TREATMENT OF HIV-1 WITH REVERSE TRANSCRIPTASE INHIBITORS (RTI'S) AND PROTEASE INHIBITORS (PI'S)

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Abstract

Treatment with antiretroviral drugs has been reported to delay progression of HIV infection to AIDS, and may even lower the infectiousness of the infectives. This study investigates the effects of treatment of HIV-1 with Reverse Transcriptase Inhibitors (RTI's) and Protease Inhibitors (PI's) at cellular level. A threshold parameter, N_{crit}, which determines the outcome of the infection is established. If $N_T < N_{crit}$, the infection dies out, while if $N_{crit} < N_T$, the infection persists where N_T is the number of virions produced by each infected $CD4^+ - T$ cell. The steady states are determined for the models under study. Numerical simulations are presented to illustrate the stability of the endemic steady states.

Declaration

No portion of the work in this thesis has been submitted for another degree or qualification of this or any other university or another institution of learning.

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DEDICATION

This work is dedicated to my father (Makidani Chirove), my mother (Mogina Chirove) and the other family members: Stellah, Enock, Tinashe, Ellah, Tapiwanashe, Tariro, Ngonidzashe, Raviro, and our beloved last born Kudzaishe for their unwavering support throughout my studies. I am proud of you.

Chapter 1

INTRODUCTION AND STATEMENT OF THE PROBLEM

1.1 General overview

We want to show, in this thesis, that mathematical models can be used to describe how therapy can help in lowering the load of the Human Immunodeficiency virus type 1 (HIV-1). This research will concentrate on the immunology of HIV/AIDS (Acquired Immunodeficiency Syndrome). Models describing the scenario are set in terms of systems of nonlinear ordinary differential equations and are analyzed for existence and stability of steady states solutions. The evolution of the disease is also analyzed numerically in order to give the projections and direction of treatment.

1.2 Research overview

AIDS is a disease caused by HIV. It is spread primarily through three routes namely: sexual intercourse, vertically (from mother to child) and intravenously [8]. Its effects are more confined to the human defence system, that is, the immunity of the human body. At the moment, AIDS as a disease cannot be cured. Hence, it remains to use control strategies such as, the use of Reverse Transcriptase inhibitors (RTI's), and Protease Inhibitors (PI's) to slow down the development of the disease within an individual and hopefully lower the infectivity of an individual [12].

A model is developed to describe the effects of RTI's in trying to reduce the impact of HIV-1 in an infected individual. Another model which incorporate the combined effects of RTI's and PI's is developed. We can measure the effects of these drugs on the number of virions produced by productively infected $CD4^+ - T$ cells, through the parameter N_T, which gives the number of virions being produced from each dying infected $CD4^+ - T$ cell. In analyzing the mathematical models, a threshold parameter, N_{crit}, is calculated across which there can be exchange of stability of the steady states. Specifically, N_{crit}, determines whether the disease will establish itself, that is, for $N_T > N_{crit}$ or whether it will fail to establish itself for $N_T < N_{crit}$.

The main aims of my thesis are :

1. To investigate the effects of RTI's on the transcription process of HIV-1.

2. To investigate the effects of the combined use of RTI's and PI's on HIV-1 infection.

3. To make recommendations towards policy formulations.

To achieve these aims, we make use of three different models and show analytic and numerical results for two of the models where treatment is administered. The computer package used is MATLAB.

1.3 Thesis Outline

This work is divided into four chapters. The first chapter is the introduction to immunology and statement of the problem, Chapter 2 looks at the review of a modified basic model without treatment by Culshaw and Ruan in [5], Chapter 3 is also a review of model by Perelson and Callaway [1] with treatment using RTI's, Chapter 4 is the main problem of this thesis which has a model with combined therapy using RTI's and PI's. The last section of this work has got the discussions and conclusions on all the models delt with followed by the references used thereof.

1.4 Motivation

The HIV/AIDS pandemic has reached epidemic proportions in most developing countries. Forty-two (42) million individuals are living with HIV/AIDS of which 29 million are Africans [11]. The rate of infection in most developing countries is very high and going up that rigorous intervention programmes are required to slow down the rate of infection. Intervention can be in two forms, namely vaccination and treatment with antiretroviral drugs. Vaccination, in the long run, would help eradicate the epidemic but there is no vaccine (a weaker version of the pathogen which elicit a primary immune response) for HIV/AIDS. However, there are candidate vaccines which are currently on trial to determine their efficacy. As a result treatment remains the most effective control strategy at the moment.

1.5 HIV and the Immune System

Lymphocytes are a type of white blood cells which are a key component of the immune system. They enable the body to produce antibodies against different types of foreign agencies (antigens) that may invade the body. It is the introduction of a foreign body into the body that stimulates an immune response to remove the object as quickly as possible. The immune system remembers and a second exposure to a foreign substance produces a more rapid and greater response [3].

The are two types of immunity, namely: Humoral immunity and Cellular immunity. Macrophages are the cells that look for foreign agencies in the body. They scavenge, engulf and examine the antigen directly. They then present their findings to the $CD4$ positive T lymphocytes ($CD4^+ - T$ cells). A type of lymphocytes called B is activated to produce antibodies into the general circulation to directly kill the antigen. On the other hand cellular immune response constitutes the major defence against infection due to viruses, fungi and a few bacteria. Lymphocytes precursors come from borne marrow and those that populate the $Thymus$ become transformed by the environment in this organ into lymphocytes responsible for cellular immunity (T lymphocytes).

$CD4^+ - T$ cells (Helper T cells) have a glycoprotein $CD4$ on their surface hence their name. They form the command center for the immune system. If an immune response is necessary, they enhance a primary immune response where they reproduce to elicit both humoral and cellular immunity. They activate the $CD8^+ - T$ cells (effector cells or killer T cells or cytotoxic cells). These have got a glycoprotein $CD8$ and hence their name. Once given a target, they seek out

and destroy cells infected with antigens and other foreign cells. If an immune response is successful, certain cells of each type retain the knowledge of the attack. These cells referred to as memory cells from B and T cells are readily converted to killer cells by a later encounter with the same or closely related antigen [2]. HIV, like any other viruses has no ability to reproduce independently and so it relies on a host to aid reproduction. HIV wreaks the most havoc on $CD4^+ - T$ cells by causing their destruction and decline, and decrease the body's ability to fight against infection. When it infects the body, it targets $CD4^+ - T$ cells receptors. A glycoprotein ($gp120$) on the surface of the HIV virion has a high affinity for the $CD4$ protein on the surface of the $CD4^+ - T$ cells. The receptors from the virions lock to those of the cell. The virus receptors then pull back and force a contact with the cell membrane of the host cell. Binding takes place and the virus penetrates the cell membrane [2].

