold quantity that helps to determine whether an outbreak of the disease dies out or spreads in a body. Later we will see, when $R_0 < 1$, the disease die out without any medical interventions but when $R_0 > 1$, the disease becomes endemic and this necessitates the introduction of some control measures in order to curtail the situation.

Remark 3.4. Using basic reproduction number R_0 the infected equilibrium point become

$$(T^*, I^*, V^*) = \left\{\frac{\lambda}{d_T R_0},\ \frac{d_T d_V}{N k d_I}(R_0 - 1),\ \frac{d_T}{k}(R_0 - 1)\right\}.$$

3.4 Local Stability of the Equilibria

For linear ODEs, it is well-known that the stability properties depend only upon the eigenvalues of the system. However, our model (3.1) is nonlinear, and thus we rely on linearization and a theorem of Hartman and Grobman [27] to unify the local behavior of the linear and nonlinear systems.

We will investigate the local stability properties of these equilibria by approximating the nonlinear system of differential equations (3.1) with a linear system at the points E^0 and E^*. Then, we locally perturb the system from equilibrium and examine the resulting long time behavior. This is done by linearizing the system about each equilibria, using the Jacobian for (3.1):

$$J = \begin{pmatrix} -kV - d_T & 0 & -kT \\ kV & -d_I & kT \\ 0 & Nd_I & -d_V \end{pmatrix}$$

Then, by studying the linearized system

$$\dot{z}(t) = J(E)z(t),$$

we can investigate the stability of each equilibrium point $E = E^0$ and $E = E^*$. As we will see below, this property depends only on a single number, referred to as the basic reproduction number, R_0 given by (3.5). As a result, we are able to examine the value of R_0 to determine whether viral persistence or viral extinction occurs as $t \to \infty$.

Theorem 3.5. *If $R_0 < 1$, then the non-infective equilibrium (E^0) is locally asymptotically stable. If $R_0 > 1$ then the non-infective equilibrium is an unstable saddle point, and the endemic equilibrium (E^*) is locally asymptotically stable.*

Proof of Theorem 3.5. We proceed by linearizing the system and using the Routh-Hurwitz criterion to determine conditions under which the linear system possesses only negative eigenvalues. Because, if the eigenvalues of the Jacobian matrix at a point have negative real parts, then that point is classified as an "attractor", meaning small perturbations from the equilibrium result in the system returning to that point over time. On the other hand, if one or more of the eigenvalues have positive real part, then small perturbations from equilibrium result in magnifications of those disturbances, and the system shifting away from the point. This point would then be known as a "repeller". Then, as a consequence of the Hartman-Grobman Theorem [27], the local behavior of the linearized system is equivalent to that of the nonlinear system.
First, we compute the Jacobian evaluated at the non-infective equilibrium $E^0 = (T^0, I^0, V^0) = \left(\frac{\lambda}{d_T}, 0, 0\right)$, resulting in

$$J(E^0) = \begin{pmatrix} -d_T & 0 & -k\frac{\lambda}{d_T} \\ 0 & -d_I & k\frac{\lambda}{d_T} \\ 0 & Nd_I & -d_V \end{pmatrix}$$

The corresponding characteristic equation can be written as

$$\begin{aligned} 0 =& \left| J(E^0) - \eta \mathbb{I} \right| \\ =& \frac{(d_T + \eta)\left\{d_T(d_I + \eta)\left(d_V + \eta\right) - d_I k \lambda N\right\}}{d_T}. \end{aligned}$$

After expanding the terms and ordering by powers of η, this equation ultimately simplifies to

$$\eta^3 + A_1\eta^2 + A_2\eta + A_3 = 0,$$

where

$$\begin{aligned} A_1 &= d_T + d_V + d_I, \\ A_2 &= -\frac{d_I k\lambda N}{d_T} + d_T\left(d_V + d_I\right) + d_I d_V, \\ A_3 &= d_I d_T d_V - d_I k\lambda N. \end{aligned}$$

According to the Routh-Hurwitz criteria (see theorem 2.11), all roots of this cubic equation possess negative real part if and only if $A_1, A_2, A_3 > 0$ and $A_1A_2 - A_3 > 0$. Clearly, $A_1 > 0$, and after rewriting A_3 in terms of R_0, we find

$$A_3 = d_I d_T d_V\left(1 - \frac{k\lambda N}{d_T d_V}\right) = d_I d_T d_V(1 - R_0).$$

Thus, if $A_3 > 0$, it is necessary that $R_0 < 1$. Similarly, we rewrite A_2 as

$$\begin{aligned} A_2 =& d_T\left(d_V + d_I\right) + d_I d_V\left(1 - \frac{k\lambda N}{d_T d_V}\right) \\ =& d_T\left(d_V + d_I\right) + d_I d_V(1 - R_0) \end{aligned}$$

and the previous condition if $R_0 < 1$, we find $A_2 > 0$.

Finally, we see that $A_2 > d_I d_V(1 - R_0)$, and clearly $A_1 > d_T$. Therefore, we find

$$A_1A_2 > d_T d_I d_V(1 - R_0) = A_3$$

and the Routh-Hurwitz criteria are satisfied. Thus, $R_0 < 1$ implies that all eigenvalues of the linearized system are negative, and hence the local asymptotic stability of E^0 follows. Conversely, if $R_0 > 1$, then the linearized system possesses at least one positive eigenvalue, and the equilibrium is unstable.

The analysis for E^* is similar to that of E^0. Linearizing (3.1) about E^*, we find the Jacobian

$$J(E^*) = \begin{pmatrix} -kV^* - d_T & 0 & -kT^* \\ kV^* & -d_I & kT^* \\ 0 & Nd_I & -d_V \end{pmatrix}$$

Using $(T^*, I^*, V^*) = \left(\frac{d_V}{kN},\ \frac{\lambda}{d_I} - \frac{d_V d_T}{Nkd_I},\ \frac{\lambda N}{d_V} - \frac{d_T}{k}\right)$, we get

$$J(E^*) = \begin{pmatrix} \frac{-k\lambda N}{d_V} & 0 & \frac{-d_V}{N} \\ \frac{k\lambda N}{d_V} - d_T & -d_I & \frac{d_V}{N} \\ 0 & Nd_I & -d_V \end{pmatrix}$$

and this results in the characteristic equation

$$0 = \left(\frac{k\lambda N}{d_V} + \eta\right)\left\{(d_I + \eta)(d_V + \eta) - d_V d_I\right\} + d_I\left(d_T d_V - k\lambda N\right).$$

After expanding the terms and ordering by powers of η, this equation ultimately simplifies to

$$\eta^3 + A_1\eta^2 + A_2\eta + A_3 = 0,$$

where

$$\begin{aligned} A_1 &= \frac{k\lambda N}{d_V} + d_V + d_I, \\ A_2 &= \frac{k\lambda N\left(d_V + d_I\right)}{d_V}, \\ A_3 &= d_I\left(k\lambda N - d_T d_V\right). \end{aligned}$$

As before, the Routh-Hurwitz criterion requires $A_1, A_2, A_3 > 0$ and $A_1A_2 - A_3 > 0$. Clearly, $A_1 > 0$ $A_2 > 0$, and after rewriting A_3 in terms of R_0, we find

$$A_3 = d_T d_V d_I\left(\frac{k\lambda N}{d_T d_V} - 1\right) = d_I(R_0 - 1).$$

Hence, it is necessary that $R_0 > 1$ in order to satisfy $A_3 > 0$. Now, we find

$$\begin{aligned} A_1A_2 &= \left(\frac{k\lambda N}{d_V} + d_V + d_I\right)\left(\frac{k\lambda N\left(d_V + d_I\right)}{d_V}\right), \\ &> k\lambda N d_I, \\ &> k\lambda N d_I - d_T d_V d_I, \\ &> A_3. \end{aligned}$$

With this, all of the criteria have been satisfied and E^* is stable if $R_0 > 1$. Conversely, if $R_0 < 1$, then the Jacobian possesses at least one positive eigenvalue, and the infected state is unstable. □

Remark 3.6. The case $R_0 = 1$ is a critical threshold point where the disease free equilibrium E^0 loses its asymptotic stability and simply becomes (neutrally) stable. Moreover, it becomes unstable immediately for $R_0 > 1$ and this will lead to the existence of a stable endemic equilibrium E^*. It is also noted that $R_0 = 1$ can literarily be viewed as a transcritical bifurcation point where stability is exchanged between E_0 and E^*.

Now we will proof a basic result concerning the non-existence of certain type of solution according to Busenberg and van den Driessche [28].

Theorem 3.7. *Let* $\mathbf{g}(T, I, V) = \{g_1(T, I, V),\ g_2(T, I, V),\ g_3(T, I, V)\}$ *be a vector field which is piecewise smooth on bounded region* $\mathcal{D}$*, and which satisfies the conditions* $\mathbf{g}.\mathbf{f} = 0$ *and curl* $\mathbf{g}.(1, 1, 1) < 0$ *in the interior of* $\mathcal{D}$*, where* $\mathbf{f} = (f_1, f_2, f_3)$ *is a Lipschitz continuous field in the interior of* $\mathcal{D}$*. Then the differential equation system* $T'(t) = f_1, I'(t) = f_2, V'(t) = f_3$ *has no periodic solutions in the bounded region* $\mathcal{D}$*.*

Proof of Theorem 3.7. Let f_1, f_2 and f_3 denote the right hand side of system (3.1), that is

$$\begin{aligned} f_1(T, I, V) &= \lambda - kTV - d_T T, \\ f_2(T, I, V) &= kTV - d_I I, \\ f_3(T, I, V) &= N d_I I - d_V V, \end{aligned}$$

and above equations are Lipschitz continuous as well as bounded (see theorem(3.1)). Let $\mathbf{g}(T, I, V) = \{g_1(T, I, V),\ g_2(T, I, V),\ g_3(T, I, V)\}$ be a vector field, where

$$\begin{aligned} g_1(T, I, V) &= f_3 - f_2 = N d_I I - d_V V - kTV + d_I I, \\ g_2(T, I, V) &= f_1 - f_3 = \lambda - kTV - d_T T - N d_I I + d_V V, \\ g_3(T, I, V) &= f_2 - f_1 = 2kTV - d_I I - \lambda + d_T T. \end{aligned}$$

It can be seen that the condition $\mathbf{g}.\mathbf{f} = 0$ is satisfied. Also

$$\begin{aligned} &curl\ \mathbf{g}.(1, 1, 1) = \\ &\{(-d_I + kT - d_V), (-d_V - kT - 2kV - d_T), (-kV - d_T - N d_I - d_I)\}.(1, 1, 1), \\ &= -2d_I - 2d_V - 2d_T - 3kV - N d_I < 0. \end{aligned}$$

Thus, by Theorem 4.1 in [28], the system (3.1) has no periodic solutions inside the bounded region $\mathcal{D}$. □

Our analysis reveals one very important fact about the overall system: for starting values sufficiently close to equilibrium, the long term behavior depends only on the value of R_0. If $R_0 > 1$ then the system tends towards an end state with a non-zero population of infected cells and virions (viral persistence), but if $R_0 < 1$ then the final equilibrium is a state with no virus or infection (viral extinction). Finally, we also establish that global asymptotic stability of the equilibria can also be shown using a Lyapunov function as in [29].

3.5 Global Stability of the Equilibria

Before proceeding with the global stability analysis for the model (3.1), we present some inequalities developed in [30], which will be used in the proofs. To begin with, we consider the function $G(x) = x - 1 - \ln(x)$. Note that $G(x) \geq 0, \forall x$ and that $G(x) = 0$ if and only if $x = 1$.
Let $x_1, x_2, \cdots, x_n$ be positive numbers. Then,

$$1 - x_i + \ln(x_i) = -G(x_i) \leq 0, \quad i = 1, 2, \cdots, n.$$

Summing over $i = 1$ to n, from above equation we obtain

$$n - \sum_{i=1}^{n} x_i + \ln\left(\prod_{i=1}^{n} x_i\right) \leq 0.$$

Choosing $x_i = \dfrac{p_i}{q_i}$, where $p_i > 0$, $q_i > 0$ for $i = 1$ to n, it followes that

$$n - \sum_{i=1}^{n} \frac{p_i}{q_i} + \ln\left(\prod_{i=1}^{n} \frac{p_i}{q_i}\right) \leq 0.$$

If $p_1, p_2, \cdots, p_n = q_1, q_2, \cdots, q_n$, then $\prod_{i=1}^{n} \dfrac{p_i}{q_i} = 1$ which leads to

$$n - \sum_{i=1}^{n} \frac{p_i}{q_i} \leq 0. \tag{3.6}$$

Theorem 3.8. *If $R_0 \leq 1$, then the non-infective equilibrium (E^0) is globally asymptotically stable and the disease dies out. If $R_0 > 1$, then the endemic equilibrium (E^*) is globally asymptotically stable and the disease persists.*

Proof of Theorem 3.8. To investigate the global stability of E^0, consider the following Lyapunov function

$$U(t) = T^0\left[\frac{T(t)}{T^0} - 1 - \ln\left(\frac{T(t)}{T^0}\right)\right] + I(t) + \frac{1}{N}V(t).$$

Notice that U is nonnegative, and U is identically zero if and only if it is evaluated at the non-infective equilibrium point $(T^0, I^0, V^0) = \left(\frac{\lambda}{d_T}, 0, 0\right)$. We compute the derivative along trajectories and find

$$\frac{dU}{dt} = \left(1 - \frac{T^0}{T}\right)\left[\lambda - kTV - d_T T\right] + \left[kTV - d_I I + \frac{1}{N}(Nd_I I - d_V V)\right].$$

After using the definition of T^0, we are left with

$$\begin{aligned}\frac{dU}{dt} &= (\lambda - d_T T)\left(1 - \frac{\lambda}{d_T T}\right) + \left(kT^0 - \frac{d_V}{N}\right)V \\ &= -\frac{1}{d_T T}(\lambda - d_T T)^2 + \frac{d_V}{N}(R_0 - 1)V.\end{aligned}$$

Thus, under the assumption that $R_0 \leq 1$, we see that $\frac{dU}{dt} \leq 0$ for all positive values of T, I, and V, and the global asymptotic stability follows by LaSalle's Invariance Principle [31].

Turning to the endemic equilibrium, none of the end values are zero, so we denote this steady state by (T^*, I^*, V^*) and define a Lyapunov function as

$$\begin{aligned}U(t) = T^*\left[\frac{T(t)}{T^*} - 1 - \ln\left(\frac{T(t)}{T^*}\right)\right] + I^*\left[\frac{I(t)}{I^*} - 1 - \ln\left(\frac{I(t)}{I^*}\right)\right] \\ + \frac{V^*}{N}\left[\frac{V(t)}{V^*} - 1 - \ln\left(\frac{V(t)}{V^*}\right)\right].\end{aligned}$$

This function is nonnegative and identically zero only when evaluated at the endemic equilibrium $E^* = (T^*, I^*, V^*)$. Computing the derivative along trajectories

yields

$$\begin{aligned}\frac{dU}{dt} &= \left(1-\frac{T^*}{T}\right)(\lambda - kTV - d_T T) + \left(1-\frac{I^*}{I}\right)(kTV - d_I I) \\ &\quad + \frac{1}{N}\left(1-\frac{V^*}{V}\right)\left(Nd_I I - d_V V\right), \\ &= \lambda - kTV - d_T T - \lambda\frac{T^*}{T} + kT^*V + d_T T^* + kTV - d_I I - kTV\frac{I^*}{I} + d_I I^* \\ &\quad + d_I I - \frac{1}{N}d_V V - d_I I\frac{V^*}{V} + \frac{1}{N}d_V V^*.\end{aligned}$$

Using the following relations

$$\begin{aligned}\lambda &= kT^*V^* + d_T T^*, \\ kT^*V^* &= d_I I^*, \\ Nd_I I^* &= d_V V^*.\end{aligned}$$

We get

$$\begin{aligned}\frac{dU}{dt} &= d_I I^* + d_T T^* - d_T T - d_I I^*\frac{T^*}{T} - d_T T^*\frac{T^*}{T} + \frac{d_I I^*}{V^*}V + d_T T^* \\ &\quad - \frac{d_I I^*}{T^*V^*}TV\frac{I^*}{I} + d_I I^* - \frac{d_I I^*}{V^*}V - d_I I\frac{V^*}{V} + d_I I^*, \\ &= d_T T^*\left(2 - \frac{T^*}{T} - \frac{T}{T^*}\right) + d_I I^*\left(3 - \frac{T^*}{T} - \frac{IV^*}{I^*V} - \frac{TVI^*}{T^*V^*I}\right).\end{aligned}$$

Since, each of the resulting terms above are nonpositive because the arithmetic mean is greater than the geometric mean, using the inequality (3.6) for $n = 3$, we obtain

$$\begin{aligned}2 - \frac{T}{T^*} - \frac{T^*}{T} &\leq 0, \\ 3 - \frac{T*}{T} - \frac{IV^*}{I^*V} - \frac{TVI^*}{T^*V^*I} &\leq 0.\end{aligned}$$

Thus, we have $\frac{dU}{dt} \leq 0$ for all positive values of T, I, V, and $\frac{dU}{dt} = 0$ if and only if $T = T^*, I = I^*$, and $V = V^*$. So the maximum invariant set in $\{(T, I, V) \in \Omega : \frac{dU}{dt} \leq 0\}$ is the singleton set $\{E^*\}$. By LaSalle's invariant principle [31], the endemic equilibrium E^* is globally asymptotically stable if $R_0 > 1$. □

3.6 Parameter Estimation

The mathematical analysis of models is very useful for understanding asymptotic behaviors and longtime qualitative outcomes, While the outcomes of a model critically depends on the values of the model parameters. Since models are confronted with disease data, an accurate estimation of parameter values is essential for reliable quantitative predictions within a finite time interval. For estimation of multiple parameters, a systematic approach for the fitting is desirable. Different tecniques was used for estimating the parameters in [32, 33, 34]. We have used a straight forward method to calculate the parameters, which is known as nonlinear least-squares method. In this least-squares approach, we assume that the time coordinates of the data are exact, but their corresponding y-coordinates (virions) may be noisy or distorted. We fit the solution curve through the data so that the sum of the squares of the vertical distances from the data points to the point on the curve is as small as possible. This distance is commonly known as least squares error.

In particular, suppose we are fitting the virions $V(t)$, with the given data $\{(t_1, \widehat{V}_1), (t_2, \widehat{V}_2), ..., (t_n, \widehat{V}_n)\}$. So the basic problem is to identify the set parameters θ such that the following sum-of-squares error (SSE) is as small as possible:

$$\underset{\min \theta}{SSE} = \sum_{i=1}^{n} \left\{ V(t_i, \theta) - \widehat{V}(t_i) \right\}^2,$$

where $V(t_i, \theta)$ represents the virus concentration at time t_i with parameter θ and $\widehat{V}(t_i)$ represents the data value at time t_i. Such a problem is clearly a nonlinear least-squares problem, since the dependence of a solution on the parameter θ is through a highly nonlinear system of differential equations. We use a Matlab functions *fminsearch* which takes the least-squares error function $SSE(\theta)$ and an initial guess of the parameter value θ_0, and uses a direct search routine to find a minimum value of least-squares error.

Certain parameters such as production rate λ of CD4$^+$T cells, natural death rates d_T of CD4$^+$T cells can be estimated directly from population data as given in Table 3.1. The rest of the parameters $\theta = (k, d_I, N, d_V)$ are estimated from the set of data gathered from plasma donor samples obtained in [35] at primary stage of HIV infection. Using intial guess $\theta_0 = (2 \times 10^{-7}, 0.5, 50, 5)$ for the parameter from

[6] and with intial conditions $(T_0, I_0, V_0) = (10^6, 0, 15.8)$, we obtained estimated parameters in the following table:

Table. 3.1. Description of parameter and values of the HIV model.

