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Mathematical modelling of In-vivo HIV optimal therapy and management

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Mathematical Modelling of In-vivo HIV Optimal Therapy and Management

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Declaration and Approval

Declaration

I declare that this work has not been previously submitted and approved for the award of a degree by this or any other University. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Abstract

Human Immunodeficiency Virus (HIV) remains the main cause of premature death globally. In 2013, Kenya was the fourth largest endemic HIV country in the world having over 1.6 million people living with the virus. The fact that there is an increase in the rate of new-HIV infections in Africa and especially in Kenya underscores the need for adequate strategies to cope with this deadly disease and to achieve vision 2020. Where the government envision that, by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression. Currently, there is no known cure for HIV, hence the most optimal way is the management of HIV infected people to prevent virus progression and HIV transmission. Although there has been progress in management of HIV by the use of antiretroviral drugs (ARTs), long-term use of these ARTs leads to overwhelming challenges. These challenges are: toxicity of the medication, non-adherence problems as a result of inaccessibility of comprehensive care centres, drug resistance-mutations and significant financial burdens. This study aimed at formulating and analysing mathematical in-vivo models for the interaction between HIV virions, $CD4^+$ T-cells, $CD8^+$ T-cells and the optimal control for effective therapy, whose numerical simulations would assist in giving more insight about the challenges aforementioned.

Various mathematical methods including ordinary differential equations, Runge-Kutta forth order scheme and optimal control theory have been applied in the development and the analysis of the model. Analysis of the formulated model indicates existence of multiple equilibria whose stability and bifurcation analysis have been presented. From the simulated results, we have noted that early initiation of HIV treatment reduce viral replication in HIV infected people. In particular, highly active antiretroviral therapy (HAART) which include the combination therapy of Fusion inhibitor (FI), Reverse Transcriptase inhibitor (RTI) and Protease inhibitor (PI) in different proportions have been found to be more effective in treating HIV than a single drug therapy. The model

simulations show how to best choose the proportions of FI, RTI and PI in order to maintain an acceptable level of $CD4^+$ T-cells and, at the same time, reduce the side effects associated with their long term use. In addition, the most optimal way of administering ART drugs that lead to maximum benefit has been predicted from optimal control simulation.

The findings give a significant explanation of why late initiation of ARTs might not be helpful to an HIV infected person and suggest that the controls ought to be optimal at the acute phase of infection where the viral replication is extremely high. If the controls are well implemented, many potential infections would be averted by lowering the viral load and increasing the number of the T-helper cells. This, in turn, will also lead to reduction in HIV transmission. Therefore, there is need for increased awareness campaigns to encourage people to know their HIV status and adhere to the prescribed treatment. The research outcomes in this study emphasizes the importance of "Anza Sasa"campaign that was launched on 15th July 2016 by the Government of Kenya through the Ministry of Health in collaboration with the National AIDS and STI Control program.

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Dedication

I dedicate this thesis to my late mother Lydia Ngina to whom I attribute my success in life. Her love, encouragement and academic support motivated me and made me who I am. Mum I will never thank you enough for your unending support, encouragement and advice. I wish you could witness this day "Nyakiega" but your words and love live on and will never be forgotten. Mami thank you for constantly reminding me that I was destined for greater things.

Eternal rest grant unto her, O Lord, and let perpetual light shine upon her. May she rest in peace. Amen

Abbreviations

CD4$^+$ T-cells	Cluster of differentiation 4 T-cells
CD8$^+$ T-cells	Cluster of differentiation 8 T-cells
HIV	Human Immunodeficiency Virus
AIDS	Acquired immunodeficiency syndrome
WHO	World Health Organisation
FIs	Fusion inhibitors
PIs	Protease inhibitors
ART	Antiretroviral Therapy
NASCOP	National AIDS and STD Control Programme (Kenya)
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
FDA	US Food and Drug Administration
CCR5	C-C chemokine receptor type 5,
CXCR4	C-X-C chemokine receptor type 4, Lysozyme Chimera
ODEs	Ordinary differential equations
R_0	Basic Reproductive Number
R_c	Critical Reproductive Number
DFE	Disease-free equilibrium
PRCCs	Partial Rank Correlation Coefficients
STIs	Sexually transmitted infections
STDs	Sexually transmitted diseases

cccDNA Covalently closed circular Deoxyribonucleic acid

Publications

The publications listed below are extracts from this thesis. The articles are appended at the end of this thesis.

1. Ngina, P. M., Mbogo, R. W., and Luboobi, L. S. (2017a). Mathematical modelling of in-vivo dynamics of HIV subject to the influence of the CD8+ T-cells. *Applied Mathematics*, 8(08):1153–1179.

2. Ngina, P. M., Mbogo, R. W., and Luboobi, L. S. (2017b). The In Vivo Dynamics of HIV Infection with the Influence of Cytotoxic T Lymphocyte Cells. *International Scholarly Research Notices*, 2017:1–10.

3. Ngina, P. M., Mbogo, R.W., and Luboobi, L. S. (2018). Modelling Optimal Control of in-host HIV Dynamics using different control strategies. *Computational and Mathematical Methods in Medicine*, 2018:1-18.

Chapter 1

Introduction

1.1 Background to the Study

Human Immunodeficiency Virus (HIV) is a retrovirus that has been associated with Acquired Immunodeficiency Syndrome (AIDS). Since the identification of the first case of HIV/AIDS, in 1983 in the United States, HIV has emerged as one of the main challenges for global public health. According to UNAIDS, UNICEF and World Health Organization (2011), more than 36.7 million people worldwide are living with HIV/AIDS, of which 22.9 million live in Sub-Sahara Africa. By the end of 2015, Kenya in particular, had over 1.6 million people living with the virus (Kimanga et al., 2014; Joint United Nations Programme on HIV/AIDS,(UNAIDS), 2015). Nonetheless, by March 2015, 15 million people representing 41% of all the cases in the world had access to antiretroviral drugs (ARTs). The drugs were aimed at reducing viral progression and improving the patients health conditions. Use of ARTs, is one of the main achievements so far in the control of HIV progression and HIV transmission (Musicco et al., 1994; Castilla et al., 2005).

Unfortunately, even with the many studies (Wodarz and Nowak, 2002; Miron and Smith, 2010; Hattaf and Yousfi, 2012b) conducted on HIV, there is no effective strategy so far that prevents the virus progression or elimination altogether. That, however, does not mean that the intervention has not made any difference as far as treatment is concerned. Even though there are challenges in the use of ARTs, it is one of the most successful intervention measures so far in the control of HIV progression and HIV prevention (Musicco et al., 1994; Castilla et al., 2005). However, eradication of the virus to zero level remains an immense challenge. In spite of the huge scientific strides made in understanding many complex biological phenomena underlying HIV dynamics, HIV remains a major challenge to the scientific world and to the public health practitioners.

Consequently, management, control and prevention of HIV requires an integrated approach, which include, awareness/education and treatment with the best ARTs combinations. Lack of awareness/education, access to early diagnosis and effective treatment has delayed the success of the global HIV programme in reducing new infections and HIV/AIDS related deaths. Therefore, there is need for new and more advanced interventions for HIV prevention, management and care.

It is in this regard that researchers hope that, in future, a solution to this pandemic will be obtained and that timely diagnosis, timely introduction of ARTs and use of mathematical modelling may be the lead to this solution.

Figure 1.1 shows a summary of people living with HIV globally by 2014.

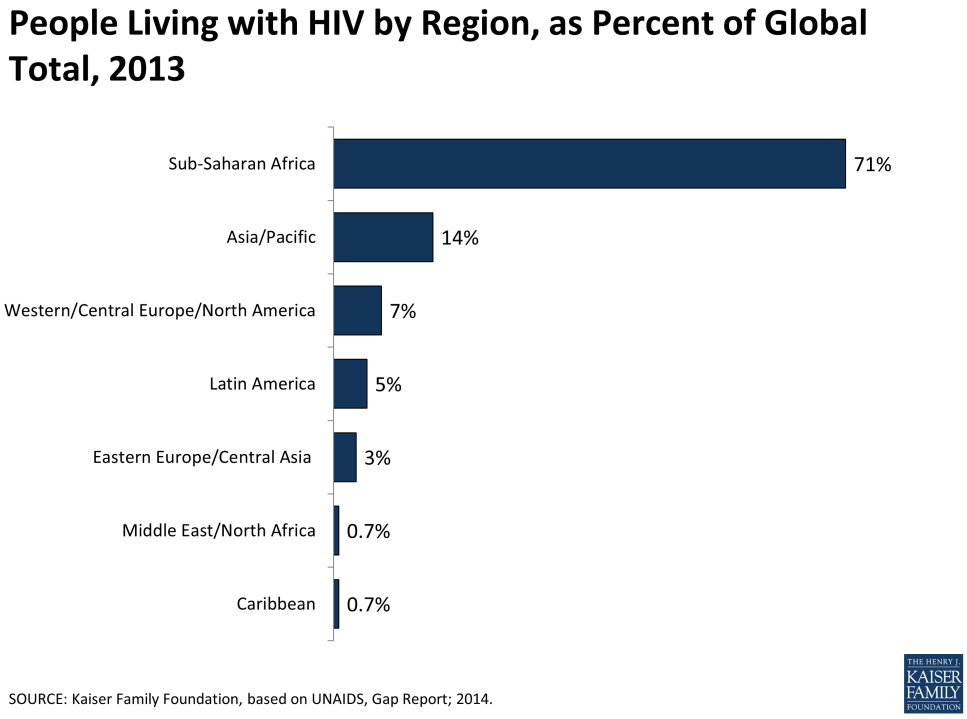


Figure 1.1: People living with HIV per region, as a percent of global total

1.1.1 HIV replication mechanism

HIV is highly concentrated in human blood, semen, vaginal fluid and breast milk. If a non-infected person is exposed to the aforementioned fluids of an infected person, one is at a risk of being infected. There are three major ways in which HIV could be

transmitted, that is, through sexual intercourse, through blood transfusion and mother-to-child transmission. However, HIV transmission through sexual intercourse accounts for the largest percentage of the HIV cases reported in the world. It is evident from past studies that the likelihood of one to be infected is directly proportional to the number of sex partners one has (Bulterys and Lepage, 1998; Pope and Haase, 2003).

Like most viruses, HIV, a retrovirus, lacks the ability to replicate on its own. HIV, therefore, relies on a host for replication and carries the copies of its own RNA (Mbogo et al., 2013). When the virus gets in the body, it mainly targets the $CD4^+$ T-cells. After the infection of the cells by the virus, it is important to note that the symptoms do not show immediately until the $CD4^+$ T-cells level reduces to about 200 cells/ mm^3 and the viral load increases to 500,000 copies /mL (Wodarz and Nowak, 2002). The process of HIV reproduction is outlined in the following steps: For HIV to replicate, it joins the membrane of the $CD4^+$ T-cell. The virus then fuses with the host cell and releases an enzyme called reverse transcriptase. Reverse transcriptase changes the genetic material of the virus from a single-stranded HIV RNA to a double-stranded HIV DNA, so that it can be integrated into the host DNA. The genetic material of the virus enters the host cell's nucleus and uses an enzyme called integrase to integrate itself into the $CD4^+$ T-cell genetic material. Once HIV is integrated in the cell's DNA, it starts using their $CD4^+$ T-cell's DNA to make long chains of HIV protein (Laskey and Siliciano, 2014). The HIV proteins are the building blocks for more HIV. These long chains of HIV proteins (immature and non-infectious) then assemble near the membrane of the $CD4^+$ T-cells and bud out.

The immature virions then release an enzyme called the protease, which cut the long HIV proteins/RNA into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new mature virion is formed. The new copies of HIV can now move on to infect other cells. This clearly shows that a single virion produces many potential threats to other cells (Yuan et al., 2016). A schematic diagram of HIV life cycle is presented in Figure 1.2.

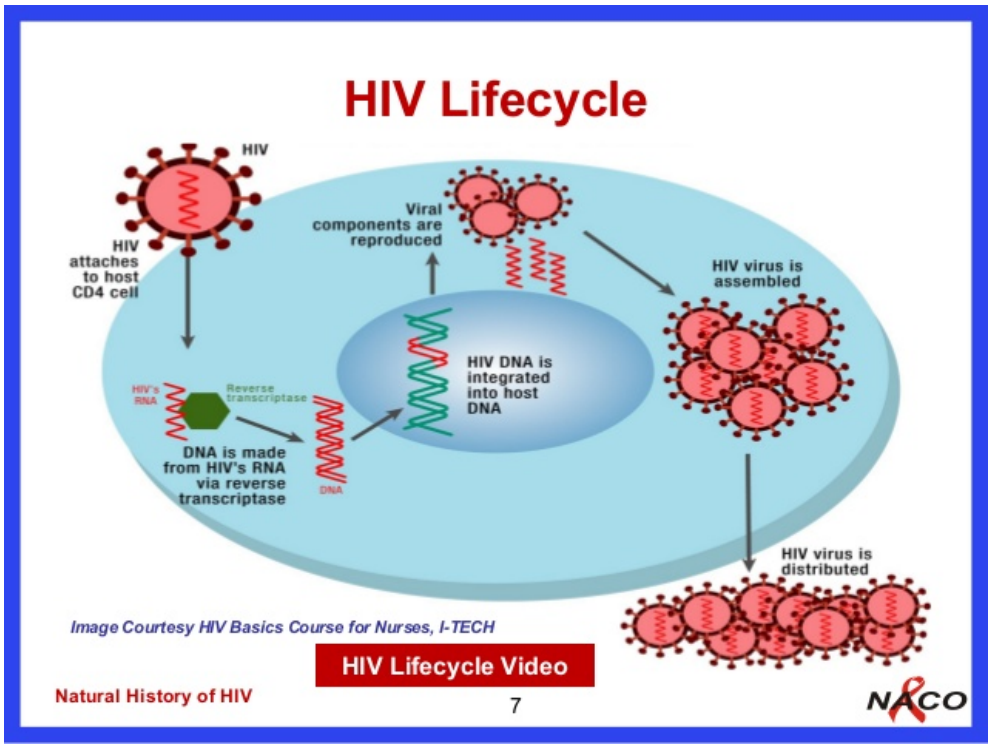


Figure 1.2: HIV life cycle.

1.1.2 Stages of HIV progression

The pattern of HIV progression in the body is divided into three stages (Kirschner, 1996).

Acute Infection

During the first few weeks of infection, patients experience a period of increasing viral load and a decline in $CD4^+$ T-cells numbers. During this period the infected person may experience the following symptoms: fever (raised temperature), body rash, sore throat, swollen glands, headache, upset stomach, joint aches and pains and muscle pains. In addition, the body immune system, in response, tries to attack the virus by producing HIV antibodies and the activation of the $CD8^+$ T-cells (Hollingsworth et al., 2008). This process is referred to as seroconversion.

It is worth noting that due to the high number of HIV virions in the blood during this stage, exposure to the blood or sexual fluid of someone in the acute phase of infection is more likely to result in an infection than exposure to someone with long-term infection. It has been estimated that the risk of infection is approximately 20 times

higher during acute HIV infection (Pinkerton, 2008).

The asymptomatic stage

This is the stage when the infected person does not experience any symptoms. In fact, the HIV virus may not reveal any other symptoms for up to 10 or even 15 years (depending on age, background and overall health). However, the virus will still be active, infecting new cells and making copies of itself. Over time this will cause a lot of damage in the infected persons immune system. In fact, during this stage, increased viral loads cause an impairment of $CD4^+$ T-cells. This compromises the longetivity of $CD8^+$ memory cells, however, there is a stimulation of the $CD8^+$ T-cells by the high antigen levels. This response help in reducing the viral load (Fiebig et al., 2003).

Symptomatic HIV infection

By the third stage of HIV infection, the immune system is completely damaged. At this point, the infected person is likely to get serious infections; bacterial and fungal diseases due to the compromised immune response. The infected person experiences symptoms such as: weight loss, chronic diarrhoea, night sweats, fever, persistent cough, mouth and skin problems, regular infections and other serious illnesses or diseases. This is the stage that leads to AIDS where the $CD4^+$ T-cells falls below 200 cells per cubic millimeter and the body is prone to many opportunistic infections. This phase also coincides with a shift in the virus population and the emergence of virus strains that are able to use CXCR4 co-receptors (instead of CCR5 co-receptors) and thus a wider range of immune cells become susceptible to the virus (Bonhoeffer et al., 2005; Regoes and Bonhoeffer, 2005). Due to the fragility of their immune system (low T-cell counts), patients suffer from a variety of opportunistic infections during the AIDS phase. Consequently, the diseases from these infections eventually lead to death of the infected person. It is worth noting that at this level the $CD8^+$ T-cells are overwhelmed by the many infections and hence not able to control any infection. A summary of the HIV stages is given in Figure 1.3.

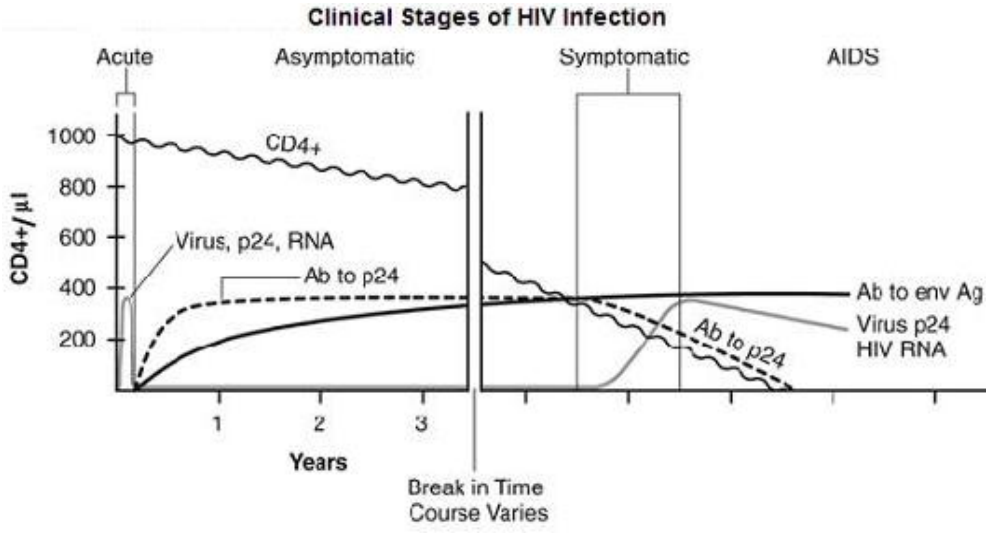


Figure 1.3: Stages of HIV progression (Pantaleo et al., 1993)

1.1.3 Relationship between CD4$^+$ T-cell count and viral load in HIV patients

According to Hogg et al. (2001), CD4$^+$ T-cell count is a blood test that health provider uses to check the level of CD4$^+$ T-cells in the body. The core role of the CD4$^+$ T-cells as far as HIV is concerned is to alert the CD8$^+$ T-cells. However, certain receptors on the CD4$^+$ T-cells make them prime targets for HIV. A normal CD4$^+$ T-cell count ranges from 500 to $1,600$ cells per cubic millimeter. In addition, if the CD4$^+$ T-cell count is below 200 cells per cubic millimeter for HIV patients the immune system becomes so compromised leading to the body being prone to many opportunistic diseases. At this stage, the body$'s$ immune system is weak due to the low number of CD4$^+$ T-cells available to alert the CD8$^+$ T-cells that fight the infections and hence the deterioration of the immune system lead to Acquired Immunodeficiency Syndrome (AIDS). On the other hand, the viral load is a test used to assess the level of HIV virions in the body. It measures the number of HIV virions in a millilitre of the blood. A low viral load is a sign of the virus copying itself in low amounts in the body and it is undetectable for levels below $40 - 75$ copies/mL. A viral load test helps in providing information on one's health status and how well antiretroviral therapy (ART treatment with HIV medicines) is controlling the HIV virions. Figure 1.4 shows the relationship between the viral load and the CD4$^+$ T-cell count at different stages of HIV infection.

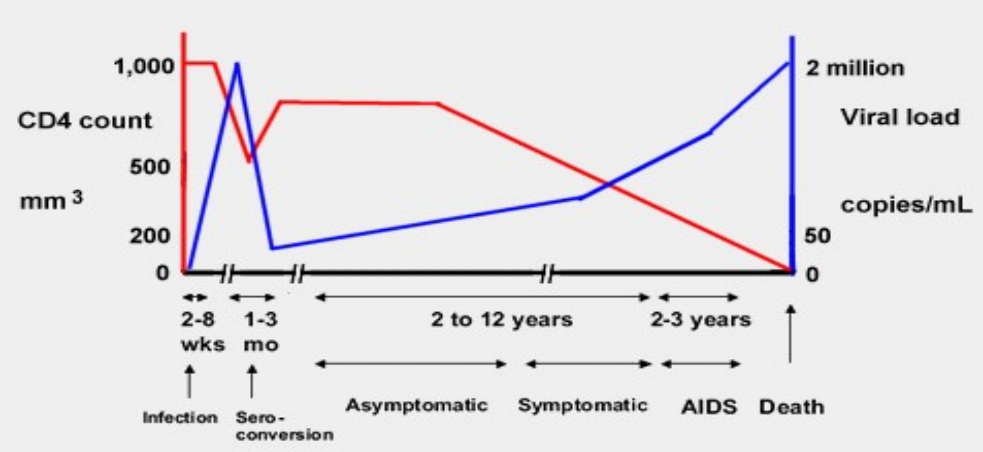


Figure 1.4: CD4$^+$ T-cell count and viral load without ART (Marcelo and Sonia, 2014)

Figure1.4 shows that after infection, the viral load level increases within the first three months. Then the immune system fights back and the viral load level drops to much lower levels. Over time though, usually after several years, viral load increases again. As the viral load increases the CD4$^+$ T-cell count decreases. Consequently, when the CD4$^+$ T-cell count is very low, the immune system is no longer strong enough to fight off infections, this lead to the body being attacked by many opportunistic diseases, where the patient finally dies.

1.1.4 The role of the CD8$^+$ T-cells in HIV infection

CD8$^+$ T-cells play a very vital role in controlling HIV replication during the early phase of infection. HIV-specific CD8$^+$T-cells are targeted at the dominant viral variant and their emergence is associated with a rapid fall in viral load before the development of an antibody response. After the HIV virions enter the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. This results to a high drop in the number of circulating CD4$^+$ T-cells. This acute viremia is associated with the activation of CD8$^+$ T-cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8$^+$ T-cell response is important in controlling virions levels, which peak and then decline, as the CD4$^+$ T-cells counts rebound (Klatt et al., 2013). Clinicians have associated a high CD8$^+$ T-cell response with slower disease progression and a better prognosis, though it does not eliminate the virus completely. However, majority of the CD8$^+$ T-cells generated during primary infection die within a few weeks, leaving a reservoir of HIV-specific CD8$^+$ memory T-cells that will persist, regardless of the presence of antigen or CD4

helper T-cells.

Researchers have found that viral load is better controlled in people whose HIV-specific $CD8^+$ T-cells mature fully into 'effector memory' T-cells (Croft et al., 1994). Without helper T-cells, which slowly disappear during HIV disease, the $CD8^+$ T-cells are unable to keep up with the increasingly diverse population of HIV inside the body (Benito et al., 2004). As HIV mutates in the body, due to several factors including pressure from antiretroviral medications, these $CD8^+$ T-cells become increasingly irrelevant. In addition, $CD8^+$ T-cells have been shown to express $CD4^+$ T-cells receptors on their surface following activation through the T-cell receptor, permitting infection by HIV. It has been suggested that this is a mechanism through which $CD8^+$ T-cells become depleted late in infection (Varela-Rohena et al., 2008).

Wodarz et al. (1998) in their study observed that the ability of HIV to infect the $CD4^+$ T-cells and a fast replication rate are the main factors that contribute to the depletion of the $CD8^+$ T-cells. This can be explained by the fact that $CD4^+$ T-cells play a vital role in the initiation of $CD8^+$ T-cells response, maturation and maintenance of $CD8^+$ T-cells memory.

1.1.5 Antiretroviral therapy

Many management options exist for control of HIV progression including use of antiretroviral therapies (ARTs), healthy diet, quitting drug abuse (alcohol, cigarettes, etc) and use pre exposure prophylaxis. However, the use of ARTs is the most effective as far as reducing viral progression and HIV prevention is concerned. Use of ARTs for the treatment of HIV has improved steadily since the introduction of potent combination therapy in 1996. ARTs have greatly reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition (Murphy et al., 2001). They are also highly effective at preventing HIV transmission. However, the most appropriate drug combinations are still under constant development and the best treatment for an HIV-infected person remains a subject of rigorous discussion (Culshaw et al., 2004; Nampala et al., 2014).

To date, the US Food and Drug Administration (FDA) has approved twenty-six ARTs and six fixed dose combinations for the treatment of HIV. These ARTs include Reverse Transcriptase Inhibitors (RTIs) also called nucleoside or nucleotide analogues, viral entry Inhibitors such as Fusion Therapy Inhibitors and Protease Inhibitors (PIs). The aim of ARTs is to reduce the replication of the HIV and prevent virus transmission. In particular, the RTIs inhibits the reverse transcription process (Joly and Pinto, 2006). This is because HIV is a retrovirus and it carries a copy of its own RNA. Consequently, HIV must be reverse transcribed into DNA using an enzyme it also carries called reverse transcriptase. Therefore, if RTIs are introduced in the human body they will block the reverse transcription process of the HIV RNA to HIV DNA, thus reducing cellular infection and the viral spread. Similarly, the PIs interfere with the viral protease enzyme necessary to produce mature virions upon budding from the host membrane. Consequently, the virions produced by the infected cells after the introduction of PIs are defective and non-infectious (Hattaf and Yousfi, 2012b). A process in which the virus become non-infectious though it is in the bloodstream plays a very important role in in-vivo dynamics. Inclusion of non-infectious virus in the optimal HIV therapy and management models would allow researchers to examine the efficacy of protease inhibitors.

The combination of RTIs and PIs has proved successful in many cases (Sullivan et al., 2009). For example, RTIs may prevent the reverse transcription process while the PIs may prevent the cells in which reverse transcription has taken place from releasing infectious HIV virions. Viral entry inhibitors such as Fusion inhibitors are a new family of ARTs whose use is not very common. Clinicians are still doing more research on the HIV entry process (Tilton and Doms, 2010). This is because the process of HIV entry into the $CD4^+$ T-cells represents a very important aspect in the search for new drug combinations to treat HIV infection. Nonetheless, researchers have identified three main steps that represent the mechanism of the virus entry process, that is, attachment of the virus to the $CD4^+$ T-cell receptor, binding of the virus to CCR5 or CXCR4 co-receptors and fusion of the viral and cellular membranes. Consequently, fusion inhibitors prevent the fusion of the virus and the $CD4^+$ T-cells. Unfortunately, up to now no drug combinations studied is known to completely shut down viral repli-

cation. HIV life-cycle with therapy is described in Figure 1.5.

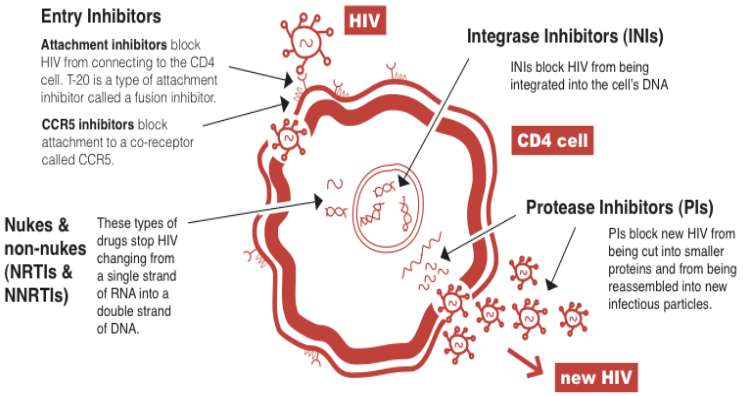


Figure 1.5: HIV life cycle with therapy (Simon, 2012)

Effects of ARTs on CD4$^+$ T-cell count and Viral load

The role played by ARTs as far as controlling the HIV is well represented in Figure 1.6.

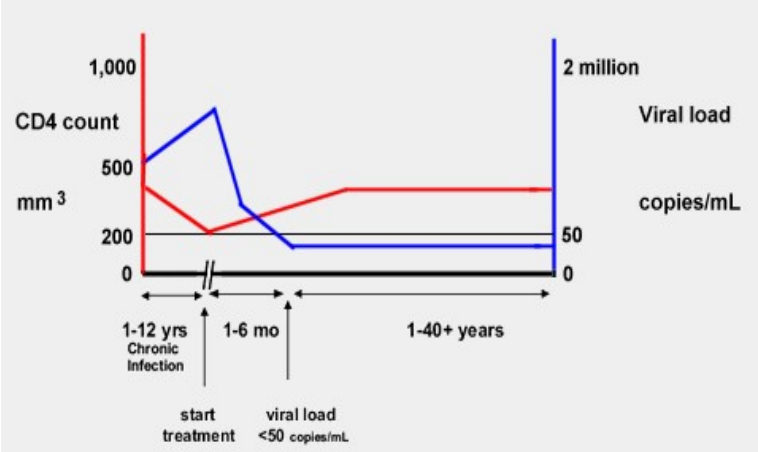


Figure 1.6: CD4$^+$ T-cell count and viral load with ART (Pantaleo et al., 1993)

Figure 1.6 shows how ARTS play a very vital role in ensuring that the level of the CD4$^+$ T-cells counts does not fall below 300 cells per cubic millimeter. It is evident from Figure 1.6 that the patient might live many years even after infection. It is therefore paramount for any HIV infected persons to adhere to the drugs. Government of Kenya through the Ministry of Health has started a campaign dubbed "Anza Sasa" where any person who test positive irrespective of their CD4$^+$ T-cells counts is put

on ARTs. This is a very noble idea since it will increase the life expectancy of HIV infected people. Many researchers (Musicco et al., 1994; Castilla et al., 2005), have pointed out that ARTs help in the reduction of HIV transmission by 80%. The results from the work done by Sullivan et al. (2009) in Zambia indicate that the infected people taking ARTs were less likely to transmit the virus to their sex partners than those who remained untreated. During acute infection there is high risk for transmission and researches have established that if patients are treated during this period there might be a reduction of latently infected cells (Chomont et al., 2009). Hence, the need for more research on the optimal use of ARTs.

1.1.6 Problems encountered during therapy

Despite the effectiveness of ARTs in suppressing the virus and reducing viral progression, it is evident that they cannot completely get rid of the virus and the patients have to rely on them for life. Use of the current combinations of ARTs for a long period is difficult to maintain and they cannot be considered as ideal drugs due to the many challenges that are associated with their use. To start with, the cost of the drugs is beyond reach for many infected patients, bearing in mind that they must continue taking ARTs for life. Most African governments have allocated a lot of financial resources to ARTs at the expense of other development projects. For instance, the National Government of Kenya allocated Ksh. 2.9 billion in the 2015/2016 national budget for HIV expense. African governments also face difficult choices in striking the right balance between prevention, treatment, and care, all of which are necessary to deal comprehensively with the epidemic (Creese et al., 2002).

The use of ARTs also leads to severe side effects such as fatigue, pain and nerve problems, anaemia, vivid dreams, and diarrhoea (Adams et al., 2005). These side effects are the main cause of therapy discontinuation and medication non-adherence in many HIV-infected people. Non-adherence to ARTs increases the level of the viral load (Ammassari et al., 2001) and could also lead to emergence of drug-resistant mutations (Miron and Smith, 2010). Drug resistance is one of the major reasons for therapeutic failure in people with HIV. It hinders complete eradication of the virus. Similar to drug resistant, it is evident that the drug may also fail to reach the target cells and this

explains why 100% viral eradication has not been achieved. Other challenges include lipid abnormalities, body habitual change, and toxicities.

In spite of these disadvantages, use of ARTs has led to prolonged life of HIV-infected persons, made them socially and economically active, less infectious to their sex partners, and has led to reduced rates of mother-to-child transmission (Kirschner, 1996). Nonetheless, many questions including who should be treated, when they should be treated, and what treatment scheme should be used are still a challenge to many health practitioners. Consequently, the optimal treatment and management scheme for HIV-positive patients that is able to address all the shortcomings associated with the use of ARTs remains the subject of intense research.

1.2 Statement of the Problem

HIV remains one of the main causes of premature deaths especially in developing countries. Even though so much research has been done on the management of HIV, most deaths in Sub-Saharan Africa are still due to HIV related opportunistic diseases that attack the body due to weak immune system. To suppress HIV, different combinations of ARTs have been recommended. Currently, HIV has no cure and long-term use of ARTs come with many challenges that require to be addressed. For instance, the cost of treatment is beyond reach of many Kenyans. Therefore, a lot of government money and donor money is used in acquiring these ARTs for infected people at the expense of other development projects. Secondly, most of these ARTs are associated with severe side effects, such as, fatigue, anaemia, pain, and nerve problems. Hence, a balance between the benefits of treatment in reducing the viral load and minimizing the side effects need to be drawn. In addition, non-adherence caused by toxicity and non-accessibility of the comprehensive care centers is a big challenge that leads to drug resistance mutations. Lastly, the optimal time to start ARTs remains a question of discussion. For all the reasons mentioned and more, it is essential that more and deeper research efforts be committed to the process until HIV is eradicated or is no longer such a debilitating global and local public health dilemma. Therefore, to address the problems aforementioned, there is a need to develop HIV optimal therapy and management models that endeavors to maximize treatment while minimizing the cost and the side effects of the ARTs.

1.3 Objectives

1.3.1 Main objective

The main objective of this work is to develop and analyze mathematical models for the in-vivo interaction between HIV virions, $CD4^+$ T-cells and $CD8^+$ T-cells and optimal control for effective therapy.

1.3.2 Specific objectives

The specific objectives are:

1. To formulate an in-vivo interaction model of HIV, the $CD4^+$ T-cells and the $CD8^+$ T-cells that would predict virus progression prior to intiation of therapy.

2. To formulate an in-vivo HIV model to investigate the effectiveness of the various HIV therapy combinations in reducing viral production.

3. To develop an optimal control model for HIV therapy.

1.4 Justification

Although strategies using ARTs for management of the infectious virus has been recommended, for HIV positive persons few studies have been carried out to examine how to manage and reduce drug non-adherence, drug toxicity, the optimal time to start ARTs for the infected people, and most importantly to establish optimal control therapy for HIV management. The benefits of ARTs can be fully realized by establishing the optimal way to manage HIV infected people. In this study the best ARTs combination that would minimize the toxicity and cost of treatment while maximizing therapeutic effects has been established. Implementation of the findings from this study will, hopefully, assist the Ministry of Health on the formulation of the guidelines and frameworks for clinical testing and monitoring of HIV/AIDS. Moreover, health practitioners could use this model in establishing the best combinations of ARTs that will lead to minimum side effects. They could also rely on the model in making informed decisions on the optimal time to start ARTs; this is in relation to the $CD4^+$ T-cell count. Similarly, the model might help the government and donors in making informed decisions on allocations of resources for HIV management. Most importantly, this research is in

line with Kenya's long-term vision for HIV control, that is, a Kenya free of new HIV infections, stigma and AIDS related deaths by 2030 and also the HIV global target of 90-90-90.

1.5 Thesis outline

This thesis is organized as follows: In Chapter 1, the study has described the biological background information on HIV/AIDS, as well as research aims and objectives. In Chapter 2, literature review based on mathematical models of HIV in-vivo dynamics both with and without therapy has been presented.

In Chapter 3, a deterministic in-vivo HIV model without therapy is formulated. Here the study focuses on the stability and bifurcation analysis to establish the existence of the equilibria and to understand the behaviour of the model, formulated in the study. The numerical simulations have been carried out and deductions made from the results obtained are presented. The model has been extended to include treatment in Chapter 4. Here, the effects of the three types of drugs (FIs, RTIs and PIs) combination on the HIV dynamics is explored and the numerical simulations for the extended model presented and discussions given.

In Chapter 5, optimal control theory has been applied to carry out economic evaluation and deriving the most optimal drug for HIV treatment. The optimality system is solved numerically using the Runge-Kutta forth order scheme. Finally, the conclusions, recommendations and ideas for future research are presented in Chapter 6.

Chapter 2

Literature Review

2.1 Introduction

According to UNAIDS, JUNPOHA (2010) HIV is one of the major causes of death worldwide. While in developed countries notable success has been obtained in terms of treatment and management of the infected persons, the situation in developing countries is pathetic. This therefore, makes HIV an important and an active field for research especially for the developing countries. Since the first HIV cases were reported in the early 1980's, there has been enormous effort made in the field of mathematical modelling of HIV/AIDS. To date, mathematical modelling is an integral part of the ongoing research on HIV dynamics. Numerous mathematical models of HIV epidemic at different levels in either population or in-host have been formulated and applied to the estimation of HIV/AIDS epidemics in a variety of settings over many years of active HIV research (Silva and Torres, 2015; Ghosh et al., 2016). The models have been known to synthesize existing knowledge and provide a framework for understanding the complex mechanisms on HIV dynamics. These models rely on almost all components of analysis and probability theory, deterministic and stochastic.

It is evident from past studies that the type of modelling methodology to be employed clearly depends on the process to be modelled and the point of view of the researchers. Many mathematical models on HIV in-host interaction use deterministic approach and are set in continuous time (use differential equations); that is not to suggest that stochastic approach has not been employed. For instance, Mbogo et al. (2013) used stochastic approach in modelling in-vivo HIV and $CD4^+$ T- cells dynamics and were able to obtain a probability generating function, the moment structures of the healthy $CD4^+$ T-cells and the virus particles at any time, and the probability of HIV clearance. Contrary to Mbogo et al. (2013) who used the stochastic approach, this study adopted the deterministic approach due to its non-complexity when dealing with

HIV dynamics.

2.2 Mathematical modelling of in-vivo HIV dynamics

HIV is a virus that causes AIDS and has led to high percentage of deaths especially in Africa. When the HIV gets in the body, it targets the CD4$^+$ T-cells, although the symptoms do not show immediately until the level of CD4$^+$ T-cells reduces and the viral load increases (Wodarz and Nowak, 2002). It should be noted that, many of the host-pathogen interaction mechanisms during HIV infection and progression to AIDS are still unknown hence, mathematical modelling of HIV infection is of interest to the medical community. This is due to the fact that no adequate animal models exist to test efficacy of drug regimes. These models test different assumptions and provide new insights into questions that are difficult to answer by clinical or experimental studies.

To date, a number of mathematical models have been formulated to describe various aspects of the interaction of HIV with healthy cells. It is evident that viral load measurements and CD4$^+$T-cell counts are important factors used in monitoring virus progression and treatment decisions. For instance, CD4$^+$ T-cell counts reflect immunological status and very low CD4$^+$T-cell counts are associated with higher mortality and increased risk of virus progression (Egger et al., 2002). Due to this fact, the earliest mathematical models were based on the interaction between the CD4$^+$ T-cells and the HIV virus. These basic non-linear models were developed and used to study the dynamics of the HIV virus and in measuring crucial parameters that led to new understanding of the disease process (Rivadeneira et al., 2014).

With the aim of providing the most fundamental information on controlling the viral progression, the most basic of these models typically include two or three of the three key/state variables. The key variables include: the susceptible CD4$^+$ T-cells, T, the already infected CD4$^+$ T-cells, I_T and the free virus, V. System (2.1) represents such models as used by: Shirazian and Farahi (2010); Hattaf and Yousfi (2012b).

$$\begin{aligned} \frac{dT}{dt} &= s - \beta T - \kappa VT, \\ \frac{dI_T}{dt} &= \kappa VT - \alpha I_T, \\ \frac{dV}{dt} &= \eta\alpha I_T - cV. \end{aligned} \tag{2.1}$$

Here s is the rate at which the CD4$^+$ T-cells are produced from the thymus and β is the decay rate of the CD4$^+$ T-cells. In addition, κ represents the rate at which the CD4$^+$ T-cells get infected by the virus. Once they are infected, the model assumes that they die at constant rate α. The free virus is generated by the infected cells at the rate η and they die at the rate c. In this simple model, it was assumed that after infection, the CD4$^+$ T-cells become actively infected and they produce the infectious- free virus. This basic model gives some insight on HIV infection dynamics. For instance, the model predicts adequately the disease progression from the initial infection stage, asymptomatic stage, to full Blown-AIDs and the viral load at the asymptomatic stage. However, as much as this simple model described by system (2.1) gives valuable information, a lot of improvement has been done and many other advanced models developed.

For instance, Duffin and Tullis (2002) formulated a mathematical model to represent complete dynamics of HIV infection:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - d_T T - k_T T V^*, \\
\frac{dTi}{dt} &= k_T T V^* - \delta_T T, \\
\frac{dM}{dt} &= \lambda_M - d_M M - k_M V, \\
\frac{dMi}{dt} &= k_M V^* - \delta_M M, \\
\frac{dV^*}{dt} &= \pi_T Ti + \pi_M Mi - cV^*,
\end{aligned} \tag{2.2}$$

where T, Ti, M, Mi and V^* represent the uninfected CD4$^+$ T-cells, the infected CD4$^+$ T-cells, macrophage cells, infected macrophage cells and the infectious virus from both the macrophage cells and the CD4$^+$ T-cells respectively. According to this model, λ_T is the rate at which the CD4$^+$ T-cells are produced from the thymus and d_T is the decay rate of the CD4$^+$ T-cells. In addition, k_T represents the rate at which the CD4$^+$ T-cells are infected by the virus. The infected CD4$^+$ T-cells die at the rate δ_T. The free virus is generated by the infected CD4$^+$ T-cells at the rate π_T and they die at the rate c. In addition, π_M is the production rate of macrophages, d_M the death rate of health macrophages, δ_M the death rate of infected macrophages, k_M represents the infection rate of macrophages and the production of virus by infected macrophages. The model aimed at showing the relationship between the CD4$^+$ T-cells, macrophage cells, and the viral load. The study suggested that infected macrophages cells are capable

of producing the large amount of virus seen late in infection period. The study provided insight on the relationship and interaction between the viral load, macrophages cells and the CD4$^+$ T-cells at early stages of infection but not after consistent infection.

This study was in agreement with other studies that have concluded on the importance of the macrophages cells in early stages of HIV infection (Orenstein et al., 1997). Although this simple model focused on the CD4$^+$ T-cells which represent the most important aspect of the HIV/ host relationship, the study did not assess the quantitative importance of the model on the dynamics on HIV infections. The inclusion of CD8$^+$ T-cells in the model would have given information valuable in the treatment of an HIV infected person. This is because when the CD4$^+$ T-cells sense there is danger they signal the CD8$^+$ T-cells to eliminate the virus by killing the infected CD4$^+$ T-cells.

However, Culshaw et al. (2004) acknowledged the importance of the immune system in HIV infection dynamics by incorporating the CD8$^+$ T-cells in HIV dynamic model. The study considered a system of three-dimensional ordinary differential equations of the untreated model. The model showed the interaction between the non-infected CD4$^+$ T-cells, infected CD4$^+$ T-cells, and the immune response as shown by system (2.3). From the model, the production of the immune CD8$^+$ T-cells depended on the infected CD4$^+$ T-cells and the non-infected CD4$^+$ T-cells. However, it is clear that the production of the CD8$^+$ T-cells do not depend precisely on the CD4$^+$ T-cell as some are produced directly from the thymus hence such an assumption is misleading.

$$\begin{aligned} \frac{dx}{dt} &= \lambda - \delta x - \beta xy, \\ \frac{dy}{dt} &= \beta' xy - ay - \rho yz, \\ \frac{dz}{dt} &= cxyz - hz, \end{aligned} \tag{2.3}$$

where $x(t)$, $y(t)$ and $z(t)$ are the variables representing the population of uninfected cells, infected CD4$^+$ T-cells and the population of immune response cells at any given time, t respectively. While the parameter λ is the source term for healthy CD4$^+$ T-cells, δ is their death rate and β is the rate at which they are infected by the HIV virus. The study considered the viral source to be directly from the infected cells. a is the death rate of the infected cells (natural death), ρ is the rate at which they are killed by the CD8$^+$ T-cells whereas c is the generation constant of the CD8$^+$ T-cells and h

is their death rate. Although this model incorporated the immune response, it made some very expensive assumptions, such as, the interaction between the infected and the non-infected $CD4^+$ T-cells; the only possible interaction is between non-infected $CD4^+$ T-cells and the virus to give infected $CD4^+$ T-cells. Moreover, the $CD8^+$ T-cells are activated by the interaction of the virus, the infected $CD4^+$ T-cells and the $CD8^+$ T-cells but not with the uninfected $CD4^+$ T-cells. The shortcomings of the model in system (2.3) need to be addressed.

Zhuang and Zhu (2013) analyzed a three dimensional in-host HIV model which include the susceptible $CD4^+$ T-cells, infected $CD4^+$ T-cells and the HIV virions. As much as this model was so basic since it had only three compartments it brought out important insight as far as HIV dynamics is concerned. The time lag from infection of the $CD4^+$ T-cells to the cells becoming actively infected was included in the model. The consideration of such a parameter is very important in HIV research. The study established the global existence of bifurcating periodic solutions with the assistance of global Hopf bifurcation theory. The numerical results in the study indicated that the latent period plays an important role in the disease spread and the disease may be controlled by shortening it.

Pankavich and Shutt (2015) analyzed an in-host model of HIV incorporating latent infection and viral mutation. The study was mainly interested in the analysis of the local behaviour of the system over time. The results indicated that the long term behaviour of the HIV model depends crucially upon parameter values, and even in the presence of viral mutation, the virus may be completely cleared from the body. Additionally, it was evident that HIV possesses a strong propensity to mutate, due to common errors in reverse transcription process. The effects of viral mutation contribute significantly to the dynamics of the disease. This is a very important insight since it allows researchers to work on the introduction of different combinations of ARTs in the body which will reduce the mutation and consequently the drug resistance. Nonetheless, the model failed to consider the body immune response which is a key variable in determining the disease dynamics and its progression.

Alshorman et al. (2017) formulated and analyzed a HIV model with time delay representing the time between initial cell infection and the establishment of latent infection, and the time between viral entry into cell and viral production in productively infected cells. The results indicated that the time delay between viral infection and viral production causes a very small change in the steady states of infected cells and viral load, but postpones the time to reach the viral peak. Inclusion of such a parameter in the model is of great importance since it will give a clear representation of the in-vivo dynamics of HIV. For instance, the intrinsic stability of latently infected $CD4^+$ T-cells explains the reason why the current HIV treatment consisting of several antiretroviral drugs cannot eradicate the latent reservoir of the infected cells. In addition, inclusion of the latently infected cells in the model gives room for the analysis of the homoeostatic proliferation of latently infected cells, latent reservoir and low-level viral load persistence during effective antiretroviral therapy.

Overall, the aforementioned modelling quests to capture the in-host dynamics of an HIV infection has improved our understanding of the progression to AIDS, but more generally, have also led to the insight that use of ARTs is very important if we want to reduce the rate of viral replication. Modelling drug treatment had a huge success in determining strategies to reduce the risk of evolution of drug resistant strains and lead to the combination therapy which is widely used in HIV treatment. These models with drug treatment are discussed in the next section.

2.3 HIV Dynamics with Therapy

To date, HIV has no cure and hence the most optimal way is to consider virus eradication up to non-detectable levels (Baryarama et al., 2006). This means that the second major components to consider in the HIV in-host model is treatment. For HIV treatment, drugs such as, viral entry inhibitors (Fusion inhibitors, PIs), Reverse Transcriptase inhibitors (RTIs) and Protease inhibitors (PIs) have been developed to attack the virus on different phases of its life cycle during HIV infection. Use of ARTs has led to a profound reduction in the viral load and has prevented the patients from progressing to full-blown stage and from AIDS-related opportunistic diseases.

In Kenya the most common ARTs in use are: Nucleoside analogue Reverse Transcrip-

tase Inhibitors (NRTIs) such as Zidovudine(AZT), Lamivudine (3TC), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) such as Efavirenz (EFV), Delavirdine (DLV) and Protease Inhibitors (PIs) such as Ritanourvir (RTV), Indinavir (IDV) (NASCOP, 2016). The NNRTIs and NRTIs inhibits the Reverse Transcription process. This is because HIV is a retrovirus and it carries a copy of its own RNA. Consequently, HIV has to be reverse transcribed into DNA using an enzyme it carries called reverse transcriptase. Therefore, if NRTIs and NNRTIs are introduced in the human body they will block the reverse transcription process of the HIV RNA to HIV DNA, thus reducing cellular infection and the viral spread. Similarly, the PIs interfere with the viral protease enzyme necessary in the production of mature virions upon budding from the host cell. Consequently, the virions produced by the infected cells after the introduction of PIs are defective and non-infectious (Hattaf and Yousfi, 2012b).

Many researchers (Musicco et al., 1994; Castilla et al., 2005), have pointed out that ARTs help in the reduction of HIV transmission by 80 percent. The results from the work done by Sullivan et al. (2009) in Zambia indicates that the infected people taking ARTs were less likely to transmit the virus to their sex partners than those who remained untreated. In addition during acute infection there is high risk for transmission and researchers have established that if patients are treated during this period there might be a reduction of latently infected cells (Chomont et al., 2009). Finaly, according to Vo et al. (2008) use of ARTs for viral suppression has a big impact as far as controlling secondary transmission is concerned. It allows HIV-status-discordant couples to live a normal life with their partner at a lower risk. It is in this regard that the WHO has recommended early HIV treatment to help in the prevention of HIV transmission.

From the various studies aforementioned it is evident that ARTs play a vital role in reducing viral replication and this in turn reduce the risk of deaths and severe HIV associated illness and more importantly the broader population level prevention benefits. However, despite the effectiveness of ARTs in suppressing the virus and reducing viral progression, it is evident that they cannot completely get rid of the virus and the patients have to rely on them for life. Use of the current combinations of ARTs for a long period is difficult to maintain and they cannot be considered as ideal drugs. This

is because prolonged use of ARTs is associated with many challenges such as drug resistance, side effects, high cost, life style change, and problems with adherence (Ammassari et al., 2001; Adams et al., 2005; Miron and Smith, 2010). Nevertheless, even with their disadvantages, use of ARTs is currently the most optimal way to manage HIV. Consequently, many researchers continue with the search of optimal treatment strategies that can decrease virus mutations, pharmaceutical side effects, and complex and expensive medication burdens (Culshaw et al., 2004).

Various mathematical models have been proposed in order to analyze the effects of ARTs. For instance, Srivastava et al. (2009) developed a simple therapy model that incorporated the use of reverse transcriptase inhibitors shown in system (2.4).

$$\begin{aligned}
\frac{dT}{dt} &= s - kVT - \mu T + (\eta a + b){T_1}^*, \\
\frac{d{T_1}^*}{dt} &= kTV - (\mu_1 + \alpha + b){T_1}^*, \\
\frac{dT^*}{dt} &= (\eta - 1)\alpha {T_1}^* - \delta T^*, \\
\frac{dV}{dt} &= N\delta T^* - cV.
\end{aligned} \tag{2.4}$$

The state variables T, T_1, T^* and V in equations (2.4) represent the susceptible CD4$^+$ T-cells, infected CD4$^+$ T-cells before reverse transcription, infected CD4$^+$ T-cells in which reverse transcription is completed and HIV virions respectively. The parameters for the model in (2.4) are described as: s is the production rate of the CD4$^+$ T-cells and μ is the rate at which they die naturally. The parameter k is the infection rate of CD4$^+$ T-cells and μ_1 is death rate of infected cells. The parameter α is the transition rate from pre-RT infected CD4$^+$ T-cells class to productively infected class (post-RT). The parameter b is the reverting rate of infected cells to uninfected class due to non-completion of reverse transcription. The parameter δ represents the death rate of actively infected CD4$^+$ T-cells and includes the possibility of death by bursting of infected CD4$^+$ T-cells, c is the clearance rate of virus and N is the total number of viral particles produced by an infected CD4$^+$ T-cell. In addition, $0 < \eta < 1$ is the efficacy of the RT inhibitor. The study established that the use of therapy when the viral load is still low could result to long-term control of HIV progression. This is because early therapy would prevent HIV from overwhelming the immune system. However, this study had some deficiencies since it only included one control variable representing

the RTIs.

Rong et al. (2008) presented mathematical models with the inclusion of treatment and time delay. The study was aimed at fitting the data to the already presented mathematical models. The research provided very important insight as far as viral replication is concerned. For instance, the study established how the ARTs affects the emergence of drug resistance during treatment, and how a low level of virus and latently infected cells can persist in infected individuals for a prolonged period of time despite an apparently effective antiretroviral therapy.

Hattaf and Yousfi (2012a) tried to address that gap by extending the model presented by Srivastava et al. (2009) by including two control variables as shown below;

$$\begin{aligned}
\frac{dx}{dt} &= s_T - dx - (1-u_1(t))\beta V_1 x + ry, \\
\frac{dy}{dt} &= (1-u_1(t))\beta V_1 x - (a+r)y, \\
\frac{dV_1}{dt} &= (1-u_2(t))ky - \mu V_1, \\
\frac{dV_{N_1}}{dt} &= u_2(t)ky - \mu V_{N_1},
\end{aligned} \tag{2.5}$$

where x, y, V_1 and V_{N_1} represent the non-infected cells, infected cells, infectious virus and the non-infectious virus respectively. Uninfected CD4$^+$ T-cells are produced at a the rate s, die at a rate d and become infected by virus at a rate β. Infected cells die at a rate α. The parameter k is the rate at which the free virus is produced and μ the rate at which they are cleared. In addition, through therapy, a part of infected cells may also revert to the uninfected state by loss of all cccDNA from their nucleus at a rate r. The control functions $u_1(t)$ and $u_2(t)$, are bounded, Lebesgue integrable functions. The control $u_1(t)$ represents the efficiency of drug therapy in blocking new infection, so that the infection rate in the presence of drug is $(1-u_1(t))\beta$. The control $u_2(t)$, represents the efficiency of drug therapy in inhibiting viral production, such that the virion production rate under therapy is $(1-u_2(t))k$.

The study developed a therapy model with two-control variables one to prevent HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome and the other prevents infected cells from replication of infectious virus par-

ticles that is, RTIs and PIs respectively. The study assumed that some of the infected cells get cured after the introduction of PIs because infected $CD4^+$ T-cells return to the uninfected state by loss of all covalently closed circular DNA from their nucleus. Inclusion of such parameters should be considered with caution since from the onset of this epidemic no cure has been reported. The study concluded that depending on the amount of the drugs used the viral load decreases. This means that the more the drug concentration the less the viral load. Unfortunately, the study failed to account for the side effects that might arise due to high concentration of the drug.

Zarei et al. (2011) developed a five dimensional in-vivo HIV model. The study included concentration of healthy $CD4^+$ T-cells, concentration of infected $CD4^+$ T-cells, cytotoxic T-cells which were divided into precursors CTLp and effectors and the free virions. This study assumed that CTL response depends on $CD4^+$ T-cell help, and that HIV virions impairs T-helper cell function. Consequently, the proliferation of the CTLp population is proportional to both infected cells in the body and the number of uninfected T-helper cells. The simulated results indicated the importance of the CTL cells in the HIV model. The study included two controls, that is, the Reverses Transcriptase inhibitors and the Protease inhibitors aimed at performing the optimal control analysis to maximize the $CD4^+$ T-cell counts and minimize both the viral load and cost of drugs. The study however, failed to put into account the entry inhibitors such as the Fusion inhibitors.

Rivadeneira et al. (2014) used mathematical modelling to study HIV dynamics after antiretroviral therapy initiation. The model described the interaction between the healthy $CD4^+$ T-cells, infected $CD4^+$ T-cells and free viruses with the inclusion of the Reverses Transcriptase inhibitors and the Protease inhibitors. However, as much as the study contained only three compartments it provided important insight as far as reducing the drug side effects is concerned. In addition, the study computed drug amounts directly, in the optimal controls which is easier to interpret by physicians and patients. The study also included the long-term drug optimization taking into account the risk of treatment-resistant mutations, within the framework of the switching systems.

Ogunlaran and Oukouomi (2016) used mathematical modelling to analyze the most effective way of managing HIV infection. The study applied two drug therapies to block the infection of new cells and to prevent the production of new free virions. This study provided very important insight on the role played by the entry inhibitors which has not been analyzed by other researchers. The results also indicated the importance of early diagnosis with immediate commencement of the use of approved antiretroviral drugs before CD4$^+$ T-cells levels fall below 350 cells$/mm^3$, regardless of whether or not a person is showing signs of HIV. This is in line with the WHO recommendations which stipulate that all people living with the HIV be put on ARTs irrespective of their CD4$^+$ counts (World Health Organization, 2014).

On the other hand, Arruda et al. (2015), constructed a system of five-dimensional non-linear ordinary differential equations (ODEs) model showing the interactions between CD4$^+$ T-cells, virions, defense cells and ARTs.

$$\begin{aligned}
\frac{dx}{dt} &= \lambda_x - \mu_x x - \beta_v x v - u_1 x, \\
\frac{dy}{dt} &= \beta_v x v - \mu_y y - \rho_y y z_a - u_2 y, \\
\frac{dv}{dt} &= k_v \mu_y y - \mu_v v - \rho_v v z_a, \\
\frac{dz}{dt} &= \lambda_z - \mu_z z - \beta_z z v, \\
\frac{z_a}{dt} &= \beta_z z v - \mu_z z_a,
\end{aligned} \tag{2.6}$$

where, x represents the CD4$^+$ T-cells, y the infected CD4$^+$ T-cells, v the virus, z the defense cells and z_a the activated defense cells. The parameters in system (2.6) are described as follows. The parameter λ_x is the rate at which the non-infected CD4$^+$ T-cells are produced and μ_x is the rate at which they decay. In addition, β_v represents the rate at which the CD4$^+$ T-cells are infected by the virus. The infected CD4$^+$ T-cells, are produced from the interaction of their uninfected counterparts and the viruses, at the rate β_v, they decay at the rate μ_y and are eliminated by the activated defense cells at the rate ρ_y. Free virions are generated from infected cells at the rate k_v, they decay at the rate μ_v and are eliminated by means of the activated defense cells at the rate ρ_v. The defense cells, in turn, are generated at a constant rate λ_z and they decay at the rate μ_z. Furthermore, they become activated by the virus at the rate β_z. The activated defense cells are generated from the defense cells in the presence of the virus at rate β_z

and decay at the rate μ_z. The controls u_1 and u_2 represent the RTIs and PIs respectively.

The study by Arruda et al. (2015) showed different compromises between the drug's effectiveness and side effects. It is evident from the study that different treatment policies must be adopted in order to maximize the benefits of treatment while keeping the medication side effects at a minimum level. As much as this model included the defense cells, it failed to account for the defective and the non-infectious viruses released by the infected $CD4^+$ T-cells after the introduction of PIs. Inclusion of such variables would provide insights on the efficiency of PIs.

2.4 Optimization Process

HIV treatment design is a field that would immensely benefit from the contributions of researchers in the field of optimization and control (Shirazian and Farahi, 2010; Gan et al., 2017). Optimization is the process of maximizing or minimizing some function relative to some set of controls, often representing a range of choices available in a certain situation aimed at determining which might be best. Optimal control (dynamic optimization) has been widely used in various studies (Rivadeneira et al., 2014; Arruda et al., 2015; Ogunlaran and Oukouomi, 2016) of HIV progression especially in analyzing the efficacy of the various ARTs combinations.

The control objective functions for all the HIV models that have been developed to date, are governed by the main purpose for the study. In particular, optimal control function for HIV model with therapy seeks to maximize on the benefits of the ARTs, minimize on the costs of treatment, reduce the side effects and decrease the viral load. The above four objectives of the study are interrelated for instance, the study may be aimed at maximizing the level of healthy $CD4^+$ T-cells and minimizing the cost of treatment, maximizing immune response and minimizing both the cost of treatment and viral load, maximizing both the level of healthy $CD4^+$ T-cells and immune response and minimizing the cost of treatment, maximizing the level of healthy $CD4^+$ T-cells while minimizing both the side effects and drug resistance or maximizing survival time of patient subject to drug cost. According to Ogunlaran and Oukouomi (2016) for the aforementioned objectives, to be achieved any optimal control problem must have an objective function $J(x(t), u(t))$, a set of state variables $(x(t) \in X)$ and

a set of control variable $(u(t) \in U)$ in time t, $0 \leq t \leq t_f$.

Various studies have examined and established therapeutic regimes of HIV through control and optimization process. For instance, Shirazian and Farahi (2010) employed the objective function defined by equation (2.7) to help in maximizing the non-infected $CD4^+$ T-cells as well as minimizing the cost of treatment after introduction of the RTIs.

$$J(T,u) = \int_0^{t_f} \left[T(t) - \frac{1}{2}\alpha u^2(t) \right] dt \tag{2.7}$$

where α is a scalar and represents the control function (RTIs). However, many factors come into play during the process of HIV infection and treatment. Therefore, the control function defined by equation (2.7) is the most basic since the study considered only one control variable. Use of one control variable is likely to give biased information since currently ARTs are taken as a combination of more than one class of drugs. To study the effects of ARTs, Arruda et al. (2015) considered two control functions to represent the effects of RTIs and the PIs. The study improved the objective function given by equation (2.7) by adding one more control variable as shown by equation (2.8).

$$J = \frac{1}{2}\int_0^T \left[c_1 x_p^2 - c_2 u_1^2 - c_3 u_2^2 \right] dt \tag{2.8}$$

where c_1, c_2 and c_3 are non-negative scalars. The control variable u_1 corresponds to RTIs, u_2 to the PIs and x_p represents the protected cells by the RTIs. The objective function aimed at maximizing the protected cells while extenuating the drug side effects.

2.5 Bifurcation Analysis

Sastry (2013) defines bifurcation as a change in the nature of a solution of trajectories due to a parameter change. A transcritical bifurcation is a bifurcation where there is an exchange of stability between two equilibrium points at a bifurcation point where the stability is transferred from one equilibrium point to another. In infectious disease models, the exchange of stability occurs between a disease free equilibrium (DFE) point and the endemic equilibrium point when the basic reproduction number is equal to one ($R_0 = 1$). At this point DFE point looses its stability and the endemic equilibrium point becomes stable depending on the conditions on R_0. A transcritical bifurcation occurs in two forms, that is, forward or backward bifurcation (Britton, 2012).

During forward bifurcation, the DFE point looses its stability when it passes through the bifurcation point and endemic equilibrium gains its stability ensuring that the endemic equilibrium point is locally stable when $R_0 > 1$. A backward bifurcation in epidemic models occurs when there is existence of two sub-critical endemic equilibria for $R_0 < 1$. The initial direction of the bifurcation curve is such that as one moves away from the bifurcation point, R_0 will decrease as the level of infection increase. Backward bifurcation is important in determining the control of the HIV infection. This is because it is possible for the disease to progress even when $R_0 < 1$. Consequently, there is need to further reduce R_0 to ensure that the disease is eliminated from the body.

Rahmoun et al. (2016) presented a four dimensional mathematical model to analyze the bifurcation of in-vivo HIV model. The study applied the Lyapunov Schmidt approach in analyzing the bifurcation around the chronic equilibrium point. The results indicated the existence of a parameter that affects the model in such away that the disease may progress even when $R_0 < 1$. Furthermore, the study emphasized on the effects that the parameter has on the qualitative dynamical properties and structural stability of the infection evolution dynamics.

Yu and Zou (2012) on their study on bifurcation analysis on the HIV-1 model with constant injection of recombinant found the existence of a bifurcation parameter in the model which represented the injection rate η. The results indicated that an appropriate injection rate can help eliminate the HIV virus. This is because the mathematical solutions indicated the presence of a critical reproduction number R_η which depended on the injection rate. The HIV free equilibrium point for the model were found to be globally asymptotically stable when the basic reproduction number, $R_0 < R_\eta$ and unstable when $R_0 > R_\eta$.

From the literature it is evident that disease models exhibit bifurcation where the stable disease free equilibrium co-exists with a stable endemic equilibrium, that is, there exist two sub-critical endemic equilibria for $R_0 < 1$. The parameters that lead to such existence have been found to have a profound impact on the control of the infections. Biologically, bi-stability may lead to unexpected adverse consequences for ARTs and

existence of backward bifurcation may provide an explanation for several phenomena observed clinically among HIV patients. It is therefore paramount for researchers in the field of HIV to put into consideration the behaviour of the model at the steady states.

2.6 Management of HIV-positive individuals

One of the threats to health in a sexually active population is sexually transmitted infections (STIs) especially HIV. To date, HIV has no cure and management of the infected persons has been and is still the most important aspect. However, with the increased survival rate of patients treated with ART, the management of HIV has become much the same as for any other long-term condition. For management purpose clinicians have outlined some areas that need to be looked into, which include: emotional aspects, education and stigmatization.

