MODELLING THE EFFECTS OF TREATMENT ON CHRONICALLY INFECTED HIV-POSITIVE PATIENTS

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Abstract

The devastating impact of HIV as a chronic infectious agent on human kind has forced a consideration of the rationale of administering combined drug therapies that incorporate fusion inhibitors, reverse transcriptase inhibitors and protease inhibitors in chronically infected HIV patients. It is also worth considering using alternative therapies, such as antioxidants, as anti-retroviral therapies are limited for economic reasons and their associated toxicity. This study models and analyzes pretreatment dynamics of viral production and progression with cellular-mediated immune responses in chronic HIV infection. The pre-treatment model is then extended to investigate the impact of administering a three drug combination regimen of reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors to chronically infected HIV-positive patients. Again from the pretreatment model we develop that considers HIV-induced free radicals as promoters of apoptosis and viral replication, incorporating antioxidants as agents of oxidative defense against the the oxidative pressures caused by the free radical molecules in chronically infected HIV patients. Deterministic mathematical models of ordinary differential equations shall be used for the three models of the thesis. An analysis of the effects of the parameters of interest is done for each one of the three models described above. In particular, this analysis is going to be centered on the reproduction numbers, stability conditions for steady states and numerical simulations. Results from the three models show that cellular-mediated immune responses, both lytic and non-lytic, play a significant role in reducing the initial impact of HIV infection. Administering combined chemotherapy helps boost CD4 count and significantly reduce viral load in chronically infected HIV patients. This treatment strategy gives positive results especially if it can be applied with relatively high efficacy rate, which might require almost perfect adherence and compliance as well as a well balanced diet and a positive psycho-social lifestyle by infected individuals. Antioxidant supplements also have great potential as far as inhibition of viral replication and maintenance of T-cell viability and survivability in chronically infected HIV patients is concerned, especially when applied right from the onset of infection. Antioxidant supplements may serve as a better alternative to chemotherapy because they are non-toxic,

affordable and do not present a problem of resistance as they need not be strain specific. It can also be deduced from the results of the antioxidant therapy models and the chemotherapy model that great clinical benefits can be realized by administering antioxidant supplements concurrently with combined drug therapy, a strategy defined in this thesis as complementary therapy.

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.

Dedication

This project is respectfully dedicated to all people involved in the quest to solve the problem of HIV and AIDS throughout the world.

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Chapter 1

Introduction and Literature Review

1.1 Background

The human immunodeficiency virus (HIV) has proven to be the bane of our times since it started decimating humanity across the globe in the twilight of the last century, and it is expected to take an increasingly negative toll on the economies of the countries most affected by it. The knowledge gained about the structure and function of this virus and its components provide a solid base from which current and future research can flourish.

The unique features of HIV infection are that it predominantly targets the economically active adult section of the human population, its random transmission dynamics, its long and random latency period, its hundred percent fatality, and the extreme complexity of its interference with the human immune system. The notorious implications of the impact of this epidemic being its silent double-edged killing of the households' economies. With one edge it attacks the health of the individual, immediately incapacitating the adult bread-earner. In sub-Sahara Africa this incapacitating seriously undercuts household income generation by reducing the amount of human capital input to the production of income time. With the other edge it depletes the household's meager resources, including production time as means

for coping with the illness. This combined attack produces and exerts direct impact on the household's income seriously sinking the entire micro-economy.

Further, there is need to at least consider the non-quantifiable costs: these could include the loss of elite cadres, the social consequences of a massive demographic imbalance, and a climate of blame, accusation and moral panic. The United States Agency for International Development (UNAIDS) and the World Health Organization (WHO) estimated that there were about 5 million people being infected, and 3 million people dying of acquired immune deficiency syndrome (AIDS) in 2006 all over the world [1]. WHO warned the International Monetary Fund (IMF) and the World Bank that (HIV/AIDS) had become a major factor in the world economy. The organization foresaw the deaths of as many as one fifth of young and middle-aged young adults over a short period of time leading to social turmoil, economic disruption and even political destabilization in many countries [2]. The illness and deaths of so many young adults has already placed immense stress on communities and resulted in hundreds of widows and orphans, many of them HIV infected.

1.1.1 HIV/AIDS in sub-Saharan Africa

Sub-Saharan Africa remains the region most affected by HIV/AIDS. In 2006, a study commissioned by the Southern Africa Trust, a regional non-profit making agency which supports and encourages inclusive policy dialogue aimed at poverty reduction, found that 24.7 million people in sub-Saharan Africa were living with HIV/AIDS, and that 59% of the figure was accounted for by women and children. In its report of the same year, the World Food Programme (WFP) said that health experts estimated that between 7 and 8 million farmers in the region have been lost to the disease over the past few years. They had evidence that the composition of households had largely changed as a result of the deaths of people still in their prime, the economically active age group. These are the people that one would least expect to be a "burden" on the society in terms of needing medical care and other related social services. Furthermore, this group comprises the labor-force, the educated and

the experienced: in other words, the people society can ill-afford to lose. With so many of the youths HIV-infected, unemployed and no free schooling, the spread of the virus among people with nothing to do and no hope of a better life is yet another matter of great concern.

The epidemic has adversely affected the economies of the countries in the region both directly and indirectly, for instance, directly, the region is losing some valuable young labor-force that are also the breadwinners of the family. Indirectly, the cost of laboratory equipment, the hospital beds, drugs and vaccines could well eat into the already depleted coffers of the national exchequer of the countries. Governments will have to spend scarce resources to buy the drugs and equipment at the expense of other developmental programmes such as primary health care and its related components *viz*; immunization, family planning, control of the environment, etc. Lack of these programmes creates many more problems (diseases and deaths). Whichever way one looks at it, this is a frightening scenario.

1.1.2 Existing control measures

Scientists have extensively studied HIV and its pathogenesis in the hope of finding targets for pharmaceuticals and immunotherapies for prevention and treatment. Accordingly, many of the secretes of HIV have now been unlocked although the challenge to develop a cure and/or a vaccine for the virus remains unsolved. Curing HIV/AIDS would mean halting the further growth of the virus, eliminating it from the human body and also lifting the depressed immune system to the levels which it can continue to police the system against foreign bodies that so constantly invade it. Cell-mediated immune response carried out by T-cells is the major weapon displayed by the immune system in its struggle against HIV [36]. Scientific intervention to preserve the health of HIV-infected persons has proven extremely difficult since the virus utilizes many cellular pathways common to immune function.

Current therapeutic approaches for resolving the AIDS problem include attempts to inhibit HIV replication or boost immune function in the presence of the virus. A number of

anti-viral agents, which have activity against viral enzymes like reverse transcriptase and protease, have been tried on HIV/AIDS patients. These drugs are meant to decelerate the multiplication of HIV and its destructive effect on the immune system.

Other available methods of reducing progression to AIDS include plasmapheresis, which is the process of removing the plasma component from the blood and thereafter reintroducing the cells into the patient. This method is not being used on a large scale at the moment because of costs associated with it. Scientists are even considering the possibility of transplanting borne marrow from healthy donors to AIDS patients. But, despite all the therapeutic advantages achieved so far, including the development of the highly active anti-retroviral therapy (HAART), once an individual has become infected, eradication of the virus still remain difficult. In addition, new problems relating to the short and long term toxicity of drug treatments and the occurrence of resistant mutants in the virus are emerging

1.2 Literature Review

HIV, a member of a subfamily of retroviruses known as the lentiviruses [3,4,5,6], is the primary aetiological agent for acquired immune deficient syndrome (AIDS). Retroviruses are fatal in virtually all cases. An understanding of the immunopathogenesis of HIV-infection is therefore a major prerequisite for rationally developing and/or improving therapeutic strategies, developing immunotherapeutics and proplylatic vaccines [7]. The virus has received more attention from scientists from across the world than any other infectious agent, and remarkable progress has so far been achieved to the extend that its biological structure has now been elucidated. Small and large text books, thesis and dissertations, circulars and reports, and many journals solely dedicated to this one virus attest to its fatality and the breath of existing knowledge about it.

Rapid advances have also been made in understanding the mode of infectiousness and the replication cycle of HIV. A detailed picture is now emerging of how HIV infects a cell and replicates itself to produce new infectious viral particles. These particles go on to infect and replicate in other cells throughout the body [8] leading to the spread of HIV and the onset of the disease AIDS. An important discovery is that HIV replication is a highly regulated process requiring a complex interplay between cellular and virus encoded proteins. Many of the processes regulated by these proteins appear to be unique for the virus and have proved to be attractive targets for anti-HIV therapies.

Infection with HIV is acquired through various routes which include sexual intercourse, transfusion of contaminated blood products, organ and tissue transplant, mother-to-child during birth (maternal-neonatal transmission) and by breast feeding. In fact, the virus is transmitted by exchange of bodily fluids, and the mode of transmission may involve the transfer of free virions or HIV-infected cells [9]. Once in the body, HIV targets among others, the $CD4^+$ T cells, which are the most abundant white blood cells of the immune system [10]. Progression to AIDS is accompanied by loss of $CD4^+$ T cells, with symptoms being noticed at blood levels less than 500 cells/mm^{-3} [11].

1.2.1 The genetic structure of HIV

As a retrovirus, HIV displays a variety of special features which include: genome composed of ribonucleic acid (RNA); a life cycle involving insertion of the viral genome into the genetic material of the host; the ability to alter its genome rapidly by mutation in the response to environmental conditions; and a common viral structure organized by three polyprotein genes: *group-specific antigen (gag)* which is the nucleocapsid core and the matrix proteins; *polymerase (pol)* that contains the reverse transcriptase, protease, integrase and ribonuclease, and *envelope (env)* which consists of the gp120 and gp41 proteins.

Every HIV particle contains two identical strands of RNA, and each of these RNA strands

contains the entire genetic blueprint coding for the structure and life cycle of HIV. The HIV genome is approximately 100 000 times smaller than the human genome, but, despite its relatively small size the genome is a remarkably complex structure that encodes at least seventeen different proteins. The viral genome also carries open reading frames (ORFs) for several regulatory proteins, and at each end of the genome is an identical sequence called the long terminal repeat (LTR), the binding site for host transmission factors. Furthermore, one of the LTRs, the 5'LTR acts as the promoter for transcription of viral messenger RNA (mRNA) [8].

There are two genetically distinct yet related HIV species called HIV-1 [12,13] and HIV-2 [14]. HIV-1 is the major cause of AIDS in the world today, and so our discussion will be primarily limited to HIV-1 infection. In terms of overall organization the HIV-1 and HIV-2 genomes are very similar. However, the two viruses actually differ by more than 55% in their primary nucleotide sequences. This means that although the viral proteins of HIV-1 and HIV-2 are functionally related, their primary amino acid structures are quite distinct. This property is reflected in the differing immunogenic characteristics of the viral proteins [8].

1.2.2 The replication cycle of HIV

The life cycle of HIV requires infection of a human cell. After initial contact and attachment to a cell of the immune system, there is a cascade of intracellular events. The end-product of these events is the production of massive numbers of new viral particles, death of the infected cells, and ultimate devastation of the immune system. The replication cycle goes as follows:

1. **Attachment, binding and fusion**- On the surface membrane of all living cells are complex protein structures called "receptors". The preferred mechanism of entry of HIV into cells begins with recognition of a cell surface receptor called CD4 [15] by the

viral surface glycoprotein gp120 [9]. This explains the marked preference of HIV for $CD4^+$ T lymphocytes. The gp120 envelope protein on the virion surface gets attached to the immunoglobulin domain of CD4 then binds to a chemokine receptor, the CXCR-4 or CCR-5 [16,17,18,19] on the target cell [20]. Although discrete binding sites on the HIV gp120, the molecular interaction requires the two proteins to be glycosylated and folded into their authentic three-dimensional conformations. After virion binding, in order for infection to become established, the target plasmalemma must fuse with the viral envelope. The conformational change in gp120 allows a fusigenic region of gp41 [21] to become exposed and mediate the fusion of the viral envelope and the host membrane [9]. Like other viruses that infect human cells, HIV commandeers the host's machinery to make multiple copies of itself.

2. **Reverse transcription**-Converting viral RNA into deoxy-ribonucleic acid (DNA). After cell fusion, the viral core enters the host cytoplasm and the genome and reverse transcriptase molecules are unpacked; the single-stranded RNA genome is reverse transcribed and eventually forms double-stranded DNA HIV genome containing all of the information originally held on the RNA genome [8]. Reverse transcriptase sometimes makes mistakes reading the RNA sequence. The result is that not all viruses produced in a single infected cell are alike. This chameleon-like nature of HIV limits the effectiveness of the class of drugs called "reverse transcriptase inhibitors".

3. **Integration**-Once the viral RNA has been reverse transcribed into a strand of DNA, the DNA is then transported to the cell nucleus where it is circularized and integrated (inserted) into a random site on the DNA of the host cell. The integrated viral DNA is called a provirus. The virus has its own enzyme called "integrase" that facilitates incorporation of the viral DNA into the cell's DNA. This enzyme is the only viral protein necessary for integration [22].

4. **Transcription**- The production of new virions requires the transcription, by host transcriptase, of the provirus, to produce multiple copies of viral RNA. This RNA codes for the production of the viral proteins and enzymes (translation) and will also

be packaged later as new viruses. Transcription of viral genes is under the control of cellular factors that bind to the long terminal repeat (LTR). Nuclear factor-κB, nuclear factor of activated T cells (NFAT) [23] and activation protein 1 (AP-1), among other factors, have been shown to activate HIV transcription [24]. Transcriptional activation by NF-κB is an absolute requirement for HIV-1 transcription [25].

5. **Translation**- viral RNA to proteins. There are only 9 genes in the HIV RNA. Those genes have the code necessary to produce structural proteins such as the viral envelope and core plus enzymes like reverse transcriptase, integrase, and a crucial enzyme called a protease. When viral RNA has been translated into a polypeptide sequence, that sequence is put in a long chain that includes several individual proteins (reverse transcriptase, protease, integrase). Before these enzymes become functional, they must be cut from the longer polypeptide chain. Viral protease cuts the long chain into its individual enzyme components which then facilitate the production of new viruses.

6. **Assembly and Budding**- Finally, viral RNA and associated proteins are packaged and released from the lymphocyte surface, taking with them a swatch of lymphocyte membrane containing viral surface proteins. These proteins will then bind to the receptors on other immune cells facilitating continued infection.

1.2.3 Cellular-mediated immune responses to HIV

The immune system works by the recognition of foreign antigens, commonly glycoproteins of the surfaces of cells. It is regulated by the activities of the T lymphocytes (helper T cells and cytotoxic T cells), derived from the thymus [26,27]. The T cells make proteins called receptors that recognize specific antigens. They do not release their receptors but hold them on their surfaces. Consequently, the T cells themselves specifically recognize and bind foreign antigens. The distinguishing features of acquired immune responses are specificity and memory [28]. Upon exposure to a given antigen, only those lymphocyte clones that specifically recognize that antigen are stimulated to proliferate and differentiate into effector cells

and memory cells [29].

Cytotoxic T cells (CTLs) carry an antigenic marker known as CD8+ antigen. Instead of attacking HIV directly, these CTLs inhibit virus spread by killing off other immune system cells infected with HIV. They directly bind to the cells carrying a foreign antigen. Once they bind to them, they attack and kill these cells thus eliminating them from the body. After carrying out this killing, they release from the target cell, which has been destroyed, and can bind and kill other cells. CTLs are also known to restrict viral load during asymptomatic phase through release of chemokines that prevent infection of new cells, and through release of cytokines that suppress viral production [29]. The CTL cells lyses the infected cells when they get into contact with each other, and they also produce cytokines that are important in the non-lytic immune response. Some cytokines work by suppressing the viral burst size of an infected T cell [30].

On the other hand, T helper cells which carry the antigenic marker CD4, do not kill cells but they play an important role in cell mediated immunity. When T cells (either CD4+ or cytotoxic) bind antigen, they become activated to proliferate. This will result in increased numbers of specific T cells to fight the foreign infectious agent, HIV. Like many other blood cells, T cells also need a growth factor in order to divide. For T cells that have bound antigen the growth factor that is required is called *interlenkin 2* (IL-2). Thus, $CD4^+$ T cells can stimulate themselves to proliferate after they bind antigen since they produce IL-2. However, most $CD8^+$ T cells do not produce IL-2 even after they bind antigen, they generally rely on IL-2 secreted by neighboring $CD4^+$ T cells in order to divide. Thus, if $CD4^+$ T cells are absent (extinct), CTL cells can proliferate at a very slow rate even if they have bound their specific antigens [31]. It is, therefore, critical to maintain $CD4^+$ T cells at high levels during HIV infection. The presence of a large number of the $CD4^+$ T cells help to mitigate opportunistic infections as they stimulate other immune cells to proliferate and differentiate into effector cells [32,33,34].

1.2.4 Chronic HIV-infection

Chronic infection is an ongoing slow progressing infection. Advances in HIV therapeutics have changed the nature of the disease, so that it has now assumed some of the characteristics of a chronic disease [35]. Chronically infected $CD4^+$ T cells contain a large number of viral particles but will have not received adequate stimuli for activation. These cells eventually lose the capacity to become activated and thus are unable to clear their viral load.

During chronic infection the number of target cells, T_S, can decrease and even be limiting. Chronically infected cells can as well act as a key reservoir for virus; virions within chronically infected cells continue to multiply if proliferation is unchecked by $CD8^+$ T cells. The viral load eventually reaches the limiting capacity leading to the killing of the chronically infected cells, releasing the viral particles into the extracellular environment. Productive or active infection, on the other hand, occurs when the virion enters the cell, successfully and effectively hijacks the cellular machinery, and efficiently produces new virions (progeny) at a steady rate .

1.2.5 Anti-HIV therapy

Highly active antiretroviral therapy (HAART) has become the standard for HIV treatment. Current HAART regimens comprise of combinations of reverse transcriptase inhibitors (RTIs) and/or protease inhibitors (PIs) [38]. A new class of anti-HIV drugs has been developed as well: these are compounds known as entry/fusion inhibitors (FIs) [41]. FIs function by preventing fusion of the virus and host cells. Initiation of HAART is generally recommended for patients with HIV-related opportunistic infections or a CD4 count less than 200 cells/mm^3. Antiretroviral (ARV) drug treatment of HIV infection causes rapid reduction in plasma viral load. These drugs work by interfering with some aspect of the viral life cycle.

RTIs are subdivided into into nucleoside (NRTIs) which inhibit viral production by acting

as chain terminators when incorporated into the viral DNA being produced in an infected cell, and nonnucleoside (NNRTIs) which are small molecule inhibitors of the enzyme reverse transcriptase [37]. Generally, RTIs prevent viral RNA from being converted into DNA, thus blocking the integration of viral code into the target cell. PIs prevent the activities of protease, an enzyme used by HIV to cleave nascent for the final assembly of new HIV virions, thereby preventing viral replication [39,40].

