

NEGLECTED TROPICAL DISEASES: MATHEMATICAL
MODELLING AND CONTROL OF WITHIN-HOST AND
TRANSMISSION DYNAMICS OF VIRAL INFECTIONS

by

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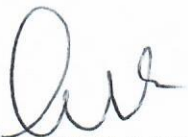
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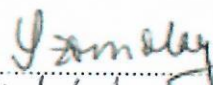
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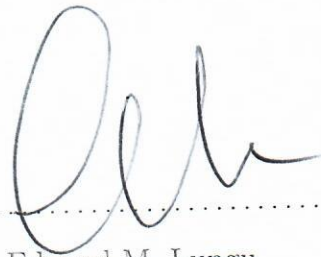
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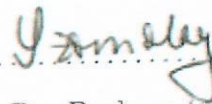
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The work presented in Chapter 6 was previously published in *Infectious Disease Modelling* as *Modeling the role of public health education in Ebola virus disease outbreaks in Sudan* by B. Levy, E. Christina, O. Gaoue, **R. Kaondera-Shava**, M. Kgosimore, S. Lenhart, B. Lephodisa, **E. Lungu**, T. Marijani, and F. Nyabadza. This study was conceived by all of the authors. I contributed to the model formulation, model analysis, literature search, sensitivity analysis, discussed results and commented on the manuscript.

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Abstract

Neglected tropical diseases (NTDs) are a health crisis that is ignored by the developed world and only starts getting attention when there is an outbreak that kills a large population. AIDS associated Kaposi sarcoma (AIDS-KS) and Ebola Virus Disease (EVD) are viral infections which are just two of the many NTDs that require attention. This thesis presents novel within-host ordinary differential equation (ODE) mathematical models in conjunction with application of the optimal control theory of AIDS-KS dynamics. Additionally, we derive an epidemiological system of ODEs to model the transmission dynamics of EVD in the presence of public health education.

AIDS-KS is caused by KS-associated herpesvirus (KSHV). Although the standard KS therapy has not changed in twenty years, not all cases of KS will respond to the same therapy. The goal of current AIDS-KS treatment modalities is to reconstitute the immune system and suppress HIV replication. We introduce novel within-host ODE mathematical models that consolidate the effect of both HIV and KSHV load on KS tumor progression by incorporating low or high viral loads (VLs) into the proliferation terms of the immune cell populations. Regulation of HIV/KSHV VL and viral reservoir cells is crucial for restoring a patient to an asymptomatic stage. Therefore, in order to devise an optimal treatment plan, optimal control theory is applied by using Pontryagin's maximum principle with control measures such as combined antiretroviral therapy (cART). The objective function is constituted to minimise the population of infected cells, VL and KS tumor and the harmful side effects of cART to the patient. The results indicate that the drug treatment strategies are capable of removing the viral reservoirs faster, consequently reducing the HIV and KS tumor burden. The predictions of the mathematical models have the potential to offer more effective therapeutic interventions based on VL and virus-infected cell load, hence support new studies addressing the superiority of VL over CD4 cell count when predicting life expectancy of HIV patients.

Public participation in Ebola virus disease (EVD) prevention efforts is essential to reduce outbreaks. Targeted education through practical health information for specific populations and sub-populations is essential to combat this disease. We study the dynamics of EVD in the presence of public health education to assess the role of behavior change instigated by health education in the dynamics of an outbreak. The intensity of behaviour change is clear in two outbreaks of EVD that occurred in Sudan just three years apart. The first occurrence turned into the primary documented outbreak of EVD and produced a sizable number of infections. The subsequent outbreak delivered far less cases, apparently on the grounds that the population in the district gained from the primary episode. We derive a system of ODEs to model these two opposite behaviors, using data from these two EVD instances to estimate parameters significant to the two opposite behaviors. We then simulate a future EVD epidemic in Sudan using our model, which includes two susceptible populations, one of which is more knowledgeable about EVD than the other. Our results show how a better educated population leads to fewer cases of EVD and features the significance of ongoing education in public health.

Keywords: : *neglected tropical diseases; viral infections; mathematical model; optimal control theory; Kaposi sarcoma; ebola virus disease; cART; viral load; HIV; KSHV; public health education; outbreak.*

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Publications

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2. B. Levy, E. Christina, O. Gaoue, **R. Kaondera-Shava**, M. Kgosimore, S. Lenhart, B. Lephodisa, **E. Lungu**, T. Marijani and F. Nyabadza, (2017). Modeling the role of public health education in Ebola virus disease outbreaks in Sudan. *Infectious Disease Modelling*, 2(3), 323-340.

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Abbreviations

KS	K aposi S arcoma
KSHV	K aposi S arcoma A ssociated H erpes V irus
HIV	H uman I mmunodeficiency V irus
HAART	H ighly A ctive A ntiretroviral T herapy
cART	combined A ntiretroviral T herapy
HHV-8	H uman H erpes V irus type 8
AIDS	A cquired I mmuno D eficiency S yndrome
DNA	D eoxyribo N ucleic A cid
WHO	W orld H ealth O rganisation
CD4	C luster of D ifferentiation 4
CD8	C luster of D ifferentiation 8
CTL	C yto T oxic L ymphocytes
VL	V iral L oad
OCP	O ptimal C ontrol P roblem
EVD	E bola V irus D isease
NTD	N eglected T ropical D isease

I dedicate this thesis to God Almighty my source of inspiration, wisdom, knowledge and understanding. I also dedicate to my dear husband Charles and my beloved daughters, Mercy, Patricia and Precious, for the encouragement and prayers they have sent my way along this journey.

Introduction

1.1 Overview of neglected tropical diseases

Neglected tropical diseases (NTDs) are a health crisis that is ignored by the developed world and begins to attract attention only when there is an outbreak that kills a large population [9]. Despite the fact that there are affordable drugs and treatments which are available to treat some NTDs, there is inadequate health interventions such as drug distribution and underfunded research [10, 11]. This group of preventable and treatable diseases is caused by parasitic, viral and bacterial and is most prevalent in tropical and subtropical conditions in 149 countries, specifically in regions such as South America, Asia and Africa [12]. NTDs affect over 1 billion people every year, hence resulting in the devastating health and economic problems for people living in poverty and end up being trapped in a cycle of poverty and disease [9]. Up to 1/2 million deaths and approximately 57 million disabilities have been attributed to NTDs [9, 13]. The first ever World NTDs day was held on 30 January 2020 [12]. Acquired immunodeficiency syndrome associated Kaposi sarcoma (AIDS-KS) and Ebola Virus Disease (EVD) are viral infections which are just two of the many NTDs that require attention. This thesis presents novel within-host ordinary differential equation (ODE) mathematical models in conjunction with application of the optimal control theory of AIDS-KS dynamics which investigates the disease's therapeutic interventions. Additionally, we derive an epidemiological system of ODEs to model the transmission dynamics of EVD to assess how behavior change induced by education can alter the dynamics of an outbreak.

KS is a cancer caused by Kaposi sarcoma associated herpes virus (KSHV) which is also referred to as human herpesvirus type 8 (HHV-8) [14]. Patients who have suppressed immune systems are the highest risk group to acquire KS [15, 16, 17, 18]. Clinically, there are four categories of KS [19, 20, 21]: classic KS which is characterised by a benign course affects especially the elderly men living in the Mediterranean area or Eastern European Jewish; endemic KS which is the most prevalent form in Central and Eastern Africa; transplant associated (iatrogenic) KS which is more frequent especially after an organ transplant and AIDS-KS which is a major AIDS-defining malignancy. The human immunodeficiency virus type 1 (HIV-1) fundamentally causes AIDS, if untreated, the disease progresses through three stages [1, 2, 22]: acute HIV-1 infection begins within a period spanning 2 to 4 weeks of being infected with the virus. At this stage some patients experience flu-like symptoms. The second stage is the chronic HIV-1 infection referred to as asymptomatic HIV-1 infection or clinical latency which lasts up to 10 years. During this stage patients may not have the HIV-related symptoms, but HIV-1 in the body will be multiplying. The final stage is AIDS, the most severe stage of infection characterised by opportunistic infections leading to death if there is no treatment. HIV-1 infection is transmitted predominantly via the exchange of body fluids, typically blood, semen and breast milk [23]. The clinical progression of untreated HIV-1 is depicted in Figure 1.1. In 2019, approximately 38 million people were living with HIV-1 worldwide, 690,000 deaths were attributed to this infection and approximately 25.4 million people were on highly active antiretroviral therapy (HAART) [24].

The HIV-era saw the AIDS-KS becoming the most prevalent of the four forms of KS, but the introduction HAART in 1996 has led to a dramatic reduction of the KS cancer load in developed countries [25, 26]. In resource-poor settings such as sub-Saharan Africa, AIDS-KS patients have a poorer prognosis than classical KS patients [27, 28]. Therefore, increasing treatment options and consequently overall survival of AIDS-KS sufferers is a vital goal to aim at. Clinical trials have shown that cART (HAART plus KS therapy) is effective in reducing the AIDS-KS burden [29, 30, 31]. Viral load (VL), which is the amount of virus in the body, is a critical risk factor in the transmission of HIV-1, hence on the basis of the World Health Organisation (WHO) 2016 guidelines [32], VL is preferred over CD4⁺ T cell count as a monitoring approach since it enables earlier and more accurate detection of treatment failure before the immune system is suppressed. After initiating HAART, VL testing occurs initially at 6 and 12 months intervals and then routinely every consecutive year [32].

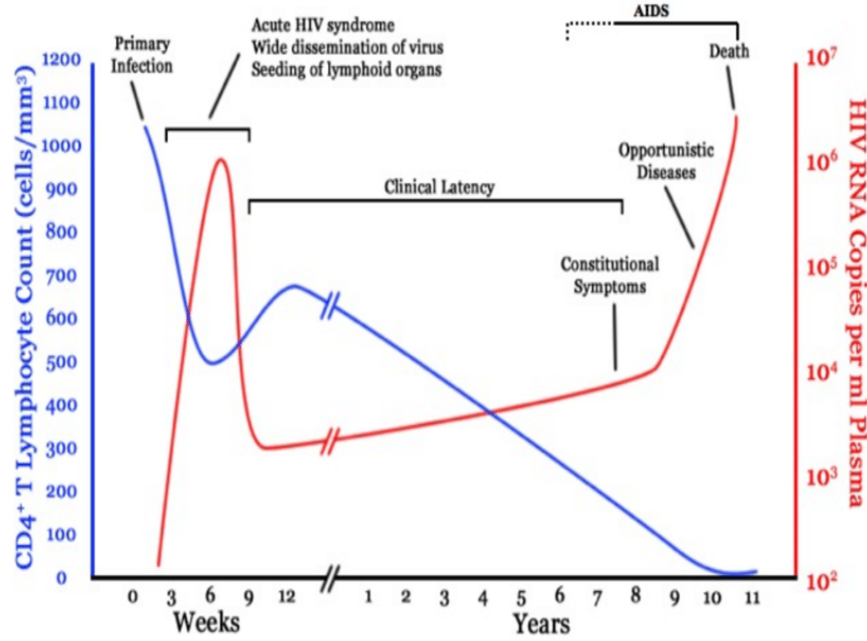


FIGURE 1.1: Clinical progression of an untreated HIV-1 infection [1].

In light of this, the growing emphasis on VL monitoring, the continued diagnosis of KS in HIV infected patients who are on HAART and the poor chances of survival after diagnosis in some cases emphasises the need for mathematical models based on VL. Despite the recommendation to use VL over $CD4^+$ T cell count when predicting HIV transmission and pathogenesis, in the past 20 years only 6% of studies related to HIV simulation included consideration of VL or VL testing [33]. This is surprising, even though the superiority of VL over $CD4^+$ T cell count in HIV progression on patients receiving ART has been shown mathematically [34]. As a consequence, the importance of understanding the within-host AIDS-KS dynamics is the key to monitoring effective treatment strategies. Nevertheless, only a very few AIDS-KS mathematical models describing within-host dynamics have been published, typically by Nani and Jin [35, 36] and Szomolay and Lungu [37]. This study therefore focuses on the VL and virus-infected cell load mathematical models that have the potential to offer more effective therapeutic interventions and render support to new studies (see [33, 34]) that address the superiority of VL over $CD4^+$ T cell count to predict life expectancy of HIV patients.