Parameter	Description	Value	Reference
λ	Production rate of CD4$^+$T cells	10^5 cells ml^{-1} d^{-1}	[6]
d_T	Death rate of CD4$^+$T cell population	0.1 d^{-1}	[6]
k	Rate of CD4$^+$T cell become infected by free virus	1.37×10^{-7} ml d^{-1}	Estimated
d_I	Death rate of Infected CD4$^+$T cell population	1.07 d^{-1}	Estimated
N	Number of free virus produced by I cells	15	Estimated
d_V	Death rate of free virions	0.25 d^{-1}	Estimated

3.7 Numerical Results

In order to further examine the behavior of the model (3.1), we conducted several numerical simulations using the estimates obtained in Table 3.1. In our simulations, we investigated the overall system dynamics as well as the stability properties of the model in order to characterize the behavior. The system under consideration being nonlinear is solved numerically using Runge-Kutta 4th order scheme.

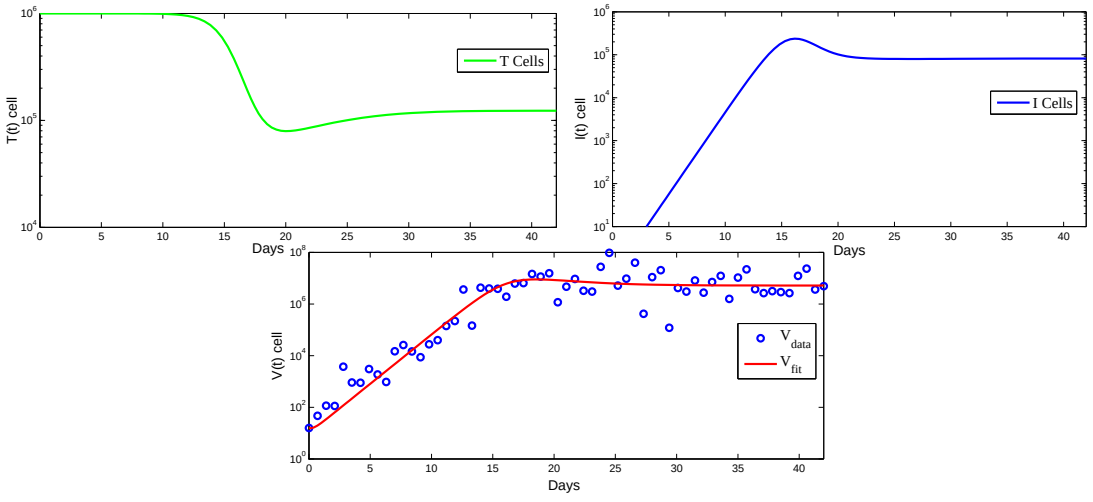


Figure. 3.2. The Basic HIV Model simulation in log scale.

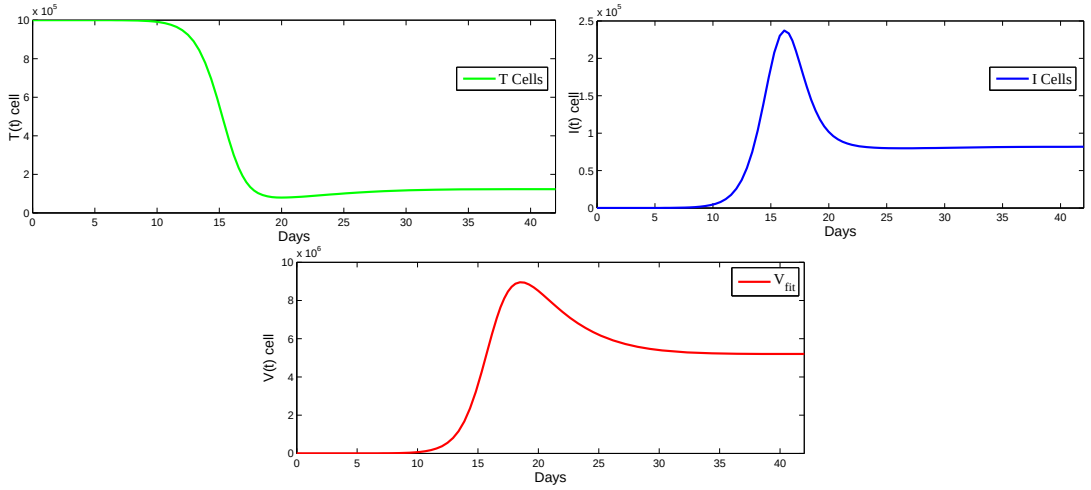


Figure. 3.3. The Basic HIV Model.

Figure 3.2 and 3.3 illustrates the system dynamic interaction between the cells $T(t), I(t)$, and $V(t)$. We can see that both the virus as well as the target cells behave exactly as expected. Upon initiation of infection, the population of the virus increases significantly until it reaches the peak viral load. After achieving the peak viral load, the virus decays until it reaches a steady state. As we see that during the increase of the virus population, the population of target cells decreases (from 10^6 cells ml^{-1} d^{-1} to 8×10^4 cells ml^{-1} d^{-1}) leaving the individual increasingly prone to further infection. However, after reaching the minimum, the target cell population begins to increases until it ultimately reaches a steady state. In this case, the steady state (1.23×10^5 cells ml^{-1} d^{-1}), which is approximately 12.3% of the original population of T-cells. This associates with a loss of long term functionality of the immune system by the virus cells, and causing damages for an infected individual. It is also important to note that the target cell population reaches its steady state after the peak viral load point. This suggests that even after the virus reaches its maximum population an infected individual is still susceptible to the long term infection. Figure 3.2 also illustrates the behavior of the infected cells during infection, which is extremely important for long term disease persistence.

Figure 3.4 presents stability of the infected steady state (E^*). By choosing the parameter values from table 3.1, the value of R_0 in this case turns out to be $R_0 = 8.12 > 1$ and thereby indicating that the infected steady state is asymptotically stable. To illustrate this we choose three different initial conditions of (T_0, I_0, V_0) as $IC1 = (10^6, 0, 15.8), IC2 = (10^4, 10, 158), IC3 = (10^5, 100, 1580)$. We ran the

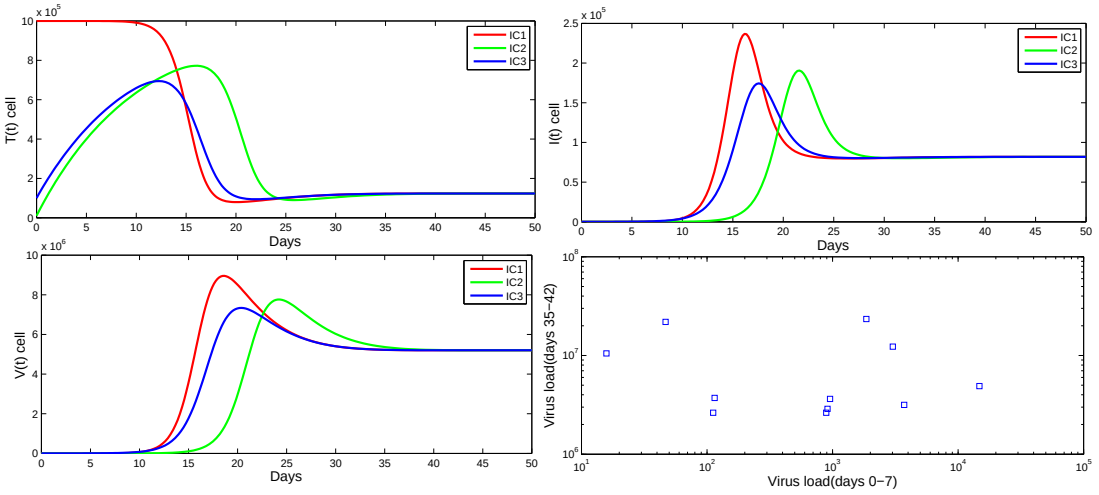


Figure. 3.4. Dynamics of HIV Model for $R_0 = 8.12 > 1$ with three different intial condition $IC1$, $IC2$, and $IC3$.

simulation for a period of 50 days and observe that the dynamics of all the system eventually converges to $E^* = (1.23 \times 10^5, 8.19 \times 10^4, 5.20 \times 10^6)$ irrespective of the initial condition. This (as can be seen in Figure 3.4) supports the result that the infected steady state is stable, thereby indicating that the patient does not eventually recover.

The last figure of Figure 3.4 illustrates the correlations between the peak and steady state viral loads. Which is crucial because it may be able to yield insights into the long term behavior of the infection, as well as inform us more of the progression of disease. For instance, a larger steady state population of the virus is associated with an increased impact of the virus on the immune system in the long term. A larger viral steady state population is commonly associated with a smaller T-cell steady state population. Since the T-cell is the primary active component of the immune system, this results in a greater propensity for long term chronic health conditions associated with HIV. We can see that in Figure 3.4, in some cases, as the peak viral load increases, the value of the steady state increases as well, suggesting a positive correlation. However, this is not true for all cases and when we conduct a linear regression fit, we receive a R (Pearson's correlation coefficient) value of 0.6932. Thus, we cannot say that there is a strong positive correlation between peak viral load and the value of the steady state. So this is evident that the disease progression does not depend on the peak viral load.

Figure 3.5, is the phase portrait for the system for diffrent intial conditions. The

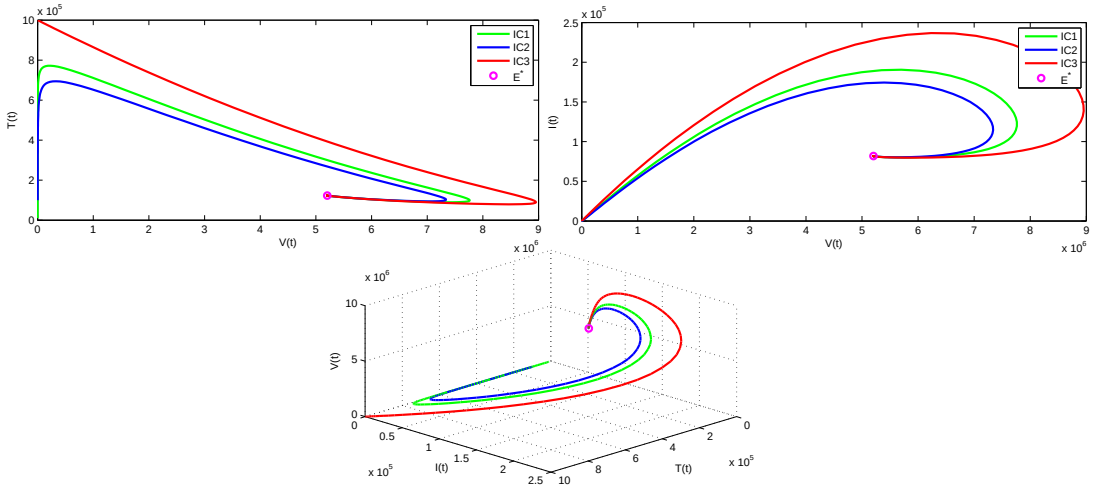


Figure. 3.5. The HIV Model in 2D & 3D Phase Portrait for $R_0 = 8.12 > 1$ with three different intial condition $IC1$, $IC2$, and $IC3$.

figure shows the stability and how all three of the populations, the target cells, infected cells, and virus interact with one another. Essentially, the figures illustrate a single trajectory to show how the populations of the target cells, infected cells and virus change relative to one another over time. However, the phase portrait in Figure 3.5, also illustrates the stability characteristics of the system. For instance, we can see that the trajectory approaches to a single point. In this case, this point is a viral persistence point. This suggests that in the long term the population of the virus as well as target cells (infected and uninfected) will remain positive. Based on our previous analysis, we know that the viral reproduction number R_0 for this system is approximately 8.12, and thus we know that it is clearly greater than one. Thus, we should expect that the system is asymptotically stable at E^* (the viral persistence equilibrium), which is exactly what we see in the figure. Figure 3.5 therefore serves to show that the trajectory approaches the long term steady state E^* and remains there as $t \to \infty$.

We now change one of the above parameter values k, to $k = 1.37 \times 10^{-8}$ ml d^{-1} which renders the value of R_0 to be $R_0 = 0.59 < 1$. In this case, we would expect the uninfected steady state E^0 to be asymptotically stable. We again choose three different initial conditions as $IC1 = (10^6, 100, 15.8), IC2 = (10^4, 10, 158)$, and $IC3 = (10^5, 0, 1580)$ and run the simulations for a period of 60 days and observe (Figure 3.6) that the three state variables converge towards $E^0 = (10^6, 0, 0, 0)$ indicating the stability of the uninfected steady state.

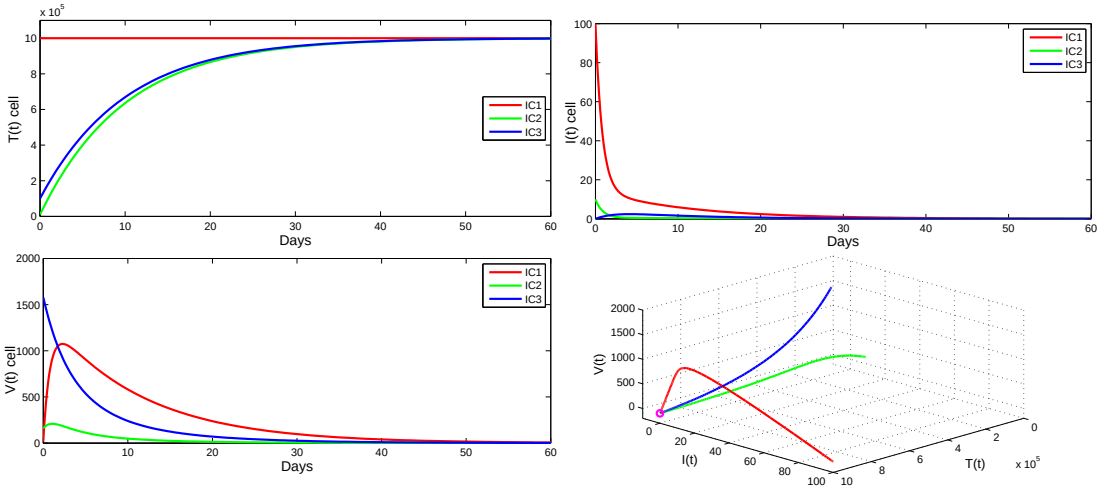


Figure. 3.6. Dynamics of HIV Model for $R_0 = 0.59 < 1$ with three different intial condition $IC1$, $IC2$, and $IC3$.

3.8 Conclusion

In this chapter, we sought to learn about the acute HIV infection within a body using basic HIV model which is driven by three coupled ODEs. We proved existence, uniqueness, positivity, and boundedness in order to justify the viability and utility of the model. The model admits two steady states, namely the uninfected and the infected steady state. Using data from HIV infected individuals, we modify the existing parameters value to determine which best fit the data. A parameter R_0 in terms of the parameters is obtained and the stability of the steady states are analyzed in terms of R_0. The uninfected steady state is proved to be stable for $R_0 \leq 1$ whereas the infected steady state is shown to be stable for $R_0 > 1$. The numerical simulations for the model was done for several initial conditions, all of which showed convergence to the appropriate steady state depending on the value of R_0.

Chapter 4

The Modified HIV Infection Model

4.1 Introduction

The HIV replicates within a host by infecting activated $CD4^+$T cells, which then produce additional copies of the virus. Though model (3.1) describes the basic mechanisms which account for the spread of HIV during acute phase, it lacks the ability to describe the latent stage of a specific subpopulation of infected T-cells. Many studies [36, 37] have determined that upon infection and transcription of viral RNA into cell DNA, a fraction of $CD4^+$T cells fail to actively produce virus until they are activated, possibly years after their initial infection. Such cells may possess a much longer lifespan than their counterparts, and are termed latently infected. Upon activation, latently infected cells do become actively productive, and hence begin to increase the viral load through viral replication. The clinical data shows that latent T-cell infection is established during early HIV infection [38]. A study [39] on HIV patients treated early in infection showed that latently infected cells are mainly generated during primary infection from initiation of infection up to the time of antiretroviral therapy (ART), and once ART is initiated, there are many fewer infections generating fewer latently infected cells. This encouraging result suggests that the initiation of ART very early during infection can limit or possibly eradicate the virus. However, an experiment with simian immunodeficiency virus (SIV) infected monkeys [40] showed that even the monkeys that were

treated on day 3 postinfection suffer from virus rebound after discontinuation of ART following 24 weeks of fully suppressive therapy.

In order to more accurately characterize the virus infection in the host, a virus dynamics model with latency is established and analyzed in this chapter by incorporating an equation for latent infected cells in model (3.1). We show the existence of the steady states and obtain the conditions for the local and global stability in terms of basic reproduction number. Further, numerical simulations are presented to support the theoretical results.

4.2 Mathematical Model

Many mathematical models have provided great insights into the dynamics of latently infected cells [4, 41, 42]. Kim and Perelson [41] studied viral persistence during therapy with the effect of latent reservoir, Rong and Perelson [42] modeled viral blips and showed that a latent reservoir could produce viral transients when activated by infection, while Perelson et al. [4] employed the latent reservoir to show that its stability was unlikely to depent on a critical value. In each of these studies, mathematical analysis was performed and parameter was used for the chronic stage (infection after years) of HIV, some nonlinear behavior of the associated model was not also fully elucidated. In our model, we describe latently infected cells using a separate compartment $L(t)$, by assuming that a proportion of target cells become latently infected upon contact with the virus, but that they are not productively infected until they leave the latent state, which occurs at a rate α proportionate to the strength of the latent cell population. We therefore propose the following modified model:

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - kT(t)V(t) - d_T T(t), \quad T(0) = T_0, \\ \dfrac{dI(t)}{dt} = (1-f)kT(t)V(t) - d_I I(t) + \alpha L(t), \quad I(0) = I_0, \\ \dfrac{dL(t)}{dt} = fkT(t)V(t) - d_L L(t) - \alpha L(t), \quad L(0) = L_0, \\ \dfrac{dV(t)}{dt} = Nd_I I(t) - d_V V(t), \quad V(0) = V_0. \end{cases} \tag{4.1}$$

We assume that a fraction, $f \in (0,1)$, of infection generates latently infected cells with replication competent genomes and the remaining fraction of infection,

$(1-f)$, leads to productively infected cells. and α is the rate at which latently infected cells transition to become actively productive. Additionally, d_L is the rate at which latent cells are cleared from the system. Rest of the parameters have the same meaning as in section 4.6. We note that the effects of viral mutation, which may continuously change model and parameter values, and the possible spatial dependence of parameters can be ignored during primary stage of the disease. A schematic representation of the model (4.1) is given in figure 4.1.

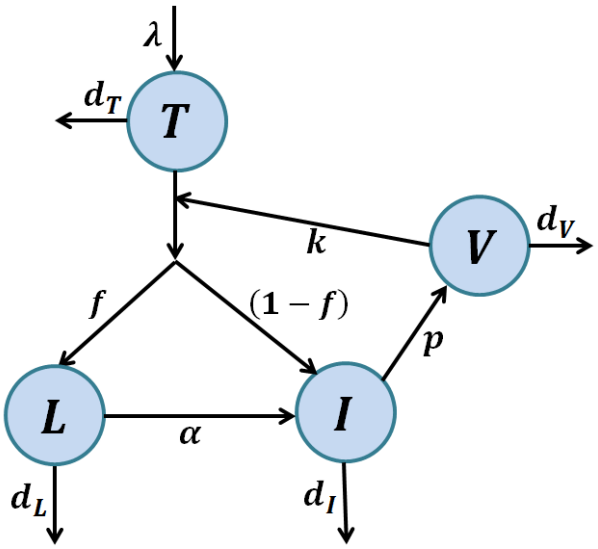


Figure. 4.1. Schematic representation of the modified HIV model.