While combined drug therapy has shown success in decreasing plasma viremia to below detectable levels in many infected patients, it has also presented the problem of resistance, due to mutations in the virus and the requirements for the complete eradication of the pathogen in infected individuals is still obscure. The high cost, the severe and the life-threatening side effects of anti-retroviral therapy are an important issue to consider as well. In fact,many have not hesitated to declare that ARVs are not cost-effective in the poorest and most heavily HIV-burdened countries [58]. Hence, notwithstanding the success of the conventional anti-retroviral therapy, it is also worthy considering the rationale of using other alternatives

Antioxidant therapy in HIV-positive patients

Many of the body's functions rely on a series of chemical reactions called oxidation. Molecules called reactive oxygen intermediates, particularly free radicals, are a natural by-product of oxidation. A free radical is a molecule characterized by the presence of free (unpaired) electron(s) in its electron structure. This type of molecule is chemically unstable, and this makes it highly reactive towards a wide variety of biological substrates and can lead to cellular damage if they are produced in "excess". The pathology of these excess free radicals is related to extensive damage to intracellular proteins, oxidation of nucleic acids, chromosome breaks and peroxidation of unsaturated fatty acids in the cell membrane, which leads to a distortion of cell membrane permeability properties [42]. Limited chromosomal damage can

be repaired whereas extensive DNA damage promotes apoptosis of the affected cell. An increase in free radical production and lipid peroxidation has been implicated in HIV infected patients [43,44]. The overproduction of the free radicals with associated pathology causes oxidative stress, especially in HIV-infection [42]. This oxidative stress and the damage due to it have also been implicated in HIV-infected individuals [45]. It, therefore, may play a role in viral replication, decreased immune cell proliferation and increased sensitivity to drug toxicity [46]. Also it may promote apoptosis [9], which is recognized as a major form of cell death of CD4+ lymphocytes in HIV infection [42,47,48,49].

The destruction of free radicals is usually carried out by molecules known as antioxidants, which react directly with free radicals to form oxidized derivatives. The body can make its own antioxidants by using some nutrients that are found in food and supplements. Plant antioxidants may also offer protection from viral replication and cell death associated with oxidation stress in patients with HIV/AIDS [46]. Supplements of *N-acetyln-cysetein* (NAC) [50], a source of cyteine, which is an important nutrient in the making of antioxidants, also increase the survivability of HIV positive patients by enhancing the functioning of their immune system [50,51]. When tested *in vitro*, virtually every antioxidant inhibits HIV replication. Hydrogen peroxide, a very strong oxidant, promotes HIV replication in infected cells by causing the release of gene stimulating cellular protein known as nuclear factor kappa B (NF-κB) [52]. The addition of the well-known antioxidant NAC counteracts this effect [52,53] The mechanism of action includes halting the stimulation of DNA by the nuclear factor (NF-κB), which is, in turn, activated by oxidation by-products [54,55]. Transcriptional activation by NF-κB is an absolute requirement for HIV-1 transcription [9,24], and this activation may be a more direct consequence of free radicals [56].

During HIV-infection, free radical damage may as well be produced by a tumor necrosis factor (TNF)-mediated generation in target cells. TNF-alpha appears to activate HIV RNA and virus production through the induction of transcription activating factors that bind to the NF-κB sequences in the HIV LTR [56]. Antioxidants have demonstrated protective capacity for TNF cytotoxicity. Thus, using antioxidants may have a positive impact as an

alternative means of treating HIV-patients. HIV can also induce chronic oxidative stress, which has been associated with apoptosis of T lymphocytes and increased rates of HIV replication through the activation of NF-κB [48,50,57].

1.2.6 Applicability of mathematical epidemiology models

Mathematical models are ideal vehicles for examining the consequences of competing effects in any system. They can take the form of a picture that depicts various processes. The model goes further and confides the picture in terms of equations which can be used to make predictions. Testing such predictions, however, depends on obtaining data and using that data to estimate parameters. There are transition values of parameters that separate one domain of behavior from another, and for different sets of parameter values, a mathematical model yields different modes of quantitative behavior. Many questions relating to disease dynamics require a quantitative understanding of the dynamics of complex systems that arise from the non-linear interactions between populations of immune cells and the invading antigen. The human immune system infected with HIV represents one such dynamical system, and this makes the use of mathematical models necessary to provide a correct interpretation of empirical results, to generate insights and hypotheses and to guide further experimental work.

More so, in epidemiology, mathematical models provide a rigorous means of thinking about and describing the immune system and its interactions with foreign bodies. Stripped of secondary detail, a good model can permit a deep analysis of the interactions that are otherwise obscured. Although they cannot include all aspects of real life situation, they can, however give insights into what happens in the real situation. Solutions or predictions based on the models can be used by public health officers to devise (better) control measures, but, perhaps like any other theoretical framework, they must be employed with taste and restrain. While

no model adequately explains all the features of the clinical data, each has its virtues; and as such models that do not give reasonable answers serve as exercises and warnings!

1.2.7 Justification

Several HIV treatment models that, among other things, seek to analyze the effects of drug therapy have been developed and have been extensively studied over the years. The results from most of these studies are in agreement with clinical observations and have in some cases helped advance medical capabilities in the treatment of HIV infections. Combined therapy has been Successful in as far as boosting the $CD4^+$ T cell count of HIV patients is concerned. However, notwithstanding the success of anti-HIV drug therapy, it is also worthy considering the rationale of using non-drug therapies, for example antioxidants, as an alternative treatment strategy in chronic HIV infection. This is particularly important considering the high costs and the severe life-threatening side effects of the conventional anti-retroviral therapy.

1.2.8 Statement of the problem

Aim

To study the effects of treatment in chronically infected HIV-positive patients.

Objectives

The main objectives of this project are to:

- Develop and analyze an HIV pretreatment model with cellular-mediated immune responses;

- Extend the pretreatment model to a treatment model that incorporates the effects of combined drug therapy on chronically infected HIV-positive patients;

- Further extend the pretreatment model by incorporating the ravaging effects of HIV-induced free radicals as promoters of apoptosis and viral replication; and the counter-effects of antioxidants as treatment in chronic HIV patients.

1.2.9 Methodology

To achieve the above set objectives the researcher is going to use deterministic ordinary differential equations to model the nonlinear dynamics/interactions between HIV particles and cells of the immune system ($CD4^+$ and $CD8^+$ T cells). The effects of combined drug therapy efficacy parameters and non-drug related variables and parameters shall be analyzed through the respective reproduction numbers, stability conditions for existence of steady states and numerical simulations of the respective models.

1.2.10 Thesis overview

The thesis is structured as follows: Chapter 1 gives a general introduction and a detailed account of the background of the HIV immuno-pathogenesis. In chapter 2 we formulate, analyze then present numerical simulations of a pretreatment model, with explicit lytic and non-lytic immune responses, for chronically infected HIV patients. The pretreatment model is then modified in chapter 3 to incorporate the effects of combined drug therapy. This chemotherapy model is also analyzed in the same way as the pretreatment model in establishing how the three drug treatment regime that includes RTIs, PIS and FIs influences the course of disease when the $CD4^+$ T cell count has fallen down to below $200 cells/mm^3$. In chapter 4 we modify the pretreatment model again by incorporating free radicals as promoters of apoptosis and viral replication in chronically infected HIV patients and antioxidants as a non-drug form of treatment that directly counteracts the effects of the free radical

molecules. An analysis of this model is carried out on the effects and counter effects of free radicals and antioxidants, respectively, on the reproduction number, the stability conditions for steady states as well as the course of disease depicted by numerical simulations. In chapter 5 we make concluding remarks and recommendations on treatment strategies in chronic HIV infections.

Chapter 2

The HIV pretreatment model

The model presented in this chapter forms a basis for the other models to be formulated and analyzed in the next two chapters. Most features of this model have been described in detail elsewhere [59,60]. Distinguishing chronically infected $CD4^+$ T cells from productively/actively infected $CD4^+$ T cells is one important feature of this blended model. The mathematical model is given by the non-linear initial value problem, where the rates of change of each variable with respect to time are:

$$\frac{dT_S(t)}{dt} = s_T + \frac{rT_S(t)V(t)}{V(t)+A} - \frac{\beta_c V(t)T_S(t)}{1+a_0C(t)} - \frac{\tau V(t)T_S(t)}{T_S(t)+B} - \mu_S T_S(t), \tag{2.1}$$

$$\frac{dT_E(t)}{dt} = \frac{\beta_c V(t)T_S(t)}{1+a_0C(t)} - \beta_\nu T_E(t) - \mu_E T_E(t), \tag{2.2}$$

$$\frac{dT_I(t)}{dt} = \alpha\beta_\nu T_E(t) - h_I T_I(t)C(t) - \mu_I T_I(t), \tag{2.3}$$

$$\frac{dT_C(t)}{dt} = (1-\alpha)\beta_\nu T_E(t) - h_C T_C(t)C(t) - \mu_T T_C(t), \tag{2.4}$$

$$\frac{dC(t)}{dt} = s_C + pV(t)T_S(t)C(t) - \mu_C C(t), \tag{2.5}$$

$$\frac{dV(t)}{dt} = \frac{N_I\mu_I T_I(t)}{1+a_1C(t)} + \frac{N_C\mu_T T_C(t)}{1+a_1C(t)} - \mu_V V(t), \tag{2.6}$$

where $T_S(t)$ is the population density of healthy $CD4^+$ T cells, also defined as susceptible $CD4^+$ T cells; $T_E(t)$ is the concentration of infected $CD4^+$ T cells where virions have only entered the cytoplasm but without transcription that has occurred, they can also be defined

as exposed CD4$^+$ T cells; $T_I(t)$ is the abundance of productively infected CD4$^+$ T cells which are a result of successful transcription; $T_C(t)$ is the density of chronically infected CD4$^+$ T cells, again resulting from successful transcription; $C(t)$ is the density of HIV specific CTLs and $V(t)$ is the abundance of HIV virions.

Equation (2.1) tracks the change in healthy (susceptible) CD4$^+$ T cells from the thymus [26,27]. The second term represents the proliferation of CD4$^+$ T cells due to HIV at rate r, where A is the maximum proliferation stimulation of CD4$^+$ T cells induced by the virus [59]. The third term represents the attachment, fusion and entry of HIV virions into the cytoplasm of CD4$^+$ T cells at rate β_c. The parameter β_c is a joint contribution of the rate at which virus and target collide, the fraction of cells which are activated and hence susceptible to infection, and the fraction of interactions between activated CD4$^+$ T cells and virus which result in successful entry of virions into the cytoplasm of CD4$^+$ T cells [60]. HIV specific CTLs release chemokines that block the entry of virions into target cells, thereby preventing infection of new cells [26] by a factor $(1 + a_0C)^{-1}$, where the parameter a_0 represents inhibition efficiency of CTLs [60]. The fourth term represents the destruction of CD4$^+$ T cells by programmed cell death (apoptosis) due to irritation induced by HIV proteins, without viral penetration, at rate τ. The last term represents the natural death of susceptible CD4$^+$ T cells at rate μ_S.

Equation (2.2) monitors the dynamics of CD4$^+$ T cells that have been exposed to the virus (that have allowed viral entry into their cytoplasm) [60], It models the transition stage that the successful infection process of CD4$^+$ T cells passes through before transcription occurs. The first term on the right hand side of equation (2.2) is the gain from the third term of equation (2.1) and is the source of CD4$^+$ T cells where virions have just entered the cytoplasm but awaiting transcription of HIV RNA to DNA to occur. After entry of viral particles into the CD4$^+$ T cells the virus then uses the CD4$^+$ T cell machinery to replicate, then transcription of viral RNA to DNA occurs at rate β_ν. Here β_ν represents three processes in the HIV-1 infection cycle, that is, (i) reverse transcription, (ii) viral DNA and host integration and (iii) transcription that result in production of many copies of HIV virions [60]. The

last term represents the death of exposed CD4$^+$ T cells at rate μ_E before transcription occurs.

Equation (2.3) marks the change in productively infected CD4$^+$ T cells that have moved from the exposed class after RNA to DNA transcription. The first term is the source of productively infected CD4$^+$ T cells, that is, a proportion α of the exposed CD4$^+$ T cells become productively infected after transcription. The other proportion, $(1-\alpha)$, become chronically infected. The second term represents the killing of productively infected CD4$^+$ T cells by the effects of HIV specific CTLs at rate h_I. the last term represents both the bursting and natural death of productively infected CD4$^+$ T cells at rate μ_I [59].

Equation (2.4) models the dynamics of chronically infected CD4$^+$ T cells. The first term is the source from the second term of equation (2.2). The second term represents the killing of chronically infected CD4$^+$ T cells by the effects of HIV specific CTLs at rate h_C. The last term represents both the bursting and natural death of the chronically infected CD4$^+$ T cells at rate μ_T [59], which we assume is less than μ_I, so that chronically infected cells are longer-lived than productively infected cells [59].

Equation (2.5) models the dynamics of HIV specific CTLs. A constant source, s_C, from the thymus, is augmented by proliferation of modeled by the term, $pCVT_S$. This term depicts the importance of CD4$^+$ T cells and antigen on CTL proliferation.. The last term is the natural death of the CTLs at rate μ_C.

Equation (2.6) tracks the dynamics of the viral load. The first and second terms represents the source of new virions from the bursting of productively and chronically infected CD4$^+$ T cells, respectively. The burst sizes of both the productively and chronically infected CD4$^+$ T cells are reduced by CTLs by factor $(1+a_1C)^{-1}$, where a_1 models the efficacy of cytokines produced by CTLs in inhibiting budding of new HIV virions. The last term represents the natural death of viral particles at rate μ_V.
A summary of variables and parameters used in the model is presented in table 2.1 below:

Variable	Description	Units
$T_S(0)$	uninfected CD4$^+$ T cells	cells/mm^{-3}
$T_E(0)$	transiently infected CD4$^+$ T cells	cells/mm^{-3}
$T_I(0)$	productively infected CD4$^+$ T cells	cells/mm^{-3}
$T_C(0)$	chronically infected CD4$^+$ T cells	cells/mm^{-3}
$C(0)$	HIV specific CTLs	cells/mm^{-3}
$V(0)$	HIV population	copies/mm^{-3}
Parameter		
s_T	supply rate of CD4$^+$ T cells	cells/mm^{-3}day^{-1}
r	proliferation rate of CD4$^+$ T cells	day^{-1}
A	proliferation stimulation constant	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$
β_c	collision-and-entry rate	$copies/\text{mm}^{-3}\text{day}^{-1}$
a_0	rate CTLs reduce infectivity	$cells/\text{mm}^3$
τ	apoptosis rate	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$
B	apoptosis saturation constant	$cells/\text{mm}^{-3}$
μ_S	CD4$^+$ T cell death rate	day^{-1}
β_ν	successful infection of CD$^+$ T cells rate	mm^{-3}day^{-1}
μ_E	"exposed" T cells death rate	day^{-1}
h_I	rate CTLs lyse productively infected cells	$cells/\text{mm}^{-3}\text{day}$
μ_I	productively infected cells "burst" rate	day^{-1}
α	proportion becoming productively infected	
h_C	rate CTLs lyse chronically infected cells	$cells/\text{mm}^{-3}\text{day}$
μ_T	chronically infected cells "burst" rate	day^{-1}
s_C	CTL supply rate	$cells/\text{mm}^{-3}\text{day}$
p	CTL proliferation rate	$\frac{\text{cells}^{-1}/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$
μ_C	natural CTL death rate	day
N_I	T_I virus burst size	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$
N_C	T_C virus burst size	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$
a_1	virion production reduction factor	$cells/\text{mm}^3$
μ_V	virus clearance rate	day^{-1}

Table 2.1: Description of variables and parameters, with their respective units, used in the pretreatment model

2.1 Positivity and boundedness of solutions

The model, equations (2.1)-(2.6), monitors human cell and viral particle densities. It is , therefore, very important that all the state variables involved are non-negative for all time and are bounded in $\mathbb{R}$. Based on biological considerations the model will be studied in the following region

$$\Omega = (T_S, T_E, T_I, T_C, C, V) \in \mathbb{R}^6_+.$$

The region $\Omega \in \mathbb{R}^6_+$ is positively invariant with respect to the system of equations (2.1)-(2.6) and a non-negative solution exists for all time, $t \in (0, \infty)$.