The Ebola virus disease (EVD) has given rise to a serious health risk to African nations since the mid 1970s. The infection was first detected in Democratic Republic of Congo

(once in the past Zaire) in a town close to the Ebola River in 1976, however 21 extra outbreaks have since happened in Central and West Africa generating over 28,000 total cases [38, 39]. While past episodes each delivered under 500 cases, the 2014 outbreak of EVD in West Africa generated more than 28,000 cases, the most cases of EVD to date [39]. The unmistakable distinction in the quantity of cases between different outbreaks makes anticipating the seriousness of future outbreaks troublesome. The specific transmission dynamics and the resulting number of cases are reliant on various factors including the particular strain of EVD, the population size in specific areas and explicit human behaviour that can either lessen or add to the spread of the disease [40].

The store for Ebola is believed to be animals, for example, bats and monkeys [41, 42]; outbreaks of Ebola start after an animal from the supply infects a human. The latency period for this disease is 2 to 21 days [43, 42]. When the virus is within the human population, people can contract the disease after coming in contact with the substantial liquids of an infected person, which can incorporate contact with somebody who has died from EVD. This transmission course is exacerbated by the infection as substantial liquids are created in those contaminated by the disease resulting in vomiting, defecation and bleeding. Since there is no immunisation accessible at the moment, Ebola patients are treated with oral or intravenous liquids with the inclusion of treating explicit manifestations [42].

Social practices in West Africa assume an enormous role in the transmission of Ebola [40]. At the point when a relative turns out to be sick, it is regular practice to renounce looking for clinical therapy and rather consult a conventional herbalist or take care of the patient at home. This is often particularly genuine within the case of Ebola as early indications are comparative to those of influenza. With relatives having to take care of the sick frequently brings about various family members getting the ailment [44]. Other exceptionally influenced zones outside the house are medical care settings. In reality, if protocols are not taken after, hospital settings are competent of producing significant number of cases amid Ebola episodes [45, 46]. It is regular practice and surely an honour for dead people to be washed, grasped, kissed and organised for burial with the aid of using own circle of relatives [47]. This is tricky as deceased individuals actually convey and are fit for spreading the infection. Indeed, even profoundly educated people who are mindful of progressing Ebola outbreak may take an interest in such social practices because of a paranoid fear of being marked elitists. Consequently, burial practices assume a significant part in spreading EVD [45].

From past episodes it is clearly apparent that taking safety measures against spreading Ebola can rapidly lessen or take out an outbreak [47]. For instance, the first estimate of the 2014 EVD epidemic in West Africa estimated that, without any intervention, 1.4 million cases would have been generated during the epidemic [48]. Be that as it may, the WHO announced the outbreak to be an “international health emergency”, dispatched a huge global intercession, facilitated help from various elements and included gigantic data missions to teach the overall population about forestalling the spread of EVD [49]. The help included medical care assets for the influenced nations and the data crusades modified character behavior, which immediately contained the outbreak and restricted the total number of infections hugely [50]. Also, considering the cases of Ebola that were exported to the United States and Europe amid the 2014 episode in West Africa, cautious safety measures were taken by the European and American population and governments, which avoided secondary outbreaks from happening both in West Africa and their nations. This study focuses on the role of public health education on the evolution EVD in the two outbreaks that took place in Sudan only 3 years apart.

1.1.1 AIDS-KS biological background

Discussion of the AIDS-KS mathematical model must be preceded by a well-developed basic understanding of the biological background that is relevant to this study. An overview of the host immune response to infection is given which is followed by a run-through of the lifecycles of HIV-1 and HHV-8 virions, how the virions interact with the immune system and how the treatment disrupts the life cycle. The pivotal role of HIV-1 in AIDS-KS pathogenesis is also discussed.

Host immune response to infection

There are two important roles performed by the immune system: detection of pathogens (such as viruses, fungi or bacteria) and elimination of these pathogens [51]. When pathogens invade the body, the body mounts two types of defence mechanisms namely the *innate* response and if this response fails it resorts to the *adaptive* response [52]. Innate immune response is instantaneous, whereas the adaptive response is a delayed response and can take a few days to fully develop. However, it is from this response that the body forms immunological memory [52]. The focus of this study is on the adaptive immune response to infection by viruses.

Three types of cells, that is, B cells, $CD4^+$ T cells and $CD8^+$ T cells (also known as effector cells or cytotoxic T lymphocyte) are critical in the adaptive immune response [53, 54]. For convenience, instead of $CD4^+$ T cells, we use T cells and for $CD8^+$ T cells, we use effector cells in the rest of the thesis. B cells produce antibodies used to detect and neutralise viruses. T cells play a central role in regulating the immune response and are considered as the “messenger” or the “control center” of the immune system because they alert the immune system that there is a pathogen that needs to be eliminated. In turn, the effector cells respond to the signals by the T cells to undertake the mission of eliminating the infected cells. Under normal circumstances, immune cells work together effectively to eliminate infection.

HIV-host interaction

The focal point of HIV-1 is its targeted infection of T cell deoxyribonucleic acid (DNA) thereby turning it into a factory producing thousands of copies of the virus [51, 55, 56]. HIV-1 does not kill the infected individual directly but over time the virus depletes the T cells. By the time the effector cells are deployed to eliminate the infection, it is sometimes too late and the infection has built up into a clinical problem and the patient’s immune system is suppressed and opportunistic infections take advantage of the compromised immune system. The two key markers which are used for monitoring HIV-1 infection are the VL and T cell count as shown in Figure 1.1.

An understanding of the viral life cycle forms the basis for the design of drugs which interfere with the life cycle [57]. The HIV-1 lifecycle consists of the following stages: binding; fusion; reverse transcription; integration; replication; assembly and budding [2] as shown in Figure 1.2. The lifecycle begins when HIV-1 binds to a T cell by fitting perfectly like a key in a lock. The virus then fuses with the T cell membrane and releases its genetic material into the host cell. Once inside the cell, reverse transcription takes place where the virus converts its genetic material into viral DNA. This is then followed by integration where the viral DNA enters the nucleus and takes control of it. Copies of the HIV-1 genetic material are created inside the cell during replication. The new HIV-1 is assembled and then released from the host cell into the bloodstream to infect other cells. The turn around time from entry to production of infectious virions is approximately 24 – 48 hours [58].

We consider two categories of antiviral drugs [51, 59, 60]; (1) reverse transcriptase inhibitors (RTIs) which target the reverse transcription stage. These antiviral drugs block

the conversion of HIV-1 genetic material into viral DNA. Hence without DNA, HIV-1 cannot make copies of itself. (2) protease inhibitors (PIs) which target the assembly stage. When PIs are used, new viruses can be formed but they will be immature and cannot infect T cells. Undetectable HIV-1 VL is when the levels are below 200 copies per mL [61, 62].

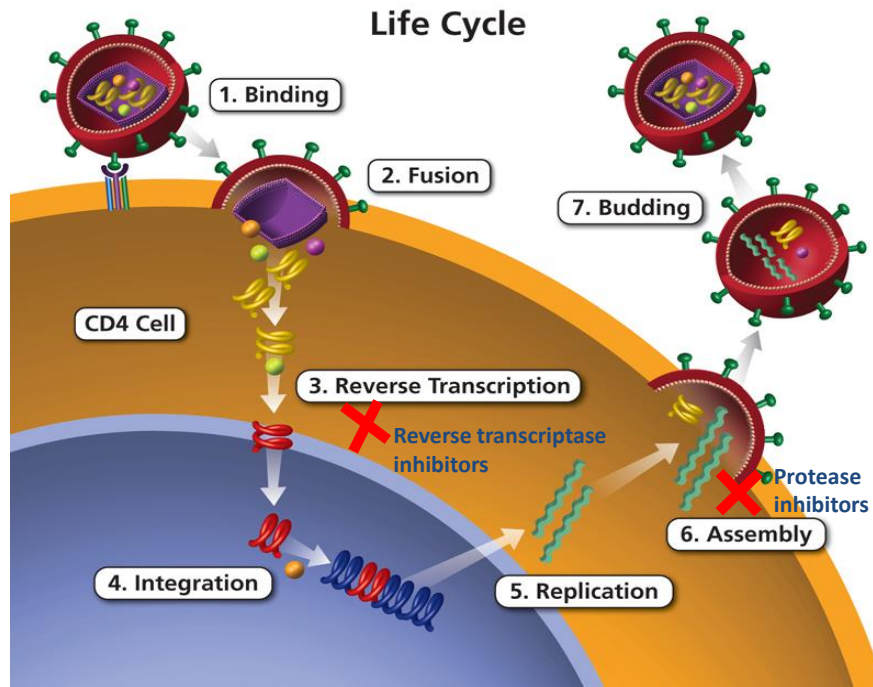


FIGURE 1.2: HIV-1 lifecycle where the red crosses illustrate the stages which are blocked by RTIs and PIs [2].

HHV-8-host interaction

HHV-8, present in all four forms of KS, was discovered in 1994 by Chang *et al.* [63] and it infects B cells primarily [3]. Transmission of the virus is predominantly via saliva, but it may also be transmitted sexually, vertically or via blood products [14, 64]. Children may acquire HHV-8 infection through saliva sharing during childhood practices of candy sharing, the premastication of food for infants and toothbrush sharing [65]. Tumors usually appear externally on the skin and also internally inside the mouth, the lymph nodes, the lungs or digestive tract which may result in severe internal bleeding [19].

HHV-8 is a double stranded DNA virus with a life cycle that consists of two distinct phases: *latent* and *lytic* replication [3, 66, 67]. The DNA is surrounded by a capsid and

then an envelope which contains several glycoproteins that are used for attachment and fusion. The virus genome is delivered to the cell nucleus where there is a choice of either becoming lytic or latent. Lytic phase creates new viral particles that later infect healthy B cells to continue the cycle. The virus production results in the killing or lysing of the host cell. Latent phase does not result in production of virions, hence the viral DNA can settle in the nucleus quietly for decades in a healthy person until it is reactivated when the immune system becomes suppressed. The HHV-8 lifecycle is shown in Figure 1.3. The target for therapy inhibits the switch from latency to lytic replication [64, 68]. When the number of HHV-8 virions is 500 copies per mL or less the VL will be undetectable [69].

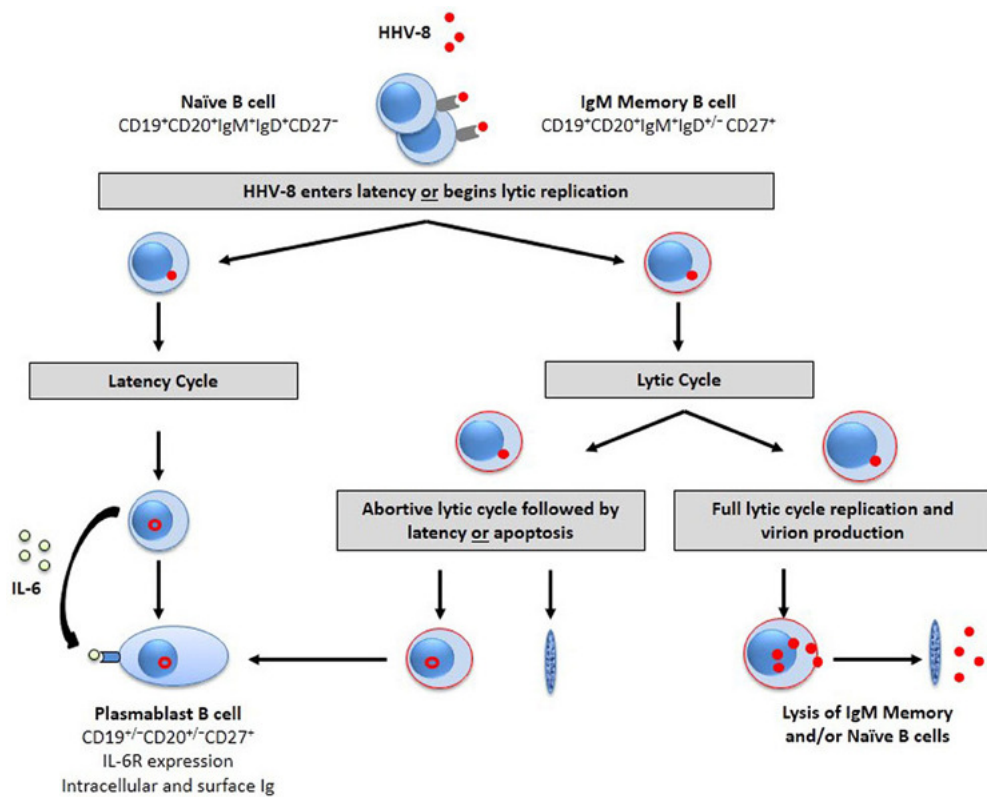


FIGURE 1.3: HHV-8 lifecycle [3].