4.3 Qualitative Analysis of the Model

As previously, in order to retain the biological validity of the model, we must prove that solutions to the system of differential equations exists and they are positive and bounded for all values of time.

Theorem 4.1. *(Existence of Solution). Let* $T_0, I_0, L_0, V_0 \in \mathbb{R}$ *be given. There exists* $t_0 > 0$ *and continuously differentiable functions* $\{T, I, L, V : [0, t_0) \to \mathbb{R}\}$ *such that the ordered quadruple* (T, I, L, V) *satisfies (4.1) and* $(T, I, L, V)(0) = (T_0, I_0, L_0, V_0)$.

Proof of Theorem 4.1. To prove the result, we utilize the classical Picard-Lindelöf theorem as stated in theorem 3.1. Since the system of ODEs is autonomous, it

suffices to show that the function $\mathbf{f} : \mathbb{R}^4 \to \mathbb{R}^4$ defined by

$$\mathbf{f}(\mathbf{y}) = \begin{pmatrix} \lambda - kTV - d_T T \\ (1-f)kTV - d_I I + \alpha L \\ fkTV - d_L L - \alpha L \\ Nd_I I - d_V V \end{pmatrix}$$

is locally Lipschitz in its $\mathbf{y}$ argument. Note that the Jacobian matrix

$$\nabla \mathbf{f}(\mathbf{y}) = \begin{pmatrix} -kV - d_T & 0 & 0 & -kT \\ (1-f)kV & -d_I & \alpha & (1-f)kT \\ fkV & 0 & -(d_L + \alpha) & fkV \\ 0 & Nd_I & 0 & -d_V \end{pmatrix}$$

is linear in $\mathbf{y} \in \mathbb{R}^3$. Thus, $\nabla \mathbf{f}(\mathbf{y})$ is continuous on a closed interval and differentiable on an open interval $I \in \mathbb{R}^4$. By the arguments used in theorem 3.1 we can conclude that $\mathbf{f}$ is locally Lipschitz in $\mathbf{y}$. According to the Picard-Lindelöf Theorem, there exists a unique solution, $y(t)$, to the ordinary differential equation $y'(t) = f(y(t))$ with initial value $y(0) = y_0$ on $[0, t_0]$ for some time $t_0 > 0$. □

The next step in analyzing our model will be to prove positivity and boundedness for the system of differential equations.

Theorem 4.2. *(Positivity and Boundedness). Assume the initial conditions of (4.1) satisfy $T_0 > 0, I_0 > 0, L_0 > 0$ and $V_0 > 0$. If the unique solution provided by Theorem 4.1 exists on the interval $[0, t_0]$ for some $t_0 > 0$, then the functions $T(t), I(t), L(t)$ and $V(t)$ will be bounded and remain positive for all $t \in [0, t_0]$.*

Proof of Theorem 4.2. We assume that $T(t), I(t), L(t)$ and $V(t)$ initially have positive values. From the previous theorem, there exists a $t > 0$ such that the solution exists on $[0, t]$. Let us denote by T^* the largest time for which all populations remain positive, or more precisely

$$T^* = \sup\{t > 0 : T(s), I(s), L(s), V(s) > 0, \ \forall s \in [0, t]\}.$$

Since each initial condition is nonnegative and the solution is continuous, there must be an interval on which the solution remains positive, and we see that $T^* > 0$. Then on the interval $[0, T^*]$ we estimate each term.

We can place lower bounds on I, L, and V instantly since the decay terms are linear.

$$\begin{aligned}\frac{dI(t)}{dt} &= (1-f)kT(t)V(t) - d_I I(t) + \alpha L(t) \geq -d_I I(t),\\ \text{i.e. } I(t) &\geq I(0)e^{-d_I t} > 0\end{aligned}$$

for $t \in [0, T^*]$. Similarly, for the latent cell

$$\begin{aligned}\frac{dL(t)}{dt} &= fkT(t)V(t) - d_L L(t) - \alpha L(t) \geq -(d_L + \alpha)L,\\ \text{i.e. } L(t) &\geq L(0)e^{-(d_L+\alpha)t} > 0\end{aligned}$$

for $t \in [0, T^*]$. Again

$$\begin{aligned}\frac{dV(t)}{dt} &= Nd_I I(t) - d_V V(t) \geq -d_V V,\\ \text{i.e. } V(t) &\geq V(0)e^{-d_V t} > 0\end{aligned}$$

for $t \in [0, T^*]$. Similarly, we can place an upper bound on $\dfrac{dT}{dt}$ so that

$$\begin{aligned}\frac{dT(t)}{dt} &= \lambda - kT(t)V(t) - d_T T(t) \leq \lambda,\\ \text{i.e. } T(t) &\leq T(0) + \lambda t \leq C(1+t),\end{aligned}$$

where the constant C depends on the upper bound of λ and $T(0)$. Next, we sum the equations for I, L, and V, and by positivity of these functions and place bounds on this sum. Then using the upper bound on $T(t)$, we find

$$\begin{aligned}\frac{d}{dt}(I+L+V) &= kT(t)V(t) + (N-1)d_I I(t) - d_L L(t) - d_V V(t),\\ &\leq kC(1+t)V + Nd_I I(t) + d_L L(t) + d_V V(t),\\ &\leq C_2(1+t)(I+L+V), \qquad \text{where } C_2 \geq \max\{kC, Nd_I, d_L, d_V\},\\ \text{i.e. } (I+L+V)(t) &\leq C_3 e^{t^2}\end{aligned}$$

for $t \in [0, T^*]$, where $C_3 > 0$ depends upon $C_2, I(0), L(0)$ and $V(0)$ only.

Since $I(t), L(t)$ and $V(t)$ are positive, we can place an upper bound on I, L and V by

$$\begin{aligned} C_3 e^{t^2} &\geq (I + L + V)(t) \geq I(t), \\ C_3 e^{t^2} &\geq (I + L + V)(t) \geq L(t), \\ C_3 e^{t^2} &\geq (I + L + V)(t) \geq V(t). \end{aligned}$$

With these bounds in place, we can now examine $T(t)$ and bound it from below using

$$\begin{aligned} \frac{dT}{dt} &= \lambda - kTV - d_T T \geq -kTV - d_T T \geq -d_T T - kC_3 e^{t^2} T, \\ &\geq -C_4(1 + e^{t^2})T, \quad \text{where } C_4 \geq \max\{kC_3, d_T\}, \\ \Rightarrow \frac{dT}{dt} &+ C_4(1 + e^{t^2})T \geq 0, \\ \text{i.e. } T(t) &\geq T(0) e^{-C_4 \int_0^t (1+e^{\tau^2} d\tau)} > 0 \end{aligned}$$

for $t \in [0, T^*]$. Thus, the values of T, I, L and V stay strictly positive for all of $[0, T^*]$, including at time T^*. By continuity, there must exist a $t > T^*$ such that $T(t), I(t), L(t)$ and $V(t)$ are still positive. This contradicts the definition of T^*, and shows that $T(t), I(t), L(t)$ and $V(t)$ are strictly positive on the entire interval $[0, t]$. Additionally, on this same interval, all of the functions remain bounded, so the interval of existence can be extended further. In fact, the bounds on T, I, L and V derived above hold on any compact time interval. Thus, we may extend the time interval on which the solution exists to $[0, t]$ for any $t > 0$ and from the above argument, the solutions remain both bounded and positive on $[0, t]$. □

4.3.1 Equilibria of the System

Let us find the steady state solutions for the system of equations (4.1) that describes the model. By setting the right-hand side of (4.1) to zero, we get

$$\lambda - kTV - d_T T = 0, \tag{4.2}$$

$$(1 - f)kTV - d_I I + \alpha L = 0, \tag{4.3}$$

$$fkTV - d_L L - \alpha L = 0, \tag{4.4}$$

$$Nd_I I - d_V V = 0. \tag{4.5}$$

We begin by solving for the nonlinear interaction term in the equations (4.2) and (4.4), that gives

$$\begin{aligned} kTV &= \lambda - d_T T, \\ fkTV &= (d_L + \alpha)L, \end{aligned}$$

and thus

$$L = \frac{f}{(d_L + \alpha)} \left(\lambda - d_T T\right).$$

Next, in equation (4.3), we find $d_I I = (1-f)kTV + \alpha L$ and thus

$$I = \frac{1}{d_I}\left(1 - f + \frac{\alpha f}{d_L + \alpha}\right)(\lambda - d_T T).$$

The last equation yields V in terms of I, so that

$$V = \frac{N d_I}{d_V} I = \frac{N}{d_V}\left(1 - f + \frac{\alpha f}{d_L + \alpha}\right)(\lambda - d_T T).$$

Finally, we may use the representation of V in terms of T within equation (4.2) and solve a simple quadratic in T to determine the possible steady state values. With this, the equation (4.2) becomes

$$\begin{aligned} &\lambda - d_T T - k\frac{N}{d_V}\left(1 - f + \frac{\alpha f}{d_L + \alpha}\right)(\lambda - d_T T)T = 0 \\ \Rightarrow &\frac{\lambda d_V\left(\alpha + d_L\right)}{kN d_T\left(\alpha + (1-f)d_L\right)} - \frac{T d_V\left(\alpha + d_L\right)}{kN\left(\alpha + (1-f)d_L\right)} - \frac{\lambda T}{d_T} + T^2 = 0 \\ \Rightarrow &T^2 - \frac{\lambda T}{d_T} - qT + \frac{\lambda q}{d_T} = 0, \qquad \left[\text{set} \quad q = \frac{d_V\left(\alpha + d_L\right)}{kN\left(\alpha + (1-f)d_L\right)}\right] \end{aligned}$$

and it follows that the only solutions are

$$T = \frac{\lambda}{d_T} \quad \text{and} \quad T = \frac{d_V\left(\alpha + d_L\right)}{kN\left(\alpha + (1-f)d_L\right)}.$$

Continuing in this manner, we obtain two corresponding values for I, L, and V. To summarize, we find two equilibria, the non-infective equilibrium (viral extinction) as

$$E^0 = (T^0, I^0, L^0, V^0) = \left(\frac{\lambda}{d_T}, 0, 0, 0\right)$$

and the infective equilibrium (viral persistence) as

$$\begin{aligned} E^* &= (T^*, I^*, L^*, V^*) \\ &= \left\{ q, \frac{d_T d_V}{kNd_I}\left(\frac{\lambda}{d_T q} - 1\right), \frac{f\lambda}{d_L + \alpha}\left(1 - \frac{d_T q}{\lambda}\right), \frac{d_T}{k}\left(\frac{\lambda}{d_T q} - 1\right)\right\}. \end{aligned}$$

4.3.2 Basic Reproduction Number

We are only concerned with compartments that spread the infection, so we need only to model the infected, I, latent, L, and virions, V, compartments. Applying the next generation method to the model (4.1), let us define the model dynamics using the equations

$$\begin{cases} \dfrac{dI(t)}{dt} = (1-f)kT(t)V(t) - d_I I(t) + \alpha L(t), \\ \dfrac{dL(t)}{dt} = fkT(t)V(t) - d_L L(t) - \alpha L(t), \\ \dfrac{dV(t)}{dt} = Nd_I I(t) - d_V V(t). \end{cases}$$

For this system, at the disease free equilibrium point

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right] = \begin{pmatrix} 0 & 0 & (1-f)k\dfrac{\lambda}{d_T} \\ 0 & 0 & fk\dfrac{\lambda}{d_T} \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right] = \begin{pmatrix} d_I & -\alpha & 0 \\ 0 & \alpha + d_L & 0 \\ -Nd_I & 0 & d_V \end{pmatrix}$$

Then, for the system (4.1), the next generation matrix is

$$FV^{-1} = \begin{pmatrix} \dfrac{(1-f)kN\lambda}{d_T d_V} & \dfrac{(1-f)kN\alpha\lambda}{(\alpha + d_L)\, d_T d_V} & \dfrac{(1-f)k\lambda}{d_T d_V} \\ \dfrac{fkN\lambda}{d_T d_V} & \dfrac{fkN\alpha\lambda}{(\alpha + d_L)\, d_T d_V} & \dfrac{fk\lambda}{d_T d_V} \\ 0 & 0 & 0 \end{pmatrix}$$

The dominant eigenvalue of FV^{-1} is given by expression

$$R_L = \rho\left[FV^{-1}\right] = \frac{k\lambda N}{d_T d_V}.\frac{(\alpha + (1-f)d_L)}{(\alpha + d_L)} \tag{4.6}$$

and it is basic reproduction number for the system (4.1).

Notice that the limiting values of T, I, and V for the infective state are of the same form as those of (3.1), with R_L replacing the role of R_0.

Remark 4.3. Using basic reproduction number R_L the infected equilibrium point $E^* = (T^*, I^*, L^*, V^*)$ becomes

$$E^* = \left\{ \frac{\lambda}{d_T R_L}, \frac{d_T d_V}{kNd_I}(R_L - 1), \frac{f\lambda}{R_L(d_L + \alpha)}(R_L - 1), \frac{d_T}{k}(R_L - 1) \right\}.$$

4.4 Local Stability of the Equilibria

By studying the linearized version of the system (4.1) at the points E^0 and E^*, we may examine the local stability of these equilibria and find that their behavior mimics that of (3.1), using the Jacobian for (4.1):

$$J = \begin{pmatrix} -kV - d_T & 0 & 0 & -kT \\ (1-f)kV & -d_I & \alpha & (1-f)kT \\ fkV & 0 & -(d_L + \alpha) & fkT \\ 0 & Nd_I & 0 & -d_V \end{pmatrix}$$

Theorem 4.4. *If $R_L < 1$, then the non-infective equilibrium is locally asymptotically stable. If $R_L > 1$ then the non-infective equilibrium is an unstable saddle point, and the endemic equilibrium is locally asymptotically stable.*

Proof of Theorem 4.4. We proceed by linearizing the system and using the Routh-Hurwitz criterion to determine conditions under which the linear system possesses only negative eigenvalues. Then, as a consequence of the Hartman Grobman Theorem [27], the local behavior of the linearized system is equivalent to that of the nonlinear system.

First, we compute the Jacobian evaluated at the non-infective equilibrium $E^0 = (T^0, I^0, L^0, V^0) = \left(\frac{\lambda}{d_T}, 0, 0, 0\right)$, resulting in

$$J(E^0) = \begin{pmatrix} -d_T & 0 & 0 & -k\frac{\lambda}{d_T} \\ 0 & -d_I & \alpha & (1-f)k\frac{\lambda}{d_T} \\ 0 & 0 & -d_L-\alpha & fk\frac{\lambda}{d_T} \\ 0 & Nd_I & 0 & -d_V \end{pmatrix}.$$

From this, we compute the associated characteristic polynomial for eigenvalues η

$$\begin{aligned} 0 =& \left|\eta\mathbb{I} - J(E^0)\right| \\ =&(\eta + d_T)\Bigg[(\eta + d_I)(\eta + \alpha + d_L)(\eta + d_V) - \frac{f\alpha Nk\lambda d_I}{d_T} \\ &- \frac{(1-f)Nk\lambda d_I}{d_T}\left(\eta + \frac{\alpha}{1-f} + d_L\right)\Bigg]. \end{aligned}$$

Since $\eta < -d_T < 0$ is the one negative eigenvalue of the system, After expanding the remaining terms and ordering by powers of η, this equation ultimately simplifies to

$$\eta^3 + A_1\eta^2 + A_2\eta + A_3 = 0,$$

where

$$\begin{aligned} A_1 &= d_I + d_L + d_V + \alpha, \\ A_2 &= d_I d_V + (d_L + \alpha)(d_I + d_V) - \frac{(1-f)Nk\lambda d_I}{d_T}, \\ A_3 &= (d_L + \alpha)d_I d_V - \frac{\lambda Nkd_I}{d_T}\left((1-f)d_L + \alpha\right). \end{aligned}$$

As before, the Routh-Hurwitz criterion requires $A_1, A_2, A_3 > 0$ and $A_1A_2 - A_3 > 0$. Clearly, $A_1 > 0$, and after rewriting A_3 in terms of R_L, we find

$$A_3 = (d_L + \alpha)d_I d_V(1 - R_L).$$

Thus, if $A_3 > 0$, it is necessary that $R_L < 1$. Similarly, we rewrite A_2 as

$$A_2 = (d_L + \alpha)(d_I + d_V) + d_I d_V\left[1 - R_L\frac{(1-f)(d_L+\alpha)}{(1-f)d_L + \alpha}\right].$$

Using the inequality

$$\frac{(1-f)(d_L+\alpha)}{(1-f)d_L+\alpha} = 1 - \frac{f\alpha}{(1-f)d_L+\alpha} < 1, \tag{4.7}$$

and the previous condition $R_L < 1$, we find $A_2 > 0$.

Finally, we see that $A_2 > d_I d_V(1-R_L)$, and clearly $A_1 > d_L + \alpha$. Therefore, we find

$$A_1 A_2 > d_I d_V (d_L+\alpha)(1-R_L) = A_3.$$

and the Routh-Hurwitz criteria are satisfied. Thus, $R_L < 1$ implies that all eigenvalues of the linearized system are negative, and hence the local asymptotic stability of E^0 follows. Conversely, if $R_L > 1$, then the linearized system possesses at least one positive eigenvalue, and the equilibrium is unstable.

