

A Control Theoretic Approach to HIV/AIDS  
Drug Dosage Design  
and  
Timing the Initiation of Therapy

by

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# A Control Theoretic Approach to HIV/AIDS Drug Dosage Design and Timing the Initiation of Therapy

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## **Abstract**

Current research on HIV therapy is diverse and multi-disciplinary. Engineers however, were late in joining the research movement and as such, engineering literature related to HIV chemotherapy is limited. Control engineers in particular, should have risen to the challenge, as it is apparent that HIV chemotherapy and control engineering have a lot in common. From a control theoretic point of view, HIV chemotherapy is control of a time varying nonlinear dynamical system with constrained controls. Once a suitable model has been developed or identified, control system theoretical concepts and design principles can be applied. The adopted control approach or strategy depends primarily on the control objectives, performance specifications and the control constraints. In principle, the designed control system can then be validated with clinical data. Obtaining measurements of the controlled variables however, has the potential to hinder effective control.

The first part of this research focuses on the application of control system analytical tools to HIV/AIDS models. The intention is to gain some insights into the HIV infection dynamics from a control theoretic perspective. The issues that need to be addressed are: Persistent virus replication under potent HAART, variability in response to therapy between individuals on the same regimen, transient rebounds of plasma viremia after periods of suppression, the attainment, or lack thereof, of maximal and durable suppression of the viral load. Such insights can help explain why an individual on antiretroviral therapy responds the way they do, as well as give the individual or practitioner the ability to preempt future responses.

The questions to answer are: When are the above mentioned observed responses from individuals on antiretroviral therapy most likely to occur as the HIV infection progresses, and does attaining one necessarily imply the other? Furthermore, the prognostic markers of virologic success, the possibility of individualizing therapy and timing the initiation

of antiretroviral therapy such that the benefits of therapy are maximized, are matters that will also be investigated.

The primary objective of this thesis is to analyze models for the eventual control of the HIV infection. HIV chemotherapy has multiple and often conflicting objectives, and these objectives had to be prioritized. The intention of the proposed control strategy is to produce practical solutions to the current antiretroviral problems. The scenario is such that, given the observed responses from individuals on antiretroviral therapy and the toxicity problems associated with this therapy, what can possibly be done to alleviate these problems? A solution should then be prescribed. The next question will then be, is such a solution implementable? The answer to this last question should be in the affirmative - Yes.

To this end, the second part of the research focuses on the addressing the HIV/AIDS control issues of sampling for effective control given the invasive nature of drawing blood from a patient and the derivation of drug dosage sequences to strike a balance between maximal suppression and toxicity reduction, when multiple drugs are concomitantly used to treat the infection.

**Keywords:** HIV/AIDS models, HIV immunology, HIV/AIDS model analysis, Initiate HIV therapy, Drug dosage design, Structured treatment interruption, Protocol design, Immune based therapy, Model predictive control, Control engineering in medicine, Biomedical engineering.

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**2 Corinthians 12:9**

But he said to me,  
“My grace is sufficient for you,  
for my power is made perfect in weakness”.

Therefore,  
I will boast all the more gladly about my weakness,  
so that Christ’s power may rest on me.

**Phillipians 4:13**

I can do everything through him who gives me strength.

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And last but not least, to Leatile and Tsaone as we tarried on together and their friendly encouragement.

Pretoria, South Africa  
July, 2006

Annah Mandu Jeffrey

...

To Afentse, Kagiso, Anwar, Nefertari and Atang.

In memory of my Father, Ben Gasennelwe, whose idea it was that I become an engineer.

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## Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
CD4	Cluster Designation 4
CD8	Cluster Designation 8
DNA	Deoxyribonucleic Acid
gp120	glycoprotein 120
FDC	Follicular Dendritic Cell
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IBT	Immune Based Therapy
LTNP	Long Term Non Progressor
SIT	Structured/Supervised/Scheduled Intermittent Therapy
STI	Structured/Supervised/Scheduled Treatment Interruptions
RNA	Ribonucleic Acid
RTI	Reverse Transcriptase Inhibitor
PI	Protease Inhibitor

# Chapter 1

## Introduction

**A**CCORDING to the United States Department of Health and Human Services (USDHHS) [1] guidelines on the use of antiretroviral agents in HIV infected adults and adolescents, HIV therapy is considered effective if it can reduce the viral load by 90% in less than 8 weeks and continue to suppress it to below 50 copies per mL of plasma in less than 6 months. The primary goals of such an effective therapy regimen are stated as: “maximal and durable suppression of the viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV related morbidity and mortality” [1]. Furthermore, the tools that are available for the attainment of these goals are: maintenance of high adherence to potent antiretroviral therapy, rational sequencing of drugs in order to maximize the benefits of antiretroviral therapy and preserve future treatment options, testing for drug resistance and adequate monitoring for predictors of virologic success .

There is no doubt that Highly Active Antiretroviral Therapy (HAART) is capable of suppressing the viral load of infected individuals to levels that are below detection by the current assays, can maintain an acceptable CD4<sup>+</sup> T cell count and consequently, prolong the life of the infected person. What is not yet clear though, and the guidelines do concede, is when, during the HIV infection progression, is the optimal time to initiate therapy.

HIV can and has been initiated during all the stages of the infection. Therapy in most cases entails the use of antiretroviral drugs that interfere with the replication cycle of the virus. Other therapies that reconstruct the immune system are also available. The issues of when best to initiate therapy have been studied in [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. Some authors, for example, [2, 8, 10] believe that early therapy, when the CD4<sup>+</sup> T cell count is still high, is best. The recent argument being put forth is that initiating therapy during the acute infection stage while the immune response to the virus is not

yet compromised, could most likely lead the individual to attain immunologic control of the virus with the use of structured treatment interruptions (STI) [13, 14, 15, 16, 17, 18]. However, in many cases, initiating therapy early during the infection is no guarantee for attaining this so called long term non-progressor (LTNP) status [19, 20, 21].

Other authors, for example [3] believe that late therapy during the final decline of the CD4<sup>+</sup> T cells is best. The arguments being put forth for delayed therapy are that the drugs are toxic and exposure should be delayed for as long as possible. Furthermore, care should be taken not to exhaust the regimen options in case resistance emerges, and as stated before, not all who initiate therapy early manage to attain LTNP status. Yet some studies [4, 5, 6] have shown that there is a higher mortality rate for patients who start therapy in the advanced stages of the disease as opposed to those who started early.

The main reason for the lack of consensus on when best to initiate therapy, as well as other HIV issues, is that the chemotherapy of HIV has multiple objectives and the studies that have been carried out had different objectives. So, the current position is that some individuals could benefit from early therapy, while for some it is better to defer therapy. How then can one predict in advance if an individual will benefit from early or late therapy?

Once the decision to initiate therapy has been made, the starting regimen should then be prescribed. It is apparent that there is variability in response to therapy among individuals. Some individuals have virologic failure on therapy that is highly effective on others. Furthermore, many experience viral load rebounds, known as blips after periods of effective suppression [22, 23, 24, 25]. Some rebounds are transient, while others lead to virologic failure. How then, can one predict in advance who will experience a rebound, and whether the rebound signals virologic failure or will be short lived? In other words, what then, are the prognostic indicators of virologic success?

The HAART regimen in most cases will manage to suppress the viral load to below detection in 3-4 months from when therapy was initiated [1]. However, the virus persistently replicates in body compartments [26, 27, 28, 29, 30, 31, 32, 33]. Furthermore, there is differential drug penetration into different compartments and target cells [34, 35, 36, 37, 38] and some latent compartments act as virus reservoirs [39, 40]. This has rendered virus eradication impossible with the currently available antiretroviral drugs.

Durable suppression of the viral load has also proven to be difficult because of the problems associated with HAART. Antiretroviral drugs are toxic, instantaneously and cumulative. There is therefore a need to design dosage regimens that can attain maximal and durable suppression of the viral load with minimal drug exposure. However, maximal

viral load suppression and minimal dosing are conflicting objectives. The objectives of therapy must therefore, be prioritized and the dosage should be designed to strike a balance between aggressive therapy and minimal side effects, now that the focus has shifted from virus eradication to managing a chronic infection.

## 1.1 Motivation

Millions of people world wide are infected by the HI virus. This HIV/AIDS pandemic has placed a heavy burden on medical workers. It is therefore, fitting that all who can assist should do so.

One of the motivations for this study is that there is a need to find plausible explanations to some currently observed clinical responses from individuals on antiretroviral therapy. These observations can be summarized as follows:

There is variability in response to therapy, as some individuals experience virologic failure on therapy that is highly effective on others [41].

For the majority who do attain viral load suppression, the maximality and duration of such suppression varies.

Persistent virus replication [28, 31, 32, 33, 40] and transient rebounds of plasma viremia (viral load blips) under HAART have also been reported [22, 23, 24, 25].

Furthermore, the optimal time to initiate therapy during the course of the HIV infection is currently not very clear.

Vigorous research in the medical field and clinical trials on HIV/AIDS and related issues mentioned above is currently ongoing. Affirmative and contradicting conclusions on most of the issues are drawn from one study to the other. This has paved the way for mathematicians and control engineers to be of assistance to medical practitioners by providing some insights and suggestions on how the above problems can be approached and solved.

The other motivating factor for this thesis is that there is a need to individualize therapy, or at least, derive dosage schedules that will apply to most HIV infected individuals. This need can be summarized as follows:

Eradication of the virus is not attainable with the currently available drugs, and now the focus has shifted from virus eradication to management of a chronic infection.

Given that antiretroviral drugs are generally toxic, the general objectives of therapy are therefore, to maximally suppress the viral load with minimal use of drugs.

Once therapy is initiated, the individual can not later choose to indefinitely discontinue therapy without undesirable effects.

## 1.2 HIV/AIDS Therapy: A Control Engineering Problem

The role that control engineering has played, and continues to play in control of biomedical systems is legendary. Examples include the automation of anaesthetic delivery during surgery, optimization of drug dosages in the management of bacterial infections and cancer chemotherapy, control of robotic endoscopic surgery systems, and so on. There is an IEEE Transaction on Automatic Control issue that addressed some of the applications of control theory in medicine. The goal of this issue, according to the guest editorial, was to “showcase some of the applications of control theory to medicine with two goals in mind. The first goal was to interest the control theory community in the idea of developing applications in medicine, and the second goal was to demonstrate to the medical community that control theory had solid applications in the medical field” [42].

Current research on HIV therapy is diverse and multi-disciplinary. Engineers however, were late in joining the research movement and as such, engineering literature related to HIV chemotherapy is limited. Control engineers in particular, should have risen to the challenge as it is apparent that chemotherapy scheduling and control engineering have a lot in common.

It is acknowledged though that HIV/AIDS models, like many biological and industrial systems, are not well defined mathematically. The main reason for the HIV/AIDS models' limitations is a lack of a good understanding of the immunology of the body against HIV. Biological systems tend to exhibit multi-compartmental interactions that are usually not well understood and as a result, can not be accurately modelled mathematically. The accuracy of the models is increasing though with new medical discoveries.

From a control theoretic perspective, HIV chemotherapy is control of a time varying nonlinear dynamical system with constrained controls. Administering an antiretroviral agent is equivalent to introducing a control signal that perturbs the current state of the HIV dynamics. The adopted control approach or strategy depends primarily on the control objectives, performance specifications and the control constraints. Obtaining

measurements of the controlled variables though, has the potential to hinder effective control.

Applying control engineering concepts to the analysis of HIV/AIDS models and therapy design is however, gaining momentum. Examples are works on viral load controllability and timing the initiation of therapy [43], optimized treatment interruptions with relation to controllability [44, 45], feedback control of the viral load [46, 47], as well as optimal control and multi-drug therapy scheduling for multiple viral strains [48, 49, 50, 51].

For the enhancement of the immune response to the virus, [52] compared continuous dose control with receding horizon control, [53] used model predictive control to derive structured treatment interruption cycles, while [54] proposed a gradual reduction of drug dosage approach that drives the patient to attain the long term non-progressor status. [55] also used predictive control to derive a dosage sequence for combination therapy. [56] presented a globally stable nonlinear control approach to HIV therapy, while [57] presented a strategy for structured treatment interruption protocol design for the chronically infected patient.

Other analytical works such as bifurcation [58], stability of the steady states [54, 59] and viral load time response analysis under therapy are also available [60]. These works are model based, and this puts an emphasis on the need to obtain, as early as possible, estimates of the individual's viral and host cell model parameters. Works related to system identifiability [61, 62, 63] and parameter estimation from clinical data [64, 65, 66, 67] are also available. [68, 69] have gone the extra mile to assess and incorporate HIV/AIDS education into the control engineering curriculum.

Most of these HIV control works are aimed at suppressing the plasma viral load of infected persons, while some focus on maintaining the  $CD4^+$  T cell count within a given range or above a specified level. There is a general view though, that treatment should vary with time and depend on the individual patient's response to treatment. This calls for frequent measurements of the controlled variables for effective feedback control.

All the foregoing call for the derivation of a control strategy for HIV therapy that can meet the goals/control objectives of therapy and simultaneously minimize the toxicities associated with the use of antiretroviral agents. This creates an ideal opportunity for control engineers to derive such control strategies. There are various approaches that the control engineer can take towards designing a control strategy for HIV therapy. A control engineering approach to HIV therapy would involve the following steps:

- Model development: This entails the translation of clinical observations into a mathematical formulation. This model should be able to adequately explain the

interaction of the virus, the host cells, and the immune system. Mathematical Biologists have paved the way by building these models and to date, such models that describe different aspects of this virus, host cell and immune systems are available in for example [70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87]. Most of these models are deterministic and based on balancing the population dynamics of the virus and target cells in plasma, while some are stochastic and take into account the random variations in the HIV dynamics.

- **Model validation:** This entails the collection of clinical data that can be used to determine the model parameters and verify that the model is representative of what is observed clinically. Model validation in this context can therefore, be considered as part of model development. There are numerous clinical trials that have been carried out and data has been collected for the determination of model parameters [64, 65, 66, 88, 89, 90, 91, 92, 93, 94]. However, the focus has been mostly on obtaining parameter estimates related to the replication competency of the virus. For these estimates, there is very wide variability between individuals, within a study and between studies. None of the above mentioned models can completely exhibit all that is observed clinically and account for the full course of the HIV infection. Most of the models though, can accurately model the dynamics from initial infection to the clinical latency stage. A point to consider is that these models do not take into account other extenuating environmental, social and welfare factors that may affect the progression of the disease.
- **Model analysis:** Extensive mathematical analysis of the model can be carried out in order to see how different drug regimens will affect viral response and preempt the type of response one can expect. To date, model parameters that are affected by various drugs that are used to treat the HIV infection have been identified and such extensive mathematical analysis has been carried out in works such as [43, 60, 61, 71, 72, 73, 75, 78, 84, 85, 86] and [95, 96, 97, 98, 99, 100]. However, very few of these works have a control theoretic analytic perspective.
- **Controller design:** Once the model is validated and analyzed, then in principle, it can be used to design suitable drug dosage regimens for HIV therapy. Such controller design related works have been presented in for example [44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 55, 56, 57]. Compared to other control design works for other medical conditions, those related to HIV are few. There is therefore, a need to derive optimal control strategies for the chemotherapy of HIV, given the multiple control objectives and constraints on the available treatment options.

- Control system simulation: Simulations can be used to gain insight into the type of response one can expect before a particular drug regimen is tried out on a patient. System simulations can also be used to guide the design of some clinical trials.

### 1.3 Thesis Objectives and Scope

In this thesis, analysis of the HIV/AIDS models will be carried out using various mathematical and control systems analytical tools. The intention is to gain some insights into the HIV infection dynamics from a control theoretic perspective. Such insights can help explain why individuals on antiretroviral therapies respond the way they do, as well as give the individual or practitioner the ability to preempt future responses. The problems or issues addressed by each analysis will be stated and the usefulness of such an analysis to clinicians will be made apparent.

The primary objective of this thesis is to analyze models for the eventual control of the infection. The intention of the proposed control strategy is to produce practical solutions to the current antiretroviral problems, and not necessarily to postulate on solutions that can not currently be implemented. This however, does not mean that issues that could enhance the solution to the problems will not be highlighted. That is, suggestions on which areas to investigate in order to improve the attained solution will be made.

The scenario is such that, given the observed responses from individuals on antiretroviral therapy and the toxicity problems associated with this therapy, what can possibly be done to alleviate these problems? A solution should then be prescribed. The next question will then be, is such a solution implementable? The answer to this last question should be in the affirmative - Yes. And finally, areas that need attention in order to further enhance the solutions will be highlighted.

The first part of this research focuses on the application of control system analytical tools to HIV/AIDS models in order to obtain insight into the following issues:

- Variability in response to therapy between individuals on the same regimen.
- Rebounds of plasma viremia after periods of suppression.
- The attainment of maximal and durable suppression of the viral load.
- The prognostic markers of virologic success.
- Timing the initiation of antiretroviral therapy such that the benefits of therapy are maximized.
- The possibility of individualizing therapy.

The second part of the research focuses on the following control issues:

- Modelling antiretroviral drugs as control inputs.

- Sampling for effective control given the invasive nature of drawing blood samples.
- Drug dosage design to strike a balance between maximal suppression (aggressive therapy) and toxicity (drug exposure) reduction.
- Design of other drug dosage schemes to further reduce total drug intake, once viral load suppression to below detectable levels is attained and maintained.
- The practicality of implementing such a dosage scheme.

## 1.4 Contribution

Contribution of this research can be found in the following published works: Journal papers [43, 60], a book chapter [61], an educational CD [101], and conference papers [102, 103, 104, 105, 106, 107]. Additional contributory works have been submitted to journals [55, 57].

## 1.5 Organization of Thesis

The thesis is arranged as follows: The thesis has a total of six chapters. Except for the concluding chapter, each chapter is concluded with a summary and other related matters or supplemental information can be found in the appendix.

Chapter 2 presents a brief background on immunology and how the virus replicates within the host cells. The interaction between the immune system and the HI virus is explained, as well as how HIV infection compromises the immune system. The chapter presents the different classes of drugs that are used to treat the infection and matters related to drugs resistance are discussed. The guidelines views and advice on the treatment of HIV/AIDS infections then follow, and the case for the need to individualize therapy is presented. Finally, the logistics and reasons for interrupting therapy are presented.

Chapter 3 gives an over view of some HIV/AIDS mathematical models and the aspects of the immune system that each model illustrates are discussed. At the end of the chapter, the models that were adopted for this thesis are presented. The validity of these adopted models and the effect of therapy on model parameters is discussed.

In chapter 4, a detailed analysis of the selected models is carried out in order to gain some insights into the HIV infection dynamics. The analysis starts with the lower order model and is then extended to the higher order model. At the end of the analysis, the usefulness of the analysis and the HIV/AIDS issues that have been addressed are stated.

Chapter 5 presents drug dosage design control strategies for HIV therapy. The chapter first presents the system to be controlled and highlights points that need to be considered

before hand. A way of modelling antiretroviral drugs as control inputs is presented. Sampling, the prioritization of objectives and Model Predictive Control as a control strategy of choice, are discussed. A sequential perturbation approach to dosage design for the treatment naïve patient is implemented. This is followed by the design of structured treatment interruption protocols.

Chapter 6 presents a summary of all the major work that was carried out in this research. This is followed by the conclusions that were drawn from this study as well as recommendations on future work.

A reference list follows and other related information is appended thereafter.

## Chapter 2

# Background

## 2.1 HIV and the Immune System

### 2.1.1 Virus Replication

**E**ACH human immunodeficiency virus (HIV) particle has a glycoprotein (gp) called gp120 on its surface. This gp120 glycoprotein can precisely fit the protein marker called cluster designation 4 (CD4), that is found on the surfaces of most immune system cells. Cells with this marker are referred to as being CD4 positive/plus (CD4<sup>+</sup>). When the HI virus enters the body, it *directly* seeks out the immune system cells because the virus can recognize the CD4 receptor on their surfaces. When a virus comes into contact with such a recognizable cell, it attaches to the CD4 receptor. However, the virus needs to attach to a second co-receptor in order to facilitate entry of the CD4-gp120 complex into the cell, or for the virus to pull itself across the cell membrane [108]. This secondary co-receptor could be CXCR4 or CCR5. After the virus attaches to the co-receptor, the host cell and virus membranes then fuse, and the virus enters the cell, as illustrated in figure 2.1.

HIV is a retrovirus. This is a type of virus that, when outside the target cell, stores its genetic information on a single-stranded ribonucleic acid (RNA) molecule instead of the more usual double-stranded molecule (DNA). However, once inside the cell cytoplasm, the virus sheds its coat and proceeds to construct a complementary DNA version of its genes. The virus enzyme called reverse transcriptase facilitates the synthesizing of this complementary double strand of viral DNA. The double stranded DNA can then proceed into the cell nucleus, where it integrates itself into the host cell's DNA. This integration process is facilitated by another viral enzyme called integrase. Once integrated, the viral DNA is called a provirus. The viral DNA then hijacks the host cell, and directs the cell to produce multiple copies of viral RNA. These viral RNA are translated into

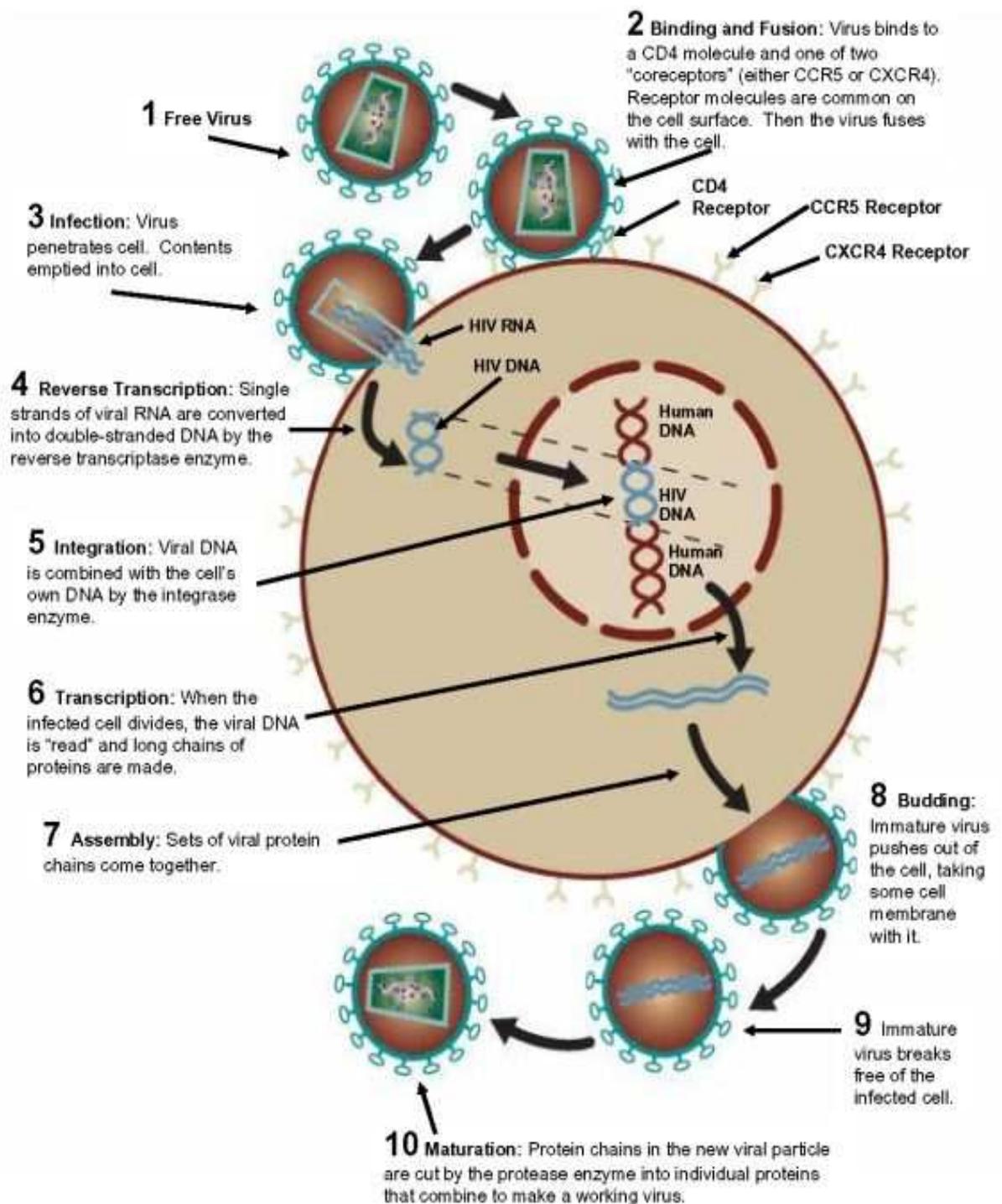


Figure 2.1: Virus Replication cycle. A reproduced picture [109].

viral proteins to be packaged with other enzymes that are necessary for viral replication. Viral core proteins, enzymes, and RNA gather just inside the cells membrane, while the viral envelope proteins aggregate within the membrane. An immature viral particle is formed and then pinches off from the cell, acquiring an envelope and the cellular and HIV proteins from the cell membrane. The immature viral particle then undergoes a maturation process. A viral enzyme called protease facilitates maturation by cutting the protein chain into individual proteins that are required for the production of new infectious viruses.

Eventually, multiple copies of the virus are released, and in the process, the immune cells are destroyed in large numbers, and certain cell pools are even depleted. This leaves the body with little or no defence against disease causing invaders. Furthermore, the replication process is error prone, and consequently, some of the virus particles released are mutants that can also replicate. This gives rise to resistance to antiretroviral drugs.

### **2.1.2 The Immune System**

The immune system is made up of different types of white blood cells (lymphocytes), antibodies and some active chemicals [108, 110], whose responsibility it is to defend the body against any disease causing foreign invaders. The immune cells work together to defend the body by identifying, disabling and destroying the invader. White blood cells are present in the blood, lymph, and lymphoid tissue and can be categorized as B cells (B lymphocytes) or T cells (T lymphocytes). B cells are derived from the bone marrow and spleen, whereas T cells are derived from the thymus gland. There are three different types of T cells that participate in a variety of cell-mediated immune reactions, namely, helper, killer, and suppressor T cells.

#### **CD4<sup>+</sup> T cells:**

CD4<sup>+</sup> T cells are also known as the helper T cells and are crucial to the immune response. In an uninfected individual, CD4<sup>+</sup> T cells constitute 60%-80% of the circulating T cells. While circulating in plasma, CD4<sup>+</sup> T cells can come across foreign invaders, or can be summoned to the infection site by macrophages. It is the CD4<sup>+</sup> T cell's responsibility to recognize viral, fungal and parasitic invaders [110]. When CD4<sup>+</sup> T cells spot a foreign antigen, they begin to proliferate or multiply and secrete a chemical alarm (lymphokines) that alerts and triggers other immune cells into action. However, once infected by the HIV, the cell does not function normally. The infected cell often does not trigger an alarm, but instead, secretes a soluble suppressor factor that blocks other T

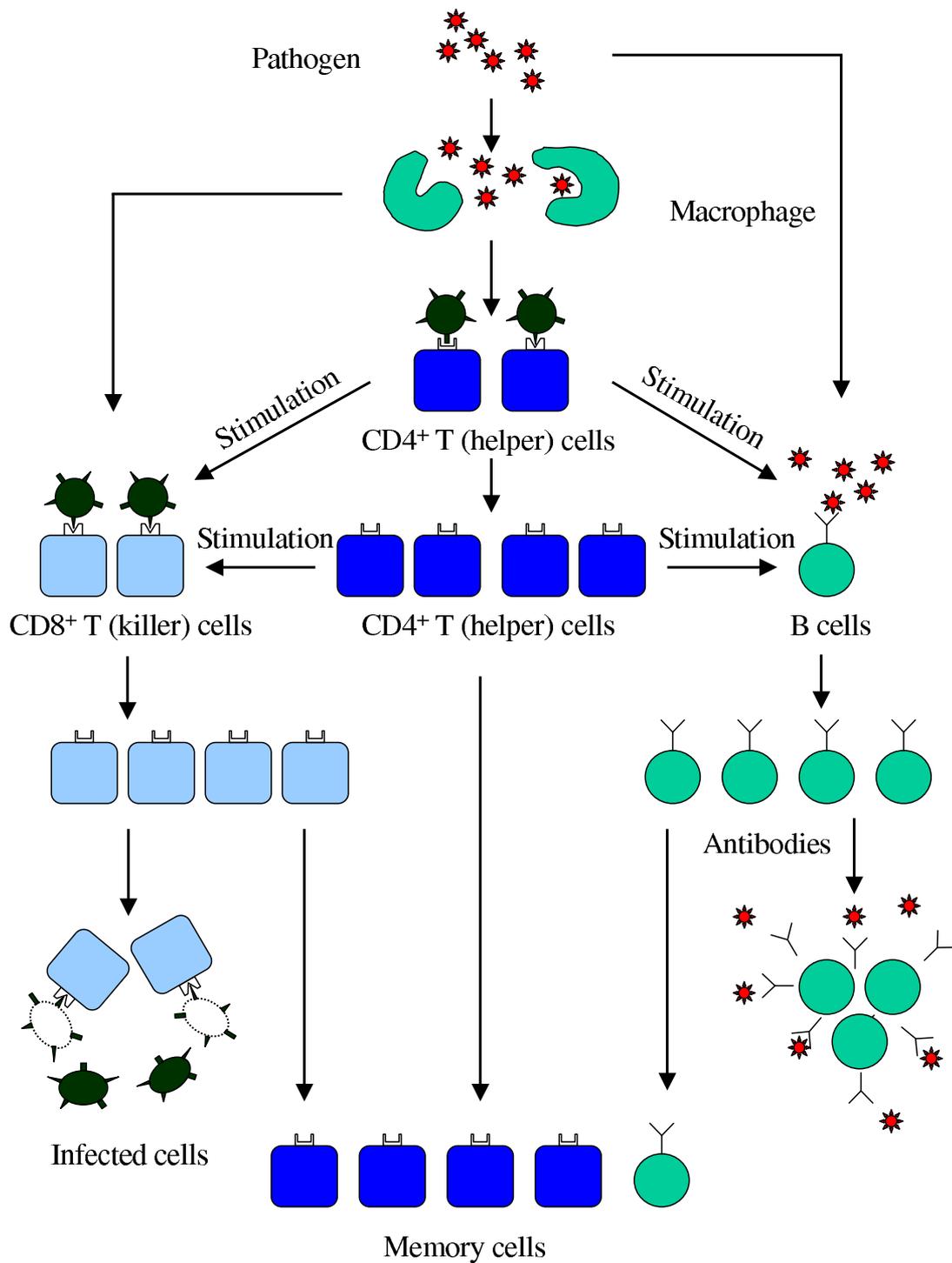


Figure 2.2: Cells of the immune system. Each cell has a receptor and co-receptor(s) on its surface that facilitate virus attachment and entry into the cell. A reproduced picture [77].

cells from responding to the HIV antigen. When the infected cell gets activated, it starts producing viruses and release of the virus destroys the cell. Infection of these  $CD4^+$  T cells by the virus therefore, leads to a drastic reduction in their numbers, and eventually, even complete depletion.

**B cells:**

During infections, B cells are transformed into plasma cells that produce large quantities of antibodies directed at specific pathogens or antigens. Antibodies are chemicals that lock onto the virus or foreign antigens, and thus marking the foreign antigen or virus and making it easier for other cells of the immune system to destroy it. This transformation of B cells to plasmas cells and to the production of antibodies, occurs through interactions with various types of T cells and other components of the immune system. However, in HIV infection or AIDS, the functional ability of both the B and the T lymphocytes is compromised or damaged. Furthermore, the production of antibodies takes time, and in the mean time, the virus multiples and goes on to infect other cells.

 **$CD8^+$  T cells:**

These are a subset of T cells that carry a cluster designation 8 ( $CD8$ ) marker on their surfaces, and are also known as killer T cells or cytotoxic T cells. Because viruses replicate inside host cells where antibodies cannot reach them, the other way viruses can be eliminated is by killing the infected host cell. It is the  $CD8^+$  T cells' responsibility to kill cells infected by intracellular pathogens and some cancer cells. However,  $CD8^+$  T cells can act only when they encounter an infected cell that carries on its surface, a distress signal or marker that links the infected cell to a foreign antigen, that being the invading virus.

Alerted by the helper  $CD4^+$  T cells, these killer  $CD8^+$  T cells likewise proliferate and their receptors then bind to an infected cell's distress signal and releases a potent chemicals that destroys the infected cell. So, while antibodies are marking free floating viruses in the blood for destruction by other cells of the immune system,  $CD8^+$  T cells are destroying cells that are infected by the virus. When the foreign antigen has been vanquished, the  $CD8^+$  T cells produces a signal that suppresses or halts antibody production and other immune responses.  $CD8^+$  T cells, are also suppressor T cells.

**Macrophages:**

These are large cells that devour invading pathogens and stimulates other immune cells by displaying the pathogen's antigen or body shape for the other immune cells to see. Macrophage infection during the primary phase of the infection may be essential for HIV to be successfully established [111]. Macrophages live longer than  $CD4^+$  T cells and are chronic virus producers that can harbour large quantities of the virus without being killed, acting as reservoirs of the virus. Thus, they facilitate virus evolution towards more replication competent strains and away from recognition by the immune system.

Unlike in  $CD4^+$  T cells, HIV replication in macrophages does not require cell activation and division [111], and macrophages have been shown to continue producing virus after  $CD4^+$  T cells have been depleted [112]. Macrophage role in virus replication and spreading of the infection is well accepted, but under-appreciated and poorly defined.

**Follicular Dendritic Cells - FDC:**

These cells are found in the germinal centers of lymphoid organs such as tonsils, lymph nodes, spleen, thymus, and other tissues. These organs act as the body's filtering system. FDCs have thread-like tentacles that form a web-like network to trap invaders and present them to other cells of the immune system that congregate there for destruction. FDCs can trap large quantities of virus, and the disassociation or release of this virus has been shown to affect the virus dynamics in plasma [113, 114].

**Memory T Cells:**

After an immune response has been successful at abating the invading pathogen, the  $CD8^+$  T cells shuts down the immune response. However, a few of each type of immune cells and antibodies remains in circulation. This subset of immune cells that have been exposed to specific antigens can then quickly proliferate on subsequent immune system encounters with the same antigen [108, 115].

### 2.1.3 Compromised Immune Response

Figure 2.3 shows a typical course of HIV infection. The course has 3 main stages, namely the acute or primary infection stage; the asymptomatic or clinical latency or chronic infection stage; and lastly the advanced or AIDS stage. The following summary for the acute and asymptomatic stages is directly extracted from [108].

- **Acute HIV Infection:** This is the period of rapid viral replication immediately following exposure to HIV. An estimated 80 to 90 percent of individuals with pri-

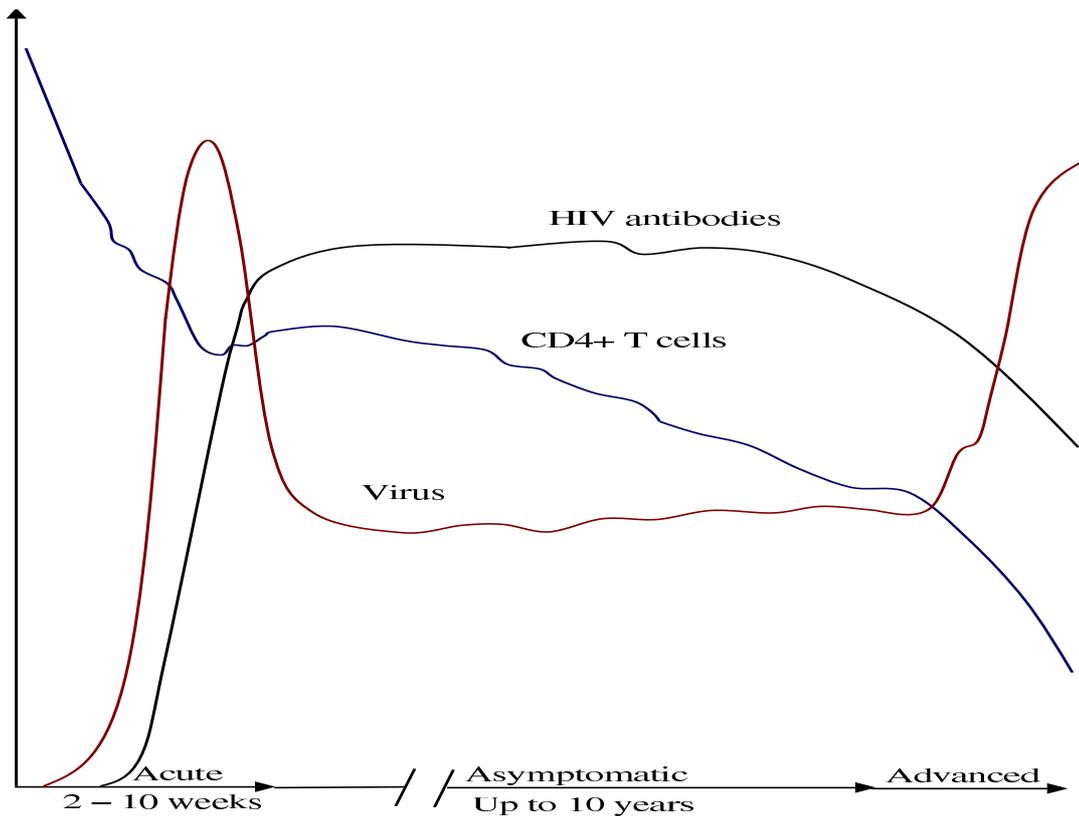


Figure 2.3: Typical HIV infection progression and stages [115].

many HIV infection develop an acute syndrome characterized by flu-like symptoms of fever, malaise, lymphadenopathy, pharyngitis, headache, myalgia, and sometimes rash. Following primary infection, seroconversion occurs. When people develop antibodies to HIV, they seroconvert from antibody-negative to antibody-positive. It may take from as little as 1 week to several months or more after infection with HIV for antibodies to the virus to develop. After antibodies to HIV appear in the blood, a person should test positive on antibody tests [108].

It was previously thought that HIV was relatively dormant during this phase. However, it is now known that during the time of primary infection, high levels of plasma HIV RNA can be documented, as illustrated in figure 2.3.

- **Asymptomatic:** Asymptomatic means “without symptoms”, and this period in infection is also known as the clinical latency period. During this period of time, a person with HIV infection does not exhibit any evidence of disease or any clinically noticeable ill effects, even though HIV is continuously infecting new cells and actively replicating. The virus is also, during this period, active within lymphoid organs where large amounts of virus become trapped in the follicular dendritic cell

network [108].

The period of clinical latency varies drastically in length from one individual to another. There are reports of this latency period lasting only 2 years, while others report it lasting for more than 15 years [115]. But normally, the duration in untreated individuals ranges from 7 to 10 years.

- **Advanced - AIDS:** After a normally long asymptomatic period, the virus eventually gets out of control and the remaining immune cells are destroyed. When the CD4<sup>+</sup> T cell count has dropped lower than 200 per  $\mu\text{L}$  ( $\text{mm}^{-3}$ ) of plasma, the individual is said to have AIDS, and will start to succumb to opportunistic infections, because of the loss of immune competence [115].

So, HIV is also a lentivirus. This is a subclass of seemingly “slow” viruses characterized by a long interval between infection and the onset of symptoms. That is why most people are HIV positive but not aware that they are infected. However, the CD4<sup>+</sup> T cell counts are gradually decreasing towards the 200 cells per  $\mu\text{L}$  AIDS cutoff during this period. This destruction of CD4<sup>+</sup> T cells is the major cause of the immunodeficiency observed in AIDS, and decreasing CD4<sup>+</sup> T cells levels appear to be the best indicator for developing opportunistic infections.

There are some individuals who progress from initial infection to AIDS within 2-3 years (fast progressors), while yet others are characterized as long term non-progressors (LTNP). These are individuals who have been infected with HIV for at least 9 to 15 years (different authors use different time spans) and have stable CD4<sup>+</sup> T cell counts of 600 or more cells per cubic millimeter of blood. Furthermore, long term non-progressors have low viral loads and no HIV-related diseases, even though they have no previous antiretroviral therapy. Data suggest that this LTNP phenomenon is associated with the maintenance of the integrity of the lymphoid tissues and with less virus trapping in the lymph nodes than is seen in other individuals living with HIV.

Besides the depletion of CD4<sup>+</sup> T cells during HIV infection, the way the immune system responds to the infection is impaired on multiple levels. There are two aspects of the immune system’s response to disease: innate and acquired. The innate part of the response is mobilized very quickly in response to infection and does not depend on recognizing specific proteins or antigens foreign to an individual’s normal tissue. It includes macrophages and dendritic cells. The acquired, or learned, immune response arises when dendritic cells and macrophages present pieces of antigen to lymphocytes, which are genetically programmed to recognize very specific amino acid sequences. The ultimate result is the creation of cloned populations of antibody-producing B cells and

cytotoxic T lymphocytes primed to respond to a unique pathogen. (Extracted from [108]).

In HIV infection, both the innate and acquired immune responses are compromised. There is a breakdown in immunocompetence and certain parts of the immune system no longer function and certain cells types are even depleted. HIV infection has been shown to lead to increased rates of cellular turnover and ultimately to deterioration of the immune system. In particular, HIV-1 infection is known to increase the turnover rates of both the CD4<sup>+</sup> and CD8<sup>+</sup> T cells, and to deplete the populations of naïve CD4<sup>+</sup> T cells, naïve CD8<sup>+</sup> T cells, and memory CD4<sup>+</sup> T cells [116]. However, the rates of turnover for these cells (even during health) are poorly characterized and this limits our understanding of the infection. Current estimates for the turnover rates of CD4<sup>+</sup> and CD8<sup>+</sup> T cells vary between 1 and 2% in normal individuals and by up to 10% in HIV- 1 infected patients [116].

The reasons for the increased turnover of T cells have been disputed widely. However, it is clear that there is over stimulation of the immune system. In any case, when follicular dendritic cells present the virus to the CD4<sup>+</sup> T cells, these cells are stimulated to proliferate. This means that the FDCs bring the virus in contact with the CD4<sup>+</sup> T cells at the time when these cells are responding to the antigen [115]. Furthermore, activated CD4<sup>+</sup> T cells are prone to apoptosis, or programmed cell suicide. This leads to the depletion of a subset of cells with specific immune response to the HI virus.

As discussed before, CD8<sup>+</sup> T cells shut down the immune response after it has wiped out invading pathogen. CD8<sup>+</sup> T cells are sensitive to high concentrations of lymphokines in circulation, and release their own lymphokines when an immune response has achieved its goal, thus signaling to all other components of the immune system to cease their coordinated attack. With HIV infection, the immune systems response coordination is impaired. CD4<sup>+</sup> T cells do not function properly and there is an over supply of lymphokines in the bloodstream. CD8<sup>+</sup> T cells then compound the problem by erroneously interpreting the oversupply of lymphokines to mean that the immune system has effectively eliminated the virus.

So while HIV is multiplying in infected CD4<sup>+</sup> T cells and macrophages, CD8<sup>+</sup> T cells are simultaneously attempting to further shut down the immune system. The stage is set for infectious agents that could normally be suppressed, to proliferate unhindered and to cause disease.

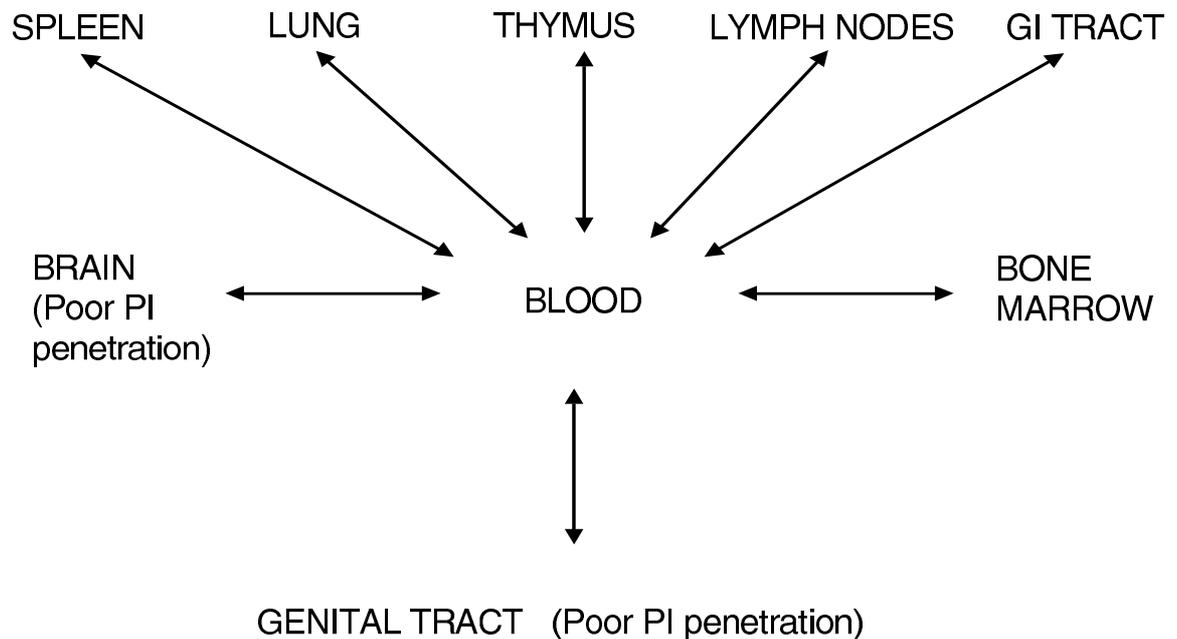


Figure 2.4: HIV Compartmentalization. Some compartments act as virus reservoirs or sanctuary sites [117].

### 2.1.4 HIV Compartmentalization

The human body is made up of different compartments as illustrated in figure 2.4. Some immune cells have the freedom to circulate in plasma or reside in any of the other compartments. Consequently, these cells not only facilitate virus replication, but its dissemination as well. Macrophages are particularly notorious for trafficking virus between compartments. Macrophages have been likened by [110] to a “Trojan horse which hides the invader and carries it to protected places”, and infected macrophages have been shown to be responsible for transporting the virus to the brain.

The release of the virus from other cells and other infected compartments has been shown to affect the virus kinetics in plasma [113]. This situation is problematic because some compartments are not easily penetrated by some drugs used to treat the HIV infection [34, 38, 117]. Furthermore, there is differential drug penetration into different cell types, even within a compartment [35, 37]. This poses a problem for virus eradication.

## 2.2 Drugs Used to Treat HIV Infection

There is a variety of antiretroviral agents that are currently being used for the treatment of HIV infection and to enhance the immune response to the virus. The antiretroviral drugs can generally be classified depending on whether they are virus replication cycle based, or are based on the immune system's response to the virus infection.

### 2.2.1 Replication Cycle Based Antiretroviral Therapies

Figure 2.1 showed the various steps of how virus replication takes place within a host cell. If any stage of the replication process is disrupted, then technically, virus replication can be halted. To this end, various antiretroviral agents that interfere or disrupt one stage or another, have been developed and/or are being currently used. These replication cycle based antiretroviral drugs are classified depending on the point in the virus replication cycle that they disrupt.

**Entry Inhibitors (EI)** are an emerging class of antiretroviral drugs. These inhibitors prevent virus replication at the very early stages of the replication cycle. These drugs are designed to disrupt the interactions between the HI virus and the potential host cell surface, and their focus is on preventing the virus from entering the target cell.

The entry inhibitor class encompasses attachment (binding) inhibitors and fusion inhibitors. Attachment inhibitors are drugs that prevent attachment of the virus gp120 protein to either the target cells CD4 receptor, the CCR4 or CXCR5 co-receptors. If the virus manages to evade the attachment inhibitors (or in the absence thereof, as is the current case) and attaches to the target cell, then the fusion inhibitors can prevent the virus and target cell membranes from fusing together. Fusion inhibitors bind to the gp41 envelope protein and blocks the structural changes necessary for the virus to fuse with the host CD4 cell. This can effectively prevent the virus from entering the target cell. The problem with current entry inhibitors is that they have short half lives and require intravenous administration.

**Reverse Transcriptase Inhibitors (RTI)** work inside the infected cell. These compounds are designed to bind to the reverse transcriptase enzyme, thus preventing nucleosides from binding to the enzyme active sites [108]. This binding interferes with the reverse transcription process and effectively reduces the chances of successful infection of the cell by the virus by halting the transcription of viral RNA into viral DNA. RTIs can further be sub-categorized as nucleoside (NRTI), nucleotide (NtRTI) or non-nucleoside (NNRTI) analogues, depending on the active enzyme site to which they bind to.

**Integrase Inhibitors:** Integrase is not a well understood viral enzyme that however, plays a vital role in the HIV infection process. After reverse transcriptase has transcribed the viral RNA to viral DNA, integrase inserts or integrates the HIVs genes into the cells normal DNA. Once integrated, the HIV DNA is called the provirus. Integrase Inhibitors are a class of currently experimental antiretroviral drugs that prevents the HIV integrase enzyme from inserting viral DNA into a host cells normal DNA.

**Zinc Finger Inhibitors.** Zinc fingers are chains of amino acids found in cellular protein, and play important roles in a cells life cycle. Zinc fingers are involved in binding and packaging viral RNA into new viruses budding from an infected host cell. There are two zinc fingers in HIVs nucleocapsid. Zinc finger inhibitors are drugs which prevents the nucleocapsid part of the gag protein of HIV, which contains the zinc finger amino acid structures, from capturing and packaging new HIV genetic material into newly budding viruses. These drugs are still experimental, and the major problem with them is that zinc fingers are found in other cells of the body. Interfering with zinc fingers in the HI virus consequently interferes with other cells' life cycles.

**Protease Inhibitors (PI)** also work within the host cell as new virus particles are budding off the cell membrane. Protease is the first HIV protein whose three-dimensional structure has been characterized. PIs inhibit the viral protease enzyme from cleaving or cutting the long protein chains into structural proteins and enzymes that make up the viral core. If the larger HIV proteins are not broken apart, they cannot assemble themselves into new functional HIV particles. This results in the production of mostly immature noninfectious virus particles. There are therefore two types of virus particles when protease inhibitors are used. The first type are the infectious virus particles that still continue to infect target cells and the other is the noninfectious type that is not capable of causing new infections, but just circulates until it is cleared from the body.

The currently approved drugs can be classified as entry inhibitors (fusion type), reverse transcriptase inhibitors and protease inhibitors. Multi-drug therapies primarily use a combination of protease and reverse transcriptase inhibitors. Entry inhibitors are also used, but not as widely as reverse transcriptase and protease inhibitors.

Antiretroviral drugs are generally toxic, and the reader is referred to the guidelines [1] for the characteristics of the FDA approved antiretroviral drugs, as well as their toxicity and resistance profiles.

### 2.2.2 The Development of Drug Resistance

HIV has nine genes. Pol is one of these nine HIV genes and codes for the enzymes protease, reverse transcriptase and integrase [108]. This pol gene is prone to mutations or sudden changes in its structure. This leads to the emergence of mutated strains that generally differ in their ability to infect and kill different cell types, as well as in their rate of replication.

The genetic mutations also lead to drug resistance, where resistance occurs when the sensitivity of the virus to a drug is reduced. In HIV, mutations can change the structure of viral enzymes and proteins so that an antiviral drug can no longer bind with them as well as it used to. Often in HIV infection, when an individual's virus strain develops resistance to a particular drug in the regimen, it also turns out to have resistance to some drug or even drugs that the virus has never been previously exposed to. This is referred to as cross-resistance, and is one of the many problems facing antiretroviral therapy.

In many instances, an individual has one or more mutants by the time they start antiretroviral therapy. This pre-existence of mutant virus strains has been cited as the primary reason for the emergence of resistance [118], and even high levels of adherence to therapy will fail to prevent the accumulation of some of these mutant strains [119]. After the initial decline in viral load as the responsive wild type viral strain is cleared, resistance emerges as the mutant strain now thrives in the absence or reduction of the wild type virus. Individuals who have only the wild type strain when they initiate therapy have better therapeutic results as they take longer to develop resistance. This is because the probability of developing resistance if there was no pre-existence of resistant strains is much lower than when mutants are present before therapy is initiated.

There are two aspects to resistance. The first is genotypic resistance and can be detected by searching the virus genetic makeup for mutations that could confer lower susceptibility to a particular drug. In essence, tests for genotypic resistance, known as genotypic assays, are used to determine if HIV has become resistant to the antiviral drug(s) by analyzing a sample of the virus from the patients blood to identify any mutations in the virus that are associated with resistance to specific drugs.

The other aspect of resistance, referred to as phenotypic resistance, is detected by successfully growing laboratory cultures of the virus in the presence of a drug. Likewise, phenotypic assays are resistance tests whereby sample DNA of a patients HIV is tested against various antiretroviral drugs to see if the virus is susceptible or resistant to these drugs. Table 2.1 has recommendations on resistance testing in HIV infection.

Table 2.1: Recommendations for using drug-resistance assays

Clinical Setting / Recommendation	Rationale
<b>Drug-resistance assay recommended:</b>	
Virologic failure during combination antiretroviral therapy (BII)	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after antiretroviral therapy initiation (BIII)	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy (BIII)	Determine if drug-resistant virus was transmitted to help design an initial regimen or to change regimen accordingly (if therapy was initiated prior to test results).
<b>Drug-resistance assay should be considered:</b>	
Chronic HIV infection before therapy initiation (CIII)	Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e., if the patient is thought to have been infected by a person receiving antiretroviral drugs).
<b>Drug resistance assay not usually recommended:</b>	
After discontinuation of drugs (DIII)	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species.
Plasma viral load < 1,000 HIV RNA copies/mL (DIII)	Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/providers may incur charges and not receive results.

Reproduced from [1].

### 2.2.3 Immune Based Therapies

Immune based therapies for HIV control entail the direct targeting of the immune system as a therapeutic strategy. Immune based therapies, as opposed to replication cycled based HAART, are not sensitive to virus mutations, and as such, are attractive as they offer the potential to minimize the emergence of drug resistance [120]. However, there is an unavoidable overlap between immune based therapy and replication cycle based therapy.

Immune based therapies can be used to augment the replication cycle based therapies. The proposed strategies include:

- Expansion of the CD4<sup>+</sup> T cell pool by direct lymphocyte transfer or Interleukin-2 [121].
  - (a) Interleukin-2 (IL-2): (Extracted from [108]) A cytokine secreted by Th1 CD4<sup>+</sup> T cells to stimulate CD8<sup>+</sup> T cytotoxic T lymphocytes. IL-2 also increases the proliferation and maturation of the CD4<sup>+</sup> T cells themselves. During HIV infection, IL-2 production gradually declines. Recent data suggest that therapy with subcutaneous IL-2, in combination with replication cycle based antiretroviral drugs, has the potential to halt the usual progression of HIV disease by maintaining an individuals CD4<sup>+</sup> T cell count in the normal range for prolonged periods of time. Long term cell expansions with its use have been recorded in clinical trials.
  - (b) Lymphocyte transfers: This entails the direct transferring of CD4<sup>+</sup> T cells to the infected individual. Transients effects in clinical trials have been recorded with this procedure.
- Enhancement of HIV specific immunity by structured treatment interruptions, therapeutic immunization or passive immunotherapy [121].
  - (a) Structured treatment interruptions (STI): These are planned interruption of treatment by discontinuation of all antiretroviral drugs. There is no evidence of enhanced antiviral activity with this approach. However, there are reports of some individuals who sustain viral control and attain LTNP status with STI, especially when HAART was initiated during the acute stage of the infection. This strategy also reduces drug exposure and the cost of treatment.
  - (b) Passive immunotherapy: (Extracted from [108]) Process in which individuals with advanced disease (who have low levels of HIV an-

tibody production) are infused with plasma rich in HIV antibodies or an immunoglobulin concentrate (HIVIG) from such plasma. The plasma is obtained from asymptomatic HIV-positive individuals with high levels of HIV antibodies.

- Suppression of immune activation by the use of immunosuppressive drugs such as hydroxyurea or cyclosporin [120].

(a) Hydroxyurea: This is an inexpensive prescription drug used for the treatment of sickle-cell anemia and some forms of leukemia. Hydroxyurea has been used investigationally for the treatment of HIV infection. Hydroxyurea does not have direct antiretroviral activity, rather, it inhibits immune activation. Some results of the use of hydroxyurea with HAART are promising [120], while others show no enhanced efficacy with its concomitant use with HAART [122, 123, 124].

(b) Cyclosporin: This drug also reduces cell activation. However, clinical trials data with its use are disappointing.

- Short-term accelerated depletion of the CD4<sup>+</sup> T cells by induced apoptosis [125].

Apoptosis: (Extracted from [108]) Also referred to as “cellular suicide,” or programmed cell death. Normally when CD4<sup>+</sup> T cells mature in the thymus gland, a small proportion of these cells is unable to distinguish self from nonself. Because these cells would otherwise attack the body’s own tissues, they receive a biochemical signal from other cells that results in apoptosis. HIV infection can also induce apoptosis in both infected and uninfected immune system cells. The adoption of this approach as a form of therapy is based on the fact that high viral loads in HIV infection are a result of an abundant supply of cells that the virus can replicate in. However, the use of drugs that induce apoptosis as a form of therapy is controversial.

## 2.3 Guidelines on the Use of Antiretroviral Agents

The guidelines referred to in this section are “Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents” [1]. These guidelines are published by the United States Department of Health and Human Services, and are available online.

Prolonged suppression of plasma viral load is attainable with the available antiretroviral agents. However, eradication of HIV infection has proven to be elusive. The reason

for this is primarily because there is a pool of latently infected CD4<sup>+</sup> T cells that is established very early during the acute HIV infection stage and persists with a long half-life, even with suppression of plasma viral load to below detectable levels.

Now that the focus has shifted from virus eradication to managing a chronic infection, the primary goals of antiretroviral therapy, according to the guidelines [1] are:

- reduce HIV-related morbidity and mortality,
- improve quality of life,
- restore and preserve immunologic function, and
- maximally and durably suppress viral load.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality.