Role of HIV-1 in AIDS-KS

HIV-1 plays a pivotal role in KS pathogenesis [4]: infected T cells release HIV-1 tat protein, inflammatory cytokines and growth factors which reactivate latently infected B cells from latency to lytic and this results in the development of KS.

1.1.2 Control and prevention of neglected tropical diseases: AIDS-KS and EVD

Interventions for neglected tropical diseases (NTDs) offer a great deal of hope for the control and prevention of the diseases [70]. The effective control of AIDS-KS requires cART (which is a combination of HAART together with KS therapy) which has been shown to be effective in clinical trials carried out in areas of high prevalence and poor resources [29, 30, 31, 71]. In spite of its success, HAART's primary concern is non-adherence, which is the most common cause of virologic failure. Non-adherence comes in the form of missing, skipping, postponing doses, not respecting food requirements and drug holiday [72].

In order to control Ebola virus disease (EVD), changes in behaviours driven by public health education can change the dynamics of an outbreak. This is evident from the first two Ebola outbreaks in Sudan, where the relative magnitude of each outbreak was an impression of readiness of health care providers and knowledge of the general public about the disease [73, 74].

1.2 Motivation

Neglected tropical diseases (NTDs) are health crises that are ignored by the developed world [9]. Affordable drugs and treatments are available to treat some NTDs [10, 11].

Despite the advent of HAART, KS is still being diagnosed in HIV-1 infected patients because they access HAART treatment too late as accessibility to drugs is based on the T cell count [15, 75, 76]. Regardless of the WHO 2016 guidelines [32] to use viral load (VL) monitoring approach over T cell count to diagnose and subsequently confirm treatment failure, in the past 20 years only 6% of studies related to HIV simulation have demonstrated the potential of VL or VL testing [33], even though the superiority of VL over T cell count in HIV progression on patients receiving ART has been shown mathematically [34]. The continued diagnosis of KS in the HAART-era, together with the poor chances of survival in some cases emphasises the importance of understanding the dynamic relationship between host and viral infections since it is the key to monitoring effective strategies of dealing with KS in patients who are infected with HIV-1 [77]. In spite of everything, only a very few AIDS-KS mathematical models describing within-host dynamics have been published. Typical examples are the mathematical models by Nani and Jin [35, 36] and Szomolay and Lungu [37]. The WHO 2016 guidelines and the immunological models [35, 36, 37]

have motivated this study to reveal the potential of this approach as a more effective therapeutic intervention based on VL.

Since the disease was first detected in the Democratic Republic of the Congo, Ebola virus disease (EVD) has posed a serious health risk in African countries. This was followed by an additional 21 outbreaks in West and Central Africa, which resulted in more than 28,000 cases. Fewer than 500 cases were reported in each of the previous outbreaks, on the other hand, the latest 2014 EVD outbreak in West Africa, generated more than 28,000 cases, the highest number of EVD cases to date. Mathematical models have been utilised by Fast *et al.* [78] and Shen *et al.* [79] to assess the impacts of public health education on the evolution of EVD. Unlike the previous models [78, 79] which basically decrease different rates because of public health education, we estimate different parameters for each group.

1.3 Objectives

This study proposes mathematical models and control of within-host models for AIDS-KS and an epidemiologic model for Ebola virus disease (EVD).

In order to achieve this, we:

- (i) formulate novel within-host ODE mathematical models which describes the KS-immune system interactions in the presence of both HIV-1 and HHV-8 by incorporating low or high VLs into the proliferation terms of the immune cell populations,
- (ii) carry out a detailed mathematical analysis together with elaborate simulations,
- (iii) investigate for what viral sources the body remains viral free and what viral sources lead to viral escape,
- (iv) apply optimal control theory to propose optimal therapeutic interventions for AIDS-KS,
- (v) derive an epidemiologic ODE mathematical model to assess the effects of public health education on the evolution EVD.

1.4 Contribution of this study

The findings of this study will be of great benefit to understanding the evolution and control of AIDS-KS and EVD:

- (i) it will assist the *health care sectors* to develop and refine optimal combinations, doses and scheduling of treatments for AIDS-KS patients,
- (ii) for *researchers*, it will provide a mathematical framework for future research in mathematical modelling of the effect of VL on AIDS-KS as well as the optimal control strategy for treatment. Consequently, it will allow for the development of more refined hypotheses that can also be tested via clinical experiments. Moreover, the study will add more knowledge to existing literature on the effects of public health education on the evolution of EVD,
- (iii) for the *government*, it will lay a foundation towards shaping the policies, programmes and control of NTDs such as AIDS-KS and EVD,
- (iv) it will also assist the *society* in general to have an understanding how AIDS-KS and EVD can be prevented and controlled,
- (v) the study will help the *public health educators* to design educational seminars and workshops that will educate people about EVD, the impact of VL on AIDS-KS and how best the diseases can be controlled.

1.5 Scope and limitation of the study

We propose within-host model for AIDS-KS and an epidemiologic model for EVD. We develop and analyse novel mathematical models based on ODEs which reveal the effect of HIV-1 and HHV-8 VL on AIDS-KS progression. Specifically, low or high VLs are incorporated into the proliferation term of the immune cell populations. Detailed mathematical analysis together with elaborate simulations is carried out. Optimal control theory is applied to the models using cART (HAART together with KS therapy) as interventions over a 20 day time horizon in order to propose an effective treatment plan for AIDS-KS. The necessary conditions for the optimal system are derived using the Pontryagin's Maximum Principle. The objective function is constituted to minimise the population of infected cells, VL, KS tumor and the harmful side effects of cART to the

patient. Existence of an optimal control is proved and the optimal control models are solved using the forward-backward sweep method. The parameter values are based on clinical and experimental results from published studies. The limitation to this study is the unavailability of some parameter values since they have not been clinically determined before in humans, typically the parameter values with regards to HHV-8.

Additionally, we formulate an ODE epidemiological EVD model which consists of two types of individuals in the Sudanese community: one who is educated about Ebola and is careful not to risk the disease and one naïve who does not take precautions against contracting or spreading the disease. We partition the susceptible population into two groups: individuals who have not yet been influenced by public health education and those who have been educated. We estimate different parameters for each group and use data from the aforementioned Ebola outbreaks in Sudan to parameterise our model and also include the effect of information on increasing the rate of infected individuals who seek professional health care.

1.6 Thesis layout

The focus of this study is on the mathematical modelling of NTDs which are caused by viral infections, typically AIDS-KS and EVD. Hence, this report consists of chapters which will cover the formulation, analysis of within-host AIDS-KS mathematical models (in conjunction with application of the optimal control theory) and an EVD epidemiological mathematical model. The thesis adopts the following layout:

Chapter 2 is dedicated to reviews of the relevant literature pertaining to mathematical models as well as existing clinical studies on AIDS-KS. This provides the context for the study. Also, a review of the mathematical models which have been used to evaluate the effects of public health education on the evolution of EVD is given.

In **Chapter 3** several mathematical concepts and results that are used throughout the thesis to qualitatively analyse and numerically implement the models are presented: well posedness of solutions, stability analysis (both local and global), sensitivity and uncertainty analysis, optimal control theory and numerical implementation by the forward-backward sweep method.

Chapter 4 presents the formulation of the novel within-host weak viral source and strong viral source (which occurs due to non adherence to treatment) models which illustrate the interaction between infected B and T cells, the viruses (HIV-1 and HHV-8), KS and the

virus-specific effector cells. Detailed mathematical analysis and numerical simulations of the AIDS-KS model is carried out to investigate the effect of VL on AIDS-KS progression. These models are then extended for the optimal control problem that will be presented in the chapter which follows.

Chapter 5 of this work deals with the optimal control for both the weak and strong viral source models in order to determine the optimal treatment plan for cART that minimise the KS tumor, infected T-cell, VL burden and the harmful side effects of cART. The existence of the optimal control pair is discussed and by using an adapted numerical technique for solving optimal control problems from forward-backward sweep method, an optimal control schedule of AIDS-KS through cART is solved.

In **Chapter 6** we derive a deterministic epidemiological mathematical model for the transmission dynamics of EVD to assess how behavior change induced by education can alter the dynamics of an outbreak in Sudan.

Finally, we conclude with a disussion of the AIDS-KS and EVD mathematical models in **Chapter 7**.

Chapter 2

Literature Review

Mathematical models have a great impact on and enrich our understanding of neglected tropical diseases (NTDs) and the efforts required to control them. This chapter reviews the mathematical models for AIDS-KS and Ebola virus disease (EVD) dynamics and discuss ways how viral infections are controlled and for those whose treatment drugs/vaccines are in clinical trials what the efficacies for the drugs should be.

2.1 AIDS-KS mathematical models reviews

Cancer growth in HIV-1 infected individuals is a hot topic area. Great efforts have been made by scientists for many years to understand the pathogenesis of AIDS-KS and how best it can be managed through clinical trials which in turn have stimulated mathematical models. The AIDS-KS reviews discussed herein will focus only on major studies relevant to the AIDS-KS and have inspired this research. These are in two categories: (i) the clinical studies on the role of HHV-8 in KS pathogenesis and (ii) the role of HIV-1 in AIDS-KS pathogenesis. To support the fore-mentioned clinical reviews and effectively quantify the processes involved, we shall also review literature on VL mathematical models and AIDS-KS mathematical models (epidemiological and immunological) which motivated this research. This study will primarily focus on within-host VL mathematical modelling of AIDS-KS and how best it can be treated. Our work is motivated by the review article by Forman [4] who proposed a model for the pathogenesis of AIDS-KS. We want to explore in chronological order the AIDS-KS clinical studies before and after Forman's publication.

2.1.1 Clinical studies on AIDS-KS

The role of HHV-8 in KS pathogenesis

There is compelling evidence tying HHV-8 to the pathogenesis of all four types of KS. DNA sequence in the studies below [63, 80, 81, 82, 83, 84] was found in biopsy samples together with anti-HHV-8 antibodies in serological studies.

Chang *et al.* [63] used a novel technique which revealed that KS was caused by a new virus, HHV-8 over a century since KS was first described by Morris Kaposi in 1872. Chang *et al.* [63] searched for foreign DNA sequences in AIDS-KS samples by using representational difference analysis (RDA). Unique sequences were detected in KS tissues from AIDS patients but absent in most non-KS tissues. However, the study could not establish the link between the sequences and AIDS-KS. Despite the shortfall, this novel discovery [63] opened up the doors to other scientists who subsequently detected the virus in KS samples.

Li *et al.* [80] carried out a study to identify the specific cells within KS tumors that contain the HHV-8 DNA. Both polymerase chain reaction (PCR) and *in situ* hybridisation techniques were applied in the study. By using the PCR technique, 14 skin biopsy samples (3 classic KS(CKS), 6 AIDS-KS, 3 normal and 2 common warts from healthy individuals) were examined for HHV-8 DNA sequences. The virus was detected in all 9 KS samples (CKS and AIDS-KS) but not in the 5 non-KS tissue samples. The *in situ* hybridisation technique on the KS samples confirmed that the viral DNA sequences were constrained to the nuclei of the endothelial cells lining the vascular slits within AIDS-KS and classical KS lesions. The findings had important suggestions about the cell of origin and the alleged role of HHV-8 in pathogenesis of KS. However, further clarification of the role of the novel HHV-8 in the pathogenesis of KS was needed.

Huang *et al.* [81] investigated the causative role of HHV-8 in the pathogenesis of KS. The study examined 31 fresh KS skin biopsy samples (3 CKS and 28 AIDS-KS) by PCR. The controls were 8 samples which were taken from healthy persons who were undergoing surgery. The virus was absent in the healthy persons samples by the PCR method. As for the samples which tested positive for HHV-8 DNA, confirmation that the extracted RNA was amplifiable was done by further examinations by performing three techniques: reverse transcription polymerase chain reaction (RT-PCR), Northern blot hybridisation analysis and *in situ* hybridisation. The results confirmed RNA expression of HHV-8 in the samples, hence supporting the pivotal role of HHV-8 in KS development. This was

an eye opener on the role of HHV-8 participating in the pathogenesis of KS. However, the study did not determine the progenitor cells as playing a role in KS pathogenesis. Moreover, the relationship between HHV-8 level of expression and the various stages of the development of KS was not determined.