2.6.1 Emotional aspects

For the achievement of vision 2030, where it is projected that there should be a Kenya free of new HIV infections, stigma, and AIDS related deaths, it is important that all stakeholders when dealing with medical aspects of sexual health and the presence of HIV infection to be sensitive to the emotive nature of all aspects of care. For instance, newly diagnosed patients are likely to need much emotional support. Some may have been unaware of their risk until diagnosed (eg, during antenatal screening). Education would play a vital role in sensitizing the stakeholders. Many infected persons fail to disclose their status, because disclosure may have potential risk for the infected individual, such as disruption of family relationship, stigma and rejection/discrimination, blame and emotional abuse (Medley et al., 2004). Lack of disclosure has increased the rate of new infections and also many people who should be on ARTs fail to take them due to the consequences.

2.6.2 Education and stigmatization

Education plays a very important role as far as HIV progression on the infected person is concerned. The main reasons for HIV/AIDS education on the infected person is to improve quality of life for HIV positive people. Too often, HIV/AIDS educa-

tion is seen as being something which should be targeted only at people who are not infected with HIV in order to prevent them from becoming infected. When AIDS education with HIV positive people is considered at all it is frequently seen only in terms of preventing new infections by teaching HIV positive people about the importance of not passing on the virus (Campbell and MacPhail, 2002). An important and commonly neglected aspect of AIDS education with HIV positive people is enabling and empowering them to improve their quality of life. HIV positive people have varying educational needs, but among them are the needs to be able to access medical services, drug provision, adherence to the ARTs and the need to be able to find appropriate emotional and practical support and help.

In Kenya, there is a great deal of fear and stigmatization of people who are HIV positive. Stigma and discrimination are some of the main issues that have made the effort on HIV prevention, treatment, care, and support unfruitful (Leary and Schreindorfer, 1998). The fear of stigma is too often accompanied by ignorance, resentment, and ultimately, anger. The people living with the virus are still treated as different by those who are uninfected. Research shows that this fear discourages people living with HIV to disclose their status, even to family members and to their sexual partners, and undermines their ability and willingness to access and adhere to treatment and may lead to drug discontinuation. It is evident that education is an integral and very fundamental aspect as far as HIV management is concerned.

Gallant and Maticka-Tyndale (2004) in their study on the School-based HIV prevention programmes for African youth established the importance of education in changing knowledge and attitudes and under certain conditions, behaviours of the youths. In Kenya the young generation contributes the highest percentage of new infections hence it is important to put in programmes that would lead to reduction of HIV transmission.

2.7 Summary

The study of in-vivo HIV infection remains a vital research area. There is an increasing need to obtain novel and efficient therapeutic mathematical models of HIV in-vivo. Many mathematical models of HIV dynamics, disease progression and therapy have been developed and exploited since the first cases of HIV were reported in Africa in

early 80s. It is evident that mathematical models on HIV dynamics analyze various processes taking place in HIV patients by use of various assumptions on the virus immune system interaction and the effects of ARTs. Irrespective of technological improvement in the different combinations of ARTs, no case has been reported on the cure of the virus. This implies that rigorous research on optimal management of the virus is paramount.

Different authors have formulated and discussed many mathematical in-vivo HIV models. These models have provided some insights into HIV progression, benefits of treatment as well as the cost and the risk of drug resistance. However, many more questions remain unanswered. It is evident that $CD8^+$ T-cells play a major role in curbing the virus progression although the exact mechanism on how they do it is not yet well understood. Nonetheless, it is unfortunate to note that, a vast majority of models in the literature have not incorporated the $CD8^+$ T-cells and their activation process in fighting the virus. Failure of models to incorporate the $CD8^+$ T-cells shows that the researchers are making the assumptions that in absence of ARTs there is no natural anti-HIV response. Such an assumption implies that the only mechanism of fighting HIV is by use of ARTs. However, in reality $CD8^+$ T-cells help in fighting the virus though their effectiveness may vary from patient to patient. Presumably, the stronger the $CD8^+$ T-cells response, the less the ARTs required to reduce the HIV progression. Therefore, it is paramount for researchers to analyze the relationship between the $CD4^+$ T-cells and the $CD8^+$ T-cells.

This study has applied mathematical modelling to establish such relationship and provide insights on what could be done to increase the strength and the effectiveness of the $CD8^+$ T-cells in fighting the HIV. Furthermore, due to lack of literature on the inclusion of Fusion inhibitors as one of the control variables as well as non-infectious virus that results from the use of PIs, this study addressed the gap by incorporating the aforementioned in the control model. The study established a treatment regime that will address the shortcomings such as the drug side effects, drug resistance, high cost of treatment, toxicity and one that have maximum benefits to the patient and the country through the social economic contribution of the infected people.

Chapter 3

In-Vivo Dynamics of HIV Subject to the Influence of the $CD8^{+}$T-cells

3.1 Introduction

Studies on in-vivo HIV dynamics have been done over the years, aimed at understanding the interaction mechanism of the immune system and the HIV virus. The information arising from such studies has proved so valuable especially in the development of ARTs and in HIV management. In the recent years, mathematical models of various complexity level have been used in the simulation and analysis of HIV dynamics (Adams et al., 2005; Chandra, 2009; Alizon and Magnus, 2012; Arruda et al., 2015). However, various issues in the in-vivo HIV dynamics remain unanswered by the current models. Therefore, there is need to come up with more models for the study of the in-vivo HIV dynamics.

In this chapter, an in-vivo HIV dynamics model with the inclusion of the immune cells, without treatment, has been formulated with the aim of establishing the core role played by the $CD8^{+}$ T-cells as far as controlling HIV replication is concerned. The positivity and boundedness of the model have been established and the expression for the basic reproduction number derived by applying the next Generation Matrix Method (van den Driessche and Watmough, 2002). In addition, both the disease free and endemic equilibrium points have been determined, their stability established and bifurcation analysis for the model carried out. Finally the numerical simulations for the in-vivo model have been presented.

3.2 Model Formulation

A mathematical model for the in-vivo interaction of the HIV virions and the immune cells has been considered. The model has been classified into five compartments. The

variables for the model are: the healthy CD4$^+$ T-cells (T), the infectious HIV virions (V), the infected CD4$^+$ T-cells (I), the CD8$^+$ T-cells (Z) and the activated CD8$^+$ T-cells (Z_a).

The healthy CD4$^+$ T-cells are recruited at a constant rate λ_T from the bone marrow and die naturally at a constant rate μ_T. The infected CD4$^+$ T-cells are as a result of the interaction between the uninfected CD4$^+$ T-cells and the HIV virions at a rate χ. They die naturally at a rate μ_I and are also eliminated by the activated CD8$^+$ T-cells at the rate α. In addition, the infected CD4$^+$ T-cells produce an average of ϵ_V virions. The new mature virions produced, infect other CD4$^+$ T-cells. The HIV virions population increases due to the budding of the infected CD4$^+$ T-cells at a rate ϵ_V and die at the rate μ_V. The CD8$^+$ T-cells (Z), are generated from the thymus at a constant rate λ_Z, and die naturally at a constant rate μ_Z. Due to the presence of the infected CD4$^+$ T-cells the CD8$^+$ T-cells became activated at the rate β. The activated CD8$^+$ T-cells (Z_a) are recruited from the CD8$^+$ T-cells in the presence of the infected CD4$^+$ T-cells, at the rate β and die naturally at a rate μ_{Z_a}. Definitions of variables and parameters for the model are summarized in Table 3.1 and Table 3.2, respectively.

Table 3.1: Variables for HIV in-vivo model

Variable	Description
$T(t)$	The concentration of the non-infected CD4$^+$T-cells per cubic millimetre at any time t.
$I(t)$	The concentration of the infected CD4$^+$T-cells per cubic millimetre at any time t.
$V(t)$	The concentration of HIV virions copies per milliliter at any time t.
$Z(t)$	The concentration of the CD8$^+$T-cells per cubic millimetre at any time t.
Z_a(t)	The concentration of the activated CD8$^+$T-cells per cubic millimetre at any time t.

Table 3.2: Parameters for HIV in-vivo model

Parameter	Description
λ_T	The rate at which the non-infected CD4$^+$ T-cells are produced per unit time.
μ_T	The rate at which the non-infected CD4$^+$T-cells decay or die.
χ	The rate at which the CD4$^+$T- cells are infected by the virus.
μ_I	The death rate of the infected CD4$^+$T-cells.
ε_V	The rate in which HIV virions are generated from the infected CD4$^+$T-cells.
μ_V	The death rate of the infectious virus.
α	The rate at which the infected cells are eliminated by the activated CD8$^+$T-cells.
λ_Z	The rate at which the CD8$^+$ T-cells are produced per unit time.
μ_Z	The death rate of the CD8$^+$ T-cells.
β	The rate at which the CD8$^+$ T-cells are activated by the presence of the virus and the infected CD4$^+$ T-cells.
μ_{Z_a}	The rate at which the activated defence cells decay.

A compartmental representation of model is presented as in Figure 3.1 which represents visually a mechanism which is governed by system (3.1).

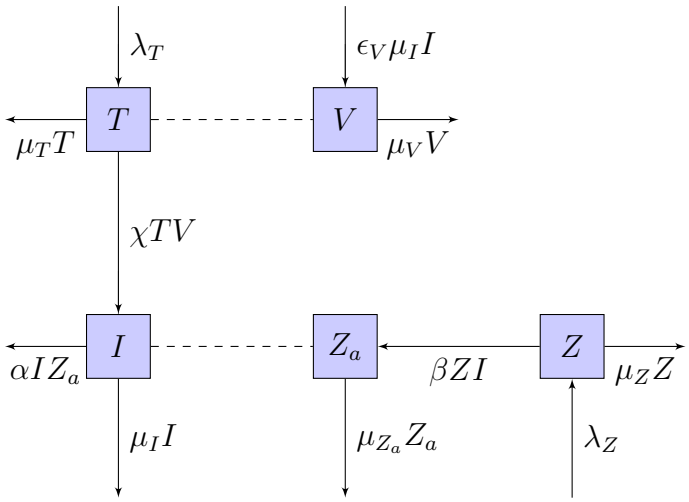


Figure 3.1: A compartmental representation of the in-vivo HIV Dynamics.

From Figure 3.1, the following model of non-linear ordinary differential equations for

the in-vivo HIV dynamics model has been derived:

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \chi TV, \\
\frac{dI}{dt} &= \chi TV - \mu_I I - \alpha I Z_a, \\
\frac{dV}{dt} &= \epsilon_V \mu_I I - \mu_V V, \\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta ZI, \\
\frac{dZ_a}{dt} &= \beta ZI - \mu_{Z_a} Z_a.
\end{aligned}\right\} \tag{3.1}$$

3.3 Model Analysis

Before commencing on the steady-states analysis of the system (3.1), it is important to look at some properties to ensure existence of biologically meaningful solutions.

3.3.1 Positivity and the boundedness of the solutions

In this section the non-negativity of the state variables of the system (3.1) implying that the solutions must be non-negative for all $t \geq 0$ and must be bounded for all $t \geq 0$ in an invariant region has been presented. The invariant region represents the domain in which the model solutions are well posed mathematically and epidemiologically meaningful.

Theorem 3.1. *Let the parameters for the system* (3.1) *be non-negative constants. A non-negative solution* $(T(t), I(t), V(t), Z(t), Z_a(t))$ *for the system* (3.1) *exists for all state variables with non-negative initial conditions* $(T(0) \geq 0, I(0) \geq 0, V(0) \geq 0, Z(0) \geq 0, Z_a(0) \geq 0)$ *for all* $t \geq 0$.

Proof. From the first equation of system (3.1) the population of the CD4$^+$ T-cells is given by

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \chi TV, \\
\frac{dT}{dt} &\geq -\mu_T T - \chi TV.
\end{aligned} \tag{3.2}$$

Separating the variables and integrating, equation (3.2) becomes,

$$\begin{aligned}
\int \frac{dT}{T} &\geq -\int (\mu_T + \chi V) dt, \\
T &\geq C e^{\int_0^t -(\mu_T + \chi V(s))ds}.
\end{aligned} \tag{3.3}$$

Taking the initial conditions at $t = 0$ and $T(0) = T_0$ then, equation (3.3) reduces to

$$T \geq T_0 e^{\int_0^t -(\mu_T + \chi V(s))ds} > 0. \tag{3.4}$$

Hence T is non-negative for all $t > 0$.

Similarly the population of the infected CD4$^+$ T-cells is given by

$$\begin{aligned} \frac{dI}{dt} &= \chi TV - \mu_I I - \alpha I Z_a, \\ \frac{dI}{dt} &\geq -(\mu_I I + \alpha I Z_a). \end{aligned} \tag{3.5}$$

By integration and separation variables equation (3.5) gives,

$$I \geq C e^{\int_0^t -(\mu_I + \alpha Z_a(s))ds}. \tag{3.6}$$

Taking the initial conditions at $t = 0$ and $I(0) = I_0$ then equation (3.6) changes to

$$I \geq I_0 e^{\int_0^t -(\mu_I + \alpha Z_a(s))ds} > 0. \tag{3.7}$$

Hence I is non-negative for all $t > 0$.

Similarly the differential equation for the HIV virions is,

$$\begin{aligned} \frac{dV}{dt} &= \epsilon_V \mu_I I - \mu_V V, \\ \frac{dV}{dt} &\geq -\mu_V V. \end{aligned} \tag{3.8}$$

By integration and separation variables equation (3.8) gives,

$$V \geq C e^{-\mu_V t}. \tag{3.9}$$

Taking the initial conditions at $t = 0$ and $V(0) = V_0$ then equation (3.9) becomes

$$V \geq V_0 e^{-\mu_V t} > 0. \tag{3.10}$$

Hence V is non-negative for all $t > 0$.

For the immune cells, part four of system (3.1) gives,

$$\begin{aligned} \frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I, \\ \frac{dZ}{dt} &\geq -(\mu_Z + \beta I) Z. \end{aligned} \tag{3.11}$$

By separation of variables and integrating both sides with respect to the corresponding variables the inequality for the population of the $CD8^+$ T-cells is given as,

$$Z \geq Ce^{\int_0^t -(\mu_Z + \beta I(s))ds}. \tag{3.12}$$

Taking the initial conditions at $t = 0$ and $Z(0) = Z_0$ then equation (3.12) becomes

$$Z \geq Z_0 e^{\int_0^t -(\mu_Z + \beta I(s))ds} > 0. \tag{3.13}$$

Hence Z is non-negative for all $t > 0$.

Finally, the differential equation for the activated immune cells is,

$$\begin{aligned} \frac{dZ_a}{dt} &= \beta ZI - \mu_{za} Z_a, \\ \frac{dZ_a}{dt} &\geq -\mu_{za} Z_a. \end{aligned} \tag{3.14}$$

By integration and separation of variables equation (3.14) becomes,

$$Z_a \geq Ce^{-\mu_{Z_a} t}. \tag{3.15}$$

Taking the initial conditions at $t = 0$ and $Z_a(0) = Z_{a_0}$ then equation (3.15) becomes

$$Z_a \geq Z_{a_0} e^{-\mu_{Z_a} t} > 0. \tag{3.16}$$

Hence Z_a is non-negative for all $t > 0$.

Thus, all the state variables are non-negative. Hence, the solutions of the system (3.1) remain positive for all $t \geq 0$. □

3.3.2 Invariant region

Notably, all the state variables of the system (3.1) have been proved to be non-negative. In addition, parameters of system (3.1) monitors cell population, hence they are also non-negative for all, $t > 0$. Consequently, the system (3.1) analysis is done in the region Γ that is biologically meaningful.

Theorem 3.2. *All solutions* $(T(t), I(t), V(t), Z(t), Z_a(t)) \in \mathbb{R}^5$ *of system* (3.1) *are bounded and there exist a biological feasible region* Γ *for the system* (3.1) *given as:*

$$\begin{aligned} \Gamma = \big\{ &(T(t), I(t), V(t), Z(t), Z_a(t)) \in \mathbb{R}^5 \mid \\ &T(t) > 0, I(t) > 0, V(t) > 0, Z(t) > 0, Z_a(t) > 0 \big\}. \end{aligned} \tag{3.17}$$

Proof. The total population of the CD4$^+$ T-cells, $T + I = N_4(t)$, is clearly a non-constant value. Hence, according to system (3.1) the evolution equation representing the change in the population of the CD4$^+$ T-cells is;

$$\begin{aligned} \frac{dN_4(t)}{dt} &= \lambda_T - \mu_T T - \mu_I I - \alpha I Z_a, \\ \frac{dN_4(t)}{dt} &\leq \lambda_T - \mu_T N_4(t). \end{aligned} \tag{3.18}$$

By separation of variables method for solving inequality, equation (3.18) becomes

$$\begin{aligned} \int \frac{dN_4(t)}{\lambda_T - \mu_T N_4(t)} &\leq \int dt, \\ \ln(\lambda_T - \mu_T N_4(t))^{-\frac{1}{\mu_T}} &\leq \ln C + t. \end{aligned} \tag{3.19}$$

Thus, inequality (3.19) can be written as

$$(\lambda_T - \mu_T N_4(t)) \leq C e^{-\mu_T t}. \tag{3.20}$$

But at $t = 0$ and denoting $N_4(0) = N_{4_0}$, inequality (3.20) reduces to,

$$C = \lambda_T - \mu_T N_{4_0}. \tag{3.21}$$

Substituting for C in inequality (3.21) in equation (3.20), then the inequality for the total population of the CD4$^+$ T-cells is

$$N_4(t) \leq \frac{\lambda_T}{\mu_T} - \frac{(\lambda_T - \mu_T N_{4_0}) e^{-\mu_T t}}{\mu_T}. \tag{3.22}$$

From inequality (3.22) we note that for

$$N_{4_0} > \frac{\lambda_T}{\mu_T} \quad \text{we have } N_4(t) \leq N_{4_0} \quad \forall \quad t \tag{3.23}$$

and for

$$N_{4_0} \leq \frac{\lambda_T}{\mu_T} \quad \text{we have } N_4(t) \leq \frac{\lambda_T}{\mu_T} \quad \forall \quad t. \tag{3.24}$$

Therefore, from inequalities (3.23) and (3.24) we have

$$N_4(t) \leq \max\left\{ N_{4_0}, \frac{\lambda_T}{\mu_T} \right\}. \tag{3.25}$$

Thus at any time $t > 0$, we have,

$$N_4(t) \leq \max\left\{ N_{4_0}, \frac{\lambda_T}{\mu_T} \right\}. \tag{3.26}$$

Hence, all feasible solutions set for the CD4$^+$ T-cells of the system (3.1) enters the region:

$$\Gamma_T = \left\{ (T(t), I(t)) \in \mathbb{R}^2 : N_4 \leq \max \left\{ N_{4_0}, \frac{\lambda_T}{\mu_T} \right\} \right\}. \tag{3.27}$$

Similarly the total number of the CD8$^+$ T-cells, $Z + Z_a = N_8(t)$, is given by;

$$\frac{dN_8(t)}{dt} = \lambda_Z - \mu_Z N_8(t). \tag{3.28}$$

By separation of variables method for solving differential equation (3.28) becomes

$$\begin{aligned} \int \frac{dN_8(t)}{\lambda_Z - \mu_Z N_8(t)} &\leq \int dt, \\ \ln(\lambda_Z - \mu_Z N_8(t))^{-\frac{1}{\mu_Z}} &\leq \ln C + t. \end{aligned} \tag{3.29}$$

Thus, inequality (3.29) can be written as

$$(\lambda_Z - \mu_Z N_8(t)) \leq C e^{\mu_Z t}. \tag{3.30}$$

At $t = 0$ and denoting $N_8(0) = N_{8_0}$ inequality (3.30) reduces to

$$C = \lambda_Z - \mu_Z N_{8_0}. \tag{3.31}$$

Substituting equation (3.31) into inequality (3.30) then, the inequality for the total population of the CD8$^+$ T-cells is

$$N_8(t) \leq \frac{\lambda_Z}{\mu_Z} - \frac{(\lambda_Z - \mu_Z N_{8_0}) e^{-\mu_Z t}}{\mu_Z}. \tag{3.32}$$

From inequality (3.32) we note that for

$$N_{8_0} > \frac{\lambda_Z}{\mu_Z}, \text{ we have, } N_8(t) \leq N_{8_0} \quad \forall \quad t \tag{3.33}$$

and for

$$N_{8_0} \leq \frac{\lambda_Z}{\mu_Z}, \text{ we have, } N_8(t) \leq \frac{\lambda_Z}{\mu_Z} \quad \forall \quad t. \tag{3.34}$$

Therefore, from inequalities (3.33) and (3.34) we have

$$N_8(t) \leq \max \left\{ N_{8_0}, \frac{\lambda_Z}{\mu_Z} \right\}. \tag{3.35}$$

Thus at any time $t > 0$ we have

$$N_8(t) \leq \max \left\{ N_{8_0}, \frac{\lambda_Z}{\mu_Z} \right\}. \tag{3.36}$$

Hence, all feasible solutions set for the CD8$^+$ T-cells of the system (3.1) enters the region;

$$\Gamma_Z = \left\{ (Z(t), Z_a(t)) \in \mathbb{R}^2 : N_8(t) \leq \max \left\{ N_{8_0}, \frac{\lambda_Z}{\mu_Z} \right\} \right\}. \tag{3.37}$$

Finally, according to system (3.1) the evolution equation representing the change in the population of the HIV virions, V, is given by,

$$\frac{dV(t)}{dt} \leq \varepsilon_V \mu_I I - \mu_V V. \tag{3.38}$$

But from inequality (3.26) $I \leq N_4(t) \leq \max \left\{ N_{4_0}, \frac{\lambda_T}{\mu_T} \right\}$, then equation (3.38) can be written as

$$\frac{dV(t)}{dt} \leq \varepsilon_V \mu_I \frac{\lambda_T}{\mu_T} - \mu_V V, \text{ since } I \leq \frac{\lambda_T}{\mu_T}. \tag{3.39}$$

By integration, inequality (3.39) gives

$$\begin{aligned} \frac{dV}{dt} + \mu_V V &\leq \varepsilon_V \mu_I \frac{\lambda_T}{\mu_T}, \\ V &\leq \frac{\mu_I \lambda_T \varepsilon_V}{\mu_T \mu_V} + Ce^{-\mu_V t}. \end{aligned} \tag{3.40}$$

At $t = 0$ and denoting $V(0) = V_0$ inequality (3.40) becomes

$$C = V_0 - \frac{\mu_I \lambda_T \varepsilon_V}{\mu_T \mu_V}. \tag{3.41}$$

Substituting C into inequality (3.41) into equation (3.40) the equality for HIV virions becomes

$$V \leq \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \left(1 - e^{-\mu_V t} \right) + V_0 e^{-\mu_V t}. \tag{3.42}$$

From inequality (3.42) we note that for

$$V_0 > \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V}, \text{ we have, } V(t) \leq V_0, \quad \forall \quad t \tag{3.43}$$

and

$$V_0 \leq \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V}, \text{ we have, } V(t) \leq \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V}, \quad \forall \quad t. \tag{3.44}$$

Therefore, from inequalities (3.43) and (3.44) we have

$$V(t) \leq \max \left\{ V_0, \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \right\}. \tag{3.45}$$

Thus at any time $t > 0$, we have

$$V(t) \leq \max \left\{ V_0 : \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \right\}. \tag{3.46}$$

Hence, all feasible solutions set for the HIV virions of the system (3.1) enters the region;

$$\Gamma_Z = \left\{ (V(t) \in \mathbb{R}, V(t) \leq \max \left\{ V_0, \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \right\} \right\}. \tag{3.47}$$

Consequently the feasible solution for the system (3.1) are bounded. Since all state variables are positive and bounded in $\mathbb{R}^5$, then the region Γ is positively invariant. □

Remark 3.1. The biologically feasible region Γ for the system (3.1) defined by the compact set

$$\begin{aligned} \Gamma = \big\{ & (T(t), I(t), V(t), Z(t), Z_a(t)) \in \mathbb{R}^5, \\ & T + I \leq \max \left\{ N_{4_0}, \frac{\lambda_T}{\mu_T} \right\}, Z + Z_a \leq \max \left\{ Z_{8_0}, \frac{\lambda_Z}{\mu_Z} \right\}, \\ & V(t) \leq \max \left\{ V_0, \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \right\} \right\}, \end{aligned} \tag{3.48}$$

with initial conditions $(T(0), I(0), V(0), Z(0), Z_a(0) > 0)$, is positively invariant and attracting for all $t > 0$. The domain Γ is positively invariant under the flow induced by system (3.1). Therefore, the system (3.1) is biologically meaningful and it is feasible to analyze the model in the domain Γ.

3.4 Equilibria and Reproductive Number

In the absence of infection by HIV virions the model as represented by system (3.1), has a unique feasible HIV-free steady state solution called the disease-free equilibrium. It is obtained by setting the derivatives of the infectious classes in system (3.1) to zero, that is, $V = I = Z_a = 0$. Thus, disease free equilibrium (DFE) of the system (3.1) is given by:

$$E_0(T, I, V, Z, Z_a) = \left[\frac{\lambda_T}{\mu_T}, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0 \right]. \tag{3.49}$$

3.4.1 Basic Reproductive Number

Researchers in the field of in-vivo HIV modelling aim at finding the threshold conditions that determine whether HIV virions will spread into susceptible CD4$^+$ T-cells when it is introduced in the body. In order to do this, researchers consider the basic reproductive number (R_0). According to Diekmann et al. (1990), the basic reproductive number represents the number of secondary infections that would result from one infected cell. In other words, it represents the average number of secondary infections

generated by a dying infected CD4$^+$ T-cell in the absence of ARTs to control the viral progression. HIV virions, once in the body, will continue infecting the CD4$^+$ T-cells. Whether the HIV virions become persistent or die out depends on the magnitude of the basic reproductive number.

Stability of equilibrium points can be analyzed using R_0. The disease free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. If $R_0 < 1$ then on average, a dying infected CD4$^+$ T-cell produces less than one newly infected CD4$^+$ T-cell over the course of the infection period. Then, the infection may die out. Conversely, if $R_0 > 1$, it implies that each infected CD4$^+$ T-cell produces, on average more than one new infection, the infection will be able to spread in the body and the infected person will eventually die due to the resulting opportunistic diseases. A large value of R_0, therefore, indicates endemicity. Consequently, in order to control viral replication it is important to ensure that the disease free equilibrium is stable, that is, $0 < R_0 < 1$.

3.4.2 Computation of R_0

In computing the basic reproduction number this study has adopted the next Generation Matrix method as given by Diekmann et al. (1990), and van den Driessche and Watmough (2002). Mathematically R_0 is given by

$$R_0 = \rho(FV^{-1}), \tag{3.50}$$

where ρ is defined as the spectral radius of the next generation matrix (Wiah and Mohammed, 2014), F is defined as the rate of appearance of new infections in a compartment while V is the transfer of individuals out of infectious compartment (van den Driessche and Watmough, 2002). The R_0 for the disease free equilibrium is calculated as the largest eigenvalue of the next generation matrix as follows. The matrix of the new infection at disease free equilibrium is given by

$$F = \begin{bmatrix} 0 & \frac{\chi\lambda_T}{\mu_T} \\ 0 & 0 \end{bmatrix}. \tag{3.51}$$

The matrix that represents the transfer of infection between compartments at the disease-free equilibrium is given by

$$V = \begin{bmatrix} \mu_I & 0 \\ -\varepsilon_V \mu_I & \mu_V \end{bmatrix}. \tag{3.52}$$

The inverse of V from equation (3.52) is

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_I} & 0 \\ \frac{\varepsilon_V}{\mu_V} & \frac{1}{\mu_V} \end{bmatrix}. \tag{3.53}$$

Thus, the next generation matrix FV^{-1} is given by,

$$FV^{-1} = \begin{bmatrix} \frac{\chi \varepsilon_V \lambda_T}{\mu_V \mu_T} & \frac{\chi \lambda_T}{\mu_T \mu_V} \\ 0 & 0 \end{bmatrix}. \tag{3.54}$$

The eigenvalues of the matrix given by (3.54) are; $\frac{\chi \varepsilon_V \lambda_T}{\mu_V \mu_T}$ and 0.
Therefore, the reproductive number, which is the largest eigenvalue is:

$$R_0 = \chi \frac{\lambda_T}{\mu_T} \frac{\epsilon_V}{\mu_V}. \tag{3.55}$$

The basic reproductive number, R_0, as given by (3.55) represents the number of secondary infections resulting from a dying infected cell over its average life time $\frac{1}{\mu_V}$. Notably, the infection would die out if $R_0 < 1$ while the HIV infection becomes endemic if $R_0 > 1$. In particular, from (3.55), it is evident that any intervention that would reduce the rate of infection, χ, would go along way in reducing the R_0.

3.5 Sensitivity Analysis of R_0 with respect to the Model Parameters

The aim of researchers especially in the field of HIV modelling is to understand the dynamics of HIV so as to control it. This is mainly done by targeting some parameters to which the R_0 is sensitive. This study has applied the normalized forward index method in the sensitivity analysis.

Definition 3.1. The normalized forward sensitivity index of R_0 with respect to the parameter P is defined as:

$$\gamma_P^{R_0} = \left(\frac{\partial R_0}{\partial P} \right) * \left(\frac{P}{R_0} \right), \tag{3.56}$$

where P represents a parameter in the expression of the basic reproductive number.

From the basic reproductive number given by equation (3.55) the sensitivity indices of R_0 with respect to the parameters $\chi, \epsilon_V, \lambda_T, \mu_V, \mu_T$ are respectively given as:

$$\frac{\partial R_0}{\partial \chi}\frac{\chi}{R_0} = 1, \tag{3.57}$$

$$\frac{\partial R_0}{\partial \varepsilon_V}\frac{\varepsilon_V}{R_0} = 1, \tag{3.58}$$

$$\frac{\partial R_0}{\partial \lambda_T}\frac{\lambda_T}{R_0} = 1, \tag{3.59}$$

$$\frac{\partial R_0}{\partial \mu_V}\frac{\mu_V}{R_0} = -1, \tag{3.60}$$

$$\frac{\partial R_0}{\partial \mu_T}\frac{\mu_T}{R_0} = -1. \tag{3.61}$$

Table 3.3 gives normalized forward sensitivity indices of R_0 irrespective of the values of the parameters .

Table 3.3: Normalized forward sensitivity indices of R_0 irrespective of the parameters value.

Parameters	Sensitivity index
ϵ_V	1
χ	1
λ_T	1
μ_V	-1
μ_T	-1

From the sensitivity indices it is evident that R_0 is most positively sensitive to parameters χ and ϵ_V. This implies that to maintain a small number of the R_0, these two parameters, χ and ϵ_V, must be reduced; whereas increasing them would lead to an increase in the R_0. Furthermore, R_0 is most negatively sensitive to parameter μ_V and ϵ_V. This implies that increasing any of these parameters (or both) would lead to a decrease in the value of R_0.

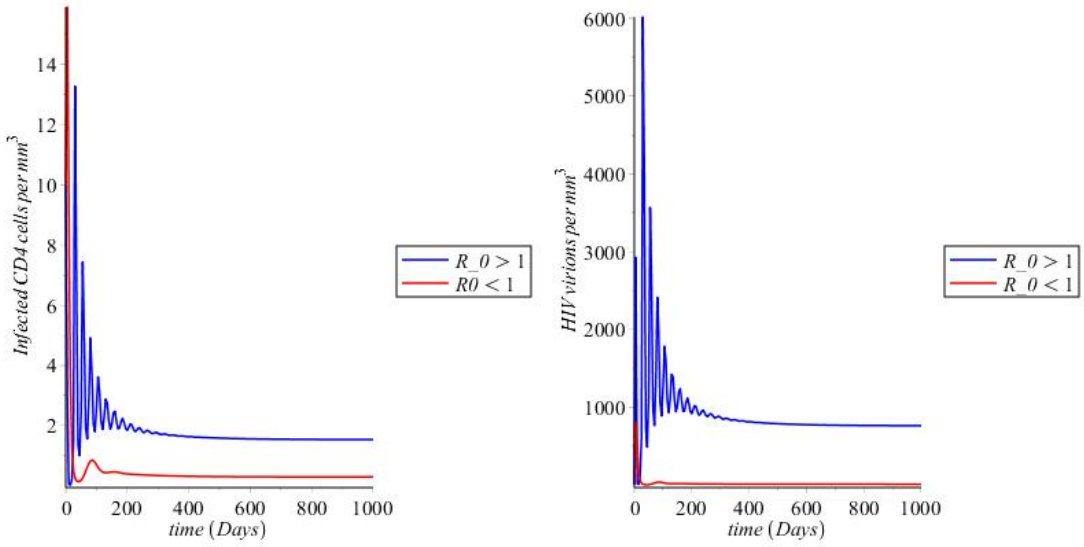
Remark 3.2. Since both λ_T and μ_T represents a naturally occurring phenomena in the body, they are not included in sensitivity analysis.

3.5.1 Effect of R_0 on the in-vivo HIV dynamics

In this subsection the effects of R_0 on the dynamics of infected cells and the HIV virions is established. The parameter values given in Table 3.4 are used in the analysis.

Table 3.4: Parameters for in-vivo HIV model

Parameters	Value	Source
λ_T	10 cell/mm^3/day	Attarian and Tran (2017).
μ_T	0.01 day^{-1}	Srivastava et al. (2009).
χ	0.000024 mm^3 vir$^-1$ day$^-1$	Attarian and Tran (2017).
μ_I	0.5 day$^-1$	Wodarz and Nowak (2000).
ϵ_V	100 vir. cell$^-1$ day$^-1$	Mbogo et al. (2013).
μ_V	3 day$^-1$	Mbogo et al. (2013).
α	0.02 day^{-1}	Arruda et al. (2015).
λ_Z	20 cell/ mm^3/day	Arruda et al. (2015).
μ_Z	0.06 day^{-1}	Arruda et al. (2015).
β	0.004 day^{-1}	Arruda et al. (2015).
μ_{Z_a}	0.004 day^{-1}	Arruda et al. (2015).



Population of the infected CD4$^+$ T-cells Population of the HIV virions

Figure 3.2: The HIV and infected CD4$^+$ T-cells dynamics for $R_0 > 1$ and $R_0 < 1$

From Figure 3.2, it is evident that change in R_0 have a big impact on the magnitude of infected cells and the HIV viral load. Notably, from Figure 3.2 an increase in R_0, that is, having $R_0 > 1$ leads to an increase in the number of the HIV virions and consequently the infected cells. This implies that the body's immunity is at risk and the infected person is likely to progress to AIDS stage. However, when $R_0 < 1$ the number of the HIV virions in the blood reduce significantly, thus, the infection is likely to die out. From the research findings on R_0 the study deduce that, for medical practitioners to reduce the magnitude of HIV infection it is important to ensure that $R_0 < 1$. This may be done by developing controls, interventions and management policies that if implemented would ensure that $R_0 < 1$.

In the next sub-section the stability of the disease-free equilibrium point of the in-vivo HIV model in system (3.1) is investigated and results presented.

3.5.2 Local stability of the disease-free equilibrium (DFE)

Theorem 3.3. *The disease-free equilibrium E_0 of system* (3.1) *is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

The epidemiological implication of the Theorem 3.3 is that whenever $R_0 < 1$ the disease would be eliminated provided the initial size of the infected CD4$^+$ T-cells

population of the model in system (3.1) is sufficiently small.

Proof. This study applies linearization method to study and prove the local stability of the disease-free equilibrium. According to this method the disease-free equilibrium, E_0, is locally asymptotically stable if all the eigenvalues of the Jacobian matrix of the system (3.1), computed at the DFE, E_0, have negative real parts. The Jacobian matrix associated with the system (3.1) is given by:

$$J = \begin{bmatrix} -\mu_T - \chi V & 0 & -\chi T & 0 & 0 \\ \chi V & -\mu_I - \alpha Z_a & \chi T & 0 & -\alpha I \\ 0 & \varepsilon_V \mu_I & -\mu_V & 0 & 0 \\ 0 & -\beta Z & 0 & -\mu_Z - \beta I & 0 \\ 0 & \beta Z & 0 & \beta I & -\mu_{Za} \end{bmatrix} \tag{3.62}$$

At the disease-free equilibrium point, E_0 (3.49), the Jacobian matrix (3.62) of system (3.1), becomes

$$J = \begin{bmatrix} -\mu_T & 0 & -\chi\frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & -\mu_I & \chi\frac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & \varepsilon_V \mu_I & -\mu_V & 0 & 0 \\ 0 & -\beta\frac{\lambda_Z}{\mu_Z} & 0 & -\mu_Z & 0 \\ 0 & \beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & -\mu_{Za} \end{bmatrix} \tag{3.63}$$

The eigenvalues of the Jacobian matrix (3.63) are $-\mu_T$,$-\mu_Z$, $-\mu_{Z_a}$ and the solutions to the characteristic equation,

$$\lambda^2 + (\mu_T + \mu_V)\lambda + \mu_I \mu_V \left(1 - \frac{\chi \lambda_T \epsilon_V}{\mu_T \mu_V}\right) = 0. \tag{3.64}$$

The solutions to equation (3.64) have negative real part if

$$\frac{\chi \lambda_T \varepsilon_V}{\mu_T \mu_V} < 1. \tag{3.65}$$

Note that $R_0 = \chi\frac{\lambda_T}{\mu_T}\frac{\epsilon_V}{\mu_V} < 1$. Therefore, the disease free equilibrium is locally asymptotically stable for $R_0 < 1$ otherwise it is unstable. □

3.6 The Endemic Equilibrium

The endemic equilibrium, E_1, is the state in which HIV infection may persist in the body, characterized by very high viral load and a decrease in the number CD4$^+$T-cells. To analyze for the stability of the endemic equilibrium this study has adopted the

assumption made by Culshaw et al. (2004) that the free virus spread the infection and there is no cell-to-cell transfer of the HIV virions. The endemic equilibrium, E_1, exists when, $T(t) > 0$, $I(t) > 0$, $V(t) > 0$, $Z(t) > 0$, $Z_a(t) > 0$. An endemic equilibrium, $E_1 = (T^*, I^*, V^*, Z^*, {Z_a}^*)$, satisfies

$$\left.\begin{aligned} \lambda_T - \mu_T T^* - \chi T^* V^* &= 0, \\ \chi T^* V^* - \mu_I I^* - \alpha I^* {Z_a}^* &= 0, \\ \epsilon_V \mu_I I^* - \mu_V V^* &= 0, \\ \lambda_Z - \mu_Z Z^* - \beta Z^* I^* &= 0, \\ \beta Z^* I^* - \mu_{Z_a} {Z_a}^* &= 0. \end{aligned}\right\} \tag{3.66}$$

Hence, the endemic equilibria of the system (3.1) correspond to the positive solutions of the model (3.66). The model (3.66) is solved in terms of ${Z_a}^*$ to obtain the endemic equilibrium as

$$\left.\begin{aligned} T^* &= \frac{\lambda_T \mu_V \beta(\lambda_Z - Z_a^* \mu_{Z_a})}{\mu_T \mu_V \beta(\lambda_Z - Z_a^* \mu_{Z_a}) + Z_a^* \epsilon_V \mu_Z \chi \mu_{Z_a} \mu_T}, \\ I^* &= \frac{Z_a^* \mu_{Z_a} \mu_Z}{\beta(\lambda_Z - Z_a^* \mu_{Z_a})}, \\ V^* &= \frac{\epsilon_V \mu_Z \mu_{Z_a} \mu_I Z_a^*}{\beta \mu_v (\lambda_Z - Z_a^* \mu_{Z_a})}, \\ Z^* &= \frac{\lambda_Z - Z_a^* \mu_{Z_a}}{\mu_Z}. \end{aligned}\right\} \tag{3.67}$$

The cubic polynomial that describes the existence of the possible equilibria is therefore obtained as

$$p(Z_a^*) = Z_a^*(\Phi_2 Z_a^{*2} + \Phi_1 Z_a^* + \Phi_0) = 0, \tag{3.68}$$

where,

$$\left.\begin{aligned} \Phi_2 &= -4\beta \mu_{Z_a} \mu_Z (\mu_{Z_a} \mu_I + \alpha \lambda_Z) \leq 0, \\ \Phi_1 &= 4\mu_{Z_a} \mu_Z \mu_T \left[-R_0 \mu_I \mu_{Z_a} (\mu_I \mu_Z - \beta \lambda_T) - \lambda_T \beta (\mu_I \mu_{Z_a} + \alpha \lambda_Z) \right], \\ \Phi_0 &= 4R_0 \mu_{Z_a}^2 \mu_Z^2 \mu_T^2 \mu_V^2 (R_0 - 1). \end{aligned}\right\} \tag{3.69}$$

System (3.69) can be re-written as

$$\left.\begin{aligned} \Phi_2 &= 4\beta \mu_{Z_a} \mu_Z (\mu_{Z_a} \mu_I + \alpha \lambda_Z), \\ \Phi_1 &= -4\mu_{Z_a} \mu_Z \mu_T \left[R_0 \mu_I \mu_{Z_a} (\mu_I \mu_Z - \beta \lambda_T) - \lambda_T \beta (\mu_I \mu_{Z_a} + \alpha \lambda_Z) \right], \\ \Phi_0 &= 4R_0 \mu_{Z_a}^2 \mu_Z^2 \mu_T^2 \mu_V^2 (1 - R_0). \end{aligned}\right\} \tag{3.70}$$

The scenario, $Z_a^* = 0$ in equation (3.68), represents the disease-free equilibrium obtained in equation (3.49). Hence equation (3.71) defines the existence of the possible endemic equilibrium.

$$\Phi_2 Z_a^{*2} + \Phi_1 Z_a^* + \Phi_0 = 0, \tag{3.71}$$

The two roots of the quadratic equation (3.71) are given by;

$$Z_a^* = \frac{-\Phi_1 \pm \sqrt{\Phi_1^2 - 4\Phi_2\Phi_0}}{2\Phi_0}. \tag{3.72}$$

Consequently, depending on the signs of Φ_1 and Φ_0 the quadratic equation (3.72) may have unique, two or no positive roots. The three scenarios are analyzed as follows.

Case 1:

If $R_0 = 1$ then $\Phi_0 = 0$, $\Phi_1 < 0$,$\Phi_2 > 0$'

$$\begin{aligned} \Phi_2 Z_a^{*2} + \Phi_1 Z_a^* &= 0, \\ Z_a^*(\Phi_2 Z_a^* + \Phi_1) &= 0. \end{aligned} \tag{3.73}$$

Therefore,

$$Z_{a1}^* = 0, Z_{a2}^* = \frac{\Phi_1}{\Phi_2}. \tag{3.74}$$

$Z_{a1}^* = 0$ corresponds to the disease free case and $Z_{a2}^* = \frac{\Phi_1}{\Phi_2}$ corresponds to a unique positive equilibrium point. This is the critical equilibrium point.

Case 2:

If $R_0 > 1$ then $\Phi_0 < 0, \Phi_1 < 0, \Phi_2 > 0$. According to Descartes rule of signs, the sign of the coefficients of the quadratic equation (3.68) changes once. So there is one unique positive equilibrium point, $Z_{a1}^* > 0$. Consequently, there exist at least one endemic equilibrium point.

Case 3:

If $R_0 < 1$ (which implies $\Phi_0 > 0$), then Φ_1 determines the existence of an equilibrium point. If $\Phi_1 \geq 0$ or $\Phi_1 > 4\Phi_2\Phi_0$ then there are no positive solutions for the quadratic equation (3.68). However, if $\Phi_1 < 0$, $\Phi_1 > 4\Phi_2\Phi_0$ or $\Phi_1 < -2\sqrt{\Phi_2\Phi_0}$ then, according to Descartes rule of signs, the sign of the coefficients of the quadratic equation (3.68)

changes twice. So there are two positive equilibrium points corresponding to two endemic equilibria. Consequently, ${Z_a}^*$ has two positive turning points, implying that at $R_0 < 1$ there is a possibility for the model to exhibit backward bifurcation.
Theorem 3.4 summarizes the existence of endemic equilibria of the system (3.1).

Theorem 3.4. *The system* (3.1) *has:*

1. *no endemic equilibrium if $R_0 < R_c < 1$, where R_c is the critical R_0.*
2. *at least one endemic equilibrium in Γ, if $R_0 > 1$.*
3. *two endemic equilibria for some parameter values for which R_0 lies within the range $R_c < R_0 < 1$.*
4. *no endemic equilibrium, otherwise.*

3.6.1 Backward bifurcation analysis

A bifurcation is defined as a change in the nature of a solution of trajectories due to a parameter change. In the simplest words backward bifurcation, in epidemic model is where a stable disease-free equilibrium co-exists with a stable endemic equilibrium for $R_0 < 1$. Thus, backward bifurcation occurs in models that have multiple endemic equilibria when $R_0 < 1$. Consequently, the classical epidemiological requirement of having $R_0 < 1$ is necessary but not a sufficient indicator for effective disease control or elimination (Mukandavire et al., 2009).

In addition, Greenhalgh and Griffiths (2009) indicated that a bifurcation diagram provides a clear picture to the modellers on how the equilibrium solutions depend on R_0. In particular, the study revealed that there is a change in the qualitative behaviour of the model when $R_0 = 1$, in that, the disease free equilibrium bifurcates into a branch representing the endemic equilibrium and another branch for the disease free equilibrium. Therefore, the basic reproductive number must be further reduced in order to avoid endemic states and guarantee viral elimination (Buonomo and Lacitignola, 2011). The aim of investigating backward bifurcation, is because it plays a fundamental role in disease control and eradication.

Various researchers such as Sharomi et al. (2008) have established that disease models exhibit the phenomenon of backward bifurcation where the stable disease free equilibrium co-exists with a stable endemic equilibrium; that is, there exists two sub-critical endemic equilibria for $R_0 < 1$. Furthermore, Huo et al. (2015) on the study of the effect of vaccines on backward bifurcation, emphasized the importance of establishing a new critical value at the turning point rather than R_0 that should work as a threshold of disease eradication. Li and Wang (2014) in their study on the use of ARTs, discovered that existence of the multiple endemic equilibria was associated with backward bifurcations which resulted in catastrophic behaviours of HIV. In particular, it indicated the rebound of HIV viral load when a patient stops taking the ARTs which also explained the viral blips during ARTs suppression of HIV. The importance of establishing the bifurcation point as documented in the literature cited is to provide insights on the best control methods that would lead to the eradication of HIV virions in the body.

In this study bifurcation analysis for the system (3.1) is carried out aimed at analyzing the behaviour of the model at the endemic state.

Remark 3.3. The system given by (3.1) exhibits a backward bifurcation point at $R_0 = 1$ if and only if $\Phi_1 < 0$ and $\Phi_1^2 - 4\Phi_2\Phi_0 > 0$.

To obtain the critical reproductive number, R_c, the discriminant $\Phi_1^2 - 4\Phi_2\Phi_0$ of the equation (3.71) is set to zero and R_0 is made the subject of the relation.

Thus, critical reproductive point is given as

$$R_c = \frac{(A_1 + 2\sqrt{A_2}))A_3}{A_4}, \tag{3.75}$$

where

$$\begin{aligned}
A_1 &= \mu_{Z_a}(\lambda_T\mu_I(-\beta\lambda_T + \mu_I\mu_Z) + 2\mu_V^2\mu_Z),\\
A_2 &= \mu_{Z_a}\mu_Z\mu_V^2\left((\lambda_T^2\beta(-\alpha\lambda_Z - 2\mu_I\mu_{Z_a}) + \mu_{Z_a}\mu_Z(\lambda_T\mu_I^2 + \mu_V^2)\right),\\
A_3 &= \beta(\alpha\lambda_Z + \mu_I\mu_{Z_a}),\\
A_4 &= \mu_{Z_a}\left((\beta\lambda_T\mu_{Z_a}\mu_I^2(\beta\lambda_T - 2\mu_I\mu_Z)) + \mu_I^4\mu_Z^2\mu_{Z_a} + 4\beta\mu_Z\mu_V^2(\alpha\lambda_Z + \mu_I\mu_{Z_a})\right).
\end{aligned} \tag{3.76}$$

If $R_c > 1$ then the system (3.1) has a trans-critical bifurcation, and if $R_c < 1$ then the system (3.1) exhibits backward bifurcation. It is important to note that existence of a backward bifurcation with endemic equilibrium when $R_c < 1$ is very interesting in applications. Notably, it has very important consequences in the strategies and

control policies designed for HIV viral eradication. Basically, a backward bifurcation implies the occurrence of multiple endemic equilibria and the coexistence of a stable endemic equilibrium with the stable disease-free equilibrium. Consequently, from the epidemiological point of view reducing R_0 below unity is no longer a guarantee that the HIV virions will be eliminated completely or reduced to non-detectable level. In addition, this affects HIV virus control since it can be possible for the disease to progress even when $R_0 < 1$. Furthermore, when backward bifurcation occurs, the diseases-free equilibrium may not be globally asymptotically stable even when the basic reproduction rate is less than unity and thus a stable endemic equilibrium coexists with the diseases-free equilibrium.

In summary, public policy makers, clinicians and researchers in the field of HIV should find ways of ensuring that the control measure put in place guarantees the existence of $R_0 < R_c < 1$. This, in turn, will lead to eradication of the HIV virions.

3.7 Global Stability of the Disease-Free Equilibrium

Due to the existence of backward bifurcation for the system (3.1) we conclude that disease-free equilibrium is globally stable if and only if $R_0 < R_c$, where R_c is the critical reproductive point. To prove this, we have applied the approach given by Castillo-Chavez et al. (2002), in studying the global stability of the disease-free equilibrium for the system (3.1). Using this approach two key conditions are listed in the study and that if met will guarantee the global asymptotic stability of the disease-free equilibrium.

Theorem 3.5. *Suppose the system* (3.1) *can be written in the following form:*

$$\begin{aligned} \frac{dX}{dt} &= H(X, W), \\ \frac{dZ}{dt} &= G(X, W), \end{aligned} \tag{3.77}$$

such that,

$$G(X, 0) = 0. \tag{3.78}$$

where the column vector components of $X \in R^M$ denote the uninfected population and the components of $W \in R^n$ denote the infected population. Let $E_0 = (X^*, 0)$ be the disease-free equilibrium for the model.

Then $E_0 = (X^*, 0)$ is globally asymptotically stable if and only if:

(1) $R_0 < 1$*, that is, locally asymptotically stable.*

(2) $\frac{dX}{dt} = H(X, 0)$*,* X^* *is globally asymptotically stable.*

(3) $G(X, W) = PG - \hat{G}(X, W), \hat{G}(X, W) \geq 0$ *for* $(X, W) \in \Omega_H$*, where* $P = D_W G(X^*, 0)$ *is an M-matrix (the off diagonal elements of P are non negative) and* Ω_H *is the region where the model makes biological sense.*

If the system (3.1) satisfies the conditions mentioned in Theorem 3.5 then the fixed point $E_0 = (X^*, 0)$ is a globally asymptotically stable equilibrium of system (3.1) provided that $R_0 < R_c$. For system (3.1) the result is stated and proved in Proposition 3.1.

Proposition 3.1. The disease-free equilibrium point, $E_0 = (X^*, 0)$, is a globally asymptotically stable equilibrium of system (3.1) provided that $R_0 < R_c$ and the conditions (2) and (3) in Theorem 3.5 are satisfied.

Proof. Following Castillo-Chavez et al. (2002), system (3.1) can be written in the form

$$\begin{aligned} \frac{dX}{dt} &= H(X, W), \\ \frac{dZ}{dt} &= G(X, W), \quad G(X, 0) = 0. \end{aligned} \tag{3.79}$$

where $X = (T, Z, Z_a)$ and $W = (I, V)$. Here, $X \in \mathbb{R}^3$ denotes the non-infected compartments and $W \in \mathbb{R}^2$ denotes the HIV infected compartments. The disease-free equilibrium for the system (3.1) is denoted as $E_0 = (X^*, 0)$.

$$H(X, W) = \begin{pmatrix} \lambda_T - \mu_T T - \chi T V \\ \lambda_Z - \mu_Z Z - \beta Z I \\ \beta Z I - \mu_{Za} Z_a \end{pmatrix}, \tag{3.80}$$

$$H(X, 0) = \begin{pmatrix} \lambda_T - \mu_T T \\ \lambda_Z - \mu_Z Z \\ -\mu_{Za} Z_a \end{pmatrix} = \frac{\mathrm{d}X}{\mathrm{d}t}. \tag{3.81}$$

The equilibrium point for system (3.81) is given by

$$X^* = \left(\frac{\lambda_T}{\mu_T}, \frac{\lambda_Z}{\mu_Z}, 0 \right). \tag{3.82}$$

Lemma 3.1. The biologically feasible region Ω_H defined by the compact set;

$$\Omega_H = \left\{ (T, Z, Z_a) \in \mathbb{R}^3 : T \leq \max \left\{ T_0, \frac{\lambda_T}{\mu_T} \right\}, Z \leq \max \left\{ Z_0, \frac{\lambda_Z}{\mu_Z} \right\}, Z_a = 0 \right\}. \tag{3.83}$$

with initial conditions $(T(0), Z(0), Z_a(0) > 0)$, is positively invariant for all $t > 0$.

Proof. Taking the first equation of the system (3.81), the population of the susceptible CD^+ T-cells is

$$\begin{aligned} \frac{dT}{dt} &= \lambda_T - \mu_T T, \\ \frac{dT}{dt} &+ \mu_T T = \lambda_T. \end{aligned} \tag{3.84}$$

Using the method of integrating factor (IF) for solving first order ordinary differential equations (ODE), where

$$I.F = e^{\int \mu_T dt}. \tag{3.85}$$

Equation (3.84) becomes

$$\int \frac{d(Te^{\mu_T t})}{dt} = \int \lambda_T e^{\mu_T t}. \tag{3.86}$$

Thus, equation (3.86) reduces to;

$$T = \frac{\lambda_T}{\mu_T} + Ce^{-\mu_T t}. \tag{3.87}$$

Applying the initial condition, at $t = 0$, and denoting $T(0) = T_0$, equation (3.87) gives

$$C = T_0 - \frac{\lambda_T}{\mu_T}. \tag{3.88}$$

Substituting (3.88) in (3.87) the inequality for the susceptible $CD4^+$ T-cells is given by;

$$T \leq \frac{\lambda_T}{\mu_T} + \left(T_0 - \frac{\lambda_T}{\mu_T} \right) e^{-\mu_T t}. \tag{3.89}$$

Hence at any time $t > 0$

$$T \leq \max \left\{ T_0, \frac{\lambda_T}{\mu_T} \right\}. \tag{3.90}$$

Similarly taking the second equation of the system (3.81), the population for the $CD8^+$ T-cells is

$$\begin{aligned} \frac{dZ}{dt} &= \lambda_Z - \mu_Z Z, \\ \frac{dZ}{dt} &+ \mu_Z Z = \lambda_Z. \end{aligned} \tag{3.91}$$

Using the method of integrating factor (IF) for solving first order ordinary differential equations (ODE), where

$$I.F = e^{\int \mu_Z dt}. \tag{3.92}$$

Equation (3.91) becomes

$$\int \frac{d(Ze^{\mu_Z t})}{dt} = \int \lambda_Z e^{\mu_Z t}. \tag{3.93}$$

Equation (3.93) reduces to

$$Z = \frac{\lambda_Z}{\mu_Z} + Z_0 e^{-\mu_Z t}. \tag{3.94}$$

Applying the initial condition, at $t = 0$, and denoting $Z(0) = Z_0$, then,

$$C = Z_0 - \frac{\lambda_Z}{\mu_Z}. \tag{3.95}$$

Thus, substituting (3.95) in (3.94) the inequality for the CD8$^+$ T-cells population is given by;

$$Z \leq \frac{\lambda_Z}{\mu_Z} + \left(Z_0 - \frac{\lambda_Z}{\mu_Z}\right) e^{-\mu_Z t}. \tag{3.96}$$

Therefore, at any time $t > 0$

$$Z \leq \max\left\{Z_0, \frac{\lambda_Z}{\mu_Z}\right\}. \tag{3.97}$$

Lastly from system (3.81) the population of the activated CD8$^+$ T-cells is given as,

$$\frac{dZ_a}{dt} = -\mu_{Z_a} Z_a. \tag{3.98}$$

By separation of variables equation (3.98) becomes

$$\frac{dZ_a}{Z_a} = -\mu_{Z_a} dt. \tag{3.99}$$

By integration, equation (3.99) reduces to

$$Z_a = Ce^{-\mu_{Z_a} t}. \tag{3.100}$$

Applying the initial conditions at $t = 0$ and denoting $Z_a(0) = Z_{a_0}$ then,

$$Z_{a_0} = C. \tag{3.101}$$

Hence substituting equation (3.101) the inequality for the activated $CD8^+$ T-cells is given by

$$Z_a \leq Z_{a_0} e^{-\mu_{Z_a} t}. \tag{3.102}$$

Thus at any time $t \geq 0$, Z_a is bounded. Equations (3.90), (3.97) and (3.102) imply that any solution $(T(t), Z(t), Z_a(t))$, at $t \geq 0$, in $\mathbb{R}^3$ will always remain confined in Ω_H. Hence, the region Ω_H is positively invariant for the system (3.81). □

For condition (2) in Theorem (3.5) the Bendixson criterion and Dulac criterion for autonomous model as described by Li et al. (1995) is applied in proving non-existence of the periodic solutions in model (3.81). This is done by first showing that the autonomous model (3.81) is an invariant linear subspace.

The Jacobian matrix, $J(T, Z, Z_a)$, of the model (3.81) is given by

$$J(T, Z, Z_a) = \begin{pmatrix} -\mu_T & 0 & 0 \\ 0 & -\mu_Z & 0 \\ 0 & 0 & -\mu_{Za} \end{pmatrix}. \tag{3.103}$$

Notably, J is a leading diagonal matrix and the eigenvalues of such a matrix are its main diagonal entries. Thus, the eigenvalues of J are $-\mu_T, -\mu_Z$ and $-\mu_{Z_a}$. Since all the eigenvalues are negative then the steady state X^* for the model (3.81) is locally asymptotically stable. We now proceed to show that this unique steady state is globally asymptotically stable. Here, Dulacs criteria is applied in ruling out the existence of periodic orbits in Ω_H.

Definition 3.2 (Bendixson-Dulacs Criterion). Suppose D is a simple connected open set of $\mathbf{R^3}$ and $B(x, y, z)$ is a real-valued function in D.

$$div(B_f, B_g, B_h) = \frac{\partial B_f}{\partial x} + \frac{\partial B_g}{\partial y} + \frac{\partial B_h}{\partial z}. \tag{3.104}$$

If the expression is not identically zero and does not change sign in D, then there are no periodic solutions of the autonomous model in D. The function $B(x, y, z)$ is called a Dulac function. It is worth noting that the Dulacs criterion is a generalization of Bendixsons Criterion, in the special case where $B(x, y, z) = 1$.

Let

$$\begin{aligned} M(T, Z, Z_a) &= \lambda_T - \mu_T T, \\ N(T, Z, Z_a) &= \lambda_Z - \mu_Z Z, \\ K(T, Z, Z_a) &= -\mu_{Z_a} Z_a. \end{aligned} \tag{3.105}$$

also let

$$\Theta(T, Z, Z_a) = \frac{1}{TZZ_a} \text{ for } \quad T > 0, Z > 0 \text{ and } Z_a > 0 \tag{3.106}$$

be a dulac function.

Let $\emptyset$ be,

$$\emptyset = \frac{\partial(M\Theta)}{\partial T} + \frac{\partial(N\Theta)}{\partial Z} + \frac{\partial(K\Theta)}{\partial Z_a} \tag{3.107}$$

then, equations (3.106) and (3.107) give

$$\begin{aligned} \emptyset &= -\frac{\mu_T}{TZZ_a} - \frac{\lambda_T - \mu_T T}{T^2 Z Z_a} - \frac{\mu_Z}{TZZ_a} - \frac{\lambda_Z - \mu_Z Z}{TZ^2 Z_a}, \\ &< 0. \end{aligned} \tag{3.108}$$

From equation (3.108) it is evident that the model (3.81) has no periodic solutions (or limit cycles) in the compact set Ω_H. Consequently, from the fact that the steady points of model (3.81) have been proved to be locally asymptotically stable, then from the Poincare- Bendixson Theorem (Dulac criterion), the unique equilibrium points X^* of the model (3.81) is globally asymptotically stable.

The study finally proves the satisfaction of condition (3) of Theorem 3.5.

Let $G(X, W) = PG - \hat{G}(X, W), \quad \hat{G}(X, 0) \geq 0 \quad \forall \quad (X, W) \in \Omega_H,$

$$G(X, W) = \begin{pmatrix} \chi TV - \mu_I I - \alpha Z_a I \\ \epsilon_V \mu_I I - \mu_V V \end{pmatrix}. \tag{3.109}$$

Since every element of the matrix $G(X, W)$ contains virions or infected components then $G(X, 0) = 0$. The M-matrix P can be constructed as

$$P = D_W G(X^*, 0), \tag{3.110}$$

$$P = \begin{pmatrix} -\mu_I & \chi \frac{\lambda_T}{\mu_T} \\ \epsilon_V \mu_I & -\mu_V \end{pmatrix}. \tag{3.111}$$

By definition of $G(X, W) = PG - \hat{G}(X, W)$ then, $\hat{G}(X, W)$ is given as

$$\hat{G}(X, W) = \begin{pmatrix} \hat{G}_1(X, W) \\ \hat{G}_2(X, W) \end{pmatrix} = \begin{pmatrix} \alpha Z_a I & 0 \\ 0 & 0 \end{pmatrix}. \tag{3.112}$$

Since $\alpha Z_a I \geq 0$ then, $\hat{G}(X, W) \geq 0$ for $(X, W) \in \Omega_H$. Hence the disease-free equilibrium (E_0) is globally stable. That is, $X^* = (\frac{\lambda_T}{\mu_T}, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0)$ is globally asymptotically stable equilibrium solution of $\frac{dX}{dt} = H(X, 0)$. Consequently, by the Proposition 3.1, the disease-free equilibrium of the system (3.1) is globally symptomatically stable. □

Proposition 3.1 implies that when $R_0 < R_c$ a small influx of free HIV virions into the body cells, would not lead to the disease progressing AIDS stage. The subsequent numbers of those infected cells would be less than that of their predecessors and eventually the disease may be reduced to non-detectable level.

Remark 3.4. From Theorem 3.1 the disease-free equilibrium, E_0, for the system (3.1) is globally asymptotically stable if $R_0 < 1$. However, due to the existence of multiple endemic equilibrium then the study conclude that system (3.1) is globally asymptotically stable if and only if $R_0 < R_c < 1$, where R_c denotes the critical reproduction number.

3.8 Numerical Simulations

Parameter values given in Table 3.4 are used in the numerical simulations and in illustrating the general dynamics of the system (3.1) with respect to time.

Figure 3.3 shows the dynamics of the $CD4^+$ T-cells. The hallmark of HIV/AIDS

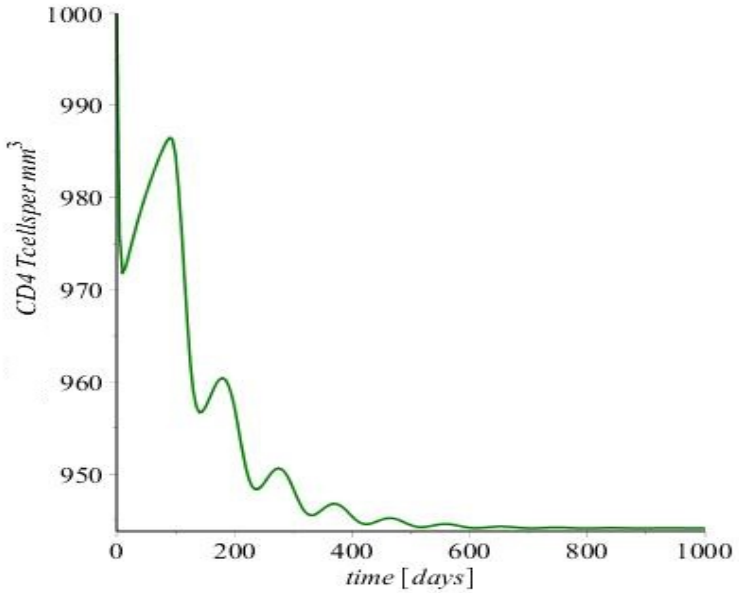


Figure 3.3: The Rate of Change of the $CD4^+$T-cells with respect to time.

pathogenesis is the depletion of $CD4^+$ T-cell populations. It is evident from Figure 3.3 that as the disease progresses the number of $CD4^+$ T-cells per micro litre decreases. However, due to the immune system mechanism the reduction of the $CD4^+$ T-cells is followed by an increase in the number of the $CD4^+$ T-cells which coincides with immune system reconstruction. This could be explained by the fact that the body mechanism will always try to be at an equilibrium. However, as the immune system weakens the body is unable to reconstruct itself, and that is why there is an occurrence of a straight line after the second year. The results in this study are in agreement with clinical observation (Reimann et al., 1996; Nishimura et al., 2005; Okoye and Picker,

2013). It has been indicated that initial destruction of the cells is counteracted by $CD4^+$ memory T-cell regeneration that preserves $CD4^+$ T-cell numbers. The number, however, does not go back to pre-infection stage. This process is not maintained for a longer period, this explains the drastic drop in the level of the $CD4^+$ T-cells. In HIV as the number of the cells decreases the body immunity lacks the ability to fight other infection. That is why HIV infected people are prone to many opportunistic deceases as the CD^+ T-cells goes below 350 cells/mm^3.