Plasma viral load is considered as a strong prognostic indicator of HIV disease progression. Reductions in plasma viral load achieved with antiretroviral therapy account for substantial clinical benefits. Therefore, suppression of plasma viral load as much as possible, for as long as possible, is a critical goal of antiretroviral therapy. This goal, however, must be balanced against the need to preserve effective treatment options in patients who do not achieve undetectable viral load due to extensive viral resistance or persistent medication non-adherence.

Viral load reduction to below limits of assay detection in a treatment-naïve patient usually occurs within the first 16-24 weeks (4-6 months) of therapy [1]. However, maintenance of excellent treatment response is highly variable. Predictors of long-term virologic success are stated as [1]:

- potency of antiretroviral regimen,
- adherence to treatment regimen,
- low baseline viral load,
- higher baseline CD4<sup>+</sup> T cell count, and
- rapid (i.e. > 1 log<sub>10</sub> in 1-4 months) reduction of viral load in response to treatment.

Successful outcomes have not been observed across all patient populations. However, achieving treatment goals requires a balance of sometimes competing considerations. The guidelines suggests the following strategies to achieve treatment objectives.

- **Selection of Combination Regimen.**

Several preferred and alternative antiretroviral regimens are recommended for use. These regimens vary in efficacy, pill burden, and potential side effects. A regimen tailored to the patient may be more successful in fully suppressing the virus with

fewer side effects. Individual tailoring is based on such considerations as lifestyle, co-morbidities, and interactions with other medications.

- **Preservation of Future Treatment Options.**

Multiple changes in antiretroviral regimens, prompted by virologic failure due to drug resistant virus or patient non-adherence, can rapidly exhaust treatment options. While these are valid reasons to prompt a change in therapy, they should be considered carefully.

- **Drug Sequencing.**

Appropriate sequencing of drugs for use in initial and subsequent salvage therapy preserves future treatment options and is another tool to maximize benefit from antiretroviral therapy. Currently recommended strategies spare at least two classes of drugs for later use and potentially avoid or delay certain class-specific side effects.

- **Improving Adherence.**

The reasons for variability in response to antiretroviral drugs are complex but may include inadequate adherence due to multiple social issues that confront patients. Patient factors clearly associated with the risk of decreased adherence such as active substance abuse, depression, and lack of social support need to be addressed with patients before initiation of antiretroviral therapy. Strategies to improve medication adherence can improve outcomes.

### 2.3.1 Recommended Regimens

There is a variety of combinations of antiretroviral drugs that are recommended for the treatment of HIV infection. These regimens are rated as illustrated in Table 2.2. A typical start up regimen could for example be a combination of Efavirenz + lamivudine + tenofovir. This combination has a rating of AII, meaning it is strongly recommended (A) and this recommendation is supported by clinical trials with laboratory results (II). These regimens are presented in Table 2.3, and all utilize replication cycle based antiretroviral agents.

### 2.3.2 The Need to Individualize Antiretroviral Therapy

The following is an extraction from the top part of table 5 in the guidelines

Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities,

Table 2.2: Rating scheme for clinical practice recommendations.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong	I: At least one randomized trial with clinical results
B: Moderate	II: Clinical trials with laboratory results
C: Optional	III: Expert opinion
D: Should usually not be offered	
E: Should never be offered	

Reproduced from [1].

drug-drug interaction potential, co-morbid conditions, and level of plasma HIV-RNA ...

Regimens are designated as “preferred” for use in treatment naïve patients when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use.

Alternative regimens are those where clinical trial data show efficacy, but it is considered alternative due to disadvantages compared to the preferred agent, such as antiviral activity, durability, tolerability, drug interaction potential, or ease of use.

In some cases, based on individual patient characteristics, a regimen listed as alternative in this table may actually be the preferred regimen for a selected patient ...

From the guidelines perspective, therapy should be individualized because some regimens are tolerable and/or have better efficacy than others. To this end, some regimens are designated as “preferred”, while others are considered alternatives. On the same note, the guidelines acknowledge that there will be variability in the way individuals respond to a particular regimen, preferred or alternative, and in a clinical environment or otherwise.

The underlying cause for this variability in response is complex. In clinical trial conditions where poor adherence has been ruled out, this variability in response has been linked to inter-individual variations in drug uptake, because HIV drug pharmacodynamics, pharmacokinetics and adverse reactions are genetically predisposed [41, 126].

Table 2.3: Antiretroviral regimens recommended for treatment of HIV-1 infection in antiretroviral naïve patients.

	Regimens	No. of pills
<b>Preferred Regimens</b>		
NNRTI-based	<b>efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF) (AII)</b>	2–3
PI-based	<b>lopinavir/ritonavir</b> (co-formulation) + (lamivudine or emtricitabine) + <b>zidovudine (AII)</b>	8–9
<b>Alternative Regimens</b>		
NNRTI-based	<b>efavirenz</b> + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine) ( <b>BII</b> )	2–4
	<b>nevirapine</b> + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir) ( <b>BII</b> ) -	3–6
PI-based	<b>atazanavir</b> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir 100mg/d) ( <b>BII</b> )	3–6
	<b>fosamprenavir</b> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) ( <b>BII</b> )	5–8
	<b>fosamprenavir/ritonavir</b> <sup>†</sup> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) ( <b>BII</b> )	5–8
	<b>indinavir/ritonavir</b> <sup>†</sup> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) ( <b>BII</b> )	7–12
	<b>lopinavir/ritonavir</b> + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine) ( <b>BII</b> )	7–10
	<b>nelfinavir</b> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) ( <b>CII</b> )	5–8
	<b>saquinavir</b> (sgc or hgc)/ <b>ritonavir</b> <sup>†</sup> + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) ( <b>BII</b> )	13–16
3 NRTI-based	<b>abacavir</b> + zidovudine + lamivudine - <i>only when a preferred or an alternative NNRTI- or a PI-based regimen cannot or should not be used</i> ( <b>CII</b> )	2

Preferred regimens are in bold type

<sup>†</sup> Low-dose (100 – 400 mg) ritonavir per day

Reproduced from [1]

## 2.4 Treatment Interruption

### 2.4.1 Reasons for Interrupting Therapy

Interruption of therapy can be for the following reasons [1]:

- Reduce drug exposure and related toxicities
- Autoimmunization or Re-immunization
- Salvage therapy

The problem with HAART interruption is that the virus starts to rebound immediately following HAART cessation, and there is an associate decline in CD4<sup>+</sup> T cell counts. The reason for this rebound of plasma viral load is because viral load suppression with HAART does not necessarily imply a reconstitution of HIV specific immune responses [127]. Other reasons for the rapid viral load rebound when HAART is interrupted are the over stimulation of the immune system during infection [92] and the availability of new target cells due to CD4<sup>+</sup> T cell gains incurred during HAART.

There are fears that therapy interruption has a similar effect on the virus as does not adhering to therapy in that they cause the virus to become resistant [128, 129, 130, 131]. Some authors argue that even high levels of adherence do not prevent the emergence of drug resistant mutants [119], and that the pre-existence of resistant mutants is the primary cause of drug resistance [118]. The later is supported by the outcome of many clinical trials where treatment interruption did not lead to drug resistance. In any case, the associated viral rebounds can also increase the transmission of the virus.

Structured treatment interruptions - STI, for the purpose of reducing the total time on HAART and drug exposure is getting a lot of attention because of the growing concern over the adverse side effects of HAART. This has been tried out primarily on patients with previous viral suppression [132]. The intention is to reduce the toxicity associated with antiretroviral drugs, given that one has to use them indefinitely. One such study on Strategies for the Management of Antiretroviral Therapies [133] aimed to “strike a balance between adequately aggressive treatment and minimal side effects”. This was a long term study that was intended to cover a period of up to nine years with some patients on either STI or continuous HAART.

STI as an immune based therapy for autoimmunization, is meant to allow short bursts of viral replication to augment HIV specific immune responses. The general intention is to use STI to shift the infected individual to a state where one can attain a degree of viral load control without antiretroviral drugs, or hopefully, attain the long term non-progressor status. Clinical studies have been carried out using this approach on patients

who had initiated therapy during the acute and chronic infection stages and had a record of sustained viral suppression to below detectable levels [15, 16, 132, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146]. Results indicate that autoimmunization has more benefit in the acute infection stage and less in the chronic stage. Individuals who initiate therapy during the acute infection stage are therefore more likely to attain long term non-progressor status, than those who wait to initiate therapy in the asymptomatic and advanced stages. Unfortunately, this favours a small percentage of HIV infected persons because the majority are already in the chronic infection stage.

One of the objectives of STI should be to improve the ability, or find ways, to determine immune competence in chronically infected patients, and to develop tests that may then predict which patients will be the best candidates for STI [127]. The general idea is that STI, just like therapeutic drug monitoring (TDM), is not for every body. This poses the question: is it possible then, for one to tell in advance, whether or not the individual will benefit from STI?.

For those patients who have virologic failure, treatment interruption can be employed for salvage purposes. The intention of this is to allow the re-emergence of the virus strain that responds to therapy. This has been tried out in [147, 148, 149] and results show that more harm than good is done in most cases, as the CD4<sup>+</sup> T cell count often drops to very low levels while the resistant virus strain remains.

### **2.4.2 Structured Treatment Interruption Protocols**

One approach to treatment interruption strategies is to monitor either the viral load or CD4<sup>+</sup> T cell count. Therapy is interrupted or resumed when the monitored variable rises above or below predetermined upper and lower bounds. In essence, it entails keeping the variable between an upper and lower bound by on/off control. Another approach to treatment interruption is to have predetermined time periods for when therapy is on and when it is interrupted. The former approach is more difficult to implement when compared to treatment interruption with predetermined on/off periods, as it requires more frequent measurements in order to check if the variable is above or below the cut off points.

Tables 2.4, 2.5 and 2.6 are summaries of clinical STI trials that had positive, neutral and negative outcomes, respectively. The criteria used to determine the success or failure of the trials is rather subjective. The trials generally had varying objectives and determinants of success or failure. Furthermore, the STI protocols that were adopted vary.

Table 2.4: Summary of clinical trials with a positive outcome

Entry Criteria		No of Patients	Treatment Schedule	Results	Reference
CD4 <sup>+</sup>	VL				
>300	<50	10	7 days on/7 days off for up to 68 weeks	Viral control maintained ↓ Side effects	[132]
$\frac{CD4}{CD8} >1$	<20	12	Off until VL > 3000 copies mL <sup>-1</sup> or max. 30 days off	Viral control maintained	[150]
$\frac{CD4}{CD8} >1$	<50	12	Off until VL > 3000 copies mL <sup>-1</sup> or max. 30 days off	Progressive ↓ in viral replication ↑ HIV-1 specific T-cell response	[145]
>500	<20	10	1 month off / 6 months on or VL > 200 copies mL <sup>-1</sup>	↓ Viral setpoint ↑ HIV-1 specific T-cell response	[139]
Varied	Varied	3	3 weeks on/1 week off	No emergence of drug resistance ↓ Viral setpoint	[14]
>500	<50	8	Off until VL > 5000 copies mL <sup>-1</sup>	↑ HIV-1 specific T-cell response	[16]
<200	<50000*	68	8 weeks off	↑ CD4 <sup>+</sup> T cell count ↓ Viral load	[147]

[151].

\* Salvage therapy

Table 2.5: Summary of clinical trials with a neutral outcome

Entry Criteria		No of Patients	Treatment Schedule	Results	Reference
CD4 <sup>+</sup>	VL				
>400	<400	8	30 days on/30 days off for 7 months	↑ HIV-1 specific T-cell response No viral control	[142]
Varied	<500	14	Range: 14-196 days off	Viral rebound to pre-HAART levels	[152]
Varied	Varied	5	Varied	↓ Latently infected cells	[153]
>150	≥5000**	10	28 days on/28 days off	No ↑ drug resistance	[154]
>400	<200	3	Median 7 days off for 11 cycles	Transient ↑ in T-cell response Virus rebound in all patients	[155]
Varied	<50	11	Varied	Resistance ≠ interruptions	[156]
>350	<50	18	Off until VL > 5000 copies mL <sup>-1</sup> or CD4 decline by 25% from baseline	Viral rebound within 2 – 3 weeks	[135]
>300	<50	97	2 weeks off/8 weeks on for 4 cycles	No change in setpoint	[143]
>300	<50	133	2 weeks off/8 weeks on for 4 cycles	Viral load similar to pre-HAART levels	[136]

[151].

\*\* Therapy naïve patients

Table 2.6: Summary of clinical trials with a negative outcome

Entry Criteria		No of Patients	Treatment Schedule	Results	Reference
CD4 <sup>+</sup>	VL				
>300	<60	14	2 weeks off/8 weeks on for 4 cycles	Viral rebound within 8 days	[137]
>300	<50	52	4 weeks off/8 weeks on	↑ Drug resistance	[157]
>350	<50	600	7 days on/7 days off or CD4 < 350	The majority of patients exhibit viral rebound > 500 copies mL <sup>-1</sup>	[20]
Varied	Varied	40	Median 214 days off	↑ AIDS events	[158]
Varied	Varied	2	Varied	↓ HIV-1 specific T-cell response	[159]

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[151].

## 2.5 Chapter Summary

The immune system is made up of different types of white blood cells (lymphocytes), antibodies and some active chemicals [108], whose responsibility it is to defend the body against any disease causing foreign invader. When the HI virus enters the body, it *directly* seeks out the immune system cells because the virus can recognize the CD4 receptor on their surfaces. Some immune cells have the freedom to circulate in plasma or reside in any of the other body compartments. Consequently, these cells not only facilitate virus replication, but its dissemination as well. Macrophage cells are particularly notorious for trafficking virus between compartments.

Besides the depletion of CD4<sup>+</sup> T cells during HIV infection, the way the immune system responds to the infection is impaired on multiple levels. There is a breakdown in immunocompetence and certain parts of the immune system no longer function and certain cells types are even depleted. There is over stimulation of the immune system, which is characterized by an over supply of lymphokines in the bloodstream. So while HIV is multiplying in infected CD4<sup>+</sup> T cells and macrophages, CD8<sup>+</sup> T cells are simultaneously attempting to further shut down the immune system. Furthermore, activated

CD4<sup>+</sup> T cells are prone to apoptosis. This leads to the depletion of a subset of cells with specific immune responses to the HI virus.

There are many antiretroviral agents that have been approved for the treatment of HIV. These agents can be categorized as replication cycle based, or immune based. Replication cycle based drugs are the reverse transcriptase, protease and entry inhibitors, so named depending on the stage of the stage of the replication cycle that they disrupt. Immune based drugs modulate the immune system.

Treatment interruptions can be for autoimmunization purposes, for salvage therapy, or to have drug holidays. Whatever the reason, viral load rebounds will be observed with each treatment interruption cycle for many patients, especially those in the asymptomatic and advanced stages of the HIV infection. Furthermore, CD4<sup>+</sup> T cell declines during HAART interruption are considered as undesirable, especially when the T cell count did not rebound adequately while one was still on HAART. To this end many clinical trials have been carried out in an attempt to come up with treatment interruption protocols that will work for most individuals.

Many individuals with chronic HIV infection will fail to attain long term non-progressor status with structured interruptions of therapy. For these individuals, who represent the majority of HIV infected persons, there is need to focus on estimating the time before the viral load rebounds, as well as monitoring both the viral load and CD4<sup>+</sup> T cell count so that therapy can be resumed before the viral rebound occurs, or T cell counts drop to dangerous levels. There is also need to explore other therapeutic options that will slow down the viral rebound and/or CD4<sup>+</sup> T cell decline during HAART interruption.

## Chapter 3

# HIV/AIDS Models

**M**ATHEMATICAL models that describe the host-pathogen interaction between the immune system and HIV should be able to explain the initial high rise in plasma viral load, its decline and settling to levels that are much lower than the peak viral load. The subsequent dramatic increase in the viral load during the later stage of the infection and timing of this increase should also be explained.

Many models explaining different aspects of the HIV infection have been developed. Most are deterministic single compartment models and are based on balancing population dynamics of the virus, the uninfected and actively infected target  $CD4^+$  T cells in plasma [7, 71, 75, 77, 80, 84, 85]. These single compartment models can be expanded to explicitly model the immune response to the virus [70, 73, 76, 77, 87] or take into consideration other target cells that are co-circulating in plasma with the  $CD4^+$  T cells [74, 78, 81, 85]. Models that include intracellular delays between cell infection and virus production [72, 82, 83], as well as stochastic models that take into account the random variations in HIV dynamics are also available [86]. The co-existence of both wild type and mutant virus strains has also been modelled [79]. Multi-compartmental models that show virus production by cells in other body compartments like tissue, as well as the trafficking of virus particles between compartments [71] have also been developed.

### 3.1 The Latently Infected Cell Model

Eradication of Human Immunodeficiency Virus - HIV infection does not seem possible with currently available antiretroviral drugs. “This is due primarily to the establishment of a pool of latently infected  $CD4^+$  T cells during the very earliest stages of acute HIV infection that persists with an extremely long half-life, even with prolonged suppression of the plasma viral load using Highly Active Anti-Retroviral Therapy - HAART” [39, 40].

The 4 dimensional model presented below by equations (3.1)-(3.4) and schematically

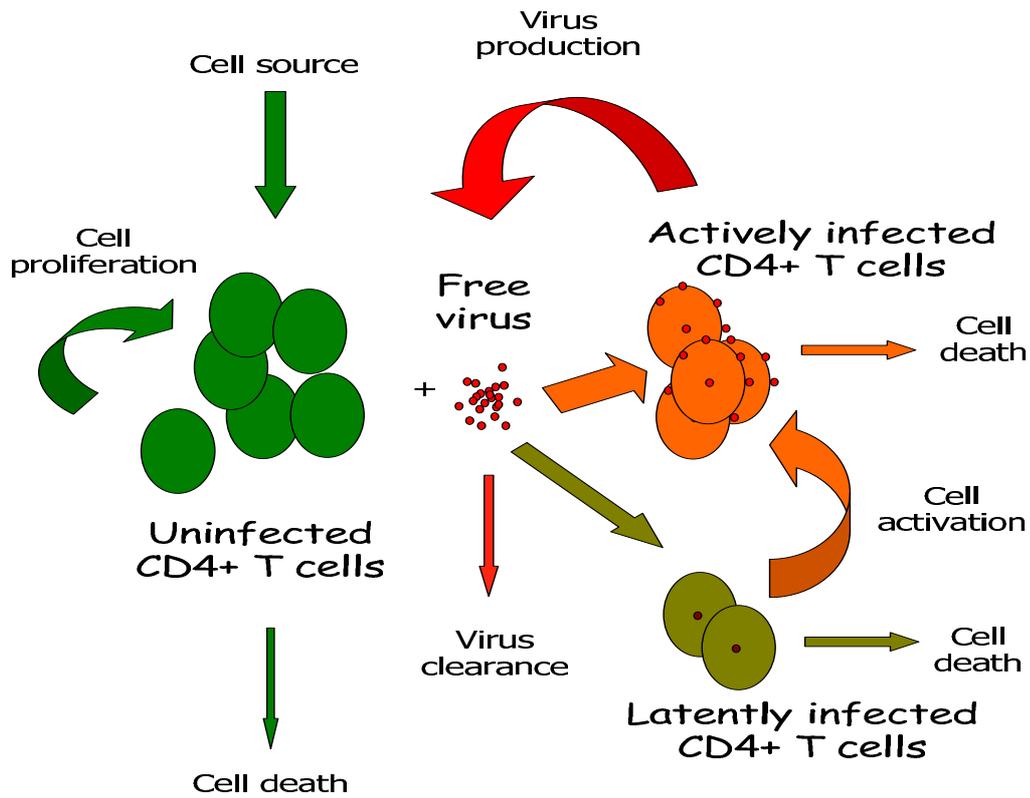


Figure 3.1: A schematic illustration of the interaction between the virus and target cells. Diagram is an expansion of that presented by [84].

illustrated in figure 3.1, has been presented in for example, [71, 77, 84, 85]. This so called latently infected cell model is single compartment and shows the interaction between the virus and the CD4<sup>+</sup> T cells in plasma. The model takes note of the fact that not all CD4<sup>+</sup> T cells actively produce virus upon infection. This is reflected by dividing the infected cell pool into latently and actively infected cells.

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.1)$$

$$\frac{dT_l}{dt} = q_l \beta_T TV - k T_l - \delta_l T_l \quad (3.2)$$

$$\frac{dT_a}{dt} = q_a \beta_T TV + k T_l - \delta_a T_a \quad (3.3)$$

$$\frac{dV}{dt} = r_T T_a - cV \quad (3.4)$$

State variables  $T$ ,  $T_l$ ,  $T_a$  and  $V$  are the plasma concentrations of the uninfected CD4<sup>+</sup> T cells, the latently infected CD4<sup>+</sup> T cells, the actively infected CD4<sup>+</sup> T cells and the

free virus particles, respectively. Equation (3.1) describes the population dynamics of the uninfected CD4<sup>+</sup> T cells. It shows that they are produced from a source at a rate  $s_T$ , die with a rate constant  $d_T$  and  $\phi(T)$  is the proliferation rate term.

Most authors assume that the source term  $s_T$  is constant. However, since HIV may be able to infect cells in the thymus and bone marrow and thus lead to a reduced production of new immunocompetent T cells, some authors believe that  $s_T$  is a decreasing function of the viral load. An expression for  $s_T$  is given by [160] as

$$s_T(V) = s_T e^{-\theta V} \quad (3.5)$$

Another form for the source rate term is given by [46, 99] as

$$s_T(V) = \theta s_T / (\theta + V) \quad (3.6)$$

A slightly different form is given by [7] as

$$s_T(V) = \theta_1 s_T + \theta_2 s_T / (B_s + V) \quad (3.7)$$

For the proliferation rate term, there are suggestions that the proliferation rate is density dependent with the rate of proliferation slowing as the T cell count gets high [90]. The most common form for proliferation is taken as the following logistic function [46, 50, 78, 85, 99]:

$$\phi(T) = pT \left(1 - \frac{T + T_l + T_a}{T_m}\right) \quad (3.8)$$

with  $p$  as the proliferation rate constant and  $T_m$  is the T cell population density at which proliferation shuts off. Given that the infected cells make a small fraction of the total CD4<sup>+</sup> T cell count, especially when antiretroviral drugs are used [26, 161], it is common to simply express the proliferation term as

$$\phi(T) = pT \left(1 - \frac{T}{T_m}\right) \quad (3.9)$$

A different form for the proliferation rate term has been suggested as [77]

$$\phi(T) = pT \frac{V}{C + V} \quad (3.10)$$

where  $C$  is referred to as the half saturation constant of the proliferation process. Some authors incorporate the proliferation effect into the constant  $d_T$ , while others suggest that these terms depend on other variables of the system to best fit the clinical data.

Uninfected CD4<sup>+</sup> T cells are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality

constant  $\beta_T$  is an indication of the effectiveness of the infection process and includes the rate at which virus particles find uninfected cells and the rate of virus entry.

Equations (3.2) and (3.3) describe the population dynamics of the latently and actively infected CD4<sup>+</sup> T cells, respectively. Parameters  $q_l$  and  $q_a$  are the probabilities that upon infection, a CD4<sup>+</sup> T cell will become latent or actively produce virus. Latently infected cells do not produce virus until they are activated, and  $k$  is the activation rate constant. The infected cells have respective death rate constants of  $\delta_l$  and  $\delta_a$ .

Initially, it was assumed that once infected, the CD4<sup>+</sup> T cell will actively produce virus and equation (3.11) is commonly used to describe the infected cell dynamics.

$$\frac{dT^*}{dt} = \beta_T TV - \delta T^* \quad (3.11)$$

where  $T^*$  represents the plasma concentration of all the infected CD4<sup>+</sup> T cells. The distinction in pools of infected CD4<sup>+</sup> T cells came about when Perelson *et al* observed that, after the rapid first phase of decay during the initial 1-2 weeks of antiretroviral therapy, plasma virus levels declined at a considerably slower rate [162]. This, and subsequent slower rates of viral decay were attributed to the turnover of a longer lived virus reservoir of infected cell population, which was determined to have a half-life of 1-4 weeks. This meant that on average, it would take between  $\frac{1}{2}$  and 3 years of perfectly effective antiretroviral therapy to eradicate the virus [163].

Equation (3.4) similarly describes the population dynamics of the free virus particles and it can be seen that an actively infected CD4<sup>+</sup> T cell produces virus particles with a rate constant  $r_T$  and  $c$  is the death rate constant at which virus particles are cleared from plasma.

Not all virus particles are infectious. Some virus particles have defective proviral RNA, and as such, are not capable of infecting cells. But generally,  $V$  in equation (3.4) describes the population dynamics of the free infectious virus particles. Some authors however, make a distinction in pools of free virus particles as reflected in equations (3.12) - (3.16)

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V_i \quad (3.12)$$

$$\frac{dT_l}{dt} = q_l \beta_T T V_i - k T_l - \delta_l T_l \quad (3.13)$$

$$\frac{dT_a}{dt} = q_a \beta_T T V_i + k T_l - \delta_a T_a \quad (3.14)$$

$$\frac{dV_i}{dt} = f_i r_T T_a - c V_i \quad (3.15)$$

$$\frac{dV_n}{dt} = (1 - f_i) r_T T_a - c V_n \quad (3.16)$$

where  $V_i$  and  $V_n$  are the infectious and noninfectious virus particles, respectively. Infectious virus particles make a fraction  $f_i$  of the total virus pool, and it is assumed that both virus particle types are cleared from plasma with the same rate constant  $c$ .

### 3.2 Time Delay Models

Other models take into consideration the fact that there is a time delay between when a cell gets infected by the virus to when it starts to actively produce virus particles. Equation (3.19) is an upgrade of equation (3.3) and a slight variation of that presented by [72].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V \quad (3.17)$$

$$\frac{dT_l}{dt} = q_l \beta_T T V - k T_l - \delta_l T_l \quad (3.18)$$

$$\frac{dT_a}{dt} = q_a \beta_T T(t - \tau) V(t - \tau) + k T_l - \delta_a T_a \quad (3.19)$$

$$\frac{dV_i}{dt} = r_T T_a - c V \quad (3.20)$$

$\tau$  is the time delay between cell infection and virus production.

Another variation of the delayed model is as presented by [83] for the actively infected CD4<sup>+</sup> T cells.

$$\frac{dT_a}{dt} = q_a \beta_T T_0 \int_0^\infty f(\tau) V(t - \tau) e^{-m\tau} d\tau + k T_l - \delta_a T_a \quad (3.21)$$

where  $e^{-m\tau}$  represents cells that die before actively producing virus. This model assumes a constant target CD4<sup>+</sup> T cell population  $T_0$  and  $f(\tau)$  is the delay distribution function. This time delay concept is usually only applied to CD4<sup>+</sup> T cells. However, the concept could be extendable to other cells such as macrophages.

### 3.3 Immune Response Models

The latently infected cell model (3.1)-(3.4) that was presented in section 3.1 does not explicitly model the immune response to the virus. Instead the effects of the said immune response are incorporated into relevant parameters. In particular, the rates at which CD8<sup>+</sup> T cells kill infected cells and antibodies kill the virus are incorporated into the death rate constants  $\delta_l$  and  $\delta_a$  of the infected cells, and the clearance rate constant  $c$  of the virus. Parameters  $\delta_l$ ,  $\delta_a$  and  $c$  therefore, “collectively reflect the immune system’s *defensive* strength against HIV infection” [80]. Similarly, parameters  $\beta_T$ , and  $r_T$  “collectively reflect HIVs *offensive* strength” [80] against the immune system.

The immune response to the virus can be explicitly modelled as illustrated by equations (3.22) - (3.26). The said immune response specifically focuses on the CD8<sup>+</sup> cytotoxic T lymphocytes - CTL. The rationale behind this model is that HIV infects immune cells which are needed in the expansion of a CTL response against infections. As a result, the ability of these cells to deliver help is compromised. This model is a variation of the one presented in [87].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T T^* \quad (3.22)$$

$$\frac{dT^*}{dt} = \beta_T T T^* - \delta T^* - b_I I T^* - b_E E T^* \quad (3.23)$$

$$\frac{dI}{dt} = \rho_I I T^* - \delta_I I \quad (3.24)$$

$$\frac{dP}{dt} = \rho_P T T^* P - k_E T^* P - \delta_P P \quad (3.25)$$

$$\frac{dE}{dt} = k_E T^* P - \delta_E E \quad (3.26)$$

State variables  $I$ ,  $P$  and  $E$  represent the helper-independent CTL response (CTL<sub>*i*</sub>), the helper-dependent CTL precursor response (CTL<sub>*p*</sub>) and the helper-dependent CTL effector response (CTL<sub>*e*</sub>), respectively. The help referred to is the uninfected CD4<sup>+</sup> T cells, whose responsibility it is to coordinate the immune response. The CTL<sub>*i*</sub> proliferates with a rate constant  $\rho_I$ , while the CTL<sub>*p*</sub> proliferates with a rate constant  $\rho_P$  and differentiates to CTL<sub>*e*</sub> in the presence of infected cells, with a rate constant  $k_E$ . Parameters  $\delta_I$ ,  $\delta_P$ ,  $\delta_E$  are the respective death rate constants. The free virus particle dynamics are not explicitly modelled, as the assumption is that the said viral load correlates with the infected CD4<sup>+</sup> T cells,  $T^*$ .

Some authors explicitly model the virus but only model the effector CTL<sub>*e*</sub> response to the virus [70]

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.27)$$

$$\frac{dT^*}{dt} = \beta_T TV - \delta T^* - b_E ET^* \quad (3.28)$$

$$\frac{dV}{dt} = r_T T^* - cV \quad (3.29)$$

$$\frac{dE}{dt} = \rho T^* - \delta_E E \quad (3.30)$$

where effectors are shown as being generated with a rate constant  $\rho$ , in the presence of infected cells. A version of the immune response model presented by [73] does not differentiate between the types of CTL responses and is given by equations (3.31)-(3.33).

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.31)$$

$$\frac{dT_8}{dt} = s_{T_8} + p_{T_8} T_8 V - d_{T_8} T_8 \quad (3.32)$$

$$\frac{dV}{dt} = r_T TV - b_v T_8 V \quad (3.33)$$

where  $T_8$  represents the CD8<sup>+</sup> T cells.

### 3.4 The Chronically Infected Cell Model

As pointed out in section 3.1, it has been observed from individuals on antiretroviral therapy that there are several distinct phases in the decay characteristics of the viral load [162]. There is a first initial rapid decline which has been associated with the clearance rate of the virus particles in plasma. The next phase, referred to as the first observable phase, has been attributed to the decay or decline of the actively infected cells. The later phase, the second observable phase, could however, be attributed to a variety of reasons: It could be due to the decline or decay of the latently infected cells or there could be a subset of the actively infected cells that has a much slower death rate.

This subset of actively infected cells is believed to produce smaller amounts of virus particles over a longer period of time, and these cells are referred to as chronically infected. Equations (3.34)-(3.37) are a representation of the chronically infected cell model and similar to that as presented by [71, 162].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.34)$$

$$\frac{dT^*}{dt} = (1 - q)\beta_T TV - \delta T^* \quad (3.35)$$

$$\frac{dC^*}{dt} = q\beta_T TV - \mu C^* \quad (3.36)$$

$$\frac{dV}{dt} = r_T T^* + r_C C^* - cV \quad (3.37)$$

where variable  $C^*$  is the plasma concentration of the chronically infected CD4<sup>+</sup> T cells. Chronically infected cells make a fraction  $q$  of the actively infected cell pool. These cells produce virus with a rate constant  $r_C$  and they die with a rate constant  $\mu$ .

### 3.5 The Extended Model

It is apparent that there are other cells in the body besides CD4<sup>+</sup> T cells that are as susceptible to the virus. The release of the virus from these cells and other infected compartments has been shown to affect the virus kinetics in plasma [113]. So while the chronically infected cell model fits the patient data, it is not the only reasonable biological model. The second observable phase of viral decay could also be linked to virus released from infected macrophages [162]. Macrophages live longer than the CD4<sup>+</sup> T cells and are chronic virus producers. An upgrade of the latently infected model is the single compartment 6 dimensional (6D) model given by equations (3.38)-(3.43), and models the target cells co-circulating in plasma [85].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.38)$$

$$\frac{dT_l}{dt} = q_l \beta_T TV - k T_l - \delta_l T_l \quad (3.39)$$

$$\frac{dT_a}{dt} = q_a \beta_T TV + k T_l - \delta_a T_a \quad (3.40)$$

$$\frac{dM}{dt} = s_M - d_M M - \beta_M MV \quad (3.41)$$

$$\frac{dM^*}{dt} = q_M \beta_M MV - \mu M^* \quad (3.42)$$

$$\frac{dV}{dt} = r_T T_a + r_M M^* - cV \quad (3.43)$$

State variables  $M$  and  $M^*$  are the uninfected and infected macrophages respectively. Equation (3.41) shows that uninfected macrophages die with a rate constant  $d_M$  and are differently infected by the virus at a rate that is also proportional to their abundance.

Parameter  $\beta_M$  is an indication of the efficiency of the infection process, while  $q_M$  is the probability of successful infection (3.42). Infected macrophages die with a rate constant  $\mu$ , and an infected macrophage cell produces virus with a rate constant  $r_M$ , as illustrated by equation (3.43). The model assumes that virus particles produced by infected CD4<sup>+</sup> T cells and macrophages are cleared from plasma with the same rate constant  $c$ . However, there are suggestions that virus produced from different cells are cleared at different rates [164].

Macrophages also reside in tissue (another compartment), and the extended model can therefore also reflect the release and trafficking of virus between tissue and plasma compartments, as given by equations (3.44)-(3.50) [71].

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T T V_T \quad (3.44)$$

$$\frac{dT_l}{dt} = q_l \beta_T T V_T - k T_l - \delta_l T_l \quad (3.45)$$

$$\frac{dT_a}{dt} = q_a \beta_T T V_T + k T_l - \delta_a T_a \quad (3.46)$$

$$\frac{dM}{dt} = s_M - d_M M - \beta_M M V_M \quad (3.47)$$

$$\frac{dM^*}{dt} = q_M \beta_M M V_M - \mu M^* \quad (3.48)$$

$$\frac{dV_T}{dt} = r_T T_a - c V_T + D_T (V_M - V_T) \quad (3.49)$$

$$\frac{dV_M}{dt} = r_M M^* - c V_M + D_M (V_T - V_M) \quad (3.50)$$

where  $V_T$  and  $V_M$  are the virus particles that are produced by CD4<sup>+</sup> T cells in plasma and by macrophages in tissue, respectively. Constants  $D_T$  and  $D_M$  represent the difference in virus concentrations between the two compartments, i.e., plasma and tissue.

### 3.6 The External Virus Source Model

There are many other models that have been developed besides the ones described above in sections 3.1 to 3.5 because there are additional reservoirs of virus. A quantitative image analysis technique was used to reveal that there is viral burden in lymphoid tissue [165], particularly on the surface of follicular dendritic cells (FDC). The source underlying the second phase kinetics might therefore also be the release of virus trapped in follicular dendritic cells (FDC).

Equation (3.51) is a variation of equation (3.43). The equation shows virus released from other sources such as macrophages and FDCs, expressed as  $v_x(V)$ , as an external

virus source. An external source in this context, is any virus releasing or producing cell or compartment, other than CD4<sup>+</sup> T cells in plasma.

$$\frac{dV}{dt} = r_T T_a + v_x(V) - cV \quad (3.51)$$

where  $v_x(V)$  is the external virus production rate. The simplest expression for the external source term would be a constant function:

$$v_x(V) = r_{ex} \quad (3.52)$$

or be plasma virus population dependent [77]:

$$v_x(V) = \frac{g_V V}{b + V} \quad (3.53)$$

where  $g_V$  is called the process growth rate and  $b$  is referred to as the half saturation constant. The later version is more applicable since most of the virus thought to be trapped and released from FDCs varies with the amount of virus that is freely circulating in plasma. This external virus source concept can be extended as given by equation (3.54):

$$\frac{dV}{dt} = r_T T_a + r_M M^* + v_x(V) - cV \quad (3.54)$$

An external source in this case (3.54), would be any virus releasing or producing cell or compartment, other than CD4<sup>+</sup> T cells and macrophages.

Some authors explicitly model virus dynamics in follicular dendritic cells as illustrated by the following model [71]:

$$\frac{dT}{dt} = s_T + \phi(T) - d_T T - \beta_T TV \quad (3.55)$$

$$\frac{dT^*}{dt} = q\beta_T TV - \delta T^* \quad (3.56)$$

$$\frac{dV}{dt} = r_T T^* - (c + b)V + uV_b \quad (3.57)$$

$$\frac{dV_b}{dt} = bV - uV_b - c_b V_b \quad (3.58)$$

where  $V_b$  represents virus particles that are trapped or bound to FDC. Parameter  $b$  is the rate constant at which free virus particles bind to FDC, and these bound virus particles unbind or dissociate from FDC with a rate constant  $u$ .

### 3.7 The Composite Long Lived Cell Model

Continued follow up of persons who have remained on HAART for extended periods of time has provided strong evidence for the existence of a possible reservoir in long-lived CD4<sup>+</sup> memory T lymphocytes, a third phase of HIV decay observed during HAART. The kinetics of decay are extremely slow, and the half-life of the memory cell reservoir has been estimated at between 6 and 44 months. As a consequence, the predicted time for effective therapy required to fully eradicate the virus from the body ranges from 9 to 72 years. This suggested that a true virologic cure is unattainable using the conventional antiretroviral drugs. Table 3.1 is a summary of these important findings. Most of the figures can be found in [166] or have been deduced from [166] by [67].

Table 3.1: Virus reservoir and life span.

Infected cell	Size	Half-life	Eradication
Active CD4	$3 \times 10^7$	1 day	25 days
FDC	$3 \times 10^8 - 10^{11}$	1 – 4 wks	0.5 – 2.8 yrs
Macrophage	n.a	1 – 4 wks	n.a
Memory CD4	$10^5 - 10^6$	6 – 44 mon	9 – 72 yrs

[67]

A composite model for the virus and all target cell dynamics can be presented to include the following sources of virus:

- Short lived actively infected CD4<sup>+</sup> T cells ( $T_a, T^*$ ).
- Latently infected CD4<sup>+</sup> T cells ( $T_l$ )
- Chronically infected CD4<sup>+</sup> T cells ( $C^*$ ).
- Infected macrophages ( $M^*$ ).
- Long lived memory CD4<sup>+</sup> T cells ( $L^*$ )
- Follicular dendritic cells ( $FDC$ ).

The composite model will be complex to analyse and can still be further extended to include the immune response to the virus and inter-compartmental trafficking of virus particles.

Given the foregoing, the resulting expression describing the virus dynamics, when taking the virus sources itemized above into consideration would be:

$$\frac{dV}{dt} = r_T T_a + r_C C^* + r_M M^* + r_L L^* + u V_b - (c + b)V \quad (3.59)$$

### 3.8 Stochastic Models

Many biological processes are known to have random variations and the HIV infection is stochastic by nature [86]. The argument being put forth in favour of stochastic models is that since stochastic models take into account the random nature of the HIV infection, they give a more realistic scenario of the HIV dynamics when compared to deterministic models. Also, the use of stochastic models paves the way to access the random variations in many of the risk variables with respect to the future course of the infection.

Equations (3.60)-(3.63) are a stochastic model of the HIV infection dynamics and are a slight variation of that presented in [86].

$$\Delta T(t) = s_T \Delta t + p(t)T(t)\Delta t - d_T T(t)\Delta t - \beta_T T(t)V(t)\Delta t + \varepsilon_1(t)\Delta t \quad (3.60)$$

$$\Delta T_l(t) = q_l \beta_T T(t)V(t)\Delta t - k T_l(t)\Delta t - \delta_l T_l(t)\Delta t + \varepsilon_2(t)\Delta t \quad (3.61)$$

$$\Delta T_a(t) = q_a \beta_T T(t)V(t)\Delta t + k T_l(t)\Delta t - \delta_a T_a(t)\Delta t + \varepsilon_3(t)\Delta t \quad (3.62)$$

$$\Delta V(t) = r_T(t)T_a(t)\Delta t - cV(t)\Delta t + \varepsilon_4(t)\Delta t \quad (3.63)$$

where  $\varepsilon_i(t)$ ,  $i = 1, 2, 3, 4$  are the random noises.

### 3.9 Models Adopted in this Thesis

The latently infected cell model (3.1)-(3.4) and the co-circulating target cell extended model (3.38)-(3.43) are the models that are adopted in this thesis and will be discussed below. However, the concepts that will be presented in the following chapters are not model specific, in that they can be extended or applied to any other model.

A summary of all the parameters in the latently infected and extended models is presented in table 3.2.

#### 3.9.1 Validity: Limitations and Adequacy of Models

None of the models presented in the preceding sections can completely exhibit all that is observed clinically and account for the full course of the infection as previously illustrated by figure 2.3 in section 2.1.3. The main reason for the models' limitation is lack of a good understanding of the immunology of the human body against HIV. Biological systems tend to exhibit multi-compartmental interactions that are usually not well understood and as a result, can not be accurately modelled mathematically. The accuracy of the models though, is increasing with new medical discoveries.

Table 3.2: Parameters in the latently infected and extended models.

Parameter and description		L	E
$s_T$	Source rate for CD4 <sup>+</sup> T cells	*	*
$p$	Proliferation rate for CD4 <sup>+</sup> T cells	*	*
$T_m$	Proliferation shut down CD4 <sup>+</sup> T cell count	*	*
$d_T$	Death rate for uninfected CD4 <sup>+</sup> T cells	*	*
$\beta_T$	Infection rate for CD4 <sup>+</sup> T cells by virus	*	*
$\delta_l$	Death rate for latently infected CD4 <sup>+</sup> T cells	*	*
$\delta_a$	Death rate for actively infected CD4 <sup>+</sup> T cells	*	*
$q_l$	Fraction of infected CD4 <sup>+</sup> T cells that becomes latent	*	*
$q_a$	Fraction of infected CD4 <sup>+</sup> T cells that becomes active	*	*
$k$	Activation rate for latently infected CD4 <sup>+</sup> T cells	*	*
$s_M$	Source rate for macrophages		*
$d_M$	Death rate for uninfected macrophages		*
$\beta_M$	Infection rate for macrophages by virus		*
$q_M$	Probability of successful infection of macrophage by virus		*
$\mu$	Death rate for infected macrophages		*
$r_T$	Virus particle production rate per infected CD4 <sup>+</sup> T cell	*	*
$r_M$	Virus particle production rate per infected macrophage		*
$c$	Death rate for virus particle	*	*
$\eta_{rt}$	Efficacy of all RTIs in regimen	*	*
$\eta_{pi}$	Efficacy of all PIs in regimen	*	*
$\alpha_{rt}$	Differential RTI penetration into macrophages		*
$\alpha_{pi}$	Differential PI penetration into macrophages		*
$\eta_{ps}$	Efficacy of all proliferation suppressors in regimen	*	*
$\eta_{da}$	Efficacy of all cell death accelerators in regimen	*	*
<b>Total: Number of parameters</b>		<b>12</b>	<b>18</b>

\*indicates the applicable parameter.

L: Latently infected cell model. E: Extended model.

All parameters except  $s_T$  and  $s_M$  are rate constants.

A point to consider is that these models do not take into account other extenuating environmental, social and welfare factors that may affect the progression of the infection. Organ health, for example, the extent to which the immune system is repairable as the infection progresses is another issue that these models do not take into consideration. Most of these models however, do adequately explain the interaction of the virus and the immune system up to the clinical latency stage.

In an attempt to account for the later or advanced stage of the infection, some model parameters are assumed to change as the infection progresses [75, 80, 167, 168]. These assumptions, though not clinically validated, do give a virus and target cell profile that complies with clinical observations. Other suggestions are that the prolonged production and destruction of the immune cells ultimately results in an immune collapse.

The models adopted for this thesis are single compartment, do not include intracellular delays, neither do they explicitly model the immune response to the virus. The reasons for adopting these models are that:

1. The latently infected cell model adequately models the virus and target cell dynamics. Its simplicity lends its self to provide analytical insights more readily, which can then be extended to other models.
2. The extended model is useful because it can simulate persistent virus replication under potent HAART that leads to the maintenance of a low steady state viral load [71].
3. It is currently difficult to get viral load measurements from tissue or any other compartment besides plasma, except in experimental settings. This thesis will therefore not consider the compartmental models.
4. The immune response to the virus can not be measurably quantified. Instead the effects of the said immune response are incorporated into relevant parameters. In particular, the rates at which CD8 T cells kill infected cells and virus are incorporated into the death rate constants  $\delta_i$  and  $\delta_a$  of the infected cells, and the clearance rate constant  $c$  of the virus. Parameters  $\delta_i$ ,  $\delta_a$  and  $c$  therefore, “collectively reflect the immune system’s *defensive* strength against HIV infection” [80]. Similarly, parameters  $\beta_T$ , and  $r_T$  “collectively reflect HIVs *offensive* strength” [80] against the immune system. This thesis will therefore not consider models that explicitly show the immune response to the virus.
5. The effect of intracellular delays in virus production from infection can be lumped into the production and clearance rate parameters of the virus. After the initial infection period, the delay effect loses its significance as all it does is shift the

virus curve to the left by the time delay. Furthermore, this delay is in the order of minutes, and when compared with the long asymptomatic period of several years, the delay is of no consequence.

### 3.9.2 Parameter Estimates

Generally, the rates of lymphocyte turnover during health and disease are poorly characterized. This limits our understanding of diseases like HIV-infection that lead to increased rates of cellular turnover and ultimately to deterioration of the immune system. HIV-1 infection is known to increase the turnover rates of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and to deplete the populations of naïve CD4<sup>+</sup> T cells, naïve CD8<sup>+</sup> T cells, and memory CD4<sup>+</sup> T cells [116]. Current estimates for the turnover rates of CD4<sup>+</sup> T cells vary between 1 and 2% in normal individuals to 1–10% in HIV-1 infected patients [116].

Various clinical studies have been carried out in order to obtain estimates for the model parameters. However, most of the studies focus on obtaining estimates for  $c$ ,  $\delta_a$ ,  $\beta_T$  and  $r_T$ . There are inter-individual variations in parameter estimates within a study. Furthermore, there are variations in estimates for a particular parameter between studies. Generally, parameters  $\beta_T$  and  $r_T$  have the widest variation, while parameters  $c$  and  $\delta_a$  are known to have the least variations. Not much effort however, has been made to determine variations in macrophage cell related parameters. However, one could intuitively expect  $\beta_M$  and  $r_M$  to have a wider variation when compared to  $\mu$ . Values for parameter estimates that were used in this thesis are presented in Appendix A.

Figure 3.2 shows how the plasma concentrations of the uninfected CD4<sup>+</sup> T cells (T), all infected CD4<sup>+</sup> T cells (T\*), uninfected macrophages (M), infected macrophages (M\*), and free virus particles (V), vary with time from initial infection to the asymptomatic stage. The initial decline of the uninfected cells and the increase in viral load are very rapid. All variables however, do eventually settle in damped oscillations to their respective infected steady state values.

## 3.10 Model Parameters Affected by Therapy

Therapy generally entails the use of reverse transcriptase and protease inhibitors (replication cycle based therapy) as well as proliferation suppressors and cell death accelerators (immune based therapy). As a control input, the model parameters that are affected by these drugs have been identified in for example [85, 169].

Reverse transcriptase inhibitors do not directly prevent cell infection. Rather, these antiretroviral agents reduce virus replication by reducing the probabilities  $q_I$ ,  $q_a$  and  $q_M$

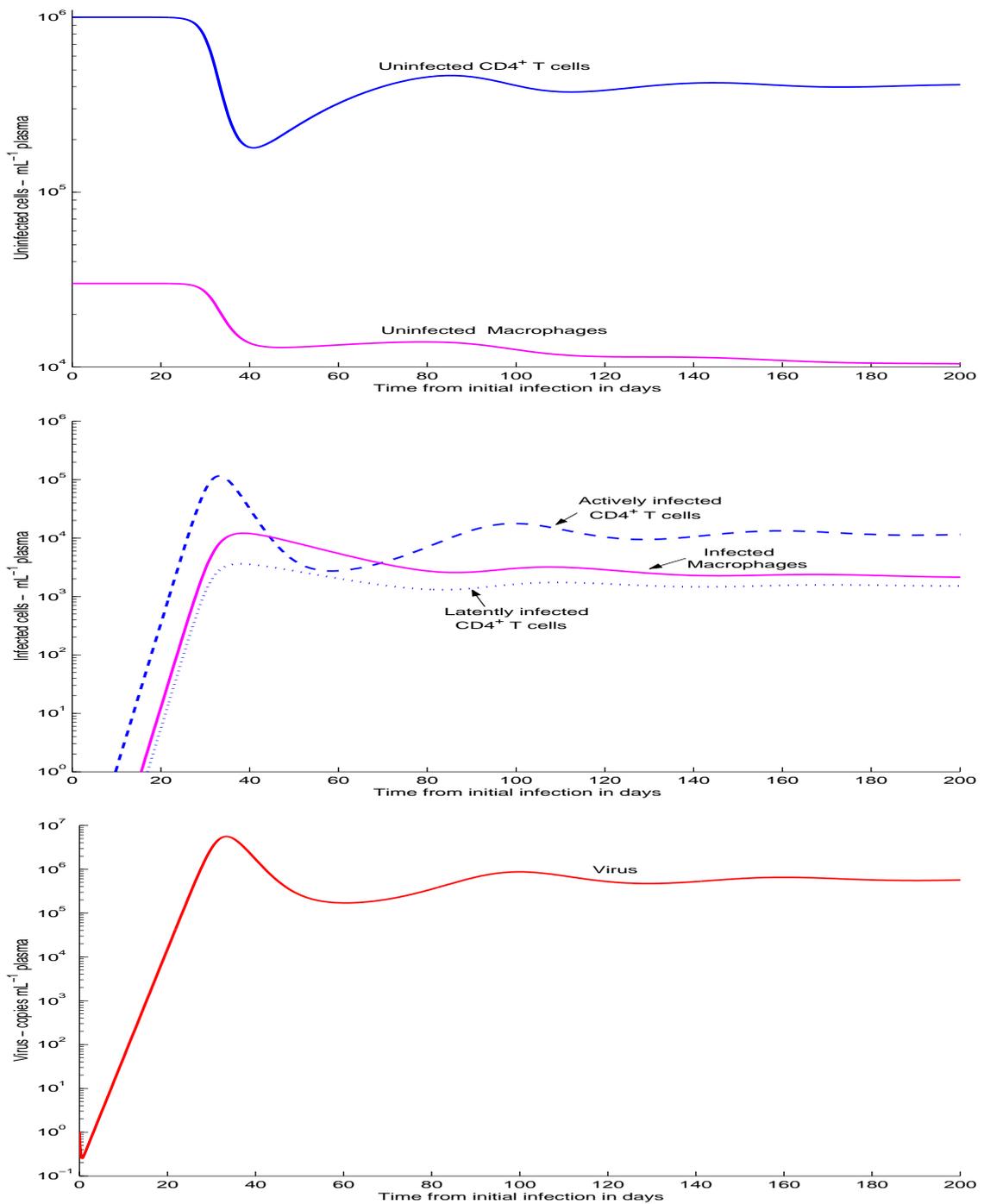


Figure 3.2: Simulated plasma concentrations for  $T$ ,  $T_a$ ,  $T_l$ ,  $M$ ,  $M^*$  and  $V$ . Parameters are as in Table A.4.

Table 3.3: Model parameters affected by therapy

Inhibitor/Drug	Parameters Affected	Efficacy
Reverse transcriptase inhibitors	$q_l, q_a, q_M$	$\eta_{rt}, \alpha_{rt}\eta_{rt}$
Protease inhibitors	$r_T, r_M$	$\eta_{pi}, \alpha_{pi}\eta_{pi}$
T cell proliferation suppressors	$p$	$\eta_{ps}$
Infected T Cell death rate accelerators	$\delta_l, \delta_a$	$\eta_{da}$
Induced CD4 <sup>+</sup> T cell death (apoptosis)	$d_T$	$\eta_{ap}$

of successful cell infection.  $\eta_{rt}$ :  $0 \leq \eta_{rt} < 1$  is the combined efficacy of all the reverse transcriptase inhibitors used. Perfect inhibition occurs when  $\eta_{rt} = 1$  and there is no inhibition when  $\eta_{rt} = 0$ . Differential reverse transcriptase inhibitor penetration into target CD4<sup>+</sup> T cells and macrophages is reflected by parameter  $\alpha_{rt}$ , where  $0 \leq \alpha_{rt} \leq 1$ . Most authors present  $\beta_T$  and  $\beta_M$  as the parameters affected by reverse transcriptase inhibitors for simplicity.

Protease inhibitors reduce the rates  $r_T$  and  $r_M$  at which infectious virus particles are produced. This leads to the production of mostly noninfectious virus particles.  $\eta_{pi}$ :  $0 \leq \eta_{pi} < 1$  is the combined efficacy of all the protease inhibitors used. Similarly, perfect inhibition occurs when all virus particles that are produced are noninfectious. That is, when  $\eta_{pi} = 1$  and there is no inhibition when  $\eta_{pi} = 0$ . In practice however, perfect inhibition does not seem attainable with any class of replication cycle based antiretroviral agents. Differential protease inhibitor penetration into target CD4<sup>+</sup> T cells and macrophages is reflected by parameter  $\alpha_{pi}$ , where  $0 \leq \alpha_{pi} \leq 1$ .

Immune based therapies only affect host cell parameters. Cell proliferation suppressors reduce parameter  $p$ , and  $\eta_{ps}$ :  $0 \leq \eta_{ps} < 1$  is the combined efficacy of all the proliferation suppressors used.

Infected CD4<sup>+</sup> T cell death rate accelerators would increase parameters  $\delta_l$  and  $\delta_a$ .  $\eta_{da}$ :  $\eta_{da} \geq 1$  is the combined efficacy of all the cell death accelerating therapies used.

Therapies that induce CD4<sup>+</sup> T cell death (apoptosis) would increase parameter  $d_T$ , and  $\eta_{ap}$ :  $\eta_{ap} \geq 1$  is the combined efficacy of all the apoptosis inducing drugs used.

Table 3.3 presents a summary of which model parameters are affected by the various types of drugs used to treat HIV infection.

### 3.11 Chapter Summary

Many models explaining different aspects of the HIV infection have been developed. Most of these are deterministic single compartment models. Though most of the models can not account for the full infection progression, they do however, adequately explain the interaction of the virus and the immune system up to the clinical latency stage. The following is a summary of virus and target cell dynamics that have been, and have yet to be modelled.

#### Modelled Dynamics:

1. Interaction between  $CD4^+$  T cells and the virus in plasma
2. Inclusion of macrophages and other long lived target cells of the HIV. These macrophages or long lived cells could be in plasma with the  $CD4^+$  T cells (co-circulating target cell model) and/or in tissue (compartmental model)
3. Trapping and release of virus from follicular dendritic cells
4. Release of virus from other unspecified external sources
5. Virus mutations: Resistance
6. Time delay from initial infection to release of virus from infected cell
7. Infection progression from initial virus inoculation to AIDS
8. Immune response to the virus:
  - (a) Inclusion of  $CD8^+$  (killer, Effector) T cells dynamics in plasma
  - (b) Inclusion of Memory T cell dynamics in plasma
9. Stochastic or Random variations in virus dynamics

#### Un-modelled Dynamics:

1. Environmental and social factors that influence infection progression.
2. Organ health. For example, the extent to which the immune system is repairable
3. Other clinically observed phenomena

Model parameters that are affected by therapy have been identified, and studies have been conducted in order to obtain estimates for the model parameters. However, most of the studies focus on obtaining estimates for  $c$ ,  $\delta_a$ ,  $\beta_T$  and  $r_T$ . There are inter-individual variations in parameter estimates within a study, as there are also variations in estimates for a particular parameter between studies. Generally, parameters  $\beta_T$  and  $r_T$  have the widest variation, while parameters  $c$  and  $\delta_a$  are known to have the least variations. Not much effort however, has been made to determine variations in macrophage cell related parameters.

# Chapter 4

## Model Analysis

**M**ODEL analysis will start with the latently infected cell model (3.1)-(3.4), with and without therapy. As pointed out before, the simpler model provides analytical insights more readily, which will then be extended to the co-circulating target cell extended model (3.38)-(3.43).

The models (3.1)-(3.4) and (3.38)-(3.43) are inherently nonlinear. Often in this chapter, approximate solutions will be derived by applying linear analytical tools to the linearized models. Linear analytical tools enable easier derivation of an analytic solution. Approximate as the solution may be, it does present the result in a simpler, more intuitive way, at least within a certain locality, given the diverse backgrounds of the intended audience. The solutions that will be obtained, or the predictions that will be made from the linear analysis will be verified by applying them to the nonlinear model. Instances where these linear analytical tools are applied will be pointed out.

As stated before, the concepts presented in this and the following chapter can be applied to any other model.

### 4.1 Steady State Analysis

Steady state analysis [170] for the HIV/AIDS models will be conducted in order to determine the dependence of the treatment viral load steady state on drug efficacy. The variation of the treatment steady state when therapy is initiated at various stages of the infection will also be examined. In particular, this section focuses on the attainment of durable suppression of the viral load. The intention is to determine when, as the HIV infection progresses, initiating therapy is most likely to attain durable suppression of the viral load. Analytical solutions for the expected steady state viral load suppression will be derived. If steady state is related to the infection stage, then this study can help decide when best to initiate therapy.

The latently infected cell model (3.1) - (3.4) in section 3.1 has two steady states or equilibrium points. The first is the pre-infection steady state and the other is the infected steady state  $[T_{ss}, T_{lss}, T_{ass}, V_{ss}]^T$ , which is given by (4.1)-(4.4). The pre-infection steady state is unstable (once infected), while the infected steady state is stable. There is therefore, only one infected stable steady state and its global asymptotic stability (attractiveness) has been proven or discussed (without  $T_l$ ) by [59], as well as [84].

$$T_{ss} = \frac{c\delta_a}{r_T\beta_T q} \quad (4.1)$$

$$T_{lss} = \frac{q_l c \delta_a}{r_T q (\delta_l + k)} V_{ss} \quad (4.2)$$

$$T_{ass} = \frac{c}{r_T} V_{ss} \quad (4.3)$$

$$V_{ss} = \frac{r_T s_T q}{c \delta_a} + \frac{p - d_T}{\beta_T} - \frac{p c \delta_a}{r_T \beta_T^2 q T_m} \quad (4.4)$$

where  $q = q_a + q_l \frac{k}{\delta_l + k}$ .  $T_{ss}$ ,  $T_{lss}$ ,  $T_{ass}$ , and  $V_{ss}$  are expressions for the uninfected CD4<sup>+</sup> T cell, latently infected CD4<sup>+</sup> T cell, actively infected CD4<sup>+</sup> T cell and viral load steady states, respectively. Equations (4.2) and (4.3) are expressed in that manner to show the proportional relationship between the virus and infected cell steady states.