Forman *et al.* [82] investigated the role of HHV-8 in the pathogenesis of KS. The study used biopsy skin lesions of KS and from pulmonary KS to determine whether HHV-8 is an etiologic agent of KS. Normal skin samples were used as the controls. Both *in situ* PCR and PCR *in situ* hybridisation was performed on 21 biopsy skin samples. The results tested negative for HHV-8 for the normal skin samples and positive for KS infected samples, hence confirming that the virus is an etiologic agent of the pathogenesis of KS. The findings for this study were that HHV-8 was constrained to endothelial cells and spindle shaped tumor cells. These experiments confirmed and extended the previously published results by Li [80]. Despite giving an insight into the active role of HHV-8 in KS development, the study was not validated by a proper animal model which demonstrated that the injection of HHV-8 can cause KS lesions.

Davis *et al.* [83] developed an enzyme-linked immunosorbent assay (ELISA) to detect the antibodies of HHV-8. The study performed serological tests on 118 serum samples where the control was the HIV-1 positive patients without KS. Overall, there was higher reactivity in the assay for HIV-1 positive patients with KS compared to HIV-1 positive patients without KS. The study concluded that HHV-8 plays a key role in KS pathogenesis. This conclusion was in agreement with previously published results [63, 80, 81, 82]. The drawback of the study [83] was that in the selection of specific peptides, there was a limitation of the sequence information on HHV-8. The study managed to identify only one peptide which reacted with 60% of sera from KS patients, hence the assay was not very sensitive to detect HHV-8 antibodies.

Kennedy *et al.* [84] carried out a study to determine the role of HHV-8 as a causative agent for KS. Sixteen (16) early KS samples derived from the skin and lymph nodes were examined for HHV-8 presence. The laboratory tests conducted were PCR and TaqMan-PCR and then *in situ* amplification was carried out to identify the candidate infected cells. The results indicated that 87% of the cases were positive. Moreover, HHV-8 amplifications were localised *in situ* to endothelial and spindle cell proliferations in early KS. The study concluded that HHV-8 plays a crucial role in the pathogenesis of KS. The limitation of this study was that the interaction between HHV-8 and other known factors involved in KS development, such as cytokines and anti-apoptosis genes, still needed clarification.

The role of HIV-1 in AIDS-KS pathogenesis

We want to review and ascertain the role of HIV-1 in the pathogenesis of AIDS-KS.

Harrington *et al.* [85] studied the role of tat protein on HHV-8 replication. A total of eleven samples of peripheral blood mononuclear cells (PBMC) were taken from three AIDS patients, four AIDS and cutaneous KS patients, one AIDS and systemic KS patient, one patient with renal transplant and two HIV-1 negative blood donors. The cells were cultured with tat protein for four days. The control consisted of mononuclear cells carrying HIV-1 long repeat chloramphenicol acetyltransferase (CAT) reporter gene that was treated with similar tat concentration used in the eleven samples of PBMC. HHV-8 infected cell line, body-cavity-based lymphoma cell line (BCBL-1) were also studied in parallel. The results indicated an increase in CAT activity which suggested that mononuclear cells can absorb the tat protein. An increase was also noted in HHV-8 DNA in tat treated BCBL-1 cells, the renal transplant HIV-1 negative patient, an HIV-1 positive patient with systemic KS, PBMCs from three HIV-1 positive patients and two HIV-1 positive patients with cutaneous KS. There was no detection of HHV-8 DNA in HIV-1 negative patient and the normal control after stimulation by tat. The study concluded that tat can activate HHV-8 replication and increase the VL. However, the study was not conducted on a large sample of HIV-1 infected and healthy individuals to determine the influence of other factors and the pathological extent of the virus.

Fiorelli *et al.* [86] considered and demonstrated the critical role of which interferon- γ , one of the inflammatory cytokines released by infected T cells, plays in promoting AIDS-KS development. *In vitro* experiments involving endothelial cells cultured in inflammatory cytokines: medium without growth supplements (CR), oncostatin M (OM), interleukin (IL)-1 ($\alpha + \beta$), tumor necrosis factor (TNF) ($\alpha + \beta$), interferon (IFN)- γ and T cell-conditioned media (TCM) were performed. Tat was then added to the cultured cells and their growth was monitored. The control to this experiment were the human umbilical vein endothelial cells which were activated by TCM. The study concluded that interferon- γ alone is the key cytokine that initiates the development of AIDS-KS by inducing endothelial cells to respond to the HIV-1 tat protein. The study recommended interferon- γ based drugs as a target for therapy for AIDS-KS treatment. Regretably, HHV-8 which causes KS lesions was not included in the experiment, the study could not confirm whether a reduction in interferon- γ would be of therapeutic benefit to KS.

Monini *et al.* [87] investigated the effect of inflammatory cytokines on HHV-8 infection. Peripheral blood mononuclear cells and purified cell populations from 45 patients with

KS and 45 at risk of KS were examined for the viral DNA. The results illustrated that the presence of inflammatory cytokines maintained HHV-8 load in cultured cells and the presence of inflammatory cytokines increased VL to detectable levels in peripheral blood mononuclear cells from serologically positive patients who were polymerase chain reaction negative before samples were cultured. This was attributed to the effects of interferon- γ which induced virus replication. The study concluded that inflammatory cytokines have effects on the target cells of HHV-8 by inducing the growth and differentiation of monocytes into KS-like spindle cells which have markers of endothelial macrophages.

Chang *et al.* [88] examined the possible links between inflammatory cytokines and KSHV replication. Latently infected body-cavity-based lymphoma cell line (BCBL-1) cells were triggered to reactivate when exposed to cytokines. The results showed that interferon- γ triggered lytic replication. Their experimental findings correlated with clinical observations [87] and confirmed for the first time that inflammatory cytokines directly adjusts KSHV replication.

Forman proposed AIDS-KS dynamics

With the aim of proposing AIDS-KS dynamics, Forman [4] reviewed some articles on the molecular pathogenesis of KS. In particular, the roles of HHV-8 and HIV-1, that is, tat protein and inflammatory cytokines from infected T cells, in the pathogenesis of AIDS-KS were extensively reviewed. Forman [4] proposed a model for the pathogenesis of AIDS-KS. The proposed model presented schematically in Figure 2.1 included all the essential elements: infected T cells, KS cells, KS progenitor cells, pre-KS cells, latently infected B cells and HIV-1 tat, inflammatory cytokines and growth factors. The model proposed that HIV-1 infected T cells are responsible for releasing HIV-1 tat, cytokines and growth factors. According to this model, HIV-1 tat is responsible for the activation of the pre-KS cells and the cytokines reactivate the latently infected B cells resulting in the release of HHV-8 virions. The role of HIV-1 in the pathogenesis, as described by Forman [4], is also supported by previously published studies [86, 87, 88]. In turn, the virions infect the pre-KS cells which progress to KS. The role of HHV-8 in the pathogenesis of KS is supported by many studies [63, 80, 81, 82, 83, 84]. The motivation of this thesis comes from this review article [4] and the models developed in this thesis are based on the schematic diagram in Figure 2.1.

Subsequent studies by Aoki and Tosato [89] analysed the possibility that HIV-tat promotes KSHV associated infection. The experiment was done by incubating together KSHV,

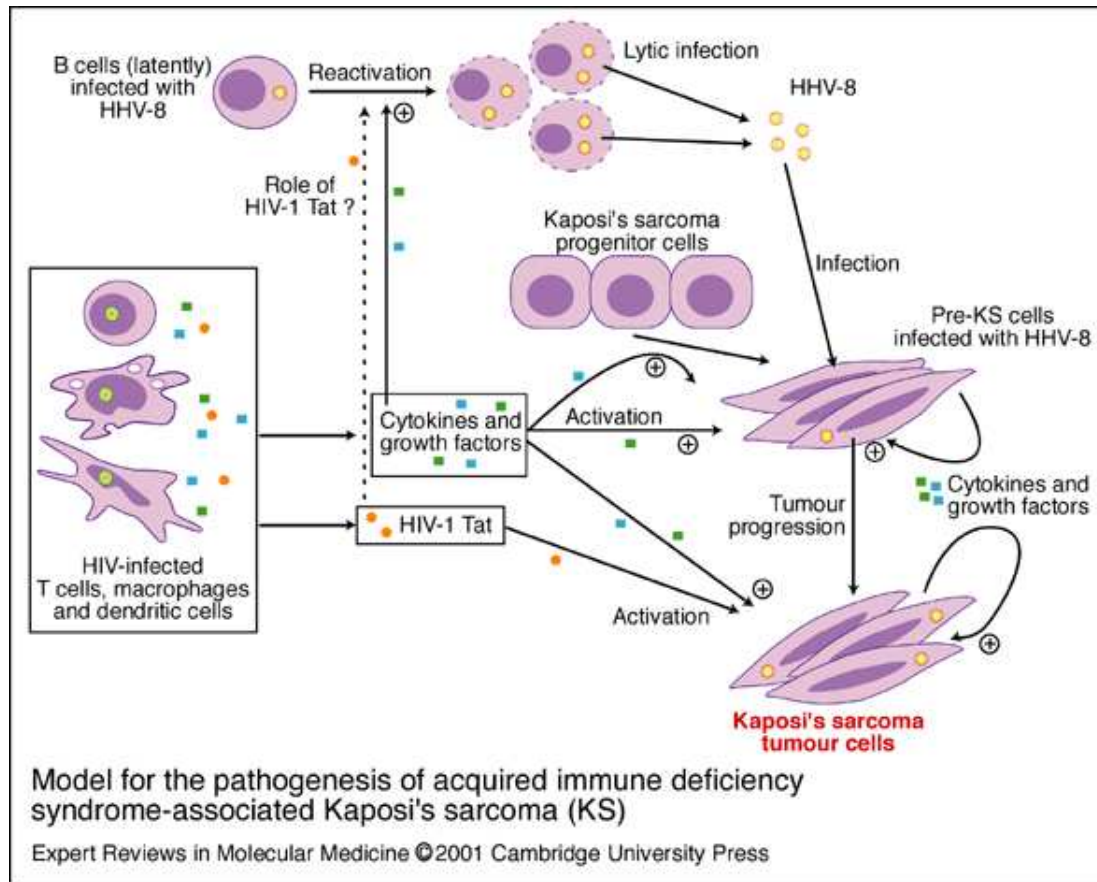


FIGURE 2.1: Forman's [4] proposed model for the pathogenesis of AIDS-KS.

endothelial cells and HIV-tat. After a period of 24 hours of incubation, the results showed that tat enhances the entry of KSHV into endothelial cells. These results were in agreement with Forman [4] and explained why the AIDS-KS is the most aggressive of all the KS clinical forms. Unfortunately, this study is not supported by clinical studies.

Clinical trials on AIDS-KS treatment

Bihl *et al.* [29] randomly selected 33 HIV patients with KS for treatment based on two treatment options over a period of 11 months: HAART combined with chemotherapy and HAART alone to evaluate HIV and KSHV VL and disease prognosis. A significant reduction in VL and a better prognosis was observed in the HAART combined with chemotherapy patients than in those receiving HAART alone. Despite the study's potential for designing immune-based therapeutic interventions, the role of the host's effector cells in the control of AIDS-KS was not included.

Mosam *et al.* [31] conducted a randomised, controlled, open-label trial on treatment-naïve HIV participants at King Edward VIII hospital in South Africa over a period of 12 months. The goal was to determine the best treatment approach for AIDS-KS patients between two approaches namely, fixed dosages of HAART alone and HAART combined with chemotherapy (CXT). Fifty-nine (59) participants were administered with HAART alone and fifty-three (53) were enrolled in the CXT trial. The trial indicated that patients who were on CXT registered better overall response rate than those on HAART alone. The study concluded that CXT may be more beneficial in reducing the AIDS-KS burden than HAART alone. However, the limitation of this study is that it was not designed to evaluate optimal chemotherapy in AIDS-KS patients.

Krown *et al.* [30] carried out a randomised, open-label non-inferiority clinical trial with the aim to investigate and recommend optimal treatment strategies for AIDS-KS in areas of high prevalence and resource-poor. The study randomly enrolled 334 HIV infected individuals who have KS from 11 AIDS clinical trial groups from 6 countries (Brazil, Kenya, Malawi, South Africa, Uganda and Zimbabwe) between October 2013 and March 2018. The results confirmed the conclusion by Mosam *et al.* [31] that treatment of AIDS-KS using combined therapy (HAART and chemotherapy) is beneficial. The advantage of this study is that it included a randomised design involving follow-up visits to evaluate for KS response, KS progression and adverse or side effects. However, the study had several limitations including difficulty in replicating the clinical trial in resource-poor countries where there is scarcity of cancer therapy and diagnostic infrastructure.