Figure 3.4 shows the dynamics of the infected $CD4^+$ T-cells. It is evident that at

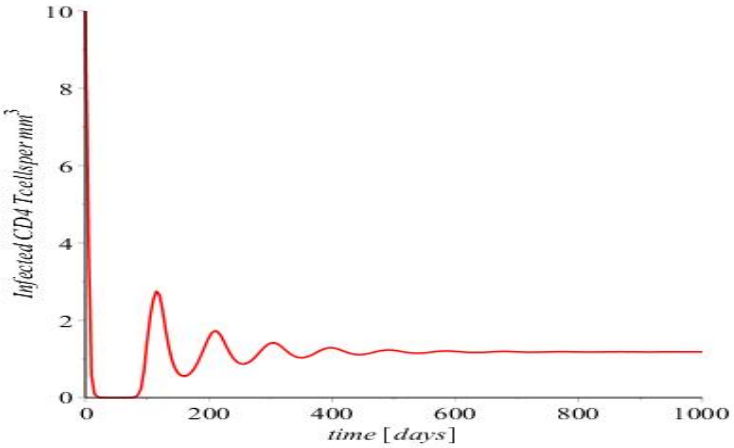


Figure 3.4: The number of the infected $CD4^+$T-cells with respect to time.

acute infection the number of the infected cells increases at a very sharp rate. Then decreases exponentially. However, after 100 days the level increases, but since the body has a way of balancing the cells, an increase is followed by a decrease hence the existence of a non-harmonic system. The non-harmonic oscillations are maintained up to 500 days. Due to the weak immune system the number of infected cells remains at a constant rate after 600 days. HIV has proved to have no cure so far, therefore, researchers need to find ways of killing all the infected cells before they bud out and produce mature HIV virions. This is because HIV-induced cell death actually increases HIV replication (Su et al., 2005; Bren et al., 2009).

Figure 3.5 represents the dynamics of the HIV virions in the first 1000 days after infection. It is evident that the number of HIV virions increases in the first few days after infection. Afterwards the number of HIV virions decreases. This is attributed to the recruitment of the cytotoxic cells to fight the free virus. After about three months

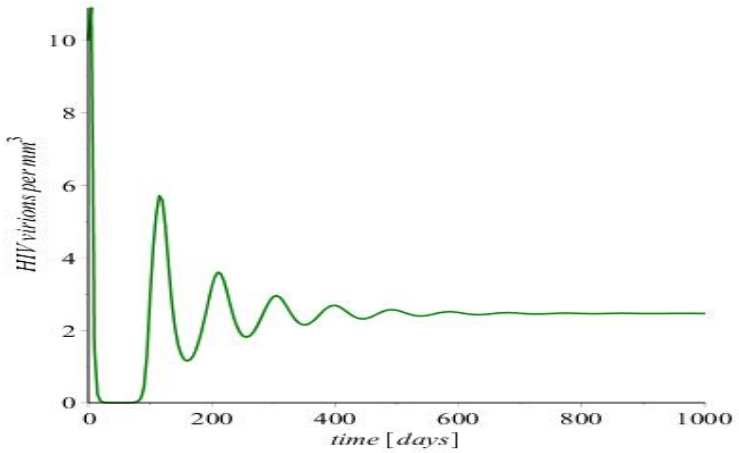


Figure 3.5: The number per mm^3 of the HIV-virions with respect to time.

the level increases exponentially; due to the many infected cells bust releasing a higher number of the virions. Since the cytotoxic cells kill the infected cells then indirectly they reduce the number of HIV virions produced. A sharp increase after three months is therefore, followed by a decrease in the number of HIV virions. After 500 days, the number of HIV virions remains at a constant rate. It is important to note that new HIV virions are released from an infected $CD4^+$ T-cell, via the bursting of the cell. This implies that a single burst produces a large pool of new HIV virions.

Figure 3.6 represents the dynamics of the of the $CD8^+$ T-cells in the first 1000 days

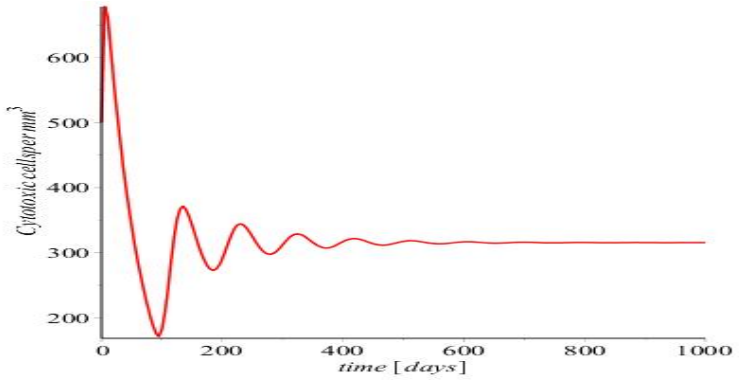


Figure 3.6: The number of cytotoxic/$CD8^+$ T-cells with respect to time.

after infection. These are specialized cells of the adaptive immune system capable of finding and eliminating pathogen-infected cells. They are responsible for destroying and killing the infected cells, and in turn helps to restore the immune system. They arise from the bone marrow and later relocate to the thymus for maturation. During this process they are able to express a unique antigen-binding molecule known as the T-cell receptor. The receptor enables them to monitor all cells of the body, ready to

destroy any cell posing as a threat to the organism. Nonetheless, for the cytotoxic cells to fight and destroy any infected cell they must be activated and the dynamics of the activated cells is shown in Figure 3.6. The activation takes place at the surface of accessory cells, which mature during the innate immune responses triggered by an infection.

From Figure 3.7 it is evident that the number of the activated $CD8^+$ T-cells increases

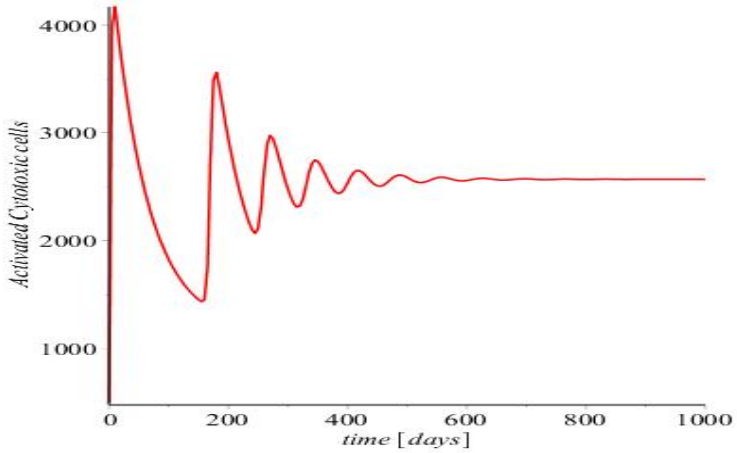


Figure 3.7: The number of the activated cytotoxic T-cells with respect to time.

exponentially for the first one month. The cells are activated in preparation to kill the already infected $CD4^+$ T-cells. The number then reduces to a minimum after 5 months (150 days) though not to the level of the pre-infection period. This coincides with the reduction in the number of the free HIV virions. Onward a non-harmonic curve is observed for the dynamics of the activated cytotoxic cells.

3.9 Conclusion

In this Chapter a deterministic model for the in-vivo HIV dynamics has been presented. The model analyzed HIV in-vivo dynamics focusing on the highly dynamic interaction between HIV virions, uninfected $CD4^+$ T-cells, infected $CD4^+$ T-cells and $CD8^+$ T-cells. The inclusion of the immune response to viral infection is a key feature in examining the course of HIV infection. The model aimed at analyzing the mechanism of the HIV virus during the entry time up to the maturation time and the role played by the activated $CD8^+$ T-cells in fighting and killing the HIV virions. The study starts by proving that the model is epidemiologically well posed. Afterwards, the expression of the basic reproductive number, R_0, is derived by use of the next generation matrix. The analytical results indicate that the disease-free equilibrium point of system

(3.1) is locally stable for $R_0 < 1$ and globally stable for $R_0 < R_c < 1$. Numerical results are presented to show the importance of maintaining the R_0 below one. The numerical simulations for the model also indicates the importance of the $CD8^+$T-cells as far as fighting the HIV virions is concerned. At the primary phase of HIV infection the patients experience a period of increasing viral load and a decline in the number of $CD4^+$T-cells. Flu like symptoms have been associated with this phase. However, as much as this study has only established the role played by the immune cells at the acute infection, researchers such as Wodarz (2001) have shown that patients who do not progress to AIDS after 15 years or longer have significantly higher levels of immune cells compared to HIV-infected patients. It is therefore, paramount to maintain a positive population of the $CD8^+$ T-cells so as to ensure that if viral load does rebound, the immune system will be in a position to fight and kill the infected $CD4^+$ T-cells. Therefore, for this to be realized the best ARTs should be administered. In this regard we extended the system (3.1) to include the various drug regimes.

Chapter 4

Mathematical Models for In-vivo HIV Dynamics Subject to Therapy

4.1 Introduction

About a third of HIV-infected individuals living in sub-Saharan Africa and who are eligible for antiretroviral therapy (ART), receive combined ARTs. Despite the increased roll-out of combined antiretroviral therapy, a meaningful decrease in the incidence of AIDS-associated malignancies is yet to be realized. It is therefore, apparent that, suppression, and not eradication, is most likely the best that can be achieved with the use of current regime of ARTs.

However, it is very unfortunate to note that the current strategy of continuous combination therapy is difficult to maintain for long periods of time due to short- and long-term toxicities (metabolic abnormalities, body habitual changes, lipid abnormalities, mitochondrial toxicity and liver toxicity) as well as adherence challenges inherent in these complicated pill regimes, cost, and the development of resistance to medications.

In this chapter, a mathematical model for the in vivo HIV dynamics with treatment has been formulated. In order to study the effect of treating HIV infection by the use of a cocktail of drugs, three control variables: u_1, u_2 and u_3 which represent Fusion inhibitors (FIs), Reverse Transcriptase inhibitors (RTIs) and the Protease inhibitors (PIs), respectively, have been introduced. This study differs from other researches that had incorporated both the HIV therapy and the $CD8^+$ T-cells in their models such as Culshaw et al. (2004); Hattaf and Yousfi (2012a); Arruda et al. (2015); Silva and Torres (2015); by considering the Fusion inhibitors as a control variable in the model and the non-infectious virus as a result of the use of Protease inhibitors. In this study it is assumed that there is no drug resistant virions before the initiation of ARTs.

4.2 Model Description

To study the effect of treating HIV infection with the use of a cocktail of drugs, an in-vivo HIV model with the three control variables u_1, u_2 and u_3 has been formulated and the analyzes given. HIV virus targets the CD4$^+$ T-cells (T). Thus, through the interaction of the CD4$^+$ T-cells and the HIV virus (V), the susceptible cells become infected at a rate χ. Then, the infected CD4$^+$ T-cells (I) produce more HIV virions through budding at a rate ϵ_V. However, if the infected person is under treatment through the use of Protease inhibitors, a small proportion of the virus produced will be immature and non-infectious (V_n). In addition, the presence of the infected CD4$^+$ T-cells, leads to the activation of the CD8$^+$ T-cells to destroy infected CD4$^+$ T-cells.

In this chapter therefore, a model with seven compartments is developed to represent the interaction between the HIV virions, the body immune cells and the HIV drugs. The state variables for the model used in this study are: susceptible CD4$^+$ T-cells, T; infected CD4$^+$ T-cells, I; latently infected CD4$^+$ T-cells, I_l; HIV virions, V; non-infectious/immature HIV virions, V_n; CD8$^+$ T-cells, Z and activated CD8$^+$ T-cells (cytotoxic cells), Z_a.

Furthermore, three treatment parameters u_1, u_2 and u_3 are introduced to the model. Parameter u_1 represents the use of FIs that inhibit the fusion process, hence the virus does not enter into the CD4$^+$ T-cells membrane. Parameter u_2 represents RTIs that prevent the reverse transcription process from taking place. Parameter u_3 represents PIs that inhibits the release of protease enzymes needed for the maturity of HIV virions hence it leads to the production of non-infectious and immature virions. This in turn reduces the amount of HIV virions in the body.

The summary for the state variables, treatment parameters and the model parameters are summarized in Tables 4.1, 4.2 and 4.3, respectively.

Table 4.1: Variables for HIV in-vivo model with therapy

Variable	Description
$T(t)$	Population of the non-infected CD4$^+$T-cells at any time t.
$I(t)$	Population of the infected CD4$^+$T-cells at any time t.
$I_l(t)$	Population of latently infected CD4$^+$ T-cells at any time t.
$V(t)$	Population of HIV virions at any time t.
$V_n(t)$	Population of the immature non-infectious virions at any time t.
$Z(t)$	Population of the CD8$^+$T-cells at any time t.
$Z_a(t)$	Population of the activated CD8$^+$T-cells at any time t.

Table 4.2: Treatment Parameters for HIV in-vivo model

Treatment Parameters	Description
u_1	Fusion inhibitors.
u_2	Reverse Trancriptase inhibitors.
u_3	Protease inhibitors.

Table 4.3: Parameters for HIV in-vivo with therapy model

Parameter	Description
λ_T	The rate at which the non-infected CD4$^+$ T-cells are produced per unit time.
μ_T	The rate at which the non-infected CD4$^+$T-cells decay.
χ	The rate at which the CD4$^+$T-cells are infected by the virus.
μ_I	The death rate of the infected CD4$^+$T-cells.
μ_{I_l}	The death rate of the latently infected CD4$^+$ T-cells.
ε_V	The rate in which HIV virions are generated from the infected CD4$^+$T-cells.
μ_V	The death rate of the infectious virus.
μ_{V_n}	The death rate of the non-infectious virions.
α	The rate at which the infected cells are eliminated by the activated CD8$^+$T-cells.
λ_Z	The rate at which the CD8$^+$ T-cells are produced per unit time.
μ_Z	The death rate of the CD8$^+$ T-cells.
β	The rate at which the CD8$^+$ T-cells are activated by the presence of the virus and the infected CD4$^+$ T-cells.
μ_{Z_a}	The rate at which the activated defense cells decay.

The interactions aforementioned are represented in the compartmental diagram in Figure 4.1.

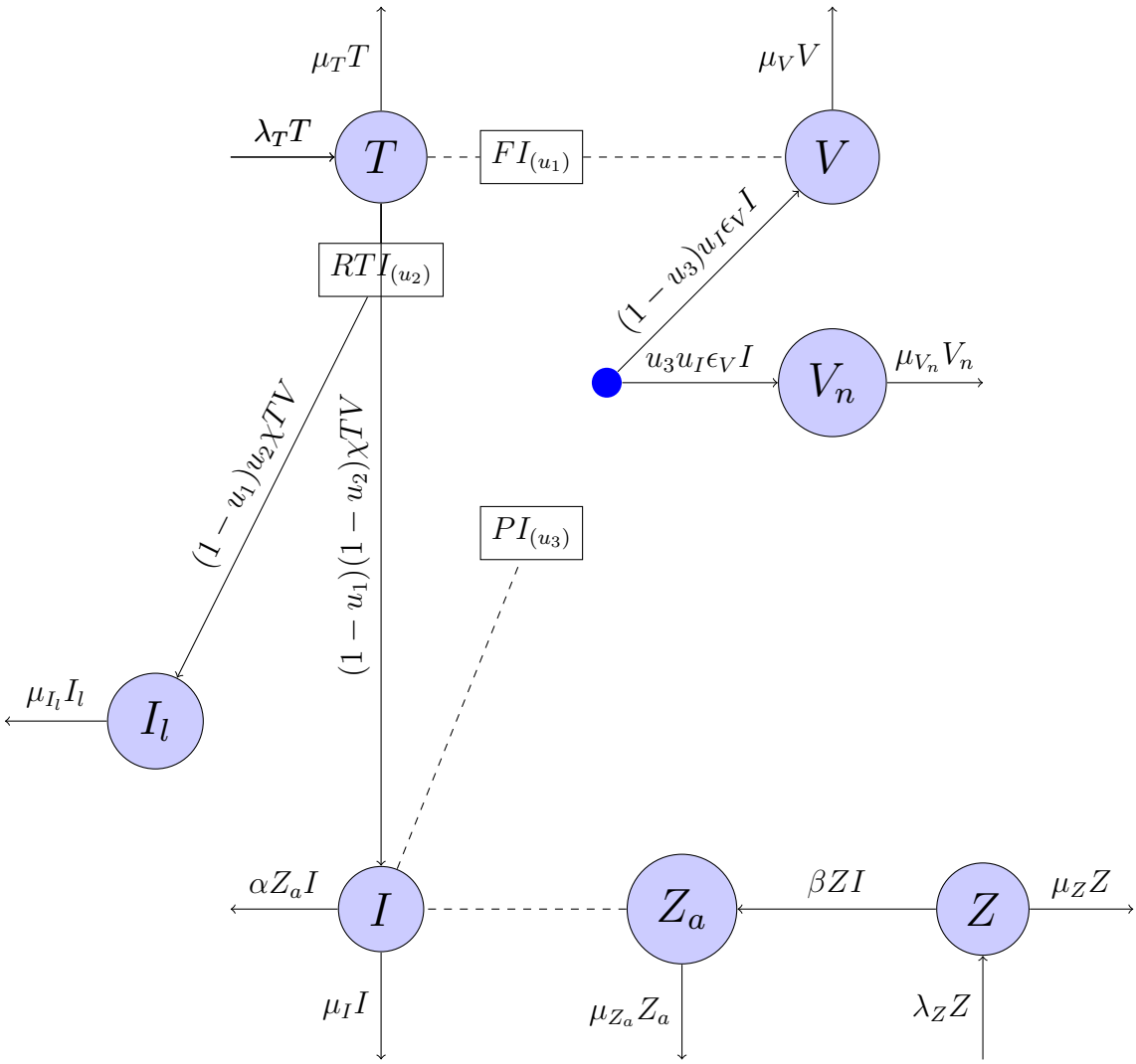


Figure 4.1: A compartmental representation of the in-vivo HIV Dynamics with therapy.

From the description of state variables, treatment parameters and the model parameters in Tables 4.1, 4.2 and 4.3 respectively and Figure 4.1, the following system of ordinary

differential equations representing the in-vivo dynamics of HIV is derived.

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - (1-u_1)\chi TV, \\
\frac{dI}{dt} &= (1-u_1)(1-u_2)\chi TV - \mu_I I - \alpha I Z_a, \\
\frac{dI_l}{dt} &= (1-u_1)u_2\chi TV - \mu_{I_l} I_l, \\
\frac{dV}{dt} &= (1-u_3)\epsilon_V \mu_I I - \mu_V V, \\
\frac{dV_n}{dt} &= u_3\epsilon_V \mu_I I - \mu_{Vn} V_n, \\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I, \\
\frac{dZ_a}{dt} &= \beta Z I - \mu_{Z_a} Z_a.
\end{aligned}\right\} \tag{4.1}$$

4.3 Model Analysis

4.3.1 Positivity of the solutions

Since the in-vivo HIV model aims at monitoring cells population, it is then paramount to show that if the model in system (4.1) starts with non-negative initial conditions of the variables and the parameters then the solutions of the model remain non-negative for all $t \in [0, \infty]$. Then there exists a suitable feasible region Γ for the system (4.1) which gives biologically meaningful solutions. That is,

$$\Gamma = \left\{(T, I, I_l, V, V_n, Z, Z_a) \in \mathbb{R}^7 : T \geq 0, I \geq 0, I_l \geq 0, V \geq 0, V_n \geq 0, Z \geq 0, Z_a \geq 0\right\}. \tag{4.2}$$

We now state and prove a theorem for the non-negativity of the variables in system (4.1) as follows:

Theorem 4.1. *Given that in system* (4.1) *the state variables,* $T(t) \geq 0$, $V(t) \geq 0$,$V_n(t) \geq 0$, $I(t) \geq 0$, $I_l(t) \geq 0$, $Z(t) \geq 0$, $Z_a(t) \geq 0$ *for all* $t > 0$. *Then, the solutions* $(T(t), V(t), V_n(t), I(t), I_l(t), Z(t), Z_a(t))$ *of the model remain positive for all time* $t > 0$*, and the region* Γ *is positively invariant.*

Proof. To show positivity of solutions, it is enough to show that each of the trajectories of system (4.1) is non-negative for all $t > 0$.

From the first part of system (4.1) the population of the CD4$^+$ T-cells is

$$\frac{dT}{dt} = \lambda_T - \mu_T T - (1-u_1)\chi TV. \tag{4.3}$$

Then, the differential inequality describing the evolution of the susceptible population of the CD4$^+$ T-cells over time is given by,

$$\begin{aligned} \frac{dT}{dt} &\geq -\mu_T T - (1-u_1)\chi T V, \\ &= -(\mu_T + (1-u_1)\chi V)T, \\ \frac{dT}{dt} &+ (\mu_T + (1-u_1)\chi V)T \geq 0. \end{aligned} \tag{4.4}$$

The resulting differential inequality can be solved by separation of variables to give,

$$\int \frac{d}{dt}(Te^{\psi(t)}) \geq \int 0, \tag{4.5}$$

where,

$$\psi(t) = \mu_T + (1-u_1)\chi V. \tag{4.6}$$

Taking the initial conditions $t = 0$ and denoting $T(0)$ by T_0 then, the complete solution to the inequality (4.5) for the susceptible population of the CD4$^+$ T-cells is given by,

$$\begin{aligned} Te^{\psi(t)} &\geq T_0, \\ T &\geq T_0 e^{-\psi(t)} \geq 0. \end{aligned} \tag{4.7}$$

The same argument can be used to prove the non-negativity of I, I_l, V, V_n, Z, and Z_a for $t > 0$. □

4.3.2 Boundedness of solutions

Similarly we show that the state variables for the system (4.1) are bounded above. Taking the total number of the CD4$^+$ T-cells as $N_4(t)$, that is, $T + I + I_l = N_4(t)$, we have from system (4.1) the differential equation for the total population of the CD4$^+$ T-cells given as

$$\frac{dN_4(t)}{dt} = \lambda_T - \mu_T T - (\mu_I + \alpha Z_a)I - \mu_{I_l} I_l. \tag{4.8}$$

From equation (4.8) the differential inequality for the total population of the CD4$^+$ T-cells is given as

$$\begin{aligned} \frac{dN_4(t)}{dt} &\leq \lambda_T - \mu_T T, \\ \frac{dN_4(t)}{dt} &+ \mu_T T \leq \lambda_T. \end{aligned} \tag{4.9}$$

Using a suitable integrating factor, that is, I.f $= e^{\mu_T t}$, the differential inequality (4.9) is solved to obtain

$$\begin{aligned} \int \frac{d}{dt}\left(N_4(t)e^{\mu_T t}\right) &\leq \int \lambda_T e^{\mu_T t}, \\ N_4(t)e^{\mu_T t} - T_0 &\leq \frac{\lambda_T}{\mu_T}e^{\mu_T t} - \frac{\lambda_T}{\mu_T}, \\ N_4(t) &\leq \left(T_0 - \frac{\lambda_T}{\mu_T}\right)e^{-\mu_T t} + \frac{\lambda_T}{\mu_T}. \end{aligned} \tag{4.10}$$

From inequality (4.10) we have

$$N_4(t) \leq \text{ max } \left\{T_0, \frac{\lambda_T}{\mu_T}\right\}. \tag{4.11}$$

From inequality (4.11) the state variables describing the evolution of the total population of the CD4$^+$ T-cells is less or equal to the maximum value between the initial conditions and the ratio of the recruitment rate over the natural mortality rate.

Similarly let the total population of the HIV virions be $N_V(t)$, that is, $V + V_n = N_V(t)$. Then from system (4.1) the differential equation for the HIV virions is;

$$\frac{dN_V}{dt} = \epsilon_V \mu_I I - \mu_V V - \mu_{V_n} V_n. \tag{4.12}$$

Since $V_n = N_V - V$, then equation (4.12) reduces to;

$$\frac{dN_V}{dt} = \epsilon_V \mu_I I - (\mu_V - \mu_{V_n})V - \mu_{V_n} N_V. \tag{4.13}$$

However, $I \leq N_4(t) \leq$ max $\left\{T_0, \frac{\lambda_T}{\mu_T}\right\}$.

Taking $max\left\{T_0, \frac{\lambda_T}{\mu_T}\right\} = H$, equation (4.13) reduces to

$$\frac{dN_V(t)}{dt} \leq \epsilon_V \mu_I H - \mu_{V_n} N_V. \tag{4.14}$$

Taking the $I.F = e^{\mu_{V_n} t}$ and by integration, inequality (4.14) becomes;

$$N_V(t) \leq \frac{\epsilon_V \mu_I H}{u_{V_n}} + V_0 e^{-u_{V_n} t}. \tag{4.15}$$

Consequently, at any $t > 0$ the HIV virions are bounded by;

$$N_V(t) \leq V_0 + \frac{\epsilon_V \mu_I H}{\mu_{V_n}}. \tag{4.16}$$

Finally, let the total population of the CD8$^+$ T-cells be denoted as, $Z + Z_a = N_Z(t)$, then from system (4.1) the differential inequality for the total population of the CD8$^+$ T-cells becomes

$$\frac{dN_8(t)}{dt} \leq \lambda_Z - \mu_Z N_8(t). \tag{4.17}$$

By separation of variables method for solving differential inequality, inequality (4.17) can be written as

$$\int \frac{dN_8(t)}{\lambda_Z - \mu_Z N_8(t)} \leq \int dt. \tag{4.18}$$

By integration, inequality (4.18) becomes

$$\ln(\lambda_Z - \mu_Z N_8(t))^{-\frac{1}{\mu_Z}} \leq C. \tag{4.19}$$

At $t = 0$ and denoting $N_8(0) = N_{8_0}$ equation (4.19) reduces to

$$C = \lambda_Z - \mu_Z N_{8_0}. \tag{4.20}$$

Substituting equation (4.20) into equation (4.19) then, the inequality for the total population of the CD8$^+$ T-cells is

$$N_8(t) \leq \frac{\lambda_Z}{\mu_Z} - \frac{(\lambda_Z - \mu_Z N_{8_0})e^{-\mu_Z t}}{\mu_Z}. \tag{4.21}$$

From inequality (4.21) we note that for

$$N_{8_0} > \frac{\lambda_Z}{\mu_Z}, \text{ we have, } N_8(t) \leq N_{8_0} \quad \forall \quad t \tag{4.22}$$

and for

$$N_{8_0} \leq \frac{\lambda_Z}{\mu_Z}, \text{ we have, } N_8(t) \leq \frac{\lambda_Z}{\mu_Z} \quad \forall \quad t. \tag{4.23}$$

Therefore, from inequalities (4.22) and (4.23) we have

$$N_8(t) \leq \max\left\{N_{8_0}, \frac{\lambda_Z}{\mu_Z}\right\}. \tag{4.24}$$

Thus at any time $t > 0$, the population of the CD8$^+$ T-cells is bounded by;

$$N_8(t) \leq \max\left\{N_{8_0}, \frac{\lambda_Z}{\mu_Z}\right\}. \tag{4.25}$$

Then for all $t > 0$ the C8$^+$ T-cells are bounded.

Since all the state variables are positive and bounded then the system (4.1) is biologically meaningful and it is feasible to analyse the model in the domain Γ.

4.4 Disease-Free Equilibrium and the Basic Reproductive Number

In this section we establish the existence of the disease-free equilibrium point of the system (4.1) and discuss its stability.

Let

$$\frac{dT}{dt} = \frac{dI}{dt} = \frac{dI_l}{dt} = \frac{dV}{dt} = \frac{dV_n}{dt} = \frac{dZ}{dt} = \frac{dZ_a}{dt} = 0. \tag{4.26}$$

Then the system (4.1) becomes

$$\left.\begin{aligned}
0 &= \lambda_T - \mu_T T - (1-u_1)\chi TV,\\
0 &= (1-u_1)(1-u_2)\chi TV - \mu_I I - \alpha I Z_a,\\
0 &= (1-u_1)u_2\chi TV - \mu_{I_l} I_l,\\
0 &= (1-u_3)\epsilon_V \mu_I I - \mu_V V,\\
0 &= u_3\epsilon_V \mu_I I - \mu_{Vn} V_n,\\
0 &= \lambda_Z - \mu_Z Z - \beta Z I,\\
0 &= \beta Z I - \mu_{Z_a} Z_a.
\end{aligned}\right\} \tag{4.27}$$

In absence of infection by the HIV virions the system (4.1), has a steady state solution called the disease-free equilibrium (DFE) given by:

$$E_0 = \left(\frac{\lambda_T}{\mu_T}, 0, 0, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0\right). \tag{4.28}$$

4.4.1 Basic Reproductive Number

In this section we derive the basic reproductive number using the next generation matrix. The infected compartments are selected for the analysis, that is, I, I_l, V and V_n.

Theorem 4.2. *The basic reproductive number R_0 of system* (4.1) *is given by*

$$R_0 = \rho(FV_1) = \frac{(1-u_1)(1-u_2)(1-u_3)\chi\varepsilon_V\lambda_T}{\mu_V\mu_T}. \tag{4.29}$$

Proof. Following Diekmann et al. (1990) and van den Driessche and Watmough (2002) the basic reproductive number R_0 of system (4.1) is calculated by using the next generation matrix. It is given by the spectral radius of the $FV^{-}1$ so that;

$$R_0 = \rho(FV^{-1}). \tag{4.30}$$

Let $F(X)$ denote the appearance of new infection in a compartment and $V(X)$ be the rate of transfer of the infection in the compartments I, I_l, V and V_n. Then

$$F = \begin{bmatrix}
0 & 0 & (1-u_1)(1-u_2)\,\chi\frac{\lambda_T}{\mu_T} & 0\\
0 & 0 & (1-u_1)u_2\chi\frac{\lambda_T}{\mu_T} & 0\\
0 & 0 & 0 & 0\\
0 & 0 & 0 & 0
\end{bmatrix}, \tag{4.31}$$

$$V = \begin{bmatrix} \mu_I & 0 & 0 & 0 \\ 0 & \mu_{I_i} & 0 & 0 \\ -(1-u_3)\varepsilon_V\mu_I & 0 & \mu_V & 0 \\ -u_3\varepsilon_V\mu_I & 0 & 0 & \mu_{V_n} \end{bmatrix}. \tag{4.32}$$

Since the reproductive number is given by the spectral radius of the matrix FV^{-1}, then from equation (4.32) V^{-1} is given as

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_I} & 0 & 0 & 0 \\ 0 & \frac{1}{\mu_{I_l}} & 0 & 0 \\ \frac{\varepsilon_V(1-u_3)}{\mu_V} & 0 & \frac{1}{\mu_V} & 0 \\ -\frac{u_3\varepsilon_V}{\mu_{V_n}} & 0 & 0 & \frac{1}{\mu_{V_n}} \end{bmatrix}. \tag{4.33}$$

The next generation matrix is given by

$$FV^{-1} = \begin{bmatrix} \frac{\lambda_T\chi\varepsilon_V(1-u_1)(1-u_2)(1-u_3)}{\mu_T\mu_V} & 0 & \frac{\lambda_T\chi(1-u_1)(1-u_2)}{\mu_V\mu_T} & 0 \\ \frac{\chi\mu_T\lambda_T\varepsilon_V(1-u_1)u_2(1-u_3)}{\mu_T\mu_V} & 0 & \frac{\chi u_2(1-u_1)\lambda_T}{\mu_T\mu_V} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}. \tag{4.34}$$

The eigenvalues of the matrix (4.34) are given by

$$\Lambda = \frac{(1-u_1)(1-u_2)(1-u_3)\chi\varepsilon_V\lambda_T}{\mu_V\mu_T}, \Lambda_2 = \Lambda_3 = \Lambda_4 = 0. \tag{4.35}$$

Hence, the basic reproductive number for the system (4.1) is

$$R_0 = \rho(FV^{-1}) = \frac{(1-u_1)(1-u_2)(1-u_3)\chi\varepsilon_V\lambda_T}{\mu_V\mu_T}. \tag{4.36}$$

□

If $R_0 < 1$ in equation (4.36), then the HIV virions cannot invade the body and the disease will die out over time. However, as much as the time before the virions goes to non-detectable level depends on how small R_0 is, the HIV patients must continue taking ARTs to avoid the recurrence of the disease. It can be seen from equation (4.36) that if the drug regimes ,that is, Fusion inhibitors, Reverse Transcriptase inhibitor and the Protease inhibitor are 100% effective which implies that, $u_1 = u_2 = u_3 = 1$, then there is no secondary infections in the cells and the disease will die out.

To determine the best ways of reducing mortality due to HIV/AIDS related illness the importance of each parameter in relation to R_0 is evaluated as shown in the next section.

4.5 Sensitivity Analysis

The aim of researchers especially in the field of HIV modelling is to understand the dynamics of HIV so as to establish conditions for controlling it through targeting some sensitive parameters. This is done by performing a sensitivity analysis on R_0. Sensitivity analysis tries to explain the importance of the parameters in relation to disease progression. In this chapter both the normalized forward index and the Partial rank correlation coefficients have been applied in the sensitivity analysis.

4.5.1 Normalized forward index

The normalized forward sensitivity index of R_0 with respect to the parameter P is given by:

$$\gamma_P^{R_0} = \left(\frac{\partial R_0}{\partial P}\right) * \left(\frac{P}{R_0}\right) \tag{4.37}$$

where P represents a parameter in the expression of the basic reproductive number. From the basic reproductive number given by equation (4.36) the sensitivity indices, of R_0 with respect to the parameters $\chi, \epsilon_V, \lambda_T, \mu_V, \mu_T$ are respectively given as:

$$\frac{\partial R_0}{\partial \chi}\frac{\chi}{R_0} = 1, \tag{4.38}$$

$$\frac{\partial R_0}{\partial \varepsilon_V}\frac{\varepsilon_V}{R_0} = 1, \tag{4.39}$$

$$\frac{\partial R_0}{\partial \lambda_T}\frac{\lambda_T}{R_0} = 1, \tag{4.40}$$

$$\frac{\partial R_0}{\partial \mu_V}\frac{\mu_V}{R_0} = -1, \tag{4.41}$$

$$\frac{\partial R_0}{\partial \mu_T}\frac{\mu_T}{R_0} = -1. \tag{4.42}$$

Table 4.4: Sensitivity indices of R_0 irrespective of the parameters value.

Parameters	sensitivity index
ϵ_V	1
χ	1
λ_T	1
μ_V	-1
μ_T	-1

From the sensitivity indices it is evident that χ and ϵ_V are the most positively sensitive parameters. This means increasing these parameter will lead to an increase in the R_0 whereas μ_V is the most negatively sensitive parameter. This means that increasing this parameter will decrease the value of R_0. In particular, a 1% increase in μ_V results to a 1% decrease in R_0. Therefore, reducing the most positively sensitive parameters in the R_0 will be the most effective way in reducing viral replication. In conclusion it is evident that at the disease-free equilibrium the most effective treatment strategy should always target the infection rate.

4.5.2 Use of Partial rank correlation coefficients (PRCCs) for sensitivity analysis

PRCC is a method that measures the monotonicity between parameters and model output after removing the linear effects of all parameters except the parameter of interest (Marino et al., 2008). The correlation provides a measure of the strength of a linear association between an input and an output. A standard correlation coefficient, ρ, for two variables, x and y, is calculated as follows:

$$\rho = \frac{\sum_i \Big(x_i - \bar{x}\Big)\Big(y_i - \bar{y}\Big)}{\sqrt{\sum_i \Big(x_i - \bar{x}\Big)^2 \Big(y_i - \bar{y}\Big)^2}}, \tag{4.43}$$

where $\{(x_i, y_i) \mid x_i \in x, y_i \in y\}$ are the set of paired, sampled data, $\bar{x}$ is the sample mean of x, and $\bar{y}$ is the sample mean of y. The PRCC determines the sensitivity of an output state variable to an input parameter as the linear correlation, ρ, between the residuals, $X_j - \hat{X}_j$ and $Y - \hat{Y}$ where X_j is the rank transformed, sampled jth input

parameter, and Y is the rank transformed output state variable, while keeping all other parameter values fixed. X_j and Y are determined for k samples by the linear regression models (Wu et al., 2013).

$$\begin{aligned} \hat{X}_j &= c_0 + \sum_{p=1\neq j}^{k} c_p X_p, \\ \hat{Y} &= b_0 + \sum_{p=1\neq j}^{k} b_p X_p. \end{aligned} \tag{4.44}$$

PRCC method has been widely used by researchers in the field of epidemiology in analyzing the parameter sensitivity to R_0. The use of PRCCs in sensitivity analysis helps in the assessment of the statistical relationship between the R_0 and the parameters and, the sign of the PRCC of an input parameter depicts the particular kind of qualitative affiliation it has with the outcome variable. When a parameter of the R_0 has a positive PRCC value, it means that if it is increased, it will lead to an increase in the value of the R_0 whereas its decrease leads to a decrease in the R_0. Using the parameter values in Table 3.4 the Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters ϵ_V, $\mu_V$andχ that influence R_0 are presented in Figure 4.2.

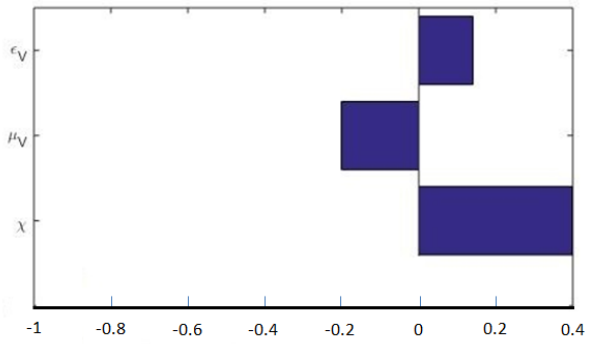


Figure 4.2: Tornado plot showing the sensitivity of R_0 to some of the parameters values

From Figure 4.2 it is evident that a decrease in the rate of HIV virions production ϵ_V would lead to a decrease in the value of R_0. This can be done, for example, by introducing HIV drugs such as the Reverse Transcriptase inhibitors (RTIs) or the Protease inhibitor (PIs). RTI prevents the production of more HIV virions since it inhibits the reverse transcription process. If the HIV RNA is not reverse transcribed to HIV DNA then the virus inside the cells fail to multiply. In addition, use of PIs inhibits the pro-

duction of protease enzyme that is necessary for the maturation of the HIV virions, consequently, the virus produced after its introduction would be non-infectious and immature. Furthermore, a strong immune response would lead to a reduction in the number of the HIV virions. Activated cytotoxic T-cells fight and kill/remove the infected cells. This, in turn, reduces the number of the HIV virions produced.

Increase in the death rate of free HIV virions would also lead to a decrease in the R_0. This could be done by introducing the ARTs drugs aforementioned. However, it is important for researchers to establish the most optimal HIV drugs that would lead to immune reconstruction with minimal side effects.

Remark 4.1. When the parameters with $PRCC > 0$ are increased, R_0 increases whereas when the parameters with $PRCC < 0$ are increased, R_0 decreases and the converse is true.

Remark 4.2. Since both λ_T and μ_T represents a naturally occurring phenomena in the body, they are not included in sensitivity analysis.

The two methods convey the same information however, the PRCC index, ranging from -1 to $+1$, is more efficient since it provides specific qualitative information on the relationship between the R_0 and its parameters.

4.6 Stability Analysis of the equilibrium points

In this section the analysis for the local stability of the disease-free equilibrium of system (4.1) is carried out. The reproductive number has been known to play an important role as far as propagation of the HIV epidemic is concerned.

4.6.1 Local stability of the disease-free equilibrium

Theorem 4.3. *The disease-free equilibrium of the HIV/AIDS system* (4.1) *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof.

$$J(P_0) = \begin{bmatrix} -\mu_T & 0 & 0 & -\chi(1-u_1)\frac{\lambda_T}{\mu_T} & 0 & 0 & 0 \\ 0 & -\mu_I & 0 & \chi\frac{(1-u_1)(1-u_2)\lambda_T}{\mu_T} & 0 & 0 & 0 \\ 0 & 0 & -\mu_{I_l} & \chi\frac{u_2(1-u_1)\lambda_T}{(1-u_1)\mu_T} & 0 & 0 & 0 \\ 0 & (1-u_3)\epsilon_V\mu_I & 0 & -\mu_V & 0 & 0 & 0 \\ 0 & u_3\epsilon_V\mu_I & 0 & 0 & -\mu_{V_n} & 0 & 0 \\ 0 & -\beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & -\mu_Z & 0 \\ 0 & \beta\frac{\lambda_Z}{\mu_Z} & 0 & 0 & 0 & 0 & -\mu_{Za} \end{bmatrix}. \tag{4.45}$$

The eigenvalues are $-\mu_T, -\mu_V, -\mu_{I_l}, -\mu_{V_n}, -\mu_Z, -\mu_{Z_a}$ and those that are solution to the equation:

$$\Lambda^2 + (\mu_I + \mu_V)\Lambda + \mu_I\mu_V\Big(1 - (1-u_1)(1-u_2)(1-u_3)\Big)\chi\frac{\lambda_T\epsilon_V}{\mu_T\mu_V} = 0. \tag{4.46}$$

The eigenvalues of equation (4.46) have negative real parts if

$$(1-u_1)(1-u_2)(1-u_3)\chi\frac{\lambda_T\epsilon_V}{\mu_T\mu_V} < 1. \tag{4.47}$$

Note that, $R_0 = (1-u_1)(1-u_2)(1-u_3)\chi\frac{\lambda_T\epsilon_V}{\mu_T\mu_V}$. Consequently, all the eigenvalues are negative when $R_0 < 1$. Hence the disease-free equilibrium of the model is locally asymptotically stable when $R_0 < 1$. □

4.7 Numerical Simulations and Analysis of HIV Dynamics during Treatment

Numerical integration is used to solve the system (4.1) in MAPLE. The initial values of the model are set as; $T_0 = 1000$ cells/mm^3, $I_0 = 10$ cells/mm^3, $I_{l0} = 0$ cells/mm^3, $V_0 = 10$ virions/mm^3, $V_{n0} = 0$ virions/mm^3, $Z_0 = 500$ cells/mm^3, $Z_{a0} = 30$ cells/mm^3. For the first simulation the same drug efficacy of the three drug combinations, that is, $u_1 = u_2 = u_3 = U$ is used. The parameter values used in the analysis are described in Tables 3.4 and 5.1.

Figure 4.3 shows the dynamics of CD4$^+$ T-cells over time. It is clear that ARTs play a very vital role. This is because the level of the susceptible CD4$^+$ T-cells remains high with increase in the level of the drug efficacy. A small decrease in the number of the CD4$^+$ T-cells is observed during treatment, which lasts for a short period. Later the

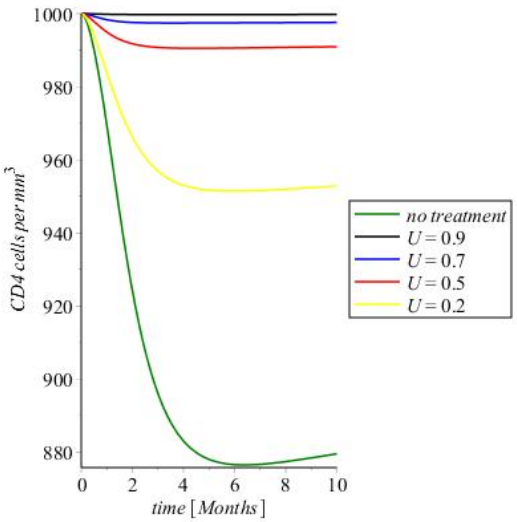


Figure 4.3: The population of the susceptible CD4$^+$T-cells.

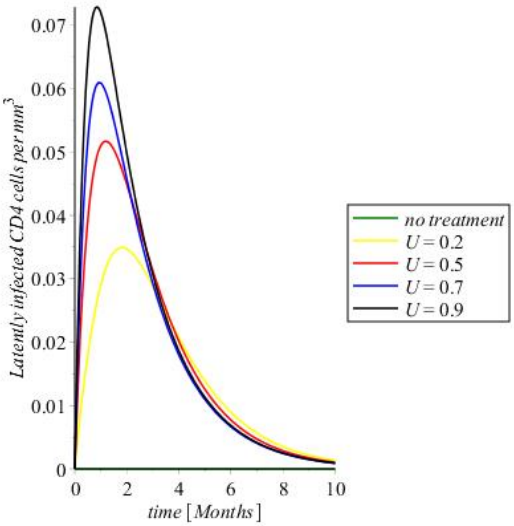


Figure 4.4: The populations of the latently infected CD4$^+$T-cells.

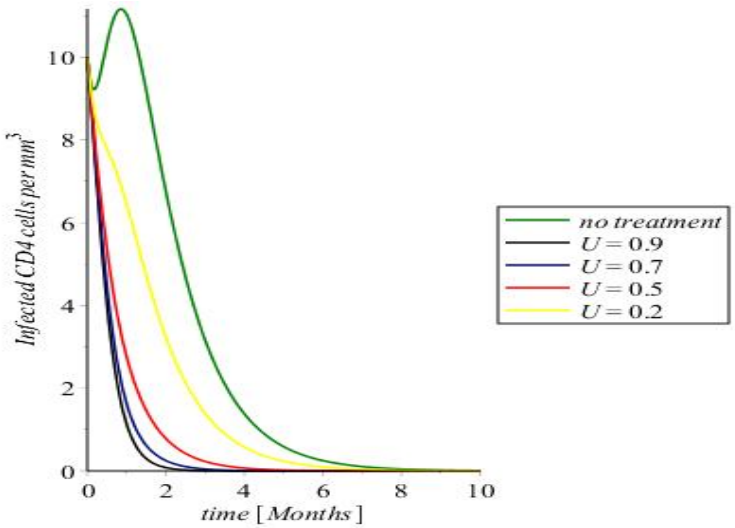


Figure 4.5: The population of the infected CD4$^+$ T-cells with time.

number of the $CD4^+$ T-cells increases although not to the pre-infection period. Furthermore, as the drug efficacy increases there is also an increase in the number of the susceptible $CD4^+$T-cells. However, without treatment the level of the $CD4^+$ T-cells decreases as one progresses to the disease stage. This can be explained by the fact that during acute infection there is high multiplication of the virus which lead to a decrease in the number of susceptible cells, hence, most of the $CD4^+$ T-cells get infected.

Figure 4.4 represents the change in population of the latently infected cells. It is evident that introduction of ARTs leads to production of the latently infected cells. The cells are only produced when RTIs drugs for HIV treatment are used. Fortunately, the latently infected cells do not produce infectious HIV virions because the RTIs inhibits the reverse transcription process.

Figure 4.5 represents the number of the infected $CD4^+$ T-cells. The research findings indicate that when no treatment is in use, there is a sharp increase in the number of infected cells. This is due the high number of HIV virions produced by a single infected cells. However, in the presence of ARTs, the number of the infected cell increases steadily during the onset of treatment but after two months, the number reduces although not to the disease free equilibrium.

Figure 4.6 shows that the number of infectious HIV virions increases when the pa-

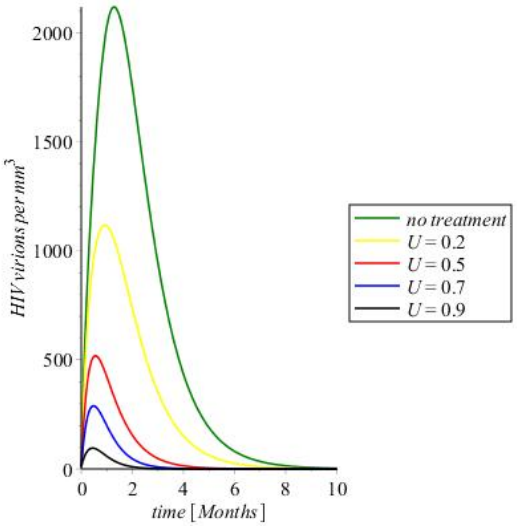


Figure 4.6: The population of the infectious virus with respect to time.

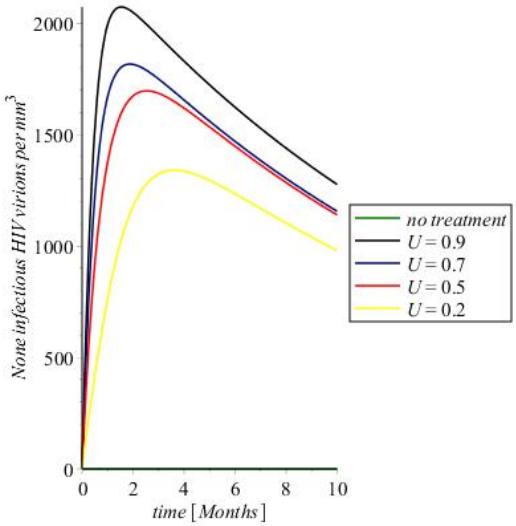


Figure 4.7: The population of the Non-infectious HIV virus.

tient is under no treatment within the first few weeks and later goes down due to the antibody response. The population however, remains at a constant level for a period of time. Nonetheless, with the introduction of treatment the drugs are able to fight the virions and this, in turn, leads to a decrease of the viral load in the body. It is evident that as U increases from 0.6 to 0.9 the viral level decreases. Thus, the higher the level of drug efficacy the lower the viral load which in turn would control HIV transmission. From the numerical simulations it is evident that, antiretroviral therapies could reduce the risk of HIV transmission and hence, ARTs should be initiated during acute infection irrespective of the $CD4^+$ counts of the infected person.

From Figure 4.7 it is evident that without treatment there is no production of non-infectious virus. This is because the immature virions are as a result of the use of Protease inhibitors. Furthermore, as the level of drug efficacy increases the number of non-infectious immature virions also increases. The study noted that, the number increases exponentially in the first three moths getting to a pick but declines on wards. It is therefore, important to consider the non-infectious virus in an HIV model. Most researchers in the field of HIV in-vivo modelling have ignored this part.

Figure 4.8 shows that the number of the $CD8^+$ T-cell decreases in both scenarios,

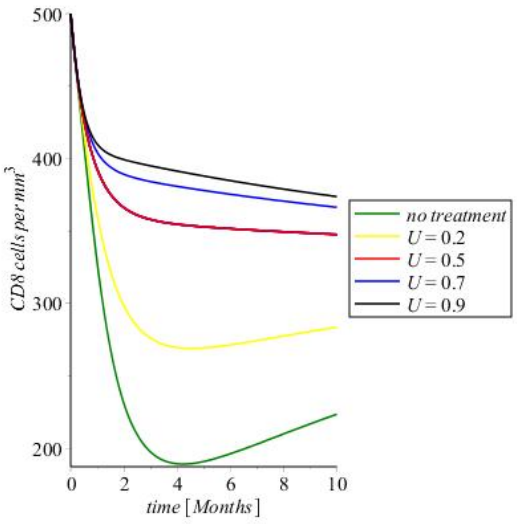


Figure 4.8: The population of the $CD8^+$ T-cells.

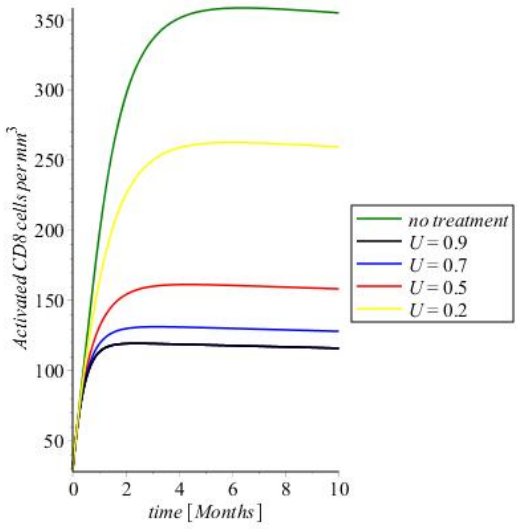


Figure 4.9: The population of the Activated $CD8^+$ T-cells.

that is, with and without treatment. However, in cases where treatment is used the

level of the CD8$^+$ T-cell decreases at a lower rate. This shows that introduction of ARTs enhances the body immunity, whereas in Figure 4.9 the recruitment of CD8$^+$ T-cells is high without treatment and decreases as the drug efficacy increases.

4.7.1 Comparison between Fusion inhibitors, Reverse Trascriptase inhibitors and the Protease inhibitors

In this section, we are interested in analyzing and determining the best ARTs between the Fusion inhibitors, Reverse Trascriptases inhibitors and the Protease inhibitors. The findings are presented in Figures 4.10– 4.16.

In each Figure, five scenarios are represented, that is, no treatment which implies that $u_1 = u_2 = u_3 = 0$, curve A which represents the scenario where $u_1 = 0.1, u_2 = 0.4$ and $u_3 = 0.9$, curve B which represents $u_1 = 0.9, u_2 = 0.4$ and $u_3 = 0.1$, curve C which represents $u_1 = 0.3, u_2 = 0.9$ and $u_3 = 0.2$ and finally curve D where, $u_1 = 0.3, u_2 = 0.2$ and $u_3 = 0.8$. In curve A and B the efficacy of Reverse Transcriptase inhibitor is held constant. As much as all the Figures 4.10– 4.16 support the importance of the ARTs as far as viral suppression is concerned they also emphasize the importance of having Proteases inhibitors in the treatment regime. In curve A where the level of protease inhibitor is high at 0.9 it is evident from Figure 4.10 that the number of CD4$^+$ T-cells remain high compared to curve B where the protease inhibitor efficacy is 0.1. This can also be deduced from Figure 4.12 where the number of infected cells in curve A are few as compared to the number of infected cells from scenario B. This clearly shows that Protease inhibitors play a major role in viral suppression compared to Fusion inhibitors. Curves C and D are mainly concerned on the effectiveness of the Reverse Trascriptase inhibitor in controlling viral load. It is evident from the number of HIV virions produced that Protease inhibitor is more effective than the Reverse Trancsriptase inhibitor. This could be deduced from Figure 4.13. The findings are similar as indicated in the number of the CD4$^+$ T-cells as shown in Figure 4.10. It is evident that Protease inhibitors are the most effective drugs in controlling viral progression. In Chapter 5, optimal control is applied to compare the results and to establish the most optimal way for administering the three drugs strategy.

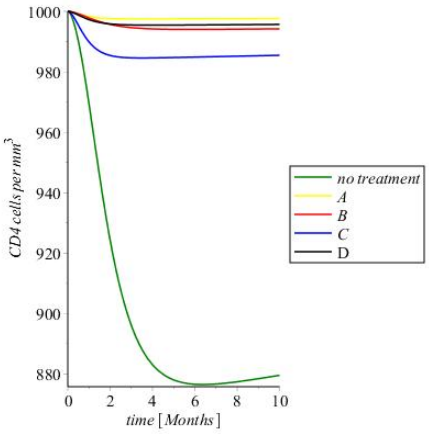


Figure 4.10: The population of the susceptible CD4$^+$T-cells.

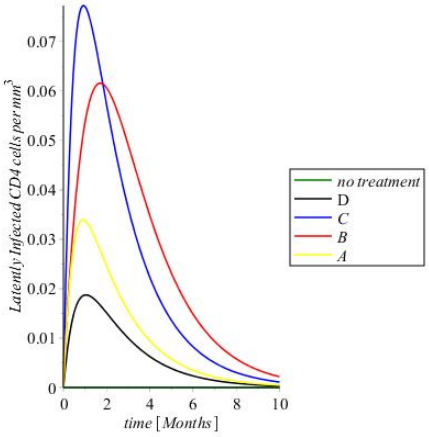


Figure 4.11: The populations of the latently infected CD4$^+$T-cells.

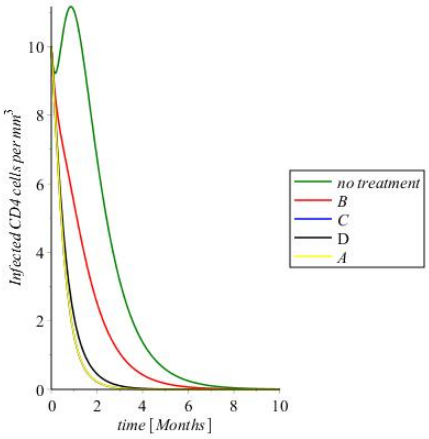


Figure 4.12: The population of the infected CD4$^+$ T-cells with time.

$A = (u_1 = 0.1, u_2 = 0.4, u_3 = 0.9)$, $B = (u_1 = 0.9, u_2 = 0.4, u_3 = 0.1)$, $C = (u_1 = 0.3, u_2 = 0.9, u_3 = 0.2)$ and $D = (u_1 = 0.3, u_2 = 0.2, u_3 = 0.8)$.

4.7.2 Delayed Treatment

In this subsection, comparison between the outcomes of early and delayed introduction of antiretroviral treatment on clinical outcomes is presented. It is evident in Figure 4.17 in treatment delay there is high multiplication of the HIV virions which in turn leads to a decrease in the level of the susceptible CD4$^+$ T-cells which is quite evident from Figure 4.18. This clearly gives us insight on the effects that early initiation of HIV treatment has on improving the infected person immune response and consequently reducing the rate of HIV transmission.

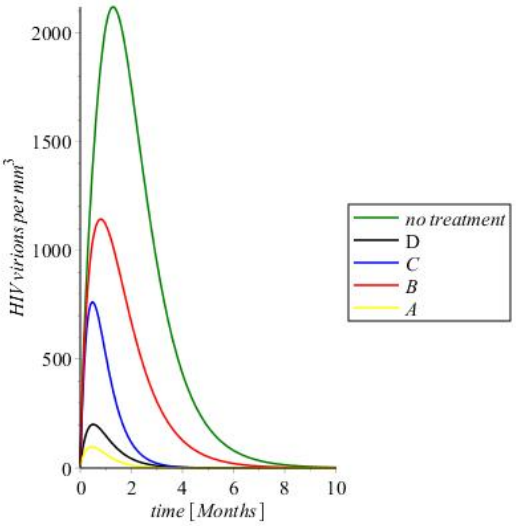


Figure 4.13: The population of the infectious virus with respect to time.

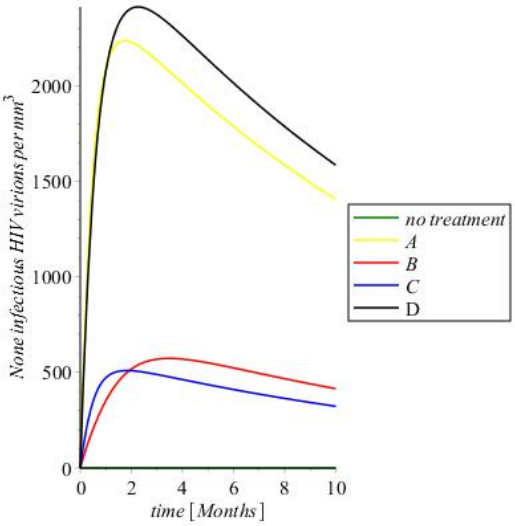


Figure 4.14: The population of the Non-infectious HIV virus.

$A = (u_1 = 0.1, u_2 = 0.4, u_3 = 0.9)$, $B = (u_1 = 0.9, u_2 = 0.4, u_3 = 0.1)$, $C = (u_1 = 0.3, u_2 = 0.9, u_3 = 0.2)$ and $D = (u_1 = 0.3, u_2 = 0.2, u_3 = 0.8)$.

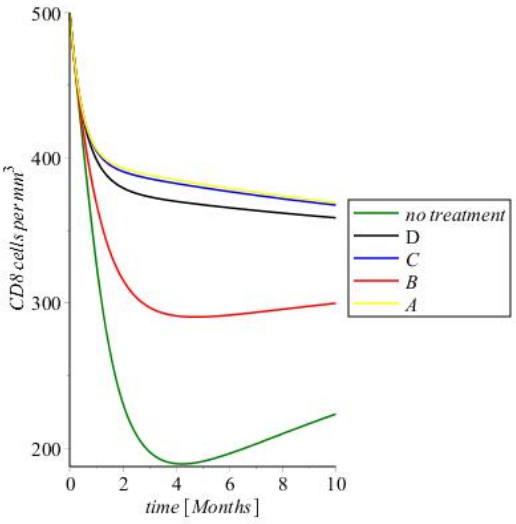


Figure 4.15: The population of the $CD8^+$ T-cells.

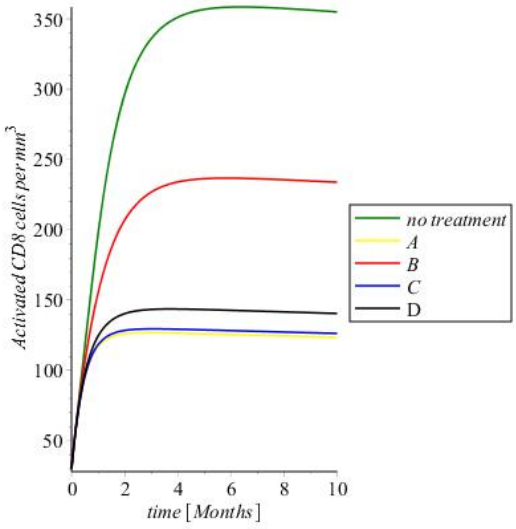


Figure 4.16: The population of the Activated $CD8^+$ T-cells.

$A = (u_1 = 0.1, u_2 = 0.4, u_3 = 0.9)$, $B = (u_1 = 0.9, u_2 = 0.4, u_3 = 0.1)$, $C = (u_1 = 0.3, u_2 = 0.9, u_3 = 0.2)$ and $D = (u_1 = 0.3, u_2 = 0.2, u_3 = 0.8)$.

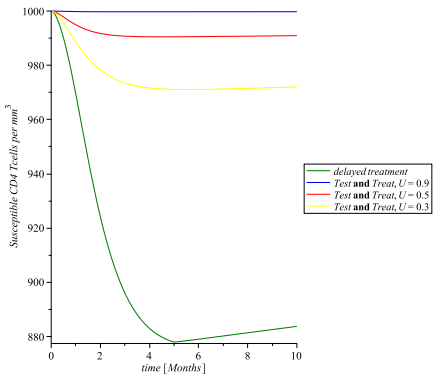


Figure 4.17: The population of the $CD4^+$ T-cells.

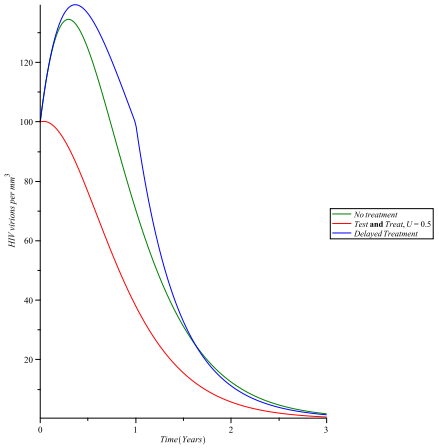


Figure 4.18: The population of the HIV virions.

4.8 Conclusion

In this chapter an in-vivo HIV dynamics model with inclusion of the immune response and administration of three drug regimes, that is, FIs, PIs and RTIs has been formulated and analysed. From the numerical simulations it is evident that the ability of various ARTs to inhibit viral production is higher when drug efficacy is high, that is, the higher the drug efficacy the less the infectious HIV virions produced. This supports the introduction of ARTs to any infected person irrespective of their $CD4^+$ counts.

As much as the cost of ARTs is high especially for the developing countries like Kenya, the social-economics benefits are worth. The findings in this study support the "Anza Sasa"campaign by the Government of Kenya through the Ministry of Health and the National AIDS and STI Control Program (NASCOP). This campaign will go a long way in assisting the Government to meet its 2020 goals that, by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression. "Anza Sasa"campaign may be very expensive at the outset, but it will be cost effective in the long run and it portends more benefits for the HIV/AIDS individuals and the society at large.