From equation (2.1) we have

$$\frac{dT_S(t)}{dt} \geq s_T - \frac{\beta_c V(t) T_S(t)}{1 + c_0 C(t)} - \frac{\tau V(t) T_S(t)}{T_S(t) + B} - \mu_S T_S(t),$$

that is,

$$(T_S(t)+B)\frac{dT_S(t)}{dt} \geq s_T(T_S(t)+B) - \frac{\beta_c V(t) T_S(t)(T_S(t)+B)}{1 + c_0 C(t)} - \tau V(t) T_S(t) - \mu_S T_S(t)(T_S(t)+B).$$

Now let $T_B(t) = T_S(t) + B$, then $\frac{dT_S(t)}{dt} = \frac{dT_B(t)}{dt}$. Substituting in the expression above we have that,

$$T_B(t)\frac{dT_B(t)}{dt} \geq s_T T_B(t) - \frac{\beta_c V(t) T_B(t)(T_B(t) - B)}{1 + c_0 C(t)} - \tau V(t)(T_B(t) - B) - \mu_S T_B(T_B(t) - B).$$

So that,

$$\frac{dT_B(t)}{dt} \geq s_T - \frac{\beta_c V(t) T_B(t)}{1 + c_0 C(t)} + \frac{\beta_c V(t) B}{1 + c_0 C(t)} - \tau V(t) - \mu_S T_B + \mu_S B.$$

Re-arranging gives,

$$\frac{dT_B(t)}{dt} + \left(\frac{\beta_c V(t)}{1 + c_0 C(t)} + \mu_S\right) T_B(t) \geq s_T + \frac{\beta_c V(t) B}{1 + c_0 C(t)} - \tau V(t) + \mu_S B. \tag{2.7}$$

Multiplying through (2.7) by the integrating factor, $e^{-\int_0^t \left(\frac{\beta_c V(p)}{1+c_0 C(p)} + \mu_S\right) dp}$, and integrating we have

$$T_B(t) e^{-\int_0^t \left(\frac{\beta_c V(p)}{1+c_0 C(p)} + \mu_S\right) dp} \geq \int_0^t \left(s_T + \frac{\beta_c V(r) B}{1 + c_0 C(r)} - \tau V(r) + \mu_S B\right) e^{-\int_0^r \left(\frac{\beta_c V(p)}{1+c_0 C(p)} + \mu_S\right) dp} dr + K,$$

where K is the constant of integration. Hence, putting

$$X = s_T + \frac{\beta_c V(r) B}{1 + c_0 C(r)} - \tau V(r) + \mu_S B$$

and

$$Y = e^{-\int_0^r \left(\frac{\beta_c V(p)}{1 + c_0 C(p)} + \mu_S \right) dp},$$

we have

$$T_B(t) \geq X^{-1}\Big(T_B(0) + \int_0^t XY dr\Big),$$

with $K = T_B(0)$. That is,

$$(T_S(t) - B) \geq X^{-1}\Big(T_S(0) - B + \int_0^t XY dr\Big),$$

and so,

$$T_S(t) \geq B + X^{-1}\Big(T_S(0) - B + \int_0^t XY dr\Big) \geq 0.$$

From equation (2.2) we have that $\frac{dT_E(t)}{dt} \geq -\beta_\nu T_E(t) - \mu_E T_E(t)$, which integrates to give $T_E(t) \geq T_E(0) e^{-(\beta_\nu + \mu_E)t} \geq 0, \ \forall \ \ t$. From equation (2.3), $\frac{dT_I(t)}{dt} \geq -h_I T_I(t) C(t) - \mu_I T_I(t)$, so that, $T_I(t) \geq T_I(0) e^{-\mu_I t - \int_0^t h_I T_I(\tau) d\tau} \geq 0, \ \forall \ \ t$. Similarly, according to equation (2.4), $T_C(t) \geq T_C(0) e^{-\mu_T t - \int_0^t h_C T_C(\tau) d\tau} \geq 0, \ \forall \ \ t$. From equations (2.5) and (2.6) it can easily be deduced that $C(t) \geq C(0) e^{-\mu_C t}$ and $V(t) \geq V(0) e^{-\mu_V t}$, respectively. Taking limits as $t \longrightarrow \infty$,

$lim_{t\to\infty} T_S(t) \geq 0$, $lim_{t\to\infty} T_E(t) \geq 0$, $lim_{t\to\infty} T_I(t) \geq 0$, $lim_{t\to\infty} T_C(t) \geq 0$, $lim_{t\to\infty} C(t) \geq 0$ and $lim_{t\to\infty} V(t) \geq 0$. It follows that $T_S(t)$, $T_E(t)$, $T_I(t)$, $T_C(t)$, $C(t)$ and $V(t)$ are positive variables for all values of time, t. Now to prove boundedness we use the fact that continuous functions are bounded on compact sets. We start by observing that $T_S(t) \to 0$ as $t \to \infty$ and thus there exists k and M where $k, M > 0$ such that for $t > k$ we have $T_S(t) < M$. On the other hand, $[0, k]$ is a closed and bounded set, hence it is a compact set; $T_S(T)$ is differentiable hence continuous. Thus $T_S(t)$ is indeed bounded on $[0, k]$. This completes the proof for boundedness of T_S for all time, $t \geq 0$, because $t \geq 0 = [0, k] \cap t > k$. The same analysis can be used for the other variables, and thus Ω is positively invariant and attracting. All solutions starting in Ω remain there for all time, $t > 0$.

2.2 Analysis of the model

The steady states for the basic model are obtained by equating the right-hand sides of equations (2.1)-(2.6) to zero. The system has two steady states: the disease-free steady state $\bar{E}_0$ and the endemically infected steady state $\bar{E}_1$.

In the absence of virus, $\bar{T}_E = 0$, $\bar{T}_I = 0$, $\bar{T}_C = 0$ and $\bar{V} = 0$. The disease-free steady state is therefore given by

$$\bar{E}_0 = (\bar{T}_S, \bar{T}_E, \bar{T}_I, \bar{T}_C, \bar{V}) = \left(\frac{s_T}{\mu_S}, 0, 0, 0, \frac{s_C}{\mu_C}, 0\right).$$

Similarly, the HIV-infected steady state can be found by equating the right hand sides of equations (2.1)-(2.6) to zero, then solving the resultant algebraic equations as follows:

$$\begin{aligned}
s_T + \frac{r\widetilde{T}_S\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} - \frac{\tau\widetilde{V}\widetilde{T}_S}{\widetilde{T}_S+B} - \mu_S\widetilde{T}_S &= 0, && (2.8)\\
\frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} - \beta_\nu\widetilde{T}_E - \mu_E\widetilde{T}_E &= 0, && (2.9)\\
\alpha\beta_\nu\widetilde{T}_E - h_I\widetilde{T}_I\widetilde{C} - \mu_I\widetilde{T}_I &= 0, && (2.10)\\
(1-\alpha)\beta_\nu\widetilde{T}_E - h_C\widetilde{T}_C\widetilde{C} - \mu_T\widetilde{T}_C &= 0, && (2.11)\\
s_C + p\widetilde{V}\widetilde{T}_S\widetilde{C} - \mu_C\widetilde{C} &= 0, && (2.12)\\
\frac{N_I\mu_I\widetilde{T}_I}{1+a_1\widetilde{C}} + \frac{N_C\mu_T\widetilde{T}_C}{1+a_1\widetilde{C}} - \mu_V\widetilde{V} &= 0. && (2.13)
\end{aligned}$$

The equilibrium value of healthy CD4$^+$ T cells is given by

$$\widetilde{T}_S = \frac{-\Pi_2 + \sqrt{(\Pi_2)^2 - 4Bs_T\Pi_1}}{2\Pi_1}, \qquad (2.14)$$

where

$$\begin{aligned}
\Pi_1 &= \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c\widetilde{V}}{1+a_0\widetilde{C}} - \mu_S,\\
\Pi_2 &= s_T + \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c B\widetilde{V}}{1+a_0\widetilde{C}} - \tau\widetilde{V} - \mu_S B.
\end{aligned}$$

For existence of this equilibrium value, $\widetilde{T}_S > 0$, that is, $\frac{-\Pi_2+\sqrt{(\Pi_2)^2-4Bs_T\Pi_1}}{2\Pi_1} > 0$. Expression (2.14) shows that the equilibrium value of uninfected CD4$^+$ T cells depends on the HIV-specific CTL activity in inhibiting infection, which is represented by factor $\frac{1}{1+a_0\widetilde{C}}$; infectivity

of CD4$^+$ T cells, β_c; proliferation rate of healthy CD4$^+$ T cells, r. The population density of exposed CD4$^+$ T cells waiting for transcription to occur is given by

$$\widetilde{T}_E = \frac{\beta_c \widetilde{V} \widetilde{T}_S}{(1 + a_0 \widetilde{C})(\beta_\nu + \mu_E)}. \tag{2.15}$$

We deduce from expression (2.15) that increased CTL activity against infection of CD4$^+$ T cells results in reduced production of CD4$^+$ T cells that have just fused with virus but successful transcription has not yet occurred. The productively infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_I = \frac{\alpha \beta_\nu \widetilde{T}_E}{h_I \widetilde{C} + \mu_I}. \tag{2.16}$$

The chronically infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_C = \frac{(1 - \alpha) \beta_\nu \widetilde{T}_E}{h_C \widetilde{C} + \mu_T}. \tag{2.17}$$

Expressions (2.16) and (2.17) show that increased CTL lytic activity on infected T cells reduces the abundance of infected T cells, which are a reservoir for new viral particles. The endemic steady state value of HIV specific CTLs is given by

$$\widetilde{C} = \frac{s_C}{\mu_C - p \widetilde{T}_S \widetilde{V}}. \tag{2.18}$$

For existence of the HIV specific CTL cells endemic equilibrium value, $\widetilde{C} > 0$. That is, $\frac{s_C}{\mu_C - p\widetilde{T}_S \widetilde{V}} > 0, \implies \frac{\mu_C}{\widetilde{T}_S} > p\widetilde{V}$. From this analysis we deduce that there is an inverse relationship between the abundance of viral particles and the population density of target cells. Expression (2.18) shows that increased interactions between healthy CD4$^+$ T cells and viral particles, as modeled by the term, $p\widetilde{T}_S \widetilde{V}$, results in increased CTL proliferation thereby increasing the abundance of CD8$^+$ T cells available for lytic and non-lytic activities. The viral steady state is given by

$$\widetilde{V} = \frac{N_I \mu_I \widetilde{T}_I + N_C \mu_T \widetilde{T}_C}{\mu_\nu (1 + a_1 \widetilde{C})}. \tag{2.19}$$

From expression (2.19) we conclude that CTL activity against viral replication is critical in reducing the endemic viral density in chronic HIV infection. On the other hand, high burst

sizes for both the productively infected and chronically infected T cells are associated with high viral burden in a chronically infected HIV patient.

The endemically infected steady state is given as

$$\bar{E}_1 = (\widetilde{T}_S, \widetilde{T}_E, \widetilde{T}_I, \widetilde{T}_C, \widetilde{C}, \widetilde{V}),$$

where the expressions for $\widetilde{T}_S$, $\widetilde{T}_E$, $\widetilde{T}_I$, $\widetilde{T}_C$, $\widetilde{C}$ and $\widetilde{V}$ are given by expressions (2.14)-(2.19), respectively

2.2.1 The reproduction number

To calculate the reproduction number for the basic model we adopt the method of O. Diekmann *et al.* [61,62]. Defining heterogeneity using groups defined by fixed characteristics the model can be written in the form:

$$\frac{dX}{dt} = f(\mathbf{X}, \mathbf{Y}, \mathbf{Z}), \tag{2.20}$$

$$\frac{dY}{dt} = g(\mathbf{X}, \mathbf{Y}, \mathbf{Z}), \tag{2.21}$$

$$\frac{dZ}{dt} = h(\mathbf{X}, \mathbf{Y}, \mathbf{Z}), \tag{2.22}$$

where $\mathbf{X} \in \mathbb{R}^2$, $\mathbf{Y} \in \mathbb{R}$, $\mathbf{Z} \in \mathbb{R}^3$, and $h(\mathbf{X}, 0, 0) = 0$. Assuming that the equation $g(\mathbf{X}^*, \mathbf{Y}, \mathbf{Z}) = 0$ implicitly determines a function $\mathbf{Y} = \bar{g}(\mathbf{X}^*, \mathbf{Z})$. We let $A = D_Z h(\mathbf{X}^*, \bar{g}(\mathbf{X}^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, with $M \geq 0$ (that is $m_{ij} \geq 0$) and $D > 0$, a diagonal matrix. The reproduction number is then evaluated from the matrix MD^{-1}.

The cell population subgroups are divided as follows, (a) $\mathbf{X}$: are cells that are uninfected by the virus, (b) $\mathbf{Z}$: are cells that are virus infected (infected $CD4^+$ T cells), and (C) $\mathbf{Y}$: the HIV pathogen. Therefore we set $\mathbf{X} = (T_S, C)$, $\mathbf{Y} = V$, $\mathbf{Z} = (T_E, T_I, T_C)$, and $\mathbf{X}^* = (\frac{s_T}{\mu_S}, \frac{s_C}{\mu_C})$. Let $\mathbf{U}_0 = (\mathbf{X}^*, 0, 0)$ denote the virus free equilibrium, that is $f(\mathbf{X}^*, 0, 0) = g(\mathbf{X}^*, 0, 0) =$

$h(\mathbf{X}^*, 0, 0) = 0$ and $\mathbf{Y} = \bar{g}(\mathbf{X}^*, \mathbf{Z})$, where

$$\bar{g}(\mathbf{X}^*, \mathbf{Z}) = \frac{N_I \mu_I \bar{T}_I + N_C \mu_T \bar{T}_C}{\mu_\nu (1 + a_1 \bar{C})}.$$

We compute $A = D_Z h(\mathbf{X}^*, \bar{g}(\mathbf{X}^*, 0), 0)$ and get

$$A = \begin{pmatrix} -\beta_\nu - \mu_E & \frac{\beta_c \bar{T}_S N_I \mu_I}{\mu_V (1+a_1\bar{C})(1+a_0\bar{C})} & \frac{\beta_c \bar{T}_S N_C \mu_T}{\mu_V (1+a_1\bar{C})(1+a_0\bar{C})} \\ \alpha\beta_\nu & -h_I \bar{C} - \mu_I & 0 \\ (1-\alpha)\beta_\nu & 0 & -h_C \bar{C} - \mu_T \end{pmatrix}.$$

So that

$$M = \begin{pmatrix} 0 & \frac{\beta_c \bar{T}_S N_I \mu_I}{\mu_V (1+a_1\bar{C})(1+a_0\bar{C})} & \frac{\beta_c \bar{T}_S N_C \mu_T}{\mu_V (1+a_1\bar{C})(1+a_0\bar{C})} \\ \alpha\beta_\nu & 0 & 0 \\ (1-\alpha)\beta_\nu & 0 & 0 \end{pmatrix}$$

and

$$D^{-1} = \begin{pmatrix} \frac{1}{(-\beta_\nu - \mu_E)} & 0 & 0 \\ 0 & \frac{1}{(-h_I\bar{C} - \mu_I)} & 0 \\ 0 & 0 & \frac{1}{(-h_C\bar{C} - \mu_T)} \end{pmatrix}.$$

Hence,

$$MD^{-1} = \begin{pmatrix} 0 & \frac{\beta_c \bar{T}_S N_I \mu_I}{-\mu_V (1+a_0\bar{C})(1+a_1\bar{C})(h_I\bar{C}+\mu_I)} & \frac{\beta_c \bar{T}_S N_C \mu_T}{-\mu_V (1+a_0\bar{C})(1+a_1\bar{C})(h_C\bar{C}+\mu_T)} \\ \frac{-\alpha\beta_\nu}{\beta_\nu + \mu_E} & 0 & 0 \\ \frac{(1-\alpha)\beta_\nu}{\beta_\nu + \mu_E} & 0 & \frac{1}{(-h_C\bar{C} - \mu_T)} \end{pmatrix}.$$

The three eigenvalues λ_1, λ_2 and λ_3 of MD^{-1} are

$$\lambda_1 = 0,$$

$$\lambda_2 = \sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S}{\mu_V (1 + a_1\bar{C})(1 + a_0\bar{C})(\beta_\nu + \mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C} + \mu_T} + \frac{\alpha N_I \mu_I}{h_I\bar{C} + \mu_I}\right)}$$

and

$$\lambda_3 = -\sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S}{\mu_V (1 + a_1\bar{C})(1 + a_0\bar{C})(\beta_\nu + \mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C} + \mu_T} + \frac{\alpha N_I \mu_I}{h_I\bar{C} + \mu_I}\right)}.$$

The reproduction ratio is given by the next generation spectral radius $\mathbf{Rho}(\mathbf{MD^{-1}})$ to be

$$R_0 = \sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S}{\mu_V (1 + a_1\bar{C})(1 + a_0\bar{C})(\beta_\nu + \mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C} + \mu_T} + \frac{\alpha N_I \mu_I}{h_I\bar{C} + \mu_I}\right)}.$$

Lemma 2.1 *The disease-free equilibrium $\bar{E}_0$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

In order to control HIV infection the reproduction number R_0 should be kept below unit. The expression for R_0 shows, as observed by Magombedze *et al.* [60], that this can be achieved by reducing: the infectivity of the virus $\frac{\beta_c}{1+a_0C}$; the effective transcription rate $\frac{\beta_\nu}{\beta_\nu+\mu_E} = 1 - \frac{\mu_E}{\beta_\nu+\mu_E} \to 0$ as $\beta_\nu \to 0$ and the rates of viral production by bursting of both the productively infected and chronically infected T cells, $\alpha N_I \mu_I$ and $(1-\alpha)N_C\mu_T$, respectively. It is also worth to note that increasing CTL activity that include lytic killing, hindrance of viral entry into CD4+ T cells and hindrance of the assembling of HIV virions from infected $CD4^+$ T cells results in reduction of the R_0 value.

2.2.2 Local stability

To discuss the local stability conditions for the steady states $\bar{E}_o$ and $\bar{E}_1$, we linearize the system of equations (2.1)-(2.6) via the Jacobian matrix, **J**, as follows.

$$\mathbf{J} = \begin{bmatrix} D_1 & 0 & 0 & 0 & D_2 & D_3 \\ \frac{\beta_c V}{1+a_0C} & -\beta_\nu - \mu_E & 0 & 0 & -D_2 & \frac{\beta_c T_S}{1+a_0C} \\ 0 & \alpha\beta_\nu & -h_I C - \mu_I & 0 & -h_I T_I & 0 \\ 0 & (1-\alpha)\beta_\nu & 0 & -h_C C - \mu_T & -h_C T_C & 0 \\ pVC & 0 & 0 & 0 & pVT_S - \mu_C & pT_S C \\ 0 & 0 & \frac{N_I\mu_I}{1+a1} & \frac{N_C\mu_T}{1+a1} & D_4 & -\mu_V \end{bmatrix},$$

where

$$D_1 = \frac{rV}{V+A} - \frac{\beta_c V}{1+a_0C} - \frac{\tau VB}{(T_S+B)^2} - \mu_S, \tag{2.23}$$

$$D_2 = \frac{a_0\beta_c V T_S}{(1+a_0C)^2}, \tag{2.24}$$

$$D_3 = \frac{rAT_S}{(V+A)^2} - \frac{\beta_c T_S}{1+a_0C} - \frac{\tau T_S}{T_S+B}, \tag{2.25}$$

$$D_4 = \frac{a_1[N_I\mu_I T_I + N_C\mu_T T_C]}{(1+a_1C)^2}. \tag{2.26}$$

Evaluated at the disease-free state, the Jacobian matrix gives $\mathbf{J}_0$ as:

$$\mathbf{J}_0 = \begin{bmatrix} -\mu_S & 0 & 0 & 0 & 0 & \Psi_1 \\ 0 & -\beta_\nu - \mu_E & 0 & 0 & 0 & \frac{\beta_c s_T}{\mu_S(1+a_0 C)} \\ 0 & \alpha\beta_\nu & \frac{-h_I s_C}{\mu_C} - \mu_I & 0 & 0 & 0 \\ 0 & (1-\alpha)\beta_\nu & 0 & \frac{-h_C s_C}{\mu_C} - \mu_T & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_C & \frac{p s_T s_C}{\mu_S \mu_C} \\ 0 & 0 & \frac{N_I \mu_I}{1+a_1 C} & \frac{N_C \mu_T}{1+a_1 C} & 0 & -\mu_V \end{bmatrix},$$

where

$$\Psi_1 = \frac{rAs_T}{\mu_S A^2} - \frac{\beta_c s_T \mu_C}{\mu_S(\mu_C + a_0 s_C)} - \frac{\tau s_T}{s_T + \mu_S B}. \tag{2.27}$$

The eigenvalues of the Jacobian matrix can be determined by solving the characteristic equation $|\mathbf{J}_0 - \lambda\mathbf{I}| = 0$, which in our case expands to become:

$$(-\mu_S - \lambda)(-\mu_C - \lambda)(\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4) = 0, \tag{2.28}$$

where

$$b_1 = \frac{s_C(h_I+h_C)}{\mu_C} + \beta_\nu + \mu_E + \mu_I + \mu_T + \mu_V, \tag{2.29}$$

$$\begin{aligned} b_2 = {} & (\beta_\nu+\mu_E)\left(\frac{s_C(h_I+h_C)}{\mu_C} + \mu_I + \mu_T + \mu_V\right) \\ & + \left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) + \mu_V\left(\frac{s_C(h_I+h_C)}{\mu_C} + \mu_I + \mu_T\right) \\ & - \left(\frac{\beta_C s_T}{\mu_S(1+a_0\bar{C})}\right)\left(\frac{\alpha\beta_\nu N_I\mu_I + (1-\alpha)\beta_\nu N_C\mu_T}{1+a_1\bar{C}}\right), \end{aligned} \tag{2.30}$$

$$\begin{aligned} b_3 = {} & (\beta_\nu+\mu_E)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T + \mu_V\right) \\ & + \mu_V\left(\frac{h_C s_C}{\mu_C} + \mu_T\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I + \beta_\nu + \mu_E\right) \\ & - \left(\frac{\beta_c s_T}{\mu_S(1+a_0\bar{C})}\right)\left(\frac{\alpha\beta_\nu N_I\mu_I}{1+a_1\bar{C}}\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\ & - (1-\alpha)\left(\frac{\beta_c s_T}{\mu_S(1+a_0\bar{C})}\right)\left(\frac{\beta_\nu N_C\mu_T}{1+a_1\bar{C}}\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right), \end{aligned} \tag{2.31}$$

$$\begin{aligned} b_4 = {} & \mu_V\left(\beta_\nu+\mu_E\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\ & - \left(\frac{\beta_c s_T}{\mu_S(1+a_0\bar{C})}\right)\left(\frac{\alpha\beta_\nu N_I\mu_I}{1+a_1\bar{C}}\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\ & + \left(\frac{(1-\alpha)\beta_\nu N_C\mu_T}{1+a_1\bar{C}}\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right). \end{aligned} \tag{2.32}$$

Two of the eigenvalues are $\lambda_1 = -\mu_S$ and $\lambda_2 = -\mu_C$. To get the other 4 eigenvalues, or at least be able to impose some conditions on them, we employ the Routh-Hurwitz criterion on the 4^{th} order characteristic polynomial:

$$q(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 \tag{2.33}$$

The roots of the characteristic polynomial above to have negative reals parts if $\frac{b_1b_2-b_3}{b_1} > 0$ and $\frac{b_3-b_4b_1^3}{b_1b_2-b_3} > 0$. That is, for a stable system $b_1b_2-b_3 > 0$ and $b_1b_2b_3-b_3^2-b_4b_1^4 > 0$. Since the expressions for the b_is are complex we are not going to do a deeper analysis of the stability conditions on the critical parameters at this stage.