The infected steady state is determined by both the host cell and virus parameters. Variations in steady state set points from one individual to the other, and ultimately variations in the response to therapy, can therefore be attributed to inter-individual variations in model parameters as has been previously observed by [41, 71, 171, 172].

A point worth noting is that the CD4<sup>+</sup> T cell steady state value (4.1) does not depend on CD4<sup>+</sup> T cell specific parameters  $s_T$ ,  $p$ ,  $T_m$  and  $d_T$ .

### 4.1.1 Analysis with Replication Cycle Based HAART

Replication cycle based HAART in this thesis, entails the concomitant use of multiple drugs from the reverse transcriptase and/or protease inhibitor classes. Model (4.5)-(4.9) incorporates the effect of HAART for the latently infected cell model (3.1)-(3.4) that was presented in section 3.1.

$$\frac{dT}{dt} = s_T + pT(1 - T/T_{max}) - d_T T - \beta_T TV_i \quad (4.5)$$

$$\frac{dT_l}{dt} = (1 - \eta_{rt})q_l\beta_T TV_i - kT_l - \delta_l T_l \quad (4.6)$$

$$\frac{dT_a}{dt} = (1 - \eta_{rt})q_a\beta_T TV_i + kT_l - \delta_a T_a \quad (4.7)$$

$$\frac{dV_i}{dt} = (1 - \eta_{pi})r_T T_a - cV_i \quad (4.8)$$

$$\frac{dV_n}{dt} = \eta_{pi}r_T T_a - cV_n \quad (4.9)$$

The treatment steady states for the uninfected CD4<sup>+</sup> T cells, infectious virus, non infectious virus and total viral load are given by:

$$T_{ss}(\eta) = \frac{c\delta_a}{(1 - \eta_{co})q\beta_T r_T} \quad (4.10)$$

$$V_{iss}(\eta) = \frac{(1 - \eta_{co})r_T s_T q}{c\delta_a} + \frac{p - d_T}{\beta_T} - \frac{pc\delta_a}{(1 - \eta_{co})r_T \beta_T^2 q T_m} \quad (4.11)$$

$$V_{nss}(\eta) = \frac{\eta_{pi}}{1 - \eta_{pi}} V_{iss} \quad (4.12)$$

$$V_{tss}(\eta) = V_{iss} + V_{nss} = \frac{1}{1 - \eta_{pi}} V_{iss} \quad (4.13)$$

where  $\eta_{co} = \eta_{rt} + \eta_{pi} - \eta_{rt}\eta_{pi}$  is the combined efficacy when both reverse transcriptase and protease inhibitors are used in the regimen. Note also that  $0 \leq \eta_{co} \leq 1$ .

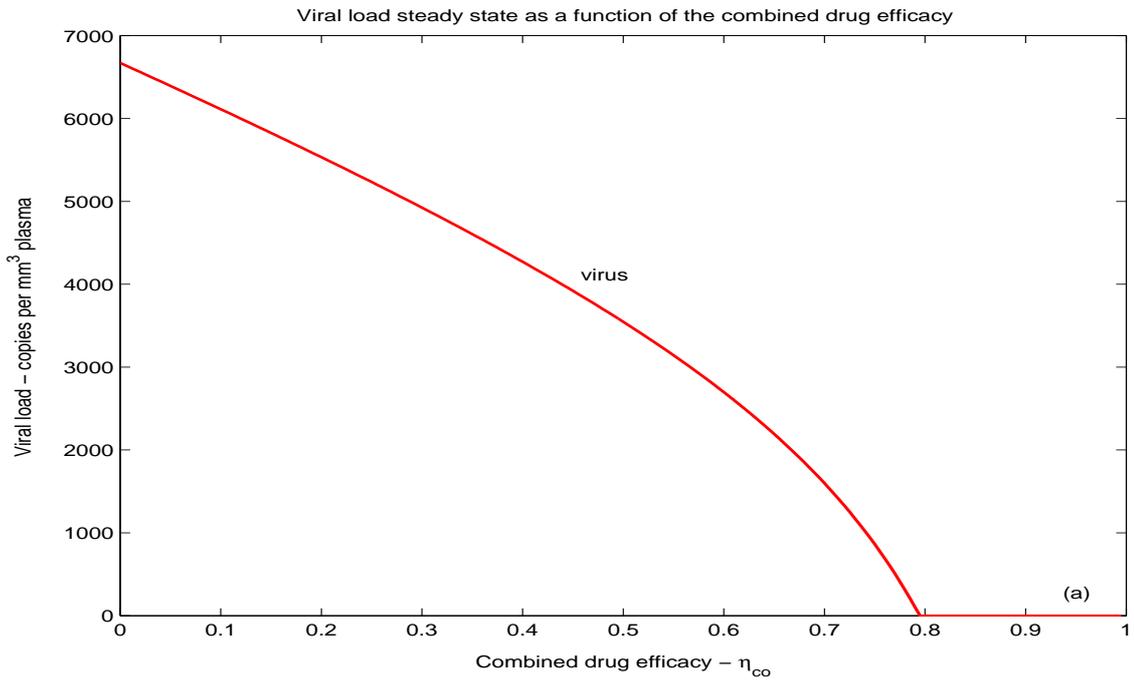
It is clear from the above equations, why and how HAART reduces the viral load and increases CD4<sup>+</sup> T cell counts. Therapy with HAART therefore, moves the states from one point to another, and the new on treatment steady states are determined by the combined drugs efficacy as illustrated in figure 4.1.

An important point to note from equations (4.10)-(4.13), is that the treatment steady states are independent of when therapy is initiated. Initiating therapy at a stage where the viral load is below this treatment steady state will result in an increasing viral load, which is interpreted as failure to control the viral load. However, initiating therapy at a stage where the viral load is higher than this treatment steady state will obviously result in some degree of viral load control even though the viral load will eventually settle to the same steady state, given the same fixed drug efficacy.

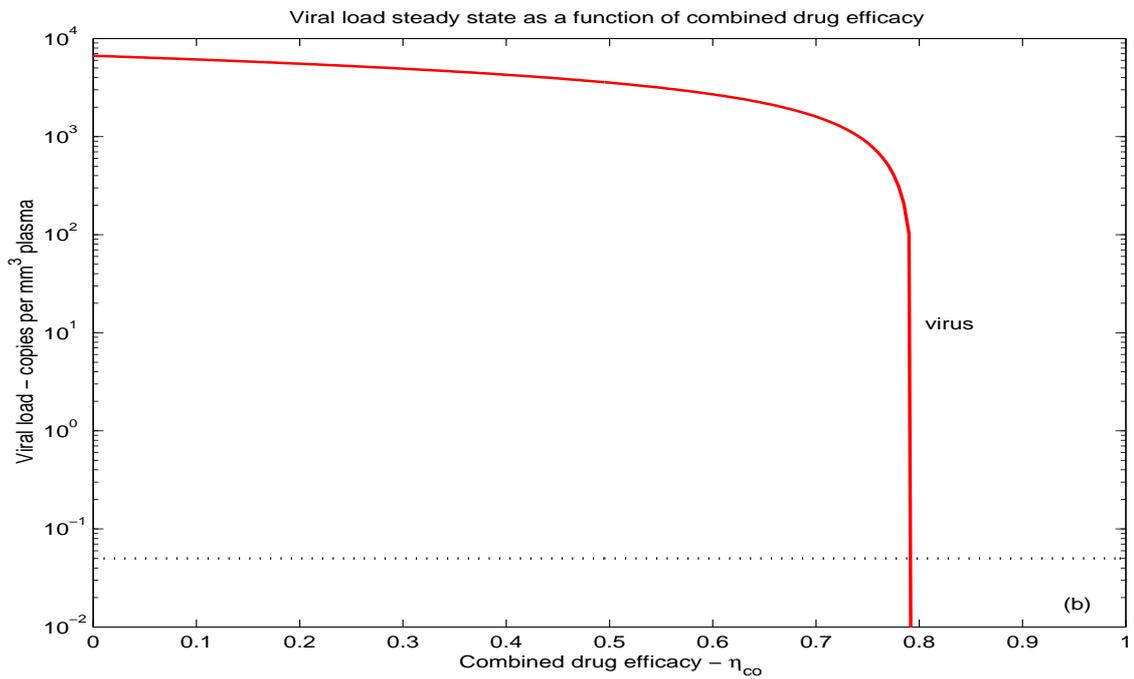
Equation (4.11) can be solved to get

$$\eta_{zss} = 1 + \frac{c\delta_a}{2\beta_T r_T s_T q} [(p - d_T) - \sqrt{(p - d_T)^2 + \frac{4s_T p}{T_m}}] \quad (4.14)$$

as the minimum combined drug efficacy that is required to obtain an on treatment steady state viral load of zero.



(a)



(b)

Figure 4.1: Viral load steady state for the latently infected cell model as determined by the combined HAART efficacy. (a) Linear plot. (b) Logarithmic plot. Parameters are in Table A.1.

Equation (4.11) can also be solved to get

$$\eta_{sup} = 1 + \frac{c\delta_a}{2\beta_T r_T s_T q} \left[ (p - d_T - 50\beta_T) - \sqrt{(p - d_T - 50\beta_T)^2 + \frac{4s_T p}{T_m}} \right] \quad (4.15)$$

as the minimum combined drug efficacy that is required to obtain a treatment steady state viral load that is below detection (below 50 copies mL<sup>-1</sup>), as depicted in figure 4.1.

It should be noted that even though attaining a zero viral load steady state corresponds to zero infected cell steady states, that does not necessarily imply perfect inhibition of virus replication, as for most parameter combinations,  $\eta_{zss} < 1$ . However, increasing the combined drug efficacy to a value above  $\eta_{zss}$  will have no further long term suppression of the virus that is produced from the CD4<sup>+</sup> T cells. This therefore means that any circulating or detectable plasma viremia is from other sources such as macrophages, follicular dendritic cells, resting memory T cells and other sources that are known to harbour pro-viral DNA [39, 40, 113, 117]. Higher drug doses are used though, because there is differential drug penetration into some compartments [34, 38, 173].

The combined drug efficacy  $\eta_{zss}$  (4.14) for a zero steady state viral load, as well as  $\eta_{sup}$  (4.15) for a below detection steady state viral load are parameter dependent. They will therefore vary from one individual to another.  $\eta_{sup}$  (4.15) can result in a combined drug efficacy as low as 60% to higher than 95% for some parameter combinations. This explains why some individuals experience virologic failure on therapy that is highly effective on others. From a vaccination point of view,  $\eta_{zss}$  (4.14) can be interpreted as the minimum drug efficacy that is required to prevent the initial virus inoculation from successfully replicating. This, however, is so if one assumes that virus replication starts in the CD4<sup>+</sup> T cells before spreading to other compartments.

For drug efficacies in the vicinity of  $\eta_{sup}$  (4.15), the viral load steady state is very sensitive to small changes in drug efficacy, as it has been previously observed by [71]. However, [71] have since demonstrated that this viral load steady state sensitivity to small changes in drug efficacy, can be reduced or eliminated when the extended model (3.38)-(3.43) is used instead. This reduced sensitivity becomes more apparent when differential drug penetration into target cells is modelled. This realization has been used to further explain why, contrary to as suggested by equation (4.14), virus eradication is not possible with the use of HAART and replication competent virus can still be recovered from individuals on potent HAART, as it has been reported in [28, 31, 33]. In any case, this variation in steady state response occurs at very low viral loads. So the use of very high drug doses above  $\eta_{sup}$  or close to  $\eta_{zss}$ , bearing in mind that virus eradication does not seem attainable with HAART, may from a clinical and toxicity perspective, not

be necessary. The drug efficacy cutoff  $\eta_{sup}$  as given by equation (4.15) is therefore, a reasonable upper limit when defining an operating therapeutic range for an individual, for each class of inhibitor that is used in the combined HAART regimen.

Equation (4.10) implies that it is possible for the uninfected CD4<sup>+</sup> T cells to rebound to pre-infection values under therapy. However, this is not true for most infected individuals as many attain virologic success with inadequate cell rebounds. Clinical studies suggest that HIV damages the immune system and the extent of T cell rebound therefore, depends on the extent to which the immune system is repairable, and not necessarily on the ability of the drugs to suppress virus replication. There is therefore, a need to find ways of quantifying the health or damage to the immune system, so that it can be factored into the equations describing the CD4<sup>+</sup> T cell dynamics. From inspecting equation (4.1), one could expect that  $\beta_T$  and infected CD4<sup>+</sup> T cell specific parameters  $\delta_a$  and  $q$  would correlate to the health or damage to the immune system.

## 4.1.2 Analysis with Immune Based Therapies

### Latently Infected Cell Model

Immune based CD4<sup>+</sup> T cell specific therapies, as discussed before, could entail:

- Reducing CD4<sup>+</sup> T cell source rate  $s$ , hence referred to as source rate limiting therapy.  $\eta_{sl}$  is the efficacy (inhibitory effect) of the source suppressing drugs used and  $0 \leq \eta_{sl} < 1$ .
- Reducing CD4<sup>+</sup> T cell proliferation rate  $p$ , hence referred to as proliferation suppressive therapy.  $\eta_{ps}$  is the efficacy of the proliferation suppressing drugs used and  $0 \leq \eta_{ps} < 1$ .
- Accelerating infected CD4<sup>+</sup> T cell death rates  $\delta_i$  and  $\delta_a$ , hence referred to as infected cell death accelerating therapy.  $\eta_{da}$  is the percentage rate at which CD4<sup>+</sup> T cell death rate is increased, or the death acceleration factor and  $\eta_{da} \geq 0$ .
- Accelerating target CD4<sup>+</sup> T cell death rate  $d_T$ , hence referred to as apoptosis inducing therapy.  $\eta_{ap}$  is the percentage rate at which apoptosis of target CD4<sup>+</sup> T is induced and  $\eta_{ap} \geq 0$ .

Immune based therapies in current practice, generally entail the independent use of the immunosuppressive drug as hydroxyurea (cell proliferation and maturation suppressor) and the immune stimulant IL-2 (infected cell death accelerator). Model (4.16)-(4.19) incorporates the effect of immune therapies for the latently infected cell model (3.1)-(3.4) that was presented in section 3.1.

$$\frac{dT}{dt} = (1 - \eta_{sl})s_T + (1 - \eta_{ps})pT(1 - T/T_{max}) - (1 + \eta_{ap})d_T T - \beta_T TV_i \quad (4.16)$$

$$\frac{dT_l}{dt} = q_l \beta_T TV_i - kT_l - (1 + \eta_{da})\delta_l T_l \quad (4.17)$$

$$\frac{dT_a}{dt} = q_a \beta_T TV_i + kT_l - (1 + \eta_{da})\delta_a T_a \quad (4.18)$$

$$\frac{dV_i}{dt} = r_T T_a - cV_i \quad (4.19)$$

When immunosuppressive therapy is used, then the uninfected CD4<sup>+</sup> T cell and viral load steady states will be:

$$T_{ss}(\eta) = \frac{c\delta_a}{r_T \beta_T q} \quad (4.20)$$

$$V_{ss}(\eta) = \frac{(1 - \eta_{sl})r_T s_T q}{c\delta_a} - \frac{d_T}{\beta_T} + \frac{(1 - \eta_{ps})p}{\beta_T} \left(1 - \frac{c\delta_a}{r_T \beta_T q T_m}\right) \quad (4.21)$$

Similarly, the steady states with immune stimulants and apoptosis inducing therapy will be:

$$T_{ss}(\eta) = \frac{(1 + \eta_{da})c\delta_a}{r_T \beta_T q_{da}} \quad (4.22)$$

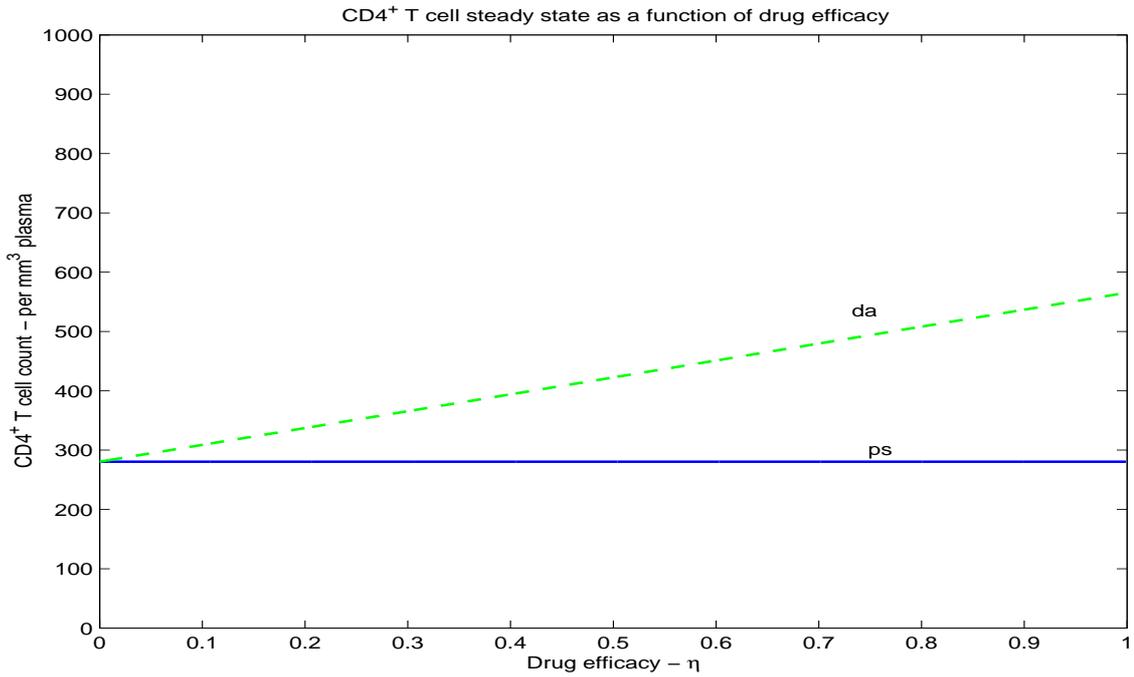
$$V_{ss}(\eta) = \frac{r_T s_T q_{da}}{(1 + \eta_{ap})c\delta_a} - \frac{(1 + \eta_{ap})d_T}{\beta_T} + \frac{p}{\beta_T} \left(1 - \frac{(1 + \eta_{da})c\delta_a}{r_T \beta_T q_{da} T_m}\right) \quad (4.23)$$

where,  $q_{da} = q_a + q_l \left(\frac{k}{k + (1 + \eta_{da})\delta_l}\right)$ .

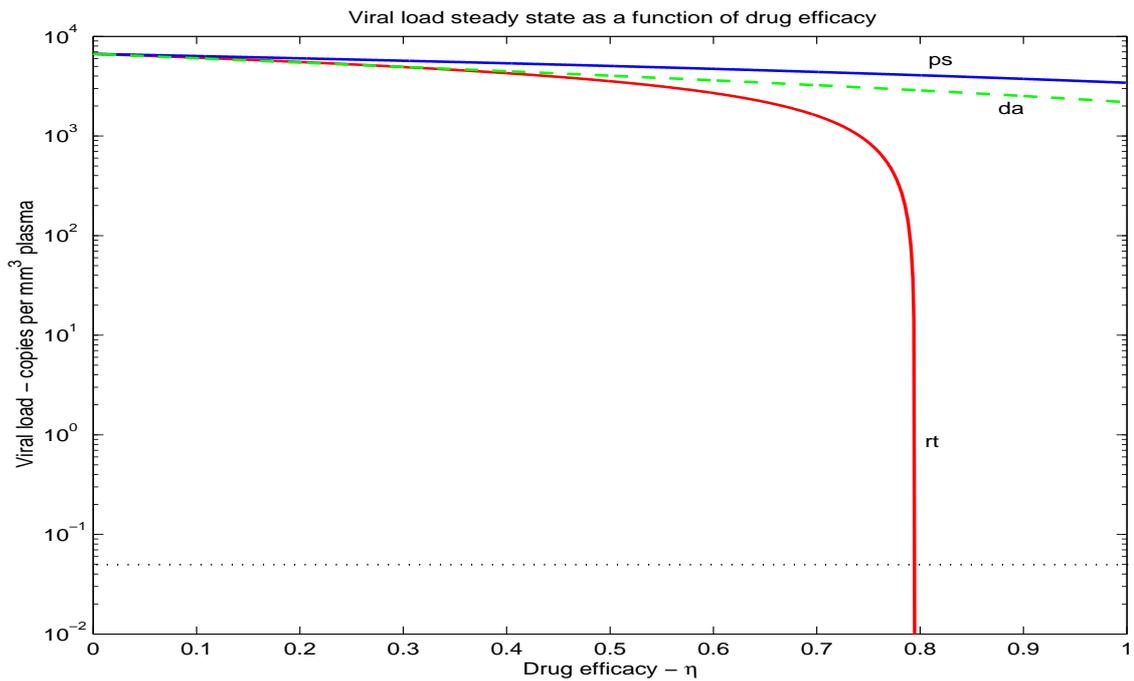
As with replication cycle based therapies, the steady states are parameter dependent, and are also independent of when, during the infection progression, therapy is initiated. As noted before,  $T_{ss}$  (4.20,4.22), unlike  $V_{ss}$  (4.21,4.23), does not depend on parameters  $s_T$ ,  $p$  and  $d_T$ . Immunosuppressive therapies that reduce  $s_T$  and  $p$ , or therapies that accelerate  $d_T$  will reduce the viral load set point  $V_{ss}$ , but will have no effect on the CD4<sup>+</sup> T cell steady state  $T_{ss}$ , as illustrated by figure 4.3. One would expect however, that the introduction of these therapies will transiently perturb the CD4<sup>+</sup> T cell dynamics, but the cell count will settle at the steady state  $T_{ss}$ , as depicted by figure 4.2.

Increasing the infected cell death rates  $\delta_l$  and  $\delta_a$  will on the other hand, increase the CD4<sup>+</sup> T cell steady state as well as reduce the viral load set point. So the above considered CD4<sup>+</sup> T cell specific therapies will reduce the viral load, but unlike replication cycle based HAART, some will not increase the CD4<sup>+</sup> T cell count in the long term.

Figures 4.2 and 4.3 show that, from an end point efficacy perspective, accelerating infected CD4<sup>+</sup> T cell death rates, is better than proliferation suppressive therapy at



(a)



(b)

Figure 4.2: CD4<sup>+</sup> T cell and viral load steady states as determined by the immune therapy drug efficacy. ps: proliferation suppressing therapy, da: infected cell death accelerating therapy, rt: reverse transcriptase. (a) CD4<sup>+</sup> T cells. (b) Viral load. Parameters are in Table A.1.

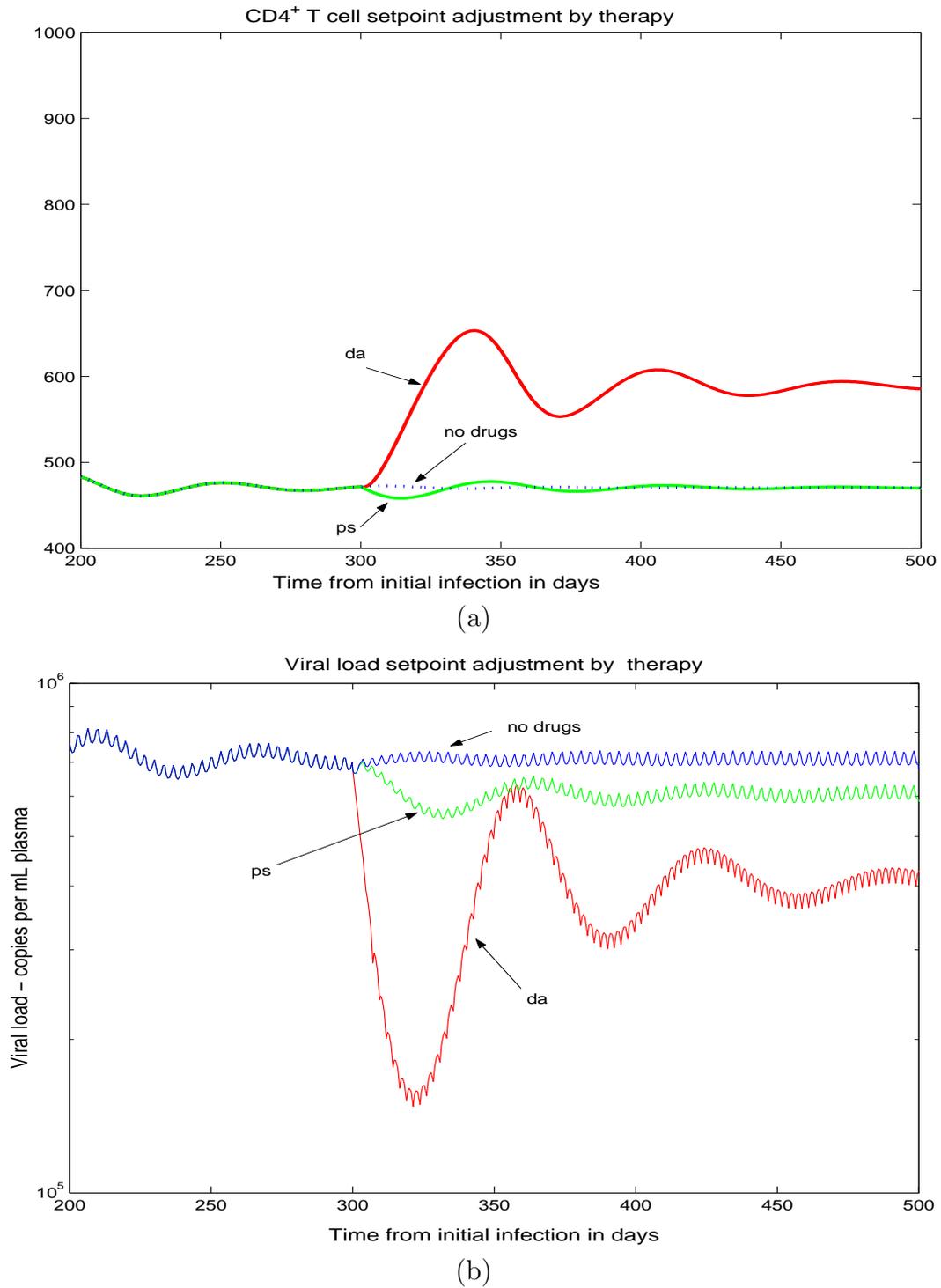


Figure 4.3: Pre-treatment set point and set point adjustment by immune therapies. ps: proliferation suppressing therapy, da: infected cell death accelerating therapy.  $\eta_{ps} = \eta_{da} = 0.25$  (a) CD4<sup>+</sup> T cell count. (b) Viral load. Parameters are in Table A.2.

reducing the viral load, given the same drug efficacy. Furthermore, cell death accelerating therapy has an added advantage of being able to also increase the CD4<sup>+</sup> T cell count. Care should be taken though, not to confuse a lower drug efficacy to automatically imply a lower pill or drug intake.

There is currently no clinical evidence that shows how immunosuppressive and cell death rate accelerating therapies affect macrophages. It can be intuitively assumed though, that these drugs would have some effect on macrophage cells as they do on CD4<sup>+</sup> T cells. However, the effect of immune based therapies on macrophage cells will not be considered in this thesis.

### 4.1.3 Combining HAART with Immune Based Therapies

There are numerous studies that have been undertaken on the concomitant use of some immune based therapies with HAART. In particular, there are some studies that have investigated the possible inclusion of the immunosuppressive drugs in HAART regimens. The intention is to improve the efficacy of HAART. This section discusses some of the results that were obtained from such clinical trials.

The non-dependence of the CD4<sup>+</sup> T cell steady state on the CD4<sup>+</sup> T cell specific therapy efficacy ( $\eta_{sl}$  and  $\eta_{ps}$ ) explains why some of the clinical trial outcomes have reported increased drug toxicity with no added efficacy, when the immunosuppressive drug hydroxyurea is added to HAART regimens [122, 123, 124]. As pointed out before in section 4.1.2, proliferation suppressive therapy has marginal reduction of the viral load, and is not capable of modifying the CD4<sup>+</sup> T cell steady state count. This analysis suggests that the addition of proliferation suppressive or source rate limiting therapy to replication cycle based HAART regimens, is an ill conceived idea. An option that could be considered is adding infected CD4<sup>+</sup> T cell death accelerators to the HAART regimen.

### 4.1.4 Conclusions

The following conclusions can be drawn from the analysis that was carried out in this section.

1. The end result of HIV therapy is to move the pre-treatment viral load to a treatment steady state. This treatment steady state is independent of when therapy is initiated, but is dependent on the individual's viral and host cell parameters, as well as the combined drug efficacy.
2. Initiating therapy when the viral load is below this treatment steady state will result in an increasing viral load, which will be perceived as failure to control the

viral load. When therapy is initiated with a viral load that is higher than this treatment steady state though, there will be an observable reduction in the viral load.

3. This dependence of the treatment steady state on model parameters and drug efficacy, also gives an indication whether or not durable viral load suppression to below detectable levels is attainable for a particular individual.
4. The best way to ensure durable suppression of the viral load to below 50 copies therefore, is to select a drug dosage that has a treatment steady state of less than 50 copies per mL of plasma.
5. The dependence of the steady states on the individuals model parameters explains why there is inter-individual variations in viral load and CD4<sup>+</sup> T cell set-points, as well as why some individuals have virologic failure on therapy that is highly effective on others.
6. For replication cycle based therapy with the latently infected cell model, the viral load steady state is sensitive to small changes in drug efficacy when one is operating around the detection cutoff (50 copies mL<sup>-1</sup> steady state efficacy. However, [71] has since shown that this sensitivity is eliminated for the extended model.
7. Immunosuppressive therapy has no effect on the CD4<sup>+</sup> T cell treatment steady state. This suggests that its concomitant use with replication cycle based HAART is a bad idea. This is further supported by some clinical trial outcomes that show increased toxicity with no added efficacy with their use in HAART regimens. The better option is adding infected CD4<sup>+</sup> T cell death accelerators to the HAART regimen. This would particularly be useful in cases where the individual has marginal cell gains with HAART.
8. The use of target cell death accelerating therapies at first sight may appear counter intuitive because current focus of therapy is to increase CD4<sup>+</sup> T cell counts. However, these therapies will not ‘harm’ the immune system in so far as the CD4<sup>+</sup> T cell counts are concerned.
9. Generally, immune based therapies, from an end point efficacy perspective, are not capable of suppressing the viral load as effectively as replication cycle based therapies.

When using replication cycle based drugs (RTI and PI), the viral load steady state is determined by the combined efficacy for these classes of antiretroviral agents. This implies that using two low efficacy drugs from each class can be as good as using moderate

efficacy therapy from a single class. Furthermore, using low efficacy and moderate efficacy from different classes can be as good as using a high efficacy therapy from a single class.

The analysis suggests that it is possible for the uninfected  $CD4^+$  T cells to rebound to pre-infection values under therapy. However, this is not true for many infected individuals who attain maximal viral load suppression with inadequate  $CD4^+$  T cell gains (virologic success with immunologic failure). There is therefore, a need to find ways of quantifying organ health or damage to the immune system, so that it can be factored into the equations describing the  $CD4^+$  T cell dynamics.

## 4.2 Transient Response Analysis

The steady state analysis presented in section 4.1 has shown that the long term end effect of therapy is to move the viral load and target cell counts from their pre-treatment values to their treatment steady states. However, the steady state analysis does not explain the dynamics underlying this transition. Transient response analysis [170] for the HIV/AIDS models therefore needs to be conducted. Maximal suppression of the viral load to below detectable levels using HAART is attainable. However, the durability of such suppression has proved in many cases, to be elusive as the virus often rebounds (blips) after periods of effective suppression [22, 23, 24, 25]. Issues that are of concern therefore, are the suppression of the viral load to below detectable levels and the ability of the drugs to maintain such suppression once attained.

This section focuses on the attainment of maximal and durable suppression of the viral load. Transient response analysis of an HIV/AIDS model will be used to determine the extent to which the viral load is suppressible at different stages of the progression of the HIV/AIDS infection. The intention is to determine when, as the HIV infection progresses, initiating therapy is most likely to attain maximal and durable suppression of the viral load, as well as the conditions that are conducive to the minimization of viral load blips. If response is related to the infection stage, then this study can also help decide when best to initiate therapy. Simulations are used to show the effect on the viral load of initiating therapy at different stages of the HIV infection.

### 4.2.1 Analysis with the Latently Infected Cell Model

An approximate analysis by linearizing the nonlinear equations in (4.5)-(4.9) with the combined use of reverse transcriptase and protease inhibitors can be obtained. The Jacobian when evaluated at an operating point  $[T^o, T_l^o, T_a^o, V_i^o, V_n^o]^T$  along the state trajectory

from initial infection is given by:

$$\mathbf{A}_L = \begin{bmatrix} \kappa_1 & 0 & 0 & -\beta_T T^o & 0 \\ q_l \beta_T V_i^o & -(\delta_l + k) & 0 & q_l \beta_T T^o & 0 \\ q_a \beta_T V_i^o & k & -\delta_a & q_a \beta_T T^o & 0 \\ 0 & 0 & r_T & -c & 0 \\ 0 & 0 & 0 & 0 & -c \end{bmatrix}$$

where  $\kappa_1 = p(1 - 2T^o/T_m) - d_T - \beta_T V_i^o$ . The assumption is that the individual is treatment naïve, that is, has no prior exposure to therapy.

It is clear from the entries in matrix  $\mathbf{A}_L$ , that the eigenvalues are functions of the viral load  $V^o$  and the  $CD4^+$  T cell count  $T^o$ , at the instance when therapy is initiated. Since these measurements vary with the stage of the HIV infection, then the eigenvalues can also be expected to vary with the stage of the HIV infection, that is, with when therapy is initiated.

The first eigenvalue is  $\lambda_1 = -c$ , while the remaining four are the solutions to

$$\begin{aligned} &(\lambda + c)(\lambda + \delta_a)(\lambda + \delta_l + k)(\lambda - \kappa_1) \\ &-r_T \beta_T T^o (\lambda - \kappa_1 - \beta_T V_i^o)(k q_l + q_a (\lambda + \delta_l + k)) = 0 \end{aligned} \quad (4.24)$$

The eigenvalues are either all real or have a complex pair depending on the stage as the infection progresses. There is therefore, a bifurcation of  $\lambda_4$  and  $\lambda_5$  as they are distinct at some infection stages and are a conjugate pair at other infection stages, as depicted in figure 4.4. For the infection stage where  $\lambda_4$  and  $\lambda_5$  are a conjugate pair, the viral load transient response will have the general form

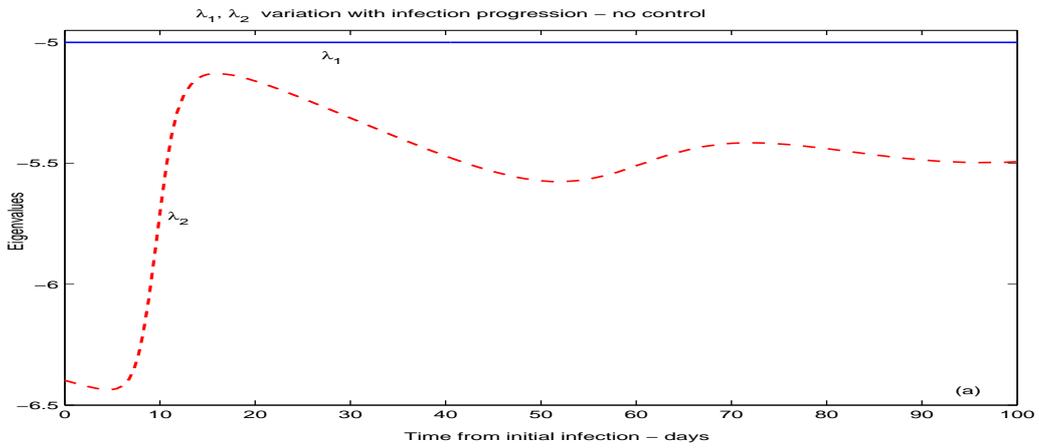
$$\tilde{v}_c(t) = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} + A_4 e^{\sigma t} \cos(\omega t + \phi) + v_{ss} \quad (4.25)$$

where  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$  are the real eigenvalues, while  $\omega$  is the frequency of oscillation and  $\sigma$  is the transient decay rate for the complex pair. This implies that when therapy is initiated, the response will oscillate about the steady state before settling. The magnitude of the oscillation and its decay rate will be parameter, drug efficacy and infection stage (timing) dependent. Figure 4.5 illustrates the variation of  $\omega$  and  $\sigma$  with the combined HAART (RTI and PI) efficacy when therapy is initiated at the asymptomatic stage.

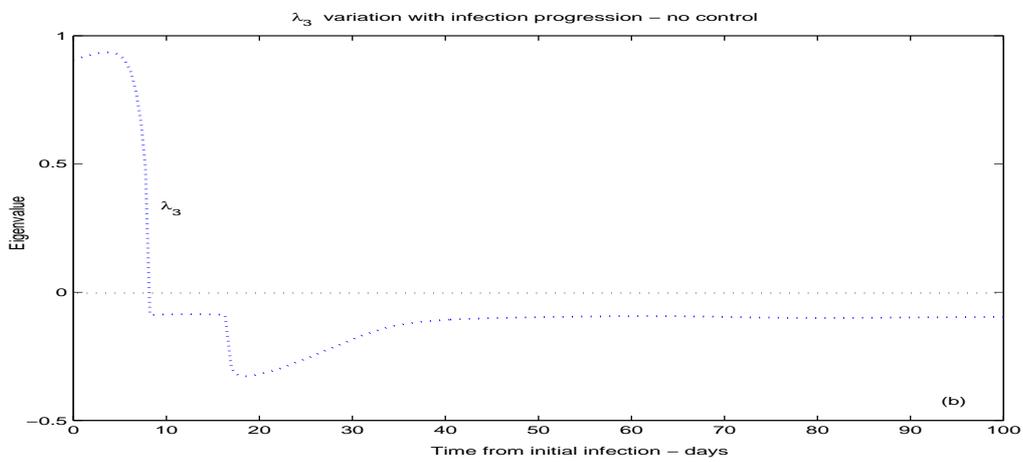
For the infection stages where  $\lambda_4$  and  $\lambda_5$  are distinct, the viral load transient response will have the general form

$$\tilde{v}_r(t) = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} + A_4 e^{\lambda_4 t} + A_5 e^{\lambda_5 t} + v_{ss} \quad (4.26)$$

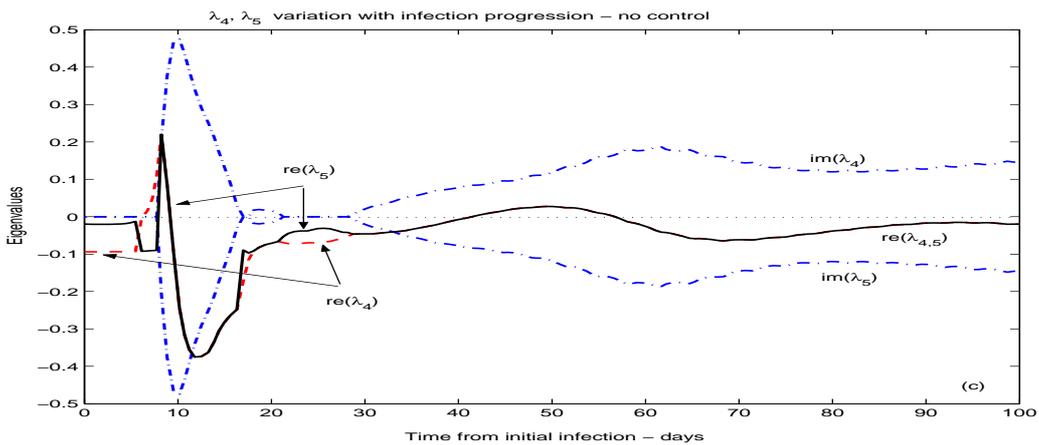
In this case, one can expect the transition to the treatment steady state to be smooth.



(a)



(b)



(c)

Figure 4.4: Eigenvalue variation with infection progression for the latently infected cell model.  $X(0) = [1000, 0, 0, 1]^T$ . Parameters are in Table A.1.

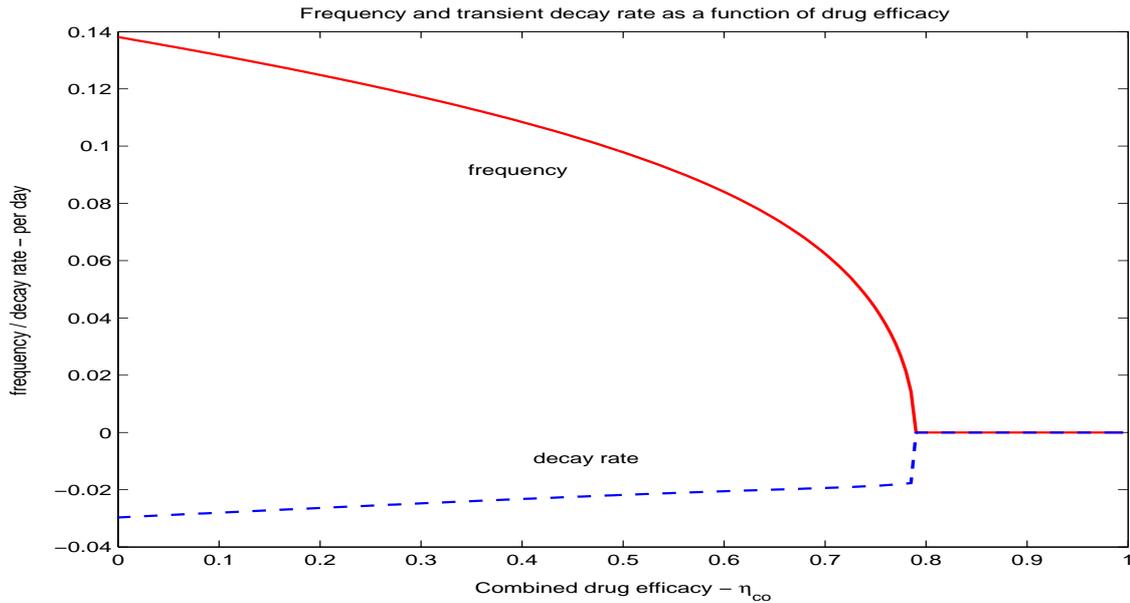


Figure 4.5: Complex eigenvalue variation with combined HAART (RTI and PI) efficacy when therapy is initiated at the asymptomatic stage. Parameters are in Table A.1.

The absolute values for  $\lambda_1$  and  $\lambda_2$  are relatively large, hence their respective transients will die out quickly ( $\tau \leq 0.2$  days). The variation in response is therefore mainly due to the variation in  $\lambda_3$  and the complex eigenvalue parameters  $\omega$  and  $\sigma$ . This variation in  $\omega$  and  $\sigma$  also implies that initiating therapy at some infection stages can be expected to result in a more oscillatory transition to the steady state than at other stages. For instances where all the eigenvalues are real, then the transition to the treatment steady state should be smoother. This analysis is consistent with the often observed ‘viral load blips’ under HAART, where a blip is defined as a transient rebound of plasma viremia after suppression has been attained.

The solutions (4.25) and (4.26) are approximations of the true response. However, the intention was more to understand the nature or form of the response that one can expect, than it was to obtain an expression for the true response. Now that the type of response one can expect is determined by this approximate linearization, it will then be verified using the nonlinear model.

Figure 4.6 shows how the viral load responds to therapy when it is initiated at various stages of the infection, using the same drug efficacy. In particular, the figure shows how viral load suppression depends on when therapy is initiated. It can be seen that a fixed drug dosage can be suppressive at one stage of the infection, but fail when therapy is initiated too early.

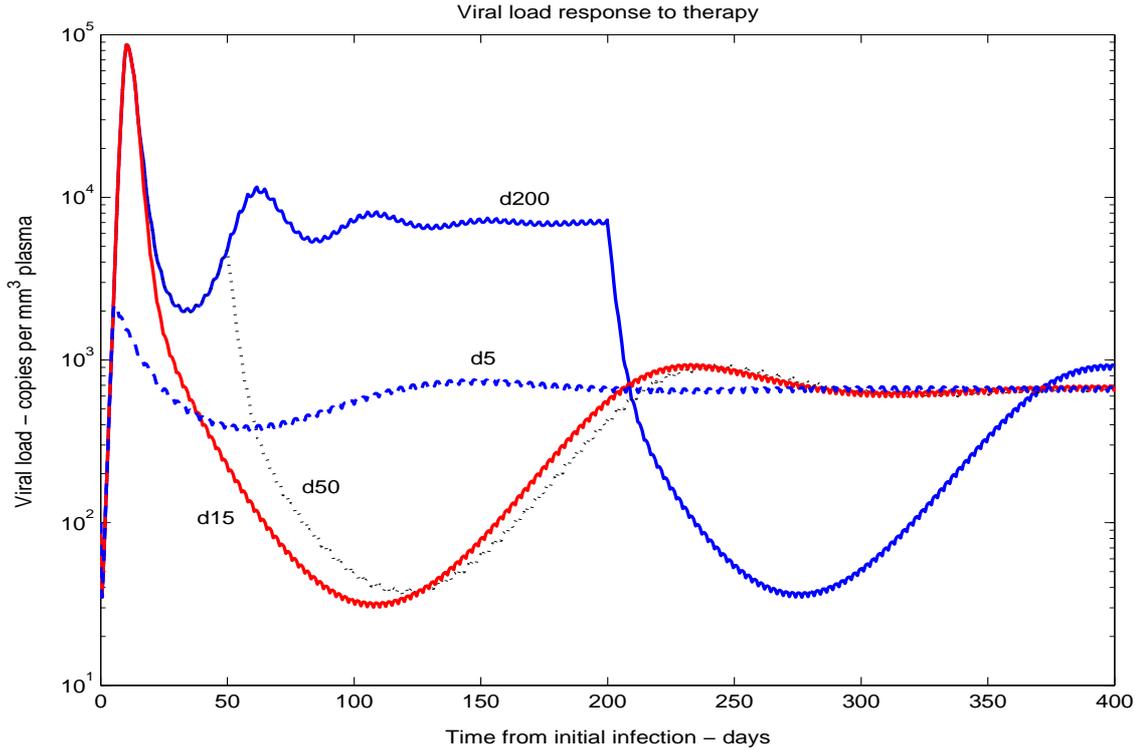


Figure 4.6: Response to therapy when initiated at various stages of the HIV infection. d200:day 200; d5:day 5; d50:day 50; d15:day 15. Drug efficacy  $\eta_{rt} = 0.7$  Parameters are in Table A.1.

On the other hand, figure 4.7 shows how the viral load responds to therapy when it is initiated at the asymptomatic stage of the infection. In this case, the figure shows how viral load suppression depends on drug efficacy.

## 4.2.2 Analysis with the Extended Model

The Jacobians for the extended model when evaluated at an operating point

$[T^o, T_l^o, T_a^o, M^o, M^{*o}, V_i^o, V_n^o]^T$  along the state trajectory from initial infection is given by:

$$\mathbf{A}_E = \begin{bmatrix} \kappa_1 & 0 & 0 & 0 & 0 & -\beta_T T_{ss} & 0 \\ q_l \beta_T V^o & -(k + \delta_l) & 0 & 0 & 0 & q_l \beta_T T^o & 0 \\ q_a \beta_T V^o & k & -\delta_a & 0 & 0 & q_a \beta_T T^o & 0 \\ 0 & 0 & 0 & -(d_M + \beta_M V^o) & 0 & -\beta_M M^o & 0 \\ 0 & 0 & 0 & q_M \beta_M V^o & -\mu & q_M \beta_M M^o & 0 \\ 0 & 0 & r_T & 0 & r_M & -c & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -c \end{bmatrix}$$

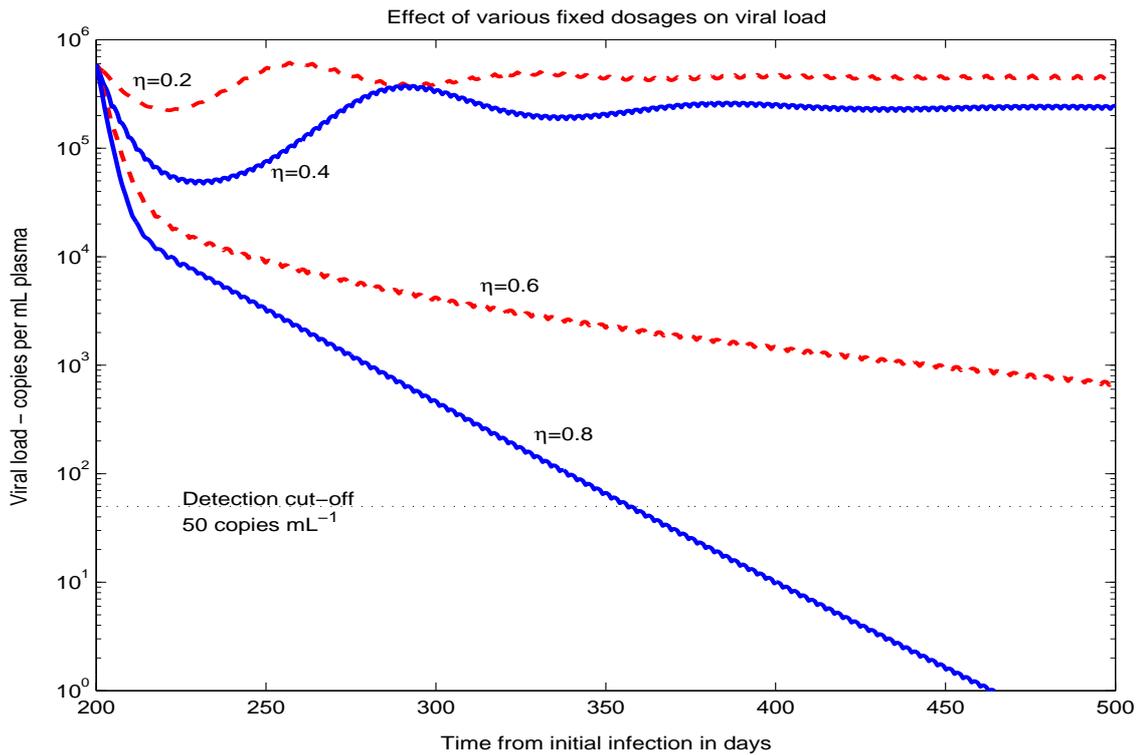


Figure 4.7: Response to therapy when initiated at the asymptomatic stage of the infection using a varying drug efficacy. Parameters are in Table A.2.

The entries in matrix  $\mathbf{A}_E$  show that the eigenvalues will be functions of the viral load  $V^o$ , the uninfected macrophage cell count  $M^o$ , and the uninfected  $CD4^+$  T cell count  $T^o$ , at the instance therapy is initiated. And similarly, the eigenvalues, and hence the response to therapy, can also be expected to vary depending on when therapy is initiated.

### 4.2.3 On Attaining Maximal and Durable Suppression of the Viral Load

Viral load suppression is considered to be maximal when the viral load reaches below levels of detection by the currently available assays. Given a fixed drug efficacy, the initial viral load and  $CD4^+$  T cell count, the minimum viral load and the duration of viral load suppression to below 50 copies per mL of plasma, if attainable, can be determined from either (4.25) or (4.26). Even though this minimum value below 50 copies per mL that the viral load can be reduced to is currently not clinically quantifiable as it can not be readily measured. However, an estimate of the minimum value that the viral load can be reduced to is useful in determining whether viral load suppression to below detectable levels can be attained, for the given drug dosage and instance when therapy is initiated.

Eigenvalue variation gives an indication of how the duration of viral load suppression is expected to vary as the infection progresses. Higher values of  $\omega$  indicate that if viral load suppression is attained, then it will be short lived. Similarly, higher values of  $\sigma$  indicate that the transition to the steady state will be more rapid. Very early initiation of therapy can therefore be expected to result in a shorter viral load suppression period and a rapid transition to the steady state, which is indicated by the relatively higher values of  $\omega$  and  $\sigma$ . Late therapy during the asymptomatic stage will most likely result in a prolonged viral load suppression period. Increasing the drug dose results in a longer period of viral load suppression, which is indicated by the decreasing values of  $\omega$  and  $\sigma$ .

Given the foregoing, maximal suppression of the viral load is most likely to be attained when therapy is initiated during the asymptomatic, very early and late acute infection stages of the infection, or when high drug doses are used. It is therefore possible for a drug dosage to be suppressive at one stage of the infection, but fail when therapy is initiated at a different stage. For a given instance when therapy is initiated, then the degree and duration of viral load suppression is drug efficacy dependent.

### **Durable Suppression**

The best way to ensure a more durable suppression of the viral load will be to select a drug dosage that has a treatment steady state of at most 50 copies per mL of plasma. Alternatively, durable viral load suppression can be attained when therapy is initiated at a time when the associated complex eigenvalues have a smaller frequency component. If any viral load suppression to below the treatment steady state is attained, then it will be long lived as the virus slowly rebounds before settling to the treatment steady state value. It is reasonable to assume that the lower to below detectable levels the viral load is suppressed to, the longer the duration of suppression will be. Maximal suppression therefore, generally implies durable suppression. Durable suppression is therefore also most likely to be attained when therapy is initiated during the asymptomatic, very early and late acute infection stages of the infection, or when a drug dosage that can attain a viral load treatment steady state below 50 copies per mL of plasma is used.

### **Viral Load Rebounds Under Therapy**

Since a viral load blip is a transient rebound of the viral load to above a specified value after maximal suppression has been attained, this means that viral load blips are more likely to occur when drug doses with steady states that are higher than the set value are used (usually over 400 or 500 copies per mL of plasma). For a fixed drug dosage and

constant frequency  $\omega$ , blips are most likely to occur when therapy is initiated at a stage where the associated transient decay rate  $\sigma$  is low. Rebounds can be expected to be more pronounced when transient viral load suppression is attained with lower drug doses, as is the case when therapy is initiated during the asymptomatic stage. Initiating therapy very early during the acute infection stage could minimize viral load blips, but result in a shorter duration of suppression. The difference in peak viral load rebounds for the different infection stages, except for the very early acute infection stage, is not really that significant, which seems to suggest that viral load rebounds are more drug efficacy and parameter variation dependent, than they are timing dependent. The sensitivity of the steady state to slight changes in efficacy could also be the cause of transient rebounds. These slight efficacy variations could be due to daily variations in drug metabolism, for example.

#### 4.2.4 Conclusions

The following conclusions can be drawn from the analysis presented in this section:

1. The transition from the pre-treatment steady state to the treatment steady state is oscillatory. The response is parameter and drug efficacy dependent, but unlike the treatment steady state, it is also dependent on when therapy is initiated.
2. If a drug is capable of driving the viral load to a particular steady state value, then the duration of the viral load suppression to below this steady state value can be maximized by choosing the right time to initiate therapy.
3. Initiating therapy during the mid acute infection stage when the viral load is high, results in a faster transition to the treatment steady state. This however, implies a shorter viral load suppression period.
4. Initiating therapy during the asymptomatic stage of the infection however, will result in a more durable suppression of the viral load. Furthermore, maximal suppression implies a more durable suppression of the viral load.
5. Viral load blips will occur whenever the drug efficacy is such that the viral load treatment steady state is higher than the figure that is set as indicative of a blip. This value in most cases is set at 500 copies per mL of plasma.
6. A point to note is that, from the steady state analysis, there is not much difference in the required drug efficacy to attain steady state viral loads of 50 or 500 copies per mL of plasma. Therefore, it is possible that blips could be caused by slight variations in efficacy due to daily variations in drug pharmacokinetics, or other such extenuating factors.

7. The stage of the infection where viral load blips are most likely to occur is not very clear, but it is clear that viral load rebounds under therapy do not necessarily imply virologic failure. It could be that the drug dosage is not capable of continued viral suppression.
8. However, if the individual's parameters are known, it is then possible to estimate the duration of viral load suppression, as well as anticipate the magnitude and timing of the viral load blip.
9. This study therefore, puts emphasis on the need to estimate parameters and individualize antiretroviral therapy.

### **4.3 Interruption of Highly Active Antiretroviral Therapy**

The viral load will rebound and CD4<sup>+</sup> T cell counts will decline during HAART interruption. This is considered as undesirable, especially when the CD4<sup>+</sup> T cell count did not rebound adequately while one was still on HAART. There is therefore, need to investigate options, therapeutic or otherwise, that will slow down the viral load rebound and/or CD4<sup>+</sup> T cell decline during HAART interruption.

It has been explained in section 4.1.3 why adding immunosuppressive drugs to HAART regimens that are already capable of maximally suppressing the viral load has marginal benefits. In any case, these drugs are on their own, only capable of slightly reducing the viral load set point. This section deals specifically with investigating the possible use of CD4<sup>+</sup> T cell specific immune based therapies as adjuvant to HAART interruptions. The intention is to slow down viral load rebounds when HAART is interrupted.

#### **4.3.1 Anti-CD4 Therapy as Adjuvant to HAART Interruption**

Viral load rebounds occur because HAART interruptions “induce sudden antigenic activation with high peaks of viral load, up to a set-point of viral load or higher, which infects new populations of activated CD4 T cells ..” [120]. More precisely, viral load rebounds occur because (refer to section 2.4):

1. Viral load suppression with HAART does not necessarily imply a reconstitution of HIV specific immune responses [127].
2. There is over stimulation of the immune system during infection [92].
3. The availability of new target cells due to cell gains incurred during HAART [174].