More experimental research however, on viral dynamics need to be carried out to improve the understanding of the dynamic nature of HIV-1 infection and the viral-drug

interaction mechanism. This is because the research findings indicated that use of ARTs is the most efficient way of eradicating HIV and also of reducing viral suppression. However, the efficacy of these ARTs depends on the possibility of halting viral replication in all biological compartments which could only be established through experimental research. Notably, development of more potent HIV drug regimens and better diagnostic tools will help a great deal in ensuring that HIV is eradicated.

Chapter 5
Modelling Optimal Control of In-vivo HIV Dynamics using Different Control Strategies

5.1 Introduction

Mathematical modelling is one of the many important tools used in understanding the dynamics of disease transmission. It is also used in developing guidelines that are important in disease control. In HIV dynamics analysis, mathematical models have provided a framework for understanding the viral dynamics and have been used in the optimal allocation of the various interventions against the HIV virions (Mbogo et al., 2013; Nampala et al., 2014; Ogunlaran and Oukouomi, 2016). A fundamental goal of developing and applying the aforementioned mathematical models of HIV is to influence treatment decisions and construct better treatment protocols for HIV-infected patients. Most of the recent mathematical models that have been developed apply the optimal control theory.

Optimal control theory is a branch of mathematics developed to find optimal ways of controlling a dynamical system (Pontryagin, 1987). It has been applied by mathematicians to assist in the analysis of how to control the spread of infectious diseases. The results are used in making key decisions that involve complex biological mechanism. In particular, it is used to determine the best dosage for various available vaccines or treatment in use for controlling infection.

For instance, Gaff and Schaefer (2009) applied optimal theory in evaluating mitigation strategy that would be highly effective in minimizing the number of people who

get infected by an infection. The study applied both vaccinations and treatment as control variables for their various models. The results indicated that as much as treatment is paramount in controlling any infection, the most optimal method would be the combinations of the two interventions. Futhemore, Bakare et al. (2014) applied optimal control to an SIR model. The study illustrated the use of optimal control theory in establishing the optimal educational campaign and treatment strategies that would minimize the population of the infected persons as well as cutting the cost of controlling the various diseases. The results indicated that for controlling infection it is important to target the uninfected populations and apply measures that will prevent them from getting the infection.

According to various articles in the literature, optimal control theory has been applied to study population level as well as in-vivo HIV dynamics. For example, Yusuf and Benyah (2012) applied optimal theory on HIV-population model. The study was aimed at determining the best method of controlling the spread of HIV/AIDS within a specified time frame. The study considered three control variables, that is, safe sex, education and ARTs. The numerical results of the objective function for the model indicated that safe sex practice as well as early initiation of ARTs are the most optimal ways of mitigating the spread of HIV/AIDS. The study established that implementation of the the aforementioned strategies would lead to a HIV free nation in 10 years time. In addition, for in-host model, optimal control theory has been applied in the search of optimal therapies for HIV infection. Drugs such as Fusion inhibitors (FIs), Reverse Transcriptase inhibitors (RTIs) and Protease Inhibitors (PIs) have been developed and applied in various optimal control problems.

In this study, optimal control theory has been applied on the in-vivo HIV treatment model aimed at establishing the optimal drug combinations for HIV in relation to their per capita cost.

5.2 Economic Evaluation

In this section the method used by Pontryagin (1987) has been applied, to economically assess the various drugs strategies. This study has considered an economic evaluation of using Fusion inhibitors, Reverse Transcriptase inhibitors and Protease inhibitors. The analysis is aimed at comparing the cost of these drugs and their effectiveness in

controlling HIV viral replication as well as assist in making informed decisions as to the most cost effective strategy among the interventions under consideration. In this regard, the study introduced a cost objective function given in equation (5.1):

$$P(u_1(t), u_2(t), u_3(t)) = \int_0^{T_f} \left\{ (c_F u_1 T(t) + (c_R(1-u_1)u_2 + c_P u_3)\,(I(t)+V(t)) \right\} e^{-\theta t} dt, \tag{5.1}$$

that needed to be minimized, subject to

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - (1-u_1(t))\chi TV, \\
\frac{dI}{dt} &= (1-u_1(t))(1-u_2(t))\chi TV - \mu_I I - \alpha I Z_a, \\
\frac{dI_l}{dt} &= (1-u_1(t))u_2(t)\chi TV - \mu_{I_l} I_l, \\
\frac{dV}{dt} &= (1-u_3(t))\epsilon_V \mu_I I - \mu_V V, \\
\frac{dV_n}{dt} &= u_3(t)\epsilon_V \mu_I I - \mu_{Vn} V_n, \\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I, \\
\frac{dZ_a}{dt} &= \beta Z I - \mu_{Z_a} Z_a,
\end{aligned}\right\} \tag{5.2}$$

where $c_F, c_R,$ and c_P represent per capita cost associated with the use of Fusion inhibitors, Reverse Transcriptase inhibitors and Protease inhibitors respectively. The parameter θ is the discount rate associated with the cost of the drugs and it is taken to be between $3\% - 5\%$ (Okosun et al., 2013; Momoh and Fügenschuh, 2017). In addition, the exponential curves guarantee a decrease on the cost function with time. Variables u_1, u_2 and u_3 represent the efficacy associated with the three drug regimes, that is, Fusion inhibitors, Reverse Transcriptase inhibitors and Protease inhibitors respectively. Let us denote the marginal price for the respective classes as various state variables as $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7$ which represent the change in the objective value of an optimal solution of an optimization problem by relaxing the constraint by one unit (Pontryagin, 1987).

The corresponding Hamiltonian is given by

$$
\begin{aligned}
H = &\{(c_F u_1(t)T(t) + (c_R(1-u_1(t))u_2(t) + c_P u_3(t))\,(I(t)+V(t))\}\,e^{-\theta t} + \\
&\lambda_1(\lambda_T - \mu_T T - (1-u_1(t))\chi T(t)V(t)) + \lambda_2((1-u_2(t))(1-u_1(t))\chi T(t)V(t) - \\
&\mu_I I(t) - \alpha I(t)Z_a(t)) + \lambda_3(u_2(1-u_1(t))\chi T(t)V(t) - \mu_{I_l} I_l(t)) + \\
&\lambda_4((1-u_3(t))\epsilon_V \mu_I I(t) - \mu_V V(t)) + \lambda_5(u_3(t)\epsilon_V \mu_I I(t) - \mu_{V_n} V_n(t)) + \\
&\lambda_6(\lambda_Z - \mu_Z Z(t) - \beta Z(t)I(t)) + \lambda_7(\beta Z(t)I(t) - \mu_{Z_a} Z_a(t)).
\end{aligned}
\tag{5.3}
$$

Pontryaginś Maximum Principle is applied in finding the marginal prices $\dot{\lambda}_i$, $i = 1, 2, ..., 7$:

$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial T}$, $\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I}$, $\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_l}$, $\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial V}$, $\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial V_n}$, $\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial Z}$, $\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial Z_a}$.

Thus,

$$
\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial H}{\partial T} = -c_F u_1(t)e^{-\theta t} + \lambda_1\left(\mu_T + (1-u_1(t))\chi V\right) - \lambda_2 \chi V(1-u_1(t)) \\
&\qquad (1-u_2(t)) - \lambda_3 u_2(t)(1-u_1(t))\chi V, \\
\dot{\lambda}_2 &= -\frac{\partial H}{\partial I} = -(c_R(1-u_1(t)u_2(t) + c_P u_3(t))\,e^{-\theta t} + \lambda_2(\mu_I + \alpha Z_a) - \lambda_4 \varepsilon_V \mu_I \\
&\qquad (1-u_3(t)) - \lambda_5 u_3(t)\epsilon_V \mu_I + \lambda_6 \beta Z - \lambda_7 \beta Z, \\
\dot{\lambda}_3 &= -\frac{\partial H}{\partial I_l} = \lambda_3 \mu_{I_l}, \\
\dot{\lambda}_4 &= -\frac{\partial H}{\partial V} = -(c_R u_2(t) + c_P u_3(t))\,e^{-\theta t} + \lambda_1 \chi T(1-u_1(t)) - \lambda_2 \chi T(1-u_1(t)) \\
&\qquad (1-u_2(t)) - \lambda_3 \chi T u_2(t)(1-u_1(t)) + \lambda_4 \mu_V, \\
\dot{\lambda}_5 &= -\frac{\partial H}{\partial V_n} = \lambda_5 \mu_{V_n}, \\
\dot{\lambda}_6 &= -\frac{\partial H}{\partial Z} = \lambda_6(\mu_Z + \beta I) - \lambda_7 \beta I, \\
\dot{\lambda}_7 &= -\frac{\partial H}{\partial Z_a} = \lambda_2 \alpha I + \lambda_7 \mu_{Z_a},
\end{aligned}
\tag{5.4}
$$

where $\lambda_i(t_f) = 0; i = 1, 2, 3, ..., 7$ are the transversality conditions. The assessment of the drug strategy is done by developing the Hamiltonian equation presented in the next subsection.

5.2.1 Economic evaluation of using Fusion inhibitor

The Hamiltonian, H, given in equation (5.3), is differentiated with respect to u_1, which represents the Fusion inhibitors, to obtain

$$\frac{\partial H}{\partial u_1} = \Big(c_F T(t) - c_R(I(t) + V(t))\Big)e^{-\theta t} + \Big(\lambda_1 - (1-u_2)\lambda_2 - u_2\lambda_3\Big)\chi TV, \quad (5.5)$$

where

$$\Big(c_F T(t) - c_R(I(t) + V(t))\Big)e^{-\theta t}$$

is the total marginal cost of using Fusion inhibitor and

$$\Big(\lambda_1 - (1-u_2)\lambda_2 - u_2\lambda_3\Big)\chi T(t)V(t)$$

is the total marginal benefit of using Fusion inhibitor.

Optimal policy is achieved if and only if the total marginal cost is equal to the total marginal benefit. The following bounds are then obtained from equation (5.5)

$$\begin{aligned}
u_1 = 0 \quad &\text{if} \quad \Big(c_F T(t) - c_R(I(t) + V(t))\Big)e^{-\theta t} > \Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2\lambda_3\Big)\chi TV, \\
u_1 \in (0,1) \quad &\text{if} \quad \Big(c_F T(t) - c_R(I(t) + V(t))\Big)e^{-\theta t} = \Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)\chi TV, \\
u_1 = 1 \quad &\text{if} \quad \Big(c_F T(t) - c_R(I(t) + V(t))\Big)e^{-\theta t} < \Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)\chi TV.
\end{aligned} \quad (5.6)$$

It is evident, from equation (5.6), that:

1. If $u_1(t) = 1$ then the total marginal benefit of using Fusion inhibitors is more than the total marginal cost; hence the gain of optimal protection of the susceptible CD4$^+$ T-cells. Thus, this drug should be recommended to an HIV infected person to prevent the entry of the virions into the CD4$^+$ T-cells.

2. If $u_1(t) \in [0, 1)$ then the marginal cost is more than the marginal benefit. Consequently, HIV virions will gain entry into the susceptible CD4$^+$. This, in turn, will lead to disease progression.

The effective use of this strategy will lead to achievement of the optimal policy which indicates that increasing the use of Fusion inhibitor will lead to an increase in the number of the susceptible CD$^+$ T-cells. Hence, the infected person will remain healthy for a longer period.

5.2.2 Economic evaluation of Reverse Transcriptase inhibitors

When the Hamiltonian, H, given in equation (5.3), is differentiated with respect to u_2 which represents the Reverse Transcriptase inhibitors, we obtain:

$$\frac{\partial H}{\partial u_2(t)} = c_R(1-u_1(t))e^{-\theta t}\left(I(t)+V(t)\right) - \left(\lambda_2-\lambda_3\right)\left(1-u_1(t)\right)\chi T(t)V(t), \quad (5.7)$$

where

$$c_R(1-u_1(t))e^{-\theta t}\left(I(t)+V(t)\right)$$

is the total marginal cost of using Reverse Transcriptase inhibitors and

$$\left(\lambda_3-\lambda_2\right)\left(1-u_1(t)\right)\chi T(t)V(t)$$

is the total marginal benefit of using Reverse Transcriptase inhibitors.
Optimal policy is achieved if and only if the total marginal cost is equal to the total marginal benefit. From equation (5.7) the following bounds are obtained:

$$\begin{aligned}
u_2 = 0 \quad &\text{if} \quad c_R(1-u_1(t))e^{-\theta t}\left(I(t)+V(t)\right) > \left(\lambda_3-\lambda_2\right)\left(1-u_1(t)\chi TV,\right.\\
u_2 \in (0,1) \quad &\text{if} \quad c_R(1-u_1(t))e^{-\theta t}\left(I(t)+V(t)\right) = \left(\lambda_3-\lambda_2\right)\left(1-u_1(t)\right)\chi TV,\\
u_2 = 1 \quad &\text{if} \quad c_R(1-u_1(t))e^{-\theta t}\left(I(t)+V(t)\right) < \left(\lambda_3-\lambda_2\right)\left(1-u_1(t)\right)\chi TV.
\end{aligned} \quad (5.8)$$

From equation (5.8) it is evident that:

1. If $u_2(t) = 1$ then the total marginal benefit of using Reverse Transcriptase inhibitors is more than the total marginal cost; hence the gain of optimal prevention of the infected CD4$^+$ T-cells from undergoing a full life cycle. This drug should be recommended to an HIV infected person since it will aid in preventing the virions from undergoing the reverse trancsription process. This will lead to production of latently infected cells and consequently, reducing the number of HIV virions released back to the blood stream.

2. If $u_2(t) \in [0,1)$ then the marginal cost is more than the marginal benefit and consequently, the HIV-RNA will be reverse transcribed to HIV-DNA, hence the virions manage to make new copies which upon maturity are released back to the body.

The effective use of this strategy will lead to the achievement of optimal policy which implies that, increasing the use of Reverse Transcriptase inhibitors will lead to an decrease in the number of the HIV virions which would emerge from the infected CD^+ T-cells.

5.2.3 Economic evaluation of Protease inhibitors

When the Hamiltonian, H, given in equation (5.3), is differentiated with respect to $u_3(t)$, which represents the Protease inhibitors, we obtain

$$\frac{\partial H}{\partial u_3(t)} = c_P e^{-\theta t}\left(I(t) + V(t)\right) - \left(\lambda_4 - \lambda_5\right)\epsilon_V \mu_I I(t), \tag{5.9}$$

where

$$c_P e^{-\theta t}\left(I(t) + V(t)\right)$$

is the total marginal cost of using Protease inhibitors and

$$\left(\lambda_5 - \lambda_4\right)\epsilon_V \mu_I I(t)$$

is the total marginal benefit of using Protease inhibitors.
Optimal policy is achieved if and only if the total marginal cost is equal to the total marginal benefit. From equation (5.9) the following bounds are obtained:

$$\begin{aligned}
u_3 &= 0 \qquad \text{if} \quad c_P e^{-\theta t}\left(I(t) + V(t)\right) > \left(\lambda_5 - \lambda_4\right)\epsilon_V \mu_I I, \\
u_3 &\in (0,1) \qquad \text{if} \quad c_P e^{-\theta t}\left(I(t) + V(t)\right) = \left(\lambda_5 - \lambda_4\right)\epsilon_V \mu_I I, \\
u_3 &= 1 \qquad \text{if} \quad c_P e^{-\theta t}\left(I(t) + V(t)\right) < \left(\lambda_5 - \lambda_4\right)\epsilon_V \mu_I I.
\end{aligned} \tag{5.10}$$

From equation (5.10) it is evident that:

1. If $u_3(t) = 1$ then the total marginal benefit of using Protease inhibitors is more than the total marginal cost; hence the gain of optimal prevention from the release of mature HIV virions from HIV infected $CD4^+$ T-cells. Hence, this drug should be recommended to an HIV infected person since it will lead to production of immature non-infectious HIV virions. This in turn will reduce the number of infectious virions in the body of the infected person.

2. If $u_3(t) \in [0,1)$ then the marginal cost is more than the marginal benefit consequently, some of the infected cells will undergo all the life cycle stages and this

will lead to production of HIV virions in the blood. The implication of this is that more CD4$^+$ T-cells will be attacked by the HIV virions, this, in turn will make the body vulnerable to many optimistic infections.

The effective use of this strategy will lead to the achievement of optimal policy which indicates that increasing the use of Protease inhibitors will lead to production of immature non-infectious HIV virions hence a decrease in the number of the free virions that results from the infected CD4$^+$ T-cells.

5.3 Optimization process

For HIV, control efforts are carried out to limit the spread of the disease, and in some cases, to prevent the the side effects associated with the various HIV drugs. Optimal control theory is a method that has been widely used to solve for an extremum value of an objective functional involving dynamic variables. In this section, optimal control theory has been applied in deriving optimal drug treatments as functions of time. The control variables as used in system (4.1) are described as follows: The control $u_1(t)$ represents the effect of Fusion inhibitors, which are the drugs that protect the uninfected CD4$^+$ T-cells by preventing the entry of the virus into the CD4$^+$T-cells membrane. The control variable $u_2(t)$ simulates the effect of Reverse Transcriptase inhibitors. These drugs hinder the reverse transcription process. The third control variable $u_3(t)$ simulates the effect of Protease inhibitors, which prevent the already infected cells from producing mature-infectious virions.

The aforementioned controls represent effective chemotherapy dosage bounded between 0 and 1. The situation $u_1(t) = u_2(t) = u_3(t) = 1$ represents total efficacy of the Fusion inhibitors, Reverse Transcriptase inhibitors and Protease inhibitors respectively and $u_1(t) = u_2(t) = u_3(t) = 0$ represents no treatment. It is worth noting that the control variables aforementioned are bounded Lebesques integrable functions. The study aimed at maximizing the levels of the healthy CD4$^+$ T-cells, as well as the levels of the CD8$^+$ T-cells $(Z(t))$ while minimizing the viral load $(V(t))$ and at the same time keeping cost and side effects of treatment at a minimum. With the above description

the following objective function (5.11) need to be maximized:

$$J(u_1(t), u_2(t), u_3(t)) = \frac{1}{2}\int_0^{T_f} (w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2(t) - A_2 u_2^2(t) - A_3 u_3^2(t))dt \tag{5.11}$$

subject to system (4.1).

$T(t)$, $Z(t)$ and $V(t)$ are the solutions of the system (4.1). The quantities w_1 and w_2 represent the cost associated with maximizing the number of CD4$^+$ T-cells and the CD8$^+$ T-cells respectively, while w_3 represents the cost associated with minimizing the viral load. In addition, A_1, A_2 and A_3 are non-negative constants representing the relative weights attached to the current cost of each treatment regime and T_f is a fixed terminal time of the treatment programme subject to the ordinary differential equations described in system (4.1). This study assumed that the cost of controls are of quadratic form. Furthermore, it is also based on the fact that there is no linear relationship between the effect of treatment on CD4$^+$ T-cells, CD8$^+$ T-cells or the HIV virions. Consequently, $u_1(t)$, $u_2(t)$ and $u_3(t)$ are Lebesgue integrable; that is, they are piecewise continuous and integrable. The fundamental aim of this therapeutic strategy is to maximize the objective functional defined in equation (5.11) by increasing the number of the uninfected CD4$^+$ T-cells and the CD8$^+$T-cells, decreasing the viral load $(V(t))$ and minimizing the harmful side effects and cost of treatment over the given time interval $[0, T_f]$. Therefore, the study aimed at determining the optimal control $u_1(t)^*$,$u_2(t)^*$ and $u_3(t)^*$ such that;

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = max\left\{J(u_1(t), u_2(t), u_3(t)) : (u_1, u_2, u_3) \in U\right\}, \tag{5.12}$$

where U is a set of all measurable controls defined by:

$$U = \left\{u = (u_1, u_2, u_3) : u_i \text{ measurable}, 0 \leq u_i(t) \leq 1, t \in [0, T_f]\right\}. \tag{5.13}$$

In the next section the existence of an optimal control for the system (4.1) is determined and the optimality system derived.

5.4 Characterization of the Optimal Control

The necessary conditions that an optimal control must satisfy come from the Pontryagins Maximum Principle (Pontryagin, 1987).

Theorem 5.1. *Suppose the objective function*

$$J(u_1(t), u_2(t), u_3(t)) = \frac{1}{2}\int_0^{T_f} (w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2(t) - A_2 u_2^2(t) - A_3 u_3^2(t))dt, \tag{5.14}$$

is maximized subject to the controls and state variables given in system (4.1) *with* $T(0) = T_0, \quad I(0) = I_0, \quad I_l(0) = I_{l0}, \quad V(0) = V_0, \quad V_n(0) = V_{n0}, \quad Z(0) = Z_0$ *and* $Z_a(0) = Z_{a0}$.

Then there exists optimal controls $(u_1^*, u_2^*, u_3^* \in U)$ *such that;*

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = max\left\{J(u_1(t), u_2(t), u_3(t)) : (u_1, u_2, u_3) \in U\right\}.$$

Proof. The existence of the solution can be shown using the results obtained in Fleming and Rishel (2012), since:

1. The class of all initial conditions with controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ in the control set U are non-negative values and are non-empty where $u_i, i = 1, 2, 3$ is a Lebesgue-integrable function on $[0, T_f]$.

2. The right hand side of system (4.1) is bounded by a linear function of the state and control variables and the solutions exist.

   By definition, each right hand side of system (4.1) is continuous and can be written as a linear function of U with coefficients depending on time and state. Furthermore, all the state and control variables $T(t), I(t), I_l(t), V(t), V_n(t), Z(t)$, $Z_a(t), u_1(t), u_2(t),$ and $u_3(t)$ are bounded on $[0, T_f]$. In particular considering the system (4.1) with initial conditions $T_0, I_0, I_{l_0}, V_0, V_{n_0}, Z_0, Z_{a_0}$, then it can be written in the form:

   $$\dot{Y} = AY + F(Y), \tag{5.15}$$

   where

   $$Y = \begin{bmatrix} T \\ I \\ I_l \\ V \\ V_n \\ Z \\ Z_a \end{bmatrix}, \tag{5.16}$$

is the vector of the state variables and A and $F(Y)$ are as defined in equations (5.17) and (5.18), respectively:

$$A = \begin{bmatrix} -\mu_T & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_I & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_{I_l} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_V & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{V_n} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_Z & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{Z_a} \end{bmatrix}, \tag{5.17}$$

$$F(Y) = \begin{bmatrix} \lambda_T - (1-u_1(t))\chi TV \\ (1-u_1(t))(1-u_2(t))\chi TV - \alpha I Z_a \\ (1-u_1(t)u_2(t)\chi TV(1-u_3)\epsilon_V \mu_I I \\ u_3 \epsilon_V \mu_I I \\ \lambda_Z - \beta Z I \\ \beta Z I \end{bmatrix}. \tag{5.18}$$

The system (5.15) is a non-linear system with a bounded coefficient. Let,

$$B(Y) = RY + F(Y) \tag{5.19}$$

then, the second term on the right-hand side of (5.19) satisfies

$$\begin{aligned} |F(Y_1) - F(Y_2)| \leq K_1 |T_1(t) - T_2(t)| + K_2 |I_1(t) - I_2(t)| + K_3 |I_{l_1}(t) \\ - I_{l_2}(t)| + K_4 |V_1(t) - V_2(t)| + K_5 |V_{n_1}(t) - V_{n_2}(t)| \\ + K_6 |Z_1(t) - Z_2(t)| + K_7 |Z_{a_1}(t) - Z_{a_2}(t)| \\ \leq K |T_1(t) - T_2(t)| + |I_1(t) - I_2(t)| + |I_{l_1}(t) - I_{l_2}(t)| + \\ |V_1(t) - V_2(t)| + |V_{n_1}(t) - V_{n_2}(t)| + |Z_1(t) - Z_2(t)| \\ + |Z_{a_1}(t) - Z_{a_2}(t)|, \end{aligned} \tag{5.20}$$

where the positive constant $K = \max\ (K_i, i = 1, 2, 3..., 7)$ is independent of the state variables. In addition, $B(Y_1) - B(Y_2) \leq K |Y_1 - Y_2|$, where $K = \sum_{i=1}^{7} K_i + ||M|| < \infty$. So, it follows that the function $B(Y)$ is uniformly Lipschitz continuous. From the definition of the controls u_1, u_2 and u_3 and the restrictions on the non-negativeness of the state variables then the solutions of the system (5.15) exists.

3. By definition the control set U is convex and closed.

   A set $K \in \mathbb{R}^{\kappa}$ is said to be a convex set if and only if

   $$\lambda x + (1-\lambda)y \in K,$$

   for all $x, y \in K$, and all $\lambda \in [0,1]$.

   This condition is satisfied by the control set U since taking any pair of controls in $u_1, u_2, u_3 \in U$ and let $\lambda \in [0,1]$ then,

   $$0 \leq \lambda u_1(t) + (1-\lambda)\, u_2(t). \tag{5.21}$$

   Clearly from (5.21), $\lambda u_1(t) \leq \lambda$ and $(1-\lambda)\, u_2(t) \leq (1-\lambda)$. Thus,

   $$\lambda u_1(t) + (1-\lambda)\, u_2(t) \leq \lambda + (1-\lambda) = 1. \tag{5.22}$$

   Then from inequalities (5.21) and (5.22) it is evident that

   $$0 \leq \lambda u_1(t) + (1-\lambda)\, u_2(t) \leq 1 \quad \forall \quad u_i \in U, i = 1,2,3 \text{ and } \lambda \in [0,1]. \tag{5.23}$$

   Therefore, the control set U is convex, and bounded and condition 3 is satisfied.

4. The integrand which is,

   $$\frac{1}{2}\left(w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2(t) - A_2 u_2^2(t) - A_3 u_3^2(t)\right), \tag{5.24}$$

   of the objective functional is concave on U. We apply the Hessian matrix method in proving that the integrand is concave as shown below. A function of many variables, $g(x_1, x_2, ..., x_n)$ is a concave function if and only if its Hessian matrix, $H(x) = \left[\frac{\partial^2 g}{\partial x_i \partial x_j}\right] \leq 0 \quad \forall \quad x \neq 0$.

   Let $L_i = -\frac{1}{2}\left(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2\right)$ where $L_i \in L$ then the Hessian matrix H of L_i is given as;

   $$H = \begin{bmatrix} \frac{\partial^2 L}{\partial {u_1}^2} & \frac{\partial^2 L}{\partial u_1 \partial u_2} & \frac{\partial^2 L}{\partial u_1 \partial u_3} \\ \frac{\partial^2 L}{\partial u_2 \partial u_1} & \frac{\partial^2 L}{\partial {u_2}^2} & \frac{\partial^2 L}{\partial u_2 \partial u_3} \\ \frac{\partial^2 L}{\partial u_3 \partial u_1} & \frac{\partial^2 L}{\partial u_3 \partial u_2} & \frac{\partial^2 L}{\partial {u_3}^2} \end{bmatrix} = \begin{bmatrix} -A_1 & 0 & 0 \\ 0 & -A_2 & 0 \\ 0 & 0 & -A_3 \end{bmatrix} \leq 0. \tag{5.25}$$

   Since $L_i \in L$, the integrand L is concave on U.

5. There exists constants $b_1 > 0$, $b_2 > 0$ and $\beta > 1$ such that the integrand of the objective function equation (5.14), $J(U,t)$ is bounded by

$$L(t,T,V,V_n,I,I_l,Z,Z_a,u_1,u_2,u_3) \leq b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\beta}{2}}. \quad (5.26)$$

From the objective function (5.14),

$$\begin{aligned} J(u_1,u_2,u_3) &= \frac{1}{2}\left(w_1T(t) + w_2Z(t) - w_3V(t) - A_1u_1^2 - A_2u_2^2 - A_3u_3^2\right), \\ J(u_1,u_2,u_3) &\leq w_1T(t) + w_2Z(t) + w_3V(t) - A_1u_1^2 - A_2u_2^2 - A_3u_3^2. \end{aligned} \quad (5.27)$$

Suppose, $A_1 = A_2 = A_3 = A$ in equation (5.27) then,

$$J(u_1,u_2,u_3) \leq w_1T(t) + w_2Z(t) + w_3V(t) - A\left(u_1^2 + u_2^2 + u_3^2\right). \quad (5.28)$$

This implies that,

$$w_1T(t) + w_2Z(t) + w_3V(t) - A\Big(u_1^2 - u_2^2 - u_3^2\Big) \leq b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_3|^2), \quad (5.29)$$

where b_1 depends on the upper bound on T, Z and V and $b_1 > 0$ since $A_1, A_2, A_3 > 0$ according to the definition. Equation (5.28) can then be written as,

$$J(u_1,u_2,u_3) \leq b_2 - b_1(u_1,u_2,u_3)^2. \quad (5.30)$$

It is evident from equation (5.30) that $\beta = 2 > 1$, and $b_1, b_2 > 0$. Thus the condition given by (5.26) is satisfied.

Since all the above conditions are satisfied then there exists optimal controls ${u_1}^*, {u_2}^*$ and ${u_3}^*$.

□

5.5 Necessary conditions of the Optimal Control

In this section we apply Pontryagin's maximum principle in defining the Lagrangian (Hamiltonian augmented) (Pontryagin, 1987) as follows:

$$\begin{aligned}
&L(T, I, I_l, V, V_n, Z, Z_a, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, u_1, u_2, u_3) \\
&\quad = w_1 T + w_2 Z - w_3 V - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2 + \lambda_1(\lambda_T - \mu_T T \\
&\quad - (1 - u_1(t))\chi T V) + \lambda_2(((1 - u_1(t))1 - u_2(t))\chi T V - \mu_I I - \alpha I Z_a) \\
&\quad + \lambda_3((1 - u_1(t))u_2(t)\chi T V - \mu_{I_l} I_l) + \lambda_4((1 - u_3(t))\epsilon_V \mu_I I - \mu_V V) \\
&\quad + \lambda_5(u_3(t)\epsilon_V \mu_I I - \mu_{V_n} V_n) + \lambda_6(\lambda_Z - \mu_Z Z - \beta Z I) + \lambda_7(\beta Z I - \mu_{Z_a} Z_a) \\
&\quad + w_{11} u_1(t) + w_{12}(1 - u_1(t)) + w_{21} u_2(t) + w_{22}(1 - u_2(t)) \\
&\quad + w_{31} u_3(t) + w_{32}(1 - u_3(t)),
\end{aligned} \tag{5.31}$$

where $w_{ij}(t) \geq 0$ are the penalty multipliers which ensure the boundedness of the control variables $u_1(t)$, $u_2(t)$ and $u_3(t)$ and satisfies the following conditions:

$$\begin{aligned}
w_{11} u_1 = w_{12}(1 - u_1) = 0 \text{ at } u_1^*, \\
w_{21} u_2 = w_{22}(1 - u_2) = 0 \text{ at } u_2^*, \\
w_{31} u_3 = w_{32}(1 - u_3) = 0 \text{ at } u_3^*,
\end{aligned} \tag{5.32}$$

where, u_1^*, u_2^*, u_3^* represent the optimal controls.

Therefore, the Pontryagin's maximum principle gives the existence of adjoint variables which are obtained by differentiating the Lagrangian given by equation (5.31), with respect to the state variables T, I, I_l, V, V_n, Z and Z_a.

The adjoint variables are given by:

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial L}{\partial T} = -w_1 + \lambda_1(\mu_T + (1-u_(t)1)\chi V) - \lambda_2\chi V(1-u_1(t))(1-u_2(t)) \\
&\quad - \lambda_3(1-u_1(t))u_2(t)\chi V, \\
\dot{\lambda}_2 &= -\frac{\partial L}{\partial I} = \lambda_2(\mu_I + \alpha Z_a) - \lambda_4\varepsilon_V\mu_I(1-u_3(t)) - \lambda_5 u_3(t)\epsilon_V\mu_I + \lambda_6\beta Z - \lambda_7\beta Z, \\
\dot{\lambda}_3 &= -\frac{\partial L}{\partial I_l} = \lambda_3\mu_{I_l}, \\
\dot{\lambda}_4 &= -\frac{\partial L}{\partial V} = w_3 + \lambda_1\chi T(1-u_1(t)) - \lambda_2\chi T(u_1(t))(1-u_2(t)) \\
&\quad - \lambda_3\chi T(1-u_1(t))u_2(t) + \lambda_4\mu_V, \\
\dot{\lambda}_5 &= -\frac{\partial L}{\partial V_n} = \lambda_5\mu_{V_n}, \\
\dot{\lambda}_6 &= -\frac{\partial L}{\partial Z} = -w_2 + \lambda_6(\mu_Z + \beta I) - \lambda_7\beta I, \\
\dot{\lambda}_7 &= -\frac{\partial L}{\partial Z_a} = \lambda_2\alpha I + \lambda_7\mu_{Z_a},
\end{aligned} \tag{5.33}$$

where,

$$\lambda_i(T_f) = 0, i = 1, ..., 7, \tag{5.34}$$

are the transversality conditions.

By maximization of the Lagrangian with respect to the control variables u_1, u_2, u_3 we get the optimal controls u_1^*, u_2^*, u_3^* for which,

$$\begin{aligned}
\frac{\partial L}{\partial u_1(t)} &= 0, \\
\frac{\partial L}{\partial u_2(t)} &= 0, \\
\frac{\partial L}{\partial u_3(t)} &= 0.
\end{aligned} \tag{5.35}$$

Therefore, differentiating the Lagrangian L given in equation (5.31) with respect to u_1 on the set $U : t|0 \leq u_1(t) \leq 1$, we obtain the following optimality equation;

$$\frac{\partial L}{\partial u_1} = -2A_1u_1 + \chi TV\Big(\lambda_1 - (1-u_2(t)) - u_2(t)\Big) + w_{11} - w_{12} = 0. \tag{5.36}$$

Let $u_1 = u_1^*$ in equation (5.36). Then, solving equation (5.36) the optimal control u_1^* becomes

$$u_1^* = \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big) + w_{11} - w_{12}}{2A_1}. \tag{5.37}$$

To determine an explicit expression for an optimal control u_1^* without w_{11} and w_{12}, the following three cases have been considered :

1. On the set $(t|0 < u_1^* < 1)$, suppose $w_{11} = w_{12} = 0$ in equation (5.37). Then the optimal u_1^* control is given by

$$u_1^* = \frac{\chi TV\Big(\lambda_1 - (1 - u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}. \tag{5.38}$$

2. Similarly, on the set $(t|u_1^* = 1)$ let $w_{11} = 0$ and $w_{12} \geq 0$. Then equation (5.37) gives

$$u_1^* = 1 = \frac{\chi TV\Big(\lambda_1 - (1 - u_2(t))\lambda_2 - u_2(t)\lambda_3\Big) - w_{12}}{2A_1}. \tag{5.39}$$

Equation (5.39) can be reduced to;

$$\frac{\chi TV\Big(\lambda_1 - (1 - u_2(t)) - u_2(t)\Big)}{2A_1} \geq 1 = u_1^*. \tag{5.40}$$

Therefore, for this set the control $u_1{}^*$ becomes

$$u_1^* = min\left(1, \frac{\chi TV\Big(\lambda_1 - (1 - u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right). \tag{5.41}$$

3. Finally, on the set $(t|u_1^* = 0)$, let $w_{12} = 0$ and $w_{11} \geq 0$ then equation (5.37) gives

$$u_1^* = 0 = \frac{\chi TV\Big(\lambda_1 - (1 - u_2(t))\lambda_2 - u_2(t)\lambda_3\Big) + w_{11}}{2A_1}, \tag{5.42}$$

which implies that

$$\frac{\chi TV\Big(\lambda_1 - (1 - u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1} \leq 0. \tag{5.43}$$

Consequently, combining all the three cases given by equations (5.38), (5.41), and (5.43) we obtain the optimal control, u_1^*, as

$$u_1^*(t) = \begin{cases} \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1} & \text{if} \quad 0 < \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1} < 1, \\ 0 & \text{if} \quad \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1} \leq 0, \\ 1 & \text{if} \quad \frac{\chi TV\lambda_1}{2A_1} \geq 1 \end{cases} \tag{5.44}$$

The control $u_1^*(t)$ is therefore, formulated as:

$$u_1^* = max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right). \tag{5.45}$$

We use the same argument to obtain an explicit expression for an optimal control u_2^* without w_{21} and w_{22}. We differentiate the Lagrangian L given in equation (5.31) with respect to u_2 on the set $U : t|0 \leq u_2(t) \leq 1$. Thus, the optimality equation is obtained as:

$$\frac{\partial L}{\partial u_2} = -2A_2u_2 + \chi TV(\lambda_3 - \lambda_2) + w_{21} - w_{22} = 0 \text{ at } u_2 = u_2^*. \tag{5.46}$$

Therefore, solving equation (5.46) the optimal control u_2^* is given as

$$u_2^* = \frac{\chi TV(1-u_1(t))(\lambda_3 - \lambda_2) + w_{21} - w_{22}}{2A_2}. \tag{5.47}$$

According to the conditions given by equation (5.32) the following distinct three cases have been derived;

1. On the set $(t|0 < u_2^* < 1)$, we let $w_{21} = w_{22} = 0$ in equation (5.47). Then the optimal u_2^* control is given by

$$u_2^* = \frac{\chi TV(1-u_1(t))(\lambda_3 - \lambda_2)}{2A_2}. \tag{5.48}$$

2. On the set $(t|u_2^* = 1)$, let $w_{21} = 0$ and $w_{22} \geq 0$ then from equation (5.47) the control u^* becomes

$$u_2^* = 1 = \frac{\chi TV(1-u_1(t))(\lambda_3 - \lambda_2) + w_{22}}{2A_2}. \tag{5.49}$$

Rearranging equation (5.49) reduces to,

$$\frac{\chi TV(1-u_1(t))(\lambda_3 - \lambda_2)}{2A_2} \geq 1 = u_2^*. \tag{5.50}$$

Thus, for the this set the control u_2^* is given as

$$u_2^* = min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3 - \lambda_2)}{2A_2}\right). \tag{5.51}$$

3. Finally, on the set $(t|u_2^* = 0)$, let $w_{22} = 0$ and $w_{21} \geq 0$. Then from equation (5.47) the control u_2^* becomes

$$u_2^* = 0 = \frac{\chi TV(1 - u_1(t))(\lambda_3 - \lambda_2)}{2A_2}. \tag{5.52}$$

which implies that

$$\frac{\chi TV(1 - u_1(t))(\lambda_3 - \lambda_2)}{2A_2} \leq 0. \tag{5.53}$$

Consequently, combining all the three cases given by equations (5.48), (5.51) and (5.53) the optimal control u_2^* is characterised as;

$$u_2^*(t) = \begin{cases} \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2} & \text{if} \quad 0 < \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2} < 1, \\ 0 & \text{if} \quad \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2} \leq 0, \\ 1 & \text{if} \quad \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2} \geq 1 \end{cases} \tag{5.54}$$

Hence, the optimal control $u_2{}^*(t)$ is formulated as follows:

$$u_2^* = max\left(0, min\left(1, \frac{\chi TV(1 - u_1(t))(\lambda_3 - \lambda_2)}{2A_2}\right)\right). \tag{5.55}$$

The expression for optimal control u_3^* is obtained by differentiating equation (5.31) with respect to u_3 on the set $U : t|0 \leq u_3(t) \leq 1$ to get the following optimality equation

$$\frac{\partial L}{\partial u_3} = -2A_3u_3 - \varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32} = 0. \tag{5.56}$$

Let $u_3 = u_3^*$ in equation (5.56) then the optimal control u_3^* is obtained as

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32}}{2A_3}. \tag{5.57}$$

1. On the set $(t|0 < u_3^* < 1)$, let $w_{31} = w_{32} = 0$ in equation (5.57). Then the optimal control u_3^* is given by

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}. \tag{5.58}$$

2. On the set $(t|u_3^* = 1)$, let $w_{31} = 0$ and $w_{32} \geq 0$ then from equation (5.57) we have

$$u_3^* = 1 = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{32}}{2A_3}. \tag{5.59}$$

Equation (5.59) can be reduced to

$$\frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \geq 1 = u_3^*. \tag{5.60}$$

Hence, for this set the control $u_3{}^*$ becomes

$$u_3^* = min\left(1, \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3}\right). \tag{5.61}$$

3. Finally, on the set $(t|u_3^* = 0)$, let $w_{32} = 0$ and $w_{31} \geq 0$ then from equation (5.57) the control u_3^* becomes

$$u_3^* = 0 = \frac{-\varepsilon_V \mu_I I \lambda_4 + w_{31}}{2A_3}, \tag{5.62}$$

which implies that

$$\frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \leq 0. \tag{5.63}$$

Consequently, combining all the three cases given by equations (5.58), (5.61) and (5.63) the optimal control, u_3^*, is characterized as;

$$u_3^*(t) = \begin{cases} \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} & \text{if} \quad 0 < \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} < 1, \\ 0 & \text{if} \quad \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \leq 0, \\ 1 & \text{if} \quad \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3} \geq 1 \end{cases} \tag{5.64}$$

Therefore, the optimal control, $u_3^*(t)$, is formulated as:

$$u_3^* = max\left(0, min\left(1, \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3}\right)\right). \tag{5.65}$$

It is worth noting that from the mathematical formulations that the optimal controls depend on the adjoint $\lambda_1, \lambda_2, \lambda_3,$ and λ_4 since the adjoint corresponds to the state variables, T, I, I_l, V and the first four equations of system (4.1) contain the control terms.

5.5.1 Optimality system

The optimality system comprising of the state system together with the adjoint system, the optimal control, and the transversality conditions is given as:

$$\left.\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right)\chi TV,\\
\frac{dI}{dt} &= \left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right)\\
&\quad \left(1 - max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right)\right)\chi TV - \mu_I I - \alpha I Z_a,\\
\frac{dI_l}{dt} &= \left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right)\\
&\quad \left(max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right)\right)\chi TV - \mu_{I_l} I_l,\\
\frac{dV}{dt} &= \left(1 - max\left(0, min\left(1, \frac{-\epsilon_V \mu_I I \lambda_4}{2A_3}\right)\right)\right)\epsilon_V \mu_I I - \mu_V V,\\
\frac{dV_n}{dt} &= max\left(0, min\left(1, \frac{-\varepsilon_V \mu_I I \lambda_4}{2A_3}\right)\right)\epsilon_V \mu_I I - \mu_V V_n,\\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I,\\
\frac{dZ_a}{dt} &= \beta Z I - \mu_{Z_a} Z_a,
\end{aligned}\right\} \tag{5.66}$$

with the initial conditions,

$$T(0) \geq 0, I(0) \geq 0, I_l(0) \geq 0, V(0) \geq 0, V_n(0) \geq 0, Z(0) \geq 0, Z_a(0) \geq 0. \tag{5.67}$$

The adjoint equations are;

$$
\left.
\begin{aligned}
\dot{\lambda}_1 &= -w_1 + \lambda_1\mu_T + \left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right)\lambda_1\chi V \\
&\quad - \lambda_2\chi V\left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right) \\
&\quad max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right) \\
&\quad - \lambda_3\chi V\left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right) \\
&\quad max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right), \\
\dot{\lambda}_2 &= \lambda_2(\mu_I + \alpha Z_a) - \lambda_4\epsilon\mu_I\left(1 - max\left(0, min\left(1, \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}\right)\right)\right) \\
&\quad - max\left(0, min\left(1, \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}\right)\right)\lambda_5\epsilon_V\mu_I + \lambda_6\beta Z - \lambda_7\beta Z, \\
\dot{\lambda}_3 &= \lambda_3\mu_{I_l}, \\
\dot{\lambda}_4 &= w_3 + \left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right)\lambda_1\chi T \\
&\quad - \lambda_2\chi T\left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right) \\
&\quad max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right) \\
&\quad - \lambda_3\chi T\left(1 - max\left(0, min\left(1, \frac{\chi TV\Big(\lambda_1 - (1-u_2(t))\lambda_2 - u_2(t)\lambda_3\Big)}{2A_1}\right)\right)\right) \\
&\quad max\left(0, min\left(1, \frac{\chi TV(1-u_1(t))(\lambda_3-\lambda_2)}{2A_2}\right)\right) + \lambda_4\mu_V, \\
\dot{\lambda}_5 &= \lambda_5\mu_{V_n}, \\
\dot{\lambda}_6 &= -w_2 + \lambda_6(\mu_Z + \beta I) - \lambda_7\beta I, \\
\dot{\lambda}_7 &= \lambda_2\alpha I + \lambda_7\mu_{Z_a},
\end{aligned}
\right\} \tag{5.68}
$$

and the transversality equations:

$$\lambda_i(T_f) = 0, i = 1, ..., 7. \tag{5.69}$$

The optimality system given by (5.66), (5.67), (5.68) and (5.69) cannot be solved analytically. Instead numerical methods are used to approximate the solutions and display

the results. The next section represents the numerical solutions for the optimality system.

5.6 Numerical Simulation

In this section, we investigate the effect of optimal strategy on HIV by applying Runge-Kutta forth order scheme on the optimality system. The optimality system is obtained by taking the state system together with the adjoint system, the optimal control, and the transversality conditions. The dynamical behaviour of the models in relation to various control are also studied. The optimal strategy is achieved by obtaining a solution for the state system (4.1) and co-state system (5.33). An iterative scheme is explored and used in determining the solution for the optimality system.

The numerical method utilized is the forward-backward sweep method which incorporates iterative Runge-Kutta fourth order progressive-regressive schemes. The progressive scheme is used in obtaining the solutions of the state ODEs given in system (4.1) with the initial conditions while the regressive scheme is applied in obtaining the solutions of the adjoint system given by system (5.33) with transversality conditions given in equation (5.34). The controls are updated at the end of each iteration using the formula for optimal controls. The iterations are carried out until convergence is achieved. This is a two-point boundary-value problem, with separated boundary conditions at times $t_0 = 0$ and $t = T_f$. This explains why the fourth-order Runge-Kutta scheme is applied in the numerical analysis. For the numerical simulation we take $T = 310$ days or 10 months. This value represent the time in which treatment is stopped. Furthermore, the values of the weight function are taken as: $A1 = A2 = A3 = 0.01$. Table 5.1 consists of the parameter values that are used in the numerical simulations of the in-vivo model while Table 5.3 consists of the proposed initial values of the state variables. The initial values given in Table 5.3 have been chosen in such away that they reflect a patient during acute infection stage. This is in line with the WHO recommendations which stipulate that all people living with the HIV be put on ARTs irrespective of their $CD4^+$ counts unlike in the past where the $CD4^+$ count had to be below 350 cell/mm^3 (World Health Organization, 2014).

Table 5.1: Parameters and controls for HIV in-vivo with therapy model

Parameters	Value	Source
λ_T	10 cell/mm^3/day	Nowak et al. (1996).
μ_T	0.01 day^{-1}	Srivastava and Chandra (2010).
χ	0.00024 mm^3 vir$^-$1 day$^-$1	Alizon and Magnus (2012).
μ_I	0.5 day$^-$1	Wodarz and Nowak (2000).
μ_{I_l}	0.5 day$^-$1	Wodarz and Nowak (2000).
ε_V	100 vir. cell$^-$1 day$^-$1	Estimate.
μ_V	2 day$^-$1	Mbogo et al. (2013).
μ_{V_n}	3 day$^-$1	Estimate.
α	0.02 day^{-1}	Arruda et al. (2015).
λ_Z	20 cell/ mm^3/day	Arruda et al. (2015).
μ_Z	0.04 day^{-1}	Arruda et al. (2015).
β	0.004 day^{-1}	Arruda et al. (2015).
μ_{Z_a}	0.004 day^{-1}	Arruda et al. (2015).

Table 5.2: Controls strategy for HIV in-vivo with therapy model

Control Variables	Possible Values
u_1	$0-1.$
u_2	$0-1.$
u_3	$0-1.$

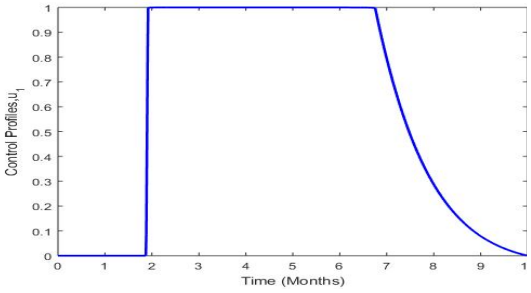
5.6.1 Results and discussion

Figure 5.1 represents the various control strategies. It is evident that the control u_1 remains at minimum for the first two months and raises to a maximum between the second up to the seventh month. It later reduces gradually to a minimum while control u_2 remains at maximum for the first four and a half months then drops to 30% between the sixth and the ninth month. In addition, the control u_2 drops to the minimum after the tenth month. The control strategy u_3 on the other hand, remains at a maximum for the first nine months only dropping to a minimum at the tenth month. From these

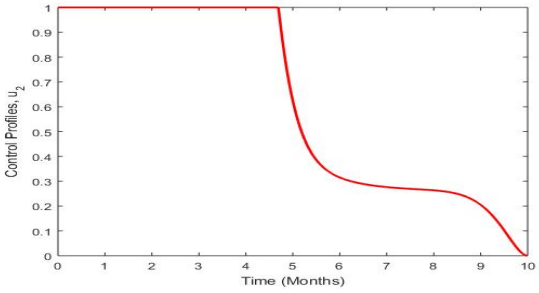
Table 5.3: The initial values for the variables for HIV in-vivo model

Variable	Values
$T(t)$	$T(0) = 500$ cell/mm^3.
$I(t)$	$I(0) = 100$ cell/mm^3.
$I_l(t)$	$I_l(0) = 0$ cell/mm^3.
$V(t)$	$V(0) = 100$ virion/mm^3.
$V_n(t)$	$V_n(0) = 0$ virion/mm^3.
$Z(t)$	$Z(0) = 100$ cell/mm^3.
Z_a(t)	$Z_a(0) = 10$ cell/mm^3.

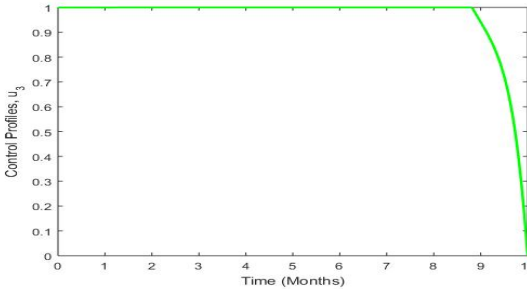
results it is evident that the Protease inhibitor could be administered for a longer period of time with minimum side effects. Furthermore, it is clear that Fusion inhibitor should not be initiated to a person who is not on any other HIV drug treatment. This is in agreement with clinical findings.



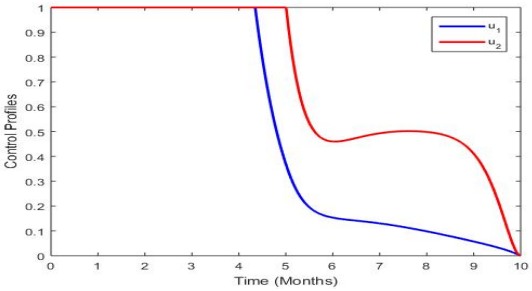
Control u_1



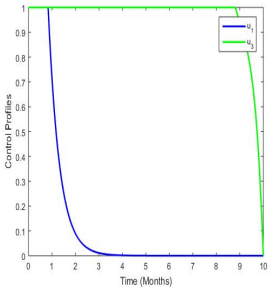
Control u_2



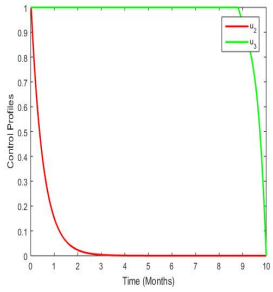
Control u_3



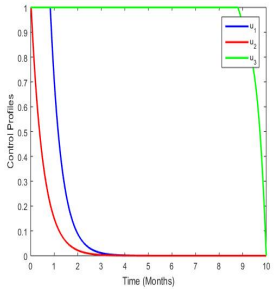
Controls u_1 and u_2



Controls u_1 and u_3

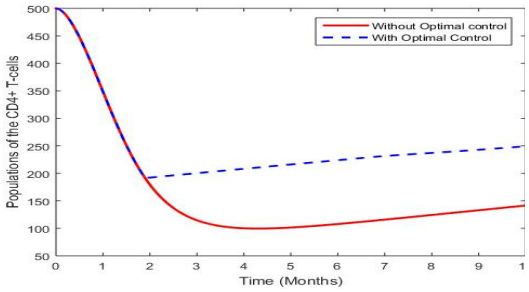


Controls u_2 and u_3

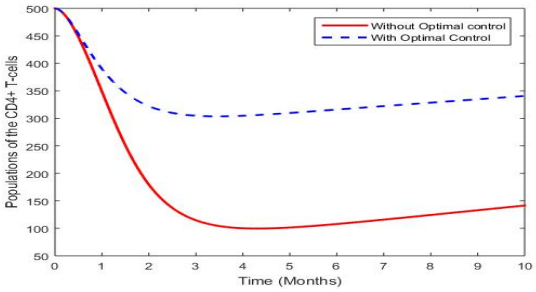


Controls u_1, u_2 and u_3

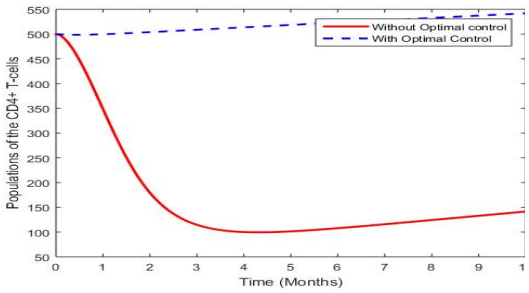
Figure 5.1: Simulated control strategies



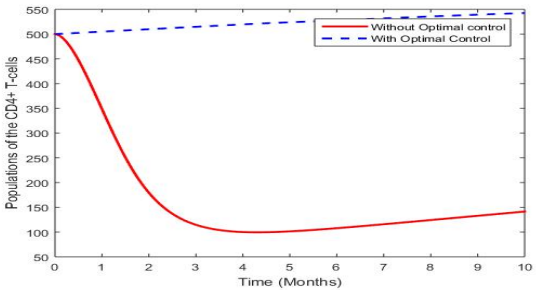
With control u_1



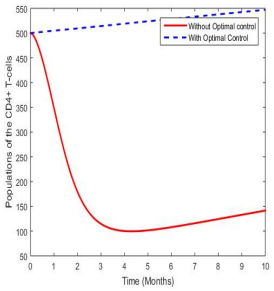
With control u_2



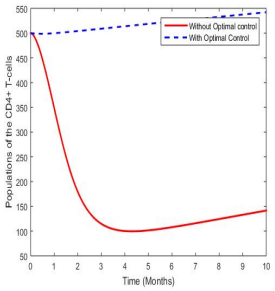
With control u_3



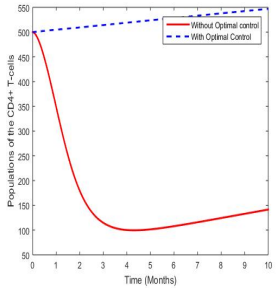
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3

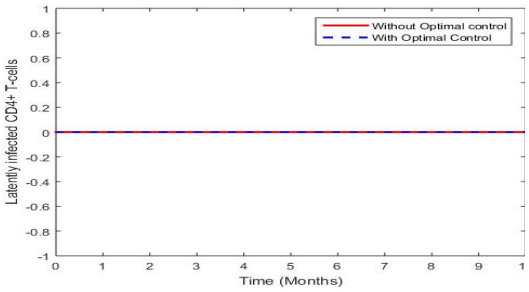


With controls u_1, u_2 and u_3

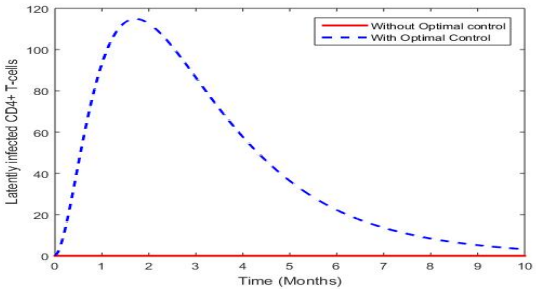
Figure 5.2: The population of the CD4$^+$ T-cells in various control strategies

Figure 5.2 presents the population of the susceptible CD4$^+$ T-cells in different treatment strategies. In all the considered cases it is evident that the introduction of the ARTs play a significant role as far as controlling HIV is concerned. Nonetheless, it is evident that when Fusion inhibitor ($u_1(t)$) is used without other controls the numbers of CD4$^+$ T-cells reduces significantly and takes a longer time before the number increases. In particular, the drug effectiveness seems to be felt after the first two months. These findings indicate that it is difficult to control the HIV virions by targeting their cell-entry mechanism at acute infection. The use of Protease inhibitors however, leads

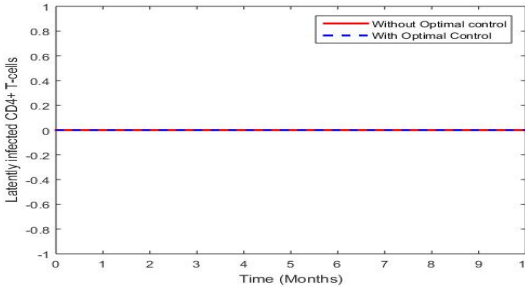
to an increase in the number of the CD4$^+$ T-cells. In addition, it is evident that a combination of the three drugs evoke a more pronounced CD4$^+$ T-cells increase than in mono therapy or two drugs combination.



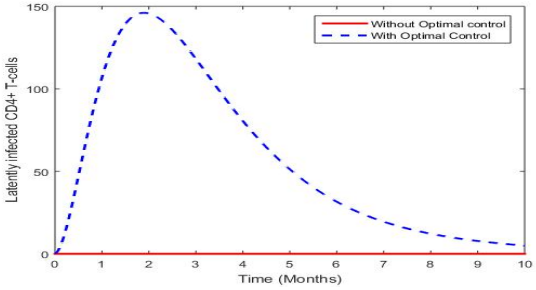
With control u_1



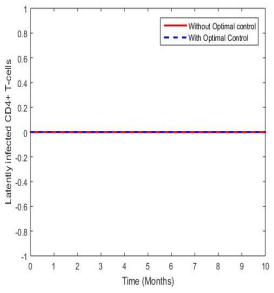
With control u_2



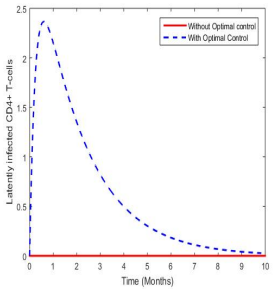
With control u_3



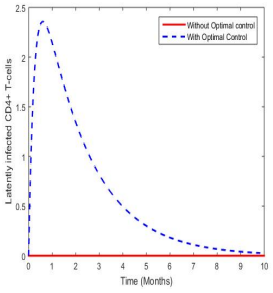
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3

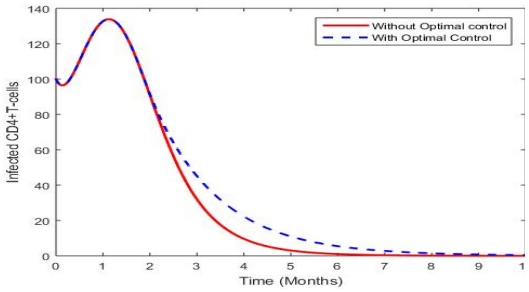


With controls u_1, u_2 and u_3

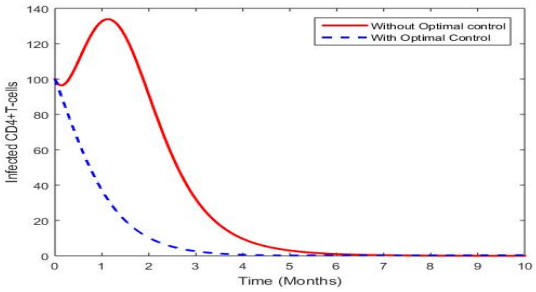
Figure 5.3: The population of the latently infected CD4$^+$ T-cells in various control strategies

the various control strategies. It is evident that the latently infected cells are produced after the initiation of Reverse Transcriptase inhibitor to an HIV infected cell. Since the latently infected cells do not produce infectious HIV virions then it is important to administer RTIs to an infected person. This would reduce the number of virions

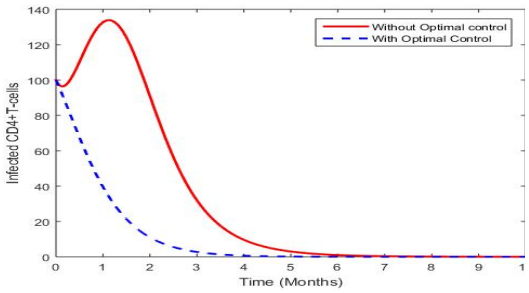
producing cells.



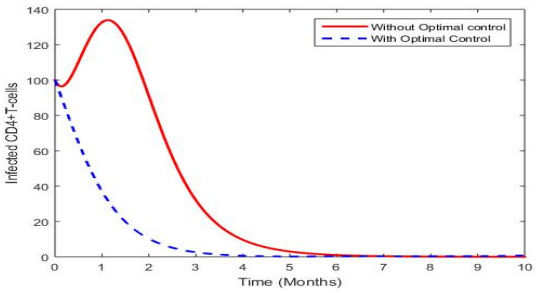
With control u_1



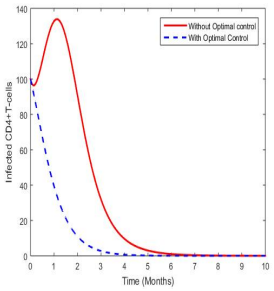
With control u_2



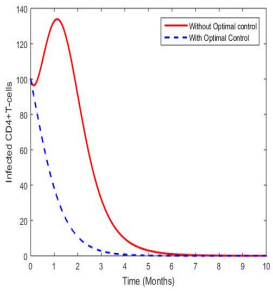
With control u_3



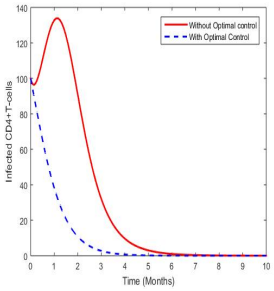
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_1 and u_2

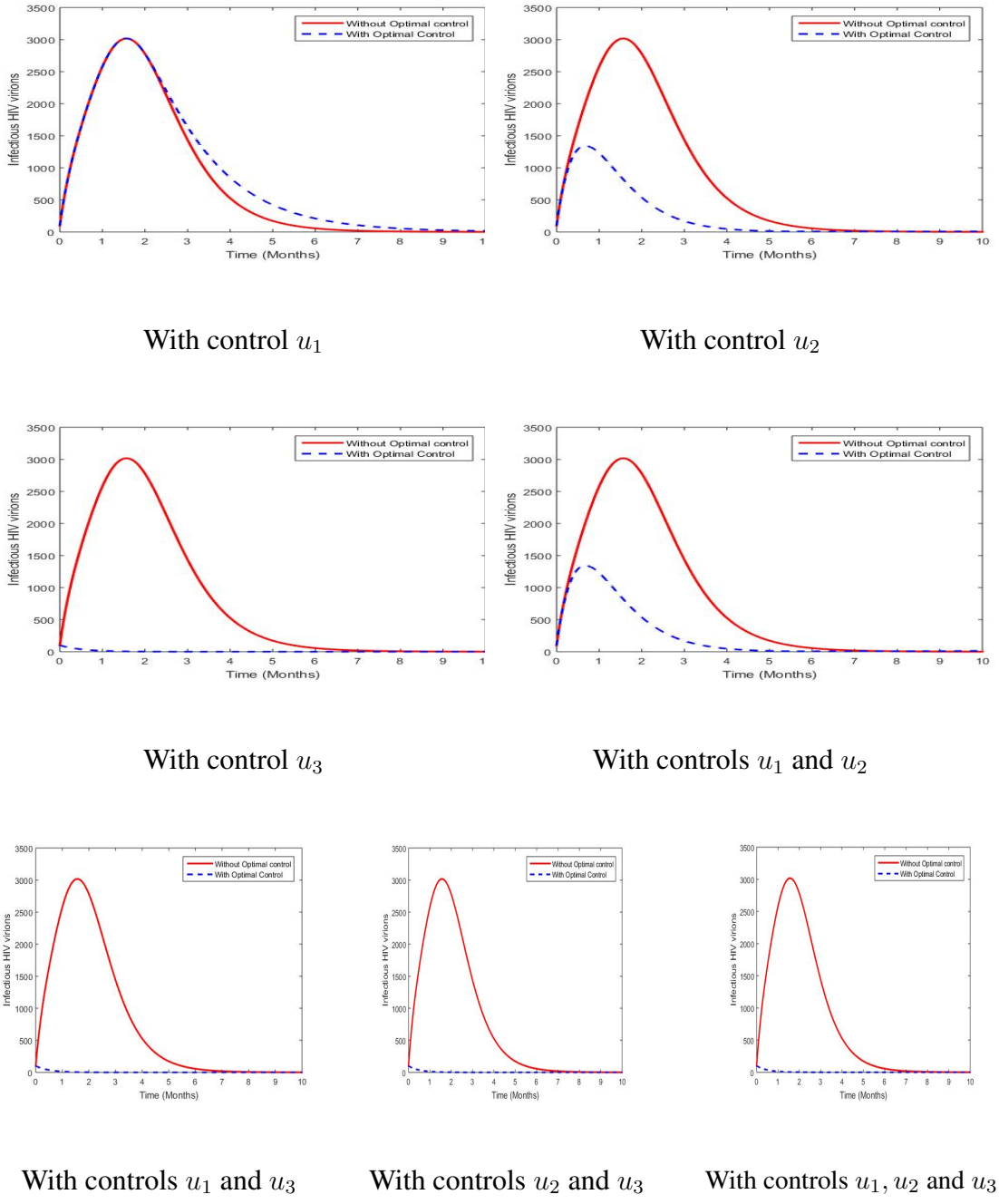


With controls u_1, u_2 and u_3

Figure 5.4: The population of the infected CD4$^+$ T-cells in various control strategies

in different control strategies. From the simulated results it is evident that ARTs play a fundamental role especially in controlling the rate of HIV infection. Notably, when the Fusion inhibitors are introduced in the body the number of the infected cells are observed to increase for the first few months. This clearly emphasizes the difficult in controlling the HIV virions at the entry level. The reason would probably be based on the fact that HIV uses a complex series of steps to deliver its genome into the host cell

cytoplasm while simultaneously evading the host immune response.