The analysis for E^* is similar to that of E^0. Linearizing (4.1) about E^*, we find the Jacobian

$$J(E^*) = \begin{pmatrix} -(d_T + kV^*) & 0 & 0 & -kT^* \\ (1-f)kV^* & -d_I & \alpha & (1-f)kT^* \\ fkV^* & 0 & -d_L-\alpha & fkT^* \\ 0 & Nd_I & 0 & -d_V \end{pmatrix}$$

and this results in the characteristic equation

$$\begin{aligned} 0 =& (\eta + d_T R_L)(\eta + d_I)(\eta + \alpha + d_L)(\eta + d_V) \\ & - \frac{(1-f)Nk\lambda d_I}{d_T R_L}\left(\eta + \frac{\alpha}{1-f} + d_L\right)(d_T + \eta). \end{aligned}$$

After expanding the terms and ordering by powers of η, this equation ultimately simplifies to a quartic polynomial

$$\eta^4 + A_1\eta^3 + A_2\eta^2 + A_3\eta + A_4 = 0,$$

where

$$
\begin{aligned}
A_1 &= d_T R_L + d_I + d_L + d_V + \alpha, \\
A_2 &= d_T R_L(d_I + d_L + d_V + \alpha) + (d_L + \alpha)(d_I + d_V) + d_I d_V - \frac{(1-f)Nk\lambda d_I}{d_T R_L}, \\
A_3 &= d_T R_L(d_L + \alpha)(d_I + d_V) + d_T R_L d_I d_V + (d_L + \alpha) d_I d_V \\
&\qquad - \frac{\lambda N k d_I}{d_T R_L}\left((1-f)d_T + (1-f)d_L + \alpha\right), \\
A_4 &= d_T R_L(d_L + \alpha) d_I d_V - \frac{\lambda N k d_I}{R_L}\left((1-f)d_L + \alpha\right).
\end{aligned}
$$

According to the Routh-Hurwitz criteria, all roots of this quartic equation possess negative real part if and only if $A_1A_2 - A_3 > 0$ and $A_3(A_1A_2 - A_3) - A_4A_1^2 > 0$. As for the E^* analysis, the positivity of A_1 follows directly from the positivity of the coefficients, and after rewriting A_4, we find

$$A_4 = d_T(d_L + \alpha)d_I d_V(R_L - 1).$$

Hence, it is necessary that $R_L > 1$ in order to satisfy the criteria. Similarly, we rewrite A_3 as

$$
\begin{aligned}
A_3 &= d_T R_L(d_L + \alpha)(d_I + d_V) + d_T R_L d_I d_V + (d_L + \alpha) d_I d_V \\
&\qquad - \left[d_T d_I d_V \frac{(1-f)(d_L + \alpha)}{(1-f)d_L + \alpha} + d_I d_V (d_L + \alpha)\right] \\
&> d_T R_L(d_L + \alpha)(d_I + d_V) + d_T d_I d_V (R_L - 1) > 0.
\end{aligned}
$$

In this inequality we have canceled the third term with the last term and utilized the inequality (4.7) to bound the fourth term. The only nonpositive term in A_2 can be rewritten as

$$A_2 > \ d_T R_L(d_I + d_L + d_V + \alpha) + (d_L + \alpha)(d_I + d_V) > 0,$$

using

$$-\frac{(1-f)Nk\lambda d_I}{d_T R_L} = -d_I d_V \frac{(1-f)(d_L + \alpha)}{(1-f)d_L + \alpha} > -d_I d_V.$$

By the definition of A_1, we have $A_1 > d_I + d_V$ and using the above inequality for A_2, we find

$$\begin{aligned} A_1A_2 &> (d_I + d_V)\left[d_T R_L(d_I + d_L + d_V + \alpha) + (d_L + \alpha)(d_I + d_V)\right] \\ &> (d_I + d_V)d_T R_L(d_L + \alpha) + d_V d_T R_L d_I + d_V d_I(d_L + \alpha) \\ &> A_3. \end{aligned}$$

Finally, we verify the last inequality $A_3(A_1A_2 - A_3) - A_4A_1^2 > 0$, thus

$$\begin{aligned} A_1A_2 - A_3 &> (d_L + \alpha)\Big[d_T R_L(d_T R_L + 2d_I + 2d_V + d_L + \alpha) + (d_L + \alpha)(d_I + 2d_V) \\ &\quad + (d_I + d_V)^2\Big]. \end{aligned}$$

Hence, we obtain

$$\begin{aligned} A_3(A_1A_2 - A_3) &> d_T R_L(d_L + \alpha)^2(d_I + d_V)\Big[d_T R_L(d_T R_L + 2d_I + 2d_V + d_L + \alpha) \\ &\quad + (d_L + \alpha)(d_I + 2d_V) + (d_I + d_V)^2\Big] \\ &\quad + d_T d_I d_V(R_L - 1)(d_L + \alpha)\Big[d_T R_L(d_T R_L + 2d_I + 2d_V + d_L + \alpha) \\ &\quad + (d_L + \alpha)(d_I + 2d_V) + (d_I + d_V)^2\Big] \\ &> d_T d_I d_V(R_L - 1)(d_L + \alpha)(d_T R_L + d_I + d_V + d_L + \alpha)^2 \\ &= A_4A_1^2. \end{aligned}$$

With this, all of the criteria have been satisfied and E^* is stable if $R_L > 1$. Conversely, if $R_L < 1$, then the Jacobian possesses at least one positive eigenvalue, and the endemic state is unstable. □

Our analysis reveals, if $R_L < 1$ and population values begin within a sufficiently close distance of E^0, then they will tend to E^0 as $t \to \infty$. Contrastingly, if $R_L > 1$ and initial populations are sufficiently close to E^*, they will tend to E^* in the long run. Theorem 4.4 also emphasizes the crucial feature that equilibria are not stable simultaneously, that is, bistability of E^0 and E^* does not occur. Furthermore, it expresses that the qualitative behavior of system (4.1) changes exactly when R_L transitions from less than one to greater than one, and hence a bifurcation occurs at $R_L = 1$.

4.5 Global Stability of the Equilibria

Finally, we also establish global asymptotic stability of the equilibria using a Lyapunov function which demonstrates the stronger result that initial values of cells have no effect on their long term ($t \to \infty$) limiting values.

Theorem 4.5. *If $R_L \leq 1$, then the non-infective equilibrium (E^0) is globally asymptotically stable and the disease dies out. If $R_L > 1$, then the endemic equilibrium (E^*) is globally asymptotically stable and the disease persists.*

Proof of Theorem 4.5. To investigate the global stability of E^0, consider the following Lyapunov function

$$\begin{aligned} U(t) = ((1-f)d_L + \alpha)T^0 \left[\frac{T(t)}{T^0} - 1 - \ln\left(\frac{T(t)}{T^0}\right)\right] \\ + (d_L + \alpha)\left[I(t) + \frac{1}{N}V(t)\right] + \alpha L(t). \end{aligned}$$

Notice that U is nonnegative, and U is identically zero if and only if it is evaluated at the non-infective equilibrium point $(T^0, I^0, L^0, V^0) = \left(\frac{\lambda}{d_T}, 0, 0, 0\right)$. We compute the derivative along trajectories and find

$$\begin{aligned} \frac{dU}{dt} &= ((1-f)d_L + \alpha)\left(1 - \frac{T^0}{T}\right)\left[\lambda - kTV - d_T T\right] \\ &\quad + (d_L + \alpha)\left[(1-f)kTV - d_I I + \alpha L + \frac{1}{N}(Nd_I I - d_V V)\right] \\ &\quad + \alpha\left[fkTV - d_L L - \alpha L\right]. \end{aligned}$$

After using the definition of T^0, we are left with

$$\begin{aligned} \frac{dU}{dt} &= ((1-f)d_L + \alpha)(\lambda - d_T T)\left(1 - \frac{\lambda}{d_T T}\right) \\ &\quad + \left[\Big((1-f)d_L + \alpha\Big)kT^0 - (d_L + \alpha)\frac{d_V}{N}\right]V \\ &= -\frac{(1-f)d_L + \alpha}{d_T T}(\lambda - d_T T)^2 + \frac{(d_L + \alpha)d_V}{N}(R_L - 1)V. \end{aligned}$$

Thus, under the assumption that $R_L \leq 1$, we see that $\frac{dU}{dt} \leq 0$ for all positive values of T, I, L, and V, and the global asymptotic stability follows by LaSalle's Invariance Principle [31].

Turning to the endemic equilibrium, none of the end values are zero, so we denote this steady state by (T^*, I^*, L^*, V^*) and define a Lyapunov function as

$$\begin{aligned}U(t) = {} & ((1-f)d_L + \alpha)T^*\left[\frac{T(t)}{T^*} - 1 - \ln\left(\frac{T(t)}{T^*}\right)\right] \\ & + (d_L + \alpha)\left[I^*\left\{\frac{I(t)}{I^*} - 1 - \ln\left(\frac{I(t)}{I^*}\right)\right\} + \frac{V^*}{N}\left\{\frac{V(t)}{V^*} - 1 - \ln\left(\frac{V(t)}{V^*}\right)\right\}\right] \\ & + \alpha L^*\left[\frac{L(t)}{L^*} - 1 - \ln\left(\frac{L(t)}{L^*}\right)\right].\end{aligned}$$

This function is nonnegative and identically zero only when evaluated at the endemic equilibrium $E^* = (T^*, I^*, L^*, V^*)$. Computing the derivative along trajectories yields

$$\begin{aligned}\frac{dU}{dt} = {} & ((1-f)d_L + \alpha)\left(1 - \frac{T^*}{T}\right)\Big[\lambda - kTV - d_T T\Big] \\ & + (d_L + \alpha)\left[\left(1 - \frac{I^*}{I}\right)\Big((1-f)kTV - d_I I + \alpha L\Big)\right. \\ & \left. + \frac{1}{N}\left(1 - \frac{V^*}{V}\right)\Big(N d_I I - d_V V\Big)\right] + \alpha\left(1 - \frac{L^*}{L}\right)\Big[fkTV - d_L L - \alpha L\Big] \\ = {} & ((1-f)d_L + \alpha)\Big[\lambda - kTV - d_T T\Big] \\ & + (d_L + \alpha)\left[(1-f)kTV - d_I I + \alpha L + \Big(d_I I - \frac{d_V}{N}V\Big)\right] \\ & + \alpha\Big[fkTV - (d_L + \alpha)L\Big] - ((1-f)d_L + \alpha)\left[\frac{\lambda T^*}{T} - kT^*V - d_T T^*\right] \\ & - (d_L + \alpha)\left[\frac{(1-f)kTVI^*}{I} + \frac{\alpha L I^*}{I} - d_I I^* + \frac{d_I I V^*}{V} - \frac{d_V V^*}{N}\right] \\ & - \alpha\left[\frac{fkTVL^*}{L} - (d_L + \alpha)L^*\right] \\ = {} & ((1-f)d_L + \alpha)\Big[\lambda - d_T T + d_T T^* - \frac{\lambda T^*}{T}\Big] \\ & + (d_L + \alpha)\Big[- \frac{(1-f)kTVI^*}{I} - \frac{\alpha L I^*}{I} + d_I I^* - \frac{d_I I V^*}{V} + \frac{d_V V^*}{N} \\ & + \alpha L^* - \frac{\alpha f k}{(d_L + \alpha)}\frac{TVL^*}{L}\Big] \\ = {} & U_1 + U_2.\end{aligned}$$

For U_1 we factor out a $d_T T^*$ term and use the form of $T^* = \dfrac{\lambda}{d_T R_L}$ to find

$$\begin{aligned}
U_1 &= ((1-f)d_L + \alpha)\Big[\lambda - d_T T + d_T T^* - \frac{\lambda T^*}{T}\Big] \\
&= ((1-f)d_L + \alpha)d_T T^*\left[R_L - \frac{T}{T^*} + 1 - R_L\frac{T^*}{T}\right] \\
&= ((1-f)d_L + \alpha)d_T T^*\left[2 - \frac{T}{T^*} - \frac{T^*}{T} + (R_L - 1)\left(1 - \frac{T*}{T}\right)\right] \\
&= ((1-f)d_L + \alpha)d_T T^*\left[2 - \frac{T}{T^*} - \frac{T^*}{T}\right] + ((1-f)d_L + \alpha)d_T T^*(R_L - 1)\left(1 - \frac{T*}{T}\right).
\end{aligned}$$

For U_2 we factor out a L^* term and use the following identities

$$T^*V^* = \frac{d_L + \alpha}{kf}L^*, \quad N d_I I^* = d_V V^*, \quad \text{and} \quad \frac{I^*}{L^*} = \frac{(1-f)d_L + \alpha}{d_I f},$$

to find

$$\begin{aligned}
U_2 &= (d_L + \alpha)\Big[- \frac{(1-f)kTVI^*}{I} - \frac{\alpha L I^*}{I} + d_I I^* - \frac{d_I I V^*}{V} + \frac{d_V V^*}{N} \\
&\qquad + \alpha L^* - \frac{\alpha f k}{(d_L + \alpha)}\frac{TVL^*}{L}\Big] \\
&= (d_L + \alpha)L^*\left[\alpha + \frac{d_I I^*}{L^*} + \frac{d_V V^*}{NL^*} - \frac{(1-f)kTVI^*}{L^*I} - \frac{d_I I^* I V^*}{L^* I^* V} - \frac{\alpha L I^*}{L^* I}\right. \\
&\qquad \left. - \frac{\alpha f k}{(d_L + \alpha)}\frac{TV}{L}\right] \\
&= (d_L + \alpha)L^*\left[\alpha + \frac{2((1-f)d_L + \alpha)}{f} - \frac{(1-f)(d_L + \alpha)}{f}\frac{TVI^*}{T^*V^*I}\right. \\
&\qquad \left. - \frac{((1-f)d_L + \alpha)}{f}\frac{IV^*}{I^*V} - \alpha\frac{LI^*}{L^*I} - \alpha\frac{TVL^*}{T^*V^*L}\right] \\
&= \frac{(d_L + \alpha)L^*}{f}\left[((1-f)d_L + \alpha)\left(2 - \frac{IV^*}{I^*V}\right) - (1-f)(d_L + \alpha)\frac{TVI^*}{T^*V^*I}\right. \\
&\qquad \left. + \alpha f\left(1 - \frac{LI^*}{L^*I} - \frac{TVL^*}{T^*V^*L}\right)\right].
\end{aligned}$$

Thus, combining the rearrangements of U_1 and U_2, we find

$$\frac{dU}{dt} = ((1-f)d_L+\alpha)d_T T^*\left[2-\frac{T}{T^*}-\frac{T^*}{T}\right] + ((1-f)d_L+\alpha)d_T T^*(R_L-1)\left(1-\frac{T*}{T}\right) + \frac{(d_L+\alpha)L^*}{f}\left[((1-f)d_L+\alpha)\left(2-\frac{IV^*}{I^*V}\right) - (1-f)(d_L+\alpha)\frac{TVI^*}{T^*V^*I} + \alpha f\left(1-\frac{LI^*}{L^*I}-\frac{TVL^*}{T^*V^*L}\right)\right].$$

Again using the following relation

$$((1-f)d_L+\alpha)d_T T^*(R_L-1) = ((1-f)d_L+\alpha)\frac{(d_L+\alpha)L^*}{f},$$

the expression becomes

$$\frac{dU}{dt} = ((1-f)d_L+\alpha)d_T T^*\left[2-\frac{T}{T^*}-\frac{T^*}{T}\right] + \frac{(d_L+\alpha)L^*}{f}\left[((1-f)d_L+\alpha)\left(3-\frac{T*}{T}-\frac{IV^*}{I^*V}\right) - (1-f)(d_L+\alpha)\frac{TVI^*}{T^*V^*I} + \alpha f\left(1-\frac{LI^*}{L^*I}-\frac{TVL^*}{T^*V^*L}\right)\right].$$

Since $(1-f)(d_L+\alpha) = (1-f)d_L+\alpha-\alpha f$, the above epression becomes

$$\frac{dU}{dt} = ((1-f)d_L+\alpha)d_T T^*\left[2-\frac{T}{T^*}-\frac{T^*}{T}\right] + \frac{(d_L+\alpha)L^*}{f}\left[(1-f)(d_L+\alpha)\left(3-\frac{T*}{T}-\frac{IV^*}{I^*V}-\frac{TVI^*}{T^*V^*I}\right) + \alpha f\left(4-\frac{T*}{T}-\frac{IV^*}{I^*V}-\frac{LI^*}{L^*I}-\frac{TVL^*}{T^*V^*L}\right)\right].$$

Since, each of the resulting terms above are nonpositive because the arithmetic mean is greater than the geometric mean, using the inequality (3.6) for $n=4$, we obtain

$$\begin{aligned} 2-\frac{T}{T^*}-\frac{T^*}{T} &\le 0,\\ 3-\frac{T*}{T}-\frac{IV^*}{I^*V}-\frac{TVI^*}{T^*V^*I} &\le 0,\\ 4-\frac{T*}{T}-\frac{IV^*}{I^*V}-\frac{LI^*}{L^*I}-\frac{TVL^*}{T^*V^*L} &\le 0. \end{aligned}$$

Thus, we have $\frac{dU}{dt} \le 0$ for all positive values of T, I, L, V, and $\frac{dU}{dt} = 0$ if and

only if $T = T^*, I = I^*, L = L^*$, and $V = V^*$. So the maximum invariant set in $\{(T, I, L, V) \in \Omega : \frac{dU}{dt} \leq 0\}$ is the singleton set $\{E^*\}$. By LaSalle′s invariant principle [31], the endemic equilibrium E^* is globally asymptotically stable if $R_L > 1$. □

This analysis reveals one very important fact about the overall system: the end states of populations are only dependent on the value of R_L, and not any other parameter or initial value. If $R_L > 1$, then the system tends to E^*, an end state with a non-zero population of infected cells and virions, but if $R_L < 1$, then the final equilibrium is E^0, which contains neither virions nor infected T-cells.

4.6 Parameter Estimation: Least-squares Method

In estimating the parameters for the modified HIV model, we adopted the same approach as we did for model (3.1), where we estimated the parameters $\theta = (k, d_I, N, d_V)$ by minimizing sum-of-squares error (SSE) defined as:

$$\underset{\min \theta}{SSE} = \sum_{i=1}^{n} \left\{ V(t_i, \theta) - \widehat{V}(t_i) \right\}^2,$$

where $V(t_i, \theta)$ represents the virus concentration at time t_i with parameter θ and $\widehat{V}(t_i)$ represents the data value at time t_i. Thus, for modified HIV model the parameters to estimate are $\theta = (k, f, d_I, \alpha, d_L, N, d_V)$. As the number of parameter increases, this time the parameters are extremely sensitive to one another, since an inaccurate initial guess can give a large residual error or negative output. We have taken most of our intial parameters from previous literature [4] and clinical output [6] except the fraction of latent infection f. Since $f \in (0, 1)$, we get an appropiate intial guess $\theta_0 = (2 \times 10^{-7}, 0.1, 0.5, 0.4, 0.004, 50, 5)$ with intial conditions $(T_0, I_0, L_0, V_0) = (10^6, 0, 0, 15.8)$, we obtained estimated parameters in the following table:

One of the important feature from the mathematical analysis reveals that long time disease dynamics depends on the infected steady state which explicitly depends on the basic reproductive number. So a larger basic reproduction number retains disease progression for larger period of time in compare to the smaller one. By choosing the new parameter values from table 4.1, the value of R_L turns out to

Table. 4.1. Description of parameter and values of the Modified HIV model.

Parameter	Description	Value	Reference
λ	Production rate of CD4$^+$T cells	10^5 cells ml^{-1} d^{-1}	[6]
d_T	Death rate of CD4$^+$T cell population	0.1 d^{-1}	[6]
k	Rate of CD4$^+$T cell become infected by free virus	3.22×10^{-7} ml d^{-1}	Estimated
f	Proportion of latent infection	0.087	Estimated
d_I	Death rate of Infected CD4$^+$T cell population	0.80 d^{-1}	Estimated
α	Activation rate of latent cells	0.45d^{-1}	Estimated
d_L	Death rate of latently CD4$^+$T cell population	0.008 d^{-1}	Estimated
N	Number of free virus produced by I cells	7	Estimated
d_V	Death rate of free virions	0.12 d^{-1}	Estimated

be $R_L = 18.37 > 1$ which is greater than $R_0 = 8.12$. Therefore, the stability of the infective state is enhanced by the inclusion of the latently-infected cell population. This result is somewhat intuitive, because (4.1) assumes that a fraction of newly infected cells become latently infected and the latter can only activate (becoming actively productive) or die, the average number of infected cells generated by the introduction of a single virus cell into a susceptible system is increased in comparison to a model without latently infected cells, namely (3.1). Hence, one should expect that the basic reproduction number, representing this average number of infected cells, does in fact increase. So from above discussion it is clear that our parameters are estimated correctly which possibly reflects the issue that HIV virus persist in an infected individuals for long time.

4.7 Numerical Results

In order to further examine the behavior of the model (4.1), we conducted several numerical simulations using the estimates obtained in Table 4.1. The results obtained for the stability of the uninfected and the infected steady states are also numerically illustrated in this section. For this purpose, we take into account two

sets of parameters corresponding to the cases of stability of the infected steady state $R_L > 1$ and uninfected steady state $R_L < 1$. Both the models are numerically solved using Runge-Kutta 4th order scheme.

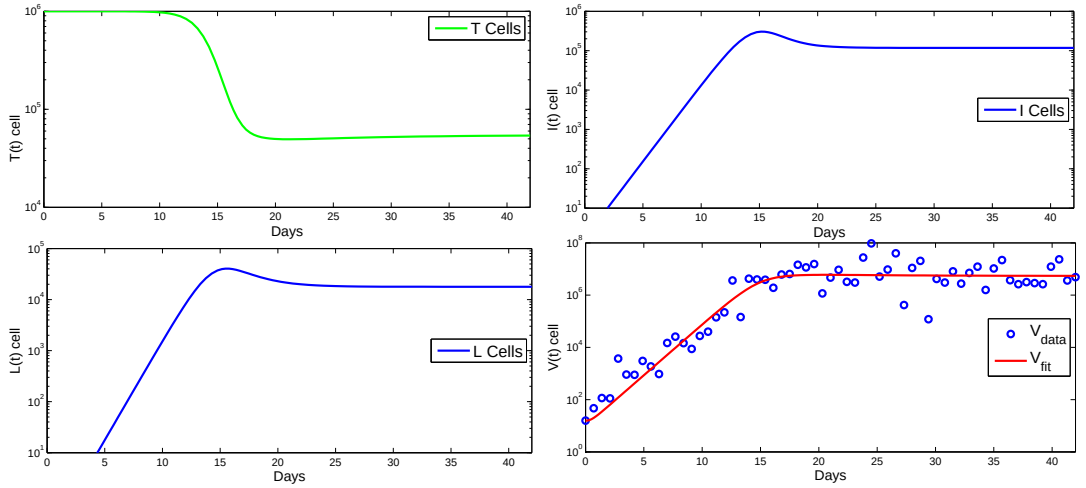


Figure. 4.2. The Modified HIV Model simulation in log scale.