2.2.3 Global stability conditions for the disease-free equilibrium

To investigate the global stability conditions for the disease-free equilibrium for this model we use the method of Castillo-chavez *et al.* [64]. We re-write the equations (2.1)-(2.6) in the form:

$$\begin{aligned} \frac{d\mathbf{X}}{dt} &= F(\mathbf{X}, \mathbf{Z}) \\ \frac{d\mathbf{Z}}{dt} &= G(\mathbf{X}, \mathbf{Z}) \end{aligned} \tag{2.34}$$

with $G(\mathbf{X}, \mathbf{0}) = 0$, where $\mathbf{X} \in \mathbb{R}^2$ denotes the vector of uninfected classes and $\mathbf{Z} \in \mathbb{R}^4$ denotes the vector of infected classes. $\mathbf{U}_0 = (\mathbf{X}^*, \mathbf{0})$ denotes the disease-free equilibrium The conditions (**H1**) and (**H2**) below must be met to guarantee global asymptotic stability.

H1: for $\frac{d\mathbf{x}}{dt} = F(\mathbf{X}, \mathbf{0})$, $\mathbf{X}^*$ is globally asymptotically stable.
H2: $G(\mathbf{X}, \mathbf{Z}) = A\mathbf{Z} - \hat{G}(\mathbf{X}, \mathbf{Z})$, $\hat{G}(\mathbf{X}, \mathbf{Z}) \geq 0$ for $(\mathbf{X}, \mathbf{Z}) \in \Omega$) where $A = D_{\mathbf{Z}} G(\mathbf{X}^*, \mathbf{0})$ is an M-matrix (the off-diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. If the above two conditions are satisfied then the following theorem holds.

Theorem 2.2 (Castillo-chavez et al. [64]): *The fixed point $\boldsymbol{U}_0 = (\boldsymbol{X}^*, \boldsymbol{0})$ is a globally stable equilibrium of the system (2.17) provided that $R_0 < 1$ and that assumptions (H1) and (H2) are satisfied.*

For the set of equations (2.1)-(2.6) we set $(X) = (T_S, C)$: the set of uninfected target CD4$^+$ T cells and HIV-specific CTLs, and $\mathbf{Z} = (T_E, T_I, T_C, V)$: the 'exposed' CD4$^+$ T cells, productively infected CD4$^+$ T cells, chronically infected CD4$^+$ T cells and the HIV particles. We compute $F(\mathbf{X}, \mathbf{0}) = 0$, $A(= D_{\mathbf{Z}} G(\mathbf{X}^*, \mathbf{0}))$ and $\hat{G}(\mathbf{X}, \mathbf{Z})$ as follows:

$$F(\mathbf{X}, \mathbf{0}) = \begin{pmatrix} s_T - \mu_S T_S \\ s_C - \mu_C C \end{pmatrix},$$

$$A = \begin{pmatrix} -\beta_\nu - \mu_E & 0 & 0 & \frac{\beta_c \bar{T}_S}{1+a_0\bar{C}} \\ \alpha\beta_\nu & -h_I\bar{C} - \mu_I & 0 & 0 \\ (1-\alpha)\beta_\nu 0 & -h_C\bar{C} - \mu_T & 0 & \\ 0 & \frac{N_I\mu_I}{1+a_1\bar{C}} & \frac{N_C\mu_T}{1+a_1\bar{C}} & -\mu_V \end{pmatrix},$$

$$A\mathbf{Z} = \begin{pmatrix} -\beta_\nu T_E - \mu_E T_E + \frac{\beta_c \bar{T}_S V}{1+a_0\bar{C}} \\ \alpha\beta_\nu T_E - h_I\bar{C}T_I - \mu_I T_I \\ (1-\alpha)\beta_\nu T_E - h_C\bar{C}T_C - \mu_T T_C \\ \frac{N_I\mu_I T_I}{1+a_1\bar{C}} + \frac{N_C\mu_T T_C}{1+a_1\bar{C}} - \mu_V V \end{pmatrix}.$$

So that using condition (**H2**) above we have,

$$\hat{G}(\mathbf{X}, \mathbf{Z}) = \begin{pmatrix} \beta_c V \left(\frac{\bar{T}_S}{1+a_0\bar{C}} - \frac{T_S}{1+a_0\bar{C}} \right) \\ h_I T_I (C - \bar{C}) \\ h_C T_C (C - \bar{C}) \\ (N_I\mu_I T_I + N_C\mu_T T_C) \left(\frac{1}{1+a_1\bar{C}} + \frac{1}{1+a_1\bar{C}} \right) \end{pmatrix}.$$

Global stability of the system at $\bar{E}_0$ requires that $\hat{G}(\mathbf{X}, \mathbf{Z}) \geq 0$. Now, examining $\hat{G}_1(\mathbf{X}, \mathbf{Z}) = \beta_c V \left(\frac{\bar{T}_S}{1+a_0\bar{C}} - \frac{T_S}{1+a_0\bar{C}} \right)$: $\frac{1}{1+a_0\bar{C}} \geq \frac{1}{1+a_0 C}$ since $C = \frac{s_C}{\mu_C - pVT_S} . \frac{s_C}{\mu_C} = \bar{C}$, when there is HIV infection. Using the equation describing the dynamics of the uninfected CD4$^+$ T cells, equation (2.1), at the endemic equilibrium

$$s_T + \frac{rVT_S}{V+A} - \frac{\beta_c V T_S}{1+a_0 C} - \mu_S T_S = 0.$$

Hence,

$$s_T + \frac{rVT_S}{V+A} - \mu_S T_S \geq 0,$$

so that

$$\frac{s_T}{\mu_S - \frac{rV}{V+A}} \geq T_S.$$

Though we can not explicitly verify that $\bar{T}_S = \frac{s_T}{\mu_S} > T_S$, biological facts and results from numerical simulations in section (2.3) provide evidences that depletion of CD4$^+$ T cells occurs after invasion by virus and so we can ascertain that $\bar{T}_S = \frac{s_T}{\mu_S} \geq T_S$.

Clearly, $\hat{G}_2(\mathbf{X},\mathbf{Z})$, $\hat{G}_3(\mathbf{X},\mathbf{Z})$ and $\hat{G}_4(\mathbf{X},\mathbf{Z}) \geq 0$ and, therefore, $\hat{G}(\mathbf{X},\mathbf{Z}) \geq 0$.
It is easy to show that $\mathbf{X}^* = (\frac{s_T}{\mu_S}, \frac{s_C}{\mu_C})$ is a globally asymptotically stable state of $\frac{d\mathbf{X}}{dt} = F(\mathbf{X},\mathbf{0})$, since, $F(\mathbf{X},\mathbf{0})$ is a limiting function of $\frac{d\mathbf{X}}{dt} = F(\mathbf{X}(t),\mathbf{Z}(t))$, that is, $lim_{t\to\infty}\mathbf{X}(t) = \mathbf{X}^*$. Therefore $\bar{E}_0$ is indeed a globally asymptotically stable equilibrium point.

2.2.4 Global stability conditions for the endemic equilibrium

To study the global stability of the endemic equilibrium we employ a "Lyapunov technique" [65] that was used by A. Fall *et al.* [66] and references mentioned therein. They used the Lyapunov function of the form $V = \sum_{i=1}^{n} a_i(x_i - \bar{x}_i \ln x_i)$. This is known as the Volterra-Lyapunov function.

Theorem 2.3 *Let V be a continuous function for a dynamical system φ on an open set D such that $x_0 \in D$, where x_0 is an equilibrium point of $\dot{x} = f(x)$. If V is positive definite and $\dot{V}$ is negative definite, then the equilibrium point x_0 is globally asymptotically stable.*

For the system of equations (2.1)-(2.6), the endemic equilibrium $\bar{E}_1$ satisfies the following relations:

$$-\frac{r\widetilde{T}_S\widetilde{V}}{\widetilde{V}+A} + \frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} + \frac{\tau\widetilde{V}\widetilde{T}_S}{\widetilde{T}_S+B} + \mu_S\widetilde{T}_S = s_T, \tag{2.35}$$

$$\frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} = \beta_\nu\widetilde{T}_E + \mu_E\widetilde{T}_E, \tag{2.36}$$

$$\alpha\beta_\nu\widetilde{T}_E = h_I\widetilde{T}_I\widetilde{C} + \mu_I\widetilde{T}_I, \tag{2.37}$$

$$(1-\alpha)\beta_\nu\widetilde{T}_E = h_C\widetilde{T}_C\widetilde{C} + \mu_T\widetilde{T}_C, \tag{2.38}$$

$$s_C + p\widetilde{V}\widetilde{T}_S\widetilde{C} = \mu_C\widetilde{C}, \tag{2.39}$$

$$\frac{N_I\mu_I\widetilde{T}_I}{1+a_1\widetilde{C}} + \frac{N_C\mu_T\widetilde{T}_C}{1+a_1\widetilde{C}} = \mu_V\widetilde{V}. \tag{2.40}$$

Let us consider a possible Lyapunov function:

$$V_{EE} = (T_S - \widetilde{T}_S \ln T_S) + (T_E - \widetilde{T}_E \ln T_E) + (T_I - \widetilde{T}_I \ln T_I) + (T_C - \widetilde{T}_C \ln T_C).$$

We are interested in the time derivative of V_{EE} along a solution curve:

$$\dot{V}_{EE} = \left(\dot{T}_S - \frac{\widetilde{T}_S \dot{T}_S}{T_S}\right) + \left(\dot{T}_E - \frac{\widetilde{T}_E \dot{T}_E}{T_E}\right) + \left(\dot{T}_I - \frac{\widetilde{T}_I \dot{T}_I}{T_I}\right) + \left(\dot{T}_C - \frac{\widetilde{T}_C \dot{T}_C}{T_C}\right).$$

Thus,

$$\dot{V}_{EE} = \dot{T}_S\left(1 - \frac{\widetilde{T}_S}{T_S}\right) + \dot{T}_E\left(1 - \frac{\widetilde{T}_E}{T_E}\right) + \dot{T}_I\left(1 - \frac{\widetilde{T}_I}{T_I}\right) + \dot{T}_C\left(1 - \frac{\widetilde{T}_C}{T_C}\right).$$

From numerical results (figure 2.1) in the next section we observe that:

$\dot{T}_S \leq 0$, $1 - \frac{\widetilde{T}_S}{T_S} \geq 0$ and so $\dot{T}_S\left(1 - \frac{\widetilde{T}_S}{T_S}\right) \leq 0$;

$\dot{T}_E \geq 0$, $1 - \frac{\widetilde{T}_E}{T_E} \leq 0$ and so $\dot{T}_E\left(1 - \frac{\widetilde{T}_E}{T_E}\right) \leq 0$;

$\dot{T}_I \geq 0$, $1 - \frac{\widetilde{T}_I}{T_I} \leq 0$ and so $\dot{T}_I\left(1 - \frac{\widetilde{T}_I}{T_I}\right) \leq 0$;

$\dot{T}_C \geq 0$, $1 - \frac{\widetilde{T}_C}{T_C} \leq 0$ and so $\dot{T}_C\left(1 - \frac{\widetilde{T}_C}{T_C}\right) \leq 0$.

Hence, ultimately $\dot{V}_{EE} \leq 0$. Since V is non-increasing, the endemic equilibrium is globally asymptotically stable.

2.3 Numerical simulations

In this section a numerical simulation of the solution to the pretreatment model is carried out using the Runge-Kutta forth order method. Matlab 6.5 is employed in programming. The initial population densities and parameter values are presented in table 2.2. Initiation of the simulations begins at inoculation, hence the initial population densities of $0 cells/mm^3$ for the "infected" cells.

Variable	Value[Source]
$T_S(0)$	1500[64]
$T_E(0)$	0[60]
$T_I(0)$	0[60]
$T_C(0)$	0[60]
$C(0)$	10[26]
$V(0)$	10[60]
Parameter	
s_T	20[26]
r	0.01[46]
A	400[46]
β_c	0.0025[60]
a_0	0.01[60]
τ	0.00001[60]
B	350.0[60]
μ_S	0.02[60]
β_ν	0.00045[60]
μ_E	0.02[60]
h_I	0.0025[26]
μ_I	0.026[est]
α	0.7[est]
h_C	0.0015[26]
μ_T	0.022[est]
s_C	10.0[59]
p	0.00001[60]
μ_C	1.5[60]
N_I	1500[67]
N_C	1200[est]
a_1	0.015[60]
μ_V	1.5[60]

Table 2.2: Table of variable and parameter values used in numerical simulations where est means estimate

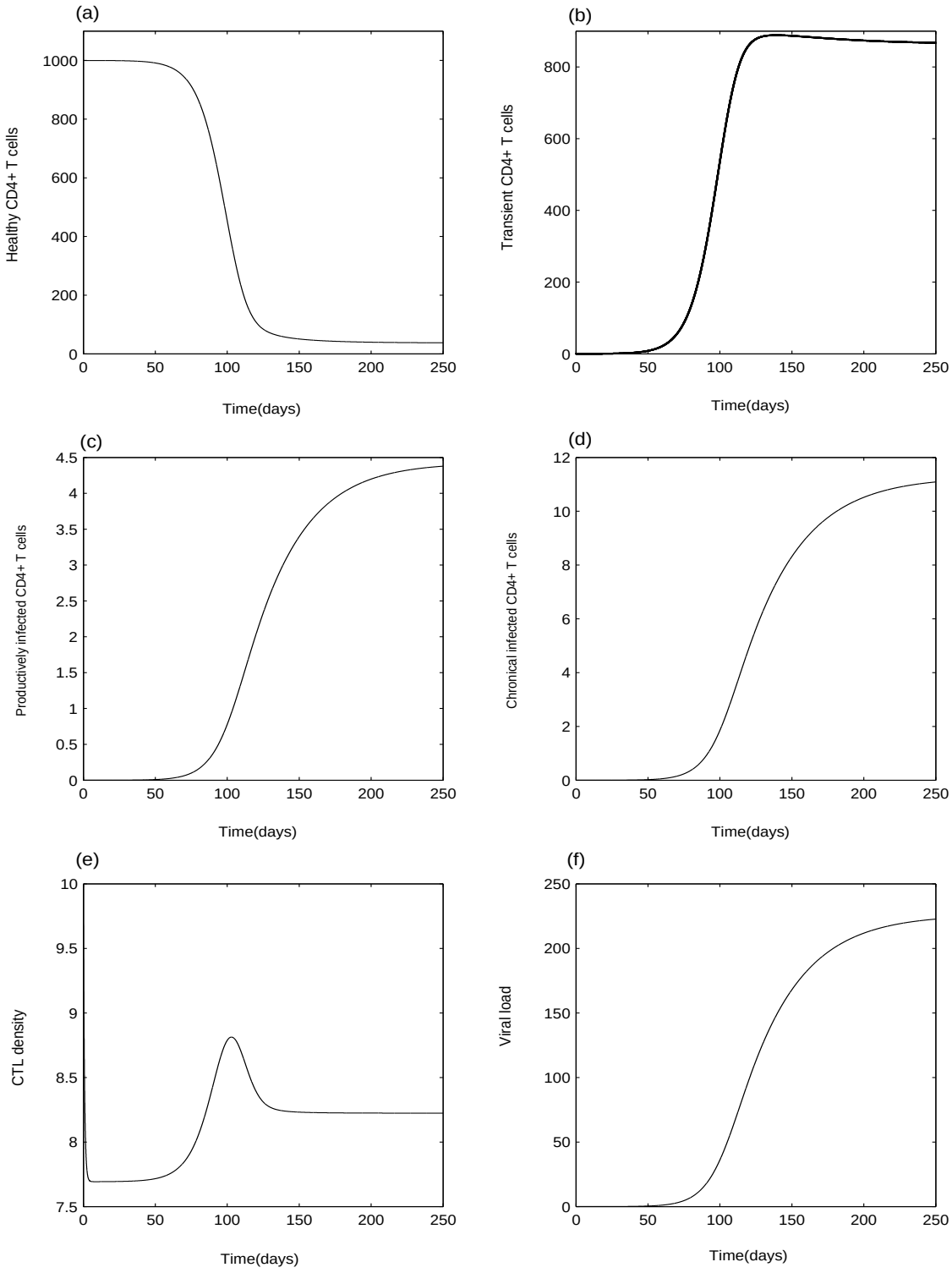

Figure 2.1: Graph of the numerical solution to equations (2.1)-(2.6), depicting the dynamics of: (a) healthy $CD4^+$ T cells, (b) transiently infected $CD4^+$ T cells, (c) productively infected $CD4^+$ T cells, (d) chronically infected $CD4^+$ T cells, (e) HIV-specific CTLs and (f) the HIV virion during the first few days of infection

2.3.1 Discussion

As depicted in figure 2.1 target-cell population remains at high levels for some days after infection, as CTL activity builds up to fight infection and viral replication. In fact, during the first 50 days after infection the population density of healthy $CD4^+$ T cells remains at approximately $1000 cells/mm^3$, CTL activity against HIV will be relatively low. This is because the virus will not have fully established itself among the cells of the immune system. After this initial period there is a rigorous build up in CTL action because there will have been enough contact between viral particles and target T cells, which facilitates the proliferation of CTL cells. This subsequent increase in cellular-mediated immune responses will be directed towards fighting new infections and suppression of viral replication. Meanwhile, the viral replication will have kick-started, slowly though, and we also observe a slow decline in the $CD4^+$ T cell count. This scenario lasts only for a short period before a sudden upsurge in the replication kinetics of virus. The strong and steady increase in the replication of the virus and the simultaneous rapid fall in CD4 count is also accompanied by a drop in cellular-mediated immune responses as the immune system succumbs due to the perversive nature of the viral replication process. The emergence of new mutants with impaired immune system recognition properties through: restricted gene expression; infection of sites not readily accessible to the immune system; down regulation of surface molecules required for T cell recognition and interference with antiviral cytokines, can be implicated for the virus' ability to eventually outclass the immune system. The continued production of virion by long-lived cells can also be cited as another main contributor to the upsurge in viral load and once the virus has established itself within the $CD4^+$ T cells, it is capable of altering the normal functioning of the cell by inducing the T-cell to produce more virion at the expense of antibody and IL-2 production, leading to the complete destruction of T-lymphocytes within the body and a total inability of the body to fight infection by foreign antigens that indicates progression to AIDS.