With control u_1 With control u_2

With control u_3 With controls u_1 and u_2

With controls u_1 and u_3 With controls u_2 and u_3 With controls u_1, u_2 and u_3

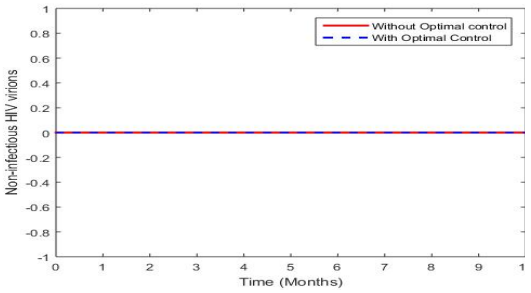
Figure 5.5: The population of the HIV-virions in various control strategies

combination(s). It is evident that control u_1 and u_2 are not very as effective as PIs in controlling viral progression. In particular, it is evident from Figure 5.5 that the number of virions are high when control u_1 is in use. This is because Fusion inhibitors block the entry of the virions into the $CD4^+$ T-cells hence reducing their removal rate from the body. Researchers such as (Kramer et al., 2012) suggest that viruses blocked by entry inhibitors such as the Fusion inhibitors are likely to be redistributed to the

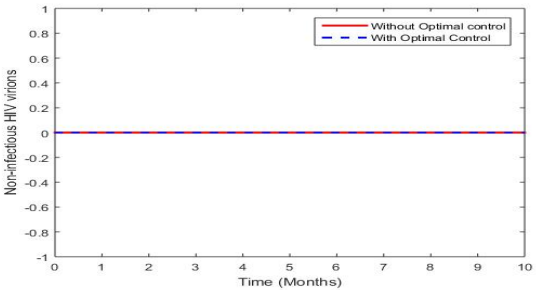
plasma, where they artificially increase the number of HIV virions. This may probably be the reason why there is an indication of having high number of viral load even when control u_1 is applied. In addition, Fusion inhibitors prevent the entry of the virions unlike the other two drugs which allow the entry of the HIV virions into the cells, confirming the absorption effect. Simulated results indicate that Protease inhibitors play a significant role in reducing viral progression and it is the best single drug in use for viral suppression. This is in agreement with some of the work done in the field of in-vivo HIV dynamics which concluded that Protease inhibitors are more effective HIV drugs than Reverse Transcriptase inhibitors and Fusion inhibitors in terms of viral load reduction in HIV infected patient (Shen et al., 2011; Allers and Schneider, 2015; Shi et al., 2016). The simulated results also emphasize the importance of using a combination of the various ARTs for HIV treatment.

From Figure 5.6 it is evident that non-infectious virus result from the introduction of the Protease inhibitor in the body. Introduction of PIs to a HIV infected cells generates a pool of immature HIV virions, that leads to the transfer of non-infectious virus across the virological synapse. This therefore implies that the virus produced would not infect more susceptible $CD4^+$ T-cells.

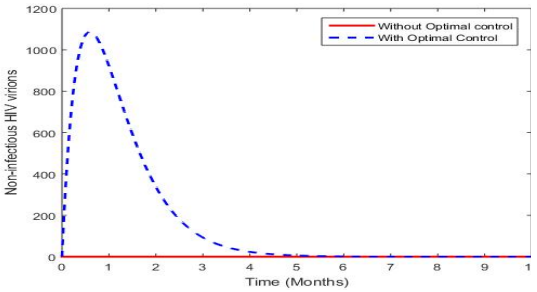
Figure 5.7 shows the population of the $CD8^+$ T-cells in different treatment strategy. From the findings it is evident that both the RTIs and PIs cause a substantial increase in the population of the $CD8^+$ T-cells in HIV-infected patients. However, it is evident that as much as these two drugs play a major role, the combination of all the three controls produces a higher immune system reconstitution with sustained increase in circulating number of $CD8^+$T-cells.



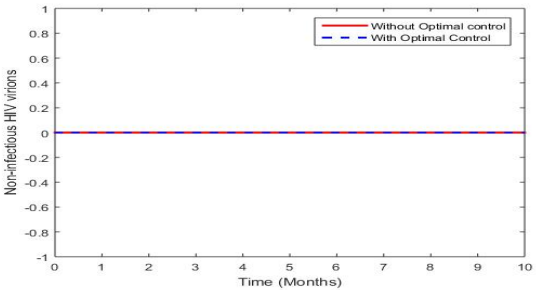
With control u_1



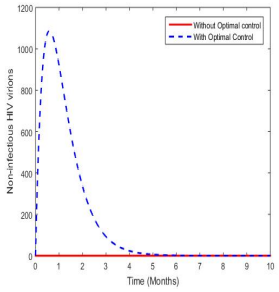
With control u_2



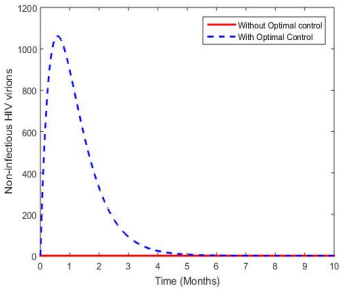
With control u_3



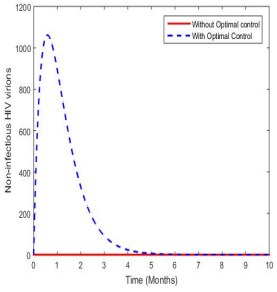
With controls u_1 and u_2



With controls u_1 and u_3

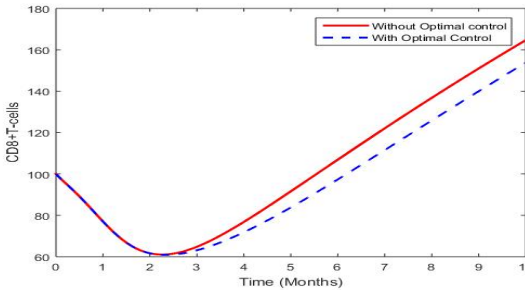


With controls u_2 and u_3

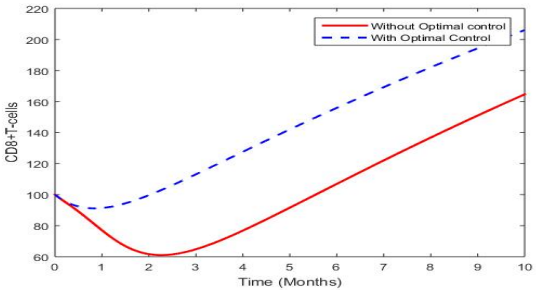


With controls u_1, u_2 and u_3

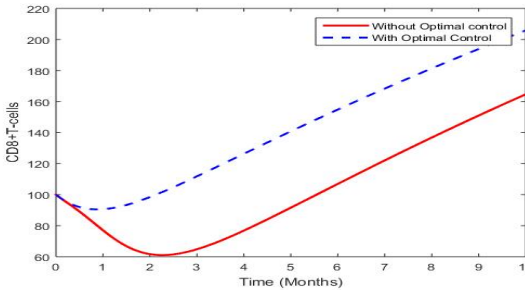
Figure 5.6: The population of the non-infectious HIV-virions in various control strategies



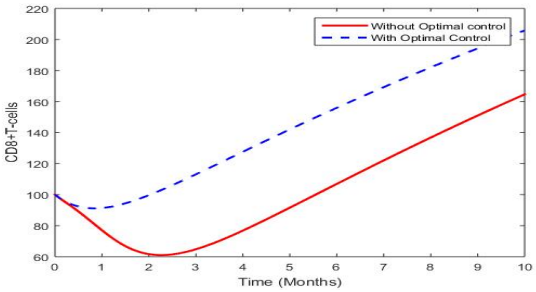
With control u_1



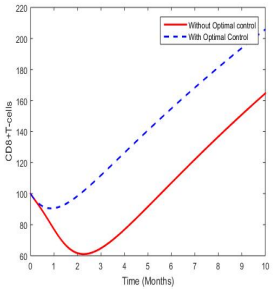
With control u_2



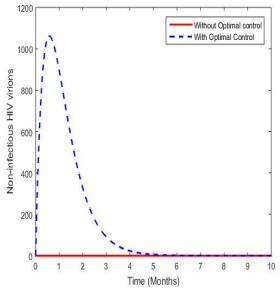
With control u_3



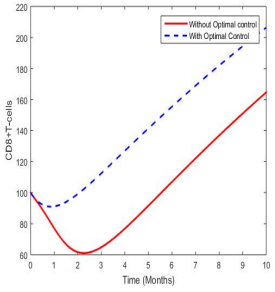
With controls u_1 and u_2



With controls u_1 and u_3

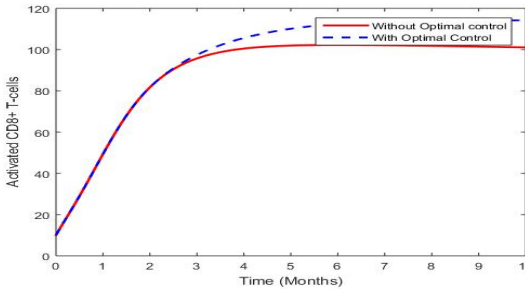


With controls u_2 and u_3

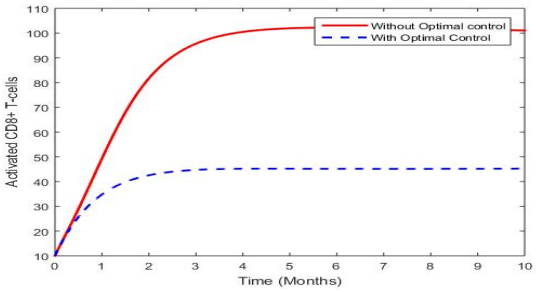


With controls u_1, u_2 and u_3

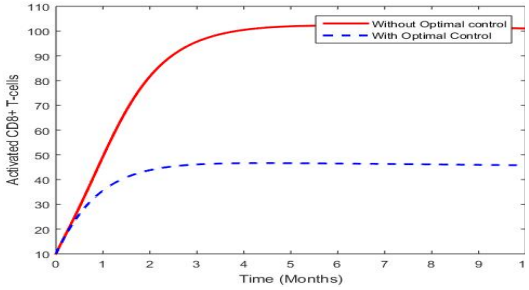
Figure 5.7: The population of the CD8$^+$ T-cells in various control strategies



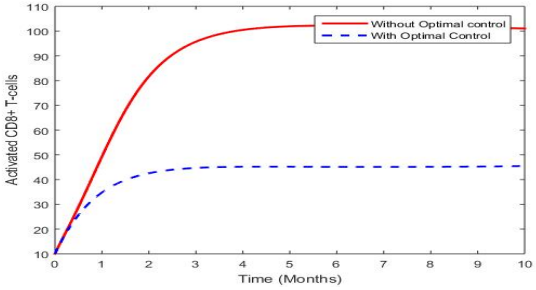
With control u_1



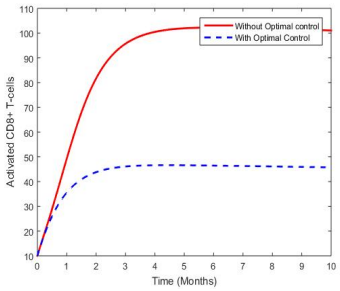
With control u_2



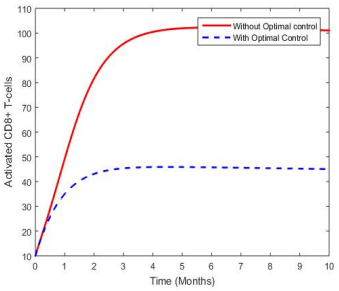
With control u_3



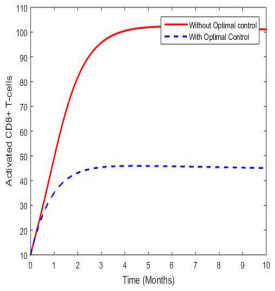
With controls u_1 and u_2



With controls u_1 and u_3



With controls u_2 and u_3



With controls u_1, u_2 and u_3

Figure 5.8: The population of the Activated CD8$^+$ T-cells in various control strategies

Figure 5.8 shows the population of the activated CD8$^+$ T-cells. The activation process plays a major role in controlling the HIV virus. This is because the cells fight, destroy and kill the infected CD4$^+$ T-cells. This, in turn, reduces the number of HIV virions produced. From the simulated results it is evident that after the introduction of the ARTs, the number of activated CD8$^+$ T-cells reduced significantly. The reduction is attributed to the reconstitution of the immune system and the reduction of the retroviral activity on the cells (Autran et al., 1997). However, the question such as the clinical benefit that result from the reduction of the CD8$^+$ T-cells activation process need to be

addressed in future.

5.7 Conclusion

In this chapter a seven-dimensional in-vivo HIV model with inclusion of three drug combinations, that is, FIs, RTIs and PIs has been formulated and analysed. Optimal control theory has been applied in determining the optimal treatment regime. In particular, the Pontryagin's maximum principle has been applied in deriving the conditions necessary for existence of optimal control drugs strategy. The systems of ordinary differential equations, the state system and the adjoint system have been solved numerically by both forward and backward Runge-Kutta forth order scheme. Results from the numerical simulations indicate that FIs and RTIs should be used for the first four months and later the doctors should consider changing the drugs and introduce another treatment regime whereas the PIs could be used for a longer period of time without necessarily leading to major side effects. However, the inferiority of mono therapy compared with combination therapies has been observed in the simulated result especially in suppression of viral replication, $CD4^+$ and $CD8^+$ T-cells reconstitution, and in controlling disease progression.

ARTs are seen to play a significant role as far as viral suppression is concerned. Therefore, they should be recommended to all patients immediately after one is diagnosed HIV positive regardless of the $CD4^+$ count. The findings in this chapter support the WHO guidelines and recommendation on ARTs for all. However, the simulated results suggest that PIs is possibly the best single drug and Fusion inhibitor the worst drug in terms of viral load and infected cells reduction. From the results the study recommends that RTIs should be used as initial therapy for HIV while FIs should be introduced to the patient after the RTIs but should never be used as a mono therapy.

Chapter 6

Conclusion and Recommendations

6.1 Summary

In this study we have developed mathematical models to study the in-vivo dynamics of HIV. At first, a five-dimensional deterministic model without treatment has been formulated and analysed. Later three drug regimes have been incorporated into the model and investigations done for optimal drug combinations.

In Chapter 2, the study reviewed some of the mathematical models that have been formulated over the years for in-vivo HIV dynamics. This Chapter also highlighted the various gaps that have not been addressed by researchers in the field of HIV modelling such as: the role played by the CD8$^+$ T-cells, the role of the Fusion inhibitors and the emergence of the non-infectious virus due to the use of Protease inhibitors.

In Chapter 3, an in-vivo HIV dynamics model that had five compartments representing the healthy CD4$^+$ T-cells (T), the infectious HIV virions (V), the already infected CD4$^+$ T-cells (I), the defence cells (Z), that is, CD8$^+$ T-cells and the activated immune cells (Z_a) has been presented. The model has been proved to be mathematically well posed and biologically meaningful. In particular, the state variables for the model have been shown to be non-negative and bounded. In addition, the existence of disease-free and endemic equilibrium points has been investigated. Next generation matrix method has been applied in deriving the expression for the basic reproductive number R_0. The results indicate that the disease-free equilibrium points is locally asymptotically stable and globally asymptotically stable for $R_0 < 1$. However, since our model has two endemic equilibrium point then having $R_0 < 1$ does not necessary mean that the system is globally stable. However, this is true if and only if the basic reproductive number is less than the critical reproductive R_c number, that is, $R_0 < R_c < 1$. Sensitivity analysis of the model has been carried out on the parameters in R_0 aimed at estab-

lishing the ones that play a significant role in the dynamics of the HIV infection. It is evident from the computations that the infection rate, χ, greatly influence the basic reproductive number. Numerical simulations have been carried out for the model and the findings presented.

In Chapter 4, the model has been extended to incorporate HIV treatment at acute infection. This analysis is motivated by the new HIV campaign in Kenya dubbed the "Anza Sasa"which recommends the initiation of ARTs at early the stages of HIV infection without any consideration of the $CD4^+$ counts. The numerical results indicate the importance of ARTs especially at acute infection. In addition, from the numerical simulations it is evident that the combination of ARTs with higher efficacy is the most effective way of HIV viral suppression. Unfortunately, from the findings, ARTs alone are unlikely to kill the HIV virions but are able to control the HIV transmission and improve the life expectancy of the infected person consequently. This will for sure alter the current trends of HIV incidence in Kenya.

In Chapter 5, optimal control theory has been applied on the treatment model. The aim is to identify the optimal therapy that would lead to improvement of the infected person immunity, at minimum cost and side effects. In particular, two objective problems have been developed. They include a cost minimization objective and a maximization objective function. The cost objective function aimed at minimizing the drug marginal cost in relation to the marginal benefit while the maximization objective function aimed at maximizing the concentration of uninfected $CD4^+$ T-cells, concentration of $CD8^+$ T-cells while minimizing the concentrations of infected cells and HIV free virions in the body with an optimal dose of combination of drug therapies in order to avert the adverse effects associated with excessive use of drug. Three control strategies representing Fusion inhibitors, Reverse Transcriptase inhibitor and Protease inhibitor have been applied in the optimal model. The Pontryagins maximum principle has been applied in characterizing the optimality control, which have been solved numerically by the Runge-Kutta fourth order progressive-regressive schemes. The numerical results emphasize the importance of early initiation of ARTs. Furthermore, the research findings indicate that Protease inhibitor is the most effective mono therapy for HIV

control. Nonetheless, any combination of the three control strategies is more beneficial in eliminating the HIV infection.

6.2 Contribution

1. This is the first time an in-vivo HIV model using non-linear ordinary differential equations has been formulated with the inclusion of the immune cells with three control variables representing three drug regimes.

2. This study applied the Pontryagins principle in evaluating the marginal cost versus the marginal benefit associated with use of each drug regime. This kind of evaluation had not been done before on in-vivo HIV models.

6.3 Recommendation

Although there is no known cure for HIV/AIDS, presently there are antiretroviral HIV drugs which block infection of new cells and reduce viral load in the body and so HIV positive individual can now enjoy relatively good health and increased life expectancy. ARTs should be initiated to the HIV infected persons immediately after they test positive. The Government of Kenya should, in particular, ensure the "Anza Sasa"campaign is launched in all the 47 counties. This will go along way in assisting the Government to meet its 2020 goals that, by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression. The government should also be aggressive in educating the citizens on the need of taking and adhering to the ARTs.

6.4 Future work

Even though the results obtained in this study are very promising in improving the quality of life of those infected by HIV, there is still a wide margin for improvement related to this work, with the primary objective of knowing more about the infection, and even improving the therapies currently available on the market. Some of the areas that could be improved in this study are listed below.

1. The deterministic models presented in this study did not consider the wild type and the naive type $CD4^+$ T-cells nor the different types of the HIV virions, such as, the drug resistant virus and wild type virus in the formulations. Considering

these state variables may provide a better understanding of the HIV dynamics, and give informative results.

2. Clinicians have indicated that the number of the $CD8^+$ T-cells in the body depends on the infected cells and not entirely on their recruitment from the thymus. Such relationship needs to be considered.

3. Our model and approach in this research is deterministic. Reviewing all analyses and comparing the results obtained with stochastic modelling approach would enable researchers to choose the best approach for analyzing HIV in-vivo dynamics.

4. Co-infection between HIV and age or lifestyle illness should be considered with inclusion of drug resistance. Drug resistance is a big issue in HIV, considering it in the HIV model presented in this thesis would go along way in improving the findings significantly.

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therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science*, 277(5322):112–116.

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Appendix A

Preliminary Mathematical Background

A.1 Introduction

This appendix is aimed at providing some useful mathematical background material, used throughout our study. In particular concepts such as existence and uniqueness of a solution, Routh-Hurwitz criteria, dilac criterion,optimal control etc. will be explained.

The mathematical introduction in this chapter will be necessarily abrupt. One can find more detail in the various textbooks on dynamical systems and bifurcation theory that aided in the preparation of this chapter (Fleming and Rishel, 2012; Athans and Falb, 2013; Lenhart and Workman, 2007; Pontryagin, 1987).

A.2 Well-posedness for ordinary differential equations

A first order ordinary differential with initial value

$$\frac{dy}{dt} = F(x, y) \quad y(x_0) = y_0 \tag{A.1}$$

whose solutions satisfy the initial constraints is said to be well possed mathematically if and only if:

1. its solutions exists
2. the solutions are unique
3. the solutions continuously depends on the initial values

We introduce the Lipschitz condition A.1 which guarantee well-posed solution of an initial value problem.

Definition A.1 (Lipschitz condition). A family of vector fields $F(x, y)$ satisfies a Lipschitz condition in a region $\mathbb{R}$ of (x, y) in the domain D there exist Lipschitz constant k such that

$$\{k > 0, (x, t) \in \mathbb{R}, \quad (y, t) \in \mathbb{R} \quad |F(x, t) - F(y, t)| \leq k(x - y|\} \tag{A.2}$$

Theorem A.1 (Existence)**.** *Suppose that $F(x, y)$ with initial values (x_0, y_0) is a continuous function defined in some region*

$$R = (x, y) : x_0 - \delta < x < x_0 + \delta, \quad y_0 - \epsilon < y < y_0 + \epsilon \tag{A.3}$$

containing the point (x_0, y_0). Then there exists a number $\delta_1 < \delta$ so that solution of (A.1)*, that is, $y = f(x)$ is defined for $x_0 - \delta_1 < x < x_0 + \delta_1$.*

Theorem A.2 (Uniqueness)**.** *Suppose that both $F(x, y)$ and $\frac{\partial F}{\partial y}(x, y)$ are continuous functions defined on a region $\mathbb{R}$ as in Theorem A.1. Then there exists a constant value $\delta_2 < \delta_1$ so that the solution $y = f(x)$ to* (A.1)*, whose existence was guaranteed by Theorem A.1, is the unique solution to* (A.1) *for $x_0 - \delta_2 < x < x_0 + \delta_2$.*

Theorem A.3 (Continuity Theorem)**.** *Let $x(t)$ and $y(t)$ be any two solutions of the differential equation* (A.1) *in $t \in [T_1, T_2]$, where F(x, y) is continuous and satisfies the Lipschitz condition A.1 in some region $\mathbb{R}$ such that $(x(t), y(t) \in \mathbb{R}$ are defined. Then*

$$\|x(x_0 + h) - y(y_0 + h)\| \leq e^{\frac{k}{h}}|x_0 - y_0| \tag{A.4}$$

Definition A.2 (Invariant region/set). A set of states $S \subseteq \mathbb{R}^n$ of (A.1) is called an invariant set of (A.1) if for all $y_0 \in S$ and for all $t \geq 0$, $y(t) \in S$ (image).

A.2.1 Stability analysis

It is paramount for modellers to analyses the stability of equilibrium points for the models at hand. This is because physical stability of an equilibrium solution to a system of differential equations addresses the behaviour of solutions that start nearby the equilibrium solution. In this study we shall first drive the basic reproductive number of the model and then analyze the local and global stability.

Definition A.3 (Equilibrium points).

An equilibrium point of (A.1) is a constant solution $y(t) = x^*$ for all $t \in R$ that satisfies

$$F\Big(x^*(t), y(t)\Big) = 0 \quad \forall \quad t \in R. \tag{A.5}$$

Definition A.4 (Stability).

An equilibrium point x^* is said to be stable if for any $\epsilon > 0$ and any $t_0 \in \mathbb{R}^+$ there exists a $\delta(t_0, \epsilon)$ such that;

$$\|x_0 - x^*\| \leq \delta \rightarrow \left\|x\Big(t, x_0, \alpha\Big) - x^*\right\| < \epsilon, \quad t \geq t_0 \tag{A.6}$$

Definition A.5 (Asymptotically stable).

An equilibrium is said to be asymptotically stable if it is stable, and $\forall \quad t_0 \in \mathbb{R}^+$ there exists a $\eta(t_0) > 0$ such that if $\|x_0 x^*\| \leq \eta$ then

$$\lim_{t\to\infty} \left\|x\Big(t, x_0, \alpha\Big) - x^*\right\| = 0. \tag{A.7}$$

The equilibrium is globally asymptotically stable if η is arbitrary.

Definition A.6 (Unstable).

An equilibrium is said to be unstable if it is not stable.

Definition A.7 (The basic reproductive number).

According to Diekmann et al. (1990) basic reproductive number represents the number of secondary infection that results from a single infected cells throughout its life. This concept is fundamental to the study of epidemiology as it helps determine whether or not an infectious disease can spread through a population. When $R_0 < 1$ the infection is likely to die off in the long run, which means each infected cells produces, on average, less than one new infected cells. Furthermore, there exist only one equilibrium, the disease-free equilibrium, and it is locally asymptotically stable. Alternatively when $R_0 > 1$ the infection will persist and invade the population. For a larger number of R_0 the researchers are advised on the best control measures, and at what size, would be most effective in reducing R_0 below unity, to prevent sustained spread of the infection, thus providing important guidance for public health initiatives.

Definition A.8 (The next generation matrix method). In this research we applied the next generation matrix method when computing R_0 (van den Driessche and Watmough, 2002).

Suppose we have n^{th} dimensional disease compartments and m^{th} non-disease compartments, and let $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ be the sizes of these compartments. Also, let F_i denote the rate of secondary infection increase of the i^{th} disease compartments and V_i be the rate of disease progression, death and recovery decrease of the i^th compartment, that is, V_i represents the transfer of infection out of the compartments. We therefore have,

$$\begin{aligned} \frac{dx_i}{dt} &= F_i(x,y) - V_i(x,y), \quad i = 1...n \\ \frac{dy_i}{dt} &= G_i(x,y), \quad i = 1...m \end{aligned} \tag{A.8}$$

The next generation method for calculation R_0 is based on the linearization of the ordinary differential equations (ODE) model at the disease free-equilibrium. Thus the following assumptions ensure that Theorem A.1 is satisfied.

1. If $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ then $F_i(x,y) > 0$, $V_i(x,y) > 0$ for $1 \leq i \leq n$. Therefore all the rate in the models will be non-negative.

2. If $x_i = 0$, then $V_i(x,y) = 0$. There can be no movement of individuals out of that compartment since there are no individuals in the infected compartment.

3. $F_i(x,y) = 0$. There can be no infections entering classes that are defined as non-infectious.

4. If $x \in y$, then $F_i(x,y) = 0$ and $V_i(x,y) = 0$ for $1 \leq i \leq n$. If there is no infection in the population, there can be no input into the infectious populations. Hence, the disease-free subspace is invariant.

5. Assume the disease-free system

$$\frac{dy}{dt} = G(0,y) \tag{A.9}$$

has a unique equilibrium that is asymptotically stable. That is, if $F_i(x) = 0$ then, all the eigenvalues of the corresponding Jacobian at the disease-free equilibrium point have negative real part. This implies that in the in absence of new infections, the disease-free equilibrium point is locally asymptotically stable.

Assuming that $F_i(x,y)$ and $V_i(x,y)$ meet above conditions then at the disease free equilibrium we have

$$F = \frac{dF_i}{dx_j} \qquad \text{and} \quad V = \frac{dV_i}{dx_j} \tag{A.10}$$

where $i, j = 1...m$

Then the basic reproductive number is given by dominant eigenvalue of the next generation matrix given by FV^{-1}.

Definition A.9 (Poincare-Perron).

Let A be a constant matrix in the system $\frac{dy}{dt} = Ay$ with eigenvalues $\lambda_i, \quad i = 1, 2, ..., n$ then,

1. the system is stable, if $Re(\lambda_i) \leq 0, \quad i = 1, 2, ..., n.$
2. the system is uniformly stable if either $Re(\lambda_i) \leq 0, \quad i = 1, 2, ..., n$, $Re(\lambda_i) < 0 \quad i = 1, 2, ..., n$ and there is no zero repeated eigenvalue.
3. the system is asymptotically stable if and only if $Re(\lambda) < 0, \quad i = 1, 2, ..., n.$
4. The solutions of the system are unstable if $Re(\lambda_i) > 0, \quad i = 1, 2, ..., n.$

Remark A.1. If any of the eigenvalues have a positive real numbers, the equilibrium is defined as a source, and thus, unstable while if all of the real parts of the eigenvalues are negative real numbers, the equilibrium is defined as a sink, and thus, stable (Perko, 2013).

Definition A.10 (Routh-Hurwitz criteria).

Given a polynomial

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n \tag{A.11}$$

where $a_i \quad i = 1, 2, ...n$ are real constants which defines the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial.

$$H = \begin{bmatrix} a_1 \end{bmatrix} \tag{A.12}$$

$$H = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix} \tag{A.13}$$

$$H = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix} \tag{A.14}$$

$$H = \begin{pmatrix} a_1 & 1 & 0 & 0 & . & . & . & 0 \\ a_3 & a_2 & a_1 & 0 & . & . & . & 0 \\ a_5 & a_4 & a_3 & a_2 & . & . & . & 0 \\ a_7 & a_6 & a_5 & a_4 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & . & . & . & a_n \end{pmatrix} \tag{A.15}$$

if $\det H_{i,j} \geq 0 \quad j = 1, 2, ...n \quad a_j = 0 \quad \text{if} \quad j > n$ then all the roots of the polynomial $P(\lambda)$ are negative hence the steady state of the model considered are stable.

Definition A.11 (Simply Connected Set).

A simply connected set in $D \subset \mathbb{R}^2$ is a connected set having the property that every simple closed curve in D cannot continuously shrink (within D) to a point, that is, whenever a simple closed curve C lies entirely in D, then its interior also lies entirely in D.

Definition A.12 (Bendixsons Criterion).

Suppose D represents a simple connected open set of $\mathbb{R}^2$. We define a two-dimensional system

$$\begin{aligned} \frac{dx}{dt} &= F(x, y) \\ \frac{dy}{dt} &= G(x, y) \end{aligned} \tag{A.16}$$

and

$$\frac{\partial F}{\partial x} + \frac{\partial G}{\partial y} \neq 0 \tag{A.17}$$

if and equation (A.17) does not change sign in D then there are no periodic orbits of the autonomous system (A.16), that is, there has no closed trajectories inside D.

Definition A.13 (Dilac Criterion).

Let D be a simply connected region of the phase plane. If there exists a continuously differentiable function $\Omega(x, y)$ such that

$$\frac{\partial}{\partial x}\left(\Omega(x, y)F(x, y)\right) + \frac{\partial}{\partial y}\left(\Omega(x, y)G(x, y)\right) \tag{A.18}$$

does not change sign in D then the dynamical system

$$\begin{aligned} \frac{dx}{dt} &= F(x,y) \\ \frac{dy}{dt} &= G(x,y) \end{aligned} \tag{A.19}$$

has no closed orbits wholly contained in D.

Definition A.14 (Convex set).

A function $V(t)$ is said to be convex on $[a,b]$ if

$$V(t_1) + (1-\chi)\, V(t_2) \geq V(t)(\chi t_1 + (1-\chi)\, t_2 \tag{A.20}$$

for all $0 \leq \chi \leq 1$ and for all $a \leq t_1, t_2 \leq b$

Definition A.15 (Concave set).

A function $V(t)$ is said to be convex on $[a,b]$ if

$$V(t)(\chi t_1 + (1-\chi)\, t_2 \geq aV(t_1) + (1-\chi)\, V(t_2) \tag{A.21}$$

for all $0 \leq \chi \leq 1$ and for all $a \leq t_1, t_2 \leq b$

Remark A.2. If V is concave and differentiable, then it is bounded above by its first-order

$$V(t_2) \leq V(t_1) - \dot{V}(t_1)[t_2 - t_1] \tag{A.22}$$

A.3 Sensitivity analysis

Sensitivity analysis technique in the context of deterministic dynamical model system refers to how sensitive a model is to changes in the values of its parameters. Sensitivity analysis is always aimed at identifying the critical inputs of a model and determining how they affect the model outcomes. In the epidemiological modelling the analysis is mainly done on the parameters on R_0. This is to determine how reactive each parameter is to disease transmission and somewhat tries to discover parameters that have a high impact on R_0 and should be targeted by intervention strategies. They are various method that have been used in calculating the basic R_0 such as the the sensitivity index and partial Rank Correlation Coefficients.

Definition A.16 (The normalized forward sensitivity). The normalized forward sensitivity index of R_0 with respect to the parameter P is defined by,

$$\frac{\partial R_0}{\partial P} * \frac{P}{R_0} \tag{A.23}$$

Definition A.17 (Partial Rank Correlation Coefficients (PRCCs)). The use of PRCCs in sensitivity analysis helps in the assessment of the statistical relationship between the R_0 and the parameters and, the sign of the PRCC of an input parameter depicts the particular kind of qualitative affiliation it has with the outcome variable.

A.4 The optimal control problem

A.4.1 Dynamical Constraints

An optimal control is an extension of the calculus of variations and optimization method for deriving control policies. It deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved (Berkovitz, 2013). Optimal control allow mathematicians to make fundamental decision on the biological problems. The optimal control can be derived using Pontryagins maximum principle or solving the Hamilton-JacobiBellman equation.

Suppose we have we have a control function $u(t)$ that we want to maximize

$$J\left(u(t)\right) = \theta[y(t), u(t), t_f] \tag{A.24}$$

subject to the state equations

$$\frac{dy}{dt} = f(y(t), u(t)) \tag{A.25}$$

and the boundary conditions

$$\Phi[y(t), u(t_f), t_f] = 0 \tag{A.26}$$

Here t represents independent time variable, indices t_0 and t_f indicates the initial and final time, respectively, $y(t) \in \mathbb{R}^n$ is a vector of representing the state variables, $u(t) \in \mathbb{R}^n$ denotes a vector of control variables to be optimized and the initial conditions are given as $y(t_0) = y_0$. Then the problem to be maximized is given by

$$\hat{J}(u(t)) = \int_{t_0}^{t_f} \left\{f(y(t), u(t))\right\} dt \tag{A.27}$$

then from Pontryagins maximum principle we have the Hamiltonian for the objective function given by

$$H = \lambda_i(t) f(y(t), u(t)) \tag{A.28}$$

where λ_i denotes the adjoint and is dependent on $(t, y(t))$ and $u(t)$ with the following properties.

1. $\lambda_i(t)f(y(t),u(t))+\mu(t)$ has a maximum value at $u(t)=u^*(t)$. where

$$\mu(t)=-\frac{\partial H(\lambda_i(t),y(t),u(t),t)}{\partial u} \tag{A.29}$$

2.

$$\frac{d\lambda_i(t)}{dt}=-\frac{\partial H(\lambda_i(t),y(t),u(t),t)}{\partial y} \tag{A.30}$$

3.

$$\frac{\partial y}{dt}=\frac{\partial H(\lambda_i(t),y(t),u(t),t)}{\partial \lambda_i} \tag{A.31}$$

4. The control u^* must maximize H. So, if the necessary partial derivatives exist, then we must have,

$$\frac{\partial H(\lambda_i(t),y(t),u(t),t)}{\partial u}=0 \tag{A.32}$$

A.5 Runge-Kutta Forth order Scheme

Due to the complexity of the optimal control problem analytical solutions can not be achieved hence the need to apply numerical methods. The fourth order Runge-Kutta method is a numerical approach used to solve ordinary differential equation and the optimality system.

$$\frac{dy}{dt}=F(x,y) \quad \text{ at } y(0)=y_0 \tag{A.33}$$

The fourth order Runge-Kutta method is based on the following general equation.

$$y_{(i+1)}=y_i+(a_1k_1+a_2k_2+a_3k_3+a_4k_4)h \tag{A.34}$$

where from knowing the value of $y=y_i$ at the point x_i, we can find the value of $y=y_{(i+1)}$ at the point x_{i+1}, and $h=x_{i+1}x_i$ is the step size. The equation (A.34) gives the first five terms of the taylors series.

$$y_{i+1}=y_i+f(x_i,y_i)h+\frac{1}{2!}f'(x_i,y_i)h^2+\frac{1}{3!}f''(x_i,y_i)h^3+\frac{1}{4!}f'''(x_i,y_i)h^4 \tag{A.35}$$

Based on the equation (A.35), we have,

$$y_{(i+1)}=y_i+\frac{h}{6}(k_1+2k_2+2k_3+k_4) \tag{A.36}$$

where,

$$\begin{aligned} k_1&=f(x_i,y_i)\\ k_2&=f(xi+\frac{1}{2},y_i+\frac{1}{2}k_1h),\\ k_3&=f(xi+\frac{1}{2},y_i+\frac{1}{2}k_2h),\\ k_4&=f(xi+\frac{1}{2},y_i+\frac{1}{2}k_3h). \end{aligned} \tag{A.37}$$

Appendix B

Numerical analysis Code

B.1 Sensitivity analysis

```
function [R_C] = calculation(para)
% lambda = 10/8.4;
% lambda = 1;
% d = 1/(12*70);
for i=1:1000;

    lambdaT(i)=para(i,1);
    muT(i)=para(i,2);
    xi(i)=para(i,3);
    muv(i)=para(i,4);
    ev(i)=para(i,5);
    % Computation of the basic reproduction number.
    R_N(i) = lambdaT (i).*xi (i).*ev(i);
    R_D(i) = muT (i).*muv(i);
    R_C(i)= R_N (i)./R_D(i);
end
```

```
% I have to run LHS first, then define a new matrix C to
   be para.

for i=1:1000;
    lambdaT(i)=para(i,1);
    muT(i)=para(i,2);
    xi(i)=para(i,3);
```

```
    muv(i)=para(i,4);
    ev(i)=para(i,5);
    % Computation of the basic reproduction number.
     R_N(i) = lambdaT (i).*xi (i).*ev(i);
    R_D(i) = muT (i).*muv(i);
    R_C(i)= R_N (i)./R_D(i);
end
```

```
clear;
% Calling program to generated PRCC for LHS; call the LHS
    program which
% generates the sample; all input variables are included
   in the LHS program
% and output of the program is the matrix CC from Blower'
   s technique paper

LHS; % call the LHS program
b = size(latin_output);
c = length(latin_output);
%      test1 = 1./latin_output(:,7);
%      test2 = 1./latin_output(:,8);
%      test3 = 1./latin_output(:,9);
%
%  latin_output(:,7) = test1;
%  latin_output(:,8) = test2;
%  latin_output(:,9) = test3;

num = b(2);

    % declare initial parameters

    rank_outcome = zeros(1000,1);
    rank = zeros(1000,10);
```

```
23      outcome = zeros(1000,100);
24      parameters = zeros(1000,10);
25      CC = zeros(10, 10);
26      lengthofmatrix = b(2);
27      % read in data from LHS; program creates matrices
            outcome and
28      % parameters that are used to calculate the PRCCs
29      % variables are then ranked and results are put into
            rank_outcome
30      % matrix which is fed into create_rank _matrix which
            creates a matrix of the ranks of each
31      % parameter for each simulation; the CC matrix then
            created in the last
32      % program
33
34      [parameters, outcome] = read_in _data(N, num,
            latin_output);
35      [rank_outcome] = create_outcome _rank(N, num, outcome
            );
36      [rank, ranks] = create_rank _matrix(N, num,
            parameters, rank, rank_outcome);
37      [CC] = make_c _matrix(N, num, rank);
38      set(0,'defaulttextinterpreter','tex');
39  fig15 = figure(15);
40  barh(CC(1:length(CC)-1,length(CC)))
41  set(gca,'YTick',1:5)
42  set(gca,'YTickLabel',{'\lambda_T','\mu_T','\chi','\mu_V',
        '\epsilon_V'})
```

B.2 Model ODE and Paarameters Values

```
1  function ymm =fuctionCC(t,y)
2   lambdaT = 10; muT = 0.01; xi = 0.000024; muI = 0.5;
```

```
alpha = 0.02; muIl = 0.5; epsV = 100; muV = 2; N1 = 100;
muVn = 3; lambdaZ = 20; muZ = 0.04; beta = 0.004; muZa =
    0.004;
% omega pg 67 eqtns 4.66
% omega = 1;
% o1 = omega; o2 = omega; o3 = omega;
% % weights of drug
% aa = 0.01;
% A1 = aa; A2 = aa; A3 = aa;
% % initia conditions
% x10 = 600; x20 = 10; x30 = 0; x40 = 10; x50 = 0; x60 =
    500; x70 = 10;
% y0=[x10,x20,x30,x40,x50,x60,x70];
% time
ymm = zeros(7,1);
ymm(1)=lambdaT-muT*y(1)-xi*y(1)*y(4);
ymm(2)=xi*y(1)*y(4)-muI*y(2)-alpha*y(2)*y(7);
      ymm(3)=-1*muIl*y(3);
      %ymm(3)=0;
      ymm(4)=epsV*muI*y(2)-muV*y(4);
      ymm(5)=-1*muVn*y(5);
      %ymm(5)=0;
      ymm(6)=lambdaZ-muZ*y(6)-beta*y(6)*y(2);
      ymm(7)=beta*y(6)*y(2)-muZa*y(7);
```

B.3 Optimality System

```
function y=purity_aa(lambdaT,muT,xi,muI,alpha,muIl,epsV,
    muV,muVn,lambdaZ,muZ,beta,muZa,o1,o2,o3,A1,A2,A3,x10,
    x20,x30,x40,x50,x60,x70,tf)
delta=0.001;
test=-1;
N=1000;
```

```
t=linspace(0,tf,N+1);
h=tf/N;
h2=h/2;

u1=zeros(1,N+1);
u2=zeros(1,N+1);
u3=zeros(1,N+1);

x1=zeros(1,N+1);
x2=zeros(1,N+1);
x3=zeros(1,N+1);
x4=zeros(1,N+1);
x5=zeros(1,N+1);
x6=zeros(1,N+1);
x7=zeros(1,N+1);

x1(1)=x10;
x2(1)=x20;
x3(1)=x30;
x4(1)=x40;
x5(1)=x50;
x6(1)=x60;
x7(1)=x70;

lambda1=zeros(1,N+1);
lambda2=zeros(1,N+1);
lambda3=zeros(1,N+1);
lambda4=zeros(1,N+1);
lambda5=zeros(1,N+1);
lambda6=zeros(1,N+1);
lambda7=zeros(1,N+1);

```

```
u=[u1 u2 u3]';
x=[x1 x2 x3 x4 x5 x6 x7]';
lambda=[lambda1 lambda2 lambda3 lambda4 lambda5 lambda6
    lambda7]';
while(test<0)

    oldu1=u1;
    oldu2=u2;
    oldu3=u3;
    oldu=u;
    oldx1=x1;
    oldx2=x2;
    oldx3=x3;
    oldx4=x4;
    oldx5=x5;
    oldx6=x6;
    oldx7=x7;
    oldlambda1=lambda1;
    oldlambda2=lambda2;
    oldlambda3=lambda3;
    oldlambda4=lambda4;
    oldlambda5=lambda5;
    oldlambda6=lambda6;
    oldlambda7=lambda7;
    oldlambda=lambda;

    for i=1:N
        k11=lambdaT-muT*x1(i)-(1-u1(i))*xi*x1(i)*x4(i);
        k12=(1-u1(i))(1-u2(i))*xi*x1(i)*x4(i)-muI*x2(i)-
            alpha*x2(i)*x7(i);
        k13=(1-u1(i))u2(i)*xi*x1(i)*x4(i)-muII*x3(i);
        k14=(1-u3(i))*epsV*muI*x2(i)-muV*x4(i);
```

```
67        k15=u3(i)*epsV*muI*x2(i)-muV*x5(i);
68        k16=lambdaZ-muZ*x6(i)-beta*x6(i)*x2(i);
69        k17=beta*x6(i)*x2(i)-muZa*x7(i);
70
71        k21=lambdaT-muT*(x1(i)++h2*k11)-(1-0.5*(u1(i)+u1(
              i+1)))*xi*(x1(i)+h2*k11)*(x4(i)+h2*k14);
72        k22=(1-0.5*(u1(i)+u1(i+1)))*(1-0.5*(u2(i)+u2(i+1)
              ))*xi*(x1(i)+h2*k11)*(x4(i)+h2*k14)-muI*(x2(i)
              +h2*k12)-alpha*(x2(i)+h2*k12)*(x7(i)+h2*k17);
73        k23=(1-0.5*(u1(i)+u1(i+1)))*0.5*(u2(i)+u2(i+1))*
              xi*(x1(i)+h2*k11)*(x4(i)+h2*k14)-muIl*(x3(i)+
              h2*k13);
74        k24=(1-0.5*(u3(i)+u3(i+1)))*epsV*muI*(x2(i)+h2*
              k12)-muV*(x4(i)+h2*k14);
75        k25=0.5*(u3(i)+u3(i+1))*epsV*muI*(x2(i)+h2*k12)-
              muVn*(x5(i)+h2*k15);
76        k26=lambdaZ-muZ*(x6(i)+h2*k16)-beta*(x6(i)+h2*k16
              )*(x2(i)+h2*k12);
77        k27=beta*(x6(i)+h2*k16)*(x2(i)+h2*k12)-muZa*(x7(i
              )+h2*k17);
78
79        k31=lambdaT-muT*(x1(i)++h2*k21)-(1-0.5*(u1(i)+u1(
              i+1)))*xi*(x1(i)+h2*k21)*(x4(i)+h2*k24);
80        k32=(1-0.5*(u1(i)+u1(i+1)))*(1-0.5*(u2(i)+u2(i+1)
              ))*xi*(x1(i)+h2*k21)*(x4(i)+h2*k24)-muI*(x2(i)
              +h2*k22)-alpha*(x2(i)+h2*k22)*(x7(i)+h2*k27);
81        k33=(1-0.5*(u1(i)+u1(i+1)))*0.5*(u2(i)+u2(i+1))*
              xi*(x1(i)+h2*k21)*(x4(i)+h2*k24)-muIl*(x3(i)+
              h2*k23);
82        k34=(1-0.5*(u3(i)+u3(i+1)))*epsV*muI*(x2(i)+h2*
              k22)-muV*(x4(i)+h2*k24);
```

```
83  k35=0.5*(u3(i)+u3(i+1))*epsV*muI*(x2(i)+h2*k22)-
        muVn*(x5(i)+h2*k25);
84  k36=lambdaZ-muZ*(x6(i)+h2*k26)-beta*(x6(i)+h2*k26
        )*(x2(i)+h2*k22);
85  k37=beta*(x6(i)+h2*k26)*(x2(i)+h2*k22)-muZa*(x7(i
        )+h2*k27);
86
87  k41=lambdaT-muT*(x1(i)++h*k31)-(1-u1(i+1))*xi*(x1
        (i)+h*k31)*(x4(i)+h*k34);
88  k42=(1-u1(i+1))*(1-u2(i+1))*xi*(x1(i)+h*k31)*(x4(
        i)+h*k34)-muI*(x2(i)+h*k32)-alpha*(x2(i)+h*k32
        )*(x7(i)+h*k37);
89  k43=(1-u1(i+1))*u2(i+1)*xi*(x1(i)+h*k31)*(x4(i)+h
        *k34)-muIl*(x3(i)+h*k33);
90  k44=(1-u3(i+1))*epsV*muI*(x2(i)+h*k32)-muV*(x4(i)
        +h*k34);
91  k45=u3(i+1)*epsV*muI*(x2(i)+h*k32)-muVn*(x5(i)+h*
        k35);
92  k46=lambdaZ-muZ*(x6(i)+h*k36)-beta*(x6(i)+h*k36)
        *(x2(i)+h*k32);
93  k47=beta*(x6(i)+h*k36)*(x2(i)+h*k32)-muZa*(x7(i)+
        h*k37);
94
95
96  x1(i+1)=x1(i)+(h/6)*(k11+2*k21+2*k31+k41);
97  x2(i+1)=x2(i)+(h/6)*(k12+2*k22+2*k32+k42);
98  x3(i+1)=x3(i)+(h/6)*(k13+2*k23+2*k33+k43);
99  x4(i+1)=x4(i)+(h/6)*(k14+2*k24+2*k34+k44);
100 x5(i+1)=x5(i)+(h/6)*(k15+2*k25+2*k35+k45);
101 x6(i+1)=x6(i)+(h/6)*(k16+2*k26+2*k36+k46);
102 x7(i+1)=x7(i)+(h/6)*(k17+2*k27+2*k37+k47);
103
```

```
104     end
105     for  i=1:N
106         j=N+2-i;
107         k11=-o1+(muT+(1-u1(j))*xi*x4(j))*lambda1(j)-xi
                *(1-u1(j))*(1-u2(j))*x4(j)*lambda2(j)-xi*(1-u1
                (j))*u2(j)*x4(j)*lambda3(j);
108         k12=(muI+alpha*x7(j))*lambda2(j)-epsV*muI*(1-u3(j
                ))*lambda4(j)-muI*N1*u3(j)*lambda5(j)+beta*x6(
                j)*lambda6(j)-beta*x6(j)*lambda7(j);
109         k13=muIl*lambda3(j);
110         k14=o3+xi*x1(j)*(1-u1(j))*lambda1(j)+xi*x1(j)*(1-
                u1(j))*(1-u2(j))*lambda2(j)+xi*lambda3(j)*x1(j
                )*(1-u1(j))*u2(j)+muV*lambda4(j);
111         k15=muVn*lambda5(j);
112         k16=-o2+(muZ+beta*x2(j))*lambda6(j)-beta*x2(j)*
                lambda7(j);
113         k17=alpha*x2(j)*lambda2(j);
114
115         k21=-o1+(muT+(1-0.5*(u1(j)+u1(j-1)))*xi*0.5*(x4(j
                )+x4(j-1)))*(lambda1(j)-h2*k11)-xi*(1-0.5*(u1(
                j)+u1(j-1)))*(1-0.5*(u2(j)+u2(j-1)))*0.5*(x4(j
                )+x4(j-1))*(lambda2(j)-h2*k12)-xi*(1-0.5*(u1(j
                )+u1(j-1)))*0.5*(u2(j)+u2(j-1))*0.5*(x4(j)+x4(
                j-1))*(lambda3(j)-h2*k13);
116         k22=(muI+alpha*0.5*(x7(j)+x7(j-1)))*(lambda2(j)-
                h2*k12)-epsV*muI*(1-0.5*(u3(j)+u3(j-1)))*(
                lambda4(j)-h2*k14)-muI*N1*0.5*(u3(j)+u3(j-1))
                *(lambda5(j)-h2*k15)+beta*0.5*(x6(j)+x6(j-1))
                *(lambda6(j)-h2*k16)-beta*0.5*(x6(j)+x6(j-1))
                *(lambda7(j)-h2*k17);
117         k23=muIl*(lambda3(j)-h2*k13);
```

```
118 k24=o3+xi*0.5*(x1(j)+x1(j-1))*(1-0.5*(u1(j)+u1(j
        -1)))*(lambda1(j)-h2*k11)+xi*0.5*(x1(j)+x1(j
        -1))*(1-0.5*(u2(j)+u2(j-1)))*(lambda2(j)-h2*
        k12)+xi*(lambda3(j)-h2*k13)*0.5*(x1(j)+x1(j-1)
        )*0.5*(u2(j)+u2(j-1))+muV*(lambda4(j)-h2*k14);
119 k25=muVn*(lambda5(j)-h2*k15);
120 k26=-o2+(muZ+beta*0.5*(x2(j)+x2(j-1)))*(lambda6(j
        )-h2*k16)-beta*0.5*(x2(j)+x2(j-1))*(lambda7(j)
        -h2*k17);
121 k27=alpha*0.5*(x2(j)+x2(j-1))*(lambda2(j)-h2*k12)
        ;
122
123 k31=-o1+(muT+(1-0.5*(u1(j)+u1(j-1)))*xi*0.5*(x4(j
        )+x4(j-1)))*(lambda1(j)-h2*k21)-xi*(1-0.5*(u1(
        j)+u1(j-1)))*(1-0.5*(u2(j)+u2(j-1)))*0.5*(x4(j
        )+x4(j-1))*(lambda2(j)-h2*k22)-xi*(1-0.5*(u1(j
        )+u1(j-1)))*0.5*(u2(j)+u2(j-1))*0.5*(x4(j)+x4(
        j-1))*(lambda3(j)-h2*k23);
124 k32=(muI+alpha*0.5*(x7(j)+x7(j-1)))*(lambda2(j)-
        h2*k22)-epsV*muI*(1-0.5*(u3(j)+u3(j-1)))*(
        lambda4(j)-h2*k24)-muI*N1*0.5*(u3(j)+u3(j-1))
        *(lambda5(j)-h2*k25)+beta*0.5*(x6(j)+x6(j-1))
        *(lambda6(j)-h2*k26)-beta*0.5*(x6(j)+x6(j-1))
        *(lambda7(j)-h2*k27);
125 k33=muIl*(lambda3(j)-h2*k23);
126 k34=o3+xi*0.5*(x1(j)+x1(j-1))*(1-0.5*(u1(j)+u1(j
        -1)))*(lambda1(j)-h2*k21)+xi*0.5*(x1(j)+x1(j
        -1))*(1-0.5*(u1(j)+u1(j-1)))*(1-0.5*(u2(j)+u2(
        j-1)))*(lambda2(j)-h2*k22)+xi*(lambda3(j)-h2*
        k23)*0.5*(x1(j)+x1(j-1))*(1-0.5*(u1(j)+u1(j-1)
        ))*0.5*(u2(j)+u2(j-1))+muV*(lambda4(j)-h2*k24)
        ;
```

```
127         k35=muVn*(lambda5(j)-h2*k25);
128         k36=-o2+(muZ+beta*0.5*(x2(j)+x2(j-1)))*(lambda6(j
                )-h2*k26)-beta*0.5*(x2(j)+x2(j-1))*(lambda7(j)
                -h2*k27);
129         k37=alpha*0.5*(x2(j)+x2(j-1))*(lambda2(j)-h2*k22)
                ;
130
131         k41=-o1+(muT+(1-u1(j-1))*xi*x4(j-1))*(lambda1(j)-
                h*k31)-xi*(1-u1(j-1))*(1-u2(j-1))*x4(j-1)*(
                lambda2(j)-h*k32)-xi*(1-u1(j-1))*u2(j-1)*x4(j
                -1)*(lambda3(j)-h*k33);
132         k42=(muI+alpha*x7(j-1))*(lambda2(j)-h*k32)-epsV*
                muI*(1-u3(j-1))*(lambda4(j)-h*k34)-muI*N1*u3(j
                -1)*(lambda5(j)-h*k35)+beta*x6(j-1)*(lambda6(j
                )-h*k36)-beta*x6(j-1)*(lambda7(j)-h*k37);
133         k43=muII*(lambda3(j)-h*k33);
134         k44=o3+xi*x1(j-1)*(1-u1(j-1))*(lambda1(j)-h*k31)+
                xi*x1(j-1)*(1-u1(j-1))*(1-u2(j-1))*(lambda2(j)
                -h*k32)+xi*(lambda3(j)-h*k33)*x1(j-1)*(1-u1(j
                -1))*u2(j-1)+muV*(lambda4(j)-h*k34);
135         k45=muVn*(lambda5(j)-h*k35);
136         k46=-o2+(muZ+beta*x2(j-1))*(lambda6(j)-h*k36)-
                beta*x2(j-1)*(lambda7(j)-h*k37);
137         k47=alpha*x2(j-1)*(lambda2(j)-h*k32);
138
139         lambda1(j-1)=lambda1(j)-(h/6)*(k11+2*k21+2*k31+
                k41);
140         lambda2(j-1)=lambda2(j)-(h/6)*(k12+2*k22+2*k32+
                k42);
141         lambda3(j-1)=lambda3(j)-(h/6)*(k13+2*k23+2*k33+
                k43);
```

```
142             lambda4(j-1)=lambda4(j)-(h/6)*(k14+2*k24+2*k34+
                    k44);
143             lambda5(j-1)=lambda5(j)-(h/6)*(k15+2*k25+2*k35+
                    k45);
144             lambda6(j-1)=lambda6(j)-(h/6)*(k16+2*k26+2*k36+
                    k46);
145             lambda7(j-1)=lambda7(j)-(h/6)*(k17+2*k27+2*k37+
                    k47);
146
147         end
148
149         temp1=xi*x1.*x4.*(lambda1-(1-u_2)*lambda2-u2*lambda3)
                /(2*A1);
150          u11=max(0, min(1,temp1));
151         %u11=min(1, max(0,temp));
152         u1=0.5*(u11 + oldu1);
153
154         temp2=xi*x1.*x4.*(1-u1)*(lambda3-lambda2)/(2*A2);
155          u22=max(0, min(1,temp2));
156         %u22=min(1, max(0,temp));
157         u2=0.5*(u22 + oldu2);
158
159         temp3=-epsV*muI*lambda4/(2*A3);
160          u33=max(0, min(1,temp3));
161         %u33=min(1, max(0,temp));
162         u3=0.5*(u33 + oldu3);
163 %u1 = zeros(1,length(u1));
164  u2 = zeros(1,length(u1));
165 u3 = zeros(1,length(u1));
166 u=[u1 u2 u3]';
167 x=[x1 x2 x3 x4 x5 x6 x7]';
```

```
168 lambda=[lambda1 lambda2 lambda3 lambda4 lambda5 lambda6
        lambda7]';
169 oldx=[oldx1 oldx2 oldx3 oldx4 oldx5 oldx6 oldx7]';
170 oldlambda=[oldlambda1 oldlambda2 oldlambda3 oldlambda4
        oldlambda5 oldlambda6 oldlambda7]';
171
172
173       temp1=delta*sum(abs(u))-sum(abs(oldu-u));
174       temp2=delta*sum(norm(x))-sum(norm(oldx-x));
175       temp3=delta*sum(norm(lambda))-sum(norm(oldlambda-
              lambda));
176       test=min(temp1,min(temp2,temp3));
177
178 end
179 y(1,:)=t;
180 y(2,:)=x1;
181 y(3,:)=x2;
182 y(4,:)=x3;
183 y(5,:)=x4;
184 y(6,:)=x5;
185 y(7,:)=x6;
186 y(8,:)=x7;
187 y(9,:)=u1;
188 y(10,:)=u2;
189 y(11,:)=u3;
```

B.4 Output Code

```
1 clear all;
2 close all;
3 clc;
4 lambdaT = 10; muT = 0.01; xi = 0.000024; muI = 0.5;
5 alpha = 0.02; muIl = 0.5; epsV = 100; muV = 2;
```

```
muVn = 3; lambdaZ = 20; muZ = 0.04; beta = 0.004; muZa =
    0.004;
%omega pg 67 eqtns 4.66
%omega = 1;
o1 = 0.1;
o2 = 0.2;
o3 = 0.3;
% Vary the values
%weights of drug
%aa = 100;
A1 = 0.03;
% A1 = 0.1;
% A2 = 0.1;
% A3 = 0.1;
% initia conditions
x10 = 500; x20 = 100; x30 = 0; x40 = 100; x50 = 0; x60 =
    100; x70 = 10;
tf=10;
y12=purity_aa(lambdaT,muT,xi,muI,alpha,muIl,epsV,muV,N1,
    muVn,lambdaZ,muZ,beta,muZa,cf,cr,cp,A1,x10,x20,x30,x40
    ,x50,x60,x70,tf);
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-5 1
    e-5 1e-5 1e-5 1e-5 ]);
to =0;
y0=[x10,x20,x30,x40,x50,x60,x70];
[t,Y]= ode45(@fuctionCC,[to tf],y0,options);
disp('                    ')
figure(1)
plot(t,Y(:,1),'r',y1(1,:),y1(2,:),'--b','LineWidth',2.0)
xlabel('Time (Months)')
ylabel('Populations of the CD4+ T-cells')
```

```
32 legend('Without Optimal control', 'With Optimal Control '
       )
33 figure(2)
34 plot(t,Y(:,2),'-r',y1(1,:),y1(3,:),'--b','LineWidth',2.0)
35 xlabel('Time (Months)')
36 ylabel('Infected CD4+T-cells')
37 legend('Without Optimal control', 'With Optimal Control '
       )
38
39 figure(3)
40 plot(t,Y(:,3),'-r',y1(1,:),y1(4,:),'--b','LineWidth',2.0)
41 xlabel('Time (Months)')
42 ylabel('Latently infected CD4+ T-cells')
43 legend('Without Optimal control', 'With Optimal Control '
       )
44
45 figure(4)
46 plot(t,Y(:,4),'-r',y1(1,:),y1(5,:),'--b','LineWidth',2.0)
47 xlabel('Time (Months)')
48 ylabel('Infectious HIV virions')
49 legend('Without Optimal control', 'With Optimal Control '
       )
50
51 figure(5)
52 plot(t,Y(:,5),'-r',y1(1,:),y1(6,:),'--b','LineWidth',2.0)
53 xlabel('Time (Months)')
54 ylabel('Non-infectious HIV virions')
55 legend('Without Optimal control', 'With Optimal Control '
       )
56
57 figure(6)
58 plot(t,Y(:,6),'-r',y1(1,:),y1(7,:),'--b','LineWidth',2.0)
```

```
59 xlabel('Time (Months)')
60 ylabel('CD8+T-cells')
61 legend('Without Optimal control', 'With Optimal Control '
   )
62 figure(7)
63 plot(t,Y(:,7),'-r',y1(1,:),y1(8,:),'--b','LineWidth',2.0)
64 xlabel('Time (Months)')
65 ylabel('Activated CD8+ T-cells')
66 legend('Without Optimal control', 'With Optimal Control '
   )
67 figure(10)
68 plot(y1(1,:),y1(9,:),'-b','LineWidth',2.0)
69 xlabel('Time (Months)')
70 ylabel('Control Profiles,u_1')
71 %  legend('u_1','u_2')
72 figure(11)
73 plot(y1(1,:),y1(9,:),'-b',y1(1,:),y1(11,:),'g','LineWidth
   ',2.0)
74 xlabel('Time (Months)')
75 ylabel('Control Profiles')
76  legend('u_1','u_3')
77 % axis([0 tf 0 1])
78 figure(12)
79 plot(y1(1,:),y1(9,:),'b', y1(1,:),y1(10,:), 'r', y1(1,:),
     y1(11,:), 'g','LineWidth',2.0)
80 xlabel('Time (Months)')
81 ylabel('Control Profiles')
82  legend('u_1','u_2','u_3')
83 % % axis([0 tfinal 0 1])
84  figure(13)
85 plot(y1(1,:),y1(11,:),'-g','LineWidth',2.0)
86 xlabel('Time (Months)')
```

```
87 ylabel('Control Profiles, u_3')
88 % legend('u1','u2')
89 %axis([0 tfinal 0 1])
90
91 %plot as many graphs as you can
```

Appendix C

Publications

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Mathematical Modelling of *In-Vivo* Dynamics of HIV Subject to the Influence of the CD8$^+$ T-Cells

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Abstract

There have been many mathematical models aimed at analysing the *in-vivo* dynamics of HIV. However, in most cases the attention has been on the interaction between the HIV virions and the CD4$^+$ T-cells. This paper brings in the intervention of the CD8$^+$ T-cells in seeking, destroying, and killing the infected CD4$^+$ T-cells during early stages of infection. The paper presents and analyses a five-component *in-vivo* model and applies the results in investigating the *in-vivo* dynamics of HIV in presence of the CD8$^+$ T-cells. We prove the positivity and the boundedness of the model solutions. In addition, we show that the solutions are biologically meaningful. Both the endemic and virions-free equilibria are determined and their stability investigated. In addition, the basic reproductive number is derived by the next generation matrix method. We prove that the virions-free equilibrium state is locally asymptotically stable if and only if $R_0 < 1$ and unstable otherwise. The results show that at acute infection the CD8$^+$ T-cells play a paramount role in reducing HIV viral replication. We also observe that the model exhibits backward and trans-critical bifurcation for some set of parameters for $R_0 < 1$. This is a clear indication that having $R_0 < 1$ is not sufficient condition for virions depletion.