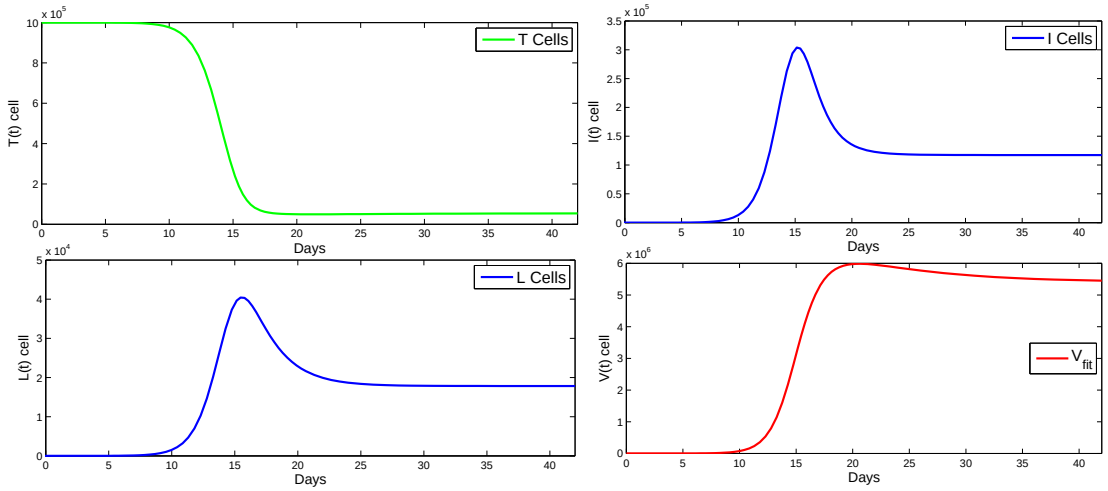


Figure. 4.3. The Modified HIV Model.

First, figure 4.2 and 4.3 illustrate the system dynamic interaction between the cells $T(t), I(t), L(t)$, and $V(t)$ almost same as model 3.1. We can see that upon initiation of infection, the population of the infected cells (I, L) and virus V-cells increases significantly until it reaches the peak. After achieving the peak, these cells decay until it reaches a steady state. As we see that during the increase of the virus cell population, the population of target T-cells decreases (from 10^6 cells ml^{-1} d^{-1} to 5×10^4 cells ml^{-1} d^{-1}). However, after reaching the minimum, the target cell population begins to increases until it ultimately reaches a steady state.

In this case, the steady state (5.4×10^4 cells ml^{-1} d^{-1}), which is approximately 5.4% of the original population of T-cells.

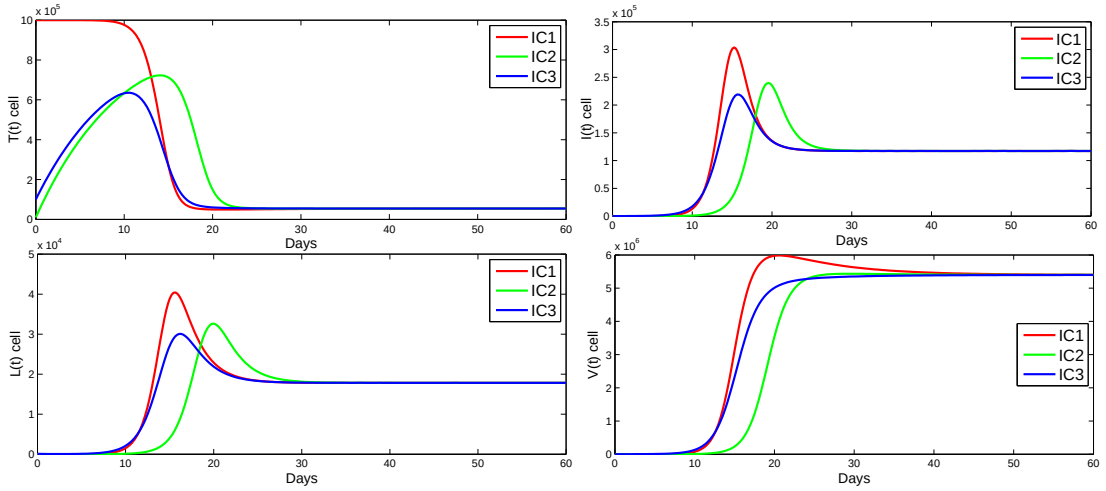


Figure. 4.4. Dynamics of HIV Model for $R_L = 18.37 > 1$ with three different intial condition $IC1$, $IC2$, and $IC3$.

Using the parameter values from table 4.1, the value of R_L turns out to be $R_L = 18.37 > 1$ and thereby indicating that the infected steady state is asymptotically stable. For this purpose, we choose three different initial conditions of (T_0, I_0, L_0, V_0) as $IC1 = (10^6, 0, 0, 15.8), IC2 = (10^4, 10, 10, 158)$, and $IC3 = (10^5, 100, 100, 1580)$. The evolution of the dynamics of the modified model for this scenario was observed for a duration of 60 days and we found the states of the system eventually converges to the infected steady state $E^* = (5.44 \times 10^4, 1.17 \times 10^5, 1.78 \times 10^4, 5.4 \times 10^6)$ for all the three initial conditions. This is illustrated in Figure 4.4 which supports the result that the infected steady state, E^* is asymptotically stable whenever $R_L > 1$ and eventually patient does not recover.

In order to study the case when $R_L < 1$, we now choose a different value of k, namely $k = 1 \times 10^{-8}$ ml d^{-1}, while retaining the other parameter values. Then the value of $R_L = 0.57 < 1$. Consequently, for this scenario, the uninfected steady state E^0 would have to be asymptotically stable. To illustrate we again choose three different initial conditions as $IC1 = (10^6, 100, 100, 15.8), IC2 = (10^4, 10, 10, 158)$, and $IC3 = (10^5, 0, 0, 1580)$ and ran the simulation for a duration of 120 days. It can be observed, from Figure 4.5, that all the state variables of the system eventually approach to the uninfected steady state $E^0 = (10^6, 0, 0, 0)$ indicating the asymptotic stability of the uninfected steady state.

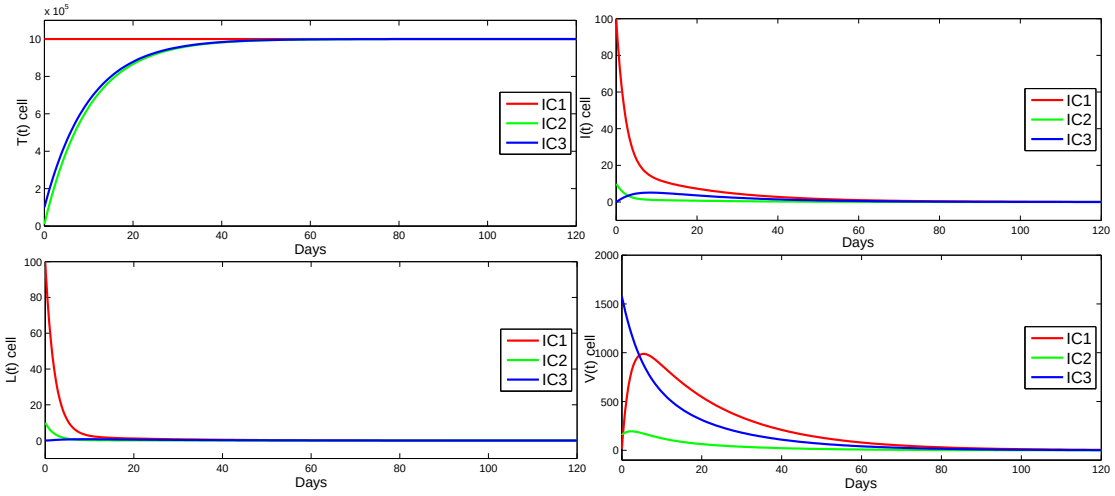


Figure. 4.5. Dynamics of HIV Model for $R_L = 0.57 < 1$ with three different intial condition $IC1$, $IC2$, and $IC3$.

4.8 Conclusion

We consider a modified model of HIV infection that describes T-cell and viral interactions, as well as, the production and activation of latently infected T-cells. The positivity and boundedness of the model is proved. Upon determining equilibrium states of the latent cell model, the local and global asymptotic behavior of solutions is examined. In particular, this implies that a wider variety of parameter values will lead to long term viral persistence as $t \to \infty$ due to the appearance of latent CD4$^+$T cells. Moreover, we prove that, when the basic reproduction number does not exceed 1, the uninfected equilibrium is globally stable, the virus can be cleared eventually; when the basic reproduction number is more than 1, the infected equilibrium is globally stable, the virus will persist in the host at a certain level. These results are further illustrated by a number of numerical simulations.

Chapter 5

Optimal Controls for HIV Infection

5.1 Introduction

The control theoretic concepts have been considered important in a wide variety of disciplines. Since, too large dosage may not be desirable for patients while too small dosage may be ineffective as therapy for the recommended therapeutic agents. Optimal treatment strategies can decrease the possibility of virus mutation, pharmaceutical side effects, and expensive medication burden. To avoid complication due to toxic effects of the drug, adequate amounts of drug in a body compartment should be maintained. To avoid the hazard of side effect of drug dose, our main aim is to find out the optimal drug dosage. Here the drug input is the control and it is through the knowledge of their size that one has a partial way of influencing the drug response behavior among patients.

Antiretroviral Therapy (ART) is administered to symptomatic human immunodeficiency virus (HIV) infected individuals to improve their health. Various administration schemes are used to improve patients' lives and at the same time suppressing development of drug resistance, reduce evolution of new viral strains, minimize serious side effects and also reduce the costs of drugs. The main purpose of this chapter is to develop a mathematical framework that deduce an optimal drug administration scheme useful in improving patients' health especially in poor resourced settings.

5.2 Mathematical Model with Treatment

Two classes of antiretroviral drugs are mostly used to reduce the viral load and limit the infected T-cell population. One class is known as Reverse Transcriptase Inhibitors (RTIs), which can block new HIV-1 infections by disrupting the conversion of viral RNA into DNA. The other category is Protease Inhibitors (PIs), which prevents the assembly of key viral proteins after they have been mistakenly produced by infected host cells. In this way, RTIs serve to reduce the rate of infection of activated CD4$^+$T cells, whereas PIs decrease the number of new infectious virions that are produced. Both drugs thus diminish the propagation of the virus. The primary attention of this chapter is to establish an optimal methodology for administering anti-viral medication therapies to fight HIV infection which specifically maximize of CD4$^+$T cell count and minimize of drug toxicity or systemic cost.

After initiation of combined chemotherapy, combination of RTIs and PIs, infection rate of CD4$^+$T cells is reduced and the number of viral particles produced by an actively infected CD4$^+$T cell is reduced. If we let $u_1(t)$ represent the normalized RTI dosage as a function of time, then k will be modified to become $(1-u_1(t))k$ and it is meant to take into account the effectiveness of the delivery. If we also let $u_2(t)$ be the normalized PI dosage, then the parameter N will be modified to become $(1-u_2(t))N$. Hence the state system becomes

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - k(1-u_1(t))T(t)V(t) - d_T T(t), \\ \dfrac{dI(t)}{dt} = (1-f)(1-u_1(t))kT(t)V(t) - d_I I(t) + \alpha L(t), \\ \dfrac{dL(t)}{dt} = f(1-u_1(t))kT(t)V(t) - d_L L(t) - \alpha L(t), \\ \dfrac{dV(t)}{dt} = N d_I (1-u_2(t))I(t) - d_V V(t). \end{cases} \tag{5.1}$$

With initial conditions

$$\begin{gathered} T(0) = T_0,\ I(0) = I_0,\ L(0) = L_0,\ V(0) = V_0, \\ \text{and } T(t),\ I(t),\ L(t),\ V(t) \text{ are free at final time } T_f. \end{gathered} \tag{5.2}$$

The optimal controls $0 \leq u_1(t),\ u_2(t) \leq 1$ represent percentage effects therapies have on the interaction of the CD4$^+$T cells with the virus (viral infectivity reduction) and the virions produced by infected cells (viral replication suppression). A

schematic representation of the model (5.1) is given in figure 5.1.

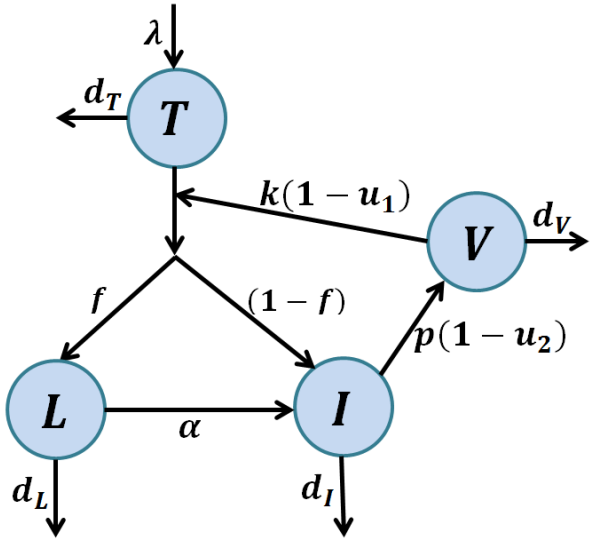


Figure. 5.1. Schematic diagram of HIV infection with the combination of treatments.

5.3 Qualitative Study of the Model

Now we must prove that solutions to the system of differential equations (5.1) exists and they are positive as well as bounded for all values of time in order to retain the biological validity of the model,

Theorem 5.1. *(Positivity). Let $t_0 > 0$, In the model (5.1), if the initial conditions satisfy $T_0 > 0, I_0 > 0, L_0 > 0$ and $V_0 > 0$, then for all $t \in [0, t_0]$ the functions $T(t), I(t), L(t)$ and $V(t)$ will be remain positive in $\mathbb{R}^4_+$.*

Proof of Theorem 5.1. Since all of the parameters used in the system are positive, we can place lower bounds on each of the equations given in the model. Thus,

$$\begin{aligned}
\frac{dT(t)}{dt} &= \lambda - k(1-u_1(t))T(t)V(t) - d_T T(t) \geq -k(1-u_1(t))T(t)V(t) - d_T T(t),\\
\frac{dI(t)}{dt} &= (1-f)(1-u_1(t))kT(t)V(t) - d_I I(t) + \alpha L(t) \geq -d_I I(t),\\
\frac{dL(t)}{dt} &= f(1-u_1(t))kT(t)V(t) - d_L L(t) - \alpha L(t) \geq -d_L L(t),\\
\frac{dV(t)}{dt} &= Nd_I(1-u_2(t))I(t) - d_V V(t) \geq -d_V V(t).
\end{aligned}$$

Through basic differential equations methods we can resolve the inequalities and produce:

$$\begin{aligned}
\frac{dT(t)}{dt} &\geq T(0)e^{-d_T t - k\int_0^{T_f}(1-u_1)Vdt}, \\
\frac{dI(t)}{dt} &\geq I(0)e^{-d_I t} > 0, \\
\frac{dL(t)}{dt} &\geq L(0)e^{-d_L t} > 0, \\
\frac{dV(t)}{dt} &\geq V(0)e^{-d_V t} > 0.
\end{aligned}$$

Thus, for all $t \in [0, t_0]$ the functions $T(t), I(t), L(t)$ and $V(t)$ will be positive and remain in $\mathbb{R}^4_+$. □

The boundedness of solutions to system (5.1-5.2) for finite time interval is needed to investigate the existence of an optimal control of our model, now we examining the priori boundedness of the state solutions.

Theorem 5.2. *(Boundedness). Given $(u_1, u_2) \in U$, there exists bounded solutions for the problems (5.1-5.2).*

Proof of Theorem 5.2. The state variables we consider here represent supersolutions for given problems (5.1-5.2). From the given equations we have

$$(T + I + L)'(t) = \lambda - d_T T - d_I I - d_L L.$$

Now, using $X(t) = T(t) + I(t) + L(t)$ and $d \geq \max\{d_T, d_I, d_L\}$, we get

$$X'(t) = \lambda - d_T T - d_I I - d_L L \leq \lambda - dX,$$

which implies that

$$\lim_{t\to\infty} \sup X(t) \leq \frac{\lambda}{d},$$

The upper bound for X is also the upper bound for T, I, and L. Lastly

$$V'(t) = Nd_I(1 - u_2(t))I(t) - d_V V(t) \leq Nd_I I(t) \leq \frac{Nd_I\lambda}{d},$$

which leads to

$$V(t) \leq \frac{Nd_I\lambda T_f}{d} \in \mathbb{R}_+, \quad \text{for all } t \in [0, T_f].$$

Since $(u_1(t), u_2(t)) \in U$, then, along with $T(t), I(t), L(t)$ and $V(t)$ are bounded above. Via a maximum principle [43] theory for first-order nonlinear differential equations, we obtain the solutions to the problems (5.1-5.2) bounded for all $t \in [0, t_0]$ and lies in the compact set

$$\mathbb{D} = \left\{ (T, I, L, V) \in \mathbb{R}^4_+ : T, I, L \leq \frac{\lambda}{d}, V \leq \frac{N d_I \lambda T_f}{d} \right\},$$

where $\mathbb{R}^4_+ = \{(T, I, L, V) : T \geq 0, I \geq 0, L \geq 0, V \geq 0\}$. □

Theorem 5.3. *(Existence of Solution). Let $t_0 > 0$, In the model (5.1), if the initial conditions satisfy $T_0 > 0, I_0 > 0, L_0 > 0$ and $V_0 > 0$, then for all $t \in \mathbb{R}$ the functions $T(t), I(t), L(t)$ and $V(t)$ will exist in $\mathbb{R}^4_+$.*

Proof of Theorem 5.3. In the case of our model the system of ODEs are defined by the function $\mathbf{f} : \mathbb{R}^4 \to \mathbb{R}^4$ as

$$\mathbf{f}(\mathbf{y}) = \begin{pmatrix} \lambda - k(1-u_1)TV - d_T T \\ (1-f)k(1-u_1)TV - d_I I + \alpha L \\ fk(1-u_1)TV - d_L L - \alpha L \\ N(1-u_2)d_I I - d_V V \end{pmatrix}$$

Note that $\mathbf{f}$ has a continuous derivative on $\mathbb{R}^4$ and thus, $\mathbf{f}$ is locally Lipschitz in $\mathbb{R}^4$. Hence, by the Fundamental Existence and Uniqueness Theorem (see Theorem 3.1) well as the theorems proved on positivity and boundedness of solutions, we know that there exists a unique, positive, and bounded solution to the ordinary differential equations given in (5.1-5.2). □

5.4 Optimal Control Problem

Our main objective is to maximize the benefit based on the CD4$^+$T cell count (increase in quality of life) and the systemic cost based on the percentage effect of the chemotherapy given (RTIs and PIs) is being minimized (toxic side effects being avoided as much as possible and not causing patient death). The objective functional is defined as,

$$J(u_1, u_2) = \int_0^{T_f} \left[T(t) - \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt, \tag{5.3}$$

where $T(t)$ is the benefit based on CD4$^+$T cells and the other terms are systemic costs of the drug treatments. The benefit of treatment is based on an increase of CD4$^+$T cells and systemic costs of drugs are minimized. The positive constants A_1 and A_2 represent desired weight on the benefit and cost, and u_1^2, u_2^2 reflect the severity of the side effects of the drugs [10]. The cost function is assumed to be nonlinear, basing on the fact that there is no linear relationship between the effects of treatment on CD4$^+$T cells or viral load hence the choice of a quadratic cost function [11]. We impose a condition for treatment time, $t \in [0, T_f]$, limited treatment window [8], that monitors global effects of these phenomena; treatment lasts for a given period of time because HIV can mutate and develop resistance to treatment after some finite time frame and in addition treatment has potentially harmful side effects, and these side effects increase with duration of treatment. The time $t = 0$ is the time when treatment is initiated and time $t = T_f$ is the time when treatment is stopped.