Chapter 3

Chemotherapy Model

In this chapter the pretreatment model is modified to incorporate the effects of drug efficacy. Numerical results in the previous chapter predict that in the absence of treatment the viral load and the concentration of productively infected and chronically infected $CD4^+$ T cells attain positive steady state values. Eventually, the cellular mediated immune responses, mainly the CTL responses, would get to a stage where it can not contain the viral density in the body, and so it is at that particular stage where treatment can be initiated. We shall incorporate three categories of anti-retroviral drugs which are: FIs, RTIs and PIs. In addition to the assumptions of the pretreatment model, we further assume that:

- When fusion inhibitors (FIs) are administered, the rate of entry of virions into the cytoplasm of $CD4^+$ T cells parameter β_c is modified to become $\beta_c(1-\gamma)$, where γ is the efficacy of FIs and $0 < \gamma < 1$.

- When RTIs are administered, the rate of transcription of HIV-1 RNA to DNA parameter β_ν, is modified to become $\beta_\nu(1-\epsilon)$, where ϵ is the efficacy of RTIs and $0 < \epsilon < 1$.

- When PIs are administered, the burst size parameters N_I and N_C are modified to become $(1-\kappa)N_I$ and $(1-\kappa)N_C$, respectively, where κ is the efficacy of PIs and $0 < \kappa < 1$.

- We further assume that there are no pharmacological and intracellular delays in drug action.

Hence, the model of multi-drug therapy which includes FIs, RTIs and PIs assumes seven interacting populations. The components being: the uninfected CD4$^+$ T cells ($T_S, cells/mm^3$), infected CD4$^+$ T cells where there virions have only entered the cytoplasm of the CD4$^+$ T cells ($T_E, cells/mm^3$), productively infected CD4$^+$ T cells($T_I, cells/mm^3$), chronically infected CD4$^+$ T cells ($T_C, cells/mm^3$), HIV specific CTLs ($C, cells/mm^3$), infectious plasma viral load ($V, copies/mm^3$) and non-infectious plasma viral load ($V^*, copies/mm^3$) With these additional assumptions we are thus lead into the following set of differential equations.

$$\frac{dT_S}{dt} = s_T + \frac{rT_SV}{V+A} - \frac{\beta_c(1-\gamma)VT_S}{1+a_0C} - \frac{\tau VT_S}{T_S+B} - \mu_S T_S, \tag{3.1}$$

$$\frac{dT_E}{dt} = \frac{(1-\gamma)\beta_c VT_S}{1+a_0C} - (1-\epsilon)\beta_\nu T_E - \mu_E T_E, \tag{3.2}$$

$$\frac{dT_I}{dt} = (1-\epsilon)\alpha\beta_\nu T_E - h_I T_I C - \mu_I T_I, \tag{3.3}$$

$$\frac{dT_C}{dt} = (1-\epsilon)(1-\alpha)\beta_\nu T_E - h_C T_C C - \mu_T T_C, \tag{3.4}$$

$$\frac{dC}{dt} = s_C + pVT_SC - \mu_C C, \tag{3.5}$$

$$\frac{dV}{dt} = \frac{(1-\kappa)N_I\mu_I T_I}{1+a_1C} + \frac{(1-\kappa)N_C\mu_T T_C}{1+a_1C} - \mu_V V, \tag{3.6}$$

$$\frac{dV^*}{dt} = \frac{\kappa N_I\mu_I T_I}{1+a_1C} + \frac{\kappa N_C\mu_T T_C}{1+a_1C} - \mu_V V^*. \tag{3.7}$$

Equations (3.1)-(3.6) are basically described in the same way as the basic model of HIV-1 infection. The difference is that the parameters β_ν, β_c, N_I and N_C are modified as a result of drug administration and that there is now presence of non-infectious virus. Equation (3.7) describes the dynamics of the non-infectious virus due to the administration of PIs.

3.1 Analysis of the chemotherapy model

The equilibrium states for the three-drug combination therapy model are obtained by setting the right-hand side of equations (3.1)-(3.7) to zero. The virus-free steady state of the

equations (3.1)-(3.7) is given by

$$\bar{E}_{T0} = (\bar{T}_S, \bar{T}_E, \bar{T}_I, \bar{T}_C, \bar{C}, \bar{V}, \bar{V}^*) = \left(\frac{s_T}{\mu_S}, 0, 0, 0, \frac{s_C}{\mu_C}, 0, 0\right).$$

The HIV-infected steady state is given by

$$\bar{E}_{T1} = (\widetilde{T}_S, \widetilde{T}_E, \widetilde{T}_I, \widetilde{T}_C, \widetilde{C}, \widetilde{V}, \widetilde{V}^*),$$

where $\widetilde{T}_S$, $\widetilde{T}_E$, $\widetilde{T}_I$, $\widetilde{T}_C$, $\widetilde{V}$ and $\widetilde{V}^*$ are given , implicitly, by expressions (3.8)-(3.14).

The equilibrium value of healthy CD4$^+$ T cells is given by

$$\widetilde{T}_S = \frac{-\Gamma_2 + \sqrt{(\Gamma_2)^2 - 4Bs_T\Gamma_1}}{2\Gamma_1}, \tag{3.8}$$

where

$$\begin{aligned}
\Gamma_1 &= \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{(1-\gamma)\beta_c\widetilde{V}}{1+a_0\widetilde{C}} - \mu_S, \\
\Gamma_2 &= s_T + \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{(1-\gamma)\beta_c B\widetilde{V}}{1+a_0\widetilde{C}} - \tau - \mu_S.
\end{aligned}$$

For existence of this equilibrium value, $\widetilde{T}_S > 0$, that is, $\frac{-\Gamma_2+\sqrt{(\Gamma_2)^2-4Bs_T\Gamma_1}}{2\Gamma_1} > 0$. Expression (3.8) shows that fusion inhibitors increase the survivability of healthy CD4$^+$ T cells. The factor $(1-\gamma)$ further reduces the value of β_c as γ increases. The population density of exposed CD4$^+$ T cells waiting for transcription to occur is given by

$$\widetilde{T}_E = \frac{(1-\gamma)\beta_c\widetilde{V}\widetilde{T}_S}{(1+a_0\widetilde{C})((1-\gamma)\beta_\nu + \mu_E)}. \tag{3.9}$$

From this expression we deduce that FIs have the effect of reducing the abundance of CD4$^+$ T cells that fused with virus but are still waiting for transcription. RTIs, on the other hand, have the effect of increasing the abundance of such. The productively infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_I = \frac{\alpha\beta_\nu(1-\epsilon)\widetilde{T}_E}{h_I\widetilde{C} + \mu_I}. \tag{3.10}$$

The chronically infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_C = \frac{(1-\alpha)(1-\epsilon)\beta_\nu\widetilde{T}_E}{h_C\widetilde{C} + \mu_T}. \tag{3.11}$$

Expressions (3.10) and (3.11) show that RTIs have the effect of reducing chances of successful transcription in chronic HIV infection, and thereby reducing the abundance of both productively and chronically infected $CD4^+$ T cells in a patient. The endemic steady state value of HIV specific CTLs is given by

$$\widetilde{C} = \frac{s_C}{\mu_C - p\widetilde{T}_S\widetilde{V}}. \tag{3.12}$$

Existence conditions deduced earlier in the previous chapter also apply for the chemotherapy model, in accordance with the earlier observation, expression (3.12) tells us that increased interactions between healthy $CD4^+$ T cells and viral particles results in increased CTL proliferation thereby increasing the abundance of $CD8^+$ T cells available for lytic and non-lytic activities. The infectious viral steady state is given by

$$\widetilde{V} = \frac{(1-\kappa)N_I\mu_I\widetilde{T}_I + (1-\kappa)N_C\mu_T\widetilde{T}_C}{\mu_\nu(1+a_1\widetilde{C})}), \tag{3.13}$$

and that of the non-infectious viral load is given by

$$\widetilde{V}^* = \frac{\kappa N\mu_I\widetilde{T}_I}{\mu_V(1+a_1\widetilde{C}).} \tag{3.14}$$

The density of non-infectious viral particles increases as the efficacy of PIs increases. Generally, administering drugs would lead to a higher turnover of healthy T cells and reduced concentration of infectious viral load by rendering some viral particles non-infectious. CTL activity continues to play a vital role in fighting infection.

3.1.1 The reproduction number

In order to determine the stability conditions of the two steady states ($\bar{E}_{T0}$ and $\bar{E}_{T1}$) obtained above we need to calculate the reproduction number. Using van den Driessche and Watmough's [61] approach, we distinguish new infections from all other changes in population. Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ be the rate of transfer of susceptible cells into compartment i by all other means and $\mathcal{V}_i^-(x)$ be the transfer out of i. Further, we assume that each function is continuously differentiable

at least twice in each variable [61]. The disease transmission model consists of nonnegative initial conditions together with the following system of equations:

$$\frac{dx_i}{dt} = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1 \cdots 7. \tag{3.15}$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$.
For the system of equations (3.1)-(3.7) and the functions, $\mathcal{F}_i(x)$ and $\mathcal{V}_i(x)$, satisfying the conditions outlined by van den Driessche and Watmough [61] we can partition the matrix $Df(x_0)$ according to the following lemma.

Lemma 3.1 (van den Driessche and Watmough) [61] *If x_0 is a disease-free equilibrium of (3.22) and $f_i(x)$ satisfies the assumptions outlined in [61], then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \qquad D\mathcal{V}(x_0) = \begin{pmatrix} F & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the m x m matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0) \right] \quad \textit{and} \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0) \right],$$

with $1 \leq i, j \leq m$, m is the number of infected compartments Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part. The matrix $\mathcal{V}$ is the "mass" balance of the compartments.

The reproductive number is therefore equal to the spectral radius of the next generation matrix FV^{-1} [61]:

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

where $\rho(A)$ denotes the spectral radius of a matrix A.

For the system of equations (3.1)-(3.7), the infection process starts when an HIV particle attaches to and enters the $CD4^+$ T cell cytoplasm, then ends when there is successful

transcription. Hence,

$$\mathcal{F} = \begin{pmatrix} \frac{(1-\gamma)\beta_c V T_S}{1+a_0 C} \\ (1-\epsilon)\alpha\beta_\nu T_E \\ (1-\epsilon)(1-\alpha)\beta_\nu T_E \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

, and

$$\mathcal{V} = \begin{pmatrix} (1-\epsilon)\beta_\nu T_E + \mu_E T_E \\ h_I T_I C + \mu_I T_I \\ h_C T_C C + \mu_T T_C \\ \frac{\beta_c(1-\gamma)VT_S}{1+a_0 C} + \frac{\tau V T_S}{T_S+B} + \mu_S T_S - s_T - \frac{rT_S V}{V+A} \\ \mu_C C - s_C - pVT_S C \\ \mu_V V - \frac{(1-\kappa)(N_I\mu_I T_I + N_C\mu_T T_C)}{1+a_1 C} \\ \mu_V V^* - \frac{\kappa(N_I\mu_I T_I + N_C\mu_T T_C)}{1+a_1 C} \end{pmatrix}.$$

The infected compartments are T_E, T_I and T_C, giving $m = 3$. Thus,

$$F = \begin{pmatrix} 0 & \frac{(1-\gamma)(1-\kappa)\beta_c\alpha\bar{T}_S N_I\mu_I}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})} & \frac{(1-\gamma)(1-\kappa)\beta_c(1-\alpha)\bar{T}_S N_C\mu_T}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})} \\ (1-\epsilon)\alpha\beta_\nu & 0 & 0 \\ (1-\epsilon)(1-\alpha)\beta_\nu & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} (1-\epsilon)\beta_\nu + \mu_E & 0 & 0 \\ 0 & h_I\bar{C} + \mu_I & 0 \\ 0 & 0 & h_C\bar{C} + \mu_T \end{pmatrix},$$

giving

$$V^{-1} = \begin{pmatrix} \frac{1}{(-(1-\epsilon)\beta_\nu - \mu_E)} & 0 & 0 \\ 0 & \frac{1}{(-h_I\bar{C} - \mu_I)} & 0 \\ 0 & 0 & \frac{1}{(-h_C\bar{C} - \mu_T)} \end{pmatrix},$$

and hence,

$$FV^{-1} = \begin{pmatrix} 0 & \frac{(1-\gamma)(1-\kappa)\alpha\beta_c\bar{T}_S N_I\mu_I}{\mu_V(1+a_0\bar{C})(1+a_1\bar{C})(h_I\bar{C}+\mu_I)} & \frac{(1-\gamma)(1-\kappa)(1-\alpha)\beta_c\bar{T}_S N_C\mu_T}{\mu_V(1+a_0\bar{C})(1+a_1\bar{C})(h_C\bar{C}+\mu_T)} \\ \frac{-(1-\epsilon)\alpha\beta_\nu}{(1-\epsilon)\beta_\nu+\mu_E} & 0 & 0 \\ \frac{-(1-\epsilon)(1-\alpha)\beta_\nu}{(1-\epsilon)\beta_\nu+\mu_E} & 0 & 0 \end{pmatrix}.$$

The three eigenvalues λ_1, λ_2 and λ_3 of FV^{-1} are

$$\lambda_1 = 0,$$

$$\lambda_2 = \sqrt{\left(\frac{(1-\epsilon)(1-\alpha)(1-\kappa)\beta_\nu\beta_c\bar{T}_S}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})((1-\epsilon)\beta_\nu+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I\mu_I}{h_I\bar{C}+\mu_I}\right)},$$

and

$$\lambda_3 = -\sqrt{\left(\frac{(1-\epsilon)(1-\alpha)(1-\kappa)\beta_\nu\beta_c\bar{T}_S}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})((1-\epsilon)\beta_\nu+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I\mu_I}{h_I\bar{C}+\mu_I}\right)}.$$

Thus,

$$R_T = \sqrt{\left(\frac{(1-\epsilon)(1-\alpha)(1-\kappa)\beta_\nu\beta_c\bar{T}_S}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})((1-\epsilon)\beta_\nu+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I\mu_I}{h_I\bar{C}+\mu_I}\right)}$$

R_T is called the chemotherapy reproductive ratio, which defines the number of secondary infections when a drug regimen constituting FIs, RTIs and PIs is administered to a chronically infected HIV-positive individual. Expressed in terms of R_0,

$$R_T = R_0\sqrt{\frac{(1-\gamma)(1-\epsilon)(1-\kappa)(\beta_\nu+\mu_E)}{((1-\epsilon)\beta_\nu+\mu_E)}}, \tag{3.16}$$

Invoking a similar version of Lemma 2.1 the disease-free equilibrium $\bar{E}_{T0}$ is locally asymptotically stable if $R_T < 1$ and unstable if $R_T > 1$. From expression (3.19) and by observing that $\sqrt{\frac{(1-\gamma)(1-\epsilon)(1-\kappa)(\beta_\nu+\mu_E)}{(1-\epsilon)\beta_\nu+\mu_E)}} \leq 1$ deduces that $R_T \leq R_0$ which implies that eradication of the viral population can be achieved by treating a chronically infected HIV-positive patient with a drug combination of RTIs, PIs and FIS, when CTL activity alone fails to curb infection.