2.1.2 Viral load mathematical models

Estill *et al.* [90] developed an individual-based mathematical model which investigated the convenience of viral load (VL) monitoring versus T cell count to reduce HIV transmission. For a cohort of 1000 HIV infected individuals in Southern Africa, the stochastic mathematical model simulated the benefit of using either VL or T cell monitoring during the first 5 years on HAART. The model predicted that VL monitoring would be an important factor in reducing mortality and could prevent or lower HIV infections. The study by Estill *et al.* [90] asserts that VL provides an additional benefit for ART as a preventative measure if treatment starts early. However, the results appear to be valid for short terms. Hence, for a long term evolution of the disease, there is a need for a dynamic transmission model involving susceptible people to HIV and partnerships of various susceptible individuals. Moreover, treatment programs are located in urban areas

where there is easy access to VL and T cell monitoring and are therefore not representative of all programs and ones of Southern Africa.

In a subsequent study, Estill *et al.* [91] adopted the previously developed individual-based mathematical model [90] to study the effect of VL on mortality over a 5-year follow-up. The study examined how VL caused higher mortality among patients accessing ART in Zambia and Malawi based on T cell counts only compared to South Africa where treatment is accessed based on VL. Results indicated that there was greater reduction in mortality in the South African group. The study experienced several limitations, firstly, the simulations considered only virologic and immunologic treatment response and ignored other factors such as gender, adherence to treatment, baseline T cell and VL values and co-infections. Secondly, due to insufficient data, the rate of immunologic failure was assumed to be constant. Thirdly, it was assumed that after virologic failure, hazard of death remained constant and finally, the study did not include economic considerations which are impediment for developing countries.

Salazar-Vizcaya *et al.* [92] developed a mathematical model for HIV positive children below the age of 16 years in seven South African cohorts. The model assessed the supremacy of VL over T cell count monitoring over a period of 5 years. Simulations were done for treatment programmes with 6-monthly T cell count or 6 to 12-monthly VL monitoring. Comparisons were made for mortality, second-line ART use, immunologic failure and time spent on failing ART when using T cell count and VL for monitoring. The results showed that for those children VL monitoring did not affect 5 year mortality, however, the benefit of VL monitoring was shown in reduced time on failing ART, improved immunological response and increased switching to second-line ART for patients with virologic failure. Hence, the study supports VL as a basis for accessing treatment and suggests that this approach could reduce drug resistance. However, the study has its limitations: with the change in clinical practices in South Africa, the data used may not reflect the current practices, for example prevention of mother-to-child transmission coverage which has increased. Due to limited data, simulations were done up to 5 years after initiating ART.

Lesosky *et al.* [93] formulated a mathematical model to simulate VL from conception to delivery to determine when and how frequently VL should be monitored in 10,000 pregnant HIV-infected women who initiated ART during pregnancy. The VL data was taken from Maternal and Child Health-Antiretroviral Therapy cohort in South Africa. The model tracked VL (both pre-ART and post-ART) by using three major components: pre-ART VL, viral decay immediately after ART initiation and viral maintenance, which examined different VL monitoring schema in predicting VL at delivery. The results provided key

insights into routine VL routine monitoring strategies for pregnant women who initiate ART during pregnancy. The study concluded that pregnant women warrant VL monitoring approaches different from non-pregnant adults where a single VL test conducted late in gestation may be used to predict approximately three-quarters of all elevated VL at delivery. Testing turnaround times require careful consideration, and point-of-care VL testing may be the best approach for measuring VL at delivery. The disadvantages of the study is that the model did not include the turnaround times for VL monitoring, it was assumed that all VL samples had results available and the cost effectiveness of the different VL monitoring approaches was not taken into consideration.

Shoko and Chikobvu [34] fitted time-homogeneous markov models on T cell count monitoring and VL monitoring in order to assess and compare the use of both monitoring methods in monitoring HIV progression in patients who are on HAART. The study concluded that VL monitoring is more superior than T cell count monitoring in HIV infected individuals who are on treatment. However, the limitation to this study was that opportunistic infections were not considered.

2.1.3 AIDS-KS epidemiology mathematical models

To the best of my knowledge, one of the few epidemiological mathematical models describing the HIV/KS coinfection dynamics was proposed by Lungu *et al.* [75]. The model for sub-Sahara Africa was designed to quantify the proportion of patients on HAART treatment who never develop KS at varying rates of treatment. This study was done during the period when the criteria for accessing HAART was made difficult and was based on economic grounds rather than clinical. The findings of this study revealed that provision of HAART to HIV-1 infected patients reduced the number of patients who end up acquiring AIDS-KS. Moreover the study emphasised that low access to proper treatment hindered the prevention of KS related complications in areas of high KS prevalence. Despite the model giving insight to the importance of intervening early with treatment before KS developed in HIV infected individuals, there are some drawbacks to the study such as lack of data resulting in most of the parameters being estimated. Furthermore, other modes of HHV-8 transmission such as interaction with an HHV-8 infected person via body fluids such as saliva, blood, vertically or sexually were not considered. The study only considered cases where there was no fluid exchange with HHV-8 infected patients. Optimal parameters to reduce the number of patients who develop AIDS-KS were not determined. Despite its drawbacks the study [75] has inspired several studies at the immunology level [37].

2.1.4 AIDS-KS immunology mathematical models

Modelling AIDS-KS at the immunology level is still an undeveloped area. Mathematical models at the immunology level were inspired by the previously published clinical studies as well as the AIDS-KS epidemiological mathematical model by Lungu *et al.* [75].

Nani and Jin [35] were the first to explore an immunological mathematical model to emphasise the KS dynamics whilst on HAART. Their investigation focused on the patho-physiodynamics of the HIV-1/HHV-8 coinfection dynamics of hypothetical patients during HAART. The study included all the key ingredients of coinfection: KS cancer cells, T cells (both infected and uninfected), HIV-1 specific effector cells, HIV-1 virions and HAART. The study concluded that both HAART and adoptive immunotherapy are required to clear both HIV-1 and KS. Adoptive immunotherapy is a type of immunotherapy that uses ones own effector cells to recognise, target and destroy cancer cells [94]. The effector cells were removed from the patient, grown in the laboratory and then injected back to the patient in increased numbers at a predetermined dose rate [94]. Despite showing the crucial role HAART plays in controlling AIDS-KS, their system [35] did not include some of the necessary variables of HHV-8 infection, that is B cells, HHV-8 specific effector cells and the HHV-8 virions, hence the underlying dynamics of KS were not fully explored. The drawback was that the study lacked clinical experimental support hence hypothetical patients were used. Optimal control to recommend an optimal dosage scheme and consequently take care of issues such as drug resistance and drug toxicity were not discussed.

In a subsequent study, Nani and Jin [36] modified their first model [35] by including Adoptive Cellular Immunotherapy (ACI) of KS during HAART. Their deterministic mathematical model consisted of the same six variables as the previous study [35]. Notably, the modification was done in the effector cell class where the supply of cells was from both the thymus and *ex vivo* incubated effector cells (ACI). The analysis of the model was discussed and more computer simulations were presented than in their first study [35]. The results of the modified model [36] indicated that ACI can lead to remission (disease has been controlled) in KS in HIV-1 patients who are undergoing HAART and the combined ACI and HAART can lead to immune reconstitution, that is improved immune function. The study [36] concluded that the combination of HAART and ACI improved the immune response and prognosis for KS.

In order to determine how varying treatment strategies would alter the spread of AIDS-KS, Szolomay and Lungu [37] proposed a model which was dependent on T cells rather than

VL and it studied the AIDS-KS dynamics during HAART. They examined the effects of adherence to drug therapy on the prognosis of KS in hypothetical patients. Their deterministic model included all the key elements of HIV-1 infection and also the crucial components of HHV-8 infection: B cells (both infected and uninfected); HHV-8 virions and HHV-8 specific effector cells. Furthermore, they also included the vital features of KS dynamics: progenitor cells (both infected and uninfected) and KS. The inclusion of progenitor cells was in compliance with Forman [4]. In this study, the pharmacodynamics of HAART treatment and KS therapy was accounted for. The study demonstrated that good adherence to treatment plays a crucial role of controlling the spread of AIDS-KS in patients. The results were compatible with those of Nani and Jin [35]. They recommended that treating HIV-1 early can be a strategy to prevent the development of KS. Once the KS has started, HAART alone will not be sufficient to clear both infections. Despite shedding some light on the AIDS-KS, the stumbling block in Szolomay and Lungu's model [37] was the lack of clinical data to estimate some model parameters. In this study, the class for latently infected B cells and T cells was not included. Also, optimal control was not addressed to cater for the issues of drug resistance and drug toxicity.

2.2 Ebola Virus Disease mathematical models reviews

The 2014 outbreak of Ebola virus disease (EVD) has driven researchers to create mathematical models which have been utilised to assess the potential role of interventions against the EVD. Interventions pointed toward reducing the burden of the 2014 EVD epidemic were incorporated into mathematical models. This section reviews the mathematical models that study the effects of public health education on the evolution of EVD.

Fast *et al.* [78] implemented an EVD transmission model involving contact networks accompanied by a model encompassing social mobilisation. By using the weekly counts of new cases, the model was fit for Lofa County in Liberia through October 2014 to analyse the dynamics with and without population behaviour change. The EVD model is an extension of the standard susceptible-infected-recovered model. The individuals were represented as nodes and disease spread contacts between them was represented as edges. The model simulated the status of each individual in the population on each day, t . The findings suggest that behavioral change in the population of Lofa County was instrumental in bringing the outbreak under control. Additionally, the model results support continued focus on social mobilisation in order to combat the spread of EVD. However, such models

still need to answer the question whether incorporating behavioral change into predictive models will be feasible given lack of available high quality data on human behaviours. Also, the model did not take into account behavioral effects which could lead to pessimistic predictions.

Shen *et al.* [79] developed an epidemiological mathematical model to study the impact of comprehensive interventions including isolation, media impact, safe burial and vaccination. The basic reproduction number was estimated by fitting the model to the reported cumulative cases and deaths in Guinea, Sierra Leone and Liberia until March 22, 2015. The model analysis showed that media coverage plays a pivotal role in reducing the spread of EVD. Among all the interventions, the study found that shortening the duration between death and burial and improving the effectiveness of isolation are two effective interventions for controlling the outbreak of Ebola virus infection. Since the interventions considered mainly addressed isolation of infected people within EVD treatment centres, the limitation of the model is that it did not explicitly account for hospital bed capacity, which plays an important role in affecting both the outbreak dynamics and the intervention efforts.

The effects of public health education on the evolution of a disease have also been studied in the cases of HIV, drinking dynamics and Hepatitis C virus transmission dynamics.

Bhunu *et al.* [95] formulated a deterministic HIV/AIDS model to theoretically explore how counselling and testing coupled with the resulting decrease in sexual activity could affect the HIV epidemic in resource-limited communities. The findings suggest that effective counselling and testing have a great potential to partially control the epidemic (especially when HIV positive individuals either willingly withdraw from risky sexual activities or disclose their status beforehand) even in the absence of antiretroviral therapy (ART). Therefore, more needs to be done in resource-limited settings, such as sub-Saharan Africa, as far as the HIV/AIDS epidemic is concerned and a formalised information, education and communication strategy should be given prominence in educational campaigns.

Del *et al.* [96] examined the effects on the epidemic after a smallpox attack of the standard smallpox interventions combined with behavioral change in the population. They formulated and analysed a mathematical model in which some individuals lower their daily contact activity rates once an epidemic has been identified in a community. It is shown that behavioral changes alone can make a huge difference, additionally, it is also shown that the impact of standard control efforts are dramatically enhanced when the individuals affected play an active role in diminishing the likelihood of transmission. Behavioral changes might seem inexpensive compared to isolation, quarantine, and vaccination, since

there is no direct cost of behavioral changes to the public health sector. However, there would be economic costs to individuals and society related to lost work or increased school absenteeism, decreased business revenues, missed events, postponed travel, etc.

Mukandavire *et al.* [97] evaluated the impact of educational campaign as a possible control measure for the spread of HIV/AIDS. The model assumed basically sexual transmission with explicit incubation period which is formulated as an integro-differential equation and shown to be equivalent to a delay differential equation. The analysis of the model illustrated that public health education campaigns can reduce the basic reproductive number to values below unity as intended for disease control thus would succeed in controlling the epidemic. The obtained results showed that effective control of the epidemic can easily be achieved when the effectiveness of education is high, and if the reproduction number is not large. The findings suggested that educating sexually immature and sexually mature individuals concurrently is more effective in slowing down HIV/AIDS than concentrating on a cohort public health educational campaign of sexually immature or sexually mature individuals only. The study concluded that in settings where education is effective and with reasonable average numbers of HIV-infected partners, public health educational campaigns can slow down the epidemic and are more effective when given to both sexually immature and sexually mature individuals concurrently.