The control set U is defined as

$$U = \big\{u_1, u_2 \text{ are Lebesgue measurable, } 0 \leq u_1(t), u_2(t) \leq 1, t \in [0, T_f]\big\}.$$

So we seek an optimal control pair, u_1^*, u_2^* such that

$$J(u_1^*, u_2^*) = \max_{u_1, u_2 \in U} J(u_1, u_2), \tag{5.4}$$

subject to state constraints (5.1-5.2).

The basic framework of this problem is to prove the existence of the optimal control, characterize the optimal control and establish uniqueness of the optimality system.

5.5 Existence of an Optimal Control Pair

Using the fact that the solution to each state equation is bounded (see Theorem 5.2). Now, the existence of an optimal control for the state system is analyzed using the theory developed by Fleming and Rishel in [44].

Theorem 5.4. *Given the objective functional*

$$J(u_1, u_2) = \int_0^{T_f} \left[T(t) - \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt,$$

where $U = \{(u_2(t), u_2(t))$, *piecewise continuous such that* $0 \leq u_1(t), u_2(t) \leq 1\}$ *for all* $t \in [0, T_f]$ *subject to equations of system (5.1-5.2) with* $T(0) = T_0$, $I(0) = I_0$, $L(0) = L_0$ *and* $V(0) = V_0$, *then there exists an optimal control pair* u_1^*, u_2^* *such that*

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) | (u_1, u_2) \in U\}.$$

Proof of Theorem 5.4. To prove this theorem, we follow the requirments from Theorem 4.1 and Corollary 4.1 developed by Fleming and Rishel in [44] and verify them. Let $\mathbf{f}(t, \mathbf{X}, \mathbf{u})$ be the right-hand side of (5.1-5.2) for $0 \leq t \leq T_f$ where $\mathbf{X} \in \mathbb{R}^4$, $\mathbf{u} \in \mathbb{R}^2$ where $\mathbf{X} = (T, I, L, V)$ and $\mathbf{u} = (u_1, u_2)$. Accordng to [44], the following coditions are need to satisfy for the existence:

(i) The class of all initial conditions with an optimal control pair u_1, u_2 in the admissible control set along with each state equation being satisfied is not empty. That is

$$|\mathbf{f}(t, 0, 0)| \leq C, \quad |\mathbf{f}_{\mathbf{X}}(t, \mathbf{X}, \mathbf{u})| \leq C(1 + |\mathbf{u}|) \text{ and } |\mathbf{f}_{\mathbf{u}}(t, \mathbf{X}, \mathbf{u})| \leq C.$$

(ii) The admissible control set U is closed and convex.

(iii) Each right hand side of equations of system (5.1-5.2) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of an optimal control pair u_1, u_2 with coefficients depending on time and the state variables. That is

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X})\mathbf{u} \text{ and } |\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|).$$

(iv) The integrand of the functional $J(u_1, u_2)$ is concave on the admissible control set and is bounded above by $C_2 - C_1|\mathbf{u}|^\beta$, where C_1, C_2 are positive constants and $\beta > 1$.

In order to verify the theorem we write the right hand side of equations of system (5.1-5.2) as

$$\mathbf{f}(t,\mathbf{X},\mathbf{u}) = \begin{pmatrix} \lambda - k(1-u_1)TV - d_T T \\ (1-f)k(1-u_1)TV - d_I I + \alpha L \\ fk(1-u_1)TV - d_L L - \alpha L \\ Nd_I(1-u_2)I - d_V V \end{pmatrix}$$

It is easy to see that $\mathbf{f}(t,\mathbf{X},\mathbf{u})$ is of class C^1 and $|\mathbf{f}(t,0,0)| = \lambda$ and we have

$$|\mathbf{f}_{\mathbf{X}}(t,\mathbf{X},\mathbf{u})| = \left| \begin{pmatrix} a_{11} & 0 & 0 & a_{14} \\ a_{21} & -d_I & \alpha & a_{24} \\ a_{31} & 0 & -(d_L+\alpha) & a_{34} \\ 0 & Nd_I(1-u_2) & 0 & -d_V \end{pmatrix} \right|$$

where $a_{11} = -k(1-u_1)V - d_T,\ a_{14} = -k(1-u_1)T,\ a_{21} = (1-f)k(1-u_1)V,\ a_{24} = (1-f)k(1-u_1)T,\ a_{31} = fk(1-u_1)V,\ a_{34} = fk(1-u_1)V$ and

$$|\mathbf{f}_{\mathbf{u}}(t,\mathbf{X},\mathbf{u})| = \left| \begin{pmatrix} kTV & 0 \\ -(1-f)kTV & 0 \\ -fkTV & 0 \\ 0 & -Nd_I \end{pmatrix} \right|$$

Since T, I, L and V are bounded, then there exits a constant C such that

$$|\mathbf{f}(t,0,0)| \leq C, \quad |\mathbf{f}_{\mathbf{X}}(t,\mathbf{X},\mathbf{u})| \leq C(1+|\mathbf{u}|) \text{ and } |\mathbf{f}_{\mathbf{u}}(t,\mathbf{X},\mathbf{u})| \leq C.$$

By definition, U is closed. Take any controls $u_1, u_2 \in U$ and $\theta \in [0,1]$. Then

$$\theta u_1 + (1-\theta)u_2 \geq 0,$$

with $\theta u_1 \leq \theta$ and $(1-\theta)u_2 \leq (1-\theta)$. Then

$$\theta u_1 + (1-\theta)u_2 \leq \theta + (1-\theta) = 1,$$

i.e $0 \leq \theta u_1 + (1-\theta)u_2 \leq 1$, for all $u_1, u_2 \in U$ and $\theta \in [0,1]$. Therefore, U is convex and condition (ii) is satisfied. The right hand side of system (5.1-5.2) is

continuous, bilinear in the control and it can be written as:

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X})\mathbf{u}.$$

Where

$$\boldsymbol{\alpha}(t, \mathbf{X}) = \begin{pmatrix} \lambda - kTV - d_T T \\ (1-f)kTV - d_I I(t) + \alpha L \\ fkTV - d_L L - \alpha L \\ Nd_I I - d_V V \end{pmatrix}, \boldsymbol{\gamma}(t, \mathbf{X}) = \begin{pmatrix} kTV & 0 \\ -(1-f)kTV & 0 \\ -fkTV & 0 \\ 0 & -Nd_I \end{pmatrix}$$

are vector-valued functions of $\mathbf{X}$. and the boundedness of solutions gives

$$|\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|),$$

where C_1 depends on the coefficients of the system. Hence, satisfies condition (iii).

In order to verify the convexity of the integrand of our objective functional, J we show that

$$(1-\epsilon)J(t, \mathbf{X}, \mathbf{u}) + \epsilon J(t, \mathbf{X}, \mathbf{v}) \leq J(t, \mathbf{X}, (1-\epsilon)\mathbf{u} + \epsilon\mathbf{v})$$

for $0 < \epsilon < 1$ and $J(t, \mathbf{X}, \mathbf{u}) = T - \Big(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\Big)$.

Now

$$\begin{aligned}
&(1-\epsilon)J(t, \mathbf{X}, \mathbf{u}) + \epsilon J(t, \mathbf{X}, \mathbf{v}) - J(t, \mathbf{X}, (1-\epsilon)\mathbf{u} + \epsilon\mathbf{v}) \\
&= (1-\epsilon)\Big[T - \Big(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\Big)\Big] + \epsilon\Big[T - \Big(\frac{A_1}{2}v_1^2 + \frac{A_2}{2}v_2^2\Big)\Big] - \Big[T - \\
&\quad \frac{A_1}{2}\big((1-\epsilon)u_1 + \epsilon v_1\big)^2 + \frac{A_2}{2}\big((1-\epsilon)u_2 + \epsilon v_2\big)^2\Big] \\
&= -\frac{A_1}{2}\Big[(1-\epsilon)u_1^2 + \epsilon v_1^2 - \big((1-\epsilon)u_1 + \epsilon v_1\big)^2\Big] \\
&\quad - \frac{A_2}{2}\Big[(1-\epsilon)u_2^2 + \epsilon v_2^2 - \big((1-\epsilon)u_2 + \epsilon v_2\big)^2\Big] \\
&= -\frac{A_1}{2}\Big(\sqrt{\epsilon(1-\epsilon)}u_1 - \sqrt{\epsilon(1-\epsilon)}v_1\Big)^2 - \frac{A_2}{2}\Big(\sqrt{\epsilon(1-\epsilon)}u_2 - \sqrt{\epsilon(1-\epsilon)}v_2\Big)^2 \\
&= -\frac{A_1}{2}\epsilon(1-\epsilon)(u_1 - v_1)^2 - \frac{A_2}{2}\epsilon(1-\epsilon)(u_2 - v_2)^2 \leq 0.
\end{aligned}$$

Since $A_1,\ A_2 > 0$, $J(t, \mathbf{T}, \mathbf{u})$ is concave in U. Finally we need to show that $J(t, \mathbf{T}, \mathbf{u}) \leq C_2 - C_1|\mathbf{u}|^\beta$, where $C_1 > 0$ and $\beta > 1$. For our case

$$J(t, \mathbf{T}, \mathbf{u}) = T - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right) \leq C_2 - C_1|\mathbf{u}|^2,$$

where C_2 depends on the upper bound on CD4$^+$T cells, and $C_1 > 0$ since A_1, $A_2 > 0$ and $\beta = 2$. So we conclude that there exists an optimal control pair. □

5.6 The Optimality Conditions

The Pontryagin's Maximum Principle [45] provides necessary conditions for an optimal control problem. This principle converted the problem of finding a control which maximizes the objective function J subject to the state system (5.1-5.2) to the problem of maximizing the Hamiltonian H, pointwisely with respect to u_1 and u_2. So it is sufficient to derive the Hamiltonian H instead of deriving the objective function J defined in (5.3) in order to characterize the optimal controls u_1^* and u_2^*. The Hamiltonian is defined from the formulation of the objective function as follows:

$$H = T(t) - \left(\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\right) + \sum_{i=1}^{4}\lambda_i(t)F_i,$$

where F_i is the right hand side of the differential equation of i-th state variable. By applying Pontryagin's Maximum Principle [45] we obtain the following theorem.

Theorem 5.5. *There exists an optimal control $u^* = (u_1^*, u_2^*)$ and corresponding solution $T(t), I(t), L(t)$ and $V(t)$, that maximizes $J(u_1, u_2)$ over U. Furthermore, there exists adjoint functions $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ and $\lambda_4(t)$ satisfying the equations*

$$\begin{cases} \lambda_1'(t) = -1 + k(1-u_1(t))V(t)\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big) + \lambda_1(t)d_T, \\ \lambda_2'(t) = \lambda_2(t)d_I - \lambda_4(t)Nd_I(1-u_2(t)), \\ \lambda_3'(t) = -\lambda_2(t)\alpha + \lambda_3(d_L + \alpha), \\ \lambda_4'(t) = k(1-u_1(t))T(t)\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big) + \lambda_4(t)d_V, \end{cases} \tag{5.5}$$

with transversality conditions

$$\lambda_i(T_f) = 0,\ \ i = 1, 2, \cdots, 4. \tag{5.6}$$

Moreover, the optimal control is given by

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big)kT(t)V(t)\right), 1\right) \quad (5.7)$$

and

$$u_2^*(t) = \min\left(\max\left(0, \frac{-1}{A_2}\lambda_4(t)Nd_I I\right), 1\right). \quad (5.8)$$

Proof of Theorem 5.5. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\begin{aligned}
\lambda_1'(t) &= -\frac{\partial H}{\partial T}, & \lambda_1(T_f) &= 0,\\
\lambda_2'(t) &= -\frac{\partial H}{\partial I}, & \lambda_2(T_f) &= 0,\\
\lambda_3'(t) &= -\frac{\partial H}{\partial L}, & \lambda_3(T_f) &= 0,\\
\lambda_4'(t) &= -\frac{\partial H}{\partial V}, & \lambda_4(T_f) &= 0.
\end{aligned}$$

Since $T(t), I(t), L(t)$ and $V(t)$ do not have fixed values at the final time T_f, the values of the associated adjoints $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ and $\lambda_4(t)$ at the final time are zero. The optimal control u_1^* and u_2^* on the interior of the control set can be solved from the optimality conditions,

$$\left.\frac{\partial H}{\partial u_1}\right|_{u_1=u_1^*} = 0, \quad \text{and} \quad \left.\frac{\partial H}{\partial u_2}\right|_{u_2=u_2^*} = 0.$$

That is

$$\frac{\partial H}{\partial u_1} = -A_1 u_1 + \Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big)kT(t)V(t) = 0,$$

and

$$\frac{\partial H}{\partial u_2} = -A_2 u_2 - \lambda_4(t)Nd_I I = 0,$$

By using the bounds on the controls, we get

$$u_1^* = \begin{cases} 0, & \text{if } \dfrac{\partial H}{\partial u_1^*} < 0\\[2ex] \dfrac{1}{A_1}\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big)kT(t)V(t), & \text{if } \dfrac{\partial H}{\partial u_1^*} = 0\\[2ex] 1 & \text{if } \dfrac{\partial H}{\partial u_1^*} > 0. \end{cases}$$

In compact notation

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big)kT(t)V(t)\right), 1\right).$$

Again, we get

$$u_2^* = \begin{cases} 0 & \text{if } \dfrac{\partial H}{\partial u_2^*} < 0, \\ \dfrac{-1}{A_2}\lambda_4(t)Nd_I I, & \text{if } \dfrac{\partial H}{\partial u_2^*} = 0 \\ 1 & \text{if } \dfrac{\partial H}{\partial u_2^*} > 0. \end{cases}$$

In compact notation

$$u_2^*(t) = \min\left(\max\left(0, \frac{-1}{A_2}\lambda_4(t)Nd_I I\right), 1\right).$$

□

In addition, the second derivative of the Hamiltonian H with respect to $u_1(t)$ and $u_2(t)$ are negative, indicating a maximum at $u^* = (u_1^*, u_2^*)$. That is

$$\frac{\partial^2 H}{\partial u_i^2} = -A_i \leq 0, \quad i = 1, 2 \quad \text{since} \quad A_i \geq 0$$

We point out that the optimality system consists of the state system (5.1) with the initial conditions (5.2), adjoint system (5.5) with transversality conditions (5.6), and optimality condition (5.7-5.8). Thus, we have the following optimality system at $u^*(t) = (u_1^*(t), u_2^*(t))$:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \lambda - k(1-u_1^*(t))T(t)V(t) - d_T T(t) \\
\dfrac{dI(t)}{dt} = (1-f)(1-u_1^*(t))kT(t)V(t) - d_I I(t) + \alpha L(t) \\
\dfrac{dL(t)}{dt} = f(1-u_1^*(t))kT(t)V(t) - d_L L(t) - \alpha L(t) \\
\dfrac{dV(t)}{dt} = N d_I (1-u_2^*(t))I(t) - d_V V(t), \\
\lambda_1'(t) = -1 + k(1-u_1^*(t))V(t)\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big) + \lambda_1(t)d_T, \\
\lambda_2'(t) = \lambda_2(t)d_I - \lambda_4(t)N d_I(1-u_2^*(t)), \\
\lambda_3'(t) = -\lambda_2(t)\alpha + \lambda_3(d_L+\alpha), \\
\lambda_4'(t) = k(1-u_1^*(t))T(t)\Big(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t)\Big) + \lambda_4(t)d_V, \\
\qquad T(0), I(0), L(0), V(0) \geq 0, \\
\qquad \lambda_i(T_f) = 0, \ i = 1, 2, \cdots, 4,
\end{cases}
\tag{5.9}
$$

where the controls $u_1^*(t)$ and $u_2^*(t)$ are given by 5.7 and 5.8 respectively.

5.7 Uniqueness of the Optimality System

Since the state system moves forward in time and the adjoint system moves backward in time, we have a challenge with uniqueness. To prove uniqueness of solutions of the optimality system for the small time interval, we use the following theorems [10].

Theorem 5.6. *The function $u^*(c) = \min(\max(c, a), b)$ is Lipschitz continuous in c, where $a < b$ are some fixed positive constants.*

Proof of Theorem 5.6. Consider c_1, c_2 real numbers and a, b as fixed positive constants. We will show that the Lipschitz continuity holds in all possible cases for $\max(c, a)$. Similar arguments hold for $\min(\max(c, a), b)$ as well.

1. $c_1 \geq a$, $c_2 \geq a$: $|\max(c_1, a) - \max(c_2, a)| = |c_1 - c_2|$.
2. $c_1 \geq a$, $c_2 \leq a$: $|\max(c_1, a) - \max(c_2, a)| = |c_1 - a| \leq |c_1 - c_2|$.
3. $c_1 \leq a$, $c_2 \geq a$: $|\max(c_1, a) - \max(c_2, a)| = |a - c_2| \leq |c_1 - c_2|$.

4. $c_1 \leq a$, $c_2 \leq a$: $|\max(c_1, a) - \max(c_2, a)| = |a - a| = 0 \leq |c_1 - c_2|$.

Hence $|\max(c_1, a) - \max(c_2, a)| \leq |c_1 - c_2|$ and we have Lipschitz continuity of u^* in c. □

Theorem 5.7. *For sufficiently small final time (T_f), bounded solutions to the optimality system (5.9), are unique.*

Proof of Theorem 5.7. Suppose $(T, I, L, V, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\overline{T}, \overline{I}, \overline{L}, \overline{V}, \overline{\lambda_1}, \overline{\lambda_2}, \overline{\lambda_3}, \overline{\lambda_4})$ are two non-identical solutions of our optimality system (5.9). To show that the two solutions are equivalent, it is convenient to make a change of variables.
Let $T = e^{mt}x_1, I = e^{mt}x_2, L = e^{mt}x_3, V = e^{mt}x_4, \lambda_1 = e^{-mt}y_1, \lambda_2 = e^{-mt}y_2$,
$\lambda_3 = e^{-mt}y_3, \lambda_4 = e^{-mt}y_4, \overline{T} = e^{mt}\overline{x_1}, \overline{I} = e^{mt}\overline{x_2}, \overline{L} = e^{mt}\overline{x_3}, \overline{V} = e^{mt}\overline{x_4}$,
$\overline{\lambda_1} = e^{-mt}\overline{y_1}, \overline{\lambda_2} = e^{-mt}\overline{y_2}, \overline{\lambda_3} = e^{-mt}\overline{y_3}, \overline{\lambda_4} = e^{-mt}\overline{y_4}$.
where $m > 0$ is a positive constant to be chosen later. With the new variables the optimality conditions become

$$
\begin{aligned}
u_1^* &= \min\left(\max\left(0, \frac{(y_1 - (1-f)y_2 - fy_3)kx_1x_4e^{mt}}{A_1}\right), 1\right),\\
u_2^* &= \min\left(\max\left(0, \frac{-Nd_Iy_4x_2}{A_2}\right), 1\right),\\
\overline{u_1^*} &= \min\left(\max\left(0, \frac{(\overline{y_1} - (1-f)\overline{y_2} - f\overline{y_3})k\overline{x_1}\ \overline{x_4}e^{mt}}{A_1}\right), 1\right),\\
\overline{u_2^*} &= \min\left(\max\left(0, \frac{-Nd_I\overline{y_4}\ \overline{x_2}}{A_2}\right), 1\right).
\end{aligned}
$$

For the first equation of system (5.9) we substitute $T = e^{mt}x_1$ and get

$$\dot{x}_1 + mx_1 = \lambda e^{-mt} - (1 - u_1^*)kx_1x_4e^{mt} - d_Tx_1$$

and for $\overline{T} = e^{mt}\overline{x_1}$ we have

$$\dot{\overline{x_1}} + m\overline{x_1} = \lambda e^{-mt} - (1 - \overline{u_1^*})k\overline{x_1}\ \overline{x_4}e^{mt} - d_T\overline{x_1}.$$

Subtracting the expression for $\overline{T}$ from the expression for T we have

$$\dot{x_1} - \dot{\overline{x_1}} + m(x_1 - \overline{x_1}) = -ke^{mt}\left[(1 - u_1^*)x_1x_4 - (1 - \overline{u_1^*})\overline{x_1}\ \overline{x_4}\right] - d_T(x_1 - \overline{x_1}).$$

Multiplying by $(x_1 - \overline{x_1})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\begin{aligned}\frac{1}{2}(x_1 - \overline{x_1})^2(T_f) + m\int_0^{T_f}(x_1 - \overline{x_1})^2 dt \\ = -k\int_0^{T_f} e^{mt}\Big[(1-u_1^*)x_1x_4 - (1-\overline{u_1^*})\overline{x_1}\ \overline{x_4}\Big](x_1 - \overline{x_1})dt \\ - d_T\int_0^{T_f}(x_1 - \overline{x_1})^2 dt.\end{aligned} \tag{5.10}$$

In order to simplify the right-hand expressions of (5.10), we need some elementary inequalities.