Strategies that reduce cell activation or limit the population of available target cells can therefore be expected to slow down the rebound rate. These immune based CD4<sup>+</sup> T cell specific therapies are referred to as anti-CD4 therapy, since they are perceived to counteract the increase of CD4<sup>+</sup> T cells. These therapies are considered to have no anti-viral activities because they do not directly interfere with the viruses replication cycle. Instead, they manipulate the population dynamics of the target CD4<sup>+</sup> T cells. As explained before, anti-CD4 therapy could include:

1. Reducing CD4<sup>+</sup> T cell proliferation rate  $p$ , referred to as proliferation suppressive therapy.
2. Reducing CD4<sup>+</sup> T cell source rate  $s_T$ , referred to as source limiting therapy.
3. Accelerating infected CD4<sup>+</sup> T cell death rates  $\delta_l$  and  $\delta_a$ , referred to as cell death accelerating therapy.
4. Accelerating target CD4<sup>+</sup> T cell death rate  $d_T$ , referred to as apoptosis inducing therapy.

These therapies are referred to as Anti-CD4 therapy, as they are perceived to be suppressing the expansion of the CD4<sup>+</sup> T cell pools.

### 4.3.2 HAART Interruption with the Latently Infected Cell Model

When HAART is on, the steady states for the viral load and uninfected CD4<sup>+</sup> T cell count for the latently infected cell model were given by equations (4.1) and (??) in section 4.1.1, and are repeated here for ease of reference.

$$T_{ss} = \frac{c\delta_a}{(1 - \eta_{co})q\beta_T r_T} \quad (4.27)$$

$$V_{iss} = \frac{(1 - \eta_{co})qr_T s_T}{c\delta_a} - \frac{d_T}{\beta_T} + \frac{p}{\beta_T} \left(1 - \frac{c\delta_a}{(1 - \eta_{co})q\beta_T r_T T_m}\right) \quad (4.28)$$

where  $q = q_a + q_l \left(\frac{k}{k + \delta_l}\right)$ . When HAART is interrupted, the system will move to another steady state. When proliferation suppressive therapy is used during this period, then the steady states will be :

$$T_{ss} = \frac{c\delta_a}{q\beta_T r_T} \quad (4.29)$$

$$V_{iss} = \frac{qr_T s_T}{c\delta_a} - \frac{d_T}{\beta_T} + \frac{(1 - \eta_{ps})p}{\beta_T} \left(1 - \frac{c\delta_a}{q\beta_T r_T T_m}\right) \quad (4.30)$$

Similarly, the steady states when cell death rate accelerating therapy is used will be:

$$T_{ss} = \frac{(1 + \eta_{da})c\delta_a}{q_{da}\beta_T r_T} \quad (4.31)$$

$$V_{iss} = \frac{q_{da}r_T s_T}{(1 + \eta_{da})c\delta_a} - \frac{(1 + \eta_{ap})d_T}{\beta_T} + \frac{p}{\beta_T} \left(1 - \frac{(1 + \eta_{da})c\delta_a}{q_{da}\beta_T r_T T_m}\right) \quad (4.32)$$

where,  $q_{da} = q_a + q_l \left( \frac{k}{k + (1 + \eta_{da})\delta_l} \right)$ .

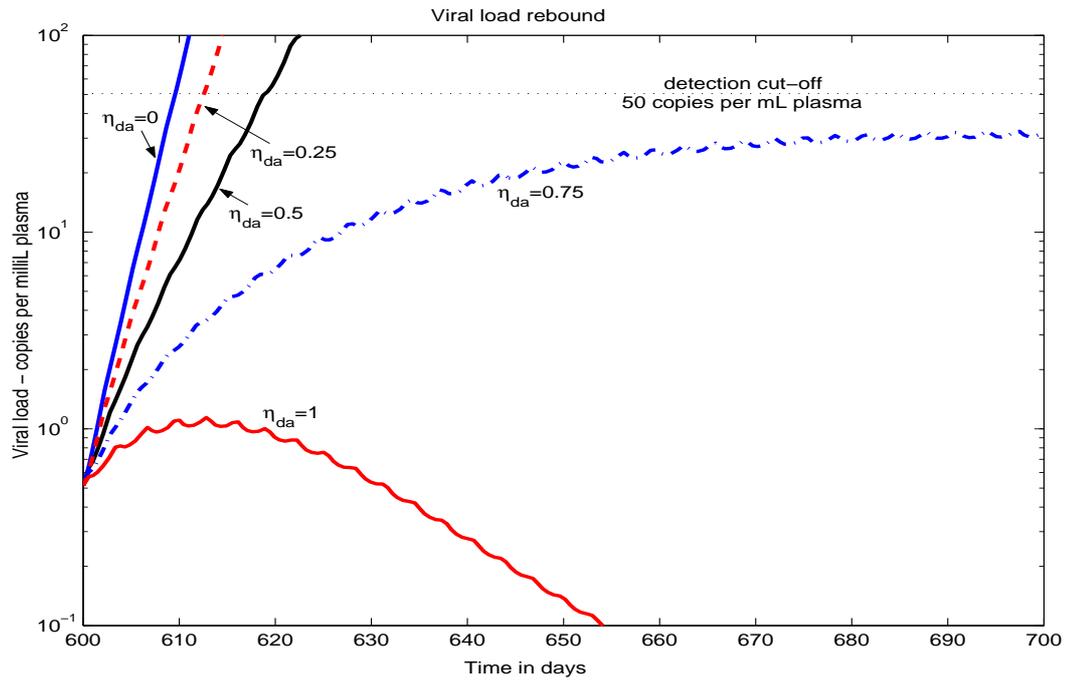
The use of anti-CD4 therapies at first sight may appear counter intuitive because current focus of therapy is to increase CD4<sup>+</sup> T cell counts. However, anti-CD4 therapies will not ‘harm’ the immune system. This is made apparent by examining equations (4.29) and (4.31). These equations show that when proliferation suppressive therapy is used during HAART interruption, then the CD4<sup>+</sup> T cell count will decline to the pre-HAART steady state value. The CD4<sup>+</sup> T cell count will also decline when cell death accelerators are used during HAART interruption. However, unlike with proliferation suppressors, this value will be higher than the pre-HAART steady state, and the percentage increase will be equal to the drug efficacy  $\eta_{da}$ .

On a similar note, it is clear from equations (4.30) and (4.32) how the use of anti-CD4 therapies during HAART interruption can prevent the viral load from rebounding to pre-HAART values. Their ability to reduce the viral load set point could imply that their use during HAART interruptions could reduce the peak viral load. This in turn could imply that the rate of viral load rebound is reduced, and consequently this would prolong the duration of HAART interruption. It is also clear that cell death accelerators, from an end point efficacy perspective, would have better viral load control than proliferation suppressors.

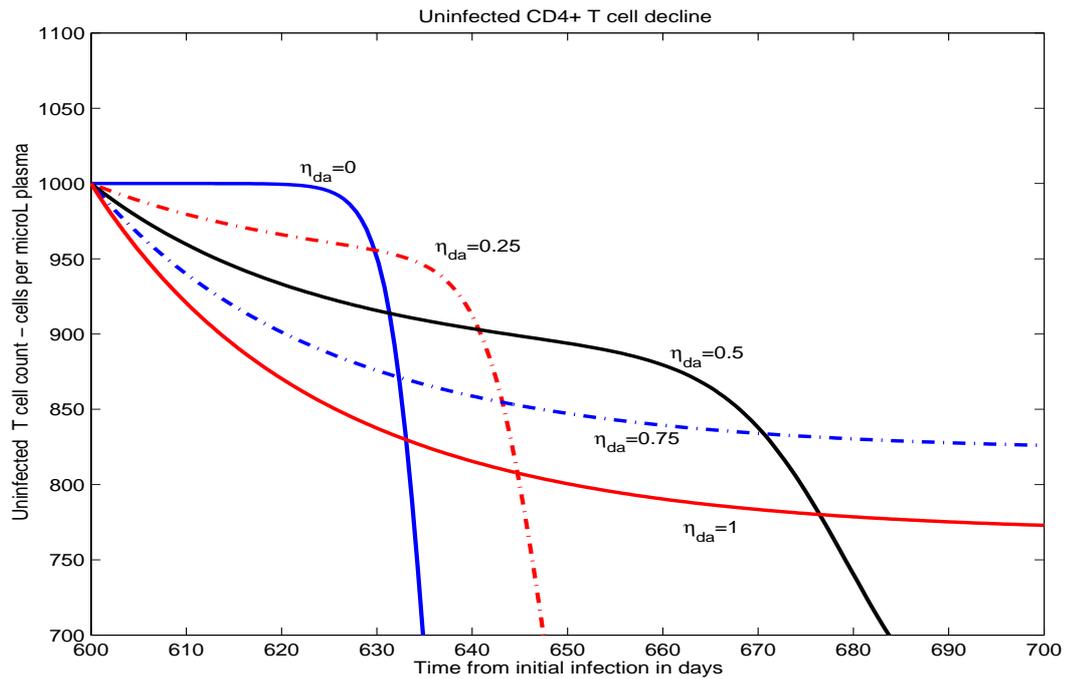
Figure 4.8(a) shows how one could expect viral load rebound to be slowed down when cell death accelerating anti-CD4 therapy is used during HAART interruption. For this case, viral suppression can be maintained for almost 10 days without therapy. Also, significantly longer HAART interruption periods can be attained by the use of anti-CD4 therapy. One however, needs to weigh the advantages of increasing OFF HAART periods against the sacrifice of having no drug free days.

Figure 4.8(b) shows that using anti-CD4 therapy results in a rapid initial decline in CD4<sup>+</sup> T cell counts. This is followed by a slower decline as CD4<sup>+</sup> T cell counts will eventually settle at a value that is higher than when no drugs are used during HAART interruption. When considering the sacrifice of having no drug free days then, one should also consider the benefits of long term CD4<sup>+</sup> T cell gains.

Analysis of the virus and target cell dynamics during HAART interruption with the extended model should illustrate the same concept: that antiCD4 therapy could be used to slow down viral load rebounds that occur when HAART is interrupted.



(a)



(b)

Figure 4.8: Viral load rebound and CD4<sup>+</sup> T cell decline when anti-CD4 therapy is used during HAART interruption.  $\eta_{da} = \eta_{ap}$ : cell death acceleration factors. HAART was previously ON for 300 days with  $\eta_{rt} = 0.7$  (a) Viral load (b) CD4<sup>+</sup> T cells. Parameters are in Table A.2.

### 4.3.3 Conclusions

It is not possible for some HIV infected individuals to attain long term viral load control when HAART is interrupted. A possible way to prolong OFF HAART periods for these individuals is to use anti-CD4 immune based therapies when HAART is interrupted. The use of anti-CD4 therapies at first sight may appear counter intuitive because current focus of therapy is to increase CD4<sup>+</sup> T cell counts. However, anti-CD4 therapy has a potential to prolong the duration of HAART interruptions without excessive reduction in CD4<sup>+</sup> T cell counts. Even though anti-CD4 therapy initially accelerates CD4<sup>+</sup> T cell depletion, it does not necessarily, in the long term harm the immune system in so far as CD4<sup>+</sup> T cell counts are concerned.

What remains then, is to determine the efficacy of the anti-CD4 therapy required for pre-determined ON/OFF HAART periods. Conversely, if the efficacy is known, then the ON/OFF HAART period can be determined. The optimal ON/OFF HAART periods also need to be determined. For the protocol considered in this section, it was assumed that the immune based therapy is to be used for the entire duration that HAART is interrupted. The possibility of whether this therapy's use during OFF HAART periods can be limited to include schedules with drug holidays, where the individual is either ON HAART, or ON Anti-CD4 therapy, or completely OFF all drugs, needs to be explored.

## 4.4 Controllability Analysis

The viral load is considered to be controllable if the control law in use can reduce it by 90% in 8 weeks from the time treatment is initiated and continue to suppress it to below 50 copies per mL of plasma in less than 6 months [1]. There are numerous reported cases where the viral load of individuals has been suppressed to below detectable levels with the use of HAART. So, from a medical/clinical perspective, it seems that the viral load of many HIV infected persons is controllable by the available antiretroviral drugs.

Controllability analysis for the basic 3D HIV/AIDS model has been previously addressed by [43, 107]. Analysis will therefore be carried out for the latently infected cell model  $\Sigma_L$  (4.33) and the co-circulating target cell extended model  $\Sigma_E$  (4.34) with both HAART and immune based therapies.

$$\Sigma_L = \begin{cases} \frac{dT}{dt} &= s_T + (1 - \eta_{ps})pT(1 - \frac{T}{T_m}) - d_T T - \beta_T TV_i \\ \frac{dT_l}{dt} &= (1 - \eta_{rt})q_l \beta_T TV_i - (1 + \eta_{da})\delta_l T_l - kT_l \\ \frac{dT_a}{dt} &= (1 - \eta_{rt})q_a \beta_T TV_i - (1 + \eta_{da})\delta_a T_a + kT_l \\ \frac{dV_i}{dt} &= (1 - \eta_{pi})r_T T_a - cV_i \end{cases} \quad (4.33)$$

$$\Sigma_{Eco} = \begin{cases} \frac{dT}{dt} &= s_T + (1 - \eta_{ps})pT(1 - \frac{T}{T_m}) - d_T T - \beta_T TV_i \\ \frac{dT_l}{dt} &= (1 - \eta_{rt})q_l \beta_T TV_i - (1 + \eta_{da})\delta_l T_l - kT_l \\ \frac{dT_a}{dt} &= (1 - \eta_{rt})q_a \beta_T TV_i - (1 + \eta_{da})\delta_a T_a + kT_l \\ \frac{dM}{dt} &= s_M - d_M M - \beta_M MV_i \\ \frac{dM^*}{dt} &= (1 - \alpha_{rt}\eta_{rt})q_M \beta_M MV_i - \mu M^* \\ \frac{dV_i}{dt} &= (1 - \eta_{pi})r_T T_a + (1 - \alpha_{pi}\eta_{pi})r_M M^* - cV_i \end{cases} \quad (4.34)$$

#### 4.4.1 Controllability

Controllability, by definition, “is a property of a system by which an input can be found that takes every state variable from a desired initial state to a desired final state in finite time” [170].

There are ways to determine if a system is controllable. The use of the controllability matrix is one such way. The controllability matrix for a linear system  $\dot{x} = \mathbf{A}x + \mathbf{B}u$  is given by  $\mathbf{M}_c = [\mathbf{B} \ \mathbf{A}\mathbf{B} \ \mathbf{A}^2\mathbf{B} \ \dots \ \mathbf{A}^{n-1}\mathbf{B}]$ , where  $n$  is the system’s order. Then the system is said to be controllable if  $\text{rank } \mathbf{M}_c = n$ . That is, if  $\mathbf{M}_c$  is not singular. In this section therefore, a linear system’s analytical tool will be applied to the linearized models.

For analysis with the latently infected cell model, the linearized model matrix  $\mathbf{A}_L$  at an operating point  $[\bar{T} \ \bar{T}_l \ \bar{T}_a \ \bar{V}_i]^T$  along the state trajectory from initial infection is:

$$\mathbf{A}_L = \begin{bmatrix} \kappa_1 & 0 & 0 & -\beta_T \bar{T} \\ q_l \beta_T \bar{V}_i & -(k + \delta_l) & 0 & q_l \beta_T \bar{T} \\ q_a \beta_T \bar{V}_i & k & -\delta_a & q_a \beta_T \bar{T} \\ 0 & 0 & r_T & -c \end{bmatrix}$$

where,  $\kappa_1 = p(1 - 2\frac{\bar{T}}{T_m}) - (d_T + \beta_T \bar{V}_i)$ .  $\bar{T}$ , and  $\bar{V}_i$  are the uninfected CD4<sup>+</sup> T cell and viral load measurements at the respective point in the HIV infection progression.

Similarly for analysis with the extended model, the linearized model matrix  $\mathbf{A}_E$  at an operating point  $[\bar{T} \ \bar{T}_l \ \bar{T}_a \ \bar{M} \ \bar{M}^* \ \bar{V}_i]^T$  along the state trajectory from initial infection is:

$$\mathbf{A}_E = \begin{bmatrix} \kappa_1 & 0 & 0 & 0 & 0 & -\beta_T \bar{T} \\ q_l \beta_T \bar{V}_i & -(k + \delta_l) & 0 & 0 & 0 & q_l \beta_T \bar{T} \\ q_a \beta_T \bar{V}_i & k & -\delta_a & 0 & 0 & q_a \beta_T \bar{T} \\ 0 & 0 & 0 & -(d_M + \beta_M \bar{V}_i) & 0 & -\beta_M \bar{M} \\ 0 & 0 & 0 & \beta_M \bar{V}_i & -\mu & \beta_M \bar{M} \\ 0 & 0 & r_T & 0 & r_M & -c \end{bmatrix}$$

where,  $\bar{M}$  is the uninfected macrophage measurement at the respective point in the HIV infection progression.

The assumption is that the individual is treatment naïve. The input matrices  $\mathbf{B}_L$  for the latently infected cell model and  $\mathbf{B}_E$  for the extended model, will depend on the type or combination of therapy that is under consideration.

#### 4.4.2 Analysis with Replication Cycle Based HAART

Under mono class therapy using Reverse transcriptase inhibitors exclusively (PI sparing regimens), the input matrices for the latently infected cell model  $\mathbf{B}_{Lrt}$  and the extended model  $\mathbf{B}_{Ert}$  are respectively given by:

$$\mathbf{B}_{Lrt} = \beta_T \bar{V}_i \bar{T} \begin{bmatrix} 0 \\ -q_l \\ -q_a \\ 0 \end{bmatrix}$$

$$\mathbf{B}_{Ert} = \bar{V}_i \begin{bmatrix} 0 \\ -q_l \beta_T \bar{T} \\ -q_a \beta_T \bar{T} \\ 0 \\ -\alpha_{rt} \beta_M \bar{M} \\ 0 \end{bmatrix}$$

The controllability matrix  $\mathbf{M}_{Lrt} = [\mathbf{B}_{Lrt} \quad \mathbf{A}_L \mathbf{B}_{Lrt} \quad \mathbf{A}_L^2 \mathbf{B}_{Lrt} \quad \mathbf{A}_L^3 \mathbf{B}_{Lrt}]$  for the latently infected cell model is given by:

$$\mathbf{M}_{Lrt} = \beta_T \bar{T} \bar{V}_i \begin{bmatrix} 0 & 0 & q_a \beta_T \bar{T} r_T & \beta_T \bar{T} r_T (q_a \kappa_1 - \kappa_4) \\ -q_l & (k + \delta_l) q_l & -q_l \kappa_2 & q_l \beta_T \bar{T} r_T (q_a \beta_T \bar{V}_i q_a + \kappa_4) + (k + \delta_l) q_l \kappa_2 \\ -q_a & -k q_l + \delta_a q_a & \kappa_3 & q_a \beta_T \bar{T} r_T (q_a \beta_T \bar{V}_i q_a + \kappa_4) - k q_l \kappa_2 - \delta_a \kappa_3 \\ 0 & -r_T q_a & r_T \kappa_4 & r_T (\kappa_3 - c \kappa_4) \end{bmatrix}$$

where

$$\kappa_2 = (k + \delta_l)^2 + q_a \beta_T \bar{T} r_T$$

$$\kappa_3 = k q_l (k + \delta_l + \delta_a) - q_a \delta_a^2 - q_a^2 \beta_T \bar{T} r_T$$

$$\kappa_4 = -k q_l + \delta_a q_a + q_a c.$$

The matrix  $\mathbf{M}_{Lrt}$  is not of full rank only when the viral load is zero or when the uninfected CD4<sup>+</sup> T cell count is zero. A zero viral load is invalid because the individual is assumed to be actively infected. When the CD4<sup>+</sup> T cell count is zero then the immune

system is completely damaged. In this case, there is no point trying to control the virus. All other states apart from when the uninfected CD4<sup>+</sup> T cell count or the viral load is zero, are therefore controllable.

The controllability matrix  $\mathbf{M}_{\text{Ert}} = [\mathbf{B}_{\text{Ert}} \quad \mathbf{A}_{\text{E}}\mathbf{B}_{\text{Ert}} \quad \mathbf{A}_{\text{E}}^2\mathbf{B}_{\text{Ert}} \quad \cdots \quad \mathbf{A}_{\text{E}}^5\mathbf{B}_{\text{Ert}}]$  for the extended model can be determined in a similar manner. The matrix  $\mathbf{M}_{\text{Ert}}$  is also not of full rank only when the viral load is zero or when both the uninfected CD4<sup>+</sup> T cell and uninfected macrophage counts are zero. Again, a zero viral load is invalid and when both the uninfected CD4<sup>+</sup> T cell and macrophage counts are zero, then the immune system is completely damaged and there is no point trying to control the virus. All other states apart from when the uninfected cell counts or the viral load are zero, are therefore controllable.

Under mono class therapy using protease inhibitors exclusively, the input matrices are respectively given by

$$\mathbf{B}_{\text{Lpi}} = r_T \bar{T}_a \begin{bmatrix} 0 \\ 0 \\ 0 \\ -1 \end{bmatrix}$$

$$\mathbf{B}_{\text{Epi}} = (r_T \bar{T}_a + \alpha_{pi} r_M \bar{M}^*) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \end{bmatrix}$$

where,  $\bar{T}_a$  and  $\bar{M}^*$  are the actively infected CD4<sup>+</sup> T cell and macrophage measurements at the respective point in the HIV infection progression.

The controllability matrix  $\mathbf{M}_{\text{Lpi}} = [\mathbf{B}_{\text{Lpi}} \quad \mathbf{A}_{\text{L}}\mathbf{B}_{\text{Lpi}} \quad \mathbf{A}_{\text{L}}^2\mathbf{B}_{\text{Lpi}} \quad \mathbf{A}_{\text{L}}^3\mathbf{B}_{\text{Lpi}}]$  for the latently infected cell model is given by:

$$\mathbf{M}_{\text{Lpi}} = r_T \bar{T}_a \begin{bmatrix} 0 & \beta_T \bar{T} & \beta_T \bar{T}(\kappa_1 - c) \\ 0 & -q_l \beta_T \bar{T} & q_l \beta_T \bar{T} \kappa_6 \\ 0 & -q_a \beta_T \bar{T} & \beta_T \bar{T}(q_a \beta_T \bar{V}_i + \kappa_4) \\ -1 & c & -\kappa_5 \\ & & \beta_T \bar{T}(\kappa_1^2 - c\kappa_1 + \kappa_5) \\ & & q_l \beta_T \bar{T}(\beta_T \bar{V}_i(\kappa_1 - c) - \kappa_6(k + \delta_l) - \kappa_5) \\ & & \beta_T \bar{T}(q_a(\beta_T \bar{V}_i(\kappa_1 - c - \delta_a) - \kappa_5) + \kappa_6 k q_l - \delta_a \kappa_4) \\ & & \beta_T \bar{T} r_T (q_a \beta_T \bar{V}_i + \kappa_4) - c\kappa_5 \end{bmatrix}$$

where

$$\kappa_5 = q_a \beta_T \bar{T} r_T + c^2$$

$$\kappa_6 = \beta_T \bar{V}_i + k + \delta_l + c$$

Matrix  $\mathbf{M}_{\text{Lpi}}$  is not of full rank when the actively infected CD4<sup>+</sup> T cell is zero or when the uninfected CD4<sup>+</sup> T cell count is zero. When the actively infected CD4<sup>+</sup> T cell count is zero, then no virus particles can be produced. All other states apart from when the actively infected or uninfected CD4<sup>+</sup> T cell counts are zero, are controllable.

The controllability matrix  $\mathbf{M}_{\text{Epi}} = [\mathbf{B}_{\text{Epi}} \quad \mathbf{A}_{\text{E}}\mathbf{B}_{\text{Epi}} \quad \mathbf{A}_{\text{E}}^2\mathbf{B}_{\text{Epi}} \quad \cdots \quad \mathbf{A}_{\text{E}}^5\mathbf{B}_{\text{Epi}}]$  for the extended model can be determined in a similar manner. The matrix  $\mathbf{M}_{\text{Epi}}$  is also not of full rank when both the actively infected CD4<sup>+</sup> T cell and infected macrophages counts are zero or when both the uninfected CD4<sup>+</sup> T cell and uninfected macrophage cell counts are zero. Again, when the infected macrophage cell and actively infected CD4<sup>+</sup> T cell counts are both zero, then no virus particles can be produced. All other states are controllable.

Under combined HAART using both reverse transcriptase and protease inhibitors, the input matrices are respectively given by

$$\mathbf{B}_{\text{Lco}} = \begin{bmatrix} 0 & 0 \\ -q_l \beta_T \bar{V}_i \bar{T} & 0 \\ -q_a \beta_T \bar{V}_i \bar{T} & 0 \\ 0 & -r_T \bar{T}_a \end{bmatrix}$$

$$\mathbf{B}_{\text{Eco}} = \begin{bmatrix} 0 & 0 \\ -q_l \beta_T \bar{V}_i \bar{T} & 0 \\ -q_a \beta_T \bar{V}_i \bar{T} & 0 \\ 0 & 0 \\ -\alpha_{rt} \beta_M \bar{V}_i \bar{M} & 0 \\ 0 & -(r_T \bar{T}_a + \alpha_{pi} r_M \bar{M}^*) \end{bmatrix}$$

The expression for the controllability matrix  $\mathbf{M}_{\text{Lco}} = [\mathbf{B}_{\text{Lco}} \quad \mathbf{A}_{\text{L}}\mathbf{B}_{\text{Lco}} \quad \mathbf{A}_{\text{L}}^2\mathbf{B}_{\text{Lco}} \quad \mathbf{A}_{\text{L}}^3\mathbf{B}_{\text{Lco}}]$  for the latently infected cell model, as well as the expression for the controllability matrix  $\mathbf{M}_{\text{Eco}} = [\mathbf{B}_{\text{Eco}} \quad \mathbf{A}_{\text{E}}\mathbf{B}_{\text{Eco}} \quad \mathbf{A}_{\text{E}}^2\mathbf{B}_{\text{Eco}} \quad \cdots \quad \mathbf{A}_{\text{E}}^5\mathbf{B}_{\text{Eco}}]$  for the extended model can likewise be determined.

### 4.4.3 Analysis with Immune Based Therapies

Without going into much detail, the input matrix  $\mathbf{B}_{\text{Lps}}$  and controllability matrix  $\mathbf{M}_{\text{Lps}}$  for the latently infected cell model, when proliferation suppressors are exclusively used, are respectively given by:

$$\mathbf{B}_{\text{Lps}} = \phi(\bar{T}) \begin{bmatrix} -1 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$\mathbf{M}_{\text{Lps}} = \phi(\bar{T}) \begin{bmatrix} -1 & -\kappa_1 & -\kappa_1^2 & -\kappa_1^3 + q_a \beta_T^2 \bar{T} \bar{V}_i r_T \\ 0 & -q_l \beta_T \bar{V}_i & q_l \beta_T \bar{V}_i (k + \delta_l - \kappa_1) & -q_l \beta_T \bar{V}_i (\kappa_1^2 + \kappa_1 (k + \delta_l) + \kappa_2) \\ 0 & -q_a \beta_T \bar{V}_i & \beta_T \bar{V}_i (q_a (\delta_a - \kappa_1) - q_l k) & \beta_T \bar{V}_i (q_a \kappa_1^2 + \kappa_1 (q_a \delta_a - k q_l) - \kappa_3) \\ 0 & 0 & -q_a \beta_T \bar{V}_i r_T & \beta_T \bar{V}_i r_T (\kappa_4 - q_a \kappa_1) \end{bmatrix}$$

where

$$\phi(\bar{T}) = p \bar{T} \left(1 - \frac{\bar{T}}{T_m}\right)$$

The matrix  $\mathbf{M}_{\text{Lps}}$  is not of full rank only when the viral load is zero or when the uninfected CD4<sup>+</sup> T cell count is zero or when the uninfected CD4<sup>+</sup> T cell count has reached the proliferation shut down cell count. In the latter case, then no proliferation can take place at any rate, suppressed or otherwise. All other states, except when  $V_i = 0$ , or when  $T = T_m$  or when  $T = 0$  are controllable.

Similarly, the input matrix  $\mathbf{B}_{\text{Lda}}$  and controllability matrix  $\mathbf{M}_{\text{Lda}}$  for the latently infected cell model, when cell death accelerators are used, are respectively given by:

$$\mathbf{B}_{\text{Lda}} = \begin{bmatrix} 0 \\ -\delta_l \bar{T}_l \\ -\delta_a \bar{T}_a \\ 0 \end{bmatrix}$$

$$\mathbf{M}_{\text{Lda}} = \begin{bmatrix} 0 & 0 & \beta_T \bar{T} r_T \delta_a \bar{T}_a & \beta_T \bar{T} (\kappa_1 r_T \delta_a \bar{T}_a - \kappa_9) \\ -\delta_l \bar{T}_l & \delta_l \bar{T}_l (k + \delta_l) & \kappa_7 & q_l \beta_T \bar{T} (\beta_T \bar{V} r_T \delta_a \bar{T}_a + \kappa_9) - \kappa_7 (k + \delta_l) \\ -\delta_a \bar{T}_a & -k \delta_l \bar{T}_l + \delta_a^2 \bar{T}_a & \kappa_8 & q_a \beta_T \bar{T} (\beta_T \bar{V} r_T \delta_a \bar{T}_a + \kappa_9) + k \kappa_7 - \delta_a \kappa_8 \\ 0 & -r_T \delta_a \bar{T}_a & \kappa_9 & r_T \kappa_8 - c \kappa_9 \end{bmatrix}$$

where

$$\kappa_7 = -\delta_l \bar{T}_l (k + \delta_l)^2 - q_l \beta_T \bar{T} r_T \delta_a \bar{T}_a$$

$$\kappa_8 = k \delta_l \bar{T}_l (k + \delta_l) + \delta_a (k \delta_l \bar{T}_l - \delta_a^2 \bar{T}_a) - q_a \beta_T \bar{T} r_T \delta_a \bar{T}_a$$

$$\kappa_9 = r_T(\delta_a^2 \bar{T}_a - k \delta_l \bar{T}_l) + cr_T \delta_a \bar{T}_a$$

The controllability matrices  $\mathbf{M}_{\mathbf{Eps}}$  and  $\mathbf{M}_{\mathbf{Eda}}$  for the extended model, or any other desired matrix, can be determined and analyzed in a similar manner.

#### 4.4.4 Singular Value Decomposition

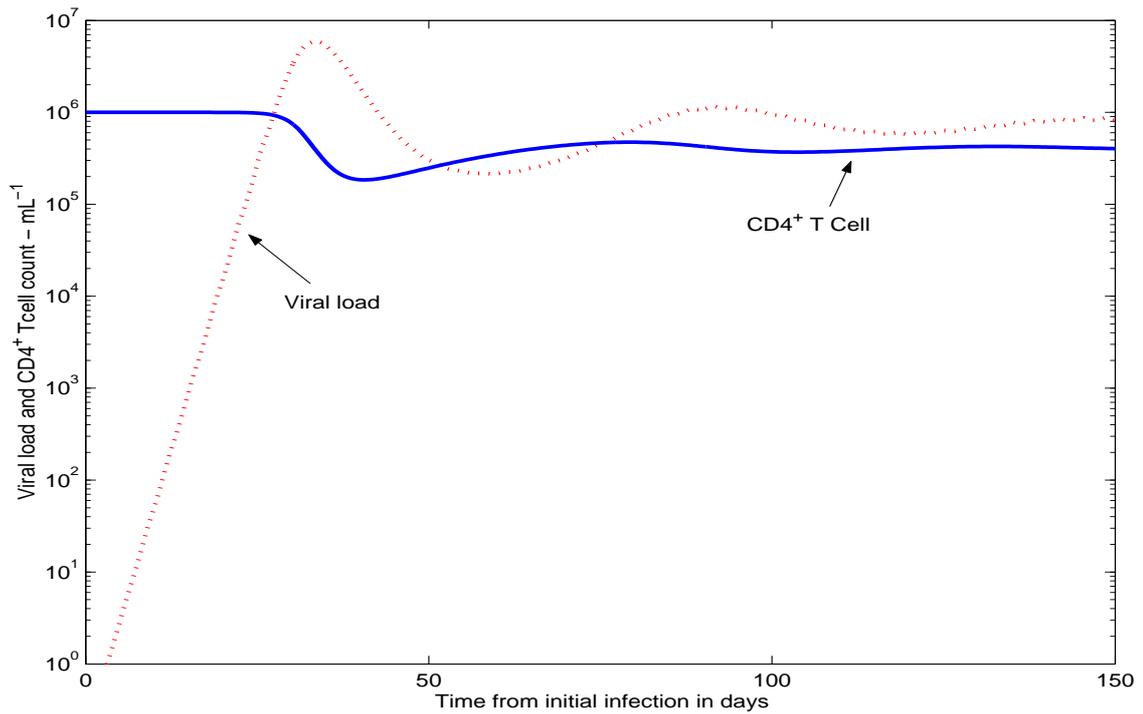
Minimum singular value (MSV) decomposition [175] will be used as a measure of controllability. Since controllability varies along the state trajectory, this means that minimum singular value as a measure of controllability is an instantaneous concept. When minimum singular value decomposition is applied to the controllability matrices, an estimate measure of how controllable the system is at a particular time during the progression of the infection can be obtained, or the extent to which the various stages of the infection progression are controllable, can be determined. Singular value decomposition as a measure of controllability is a valid method to use here because the same variables are used to measure controllability and compared at different times as the infection progresses. It is usually desirable to have a relatively large singular value, as that implies an easier to control infection stage. The reasoning is that, the more controllable the viral load at a particular instance when therapy is initiated, the faster the transition to the treatment steady state, the lower the total drug intake during the transition period.

These easier to control stages will therefore be identified and simulations will be used to demonstrate the effect on the viral load of initiating various types of therapies at different stages as the infection progresses. Comparison will be made between when therapy is initiated in the acute infection and asymptomatic stages of the infection. Comparisons will also be made between the different types and combinations of therapy.

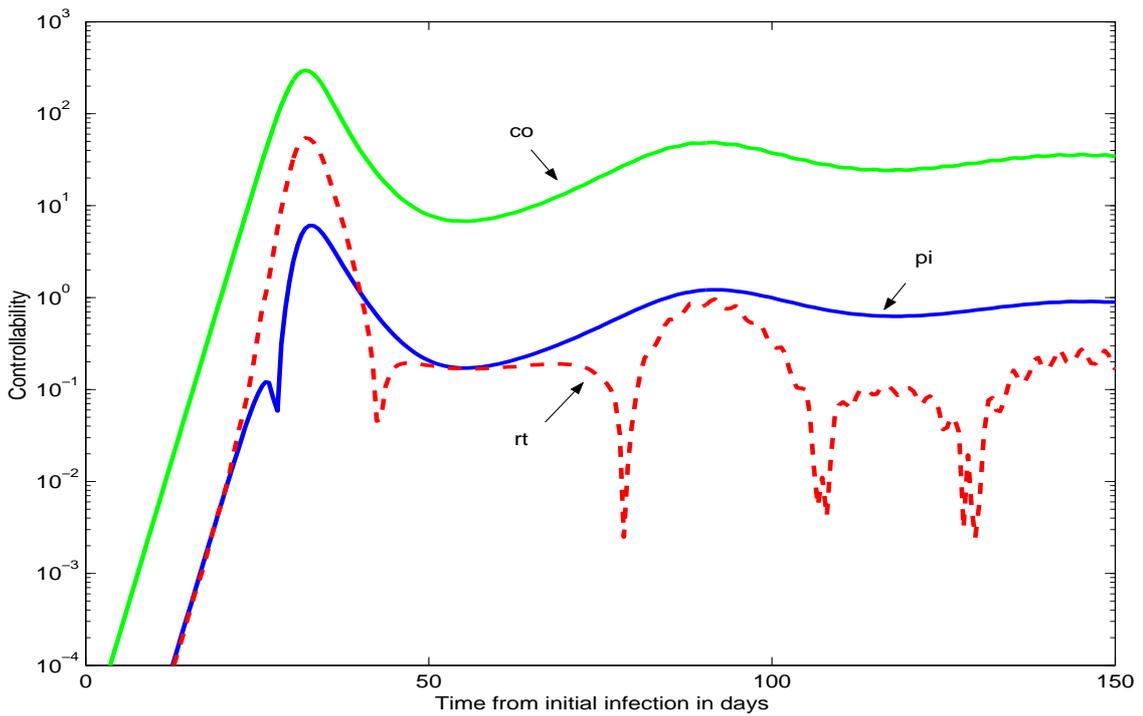
The graphs labelled *pi*, *rt* and *co* in figure 4.9(b) show how the minimum singular value varies with time for the latently infected cell model. These graphs were generated using matrices  $\mathbf{M}_{\mathbf{Lrt}}$ ,  $\mathbf{M}_{\mathbf{Lpi}}$  and  $\mathbf{M}_{\mathbf{Lco}}$ , respectively. Similarly, figure 4.10 shows how the minimum singular value varies with time for the extended model. Graphs were generated using matrices  $\mathbf{M}_{\mathbf{Ert}}$ ,  $\mathbf{M}_{\mathbf{Epi}}$  and  $\mathbf{M}_{\mathbf{Eco}}$ , respectively.

The controllability profiles for the reverse transcriptase and protease inhibitors are similar in that where one controls most effectively, the other one does also. One can not however, draw any conclusions on which type of drug is more capable of suppressing the virus. Singular value decomposition as a controllability measure is not valid in this case.

Some stages of the HIV infection are more (or less) controllable than others. This is so because, for a particular drug, the minimum singular value varies with the instance



(a)



(b)

Figure 4.9: (a) Viral load and  $CD4^+$  T cells. (b) Controllability to the asymptomatic stage for the latently infected cell model with replication cycle based therapies. rt: reverse transcriptase inhibitors, pi: protease inhibitors, co: combined rt and pi. Parameters are in Table A.4.

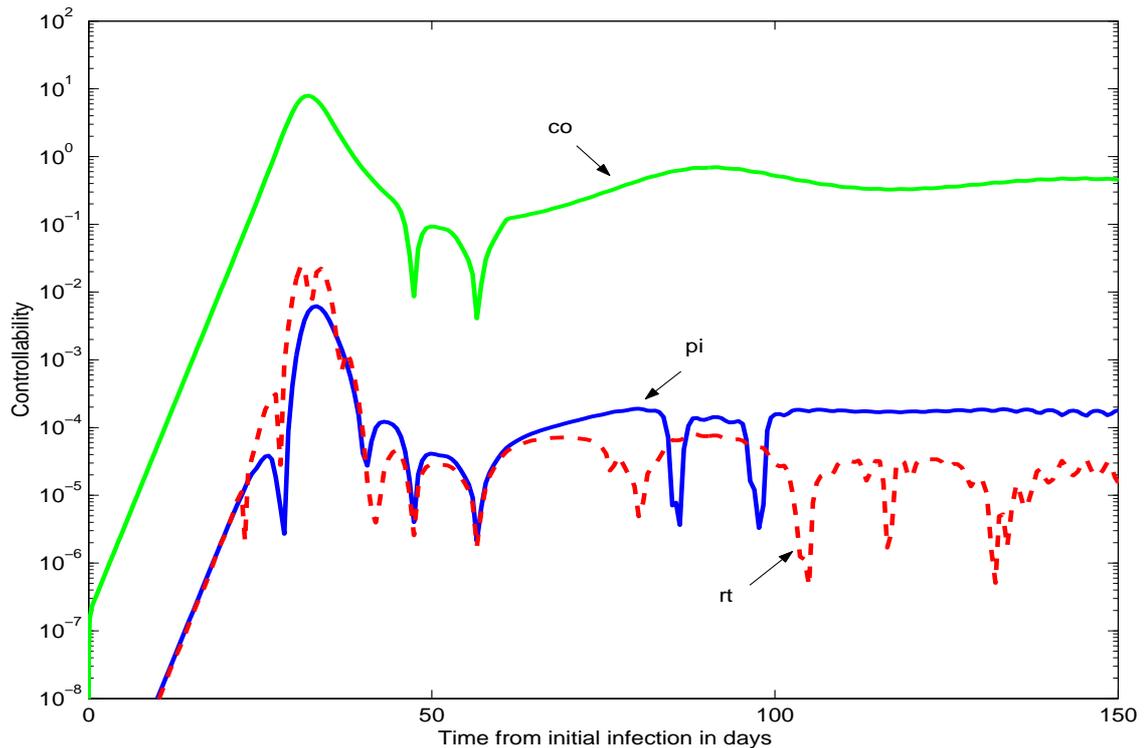


Figure 4.10: Controllability to the asymptomatic stage for the extended model with replication cycle based therapies. rt: reverse transcriptase inhibitors, pi: protease inhibitors, co: combined rt and pi. Parameters are in Table A.4.

during the infection, when therapy is initiated. A higher singular value indicates an easier to control viral load in the sense that the transition to the treatment steady state is faster. A lower singular value indicates a more difficult to control viral load characterized by a slow transition to the final state, given the same control effort. Initiating therapy therefore, when the viral load is easier to control implies the use of lower drug doses and consequently more bearable side effects.

Figures 4.9(b) and 4.10 show that the very early stages of the acute infection stage are relatively more difficult to control as compared to the asymptomatic stage. The section of the acute infection stage where the viral load is much higher than the steady state viral load is relatively the easiest to control. It can also be seen from figure 4.9 that up to the asymptomatic stage, controllability and viral load are correlated, whereas there is no obvious correlation between the  $CD4^+$  T cell or macrophage cell count with controllability. So it seems that from a viral load controllability perspective, the measured viral load at the initiation of therapy is a better prognostic indicator of virologic success, when compared to the  $CD4^+$  T cell or macrophage cell counts.

For controllability with the use of immune based therapies, graphs ‘ps’ and ‘da’ in

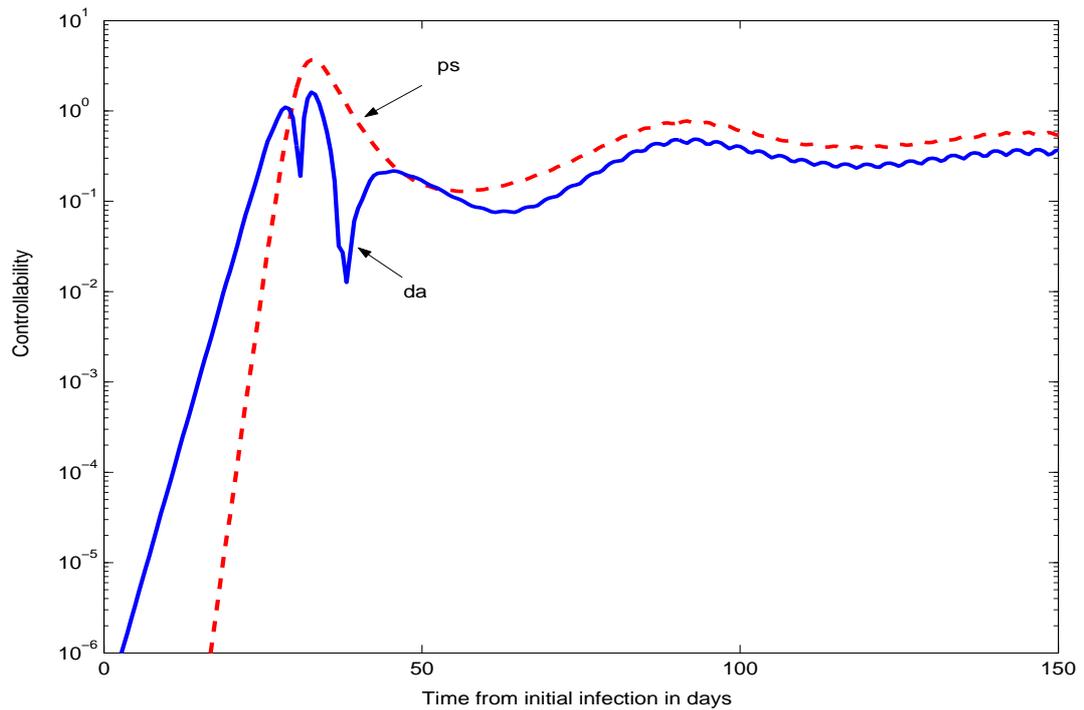


Figure 4.11: Controllability to the asymptomatic stage for the latently infected cell model with immune based therapies. ps: proliferation suppressors, da: death accelerators. Parameters are in Table A.4.

figure 4.11 were generated using matrices  $\mathbf{M}_{Lps}$  and  $\mathbf{M}_{Lda}$ , respectively. When figure 4.11 is compared with figure 4.9, the results show that viral load controllability characteristics are independent of the type of immune based therapy that is used, as it was also the case with replication cycle based therapy.

#### 4.4.5 Controllability to the Advanced Stage

Model parameters are thought to vary with time as has been shown in [84, 167]. For this section, in an attempt to account for the slow decline in  $CD4^+$  T cells counts during the asymptomatic stage, and for the rapid increase of the viral load at the advanced stage of the infection, parameters  $r_T$  and  $\beta_T$  are assumed to increase linearly with time as given by equation (4.35) as

$$y(t) = \begin{cases} y_o, & 0 \leq t \leq t_b \\ y_o(1 + m_y(t - t_b)), & t > t_b \end{cases} \quad (4.35)$$

where the variable  $y$  represents the concerned parameter ( $r_T$  or  $\beta_T$ ),  $y_o$  is the original value, and  $m_y$  is the rate at which the parameter changes. All parameters are assumed

to be constant during the acute infection stage. The parameters change at a slower rate during the asymptomatic stage, which is then followed by a higher rate during the advanced stage. These assumptions, though not clinically validated, do give virus and CD4<sup>+</sup> T cell profiles that comply with clinical observations.

For illustrative purposes, clinical latency is attained after 200 days and the immune system is taken to break down 400 days from initial infection. Figure 4.12(a) illustrates the relatively slower CD4<sup>+</sup> T cell decline during the asymptomatic stage, and figure 4.12(b) shows the minimum singular value plots to the advanced stage.

It can be seen that in all cases, the advanced stage is not as controllable as the asymptomatic stage and that controllability now correlates with the CD4<sup>+</sup> T cells. There is a period of time from just when the virus rebounds and the CD4<sup>+</sup> T cells decline, when the viral load controllability slightly increases.

Virus dynamics are oscillatory, so the response when therapy is initiated will initially either overshoot or undershoot before settling to the new steady state. Initiating therapy when the viral load is easier to control implies that the viral load will rebound and settle to the treatment steady state faster than when therapy is initiated where the viral load is more difficult to control. If any viral load suppression to below the treatment steady state is attained, then it will be short lived as the virus quickly rebounds and settles. This will call for early changes or an increase in dosage in order to re-suppress the virus.

On the other hand, initiating therapy when the viral load is more difficult to control implies that the viral load will slowly rebound and settle to the treatment steady state. Any viral load suppression attained will therefore, be relatively durable as the virus slowly rebounds and settles.

The reciprocal of the minimum singular value will give an indication of the viral load settling time and consequently, an indication of the duration of viral load suppression. In terms of the objectives of therapy, therapy is best initiated at a time when treatment will effectively suppress the viral load for as long as possible before it rebounds. If a drug is capable of driving the viral load to a particular steady state value, then the durability of the viral load suppression to below this steady state value can be maximized by choosing the right time to initiate therapy. This would be at a time when the viral load is higher than this steady state value and more difficult to control.

The viral load controllability analysis that has been carried out in this section complements the transient response analysis that was presented in the previous section 4.2. This controllability analysis further explains why differing responses to therapy, as previously illustrated in figure 4.6 (section 4.2.2), can be attained depending on when, during

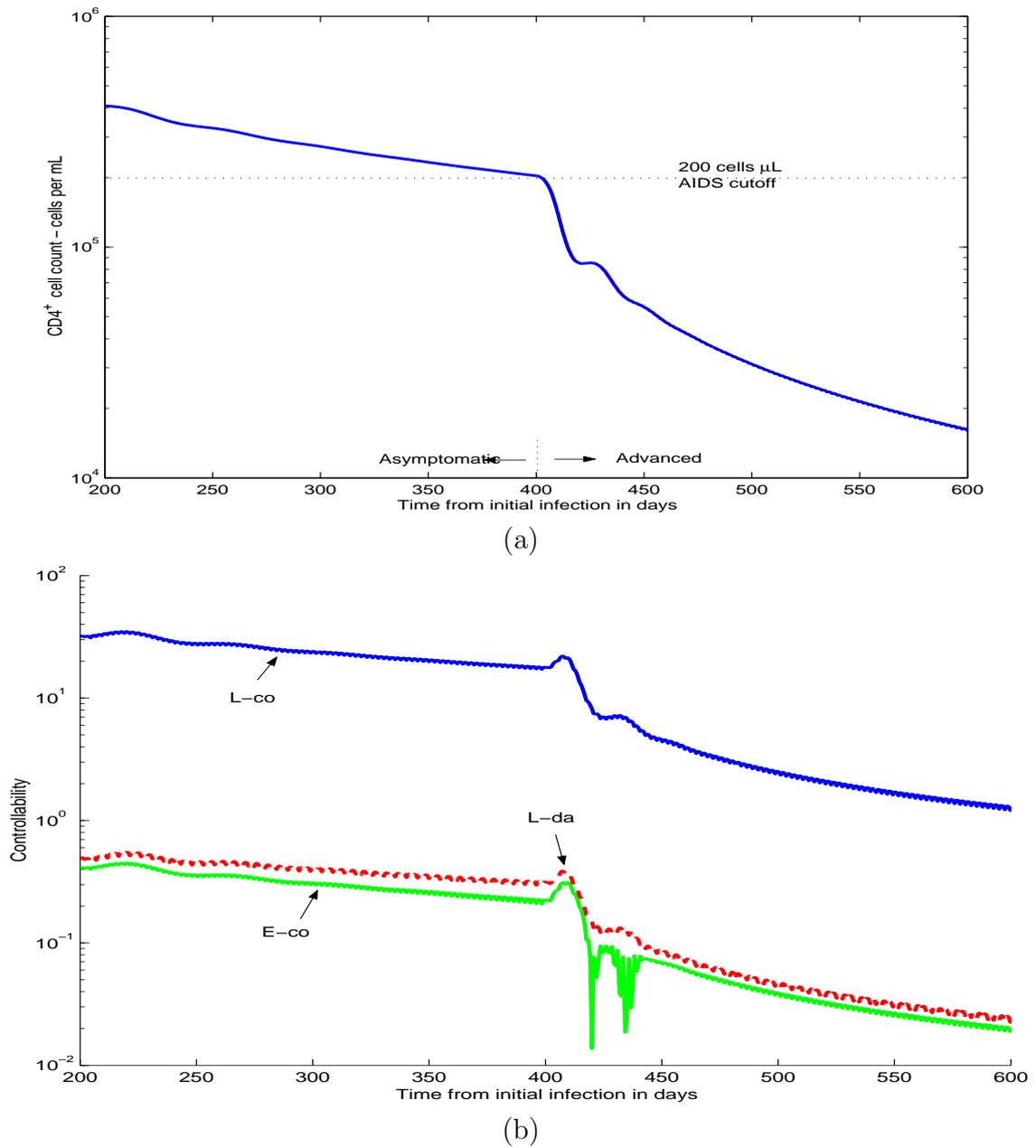


Figure 4.12: Controllability to the advanced stage with a progressive asymptomatic stage. Parameters  $r_T$  and  $\beta_T$  slowly changing at rates  $m_{r1} = m_{\beta1} = 0.005$ , then rapidly at rates  $m_{r2} = m_{\beta2} = 0.1$ . (a)  $CD4^+$  T cell decline. (b) Controllability. L-co: Latently infected cell model with combined  $r_t$  and  $\pi_i$ ; L-da: Latently infected cell model with cell death accelerators; E-co: Extended model with combined  $r_t$  and  $\pi_i$ . Parameters are in Table A.4.

the HIV infection, therapy is initiated.

#### 4.4.6 Conclusions

The following conclusions can be drawn from this study.

1. It is apparent that the controllability profiles for the different therapies are similar, or that viral load controllability characteristics are independent of the type of therapy that is used.
2. Even though any viral load for all stages of the infection, apart from when the associated T cell count is zero, is theoretically controllable, some stages are more controllable than others.
3. The early acute infection stage and the advanced stages are the most difficult stages to control.
4. The mid-acute infection stage, when the viral load is very high is the easiest stage to control.
5. There is a strong correlation between the viral load and controllability up to the asymptomatic stage, while controllability strongly correlates with the CD4<sup>+</sup> T cell count during the advanced stage of the infection.
6. From a viral load controllability point of view, therapy is best initiated when the viral load is easier to control because this implies the use of lower drug doses and consequently bearable sides effects.
7. This study seems to indicate that when therapy is initiated at the appropriate time, the use of highly potent HAART may not be necessary. However, caution is needed due to resistance issues.

### 4.5 Identifiability Analysis

There is a need to accurately estimate all viral, host cell and immune response specific parameters. Before such an extensive parameter estimation exercise can be carried out, an identifiability analysis needs to be carried out to investigate whether or not it is possible to determine all the parameters. If it is found to be possible, then the conditions or restrictions that apply need to be known before hand. The issues to address are the variables to be measured, the minimal number of measurements for a complete determination of all parameters, the frequency and when, during the course of the viral infection, such measurements can be taken. It is important to know this in advance, especially where budgets are concerned. The measured variable combination and conditions that

result in the least number of measurements or costs less, could then be selected. All the foregoing will be investigated in this chapter using a well established nonlinear system identifiability theory.

Identifiability is a basic system property of whether all parameters can be calculated from the measured output. The identifiability concept applied here was presented and analyzed by [63]. The concept is based on the practical requirement that if parameters can be expressed as functions of known quantities of the model, then it is possible to work in the algebraic framework. In essence, if as many such function expressions as there are unknown parameters can be generated, then it is possible to solve for all the unknown parameters.

There are other identifiability analysis tools for nonlinear systems that are available in literature besides the one that is adopted in this thesis. However, the approach as presented by [63] is more practically applicable because it explicitly addresses the issue of the minimum number of measurements that would be required for the eventual determination of the model parameters.

According to [63], if the system is algebraically identifiable, then this enables one to construct the parameters from solving algebraic equations depending only on the information of the input and output. Also, if the system is geometrically identifiable, then this enables one to construct the parameters from solving algebraic equations depending on the information of the input, the output and the initial conditions of the system.

### **4.5.1 The Need for Parameter Estimates**

The preceding model analysis of sections 4.1 to 4.4, as well as the eventual design of individualized dosage schedules will all depend on model parameters. If model parameter estimates can be obtained during the early stages of the HIV infection, they can be used to predict viral load set points, which are an important indicator of disease progression [166]. In this case, if such estimates can be obtained, then it must be within a reasonably short period of time. From an HIV vaccination point of view, such estimates can be used to determine the vaccine efficacy. Estimates for model parameters are available in for example, [50, 84, 85, 176]. Not much effort however, has been put into simultaneously estimating all of these parameters [63]. The available estimates, especially for the compartmental models, are sparse and incomplete. There are indications though, that accuracy of estimates for some of the model parameters is increasing as more innovative approaches for their estimation are employed.

Another reason for the need for accurate parameter estimates is the fact that there

are inter-individual variations in parameters [98, 171]. Furthermore, parameters are thought to vary from one stage to the next as the infection progresses [80, 84]. There is a possibility though, that what seems to be changes in model parameters with time could just be the effect of un-modelled dynamics or external disturbances. Obtaining an individual's parameters at different stages of the viral infection could therefore, settle this issue.

HIV drug pharmacokinetics, pharmacodynamics and adverse reactions are genetically predisposed [41, 126]. Furthermore, the response time to therapy, for example, the time to effectively suppress the viral load are parameter dependent [60]. Given this parameter dependence of the response to therapy, one can therefore consider exploiting inter-individual variations in parameters to individualize treatment and enhance the benefits of antiretroviral therapy [177, 178]. There will be a need then, for test measurements to be done over a short period of time.

All variables in the models presented in this and chapter 3 can essentially be measured, though some with less accuracy and high cost. However, variables that are routinely measured for deciding when to initiated therapy and for monitoring of patients on antiretroviral therapy are the viral load and the total CD4<sup>+</sup> T cell count  $T_{tot}$ , which is the sum of the uninfected and infected CD4<sup>+</sup> T cells. In settings where all variable measurements are obtainable, this will improve the identifiability properties of the system.

It has been observed that for individuals in the asymptomatic stage of the infection and those on antiretroviral drugs, the infected CD4<sup>+</sup> T cell pool makes a very small percentage (< 1%) of the total CD4<sup>+</sup> T cell count [26, 161]. This means that in this case, the assumption that the uninfected CD4<sup>+</sup> T cell count is approximately equal to the total CD4<sup>+</sup> T cell count can be made. The same is assumed to apply to macrophage measurements. This thesis has therefore, opted to take the uninfected CD4<sup>+</sup> T cell count as the measured output instead of the total CD4<sup>+</sup> T cell count. The same applies to macrophage measurements. The actual parameter extraction is outside the scope of this thesis.

## 4.5.2 Identifiability Properties of the Latently Infected Cell Model

The identifiability analysis of the latently infected cell model  $\Sigma_{Lnp}$ (4.36) has already been carried out by [63]. A summary of their findings will be presented in this section for comparative purposes.

Table 4.1: Identifiability of system  $\Sigma_{Lnp}$  with some known parameters.