Most viruses carry copies of their DNA and insert this into the host cell's DNA. HIV is a special type of retrovirus meaning that it stores its genetic information as RNA rather than DNA. Single stranded RNA (ssRNA) is transcribed into single stranded DNA (ssDNA) by the enzyme called reverse transcriptase. A second strand of DNA is synthesized to form double stranded DNA. New virus particles bud off from the surface of the host cell. This is the major difference between HIV and other viruses. HIV has four stages of progression. The first stage is the initial inoculation where the virus is introduced into the body, the second stage is the initial transient which is a relatively short period of time when both T-cell population and virus population are in great flux, the third stage is the clinical latency which is the period of time when there are extremely large numbers of virus and T cells undergoing incredible dynamics the result of which is an appearance of latency (disease steady state), and the fourth stage, the AIDS stage

when T cells will drop to very low numbers and the virus growing without bound resulting in death [2].

There are two main forms of HIV, HIV-1, and HIV-2. HIV-1 was discovered by Luc Montagnier and his associates at the Institute of Pasteur in Paris 1983. HIV-2 was first identified among patients in Cameroon in 1985. It is less virulent and does not result in full blown AIDS though it is fatal. It is $HIV-1$ which is of particular importance in this thesis and we refer to it as simply HIV for the sake of simplicity.

1.6 Statement of the problem

So many models have been developed to model the immunology of HIV. These models have been used to explain different phenomena.

In [2], Kirschner looked at a basic three stage HIV model which he modified to include treatment, time delay and to be age dependant. He established, using computer simulations, that $CD4^{+}-T$ cell count is higher overally when treatment is initiated at a later stage and chemotherapy administration does not affect the overall outcome of treatment.

In [5], Culshaw and Ruan considered a threee stage model on HIV immunology and also carried out computer simulations after introducing time delay. Their results showed that the introduction of time delay on drug efficacy only produced transient oscillations and does not disturb the stability of the endemic steady state.

In [1], Perelson and Callaway considered various models on HIV/AIDS including the one where there was administration of RTI's monotherapy. They established

that there is a linear relationship between the strength of the drug and the viral load which is more appropriate for HIV modelling during RTI's monotherapy. It is this model that we modify to study the combined effects of RTI's and PI's on the infectiousness of HIV.

Chapter 2

A MODEL WITHOUT TREATMENT

2.1 Introduction

In this chapter a model for HIV is considered when there is no treatment. We begin by presenting a three-stage model in [5]. Culshaw and Ruan looked at a model with time delay. In this model we modify their model to ignore the time delay part. We therefore concentrate on the rates of change of the populations of $CD4^+ - T$ cells susceptible to infection (T), Infected $CD4^+ - T$ cells (I) and the free virus population (V) as follows:

2.2 Model formulation

2.2.1 Susceptible $CD4^+ - T$ cells (T)

All uninfected $CD4^+ - T$ cells which proliferate at a rate λ per unit time are assumed to be susceptible. The susceptible population is diminished by natural

death (at a rate d) and by infection following contact with the virus (with probability k). The nonlinear ordinary differential equation describing the dynamics of the susceptible $CD4^+ - T$ cells is given by

$$\dot{T} = \lambda - dT - kVT,$$

where the force of infection kVT is the rate of infection for a susceptible T cell with a viral particle within the body of an individual. This also measures the incidence of infection.

2.2.2 Infected $CD4^+ - T$ cells (I)

This population increase through progression to infected cells of susceptible $CD4^+ - T$ cells. They are cleared by a blanket death (those that burst into virions and those that die naturally) at a rate δ. This gives

$$\dot{I} = kVT - \delta I.$$

2.2.3 Virus cells (V)

These proliferate through progression to virus cells of virions from bursting infected cells (by a rate $N_T\delta$). They diminish at a constant death rate c. This gives

$$\dot{V} = N_T\delta I - cV,$$

where N_T is the number of virions produced by each infected dying $CD4^+ - T$ cell.

In summary, we have the model given by the nonlinear system of ordinary differential equations. The model describing the scenario is

$$\begin{aligned} \dot{T} &= \lambda - dT - kVT, \\ \dot{I} &= kVT - \delta I, \\ \dot{V} &= N_T \delta I - cV. \end{aligned} \tag{2.1}$$

2.3 Finding the equilibrium points

The equilibrium solutions can be obtained from equating the right hand side of (2.1) to zero, that is,

$$\lambda - dT^* - kV^*T^* = 0, \tag{2.2}$$

$$kV^*T^* - \delta I^* = 0, \tag{2.3}$$

$$N_T \delta I^* - cV^* = 0. \tag{2.4}$$

The disease free steady state is obtained when $V^* = I^* = 0$. This gives $E_o = (\frac{\lambda}{d}, 0, 0)$. The disease free steady state exists for all values of $N_T > 0$. The endemic steady state is obtained as follows: From (2.3)

$$V^*T^* = \frac{\delta}{k} I^*, \tag{2.5}$$

then multiplying (2.4) by T^*, we obtain

$$\begin{aligned} N_T \delta I^* T^* - cV^*T^* &= 0, \\ N_T \delta I^* T^* - \frac{c\delta}{k} I^* &= 0, \\ (N_T \delta T^* - \frac{c\delta}{k}) I^* &= 0. \end{aligned}$$

This gives

$$T^* = \frac{c}{kN_T}, \tag{2.6}$$

substituting (2.6) into (2.2), we obtain

$$\begin{aligned}
\lambda - \frac{cd}{kN_T} - \frac{c}{N_T}V^* &= 0, \\
V^* &= \frac{\lambda N_T}{c} - \frac{d}{k}, \\
&= \frac{\lambda}{c}(N_T - \frac{cd}{k\lambda}), \\
&= \frac{\lambda}{c}(N_T - N_{crit}).
\end{aligned}$$

where

$$\begin{aligned}
N_{crit} &= \frac{cd}{k\lambda}, \\
I^* &= \frac{\lambda}{\delta N_T}(N_T - N_{crit}).
\end{aligned}$$

The endemic steady state is given by

$$\overline{E} = \left(\frac{c}{kN_T}, \frac{\lambda}{\delta N_T}(N_T - N_{crit}), \frac{\lambda}{c}(N_T - N_{crit})\right).$$

We therefore, have the following theorem

Theorem 1 *The endemic steady state exists if and only if* $N_{crit} < N_T$.

2.4 Stability analysis for the disease-free steady state

Let

$$y_1 = T - \frac{\lambda}{d}, y_2 = I, y_3 = V,$$

$$\dot{y_1} = \dot{T}, \dot{y_2} = \dot{I}, \dot{y_3} = \dot{V},$$

then substituting these into the system (2.1) we obtain

$$\begin{aligned}
\dot{y_1} &= -dy_1 - \frac{k\lambda}{d}y_3 - ky_3y_1, \\
\dot{y_2} &= -\delta y_2 + \frac{k\lambda}{d}y_3 + ky_3y_1, \\
\dot{y_3} &= N_T\delta y_2 - cy_3.
\end{aligned}$$

We extract the linearized system to get

$$\begin{pmatrix} \dot{y_1} \\ \dot{y_2} \\ \dot{y_3} \end{pmatrix} = \begin{pmatrix} -d & 0 & -\frac{k\lambda}{d} \\ 0 & -\delta & \frac{k\lambda}{d} \\ 0 & N_T\delta & -c \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix},$$

which is of the form $\dot{Y} = AY$, where $\dot{Y} = (\dot{y_1}, \dot{y_2}, \dot{y_3})^T$ and $y = (y_1, y_2, y_3)^T$.