By the elementary inequality $(a+b)^2 \le 2(a^2+b^2)$, we have

$$\begin{aligned}(x_1y_1 - \overline{x_1}\ \overline{y_1})^2 &= (x_1y_1 - x_1\overline{y_1} + x_1\overline{y_1} - \overline{x_1}\ \overline{y_1})^2 \\ &= [x_1(y_1 - \overline{y_1}) + \overline{y_1}(x_1 - \overline{x_1})]^2 \\ &\le \max\{2x_1^2, 2\overline{y_1}^2\}[(x_1 - \overline{x_1}) + (y_1 - \overline{y_1})]^2 \\ &\le C[(x_1 - \overline{x_1}) + (y_1 - \overline{y_1})]^2,\end{aligned}$$

where C depends on bounds for $x_1, \overline{y_1}$. Another common expression can be used repeatedly,

$$\begin{aligned}(xy - \overline{x}\ \overline{y})(w - \overline{w}) &= (xy - \overline{x}y + \overline{x}y - \overline{x}\ \overline{y})(w - \overline{w}) \\ &= y(x - \overline{x})(w - \overline{w}) + \overline{x}(y - \overline{y})(w - \overline{w}) \\ &\le y^2(x - \overline{x})^2 + \overline{x}^2(y - \overline{y})^2 + 2(w - \overline{w})^2 \\ &\le C[(x - \overline{x})^2 + (y - \overline{y})^2 + (w - \overline{w})^2],\end{aligned}$$

where C depends on bounds for $\overline{x}, y$.

Based on the above arguments and theorem 5.6, we find

$$\begin{aligned}&\int_0^{T_f}(u_1^* - \overline{u_1^*})^2 dt \\ &= \frac{k^2}{A_1^2}\int_0^{T_f}\left[e^{mt}\left\{x_1x_4\Big(y_1 - (1-f)y_2 - fy_3\Big) - \overline{x_1}\ \overline{x_4}\Big(\overline{y_1} - (1-f)\overline{y_2} - f\overline{y_3}\Big)\right\}\right]^2 dt \\ &\le C_2\frac{k^2e^{2mT_f}}{A_1^2}\int_0^{T_f}\Big[(y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2\Big]dt.\end{aligned}$$

Also,

$$
\begin{aligned}
&k\int_0^{T_f} e^{mt}\Big[(1-u_1^*)x_1x_4-(1-\overline{u_1^*})\overline{x_1}\ \overline{x_4}\Big](x_1-\overline{x_1})dt\\
&\le C_3e^{mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_4-\overline{x_4})^2+(u_1^*-\overline{u_1^*})^2\Big]dt\\
&\le C_2'e^{3mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_4-\overline{x_4})^2+(y_1-\overline{y_1})^2+(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt.
\end{aligned}
$$

Substituting above relations in equation (5.10), it becomes

$$
\begin{aligned}
&\frac{1}{2}(x_1-\overline{x_1})^2(T_f)+m\int_0^{T_f}(x_1-\overline{x_1})^2dt\\
&\le C_1'\int_0^{T_f}(x_1-\overline{x_1})^2dt\\
&\quad+C_2'e^{3mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_4-\overline{x_4})^2+(y_1-\overline{y_1})^2+(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt
\end{aligned}
$$

where the contant C_2, C_1' and C_2' obtained above are dependent on the system coefficients as well as the bounds on the state and adjoint variables.

Similarly, for $\lambda_1 = e^{-mt}y_1$ and $\overline{\lambda_1} = e^{-mt}\overline{y_1}$ we have

$$
-\dot{y}_1+my_1=e^{mt}-d_Ty_1-ke^{mt}(1-u_1^*)x_4\Big[y_1-(1-f)y_2-fy_3\Big]
$$

and

$$
-\dot{\overline{y_1}}+m\overline{y_1}=e^{mt}-d_T\overline{y_1}-ke^{mt}(1-\overline{u_1^*})\overline{x_4}\Big[\overline{y_1}-(1-f)\overline{y_2}-f\overline{y_3}\Big]
$$

respectively. Subtracting the expression for $\overline{\lambda_1}$ from the expression for λ_1 and multiplying by $(y_1-\overline{y_1})$ and integrating from $t=0$ to $t=T_f$ we have

$$
\begin{aligned}
&\frac{1}{2}(y_1-\overline{y_1})^2(0)+m\int_0^{T_f}(y_1-\overline{y_1})^2dt\\
&=-d_T\int_0^{T_f}(y_1-\overline{y_1})^2dt-k\int_0^{T_f}e^{mt}\Big[(1-u_1^*)x_4\Big(y_1-(1-f)y_2-fy_3\Big)\\
&\qquad-(1-\overline{u_1^*})\overline{x_4}\Big(\overline{y_1}-(1-f)\overline{y_2}-f\overline{y_3}\Big)\Big](y_1-\overline{y_1})dt\\
&\le C_3'\int_0^{T_f}(y_1-\overline{y_1})^2dt\\
&\quad+C_4'e^{3mT_f}\int_0^{T_f}\Big[(x_4-\overline{x_4})^2+(y_1-\overline{y_1})^2+(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt
\end{aligned}
$$

where the contant C_3' and C_4' ontained above are dependent on the system coefficients as well as the bounds on the state and adjoint variables.

Similarly, after appropriate substitutions the equations for I and $\overline{I}$, L and $\overline{L}$, V and $\overline{V}$, λ_2 and $\overline{\lambda_2}$, λ_3 and $\overline{\lambda_3}$, λ_4 and $\overline{\lambda_4}$ are subtracted, then each expression is multiplied by an appropriate function and integrated from $t = 0$ to $t = T_f$. We obtain total eight integral equations and to show uniqueness, the integral equations are combined. Adding all the eight estimates gives

$$\begin{aligned}
&\frac{1}{2}(x_1 - \overline{x_1})^2(T_f) + \frac{1}{2}(x_2 - \overline{x_2})^2(T_f) + \frac{1}{2}(x_3 - \overline{x_3})^2(T_f) + \frac{1}{2}(x_4 - \overline{x_4})^2(T_f) \\
&\quad + \frac{1}{2}(y_1 - \overline{y_1})^2(0) + \frac{1}{2}(y_2 - \overline{y_2})^2(0) + \frac{1}{2}(y_3 - \overline{y_3})^2(0) + \frac{1}{2}(y_4 - \overline{y_4})^2(0) \\
&\quad + m\int_0^{T_f} [(x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 \\
&\quad + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2]dt \\
\leq &(\tilde{C_1} + \tilde{C_2}e^{3mT_f})\int_0^{T_f} \Big[(x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 \\
&\quad + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2\Big]dt.
\end{aligned}$$

Thus from the above expression, using the non-negativity of the variable expressions evaluated at the initial and the final time and simplifying, the inequality is reduced to

$$\begin{aligned}
&\big(m - \tilde{C_1} - \tilde{C_2}e^{3mT_f}\big)\int_0^{T_f} \Big[(x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 \\
&\quad + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2\Big]dt \leq 0.
\end{aligned}$$

where $\tilde{C_1}$ and $\tilde{C_2}$ depend on the syatem coefficients as well as the bounds on state and adjoint variables. If we choose m such that $m - \tilde{C_1} - \tilde{C_2}e^{3mT_f} > 0$, the above inequality holds if the integrand is identically zero. Since the natural logarithm is an increasing function, then $\ln\big(\frac{m - \tilde{C_1}}{\tilde{C_2}}\big) > 3mT_f$ if $m > \tilde{C_1} + \tilde{C_2}$. This gives that $T_f < \frac{1}{3m}\ln\big(\frac{m - \tilde{C_1}}{\tilde{C_2}}\big)$, then $x_1 = \overline{x_1}$, $x_2 = \overline{x_2}$, $x_3 = \overline{x_3}$, $x_4 = \overline{x_4}$, $y_1 = \overline{y_1}$, $y_2 = \overline{y_2}$, $y_3 = \overline{y_3}$, $y_4 = \overline{y_4}$. Hence the solution is unique for small time. □

5.8 Critical Drug Efficacy

To analyze the steady states and basic reproduction number for (5.1), we may reproduce the analysis of (4.1), but clearly the new terms are introduced only where the parameters k and N appear. Thus, we need only replace k with $k(1-u_1)$ and N with $N(1-u_2)$. The new basic reproduction number then becomes

$$R_L^u = \frac{k\lambda N(1-u_1)(1-u_2)}{d_T d_V}.\left(1-\frac{fd_L}{\alpha+d_L}\right).$$

Notice that in the presence of drugs, R_L^u is usually called the (on-treatment) reproductive number. As per previous dicussion (see theorem 4.5), we know that the condition for the existence of the uninfected (E^0) and infected (E^*) steady state are given in terms of the basic reproduction number as $R_L^u < 1$ and $R_L^u > 1$.

In the system (5.1), the efficacies of RTIs and PIs are incorporated through the terms $(1-u_1)$ and $(1-u_2)$ respectively. The values, $u_i = 0$ and $u_i = 1$, reflect completely ineffective and perfectly effective therapy respectively. For brevity, the efficacies of RTIs and PIs are combined to obtain a new term to reflect the overall efficacy for this combination therapy and is given by $1-u = (1-u_1)(1-u_2)$, this rearrangement indicates that the drugs act independently of one another. Note that $u = u_1 + u_2 - u_1u_2$ represents the total combined drug efficacy. This choice is motivated by the condition for stability of E^0 and E^*. Recalling that the stability criterion for E^0 is , which equivalent to $R_L^u < 1$, which equivalent to

$$\frac{k\lambda N(1-u)}{d_T d_V}\left(1-\frac{fd_L}{\alpha+d_L}\right) < 1 \Rightarrow R_L(1-u) < 1 \Rightarrow 1-u < \frac{1}{R_L}.$$

Similarly the condition $R_L^u > 1$, for E^* to be stable is equivalent to

$$\frac{k\lambda N(1-u)}{d_T d_V}\left(1-\frac{fd_L}{\alpha+d_L}\right) > 1 \Rightarrow R_L(1-u) > 1 \Rightarrow 1-u > \frac{1}{R_L}.$$

Thus, there is a transcritical bifurcation point given by

$$1-u = \frac{1}{R_L}.$$

Motivated by this we define the critical efficacy, u_c by

$$u_c = 1-\frac{1}{R_L}.$$

Thus, in order to achieve a successful therapy by way of elimination of HIV, i.e., the uninfected steady state E^0 being stable we need $u > u_c(\equiv R_L^u < 1)$. On the other hand, whenever $u < u_c(\equiv R_L^u > 1)$, the infected steady state E^* remains stable and the infection persists. With the base-case parameters given in Table 1, in the absence of drugs, i.e., $u = 0$, the basic reproductive number is $R_L^u = R_L = 18.37$. This shows that to avoid infection the combination drug efficacy u_c should be maintained at a constant greater than

$$u_c > 1 - \frac{1}{R_L} = 0.95,$$

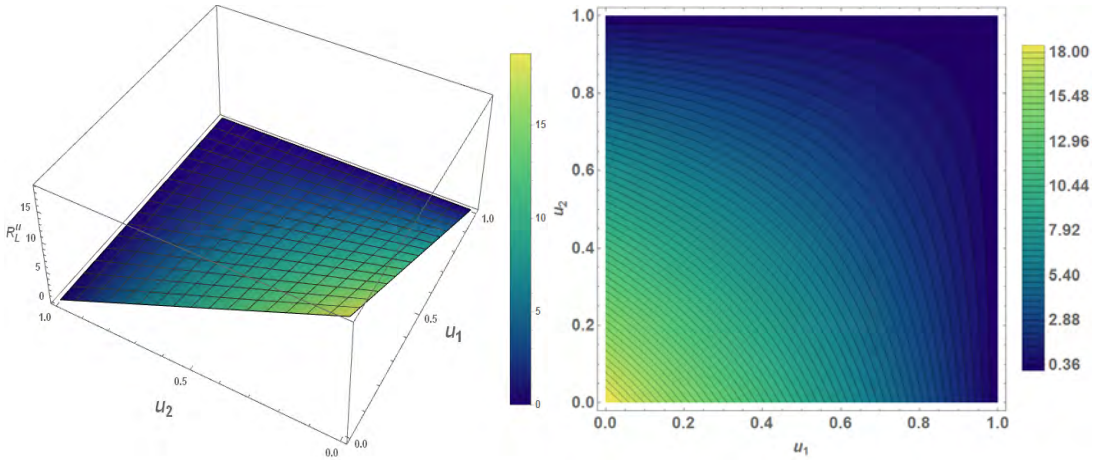
i.e., maintaining constant drug effectiveness of at least 95% should theoretically avoid infection. The goal is to choose u_1 and u_2 so that $u_c > 0.95(\equiv R_L^u < 1)$ hereby resulting in a stable uninfected steady state.

5.9 Numerical Results

In this section, we utilize the data as discussed in section 4.6 to simulate the impact of different treatments strategy on the dynamics of HIV primary infection. We explore the model 5.1 to study the effects of both RTIs and PIs on the proliferation of the viral and infected cells within the host. Since HIV symptoms are exposed during symptomatic phase (7-12 days after infection), so treatment was assumed to be given during this phase. Using various combinations of the two drugs, one at a time and combined, we investigate and compare the numerical results from simulations. In doing so, we are able to numerically illustrate how the efficacy of the drugs effect the level of infection in order to achieve viral clearance. Numerical simulations are doing with the base-case parameters given in Table 1, when the basic reproductive number is $R_L = 18.37 > 1$.

5.9.1 Constant Treatment Strategy

First, we numerically examine the impact of the constant efficacies u_1 and u_2 (of RTIs and PIs respectively) on the basic reproduction number R_L^u. Recall that the infection clears out or persists whenever $R_L^u < 1$ or $R_L^u > 1$, which is equivalent to $u > u_c$ or $u < u_c$. In previous section 5.8, we show that our goal is to choose u_1 and u_2 such that R_L^u is driven to a value less than 1 and combined drug efficacy



(a) Surface plot of R_L^u. (b) Contour plot of R_L^u.

Figure. 5.2. Surface and contour plot of R_L^u for various values of u_1 and u_2.

$u(= 1 - (1 - u_1)(1 - u_2)) > u_c = 0.95$. We illustrate this by a surface plot and a contour plot in Figure 5.2. We can easily observe that for $u_1 = 0$ and $u_2 = 0$ the value of R_L^u attains its maximum value of $R_L^u = R_L = 18.37$. We increase u_1 and u_2 from 0 to 1 and observe that the value of R_L^u gradually decreases and eventually tends towards 0 (corresponding to $u_1 = 1$, $u_2 = 1$). This clearly reflects the impact of the efficacies in terms of clearance of the infection.

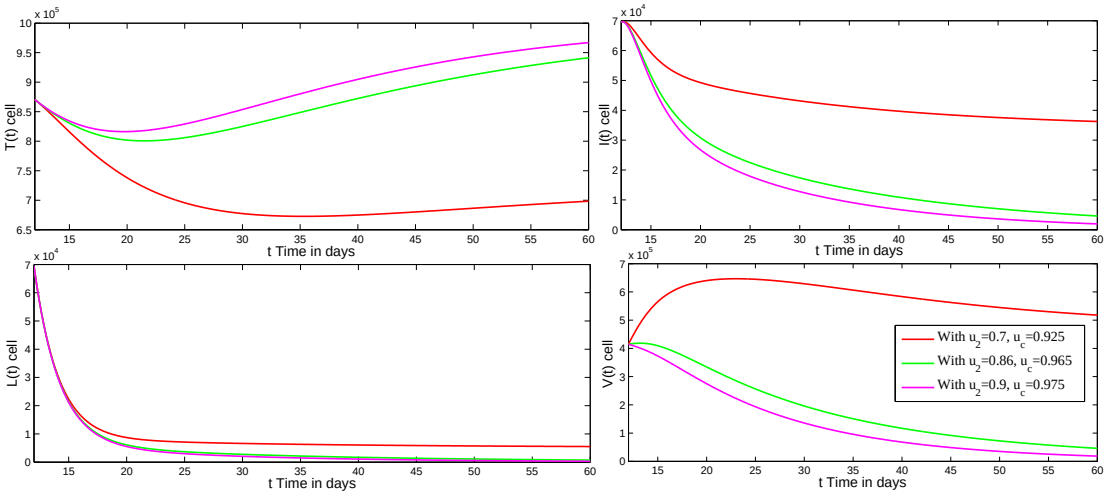


Figure. 5.3. Various cell dynamics in contact with HIV during various values of u_2(PIs) with fix u_1(RTIs).

Now, we simulated the dynamics of the system as a result of administration of the combination constant therapy. Recall that the parameter values (without treatment) chosen are for $R_L^u > 1$. In Figure 5.3, we fix the efficacy of RTIs as $u_1 = 0.75$ and consider three different efficacies of PIs, namely, $u_2 = 0.7,\ 0.86,\ 0.9$.

For $u_2 = 0.7$, the combination efficacy, $u = 0.925$, which is less than the critical efficacy $u_c = 0.95$ with $R_L^u = 1.38 > 1$. In this case, the levels of infected I-cell, Latent L-cell and virions V show some signs of decline over a period of 60 days as can be seen in Figure 5.3. But if the simulation is run for a longer time period, then we can see that despite the initial signs of patient recovery, the levels of all three cells will rebound and eventually move towards the infected steady state. Further, for $u_2 = 0.86,\ 0.9$, the combination efficacy u is always greater than the critical efficacy u_c i.e., $R_L^u < 1$. For these cases, the levels of I, L and V show a gradual decline over the period of 60 days and simulation for a longer period also confirms that the populations tend towards the levels for the uninfected steady state E^0. We observe that this decline is biphasic in nature in case of V with a more rapid decline in the first phase of a couple of days followed by a slower decline, which is consistent with clinical results [48]. We observe similar results by fixing $u_2 = 0.75$ and varying the values of $u_1 = 0.7,\ 0.86,\ 0.9$. These results are presented in Figure 5.4. We note that in this case also there is a biphasic decline that is observed earlier.