Known parameters	Identifiability of remaining parameters
$q_l, q_a$	identifiable
$q_l, \delta_l$	identifiable
$q_l, k$	identifiable
$q_l, \delta_a$	not identifiable
$q_l, r_T$	identifiable
$q_l, c$	not identifiable
$q_a, \delta_l$	identifiable
$q_a, k$	identifiable
$q_a, \delta_a$	not identifiable
$q_a, r_T$	identifiable
$q_a, c$	not identifiable
$\delta_l, k$	not identifiable
$\delta_l, \delta_a$	not identifiable
$\delta_l, r_T$	identifiable
$\delta_l, c$	not identifiable
$k, \delta_a$	not identifiable
$k, r_T$	identifiable
$k, c$	not identifiable
$\delta_a, r_T$	not identifiable
$\delta_a, c$	not identifiable

[63]

$$\Sigma_{Lnp} = \begin{cases} \frac{dT}{dt} & = s_T - d_T T - \beta_T TV \\ \frac{dT_l}{dt} & = q_l \beta_T TV - k T_l - \delta_l T_l \\ \frac{dT_a}{dt} & = q_a \beta_T TV + k T_l - \delta_a T_a \\ \frac{dV}{dt} & = r_T T_a - cV \end{cases} \quad (4.36)$$

If the viral load (V) and uninfected CD4<sup>+</sup> T cell count (T) are taken as the measured system outputs, system  $\Sigma_{Lnp}$  has been shown not to be algebraically identifiable. Besides the identification of  $s_T$ ,  $d_T$  and  $\beta_T$ , five of the seven remaining parameters may be computed in terms of the measurements if two of the remaining parameters are known. A summary on the identifiability of system  $\Sigma_{Lnp}$  when various combinations of two model parameters are known is presented in Table 4.1.

However,  $\Sigma_{Lnp}(4.36)$  has been shown to be geometrically identifiable. Therefore, all the original parameters of  $\Sigma_{Lnp}$  are identifiable from the measurements of the viral load and uninfected CD4<sup>+</sup> T cell count if the initial values for both the actively and latently infected CD4<sup>+</sup> T cells for the individual are known. And as [63] put it, one needs to

Table 4.2: Minimum number of measurements for the latently infected cell model  $\Sigma_{Lnp}$ .

Measured	Property	$T$	$T_l$	$T_a$	$V$	Total
$T, V$	Geometric	6	1	1	8	16

[63]

have a “comprehensive test” done before measurements are taken.

The required minimum number of measurements for a complete first determination of all ten parameters are as summarized in Table 4.2.

### 4.5.3 Identifiability Properties of the Extended Model

An analysis of the extended model  $\Sigma_{Enp}$  in (4.37) will be presented for when different combinations of model variables are the measured outputs.

$$\Sigma_{Enp} = \begin{cases} \frac{dT}{dt} &= s_T - d_T T - \beta_T TV \\ \frac{dT_l}{dt} &= q_l \beta_T TV - k T_l - \delta_l T_l \\ \frac{dT_a}{dt} &= q_a \beta_T TV + k T_l - \delta_a T_a \\ \frac{dM}{dt} &= s_M - d_M M - \beta_M MV \\ \frac{dM^*}{dt} &= q_M \beta_M MV - \mu M^* \\ \frac{dV}{dt} &= r_T T_a + r_M M^* - cV \end{cases} \quad (4.37)$$

#### Identifiability with viral load and uninfected CD4<sup>+</sup> T cell count measurements

In the first instance, take outputs as the uninfected CD4<sup>+</sup> T cell count,  $T$  and the viral load  $V$ . That is,

$$y_1 = T, \quad y_2 = V.$$

For output  $y_1$ , compute

$$\dot{y}_1 = s_T - d_T y_1 - \beta_T y_1 y_2. \quad (4.38)$$

Thus, output  $y_1$  has an observability index equal to 1 and three parameters that may be identified. Higher order derivatives yield

$$\ddot{y}_1 = -d_T \dot{y}_1 - \beta_T (y_1 y_2)^{(1)}, \quad (4.39)$$

$$y_1^{(3)} = -d_T \ddot{y}_1 - \beta_T (y_1 y_2)^{(2)}. \quad (4.40)$$

where  $(y)^{(n)}$  is the  $n^{th}$  derivative of  $y$ .

Now there are three equations (4.38), (4.39) and (4.40) with three unknown parameters.

Parameters  $s_T$ ,  $d_T$  and  $\beta_T$  can therefore, be computed from any persistently exciting trajectory  $y(t)$  such that  $\text{rank } \partial(\dot{y}_1, \ddot{y}_1, y_1^{(3)}) / \partial(s_T, d_T, \beta_T) = 3$ . That is, if

$$\text{rank} \begin{bmatrix} 1 & -y_1 & -y_1 y_2 \\ 0 & -\dot{y}_1 & -(y_1 y_2)^{(1)} \\ 0 & -\ddot{y}_1 & -(y_1 y_2)^{(2)} \end{bmatrix} = 3.$$

The three equations (4.38), (4.39) and (4.40) can be solved to get a unique solution for  $s_T$ ,  $d_T$  and  $\beta_T$ . At least four measurements of the uninfected CD4<sup>+</sup> T cell count  $y_1$  and at least three measurements of the viral load  $y_2$ , are needed for a complete first determination of these three parameters.

For the remaining twelve parameters  $(\delta_l, \delta_a, q_l, q_a, k, r_T, s_M, d_M, \beta_M, r_M, \mu, c)$ , compute

$$\begin{aligned} \dot{y}_2 &= r_T T_a + r_M M^* - c y_2, & (4.41) \\ &\vdots \\ y_2^{(5)} &= r_T q_a \beta_T (y_1 y_2)^{(3)} + r_T \beta_T (\theta_2 + \mu q_a) (y_1 y_2)^{(2)} \\ &\quad + r_T \beta_T \mu \theta_2 (y_1 y_2)^{(1)} - (\theta_1 + c + \delta_a) y_2^{(4)} - (\theta_4 + (k + \delta_l) \theta_3) y_2^{(3)} \\ &\quad + (\theta_5 + s_M - (k + \delta_l) \theta_4) \dot{y}_2 + (k + \delta_l) \theta_5 \dot{y}_2 \\ &\quad + s_M (\Sigma + (\psi_1 - \beta_M y_2) \dot{y}_2) + \frac{\dot{\Sigma}}{\Sigma} - (d_M - \beta_M y_2) \Lambda, & (4.42) \end{aligned}$$

where,

$$\begin{aligned} \theta_1 &= k + \delta_l + \mu, \\ \theta_2 &= k q_l + (k + \delta_l) q_a, \\ \theta_3 &= \mu + c + \delta_a, \\ \theta_4 &= \mu c + \delta_a (\mu + c), \\ \theta_5 &= r_M \beta_M s_M - \mu c \delta_a, \\ \psi_1 &= \delta_a - d_M - \beta_M y_2, \\ \Sigma &= \dot{y}_2 + (\psi_1 - \beta_M y_2) \dot{y}_2, \\ \Lambda &= y_2^{(4)} - r_T q_a \beta_T (y_1 y_2)^{(2)} - r_T \beta_T (\theta_2 + \mu q_a) (y_1 y_2)^{(1)} \\ &\quad - r_T \beta_T \mu \theta_2 y_1 y_2 + (k + \delta_l + \theta_3) y_2^{(3)} + (\theta_4 + \theta_3 (k + \delta_l)) \dot{y}_2 \\ &\quad - (\theta_5 + s_M - \theta_4 (k + \delta_l)) \dot{y}_2 - \theta_5 (k + \delta_l) y_2 - \psi_1 s_M y_2. \end{aligned}$$

However, the system is not algebraically identifiable. Besides the identification of  $s_T$ ,  $d_T$  and  $\beta_T$ , only eight of the remaining twelve parameters can be computed in terms of the measured outputs and the other four parameters. The system can be shown to be geometrically identifiable, or identifiable with known initial conditions. One therefore,

needs a comprehensive test to obtain initial measurements for both the actively and latently infected CD4<sup>+</sup> T cells, as well as for the infected and uninfected macrophages. Even though this system is geometrically identifiable with measured outputs taken as the viral load and uninfected CD4<sup>+</sup> T cells, the required minimum number of measurements of these outputs is too high as outlined in Table 7. Attempts to obtain estimates of all 15 parameters of this model, with the viral load and uninfected CD4<sup>+</sup> T cell counts as the measured outputs will therefore, not be a practical approach when cost and patient discomfort are taken into consideration. One therefore needs to consider measuring something else or increasing the number of measured outputs.

**Identifiability with viral load and uninfected CD4<sup>+</sup> T cell count and macrophage measurements**

The identifiability property of system  $\Sigma_{Enp}$  (4.37) can be improved by also measuring the uninfected macrophages. Then, taking the outputs as

$$y_1 = T, \quad y_2 = V, \quad y_3 = M, \quad \text{and let } x_1 = y_1 y_2, \quad x_2 = y_1 y_3,$$

and compute

$$\dot{y}_1 = s_T - d_T y_1 - \beta_T x_1. \tag{4.43}$$

Then,  $s_T$ ,  $d_T$  and  $\beta_T$  can therefore, as illustrated before, be computed from any persistently exciting trajectory  $y(t)$  such that  $\text{rank } \partial(\dot{y}_1, \ddot{y}_1, y_1^{(3)})/\partial(s_T, d_T, \beta_T) = 3$ . That is, if

$$\text{rank} \begin{bmatrix} 1 & -y_1 & -x_1 \\ 0 & -\dot{y}_1 & -\dot{x}_1 \\ 0 & -\ddot{y}_1 & -\ddot{x}_1 \end{bmatrix} = 3.$$

For output  $y_3$ , compute

$$\dot{y}_3 = s_M - d_M y_3 - \beta_T x_2. \tag{4.44}$$

Similarly,  $s_M$ ,  $d_M$  and  $\beta_M$  can be computed from any persistently exciting trajectory  $y(t)$  such that  $\text{rank } \partial(\dot{y}_3, \ddot{y}_3, y_3^{(3)})/\partial(s_M, d_M, \beta_M) = 3$ . That is, if

$$\text{rank} \begin{bmatrix} 1 & -y_3 & -x_2 \\ 0 & -\dot{y}_3 & -\dot{x}_2 \\ 0 & -\ddot{y}_3 & -\ddot{x}_2 \end{bmatrix} = 3.$$

For the remaining nine parameters  $(\delta_l, \delta_a, q_l, q_a, k, r_T, r_M, \mu, c)$ , define

$$\begin{aligned}
 \theta_1 &= k + \delta_l + \mu, \\
 \theta_2 &= kq_l + (k + \delta_l)q_a, \\
 \theta_3 &= \mu + c + \delta_a, \\
 \theta_4 &= \mu c + \delta_a(\mu + c), \\
 \theta_5 &= \mu c(\mu + c)(k + \delta_l), \\
 \theta_6 &= c\delta_a(c + \delta_a)(k + \delta_l), \\
 \theta_7 &= \delta_a\mu(\delta_a + \mu)(k + \delta_l).
 \end{aligned}$$

Then compute

$$\dot{y}_2 = r_T T_a + r_M M^* - c y_2, \quad (4.45)$$

$$\begin{aligned}
 \ddot{y}_2 &= q_a r_T \beta_T x_1 + r_M \beta_M x_2 + r_T k T_l \\
 &\quad - (\mu + c) \dot{y}_2 - \mu c y_2 - r_T (\delta_a - \mu) T_a,
 \end{aligned} \quad (4.46)$$

$$\begin{aligned}
 y_2^{(3)} &= q_a r_T \beta_T \dot{x}_1 + r_M \beta_M \dot{x}_2 + r_T \beta_T (k q_l + \mu q_a) x_1 \\
 &\quad + r_M \beta_M \delta_a x_2 - \theta_3 \ddot{y}_2 - \theta_4 \dot{y}_2 - \delta_a \mu c y_2 \\
 &\quad - r_T k (k + \delta_l - \mu) T_l,
 \end{aligned} \quad (4.47)$$

$$\begin{aligned}
 y_2^{(4)} &= q_a r_T \beta_T \ddot{x}_1 + r_M \beta_M \ddot{x}_2 + r_T \beta_T (\theta_2 + \mu q_a) \dot{x}_1 \\
 &\quad + r_M \beta_M (k + \delta_l + \delta_a) \dot{x}_2 + r_T \beta_T \mu \theta_2 x_1 \\
 &\quad + r_M \beta_M \delta_a (k + \delta_l) x_2 - (\theta_3 + k + \delta_l) y_2^{(3)} \\
 &\quad - (\theta_4 + \theta_3 (k + \delta_l)) \ddot{y}_2 - (\delta_a \mu c + \theta_4 (k + \delta_l)) \dot{y}_2 \\
 &\quad - (k + \delta_l) \delta_a \mu c y_2.
 \end{aligned} \quad (4.48)$$

The remaining nine parameters can therefore be computed from any persistently exciting trajectory  $y(t)$  such that  $\text{rank } \partial(y_2^{(4)}, \dots, y_2^{(12)}) / \partial(\delta_l, \delta_a, q_l, q_a, k, r_T, r_M, \mu, c) = 9$ .

That is, if

$$\text{rank} \begin{bmatrix} \psi_1 & \psi_2 & \psi_3 & \dots & \psi_8 & \psi_9 \\ \dot{\psi}_1 & \dot{\psi}_2 & \dot{\psi}_3 & \dots & \dot{\psi}_8 & \dot{\psi}_9 \\ \vdots & \vdots & \vdots & \dots & \vdots & \vdots \\ \psi_1^{(8)} & \psi_2^{(8)} & \psi_3^{(8)} & \dots & \psi_8^{(8)} & \psi_9^{(8)} \end{bmatrix} = 9,$$

where,

$$\begin{aligned}
 \psi_1 &= r_T \beta_T q_a (\dot{x}_1 + \mu x_1) + r_M \beta_M (\dot{x}_2 + \delta_a x_2) \\
 &\quad - y_2^{(3)} - \theta_3 \ddot{y}_2 - \theta_4 \dot{y}_2 - \delta_a \mu c y_2, \\
 \psi_2 &= r_M \beta_M (\dot{x}_2 + (k + \delta_l) x_2) - y_2^{(3)} \\
 &\quad - (\theta_4 + c) \ddot{y}_2 - \theta_5 \dot{y}_2 - (k + \delta_l) \mu c y_2, \\
 \psi_3 &= r_T \beta_T k (\dot{x}_1 + \mu x_1), \\
 \psi_4 &= r_T \beta_T (\ddot{x}_1 + \theta_1 \dot{x}_1 + \mu (k + \delta_l) x_1), \\
 \psi_5 &= r_T \beta_T (q_l + q_a) (\dot{x}_1 + \mu x_1) + r_M \beta_M (\dot{x}_2 + \delta_a x_2) \\
 &\quad - y_2^{(3)} - \theta_3 \ddot{y}_2 - \theta_4 \dot{y}_2 - \delta_a \mu c y_2, \\
 \psi_6 &= \beta_T (q_a \ddot{x}_1 + (\theta_3 + \mu q_a) \dot{x}_1 + \mu \theta_3 x_1), \\
 \psi_7 &= \beta_M (\ddot{x}_2 + \delta_a (k + \delta_l) x_2), \\
 \psi_8 &= r_T \beta_T (q_a \dot{x}_1 + \theta_3 x_1) - y_2^{(3)} \\
 &\quad - (k + \delta_l + \mu + \delta_a) \ddot{y}_2 - \theta_6 \dot{y}_2 - (k + \delta_l) \delta_a c y_2, \\
 \psi_9 &= -y_2^{(3)} - (\delta_a + \theta_1) \ddot{y}_2 - \theta_7 \dot{y}_2 - (k + \delta_l) \delta_a \mu y_2.
 \end{aligned}$$

System  $\Sigma_E$  (4.37) can be shown to be algebraically identifiable, and all fifteen parameters can be computed for measurements of the uninfected CD4<sup>+</sup> T cells, the viral load and uninfected macrophages, if

$$r_T \beta_T \beta_M k q_l q_a (k - q_l) (k + \delta_l - \delta_a) \neq 0,$$

$$\delta_a \neq c \quad \text{and} \quad c \neq \mu.$$

Again, bearing in mind that the infected cells are a small portion of the total cell count, then in most instances where it is not possible to obtain discriminatory macrophage and CD4<sup>+</sup> T cell count measurements, one can take the total cell count as representative of the uninfected cells.

### **Identifiability with viral load and discriminatory CD4<sup>+</sup> T cell count measurements**

Considering that macrophage measurements are currently more difficult to obtained compared to discriminatory CD4<sup>+</sup> T cell count measurements, one option would be to measure the actively infected CD4<sup>+</sup> T cells instead of the uninfected macrophages.

Setting

$$y_1 = T, \quad y_2 = V, \quad y_4 = T_a, \quad \text{and} \quad x_1 = y_1 y_2,$$

then outputs  $y_1$ ,  $y_2$  and  $y_4$  have observability indices  $r_1 = 1$ ,  $r_2 = 3$  and  $r_4 = 2$ , respectively. Identifiability of parameters  $s_M$ ,  $d_M$  and  $\beta_M$  is as presented earlier in this

section 4.5.3. For identifiability of the remaining twelve parameters, define

$$\begin{aligned}\Delta_1 &= \frac{\dot{y}_2}{y_2} - d_M - \beta_M y_2, \\ \Delta_2 &= \ddot{y}_2 - r_T \dot{y}_4 + (\mu + c) \dot{y}_2 - r_T \mu y_4 + \mu c y_2,\end{aligned}$$

and compute

$$\dot{y}_2 = r_T y_4 + r_M M^* - c y_2, \quad (4.49)$$

$$\ddot{y}_2 = r_T \dot{y}_4 + r_T \mu y_4 - (\mu + c) \dot{y}_2 - \mu c y_2 + r_M \beta_M y_2 M, \quad (4.50)$$

$$\begin{aligned}y_2^{(3)} &= r_T \ddot{y}_4 - (\mu + c + d_M) \ddot{y}_2 + r_T (\mu + d_M) \dot{y}_4 \\ &\quad - (\mu c + d_M (\mu + c)) \dot{y}_2 + r_T d_M \mu y_4 \\ &\quad - (d_M \mu c - r_M \beta_M s_M) y_2 + \left( \frac{\dot{y}_2}{y_2} - \beta_M y_2 \right) \Delta_2.\end{aligned} \quad (4.51)$$

Then the seven parameters  $(r_T, r_M, \mu, c, s_M, d_M, \beta_M)$  in (4.51) can be computed from any persistently exciting trajectory  $y(t)$  such that

$\text{rank } \partial(y_2^{(3)}, \dots, y_2^{(9)}) / \partial(r_T, r_M, \mu, c, s_M, d_M, \beta_M) = 7$ . That is, if

$$\text{rank} \begin{bmatrix} v_1 & s_M v_6 & v_2 & v_3 & r_M v_6 & v_4 & v_5 \\ \dot{v}_1 & s_M \dot{v}_6 & \dot{v}_2 & \dot{v}_3 & r_M \dot{v}_6 & \dot{v}_4 & \dot{v}_5 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ v_1^{(6)} & s_M v_6^{(6)} & v_2^{(6)} & v_3^{(6)} & r_M v_6^{(6)} & v_4^{(6)} & v_5^{(6)} \end{bmatrix} = 7,$$

where,

$$\begin{aligned}v_1 &= \ddot{y}_4 + (\mu \Delta_1) \dot{y}_4 - \mu \Delta_1 y_4, \\ v_2 &= -\ddot{y}_2 + r_T \dot{y}_4 - (c - \Delta_1) \dot{y}_2 - r_T \Delta_1 y_4 + \Delta_1 c y_2, \\ v_3 &= -\ddot{y}_2 - (\mu - \Delta_1) \dot{y}_2 + \Delta_1 \mu y_2, \\ v_4 &= -\ddot{y}_2 + r_T \dot{y}_4 - (\mu + c) \dot{y}_2 + r_T \mu y_4 - \mu c y_2, \\ v_5 &= (r_M s_M + \Delta_2) y_2, \\ v_6 &= \beta_M y_2.\end{aligned}$$

However, the above matrix only has rank = 6, and therefore not all the seven parameters can be estimated. It can be shown that one needs prior knowledge of either  $s_M$  or  $r_M$  in order to determine the other six parameters.

For the still remaining parameters  $(\delta_l, \delta_a, q_l, q_a, k)$ , compute

$$\dot{y}_4 = q_a \beta_T x_1 + k T_l - \delta_a y_4, \quad (4.52)$$

$$\begin{aligned}\ddot{y}_4 &= q_a \beta_T \dot{x}_1 + \beta_T (k q_l + (k + \delta_l) q_a) x_1 \\ &\quad - (k + \delta_l + \delta_a) \dot{y}_4 - \delta_a (k + \delta_l) y_4.\end{aligned} \quad (4.53)$$

The five parameters can be computed from any persistently exciting trajectory  $y(t)$  such that

$$\text{rank } \partial(\dot{y}_4, \dots, y_4^{(6)})/\partial(\delta_l, \delta_a, q_l, q_a, k) = 5.$$

That is, if

$$\text{rank} \begin{bmatrix} \phi_1 & \phi_2 & \phi_1 + \beta_T q_a x_1 & \beta_T k x_1 & \phi_1 \\ \dot{\phi}_1 & \dot{\phi}_2 & \dot{\phi}_1 + \beta_T q_a \dot{x}_1 & \beta_T k \dot{x}_1 & \dot{\phi}_3 \\ \ddot{\phi}_1 & \ddot{\phi}_2 & \ddot{\phi}_1 + \beta_T q_a \ddot{x}_1 & \beta_T k \ddot{x}_1 & \ddot{\phi}_3 \\ \phi_1^{(3)} & \phi_2^{(3)} & \phi_1^{(3)} + \beta_T q_a x_1^{(3)} & \beta_T k x_1^{(3)} & \phi_3^{(3)} \\ \phi_1^{(4)} & \phi_2^{(4)} & \phi_1^{(4)} + \beta_T q_a x_1^{(4)} & \beta_T k x_1^{(4)} & \phi_3^{(4)} \end{bmatrix} = 5,$$

where,

$$\begin{aligned} \phi_1 &= -\dot{y}_4 + \beta_T q_l x_1 - \delta_a y_4, \\ \dot{\phi}_1 &= -\dot{y}_4 - (k + \delta_l) y_4, \\ \phi_3 &= \beta_T (\dot{x}_1 + (k + \delta_l) x_1). \end{aligned}$$

However, the above matrix has rank  $< 5$ , and therefore not all five remaining parameters can be estimated. One needs prior knowledge of either  $\delta_l$ ,  $q_l$  or  $k$  in order to determine the other four parameters. The system is therefore not algebraically identifiable if the viral load, uninfected and actively infected CD4<sup>+</sup> T cell counts are the measured outputs.

To test for geometric identifiability of the remaining parameters, use (4.50) and (4.52)

$$\begin{aligned} \ddot{y}_2 &= r_T \dot{y}_4 + r_T \mu y_4 \\ &\quad - (\mu + c) \dot{y}_2 - \mu c y_2 + r_M \beta_M y_2 M, \\ \dot{y}_4 &= q_a \beta_T x_1 + k T_l - \delta_a y_4. \end{aligned}$$

to generate a 7<sup>th</sup> equation for the  $y_2$  dynamics and a 5<sup>th</sup> equation for the  $y_4$  dynamics. The system is geometrically identifiable if the viral load, the uninfected and actively infected CD4<sup>+</sup> T cells counts are the measured outputs. The initial measurements for the latently infected CD4<sup>+</sup> T cells,  $T_l$  and uninfected macrophages,  $M$  will also be required.

For the output options considered in this section, measuring the actively infected CD4<sup>+</sup> T cells instead of the uninfected macrophage cells significantly reduces the number of required measurements, even though the system is no longer algebraically identifiable. This illustrates that, improving the identifiability property of a system does not necessarily imply a reduction in the required number of measurements. More importantly, the point that is being illustrated here is that, careful consideration of what needs to be measured is necessary. Table 4.3 summarizes the results for when various model variables are the measured outputs.

Table 4.3: Minimum number of measurements for the extended model  $\Sigma_{Emp}$ .

Measured	Property	$T$	$T_l$	$T_a$	$M$	$M^*$	$V$	Total
$T, V$	Geometric	15	1	1	1	1	17	36
$T, M, V$	Algebraic	11	0	0	11	0	13	35
$T, T_a, V$	Geometric	5	1	6	1	1	10	24

#### 4.5.4 When to Take Measurements

If either one of the measured outputs  $y_1, y_2$  or  $y_3$  is constant, the higher order derivatives will be zero and parameter extraction from the measured outputs will not be possible. When one therefore, considers the variation of the model variables with time as depicted in Figure 4.13, then one can see that the measured outputs are constant for the asymptomatic stage. It has been observed that for HIV infected individuals, the viral load remains relatively constant during this long asymptomatic stage, while the  $CD4^+$  T cell count slowly declines. This means that measurements should be taken during the acute infection stage and during the advanced stage of the HIV infection.

For individuals in the asymptomatic stage of the infection, one then needs to use antiretroviral drugs to perturb the quasi-steady state. When measurements are taken during the acute infection stage of the infection, then the assumption that the measured total  $CD4^+$  T cell count is representative of the uninfected cell population does not hold. This will necessitate for discriminatory  $CD4^+$  T cell measurements to be the standard practice, unless antiretroviral agents are again used, but in this case to reduce the proportion of infected cells in the total cell count.

#### 4.5.5 Identifiability With the Use of Antiretroviral Agents

It has again been observed that in the short period following the initiation of therapy, the  $CD4^+$  T cell count does not change much [90, 179]. Therefore, during this short period, a complete determination of all the parameters will not be possible. Another point worth noting is that, current assays do not differentiate between infectious and noninfectious virus particles. That is,  $V_{tot} = V_i + V_n$  is the measured viral load. It would be better then, for parameter estimation purposes, if reverse transcriptase inhibitors were exclusively used when measurements are taken.

A summary of the model parameters that are affected by therapy has been presented in Table 3.3 in section 3.10.

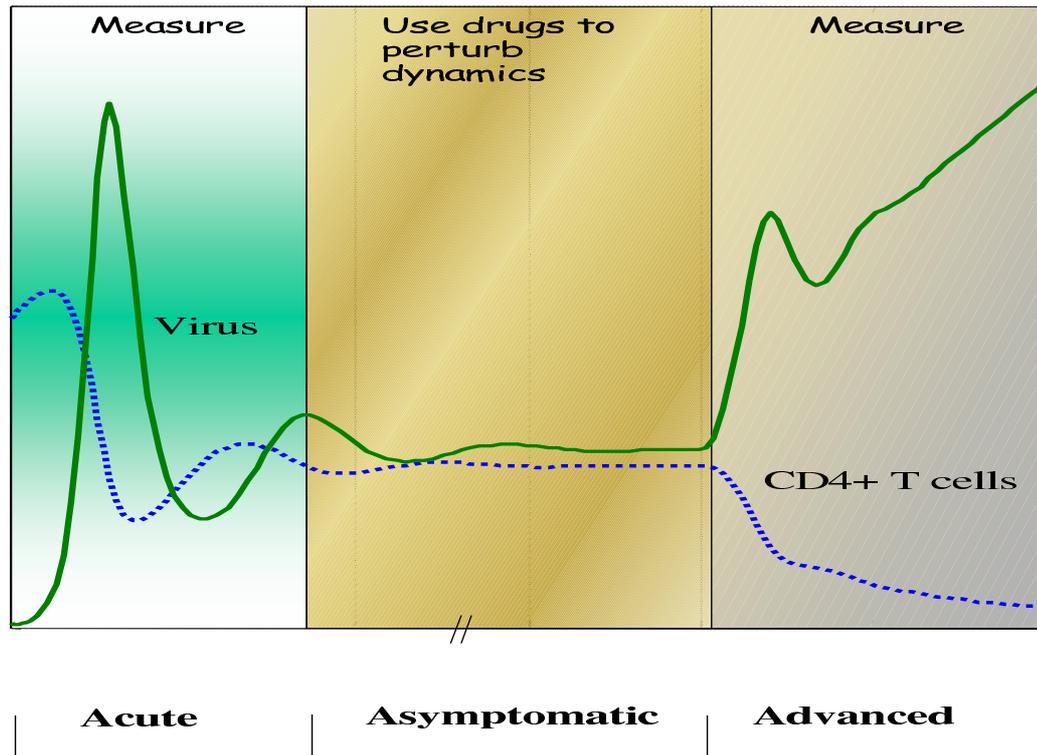


Figure 4.13: When to take measurements.

For parameter identifiability under the use of antiretroviral agents, the effect of the drugs will affect the identification of the affected model parameters. In fact, for the models  $\Sigma_{Lnp}$  (4.36) and  $\Sigma_{Enp}$  (4.37), with the use of replication cycle based reverse transcriptase and protease inhibitors, the identifiable parameters will be the composite parameters. That is,  $\eta_{rt}q_l$ ,  $\eta_{rt}q_a$ ,  $\eta_{pi}r_T$ ,  $\alpha_{rt}\eta_{rt}q_M$  and  $\alpha_{pi}\eta_{pi}r_M$  would be obtainable, instead of the original parameters  $q_l$ ,  $q_a$ ,  $r_T$ ,  $q_M$  and  $r_M$ . This means that the drug control effect or efficacy can not be separated from the parameter it affects.

The same holds when immune based therapies are used.

It would be better when using replication cycle based therapies, to use reverse transcriptase inhibitors exclusively. Protease inhibitors increase the proportion of non-infectious virus particles in the measured viral.

#### 4.5.6 Conclusions

In this section, a nonlinear system identifiability theory has been applied to analyze the identifiability properties of some HIV/AIDS models. The intention was to investigate the possibility of simultaneously estimating all the model parameters from measured system outputs, such as the viral load and CD4<sup>+</sup> T cell count. Other issues addressed

include the minimum number of measurements for a complete first approximation of all parameters, the timing and the conditions under which such measurements can be taken.

The extended system  $\Sigma_{Enp}$  given by equation (4.37) is identifiable with proper measurements. The identifiability property of the system has been analyzed when various system variable combinations are taken as the measured outputs.

- System  $\Sigma_{Enp}$  is geometrically identifiable when the viral load and the uninfected CD4<sup>+</sup> T cells are the measured system outputs. That is, it is possible to obtain all 16 model parameters from viral load and uninfected CD4<sup>+</sup> T cell count measurements if the initial conditions for both the latently and actively infected CD4<sup>+</sup> T cells, and both the uninfected and infected macrophages are known.
- System  $\Sigma_{Enp}$  is algebraically identifiable when the viral load, the uninfected CD4<sup>+</sup> T cells and the uninfected macrophages are the measured system outputs. It is therefore possible to obtain all model parameters from the measured system outputs.
- System  $\Sigma_{Enp}$  is geometrically identifiable when the viral load, the uninfected CD4<sup>+</sup> T cells and actively infected CD4<sup>+</sup> T cells are the measured system outputs. It is possible to obtain all the model parameters from the measured system outputs if the initial conditions for both the latently infected CD4<sup>+</sup> T cells, and both the uninfected and infected macrophages are known.

This shows that careful consideration of what should be to measured is necessary.

If antiretroviral drugs are used when measurements are taken, then composite parameters  $\eta_{rt}q_l$ ,  $\eta_{rt}q_a$ ,  $\eta_{pi}r_T$ ,  $\alpha_{rt}\eta_{rt}q_M$  and  $\alpha_{pi}\eta_{pi}r_M$  would be obtainable, instead of the original parameters  $q_l$ ,  $q_a$ ,  $r_T$ ,  $q_M$  and  $r_M$ .

This information will be useful for the eventual parameter estimation, as well as for formulating guidelines for clinical practice.

## 4.6 Model Reduction

The HIV/AIDS models analyzed in this thesis have been shown to be identifiable with proper measurements (refer to section 4.5), and the conditions that apply have been outlined. However, there are too many parameters to be identified, and in some cases, too many measurements would be required to obtain these parameters for some medical settings. The model reduction exercise was carried out to reduce the total number of parameters and lessen the eventual cost of the parameter estimation. However, the resulting or composite parameter set must have clinical significance or meaning.

### 4.6.1 Residualization of the Latently Infected Cell Model

Reduction of the latently infected cell model  $\Sigma_{Lnp}$ (4.36) without proliferation as it was presented and analyzed in section 4.5 will be carried out. The model is re-presented here for ease of reference as:

$$\frac{dT}{dt} = s_T - d_T T - \beta_T TV \quad (4.54)$$

$$\frac{dT_l}{dt} = q_l \beta_T TV - k T_l - \delta_l T_l \quad (4.55)$$

$$\frac{dT_a}{dt} = q_a \beta_T TV + k T_l - \delta_a T_a \quad (4.56)$$

$$\frac{dV}{dt} = r_T T_a - cV \quad (4.57)$$

Equations (4.54) - (4.57) are a minimal realization of the system. The Jacobians at some operating point  $\bar{\mathbf{x}} = [T^o, T_l^o, T_a^o, V_i^o]^T$  are given by

$$\mathbf{A} = \begin{bmatrix} -(d_T + \beta_T V_i^o) & 0 & 0 & -\beta_T T^o \\ q_l \beta_T V_i^o & -(\delta_l + k) & 0 & q_l \beta_T T^o \\ q_a \beta_T V_i^o & k & -\delta_a & q_a \beta_T T^o \\ 0 & 0 & r_T & -c \end{bmatrix}$$

The eigenvalues of matrix  $\mathbf{A}$  are the solutions to

$$(\lambda + c)(\lambda + \delta_a)(\lambda + k + \delta_l)(\lambda + d_T + \beta_T V_i^o) - r_T \beta_T T^o (\lambda + d_T)(q_l k - q_a(\lambda + k + \delta_l)) = 0$$

When suppressive therapy is initiated at the asymptomatic stage, then for a typical parameter estimate set in table A.3,

$$0 < r_T \beta_T T^o q_l k < 0.005$$

The eigenvalues can therefore be approximated very well by

$$\bar{\lambda}_1 = -c; \bar{\lambda}_2 = -\delta_a; \bar{\lambda}_3 = -(k + \delta_l); \bar{\lambda}_4 = -d_T$$

From all the available parameter estimates,

$$\bar{\lambda}_1 < \bar{\lambda}_2 < \bar{\lambda}_3 < \bar{\lambda}_4$$

The dynamics of  $T_l$  and  $T$  are much slower than those of  $V$  and  $T_a$ , hence  $T_l$  and  $T$  can be residualized.

Note that residualizing the slower transients  $T_l$  and  $T$  is equivalent to assuming that their values remain constant for some time after therapy is initiated, as has been observed in practice. A residualization can be obtained by setting  $\frac{dT_l}{dt}$  and  $\frac{dT}{dt}$  to zero to obtain

$$T = \frac{s_T}{d_T + \beta_T V} \quad (4.58)$$

$$T_l = \frac{q_l \beta_T s_T V}{(d_T + \beta_T V)(k + \delta_l)} \quad (4.59)$$

A second order approximation of the full order system is therefore given by

$$\frac{dV}{dt} = r_T T_a - cV \quad (4.60)$$

$$\frac{dT_a}{dt} = \frac{\beta_T s_T}{(d_T + \beta_T V)} \left( q_l \frac{k}{k + \delta_l} + q_a \right) V - \delta_a T_a \quad (4.61)$$

and has non trivial steady states given by

$$V_{ss} = \frac{s_T r_T}{c \delta_a} \left( q_l \frac{k}{k + \delta_l} + q_a \right) - \frac{d_T}{\beta_T} \quad (4.62)$$

$$T_{a,ss} = \frac{c}{r_T} V_{ss} \quad (4.63)$$

The nonlinear term in Equation (4.61) can be expanded to give

$$\frac{dT_a}{dt} = \frac{\beta_T s_T}{d_T} \left( q_l \frac{k}{k + \delta_l} + q_a \right) V \left( 1 - \frac{\beta_T}{d_T} V + \dots \right) - \delta_a T_a \quad (4.64)$$

and when the higher order terms are ignored, the reduced order system can be linearized as

$$\frac{dV}{dt} = r_T T_a - cV \quad (4.65)$$

$$\frac{dT_a}{dt} = \frac{\beta_T s_T}{d_T} \left( q_l \frac{k}{k + \delta_l} + q_a \right) V - \delta_a T_a \quad (4.66)$$

This linearized system's characteristic equation is given by

$$\lambda^2 + (c + \delta_a)\lambda + c \delta_a (1 - R_0) = 0 \quad (4.67)$$

where

$$R_0 = \frac{\beta_T s_T r_T}{c \delta_a d_T} \left( q_l \frac{k}{k + \delta_l} + q_a \right) \quad (4.68)$$

is the basic reproductive number [85] and defined as the number of secondary infections resulting from one infected T cell. At steady state, then on average, only one secondary infection results per infected  $CD4^+$  T cell. That is,  $R_{0(ss)} = 1$ .

### 4.6.2 Response Time Estimation with Reduced Model

Medically, the viral load is considered to be controllable if the antiretroviral drugs in use can reduce the viral load by 90% or by 1 log<sub>10</sub> scale, in 8 weeks from when treatment is initiated and continue to suppress it to below 50 copies per milliliter of plasma in less than 6 months [1]. The time taken from when therapy is initiated to reduce the viral load by 90% is here referred to as the response time,  $t_{res}$  and the time taken to suppress the viral load to below 50 copies is the suppression time,  $t_{sup}$ . Similarly, the time from when suppressive therapy is terminated to when the viral load rebounds to more than 50 copies is referred to as the rebound time,  $t_{reb}$ . This section only estimates the response and suppression times  $t_{res}$  and  $t_{sup}$  when therapy is initiated at the asymptomatic stage of the infection.

Equations (4.65) and (4.66) under combined antiretroviral therapy are expressed as

$$\frac{dV}{dt} = u_{pi}r_T T_a - cV \quad (4.69)$$

$$\frac{dT_a}{dt} = \frac{u_{rt}\beta_T s}{d} \left( q_l \frac{k}{k + \delta_l} + q_a \right) V - \delta_a T_a \quad (4.70)$$

where  $u_{pi} = (1 - \eta_{pi})$  is the control effort for the protease inhibitors used, while  $u_{rt} = (1 - \eta_{rt})$  is for the reverse transcriptase. For a reduction in viral load therefore, as is the case with effective therapy, the clearance rate of the virus must exceed its replication rate [85]. This means that

$$c > \frac{u\beta_T s r_T}{\delta_a d_T} \left( q_l \frac{k}{k + \delta_l} + q_a \right)$$

where  $u = u_{rt}u_{pi}$  is the combined control effect of the drug combination used and  $0 \leq u \leq 1$ . The system is therefore stable and its eigenvalues are

$$\lambda_{1,2} = \frac{-c - \delta_a \pm \sqrt{(c + \delta_a)^2 - 4c\delta_a(1 - R_{0(u)})}}{2}$$

where

$$R_{0(u)} = uR_{0(ss)} = u$$

is the number of secondary infections resulting from an infected CD4<sup>+</sup> T cell under therapy.

The solution for the viral load  $V(t)$  for equations (4.69) and (4.70) has the form

$$V(t) = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} \quad (4.71)$$

where

$$A_1 = \frac{\lambda_2}{\lambda_2 - \lambda_1} \bar{V} \quad (4.72)$$

$$A_2 = \frac{\lambda_1}{\lambda_1 - \lambda_2} \bar{V} \quad (4.73)$$

and  $\bar{V}$  could be the steady state or viral load measurement before therapy.

A first estimate for the response time to therapy as well as the time to suppress the viral load can be obtained by solving equation (4.71). In order to do that, one only needs to know the death rate of the actively infected  $CD4^+$  T cells  $\delta_a$ , the clearance rate of the virus  $c$ , as well as the reproductive number  $R_{0(u)}$ . It is interesting to note that these three parameter estimates are attainable. For how to estimate  $\delta_a$ ,  $c$  and  $R_{0(u)}$  from viral load measurements under therapy, refer to [84, 85, 90]. Methods for obtaining parameter estimates by using control theory techniques are presented in [62, 64, 66].

The estimation error due to residualization is bounded [175]. If one assumes that the absolute error in time estimation is constant for high enough drug efficacies, including  $u = 0$ , (even though perfect inhibition of virus replication is not practically attainable) then, this could be utilized to derive an expression for the difference in time estimates due to residualization. For  $u = 0$ , the equations for the residualization difference model are given by

$$\frac{dV_r}{dt} = r_T T_{ar} - cV_r \quad (4.74)$$

$$\frac{dT_{ar}}{dt} = -\delta_a T_{ar} + kT_{lr} \quad (4.75)$$

$$\frac{dT_{lr}}{dt} = -kT_{lr} - \delta_l T_{lr} \quad (4.76)$$

These equations are linear and the solution for the residualization difference in viral load  $V_r(t)$  has the form

$$V_r(t) = B_1 e^{\gamma_1 t} + B_2 e^{\gamma_2 t} + B_3 e^{\gamma_3 t} \quad (4.77)$$

where

$$\gamma_1 = -\delta_a; \quad \gamma_2 = -(k + \delta_l); \quad \gamma_3 = -c$$

and

$$B_1 = \frac{\gamma_1}{\gamma_2 - \gamma_1} \frac{\gamma_3}{\gamma_3 - \gamma_1} \bar{V} \quad (4.78)$$

$$B_2 = \frac{\gamma_1}{\gamma_1 - \gamma_2} \frac{\gamma_3}{\gamma_3 - \gamma_2} \bar{V} \quad (4.79)$$

$$B_3 = \frac{\gamma_1}{\gamma_1 - \gamma_3} \frac{\gamma_3}{\gamma_2 - \gamma_3} \bar{V} \quad (4.80)$$

Time estimates can be obtained by adding Equations (4.71) and (4.77) and solving for  $t_{res}$  and  $t_{sup}$ . This however, would increase the number of required parameters to include a not readily attainable estimate for the combined rate  $k + \delta_l$ , at which latently infected

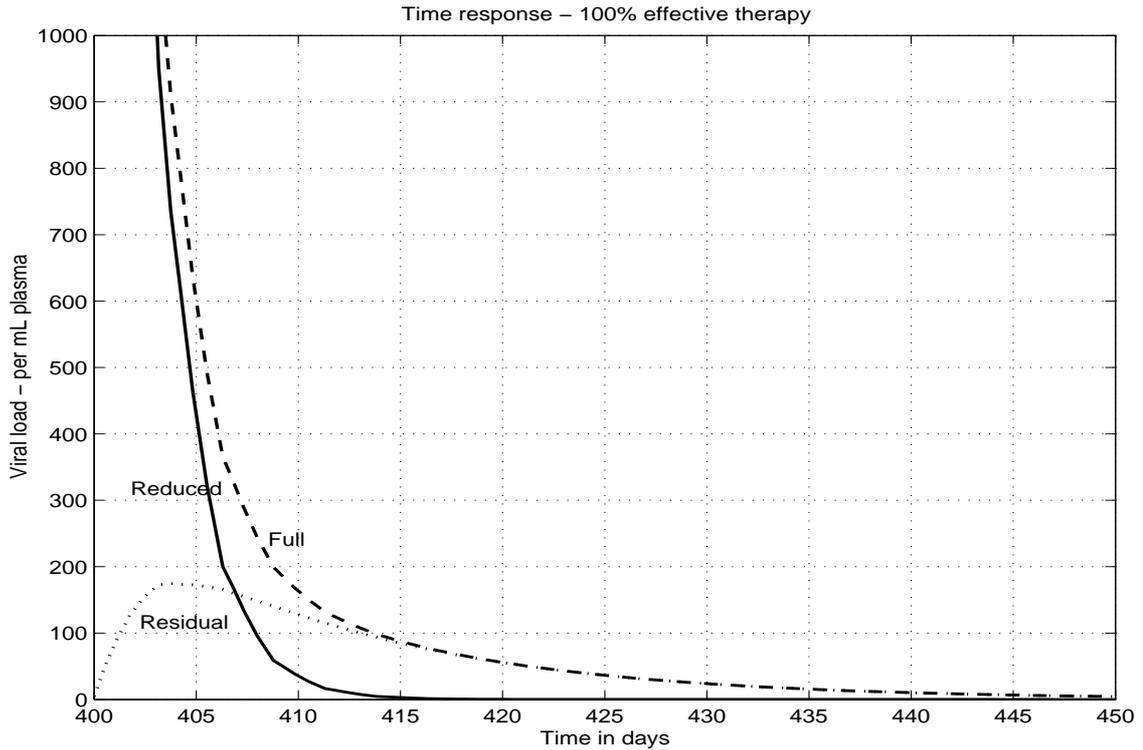


Figure 4.14: Viral load time response for  $u = 0$ . Full (4D nonlinear), reduced (2D linear) and difference(residual) models. Viral load at start of therapy is 5000 copies per mL plasma. Parameters are in Table A.3.

$CD4^+$  T cells are cleared from plasma. Figure 4.14 shows the viral load time response for when perfect inhibition is assumed for the full, reduced and difference models.

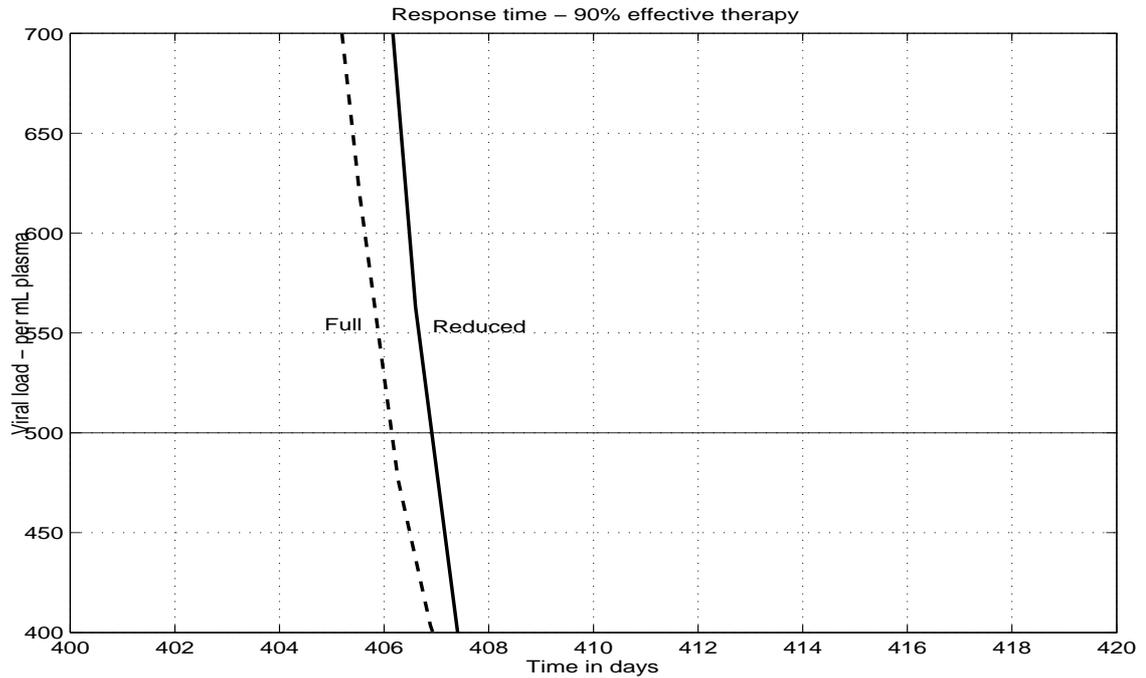
An alternate approach is to consider that simulations show that the differences in response and suppression time estimates due to residualization can be approximated as

$$dif_{res} = t_{res}/R_0 \quad (4.81)$$

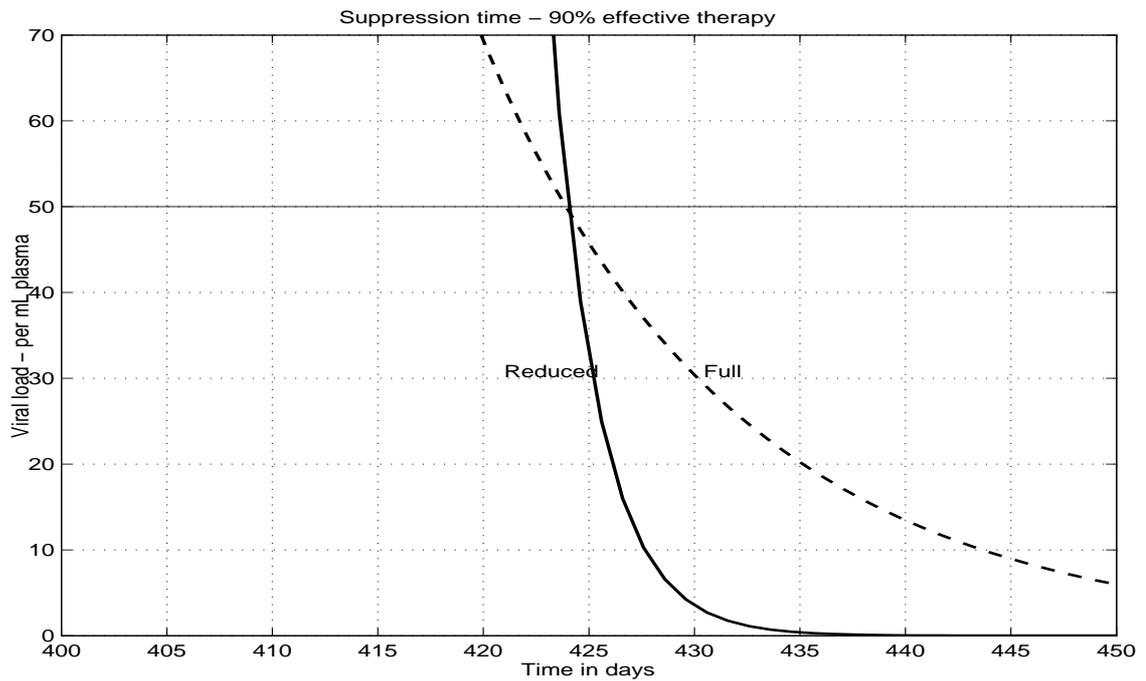
$$dif_{sup} = t_{sup}(1 + 1/R_0) \quad (4.82)$$

where  $R_0$  can be obtained. This means that residualization differences in time estimates can be obtained if the basic reproductive number is known, by adding the respective difference to the appropriate solution of equation (4.71).

Figures 4.15, 4.16 and 4.17 show the response and suppression time graphs for the full and the reduced order systems when therapy is on and varying drug efficacies are used. Table 4.4 summarizes the results for the response time estimates, with the associated absolute errors in brackets. Table 4.5 does likewise for the suppression time estimates.

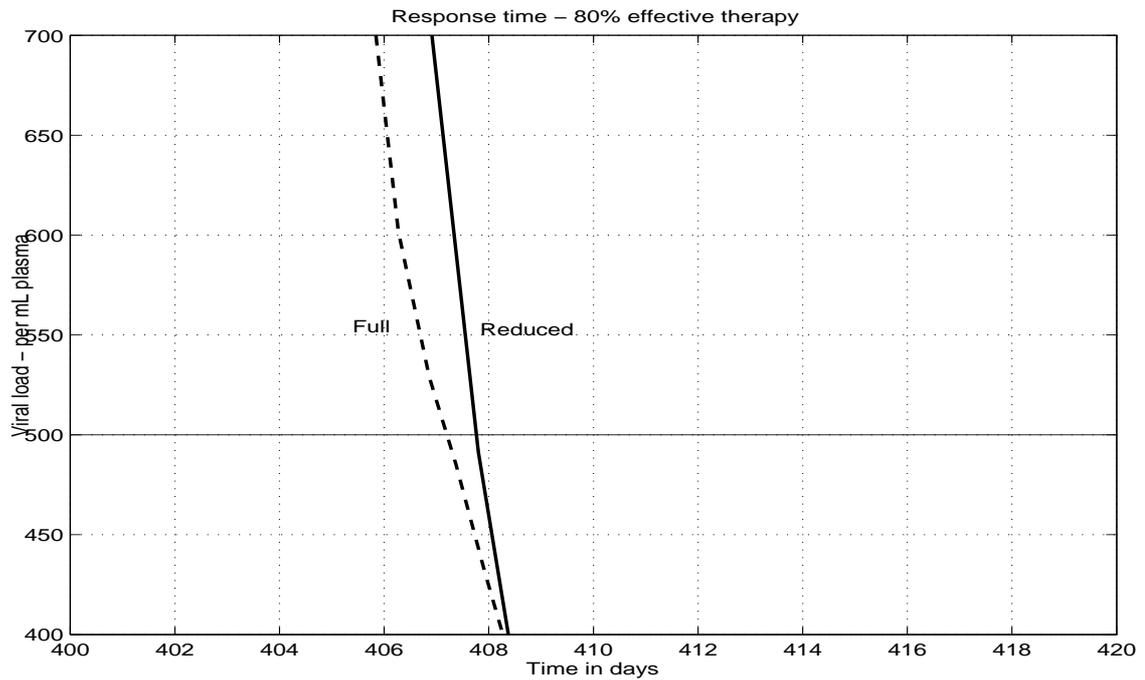


(a)

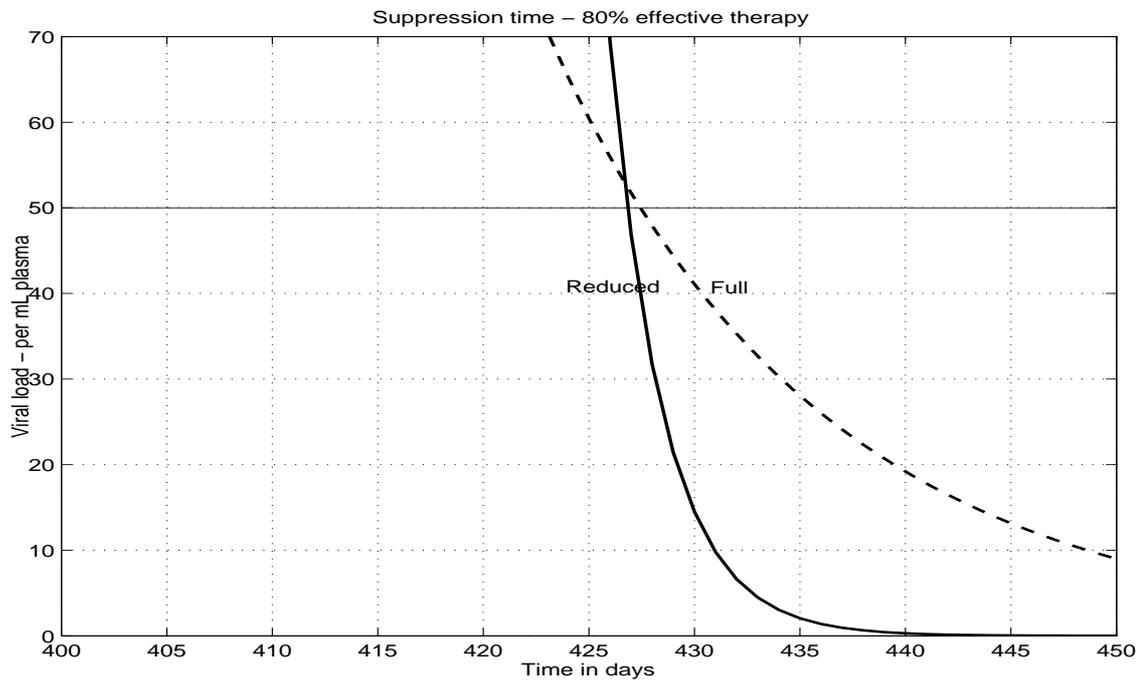


(b)

Figure 4.15: Response and suppressions times for full (4D nonlinear) and reduced (2D linear) order systems: chemotherapy effectiveness: 90% ( $u = 0.1$ ). Viral load at start of therapy (day 400) is 5000 copies per mL plasma. Parameters are in Table A.3.

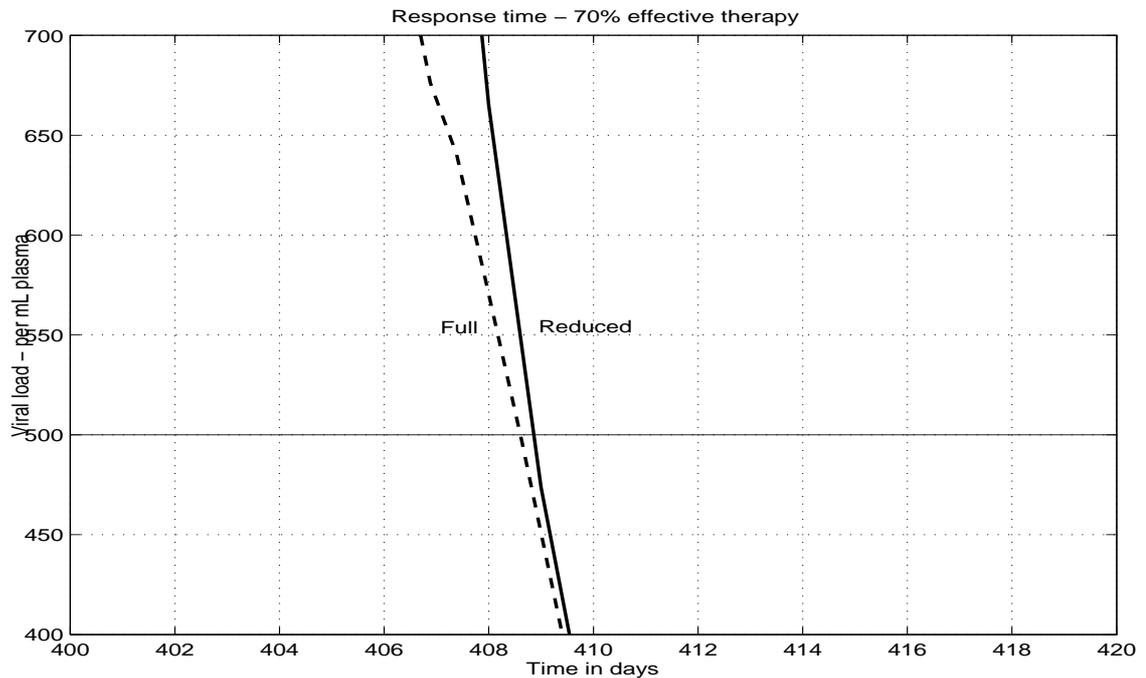


(a)

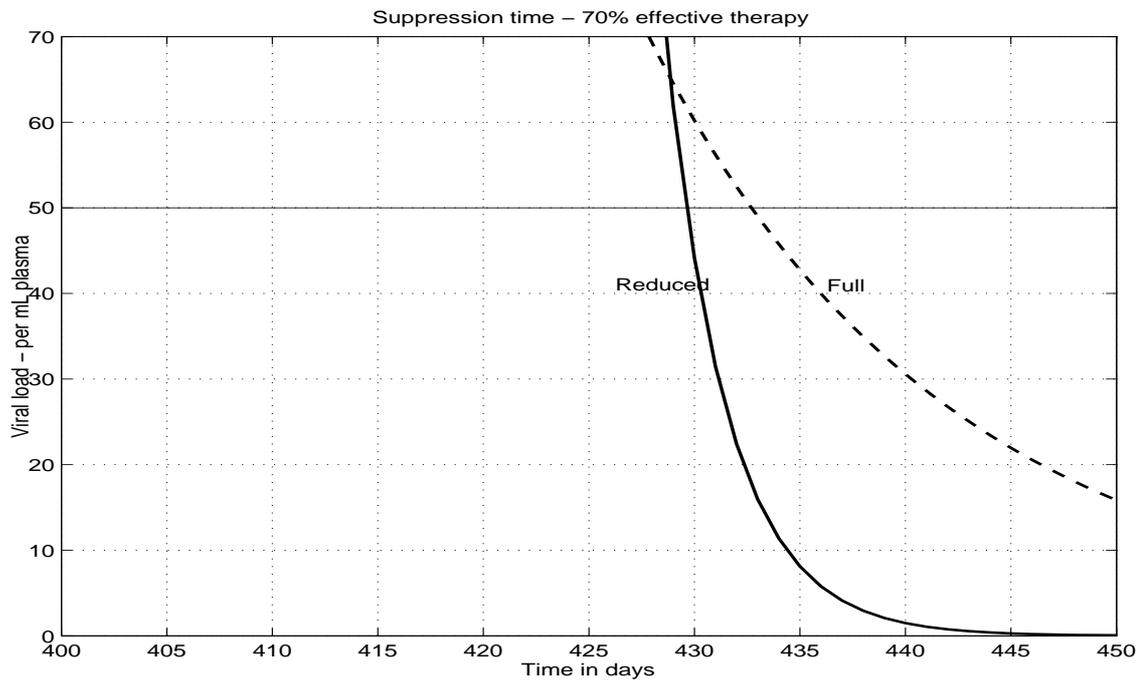


(b)

Figure 4.16: Response and suppression times for full (4D nonlinear) and reduced (2D linear) order systems: chemotherapy effectiveness: 80% ( $u = 0.2$ ). Viral load at start of therapy (day 400) is 5000 copies per mL plasma. Parameters are in Table A.3.