We find the eigenvalues, β, of the Jacobian, A, of the linearized system by considering $det(A - \beta I) = 0$ as follows

$$\begin{vmatrix} -d-\beta & 0 & -\frac{k\lambda}{d} \\ 0 & -\delta-\beta & \frac{k\lambda}{d} \\ 0 & N_T\delta & -c-\beta \end{vmatrix} = 0$$

$$-(d+\beta)[(\delta+\beta)(c+\beta) - \frac{kN_T\delta\lambda}{d}] \;=\; 0.$$

We observe that the eigenvalues are $\beta = -d$ and the solutions of the quadratic expression $\beta^2 + (\delta + c)\beta + \delta c\left(1 - \frac{N_T}{N_{crit}}\right) = 0$. Then the eigenvalues are

$$\beta_1 = -d$$

$$\beta_{2,3} = -\frac{\delta + c}{2} \pm \sqrt{\left(\frac{\delta + c}{2}\right)^2 - \delta c\left(1 - \frac{N_T}{N_{crit}}\right)}$$

If $N_T < N_{crit}$ then all the eigenvalues are negative and we thus have the following theorem

Theorem 2 *The disease free steady state is stable for $N_T < N_{crit}$ and is unstable for $N_T > N_{crit}$.*

2.5 Stability analysis for the endemic steady state

To establish the stability of the endemic steady state we linearize the system (2.1) about $\overline{E}$.

Let

$$y_1 = T - \frac{c}{kN_T}, y_2 = I - \frac{\lambda}{\delta}\left(1 - \frac{N_T}{N_{crit}}\right), y_3 = V - \frac{\lambda}{c}(N_T - N_{crit}),$$

$$\dot{y_1} = \dot{T}, \dot{y_2} = \dot{I}, \dot{y_3} = \dot{V}.$$

On substituting this into the system (2.1) we obtain the following nonlinear system

$$\begin{aligned}
\dot{y_1} &= -(d + \frac{k\lambda}{c}(N_T - N_{crit}))y_1 - \frac{c}{N_T}y_3 - ky_1y_3, \\
\dot{y_2} &= \frac{k\lambda}{c}(N_T - N_{crit})y_1 - \delta y_2 + \frac{c}{N_T}y_3 + ky_1y_3, \\
\dot{y_3} &= N_T\delta y_2 - cy_3.
\end{aligned}$$

The associated linear system is given by

$$\begin{pmatrix} \dot{y_1} \\ \dot{y_2} \\ \dot{y_3} \end{pmatrix} = \begin{pmatrix} -(d + \frac{k\lambda}{c}(N_T - N_{crit})) & 0 & -\frac{c}{N_T} \\ \frac{k\lambda}{c}(N_T - N_{crit}) & -\delta & \frac{c}{N_T} \\ 0 & N_T\delta & -c \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}.$$

We Find the eigenvalues, β, of the linearized system by considering the determinant.

$$\begin{vmatrix} -e_1 - \beta & 0 & -\frac{c}{N_T} \\ e_2 & -\delta - \beta & \frac{c}{N_T} \\ 0 & N_T\delta & -c - \beta \end{vmatrix} = 0,$$

where $e_1 = d + \frac{k\lambda}{c}(N_T - N_{crit}), e_2 = \frac{k\lambda}{c}(N_T - N_{crit})$.

$$-(e_1 + \beta)\begin{vmatrix} -(\delta + \beta) & \frac{c}{N_T} \\ N_T\delta & -(c + \beta) \end{vmatrix} + \frac{c}{N_T}\begin{vmatrix} e_2 & -(\delta + \beta) \\ 0 & N_T\delta \end{vmatrix} = 0,$$

$$\begin{aligned}
-(e_1 + \beta)[(\delta + \beta)(c + \beta) - \delta c] + \delta c e_2 &= 0, \\
\beta^3 + (e_1 + (\delta + c))\beta^2 + e_1(\delta + c)\beta - \delta c e_2 &= 0, \\
\beta^3 + A\beta^2 + B\beta - C &= 0,
\end{aligned}$$

where $A = e_1 + \delta + c, B = e_1(\delta + c), C = \delta c e_2$,

$$\begin{aligned} A &= d + \delta + c + \frac{k\lambda}{c}[N_T - N_{crit}], \\ B &= \frac{k\lambda}{c}(\delta + c)[N_T - N_{crit}], \\ C &= k\delta\lambda[N_T - N_{crit}]. \end{aligned}$$

Applying the Routh-Hurwitz conditions we observe that A, B, C are positive if and only if $N_T > N_{crit}$ and

$$\begin{aligned} AB - C &= (\delta + c)(e_1 + \delta + c)e_1 - \delta e_2, \\ &= (\delta + c)e_1^2 + (\delta + c)^2 e_1 - \delta e_2, \\ &= (\delta + c)e_1^2 + (\delta^2 + c^2)e_1 + \delta c(2e_1 - e_2), \\ &= (\delta + c)e_1^2 + (\delta^2 + c^2)e_1 + \delta c(2d + e_2), \\ &> 0. \end{aligned}$$

It follows that all the eigenvalues of the system have negative real parts. We can summarize the results as follows:

Theorem 3 *The endemic steady state* $\overline{E}$ *is asymptotically stable if* $N_T > N_{crit}$

Chapter 3

THE MODEL WITH RTI's TREATMENT

3.1 Introduction

Reverse Transcriptase Inhibitors (RTI's) prevent HIV-1 from infecting $CD4^+ - T$ cells by hindering the reverse transcription of HIV-1 RNA into DNA. The most effective way of modelling RTI's is to consider the effect of the drug at cellular level. Uninfected $CD4^+ - T$ cells are grouped into those which do and do not respond to the drug. The effects of the drug is measured by the rate at which target cells are transferred to a pool of infection resistant cells and by the amount the viral infectivity is reduced in the pool of infection resistant cells [1].

3.2 Model formulation

We present a four-stage model in [1]. The model shows the rate of change of the populations of $CD4^+ - T$ cells susceptible to infection (T), $CD4^+ - T$ cells containing active drugs with susceptibility to infection (T_d), Infected $CD4^+ - T$ (I) cells and the free virus population (V) as follows:

3.2.1 Susceptible $CD4^+ - T$ cells (T)

All uninfected $CD4^+ - T$ cells which proliferate at a rate λ per unit time are assumed to be susceptible. The susceptible population is diminished by natural death (at a rate d) and by infection following contact with the virus (with probability k). Upon treatment they are moved to a class of T_d cells (at a rate r). The nonlinear ordinary differential equation describing the dynamics of the T cells is given by:

$$\dot{T} = \lambda - dT - kVT - rT,$$

where the force of infection kVT is the rate of infection for a susceptible T cells with a viral particle within the body of an individual. This also measures the incidence of infection.