Xiang *et al.* [98] formulated a drinking model with public health educational campaigns and liner relapse. The study considered the effect of public health educational campaigns on the drinking dynamic. To describe how alcoholism spreads, how reformed alcoholics relapse and the effect of the public health educational campaigns, the drinking population was subdivided into five groups. The basic reproductive for the model was compared with the basic reproductive number for the absence of public health educational campaigns. The study concluded that the public health educational campaigns of drinking individuals can slow down the drinking dynamics. This means that public health education campaigns is one of the effective measure to control the alcohol problems.

Mushaybasa and Bhunu [99] developed a mathematical model to assess the impact of educational campaigns on controlling HCV among women in prison settings. Equilibria for the model are determined and their stability are examined. Population-level effects of increased educational campaigns to encourage safe injecting practices among women in prison were evaluated through numerical simulations. The results suggested that educating women prisoners about abstaining from intravenous drug misuse may significantly reduce HCV prevalence among women in prison settings. Targeted education campaigns, which are effective at stopping transmission of HCV more than 80% of the time, will be highly

effective at controlling the disease among women in prisons. However, the model has several limitations, it was assumed a constant release rate, rather than staggered release rates.

2.3 Summary

Mathematical models have a great impact to enrich our understanding of NTDs (such as AIDS-KS and EVD) and the efforts required to control them.

Since this study is motivated by Forman [4], we explored some clinical studies that were carried out before and after Forman's publication. The clinical studies gave a demonstration of the crucial roles played by HIV-1 and HHV-8 in the AIDS related KS pathogenesis: (i) HHV-8 is the etiologic agent in KS development [63, 80, 81, 82, 83, 84], (ii) HIV-1 infected T cells produce cytokines which induce HHV-8 viral replication [86, 87, 88] and (iii) HIV-1 Tat promotes KSHV infection by enhancing the entry of KSHV into endothelial cells [85, 89]. Using cART in the treatment of AIDS-KS improves response rate of patients [29, 30, 31]. VL mathematical models [90, 91, 92, 93, 34] demonstrated the supremacy of VL monitoring over T cell count monitoring on patients who are on treatment. Currently, there is only one epidemiological mathematical model which was proposed by Lungu *et al.* [75] which focused on resource-poor settings in sub Saharan Africa. The findings revealed that early provision of HAART to HIV infected patients reduced the number of people who develop AIDS-KS. Additionally, the study has inspired several AIDS-KS studies at the immune level. However, the drawbacks to this study were that most of the parameters were estimated due to lack of data and the model is only valid in sub Saharan Africa.

Mathematical modelling at the immunology level is still at its infancy. Immune models were inspired by the previously published AIDS-KS clinical studies as well as the AIDS-KS epidemiological mathematical model by Lungu *et al.* [75]. Nani and Jin [35] explored the first immunological HIV-1/KS model with a focus on the patho-physiodynamics of coinfection during HAART. Their study highlighted the requirement for both HAART and adoptive immunotherapy in controlling KS infection. In their successive study, Nani and Jin [36] modified their earlier model [35] to include ACI of KS during HAART. They concluded that both HAART and ACI boosts the immune response. However, both models [35, 36] lacked the crucial KS dynamics. Szolomay and Lungu [37] constructed an AIDS-KS mathematical model to determine the effect of varying adherence on AIDS-KS prognosis.

They concluded that strict adherence to treatment significantly reduces KS infection. Despite the inclusion of all the key ingredients in their model, there was lack of clinical data and also optimal control which addresses the drug toxicity and resistance was not catered for. Additionally, the model [37] was T cell dependent rather than VL dependent.

Interventions aimed at reducing the burden of the 2014 EVD epidemic were incorporated into mathematical models [78, 79]. We reviewed the mathematical models that study the effects of public health education on the evolution of EVD. The studies showed that behavioral change plays a very important role in combatting the spread of EVD. Fast *et al.* [78] implemented an EVD transmission model on a contact network accompanied by a model of social mobilisation. The findings suggest that behavioral change in the population of Lofa County was instrumental in bringing the outbreak under control. Shen *et al.* [79] developed an epidemiological mathematical model to study the impact of comprehensive interventions including isolation, media impact, safe burial and vaccination. Model analysis showed that media coverage plays a pivotal role in reducing the spread of EVD.

Given the gaps in literature, there is need to develop within-host AIDS-KS mathematical models which accounts for the VL and the effect of infected cell populations with the inclusion of optimal control. Motivated by Forman [4] and Szomolay and Lungu's model [37], we modify [37] by constructing novel models which are based on VL rather than T cells count. As for the EVD, motivated by the data of two outbreaks that took place in Sudan only 3 years apart and the epidemiological models by Fast *et al.* [78] and Shen *et al.* [79], we estimate different parameters for each population in the two Sudan outbreaks, unlike the previous studies [78, 79] which simply reduced various rates as a result of public health education.

Prior to presenting the proposed models, we look at the mathematical preliminaries that are used throughout the thesis in the chapter which follows.

Mathematical preliminaries

This chapter introduces basic mathematical concepts and results that are used throughout the thesis to qualitatively analyse and numerically implement the models presented in this thesis such as well posedness of solutions, stability analysis (both local and global), sensitivity and uncertainty analysis, optimal control theory and numerical implementation by the forward-backward sweep method.

3.1 Well posedness fundamentals

A mathematical model developed using biological considerations must make sense both biologically and mathematically. For determining the well posedness of our model, the following mathematical basics are required: existence and uniqueness theorems, locally Lipschitz and Gronwall's inequality. The proofs of the theorems are found in [100].

Definition 3.1. (Locally Lipschitz Functions). Let $f : \mathbb{R}^m \rightarrow \mathbb{R}^m$. A function is locally Lipschitz if for each $x_0 \in \mathbb{R}^m$, there is a $B(x_0) \in \mathbb{R}^m$ which is a neighborhood of x_0 and a constant $K \geq 0$ such that

$$|f(x) - f(y)| \leq K|x - y|, \quad \forall x, y \in B(x_0).$$

Theorem 3.1. (Existence and Uniqueness Theorem). *Suppose the function $f : \mathbb{R}^m \rightarrow \mathbb{R}^m$ is continuously differentiable. Then $x(t)$ is a solution of the differential equation $\frac{dx}{dt} = f(x)$ on an interval I if $x(t)$ is differentiable on I and if $\forall t \in I, x(t) \in \mathbb{R}^m$ and $\frac{dx}{dt} = f(x(t))$*

and given $x_0 \in \mathbb{R}^m$, $x(t)$ is a solution of the initial value problem

$$\begin{aligned}\frac{dx}{dt} &= f(x(t)) \\ x(t_0) &= x_0\end{aligned}$$

Remark 3.1. The Existence and Uniqueness Theorem ensures that the solution to a first order differential equation exists and is unique in the neighbourhood of x_0 , i.e., the function is locally Lipschitz.

3.2 Stability (local and global) fundamentals

Stability analysis allows the establishment of the stability of the system of ordinary differential equations (ODEs) around the equilibrium points. There are two types of stability: local stability and global stability. The local stability provides insights into the system's behaviour and provide a basis for global analysis.

Definition 3.2. (Equilibrium point). For a given ODE, $\frac{dx}{dt} = f(\bar{x}(t))$, a point $\bar{x} \in \mathbb{R}^m$ is an equilibrium point when $\frac{dx}{dt} = f(\bar{x}(t)) = 0$ [100].

Remark 3.2. At equilibrium points, there is no adjustment in the populations, subsequently these points are acquired by setting each differential equation to zero. Equilibrium points can be classified as elimination or persistence points, which happen when the values of the infected populations equivalent to zero and not equivalent to zero respectively. As soon as the system obtains the equilibrium point value at any moment, it remains at that point for the rest of the time. Finding the equilibria marks the beginning of understanding the long term behaviour of our system: the system can move closer to or away from equilibrium, or even change cyclically between specific equilibria, thus the need for a stability analysis.

Theorem 3.2. (The Hartman-Grobman Theorem). Let E be an open subset of $\mathbb{R}^m$ containing the origin, let $f \in C^2(E)$ and let ϕ_t be the flow of a nonlinear system. Suppose that $f(0) = 0$ and that the matrix $J(0)$ has no eigenvalue with zero real part. Then there exists a homeomorphism H of an open set U containing the origin onto an open set V containing the origin such that for each $x_0 \in U$ there is an open interval $I_0 \subset \mathbb{R}$ containing zero such that for all $x_0 \in U$ and $t \in I_0$, the mapping $H \circ \phi_t(x_0) = e^{At}H(x_0)$.

Remark 3.3. The above theorem essentially shows how the analysis of the linearised system relates to the nonlinear system, that is, near the equilibrium points, H maps the

trajectories of the nonlinear system onto the trajectories of the linear system. Hence, if the Jacobian matrix does not have zero or purely imaginary values, the stability properties of the nonlinear system of ODEs is equivalent to the linear ODE system at the equilibrium point. The proof of the theorem is found in [100].

Definition 3.3. The Jacobian matrix, J , is a matrix that is made up of all first order partial derivatives of a vector-valued function, that is,

$$J = \begin{bmatrix} \frac{\partial F_1}{\partial x_1} & \cdots & \frac{\partial F_1}{\partial x_m} \\ \vdots & \ddots & \vdots \\ \frac{\partial F_m}{\partial t} & \cdots & \frac{\partial F_m}{\partial x_m} \end{bmatrix}, \quad \text{for } F : \mathbb{R}^n \rightarrow \mathbb{R}^m \text{ [100].}$$

Definition 3.4. (Reproduction number, $\mathcal{R}_0$). It is the average number of secondary infections caused by a single infectious individual during the entire period of infection [101, 102]. Note, “secondary” depends on the context:

- (i) number of individuals infected within a single infected individual’s entire infectious lifetime (epidemiology),
- (ii) number of newly infected cells produced by a single infected cell (within-host dynamics).

Remark 3.4. If $\mathcal{R}_0 < 1$, the disease dies out and if $\mathcal{R}_0 > 1$, the disease persists.

Definition 3.5. (Characteristic polynomial). The polynomial side of the characteristic equation, $\det(A - \lambda I)$ derives the characteristic polynomial, where A represents the square matrix, I represents the identity matrix and λ is the eigenvalue.

Computation of $\mathcal{R}_0$ from the Jacobian

A formula for $\mathcal{R}_0$ is derived by imposing a stability condition. Typically, the Jacobian is calculated at the disease free equilibrium (DFE) and is subject to the condition that all eigenvalues of the corresponding characteristic equations must have a negative real part. Now, if the calculated Jacobian is a characteristic polynomial of degree 3 or higher, $\mathcal{R}_0$ can be calculated from the constant term of the characteristic polynomial. In order to give the necessary and sufficient condition of the eigenvalue to satisfy the imposed condition, we need a tool that satisfies the necessary and sufficient conditions for the eigenvalues to

have negative real parts. The Routh-Hurwitz criterion described in the following theorem gives these conditions:

Theorem 3.3. (Routh-Hurwitz Criteria). *Given the characteristic polynomial*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n,$$

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

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

where $a_i = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real parts iff the determinants of all Hurwitz matrices are positive: $\det(H_j) > 0, j = 1, 2, \dots, n$. The Routh-Hurwitz criteria for polynomials is given in Table 3.1.

TABLE 3.1: Routh-Hurwitz criteria

n	Sign of the coefficient	Additional conditions
2	$a_1 > 0, a_2 > 0$	-
3	$a_1 > 0, a_2 > 0, a_3 > 0$	$a_1 a_2 > a_3$
4	$a_1 > 0, a_2 > 0, a_3 > 0, a_4 > 0$	$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$
5	$a_1 > 0, a_2 > 0, a_3 > 0, a_4 > 0, a_5 > 0$	$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2$

Proof. The proof of the above theorem can be found in [103]. □

Theorem 3.4. (Poincare-Perron). *Let A be a constant matrix in the system $\frac{dx}{dt} = Ax$ with eigenvalues $\lambda_i, i = 1, 2, \dots, n$*

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

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

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

Remark 3.5. The equilibrium is stable if any of the values have negative real numbers, otherwise the equilibrium is unstable. Routh-Hurwitz Criteria can be applied to investigate the sign of the eigenvalue. The proof of the above theorem is found in [100].