(a)



(b)

Figure 4.17: Response and suppression times for full (4D nonlinear) and reduced (2D linear) order systems: chemotherapy effectiveness: 70% ( $u = 0.3$ ). Viral load at start of therapy (day 400) is 5000 copies per mL plasma. Parameters are in Table A.3.

Table 4.4: Response times

Control $u$ (%effect)	Full system days	Reduced days(error)
0.05 (95%)	6	7 (1)
0.10 (90%)	6	7 (1)
0.15 (85%)	7	8 (1)
0.20 (80%)	7	8 (1)
0.25 (75%)	8	9 (1)
0.30 (70%)	9	9 (0)

Table 4.5: Suppression times

Control $u$ (%effect)	Full system days	Reduced days(error)
0.05 (95%)	23	23 (0)
0.10 (90%)	24	24 (0)
0.15 (85%)	26	25 (-1)
0.20 (80%)	28	26 (-2)
0.25 (75%)	30	28 (-2)
0.30 (70%)	33	29 (-4)

### 4.6.3 Conclusions

The following conclusions can be drawn from this study.

1. Estimates for the response time to therapy and the time to suppress the viral load, can be determined from values for the death rate of the actively infected CD4<sup>+</sup> T cells  $\delta_a$ , the clearance rate of the virus  $c$ , the drug efficacy  $u$  and either, the basic reproductive number  $R_0$ , or the combined rate  $k + \delta_l$  at which latently infected CD4<sup>+</sup> T cells are cleared from plasma.
2. The time estimates are parameter dependent and will therefore vary from one individual to the other.
3. The estimated response times, unlike the suppression times, do not exhibit any significant variation with drug efficacy.
4. The initial response is heavily influenced by the virus clearance rate constant  $c$ , which is much larger than the actively infected CD4<sup>+</sup> T cell clearance rate constant  $\delta_a$ .
5. The estimated suppression times are shorter than the actual suppression times. When designing a therapy based on the estimates, the drug dosage is always

- conservative. In some of the cases of HIV patients, this is desirable.
6. The error in suppression time estimation increases with decreasing drug efficacy. This is because the perfect inhibition assumption used to determine the difference in estimation due to residualization, does not hold for low drug efficacies.
  7. This approach enables the determination of the drug efficacy in order to obtain predetermined response and suppression times.
  8. This approach can be incorporated into an interruptible control strategy for the viral load.
  9. Viral response and suppression time estimates can aid clinicians in scheduling therapy and viral load measurements.

## 4.7 Chapter Summary

Linear analytical tools were used in some sections of this chapter to derive approximate solutions. The approximate solutions that were obtained, or the predictions that were made from the linear analysis were verified by applying them to the nonlinear model. Since the response was usually as expected or predicted, one can conclude that the linear solution gives a very good approximation.

The following is a summary of the antiretroviral issues that have been addressed by the model analysis that was carried out in this chapter.

### 4.7.1 Persistent Virus Replication under HAART

The continuous virus replication that has been observed under potent HAART is because the currently used antiretroviral agents are not capable of completely inhibiting virus replication in all the virus producing compartments. However, if the reported virus replication occurs elsewhere and not in the  $CD4^+$  T cells, then this suggests that the drugs' efficacy at least equals that required for a zero viral load steady state, as given by equation (4.14).

### 4.7.2 Variable Response to Therapy

Results from the steady state analysis in section 4.1 indicate that antiretroviral therapy moves the viral load from the pre-treatment value to a treatment steady state. This steady state is drug efficacy and parameter dependent, and will therefore, vary from one individual to the other, given the same drug efficacy. However, the treatment steady state is independent of when therapy is initiated during the course of the infection.

The dependence of the treatment steady states on the model parameters and drug efficacy suggests that if the said model parameters and drug efficacy are known, then it is possible to assess whether or not the individuals viral load can be suppressed to below detectable levels, as well as to determine the individual's operating therapeutic range. This steady state analysis can conversely, be used to determine the drug efficacy required in order to attain and maintain a certain degree of viral load suppression.

The analysis therefore, provides some insight on the issue of variability in response between individuals on the same regimen. The study confirms previous observations that, for a fixed drug efficacy, this variation in response to therapy between individuals is due to inter-individual variations in parameters.

Results from the transient response analysis in section 4.2 show that the transition from the pre-treatment viral load to the treatment steady state is generally oscillatory. The magnitude and frequency of these oscillations are parameter, drug efficacy and timing dependent. The controllability analysis that was presented in section 4.4 shows that from a viral load controllability perspective, some stages of the HIV infection are more controllable than others. The transition from the pre-treatment viral load to the treatment steady state will therefore depend on when therapy is initiated. The transient response and controllability analysis therefore, collectively suggest that a particular individual can have variable response to antiretroviral therapy depending on when therapy is initiated.

### **4.7.3 Transient Viral Load Rebounds or Virologic Failure?**

As discussed before, for a fixed drug efficacy, the transition from the pre-treatment viral load to the treatment steady state is generally oscillatory. The viral load will therefore transiently oscillate about the treatment steady state before settling. When therapy is initiated therefore, the viral load will initially be suppressed to a value that is below the treatment steady state, then rebound to a value above this treatment steady state, before settling. Viral load rebounds are therefore, from a treatment steady state perspective, all transient.

As the viral load oscillates about the steady state value, some oscillations will be larger than others and the viral load will take longer to settle in some cases, depending on the individuals parameters, drug efficacy and when therapy is initiated. However, given that the treatment steady state is independent of when therapy is initiated, it can be concluded that what a viral load rebound is indicative of, does not depend on when therapy is initiated.

This generally means that for an individual, if the drug efficacy is such that the treatment steady state will be at or above a value that is considered indicative of virologic failure, then the viral ‘blip’ will, in the clinical context, also be indicative of virologic failure. On the other hand, if the drug efficacy is such that the treatment steady state is below detectable levels, then the viral blip will be, in the clinical context again, transient.

#### 4.7.4 Indicators of Virologic and Immunologic Success

Given the preceding analysis, how can one tell in advance, what benefits an individual initiating therapy can expect to obtain, and who will fail to attain viral load suppression? On an individual basis, the attainment of maximal suppression of the viral load, as well as the duration of such suppression once attained, depend on:

1. The HIV infection stage at which therapy is initiated. This stage in turn is defined by the viral load cell count measurements at that time.
2. The virus and target cell parameters.
3. The combined efficacy of the drugs used in the regimen.

However, the maximum cell count to which the cell counts can rebound to depend on the drug efficacy.

This analysis therefore, seems to confirm the findings of some clinical studies that suggests that the virologic and immunologic conditions (viral load and T cell counts) at the start of therapy, determine the outcome of therapy. On the other hand, durable suppression depends on the treatment steady state that the given drug combination efficacy can attain. This also depends on the model parameters and is independent of when therapy is initiated. Does this then disqualify the viral load and cell counts as the indicators of virologic success?

It appears that viral load and T cell counts at the start of therapy are more indicators of virologic response than they are of virologic success. True virologic success, for a particular individual, is determined by the end point drug efficacy. And this lends support to findings that have suggested that virologic failure can be attributed to the regimen used.

It has been argued before that the basic reproductive ratio  $R_o$ , is one of the prognostic indicators of virologic success. Given that  $R_o$  is exclusively determined by the individual’s model parameters, which are in turn co-determinants of virologic success, then the argument is justified.

### 4.7.5 When Best to Initiate Antiretroviral Therapy?: Clarifying the Confusion

Results from all the preceding sections in this chapter will be analyzed together in order to determine the best time to initiate therapy during the course of the HIV infection. This will be compared with the recommendations from the guidelines, as well as outcomes of some clinical trials. Timing the initiation of therapy can be looked at from different perspectives.

#### **A maximal viral load suppression perspective:**

For a particular regimen, the maximality of viral load suppression to below the treatment steady state is highest when therapy is initiated during the early-acute, late-acute and asymptomatic stages of the infection.

#### **A durable viral load suppression perspective:**

For a truly durable suppression of the viral load, the drug efficacy should be high enough to attain a treatment steady state that is below levels of detection. The treatment steady state does not depend on when therapy is initiated.

#### **A viral load point to point controllability perspective:**

The degree of viral load controllability is highest during the mid-acute infection stage, as the viral load will reach the treatment steady state in a shorter period of time. In this case, one can know if there is need to adjust dosage sooner if viral load suppression is not attained. Also, initiating therapy at this stage will minimize viral load blips.

#### **An Immunologic success perspective:**

It appears target cells will rebound irrespective of when therapy is initiated. The maximum to which they can rebound to depends on the model parameters and drug efficacy. No conclusion on timing the initiation of therapy can be drawn from this perspective.

**A Virologic success perspective:** True virologic success is attained if the drug efficacy is such that the treatment steady state is below levels of detection.

#### **A clinical trial perspective:**

From the trial outcomes with STI for autoimmunization, the best time to initiate therapy is during the early acute infection stage.

**Guidelines recommendation:**

Not very clear. On an individual basis, the objectives range from suppressing the viral load to below detectable levels, to maintaining CD4<sup>+</sup> T cell counts at levels that are just sufficient to delay the onset of AIDS and opportunistic infections. But the guidelines are more inclined towards initiating therapy during the mid-asymptomatic stage.

**Compromise: When best to initiate?**

The compromise is objective driven and some objectives are in conflict. There is need therefore, to prioritize one's objectives in order to find an optimal solution.

**4.7.6 The Possibility of Individualizing Antiretroviral Therapy**

The bottom line is that, therapy should be individualized and objectives need to be prioritized. Then the benefits of therapy can be maximized by appropriate drug dosing to attain the desired effect as well as selecting the right time to initiate therapy. Determining the appropriate dose however, places an emphasis on the need to obtain the individual's parameter estimates.

Since the identifiability and model reduction studies have indicated the possibility of attaining the full parameters estimates from system measurements, and the reducibility of this parameter set if need be, then this affirms that it is possible to individualize antiretroviral therapy. If parameters are obtained, then one can determine the individuals therapeutic range. However, if antiretroviral drugs are used when measurements are taken, then it may not be possible to separate the drug efficacy from the model parameter that it affects.

## Chapter 5

# Drug Dosage Design

**A**NTIRETROVIRAL therapy generally entails the application of drugs in a fixed dosage regimen. A typical initial regimen would consist of 2 reverse transcriptase inhibitors - nucleoside/nucleotide (NRTI/NtRTI) as the basis of the regimen, plus either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1]. But generally, selection of an initial regimen is subject to considerations such as efficacy, toxicity, resistance profile and durability. Other issues to address, besides what regimen to start with, are when to change the initial regimen; and when deciding to change, what should the regimen be change to?

From a control theoretic point of view, HIV chemotherapy is control of a time varying nonlinear dynamical system with constrained controls. Once a suitable model has been developed or identified, control system theoretical concepts and design principles can be applied. The adopted control approach or strategy depends primarily on the control objectives, performance specifications and the control constraints. In principle, the designed control system can then be validated with clinical data.

This chapter focuses on the rational sequencing of antiretroviral drugs in order to maximize the benefits of therapy, when replication cycle based HAART (reverse transcriptase inhibitors - RTIs, protease inhibitors - PIs) and immune based therapies - IBT (Hydroxyurea - HU, Interleuken 2 - IL2) are available and therapy is initiated during the asymptomatic stage of the infection. This will be done taking into account the constraints on the admissible controls imposed by the narrow therapeutic range of the antiretroviral agents, as well as the possible emergence of drug resistant mutants with inadequate viral load suppression. The practicality of applying the derived dosage schemes to a patient will be discussed.

## 5.1 The Dynamical System to be Controlled

Equations (5.1) represent the HIV/AIDS system to be controlled. This system has been described in detail in the preceding chapters, with two notable exceptions - the parameter  $u_H$ , which takes the binary value 1 when HAART is ON, and 0 when HAART is OFF, and the parameter  $u_I$ , which takes the binary value 1 when IBT is ON, and 0 when IBT is OFF. The  $CD4^+$  T cell and macrophage counts prior to infection (pre-infection) as well as the system states at the initiation of therapy (pre-treatment/pre-HAART measurements) are presented in Table 5.2. Model parameters are re-presented in Table 5.1 for ease of reference.

$$\Sigma_{Eco} = \begin{cases} \frac{dT}{dt} &= s_T + (1 - u_I \eta_{ps}) p T (1 - \frac{T}{T_m}) - d_T T - \beta_T T V_i \\ \frac{dT_l}{dt} &= (1 - u_H \eta_{rt}) q_l \beta_T T V_i - (1 + u_I \eta_{da}) \delta_l T_l - k T_l \\ \frac{dT_a}{dt} &= (1 - u_H \eta_{rt}) q_a \beta_T T V_i - (1 + u_I \eta_{da}) \delta_a T_a + k T_l \\ \frac{dM}{dt} &= s_M - d_M M - \beta_M M V_i \\ \frac{dM^*}{dt} &= (1 - u_H \alpha_{rt} \eta_{rt}) \beta_M M V_i - \mu M^* \\ \frac{dV_i}{dt} &= (1 - u_H \eta_{pi}) r_T T_a + (1 - u_H \alpha_{pi} \eta_{pi}) r_M M^* - c V_i \\ \frac{dV_n}{dt} &= u_H \eta_{pi} r_T T_a + u_H \alpha_{pi} \eta_{pi} r_M M^* - c V_n \end{cases} \quad (5.1)$$

Table 5.1: Parameter estimates

Parameter	Value	Parameter	Value
$s_T$	$10^4 \text{ mL}^{-1} \text{ day}^{-1}$	$s_M$	$150 \text{ mL}^{-1} \text{ day}^{-1}$
$d_T$	$0.01 \text{ day}^{-1}$	$d_M$	$0.005 \text{ day}^{-1}$
$\beta_T$	$4.5 \times 10^{-8} \text{ mL day}^{-1}$	$\beta_M$	$1.75 \times 10^{-8} \text{ mL day}^{-1}$
$p$	$0.02 \text{ day}^{-1}$	$q_M$	1
$T_m$	$10^6 \text{ mL}^{-1}$	$\mu$	$0.05 \text{ day}^{-1}$
$q_l$	0.005	$r_M$	$35 \text{ cell}^{-1} \text{ day}^{-1}$
$q_a$	0.55	$\alpha_{rt}$	0.85
$\delta_l$	$0.01 \text{ day}^{-1}$	$\alpha_{pi}$	0.55
$\delta_a$	$0.5 \text{ day}^{-1}$		
$k$	$0.025 \text{ day}^{-1}$		
$r_T$	$240 \text{ cell}^{-1} \text{ day}^{-1}$	$c$	$5 \text{ day}^{-1}$

[46, 71, 50, 176]

$u_H$	0	Off HAART
	1	On HAART
$u_I$	0	Off IBT
	1	On IBT

Table 5.2: System states prior to infection and at the initiation of therapy

Variable	Value	Note
<b>Pre-infection</b>		
$T(0)$	$10^6 \text{ mL}^{-1}$	CD4 <sup>+</sup> T cell count
$M(0)$	$3 \times 10^4 \text{ mL}^{-1}$	Macrophage cell count
<b>Pre-treatment/Pre-HAART</b>		
$\bar{T}$	$4.08 \times 10^5 \text{ mL}^{-1}$	Uninfected CD4 <sup>+</sup> T cell count
$\bar{T}_l$	$1.54 \times 10^3 \text{ mL}^{-1}$	Latently infected CD4 <sup>+</sup> T cell count
$\bar{T}_a$	$1.19 \times 10^4 \text{ mL}^{-1}$	Actively infected CD4 <sup>+</sup> T cell count
$\bar{M}$	$9.85 \times 10^3 \text{ mL}^{-1}$	Uninfected macrophage cell count
$\bar{M}^*$	$2.02 \times 10^3 \text{ mL}^{-1}$	Infected macrophage cell count
$\bar{V}_i$	$5.94 \times 10^5 \text{ mL}^{-1}$	Infectious viral load
$\bar{V}_n$	0	Non-infectious viral load

Figure 5.1 shows the control system block diagram where the patient's virus and host cell dynamics are modelled by (5.1). The model is known to have some inaccuracies and there are some un-modelled dynamics. The model parameters are also inaccurate and are also thought to change as the infection progresses.

It is clear from the illustrations in figure 5.1 that there are many issues that need to be addressed or taken into consideration when designing a controller. There are disturbances, many sources of error and generally much uncertainty in the system. Furthermore, the objectives of therapy are multiple and conflicting.

In essence then, one has to design a drug regimen that optimizes a performance criterion, and also explores future dosing and sampling scenarios in advance. Besides optimizing performance, the intention should also be to optimize the process of learning about the patient. All this has to be done while having to treat the patient at the same time [180].

## 5.2 Modelling Antiretroviral Drugs As Control Inputs

Administering an antiretroviral drug is equivalent to introducing an input signal that perturbs the HIV dynamics. A point to note is that these drugs are administered periodically, and that the instantaneous inhibitory effect of the antiretroviral agent is a time varying function [43, 77, 97, 182]. Furthermore, HIV drug pharmacodynamics,

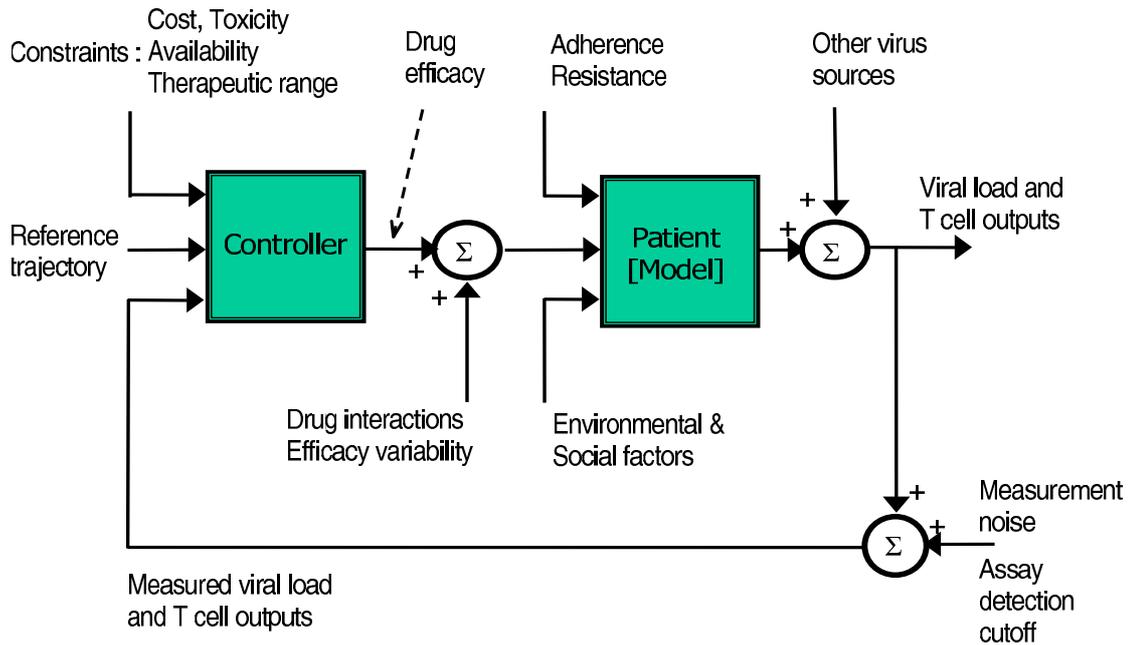


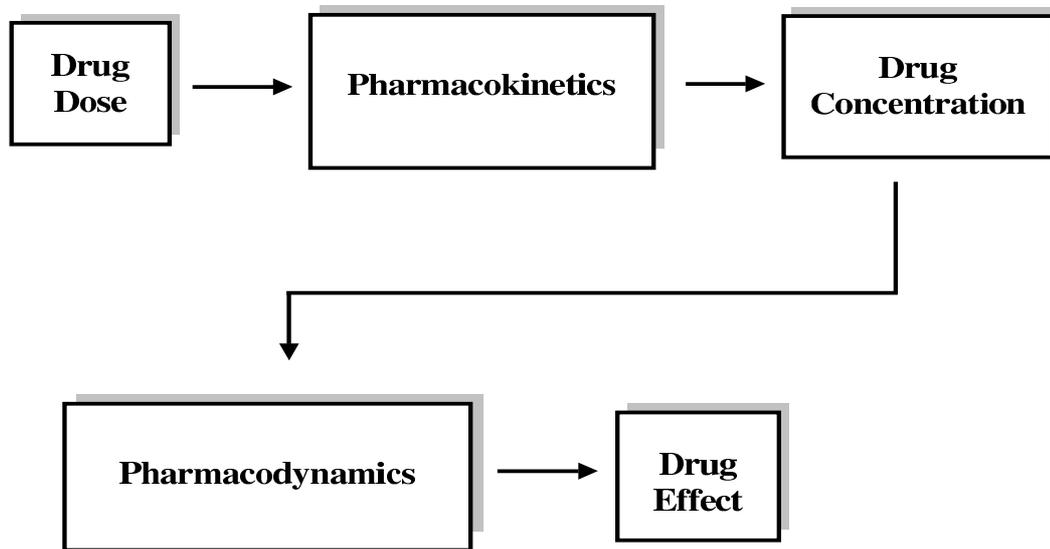
Figure 5.1: Control system block diagram.

pharmacokinetics and adverse reactions are genetically predisposed [41, 126].

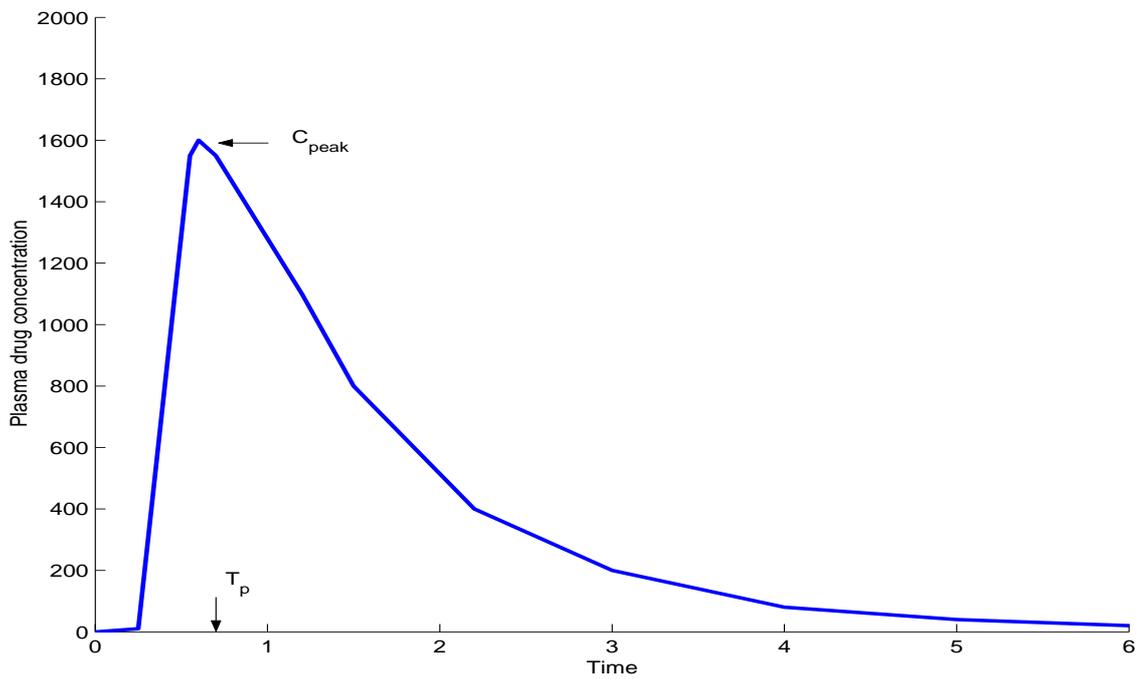
### 5.2.1 Drug Pharmacology

Drug pharmacokinetics deals with the relationship between dosage and plasma concentration of the drug, and involves the processes of absorption, distribution, metabolism and excretion of the drug. Pharmacodynamics on the other hand, deals with the relationship between the drug plasma concentration and the end point effect of the drug. For a particular drug dose, there will be inter individual variations in drug plasma concentrations. Similarly, for a particular plasma drug concentration, there will be inter individual variations in the end point effect of the drug.

The drug dosage to end effect process is illustrated in figure 5.2(a). From ingestion, the increase in plasma drug concentration is determined by the rate at which the drug enters the plasma by absorption and simultaneously removed from plasma by either distribution to other body compartments or by elimination. A peak concentration, as illustrated in figure 5.2(b), is reached when there is a balance between the entry and removal rates of the drug into and out of the plasma. Thereafter, the drug plasma concentration declines because the combined rate at which it is distributed and elimi-



(a)



(b)

Figure 5.2: (a) Drug dosage to end effect process [181]. (b) Single dose plasma drug concentration variation [177].  $C_{peak}$  : peak drug concentration,  $T_p$  : time to reach peak concentration.

Table 5.3: Suggested minimum target trough concentrations for persons with wild-type HIV-1

Drug	Concentration (ng/mL)
Amprenavir (Agenerase)	400
Indinavir (Crixivan)	100
Lopinavir/ritonavir (Kaletra)	1000
Nelfinavir (Viracept) <sup>a</sup>	800
Ritonavir (Norvir) <sup>b</sup>	2100
Saquinavir (Fortovase, Invirase)	100–250
Efavirenz (Sustiva)	1000
Nevirapine (Viramune)	3400

Reproduced from [1].

nated exceeds the rate at which it is absorbed [177]. The expression for the plasma drug concentration for a single dose can be represented as

$$\text{conc}_0(t) = a_0(e^{-t/\tau_x} - e^{-t/\tau_a}) \tag{5.2}$$

where  $\tau_x$  and  $\tau_a$ ,  $\tau_x > \tau_a$  are the respective elimination and absorption time constants, and  $a_0$  is drug and dosage dependent.

Figure 5.3(a) shows how the plasma drug concentration is expected to vary between multiple doses. This actually is the accumulation of all the single dosages taken at specified intervals and can be expressed as

$$\text{conc}(t) = \sum_{i=0}^{n-1} a_i(e^{-(t-t_i)/\tau_x} - e^{-(t-t_i)/\tau_a}) \tag{5.3}$$

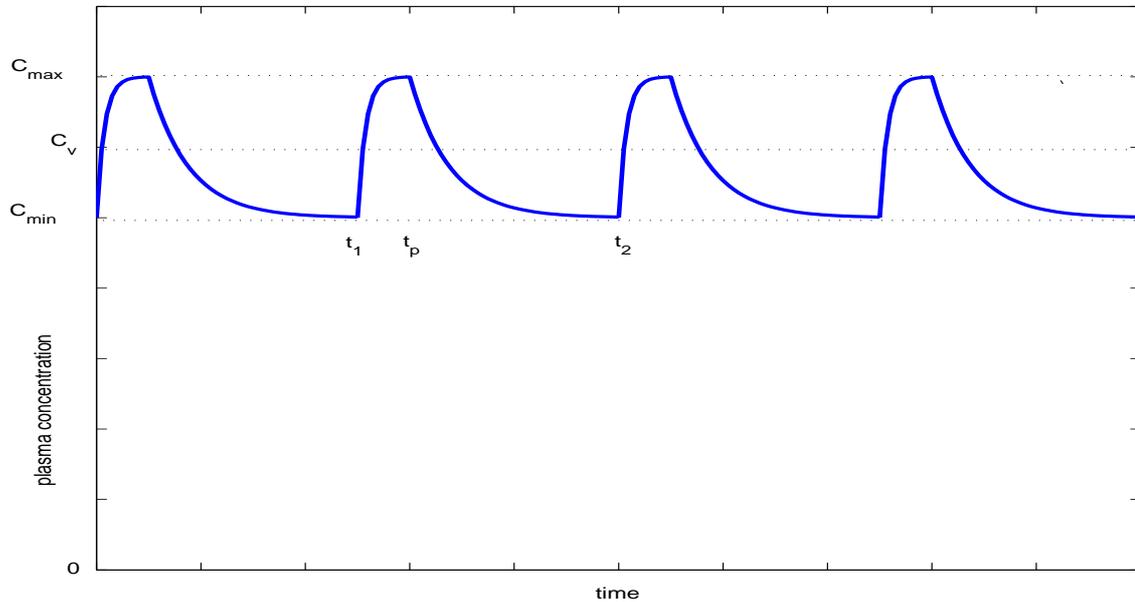
where  $t_i$  is the instance when the dosage is administered.

Table 5.3 presents a summary of the recommended minimum concentrations for some antiretroviral drugs [1].

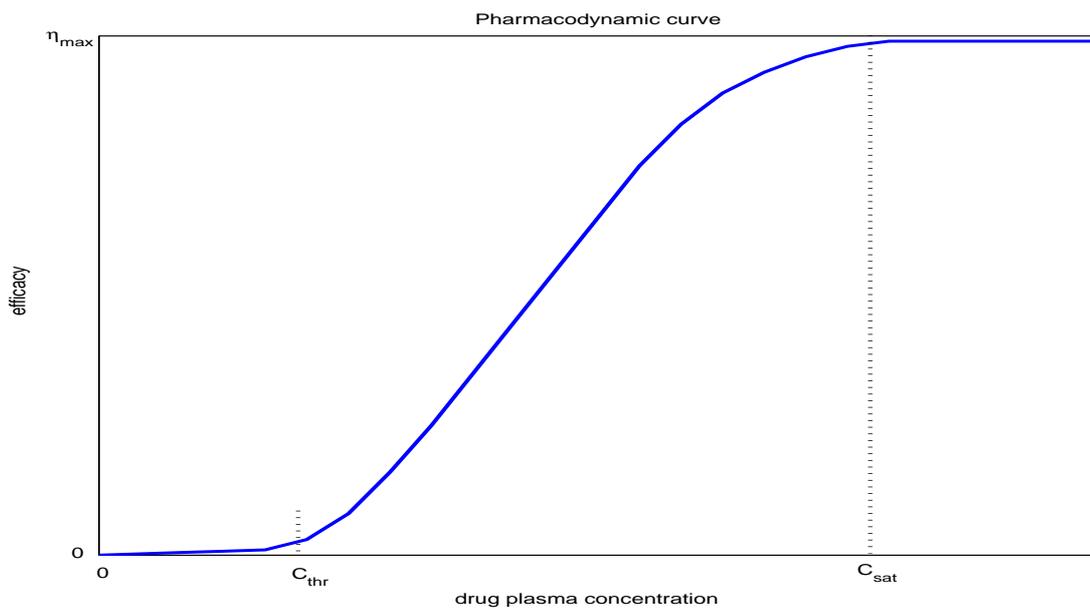
If one assumes that the plasma concentration of a drug at a particular point in time is an indication of the efficacy or instantaneous inhibition of virus replication by the drug, as illustrated in figure 5.3(b), then the variation of the drug’s efficacy  $\eta(t)$  over one dosing cycle can be approximated as

$$\eta(t) = \begin{cases} \eta_v + \eta_w(\frac{1}{2} - e^{-(t-t_1)/\tau_r}), & t_1 \leq t \leq t_p \\ \eta_v + \eta_w(e^{-(t-t_p)/\tau_d} - \frac{1}{2}), & t_p < t < t_2 \end{cases} \tag{5.4}$$

where  $\eta_w$  is the difference between the upper and lower efficacy bounds,  $\eta_v$  is the average efficacy value, while  $\tau_r$  and  $\tau_d$  are the rise and decay time constants after each dose.



(a)



(b)

Figure 5.3: (a) Plasma drug concentration variation with time for multiple doses.  $C_{max}$  : maximum concentration,  $C_v$  : average concentration,  $C_{min}$  : minimum concentration. (b) Drug pharmacodynamics: Variation of end point drug efficacy with drug plasma concentration.  $\eta_{max}$  : maximum attainable efficacy,  $C_{thr}$  : threshold drug concentration,  $C_{sat}$  : saturation drug concentration.

Refer to, for example, [95, 183] for the relationship between plasma drug concentration and efficacy, and to [173] for a summary of the clinical pharmacokinetic properties of some antiretroviral drugs. Techniques to estimate the instantaneous inhibitory effect from end point data are proposed in [182]. The drug efficacy is therefore an oscillatory function of time. If however, the interval between dosing, or the release mechanism of the drug is such that the variation between the peak drug concentration and the minimum concentration is minimal, then the average value  $a_v$  in equation (5.4) gives a good approximation of the drug's efficacy over time, and the efficacy can therefore be assumed to be constant.

The drug is usually effective until the time when resistance emerges. The effectiveness  $\eta$  can also be assumed to decline exponentially with time, and the expression for  $\eta(t)$  over one cycle can be modified to

$$\eta(t) = \begin{cases} (\eta_v + \eta_w(\frac{1}{2} - e^{-(t-t_1)/\tau_r}))e^{-(t-t_i)/\tau_e}, & t_1 \leq t \leq t_p \\ (\eta_v + \eta_w(e^{-(t-t_p)/\tau_d} - \frac{1}{2}))e^{-(t-t_i)/\tau_e}, & t_p < t < t_2 \end{cases} \quad (5.5)$$

where  $t_i$  is the time when resistance emerges and the time constant  $\tau_e$  of the drug's effectiveness due to resistance is drug dependent. Alternative descriptions for the drug dosage to end point effect are available in [77, 97, 182].

Besides the development of resistance to drugs, there are other factors that can affect the end point drug efficacy, such as non-adherence to a regimen and drug-drug interactions that arise when more than one drug is taken. The reader is referred to the guidelines [1] for allowable drug combinations and drug-drug interactions between some compounds.

### 5.2.2 Therapeutic Range

Antiretroviral agents are known to have, or there are indications that they have a narrow therapeutic range [184], where the therapeutic range for a drug is the dosage range within which most patients will experience significant therapeutic effect without an undesirable degree of adverse reactions. It is therefore desirable to administer drug doses that are within this therapeutic range. However, one needs to bear in mind that the therapeutic range for a particular drug is the average for many individuals on the therapeutic trial, and that it approximates single drug therapy when the dosage is as prescribed. The combined therapeutic effect when more than one drug is used to treat a single condition needs to be considered.

A point to note is that inadequate viral load suppression, inadequate concentrations/efficacy of each class of antiretroviral agent in the regimen and the pre-existence

of drug resistant mutants are the primary reasons why drug resistance emerges [118], and not necessarily the use of low drug doses. If for a particular individual, a drug dose that is below the specified therapeutic range can adequately suppress the viral load, then there is no need to increase the dosage.

### 5.3 Prioritization of Objectives of Therapy

Eradication of HIV infection cannot be achieved with available antiretroviral regimens and now the focus has shifted from virus eradication to managing a chronic infection. Therefore, once the decision is made to initiate therapy, the primary goals of antiretroviral therapy, according to [1] are to:

- reduce HIV-related morbidity and mortality,
- improve quality of life,
- restore and preserve immunologic function, and
- maximally and durably suppress viral load.

The maximum count to which the T cells can rebound depends on the state of the immune system or the extent to which the immune system is repairable, and not necessarily on the ability of the drugs to suppress the viral load. However, it is currently not clear how one can quantify the health of the immune system, especially so for the chronically infected patient. One could intuitively, expect the health of the immune system to correlate with the source rates  $s_T$  and  $s_M$  at which uninfected CD4<sup>+</sup> T cells and macrophages are produced. However, this expectation can not be upheld because the CD4<sup>+</sup> T cell steady state value does not depend on parameter  $s_T$ , as illustrated by equation (4.1) in section 4.1.1.

Given that there are problems associated with current antiretroviral agents, therapy should ideally entail the use of minimal drug dosage schemes that reduce toxic effects, and simultaneously maximally/effectively suppress the viral load for as long as possible. However, minimal dosing and maximal suppression of the viral load are conflicting objectives. There is therefore a need to prioritize ones objectives in order to strike a balance between aggressive therapy and toxicity reduction.

Numerous clinical trial have shown that if one can suppress the viral load, there will be some degree of CD4<sup>+</sup> T cell and macrophage cell rebounds. It is therefore, more practical to aim to suppress the viral load than to try and maintain a pre-determined CD4<sup>+</sup> T cell count. That is, more emphasis should be placed on viral load control. A reference trajectory that specifies the limits to the time available to suppress the viral load from when therapy is initiated should be determined, bearing in mind that

antiretroviral drugs are generally toxic.

## 5.4 Model Predictive Control

Model Predictive Control - MPC is a technique in which the control is determined by solving, at each sampling instance, a finite-horizon optimal control problem [53]. The optimal solution is attained while respecting the constraints on the system. MPC's "constraint-tolerance" is what differentiates it from other optimal control strategies [185].

The MPC controller is a discrete-time controller and only computes the control move at regularly spaced, discrete time instants. Furthermore, the controller does not accept updates on the measured plant outputs between sampling instances. Once the optimal control sequence is computed, it is sent to the plant, but only for one sampling period. The plant operates with this constant input until the next sampling instant [185]. At the next sampling instant, the controller accepts new plant measurements and a new optimal solution is computed. It is hence, assumed that the output measurement is available when computing the control sequence.

Predictive control is model based in the sense that the controller explicitly uses an internal plant model to make predictions of future plant behaviour [186]. Model based control could therefore, be a drawback if the model or parameters are not accurate, as is the case with HIV/AIDS models. However, MPC has a certain degree of robustness to model inaccuracies [187].

### 5.4.1 Overview

The following summary of how Model Predictive Control works is a direct extraction from [186, 187]:

A predictive controller assumes a discrete time setting and the current time is referred to as  $k$ .

For a discrete system of the form  $X_{k+1} = f(X_k, u_k)$ , and a current state  $X_k$  a length  $H_u$  sequence  $U = \{u_k, u_{k+1}, \dots, u_{k+H_u-1}\}$  is derived which minimizes a cost function of the form

$$V(k) = \sum_{j=H_w}^{H_p} \|\hat{z}(k+j|k) - r(k+j|k)\|_{Q(j)}^2 + \sum_{j=0}^{H_u-1} \|\Delta\hat{u}(k+j|k)\|_{R(j)}^2$$

The cost function  $V$  penalizes deviations of the predicted controlled outputs  $\hat{z}(k+j|k)$  from a (vector) reference trajectory  $r(k+j|k)$ . The prediction horizon has length  $H_p$ , but

it is not necessary to start penalizing deviations of  $z$  from  $r$  immediately (if  $H_w > 1$ ). The prediction and control horizons  $H_p$  and  $H_u$ , the ‘window’ parameter  $H_w$ , the weights  $Q(j)$  and  $R(j)$ , and the reference trajectory  $r(k+j)$ , all affect the behaviour of the closed-loop combination of plant and predictive controller. Some of these parameters, particularly the weights, may be dictated by the economic objectives of the control system, but usually they are in effect tuning parameters which are adjusted to give satisfactory dynamic performance.

The controller has an internal model which is used to predict the behaviour of the plant, starting at the current time, over a future prediction horizon. This predicted behaviour depends on the assumed input trajectory  $\hat{u}(k+j|k)$ , ( $j = 0, 1, \dots, H_p - 1$ ) that is to be applied over the prediction horizon, and the idea is to select that input which promises the best predictive behaviour. The procedure therefore entails calculation of a control sequence minimizing an objective function, and relies on the explicit use of the model to predict the process output at future time instants. It is assumed that the output measurement  $y(k)$  is available when deciding the value of the input.

Once a future input trajectory has been chosen, only the first element of that trajectory is applied as the input signal to the plant. Then the whole cycle of output measurement, prediction and input trajectory is repeated, one sampling interval later: a new output measurement  $y(k+1)$  is obtained; a new reference trajectory  $r(k+j|k+1)$ , ( $j = 2, 3, \dots$ ) is defined; predictions are made over the horizon  $k+1+j$ , with ( $j = 1, 2, \dots, H_p$ ); a new input trajectory  $\hat{u}(k+1+j|k+1)$ , with ( $j = 0, 1, \dots, H_p - 1$ ) is chosen; and finally the next input is applied to the plant:  $u(k+1) = \hat{u}(k+1|k+1)$ . Since the prediction horizon remains the same length as before, but slides along by one sampling interval at each step, this way of controlling a plant is often called a receding horizon strategy. This concept is illustrated in figure 5.4.

Constraints of the following form are assumed to hold over the control and prediction horizons:

$$E \text{ vec}(\Delta\hat{u}(k|k), \dots, \Delta\hat{u}(k+H_u-1|k), 1) \leq \text{vec}(0)$$

$$F \text{ vec}(\hat{u}(k|k), \dots, \hat{u}(k+H_u-1|k), 1) \leq \text{vec}(0)$$

$$G \text{ vec}(\hat{z}(k+H_w|k), \dots, \hat{z}(k+H_p|k), 1) \leq \text{vec}(0)$$

It is also possible to have the converse situation, of variables which are constrained but do not appear in the cost function (*zone objectives*). This is only likely to occur with the  $z$  variables, and is represented in the standard formulation by having appropriate zero entries in the weighting matrices  $Q(j)$ .

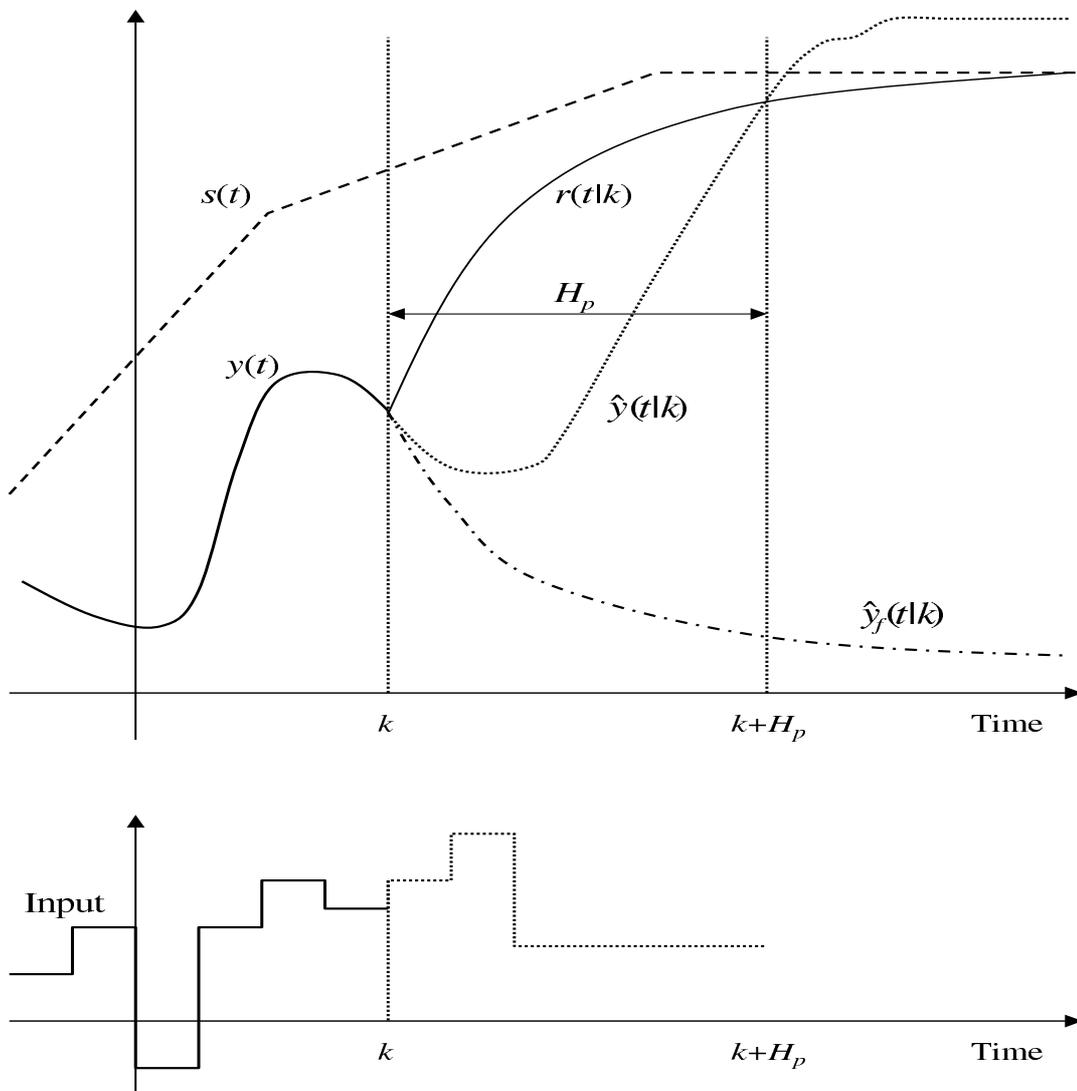


Figure 5.4: Predictive control - receding horizon concept. The current time is referred to as step time  $k$ .  $y(t)$ : plant output,  $s(t)$ : set-point trajectory,  $r(t|k)$ : reference trajectory,  $\hat{y}(t|k)$ : Assumed plant output,  $H_p$ : prediction horizon [186].

### 5.4.2 Suitability for HIV/AIDS Drug Dosage Design

MPC has many uses in drug delivery systems. [53] used MPC to derive an On/Off dosage sequence that enhances immune response to HIV infection, while [181] used MPC in a complex physiologically based drug model. MPC is attractive to use in drug delivery systems because it has a certain degree of robustness to model inaccuracies and can be easily tuned [187].

For HIV/AIDS control, MPC offers the flexibility to incorporate some clinically observed but not modelled phenomena, such as the fact that the CD4<sup>+</sup> T cell count does not usually rebound to pre-infection values, even with prolonged viral load suppression. Weights can also be adjusted to favour the use of one class of antiretroviral inhibitor over the other, and the limits for the operating therapeutic range can be directly set. The time between samples is long enough to allow for computation and an observer can be used for states that are not readily measured. MPC is easily adaptable and this allows for other improved HIV/AIDS models to be integrated as they are developed [53].

Recalculation of a new optimal control sequence at each sampling instance serves viral load control very well, since the predictions that were made during the previous optimization stage are not perfect. As illustrated in figure 5.1, the plant is subjected to various unexpected disturbances. Measurement feedback and reformulation therefore allows the controller to correct for these errors and unexpected disturbances.

MPC is therefore well suited for HIV control.

## 5.5 Sampling

After therapy is initiated, blood samples are taken after about 2-8 weeks in order to assess the initial effect of the drugs. Thereafter, guidelines call for sampling every 3-4 months to monitor for virologic failure and the emergence of resistance, as presented in Table 5.4 [1].

Clearly, the recommended measurement schedule is inadequate for feedback control. There are also indications from various studies that antiretroviral therapy should be individualized and depend on the individuals response to therapy [50, 51, 177, 184]. This in turn calls for more frequent or adequate sampling of the viral load and host cell counts. As a rule of thumb, one should sample at a rate that is 5-10 times the signal bandwidth, for feedback control [188]. However, due to the invasive nature of taking blood samples, it is desirable to keep sampling at a minimum with due consideration to patient discomfort, the need for one to avail themselves and cost.

Table 5.4: Indications for plasma HIV RNA testing

<b>Clinical Indication</b>	<b>Information</b>	<b>Use</b>
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis
Initial evaluation of newly diagnosed HIV infection	Baseline viral load set-point	Use in conjunction with CD4 <sup>+</sup> T cell count for decision to start or defer therapy
Every 3–4 months in patients not on therapy	Changes in viral load	Use in conjunction with CD4 <sup>+</sup> T cell count for decision to start therapy
2–8 weeks after initiation of or change in antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3–4 months after start of therapy	Assessment of virologic effect of therapy	Decision to continue or change therapy
Every 3–4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4 <sup>+</sup> T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

Reproduced from [1].

As stated before, there are inter-individual variations in parameter estimates. These variations in parameter values lead to variations in steady state cell counts and viral load set points from one individual to the other [171] and consequently, to inter individual variations in the response to therapy. Furthermore, these parameter ranges are very wide for some of the model parameters. This explains, in part, why some individuals have virologic failure on therapy that is highly effective on others. There is a need therefore, to determine the individual's sampling interval from one's parameters.

## 5.6 A Sequential Perturbation Approach to Dosage Design

### 5.6.1 Strategy

The strategy, in light of the objectives of therapy and the issues discussed in sections 5.1 - 5.3 is: Determine the operating therapeutic range and an appropriate sampling interval for the individual. The next step is then to design or select a desired viral load trajectory. Finally, a control input sequence to attain the desired viral load trajectory is obtained using MPC with the appropriate constraints in place. Only the use of replication cycle based HAART (RTI and PI containing regimens) will be considered in this section. That is,  $u_H = 1$ , while  $u_I = 0$ .

### 5.6.2 Objective Function and Constraints

#### Measured Outputs:

The measured outputs are taken as the uninfected CD4<sup>+</sup> T cells  $T$  and the infectious virus particles  $V_i$ .

In current practice however, discriminatory T cell count measurements are not readily attainable. The total cell count  $T_{tot} = T + T_l + T_a$  is what is measured. However, it has been observed that, under therapy, the infected cells make a very small percentage of the total T cell count. Therefore, in this case, it is reasonable to assume that  $T \simeq T_{tot}$ .

The measured viral load is also the total of the infectious and noninfectious particles, that is,  $V_{tot} = V_i + V_n$  is what is currently measured. If reverse transcriptase inhibitors are exclusively used in the regimen, then the measured viral load is the infectious virus particles, and  $V_{tot} = V_i$ . If the regimen includes protease inhibitors with a known efficacy, then one can calculate the infectious virus particles from the total measured viral load.

#### Objective Function:

The intention of therapy is to suppress the viral load as much as possible. However, given the cost and undesirable side effects of the antiretroviral drugs, it would be best if such viral load suppression is attained with the least amount of drugs. No attempt is made to control the uninfected CD4<sup>+</sup> T cell count.

The objective function is therefore selected as

$$\min J(v, \eta) = \sum_{j=1}^{N_p} \delta(j) [\hat{v}(t+j|t) - r(t+j)]^2 + \sum_{j=0}^{N_\eta-1} \lambda(j) [\eta(t+j-1)]^2 \quad (5.6)$$

where  $N_p$  is the prediction horizon and  $N_\eta$  is the control horizon. The intention is that the future viral load output ( $\hat{v}$ ) on the considered horizon should follow a determined reference trajectory ( $r$ ), and at the same time, the drug dosage ( $\eta$ ) necessary for doing so should be penalized [187].  $\delta(j)$  and  $\lambda(j)$  are weights that consider the future behaviour and are used as tuning parameters.

### Sampling Interval:

There are numerous reports of viral load rebounds for individuals on HAART, whose viral load had been previously suppressed to below detectable levels. This phenomena is referred to as viral ‘blips’ [22, 23, 25]. Some rebounds are transient, while others lead to virologic failure. Predicting the timing and frequency of these blips, as well establishing which blips are transient and which are indicative of virologic failure, is currently the subject of intense research.

A step response analysis of the system has shown that it is also possible to obtain short term viral load suppression with low drug doses due to the transient undershoot attained when therapy is initiated [104], as illustrated in figure 5.5. This figure 5.5 was generated with the nonlinear model when therapy is initiated 200 days from initial infection, using a constant low efficacy dosage. The point being made is that there is a transient undershoot after therapy is initiated and the dosage has to be adjusted before the viral load rebounds, with the arrow indicating the desired viral load direction.

The sampling interval was accordingly determined as the time to reach the undershoot, as the dosage needs to be adjusted before the viral load rebounds. The intention of the proposed sampling interval is to have as few samples as possible, with due consideration to the invasive nature of taking blood samples and patient discomfort. The sampling interval was estimated from the step response of the linearized system when therapy is initiated at the asymptomatic stage. The sampling interval thus chosen is parameter dependent and will vary from one individual to the other. For the parameter set presented in Table 5.1, the sampling interval was determined to be 15 days, ie.  $t_s = 15$  days.

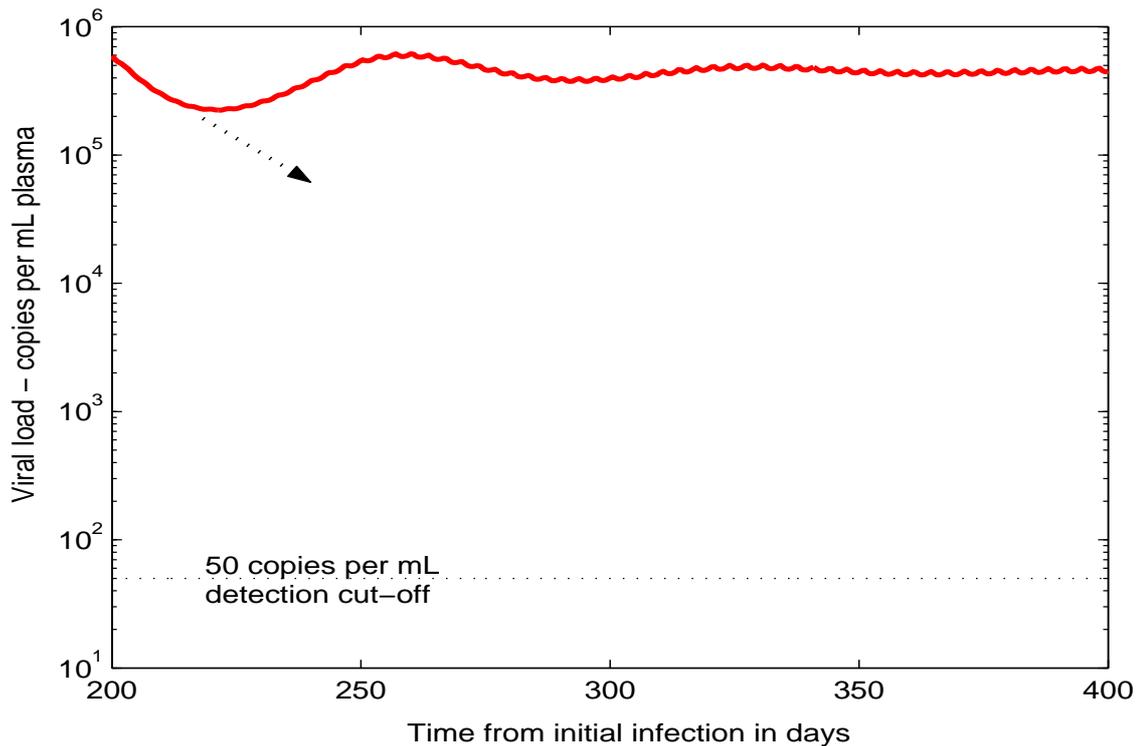


Figure 5.5: Transient effect of a fixed low efficacy dosage on viral load when therapy is initiated.

#### Prediction and Control Horizons:

Prediction was done over 120 days. With the sampling interval determined as  $t_s = 15$  days, then  $N_p = 8$  and the control horizon of  $N_\eta = 3$  was selected. This configuration is motivated by the guidelines' recommendation on plasma HIV testing (presented as Table 5.4). The guidelines call for testing 2-8 weeks after initiation of therapy for the initial assessment of drug efficacy. Thereafter, test 3-4 months after start of therapy for assessment of virologic effect of therapy and the durability of antiretroviral effect.

#### Reference Trajectory:

The desired viral load trajectory was selected based on the guidelines notion of a controllable viral load. The guidelines consider antiretroviral therapy to be effective if it can reduce the viral load by 90% in less than 8 weeks and continue to suppress it to below 50 copies per mL of plasma in less than 6 months [1].

These conditions are loosely stated, hence for this thesis, an additional requirement that such viral load suppression to below 50 copies per mL of plasma, should not be

attained before 5 months of initiating therapy is added.

The weight  $\delta(j)$ , penalizing any deviations of the viral load ( $\hat{v}$ ) from the reference trajectory ( $r$ ), was selected as the increasing function

$$\delta(j) = \sigma^{N_p - j} \quad 0 < \sigma < 1 \quad (5.7)$$

because more emphasis is placed on viral load suppression than on the initial viral load response.

### **Efficacy Constraints:**

As stated before, perfect inhibition of virus replication occurs if  $\eta = 1$ , and there is no inhibition if  $\eta = 0$ . The assumption is usually that perfect inhibition is not possible with the currently available antiretroviral agents. That is  $0 \leq \eta < 1$  for both types of inhibitors.