3.2.2 $CD4^+ - T$ cells containing active drug with susceptibility to infection (T_d)

This population increases through resistance by T cells to infection (at a rate r) when treatment has been applied. It diminishes by natural death (at a rate d) and by infection through contact with the virus (with probability $k(1 - \epsilon_{RT})$). This gives:

$$\dot{T}_d = rT - dT_d - (1 - \epsilon_{RT})kVT_d,$$

where ϵ_{RT} denotes the drug efficacy and $1 - \epsilon_{RT}$ denotes the proportion of T_d cells susceptible to infection. The force of infection $k(1 - \epsilon_{RT})VT_d$ is the rate of infection for a susceptible T_d cell with a virus. We note that when the drug is perfect, that is $\epsilon_{RT} = 1$, no T_d cells are infected and when the drug is ineffective, that is $\epsilon_{RT} = 0$, all T_d cells are infected because they have no protection.

3.2.3 Infected $CD4^+ - T$ cells (I)

This population increase through progression to infected cells of susceptible $CD4^+ - T$ cells and susceptible $CD4^+ - T$ cells with active drug. They are cleared (by bursting and natural death) at a rate δ. This gives:

$$\dot{I} = kV(T + (1 - \epsilon_{RT})T_d) - \delta I.$$

If the drug is perfect, then the gain to this population is through the infection of unprotected T cells only.

3.2.4 Virus cells (V)

These proliferate through progression to virus cells of virions from bursting infected cells (by a rate $N_T\delta$). They diminish at a constant death rate c. This gives:

$$\dot{V} = N_T\delta I - cV,$$

where N_T is the number of virions produced by each productively infected cell.

In summary, we have the model given by the nonlinear system of differential equations. The model describing the scenario is

$$\begin{aligned} \dot{T} &= \lambda - dT - kVT - rT, \\ \dot{T}_d &= rT - dT_d - (1-\epsilon_{RT})kVT_d, \\ \dot{I} &= kV(T + (1-\epsilon_{RT})T_d) - \delta I, \\ \dot{V} &= N_T\delta I - cV. \end{aligned} \tag{3.1}$$

3.3 Finding the disease free steady state

The disease free steady state is obtained when $V^* = I^* = 0$ and is given by

$$E_o = (T_o, T_{d_o}, I_o, V_o) = (\frac{\lambda}{d+r}, \frac{r\lambda}{d(d+r)}, 0, 0).$$

3.4 Determining the Basic reproduction number

The most fundamental quantity of any model of pathogen dynamics is the Basic reproduction number, R_o, which quantifies replicative capacity of HIV [14]. We proceed using the method in [13]. The distinction between the infected and uninfected compartments plays a vital role in the definition and calculation of R_o of the model. For this reason, the definition and calculation of R_o of the model is not inferred from the structure of the model alone but also from the distinction between infective compartments and uninfected compartments in the cell compartments. We sort the compartments of infected and uninfected cells. The first m compartments should correspond to infected cells and the rest to

uninfected cells. We then define $\mathcal{F}_i$ as the rate of appearance of new infections in compartment i, $\mathcal{V}^-{}_i$ as the rate of transfer of cells out of compartment i, $\mathcal{V}^+{}_i$ as the rate of transfer of cells into compartment i. We also define matrices $\mathcal{F}$=$\mathcal{F}_i$, $\mathcal{V}$=$\mathcal{V}^-{}_i - \mathcal{V}^+{}_i$ and the model is then defined as $\dot{u} = \mathcal{F} - \mathcal{V}$

$$D(\mathcal{F}(E_o)) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, D(\mathcal{V}(E_o)) = \begin{pmatrix} V & 0 \\ P & Q \end{pmatrix}$$

where the matrices F and P are nonnegative, matrix Q has eigenvalues with positive real part, and V is a nonsingular M-matrix. We then define the next generation matrix as FV^{-1}. The dorminant eigenvalue of FV^{-1} gives R_o [13].

3.5 The sorted system

$$\begin{aligned} \dot{I} &= kV(T + (1-\epsilon_{RT})T_d) - \delta I, \\ \dot{V} &= N_T \delta I - cV, \\ \dot{T} &= \lambda - dT - kVT - rT, \\ \dot{T}_d &= rT - dT_d - (1-\epsilon_{RT})kVT_d. \end{aligned}$$

$$\mathcal{F} = \begin{pmatrix} kV(T + (1-\epsilon_{RT})T_d) \\ 0 \\ 0 \\ 0 \end{pmatrix}, \mathcal{V}^-{}_i = \begin{pmatrix} \delta I \\ cV \\ (d + kV + r)T \\ (d + k(1-\epsilon_{RT}))T_d \end{pmatrix}, \mathcal{V}^+{}_i = \begin{pmatrix} 0 \\ N_T \delta I \\ \lambda \\ rT \end{pmatrix}$$

$$\mathcal{V} = \begin{pmatrix} \delta I \\ cV - N_T \delta I \\ (d + kV + r)T - \lambda \\ (d + k(1 - \epsilon_{RT}))T_d - rT \end{pmatrix}, \mathcal{D}(\mathcal{F}) = \begin{pmatrix} 0 & k(T + (1 - \epsilon_{RT})T_d) & kV & k(1 - \epsilon_{RT})V \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$D(\mathcal{F}(E_o)) = \begin{pmatrix} 0 & \frac{k\lambda(d+r(1-\epsilon_{RT}))}{d(d+r)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$D(\mathcal{V}) = \begin{pmatrix} \delta & 0 & 0 & 0 \\ -N_T \delta & c & 0 & 0 \\ 0 & kT & d + kV + r & 0 \\ 0 & k(1 - \epsilon_{RT})T_d & -r & d + k(1 - \epsilon_{RT})V \end{pmatrix}$$

$$D(\mathcal{V}(E_o)) = \begin{pmatrix} \delta & 0 & 0 & 0 \\ -N_T \delta & c & 0 & 0 \\ 0 & \frac{k\lambda}{d+r} & d + r & 0 \\ 0 & \frac{kr\lambda(1-\epsilon_{RT})}{d(d+r)} & -r & d \end{pmatrix}, F = \begin{pmatrix} 0 & \frac{kr\lambda(1-\epsilon_{RT})}{d(d+r)} \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \delta & 0 \\ -N_T \delta & c \end{pmatrix}$$

$$P = \begin{pmatrix} 0 & \frac{k\lambda}{d+r} \\ 0 & \frac{kr\lambda(1-\epsilon_{RT})}{d(d+r)} \end{pmatrix}, Q = \begin{pmatrix} d + r & 0 \\ -r & d \end{pmatrix}, V^{-1} = \begin{pmatrix} \frac{1}{\delta} & 0 \\ \frac{N_T}{c} & \frac{1}{c} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} 0 & \frac{kr\lambda(1-\epsilon_{RT})}{d(d+r)} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\delta} & 0 \\ \frac{N_T}{c} & \frac{1}{c} \end{pmatrix} = \begin{pmatrix} \frac{k\lambda(d+r(1-\epsilon_{RT}))N_T}{cd(d+r)} & \frac{k\lambda(d+r(1-\epsilon_{RT}))}{cd(d+r)} \\ 0 & 0 \end{pmatrix}$$

let

$$b_0 = \frac{k\lambda(d + r(1 - \epsilon_{RT}))N_T}{cd(d + r)}$$

We proceed to find the eigenvalues, β, of FV^{-1}.