Keywords

HIV, Endemic Equilibrium, Global Stability *In-Vivo*, Disease-Free Equilibrium, Basic Reproductive Number, Backward Bifurcation

1. Introduction

One of the most threatening retrovirus in the world is the Human Immunodeficiency Virus (HIV) that leads to Acquired Immunodeficiency Syndrome (AIDS). Unlike other viruses, HIV is encoded in ribonucleic acid (RNA) rather than

deoxyribonucleic acid (DNA). HIV attacks the immune system, weakening it and eventually if not treated it makes the infected people highly vulnerable to various opportunistic infections. In absence of any HIV-management mechanism, infected people progresses to AIDS stage after 10 - 15 years [1]. HIV can be transmitted through various modes such as: Sharing sharp objects with infected people, having unprotected sex, transfusion using HIV-contaminated blood and mother to child transmission during either breast-feeding or via delivery.

Since the first case of HIV was reported in the early 1980's, HIV/AIDS has been associated to the deaths of more than 35 million people while over 36.9 million are living with the virus worldwide, making it one of the worst menace in the recorded history [2] [3] [4]. However, HIV remains a major cause of mortality in the world, having severe consequences mainly in sub-Saharan Africa, with a prevalence range of between 12% to 42% [3]. The greatest burden of HIV/AIDS lies with the poor communities, who also have the least access to antiretroviral therapy (ARTs) and interventions against HIV. Management, control and prevention of HIV require an integrated approach, which include, awareness/education and treatment with the best ARTs combinations. Lack of awareness/education, in access to early diagnosis and effective treatment has delayed the success of the global HIV programme in reducing new infection and severe HIV/AIDS related deaths. Therefore, there is need for new and more advanced interventions for HIV prevention, management and care.

According to [5], Kenya is among the six HIV high burden countries in the world having over 1.6 million individual living with the virus. Although Kenya had over 79,000 cases of new infection by 2015, she has however, made notable and outstanding strides in controlling and preventing HIV. For instance, the country has one of the world's highest HIV testing rates with about 72% of the total population having been tested at least once and 900,000 of the infected persons are on ARTs. However, not all efforts are reaching those who need these services. Consequently, concentrated epidemics are emerging among vulnerable groups such as youths, women, truck drivers, sex workers, prisoners, injecting-drug users, men who have sex with men, persons living with disabilities, discordant couples, orphan and vulnerable children. Therefore, control and prevention approaches should be tailored towards the aforementioned HIV special populations as part of wider efforts to control and curb the HIV/AIDS in Kenya. In addition, even with all the interventions, there are still a big number of Kenyans who do not know their HIV status. Therefore, it is important to increase HIV testing in order for people to be aware of their HIV status and be referred onto the best treatment, support and care according to the test outcomes. Kenyans economy and development has been affected severely by this menace. The Kenyan Government therefore, need to come up with sustainable methods of funding to improve existing HIV management efforts and to reduce the country's dependence on funding from donors and development partners.

In-vivo study for HIV dynamics have been done over the years, aimed at understanding the interaction mechanism of the body cells and the HIV virus.

Such information has proved so valuable especially in the development of ARTs and in HIV management. In the recent years, mathematical models of various complexity level have been used to simulate and analyse such interactions unlike in the past where researches relied on clinical trials [6]. Consequently, many researchers [7] [8] [9] [10] in the field of epidiemiological modelling have embarked on the process of developing new models that could be used in the analysis of HIV dynamics. Many of the developed models describe and give insight on the various aspects that result from the interaction of HIV with healthy immune cells. The earliest mathematical models were based on the interaction between the $CD4^+$ T-cells and the HIV virions. These basic non-linear models were developed and used in the analysis of HIV dynamics and consequently, in estimating fundamental parameters that brought in new concepts of the disease processes and its progression [11]. With the aim of providing the most fundamental information on controlling the viral progression, most of these basic models include atleast three state variables, which include: the susceptible $CD4^+$ T-cells, free HIV virions and the already infected $CD4^+$ T-cells. For instance, [12], formulated and analyzed an HIV model with three state variables, that is, the susceptible $CD4^+$ T-cells, the already infected $CD4^+$ T-cells and the free HIV virions. The model for instance, predicts adequately the disease progression from the early infection stage, asymptomatic stage, to full blown-AIDs and the viral load at the asymptomatic stage. However, great improvement on the model has been done and many other advanced models developed. [13] formulated a mathematical model representing a complete dynamic of HIV infection. The model aimed at analyzing the interaction between the $CD4^+$ T-cells, macrophage cells and the viral load. The results indicate that the $CD4^+$ T-cells play a very vital role as far as HIV virions replication is concerned. Similarly [6] analyzed a three component model for HIV. The model was aimed at analyzing the HIV dynamics during the initial stages of infection. The results showed that viral persistence was very high during initial stage of HIV infection.

Other researches have sought to study the role played by the killer T-cells in preventing virions replication in the body. In particular, [14] acknowledged the importance of the immune system in HIV infection dynamics by incorporating the $CD8^+$ T-cells in HIV dynamic model. The study developed a three-dimensional ordinary differential equations of the untreated model. The model showed the interaction between the non-infected $CD4^+$ T-cells, infected $CD4^+$ T-cells and the immune response. The model had a major shortcoming for its failure to incorporate the HIV virions. On other hand, [9], used a five-dimensional nonlinear ordinary differential equations (ODEs) model in showing the relationship between $CD4^+$ T-cells, virions, defense cells and ARTs. The results emphasized the importance of the $CD8^+$ T-cells in fighting the HIV virions during acute infection. It has been established that the disease become more endemic due to exponential virions replication and the failure of the ARTs to reach all the cells. Therefore, the focus on how to reduce virions replication by targeting the defense cell is inevitable and it will play a big role in ensuring that

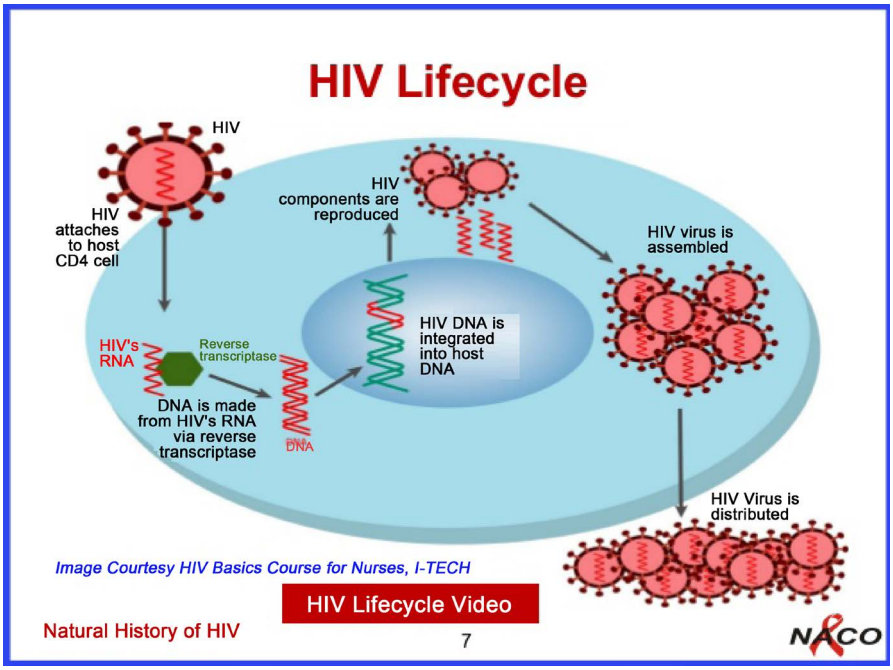
the endemicity of the infection is reduced.

In this paper, we shall mainly focus on HIV dynamics at acute HIV infection stage without any focus on the disease progression to AIDS stage which may come as a result of not using ARTs. The motivation behind this simple initial infection model is the fact that most of the new strategies for HIV management in Kenya such as the pre-exposure antiviral treatment and post-exposure antiviral treatment targets the HIV virions at the early stages of HIV-infection. For this study to be successful we develop a non-linear, five-dimensional deterministic model for *in-vivo* dynamics of HIV with inclusion of the $CD8^+$ T-cells.

HIV Life Cycle

HIV, like most viruses lacks the ability to replicate on its own and therefore, relies on a host for replication. Although, unlike all other viruses HIV is a retrovirus and hence carries the copies of its own RNA [2]. Once the virus gets in the body it mainly targets the $CD4^+$ T cells by attaching itself on the membrane of the cell. After the infection of the cells by the virus, it is important to note that the symptoms do not show immediately until their level reduces to about 200 cells per mm^3, and the viral load increases to 500 copies per ml [12]. The process of HIV replication is outlined in the following steps: First HIV virion joins the membrane of the $CD4^+$ T-cell. Then it fuses with the harbour cell and releases an enzyme known as reverse transcriptase. Reverse transcriptase enzyme transform the genome of the HIV virus to a double-stranded HIV DNA from a single-stranded HIV RNA. The transcription process ensures that integration of the HIV virion into the host DNA. Once HIV is integrated in the cells DNA, it starts to manufacture long chains of HIV protein using their DNA. The HIV proteins are the support system for more HIV virions. These long chains of HIV proteins (immature and non-infectious) assembles closer the membrane of the $CD4^+$ cells and bud out. The immature virions then release an enzyme called the protease, which cut the long HIV proteins RNA into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, they form a new mature virus particle. Other cells can now be infected by the new HIV copies. This clearly shows that a single virion lead to the production of many other virions [15].

After infection the $CD4^+$ T-cells sends a signal to the $CD8^+$ T-cells. The $CD8^+$ T-cells are aimed at destroying and killing the virions [9]. Unfortunately, despite immense effort from the mathematician in the field of mathematical modeling on HIV/AIDS analysis, the intervention of $CD8^+$ T-cells need to be analyzed further. Although researchers suggest that $CD8^+$ T-cells play a paramount role in host defense against the HIV virions nothing much has been done to show it especially during AIDS stage. One of the objectives of this paper is to present a realistic model that will analyze the importance of the $CD8^+$ T-cells in destroying the HIV virions. The $CD4^+$ T-cells play critical roles in controlling viral infections by prompting $CD8^+$ T-cells to eliminate the free HIV virions. The



Source: HIV Basics Course for Nurses.

Figure 1. HIV Life Cycle.

HIV virus life cycle is presented in **Figure 1**.

2. Mathematical Model for HIV Dynamics *in-Vivo*

2.1. Introduction

An in-host HIV dynamics model with the inclusion of the immune cells is formulated. We show the model is positively invariant. The basic reproduction number expression is derived using the next generation matrix method. We also do the analyses on the stability of the steady points of the model.

2.1.1. HIV Model Formulation

We shall put into consideration a mathematical model for the *in-vivo* interaction of the HIV virions and the immune system cells. The model is classified into five compartments. The following are the variables used in the model (1) the healthy $CD4^+$ T-cells (T), the infectious HIV virions (V), the already infected $CD4^+$ T-cells (I), the immune cells (Z), that is, $CD8^+$ T-cells and the activated immune cells (Z_a).

The healthy $CD4^+$ T-cells are recruited at a constant rate λ_T from the bone marrow and die naturally at a constant rate μ_T. The healthy $CD4^+$ T-cells are as a result of the interaction between the uninfected $CD4^+$ T-cells and the virus at a rate χ. They die naturally at a rate μ_I, they are also eliminated by the activated $CD4^+$ T-cells at the rate α. In addition, the infected healthy $CD4^+$ T-cells produces an average of ϵ_V viral particles. The new mature virions produced will infect other $CD4^+$ T-cells. The HIV virions population increases due to the budding of the infected $CD4^+$ T-cells at a rate ϵ_V and die at the rate μ_V. The

$CD8^+$ T-cells, are generated from the thymus at a constant rate λ_Z, and die naturally at a constant rate μ_Z. Due to the presence of the HIV virions the $CD8^+$ T-cells become activated at the rate β. The activated $CD8^+$ T-cells are produced from the $CD8^+$ T-cells the in the presence of the HIV virions, at rate β and die naturally at rate μ_{Z_a}. The interaction description can be summarized in Table 1 and Table 2 which represent the Variables and parameters respectively.

We present the model diagram in Figure 2. The diagram represent visually a mechanisms which govern the system of differential equations for system (1).

From Figure 2, we derive the following system of initial value non-linear differential equation for the *in-vivo* HIV dynamics model;

$$\left.\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= \lambda_T - \mu_T T - \chi TV,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \chi TV - \mu_I I - \alpha I Z_a,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \epsilon_V \mu_I I - \mu_V V,\\
\frac{\mathrm{d}Z}{\mathrm{d}t} &= \lambda_Z - \mu_Z Z - \beta ZI,\\
\frac{\mathrm{d}Z_a}{\mathrm{d}t} &= \beta ZI - \mu_{Z_a} Z_a
\end{aligned}\right\} \quad (1)$$

Table 1. Variables for HIV *in-vivo* model.

Variable	Description
$T(t)$	The concentration of the susceptible $CD4^+$ T cells at any time t
$I(t)$	The concentration of the infected $CD4^+$ T cells at any time t
$V(t)$	The concentration of infectious HIV virions at any time t
$Z(t)$	The concentration of the $CD8^+$ T-cells at any time t
$Z_a(t)$	The population of the activated $CD8^+$ T-cells at any time t

Table 2. Parameters for HIV *in-vivo* model.

Parameter	Description
λ_T	The recruitment rate of the susceptible $CD4^+$ T-cells per unit time.
μ_T	The decay rate of the susceptible $CD4^+$ T-cells.
χ	The infection rate of the $CD4^+$ T-cells by the virus.
μ_I	The natural death rate of the infected $CD4^+$ T-cells.
ϵ_V	The HIV virions generation rate from the infected $CD4^+$ T-cells.
μ_V	The death rate of the infectious virus.
α	The rate at which the infected cells are eliminated by the activated $CD8^+$ T-cells.
λ_Z	The recruitment rate of the $CD8^+$ T-cells per unit time.
μ_Z	The death rate of the $CD8^+$ T-cells.
β	The activation rate of the $CD8^+$ T-cells due to the presence the infected $CD4^+$ T-cells.
μ_{Z_a}	The decay rate at of the activated defence cells decay per unit time.

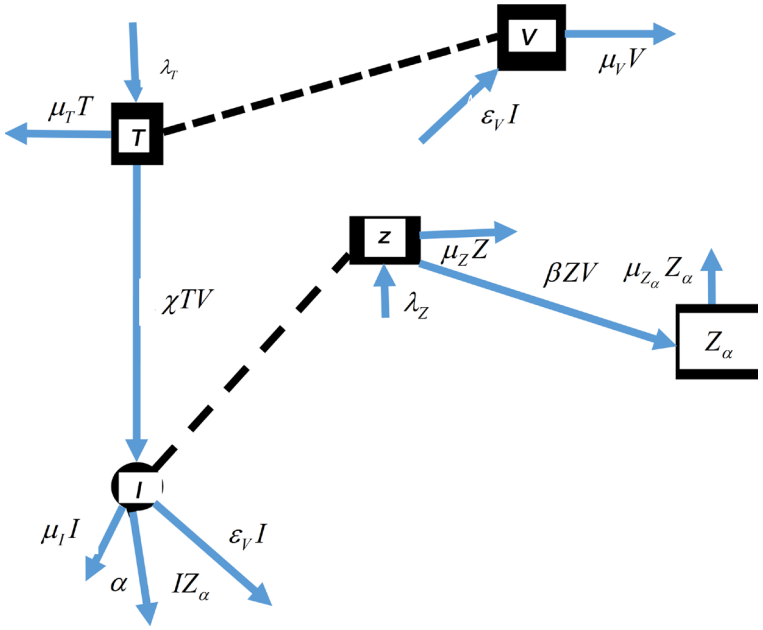


Figure 2. A compartmental representation of the *in-vivo* HIV Dynamics.

3. Basic Properties of the Model

Before commencing the steady-states analysis of the model (1), it is important to look at some properties to ensure existence of biologically meaningful solutions.

3.1. Boundedness and the Positivity of the Model Solutions

Before we analyze the model (1) it is paramount to prove that the key variables are non-negative implying that the model solutions will be positive for all $t>0$ and must be bounded for all $t>0$ in an invariant region. Invariant region is the area in which the model is well posed mathematically and has biological meaning.

Theorem 1. *Let the initial values of the state variables be* $T(0)\geq 0$, $V(0)\geq 0$, $I(0)\geq 0$, $Z(0)\geq 0$, $Z_a(0)\geq 0$. *Then show that, for every* $t>0$ *the solution set* $\Gamma=\{T(t),V(t),I(t),Z(t),Za(t)\}$ *of the model* (1) *is non-negative and* Γ *is the invariant region.*

Proof. Taking the first part of Equation (1) we have,

$$\begin{aligned}&\frac{\mathrm{d}T(t)}{\mathrm{d}t}\geq -\mu_T T-\chi TV\\ &T(t)\geq T(0)\mathrm{e}^{\int-(\mu_T+\chi V)\mathrm{d}t},\end{aligned}\tag{2}$$

Hence T is non-negative for all $t>0$.

Similarly for the infected $CD4^+$ T-cells we have,

$$\frac{\mathrm{d}I}{\mathrm{d}t}=\chi TV-\mu_I I-\alpha IZ_a\geq -(\mu_I-\alpha Z_a)I\tag{3}$$

By integration and separation of variables Equation (3) gives,

$$I\geq I(0)\mathrm{e}^{\int-(\mu_I+\alpha Z_a)\mathrm{d}t}\tag{4}$$

Hence I is non-negative for all $t>0$.

Similarly for the HIV virions we have,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \epsilon_V \mu_I I - \mu_V V \geq -\mu_V \tag{5}$$

By integration and separation variables Equation (3) gives,

$$V \geq V(0)\mathrm{e}^{\int -(\mu_V)\mathrm{d}t}$$

Hence V is non-negative for all $t > 0$.

For the $CD8^+$, part four of model (1) gives

$$\begin{aligned} \frac{\mathrm{d}Z}{\mathrm{d}t} &= \lambda_Z - \mu_Z Z - \beta ZI \geq -(\mu_Z + \beta I)Z \\ \frac{\mathrm{d}Z}{\mathrm{d}t} &\geq -(\mu_Z + \beta I)Z \end{aligned} \tag{6}$$

We separate variables and integrate both sides with respect to the corresponding variables as follow,

$$Z \geq Z(0)\mathrm{e}^{\int -(\mu_Z + \beta I)\mathrm{d}t} \tag{7}$$

Hence Z is non-negative for all $t > 0$.

Finally for the activated immune cells we have;

$$\begin{aligned} \frac{\mathrm{d}Z_a}{\mathrm{d}t} &= \beta ZI - \mu_{za} Z_a \geq -(\mu_{za} Z_a) \\ \frac{\mathrm{d}Z_a}{\mathrm{d}t} &\geq -(\mu_{za} Z_a) \end{aligned} \tag{8}$$

By integration and separation of variables we get;

$$Z_a \geq Z_a(0)\mathrm{e}^{\int -(\mu_{za})\mathrm{d}t} \tag{9}$$

Hence Z_a is non-negative for all $t > 0$. □

3.2. Invariant Region

Notably, all the state variables of system (1) have been proved to be non-negative. In addition, parameters of model (1) monitors cell population, hence they are also non-negative for all, $t > 0$. Consequently the model (1) analysis is done in the region Γ that is biologically meaningful.

Theorem 2. *Let* $T(t) \geq 0$, $V(t) \geq 0$, $I(t) \geq 0$, $Z(t) \geq 0$, $Z_a(t) \geq 0$. *Then the solutions of* $T(t)$, $V(t)$, $I(t)$, $Z(t)$, $Z_a(t)$ *are bounded and the region* Γ *is positively invariant for all* $t \geq 0$.

$$\Gamma = \left\{ \left(T(t), I(t), V(t), Z(t), Z_a(t)\right) \in \mathbb{R}^5, T + I \leq \frac{\lambda_T}{\mu_T}, Z + Z_a \leq \frac{\lambda_Z}{\mu_Z}, V \leq \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} + V_0 \right\} \tag{10}$$

Proof. The total population of the $CD4^+$ T-cells, $T + I = N_4(t)$, is clearly non-constant value. Hence the evolution equation representing the change in the population of the $CD4^+$ T-cells is;

$$\begin{aligned} \frac{\mathrm{d}N_4(t)}{\mathrm{d}t} &= \lambda_T - \mu_T T - \mu_I I - \alpha I Z_a, \\ \frac{\mathrm{d}N_4(t)}{\mathrm{d}t} &\leq \lambda_T - \mu_T N_4(t) \end{aligned} \tag{11}$$

By separation of variables method for solving differential inequality, Equation (11) becomes;

$$\begin{aligned} &\frac{\mathrm{d}N_4(t)}{\lambda_T - \mu_T N_4(t)} \le \mathrm{d}t, \\ &\ln\left(\lambda_T - \mu_T N_4(t)\right)^{-} \frac{1}{\mu_T} \ge \ln C + t \end{aligned} \tag{12}$$

Thus, Equation (12) reduces to;

$$\ln\left(\lambda_T - \mu_T N_4(t)\right)^{-\frac{1}{\mu_T}} \ge C\mathrm{e}^{\mu_T t} \tag{13}$$

But

$$C = \lambda_T - \mu_T N_0 \tag{14}$$

Therefore, Equation (12) becomes;

$$N_4(t) \le \frac{\lambda_T}{\mu_T} - \frac{\left(\lambda_T - \mu_T N_0\right)\mathrm{e}^{-\mu_T t}}{\mu_T} \tag{15}$$

Thus at any time $t > 0$ we have;

$$N_4(t) \le \max\left\{N_0, \frac{\lambda_T}{\mu_T}\right\} \tag{16}$$

Hence, all feasible solutions set for the $CD4^+$ T-cells of the model (1) enters the region:

$$\Gamma_T = \left\{\left(T(t), I(t)\right) \in \mathbb{R}^2, N_4 \le \max\left\{N_0, \frac{\lambda_T}{\mu_T}\right\}\right\} \tag{17}$$

Similarly the total number of the $CD8^+$ T-cells, $Z + Z_a = N_8(t)$, at disease free equilibrium are given by;

$$\frac{\mathrm{d}N_8(t)}{\mathrm{d}t} = \lambda_Z - \mu_Z N_8(t) \tag{18}$$

By separation of variables method for solving differential inequality Equation (18) becomes;

$$\frac{\mathrm{d}N_8(t)}{\lambda_Z - \mu_Z N_8(t)} \le \mathrm{d}t \tag{19}$$

Integrating Equation (19) we have

$$N_8(t) \le \frac{\lambda_Z}{\mu_Z} - \frac{\left(\lambda_Z - \mu_Z N_0 c\right)\mathrm{e}^{-\mu_Z t}}{\mu_Z} \tag{20}$$

Thus at any time $t > 0$ we have;

$$N_8(t) \le \max\left\{N_0 c, \frac{\lambda_Z}{\mu_Z}\right\} \tag{21}$$

Hence, all feasible solutions set for the $CD8^+$ T-cells of the model (1) enters the region;

$$\Gamma_Z = \left\{ \left(Z(t), Z_a(t) \right) \in \mathbb{R}^2, N_8(t) \le \max \left\{ N_0 c, \frac{\lambda_Z}{\mu_Z} \right\} \right\} \tag{22}$$

Considering the V population of the model (1) we have'

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \le \varepsilon_V \mu_I \frac{\lambda_T}{\mu_T} - \mu_V V, \text{ since } I \le \frac{\lambda_T}{\mu_T} \tag{23}$$

Integration gives

$$\begin{aligned} &\frac{\mathrm{d}V}{\mathrm{d}t} + \mu_V V \le \varepsilon_V \mu_I \frac{\lambda_T}{\mu_T} \\ &V \le \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} + V_0 \end{aligned} \tag{24}$$

Hence V is bounded. Consequently the feasible solution for the model (1) is;

$$\Gamma = \left\{ \left(T(t), V(t), I(t), Z(t), Z_a(t) \right) \in \mathbb{R}^5, T + I \le \frac{\lambda_T}{\mu_T}, Z + Z_a \le \frac{\lambda_Z}{\mu_Z}, V \le \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} + V_0 \right\} \tag{25}$$

All the state variables are positive and bounded. Consequently, from Equation (25), Γ is positively invariant of model (1). Hence, it is possible to study the dynamics of the HIV model (1) in Γ. □

With theorem 2 we conclude that the model is valid and will remain so during the whole course of study if and only if the initial data are biologically meaningful. In addition it is evident that with time the number of virions will reduce to non-detectable level.

Remark 1. *Suppose* $T(0), I(0), V(0), Z(0), Z_a(0) > 0$ *be given. Then there exist a differentiable continuous function* $T, I, V, Z, Z_a : [0, T_f]$ R *such that* (T, I, V, Z, Z_a) *is bounded and* $(T, I, V, Z, Z_a)(0) = \left(T(0), I(0), V(0), Z(0), Z_a(0) \right)$.

Therefore, the model solutions will always be positive if the initial values for the state variables are non-negative for all $t > 0$ in the closed interval $[0, T_f]$.

4. Equilibria and Reproductive Number

For us to fully understand the dynamics of the five component HIV model we study its stability. In this model there exist two critical points. The critical points represent the case before the virions get to the body, that is virions-free equilibrium point that is, $V = I = Z_a = 0$, and when the virus persist in the body, that is, $V \neq 0, I \neq 0$ and $Z_a \neq 0$.

Before infection by HIV virions, the model as represented by Equation (1), has a unique feasible HIV-free steady state solution to be referred to as the virions-free equilibrium (VFE). The virions-free equilibrium of the model (1) is given by:

$$E_0(T, I, V, Z, Z_a) = \left[\frac{\lambda_T}{\mu_T}, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0 \right] \tag{26}$$

4.1. Basic Reproductive Number

Researchers in the field of *in-vivo* HIV modelling aims at finding the optimal

conditions that determine the spread of the HIV virions in the susceptible $CD4^+$ T-cells. In order to do this, researchers consider the basic reproductive number (R_0). According to [16], the basic reproductive number represent the number of secondary infection that result from single infected T-cell. R_0 measures the potential of HIV spread in the host and probably attacking a large number of the T-cells. The R_0 obtained for the virions-free equilibrium by the next generation matrix guarantee local stability of the model (1). R_0 is used in stability analysis of the critical points. If $R_0 < 1$ the virions-free equilibrium is locally asymptotically stable and if $R_0 > 1$ it is said to be unstable. Notably, a large value of R_0 indicates disease epidemic. Consequently, in order to control viral replication it is important to ensure that $0 < R_0 < 1$.

Computation of R_0

In this paper we shall adopt the next generation matrix method for the derivation of R_0 [16]. Mathematically, R_0 is given by $R_0 = \rho\left(FV^{-1}\right)$ where ρ is the spectral radius of the next generation matrix [17] and F is the matrix of the infections while V is the transfer of individuals out of compartment [18]. The expression of R_0 is the dominant eigenvalue of the next generation matrix. In model (1) we have two infection classes, therefore, the matrix of new infection at the virions-free equilibrium is given by;

$$F = \begin{bmatrix} 0 & \frac{\chi\lambda_T}{\mu_T} \\ 0 & 0 \end{bmatrix} \tag{27}$$

The matrix that represent the transfer between compartments at the disease-free equilibrium given respectively by,

$$V = \begin{bmatrix} \mu_I & 0 \\ -\varepsilon_V\mu_I & \mu_V \end{bmatrix} \tag{28}$$

The inverse of V is given by;

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_I} & 0 \\ \frac{\varepsilon_V}{\mu_V} & \frac{1}{\mu_V} \end{bmatrix} \tag{29}$$

The next generation matrix FV^{-1} is given by;

$$FV^{-1} = \begin{bmatrix} \frac{\chi\varepsilon_V\lambda_T}{\mu_V\mu_T} & \frac{\chi\lambda_T}{\mu_T\mu_V} \\ 0 & 0 \end{bmatrix} \tag{30}$$

The eigenvalues of the matrix above are; $\frac{\chi\varepsilon_V\lambda_T}{\mu_V\mu_T}$ and 0, therefore, the reproductive number (which is the largest eigenvalue) is given by;

$$\mathcal{R}_0 = \frac{\chi\varepsilon_V\lambda_T}{\mu_V\mu_T} \tag{31}$$

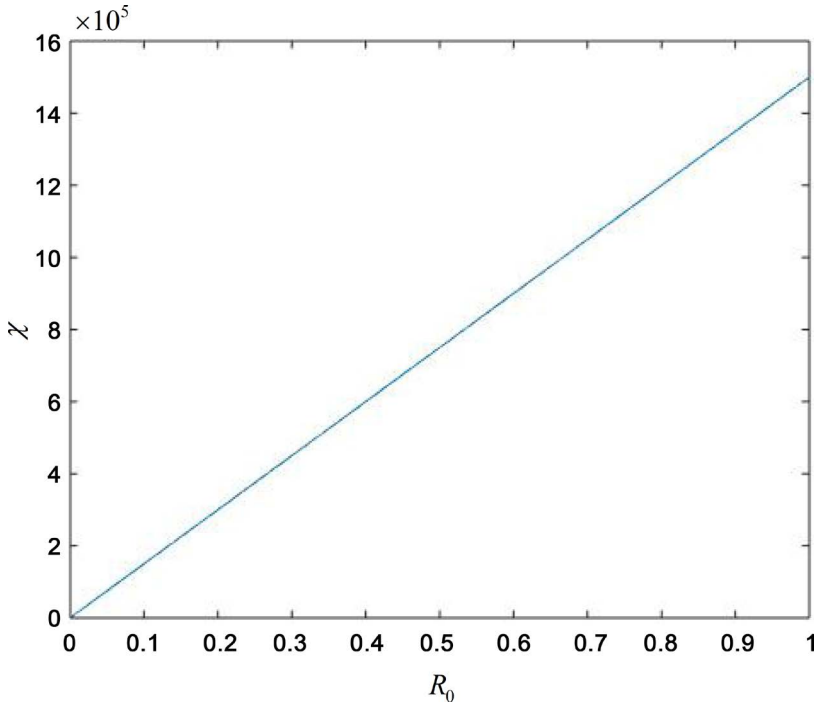


Figure 3. Basic Reproductive number increases with the infection rate.

Figure 3 illustrates how R_0 is affected by the change of χ.

Increasing the infection rate would lead to a rise in the number of secondary infection this is clearly depicted from the reproductive number given in Equation (31). The only way of reducing this is by introducing ARTs that target the HIV lifecycle at the entry level of the HIV virions to the $CD4^+$ T-cells, that is, during fusion stage and hence the recommended drugs are the Fusion Inhibitors. Similarly, increasing the rate at which free HIV virions are generated from the infected cells would lead to an increase in the reproductive number. This means that it is paramount to bring in treatment at the budding level or to introduce ARTs drugs that would help in ensuring that the HIV virions generated from the infected $CD4^+$ T-cells are defective and non-infectious. The ARTs that can play that role are the protease inhibitors. The protease inhibitors (PIs) inhibits the release of the viral protease enzyme that ensures the maturity of HIV virions upon budding from the host membrane. Consequently, the virions produced by the infected cells after the introduction of PIs are defective and non-infectious [19]. Conversely, if the rate at which the virus dies increases the rate of secondary infection would be at the minimum level. The HIV virions can die naturally or triggered by the $CD8^+$ T-cells. According to [9], the $CD8^+$ T-cells seek, destroy, and kill the cells infected by the HIV virions. This means that if the $CD8^+$ T-cells are able to fight the virions by killing the infected CD^+ T-cells the number of secondary infection would reduce and eventually the virions maybe eliminated from the body. This shows that during the initial HIV infection stage $CD8^+$ T-cells are very important as far as fighting and reducing HIV virions replication is concerned. The most fundamental thing would for

researcher to establish what happens to $CD8^+$ T-cells at the chronic level. Do they still fight the virus? Or probably are the $CD4^+$ T-cells so worn out that they are not able to alert the $CD8^+$ T-cells?

4.2. Local Stability of the Virions-Free Equilibrium (VFE)

Theorem 3. *The virions-free equilibrium* E_0 *of the model* (1) *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$

Proof. In this study we have a non-linear differential equations model hence we shall use linearization method by [20] to study and prove the local stability of the virions-free equilibrium. The Jacobian matrix of the DFE for the model (1) is given by:

$$J = \begin{vmatrix} -\mu_T & 0 & -\chi T & 0 & 0 \\ 0 & -\mu_I & \chi T & 0 & 0 \\ 0 & \varepsilon_V \mu_I & -\mu_V & 0 & 0 \\ 0 & -\beta Z & 0 & -\mu_Z & 0 \\ 0 & \beta Z & 0 & 0 & -\mu_{Za} \end{vmatrix} \tag{32}$$

Substituting Equation (26) into Equation (32) we have;

$$J(E_0) = \begin{vmatrix} -\mu_T & 0 & -\chi \dfrac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & -\mu_I & \chi \dfrac{\lambda_T}{\mu_T} & 0 & 0 \\ 0 & \varepsilon_V \mu_I & -\mu_V & 0 & 0 \\ 0 & -\beta \dfrac{\lambda_Z}{\mu_Z} & 0 & -\mu_Z & 0 \\ 0 & \beta \dfrac{\lambda_Z}{\mu_Z} & 0 & 0 & -\mu_{Za} \end{vmatrix} \tag{33}$$

The characteristic equation in Λ for Equation (33) is given by

$$\Lambda^5 - b_4\Lambda^4 - b_3\Lambda^3 - b_2\Lambda^2 - b_1\Lambda + b_0 = 0 \tag{34}$$

where,

$$b_4 = -\mu_{Za} - \mu_Z + \mu_V - \mu_I + \mu_T$$

$$b_3 = \chi \frac{\lambda_T}{\mu_T} \varepsilon_V \mu_I - \lambda_T \mu_{Za} - \lambda_T \mu_Z - \lambda_T \mu_I - \lambda_T \mu_V - \mu_{Za} \mu_Z - \mu_{Za} \mu_I - \mu_{Za} \mu_V - \mu_Z \mu_I - \mu_Z \mu_V - \mu_I \mu_V$$

$$b_2 = \lambda_T \chi \frac{\lambda_T}{\mu_T} \varepsilon_V \mu_I + \chi \frac{\lambda_T}{\mu_T} \mu_{Za} \varepsilon_V \mu_I + \mu_Z \varepsilon_V \mu_I \chi \frac{\lambda_T}{\mu_T} - \lambda_T \mu_{Za} \mu_Z - \lambda_T \mu_{Za} \mu_I - \lambda_T \mu_{Za} \mu_V - \lambda_T \mu_Z \mu_I - \lambda_T \mu_Z \mu_V - \lambda_T \mu_I \mu_V - \mu_{Za} \mu_Z \mu_I - \mu_{Za} \mu_Z \mu_V - \mu_{Za} \mu_I \mu_V - \mu_Z \mu_I \mu_V$$

$$b_1 = \lambda_T \mu_{Za} \varepsilon_V \mu_I \chi \frac{\lambda_T}{\mu_T} + \lambda_T \mu_Z \varepsilon_V \mu_I \chi \frac{\lambda_T}{\mu_T} + T \mu_{Za} \mu_Z \varepsilon_V \mu_I \chi \frac{\lambda_T}{\mu_T} + \lambda_T \mu_{Za} \mu_Z \mu_I - \lambda_T \mu_{Za} \mu_Z \mu_V - \lambda_T \mu_{Za} \mu_I \mu_V - \lambda_T \mu_Z \mu_I \mu_V - \mu_{Za} \mu_Z \mu_I \mu_V$$

$$b_0 = \mu_{Za}\mu_Z\mu_I\lambda_T\left(\varepsilon_V\frac{\lambda_T}{\mu_V}-\mu_V\right)$$

The eigenvalues for the Jacobian matrix are given by; $\Lambda_1 = -\mu_T$, $\Lambda_2 = -\mu_Z$, $\Lambda_3 = -\mu_{Za}$,

$$\Lambda_4 = \frac{-\mu_I\mu_T - \mu_V\mu_T + \sqrt{4\chi\lambda_T\mu_I\mu_T\varepsilon_V + \mu_I^2\mu_T^2 - 2\mu_I\mu_T^2\mu_V + \mu_T^2\mu_V^2}}{2\mu_T},$$

$$\Lambda_5 = -\frac{\mu_I\mu_T + \mu_V\mu_T + \sqrt{4\chi\lambda_T\mu_I\mu_T\varepsilon_V + \mu_I^2\mu_T^2 - 2\mu_I\mu_T^2\mu_V + \mu_T^2\mu_V^2}}{2\mu_T}$$

It is evident that Λ_1, Λ_2, Λ_3 and Λ_5. However we need to determine the conditions that would guarantee that Λ_4 is also negative, since for local stability all the eigenvalues must be negative.

Suppose $\Lambda_4 < 0$, we have:

$$\begin{aligned}&\frac{-\mu_I\mu_T - \mu_V\mu_T + \sqrt{4\chi\lambda_T\mu_I\mu_T\varepsilon_V + \mu_I^2\mu_T^2 - 2\mu_I\mu_T^2\mu_V + \mu_T^2\mu_V^2}}{2\mu_T} < 0,\\ &\left(\mu_I\mu_T + \mu_V\mu_T\right)^2 > 4\chi\lambda_T\mu_I\mu_T\varepsilon_V + \mu_I^2\mu_T^2 - 2\mu_I\mu_T^2\mu_V + \mu_T^2\mu_V^2,\\ &\mu_V\mu_T > \chi\lambda_T\varepsilon_V\end{aligned} \tag{35}$$

Thus, from Equation (35) we have;

$$\frac{\chi\lambda_T\varepsilon_V}{\mu_V\mu_T} < 1 \tag{36}$$

From (36) we deduce that $R_0 = \frac{\chi\lambda_T\varepsilon_V}{\mu_V\mu_T} < 1$. Thus, the virions-free equilibrium is locally asymptotically stable. □

4.3. The Endemic Equilibrium

To analyze the endemic equilibrium, this study adopt the assumption made by [14] that the free virus spread of infection and there is no cell-to-cell transfer of the HIV virions. The endemic equilibrium E_1 exist when, $T(t) > 0$, $I(t) > 0$, $V(t) > 0$, $Z(t) > 0$, $Z_a(t) > 0$. An endemic equilibrium $E_1 = \left(T^*, I^*, V^*, Z^*, Z_a^*\right)$, satisfies;

$$\left.\begin{aligned}&\lambda_T^* - \mu_T T^* - \chi T^* V^* = 0,\\ &\chi T^* V^* - \mu_I I^* - \alpha I^* Z_a^* = 0,\\ &\epsilon_V\mu_I I^* - \mu_V V^* = 0,\\ &\lambda_Z - \mu_Z Z^* - \beta Z^* I^* = 0,\\ &\beta Z^* I^* - \mu_{za} Z_a^* = 0\end{aligned}\right\} \tag{37}$$

Hence, the endemic equilibria of the model (1) correspond to the non-negative solutions of the Equation (37). Therefore, we solve the system (37) in terms of Z_a^* and obtain the endemic equilibrium as;

$$\left.\begin{aligned} T^* &= \frac{\lambda_T \mu_v \beta\left(\lambda_Z - Z_a^* \mu_{za}\right)}{\mu_T \mu_v \beta\left(\lambda_Z - Z_a^* \mu_{Za}\right) + Z_a^* \epsilon_v \mu_z \chi \mu_{Za} \mu_T}, \\ I^* &= \frac{Z_a^* \mu_{za} \mu_Z}{\beta\left(\lambda_Z - Z_a^* \mu_{Za}\right)}, \\ V^* &= \frac{\epsilon_V \mu_Z \mu_{Za} \mu_I Z_a^*}{\beta \mu_v \left(\lambda_Z - Z_a^* \mu_{Za}\right)}, \\ Z^* &= \frac{\lambda_Z - Z_a^* \mu_{za}}{\mu_Z}. \end{aligned}\right\} \tag{38}$$

We then obtain the following cubic polynomial that describes the existence of the possible equilibria.

$$p\left(Z_a^*\right) = Z_a^*\left(\Phi_2 Z_a^{*2} + \Phi_1 Z_a^* + \Phi_0\right) = 0, \tag{39}$$

where,

$$\left.\begin{aligned} \Phi_2 &= -4\beta\mu_{Za}\mu_Z\left(\mu_{Za}\mu_I + \alpha\lambda_Z\right), \\ \Phi_1 &= 4\mu_{Za}\mu_Z\mu_T\left[-R_0\mu_I\mu_{Za}\left(\mu_I\mu_Z - \beta\lambda_T\right) - \lambda_T\beta\left(\mu_I\mu_{Za} + \alpha\lambda_Z\right)\right], \\ \Phi_0 &= 4R_0\mu_{Za}^2\mu_Z^2\mu_T^2\mu_V^2\left(R_0 - 1\right). \end{aligned}\right\} \tag{40}$$

We re-write Equation (40) to ensure that $\Phi_2 > 0$ as;

$$\left.\begin{aligned} \Phi_2 &= 4\beta\mu_{Za}\mu_Z\left(\mu_{Za}\mu_I + \alpha\lambda_Z\right), \\ \Phi_1 &= -4\mu_{Za}\mu_Z\mu_T\left[R_0\mu_I\mu_{Za}\left(\mu_I\mu_Z - \beta\lambda_T\right) + \lambda_T\beta\left(\mu_I\mu_{Za} + \alpha\lambda_Z\right)\right], \\ \Phi_0 &= 4R_0\mu_{Za}^2\mu_Z^2\mu_T^2\mu_V^2\left(1 - R_0\right). \end{aligned}\right\} \tag{41}$$

From Equation (39), if $Z_a^* = 0$, then we have disease-free equilibrium treated earlier in Equation (26). The solution to the following equation defines the existence of the possible endemic equilibrium.

$$\Phi_2 Z_a^{*2} + \Phi_1 Z_a^* + \Phi_0 = 0, \tag{42}$$

The two roots of the quadratic Equation (42) is given by;

$$Z_a^* = \frac{-\Phi_1 \pm \sqrt{\Phi_1^2 - 4\Phi_2\Phi_0}}{2\Phi_0} \tag{43}$$

Consequently, depending on the signs of Φ_2, Φ_1 and Φ_0 the model (1) may have unique, two or no positive roots. We now analyze the three scenarios as follows.

Case 1:

If $R_0 = 1$ then $\Phi_0 = 0$, $\Phi_1 < 0$, $\Phi_2 > 0$,

$$\left.\begin{aligned} \Phi_2 Z_a^{*2} - \Phi_1 Z_a^* &= 0, \\ Z_a^*\left(\Phi_2 Z_a^* - \Phi_1\right) &= 0 \end{aligned}\right\} \tag{44}$$

Therefore,

$$Z_{a1}^* = 0, Z_{a2}^* = \frac{\Phi_1}{\Phi_2} \tag{45}$$

$Z_{a1}^{*}=0$ represents the disease free case and $Z_{a2}^{*}=\frac{\Phi_1}{\Phi_2}$ represent a unique positive equilibrium point. This is the critical equilibrium point.

Case 2:

If $R_0>1$ then $\Phi_0>0,\Phi_1<0,\Phi_2>0$ and using the signs rule Descartes, the sign of the coefficients of the quadratic Equation (39) changes once. So there is a unique positive equilibrium point, $Z_{a1}^{*}>0$. Consequently, there exist at least one endemic equilibrium point.

Case 3:

If $R_0<1$ then $\Phi_0>0,\Phi_1<0$ and using the signs rule by Descartes, the sign of the coefficients of the quadratic Equation (31) changes twice. So there are two unique positive equilibria point. Consequently, Z_a^{*} has two positive endemic turning points, implying that at $R_0<1$ there is a possibility for the model to exhibit backward bifurcation. So the existence of the threshold R_c is assumed in the result.

4.4. Bifurcation Analysis of the Endemic Equilibria

Backward bifurcation plays a fundamental role in controlling and eradicating diseases. Backward bifurcation occurs in models that have multiple equilibria when $R_0<1$. Consequently, having $R_0<1$ is important but not a sufficient indicator for the control and elimination of the infection [21]. Therefore, there is need to reduce the basic reproductive to avoid endemic states and in turn guarantee viral elimination [22]. Various researchers [23], [24] have established that HIV dynamics models exhibit backward bifurcation phenomenon where the stable virions-free equilibrium co-exist with an endemic equilibrium, for $R_0<1$. This section focuses on bifurcations of the model in order to analyze the stability of the endemic equilibrium point. In many epidemic models, the virions-free equilibrium loses the stability when $R_0>1$, which results in a bifurcation. From the model (1) we have critical R_0 denoted by R_c as;

$$R_c=\frac{\beta\lambda_T\left(\mu_{Za}\mu_I+\alpha\lambda_Z\right)}{\mu_{Za}\mu_I\left(\mu_Z\mu_I-\beta\lambda_T\right)} \tag{46}$$

If $R_c>1$ in Equation (46) then we have a forward bifurcation and if $R_c<1$ then the model exhibit backward bifurcation. It is important to note that existence of a backward bifurcation with endemic equilibrium when $R_c<1$ is very important in epidemiological applications. Notably, it has very important consequences in the strategies and control policies designed for HIV viral eradication. From the epidemiological point of view reducing R_0 below unity is no longer a guarantee that the HIV virions will be eliminated completely or reduced to non-detectable level. In addition, this affects HIV virus control since the disease progresses even when $R_0<1$. Furthermore, existence of backward bifurcation may result to a model that is globally unstable. From Equation (46) backward bifurcation is only possible if the rate μ_I at which the infected $CD4^+$ T-cells dies increases. From model (1) the infected cells may either die naturally

or they can be destroyed and killed by the activated $CD8^+$ T-cells. Another parameter of interest as far as backward bifurcation is concerned is the β, the rate at which the $CD8^+$ T-cells are activated. Reducing β would lead to backward bifurcation. Biologically, bi-stability may lead to unexpected adverse consequences for ARTs and backward bifurcation may provide an explanation for several phenomena observed clinically among HIV patients.

Epidemiological Implication of Backward Bifurcation

It is paramount to carry out a deep discussion under epidemiological point of view. From the results it is evident that the bifurcation depends mainly on immunity of the infected person and Treatment, that is, efficacy of the ARTs. Use of ARTs as a way of managing an HIV persons may help in reducing the transmission rate. However, this may only be possible if the person adhere to the drugs. In the model the transmission rate is presented by χ. For the immunity of the infected person it is important to analyze the role played by the $CD8^+$ T-cells. From (46) it can be seen clearly the immune cells plays a very vital role. Therefore, it is fundamental, for HIV eradication, to find ways in which the immunity of the infected person may be boosted. This may be done through proper diet or through use of prescribed medication. Thus it is very important to education people living with HIV/AIDS (PLWHAs) on proper nutrition and the availability on the drugs to boost the immunity.

From the point of HIV virions eradication public policy makers must work to ensure information education material (IEC) are available in all public places. They must also ensure that the drugs are accessible and available. This may play a major role in ensuring that the backward bifurcation scenario are avoided.

In summary if the backward bifurcation cannot be avoided, public policy makers have to particularly be careful since having $R_0 < 1$ does not guarantee that the viral load may get to non-detectable level, the disease might eventually progress to AIDS. However, from the numerical values used in model (1) results to a forward bifurcation as shown in the **Figure 4** From an epidemiological point of view, forward bifurcations means that when $R_0 < 1$ small perturbations from E_0 are unable to generate an endemic disease.in addition, when $R_0 > 1$, such small perturbations move the system (1) away from VFE the epidemic outbreak takes place and the disease might stabilize in an endemic state.

Remark 2. *The existence of a backward bifurcation shows that even if* $R_0 < 1$ *by some control measures, HIV may still persist. The control of HIV becomes more difficult.*

4.5. Global Stability of the Virions-Free Equilibrium

Using the approach of [25] we investigate the global stability of the virions-free equilibrium for the model (1). Using this approach we list two conditions that if met will guarantee the global asymptotic stability of the virions-free equilibrium.

Theorem 4. *Suppose we can express model* (1) *as*;

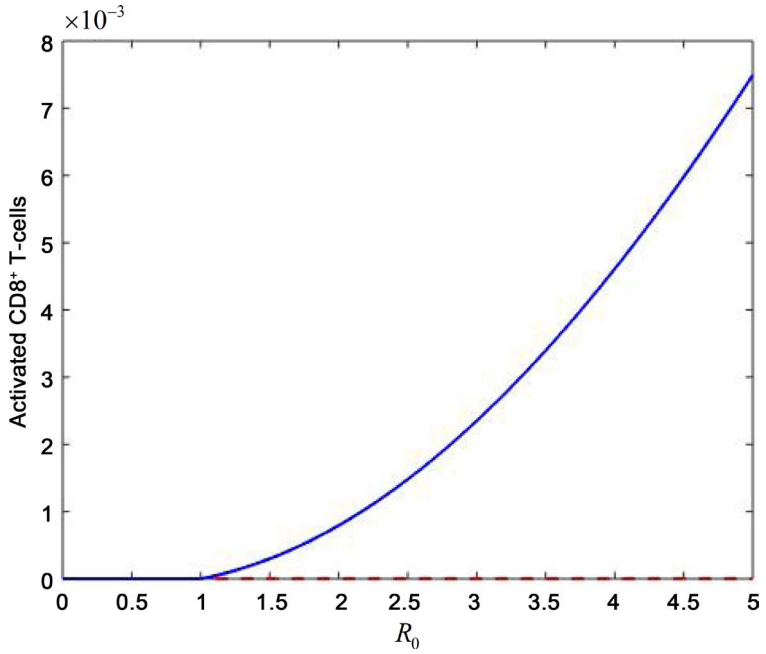


Figure 4. Forward bifurcation (the blue lines denote stability while the red line denote instability).

$$\begin{aligned}\frac{\mathrm{d}X}{\mathrm{d}t} &= H(X,W)\\ \frac{\mathrm{d}Z}{\mathrm{d}t} &= G(X,W)\end{aligned} \tag{47}$$

such that,

$$G(X,0)=0 \tag{48}$$

where the column vector components of $X \in R^M$ denote the uninfected population and the components of $W \in R^n$ denote the infected population. Let $E_0=(X^*,0)$ be the virions-free equilibrium for the system.

Then $E_0=(X^*,0)$ is globally asymptotically stable if and only if:

1) The $R_0<1$, that is, locally asymptotically stable.

2) $\frac{\mathrm{d}X}{\mathrm{d}t}=H(X,0)$, X^* is globally asymptotically stable.

3) $G(X,W)=PG-\hat{G}(X,W), \hat{G}(X,W)\geq 0$ for $(X,Z)\in\Omega_H$.

where $P=D_W G(X^*,0)$ represents an M-matrix (the off diagonal elements of P are non negative) and Ω_H is the feasible reqion for the model.

If model (1) satisfies the conditions mentioned above then the fixed point $E_0=(X^*,0)$ is a globally asymptotic stable equilibrium of model system (1) provided that $R_0<R_c$. For model (1) the result is stated and proved in Theorem 5.

Theorem 5. *The virions-free equilibrium point* $E_0=(X^*,0)$ *is a globally asymptotically stable equilibrium of system* (1) *provided that* $R_0<R_c$ *and the conditions* (2) *and* (3) *of Theorem* 4 *are satisfied.*

Proof. From the system (1) we let $X=(T,Z,Z_a)$ and $W=(I,V)$, then we

have;

$$H(X,0)=\begin{pmatrix}\lambda_T-\mu_T T\\ \lambda_Z-\mu_Z\\ -\mu_{Za}Z_a\end{pmatrix} \tag{49}$$

$$G(X,W)=PG-\hat{G}(X,W) \tag{50}$$

where

$$P=\begin{pmatrix}-\mu_I & \chi\dfrac{\lambda_T}{\mu_T}\\ \varepsilon_V\mu_I & -\mu_V\end{pmatrix} \tag{51}$$

and

$$\hat{G}=\begin{pmatrix}\alpha Z_a I & 0\\ 0 & 0\end{pmatrix} \tag{52}$$

Since $\alpha Z_a I \geq 0$ then, $\hat{G}(X,W)\geq 0$. In addition, the matrix P is an M-Matrix since all its off-diagonal elements are non-negative. This therefore, proves the global stability of the virions-free Equilibrium (E_0). That is, $X^*=\left(\dfrac{\lambda_T}{\mu_T},0,0,\dfrac{\lambda_Z}{\mu_Z},0\right)$ is globally asymptotic stable equilibrium solution of $\dfrac{\mathrm{d}X}{\mathrm{d}t}=H(X,0)$. Consequently, by Theorem 5, the disease free equilibrium of the model (1) is globally asymptomatically stable. □

Theorem 5 implies that when $R_0 < R_c$ a small influx of free HIV virions into the body cells, will not lead to AIDS. The subsequent numbers of those infected cells will be less than that of their predecessors and eventually the disease maybe reduced to non-detectable level.

5. Numerical Analysis

In order to observe the variables on the HIV model given in Equation (1) over a period of time, the study applied Matlab programming language. The initial values of the model were set as; $T_0=1000$, $I_0=10$, $V_0=1$, $Z_0=500$, $Z_{a0}=10$. This section is aimed at investigating numerically the behaviour of each compartment on the onset of infection without any medical treatment. The values for the parameter are described in **Table 3**.

Discussion

Figure 5 shows that at initial infection stage the level of the susceptible $CD4^+$ T-cells reduces for the first three months and later the body immunity stabilizes and the number of the susceptible $CD4^+$ T-cells increases. However, it fails to go back to the pre-infection stage. Clinicians have established that the depletion of $CD4^+$ T-cells is a indication of HIV infection. Clinicians have established that the first few weeks after infection the virus is characterized by inflammatory response including extreme flu like symptoms such as swollen nodes, fever, sore

Table 3. Parameters for *in-vivo* HIV model.

Parameters	Description	Value	Source
λ_T	The recruitment rate of non-infected $CD4^+$ T-cells produced per unit time	10 cell/mm^3/day	[26]
μ_T	The rate at which the non-infected $CD4^+$ T-cells decay	0.01 day^{-1}	[27]
χ	The rate at which the $CD4^+$ T-cells are infected by the virus	0.000024 mm^3 vir^{-1} day^{-1}	[8]
μ_I	The death rate of the infected $CD4^+$T-cells	0.5 day^{-1}	[28]
ε_V	The rate in which HIV virions are generated from the infected $CD4^+$T-cells	100 vir. $cell^{-1}$ day^{-1}	[2]
μ_V	The death rate of the infectious virus	3 day^{-1}	[2].
α	The rate at which the infected cells are eliminated by the activated $CD8^+$T-cells	0.02 day^{-1}	[9]
λ_Z	The rate at which the $CD8^+$ T-cells are produced per unit time	20 cell/mm^3/day	[9]
μ_Z	The death rate of the $CD8^+$ T-cells	0.06 day^{-1}	[9]
β	The rate at which the $CD8^+$ T-cells are activated by the presence of the virus and the infected $CD4^+$ T-cells	0.004 day^{-1}	[9]
μ_{Z_a}	The rate at which the activated defence cells decay	0.004 day^{-1}	[9]

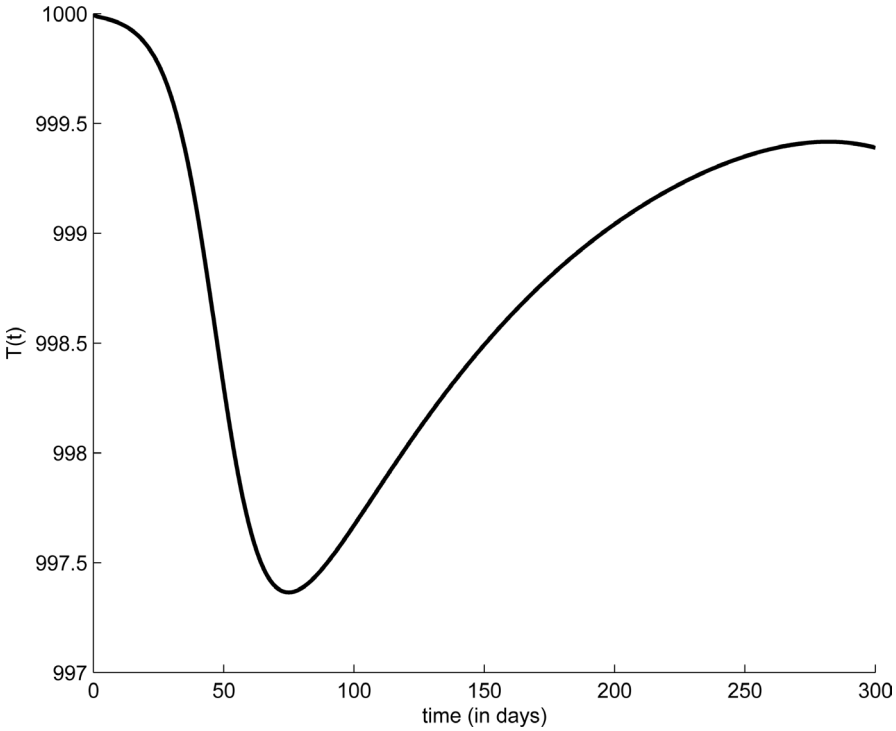


Figure 5. A Figure showing the number of the susceptible $CD4^+$ T-cells with change.

throat, rashes, muscles and joint pains and headache. This takes place up to the forth week. In this phase the natural immune response changes to "allergy-like" immune response replica of a mild anaphylactic reaction. Due to these changes the viral replication is high, infection of the $CD4^+$ T-cells is high and the activation of the $CD8^+$ T-cells and B-lymphocytes rises. As a result, the amount of $CD4^+$ T-cells falls very drastically. Later, due to the immune response, new $CD4^+$ T-cells are generated rapidly by the thymus to replace the already infected

ones and hence their level rise again as depicted by the Figure 5.

In Figure 6, the person has just been infected with HIV virions, the acute infection takes place two to four weeks later. At this time, when the HIV virions infect a few number of the susceptible $CD4^+$ T-cells, replications take place and new HIV virions are produced. The high number of infectious virions attaches themselves to the membrane of the $CD4^+$ T-cells infecting them. The cycle continues and more virions are produced hence more $CD4^+$ T-cells are infected. This explains why the number of the infected $CD4^+$ T-cells increases rapidly for the first 2 months as depicted by the Figure 6. Meanwhile at this stage the body is relaying on the natural immune response while waiting for the $CD4^+$ T-cells Adaptive Immune response. Consequently, the adaptive immune response sets in and kill most of the infected $CD4^+$ T-cells causing a drastic fall on the number of infected $CD4^+$ T-cells to almost nil as depicted in the Figure 6. Unfortunately, a few mutants develop. The new mutants start infecting the uninfected $CD4^+$ T-cells. As a result to this the infected $CD4^+$ T-cells count rises but at a slower rate. After 300 days the level start to rise again.

Figure 7 shows that at early HIV infection stage the level of the HIV virions reduces to almost zero during. This is the phase in which the virions attaches themselves to the membrane of the $CD4^+$ T-cells. However, after about three days the infected $CD4^+$ T-cells burst releasing infectious HIV virus. This explain why at acute stage of infection, large number of HIV virions are produced in the

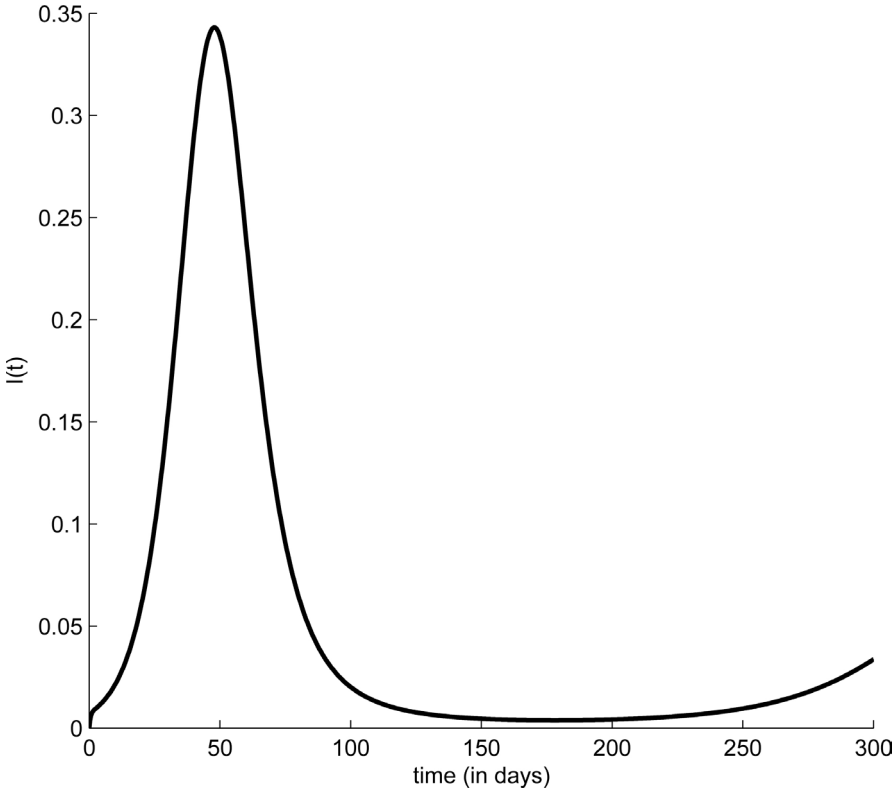


Figure 6. A Figure showing the population of the infected $CD4^+$T-cells with respect to time.

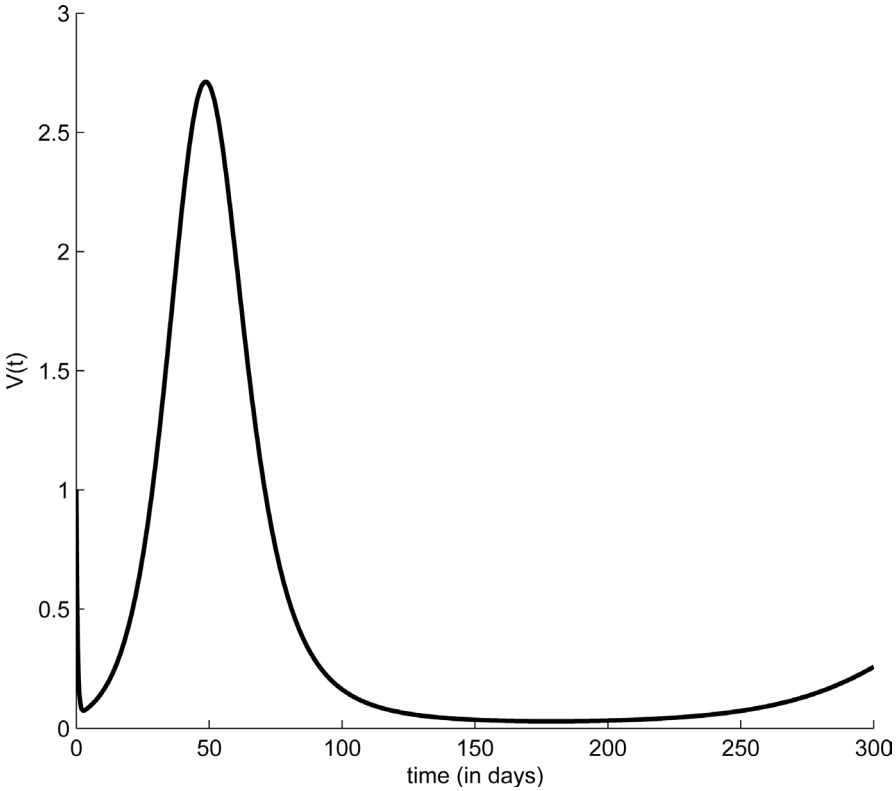


Figure 7. A Figure showing the number of the HIV virions with respect to time.

patients body. With time the HIV virions continue to replicate and infecting more $CD4^+$ T-cells. This explains the decline on the level of the susceptible $CD4^+$ T-cells as depicted in **Figure 5**. However, after the immune response sets in it destroys the infected cells, suppresses viral replication and inhibits more production of the infectious virus since the cells available for infection are decimated. Furthermore, comparing **Figure 5** and **Figure 7** the number of HIV virions reduces as the number of the susceptible $CD4^+$ T-cells this is contrarily to the work done by [29]. Their study, which has been criticized by many researches, established that the fall of the viral load was due to a decline in the target cells ($CD4^+$ T-cells), a process called target cell limitation. Consequently, due to the incerase on the number of the infected $CD4^+$ T-cells, a signal is sent to the $CD8^+$ T-cell and consequently the cells are activated to kill the infected cells. This helps in reducing the level of the viral load in the body. The number of the $CD4^+$ T-cells count begins to increase during this point, though it may never return to the pre-infection levels. It may be paramount for the patient to begin ARTs during this stage. The virus level cannot reduce to non-detectable level since it is very difficult to control the HIV virions free in circulation when not attached to the $CD4^+$ T-cells.