3.1.2 Local stability

To discuss the local stability conditions for the steady states $\bar{E}_{T0}$ and $\bar{E}_{T1}$, we linearize the system of equations (3.1)-(3.7) via the Jacobian matrix, $\mathbf{J}$, as follows.

$$\mathbf{J} = \begin{bmatrix} G_1 & 0 & 0 & 0 & G_2 & G_3 & 0 \\ \frac{\beta_c(1-\gamma)V}{1+a_0C} & -(1-\epsilon)\beta_\nu - \mu_E & 0 & 0 & -G_2 & \frac{\beta_c(1-\gamma)T_S}{1+a_0C} & 0 \\ 0 & (1-\epsilon)\alpha\beta_\nu & -h_IC - \mu_I & 0 & -h_IT_I & 0 & 0 \\ 0 & (1-\epsilon)(1-\alpha)\beta_\nu & 0 & -h_CC - \mu_T & -h_CT_C & 0 & 0 \\ pVC & 0 & 0 & 0 & pVT_S - \mu_C & pT_SC & 0 \\ 0 & 0 & \frac{(1-\kappa)N_I\mu_I}{1+a_1C} & \frac{(1-\kappa)N_C\mu_T}{1+a_1C} & G_4 & -\mu_V & 0 \\ 0 & 0 & \frac{\kappa N_I\mu_I}{1+a_1C} & \frac{\kappa N_C\mu_T}{1+a_1C} & \frac{\kappa}{1-\kappa}G_4 & 0 & -\mu_V \end{bmatrix}$$

$$G_1 = \frac{rV}{V+A} - \frac{\beta_c(1-\gamma)V}{1+a_0C} - \frac{\tau BV}{(T_S+B)^2} - \mu_S, \tag{3.17}$$

$$G_2 = \frac{a_0\beta_c(1-\gamma)VT_S}{(1+a_0C)^2}, \tag{3.18}$$

$$G_3 = \frac{rAT_S}{(V+A)^2} - \frac{\beta_c(1-\gamma)T_S}{1+a_0C} - \frac{\tau T_S}{T_C+B}, \tag{3.19}$$

$$G_4 = \frac{a_1(1-\kappa)[N_I\mu_IT_I + N_C\mu_TT_C]}{(1+a_1C)^2}. \tag{3.20}$$

Evaluated at the disease-free state, $\bar{E}_{T0}$, the Jacobian matrix gives $\mathbf{J}_0$ as:

$$\mathbf{J}_0 = \begin{bmatrix} -\mu_S & 0 & 0 & 0 & 0 & \Psi_2 & 0 \\ 0 & -(1-\epsilon)\beta_\nu - \mu_E & 0 & 0 & 0 & \frac{(1-\gamma)\beta_c s_T}{\mu_S(1+a_0C)} & 0 \\ 0 & (1-\epsilon)\alpha\beta_\nu & \frac{-h_Is_C}{\mu_C} - \mu_I & 0 & 0 & 0 & 0 \\ 0 & (1-\epsilon)(1-\alpha)\beta_\nu & 0 & \frac{-h_Cs_C}{\mu_C} - \mu_T & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_C & \frac{ps_Ts_C}{\mu_CS} & 0 \\ 0 & 0 & \frac{(1-\kappa)N_I\mu_I}{1+a_1C} & \frac{(1-\kappa)N_C\mu_T}{1+a_1C} & 0 & -\mu_V & 0 \\ 0 & 0 & \frac{\kappa N_I\mu_I}{1+a_1C} & \frac{\kappa N_C\mu_T}{1+a_1C} & 0 & 0 & -\mu_V \end{bmatrix}$$

where

$$\Psi_2 = \frac{rs_TA}{\mu_SA^2} - \frac{\mu_C\beta_cs_T(1-\gamma)}{\mu_S(\mu_C+a_0s_C)} - \frac{\tau s_T}{s_T+\mu_S(B)}. \tag{3.21}$$

The eigenvalues of the Jacobian matrix can be determined by solving the characteristic equation $|\mathbf{J}_0 - \lambda\mathbf{I}| = 0$, which in our case expands to become:

$$(-\mu_S - \lambda)(-\mu_C - \lambda)(-\mu_V - \lambda)(\lambda^4 + f_1\lambda^3 + f_2\lambda^2 + f_3\lambda + f_4) = 0, \tag{3.22}$$

where

$$\begin{aligned}
f_1 &= \frac{s_C(h_I + h_C)}{\mu_C} + (1-\epsilon)\beta_\nu + \mu_E + \mu_I + \mu_T + \mu_V, \\
f_2 &= ((1-\epsilon)\beta_\nu + \mu_E)\left(\frac{s_C(h_I + h_C)}{\mu_C} + \mu_I + \mu_T + \mu_V\right) \\
&\quad + \left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) + \mu_V\left(\frac{s_C(h_I + h_C)}{\mu_C} + \mu_I + \mu_T\right) \\
&\quad - \left(\frac{\beta_C s_T}{\mu_S(1 + a_0\bar{C})}\right)\left(\frac{\alpha(1-\epsilon)\beta_\nu(1-\kappa)N_I\mu_I + (1-\alpha)(1-\epsilon)\beta_\nu(1-\kappa)N_C\mu_T}{1 + a_1\bar{C}}\right), \\
f_3 &= (1-\epsilon)\beta_\nu + \mu_E)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T + \mu_V\right) \\
&\quad + \mu_V\left(\frac{h_C s_C}{\mu_C} + \mu_T\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I + (1-\epsilon)\beta_\nu + \mu_E\right) \\
&\quad - \left(\frac{(1-\gamma)\beta_c s_T}{\mu_S(1 + a_0\bar{C})}\right)\left(\frac{\alpha(1-\epsilon)\beta_\nu(1-\kappa)N_I\mu_I}{1 + a_1\bar{C}}\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\
&\quad - (1-\alpha)\left(\frac{(1-\gamma)\beta_c s_T}{\mu_S(1 + a_0\bar{C})}\right)\left(\frac{(1-\epsilon)\beta_\nu(1-\kappa)N_C\mu_T}{1 + a_1\bar{C}}\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right), \\
f_4 &= \mu_V\left((1-\epsilon)\beta_\nu + \mu_E\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\
&\quad - \left(\frac{(1-\gamma)\beta_c s_T}{\mu_S(1 + a_0\bar{C})}\right)\left(\frac{\alpha(1-\epsilon)\beta_\nu(1-\kappa)N_I\mu_I}{1 + a_1\bar{C}}\right)\left(\frac{h_C s_C}{\mu_C} + \mu_T\right) \\
&\quad + \left(\frac{(1-\alpha)(1-\epsilon)\beta_\nu(1-\kappa)N_C\mu_T}{1 + a_1\bar{C}}\right)\left(\frac{h_I s_C}{\mu_C} + \mu_I\right).
\end{aligned} \tag{3.23}$$

Three of the eigenvalues are $\lambda_1 = -\mu_S$, $\lambda_2 = -\mu_V$ and $\lambda_3 = -\mu_C$. To get the other 4 eigenvalues, or at least be able to determine stability conditions on them, we use the Routh-Hurwitz criterion again on the 4^{th} order characteristic polynomial:

$$q(\lambda) = \lambda^4 + f_1\lambda^3 + f_2\lambda^2 + f_3\lambda + f_4. \tag{3.24}$$

The roots of the characteristic polynomial above to have negative reals parts if $\frac{f_1 f_2 - f_3}{f_1} > 0$ and $\frac{f_3 - f_4 f_1^3}{f_1 f_2 - f_3} > 0$. That is, for a stable system $f_1 f_2 - f_3 > 0$ and $f_1 f_2 f_3 - f_3^2 - f_4 f_1^4 > 0$. The coefficients, f_is, are so complex again that we are not going to do an analysis of the stability conditions on the critical parameters at this stage.

3.1.3 Global stability conditions for the disease-free equilibrium

Using the method of Castillo-chavez *et al.* [64] we re-write the equations (3.1)-(3.7) in the form:

$$\begin{aligned} \frac{d\mathbf{X}_T}{dt} &= F_T(\mathbf{X}_T, \mathbf{Z}_T) \\ \frac{d\mathbf{Z}_T}{dt} &= G_T(\mathbf{X}_T, \mathbf{Z}_T) \end{aligned} \tag{3.25}$$

with $G_T(\mathbf{X}_T, \mathbf{0}) = 0$, where $\mathbf{X}_T \in \mathbb{R}^2$ denotes the vector of uninfected classes and $\mathbf{Z}_T \in \mathbb{R}^5$ denotes the vector of infected classes. $\mathbf{U}_0 = (\mathbf{X}_T^*, \mathbf{0})$ denotes the disease-free equilibrium The conditions (**H1**) and (**H2**) below must be met to guarantee global asymptotic stability.

H1: for $\frac{d\mathbf{X}_T}{dt} = F_T(\mathbf{X}_T, \mathbf{0})$, $\mathbf{X}_T^*$ is globally asymptotically stable.
H2: $G_T(\mathbf{X}_T, \mathbf{Z}_T) = A_T \mathbf{Z}_T - \hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T)$, $\hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T) \geq 0$ for $(\mathbf{X}_T, \mathbf{Z}_T) \in \Omega$) where $A_T = D_{\mathbf{Z}_T} G_T(\mathbf{X}_T^*, \mathbf{0})$ is an M-matrix (the off-diagonal elements of A_T are non-negative) and Ω is the region where the model makes biological sense.

If the above two conditions are satisfied then Castillo-chavez *et al.*'s [64] theorem holds. For the set of equations (3.1)-(3.7) we set $(X) = (T_S, C)$: the set of uninfected target CD4$^+$ T cells and HIV-specific CTLs, and $\mathbf{Z}_T = (T_E, T_I, T_C, V, V^*)$: the 'exposed' CD4$^+$ T cells, productively infected CD4$^+$ T cells, chronically infected CD4$^+$ T cells, the infectious HIV particles and the non-infectious HIV particles. We compute $F_T(\mathbf{X}_T, \mathbf{0}) = 0$, $A_T (= D_{\mathbf{Z}_T} G_T(\mathbf{X}_T^*, \mathbf{0}))$ and $\hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T)$ as follows:

$$F_T(\mathbf{X}_T, \mathbf{0}) = \begin{pmatrix} s_T - \mu_S T_S \\ s_C - \mu_C C \end{pmatrix},$$

$$A_T = \begin{pmatrix} -(1-\epsilon)\beta_\nu - \mu_E & 0 & 0 & \frac{(1-\gamma)\beta_c \bar{T}_S}{1+a_0\bar{C}} & 0 \\ \alpha(1-\epsilon)\beta_\nu & -h_I\bar{C} - \mu_I & 0 & 0 & 0 \\ (1-\alpha)(1-\epsilon)\beta_\nu 0 & -h_C\bar{C} - \mu_T & 0 & 0 & \\ 0 & \frac{(1-\kappa)N_I\mu_I}{1+a_1\bar{C}} & \frac{(1-\kappa)N_C\mu_T}{1+a_1\bar{C}} & -\mu_V & 0 \\ 0 & \frac{\kappa N_I\mu_I}{1+a_1\bar{C}} & \frac{\kappa N_C\mu_T}{1+a_1\bar{C}} & 0 & -\mu_V \end{pmatrix},$$

$$A\mathbf{Z}_T = \begin{pmatrix} -(1-\epsilon)\beta_\nu T_E - \mu_E T_E + \frac{(1-\gamma)\beta_c \bar{T}_S V}{1+a_0\bar{C}} \\ \alpha(1-\epsilon)\beta_\nu T_E - h_I\bar{C}T_I - \mu_I T_I \\ (1-\alpha)(1-\epsilon)\beta_\nu T_E - h_C\bar{C}T_C - \mu_T T_C \\ \frac{(1-\kappa)N_I\mu_I T_I}{1+a_1\bar{C}} + \frac{(1-\kappa)N_C\mu_T T_C}{1+a_1\bar{C}} - \mu_V V \\ \frac{\kappa N_I\mu_I T_I}{1+a_1\bar{C}} + \frac{\kappa N_C\mu_T T_C}{1+a_1\bar{C}} - \mu_V V^* \end{pmatrix}.$$

So that using condition (**H2**) above we have,

$$\hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T) = \begin{pmatrix} (1-\gamma)\beta_c V\left(\frac{\bar{T}_S}{1+a_0\bar{C}} - \frac{T_S}{1+a_0 C}\right) \\ h_I T_I(C - \bar{C}) \\ h_C T_C(C - \bar{C}) \\ (1-\kappa)(N_I\mu_I T_I + N_C\mu_T T_C)\left(\frac{1}{1+a_1\bar{C}} + \frac{1}{1+a_1 C}\right) \\ \kappa(N_I\mu_I T_I + N_C\mu_T T_C)\left(\frac{1}{1+a_1\bar{C}} + \frac{1}{1+a_1 C}\right) \end{pmatrix}.$$

Global stability of the system at $\bar{E}_0$ requires that $\hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T) \geq 0$. Since $(1-\gamma)$ and $(1-\kappa) \geq 0$, and using the deductions made on the components of $G_T(\mathbf{X}, \mathbf{Z})$ in the previous chapter we have that $\hat{G}_T(\mathbf{X}_T, \mathbf{Z}_T) \geq 0$.

It is easy to show that $\mathbf{X}_T^* = (\frac{s_T}{\mu_S}, \frac{s_C}{\mu_C})$ is a globally asymptotically stable state of $\frac{d\mathbf{X}_T}{dt} = F_T(\mathbf{X}_T, \mathbf{0})$, since, $F_T(\mathbf{X}_T, \mathbf{0})$ is a limiting function of $\frac{d\mathbf{X}_T}{dt} = F_T(\mathbf{X}_T(t), \mathbf{Z}_T(t))$, that is, $lim_{t\to\infty}\mathbf{X}_T(t) = \mathbf{X}_T^*$. Therefore $\bar{E}_{T0}$ is a globally asymptotically stable equilibrium point.

3.2 Numerics

The numerical solutions presented in this section are produced using a mathematical progamming language called Matlab. In figure 3.1 we investigate the general effect of chemotherapy by looking at how a relatively low common drug efficacy ($\epsilon = \gamma = \kappa = 0.65$) and a relatively high common drug efficacy ($\epsilon = \gamma = \kappa = 0.95$) affect the dynamics of infection in an HIV infected patient. The parameter values used are as given in table 2.2 in the previous chapter and the initial variable values are given in table 3.1 below

Variable	Value	Units
$T_S(0)$	100	cells/mm^{-3}
$T_E(0)$	500	cells/mm^{-3}
$T_I(0)$	50	cells/mm^{-3}
$T_C(0)$	50	cells/mm^{-3}]
$C(0)$	10	cells/mm^{-3}
$V(0)$	400	copies/mm^{-3}
$V^*(0)$	10	copies/mm^{-3}

Table 3.1: Table of initial variable values used in chemotherapy model numerical simulations

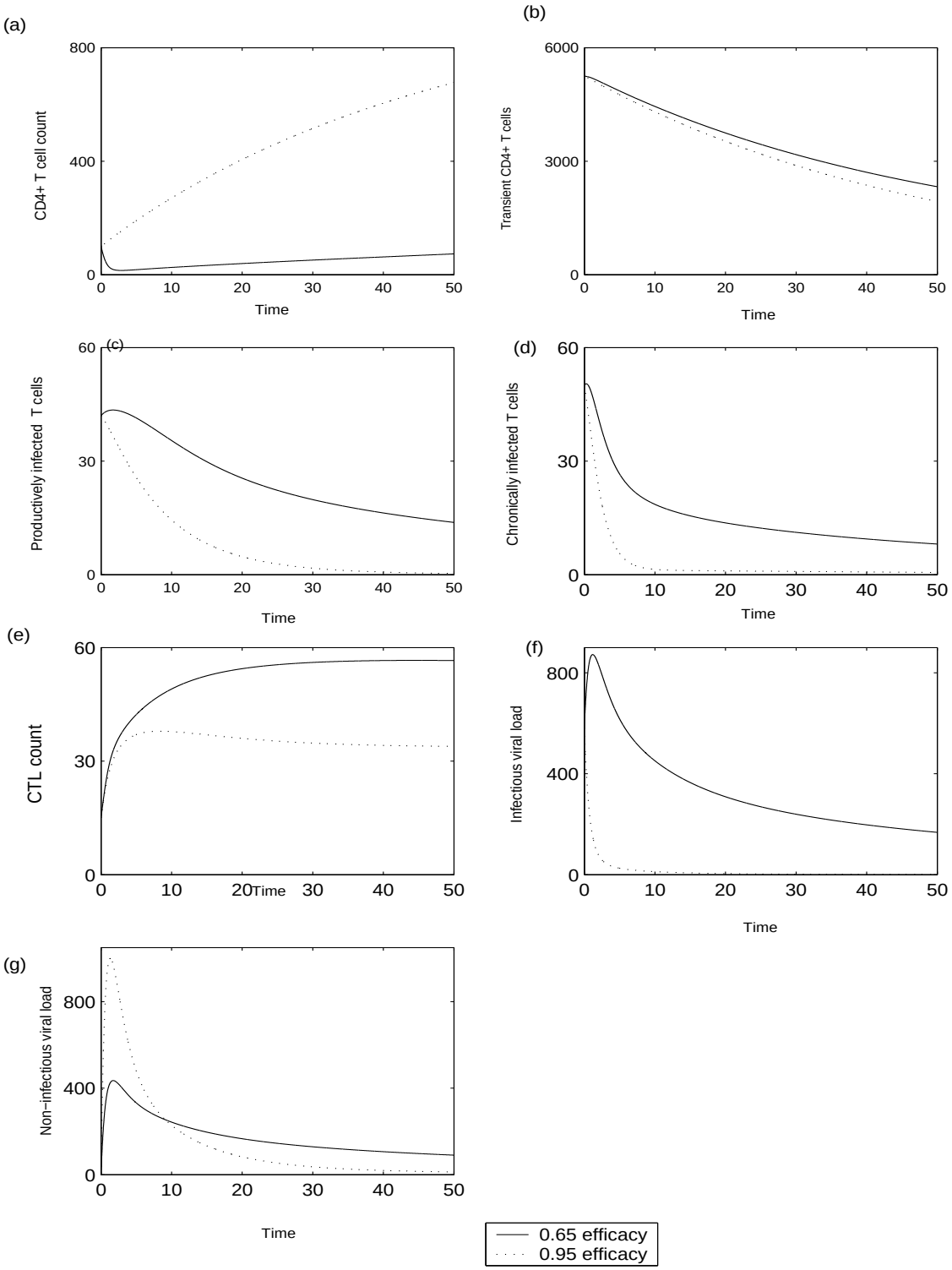

Figure 3.1: Graph of the numerical solution to equations (3.1)-(3.7), depicting the dynamics of: (a) healthy $CD4^+$ T cells, (b) transiently infected $CD4^+$ T cells, (c) productively infected $CD4^+$ T cells, (d) chronically infected $CD4^+$ T cells, (e) HIV-specific CTLs, (f) the non-infectious HIV virion during the first days of infection and (g) the infectious HIV virion during the first few days of infection

3.2.1 Discussion

The results presented in figure 3.1 predict that initiation of HAART with a drug combination of RTIs, PIs and FIs with both the relatively low (0.65) and the relatively high (0.95) efficacy levels ultimately reduces the viral load and hence increase the CD4 count in a chronically infected HIV patient. The results suggest that the patient's CD4 count rises at a faster rate if a drug regimen of a higher efficacy rate, 0.95, is administered whereas a drug regimen of relatively lower efficacy rate, 0.65, is associated with a slower gain in CD4 count. The 0.65 efficacy level is slow though in boosting the CD4 count. This three-drug combination treatment intervention is initiated when the patient's CD4 count has fallen to below $200 cells/mm^3$, at that stage CTL activity will has significantly subdued leaving the patient at risk of quickly progressing to the AIDS stage. However, CTL activity bounces back, upon initiation of therapy, from an impaired low level reaching a high equilibrium level in a couple of weeks. This enhanced cellular-mediated immune response helps keep both infection and viral replication under check.