$$\begin{vmatrix} b_o - \beta & N_T b_o \\ 0 & -\beta \end{vmatrix} = 0$$

$$\beta = 0 \quad \text{or} \quad \beta = \mathrm{b_o}$$

$$R_o = \frac{k\lambda(d + r(1 - \epsilon_{RT}))N_T}{cd(d + r)}$$

All that is required of an infection to go into decline is that each case should generate, on average less than one case over the course of its infectious period. The critical treatment proportion that will achieve eradication, N_{crit}, is that for which the Basic reproduction number, R_o, under treatment to just equal to 1.

$$N_{crit} = \frac{cd(d + r)}{k\lambda(d + r(1 - \epsilon_{RT}))}$$

3.6 Finding the endemic steady state

To find the endemic steady state (that is solutions as $t \to \infty$) we equate the right hand side of the system 3.1 to zero as follows

$$\lambda - dT^* - kV^*T^* - rT^* = 0, \quad (3.2)$$

$$rT^* - dT_d^* - (1-\epsilon_{RT})kV^*T_d^* = 0, \quad (3.3)$$

$$kV^*(T^* + (1-\epsilon_{RT})T_d^*) - \delta I^* = 0, \quad (3.4)$$

$$N_T\delta I^* - cV^* = 0. \quad (3.5)$$

The infected steady state in terms of N_{crit} is given by

$$\overline{E} = (\overline{T}, \overline{T_d}, \overline{I}, \overline{V}),$$

where

$$\overline{T} = \frac{cd + ck(1-\epsilon_{RT})[-\frac{1}{2}a_o + \sqrt{(\frac{a_o}{2})^2 - \frac{d(d+r)}{k^2(1-\epsilon_{RT})}[1-\frac{N_T}{N_{crit}}]}]}{kN_T(d+r(1-\epsilon_{RT})) + k^2N_T(1-\epsilon_{RT})[-\frac{1}{2}a_o + \sqrt{(\frac{a_o}{2})^2 - \frac{d(d+r)}{k^2(1-\epsilon_{RT})}[1-\frac{N_T}{N_{crit}}]}]},$$

$$\overline{T_d} = \frac{rc}{kN_T(d+r(1-\epsilon_{RT})) + k^2N_T(1-\epsilon_{RT})[-\frac{1}{2}a_o + \sqrt{(\frac{a_o}{2})^2 - \frac{d(d+r)}{k^2(1-\epsilon_{RT})}[1-\frac{N_T}{N_{crit}}]}]},$$

$$\overline{I} = \frac{C}{N_T\delta}[-\frac{1}{2}a_o + \sqrt{(\frac{a_o}{2})^2 - \frac{d(d+r)}{k^2(1-\epsilon_{RT})}[1-\frac{N_T}{N_{crit}}]}],$$

$$\overline{V} = \frac{1}{2}a_o + \sqrt{(\frac{a_o}{2})^2 - \frac{d(d+r)}{k^2(1-\epsilon_{RT})}[1-\frac{N_T}{N_{crit}}]},$$

where

$$a_o = \frac{d + (d+r)(1-\epsilon_{RT})[1 - \frac{dN_T}{(d+r(1-\epsilon_{RT}))N_{crit}}]}{k(1-\epsilon_{RT})}.$$

$\overline{V}$ exists if and only if $1 - \frac{N_T}{N_{crit}} < 0$, that is, $N_{crit} < N_T$. The infected steady state does not exist below N_{crit}. It follows that the infected steady-state exists if $N_{crit} < N_T$.

3.7 Stability analysis of the disease free steady state

The partitioning of the Jacobian of the model into infected and uninfected compartments enables us to determine the eigenvalues of the compartments. The eigenvalues of $-Q$ are negative by the definition of the matrix Q, hence the stability of the disease free steady state can be determined from the eigenvalues, β, of the matrix $A = F - V$ [13].

$$A = \begin{pmatrix} -\delta & \frac{k\lambda(d+r(1-\epsilon_{RT}))}{d(d+r)} \\ N_T\delta & -c \end{pmatrix},$$

$$|A - \beta I| = \begin{vmatrix} -\delta-\beta & \frac{k\lambda(d+r(1-\epsilon_{RT}))}{d(d+r)} \\ N_T\delta & -c-\beta \end{vmatrix} = 0$$

$$\begin{aligned} \beta^2 + (\delta+c)\beta + \delta c - \frac{\delta k\lambda}{d(d+r)}(d+r(1-\epsilon_{RT}))N_T &= 0 \\ \beta^2 + (\delta+c)\beta + \delta c(1-\frac{N_T}{N_{crit}}) &= 0 \end{aligned}$$

$$\beta_{1,2} = -\frac{1}{2}(\delta+c) \pm \sqrt{(\frac{\delta+c}{2})^2 - \delta c(1-\frac{N_T}{N_{crit}})}$$

The disease free state is stable if $1 > \frac{N_T}{N_{crit}}$, that is, $N_T < N_{crit}$

We can summarize the results as follows:

Theorem 4 *1. The disease free steady state exists for all values of N_T*

2. *The disease free steady state is stable for $N_T < N_{crit}$ and is unstable for $N_T > N_{crit}$*

3. *The endemic steady state exist and is stable for $N_T > N_{crit}$*

Remark 1 *The proof for the stability of the infected steady state is so tedious that the details are omitted here. We can illustrate these details numerically as shown in the next section.*

3.8 Tables

The variables and parameters used in the model are defined in the table below. The values for rates and constants are adopted from [5], [2] and [10]