### **Therapeutic Range Constraints:**

The upper limit for the operating therapeutic range was determined from the steady state analysis that was carried out in section 4.1.1, as the 50 copies per mL viral load steady drug efficacy  $\eta_{sup}$  as given by equation (4.15). The rationale for selecting  $\eta_{sup}$  as the upper therapeutic range limit was presented in that section. For the parameter set presented in Table 5.1, the therapeutic limit was determined to be  $\eta_{th} = \eta_{sup} = 0.72$ . This constraint is lifted however, when only one class of inhibitor is available for use in the regimen.

### **CD4<sup>+</sup> T Cell Count Rebound:**

No attempt is made to control either the CD4<sup>+</sup> T cell or macrophage cell counts. The assumption is that cell counts will increase from their pre-treatment values. However, the CD4<sup>+</sup> T cell count under therapy can not rebound to values higher than the pre-infection steady state value. That is,  $\bar{T} \leq T \leq T(0)$  during therapy. Values for the pre-infection CD4<sup>+</sup> T cell count  $T(0)$ , the pre-treatment CD4<sup>+</sup> T cell measurement,  $T_{ss}$  and the pre-treatment viral load measurement,  $\bar{V}_i$  are presented in Table 5.2.

## **5.6.3 Dosage Sequence Design**

MPC is applied to derive the required drug efficacy input sequences for the HIV/AIDS model  $\Sigma_{Eco}$  (5.1) with multiple target cells and differential drug penetration into these cells. Only the extended cell model is used in this section because this model can realis-

Table 5.5: Summary of constraints

Type	Lower and Upper Limits	Notes
Efficacy - RTI	$0 \leq \eta_{rt} < 1$	Perfect inhibition not possible.
Efficacy - PI	$0 \leq \eta_{pi} < 1$	Perfect inhibition not possible.
Therapeutic - RTI	$\eta_{th(rt)} = 0.72$	Lower limit not established.
Therapeutic - PI	$\eta_{th(pi)} = 0.72$	Lower limit not established.
CD4 <sup>+</sup> T cell rebound	$\bar{T} \leq T \leq T(0)$	$T(0)$ : Pre-infection CD4 <sup>+</sup> T cell count.
Viral load	$0 < V_i \leq \bar{V}_i$	$\bar{V}_i$ : Pre-treatment viral load measurement.

$t_s$	15 days
$N_p$	8 (120 days)
$N_\eta$	3
$\lambda$	<b>1</b>

tically simulate low viral loads under potent HAART. The assumption is that both the reverse transcriptase and protease inhibitors are available for therapy.

- Since MPC normally requires a linear discrete-time controller, the extended model  $\Sigma_{Eco}$  (5.1) was first linearized, then discretized to obtain the internal controller model.
- The nonlinear plant was maintained as is given by system  $\Sigma_{Eco}$  (5.1).
- The applicable constraints are summarized in Table 5.5.

### 5.6.4 Results

For dosage sequence design, the algorithm presented in the preceding section was implemented using Matlab. Unless otherwise stated, parameters and constraints are as presented in Table 5.1 and Table 5.5.

As a bench mark, dosage efficacy sequences were derived with no therapeutic range constraints. That is, when  $0 \leq \eta_{rt} < 1$ ,  $0 \leq \eta_{pi} < 1$  was the only constraint on the inputs. Simulations were performed for a prediction horizon of 120 days and 3 control moves ( $N_p = 8$  and  $N_\eta = 3$ ). The results are presented in figures 5.6 and 5.7.

Please note that mono class therapy does not necessarily imply the use of a single inhibitor as in mono drug therapy. An example of mono class therapy is the currently

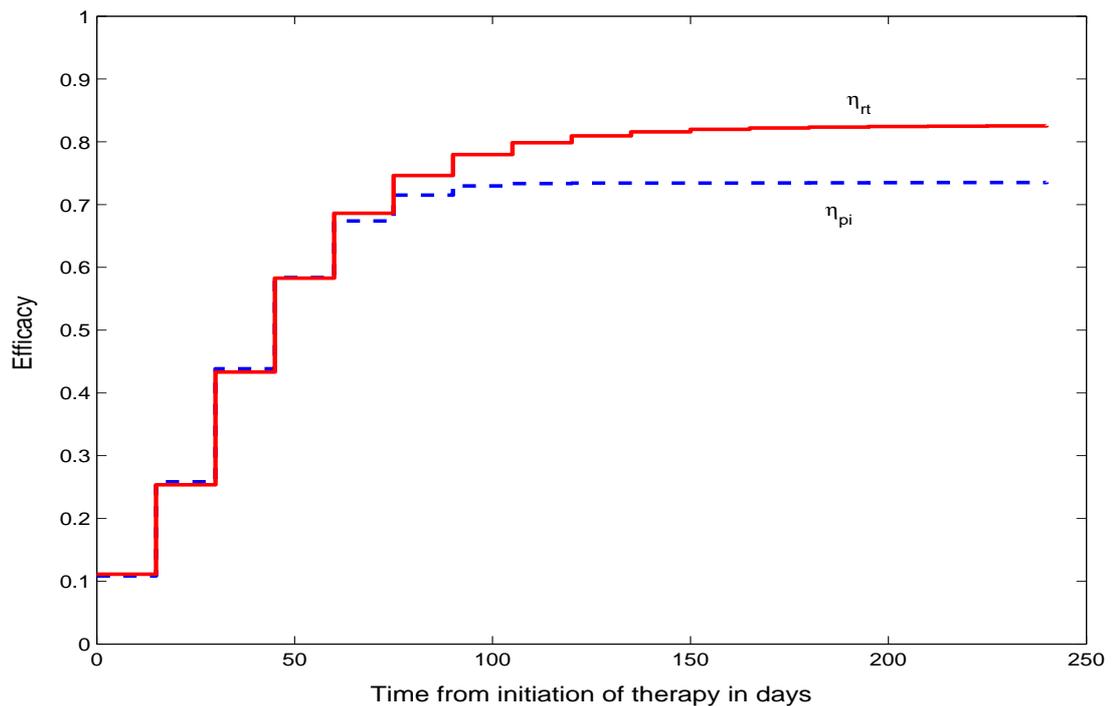


Figure 5.6: Control input sequence for mono (single) class therapy with no therapeutic range constraint.  $\eta_{rt}$  : RTI efficacy;  $\eta_{pi}$  : PI efficacy. Sampling interval  $t_s=15$  days.

used 2NRTI plus 1NNRTI regimen consisting of didanosine, lamivudine and efavirenz [1], where all drugs are from the reverse transcriptase class of antiretroviral agents.

For mono class therapy, figure 5.6 suggests that from an end point efficacy perspective, protease inhibitors are slightly better than reverse transcriptase inhibitors at controlling the infectious viral load because the end efficacy for the PIs is less than than of the RTIs. This is understandable when one considers that under reverse transcriptase inhibitors, the viral load is exclusively infectious, while the viral load is split between infectious and noninfectious types when protease inhibitors are used. However, care should be taken not to confuse a lower end point efficacy of an inhibitor to automatically imply a lower pill intake.

When both classes of inhibitors are available or used in the regimen, then for this combined therapy, figure 5.7 shows that for an individual with a typical set of parameters as in Table 5.1, the resulting dosage efficacy sequence suggests starting therapy with a low efficacy reverse transcriptase inhibitor, and sequentially increasing the efficacy over time. The protease inhibitors are later added to the regimen. The protease inhibitor efficacy also starts low, then is sequentially increased while the reverse transcriptase inhibitors

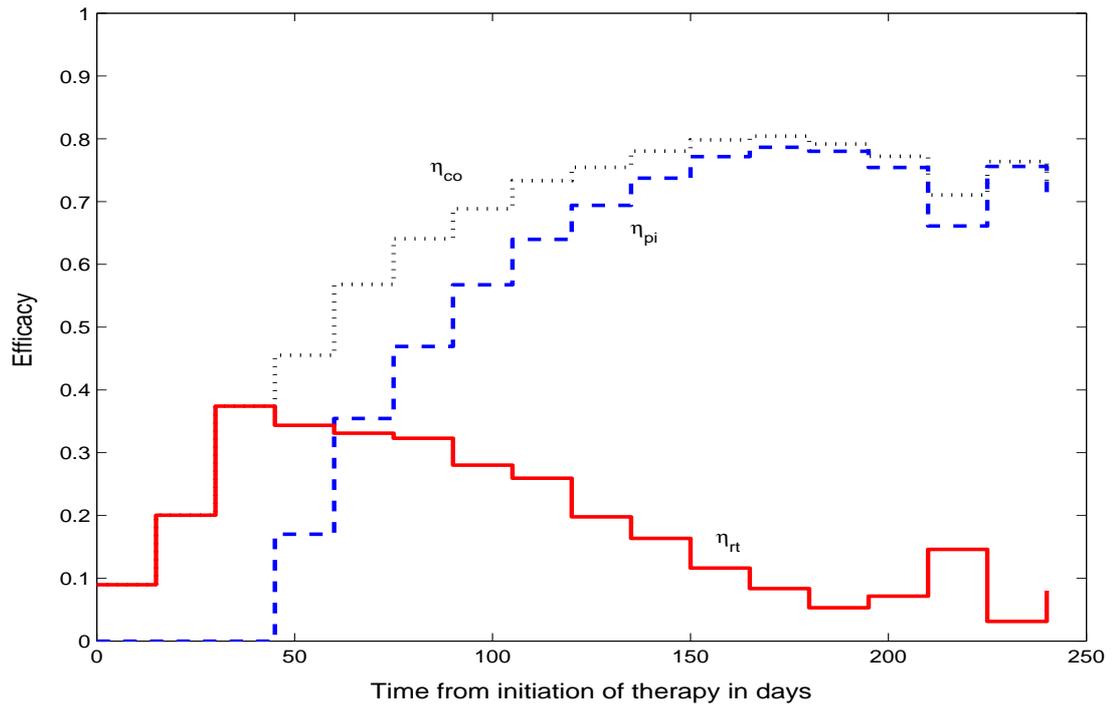


Figure 5.7: Control input sequence for combined therapy with no therapeutic range constraint.  $\eta_{rt}$  : RTI efficacy;  $\eta_{pi}$  : PI efficacy;  $\eta_{co}$  : Combined efficacy. Sampling interval  $t_s=15$  days.

are eventually removed from the regimen. Of interest is the distinct switching from the reverse transcriptase class of inhibitors to the protease inhibitors during therapy. This switch could be explained by figure 5.6 because the eventual efficacy for the protease inhibitors is lower than that of the reverse transcriptase inhibitors.

The derived dosage sequence as depicted in figure 5.7 therefore inherently favours a protease inhibitor intensive regimen for the eventual suppression of the viral load, and to keep it below detectable levels. This may pose a problem when one considers that protease inhibitors are generally more toxic (long term) than the reverse transcriptase inhibitors [189], and most regimens are currently more inclined towards the use of reverse transcriptase inhibitors. Furthermore, the eventual elimination of the reverse transcriptase inhibitors from the regimen may be undesirable, as the protease inhibitor's efficacy ends up being high. The eventual combined drug efficacy

$$\eta_{co} = 1 - (1 - \eta_{rt})(1 - \eta_{pi}) \quad (5.8)$$

is the efficacy that attains a viral load steady state below 50 copies per mL of plasma, as is illustrated in figure 5.7. Figure 5.8(a) shows the resulting viral load outputs for

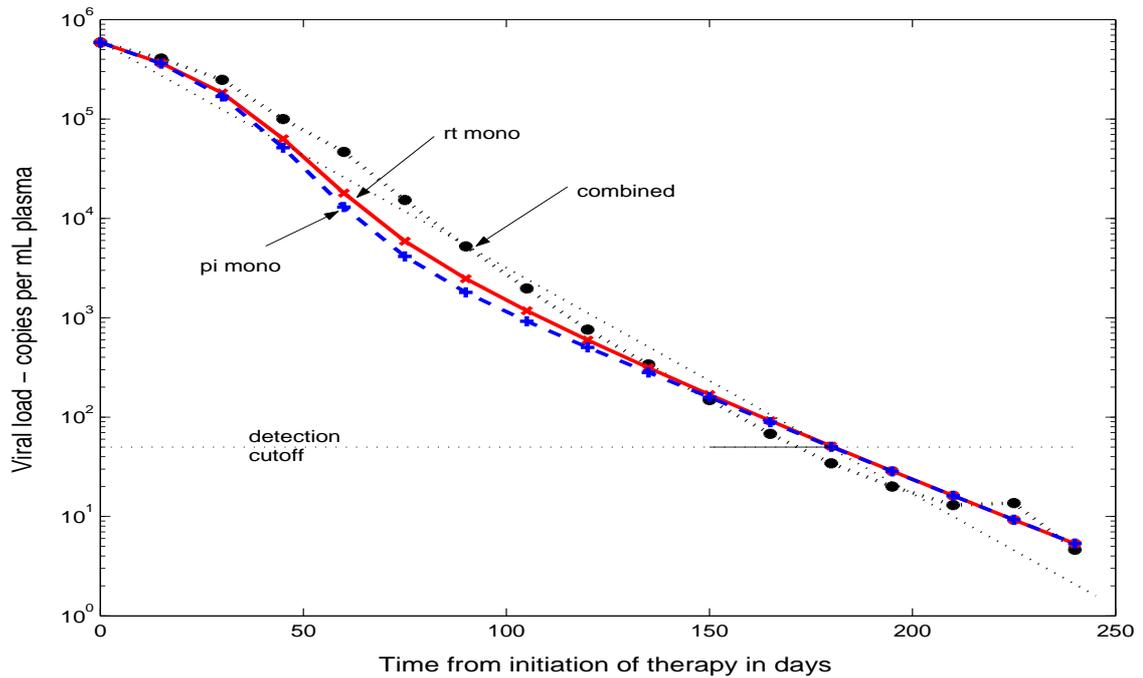
the dosage input sequences in figures 5.6 and 5.7, and shows that combined therapy has better viral load control when compared with mono class therapy. However, there is no significant difference in  $CD4^+$  T cell count outputs between mono class and combined therapy, as illustrated in figure 5.8(b).

So, for this particular case, if drug resistance and long term protease inhibitor toxicity were not an issue, then the results suggest that reverse transcriptase inhibitors should be the choice basis for the starting regimen, while protease inhibitors should be the choice basis for the subsequent suppression and maintenance regimen. The general outlook is that there is no need to start treatment with high dosages. The dosage should start low and be sequentially increased over time. Also, there may be no need to start therapy with inhibitors from both classes. Therapy can start with one class, and the other class can be added later.

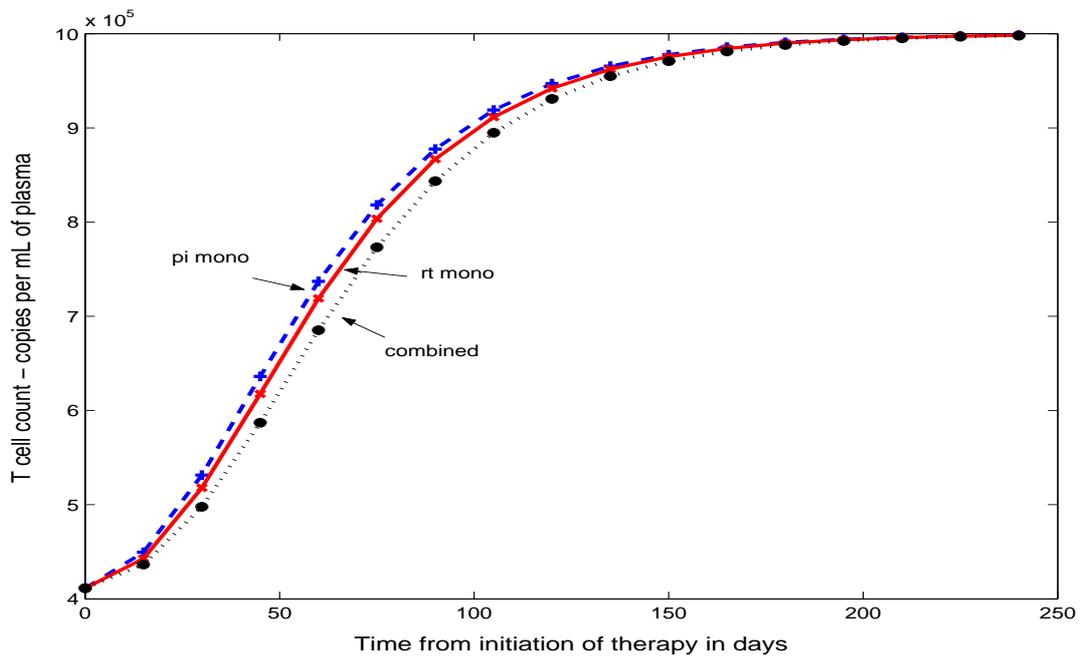
The problem of high efficacies for a particular class of antiretroviral agent can be reduced by imposing an individualized operating therapeutic efficacy range. A lower efficacy limit will prevent the elimination or exclusion of the class from the regimen. An upper efficacy limit should reduce cumulative and instantaneous toxicity, and could also prevent class exclusion or elimination. Figure 5.9 shows the resulting dosage efficacy sequence when an upper operating limit is imposed on the protease inhibitor efficacy. Still, the derived dosage sequence favours the use of protease inhibitors for the eventual suppression of the viral load. The upper limit on the protease inhibitor efficacy however, keeps the reverse transcriptase inhibitors as part of the regimen. This however, has no significant effect on the viral load and  $CD4^+$  T cell count output. Figure 5.9 also shows the fixed dosage efficacy  $\eta_{fix}$  that is equally capable of suppressing the viral load.

A comparison between the MPC derived dosage input sequence and the fixed dosage approach to therapy is made in figures 5.10, 5.11 and 5.12. The initial viral load and  $CD4^+$  T cell responses are much faster for the fixed dosage regimen. This is understandable considering that the fixed regimen starts therapy with a much higher efficacy. However, the viral loads for both therapy approaches reach the 50 copies per mL detection cutoff almost at the same time. For the infected  $CD4^+$  T cells, the decline pattern for the actively infected  $CD4^+$  T cells as illustrated by figure 5.11(b) is similar to that of the viral load (figure 5.10(a)). Macrophage rebound and decline is slower than that of the  $CD4^+$  T cells.

What is clear from these simulations is that, if the intention is to reduce drug toxicities, the logical way to schedule drugs is to take advantage of the initial viral load undershoot when dynamics are perturbed and start therapy with a low drug efficacy.



(a)



(b)

Figure 5.8: System outputs with no therapeutic range constraint. rt mono : RTI mono class therapy; pi mono : PI mono class therapy; combined : Combined therapy; Sampling interval  $t_s = 15$  days. (a) Viral load (b)  $CD4^+$  T cells

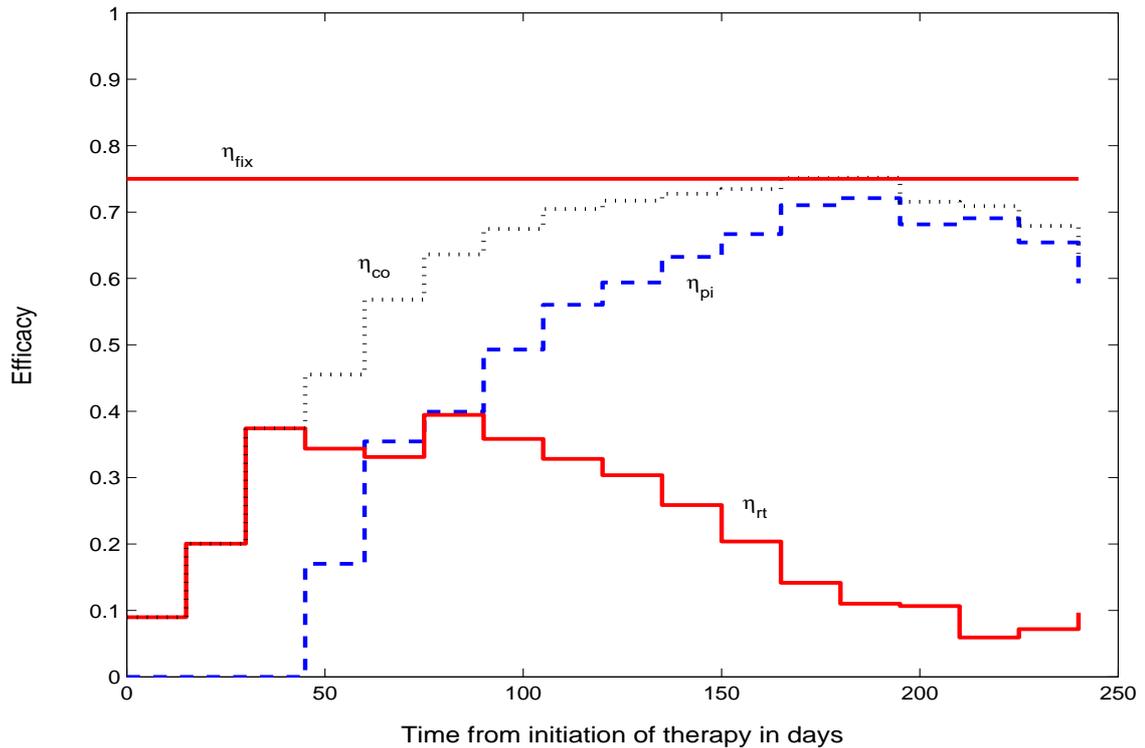
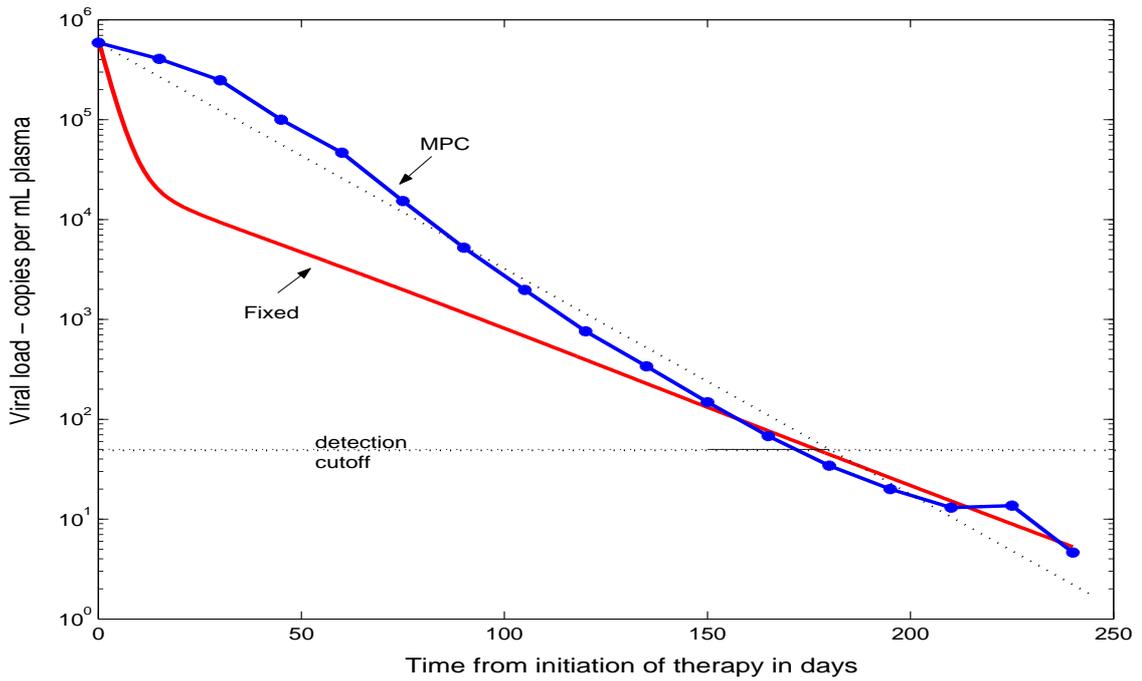


Figure 5.9: Control input sequence for therapeutic range constrained combined therapy ( $t_s = 15$  days) and fixed dosage therapy. Fixed efficacy  $\eta_{fix} = 0.75$ .

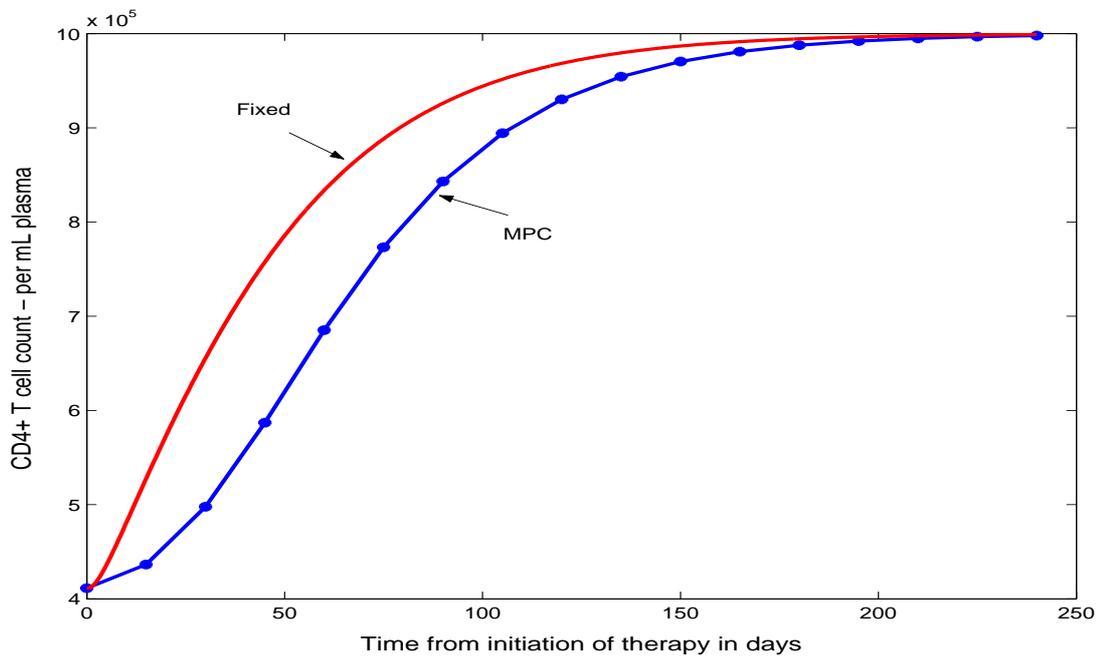
Then the dosage must be sequentially increased over time to prevent the viral load from rebounding, increased again to reduce the viral load further, and eventually increased to suppress and keep the viral load below detectable levels. This results in a sequential perturbation approach to antiretroviral therapy.

The derived dosage sequences as presented in figures 5.6, 5.7 and 5.9 suggest that the dosage should start low and be sequentially increased over time. This suggested dosage schedule could be seen as being contrary to how ARVs are currently scheduled. However, one needs to take note of the following points:

1. Starting therapy with a low efficacy dosage does not necessarily imply that it will take longer to suppress the viral load. This point is illustrated in figures 5.10 and from that perspective, the proposed MPC dosage schedule and the fixed, high all the time efficacy dosage are equally aggressive.
2. Given that the objective is to strike a balance between aggressive therapy and toxicity reduction (instantaneous and accumulative), then an equally aggressive therapy schedule that uses less drugs is better.

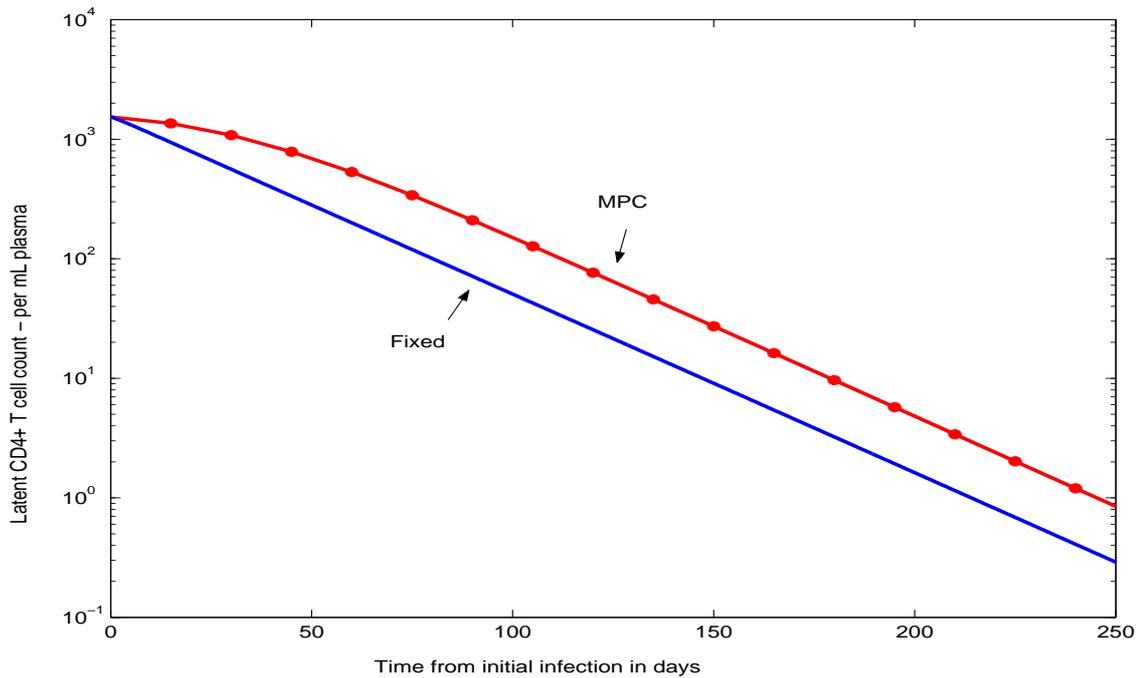


(a)

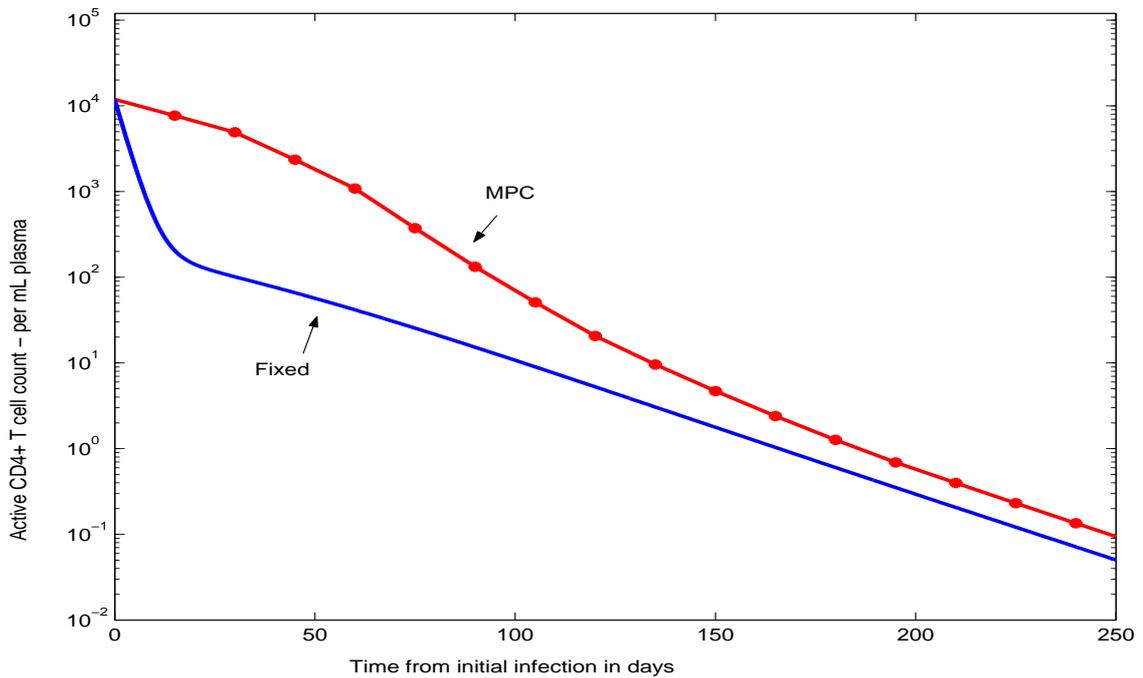


(b)

Figure 5.10: System outputs for therapeutic range constrained combined therapy ( $t_s = 15$  days) and fixed dosage therapy. Control input sequences are in figure 5.9. (a) Viral load, (b) CD4<sup>+</sup> T cells.

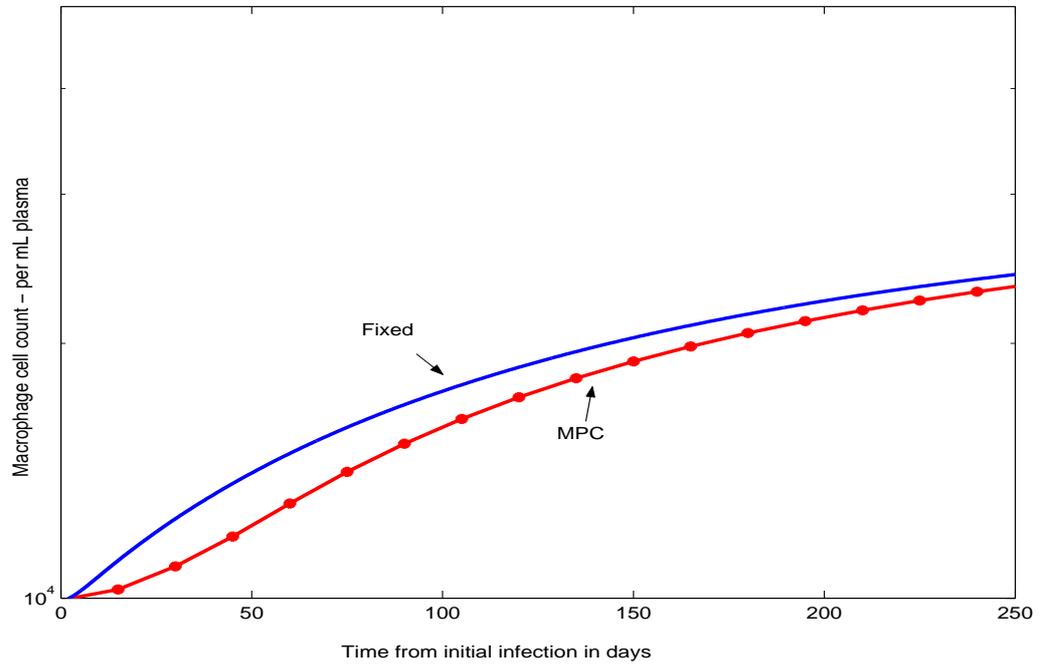


(a)

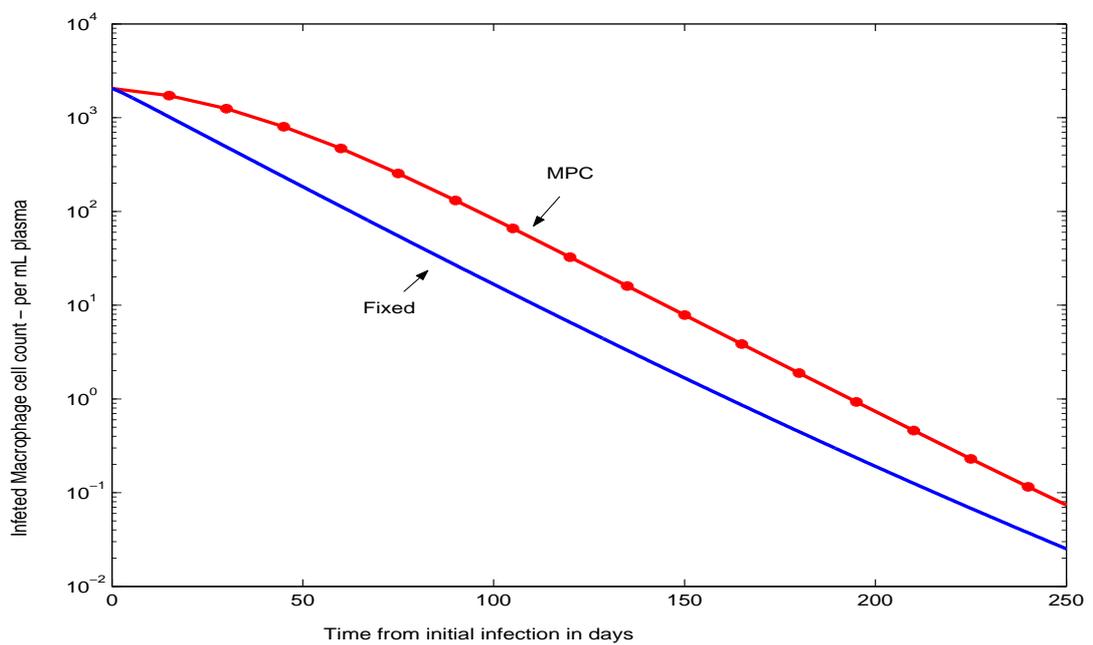


(b)

Figure 5.11: System outputs for therapeutic range constrained combined therapy ( $t_s = 15$  days) and fixed dosage therapy. Control input sequences are in figure 5.9. (a) Latently infected CD4<sup>+</sup> T cells, (b) Actively infected CD4<sup>+</sup> T cells.



(a)



(b)

Figure 5.12: System outputs for therapeutic range constrained combined therapy ( $t_s = 15$  days) and fixed dosage therapy. Control input sequences are in figure 5.9. (a) Uninfected macrophage cells, (b) Infected macrophage cells.

Table 5.6: Initial efficacy and drug exposure variation with sampling interval

Sampling interval	Initial efficacy	Drug exposure
15 days	0.10	0.73
30 days	0.43	0.88
60 days	0.70	0.97
Fixed dosage	0.75	1

Calculated from initiation of therapy up to day 180

### 5.6.5 Effect of Inadequate Sampling

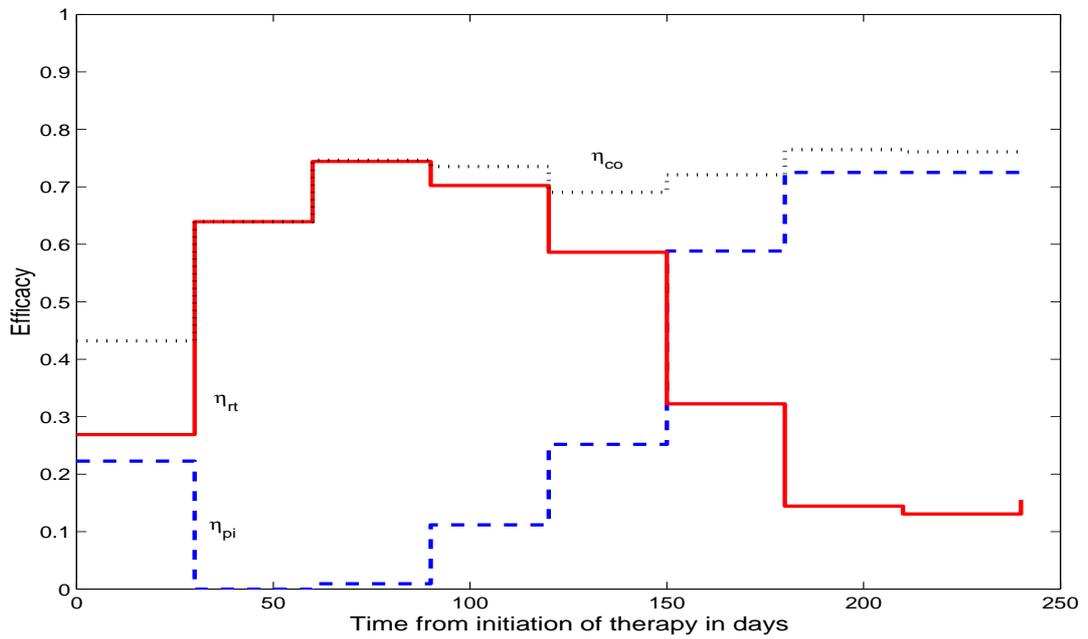
In this section, the sampling interval was varied in order to assess its effect on the resulting dosage efficacy input sequence. Figures 5.13(a) and 5.13(b) show the resulting input sequences when samples were taken every month (30 days) and every 2 months (60 days), respectively. Increasing the interval between taking samples increases the required initial drug efficacy when starting therapy from as low as 11% for a 2 week sampling interval, to 35% for a monthly interval, and as high as 68% when samples are taken once every 2 months.

The once every 2 months dosage efficacy sequence is more like how antiretroviral therapy is currently administered, as it is more inclined towards a fixed dosage regimen. This puts an emphasis on adequate sampling in order to reduce total drug intake. This could explain why current regimens dictate the use of potent HAART from the start. The relative increase in total drug exposure due to increasing the sampling interval is summarized in Table 5.6. Adequate viral load sampling therefore can reduce total drug exposure by up to 27%, as is the case for a 15 day sampling interval.

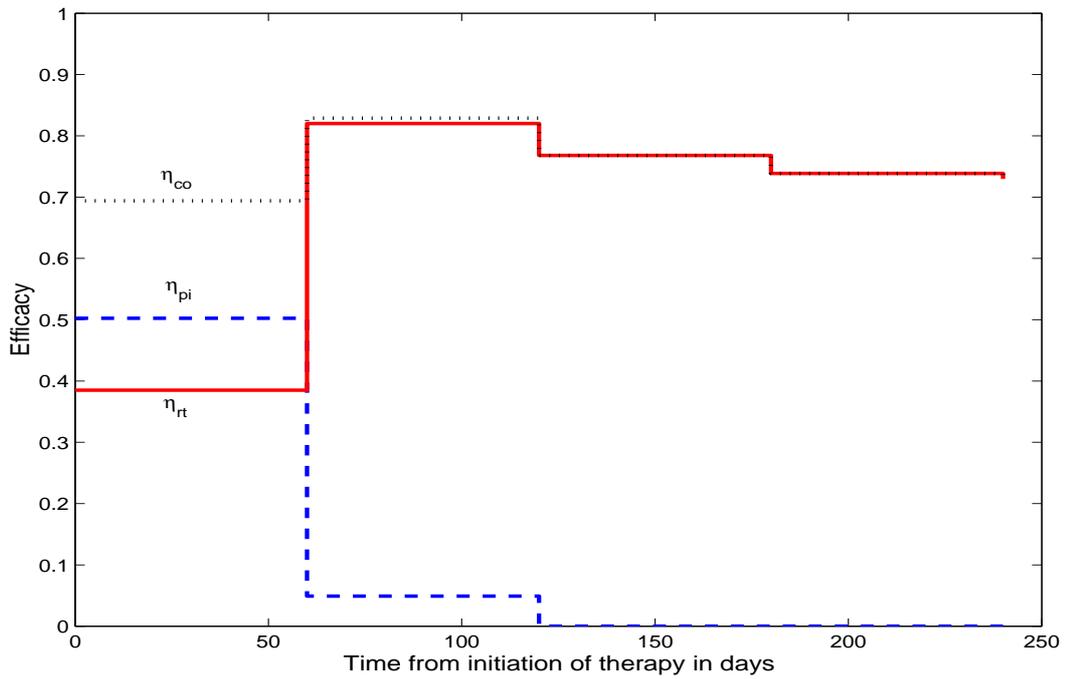
Figure 5.14(a) shows the resulting viral load and figure 5.14(b) the CD4<sup>+</sup> T cell outputs for the dosage schedules in figures 5.13(a) and 5.13(b), respectively.

### 5.6.6 Conclusions

Now that virus eradication does not seem attainable, the focus has shifted to striking a balance between adequately suppressive therapy and toxicity reduction. Therefore, a logical way to minimize cumulative toxicities is to start therapy with a low dosage (take advantage of the transient undershoot when dynamics are perturbed) and sequentially increase the dosage to further suppress and maintain the viral load below detectable levels. This results in a sequential perturbation approach to therapy. The eventual dosage required to keep the viral load below detectable levels will be high. However, once viral load suppression is attained, other strategies like Structured Treatment Interruptions

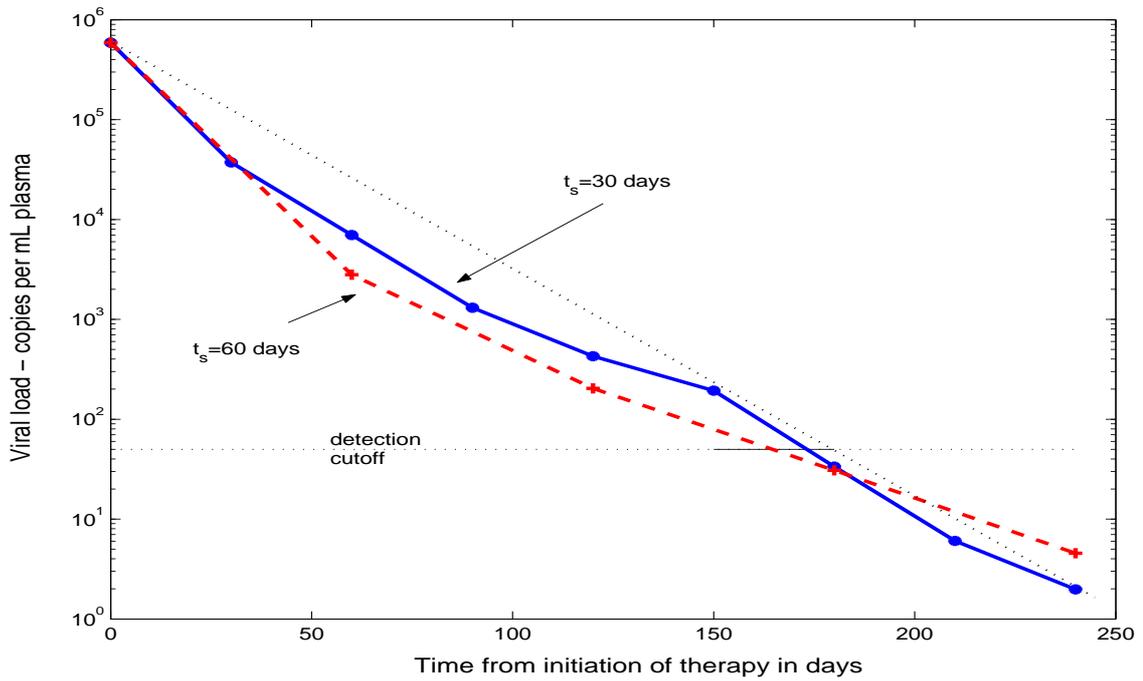


(a)

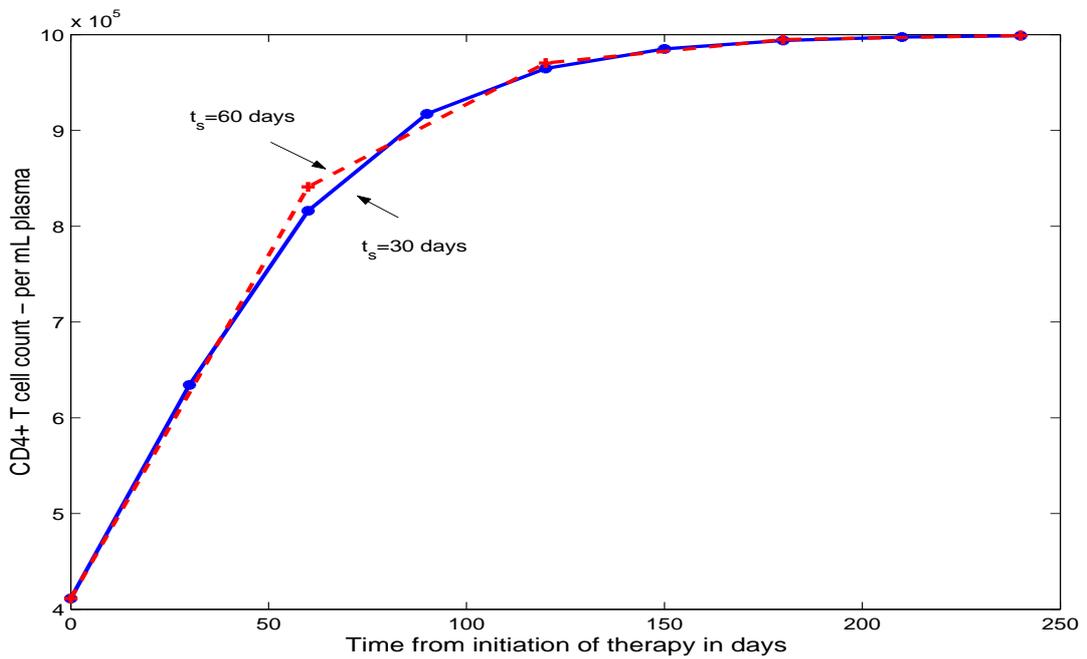


(b)

Figure 5.13: Control input sequences for combined therapy with no therapeutic range constraint when sampling interval is increased.  $\eta_{rt}$  : RTI efficacy;  $\eta_{pi}$  : PI efficacy;  $\eta_{co}$  : combined efficacy. (a)  $t_s=30$  days (b)  $t_s=60$  days.



(a)



(b)

Figure 5.14: System’s outputs for combined therapy with no therapeutic range constraint when sampling interval is increased.  $t_s$ : Sampling interval. Control input sequences are in figure 5.13. (a) Viral load. (b)  $CD4^+$  T cell count.

can be employed to further reduce total drug use.

Firstly, the study suggests that the selection of both the starting and the subsequent regimens will depend on the frequency at which the viral load is sampled. The initial dosage efficacy also depends on the sampling interval, and the prescribed regimen is more inclined towards a fixed dosage regimen as the sampling interval increases. And as expected, the sampling interval is parameter dependent and will vary from one individual to the other. This puts emphasis on the need for more frequent sampling.

Secondly, for mono class therapy, the eventual protease inhibitor efficacy is lower than that of the reverse transcriptase inhibitors. This could explain why for combined therapy, protease inhibitors are preferred for the eventual suppression of the viral load, even though the initial regimen was more inclined towards the use of reverse transcriptase inhibitors.

When both drug options are available for therapy, there is a distinct switch from one class of antiretroviral agent to the other during treatment. The underlying dynamics, or criteria for switching the regimen basis from one class to the other, and the eventual elimination of one class from the regimen in some cases, requires further investigation. Further investigation could add some insight into the ‘what to start with, when and what to change to’ questions that arise when selecting regimens.

The issue is whether such a dosage scheme can be practically implemented. Given that an individual’s model parameter estimates can be obtained, the results from this study indicate that if the sampling interval is reasonable, which it is in this case, then such a dosage scheme can be practical. However, even though the models predict that any drug efficacy can result in some degree of viral load reduction, one needs to consider or investigate the clinical implications of under dosing, or more generally, the implications of not taking drugs as prescribed.

## 5.7 Interruptible Drug Dosage Design

The preceding section 5.6 has shown how viral load suppression can be attained with a reduction in total drug exposure. This consequently minimizes cumulative toxicities and the cost of therapy. The approach that was presented also eliminated the problem of viral load rebounds after suppression has been attained. However, as pointed out, the eventual dosage efficacy required to keep the viral load suppressed at below detectable levels will generally be high. This eventually high drug efficacy reintroduces the toxicity problem. Other strategies that can further reduce drug exposure, once suppression is attained and maintained, need to be employed. One such strategy that has been tried

out in numerous clinical trials is structured treatment interruptions - STI.

As explained before in section 2.4, STI for reducing total drug exposure and invoking immunologic control of the virus, has been shown to have more success if HAART was initiated while the patient was in the acute infection stage, than the chronic infection stage. However, the acute infection stage does not last long enough, and most HIV infected persons are in the chronic infection stage. Furthermore, virus suppression with HAART, especially at the chronic infection stage, does not necessarily imply a reconstitution of the immune system. There is therefore, a need to employ other therapeutic options that will slow down viral load rebound and/or CD4<sup>+</sup> T cell decline during HAART interruption for the chronically infected individual.

This section presents a model based approach to STI protocol design for patients who initiate therapy during the chronic infection stage. For these patients, the purpose of treatment interruptions is primarily to reduce the time on HAART and the related toxicity. This reduction in total drug exposure should be attained while keeping the viral load either below the level of detection, or below some preset viral load cut off value.

The resulting STI schedules will be compared with STI protocols that have been tried out in clinical trials. The results from this section will therefore, be interpreted in the context of these trials, the objective being to highlight the strengths and weaknesses of those trials. This section also shows how, if need be, the duration of the STI cycles can be adjusted by CD4<sup>+</sup> T cell specific therapies, as well as how these CD4<sup>+</sup> T cell specific therapies can be used to make a patient conform to pre-arranged STI schedules.

### 5.7.1 Bottlenecks and Advances in STI Protocol Design

Clinical trials have been conducted in an attempt to determine the immunological and virological benefits of STI for patients with chronic HIV infection, as well as determine the best protocol. However, coming up with an STI protocol that will benefit most patients is still elusive. It is clear from almost all the STI trial that have been carried out to date, that STI protocols with fixed or predetermined on/off periods are not for every body.

Bottlenecks in STI protocol design, generally can be summarized as follows:

- The viral load rebound and T decline rates during treatment interruption will vary from one individual to the other [15, 137, 144]. In essence, there is variability in response between individuals within a trial, as well as between individuals in trials with similar protocols. In clinical trial settings where poor adherence has been

ruled out, this variation in response is primarily due to inter-individual variations in viral and cell parameters, as well as the individual's stage of infection, and not necessarily on the stimulation of HIV specific immunity [143].

- Most assays used in clinical practice have a detection cutoff limit of 50 copies per mL of plasma. This makes timing viral load rebounds and deriving a suitable STI schedule problematic because the virus dynamics under consideration, occur at viral loads that are below the level of detection. The current situation is such that, attempts are being made to maintain a variable at a level that can not be readily measured. In other words, the maximality of virus suppression below the detection cutoff is unknown because there usually is no model that one can use as a guide. This is problematic because these unknown initial system conditions when therapy is interrupted, do influence its transient response.
- In the absence of a model and parameters, how then can a practitioner pre-empt the viral load response when HAART is interrupted? This means that, in order to understand the underlying viral dynamics below the level of detection, one will have to use viral load measurements that are obtainable only when the viral load has rebounded to above detectable levels. In this case, how then is the practitioner supposed to keep the viral load below detection and simultaneously collect data? This problem has in many STI trial instances, made it necessary for viral load cut off points to be increased from 50 copies per mL of plasma, to 200, 500 and even 5000 copies per mL.

In spite of all the problems with STI protocols, significant advances have been made:

- It has long been observed that re-initiation of HAART after an interruption results in re-suppression of the viral load to below detectable levels (for patients who had prior viral load suppression before treatment interruption) [154]. This observation has since been supported by almost all the clinical trials referenced above.
- As supported by the outcome of many clinical trials, STI does not necessarily facilitate or accelerate the selection of resistant mutants [156], though there are some instances of the emergence of drug resistance during repeated STI [128, 129, 130, 131].
- Even though coming up with an STI protocol that will benefit most patients is still illusive, there are compelling reasons to believe that short cycle STI schedules have more success than schedules with long cycles.

### 5.7.2 Strategy

Having highlighted the bottlenecks in STI protocol design, the strategy then, is as follows: Determine the conditions for interrupting and resuming therapy. The next step is then to identify STI schedule options that would work for the chronically infected individual, under the stipulated conditions.

For each schedule option, the following should be evaluated or considered:

- Percentage reduction in total drug exposure when compared with continuous HAART.
- The ease of implementation, or lack thereof.
- Ways of improving the appeal of the schedule.

Finally, ways of making an individual conform to pre-defined STI schedules, as is the case in clinical trials, needs to be investigated.

#### Assumptions:

- The assumption in most clinical trials is usually that the individual has been on HAART long enough and has a record of sustained viral load suppression below 50 copies per mL of plasma. This assumption is also made in this thesis.
- When HAART is re-initiated after an interruption, it is also assumed that the patient will resume the regimen they were previously on. In this case, this will be the RTI and PI containing HAART regimen that was derived in section 5.6.
- By interrupting HAART, it is understood to imply the discontinuation of all replication cycle based drugs (RTI and PI) in the regimen.
- Also, by interrupting IBT, it is understood to imply the discontinuation of all immune based drugs in the regimen.

This section is therefore, a logical continuation of the preceding section. So HAART is considered to have been initiated and day 300 from initial infection for a period of 300 days. The end point data, that is, the combined RTI and PI drug efficacy and the system states at day 600 are presented at the bottom of Table 5.7.

### 5.7.3 Off/On HAART: Getting the Timing Right

When HAART is discontinued, the viral load will in most cases rebound and target cell counts decline to pre-HAART levels [152], as illustrated in figure 5.15. The objective then, is to maintain the viral load between an upper  $V_{max}$  and lower  $V_{min}$  cut off limit by Off/On control.