The diagram shows that soon after administering therapy, the viral load rises to relatively high levels for a short time. When therapy of relatively high efficacy is administered it is the population density of non-infectious viral particles the increases during this initial stage as the PIs render almost all the viral particles produced by the productively infected $CD4^+$ T cells non-infectious. On the other hand, when therapy of relatively low efficacy is administered the initial increase in viral load is mainly infectious. However, after the initial rise the viral load subsequently declines, rapidly at first then slowly at the end. Meanwhile the population densities of the both the productively infected and chronically infected $CD4^+$ T cells will be depreciating, especially the long-lived ones that sharply fall to low levels quicker than the actively infected ones. This is a manifestation of the combined works of the RTIs and PIs. The RTIs decelerates the transcription rate of virus thereby reducing the population densities of infected cells which happen to be the only source of new virion. The PIs complement by rendering the virus produced by "bursting" of infected cells non-infectious. This is so with no much difference between the relatively high and the relatively low efficacy

levels of the tree-drug combination therapy

The three-drug combination therapy also brings about a rebound in CD4 count. This is as a result the work of FIs, which deter the viral envelop protein from successfully engaging with the CD4 receptor as well as down-regulating the chemokine co-receptors (CCR5 and CXCR4). The relatively high efficacy level therapy rapidly boosts the abundance of healthy $CD4^+$ T cells to very high levels from the "dangerous" zone of below $200 cells/mm^3$. Yet the relatively low efficacy level therapy shows some positive but very slow progress in boosting the CD4 count in a chronically infected HIV patient, exposing the patient to opportunistic infections. This comparison is depicted in figure 3.1(a). The main challenges in the efficient application of FIs include: env density, receptor expression levels, differences in affinity and receptor presentation. These are some of the factors that could require that FIs be administered with relatively high efficacy if positive results are to be realized.

Generally, administering the three-drug combination therapy with relatively high efficacy level yields positive results with respect to boosting CD4 count and CTL response as well as significantly reducing viral load in chronically infected HIV patients. On the other hand, administering therapy with relatively low efficacy level gives positive results mainly with respect to reducing viral load and increasing CTL response, and is not effective in boosting CD4 count in HIV patients.

Chapter 4

Antioxidant therapy model

In this chapter the pretreatment model is extended to incorporate the effects of free radicals proponents of apoptosis and viral replication; and the counter effects of antioxidant therapy in chronically infected HIV patients in order to analyze how this type of treatment affects the dynamics of chronic HIV-infection. We therefore add and/or refine some of the the assumptions of the pretreatment model as follows:

- There is excessive production of free radical molecules, $Rmols/mm^3$, within the healthy $CD4^+$ T cells that will have just "sensed" invasion by virus.
- Antioxidant molecules, $Mmols/mm^3$, which are taken through supplements at a constant rate, $M_0 mols/mm^3/day$, find their way into the healthy $CD4^+$ T cells that will have just "sensed" invasion by virus to react with the free radicals.
- The concentration of antioxidant molecules is cleared by reacting with free radical molecules within the affected $CD4^+$ T cells at a constant rate, q, and this clearance depends on the abundance of free radical particles and antioxidant molecules themselves.
- Free radicals are generated, within healthy $CD4^+$ T cells, after successful $CD4^+$ T cells receptor stimulation by HIV without viral penetration at a constant rate, δ. The proliferation rate depends on the viral density with a half-saturation constant, K.

- Free radical molecules are therefore cleared in the same way as they react with the antioxidant molecules.

- Apoptosis of healthy $CD4^+$ T cells is induced by the activities of free radical molecules [46,49,50,57,64], at a constant rate, τ.

- Successful transcription and hence infection of $CD4^+$ T cells is directly proportional to the abundance of both the free radical molecules and the $CD4^+$ T cells that will have fused with virus but waiting for transcription to occur, and it occurs at a constant rate, β_ν.

Hence, the model of antioxidant therapy has two additional components to those in the pre-treatment model and these are: the free radical molecules ($Rmols/mm^3$) and antioxidant dosage ($Mmols/mm^3$). With these additional assumptions, the model is now given by the following set of ordinary differential equations:

$$\begin{aligned}
\frac{dM(t)}{dt} &= M_0 - qM(t)R(t), && (4.1)\\
\frac{dR(t)}{dt} &= \frac{\delta V(t)T_S(t)}{V(t)+K} - qM(t)R(t), && (4.2)\\
\frac{dT_S(t)}{dt} &= s_T + \frac{rT_S(t)V(t)}{V(t)+A} - \frac{\beta_c V(t)T_S(t)}{1+a_0C(t)} - \frac{\tau R(t)T_S(t)}{T_S(t)+B} - \mu_S T_S(t), && (4.3)\\
\frac{dT_E(t)}{dt} &= \frac{\beta_c V(t)T_S(t)}{1+a_0C(t)} - \beta_\nu T_E(t)R(t) - \mu_E T_E(t), && (4.4)\\
\frac{dT_I(t)}{dt} &= \alpha\beta_\nu T_E(t)R(t) - h_I T_I(t)C(t) - \mu_I T_I(t), && (4.5)\\
\frac{dT_C(t)}{dt} &= (1-\alpha)\beta_\nu T_E(t)R(t) - h_C T_C(t)C(t) - \mu_T T_C(t), && (4.6)\\
\frac{dC(t)}{dt} &= s_C + pV(t)T_S(t)C(t) - \mu_C C(t), && (4.7)\\
\frac{dV(t)}{dt} &= \frac{N_I\mu_I T_I(t)}{1+a_1C(t)} + \frac{N_C\mu_T T_C(t)}{1+a_1C(t)} - \mu_V V(t). && (4.8)
\end{aligned}$$

Equation (4.1) monitors the changes in the antioxidant concentration. Here the first term represents the dose of antioxidant administered to the patient at a constant rate. The second

term is the clearance by reacting with free radical molecules.

Equation (4.2) describes the dynamics of the "excess" free radical particles and the first term is a gain due to the massive production of the free radicals induced by HIV-invasion. The second term, like that in equation (4.1), is a loss term as the free radicals react with antioxidant particles. So the reaction between the antioxidant and free radical molecules is a neutralization process known as the *redox reaction*.

Equation (4.3) tracks the change in healthy (susceptible) $CD4^+$ T cells. All the other terms are as explained in the previous model except for the fourth term, which explains the programmed cell death (apoptosis) as being mainly a consequence of the activities of free radical molecules on the cells. Oxidative stress is implicated as the main cause of apoptosis in HIV-infected patients [46,49,50,57,64].

Equation (4.4) monitors the dynamics of $CD4^+$ T cells that have been exposed to the virus (that have allowed viral entry into their cytoplasm) [60]. The first term on the right hand side of equation (4.4) is from the third term of equation (4.3) and is the source of $CD4^+$ T cells where virions have just entered the cytoplasm but awaiting transcription of HIV RNA to DNA to occur. The second term models the loss of exposed cells due to successful transcription. The transcription of viral RNA to DNA is enhanced by the activities of the free radical molecules in the cell at a constant rate. A proportion, α, of these cells become productively infected and $(1-\alpha)$ become chronically infected.

Equations (4.5)-(4.8) are basically described in the same way as equations (2.3) to (2.6) in the model. The gain terms in equations (4.5) and (4.6) are a result of successful infection of the $CD4^+$ T cells. A proportion, α, become productively infected and the other proportion, $1-\alpha$, become chronically infected. Thus, the production of chronically infected cells occurs at a fraction of the rate productively infected cells are generated [59].

4.1 Analysis of the antioxidant model

The steady states for the antioxidant model are obtained by equating the right-hand sides of equations (4.1)-(4.8) to zero. The system has two steady states: the disease-free steady state,

$\bar{E}_{A0}$ and the endemically infected steady state, $\bar{E}_{A1}$. In the absence of virus, no HIV-induced "excess" free radicals are produced, $R = 0$. Hence no antioxidant supplementation should be administered as anti-HIV therapy, lest the "excess" antioxidants become a nuisance as well to the body. So the disease-free steady state is:

$$\bar{E}_{A0} = (\bar{M}, \bar{R}, \bar{T}_S, \bar{T}_E, \bar{T}_I, \bar{T}_C, \bar{V}) = \left(0, 0, \frac{s_T}{\mu_S}, 0, 0, 0, \frac{s_C}{\mu_C}, 0\right).$$

Similarly, the HIV-infected steady state can be found by equating the right hand sides of equations (4.1)-(4.8) to zero, then solving the resultant algebraic equations as follows:

$$\begin{aligned}
M_0 - q\widetilde{M}\widetilde{R} &= 0, && (4.9)\\
\frac{\delta\widetilde{V}\widetilde{T}_S}{\widetilde{V}+K} - q\widetilde{M}\widetilde{R} &= 0, && (4.10)\\
s_T + \frac{r\widetilde{T}_S\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} - \frac{\tau\widetilde{R}\widetilde{T}_S}{\widetilde{T}_S+B} - \mu_S\widetilde{T}_S &= 0, && (4.11)\\
\frac{\beta_c\widetilde{V}\widetilde{T}_S}{1+a_0\widetilde{C}} - \beta_\nu\widetilde{T}_E\widetilde{R} - \mu_E\widetilde{T}_E &= 0, && (4.12)\\
\alpha\beta_\nu\widetilde{T}_E\widetilde{R} - h_I\widetilde{T}_I\widetilde{C} - \mu_I\widetilde{T}_I &= 0, && (4.13)\\
(1-\alpha)\beta_\nu\widetilde{T}_E\widetilde{R} - h_C\widetilde{T}_C\widetilde{C} - \mu_T\widetilde{T}_C &= 0, && (4.14)\\
s_C + p\widetilde{V}\widetilde{T}_S\widetilde{C} - \mu_C\widetilde{C} &= 0, && (4.15)\\
\frac{N_I\mu_I\widetilde{T}_I}{1+a_1\widetilde{C}} + \frac{N_C\mu_T\widetilde{T}_C}{1+a_1\widetilde{C}} - \mu_V\widetilde{V} &= 0. && (4.16)
\end{aligned}$$

The endemic equilibrium value for the antioxidant dosage is defined by:

$$\widetilde{M} = \frac{M_0}{q\widetilde{R}}. \quad (4.17)$$

There is an inverse relationship between the antioxidant dosage and the abundance of free radical particles. This means that the amount of antioxidant dosage found in an HIV patient decreases as the abundance of free radicals being produced due to infection by HIV increases, and vice versa. The steady state value for the free radical molecules is defined by

$$\widetilde{R} = \frac{\delta\widetilde{V}\widetilde{T}_S}{q\widetilde{M}(\widetilde{V}+K)}. \quad (4.18)$$

The inverse relationship observed in expression (4.17) is also witnessed in expression (2.18). We further observe from expression (4.18) the increased interactions between target T-cells

and virion results in increased production of free radical particles. The equilibrium value of healthy CD4$^+$ T cells is given by

$$\widetilde{T}_S = \frac{-\Pi_4 + \sqrt{(\Pi_4)^2 - 4Bs_T\Pi_3}}{2\Pi_3}, \tag{4.19}$$

where

$$\begin{aligned}\Pi_3 &= \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c\widetilde{V}}{1+a_0\widetilde{C}} - \mu_S,\\ \Pi_4 &= s_T + \frac{r\widetilde{V}}{\widetilde{V}+A} - \frac{\beta_c B\widetilde{V}}{1+a_0\widetilde{C}} - \tau\widetilde{R} - \mu_S B.\end{aligned}$$

From this expression it can be observed that an inflated abundance of free radical particles results in a depleted CD4 count as a direct result of apoptosis. The population density of exposed CD4$^+$ T cells waiting for transcription to occur is given by

$$\widetilde{T}_E = \frac{\beta_c\widetilde{V}\widetilde{T}_S}{(1+a_0\widetilde{C})(\beta_\nu\widetilde{R}+\mu_E)}. \tag{4.20}$$

Expression (4.20) shows that the abundance of CD4$^+$ T cells that will have fuse with virus but still waiting for transcription decreases as the abundance of free radical particles increases. This because the free radical particles create a a highly oxidized environment favorable to transcription promoting factors like NF-κB. The productively infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_I = \frac{\alpha\beta_\nu\widetilde{T}_E\widetilde{R}}{h_I\widetilde{C}+\mu_I}. \tag{4.21}$$

The chronically infected CD4$^+$ T cell endemic equilibrium is given by

$$\widetilde{T}_C = \frac{(1-\alpha)\beta_\nu\widetilde{T}_E\widetilde{R}}{h_C\widetilde{C}+\mu_T}. \tag{4.22}$$

Expressions (4.21) and (4.22) show that the over-production of free radical molecules results in higher magnitudes of both the productively infected and chronically infected cell densities. Lytic CTL activity continues to play a significant role in reducing the abundance of infected cells as these are the main sources of new virion. The endemic steady state value of HIV specific CTLs is given by

$$\widetilde{C} = \frac{s_C}{\mu_C - p\widetilde{T}_S\widetilde{V}}. \tag{4.23}$$

Existence conditions for the endemic steady state value of the CTL cells to be biologically meaningful are the same as those derived from the pretreatment model in chapter 1. The viral steady state is given by

$$\widetilde{V} = \frac{N_I\mu_I\widetilde{T}_I + N_C\mu_T\widetilde{T}_C}{\mu_\nu(1+a_1\widetilde{C})}. \tag{4.24}$$

From expression (4.24) it can be deduced that the abundance of the productively infected as well as the chronically infected cells greatly contribute to the amount of virion in a chronically infected HIV patient. This is a critical observation to consider given that the presence of free radical particles directly results in inflated abundances of the infected cells.
Thus, the endemically infected steady state of the antioxidant therapy model is:

$$\bar{E}_{A1} = (\widetilde{M}, \widetilde{R}, \widetilde{T}_S, \widetilde{T}_E, \widetilde{T}_I, \widetilde{T}_C, \widetilde{C}, \widetilde{V})$$

where the expressions for $\widetilde{M}$, $\widetilde{R}$, $\widetilde{T}_S$, $\widetilde{T}_E$, $\widetilde{T}_I$, $\widetilde{T}_C$, $\widetilde{C}$ and $\widetilde{V}$ are given by expressions (4.17)-(4.24), respectively

4.1.1 The reproduction number

We now investigate threshold conditions that determine whether the disease will persist in a susceptible population when the virus is introduced into the population, and the threshold conditions are usually characterized by the reproductive number. To calculate the reproduction number for the antioxidant therapy model we adopt the method of O. Diekmann *et al.* [62]. We define heterogeneity using groups defined by fixed characteristics; that is, the model can be written in the form:

$$\frac{dX_A}{dt} = f_A(\mathbf{X}_A, \mathbf{Y}_A, \mathbf{Z}_A), \tag{4.25}$$

$$\frac{dY_A}{dt} = g_A(\mathbf{X}_A, \mathbf{Y}_A, \mathbf{Z}_A), \tag{4.26}$$

$$\frac{dZ_A}{dt} = h_A(\mathbf{X}_A, \mathbf{Y}_A, \mathbf{Z}_A), \tag{4.27}$$

where $\mathbf{X}_A \in \mathbb{R}^4$, $\mathbf{Y}_A \in \mathbb{R}$, $\mathbf{Z}_A \in \mathbb{R}^3$, and $h_A(\mathbf{X}_A, 0, 0) = 0$. Assuming that the equation $g_A(\mathbf{X}_A^*, \mathbf{Y}_A, \mathbf{Z}_A) = 0$ implicitly determines a function $\mathbf{Y}_A = \bar{g}_A(\mathbf{X}_A^*, \mathbf{Z}_A)$. We let

$A_A = D_{Z_A} h_A(\mathbf{X}_A^*, \bar{g}_A(\mathbf{X}_A^*, 0), 0)$ and further assume that A_A can be written in the form $A_A = M_A - D_A$, with $M_A \geq 0$ (that is $m_{ij} \geq 0$) and $D_A > 0$, a diagonal matrix. The reproduction ratio is then evaluated from the matrix $M_A D_A^{-1}$.

The cell population subgroups are divided as follows,

(a) $\mathbf{X}_A$: are components that are uninfected by the virus,

(b) $\mathbf{Z}_A$: are components that are virus infected (infected CD4$^+$ T cells), and

(C) $\mathbf{Y}_A$: the HIV pathogen. Therefore we set $\mathbf{X}_A = (M, R, T_S, C)$, $\mathbf{Y}_A = V$, $\mathbf{Z}_A = (T_E, T_I, T_C)$, and $\mathbf{X}_A^* = (0, 0, \frac{s_T}{\mu_S}, \frac{s_C}{\mu_C})$. Let $\mathbf{U}_{A0} = (\mathbf{X}_A^*, 0, 0)$ denote the virus free equilibrium, that is $f_A(\mathbf{X}_A^*, 0, 0) = g_A(\mathbf{X}_A^*, 0, 0) = h_A(\mathbf{X}_A^*, 0, 0) = 0$ and $\mathbf{Y}_A = \bar{g}_A(\mathbf{X}_A^*, \mathbf{Z}_A)$, where

$$\bar{g}_A(\mathbf{X}_A^*, \mathbf{Z}_A) = \frac{N_I \mu_I \bar{T}_I + N_C \mu_T \bar{T}_C}{\mu_\nu (1 + a_1 \bar{C})}.$$

We compute $A_A = D_{Z_A} h_A(\mathbf{X}_A^*, \bar{g}_A(\mathbf{X}_A^*, 0), 0)$ and get

$$A_A = \begin{pmatrix} -\beta_\nu R - \mu_E & \frac{\beta_c \bar{T}_S N_I \mu_I}{\mu_V (1+a_1 \bar{C})(1+a_0 \bar{C})} & \frac{\beta_c \bar{T}_S N_C \mu_T}{\mu_V (1+a_1 \bar{C})(1+a_0 \bar{C})} \\ \alpha \beta_\nu R & -h_I \bar{C} - \mu_I & 0 \\ (1-\alpha)\beta_\nu R & 0 & -h_C \bar{C} - \mu_T \end{pmatrix}.$$

So that

$$M_A = \begin{pmatrix} 0 & \frac{\beta_c \bar{T}_S N_I \mu_I}{\mu_V (1+a_1 \bar{C})(1+a_0 \bar{C})} & \frac{\beta_c \bar{T}_S N_C \mu_T}{\mu_V (1+a_1 \bar{C})(1+a_0 \bar{C})} \\ \alpha \beta_\nu R & 0 & 0 \\ (1-\alpha)\beta_\nu R & 0 & 0 \end{pmatrix}$$

, and

$$D_A^{-1} = \begin{pmatrix} \frac{1}{(-\beta_\nu R - \mu_E)} & 0 & 0 \\ 0 & \frac{1}{(-h_I C - \mu_I)} & 0 \\ 0 & 0 & \frac{1}{(-h_C \bar{C} - \mu_T)} \end{pmatrix}.$$

Hence,

$$M_A D_A^{-1} = \begin{pmatrix} 0 & \frac{\beta_c \bar{T}_S N_I \mu_I}{-\mu_V (1+a_0 \bar{C})(1+a_1 \bar{C})(h_I C + \mu_I)} & \frac{\beta_c \bar{T}_S N_C \mu_C}{-\mu_V (1+a_0 \bar{C})(1+a_1 \bar{C})(h_C C + \mu_C)} \\ \frac{-\alpha \beta_\nu R}{\beta_\nu + \mu_E} & 0 & 0 \\ \frac{(1-\alpha)\beta_\nu R}{\beta_\nu R + \mu_E} & 0 & \frac{1}{(-h_C \bar{C} - \mu_T)} \end{pmatrix}.$$

The three eigenvalues λ_1, λ_2 and λ_3 of $M_A D_A^{-1}$ are

$$\lambda_1 = 0,$$

$$\lambda_2 = \sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S R}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})(\beta_\nu R+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I \mu_I}{h_I\bar{C}+\mu_I}\right)},$$

and

$$\lambda_3 = -\sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S R}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})(\beta_\nu R+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I \mu_I}{h_I\bar{C}+\mu_I}\right)}.$$

The reproduction ratio is given by the next generation spectral radius $\rho(MD^{-1})$ to be

$$R_{A0} = \sqrt{\left(\frac{\beta_\nu \beta_c \bar{T}_S R}{\mu_V(1+a_1\bar{C})(1+a_0\bar{C})(\beta_\nu R+\mu_E)}\right)\left(\frac{(1-\alpha)N_C\mu_T}{h_C\bar{C}+\mu_T}+\frac{\alpha N_I \mu_I}{h_I\bar{C}+\mu_I}\right)}.$$

Expressed in terms of R_0, the pretreatment reproduction number,

$$R_{A0} \quad = \quad R_0\sqrt{\frac{R(\beta_\nu+\mu_E)}{\beta_\nu R+\mu_E}}, \tag{4.28}$$

which can be re-written as,

$$R_{A0} = R_0\sqrt{\frac{(\beta_\nu+\mu_E)}{\beta_\nu+\frac{\mu_E}{R}}},$$

If the abundance of free radical particles is less than $1 mol/mm^3$, then the antioxidant reproduction number will be less than the pretreatment reproduction number, $R_{A0} < R_0$. If the abundance of free radical particles is greater than $1 mol/mm^3$, then the antioxidant reproduction number will be greater than the pretreatment reproduction number, $R_{A0} > R_0$. Thus, maintaining the abundance of free radical particles below $1 mol/mm^3$ ensures that the disease is at least manageable.