Table 3.1: Variables and parameters for viral spread

Dependant Variables		
T	Uninfected $CD4^+ - T$ cell population	$2000mm^{-3}$
T_d	$CD4^+ - T$ cell population with active drug	0
I	Infected $CD4^+ - T$ cell population	0
V	Infectious HIV population	$1.0 \times 10^{-3}mm$
Parameters and constants		
λ	Source of new $CD4^+ - T$ cells	$10(dy)^{-1}(mm^{-3})$
d	Death rate of uninfected $CD4^+ - T$ cell population	$0.02dy^{-1}$
r	Rate at which $CD4^+ - T$ cell acquire active drug	0.003
k	Rate of infection of $CD4^+ - T$ cells	$2.4 \times 10^{-5}mm^3dy^{-1}$
δ	Blanket death rate of Infected $CD4^+ - T$ cells	$0.24dy^{-1}$
N_T	Number of virions produced by infected cells	500
c	Death rate of free virus	$2.4dy^{-1}$
ϵ_{RT}	Drug efficacy for $RTI's$	$0 \leq \epsilon_{RT} \leq 1$
ϵ_{PI}	Drug efficacy for $PI's$	$0 \leq \epsilon_{PI} \leq 1$

3.9 Numerical results for stability analysis of the endemic steady state

Figure 3.1, shows the dynamics of the endemic steady state. All the graphs for the different classes are characterized by initial transients followed by the levelling off of the curves with time. This shows with the administration of RTI's as an intervention strategy, the infection will persist whenever $N_{crit} < N_T$. Thus the graphs shows that the endemic steady state is asymptotically stable in this region.

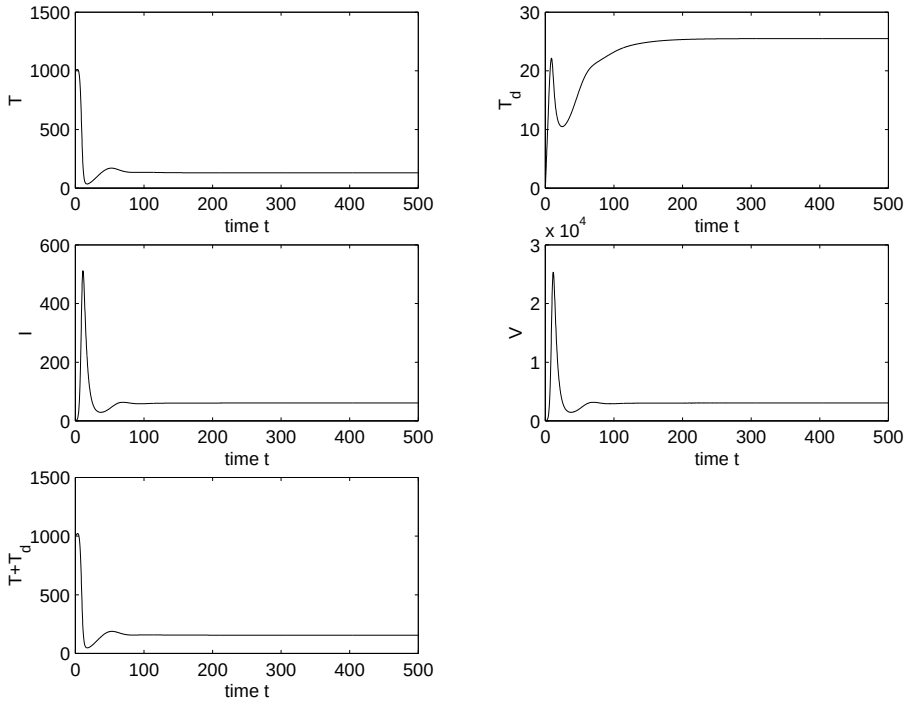

Figure 3.1: The model with RTI's treatment $N = 500, \epsilon_{RT} = 0.8$. The other parameters are given in Table 3.1

Chapter 4

THE MODEL WITH BOTH RTI'S AND PI'S THERAPY

4.1 Introduction

Protease inhibitors (PI's) pose their effects on infected $CD4^+ - T$ cells by inhibiting their lytic death and rendering those that are produced non-infectious. The previous Four-stage model considered the monotherapy with RTI's. We modify this model by introducing another type of drug, PI's. In the end we want to establish how far the two drugs can be effective in reducing the infectiousness of HIV. We also take into consideration that when a virus binds to an uninfected $CD4^+ - T$ cell, the result is an infected $CD4^+ - T$ cell. Thus we lose an uninfected $CD4^+ - T$ cell and a virus. This will further change the dynamics of the free virus population as follows

$$\dot{V} = N_T(1 - \epsilon_{PI})\delta I - cV - kVT,$$

where ϵ_{PI} is the drug efficacy of PI's and the new loss term becomes $(c + kT)V$. We note that when the drug, PI's, is perfect, that is $\epsilon_{PI} = 1$, then the virus

population will never multiply and those that are available will be left to die. When the drug is ineffective then we experience the same situation as in the previous model. In summary, the inclusion of RTI's and PI's together improves the model for better results and the dynamics of the system is given below as:

$$\begin{aligned}
\dot{T} &= \lambda - dT - kVT - rT, \\
\dot{T}_d &= rT - dT_d - (1-\epsilon_{RT})kVT_d, \\
\dot{I} &= kV(T + (1-\epsilon_{RT})T_d) - \delta I, \\
\dot{V} &= N_T(1-\epsilon_{PI})\delta I - cV - kVT.
\end{aligned}$$

4.2 Equilibrium points

To find the equilibrium points we equate the right hand side of the model to zero as follows:

$$\lambda - dT^* - kV^*T^* - rT^* = 0, \tag{4.1}$$

$$rT^* - dT_d^* - (1-\epsilon_{RT})kV^*T_d^* = 0, \tag{4.2}$$

$$kV^*(T^* + (1-\epsilon_{RT})T_d^*) - \delta I^* = 0, \tag{4.3}$$

$$N_T(1-\epsilon_{PI})\delta I^* - cV^* - kV^*T^* = 0. \tag{4.4}$$

From (4.4) we obtain

$$I^* = \frac{c + kT_o}{N_T(1-\epsilon_{PI})\delta}V^*, \tag{4.5}$$

and from (4.3) we have

$$I^* = \frac{k(T^* + (1-\epsilon_{RT})T_d^*)V^*}{\delta}. \tag{4.6}$$

Equating (4.5) and (4.6) gives

$$V^*\left[\frac{k(T^*+(1-\epsilon_{RT})T_d^*)}{\delta}-\frac{c+kT_o}{N_T(1-\epsilon_{PI})\delta}\right] = 0,$$

$$V^*=0 \text{ or } \frac{\mathrm{k(T^*+(1-\epsilon_{RT})T_d^*)V^*}}{\delta}-\frac{\mathrm{c+kT^*}}{\mathrm{N_T(1-\epsilon_{PI})}\delta}\mathrm{V^*} = 0.$$

The disease free steady state is obtained when $V^* = I^* = 0$ and is given as $E_o = (\frac{\lambda}{d+r}, \frac{r\lambda}{d(d+r)}, 0, 0)$