In **Figure 8** we monitor the change in the number of $CD8^+$ T-cells during initial infection stage. From **Figure 8** the level of $CD8^+$ T-cells reduces during for the first three months. This may be due to the fact that a big number of the $CD8^+$ T-cells die within few weeks, leaving a reservoir of $CD8^+$ memory T-cells which

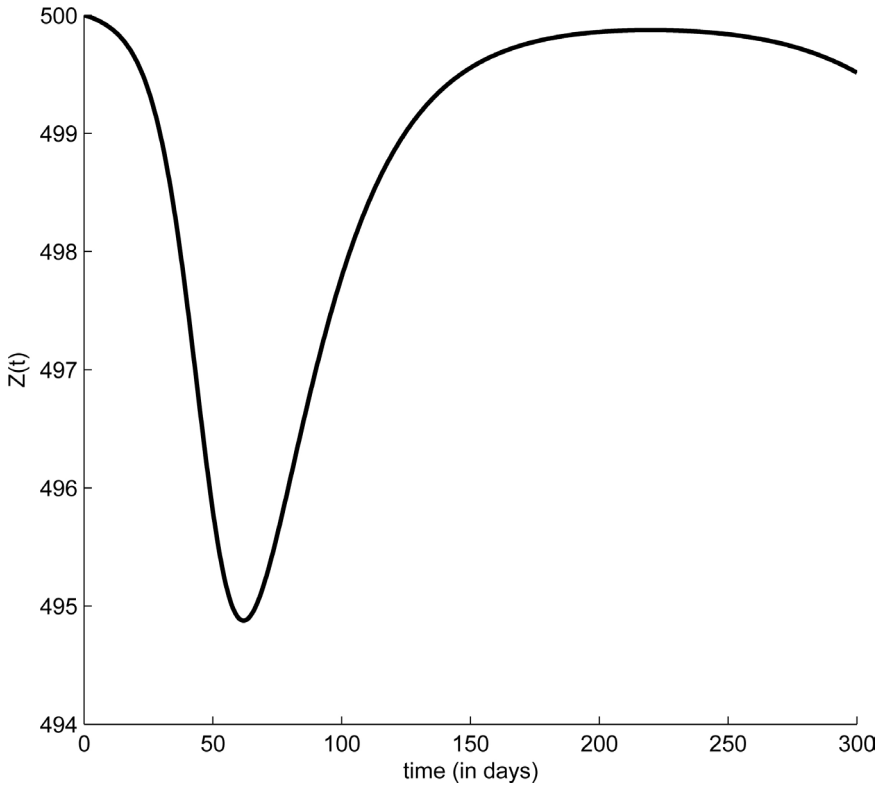


Figure 8. A Figure showing the number of $CD8^+$ T-cells with respect to time.

are HIV-specific which persist, irrespective of the presence of antigen or $CD4^+$ T-cells. In addition, many of the cells get activated to fight the virus. However, after three months the number increases gradually, this is because of the reduction of the viral load and the infected $CD4^+$ T-cells.

In **Figure 9**, we monitor the number of the activated $CD8^+$ T-cells. The number of the activated cells rises after the first 3 days. This correspond to the time in which the infected $CD4^+$ T-cells start to increase. Most of the cells are activated to kill the infected T-cells and consequently control the viral replication. According to [30] $CD4^+$ T-cells plays an important role in the initiation and persistence of $CD8^+$ T-cells responses. The $CD8^+$ T-cell activation can lead to a number of immune responses such as antibody production, activation of phagocytic cells and direct cell killing. Therefore, the best immune response for different types of diseases is implemented by natural mechanism. $CD8^+$ T-cells have been shown to express $CD4^+$ T-cells receptors on their surface after activation through the T-cell receptor, allowing infection by HIV. Some researchers such as [28] suggest this is a mechanism through which $CD8^+$ T-cells get destroyed late in infection. From **Figure 9** it is evident that during infection most of the $CD8^+$T-cells get activated to fight the virus. This explain the exponential rise.

6. Conclusion

In this paper, we have presented an *in-vivo* HIV dynamics model with inclusion

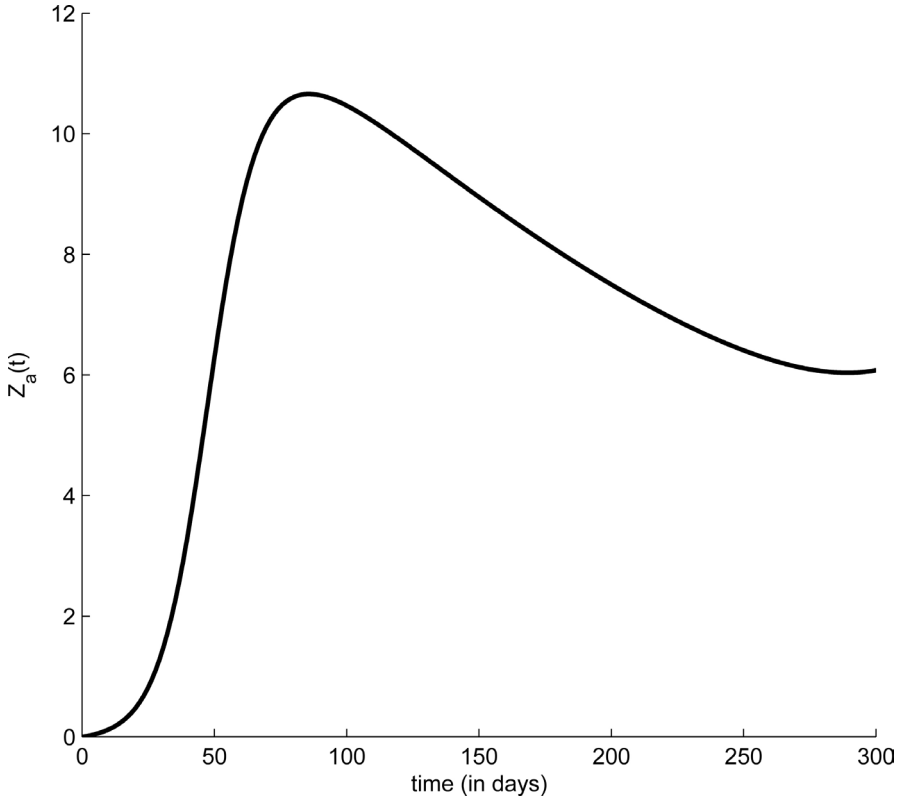


Figure 9. A Figure showing the number of the activated $CD8^+$ T-cells with respect to time.

of the $CD8^+$ T-cells. We first showed that the key variables of the model were non-negative and bounded to ensure that it is biologically relevant. We have computed the expression for the basic reproductive number R_0 and the equilibria of the model. It is evident that the rate of infection greatly influences the basic reproductive number. The mathematical analysis of the model showed the existence of virions-free equilibrium. In addition, the system exhibits backward and trans-critical bifurcation under some restriction on parameters. This shows that having $R_0 < 1$ is not enough to eradicate the HIV-virions to non-detectable level. Numerical analysis were done to give more insight regarding the model. The results clearly show the introduction of HIV virions in the body without the use of ARTs does not mean that the disease is likely to persist in the body. The body have a way of reducing the HIV virions to very low level after three months of infection. This is in agreement with the biological mechanism of the HIV-cells interaction. However, as much as it is so in this study, the parameters were not varied; this means that the behavior might slightly be different between individuals. Furthermore, the simulations for the model have showed the importannce of the $CD8^+$ T-cells in fighting the HIV virions. At the primary phase of HIV infection, there is an increase in the level viral load and a reduction in the population of the $CD4^+$ T-cells, which reduces after three months due to the presence of the killer cells. However, as much as this study has only established the role played by the immune cells at the acute

infection other researches such as [31] has shown that patients who fail to develop HIV/AIDS after 15 years or longer have significantly higher levels of immune cells compared to a normal HIV-infected patients. Therefore, it is fundamental to maintain a high population of the immune cells which in turn will lead to low level of the viral load. In addition, due to the high increase of the virions during the first three months it is important to introduce ARTs to prevent HIV transmission. This will help in the reduction of new infection.

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Research Article

The *In Vivo* Dynamics of HIV Infection with the Influence of Cytotoxic T Lymphocyte Cells

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The *in vivo* dynamics of HIV infection, the infection mechanism, the cell types infected, and the role played by the cytotoxic cells are poorly understood. This paper uses mathematical modelling as a tool to investigate and analyze the immune system dynamics in the presence of HIV infection. We formulate a six-dimensional model of nonlinear ordinary differential equations derived from known biological interaction mechanisms between the immune cells and the HIV virions. The existence and uniqueness as well as positivity and boundedness of the solutions to the differential equations are proved. Furthermore, the disease-free reproduction number is derived and the local asymptotic stability of the model investigated. In addition, numerical analysis is carried out to illustrate the importance of having $R_0 < 1$. Lastly, the biological dynamics of HIV *in vivo* infection are graphically represented. The results indicate that, at acute infection, the cytotoxic T-cells play a paramount role in reducing HIV viral replication. In addition, the results emphasize the importance of developing controls, interventions, and management policies that when implemented would lead to viral suppression during acute infection.

1. Introduction

For the last three decades Human Immunodeficiency Virus (HIV) has been a big challenge in the whole world though its impact is mostly felt in Sub-Saharan Africa. Over 36 million people have been infected since early 1980s and over 25 million of died [1]. Due to the high mortality associated with the virus, HIV has become a major problem for human Health. Many researchers [2–5] have sought to analyze the infection mechanism of the virus. It has been found that HIV targets and infects $CD4^+$ T-cells. This is because $CD4^+$ T-cells have a protein on its surface that can bind to foreign substances such as HIV, that is, through exploitation of the CCR5 and CXCR4 coreceptors expressed on their surfaces. Once inside the $CD4^+$ T-cells, the HIV, which is a retrovirus, is converted to DNA. The virus then multiplies inside the cells that burst releasing more mature virions. This in turn triggers the thymus to produce more $CD4^+$ T-cells. Consequently, more HIV virions are produced. Hence, the major hallmarks of HIV infection include the destruction of helper $CD4^+$ T lymphocytes and subsequent loss of immune competence. HIV virions in particular weakens the cell function by damaging the helper cells necessary in building a robust immune response. Depletion of the $CD4^+$ T-cells results in a weakened immune system [6].

During the initial infection stage, high level of viral replication takes place lasting for about three to six weeks upon infection [3]. This period is followed by the asymptomatic stage which is characterized by high level of immune response; this helps in stabilizing the viral load in the infected person. This stage lasts for several years and varies from patient to patient. It is important to note that during this period the infected person shows no sign of the infection. However, if not treated the virus may progress to disease/symptomatic/AIDS stage. This is when the body is prone to many opportunistic infections. It is characterized by a decrease in the number of $CD4^+$ T-cells and an increase in the viral load. In addition, within-host virus genetic diversity decreases [7, 8].

Mathematicians in the field of epidemiological modelling have developed models to analyze the HIV infection mechanism *in vivo*. These models have provided important insights into diseases behaviors and how best it could be controlled. To date, mathematical modelling has become

a paramount tool, in understanding the dynamics of HIV and in decision making processes regarding intervention programmes for controlling and managing the virus in many countries. Arruda et al. [9] proposed and analyzed a five-dimensional model for HIV infection *in vivo* with the inclusion of the $CD8^+$ T-cells. As much as the study included the activation process in the *in vivo* model the argument that the $CD8^+$ T-cells kills the virus directly is clinically wrong. Hattaf and Yousfi [10] analyzed an *in vivo* HIV model. However, the model only included the $CD4^+$ T-cells and the virus and omitted the infected $CD4^+$ T-cells. Ogunlaran and Oukouomi Noutchie [11] analyzed a three-dimensional model, which included the $CD4^+$ T-cells, the infected $CD4^+$ T-cells, and the HIV virions. This study was more interested in establishing how to maximize the number of the infected cells after introduction of ARTs. Nonetheless, the study failed to put in account the role played by the $CD8^+$ T-cells in fighting the virions. Omission of such important variables in the model paints the wrong picture of the disease dynamics. The question of the role played by one's immune system could not be answered by such a model.

Zarei et al. [12] developed a five-dimensional *in vivo* HIV model. The study included concentration of healthy $CD4^+$ T-cells, concentration of infected $CD4^+$ T-cells, and cytotoxic T-cells which were divided into precursors CTLp and effectors and the free virus particles. This study assumed that cytotoxic T lymphocyte (CTL) response depends on $CD4^+$ T-cell help and that HIV virions impairs T-helper cell function. Consequently, the proliferation of the CTLp population is proportional to both infected cells in the body and the number of uninfected T-helper cells. The simulated results indicated the importance of the CTL cells in the HIV model. The study had some few shortcomings since it failed to account for the resistant and the wild type $CD4^+$ T-cells. The rate in which the two types of the $CD4^+$ T-cells are infected by the HIV virions is quite different, hence the need to include them in the model.

Zhuang and Zhu [13] analyzed a three-dimensional in-host HIV model. As much as this model was so basic since it had only three compartments it brought out important insight as far as HIV dynamics are concerned. The time lag from infection of the $CD4^+$ T-cells to the cells becoming actively infected was included in the model. The consideration of such a parameter is very important in HIV research. The study established the global existence of bifurcating periodic solutions with the assistance of global Hopf bifurcation theory. The numerical results in the study indicated that the latent period plays an important role in the disease spread and the disease may be controlled by shortening it.

Ngina et al. [3] analyzed a five-dimensional in-host model. The results from the study established the importance of the $CD8^+$ T-cells in controlling HIV viral progression. The stability analysis of the model indicated the presence of backward bifurcation implying that having $R_0 < 1$ does not guarantee eradication of the virus in the body.

This study wishes to improve the research by Ngina et al. [3] by introducing the wild type and and the resistant $CD4^+$ T-cells. The study will also be aimed at addressing the gaps noted from the cited literature.

2. Model Description

We shall put into consideration a mathematical model for the *in vivo* interaction of the HIV virions and the immune system cells. The model is classified into six compartments. The following are the variables used in the model: the wild type healthy $CD4^+$ T-cells (T_w); resistant type healthy $CD4^+$ T-cells (T_r); the infectious HIV virus particles (V); the already infected $CD4^+$ T-cells (I); and the cytotoxic T-cells (CTL), that is, $CD8^+$ T-cells (Z) and the activated cytotoxic T-cells (Z_a).

The wild type healthy $CD4^+$ T-cells are recruited at a constant rate λ_{T_w} from the thymus and die naturally at a constant rate μ_{T_w}. These cells are infected by the virus at the rate $\chi_w T_w V$. The resistant type healthy $CD4^+$ T-cells are recruited from the thymus at a constant rate λ_{T_r} and die naturally at a constant rate μ_{T_r}. These cells are infected by the virus at the rate $\chi_r T_r V$. The infected $CD4^+$ T-cells result from the infection of both the wild and resistant type healthy $CD4^+$ T-cells and die at a rate $\mu_I I$, and are killed by activated cytotoxic T-cells at the rate $\alpha I Z_a$. They could also be recruited directly from the thymus at a constant rate λ_Z. Clinical finding indicates that CTL response depends on infected $CD4^+$ T-cells. Consequently, the recruitment into the population of the CTL cells is given by cZI. This results from the stimulation by the viral antigen of the infected cells. CTLs are activated at the rate βZI. Due to the absence of the viral antigen the CTL T-cells die at the rate $\mu_Z Z$ while the activated CTL cells die at the rate $\mu_{Z_a} Z_a$. The free HIV virions are produced by the infected $CD4^+$ T-cells at the rate $\epsilon_V \mu_I I$ and they die at the rate $\mu_V V$.

$$\begin{aligned}
\frac{dT_w}{dt} &= \lambda_{T_w} - \mu_{T_w} T_w - \chi_w T_w V,\\
\frac{dT_r}{dt} &= \lambda_{T_r} - \mu_{T_r} T_w - \chi_r T_r V,\\
\frac{dI}{dt} &= V\left(\chi_w T_w + \chi_r T_r\right) - \mu_I I - \alpha I Z_a,\\
\frac{dV}{dt} &= \epsilon_V \mu_I I - \mu_V V,\\
\frac{dZ}{dt} &= \lambda_Z + cZI - \mu_Z Z - \beta ZI,\\
\frac{dZ_a}{dt} &= \beta ZI - \mu_{Z_a} Z_a.
\end{aligned} \tag{1}$$

The parameters used in model (1) are described in Table 1

3. Properties of the HIV Model

3.1. Positivity of Solutions. The *in vivo* HIV model monitors cell population. Hence, there is a need to prove that the state variables for model (1) remain nonnegative. In particular we show that, with nonnegative initial conditions, the solutions of model (1) will remain nonnegative for all time values $t \geq 0$. We thus have the following theorem.

Table 1: Parameters for *in vivo* HIV dynamics with therapy model.

Parameter	Description
λ_{T_w}	The rate at which the wild type non-infected $CD4^+$ T-cells are produced.
λ_{T_r}	The production rate of the resistant type non-infected $CD4^+$ T-cells per unit time.
χ_w	The rate at which the wild type $CD4^+$ T-cells are infected by the HIV virions.
χ_r	The rate at which the resistant $CD4^+$ T-cells are infected by the HIV virions.
μ_{T_w}	The death rate of the wild type $CD4^+$ T-cells.
μ_{T_r}	The death rate of the resistant type $CD4^+$ T-cells.
μ_I	The death rate of the infected $CD4^+$ T-cells.
ϵ_V	The number of virions releases per bursting infected cells.
μ_V	The death rate of the infectious virus.
α	The rate at which the infected cells are eliminated by the activated CTL T-cells.
c	Proliferation rate of CTL T-cells.
λ_Z	The rate at which the cytotoxic T-cells are produced.
μ_Z	The death rate of the CTL T-cells.
β	The rate at which the CTL T-cells are activated due to the presence infected $CD4^+$ T-cells.
μ_{Z_a}	The rate at which the activated defense cells decay.

Theorem 1. *Let the parameters for model (1) be nonnegative constants. A nonnegative solution* $(T_w(t), T_r(t), I(t), V(t), Z(t), Z_a(t))$ *for model (1) exists for all state variable with nonnegative initial conditions* $(T_w(0) \geq 0,\ T_r \geq 0,\ I(0) \geq 0,\ V(0) \geq 0,\ Z(0) \geq 0,\ Z_a \geq 0)$ *for all* $t \geq 0$.

Proof. From the first equation of model (1) we have

$$\begin{aligned}\frac{dT_w}{dt} &= \lambda_{T_w} - \mu_{T_w}T_w - \chi_w T_w V \\ &= \lambda_{T_w} - \left(\mu_{T_w} + \chi_w V\right)T_w > -\left(\mu_{T_w} + \chi_w V\right)T_w.\end{aligned} \tag{2}$$

By separation of variable method we have

$$\frac{dT_w}{T_w} > -\left(\mu_{T_w} + \chi_w V\right)dt. \tag{3}$$

Integrating (3) we have

$$T_w > Ce^{-\int_0^t (\mu_{T_w} + \chi_w V(s))ds}. \tag{4}$$

Taking the initial conditions at $t = 0$ and $T_w(0) = T_{w_0}$ then from (4) we have

$$C = T_{w_0}. \tag{5}$$

Therefore, (4) can be written as

$$T_w > T_{w_0}e^{-\int_0^t (\mu_{T_w} + \chi_w V(s))ds}. \tag{6}$$

Thus,

$$T_w(t) > 0 \quad \forall t \geq 0. \tag{7}$$

Similarly, using the same argument, it can be shown that the state variables $T_r(t) > 0, I(t) > 0, V(t) > 0, Z(t) > 0, Z_a(t) > 0$ are nonnegative for all $t > 0$. Therefore, the solutions of system (1) remain positive for all $t \geq 0$. This completes the proof. □

3.2. Boundedness of Solutions

Theorem 2. *All solutions* $(T_w(t), T_r(t), I(t), Z(t), Z_a(t)) \in \mathbb{R}^6$ *of model (1) are bounded and there exists a biological feasible region* Γ *for model (1) given as*

$$\begin{aligned}\Gamma = \Big\{&\left(T_w(t), T_r, I(t), V(t), Z(t), Z_a(t)\right) \\ &\in \mathbb{R}^6 \mid T_w(t) > 0,\ T_r(t) > 0,\ I(t) > 0,\ V(t) \\ &> 0,\ Z(t) > 0,\ Z_a(t) > 0\Big\}.\end{aligned} \tag{8}$$

Proof. The total population of the $CD4^+$ T-cells, $T_w + T_r + I = N_4(t)$, is a nonconstant value. Hence, according to (1), the evolution equation representing the change in the population of the $CD4^+$ T-cells is given by

$$\begin{aligned}\frac{dN_4(t)}{dt} &= \lambda_{T_w} + \lambda_{T_r} - \mu_{T_w}T_w - \mu_{T_r}T_r - \left(\mu_I + \alpha Z_a\right)I, \\ \frac{dN_4(t)}{dt} &\leq \lambda_{T_w} + \lambda_{T_r} - \mu_{T_w}T_w - \mu_{T_r}T_r - \mu_I I, \\ \frac{dN_4(t)}{dt} &\leq \lambda_{T_w} + \lambda_{T_r} - \left(\mu_{T_w} + \mu_{T_r} + \mu_I\right)N_4(t).\end{aligned} \tag{9}$$

We solve (9) using the separation of variable method for solving differential inequality.

$$\frac{dN_4(t)}{dt} + \left(\mu_{T_w} + \mu_{T_r} + \mu_I\right)N_4(t) \leq \lambda_{T_w} + \lambda_{T_r}. \tag{10}$$

Integrating factor for (10) is given by

$$\text{I.F} = e^{(\mu_{T_w} + \mu_{T_r} + \mu_I)t}. \tag{11}$$

Multiplying (10) by the integrating factor given in (11) we have,

$$N_4(t)\,e^{(\mu_{T_w} + \mu_{T_r} + \mu_I)t} \leq \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I}e^{(\mu_{T_w} + \mu_{T_r} + \mu_I)t} + C. \tag{12}$$

Applying the initial condition in (12), at $t = 0$, and letting $N(0) = N_{4_0}$, we obtain

$$N_{4_0} = \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I} + C. \tag{13}$$

Hence,

$$C = N_{4_0} - \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I} \tag{14}$$

Substituting (14) into (12) we have

$$\begin{aligned} N_4(t) &\le e^{-(\mu_{T_w}+\mu_{T_r}+\mu_I)t}\left[\frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I} e^{(\mu_{T_w}+\mu_{T_r}+\mu_I)t}\right. \\ &\left. + N_{4_0} - \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I}\right], \\ N_4(t) &\le \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I} + \left(N_{4_0} - \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I}\right) \\ &\cdot e^{-(\mu_{T_w}+\mu_{T_r}+\mu_I)t} \end{aligned} \tag{15}$$

As $t \to \infty$ (15) becomes

$$\lim_{t\to\infty} N_4(t) \le \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r} + \mu_I}. \tag{16}$$

Similarly as $t \to 0$ (15) becomes

$$\lim_{t\to 0} N_4(t) \le N_{4_0}. \tag{17}$$

From (16) and (17) we conclude that $N_4(t)$ is bounded above by

$$N_4(t) \le \max\left\{N_{4_0}, Q\right\}, \tag{18}$$

where $Q = (\lambda_{T_w} + \lambda_{T_r})/(\mu_{T_w} + \mu_{T_r} + \mu_I)$.

From (18) the state variables describing the evolution of the total population of the $CD4^+$ T-cells are less than or equal to the ratio of the recruitment rate and the decay rate.

The same procedure can be used to show that all the state variables are bounded. Since all state variables are positive and bounded in $\mathbb{R}^6$, then the region Γ is positively invariant.

Remark 3. The biologically feasible region Γ for model (1) defined by the compact set

$$\begin{aligned} \Gamma = \Big\{&\left(T_w(t), T_r, I(t), V(t), Z(t), Z_a(t)\right) \in \mathbb{R}^6,\ T_w \\ &+ T_r + I \le \frac{\lambda_{T_w} + \lambda_{T_r}}{\mu_{T_w} + \mu_{T_r}},\ Z + Z_a \le \frac{\lambda_Z}{\mu_Z},\ V \le \frac{\varepsilon_V \mu_I \lambda_T}{\mu_T \mu_V} \\ &+ V_0\Big\} \end{aligned} \tag{19}$$

with initial conditions $T_w(0), T_r(0), I(0), V(0), Z(0), Z_a(0) > 0$ is positively invariant and attracting for all $t > 0$. The domain Γ is positively invariant under the flow induced by the system (1). Therefore, system (1) is biologically meaningful and it is feasible to analyse the model in the domain Γ. □

4. Disease-Free Equilibrium and Its Stability

The disease-free equilibrium point occurs when there is no infection in the body and hence it is obtained by setting infectious classes in (1) to zero; that is, $V = I = Z_a = 0$,

$$\begin{aligned} E_0 &= (T_{w0}, T_{r0}, 0, 0, Z_0, 0) \\ &= \left(\frac{\lambda_{T_w}}{\mu_{T_w}}, \frac{\lambda_{T_r}}{\mu_{T_r}}, 0, 0, \frac{\lambda_Z}{\mu_Z}, 0\right). \end{aligned} \tag{20}$$

4.1. Basic Reproductive Number. We apply the next generation matrix method for the derivation of R_0 [16]. R_0 is given by $R_0 = \rho(FV^{-1})$, where ρ is defined as the spectral radius of the next generation matrix [17] and F represents the appearance of new infections while V is the rate of transfer of the infections [18]. Using the Van den Driessche and Watmough [18] method we have three infection classes, that is, $I(t), V(t)$, and $Z(t)$, and hence the matrix of new infections is given by

$$F = \begin{bmatrix} 0 & \dfrac{\chi_w \lambda_{T_w}}{\mu_{T_w}} + \dfrac{\chi_r \lambda_{T_r}}{\mu_{T_r}} & 0 \\ 0 & 0 & 0 \\ c\dfrac{\lambda_Z}{\mu_Z} & 0 & 0 \end{bmatrix}. \tag{21}$$

The matrix that represents the transfer of the infections between compartments at the disease-free equilibrium is given by

$$V = \begin{bmatrix} \mu_I & 0 & 0 \\ -\epsilon_V \mu_I & \mu_V & 0 \\ \beta\dfrac{\lambda_Z}{\mu_Z} & 0 & \mu_Z \end{bmatrix}. \tag{22}$$

The inverse of V^{-1} is given by

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\mu_I} & 0 & 0 \\ \dfrac{\epsilon_V}{\mu_V} & \dfrac{1}{\mu_V} & 0 \\ -\beta\dfrac{\lambda_Z}{\mu_I \mu_Z^2} & 0 & \dfrac{1}{\mu_Z} \end{bmatrix}. \tag{23}$$

The next generation matrix FV^{-1} is given by

$$\begin{aligned} &FV^{-1} \\ &= \begin{bmatrix} \left(\dfrac{\chi_w \lambda_{T_w}}{\mu_{T_w}} + \dfrac{\chi_r \lambda_{T_r}}{\mu_{T_r}}\right)\dfrac{\epsilon_V}{\mu_V} & \left(\dfrac{\chi_w \lambda_{T_w}}{\mu_{T_r}} + \dfrac{\chi_r \lambda_{T_r}}{\mu_{T_r}}\right)\dfrac{1}{\mu_V} & 0 \\ 0 & 0 & 0 \\ c\dfrac{\lambda_Z}{\mu_Z}\dfrac{1}{\mu_I} & 0 & 0 \end{bmatrix}. \end{aligned} \tag{24}$$

The eigenvalues for the matrix given by (24) are 0, 0 and $((\lambda_w \mu_{T_r} \chi_{T_w} + \lambda_{T_r} \mu_{T_w} \chi_{T_r})/\mu_{T_r} \mu_{T_w} \mu_V)\epsilon_V$.

Thus the reproductive number R_0, which is given by the greatest eigenvalue, is

$$R_0 = \left(\frac{\lambda_w \mu_{T_r} \chi_{T_w} + \lambda_{T_r} \mu_{T_w} \chi_{T_r}}{\mu_{T_r} \mu_{T_w} \mu_V} \right) \epsilon_V = \left(\frac{\lambda_{T_w} \chi_{T_w}}{\mu_{T_w}} + \frac{\lambda_{T_r} \chi_{T_r}}{\mu_{T_r}} \right) \frac{\epsilon_V}{\mu_V}. \tag{25}$$

R_0 as given by (25) represents the number of secondary infection that results from a single infected cell over its average life time $1/\mu_V$. In addition, it is important to note that the infection will die out if $R_0 < 1$ while the HIV infection may become endemic if $R_0 > 1$.

4.2. Sensitivity Analysis of R_0 with respect to the Model Parameters. The aim of researchers especially in the field of HIV modelling is to understand the dynamics of HIV so as to control it. This is mainly done by targeting some parameters to which R_0 is sensitive.

We apply the normalized forward index method in the analysis. The normalized forward sensitivity index of R_0 with respect to the parameter P is given by

$$\frac{\partial R_0}{\partial P} * \frac{P}{R_0}, \tag{26}$$

where P represents the parameters on the basic reproductive number. From the basic reproductive number given by (25) we get

$$\begin{aligned}
\frac{\partial R_0}{\partial \lambda_{T_w}} \frac{\lambda_{T_w}}{R_0} &= \frac{\chi_{T_w} \lambda_{T_w} \mu_{T_r}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \lambda_{T_r}} \frac{\lambda_{T_r}}{R_0} &= \frac{\chi_{T_r} \lambda_{T_r} \mu_{T_w}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \chi_{T_w}} \frac{\chi_{T_w}}{R_0} &= \frac{\chi_{T_w} \lambda_{T_w} \mu_{T_r}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \chi_{T_r}} \frac{\chi_{T_r}}{R_0} &= \frac{\chi_{T_r} \lambda_{T_r} \mu_{T_w}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \mu_{T_w}} \frac{\mu_{T_w}}{R_0} &= -\frac{\chi_{T_w} \lambda_{T_w} \mu_{T_r}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \mu_{T_r}} \frac{\mu_{T_r}}{R_0} &= -\frac{\chi_{T_r} \lambda_{T_r} \mu_{T_w}}{\lambda_{T_w} \chi_{T_W} \mu_{T_r} + \lambda_{T_r} \chi_{T_r} \mu_{T_w}}, \\
\frac{\partial R_0}{\partial \epsilon_V} \frac{\epsilon_V}{R_0} &= 1, \\
\frac{\partial R_0}{\partial \mu_V} \frac{\mu_V}{R_0} &= -1.
\end{aligned} \tag{27}$$

From the sensitivity index represented as in Table 2 it is evident that ϵ_V is the most positively sensitive parameter. This means that to maintain a small number on R_0 we have to reduce this parameter whereas increasing these parameters will lead to an increase in the R_0 whereas μ_V is the most negatively sensitive parameter. This means that increasing this parameter will decrease the value of R_0.

Table 2: Sensitivity indices of R_0 evaluated at the baseline parameter.

Parameters	Parameter value	sensitivity index
λ_{T_w}	10	0.428724544
λ_{T_r}	0.03198	0.571275455
χ_{T_w}	0.000024	0.428724544
χ_{T_r}	0.01	0.571275455
μ_{T_w}	0.01	−0.428724544
μ_{T_r}	0.01	−0.571275455
ϵ_V	100	1
μ_V	3	−1

Table 3: Parameters for *in vivo* HIV model.

Parameters	Value	Source
λ_{T_w}	10 cell/mm^3/day	Attarian and Tran [2]
λ_{T_r}	0.03198 cell/mm^3/day	Attarian and Tran [2]
μ_{T_w}	0.01 day^{-1}	Srivastava et al. [14]
μ_{T_r}	0.01 day^{-1}	Attarian and Tran [2]
χ_w	0.000024 mm^3 vir^{-1} day^{-1}	Attarian and Tran [2]
χ_r	0.01 mm^3 vir^{-1} day^{-1}	Attarian and Tran [2]
μ_I	0.5 day^{-1}	Wodarz and Nowak [7]
ε_V	100 vir. cell^{-1} day^{-1}	Mbogo et al. [15]
μ_V	3 day^{-1}	Mbogo et al. [15].
α	0.02 day^{-1}	Arruda et al. [9]
λ_Z	20 cell/mm^3/day	Arruda et al. [9].
μ_Z	0.06 day^{-1}	Arruda et al. [9]
c	0.000005 L^2 cells^2 day^1	Zarei et al. [12]
β	0.004 day^{-1}	Arruda et al. [9]
μ_{Z_a}	0.004 day^{-1}	Arruda et al. [9]

Using the parameters values in Table 3 we present the Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters that influence R_0 in Figure 1.

From Figure 1 it is evident that a decrease in the rate of HIV virions production (ϵ_V) would lead to a decrease in the value of R_0. This can be done by introducing HIV drugs such as the reverse transcriptase inhibitors (RTI) or the protease inhibitor (PI). RTI prevents the production of more HIV virions since it inhibits the reverse transcription process. If the HIV RNA is not reverse transcribed to HIV DNA, then the virus inside the cells cannot multiply. In addition, use of PIs inhibits the production of protease enzyme that is necessary for the maturation of the HIV virions; consequently, the virus produced after its introduction would be noninfectious and immature. Furthermore, a strong immune response would lead to a reduction in the number of the HIV virions. Activated cytotoxic T-cells fight and kill/remove the infected cells. This in turn reduces the number of the HIV virions produced.

Increase in the death rate of free HIV virions would also lead to a decrease in R_0. This could be done by introducing

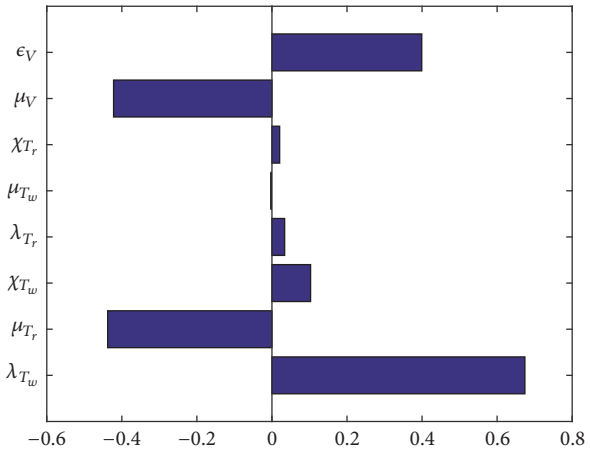


FIGURE 1: Tornado plot showing the sensitivity of R_0 to some of the parameters values.

the ARTs drugs aforementioned. However, it is important for researchers to establish the most optimal HIV drugs that would lead to immune reconstruction with minimal side effects.

4.3. Effect of R_0 on the In Vivo Dynamics of HIV. In this subsection we establish the effects of R_0 on the dynamics of infected cells and the HIV virions. We apply the parameter values described in Table 3.

From Figure 2 it is evident that change in R_0 has a big impact on the magnitude of infected cells and the HIV viral load. It is evident from the graphs in Figure 2 that an increase in R_0; that is, having $R_0 > 1$ leads to an increase in the number of the HIV virions and the infected cells. This implies that the body immunity is threatened and the infected person may progress to AIDS stage if not treated with the ARTs. However, when $R_0 < 1$ the number of the HIV virions in the blood reduces significantly; therefore the infection may die out. For medical practitioners to reduce the effect of the infection it is important to ensure that $R_0 < 1$. This is by developing control, interventions, and management policies that if implemented would ensure that $R_0 < 1$. In the next section we analyze the stability of the disease-free equilibrium point.

4.4. Local Stability of the Disease-Free Equilibrium (DFE)

Theorem 4. *The disease-free equilibrium E_0 of system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. Van den Driessche and Watmough [18] indicated that the stability of the disease-free equilibrium point of a dynamical system is determined by the stability of the matrix $F - V$ given by

$$F - V = \begin{bmatrix} -\mu_I & \dfrac{\chi_w \lambda_{T_w}}{\mu_{T_w}} + \dfrac{\chi_r \lambda_{T_r}}{\mu_{T_r}} & 0 \\ \epsilon_V \mu_I & -\mu_V & 0 \\ \dfrac{\lambda_Z}{\mu_Z}(c-\beta) & 0 & -\mu_Z \end{bmatrix}. \quad (28)$$

We solve the following to obtain the eigenvalues of (28):

$$|F - V - \Lambda I| = \begin{vmatrix} -\mu_I - \Lambda & \dfrac{\chi_w \lambda_{T_w}}{\mu_{T_w}} + \dfrac{\chi_r \lambda_{T_r}}{\mu_{T_r}} & 0 \\ \epsilon_V \mu_I & -\mu_V - \Lambda & 0 \\ \dfrac{\lambda_Z}{\mu_Z}(c-\beta) & 0 & -\mu_Z - \Lambda \end{vmatrix} = 0. \quad (29)$$

The characteristic equation of (28) is given by

$$\Lambda^3 + b_2 \Lambda^2 + b_1 \Lambda + b_0 = 0, \quad (30)$$

where

$$b_2 = \mu_Z + \mu_V + \mu_I,$$

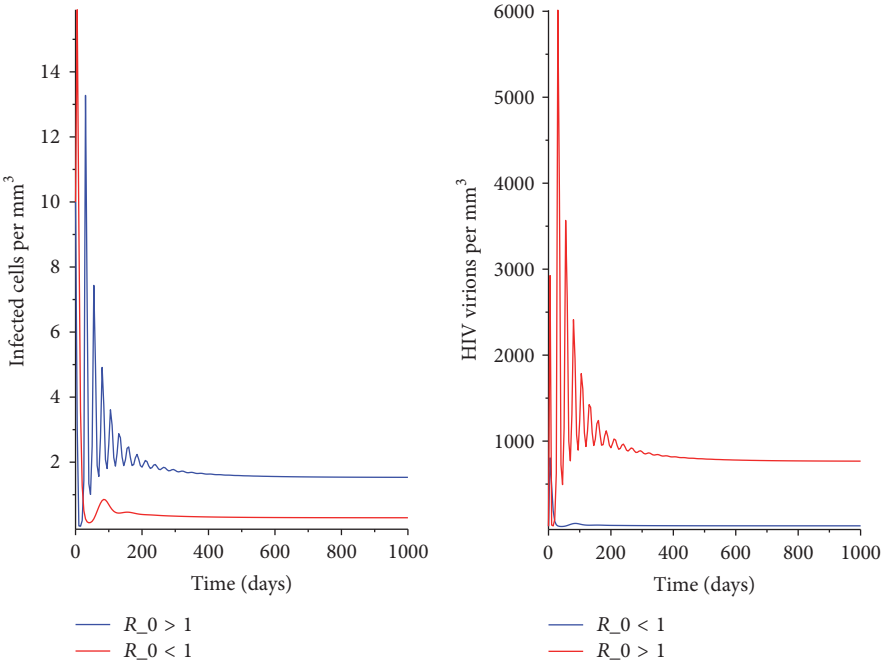
$$b_1 = \frac{\mu_V \mu_Z \mu_{T_r} \mu_{T_w} + \mu_V \mu_{T_r} \mu_{T_w} \mu_I + \mu_Z \mu_{T_r} \mu_{T_w} \mu_I - \mu_{T_r} \chi_w \mu_{T_w} \lambda_{T_w} \epsilon_V - \mu_{T_w} \chi_r \mu_{T_w} \lambda_{T_r} \epsilon_V}{\mu_{T_w} \mu_{T_r}}, \quad (31)$$

$$b_0 = \frac{\mu_Z \mu_1 \left(\mu_V \mu_{T_r} \mu_{T_w} - \mu_{T_r} \chi_w \lambda_{T_w} \epsilon_V - \mu_{T_w} \chi_r \lambda_{T_r} \epsilon_V \right)}{\mu_{T_w} \mu_{T_r}}.$$

Using the Routh-Hurwitz criterion [19], to determine the conditions for the real part of the roots of the characteristic equation (30) $\mathrm{Re}(\Lambda) < 0$ for 3rd-degree polynomial we require

$$b_2 > 0, \quad b_0 > 0, \quad b_2 b_1 - b_0 > 0. \quad (32)$$

We can clearly observe from (31) that all the Routh-Hurwitz conditions are satisfied. Thus all the eigenvalues according to the characteristic equation are negative and real. This implies that the virions-free equilibrium point is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. The epidemiological implication of Theorem 4 is that the HIV virions could be cleared from the body if and only if $R_0 < 1$. □



(a) Population of the infected CD4$^+$ T-cells (b) Population of the HIV virions

FIGURE 2: The HIV dynamics with varying R_0.

5. Numerical Simulation

This section is aimed at investigating numerically the behavior of each compartment on the onset of infection without any medical treatment. We use Maple software to analyze the HIV dynamics *in vivo* without any interventions apart from the body immunity. The initial values of the model were set as $T_{w0} = 1000$, $T_{r0} = 10$, $I_0 = 10$, $V_0 = 10$, $Z_0 = 500$, and $Z_{a0} = 30$. The values for the parameter are adopted from Table 3.

Figure 3 shows the dynamics of the wild type CD4$^+$ T-cells. The hallmark of HIV/AIDS pathogenesis is the depletion of CD4$^+$ T-cell populations. It is evident from Figure 3 that as the disease progresses the number of the CD4$^+$ T-cells decreases. However, due to the immune system mechanism the reduction of the CD4$^+$ T-cells is followed by an increase in the number of the CD4^T which coincides with immune system reconstruction. This can be explained by the fact that the body mechanism will always try to be at an equilibrium. However, as the immune system weakens the body is unable to reconstruct itself, and that is why we get a straight line after the second year. The results in this study agrees with clinical observation [20–22]. It has been indicated that initial destruction of the cells is counteracted by CD4$^+$ memory T-cell regeneration that preserves CD4+ T-cell numbers. The number, however, does not go back to preinfection stage. This process is not maintained for a longer period and that is why we see a drastic drop in the level of the CD4$^+$ T-cells. In HIV as the number of the cells decreases the body immunity lacks the ability to fight other infections. That is why HIV infected people are prone to many opportunistic deceases as the CD$^+$ T-cells go below 350 cells/mm^3.

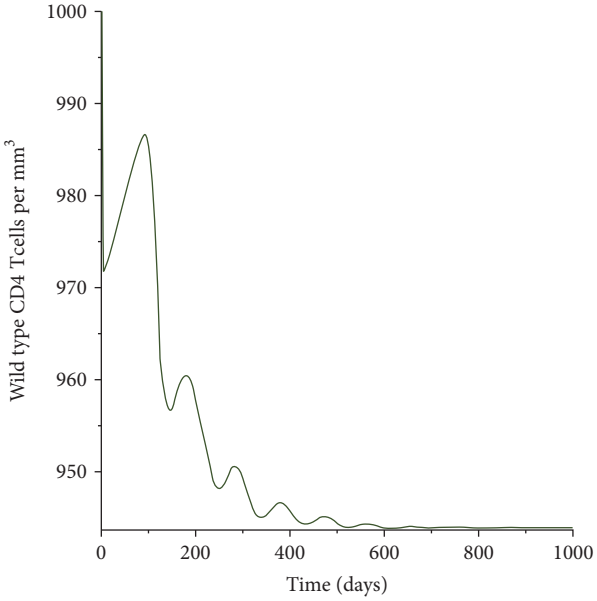


FIGURE 3: Population of the wild type CD4$^+$ T-cells.

Figure 4 shows the dynamic of the resistant CD4$^+$ T-cells. The dynamics of these cells are similar to that of the wild type cells. Nonetheless since the cells resist infection they remain at a low level after the third month, which is not the case with the wild type CD4$^+$ T-cells.

Figure 5 shows the dynamics of the infected CD4$^+$ T-cells. It is evident that at acute infection the number of the infected cells increases at a very sharp rate and then decreases

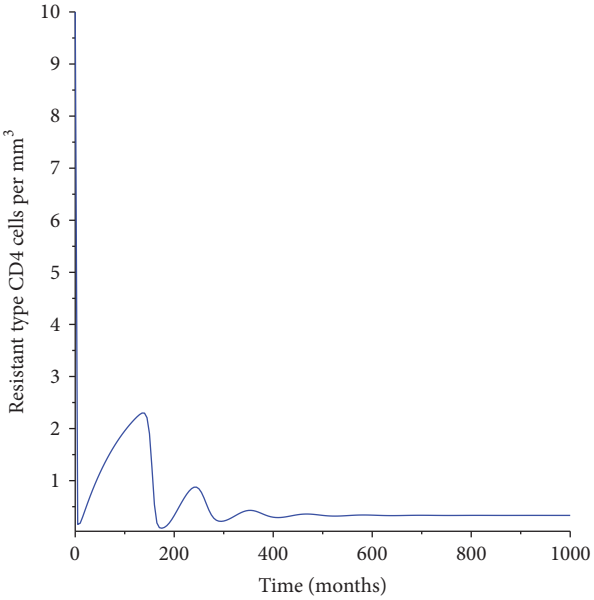


Figure 4: Population of the resistant type $CD4^+$ T-cells.

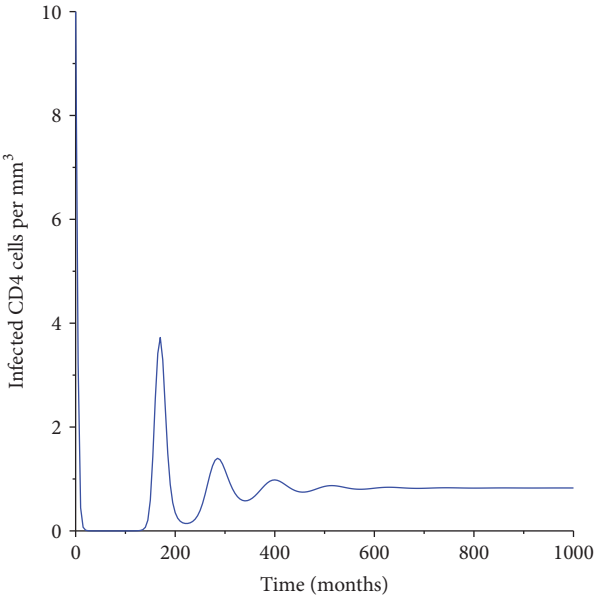


Figure 5: Population of the infected $CD4^+$ T-cells.

exponentially. However, after the 100 days the level increases, but since the body has a way of balancing the cells, we see an increase is followed by a decrease. The harmonic oscillations is maintained up to 500 days. Due to the weak immune system the number of infected cells remains at a constant rate from 600 days which might remain so for several years. HIV has proved to have no cure so far. However, as researchers we need to find a way of killing all the infected cells before they bud out and produce mature HIV virions. So far clinicians have indicated that HIV-induced cell death actually increases HIV replication [23, 24].

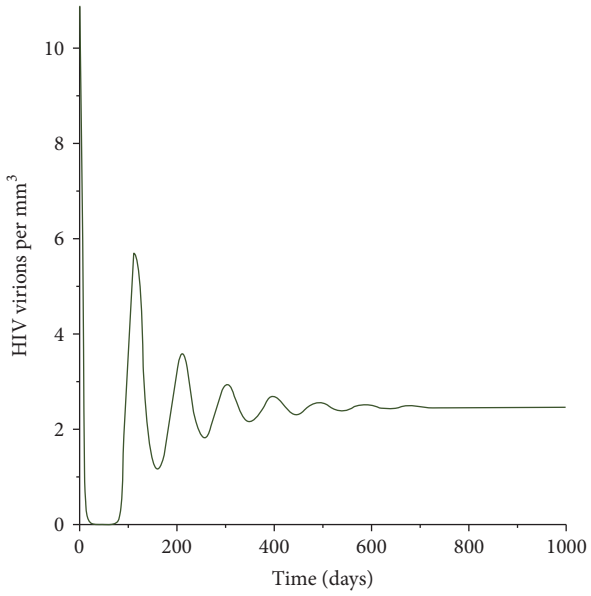


Figure 6: Population of the HIV virus particles.

Figure 6 represents the dynamics of the HIV virions for the first 1000 days after infection. It is evident that the number of HIV virions increases in the first few days after infection. Afterwards the number of virions decreases. This is because of the recruitment of the cytotoxic cells to fight the free virus. After about three months the level increases exponentially; this is because many infected cells burst releasing a higher number of the virions. Since the cytotoxic cells kill the infected cells then indirectly they reduce the number of HIV virions produced. A sharp increase after three months is, therefore, followed by a decrease in the number of HIV virions. After 500 days, the number of HIV virions remains at a constant rate. It is important to note that new HIV virions are emitted from an infected $CD4^+$ T-cell, via bursting of the cell. This implies that a single burst produces a big number of new HIV particles.

Figure 7 represents the dynamics of the of the cytotoxic cells in the first 1000 days after infection. These are specialized cells of the adaptive immune system capable of finding and eliminating pathogen-infected cells. They are responsible for destroying and killing the infected cells and in turn help to restore the immune system. They arise from the bone marrow and later relocate to the thymus for maturation. During this process they are able to express a unique antigen-binding molecule known as the T-cell receptor. The receptor enables them to monitor all cells of the body, ready to destroy any cell posing a threat to the organism. Nonetheless, for the cytotoxic cells to fight and destroy any infected cell they must be activated and the dynamics of the activated cells is shown in Figure 8. The activation takes place at the surface of accessory cells, which mature during the innate immune responses triggered by an infection.

From Figure 8 it is evident that the number of the activated $CD8^+$ T-cells increases exponentially for the first month. The cells are activated in preparation to kill the

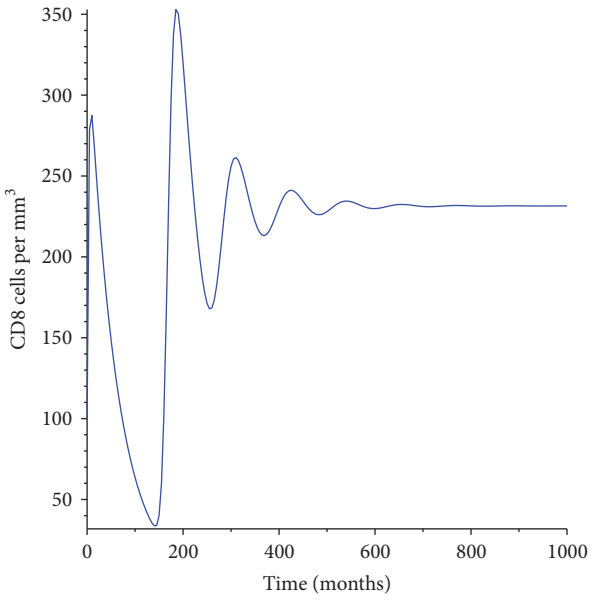


Figure 7: Population of the cytotoxic T-cells.

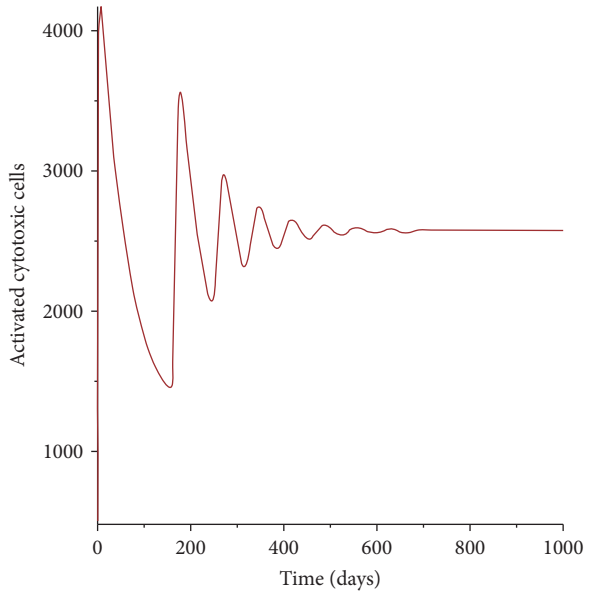


Figure 8: Population of the activated cytotoxic T-cells.

already infected $CD4^+$ T-cells. The number then reduces to a minimum after 5 months (150 days) though not to the level of the preinfection period. This coincides with the reduction in the number of the free HIV virions. Onward a nonharmonic curve is seen for the dynamics of the activated cytotoxic cells.

6. Conclusion

This paper presented a six-dimensional *in vivo* HIV dynamics model. The model analyzes HIV virus dynamics focusing on the highly dynamic interaction between HIV virions, uninfected wild and resistant type $CD4^+$ T-cells, infected $CD4^+$ T-cells, and CTLs. The inclusion of the immune response to viral infection was a key feature in examining the course of HIV infection. The model was aimed at analyzing the mechanism of the HIV virus during the entry time up to the maturation time and the role played by the activated $CD8^+$ T-cells in fighting and killing the HIV virions. We started by proving that the model was epidemiologically well posed. We later derived the expression of the basic reproductive number, R_0. It was evident that the model was locally stable and the simulated results from the model emphasized the importance of maintaining R_0 below one. The cytotoxic cells play a very crucial role in our system as far as infection control is concerned. It is evident from the numerical results that high level of the virus and infected cells in the body result in an increase in the level of the activated defense cells. The activated cells fight the infected cells and indirectly reduce the viral load. In addition, due to the high increase of the virions during the first three months it is important to introduce ARTs to prevent HIV transmission. This will help in the reduction of new infection. From this study we note that there is production of high number of HIV virions during the early stages of infection; it is therefore paramount to initiate ARTs to prevent HIV transmission. In addition, the medical practitioners and the government should initiate HIV programs and management polices that will lead to having $R_0 < 1$.

In conclusion, lessons learnt by the various researchers, governmental and nongovernmental organizations, and clinicians in addressing the HIV for the last three decades must be collaboratively collected and the findings implemented. In future it is important to carryout the optimal control to establish the role played by the HIV drugs and also the optimal drug combinations.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Modelling Optimal Control of In-Host HIV Dynamics Using Different Control Strategies

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HIV is one of the major causes of deaths, especially in Sub-Saharan Africa. In this paper, an in vivo deterministic model of differential equations is presented and analyzed for HIV dynamics. Optimal control theory is applied to investigate the key roles played by the various HIV treatment strategies. In particular, we establish the optimal strategies for controlling the infection using three treatment regimes as the system control variables. We have applied Pontryagin's Maximum Principle in characterizing the optimality control, which then has been solved numerically by applying the Runge-Kutta forth-order scheme. The numerical results indicate that an optimal controlled treatment strategy would ensure significant reduction in viral load and also in HIV transmission. It is also evident from the results that protease inhibitor plays a key role in virus suppression; this is not to underscore the benefits accrued when all the three drug regimes are used in combination.

1. Introduction

There is an ever-changing need for new and useful treatment regimes that will provide assistance and relief in all aspects of the human condition. Subsequently, many researchers have embarked on the journey of analyzing the dynamics of various diseases affecting mankind with the aim of improving control and effect and finally eradicating the diseases from the population. Modelling and numerical simulations of the infectious diseases have been used as tools to optimize disease control. This is due to the fact that medical community has insufficient animal models for testing efficacy of drug regimes used in controlling infections. Human immunodeficiency virus (HIV) is one of the major problems that researchers have been working on for over three decades. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS), there were 36.7 million people living with HIV/AIDS in 2016, 1.6 million of which live in Kenya [1]. Nonetheless, many treatment regimes for HIV have been approved by the US Food and Drug Administration. Among them, is the Highly Active Antiretroviral Therapy (HAART) which is the latest combinations in use, in most countries. HAART has been proven to be highly effective in viral suppression, prolongs life of the infected person, and also reduces the rate of HIV transmission. However, even over three decades since the first HIV cases were reported, the virus had no cure and hence various control methods for HIV/AIDS have been recommended. These controls range from preventive measures to treatment regimes. Preventive measures aim at reducing the number of new HIV infections, while treatment regimes target the already infected persons to increase their life expectancy and reduce the rate of HIV transmission. Various treatment strategies are still the subject of many ongoing clinical trials that are investigating their benefits versus risks aimed at determining the most optimal treatment for HIV. Unfortunately, various host-pathogen interaction mechanisms during HIV infection and progression to AIDS are still unknown. Consequently, many questions like which is the best combination, when is the best time to start treatment, and how the treatment should be administered are yet to be answered fully.

Mathematical modelling is one of the many important tools used in understanding the dynamics of disease transmission. It is also used in developing guidelines important in disease control. In HIV, mathematical models have provided a framework for understanding the viral dynamics and have

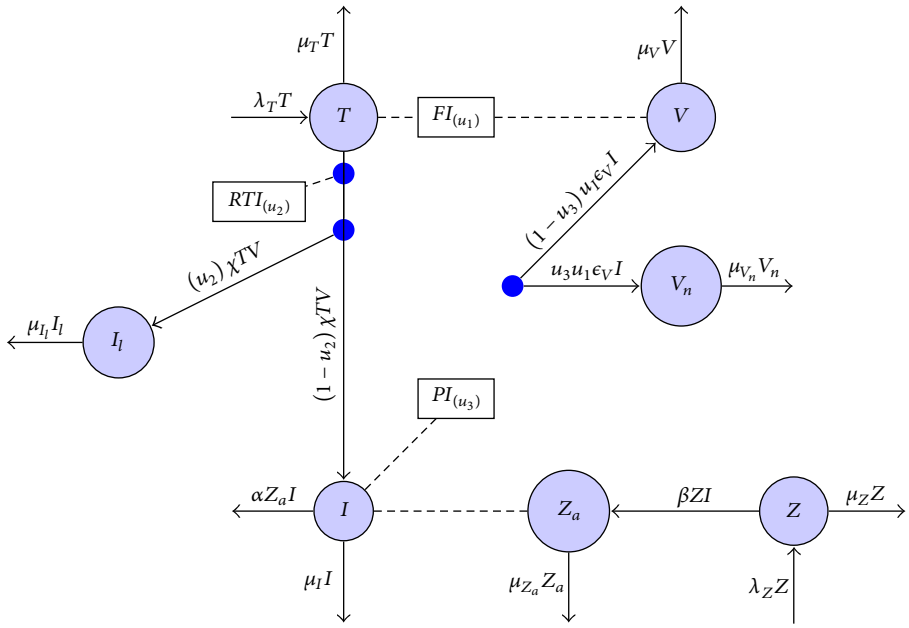

Figure 1: A compartmental representation of the in vivo HIV dynamics with therapy.

been used in the optimal allocation of the various interventions against the HIV virions [2–4]. A fundamental goal of developing and applying the aforementioned mathematical models of HIV is to influence treatment decisions and construct better treatment protocols for infected patients. Most of the modern mathematical models that have been developed apply the optimal control theory. Optimal control theory is a branch of mathematics developed to find optimal ways of controlling a dynamical system [5]. It has been applied by mathematicians to assist in the analysis of how to control the spread of infectious diseases. The results are used in making key decisions that involve complex biological mechanism. In particular, it is used to determine the best dosage for various available vaccines or treatment in use for controlling infection. For instance, Gaff and Schaefer [6] applied optimal theory in evaluating mitigation strategy that would be highly effective in minimizing the number of people who get infected by an infection. The study applied both vaccinations and treatment as control variables for their various model. The results indicated that as much as treatment is paramount in controlling any infection, the most optimal method would be the combination of the two interventions. Furthermore, Bakare et al. [7] applied optimal control in an SIR model. The study illustrated the use of optimal control theory in establishing the optimal educational campaign and treatment strategies that would minimize the population of the infected persons as well as cutting the cost of controlling the various diseases. The results indicated that, for controlling infection, it is important to target the uninfected populations and apply measures that will prevent them from getting the infection.

In the literature, optimal control theory has also been applied both in-host and population HIV dynamics model. For instance, Yusuf and Benyah [14] applied optimal theory on HIV population model. The study aimed at determining the best method of controlling the spread of HIV/AIDS within a specified time frame. The study considered three control variables, that is, safe sex, education, and ARTs. The numerical results of the objective function for the model indicated that safe sex practice and early initiation of ARTs are the most optimal ways of mitigating the spread of HIV/AIDS. The study established that if the aforementioned strategies are well implemented, this would lead to an HIV-free nation in 10 years. In addition, for in-host model, optimal control theory has been applied in the search for optimal therapies for HIV infection.

Drugs such as fusion inhibitors (FIs), reverse transcriptase inhibitors (RTIs), and protease inhibitors (PIs) have been developed and applied in the various optimal control problems. Srivastava et al. [15] analyzed an initial infection model with reverse transcriptase inhibitors (RTIs). The study argued that the use of RTIs reverts back an infected cell to susceptible. However, this is unlikely since once a $CD4^+$ T-cell is infected it cannot go back to susceptible. The only possible way is for it to remain latently infected but fail to produce infectious virus, since RTIs inhibit the reverse transcription process. Hattaf and Yousfi [16] analyzed two optimal treatments of HIV infection model. The study aimed at measuring the efficiency of RTIs and PIs. This was done by maximizing objective function aimed at increasing the number of the uninfected cells, decreasing the viral load, and minimizing the treatment cost. The results indicated that use of therapy is important in HIV control. It is also important to note that the study included two types of viruses, that is, the infectious virus and the noninfectious virus. Noninfectious virus is due to the use of PIs as a treatment regime.

Karrakchou et al. [17] applied optimal control theory on HIV. Like Hattaf and Yousfi [16], the study applied the two

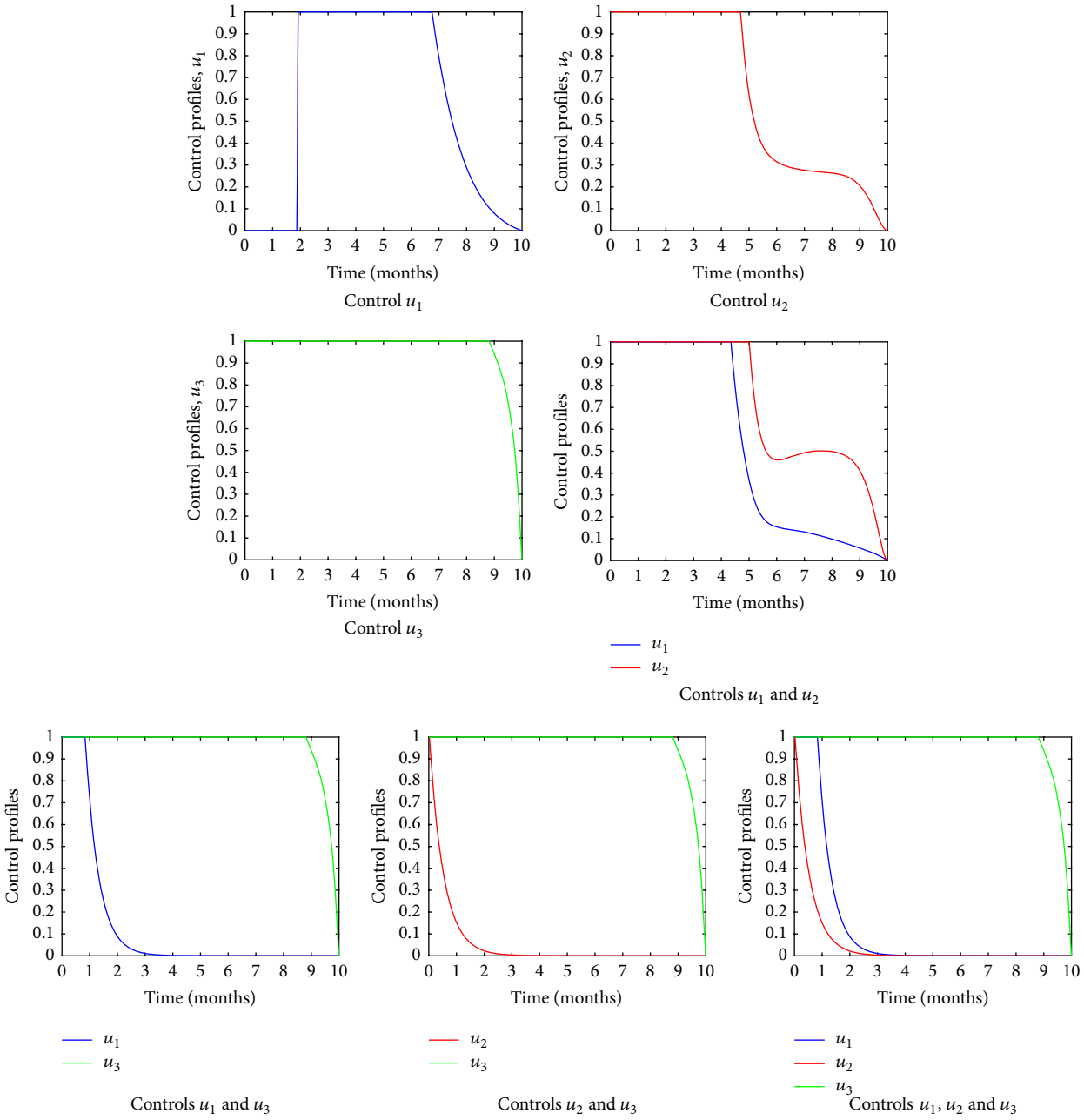

Figure 2: Simulated control strategies.