Global stability conditions

The system of ODEs must be written in the form

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z) \\ \frac{dZ}{dt} &= G(X, Z), \quad G(X, 0) = 0 \end{aligned} \tag{3.1}$$

where, $X \in \mathbb{R}^m$ denotes the uninfected states and $Z \in \mathbb{R}^n$ denotes the infected states. $\mathcal{E}_0 = (x^*, 0)$ denotes the DFE of the system. In order to guarantee asymptotic stability, the two conditions (H1) and (H2) given below must be met:

(H1) For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable (GAS),

(H2) $G(X, Z) = AZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$, where $A = D_Z G(X^*, 0)$ is an M -matrix (the off diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense. If the above two conditions are met, then the following theorem holds:

Theorem 3.5. (Global asymptotic stability of $\mathcal{E}_0$). *The equilibrium point, $\mathcal{E}_0 = (x^*, 0)$, is GAS provided $\mathcal{R}_0 < 1$ and the conditions (H1) and (H2) are satisfied.*

Proof. The proof of the above theorem can be found in [104]. □

3.3 Sensitivity and uncertainty analysis fundamentals

Mathematical models are commonly used as decision-making tools and are influenced by parameter-driven uncertainties. A small adjustment to a parameter may indicate the convergence to disease-free or disease persistence state. A sensitive parameter has a great

influence on the model output. Due to the high degree of uncertainty in the estimation of parameters, sensitivity analysis and uncertainty analysis play an important role. The parameter space is explored by performing an uncertainty analysis using Latin Hypercube Sampling (LHS) method as described by Blower and Gomero [105, 106]. Subsequently, a sensitivity analysis is carried out to identify the inputs with the greatest impact. This is done by calculating the Pearson Partial Rank Correlation Coefficient (PRCC) sampled first by the LHS scheme. The purpose of uncertainty analysis and sensitivity analysis is to examine the effect on the model output, based on the changes in input parameters by:

- (i) *understanding the behavior of the system* that is being modelled,
- (ii) *determining the parameters* which can significantly alter the predictions of the model,
- (iii) *estimating potential errors in model forecasts* that could be due to parameter value errors. This helps to understand underestimation and overestimation.

The model output can be of two types: constant in time, for example $\mathcal{R}_0$ and a function of time, for example $I(t)$, that is, number of infected individuals at time t . The LHS/PRCC procedure [105] which can be implemented in MATLAB is given below:

1. Design the model.
2. Identify parameters of interest.
3. Determine the number of simulations (N).
4. Implement LHS method.
5. Analysis of model output: perform an uncertainty and sensitivity analysis.

3.4 Optimal control problem fundamentals

Optimal control techniques can be utilised to guide molecular dynamics to achieve specific physical goal. An optimal control problem consists of the following elements:

- (i) cost functional, $J[x(t), u(t)]$,
- (ii) state variables, $x(t) \in X$,

(iii) control variables, $u(t) \in U$ in a time t , $t_0 < t < t_f$.

The main goal of the optimal control problem is to find a piecewise control $u(t)$ and the associated state variable to maximise a given objective functional. This section is adapted from the work by Lenhart and Workman [5].

Definition 3.6. (Basic optimal control problem).

$$\begin{aligned} \max_u \quad J[x(t), u(t)] &= \int_{t_0}^{t_f} f(t, x(t), u(t)) dt \quad \text{such that} \\ \dot{x} &= g(t, x(t), u(t)) \\ x(t_0) &= x_0 \end{aligned} \tag{3.2}$$

$x(t_f)$ could be free or fixed, i.e $x(t_f) = t_f$.

f and g will always be continuously differentiable functions. The assumption is that the control set U is a Lebesgue measurable function. Switching back and forth between maximisation and minimisation is possible by simply negating the cost functional:

$$\min(J) = -\max(-J).$$

Pontryagin's Maximum Principle

Pontryagin's Maximum Principle provides the necessary conditions for an optimal control problem. Pontryagin introduced the idea of adjoint functions to append the differential equation to the objective functional.

Definition 3.7. (Hamiltonian). Consider the optimal control problem (3.2). The function

$$\begin{aligned} H(t, x(t), u(t), \lambda(t)) &= f(t, x(t), u(t)) + \lambda(t)g(t, x(t), u(t)) \\ &= (\text{integrand}) + (\text{adjoint}) \times (\text{right hand side of the ODE}) : \end{aligned}$$

is called Hamiltonian function and λ is the adjoint variable.

Theorem 3.6. (Pontryagin's Maximum Principle). *If $u^*(t)$ and $x^*(t)$ are optimal for problem (3.2) then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

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

for all controls u at each time t , where H is the Hamiltonian previously defined and

$$\begin{aligned}\dot{\lambda}(t) &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \\ \lambda(t_f) &= 0.\end{aligned}$$

Proof. The proof can be found in Clarke's book [107]. □

Remark 3.6. The transversality condition, $\lambda(t_f) = 0$ is only used when the optimal control problem does not have terminal value in the state variable, i.e., $x(t_f)$ is free.

This principle converts the problem of finding a control which maximises the objective functional subject to the state ODE and initial condition into the problem of optimising the Hamiltonian pointwise. As consequence, with this adjoint equation and Hamiltonian, we have

$$\frac{\partial H}{\partial u} = 0. \tag{3.3}$$

at u^* for each t , namely, the Hamiltonian has a critical point; usually this condition is called *optimality condition*. Hence, to find the necessary conditions, we only use the Hamiltonian.

Optimal control with bounded controls

Definition 3.8. (optimal control with bounded control). An optimal control with bounded control can be written in the form

$$\begin{aligned} \max_u \quad J[x(t), u(t)] &= \int_{t_0}^{t_f} f(t, x(t), u(t)) dt \quad \text{such that} \\ \dot{x} &= g(t, x(t), u(t)) \\ x(t_0) &= x_0 \\ a &\leq u(t) \leq b \end{aligned} \tag{3.4}$$

where a, b are fixed real constants and $a < b$.

Alternative necessary conditions are necessary to solve problems with bounds on the control.

Proposition 1. (Necessary conditions). *If $u^*(t)$ and $x^*(t)$ are optimal for problem (3.4) then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

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

for all controls u at each time t , where H is the Hamiltonian previously defined and

$$\begin{aligned} \dot{\lambda}(t) &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \quad (\text{adjoint condition}), \\ \lambda(t_f) &= 0 \quad (\text{transversality condition}). \end{aligned}$$

By an adaptation of the Pontryagin's Maximum Principle, the optimal control must satisfy the optimality condition:

$$u^* = \begin{cases} a & \text{if } \frac{\partial H}{\partial u} < 0 \\ a \leq \tilde{u} \leq b & \text{if } \frac{\partial H}{\partial u} = 0 \\ b & \text{if } \frac{\partial H}{\partial u} > 0 \end{cases} \quad (\text{optimality condition})$$

Proof. The proof of this result can be found in [108]. □

Remark 3.7. For a minimisation problem, then $\tilde{u}$ is instead chosen to minimise H pointwise, hence reversing $<$ and $>$ in the first and third lines of optimality condition.

For implementation in MATLAB, the optimality condition can be written in compact form:

$$u^* = \max \left\{ 0, \min \left(\frac{\partial H}{\partial u}, 1 \right) \right\}$$

The optimality system

The optimality system is formed from the optimal control system (the state system) and the adjoint system by incorporating the characterised control set, initial and transversed condition.

Uniqueness of the optimality system

Due to the priori boundedness of the state, adjoint functions and the resulting Lipschitz structure of the ODEs, we can obtain the uniqueness of solutions of the optimality system for the small time interval. Hence the following theorem:

Theorem 3.7. *For $t \in [0, t_f]$, the bounded solutions to the optimality system is unique.*

Proof. The proof of the theorem can be found in [109]. □

Application of the optimal control theory is outlined in the following steps:

1. Formulation of the Hamiltonian for the problem

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

2. Give the adjoint differential equation, transversality boundary condition and optimality condition.

$$\begin{aligned} \dot{\lambda}(t) &= -\frac{\partial H}{\partial x} \quad (\text{adjoint condition}), \\ \lambda(t_f) &= 0 \quad (\text{transversality condition}), \\ \frac{\partial H}{\partial x} &= 0 \quad \text{at } u = u^* \quad (\text{optimality condition}). \end{aligned}$$

3. Solve for u^* in terms of x^* and λ .
4. After finding the optimal state and adjoint, solve for the optimal control.

Forward-Backward Sweep Method to solve optimal control problems

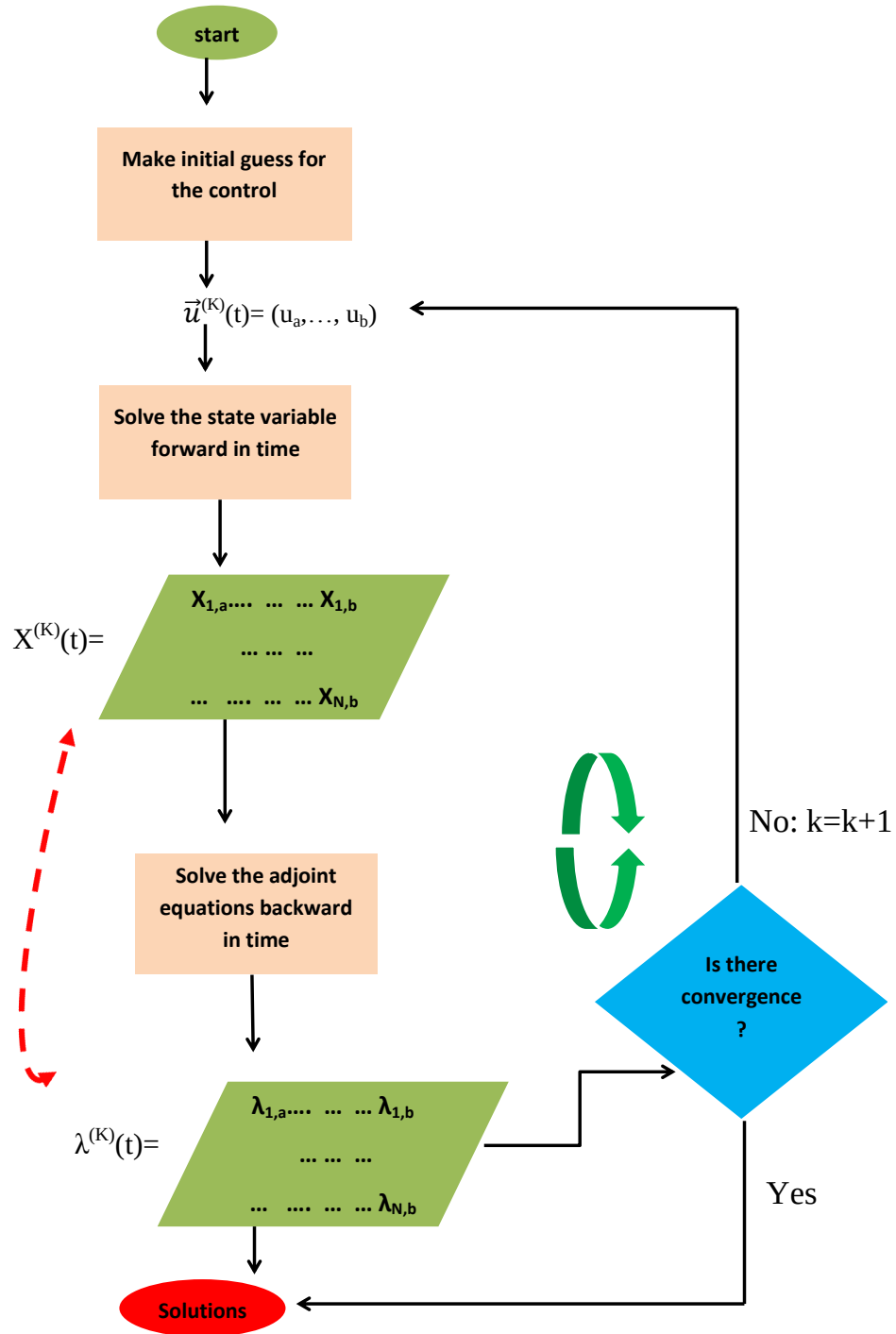


FIGURE 3.1: FBSM flow diagram as described by Lenhart and Workman[5].

FBSM is a numerical technique for solving OC problems which is implemented with MATLAB. The method was developed by Lenhart and Workman [5] and the flow chart of the algorithm which was adapted from [5] is illustrated in Figure 3.1. Firstly, the initial estimates of the control is made. Then the state equations are solved forward in time using a Runge-Kutta 4th order method. The output is then plugged into the adjoint equations. Then the adjoint equations with given final conditions are solved backward in time, applying the Runge-Kutta 4th order method again. The updated controls are used to solve the state and then the adjoint system. This iterative process is repeated until the current state, adjoint and controls converge sufficiently [5].