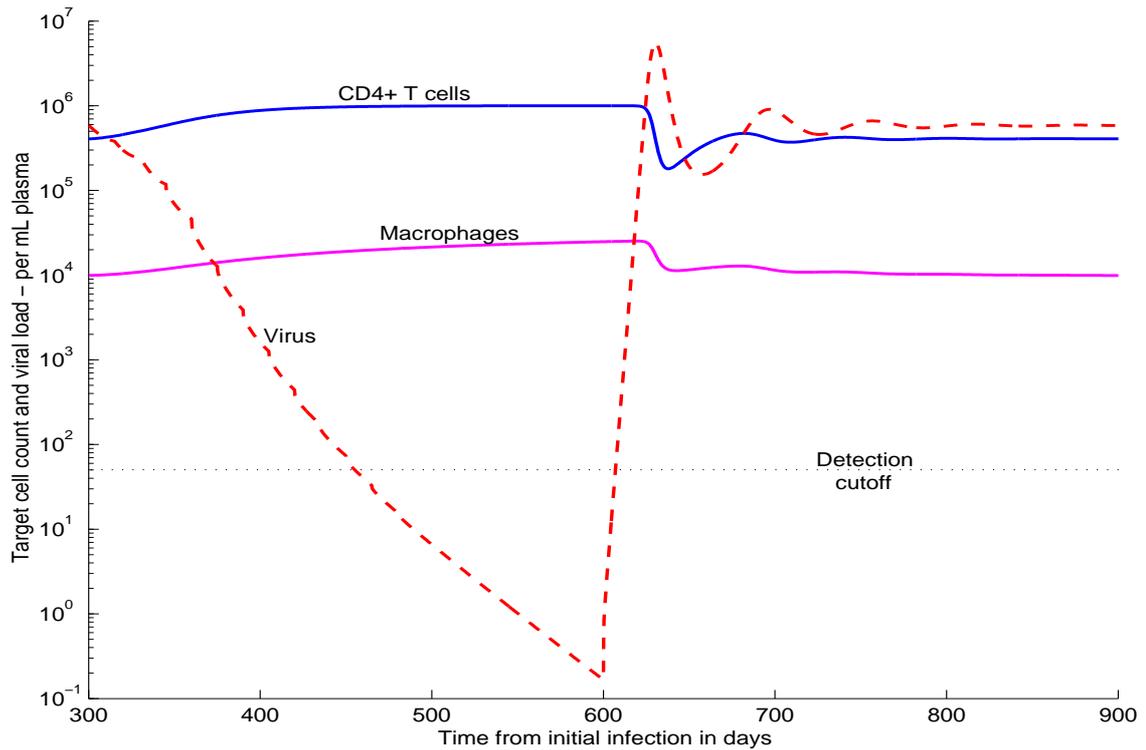


Figure 5.15: Viral load rebound and cell loss to pre-HAART values when therapy is discontinued. HAART was On from day 300 for 300 days, then discontinued at day 600.

**Upper Viral Load Limit:**

Choices for the upper viral load limit  $V_{max}$ , was based on similar choices that were made in various clinical trials, where  $V_{max}$  was selected as, for example, 200 copies per mL plasma [139] and even as high as 5000 copies per mL plasma [135].

In this thesis, the upper viral load limit varied from  $V_{max} = 50$  copies per mL plasma, to  $V_{max} = 200$  copies per mL plasma, and to  $V_{max} = 500$  copies per mL plasma. The appropriateness of imposing each upper viral limit will be assessed.

**Lower Viral Load Limit:**

The lower limit,  $V_{min}$  will simply be taken as the viral load measurement when STI is initiated (pre-STI). This is the viral load measurement at day 600.

**CD4<sup>+</sup> T cells decline and rebound:**

It is undesirable for the CD4<sup>+</sup> T cells count to drop during HAART interruption, by more than half of the cell gain that has been attained prior to STI. That is CD4<sup>+</sup> T cells count should not drop below  $\hat{T} = \bar{T} + \frac{T_H - \bar{T}}{2}$ , where  $T_H$  is the pre-STI CD4<sup>+</sup> T cells count.

Table 5.7: Summary of constraints for interruptible dosage scheduling

Type	Lower and Upper Limits	Notes
HAART Efficacy	$\eta_{co} = 0.82$	Fixed. Pre-determined from section 5.6.
IBT Efficacy	$0 \leq \eta_{ps} < 1$ $0 \leq \eta_{da} < 1$	Varies. Varies.
$u_H$	0 1	HAART interrupted. HAART resumed.
$u_I$	0 1	IBT interrupted. IBT resumed.
CD4 <sup>+</sup> T cell decline and rebound	$\hat{T} \leq T \leq T(0)$	Maintain asymptomatic status. $\hat{T} = \bar{T} + \frac{\bar{T} + T_H}{2}$
Viral load	$V_{iH} < V_i \leq V_{max}$	$V_{max} : [50 \ 200 \ 500]$ .
<b>Pre-HAART conditions</b>		
	$\bar{T}$	408 cells per $\mu\text{L}$ plasma
<b>Pre-STI conditions</b>		
	$T_H$	1000 cells per $\mu\text{L}$ plasma
	$V_{iH}$	0.17 copies per mL plasma
	$\eta_{co}$	0.82

The assumption is that  $\hat{T} > 350$  cells per  $\mu\text{L}$  of plasma, or equivalently  $\hat{T} > 3.5 \times 10^5$  cells per mL of plasma. The intention is to keep the patient clearly in the asymptomatic stage.

The CD4<sup>+</sup> T cells are not expected to rebound to higher than pre-infection values.

**Off/On Control Sequence:**

The criteria for switching OFF and ON HAART, or the control sequence rather, can be summarized as follows:

- Interrupt HAART ( $u_H=0$ ) until  $V_i \geq V_{max}$  [50, 200 or 500 mL<sup>-1</sup>] or  $T \leq \hat{T}$
- Resume and maintain HAART ( $u_H=1$ ) until  $V_i \leq V_{min}$
- Repeat Off/On cycle for 300 days

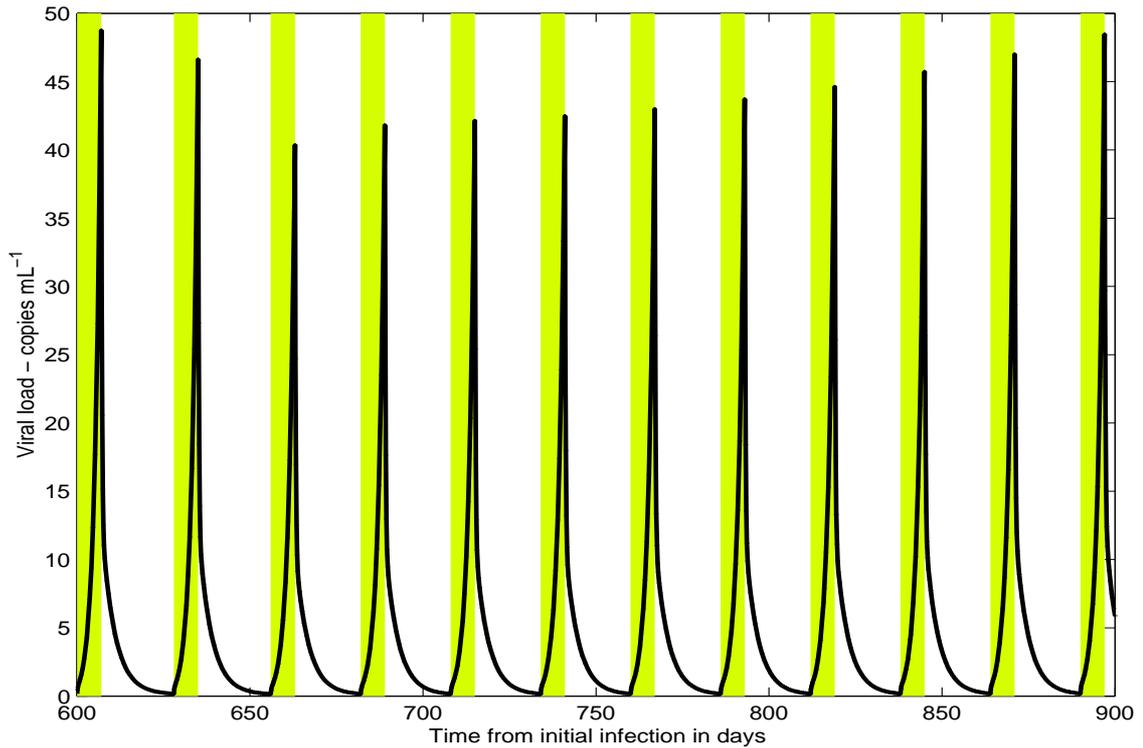


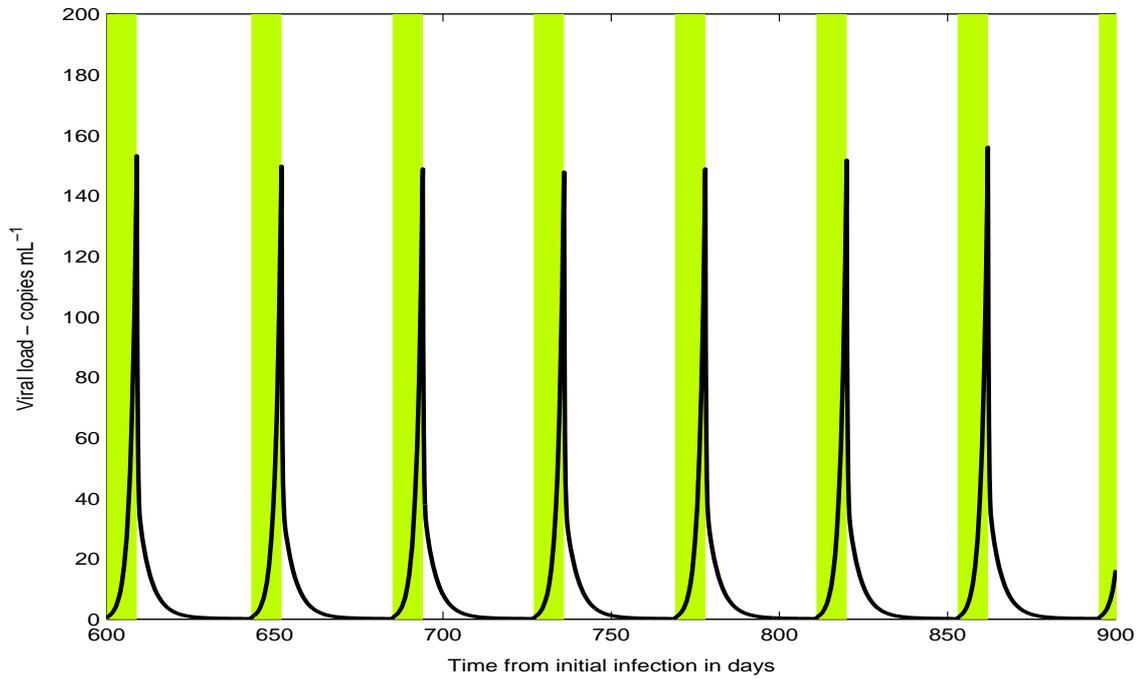
Figure 5.16: Getting the timing right.  $V_{max} = 50$ . Pre-STI conditions are presented in Table 5.7. Shaded areas indicate Off HAART periods.  $\eta_{co} = 0.82$ .

$u_H$  is as presented by  $\Sigma_{Eco}$  (5.1) in section 5.1. The applicable constraints, together with the pre-STI viral load and  $CD4^+$  T cell count are summarized in Table 5.7.

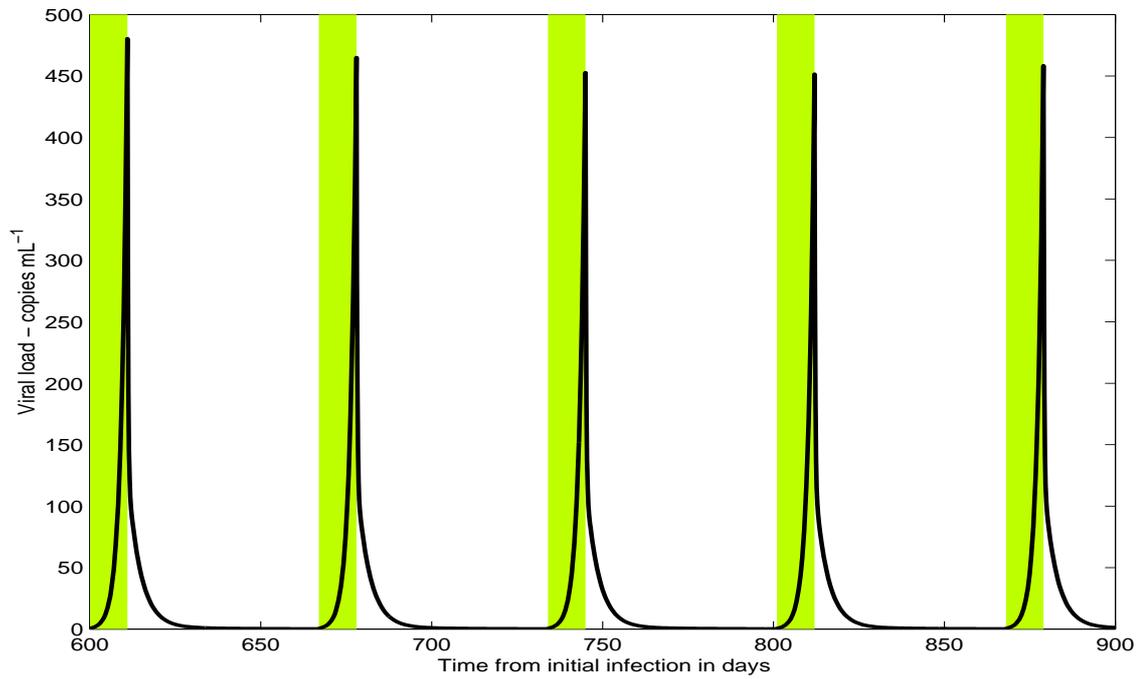
#### 5.7.4 Off/On HAART: Results

Off/On HAART sequence was first derived for the 50 copies per mL of plasma upper viral load cutoff limit  $V_{max} = 50$ , then for  $V_{max} = 200$  and  $V_{max} = 500$ . The assumption that only replication cycle based HAART is used still applies. Therapy is considered to have failed if the viral load can not be kept below the respective  $V_{max}$ .

Figure 5.16 shows the viral load response for  $V_{max} = 50$  copies per mL plasma. The shaded area indicates Off HAART periods. The resulting STI input sequence starts with an Off/On cycle with 7 days Off HAART/21 days On HAART (7/21), for the first two cycles. Thereafter, the On HAART period decreases slightly to 19 days, while the time Off HAART remains as 7 days. But generally, the resulting input sequence approximates the fixed 7/21 Off/On schedule that was used in the clinical trial by Lori *et al* [14]. For practical purposes, it is better to have STI schedules with fixed Off/On cycles, as they are easier to administer.



(a)



(b)

Figure 5.17: Getting the timing right. Viral load response with varying  $V_{max}$ . Pre-STI conditions are presented in Table 5.7.  $\eta_{co} = 0.82$ . (a)  $V_{max}=200$ ; (b)  $V_{max}=500$

Table 5.8: Getting the timing right with varying viral load upper cutoff limits

<b>Viral load cutoff</b>	<b>Off/On HAART</b>	<b>Drug Reduction*</b>
$V_{max} = 50 \text{ mL}^{-1}$	7/21 days (28 day cycle)	25%
$V_{max} = 200 \text{ mL}^{-1}$	9/34 days (43 day cycle)	20.9%
$V_{max} = 500 \text{ mL}^{-1}$	11/56 days (67 day cycle)	16.4%

\*Percentage reduction in total drug exposure when compared with continuous HAART.

Similarly, figure 5.17 shows the viral load response for  $V_{max} = 200$  and  $V_{max} = 500$  copies per mL plasma. For  $V_{max} = 200$  (figure 5.17(a)), the derived STI input sequence starts with an Off/On cycle with 9 days Off HAART/34 days On HAART (9/34), for the first cycle only, which is followed by a slightly shorter 9/33 day Off/On cycle for the subsequent cycles. The resulting input sequence can be approximated very well by the fixed 9/34 day Off/On schedule.

For  $V_{max} = 500$  (figure 5.17(b)), the derived STI input sequence has fixed 11 days Off HAART/56 days On HAART (11/56) cycles. All the resulting fixed duration Off/On schedules that can be used to approximate the derived input sequences and the percentage reduction in total drug intake are summarized in Table 5.8. Figure 5.18 shows the resulting viral load response for the various upper cut off limits when the approximate fixed duration Off/On schedules are used.

It seems, from figure 5.18, figure 5.17 and Table 5.8, that there is no obvious correlation between the Off HAART period and the On HAART period. However, it is clear that it takes longer to re-suppress the viral load after an interruption, than it does for the viral load to rebound during an interruption. This is reflected by the systematically longer On HAART periods with relatively shorter Off HAART periods.

This simple fact, seems to suggest that in the absence of immune control of the virus, as is usually the case in chronic infection, STI clinical trials that have been carried out with equal Off/On periods, were designed to fail. Examples of such designed to fail trials are the 30 days On HAART/30 days Off HAART (30/30) trial by Ortiz *et al* [142] and the 7 days On HAART/7 days Off HAART (7/7) trial by Ananworanich *et al* [20]. Seemingly unexplainable, is the positive outcome of the 7/7 trial by Dybul *et al* in which the participants attained viral load control. However, analysis of the trial's protocol shows that the HAART regimen that was used during STI was more potent than the one originally used to suppress the viral load. Refer to Tables 2.5, 2.6 and 2.4, respectively in section 2.4 for a summary of these trials.

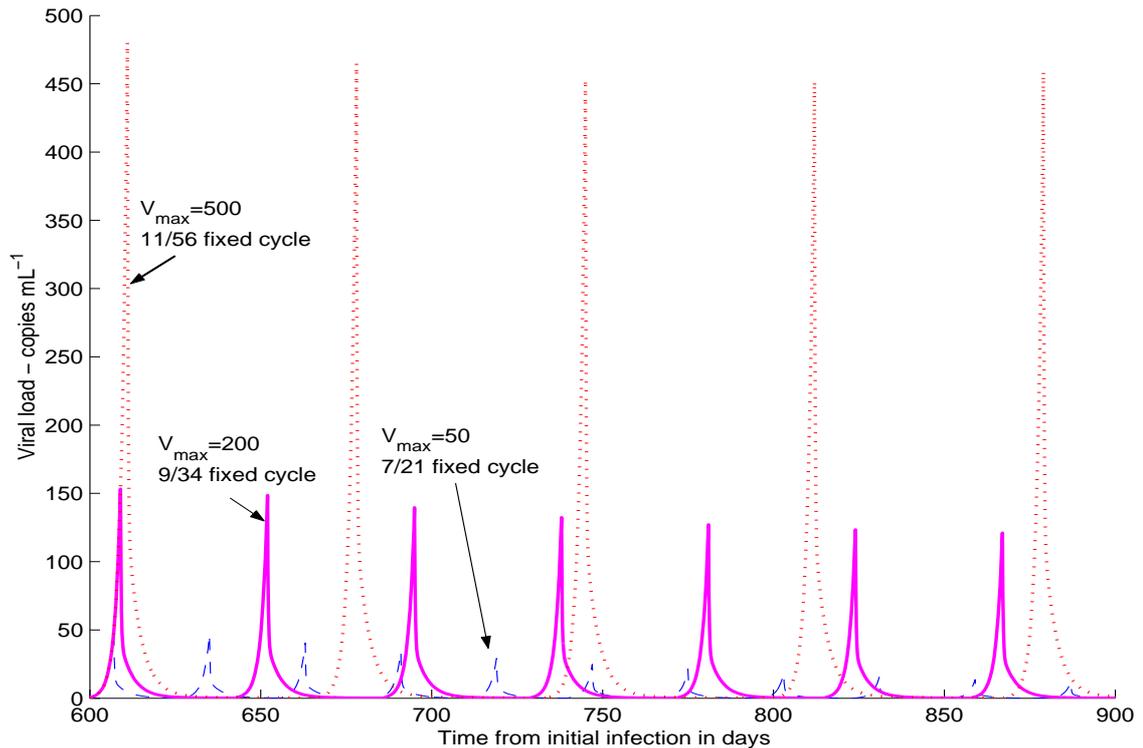


Figure 5.18: Getting the timing right. Viral load response with varying  $V_{max}$ . Pre-STI conditions are presented in Table 5.7.  $\eta_{co} = 0.82$ .

The reason for failure is that On HAART period, relative to the Off HAART period, was not long enough to adequately re-suppress the virus when therapy is re-initiated after an interruption. This effect is illustrated in figure 5.19.

Results also show that the resulting input sequences for lower  $V_{max}$  have shorter Off/On cycles than the derived input sequences with higher  $V_{max}$ . For example, setting  $V_{max} = 50$  copies per mL plasma results in a 28 day (7/21) Off/On cycle, while setting  $V_{max} = 500$  copies per mL plasma results in a 67 day (11/56) Off/On cycle. This can be intuitively deduced because, the higher you let the virus rebound, the longer it will take to re-suppress it, and this will result in a longer Off/On cycle.

The real advantage of setting a lower value for  $V_{max}$ , is that the resulting Off/On schedule has a relatively higher percentage reduction in total drug intake. For example, setting  $V_{max} = 50$  copies per mL plasma results in at least a 25% reduction in total drug use when compared with continuous HAART, while setting  $V_{max} = 500$  copies per mL plasma reduces drug exposure by only 16%. This seems to suggest that short cycle STI schedules are better than schedules with long Off/On cycles.

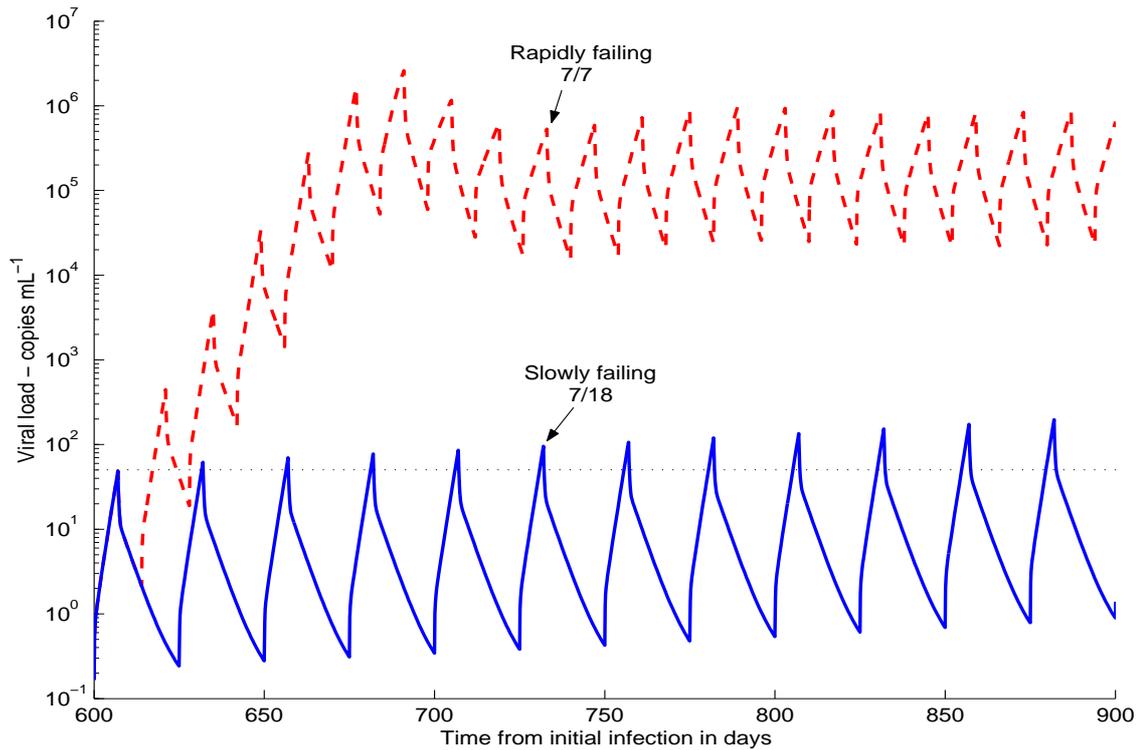


Figure 5.19: Designed to fail: Effect of failure to adequately re-suppress the viral load after an interruption. 7/7: 7 days Off HAART/7 days On HAART; 7/18: 7 days Off HAART/18 days On HAART.

As it appears, increasing the upper viral load cutoff limit, is a case of increased risk of drug resistance with no reward. However, this increase in  $V_{max}$  does not seem to have any adverse effect of the  $CD4^+$  T cell count, as long as there is viral load control, as illustrated in figure 5.20.

The results suggests that an individual with a parameter set similar to the one presented in this chapter (Table 5.1) then, would have had a negative outcome in the following clinical trials:

- the 7days/7days trial by Ananworanich, *et al* [20] because the 7 days given to re-suppress the viral load would have been inadequate. This could explain why the trial's outcome was negative.
- the 2weeks/8weeks trials by Fischer, *et al* [137] and Oxenius, *et al* [143] because the 2 weeks off therapy is too long and would allow the viral load to rebound to high levels.

On a similar note, the said individual would have had a positive outcome in the following clinical trials:

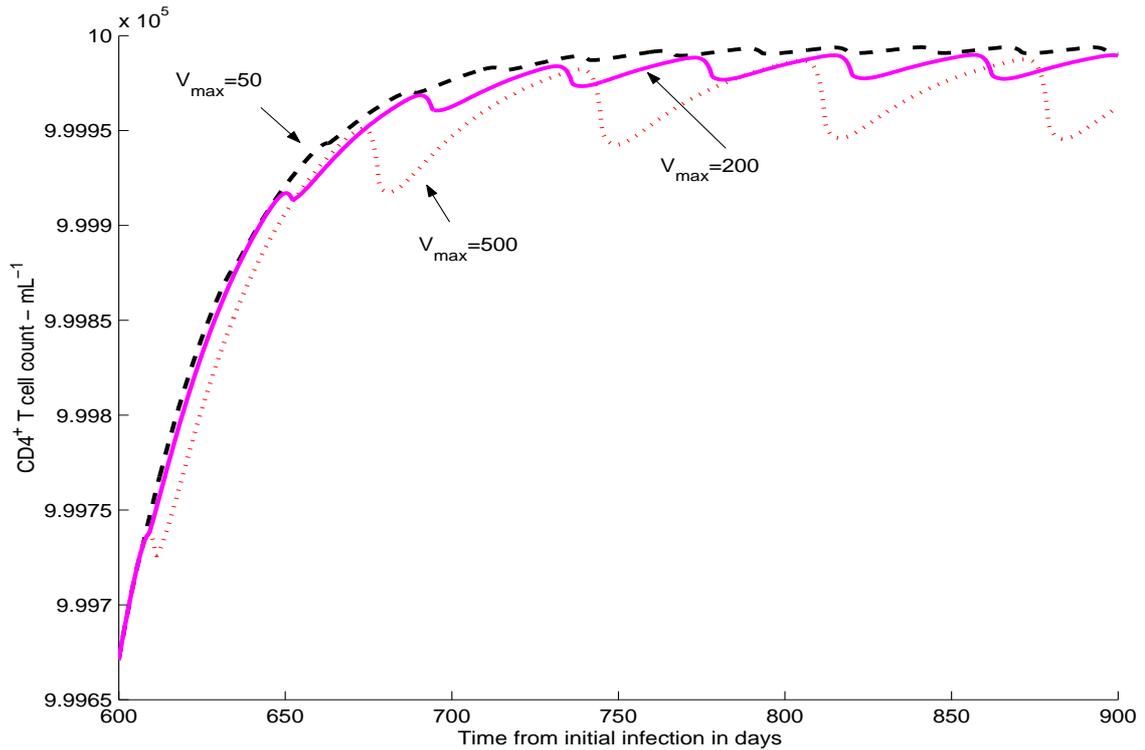


Figure 5.20: Getting the timing right.  $CD4^+$  T cell response with varying  $V_{max}$ . Pre-STI conditions are presented in Table 5.7.  $\eta_{co} = 0.82$ .

- the 1week/3weeks trial by Lori, *et al* [14] though no conclusions about resistance can be drawn in this case.

It is acknowledged that 50, 200 and 500 are not the only viable options for  $V_{max}$ . Table 5.9 presents a summary of the derived Off/On schedules for various viral load cut off limits, and mostly for those that are below the level of detection, that is for  $V_{max} < 50$  copies  $mL^{-1}$ . As expected, setting lower values for  $V_{max}$  further shortens the duration of the Off/On cycles. However, this does not imply a further reduction in total drug exposure. Care should therefore be taken when selecting the value for  $V_{max}$ .

### 5.7.5 Including Protease Inhibitors in the STI Regimen

As pointed out, in current practice, there is no differential measuring of neither the viral load nor the  $CD4^+$  T cell count. The total viral load, which is the sum of the infectious and noninfectious virus particles is what is measured. This therefore, nullifies the effect of protease inhibitors in the regimen, and consequently, could result in over prescribed regimens. Similarly, measuring the total  $CD4^+$  T cell count over estimates the availability of target cells.

Table 5.9: STI schedule options for  $V_{max} < 50$  copies  $\text{mL}^{-1}$

$V_{max}$	Off/On Schedule	Drug Reduction*
500 $\text{mL}^{-1}$	11/56 (67 day cycle)	16.4%
300 $\text{mL}^{-1}$	10/45 (65 day cycle)	18.2%
200 $\text{mL}^{-1}$	9/34 (43 day cycle)	20.9%
100 $\text{mL}^{-1}$	8/27 (35 day cycle)	22.9%
50 $\text{mL}^{-1}$	7/21 (28 day cycle)	25%
30 $\text{mL}^{-1}$	6/18 (24 day cycle)	25%
20 $\text{mL}^{-1}$	5/16 (21 day cycle)	23.8%
10 $\text{mL}^{-1}$	4/13 (17 day cycle)	23.5%
5 $\text{mL}^{-1}$	3/11 (14 day cycle)	21.4%
3 $\text{mL}^{-1}$	2/9 (11 day cycle)	18.2%
2 $\text{mL}^{-1}$	1/6 (7 day cycle)	14.3%

\*Percentage reduction in total drug exposure when compared with continuous HAART.

Figure 5.21 shows the infectious and total viral load responses to the previously derived 7/21 STI schedule with PI containing regimens. The peak for the total viral load is slightly higher than that of the infectious particles. This is so because no noninfectious virus particles are produced when therapy is interrupted. So whether or not PIs are used in the regimen should not determine the failure or success of the schedule, especially so when operating at viral loads below levels of detection.

### 5.7.6 Immune Based Therapy to Augment HAART Interruptions

The preliminary analysis that was carried out in section 4.3 has suggested the potential use of immune based therapies - IBT, to augment HAART interruptions. This section presents simulation results when infected  $\text{CD4}^+$  T cell death rates  $\delta_i$  and  $\delta_a$  are accelerated, and when  $\text{CD4}^+$  T cell proliferation is suppressed. Such immune based therapies include the use of hydroxyurea (HU) and interleukin-2 (IL-2).

The rationale for accelerating the death rates of infected cells is clear.  $\text{CD4}^+$  T cell proliferation suppressing therapies in any case, can also be considered because even though they are not capable of long term enhancement of antiviral efficacy, they do have an effect on the viral load transient response, with and without HAART.

The objective of using IBT to augment HAART interruptions could be to:

- Slow down viral load rebound when HAART is interrupted, and consequently, extend the Off HAART period. This implies alternating HAART with IBT such

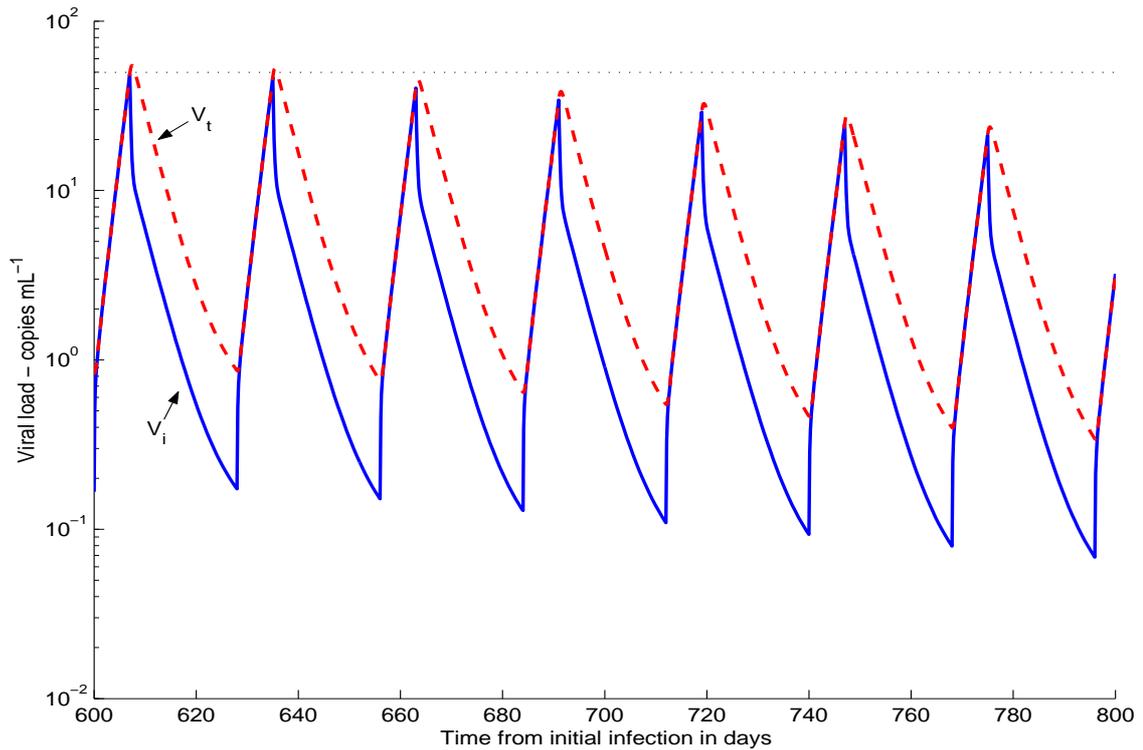


Figure 5.21: Viral load response to Off/On cycles with PI containing regimens.  $\eta_{pi} = 0.8$ ,  $\eta_{rt} = 0.1$ . Pre-STI conditions are presented in Table 5.7.  $V_t$ : Total viral load.  $V_i$ : Infectious virus particles.

that, when HAART is interrupted, IBT is initiated and when HAART is resumed, IBT is interrupted. The switching is as follows :

$$(u_H = 1, u_I = 0)/(u_H = 0, u_I = 1)$$

As this entails the use of IBT during HAART interruptions, this approach will sacrifice one's drug free days, or drug holidays.

- Accelerate viral load re-suppression after HAART interruption, and consequently, reduce the On HAART period. This implies the concomitant use of HAART and IBT such that, when HAART is interrupted, IBT is also interrupted and when HAART is resumed, IBT is also resumed. The switching is as follows :

$$(u_H = 1, u_I = 1)/(u_H = 0, u_I = 0)$$

As this entails the use of IBT during HAART periods, this approach will preserve one's drug free days.

Only the option that preserves drug holidays will be presented here.

Even though maximal reduction of the time on therapy is desirable, the use of IBT must be limited, so as not to make an already potent regimen more toxic. The advantages

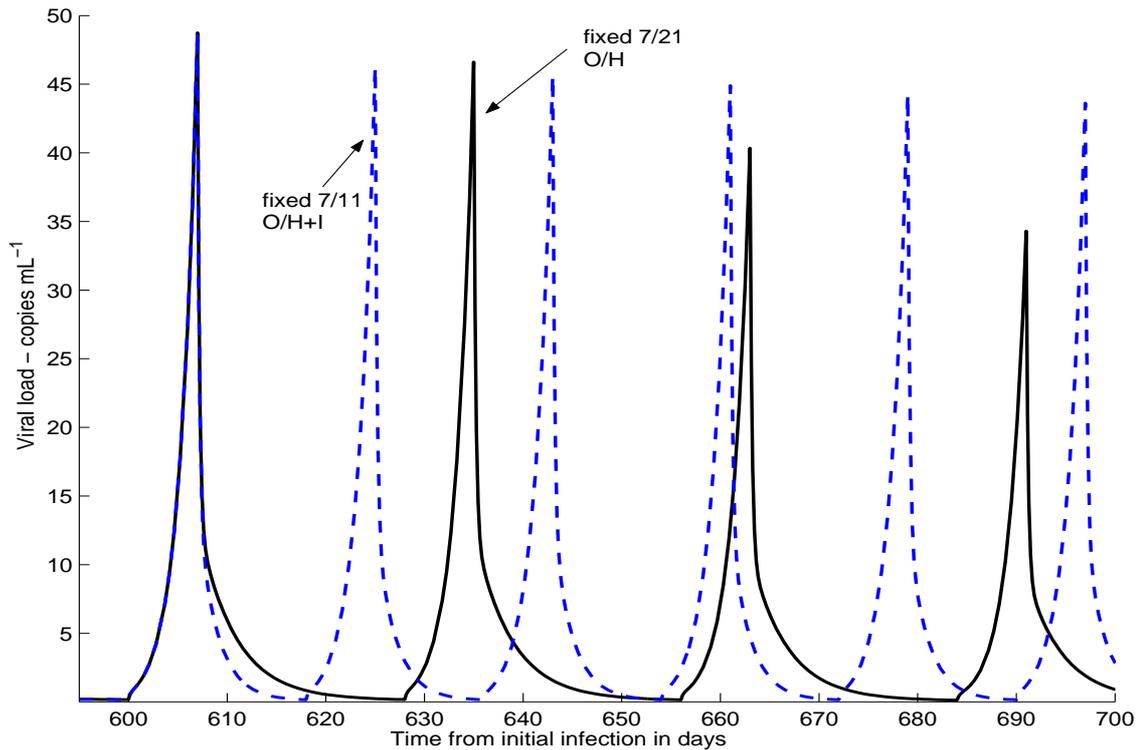


Figure 5.22: Viral load response when IBT is added to HAART when therapy is On.  $\eta_{da} = 0.5$ . Pre-STI conditions are as presented in Table 5.7. 7/21 O/H: 7 days Off all therapies /7 days On HAART only; 7/11 O/H+I: 7 days Off all therapies/11 days On HAART plus IBT.

and disadvantages of adding IBT to a HAART regimen that is already capable of viral load suppression should be evaluated. That is, one should assess if further reducing HAART exposure is worth the possible compounded regimen toxicity.

Figure 5.22 shows how concurrently administering HAART and IBT (cell death accelerators) can accelerate viral load suppression and consequently, reduce the time On therapy. However, one needs to weigh the advantages of reducing On therapy periods against the sacrifice of increased toxicity. The results are summarized in Table 5.10.

This approach can also be used to force conformation to STI schedules with pre-determined Off/On periods.

### 5.7.7 Conclusions

In this section, structured treatment interruptions schedules of HAART were derived for when varying upper viral load limits for the virus rebound were set. The intention was to reduce drug exposure (when compared with continuous HAART), the associated toxicity and cost of therapy. The appropriateness of imposing each viral load upper limit

Table 5.10: STI schedules with HAART plus IBT.  $V_{max} = 50$  copies mL<sup>-1</sup>.

Schedule	Cycle	Drug Reduction*
Off/HAART	7/21 days (28 day cycle)	25%
Off/(HAART+IBT)	7/11 days (18 day cycle)	39% <sup>†</sup>

\*Percentage reduction in total drug exposure when compared with continuous HAART.

<sup>†</sup>Increased IBT exposure.

was assessed, and the derived Off/On HAART schedules were compared with schedules that have been used in some STI clinical trials.

The preliminary analysis that was carried out in section 4.3 has suggested the potential use of immune based therapies to augment HAART interruptions. STI schedules with shorter cycles were derived when IBT was added to HAART when therapy was resumed after an interruption.

The following conclusions can be drawn for this section:

1. It is clear that it takes longer to re-suppress the viral load with HAART after an interruption, than it does for the viral load to rebound during an interruption. This means that for STI schedule design with HAART, the Off HAART period will always be shorter than the On HAART period, for all viral load upper cutoff limits.
2. STI schedules with equal Off/On periods that have been used in some clinical trials were designed to fail.
3. Results show that setting lower viral load limits result in Off/On schedules with shorter cycles. This can be intuitively deduced because, the higher you let the virus rebound, the longer it will take to re-suppress it, and this will result in long Off/On cycles.
4. It can also be seen that these short Off/On cycle STI schedules have a relatively higher percentage reduction in total drug intake. As it appears, increasing the viral load cutoff limit is a case of increased risk of drug resistance with no reward.
5. From a total drug intake perspective, selecting a viral load upper limit  $V_{max} = 50$  copies per mL of plasma produced the best STI schedule, as it resulted in the highest reduction in total drug intake of at least 25%. Another advantage with this schedule is that it can be approximate very well by a 28 day (1 month) cycle with 7 days (1 week) Off HAART and 21 days (3 weeks) On HAART. This Off/On cycle can be easily implemented as it is convenient to use.

6. The use of IBT to augment HAART interruptions that was presented in this section was to accelerate viral load re-suppression after an interruption, and consequently reduce the time on therapy. This resulted in shorter Off/On cycles and further reduction in HAART exposure. However the resulting regimen was more potent.
7. The approach presented above can be used to force conformation to STI schedules with pre-determined Off/On periods. Similar results can be achieved by selecting a more potent HAART regimen for use during STI.

## 5.8 Chapter Summary

It is clear that the rational sequencing of antiretroviral drugs is needed. There is also a pressing need to individualize therapy and schedule drugs depending on the individual's response. Furthermore, drug dosages should be within the individuals operating or therapeutic range, and this operating efficacy range for an individual can be determined if the model parameters are known.

Antiretroviral drugs have a narrow therapeutic range. So while it is desirable to administer drugs within the prescribed therapeutic range, the fact that this range is an average taken over many clinical trials should be taken into consideration. Furthermore, and as pointed out by the guidelines, a regimen that is not effective or is considered alternative for a certain individual can turn out to be another individuals preferred and effective regimen. Better response to therapy can therefore be attained by true individualization of therapy, where the underlying causes for variability in response are factored in when selecting a regimen.

It would not be practical to determine the dosage to end point efficacy for each drug for each individual because the co-administration of multiple drugs leads to drug-drug interactions. A more viable option would be to determine the dosage to end point efficacy for a particular regimen, when administered to an individual. That is, defining the dosage to end point efficacy relationship for the administered regimen would be a step in that direction.

This study has provided some insights on the way antiretroviral agents could be administered. Firstly, the study suggests that the selection of both the starting and the subsequent regimens will depend on the frequency at which the viral load is sampled. The initial dosage efficacy also depends on the sampling interval, and the prescribed regimen is more inclined towards a fixed dosage regimen as the sampling interval increases. And as expected, the sampling interval is parameter dependent and will vary from one individual

to the other. Secondly, for mono class therapy, the eventual protease inhibitor efficacy is lower than that of the reverse transcriptase inhibitors. When both drug options are available for therapy, there is a distinct switch from one class of antiretroviral agent to the other during treatment.

The study did not address the issue of stability for the model predictive controller. Furthermore, for the linearized internal model, the exact linearization about a non-equilibrium system trajectory is a time varying linear model, since the state does not remain constant [186]. Even though one does not have to re-linearize at each sampling instance, re-linearizing often enough could improve the performance of the controller.

The issue was whether such a dosage scheme can be practically implemented. Given that an individual's model parameter estimates can be obtained, the results from this study indicate that if the sampling interval is reasonable, which it is in this case, then such a dosage scheme can be practical.

The eventual dosage required to keep the viral load below detectable levels will be high. However, once viral load suppression is attained, other strategies like Structured Treatment Interruptions were employed to further reduce total drug use.

Setting lower viral load cutoff limits resulted with STI input sequences with shorter Off/On cycles and relatively higher percentage reduction in total drug intake. As it appears, increasing the viral load cutoff limit is a case of increased risk of drug resistance with no reward.

The viral load rebound when HAART is interrupted may be too rapid for some individuals. This may render STI of HAART an inviable option. A possible way to prolong Off HAART periods for these individuals is to alternate HAART with immune based therapy. However, this could sacrifice the drug free days or holidays that one had. A more viable option is the co-administration of IBT with HAART when therapy is resumed after an interruption. This further reduced the duration of the Off/On cycle, further reduced HAART exposure and preserved one's drug free days.

# Chapter 6

## Conclusions and Future Work

### 6.1 Summary

The first chapter presented an overview of the problem at hand. The problems with antiretroviral therapy, the advances so far made in this area, and hence the motivation for conducting this research was presented. The case for HIV/AIDS therapy as a control engineering problem was made, and the role that Control Engineers have played, continue to play and should play in helping to combat the infection was made apparent.

As a foundation, Chapter 2 presented a brief background on immunology, virus replication mechanism and the events that lead to the immune system being compromised. The chapter presented replication cycle based HAART and immune based therapies - IBT, as drugs that are used to treat the infection. The guidelines perspective and advice on the treatment of HIV/AIDS infection then followed, and the case for the need to individualize antiretroviral therapy was presented. Issues relating to the interruption of HAART were discussed.

In Chapter 3, an over view of some HIV/AIDS mathematical models in the literature and the aspects of the immune system that each model illustrates were discussed. Justification for the choice of models that were adopted for this thesis was made. Issues of antiretroviral drug efficacy were discussed and the model parameters that are affected by therapy were presented.

Extensive analysis of the selected models, with and without therapy was carried out in Chapter 4. Therapy in this context, entailed the exclusive or concomitant use of replication cycle based antiretroviral and immune based therapies. This analysis endeavoured to find explanations, from a control theoretic perspective, to some clinically observed responses of individuals on antiretroviral therapy, as well as gain some insight into the following HIV/AIDS therapy issues:

- Variability in response to therapy between individuals on the same regimen.

- Transient rebounds of plasma viremia after periods of suppression.
- The attainment of maximal and durable suppression of the viral load.
- The prognostic markers of virologic success.
- Timing the initiation of antiretroviral therapy such that the benefits of therapy are maximized.
- The possibility of individualizing therapy.

The analysis started with the latently infected cell model and was where necessary, extended to the higher order extended model. At the end of the analysis, the usefulness of the analysis was made apparent as explanations to the above mentioned HIV/AIDS issues were made.

The models were analyzed for the eventual control of the HIV infection. To this end, Chapter 5, after presenting the control problem, also presented antiretroviral drugs as control inputs. Sampling issues, therapeutic range estimation, prioritization of objectives and Model Predictive Control as a control strategy of choice, were discussed.

A sequential perturbation dosage scheme that attained maximal suppression of the viral load with minimal drug exposure, for the treatment naïve individual in the asymptomatic stage of the infection, when replication cycle based HAART was used, was implemented. Once viral load suppression to below detectable levels was attained and maintained, a structured treatment interruption dosage schedule to further reduce total drug intake was implemented, when both replication cycle based HAART and immune based therapies were used. The designed control strategies were assessed for practicality and ease of implementation.

## 6.2 Conclusions

The following are the conclusions that were drawn from this research and are presented according to the problem that had to be addressed:

### **Variable response to therapy:**

- The treatment steady state is drug efficacy and parameter dependent, but is independent of when, during the course of the infection, therapy is initiated. This exclusive dependence of the treatment steady state on the model parameters confirms previous observations that for a fixed drug efficacy, the variability in response to therapy between individuals is primarily due to inter-individual variations in parameters.

- From a viral load point to point controllability perspective, some stages of the HIV infection are more controllable than others. The transition pattern from the pre-treatment state to the treatment steady state will therefore depend on when therapy was initiated. This suggests that an individual can have variable response to therapy depending on when therapy is initiated.

**Rebounds of plasma viremia after periods of suppression:**

- For a fixed drug efficacy, the transition from the pre-treatment viral load to the treatment steady state is generally oscillatory and the viral load will transiently oscillate about the treatment steady state before settling. Viral load rebounds are therefore, from a treatment steady state perspective, all transient.
- The magnitude and frequency of the viral load rebounds about the treatment steady state depend on when during the course of the infection, therapy was initiated.
- For an individual, if the drug efficacy is such that the treatment steady state is above a value that is considered indicative of virologic failure, then the viral ‘blip’ will, in the clinical context, also be indicative of virologic failure. On the other hand, if the drug efficacy is such that the treatment steady state is below detectable levels, then the viral blip will be, again in the clinical context, transient.

**Prognostic indicators of virologic success:**

- The maximality of viral load suppression and the durability of such suppression once attained, depend on the infection stage at which therapy is initiated. As such, the viral load and cell count at the start of therapy are more prognostic indicators of virologic response, than they are of virologic success. This study therefore, partially lends support to some clinical study findings that have suggested that the virologic and immunologic conditions at the start of therapy, determine the outcome.
- The real determinant of virologic success on an individual basis, is the combination of the virus and host cells’ parameters and the end point efficacy of the drugs used. This finding, fully supports the reported cases where virologic failure has been attributed to the regimen used.
- It has been argued before that the basic reproductive ratio  $R_o$ , is one of the prognostic indicators of virologic success. Given that  $R_o$  is exclusively determined by the individuals virus and host cells’ parameters, which are in turn co-determinants of virologic success, then the argument is justified.

**The possibility of individualizing antiretroviral therapy:**

- This study has indicated that it could be possible to obtain the full parameter estimate set for the HIV/AIDS models considered in this thesis, with appropriate system measurements, and that this parameter estimate set can be reduced if need be. This affirms that it is possible to individualize antiretroviral therapy.

**The best time to initiate antiretroviral therapy:**

- From a maximal viral load suppression perspective, it is best to initiate antiretroviral therapy during the early-acute infection stages. Failing which, then therapy should be initiated during the asymptomatic stage.
- Maximal viral load suppression generally implies durable suppression. From a durable viral load suppression perspective then, it is best to initiate therapy also during the early acute infection stages. For a truly durable suppression of the viral load however, a drug efficacy that is high enough to attain a treatment steady state that is below levels of detection should be used.
- Some stages of the HIV infection are more controllable than others, and the degree of viral load controllability is highest during the mid-acute infection stage. From a viral load point to point controllability perspective then, is the best time to initiate therapy during this stage. Failing which, then therapy should be initiated during the early asymptomatic stage.

**Modelling antiretroviral drugs as control inputs:**

- The instantaneous inhibitory effect of virus replication has been modelled as an oscillatory function of time. If however, the interval between dosing, or the release mechanism of the drug is such that the variation between the peak drug concentration and the minimum concentration is minimal, then the drug efficacy can be assumed to be constant.

**Sampling for effective control:**

- The sampling interval has been determined from the viral load transient response analysis and corresponds to the minimum sampling rate to prevent aliasing. This sampling interval is parameter dependent and will vary between individuals.

**The rational sequencing of drugs:**

This study has provided some potentially interesting insights on the way antiretroviral agents could be administered.

- Firstly, the study suggests that the initial dosage efficacy and the selection of

both the starting and subsequent regimens will depend on the frequency at which the viral load is sampled. The prescribed regimen is more inclined towards a fixed dosage regimen as the sampling interval increases and there is an associated increase in drug intake. This puts emphasis on the need for sampling to be more frequent than as recommended by the guidelines.

- Secondly, for mono class therapy, the eventual protease inhibitor efficacy is lower than that of the reverse transcriptase inhibitors. This suggests that protease inhibitors are better than reverse transcriptase inhibitors at suppressing the infectious viral load.
- When both drug options are available for therapy, there is a distinct switch from one class of antiretroviral agent to the other during treatment. Protease inhibitors were preferred for the eventual suppression of the viral load, even though the initial regimen was more inclined towards the use of reverse transcriptase inhibitors. The underlying dynamics, or criteria for switching the regimen basis from one class to the other, and the possible elimination of one antiretroviral class from the regimen, requires further investigation.
- Results from this study suggest that a logical way to minimize cumulative toxicities is to start therapy with a low dosage (take advantage of the transient undershoot when dynamics are perturbed) and sequentially increase the dosage to further suppress and eventually maintain the viral load below detectable levels. This results in a sequential perturbation approach to therapy.
- The eventual dosage required to keep the viral load below detectable levels will be high.

#### **Structured treatment interruption protocol design:**

- Immune based proliferation suppressors have been found, in this study, to have marginal effect on the viral load treatment steady state and no effect at all on the CD4<sup>+</sup> T cell steady state counts. Adding immunosuppressive hydroxyurea to replication cycle based HAART for the initial suppression of the viral load, as it has been done in some clinical trials, was therefore, an ill conceived idea. However, proliferation suppressors do have a transient effect on the viral load response and could be added to the STI regimen.
- In the absence of immune control of the virus, it takes longer to re-suppress the viral load after a HAART interruption, than it does for the viral to rebound during an interruption. This means that with the use of replication cycle based HAART, STI treatment schedules with equal Off/On periods, such as those that have been

used in some clinical trials were designed to fail.

- Setting lower viral load upper limits has been found to result in shorter Off/On cycles. The derived shorter Off/On cycles that result with lower viral load upper limits have a relatively higher percentage reduction in total drug intake, when compared with the longer Off/On cycles that resulted with higher viral load upper limits. As it appears, increasing the viral load cutoff limit is a case of increased risk of drug resistance with no reward.
- Intensifying the STI HAART regimen by adding immune based therapies to it results in even shorter Off/On cycles and further reduces HAART exposure. However, care should be taken not to make the already toxic HAART regimen more toxic. Conformation to pre-designed STI Off/On schedules can be attained by such intensification of the STI HAART regimen.

#### **Practicality of implementation:**

The issue is whether such a dosage scheme can be practically implemented. Given that an individual's model parameter estimates could be obtained, the results from this study indicate that if the sampling interval is reasonable, which it is in this case, then such a dosage scheme can be practically implemented. However, even though the models predict that any drug efficacy can result in some degree of viral load reduction, one needs to consider or investigate the clinical implications of under dosing, or more generally, the implications of not taking drugs as prescribed.

### **6.3 Recommendations and Future Work**

A lot has been done in model development and a lot more still needs to be done. Model accuracy needs to be further improved, though this will ultimately make model analysis more difficult.

Issues of resistance, though not considered in this thesis, are real. This is especially so if dosage sequences with variable drug intake are considered. This area also needs to be addressed.

Items that still need to be properly formulated are:

1. Environmental and social factors that influence infection progression.
2. Organ health, as in quantifying the extent to which the immune system is repairable.

Besides facilitating the simulation of a more realistic infection progression, it can also

explain such cases of attaining virologic success with immunologic failure (durable viral load suppression to below detectable levels with suboptimal T cell gains). Being able to quantify organ health can also improve the determination of immune competence in chronically infected patients, and facilitate the development of tests that may then predict which patients will be the best candidates for STI. This should be one of the objectives of STI.

The HIV/AIDS models presented in this thesis are inherently nonlinear regarding the states and parameters are known to change over time. Even though results based on linear time-invariant system analysis are valid (at least locally), an in-depth nonlinear analysis of the system still has to be carried out. This could unveil some model characteristics or properties that were not made apparent or addressed in this thesis and give more insights into the disease dynamics and possible treatment strategies.

Explicitly modelling the immune response to the virus would make the HIV control problem more challenging for the control engineer. Modelling the immune response would actually increase in number, the equilibrium points of the system. Other challenges that the control engineer could take up are including the trafficking of virus particles between compartments. Macrophages residing in tissue in particular, are one of the obstacles of virus eradication.

The control strategy that has been presented in this thesis needs to be upgraded. There is much uncertainty in model parameters estimates and these estimates are known to change with time. Even though MPC has some degree of robustness to model inaccuracies, the controller's performance in the presence of disturbances and parameter changes has to be assessed and issues relating to the controller's stability have to be addressed. Adaptive strategies need to be explored.

For control purposes, the derived input drug sequences are specified from an end point drug efficacy perspective and this efficacy can be assumed to be constant for the interval that the dosage is fixed. However, determining the actual required dosage that corresponds to the derived input efficacy sequences will be problematic as it involves firstly, that the relationship between the two be defined for each individual and for each regimen that the individual uses. A lot of research work needs to be done in that area.

All the foregoing calls for collaborative research with immunologists and related medical practitioners in order to take the research work of control engineers further and make it more applicable and of use.

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# Appendix A

## Parameter Estimates

Table A.1: Parameter estimates for the latently infected model : Set 1.

Parameter	Value
$s_T$	$10 \text{ mm}^{-3} \text{ day}^{-1}$
$p$	$0.03 \text{ day}^{-1}$
$T_{max}$	$1500 \text{ mm}^{-3}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$7.5 \times 10^{-6} \text{ mm}^3 \text{ day}^{-1}$
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	0.075
$q_l$	0.05
$q_a$	0.55
$r_T$	$2000 \text{ cell}^{-1} \text{ day}^{-1}$
$c$	$5 \text{ day}^{-1}$

[84, 85, 50, 46]

Table A.2: Parameter estimates for the latently infected model : Set 2.

Parameter	Value
$s_T$	$10 \text{ mm}^{-3} \text{ day}^{-1}$
$p$	$0.03 \text{ day}^{-1}$
$T_{max}$	$1000 \text{ mm}^{-3}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$4 \times 10^{-5} \text{ mm}^3 \text{ day}^{-1}$
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	$0.025$
$q_l$	$0.005$
$q_a$	$0.55$
$r_T$	$240 \text{ cell}^{-1} \text{ day}^{-1}$
$c$	$5 \text{ day}^{-1}$

Table A.3: Parameter estimates for the latently infected model : Set 3.

Parameter	Value
$s_T$	$10 \text{ mm}^{-3} \text{ day}^{-1}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$7.5 \times 10^{-6} \text{ mm}^3 \text{ day}^{-1}$
$q_l$	$0.05$
$q_a$	$0.8$
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	$0.075$
$r_T$	$2000 \text{ virions cell}^{-1} \text{ day}^{-1}$
$c$	$5 \text{ day}^{-1}$

[85, 50, 84, 7, 90].

Table A.4: Typical parameters estimates for the extended model.

Parameter	Typical Value
$T(0)$	$10^6 \text{ mL}^{-1}$
$M(0)$	$3 \times 10^4 \text{ mL}^{-1}$
$V(0)$	$10 \text{ mL}^{-1}$
$s_T$	$10^4 \text{ mL}^{-1}\text{day}^{-1}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$4.5 \times 10^{-8} \text{ mL day}^{-1}$
$p$	$0.02 \text{ day}^{-1}$
$T_m$	$10^6 \text{ mL}^{-1}$
$q_t$	0.005
$q_a$	0.55
$\delta_t$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	$0.025 \text{ day}^{-1}$
$s_M$	$150 \text{ mL}^{-1}\text{day}^{-1}$
$d_M$	$0.005 \text{ day}^{-1}$
$\beta_M$	$1.75 \times 10^{-8} \text{ mL day}^{-1}$
$q_M$	1
$\mu$	$0.05 \text{ day}^{-1}$
$r_T$	$240 \text{ cell}^{-1}\text{day}^{-1}$
$r_M$	$35 \text{ cell}^{-1}\text{day}^{-1}$
$c$	$5 \text{ day}^{-1}$
$\eta_{rt}$	$[0, 1)$
$\eta_{pi}$	$[0, 1)$
$\alpha_{rt}$	$(0, 1]$
$\alpha_{pi}$	$(0, 1]$
$\eta_{ps}$	$[0, 1)$
$\eta_{da}$	$[0, 1]$

[46, 71, 78, 84, 176]