Table 1: Variables for HIV in vivo model with therapy.

Variable	Description
$T(t)$	The concentration of the noninfected $CD4^+$ T-cells per cubic millimetre at any time t
$I(t)$	The concentration of the infected $CD4^+$ T-cells per cubic millimetre at any time t
I_l	The concentration of latently infected $CD4^+$ T-cells per cubic millimetre at any time t
$V(t)$	The concentration of HIV virions, copies/mL, at any time t
$V_n(t)$	The concentration of the immature noninfectious virions, copies/mL, at any time t
$Z(t)$	The concentration of the $CD8^+$ T-cells per cubic millimetre at any time t
$Z_a(t)$	The concentration of the activated $CD8^+$ T-cells per cubic millimetre at any time t

Table 2: Parameters for HIV in vivo model with therapy.

Parameter	Description
λ_T	The rate at which the noninfected $CD4^+$ T-cells are produced per unit time.
μ_T	The rate at which the noninfected $CD4^+$ T-cells decay.
χ	The rate at which the $CD4^+$ T-cells are infected by the virus.
μ_I	The death rate of the infected $CD4^+$ T-cells.
μ_{I_l}	The death rate of the latently infected $CD4^+$ T-cells.
ε_V	The rate in which HIV virions are generated from the infected $CD4^+$ T-cells.
μ_V	The death rate of the infectious virus.
μ_{V_n}	The death rate of the noninfectious virions.
α	The rate at which the infected cells are eliminated by the activated $CD8^+$ T-cells.
λ_Z	The rate at which the $CD8^+$ T-cells are produced per unit time.
μ_Z	The death rate of the $CD8^+$ T-cells.
β	The rate at which the $CD8^+$ T-cells are activated by the presence of the virus and the infected $CD4^+$ T-cells.
μ_{Z_a}	The rate at which the activated defense cells decay.

Table 3: Control variables for HIV in vivo model.

Control variable	Description	Purpose
$0 \le u_1 \le 1$	Fusion inhibitors	Are a class of antiretroviral drugs that work on the outside of the host $CD4^+$ T-cell to prevent HIV from fusing with and infecting it.
$0 \le u_2 \le 1$	Reverse transcriptase inhibitors	Are a class of antiretroviral drugs used to treat HIV infection by inhibiting the reverse transcription process.
$0 \le u_3 \le 1$	Protease inhibitors	Are a class of antiviral drugs that are widely used to treat HIV/AIDS by inhibiting the production of protease enzyme necessary for the production of infectious viral particles.

control strategies, that is, RTIs and the PIs. However, the study failed to put into account both the latently infected cells and the noninfectious virus that results due to the use of RTIs and PIs, respectively. Failure to include such important variables in the model underscores the adequacy of the model in representing the actual HIV in-host mechanism. In addition, Arruda et al. [12] applied optimal control theory in HIV immunology. The study used two control variables in fighting HIV with the inclusion of the $CD8^+$ T-cells. However, the study has some shortcomings; for instance, the study suggested that activated $CD8^+$ T-cells kill the HIV virions and also the infected cells. This is not the scenario, since the activated $CD8^+$ T-cells are only able to kill infected $CD4^+$ T-cells which in turn reduce the population of the HIV virions. Unfortunately, even with the aforementioned work done on HIV, the implementation of some of the recommendations has been proven to be inefficient and in most cases not economically viable, especially to the developing countries.

As per the literature cited, it is clear that as much as ARTs have been used for viral suppression, the optimal treatment schedule necessary to maintain low viral load is always an approximation. Until the time when HIV cure is found, physicians will try as much as possible to apply the control strategy that will inhibit viral progression while simultaneously holding the side effects of treatment to a minimum. Most of the treatment regimes have many side effects that must be maintained at a low level. For example, long-term use of protease inhibitors is associated with insulin intolerance, cholesterol elevation, and the redistribution of body fat. Therefore, there is a need to establish the optimal treatment strategy, that is, the one which both maximizes the patient's uninfected $CD4^+$ T-cells and minimizes the harmful side effects due to the drugs.

This study has addressed some of the shortcomings noted from the in-host HIV dynamics models by applying three control variables representing the three drug regimes on the market, that is, the fusion inhibitor, reverse transcriptase inhibitors, and the protease inhibitors, in the in vivo HIV model. In addition, the study has incorporated the $CD8^+$ T-cells in the model. For the analysis, the study will apply optimal control theory together with Pontryagin's Maximum Principle in solving the objective function with the aim of establishing the optimal treatment strategy.

2. Model Formulation

2.1. Model Description. In order for us to carry out optimal control processes, it is paramount to formulate a model that describes the basic interaction between the HIV virions and the body immune system. We develop a mathematical model for HIV in-host infection with three combinations of drugs. We define eight variables for the model as follows: susceptible $CD4^+$ T-cells (T), latently infected $CD4^+$ T-cells (I_l), infected $CD4^+$ T-cells (I), HIV infectious virions (V), noninfectious HIV virions (V_n), $CD8^+$ T-cells (Z), and the activated $CD8^+$ T-cells (Z_a).

The parameters for the model are as follows. The susceptible $CD4^+$ T-cells are produced from the thymus at a

Table 4: Parameters and controls for HIV in vivo model with therapy.

Parameters	Value	Source
λ_T	10 cell/mm^3/day	Nowak et al. [8]
μ_T	0.01 day^{-1}	Srivastava and Chandra [9]
χ	0.000024 mm^3 vir^{-1} day^{-1}	Alizon and Magnus [10]
μ_I	0.5 day^{-1}	Wodarz and Nowak [11]
μ_{I_l}	0.5 day^{-1}	Wodarz and Nowak [11].
ε_V	100 vir. cell^{-1} day^{-1}	Estimate
μ_V	3 day^{-1}	Mbogo et al. [2].
μ_{V_n}	0.06 day^{-1}	Estimate
α	0.02 day^{-1}	Arruda et al. [12]
λ_Z	20 cell/mm^3/day	Arruda et al. [12]
μ_Z	0.06 day^{-1}	Arruda et al. [12]
β	0.004 day^{-1}	Arruda et al. [12]
μ_{Z_a}	0.004 day^{-1}	Arruda et al. [12]
u_1	0-1 variable	Estimate
u_2	0-1 variable	Estimate
u_3	0-1 variable	Estimate

Table 5: The initial values for the variables for HIV in vivo model.

Variable	Values
$T(t)$	$T(0) = 500$ cell/mm^3
$I(t)$	$I(0) = 100$ cell/mm^3
I_l	$I_l(0) = 0$ cell/mm^3
$V(t)$	$V(0) = 100$ virion/mm^3
$V_n(t)$	$V_n(0) = 0$ virion/mm^3
$Z(t)$	$Z(0) = 100$ cell/mm^3
$Z_a(t)$	$Z_a(0) = 10$ cell/mm^3

constant rate λ_T, die at a constant per capita rate μ_T, and become infected by the HIV virions at the rate χTV. However, due to the use of fusion inhibitor (u_1) which prevents the entry of the HIV virions into the CD4$^+$ T-cells, a fraction $u_1\chi VT$ reverts back to susceptible class. In addition, when the infected CD4$^+$ T-cells are exposed to the HIV virions in presence of reverse transcriptase inhibitor (u_2), the HIV virions RNA may not be reverse-transcribed. This results in a proportion $u_2\chi VT$ of the infected cells becoming latently infected. The infected cells are killed by the CD8$^+$ T-cells at the rate α and they die naturally at the rate μ_I, whereas latently infected cells die at the rate μ_{I_l}. This study assumes that the latently infected cells will die naturally and have no possibility of producing infectious virions nor becoming activated to become infectious. However, if the protease inhibitor (u_3) is used as a treatment strategy, it inhibits the production of protease enzyme, which is necessary for production of mature HIV virions. This therefore means that we have two kinds of HIV virions produced from infected CD4$^+$ T-cells, that is, the infectious HIV virions and the immature noninfectious virions. The infectious HIV virions are produced at the rate $(1-u_3)\epsilon_V$ and die at the rate μ_V, while the noninfectious HIV virions are produced at the rate $u_3\epsilon_V$ and die at the rate μ_{V_n}. Furthermore, the CD8$^+$ T-cells are produced naturally from the thymus at the rate λ_Z, they die naturally at the rate μ_Z, and they can also be activated to kill the infected cells at the rate β. The activated CD8$^+$ T-cells die naturally at the rate μ_{Z_a}. It is very important to point out that the CD8$^+$ T-cells are activated to kill the infected CD4$^+$ T-cells and not the virus as suggested by Arruda et al. [12].

The summary for the model description is given as follows. The variables, parameters, and the control variables for the in-host model are described in Tables 1, 2, and 3, respectively.

From Figure 1 and the description above, we derive the following system of ordinary differential equations to describe the in vivo dynamics of HIV:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - \mu_T T - \left(1 - u_1(t)\right)\chi TV,\\
\frac{dI}{dt} &= \left(1 - u_2(t)\right)\chi TV - \mu_I I - \alpha I Z_a,\\
\frac{dI_l}{dt} &= u_2(t)\,\chi TV - \mu_{I_l} I_l,\\
\frac{dV}{dt} &= \left(1 - u_3(t)\right)\epsilon_V \mu_I I - \mu_V V,\\
\frac{dV_n}{dt} &= u_3(t)\,\epsilon_V \mu_I I - \mu_{Vn} V_n,\\
\frac{dZ}{dt} &= \lambda_Z - \mu_Z Z - \beta Z I,\\
\frac{dZ_a}{dt} &= \beta Z I - \mu_{Z_a} Z_a.
\end{aligned} \tag{1}$$

3. Optimization Process

Control efforts are carried out to limit the spread of the disease and, in some cases, to prevent the emergence of drug

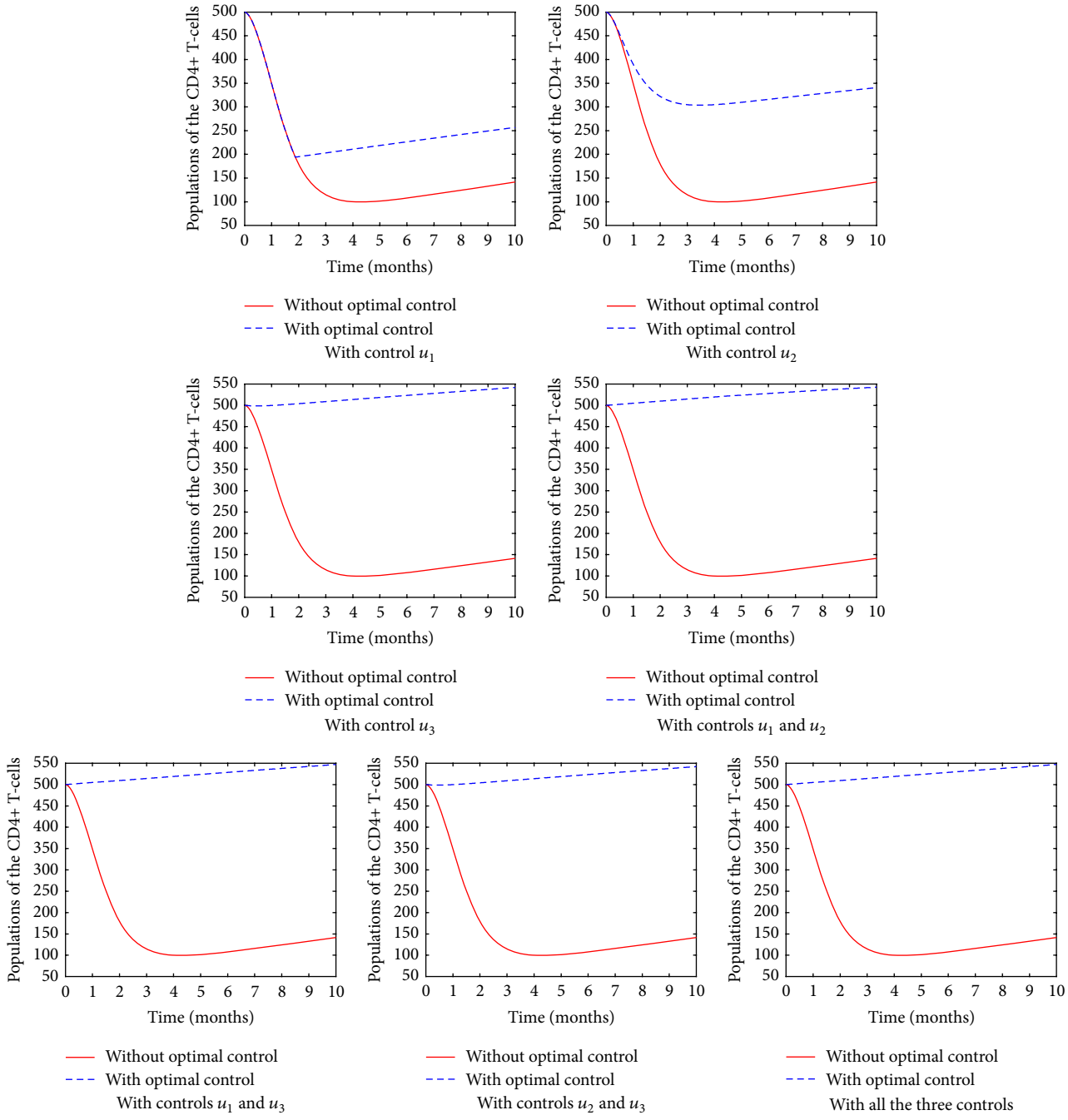

FIGURE 3: The population of the $CD4^+$ T-cells in various control strategies.

resistance. Optimal control theory is a method that has been widely used to solve for an extremum value of an objective functional involving dynamic variables. In this section, we consider optimal control methods to derive optimal drug treatments as functions of time. The control variables as used in (1) are described as follows. The control u_1 represents the effect of fusion inhibitors, which are the drugs that protect the uninfected $CD4^+$ T-cells by preventing the entry of the virus into the $CD4^+$ T-cells membrane. The control variable u_2 simulates the effect of reverse transcriptase inhibitors. These drugs hinder the reverse transcription process. The third control variable u_3 simulates the effect of protease inhibitors, which prevent the already infected cells from producing mature infectious virions. The aforementioned controls represent effective chemotherapy dosage bounded between 0 and 1. The situation $u_1(t) = u_2(t) = u_3(t) = 1$ represents total efficacy of the fusion inhibitors, reverse transcriptase inhibitors, and protease inhibitors, respectively, and $u_1(t) = u_2(t) = u_3(t) = 0$ represents no treatment. It is worth noting that the aforementioned control variables are

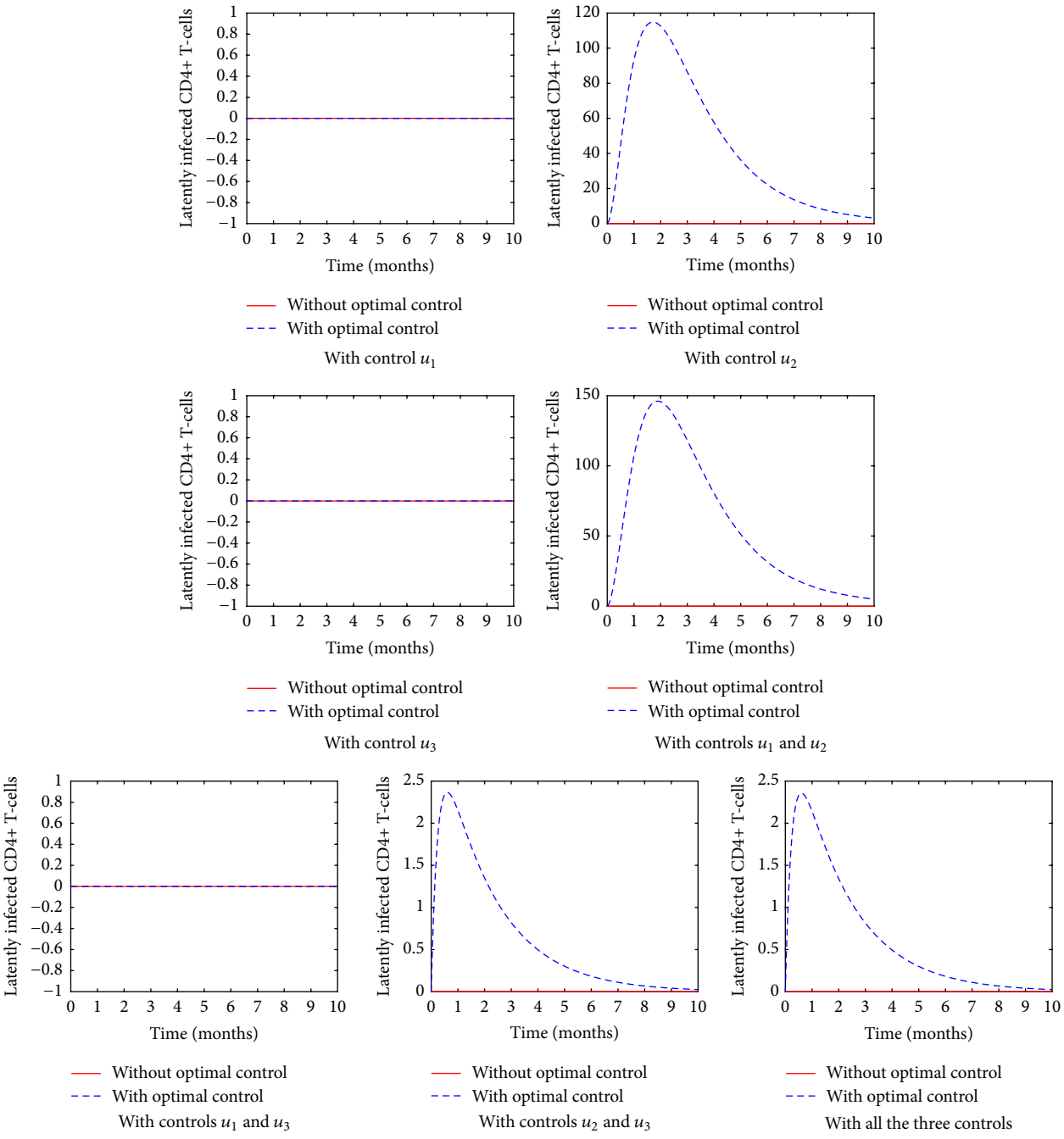

FIGURE 4: The population of the latently infected $CD4^+$ T-cells in various control strategies.

bounded Lebesgue-integrable functions. The study aims at maximizing the levels of the healthy $CD4^+$ T-cells, as well as the levels of the $CD8^+$ T-cells (Z), while minimizing the viral load (V) and at the same time keeping cost and side effects of treatment at a minimum. With the above description, the following objective function (2) needs to be maximized:

$$J\left(u_1(t), u_2(t), u_3(t)\right) = \frac{1}{2}\int_0^{T_f}\left(w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2\right) dt \quad (2)$$

subject to the ordinary differential equations given in model (1).

$T(t)$, $Z(t)$, and $V(t)$ are the solutions of the ODEs (1). The quantities w_1 and w_2 represent the cost associated with maximizing the number of $CD4^+$ T-cells and the $CD8^+$ T-cells, respectively, while w_3 represents the cost associated with minimizing the viral load. In addition, A_1, A_2, and A_3 are nonnegative constants representing the relative weights attached to the current cost of each treatment regime and T_f is a fixed terminal time of the treatment program subject

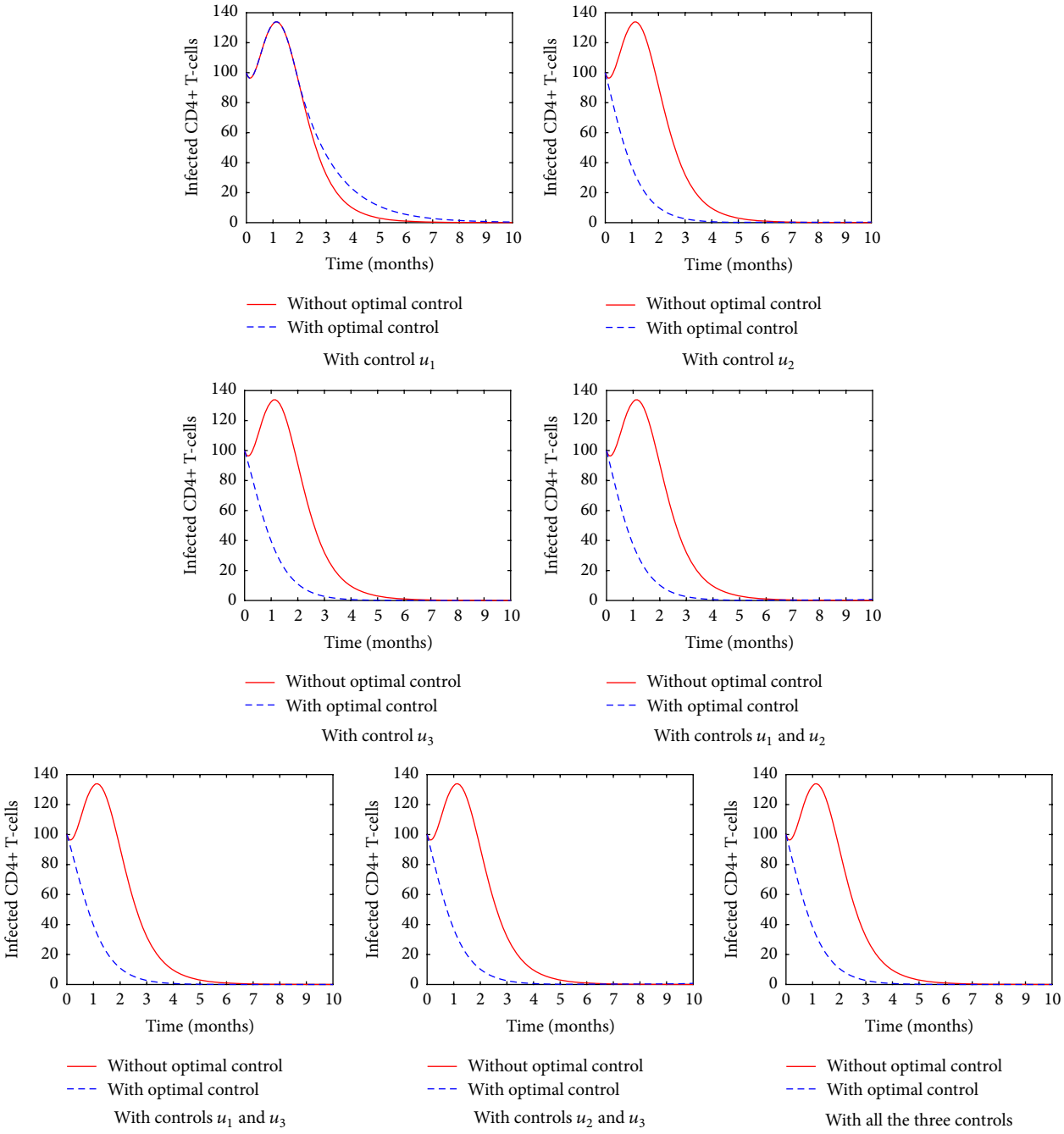

FIGURE 5: The population of the infected $CD4^+$ T-cells in various control strategies.

to the ordinary differential equations described in model (1). This study assumes that the cost of controls is of quadratic form. Furthermore, it is also based on the fact that there is no linear relationship between the effect of treatment on $CD4^+$ T-cells and $CD8^+$ T-cells and the HIV virions. Consequently, u_1, u_2, and u_3 are Lebesgue-integrable; that is, they are piecewise continuous and integrable. The fundamental aim of this therapeutic strategy is to maximize the objective functional defined in (2) by increasing the number of the uninfected $CD4^+$ T-cells and the $CD8^+$ T-cells, decreasing the viral load (V), and minimizing the harmful side effects and cost of treatment over the given time interval $[0, T_f]$. Therefore, we aim at determining the optimal controls u_1^*, u_2^*, and u_3^* such that

$$J\left(u_1^*(t), u_2^*(t), u_3^*(t)\right) = \max\left\{J\left(u_1(t), u_2(t), u_3(t)\right) : \left(u_1, u_2, u_3\right) \in U\right\}, \tag{3}$$

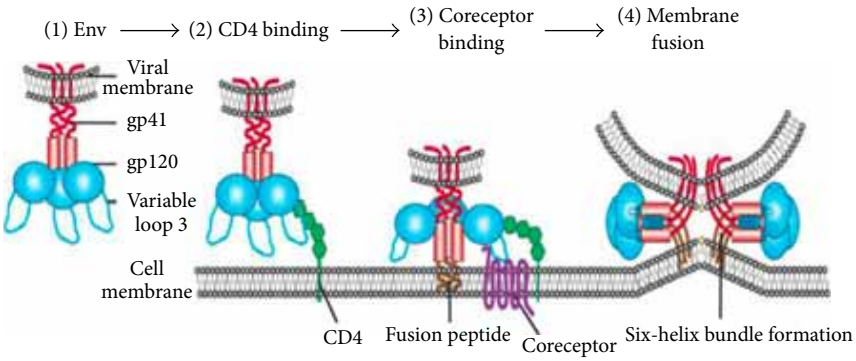

Figure 6: HIV entry mechanism [13].

where U is a set of all measurable controls defined by

$$U = \left\{u = (u_1, u_2, u_3) : u_i \text{ measurable},\ 0 \le u_i(t) \le 1,\ t \in \left[0, T_f\right]\right\}. \tag{4}$$

In the next section, we show the existence of an optimal control for system (1) and later derive the optimality system. This study will employ Pontryagin's Maximum Principle.

4. Characterization of the Optimal Control

The necessary conditions that an optimal control must satisfy come from Pontryagin's Maximum Principle [5].

Theorem 1. *Suppose that the objective function*

$$J(u_1(t), u_2(t), u_3(t)) = \frac{1}{2}\int_0^{T_f} \left(w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2\right) dt \tag{5}$$

is maximized subject to the controls and state variables given in model (1) with

$$\begin{aligned} T(0) &= T_0, \\ I(0) &= I_0, \\ I_l(0) &= I_{l0}, \\ V(0) &= V_0, \\ V_n(0) &= V_{n0}, \\ Z(0) &= Z_0, \\ Z_a(0) &= Z_{a0}. \end{aligned} \tag{6}$$

Then there exist optimal controls $(u_1^*, u_2^*, u_3^* \in U)$ *such that*

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = \max\left\{J(u_1(t), u_2(t), u_3(t)) : (u_1, u_2, u_3) \in U\right\}. \tag{7}$$

Proof. The existence of the solution can be shown using the results obtained in Fleming and Rishel [18], since

(1) the class of all initial conditions with controls u_1, u_2, and u_3 in the control set U are nonnegative values and are nonempty, where u_i, $i = 1, 2, 3$, is a Lebesgue-integrable function on $[0, T_f]$,

(2) the right-hand side of system (1) is bounded by a linear function of the state and control variables,

by definition, each right-hand side of system (1) is continuous and can be written as a linear function of U with coefficients depending on time and state. Furthermore, all the state and control variables T, I, I_l, V, V_n, Z, Z_a, u_1, u_2, and u_3 are bounded on $[0, T_f]$,

(3) by definition, the control set U is convex and closed.A set $K \in \mathbb{R}^{\kappa}$ is said to be a convex set if and only if

$$\lambda x + (1 - \lambda) y \in K \tag{8}$$

for all $x, y \in K$ and all $\lambda \in [0, 1]$,

this condition is satisfied by the control set U,

(4) the integrand which is $(1/2)(A_1 u_1^2 + A_2 u_2^2 + A_3 u_3^2)$ of the objective functional is concave on U,

(5) there exist constants $b_1 > 0$, $b_2 > 0$, and $\beta > 1$ such that the integrand of the objective function $J(U, t)$ is bounded by $L(t, T, V, V_n, I, I_l, Z, Z_a, u_1, u_2, u_3) \le b_2 - b_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\beta/2}$,

this implies that

$$\begin{aligned} &w_1 T(t) + w_2 Z(t) - w_3 V(t) - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2 \\ &\quad \le b_2 - b_1\left(|u_1|^2 + |u_2|^2 + |u_3|^2\right), \end{aligned} \tag{9}$$

where b_1 depends on the upper bound on T, Z, V while $b_1 > 0$ since $A_1, A_2, A_3 > 0$ according to the definition.

Since all the above conditions are satisfied, we conclude that there exist optimal controls ${u_1}^*$, ${u_2}^*$, and ${u_3}^*$. □

5. Necessary Conditions of the Control

We now proceed by applying Pontryagin's Maximum Principle [5]. We begin by defining Lagrangian (Hamiltonian augmented):

$$\begin{aligned}
&L\left(T, I, I_l, V, V_n, Z, Z_a, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, u_1, u_2, u_3\right)\\
&\quad = w_1 T + w_2 Z - w_3 V - A_1 u_1^2 - A_2 u_2^2 - A_3 u_3^2\\
&\quad + \lambda_1\left(\lambda_T - \mu_T T - \left(1 - u_1\left(t\right)\right)\chi TV\right)\\
&\quad + \lambda_2\left(\left(1 - u_2\left(t\right)\right)\chi TV - \mu_I I - \alpha I Z_a\right) + \lambda_3\left(u_2\left(t\right)\right.\\
&\quad \left.\cdot\, \chi TV - \mu_{I_l} I_l\right) + \lambda_4\left(\left(1 - u_3\left(t\right)\right)\epsilon_V \mu_I I - \mu_V V\right)\\
&\quad + \lambda_5\left(u_3\left(t\right)\epsilon_V \mu_I I - \mu_{V_n} V_n\right) + \lambda_6\left(\lambda_Z - \mu_Z Z\right.\\
&\quad \left. - \beta ZI\right) + \lambda_7\left(\beta ZI - \mu_{Z_a} Z_a\right) + w_{11} u_1 + w_{12}\left(1\right.\\
&\quad \left. - u_1\right) + w_{21} u_2 + w_{22}\left(1 - u_2\right) + w_{31} u_3 + w_{32}\left(1\right.\\
&\quad \left. - u_3\right),
\end{aligned} \tag{10}$$

where $w_{ij}(t) \leq 0$ are the penalty multipliers that ensure the boundedness of the control variables $u_1(t)$, $u_2(t)$, and $u_3(t)$ and satisfy the following conditions:

$$\begin{aligned}
w_{11} u_1 &= w_{12}\left(1 - u_1\right) = 0 \quad \text{at } u_1^*\\
w_{21} u_2 &= w_{22}\left(1 - u_2\right) = 0 \quad \text{at } u_2^*\\
w_{31} u_3 &= w_{32}\left(1 - u_3\right) = 0 \quad \text{at } u_3^*,
\end{aligned} \tag{11}$$

where u_1^*, u_2^*, and u_3^* represent the optimal controls.

Therefore, Pontryagin's Maximum Principle gives the existence of adjoint variables that are obtained by differentiating the Lagrangian given by (10) with respect to the state variables T, V, I, I_l, Z, and Z_a.

The adjoint variables are given by

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial L}{\partial T}\\
&= -w_1 + \lambda_1\left(\mu_T + \left(1 - u_1\right)\chi V\right) - \lambda_2 \chi V\left(1 - u_2\right)\\
&\quad - \lambda_3 u_2 \chi V,\\
\dot{\lambda}_2 &= -\frac{\partial L}{\partial I}\\
&= \lambda_2\left(\mu_I + \alpha Z_a\right) - \lambda_4 \epsilon_V \mu_I\left(1 - u_3\right) - \lambda_5 u_3 \epsilon_V \mu_I\\
&\quad + \lambda_6 \beta Z - \lambda_7 \beta Z,\\
\dot{\lambda}_3 &= -\frac{\partial L}{\partial I_l} = \lambda_3 \mu_{I_l},\\
\dot{\lambda}_4 &= -\frac{\partial L}{\partial V}\\
&= w_3 + \lambda_1 \chi T\left(1 - u_1\right) - \lambda_2 \chi T\left(1 - u_2\right) - \lambda_3 \chi T u_2\\
&\quad + \lambda_4 \mu_V,\\
\dot{\lambda}_5 &= -\frac{\partial L}{\partial V_n} = \lambda_5 \mu_{V_n},\\
\dot{\lambda}_6 &= -\frac{\partial L}{\partial Z} = -w_2 + \lambda_6\left(\mu_Z + \beta I\right) - \lambda_7 \beta I,\\
\dot{\lambda}_7 &= -\frac{\partial L}{\partial Z_a} = \lambda_2 \alpha I + \lambda_7 \mu_{Z_a},
\end{aligned} \tag{12}$$

where

$$\lambda_i\left(T_f\right) = 0, \quad i = 1, \ldots, 7, \tag{13}$$

are the transversality conditions.

By maximization of the Lagrangian with respect to the control variables u_1, u_2, u_3 at the optimal controls (u_1^*, u_2^*, and u_3^*), we have

$$\begin{aligned}
\frac{\partial L}{\partial u_1} &= 0,\\
\frac{\partial L}{\partial u_2} &= 0,\\
\frac{\partial L}{\partial u_3} &= 0.
\end{aligned} \tag{14}$$

Therefore, differentiating the Lagrangian L given in (10) with respect to u_1 on the set $U : t \mid 0 \leq u_1(t) \leq 1$, we get the following optimality equation:

$$\frac{\partial L}{\partial u_1} = -2A_1 u_I + \chi TV\lambda_1 + w_{11} - w_{12} = 0. \tag{15}$$

Let $u_1 = u_1^*$ in (15). Then, solving (15), we obtain the optimal control u_1^* as

$$u_1^* = \frac{\chi TV\lambda_1 + w_{11} - w_{12}}{2A_1}. \tag{16}$$

To determine an explicit expression for an optimal control u_1^* without w_{11} and w_{12}, we consider the following three cases:

(1) On the set $(t \mid 0 < u_1^* < 1)$, suppose we set $w_{11} = w_{12} = 0$ in (16). Then the optimal u_1^* control is given by

$$u_1^* = \frac{\chi TV\lambda_1}{2A_1}. \tag{17}$$

(2) Similarly, on the set $(t \mid u_1^* = 1)$, we have $w_{11} = 0$ and $w_{12} \geq 0$; then from (16), we have

$$u_1^* = 1 = \frac{\chi TV\lambda_1 - w_{12}}{2A_1}. \tag{18}$$

Equation (18) can be reduced to

$$\frac{\chi TV\lambda_1}{2A_1} \geq 1 = u_1^*. \tag{19}$$

Therefore, for this set, we have

$$u_1^* = \min\left(1, \frac{\chi TV\lambda_1}{2A_1}\right). \tag{20}$$

(3) Finally, on the set $(t \mid u_1^* = 0)$, we have $w_{12} = 0$ and $w_{11} \geq 0$; then from (16), we have

$$u_1^* = 0 = \frac{\chi TV\lambda_1 + w_{11}}{2A_1}, \tag{21}$$

which implies that

$$\frac{\chi TV\lambda_1}{2A_1} \leq 0. \tag{22}$$

Consequently, combining all the three cases given by (17), (20), and (22), we obtain the optimal control, u_1^*, as follows:

$$u_1^*(t) = \begin{cases} \dfrac{\chi TV\lambda_1}{2A_1} & \text{if } 0 < \dfrac{\chi TV\lambda_1}{2A_1} < 1 \\ 0 & \text{if } \dfrac{\chi TV\lambda_1}{2A_1} \leq 0 \\ 1 & \text{if } \dfrac{\chi TV\lambda_1}{2A_1} \geq 1. \end{cases} \tag{23}$$

This implies that the control $u_1^*(t)$ is formulated as follows:

$$u_1^* = \max\left(0, \min\left(1, \frac{\chi TV\lambda_1}{2A_1}\right)\right). \tag{24}$$

We use the same argument to obtain an explicit expression for an optimal control u_2^* without w_{21} and w_{22}. We differentiate the Lagrangian L given in (10) with respect to u_2 on the set $U : t \mid 0 \leq u_2(t) \leq 1$. We therefore obtain the optimality equation as

$$\frac{\partial L}{\partial u_2} = -2A_2u_2 + \chi TV(\lambda_3 - \lambda_2) + w_{21} - w_{22} = 0 \quad \text{at } u_2 = u_2^*. \tag{25}$$

Therefore, solving (25), we obtain the optimal control u_2^* as follows:

$$u_2^* = \frac{\chi TV(\lambda_3 - \lambda_2) + w_{21} - w_{22}}{2A_2}. \tag{26}$$

According to the conditions given by (11), we derive the following distinct three cases:

(1) On the set $(t \mid 0 < u_2^* < 1)$, we have $w_{21} = w_{22} = 0$ in (26). Then the optimal u_2^* control is given by

$$u_2^* = \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}. \tag{27}$$

(2) On the set $(t \mid u_2^* = 1)$, we have $w_{21} = 0$ and $w_{22} \geq 0$; then from (26), we have

$$u_2^* = 1 = \frac{\chi TV(\lambda_3 - \lambda_2) + w_{22}}{2A_2}. \tag{28}$$

Rearranging (28) we have

$$\frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \geq 1 = u_2^*. \tag{29}$$

Thus, for the this set, we have

$$u_2^* = \min\left(1, \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}\right). \tag{30}$$

(3) Finally, on the set $(t \mid u_2^* = 0)$, we have $w_{22} = 0$ and $w_{21} \geq 0$; then from (26), we have

$$u_2^* = 0 = \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}, \tag{31}$$

which implies that

$$\frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \leq 0. \tag{32}$$

Consequently, combining all the three cases given by (27), (30), and (32), we obtain the optimal control u_2^* as follows:

$$u_2^*(t) = \begin{cases} \dfrac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} & \text{if } 0 < \dfrac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} < 1 \\ 0 & \text{if } \dfrac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \leq 0 \\ 1 & \text{if } \dfrac{\chi TV(\lambda_3 - \lambda_2)}{2A_2} \geq 1. \end{cases} \tag{33}$$

Hence, the optimal control $u_2^*(t)$ is formulated as follows:

$$u_2^* = \max\left(0, \min\left(1, \frac{\chi TV(\lambda_3 - \lambda_2)}{2A_2}\right)\right). \tag{34}$$

To obtain the expression for optimal control u_3^*, we differentiate (10) with respect to u_3 on the set $U : t \mid 0 \le u_3(t) \le 1$ to get the following optimality equation:

$$\frac{\partial L}{\partial u_3} = -2A_3u_3 - \varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32} = 0. \quad (35)$$

Let $u_3 = u_3^*$ in (35); then we obtain the optimal control u_3^*:

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{31} - w_{32}}{2A_3}. \quad (36)$$

(1) On the set $(t \mid 0 < u_3^* < 1)$, we have $w_{31} = w_{32} = 0$ in (36). Then the optimal control u_3^* is given by

$$u_3^* = \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}. \quad (37)$$

(2) On the set $(t \mid u_3^* = 1)$, we have $w_{31} = 0$ and $w_{32} \ge 0$; then from (36), we have

$$u_3^* = 1 = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{32}}{2A_3}. \quad (38)$$

Equation (38) can be reduced to

$$\frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \ge 1 = u_3^*. \quad (39)$$

Hence, for this set, we have

$$u_3^* = \min\left(1, \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}\right). \quad (40)$$

(3) Finally, on the set $(t \mid u_3^* = 0)$, we have $w_{32} = 0$ and $w_{31} \ge 0$; then from (36), we have

$$u_3^* = 0 = \frac{-\varepsilon_V\mu_I I\lambda_4 + w_{31}}{2A_3}, \quad (41)$$

which implies that

$$\frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \le 0. \quad (42)$$

Consequently, combining all the three cases given by (37), (40), and (42), the optimal control, u_3^*, is characterized as

$$u_3^*(t) = \begin{cases} \dfrac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} & \text{if } 0 < \dfrac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} < 1 \\ 0 & \text{if } \dfrac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \le 0 \\ 1 & \text{if } \dfrac{-\varepsilon_V\mu_I I\lambda_4}{2A_3} \ge 1. \end{cases} \quad (43)$$

Therefore, the optimal control, $u_3^*(t)$, is formulated as

$$u_3^* = \max\left(0, \min\left(1, \frac{-\varepsilon_V\mu_I I\lambda_4}{2A_3}\right)\right). \quad (44)$$

It is worth noting that the optimal controls depend on the adjoint variables λ_1, λ_2, λ_3, and λ_4, since the adjoint variables correspond to the state variables, T, I, I_l, V, and the first four equations in (1) contain the control terms.

6. Numerical Simulation

In this section, we investigate the effect of optimal strategy on HIV by applying Runge-Kutta forth-order scheme on the optimality system. The optimality system is obtained by taking the state system together with the adjoint system, the optimal control, and the transversality conditions. The dynamical behaviour of the models in relation to various control is also studied. The optimal strategy is achieved by obtaining a solution for the state system (1) and costate system (12). An iterative scheme is explored and used to determine the solution for the optimality system. The numerical method utilized is the forward-backward sweep method that incorporates iterative Runge-Kutta fourth-order progressive-regressive schemes. The progressive scheme is used in obtaining the solutions of the state ODEs given in (1) with the initial conditions, while the regressive scheme is applied in obtaining the solutions of the adjoint system given by (12) with transversality conditions given in (13). The controls are updated at the end of each iteration using the formula for optimal controls. We continue with the iterations until convergence is achieved. This is a two-point boundary-value problem, with separated boundary conditions at times $t_0 = 0$ and $t = T_f$. This explains our choice in using the fourth-order Runge-Kutta scheme. For the numerical simulation, we take $T = 310$ days or 10 months. This value represents the time in which treatment is stopped. Furthermore, the values of the weight function are taken as $A_1 = A_2 = A_3 = 0.01$. Table 4 consists of the parameter values that are used in the numerical simulations of the in vivo model, while Table 5 consists of the proposed initial values of the state variables.

The initial values given in Table 5 are chosen in such a way that they reflect a patient during acute infection. This is in line with the WHO recommendations that stipulate that all people living with the HIV be put on ARTs irrespective of their $CD4^+$ counts unlike in the past where the $CD4^+$ count had to be less than 500 cells/mm^3 [19].

6.1. Results and Discussion. Figure 2 represents the various control strategies. It is evident that the control u_1 remains at the maximum for the first two months and drops to zero onward, while control u_2 remains at maximum for the first four and a half months and then drops to 30% the sixth and the ninth months and drops to the minimum after the 10th month. In addition, the control strategy u_3 remains at a maximum for the first ninth months, only dropping to a minimum at the tenth month. From these results, we can see that protease inhibitor can be administered for a longer period of time.

Figure 3 shows the population of the $CD4^+$ T-cells in different treatment strategy. In all the cases, it is evident that the introduction of the ARTs plays a significant role as far as controlling HIV is concerned. Nonetheless, it is clear that when fusion inhibitor (u_1) is used without other controls, the number of $CD4^+$ T-cells reduces significantly and a longer time is taken before the number increases. In particular, the drug effectiveness seems to be felt after the first two months. We interpret the results to mean that it is difficult to control

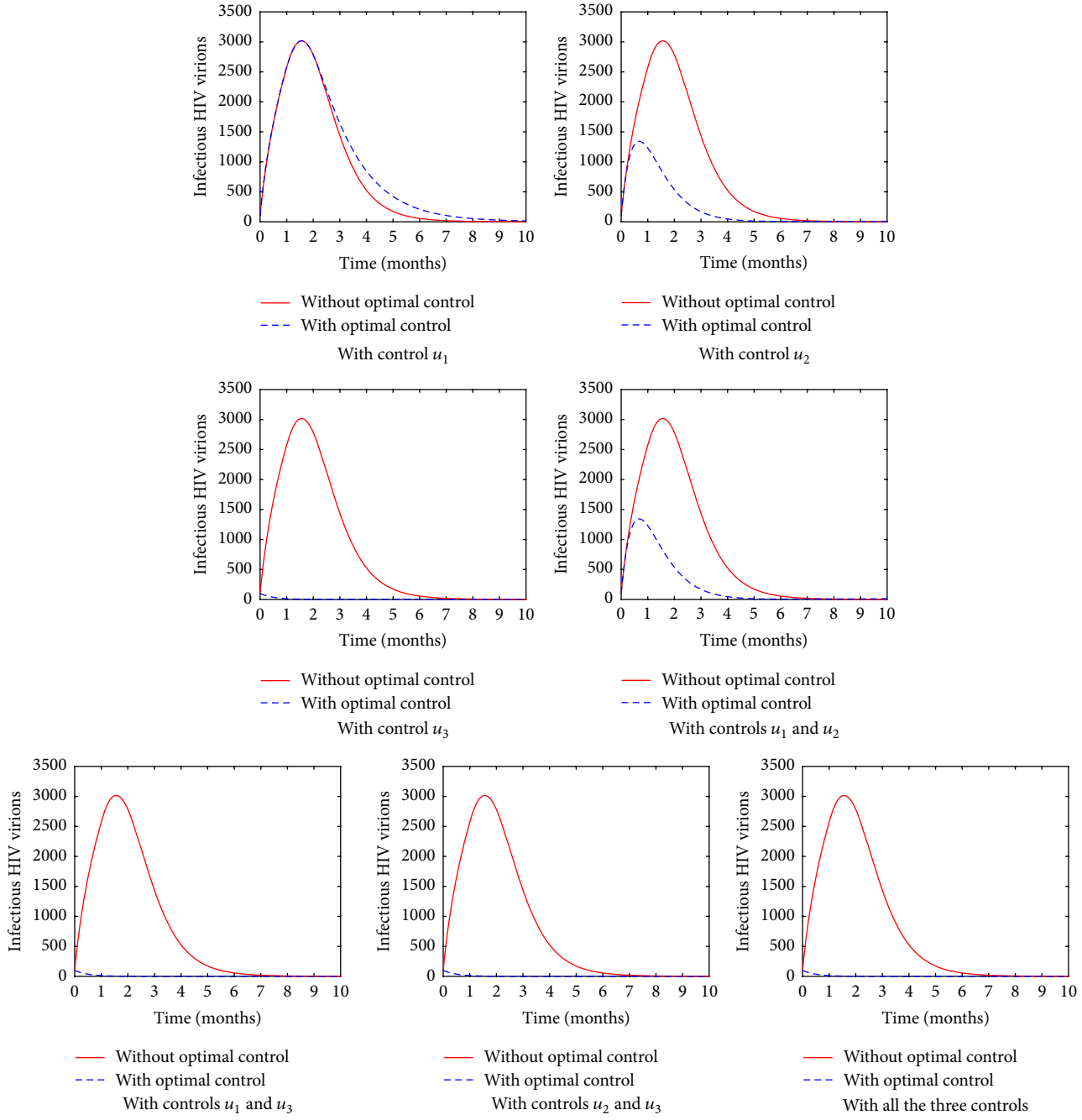

Figure 7: The population of the HIV virions in various control strategies.

the HIV virions by targeting its cell-entry mechanism. The use of protease inhibitor, however, leads to an increase in the number of the $CD4^+$ T-cells. In addition, it is evident that a combination of the three drugs evokes a more pronounced $CD4^+$ T-cells increase than in monotherapy or combination of two drugs.

It is important to point out that $CD4^+$ T-cell responses in number of cells gained were similar for patients treated with combination of two drugs therapies and patients treated with combination of three drugs therapies.

Figure 4 presents the dynamics of the latently infected cells after the introduction of the various control strategies. It is evident that the latently infected cells are produced after the introduction of reverse transcriptase inhibitor to an HIV infected cell. Since the latently infected cells do not produce infectious virions, it is important to administer RTIs to an infected person. This will reduce the number of virions producing cells.

Figure 5 shows the change in the population of the infected $CD4^+$ T-cells with time in different control strategies. From the simulated results, we see that use of ARTs plays a

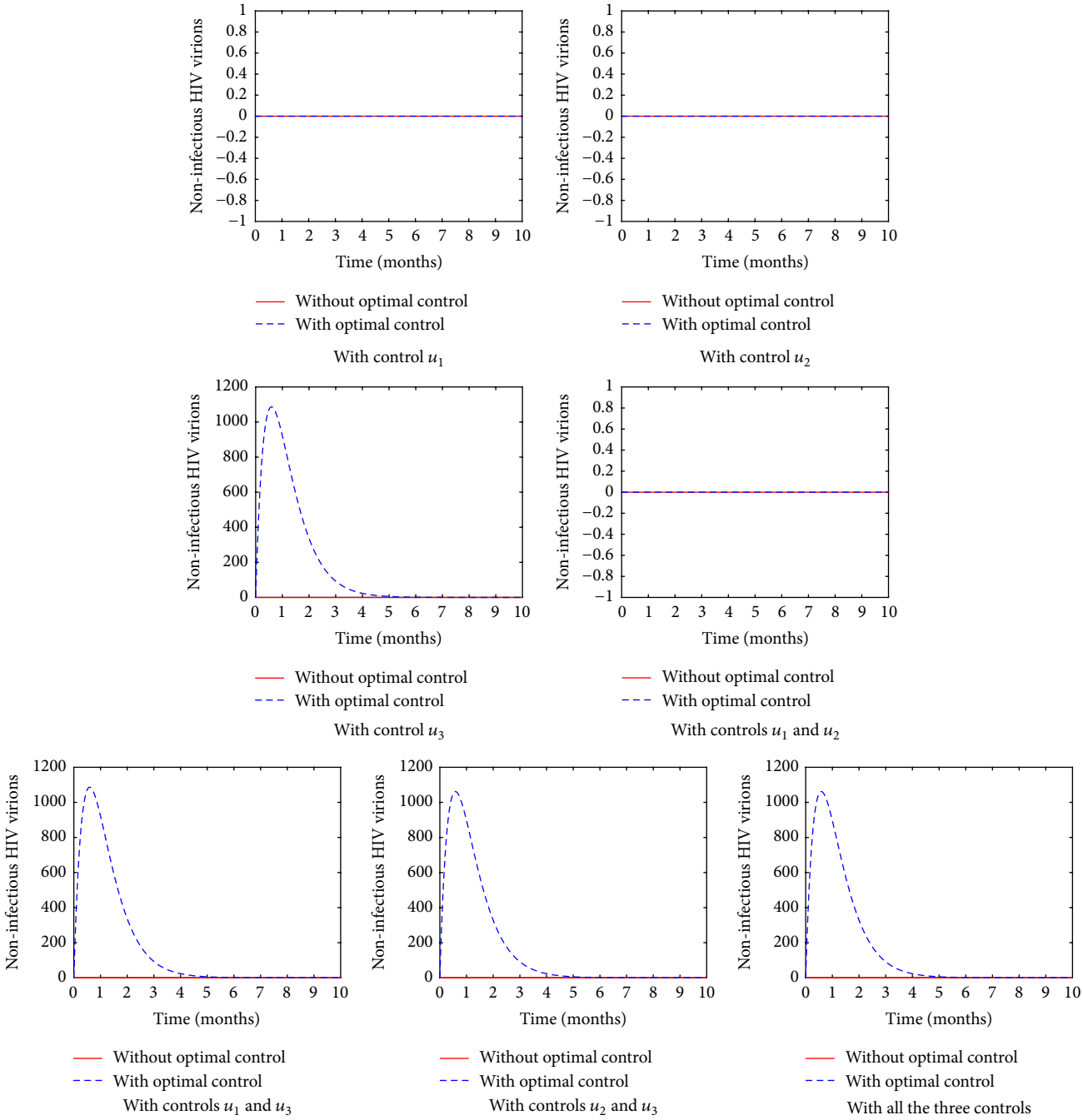

Figure 8: The population of the noninfectious HIV virions in various control strategies.

fundamental role, especially in controlling the rate of infection. Nonetheless, when the fusion inhibitors are introduced in the body, the number of the infected cells still increases for the first few months. This clearly shows that it is very difficult to control the HIV virions at the entry level. The reason would probably be based on the fact that HIV uses a complex series of steps to deliver its genome into the host cell cytoplasm while simultaneously evading the host immune response as shown in Figure 6.

Figure 7 shows the change in the population of the HIV virions in different drug combination(s). It is evident that controls u_1 and u_2 are not as very effective as PIs in controlling viral progression. In particular, there is no significant difference when the control u_1 is used and when no control is used at all. Researches such as [20] suggest that viruses blocked by entry inhibitors such as the fusion inhibitors are likely redistributed to plasma, where they artificially increase the number of HIV virions. This may probably be the reason why there is an indication of having

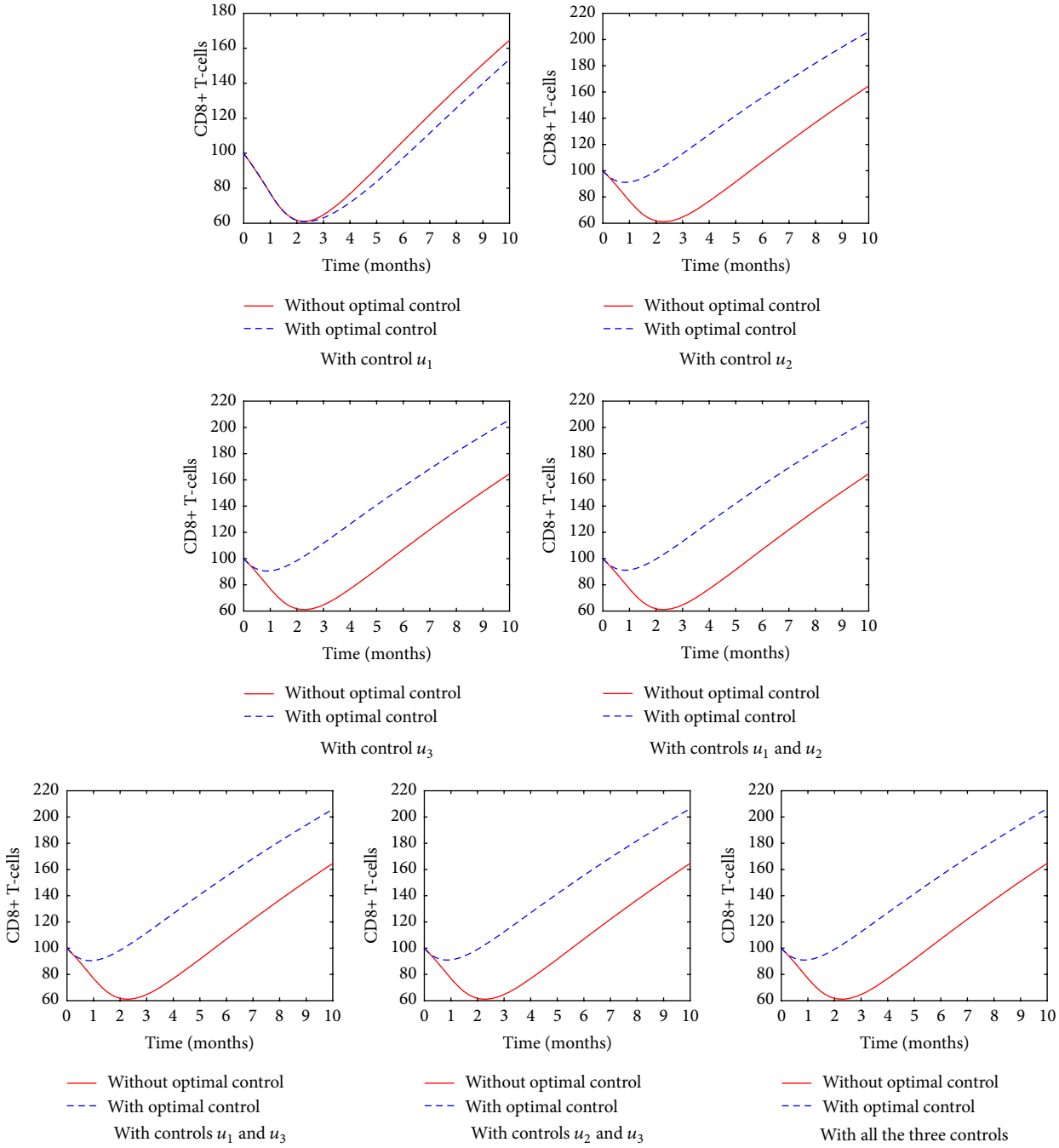

Figure 9: The population of the $CD8^+$ T-cells in various control strategies.

high number of viral loads even when control u_1 is applied. In addition, the fusion inhibitor prevents the entry of the virions unlike the other two drugs that allow the entry of the HIV virions into the cells, confirming the absorption effect. Simulated results shows that protease inhibitor plays a significant role in reducing viral progression and it is the best single drug in use for viral suppression. This is in agreement with some of the works done in the field of in vivo HIV dynamics which have concluded that protease inhibitors are more effective than reverse transcriptase inhibitors and fusion inhibitors in terms of viral load reduction in HIV infected patient [21–23]. The simulated results also emphasize the importance of using a combination of the various ARTs when treating HIV.

From Figure 8, it is evident that noninfectious viruses are produced after the introduction of the protease inhibitor in the body. Introduction of PIs to HIV infected cells generates a pool of immature HIV virions; this leads to the transfer of noninfectious virus across the virological synapse. This

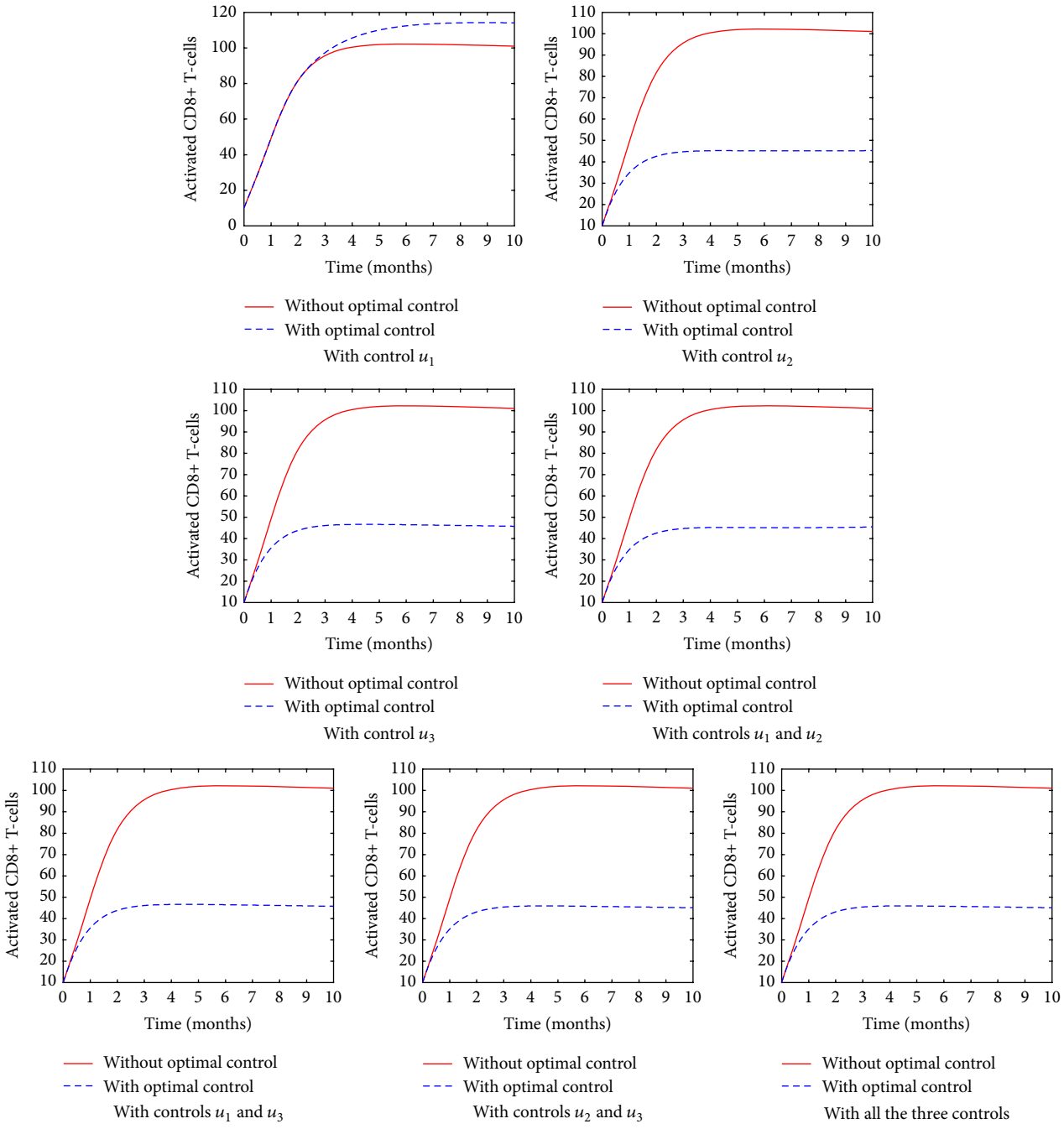

FIGURE 10: The population of the activated $CD8^+$ T-cells in various control strategies.

therefore implies that the virus produced will not infect more susceptible $CD4^+$ T-cells.

Figure 9 shows the population of the $CD8^+$ T-cells in different treatment strategy. Both the RTIs and PIs cause a substantial increase in the population of the $CD8^+$ T-cells in HIV infected patients. However, it is evident that as much as these two drugs plays a major role, the combination of all the three controls produces a higher immune system reconstitution with sustained increases in circulating number of $CD8^+$ T-cells.

Figure 10 shows the population of the activated $CD8^+$ T-cells. The activation process plays a major role in controlling the HIV virus particles. This is because the cells fight, destroy, and kill the infected $CD4^+$ T-cells. This in turn reduces the number of HIV virions produced. From the simulated results, it is evident that, after the introduction of the ARTs, the number of activated $CD8^+$ T-cells reduced significantly. The reduction may be attributed to the reconstituted immune system or due to the reduction of the retroviral activity on the cells [24]. However, the question we need to ask ourselves is

whether this reduction has any clinical benefit. In the future, it is important to analyze the clinical benefit accrued from the reduction of the $CD8^+$ T-cells activation process.

7. Conclusion

In this paper, we have analyzed a seven-dimension in vivo HIV model with inclusion of three drug combinations, that is, FIs, RTIs, and PIs. Optimal control theory is applied to determine the optimal treatment regime. The study applied Pontryagin's Maximum Principle in deriving the conditions for optimal control, which maximizes the objective function. The systems of ODEs, the state system, and the adjoint system were solved numerically by both forward and backward Runge-Kutta forth-order scheme. Results from the numerical simulations show that FIs and RTIs should be used within the four months and later the doctors should change the drugs and introduce another type, whereas the PIs can be used for a longer period of time without necessarily leading to major side effect. However, the inferiority of monotherapy compared with combination of therapies has been observed in the simulated result, especially in suppression of viral replication, $CD4^+$ and $CD8^+$ T-cells reconstitution, and controlling disease progression.

ARTs have been seen to play a significant role as far as viral suppression is concerned. Therefore, they should be recommended for all patients immediately after one is diagnosed as HIV-positive regardless of the $CD4^+$ count. This supports the guidelines by WHO. However, the simulated results suggest that PI is possibly the best single drug and fusion inhibitor is the worst drug in terms of viral load and infected cells reduction. From the results, we recommend that RTIs be used as initial therapy for HIV. FI should be introduced to the patient after the RTIs but should never be used alone.

In the future, it is important to develop the model in such a way that it brings out the relationship between the number of the $CD8^+$ T-cells and the $CD4^+$ T-cells produced in the thymus.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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