Lemma 4.1 *The disease-free equilibrium $\bar{E}_{A0}$ is locally asymptotically stable if $R_{A0} < 1$ and unstable if $R_{A0} > 1$.*

Therefore in order to control HIV infection the reproduction ratio R_{A0} should be kept below unit by significantly suppressing the abundance of free radical particles in chronically infected HIV patients.

4.2 Numerical simulations

The numerical solutions presented in this section are produced using a mathematical programming language called Matlab. Figure 4.1 depicts the effects of two different antioxidant dosages, $M_0 = 2mols/mm^3$ and $M_0 = 5mols/mm^3$, in comparison with a situation when no antioxidant therapy is being administered to a chronically infected HIV patient. The parameter values used in the simulations, some of which are estimates based on some insights from literature, are given in table 4.1 below.

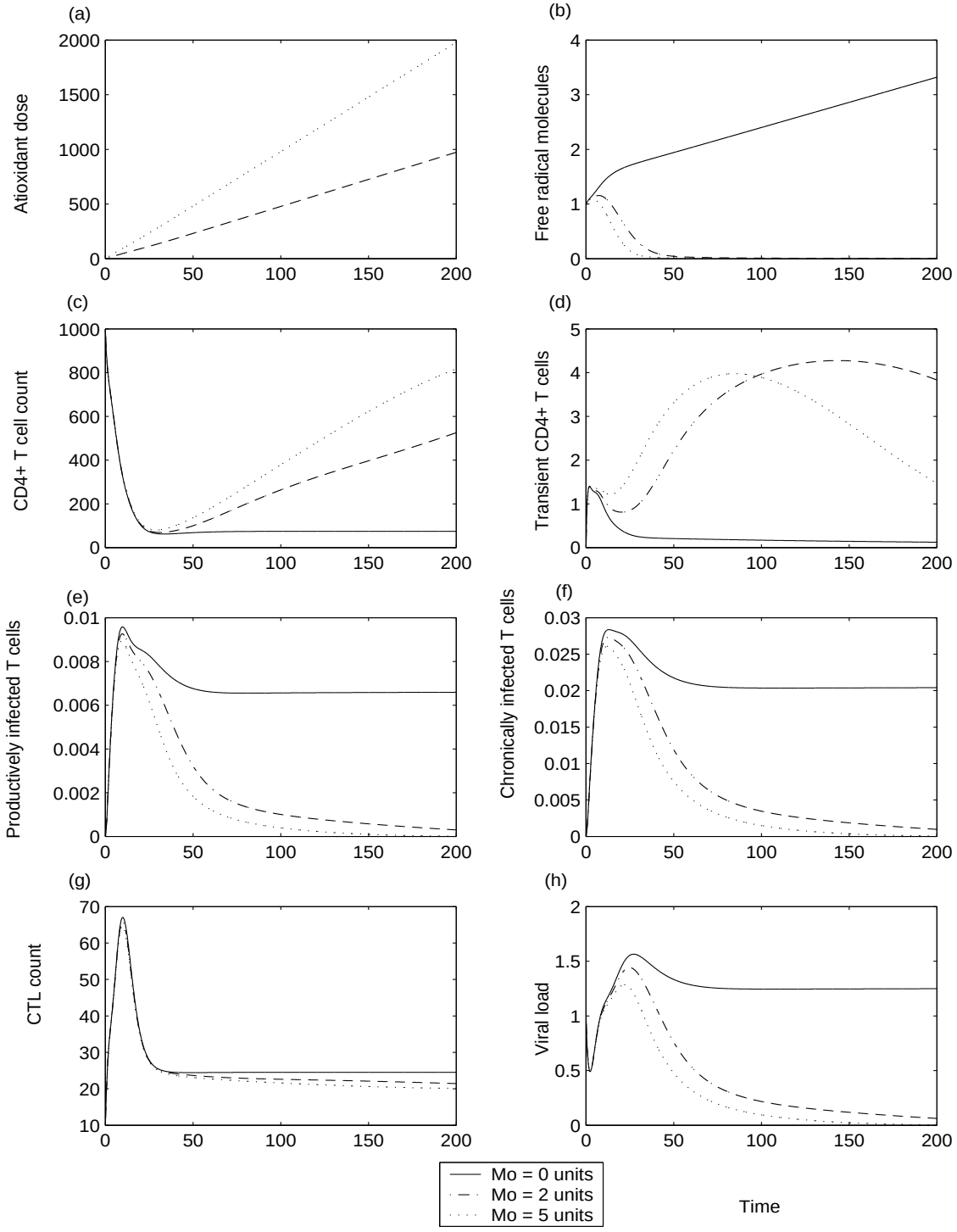

Figure 4.1: Graph of the numerical solution to equations (4.1)-(4.8), depicting the dynamics of: (a) antioxidant dosage, (b) free radical molecules, (c) healthy $CD4^+$ T cells, (d) transiently infected $CD4^+$ T cells, (e) productively infected $CD4^+$ T cells, (f) chronically infected $CD4^+$ T cells, (g) HIV-specific CTLs, and (h) the HIV viral particles.

4.2.1 Discussion

Fig 4.1 shows that antioxidant supplements have the effect of boosting CD4 count as well as significantly reducing viral load in chronically infected HIV patients. The graph also depicts that as far as effectiveness is concerned there is no significant difference between a relatively low dosage (2 $mols/mm^3$) and a relatively high dosage (5 $mols/mm^3$) of antioxidant, although a higher dosage is associated with a slightly faster rate of gain of CD4 count of the chronically infected HIV patients. The ravaging effects of the excessive production of free radicals due to infection infection by HIV is particularly observed when there is no antioxidant therapy being administered to a chronically infected HIV patient. These unstable molecules aggressively seek to stabilize themselves by reacting with other molecules and atoms within the $CD4^+$ T cells leading to a rapid decline of the CD4 count through decreased immune cell proliferation and oxidative stress induced apoptosis.

The decline in CD4 count which is observed from the onset of infection by HIV even when there is antioxidant therapy being administered to the patient can be attributed to the activities of the free radical molecules that are produced just upon invasion by virus. These free radicals further promote transcription of virus, hence the initial rise in the population densities of both the productively infected and chronically infected T cells. The end result of this is an increase in the abundance of viral particles directly from "bursting" of the infected cells, especially the productively infected ones. This happens only for a short while and CTL activity plays a very important role during this initial stage of infection. The activities of antioxidants to neutralize the highly oxidative environment that would have been brought about by HIV-induced free radicals begin to manifest themselves only after a couple of days. This initial delay can be attributed to the drug pharmacokinetics: from the administration of the drug to the beginning of drug action within cells. Continuous administration of antioxidants maximally inhibits viral replication and infection of virgin cells. This worthwhile and intriguing observation can be realized especially when antioxidant supplements are applied right from the early stages of infection when viral spread has not occurred and when an individual's digestive functions are not too greatly impaired, otherwise the absorption is

likely to be too low.

Comparison between antioxidant therapy model and pretreatment model as well as chemotherapy model

There are some differences, but not contradictions, between the dynamics depicted by the antioxidant therapy model and the pretreatment model as well as the chemotherapy model. For instance, in the absence of antioxidant therapy being administered to a chronically infected HIV patient, the antioxidant therapy model does mot mimic some features of pretreatment model. The initial "shoulder" or delay in the depletion of CD4 count observed from the pretreatment results is not depicted in the antioxidant results with $M_0 = 0units$. Also, the initial delay (or "foot") in the increase of the population densities of the infected cells and subsequently the viral load is shown on the pretreatment model yet the antioxidant model does not reveal it. In general, the antioxidant model portrays a more aggressive picture of HIV infection and progression than the pretreatment model. This is possibly due to the apoptosis rate parameter which is assumed to be of the same value for both the antioxidant therapy model and pretreatment model. This parameter value was taken directly from literature [60]. This parameter value can be determined, at least approximately, through sensitivity analysis of the antioxidant model.

Results from the antioxidant model may not be comparable with those from the chemotherapy model because the timing of administering therapy is different. In fact, both treatment strategies have the same ultimate benefit of boosting CD4 count and reducing the viral load in a chronically infected HIV patient, provided optimum dosage levels can be applied for optimum efficacy. Since antioxidants therapy is administered during the early stages in order realize the potential benefit yet on the other hand, the three-drug combination intervention is advisably administered at a later stage after infection when the patient's CD4 count is

below $200 cells/mm^3$, it can be envisaged that combining antioxidants and chemotherapy may have several (better) cellular and clinical benefits.

Variable	Description	Units	Value[Source]
$M(0)$	antioxidant dosage	mols/mm^{-3}	0, 2 and 5[est]
$R(0)$	free radical molecules	mols/mm^{-3}	1.0[est]
$T_S(0)$	uninfected $CD4^+$ T cells	cells/mm^{-3}	1500[64]
$T_E(0)$	transiently infected $CD4^+$ T cells	cells/mm^{-3}	0[60]
$T_I(0)$	productively infected $CD4^+$ T cells	cells/mm^{-3}	0[60]
$T_C(0)$	chronically infected $CD4^+$ T cells	cells/mm^{-3}	0[60]
$C(0)$	HIV specific CTLs	cells/mm^{-3}	10[26]
$V(0)$	HIV population	copies/mm^{-3}	10[60]
Parameter			
q	redox rate	$\text{mol}^{-1}\text{mm}^3\text{days}$	0.002[est]
δ	proliferation rate of free radicals	$\text{cells/mm}^{-3}\text{day}^{-1}$	20[26]
K	proliferation stimulation constant	$\frac{cells/\text{mm}^{-3}}{mols/\text{mm}^{-3}\text{day}^{-1}}$	500[est]
s_T	supply rate of $CD4^+$ T cells	$\text{cells/mm}^{-3}\text{day}^{-1}$	20[26]
r	proliferation rate of $CD4^+$ T cells	day^{-1}	0.01[46]
A	proliferation stimulation constant	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$	400[46]
β_c	collision-and-entry rate	$copies/\text{mm}^{-3}\text{day}^{-1}$	0.0025[60]
a_0	rate CTLs reduce infectivity	$cells/\text{mm}^3$	0.01[60]
τ	$CD4^+$ T cell apoptosis rate	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$	0.00001[60]
B	apoptosis saturation constant	$cells/\text{mm}^{-3}$	350.0[60]
μ_S	$CD4^+$ T cell death rate	day^{-1}	0.02[60]
β_ν	successful infection of CD^+ T cells rate	$\text{mm}^{-3}\text{day}^{-1}$	0.00045[60]
μ_E	"exposed" T cells death rate	day^{-1}	0.02[60]
h_I	rate CTLs lyse productively infected cells	$cells/\text{mm}^{-3}\text{day}$	0.0025[26]
μ_I	productively infected cells "burst" rate	day^{-1}	0.026[est]
α	proportion becoming productively infected		0.7[est]
h_C	rate CTLs lyse chronically infected cells	$cells/\text{mm}^{-3}\text{day}$	0.0015[26]
μ_T	chronically infected cells "burst" rate	day^{-1}	0.022[est]
s_C	CTL supply rate	$cells/\text{mm}^{-3}\text{day}$	10.0[59]
p	CTL proliferation rate	$\frac{\text{cells}^{-1}/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$	0.00001[60]
μ_C	natural CTL death rate	day	1.5[60]
N_I	T_I virus burst size	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$	1500[67]
N_C	T_C virus burst size	$\frac{cells/\text{mm}^{-3}}{copies/\text{mm}^{-3}\text{day}^{-1}}$	1200[est]
a_1	virion production reduction factor	$cells/\text{mm}^3$	0.015[60]
μ_V	virus clearance rate	day^{-1}	1.5[60]

Table 4.1: Table of variable and parameter values used in numerical simulations where est means estimate

Chapter 5

Conclusions and Recommendations

An exploration of the general dynamics of HIV immuno-pathogenesis without any treatment intervention reveals some important aspects of cellular-mediated immune responses against chronic HIV infections. Impairment of the immune system is one of the means employed by HIV to eventually subvert CTL activities (both lytic and non-lytic). Results from the model of combined drug therapies based upon three anti-HIV medications that incorporate FIs, RTIs and PIs, show some significant improvements with respect to boosting the CD4 count as well as reducing the viral load in chronically infected HIV patients. These results reveal that if combined chemotherapy can be applied with relatively high efficacy then the viral can be significantly suppressed, raising hopes that the infection, sometimes considered as an inexorable fatal disease, can actually be a chronic manageable problem. Non-drug therapies are an option worthy considering in the fight against HIV infections. As evidenced by the results of the antioxidant therapy model, there could be great benefits from administering the relatively less expensive and non-toxic antioxidant supplements on chronically infected HIV patients.

Analysis of the pretreatment model shows that in the absence of treatment intervention, cellular-directed immune responses that include CTL-mediated lysis, inhibition of viral entry into target cells and inhibition of virion production, play a crucial role in containing

viral replication in HIV infection; otherwise a patient would advance to AIDS in a matter of weeks. However, the immune system will eventually succumb to virus mainly because of the perversive nature of the viral replication process. Subversion of the CTL activities by HIV is a direct consequent of viral escape from cellular immune responses as well as virus-induced immune impairment. Once the immune system is sufficiently debilitated, the patient's health rapidly diminishes towards the AIDS stage characterized with a very low T cell count, a very high viral load and uncontrolled opportunistic infections.

Initiation of combined chemotherapy incorporating FIs, RTIs and PIs to chronically infected HIV-positive patients substantially reduces the severity of the HIV epidemic. Positive results can be realized if this three-drug combination regimen can be administered with relatively high efficacy, especially the FIs. The main challenges in the efficient application of FIs include: env density, receptor expression levels, differences in affinity and receptor presentation. These are some of the factors that could require that FIs be administered with relatively high efficacy. Complete eradication of HIV infection is not possible. In other words, 100% drug efficacy is not attainable. Even "high" drug efficacy levels may require almost perfect adherence and compliance coupled with a well balanced diet and a positive psycho-social lifestyle among other ideals. Further, drug efficacy level may be positively correlated with drug dosage which might in turn correlate with toxicity. Thus, combined chemotherapy does well in delaying disease progression in HIV infected patients but may also caused unpredictable side effects. Further, due to high costs of using polydrug therapy "drug cocktails" and the lack of proper healthcare infrastructure in most developing countries, the widespread use of combined chemotherapy is difficult. It is therefore imperative to consider the rationale of using alternative therapeutic approaches in the management of chronic HIV infections.

Antioxidant therapy has the potential to suppress viral replication and restore cellular immunity, especially when antioxidant supplements are applied right from the early stages of infection when viral spread has not occurred and when an individual's digestive functions are

not too greatly impaired, otherwise the absorption is likely to be too low. Apart from neutralizing the highly oxidized environment created by HIV-induced free radicals, these natural and safe micro-nutrients target NF-κB, a transcription factor that regulates HIV activation, and have a protective capacity for tumor necrosis factor (TNF) cytotoxicity. TNF-induced free radicals can increase the replication of HIV and destroy T-cells [22]. Results from the antioxidant therapy model confirm the ability of antioxidants to increase the viability and survivability of T-lymphocytes as well as enhancing the functioning of the immune system. Thus, antioxidants are a promising therapeutic option for HIV infected patients: they can be taken in through food, fruits and vitamin supplements which can be afforded by many and do not present the problem of resistance as they need not be strain specific.

Recommendations

Findings from the two treatment strategies studied in this thesis have implications on initiatives to delay or prevent the onset of AIDS. Antioxidant therapy gives good results especially if applied during the early stages of infection, yet, on the other hand, administering combined chemotherapy gives good results if applied at a later stage when the patient's CD4 count has fallen below $200 cells/mm^3$ so as to delay the development of drug resistance and unpredictable side effects. It is recommended that clinical work be initiated towards developing both the three-drug combination therapy regimen incorporating FIs, RTIs and PIs as well as antioxidant supplementation for chronically infected HIV patients. Antioxidant supplementation can actually be applied as first line treatment, that is during the early stages of infection when viral spread has not occurred and when the immune system is not severely depleted. While on the other hand, the three-drug combination treatment strategy can be applied at a later stage. Also it can be envisaged that combining antioxidants and the three-drug combination may have several (better) cellular and clinical benefits in mitigating the HIV/AIDS pandemic. This combination of the drug and non-drug therapies is defined

in this study as complementary therapy. Reductions in drug dosage requirements through combination with antioxidants would lessen drug toxicity as well as resistance while maximally inhibiting viral replication and maintaining T-cells viability. In addition, this notion of complementary therapy which can be applied at low cost should be administered in a single tablet, also known as fixed drug combination, that integrates antioxidant supplements with the combined drug component incorporating FIs, RTIs and PIs, that is when the drug component is due to come on board following a properly crafted programme for the management of HIV infection. This will help facilitate drug synergism as well as reduce the risk of non-adherence and non-compliance.

Suggestions for future research work

A more comprehensive study of complementary therapy may reveal some interesting aspects that can be valuable in the management of HIV/AIDS. Additional work needs to be done to identify antioxidant related parameter values. A planned experimental phase will allow parameter identification techniques to be applied for more accurate parameters values and verification of model modifications. Determining optimum levels of antioxidant and chemotherapy dosages that should be administered to chronically infected HIV patients warrants further investigation using optimal control techniques.

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