The endemic equilibrium point is given by $\overline{E} = (\overline{T}, \overline{T_d}, \overline{I}, \overline{V})$ where

$$\begin{aligned}
\overline{T_d} &= \frac{rc}{\alpha_1+\alpha_2\left[-\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}\right]},\\
\overline{T} &= \frac{cd-c(1-\epsilon_{RT})k\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}}{\alpha_1+\alpha_2\left[-\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}\right]},\\
\overline{I} &= \frac{\alpha_3\left(-\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}\right)\Big)^2+\alpha_4\left(-\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}\right)}{\alpha_5+\alpha_6\left(-\frac{e_o}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}\right)},\\
\overline{V} &= -\frac{e_0}{2}+\sqrt{\left(\frac{e_0}{2}\right)^2-\alpha_7}.
\end{aligned}$$

where $\overline{V}$ exists if and only if $1 < \frac{(1-\epsilon_{PI})N_T}{N_{crit}}$, that is, $N_{crit} < (1-\epsilon_{RT})N_T$

and

$$\begin{aligned}
\alpha_1 &= k(N_T(1-\epsilon_{RT})-1),\\
\alpha_2 &= kN_T(1-\epsilon_{RT})(k(N_T(1-\epsilon_{PI})-1)),\\
\alpha_3 &= ckN_T(1-\alpha_{RT})(1-\epsilon_{PI}),\\
\alpha_4 &= cN_T(1-\epsilon_{PI})(d+(1-\epsilon_{RT})),\\
\alpha_5 &= \delta dN_T(N_T(1-\epsilon_{PI})-1))(1-\epsilon_{PI})+\delta N_T(N_T(1-\epsilon_{PI})-1)^2(1-\epsilon_{PI})^2(1-\epsilon_{RT}),\\
\alpha_6 &= \delta N_T(N_T(1-\epsilon_{PI})-1))(1-\epsilon_{PI})((1-\epsilon_{RT})),\\
\alpha_7 &= e_1+e_1c(d+r)\left[1-\frac{(1-\epsilon_{PI})N_T}{N_{crit}}\right].
\end{aligned}$$

4.3 Stability analysis of the disease free steady state

To establish the stability of the disease free steady state we linearize the system about the point E_o.

Let $y_1 = T - \frac{\lambda}{d+r}, y_2 = T_d - \frac{r\lambda}{d(d+r)}, y_3 = I, y_4 = V,$

$\dot{y_1} = \dot{T}, \dot{y_2} = \dot{T_d}, \dot{y_3} = \dot{I}, \dot{y_4} = \dot{V}.$

substituting this into the original system we get

$$\begin{aligned}
\dot{y_1} &= -(d+r)y_1 - \frac{k\lambda}{d+r}y_4 - ky_4y_1,\\
\dot{y_2} &= ry_1 - dy_2 - \frac{(1-\epsilon_{RT})kr\lambda}{d(d+r)}y_4 - r(1-\epsilon_{RT})y_4y_2,\\
\dot{y_3} &= -\delta y_3 + \left(\frac{k\lambda}{d+r} + \frac{(1-\epsilon_{RT})kr\lambda}{d(d+r)}\right)y_4 + ky_4y_1 + k(1-\epsilon_{RT})y_4y_2,\\
\dot{y_4} &= N_T(1-\epsilon_{PI})\delta y_3 - \left(\frac{c(d+r)+k\lambda}{d+r}\right)y_4 - ky_4y_1.
\end{aligned}$$

The associated linearized system is given by

$$\begin{pmatrix} \dot{y_1} \\ \dot{y_2} \\ \dot{y_3} \\ \dot{y_4} \end{pmatrix} = \begin{pmatrix} -(d+r) & 0 & 0 & -\frac{k\lambda}{d+r} \\ r & -d & 0 & -\frac{(1-\epsilon_{RT})kr\lambda}{d(d+r)} \\ 0 & 0 & -\delta & \frac{k\lambda(d+r(1-\epsilon_{RT})}{d(d+r)} \\ 0 & 0 & N_T(1-\epsilon_{PI})\delta & -\frac{c(d+r)+k\lambda}{d+r} \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{pmatrix}$$

,

Let $c_o = d + r, c_1 = \frac{k\lambda}{c_o}, c_2 = \frac{rc_1(1-\epsilon_{RT})}{d}, c_3 = c_1 + c_2, c_4 = \frac{c(d+r)+k\lambda}{d+r}$,

The linearized system gives the following eigenvalues:

$$\beta_1 = -c_o, \beta_2 = -d$$

,

$$\beta_{3,4} = -\frac{(\delta + c_4)}{2} \pm \sqrt{\left(\frac{\delta + c_4}{2}\right)^2 - \delta c_3(N_{crit} - N_T(1-\epsilon_{PI}))}$$

Clearly the disease-free state is stable if $(1-\epsilon_{PI})N_T < N_{crit}$, where

$$N_{crit} = \frac{cd(d+r)}{k\lambda(d+r(1-\epsilon_{RT}))}.$$

When $\epsilon_{PI} \to 0$, then the drug will not be very effective N_T will be slightly below N_{crit}. This means the virus has higher chances to cause an infection. When $\epsilon_{PI} \to \infty$, then the drug's effectiveness will be improving and N_T will be reduced towards zero. This is a situation where we may eradicate infection or render the virus less infectious. We then summarize all these results in the following theorem

Theorem 5 *1. The uninfected steady state exists for all values of N_T.*

2. *The uninfected steady state is stable for* $(1-\epsilon_{PI})N_T < N_{crit}$ *and is unstable for* $(1-\epsilon_{PI})N_T > N_{crit}$.

3. *The infected steady state exist and is stable for* $(1-\epsilon_{PI})N_T > N_{crit}$.

Remark 2 *The proof for the stability of the infected steady state is cumbersome and the details are omitted here. We can illustrate these details numerically as shown in the following section.*

4.4 Numerical results for stability analysis of the endemic steady state

Figure 4.1, shows the dynamics of the endemic steady state. All the trajectories for the different classes are characterised by initial transients followed by the levelling off of the curves with time. This shows that with the administration of both RTI's and PI's as an intervention strategy, the infection will persist whenever $N_{crit} < N_T(1 - \epsilon_{PI})$. Thus the graphs shows that the endemic steady state is asymptotically stable in this region.