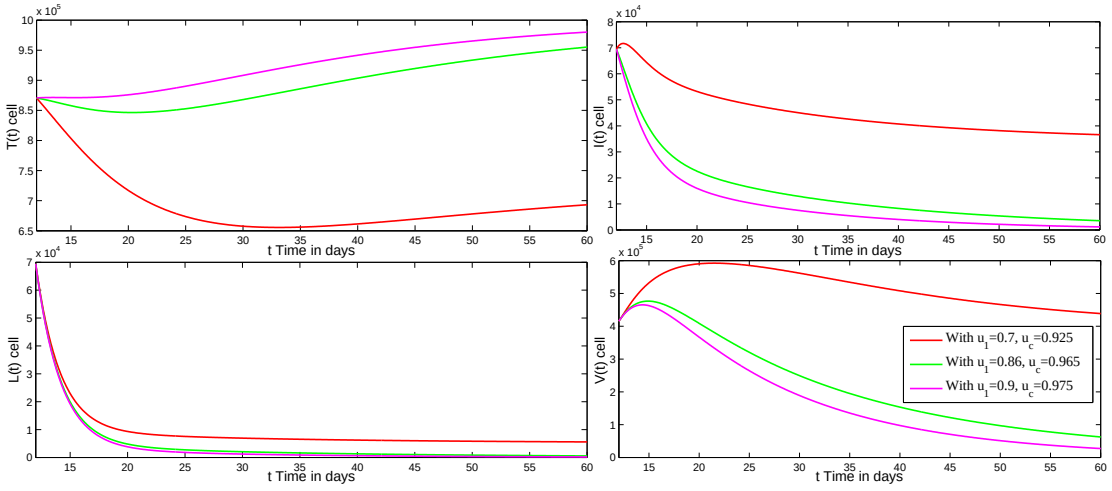


Figure. 5.4. Various cell dynamics in contact with HIV during various values of u_1(RTIs) with fix u_2(PIs).

Interruptions in treatment can happen due to a variety of reasons such as side effects and financial constraints for a continued long term treatment [26]. To illustrate one such scenario, we consider three sets of combination therapy (u_1, u_2) as $(0.88, 0.6), (0.83, 0.75)$, and $(0.83, 0.75)$ for a period of 60 days. For these three pairs of $(u_1, u_2), u > u_c$. We see in Figure 5.5, as to how the viral load declines in a biphasic manner if full treatment is adminstrated. The decline is significant (approximately 10^2 folds). The discontinuation of treatment after 45 days results

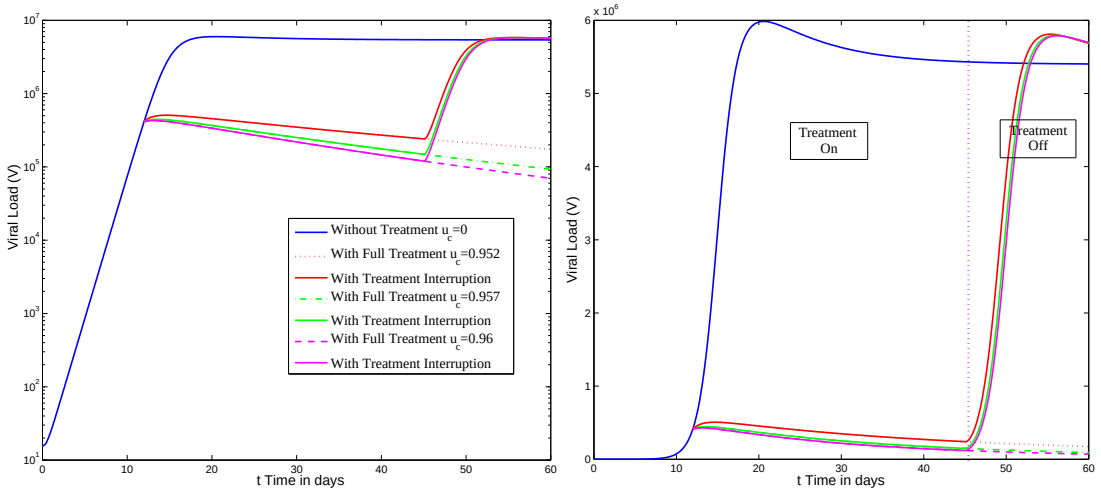


Figure. 5.5. Pattern of viral load with an on-off treatment with the treatment being administered for 45 days and then the treatment being interrupted for the next 15 days.

in the rebound of the levels of HIV virions. Once the treatment period of 45 days is over, we observed the dynamics of the system for another 15 days starting from the levels at the cessation of treatment after 45 days. It can be seen that the peak viral load on an average is lower with this on-off therapeutic protocol as compared to the scenario when no treatment is administered over the entire period of 60 days.

5.9.2 Optimal Treatment Strategy

The optimal control problem comprising of the optimality system in 5.9 is solved using an iterative method with Runge-Kutta of order four scheme. The optimality system is a two-point boundary value problem, where initial conditions are specified for the state system and terminal conditions are specified for the adjoint system. The method of obtaining the optimal control is as follows [26]:

1. Take a guess for the two controls.
2. Solve the state system forward using those controls and using a Runge-kutta method of order four algorithm with state variables initial conditions.
3. Using the new state values, solve the adjoint system backwards using the final time zero boundary conditions and Runge-Kutta of order four scheme.
4. Calculate the new control values from the characterization.

5. Go to steps 2, 3 again with new control from step 4.

6. Calculate other new control values from step 5. Compare controls from last iteration to new iteration and compare states also. Keep repeating control updates and forward and backward solving until the iterates converge.

Most individuals in the acute phase of HIV infection are highly infectious to others, primarily because of high HIV RNA levels, and often lack of awareness of their HIV status [46]. Thus, accurate and timely detection of primary HIV infection is critical to both the future health of the infected individual and for preventing forward transmission of HIV. To understand the impact of treatment strategy, we first look at the dyamics with and without treatment. We vary initiation of treatment during later days of symptomatic phase with the following intial values:

Table. 5.1. The cell populations at different moments of time following the infection.

Days after infection	Initial $T(t)$	Initial $I(t)$	Initial $L(t)$	Initial $V(t)$
$t = 12$	870691	69466	8130	415083
$t = 18$	56088	179896	29738	5684380
$t = 24$	50148	119087	18679	5863112
$t = 30$	52185	117373	17888	5628812

For the purpose of the simulation we take the minimum and maximum control to be $0 \leq u_1, u_2 \leq 1$ and the cost coefficients that were introduced in the definition of the objective functional 5.3 were set at $A_1 = A_2 = 1$ [10]. Figure 5.6 shows that without any preventive control the uninfected T cells continue to decrease, the number of infected cells (I & L) and virus V cells increases, at the end of the time interval these cells achieving a infected state at $t = 60$. By using therapy at any time we can alter the situation.

For better understanding the treatment dynamics starting at different time, we summarize the end state variables in the following tables:

According to table 5.2, it signifies that treatment must be started immediately regardless the time elapsed since infection. We also notice the cases when the

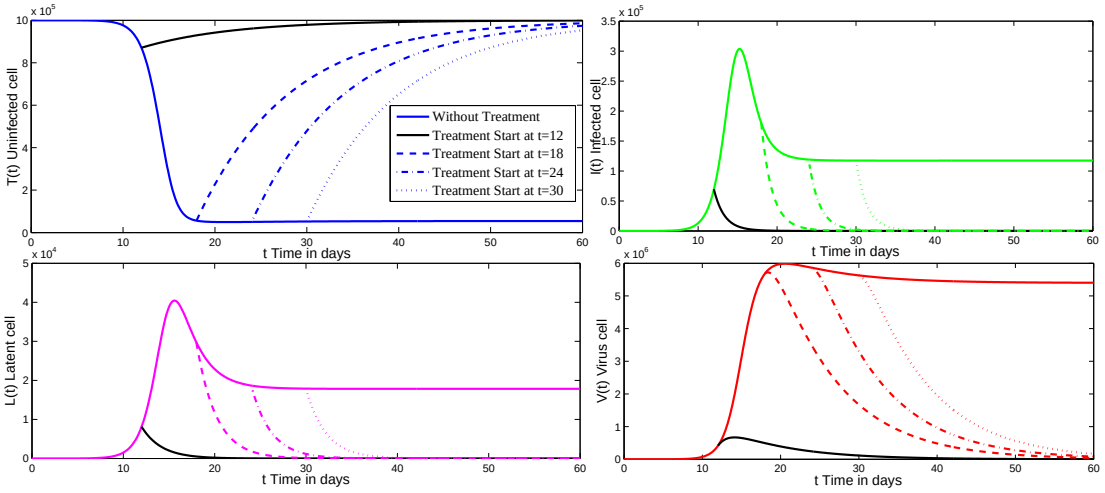


Figure. 5.6. The evolution of the immune system dynamics in contact with HIV with and without optimal treatment. Here we initiate treatment at different days after infection.

Table. 5.2. The cell populations at the end of time following the treatment.

Treatment initiate at	End $T(t)$	End $I(t)$	End $L(t)$	End $V(t)$	$J(u^*)$
$t = 12$	998936	2.5×10^{-6}	1.9×10^{-6}	2781	7.8×10^{8}
$t = 18$	985846	0.00015	0.00011	40462	5.5×10^{8}
$t = 24$	974047	0.0015	0.0011	80627	4.5×10^{8}
$t = 30$	952811	0.023	0.017	163588	3.5×10^{8}

objective function values are larger, i.e., when initial T cell counts are higher. So, for the patients who are in the early stage of infection, the greatest effect does occur when treatment is initiated earlier with maximum value of the objective function. This result resembles the clinical output given by D. Ho [47] which confered that "Time to hit HIV, early and hard!". "The acute infection stage, when the viral load is very high is the easiest stage to control" results given by P. Paci et al. [48] also confirms our output.

Now we turn our attention to why we use combined drug treatment strategy. Figure 5.7 shows the graph of the solution to the optimality system when drugs (RTIs and PIs) are administered individually and combinedly for 60 days. The figure depicts that except administrating only PIs both combined and only RTIs show almost same result at the end. By covering different path during treatment

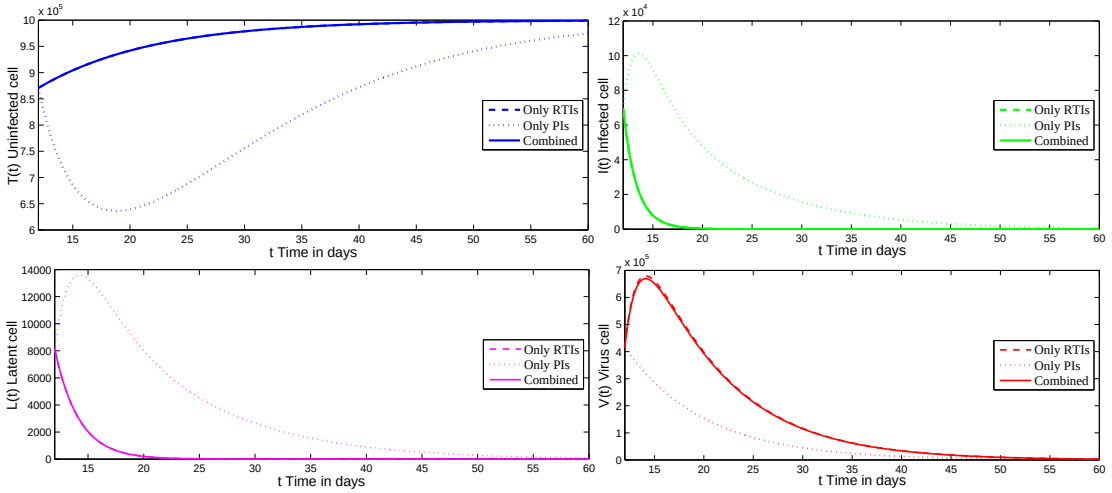


Figure. 5.7. State dynamics in various optimal treatment strategy.

period all treatment strategies attain optimal level at the end. Figure 5.8 shows corresponding drug dosage during optimal treatment, which shows each treatment strategy used 100% drug efficacy to attain optimal level except PIs during combined therapy.

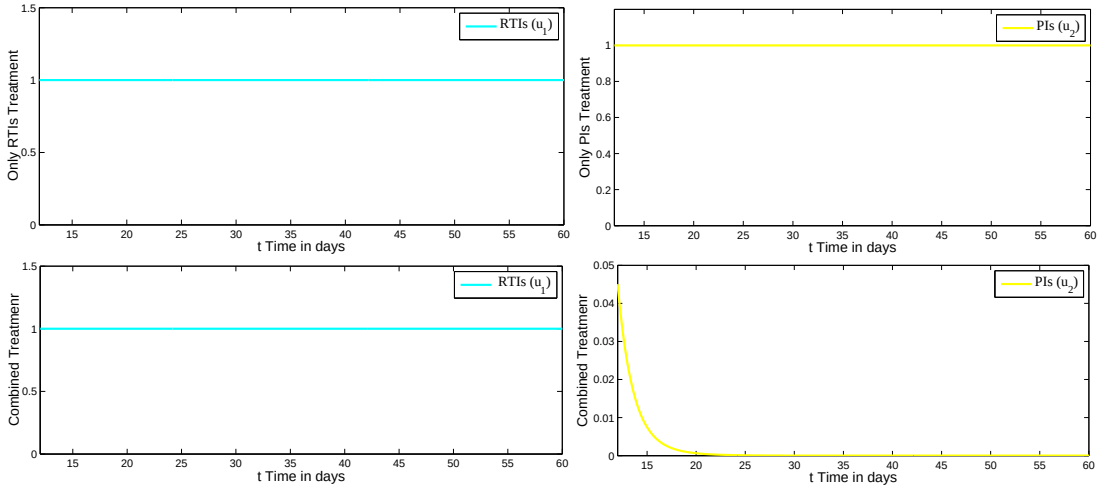


Figure. 5.8. Optimal drug profile during treatment.

For better understanding insight the treatment dynamics, we summarize the state variables at different time of the treatment in the following tables:

Regarding the question of optimizing treatment scheduling, i.e. which treatment should be given, whatever the stage of infection would be, the results from the table 5.3 to 5.5 are conclusive. More or less each strategy is efficient to increase T cell but in contest of decrease virus cell only PIs treatment clearly dominate to others. However, when comparing the objective function values in case of different

Table. 5.3. A summary of the cell populations at different moments of time administering only RTIs.

	Only RTIs			
Time	$T_R(t)$	$I_R(t)$	$L_R(t)$	$V_R(t)$
$t = 21$	9.5×10^5	213	127	3.5×10^5
$t = 45$	9.95×10^5	0.14	0.024	18159
$t = 60$	9.989×10^5	0.02	0.004	2824
$J(u^*)$	779554636			

Table. 5.4. A summary of the cell populations at different moments of time administering only PIs.

	Only PIs			
Time	$T_P(t)$	$I_P(t)$	$L_P(t)$	$V_P(t)$
$t = 21$	6.4×10^5	42311	7125	1.3×10^5
$t = 45$	9.1×10^5	3023	509	6913
$t = 60$	9.7×10^5	508	86	1075
$J(u^*)$	655996592			

treatment strategy following the infection (only RTIs, only PIs and combined therapy) we remark that the best result is obtained in the last situation.

Our simulations showed that earlier treatment with a better pharmacodynamic profile is always associated with more substantial suppression of the viral load and latently infected cells in the early stage of infection. So early antiretroviral therapy can prevents the explosive burst of viremia during with acute infection and thus may improve long-term health outcomes for acutely infected individuals and decrease the likelihood of viral transmission.

Table. 5.5. A summary of the cell populations at different moments of time during combined treatment strategy.

	Combined Therapy			
Time	$T_C(t)$	$I_C(t)$	$L_C(t)$	$V_C(t)$
$t = 21$	9.5×10^5	210	127	3.5×10^5
$t = 45$	9.95×10^5	0.0026	0.0019	17893
$t = 60$	9.99×10^5	2.52×10^{-6}	1.9×10^{-6}	2781
$J(u^*)$	779560365			

5.10 Conclusion

In this chapter, we presented a model for HIV infection where the patient is subjected to the combination therapy of RTIs and PIs. The controls represent the efficiency of drug treatment in inhibiting viral production and preventing new infections. We formulated an optimal control problem with the objective of maximize the benefit relied on T-cells count as well as minimize the systemic cost based on the percentage of chemotherapy. Existence for the optimal control pair is established and the Pontryagin's maximum principle is used to uniquely characterized these optimal controls. Our results show that the optimal treatment strategies reduce the viral load and increase the uninfected T-cell count, which improves the quality of life of the patient. The key finding is that the greatest effect of treatment does occur when it is initiated earliest. This optimal moment corresponds to the highest number of T cells.

Chapter 6

Conclusion and Future Works

In this study, we sought to learn more about HIV by introducing and analyzing mathematical models of immune system dynamics in the presence of anti-viral therapy. We began by developing and analyzing several models for HIV infection and, using data from HIV infected individuals, compared the models to determine which best fit the data for long time dynamics. We proved existence, uniqueness, positivity, and boundedness for the models and derived the conditions on basic reproduction number that guarantees the asymptotic stability of the equilibria. Both models determined that during primary infection the interaction between the cells plays a key role in characterizing HIV infection. The modified model, which included a latent compartment, maintained the greater basic reproduction number which suggests that the modified model was the best at capturing the long term dynamics and behavior of the infection. In addition to examining untreated systems, we also examined how treatment impacts the proliferation of HIV. In doing so, we used asymptotic stability analyses to define treatment thresholds in order to eliminate the virus and clear the infection. Additionally, we were able to estimate necessary drug efficacy of treatment for infected patients and apply optimal control theory to prove the existence of the optimal treatment solution. This would allow doctors to prescribe an optimal treatment for the patient in order to clear the virus while limiting the negative side effects associated with treatment therapies. Furthermore, our findings illustrate that combination therapy can provide the same level of effectiveness as individual treatments with much lower levels of toxicity. The values of the objective function at the optimal control shows that the greatest effects do occur when treatment is initiated earliest. Also,

results of the numerical simulations indicate that the rate of uninfected CD4$^+$T increased and virus population decreased due to treatment parameter.

Some of the possible future directions of this work are briefly outlined below.

1. In many literature [4], to make the production of T-cells desensity dependent, the logistic growth has been considered during the chronic infection of HIV. To trace out long term disease infectious from the beginning the proliferation rate of target T-cells can be considered to be a logistic growth function.

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda + rT(t)\left(1 - \dfrac{T(t)}{T_{max}}\right) - kT(t)V(t) - d_T T(t), \\ \dfrac{dI(t)}{dt} = (1-f)kT(t)V(t) - d_I I(t) + \alpha L(t), \\ \dfrac{dL(t)}{dt} = fkT(t)V(t) - d_L L(t) - \alpha L(t), \\ \dfrac{dV(t)}{dt} = Nd_I I(t) - d_V V(t). \end{cases}$$

2. Our mathematical descriptions have generally been limited to nonlinear ordinary differential equations describing the average behavior throughout the whole body under the assumption that the environment is well-mixed or spatially-homogeneous. Unfortunately, such an assumption is not valid during infection or at sites of viral entry [49]. So the propagation of Virus cells into the body not only depends on time but also to the space. Proposed spatial model:

$$\begin{cases} \dfrac{\partial T}{\partial t} = \lambda - kT(x,t)V(x,t) - d_T T(x,t), \\ \dfrac{\partial I}{\partial t} = (1-f)kT(x,t)V(x,t) - d_I I(x,t) + \alpha L(x,t), \\ \dfrac{\partial L}{\partial t} = fkT(x,t)V(x,t) - d_L L(x,t) - \alpha L(x,t), \\ \dfrac{\partial V}{\partial t} = q\Delta V(x,t) + Nd_I I(x,t) - d_V V(x,t). \end{cases}$$

   Here, $d > 0$ is the diffusion coefficients of virions with Δ being the Laplacian operator.

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