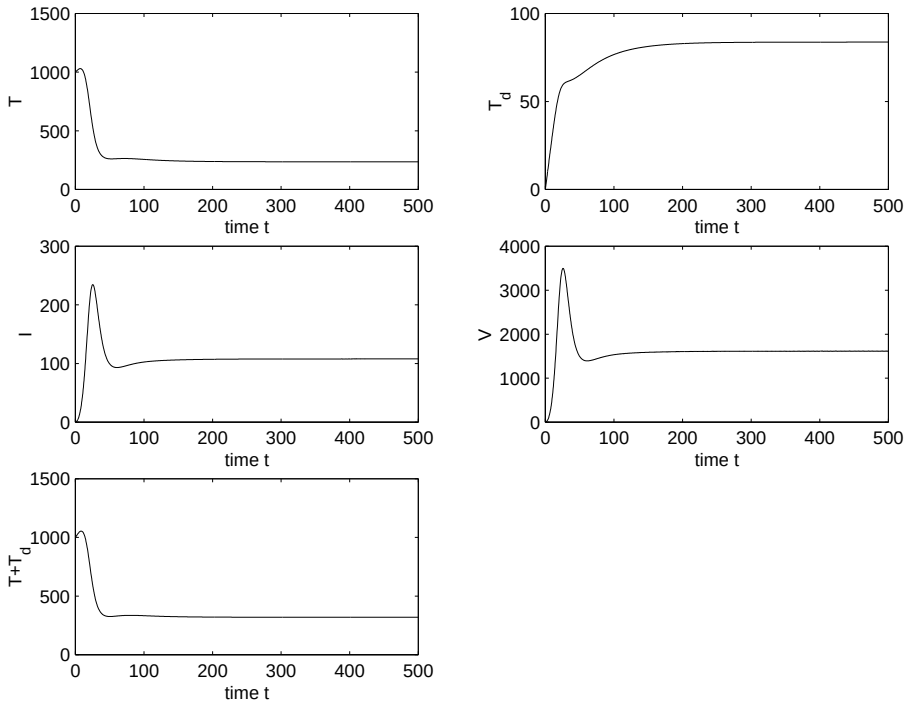

Figure 4.1: The model with both RTI's and PI's treatment, $N = 500$, $\epsilon_{RT} = 0.8, \epsilon_{PI} = 0.7$. The other parameters are given in Table 3.1

Chapter 5

DISCUSSIONS AND CONCLUSION

We first reviewed the model without treatment by Culshaw and Ruan [5]. We obtained a threshold parameter, N_{crit}. The disease free steady state was established and existed for all N_T while the endemic steady state existed for $N_T > N_{crit}$. The local stability for the steady states was established based on N_{crit}. This determines whether the disease will persist or not. Thus if $N_T < N_{crit}$, it is possible for the infection to die out in the sense that uninfected $CD4^+ - T$ cells stay healthy all times. If $N_T > N_{crit}$, then the infection becomes endemic in the sense that the immune system is weakened by the high free virus load.

We also reviewed a model with RTI's monotherapy where N_{crit} was improved by the introduction of the drug term. Numerical simulations on the stability analysis of the endemic steady state for the model with RTI's treatment showed that it is stable. The results showed that the administering of RTI's monotherapy

reduces the number of virions and slightly increases the total number of uninfected $CD4^+ - T$ cell. This means that the infection will always persist if no further intervention measures are taken. We established that when the drug is not effective, that is $\epsilon_{RT} \to 0$, then we experience the same situation as in the model without treatment. If $\epsilon_{RT} \to \infty$, that is when every $CD4^+ - T$ cell gets protection from RTI's then the value of N_{crit} is reduced towards zero and this leads to a possible eradication of the infection.

When we investigated the model with a combination of RTI's and PI's in the third model we established that the additional drug has remarkable effect on reducing the number of free virions. For infection not to progress, $(1-\epsilon_{PI})N_T < N_{crit}$ and for the infection to progress, $(1-\epsilon_{PI})N_T > N_{crit}$. From the computer simulations for the stability analysis of the endemic steady state, we established that it is also stable at a certain proportion which showed a remarkable improvement from the one on monotherapy. The trajectories are characterised by initial transients which are a result of the immune response which is present early in the infection. Thus it has the effect of lengthening the period over which an infective should survive. However, there is a possibility of the virus gaining resistance and blowing up again. Considering the conditions for the progression and reduction of infection, the drug is useless, that is $\epsilon_{PI} = 0$, then we have the same effects as in the model with RTI's treatment where every cell is only protected by one drug. This will not be good enough since multiple virions may infect one cell and only one of them might be hindered to get through and others allowed to get through or around the drug barrier [8]. Only when the additional drug is perfect, that is $\epsilon_{PI} = 1$, that we are able to further reduce the number of free virions produced by an infected cell towards zero. In this case it will be possible to get rid of the

infection at a faster rate than when we administer monotherapy. Thus we note that a combination of two types of drugs is more effective in reducing infection than one drug.

The results from the models are also in agreement with the previous findings by other modellers. In [7] They noted that the use of combination therapies raises many public health issues where they offer the promise of an important advance in the global fight against HIV/AIDS. However, it is possible that we may have an ill-planned combined treatment programme that may cause the progression of an infection as cited by Y. Hsieh and J.X. Velasco-Hernandez in [9]. The most important thing is the implementation of a comprehensive drug combinations that will arrest a large number of future infections and reverse the course of the AIDS pandemic [6]

References

[1] A.S. Perelson and D.S. Callaway: HIV-1 Infection and Low Steady State Viral Loads, Bulleting of Mathematical Biology. 2002; 64 (1): 29-64.

[2] D. Kirschner: Using Mathematics to understand HIV immune Dynamics, Journal of Anthology, 1996; 43:191-202.

[3] W.F Ganong: Review of Medical Physiology,Appleton and Lange publishing co., 1995.

[4] M. Kgosimore and E.M. Lungu: The effects of Vaccination and Treatment on the spread of HIV/AIDS, Journal of Biological Systems, pp 399-417, 2004.

[5] R.V. Culshaw and S. Ruan: A Delay-differential equation model of HIV infection of $CD4^+ - T$ cells, Mathematical Biosciences, 2000; 165: 27-39.

[6] J. Stover *et al*: Can we reverse the HIV/AIDS pandemic with an expanded response, Lancet. 2002; 360: 73-77.

[7] N. Hicks: A report on HIV/AIDS-A public health perspective.

[8] J.X. Velasco-Hernandez *et al*: Remarks on modelling Host-Viral Dynamics and Treatment: in Vol 125: Mathematical approaches for emerging and reemerging Diseases Part I: An Introduction to Models, Methods and Theory, 2001

[9] Y. Hsieh and J.X. Velasco-Hernandez: Community treatment of HIV-1: initial stage and asymptotic dynamics; Biosystems 35 (1995) 75-81.

[10] Ping Ye and D.E. Kirschner: Reevaluation of T Cell Receptor Excision Circles as a Measure of Human Recent Thymic Emigrants, Journal of Immunology, 2002; 169: 4968-4979.

[11] Baylor International Pediatric AIDS Initiative (Botswana): HIV/AIDS in Southern Africa,Technical Report, 2005.

[12] S. Blower and P. Farmer: Predicting the public health impact of antiretrovirals: Preventing HIV in developing countries, 2003.

[13] P. van den Driessche and J. Watmough: Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission, Mathematical Biosciences 180 (2002) 29-48.

[14] C. Fraser *et al*: The role of antigenic stimulation and cytotoxic T cell activity in regulating the long-term immunopathogenesis of HIV: mechanisms and clinical implications, Proc. R. Soc. lond B (2001); 268: 2085-2095.