Runge-Kutta 4th order method

The Runge-Kutta4th order method numerical technique used to solve first order ODEs. Given a step size h and an ODE $\dot{x} = f(t, x(t))$, we can make an convenient approximation of $x(t+h)$ given $x(t)$ is

$$x(t+h) \approx x(t) + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

where

$$\begin{aligned} k_1 &= f(t, x(t)) \\ k_2 &= f\left(t + \frac{h}{2}, x(t) + \frac{h}{2}k_1\right) \\ k_3 &= f\left(t + \frac{h}{2}, x(t) + \frac{h}{2}k_2\right) \\ k_4 &= f(t+h, x(t) + hk_3) \end{aligned}$$

Novel mathematical models of AIDS-KS

Based on a study by Foreman [4] and motivated by the work of Szomolay and Lungu [37], novel weak viral source and strong viral source mathematical models are formulated to provide a description of the interactions between the infected B-cells, B_i , infected T-cells, I , the viruses, HIV-1, V_1 , HHV-8, V_8 , KS, K , and the virus-specific effector cells, E_1 and E_8 for lysing of infected T and B cells respectively. Unlike [37] which is T-cell dependent, our models are viral load (VL) dependent, hence, are amenable to include the effect of low and high VL in the proliferation terms of the infected cells and virus-specific effector cells. This approach is supported by the literature on VL we reviewed [34, 90, 91, 92, 93]. We assume that the viral production begins immediately upon infection of the cell.

The objective of this chapter is to develop VL dependent treatment mathematical models. To the best of my knowledge, this approach has not been implemented despite numerous biological and clinical evidence suggesting the superiority of this approach over T cell count protocols to determine HIV-1 treatment access [34, 90, 91, 92, 93].

From a modelling point of view, the impediment to implementation of this approach has been the lack of experimental or clinical evidence to suggest the type of source terms for infected T-cell and B-cell terms to represent the growth of the two classes of cells and their associated specific effector cells.

From a reported clinical trial involving sixty-seven (67) HIV-1 infected patients who suffered from various underlying opportunistic infections, we propose to construct growth

terms for infected T-cells and B-cells and the associated HIV-1 and HHV-8 specific effector cells, respectively from responses of HIV-1 patients with Cryptococcus [6]. The response curve is given in Figure 4.1 below:

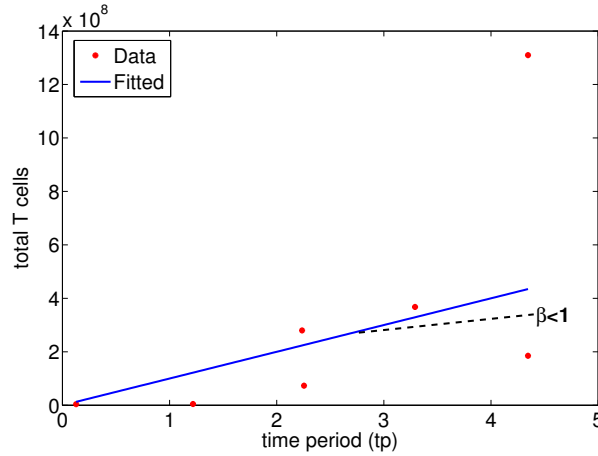


FIGURE 4.1: T cell responses of HIV-1 patients with Cryptococcus adapted from Mahnke *et al.* [6].

We have fitted a curve approximated by $f(x) = x^\beta$ for $\beta = 1$ and $\beta < 1$. We shall use functions of the type x^β to represent the growth terms for infected T-cells and infected B-cells where x represents the associated pathogen. This representation is not unique as other opportunistic infections yielded different responses. This approach seems reasonable to represent various phases of infection, that is low and high VL for $0 \leq \beta \leq 1$ [7].

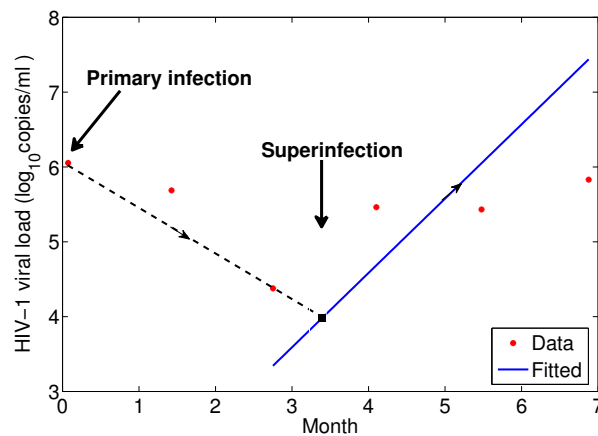


FIGURE 4.2: HIV-1 VL in a patient adapted from Doyle [7].

Figure 4.2 (Doyle [7]) shows that $f(x) = x^\beta$ can represent both subinfection $\beta < 1$ and superinfection $\beta \geq 1$.

4.1 General AIDS-KS model

For simplicity of notation, we let $\{x_1, x_2, x_3, x_4, x_5, x_6, x_7\} = \{B_i, K, E_1, I, E_8, V_1, V_8\}$. We construct a mathematical model describing the dynamics of viruses and associated immune cells described in Figure 4.3 for viral sources of the type $H_1(x_6, \beta) = x_6^\beta$, for infection of T cells, and $H_8(x_7, \gamma) = x_7^\gamma$, for infection of B cells where the exponents β and γ are assumed to be $0 \leq \beta \leq 1$ and $0 \leq \gamma \leq 1$. β and γ express the magnitude of proliferation. As alluded in the literature review these sources are consistent with clinical observation of infection of T cells (as an example).

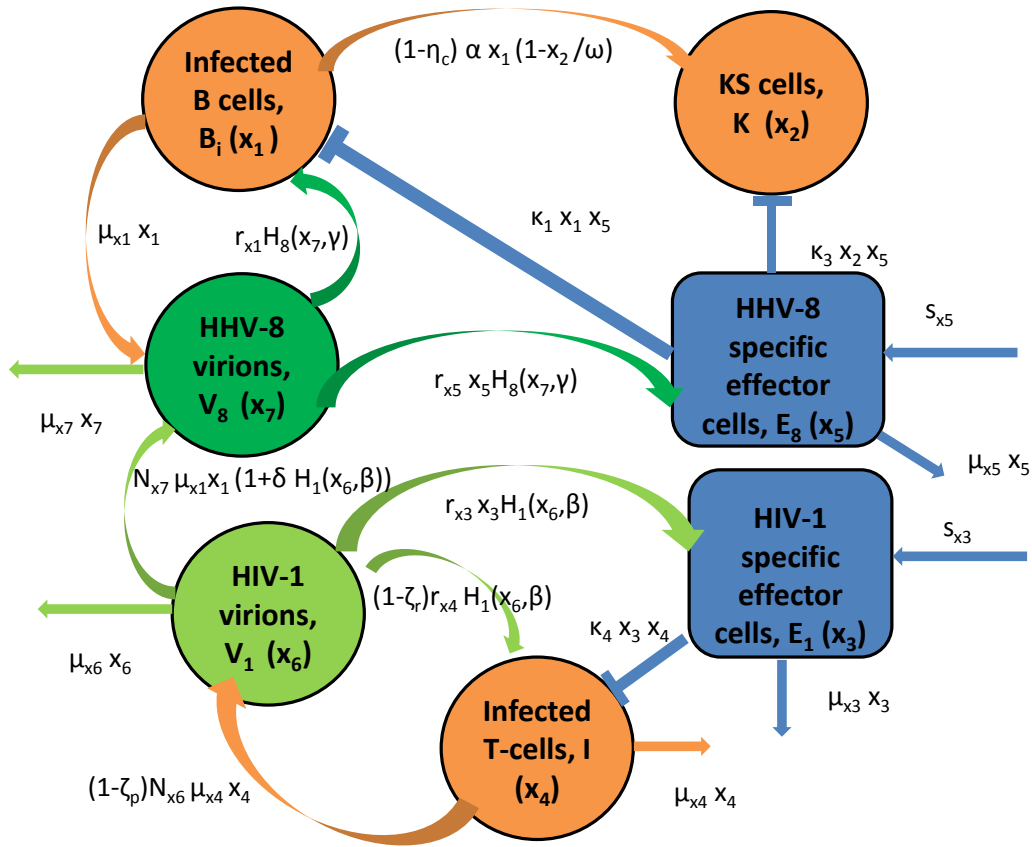


FIGURE 4.3: Schematic presentation of the mathematical model showing the KS-immune system interactions in the presence of HIV-1 and HHV-8. Blocked arrows indicate killing of infected cells by the effector cells and sharp arrows indicate interaction.

Table 4.1 gives a description of the model variables and parameters. The HIV-1-KS model is described below:

TABLE 4.1: Model variables and parameters

Symbols	Description
x_1	density of infected B-cells
x_2	density of KS cells
x_3	density of HIV-1 specific effector cells
x_5	density of HHV-8 specific effector cells
x_4	density of infected T-cells
x_6	density of HIV-1 virions
x_7	density of HHV-8 virions
s_{x_3}, s_{x_5}	source of HIV-1 and HHV-8 virus-specific effector cells respectively
r_{x_1}	growth rate of infected B-cells
r_{x_4}	growth rate of infected T-cells
r_{x_3}, r_{x_5}	growth rate of HIV-1 and HHV-8 specific effector cells respectively
ω	maximum carrying capacity of KS cells
κ_1	lysis of infected B-cells
κ_3	lysis of KS cells
κ_4	lysis of infected T-cells
μ_{x_1}	lytic death of infected B-cells
μ_{x_3}, μ_{x_5}	natural death of HIV-1 and HHV-8 virus specific effector cells respectively
μ_{x_4}	lytic death of infected T-cells
μ_{x_6}	clearance of HIV-1 virions
μ_{x_7}	clearance of HHV-8 virions
α	growth rate of KS cells
δ	proliferation rate of HIV-1 virions
N_{x_6}	maximum carrying capacity of infected T-cells
N_{x_7}	maximum carrying capacity of infected B-cells
η_c	efficacy of KS therapy
ζ_p	efficacy of PIs
ζ_r	efficacy of RTIs
β, γ	magnitude of proliferation

Infected B-cell dynamics:

$$\dot{x}_1 = r_{x_1} H_8(x_7, \gamma) - \kappa_1 x_1 x_5 - \mu_{x_1} x_1. \quad (4.1)$$

Equation (4.1) describes the rate of change of actively infected B-cells, x_1 . In this model we have ignored the class of latently infected B-cells. The actively infected B-cells are generated by infection of susceptible B-cells by HHV-8 as well as proliferation of infected B-cells. We account for these two mechanisms through the first term. The second and third terms describe the loss due to lytic death and the killing of infected B-cells by HHV-8-specific effector cells.

KS cell dynamics:

$$\dot{x}_2 = (1 - \eta_c)\alpha x_1 \left(1 - \frac{x_2}{\omega}\right) - \kappa_3 x_2 x_5. \quad (4.2)$$

Equation (4.2) describes the rate of change of KS cells, x_2 . The first term assumes logistic growth for these cells [110, 111] and the second term represents the killing of KS cells by HHV-8-specific effector cells. The growth of this population is dependent on the population of infected B-cells, x_1 , but it is self-regulated. When the KS population increases towards the carrying capacity, ω , the cancer goes into remission. This can be also achieved due to KS therapy, expressed by the efficacy function ($0 \leq \eta_c \leq 1$).

HIV-1 specific effector cells dynamics:

$$\dot{x}_3 = s_{x_3} + r_{x_3} x_3 H_1(x_6, \beta) - \mu_{x_3} x_3. \quad (4.3)$$

The dynamics of HIV-1 specific effector cells is given by Equation (4.3). The first two terms represent the constant source of the effector cells and the proliferation due to the presence of HIV-1, respectively. The third term accounts for natural death.

Infected T-cells dynamics:

$$\dot{x}_4 = (1 - \zeta_r) r_{x_4} H_1(x_6, \beta) - \kappa_4 x_3 x_4 - \mu_{x_4} x_4. \quad (4.4)$$

Equation (4.4) describes the rate of change of infected CD4⁺ T-cells, x_4 . This population increases by infection of healthy T-cells by HIV-1 and proliferation. These two sources are represented by the first term which is assumed to depend on the density of HIV-1, x_6 . The second term accounts for the killing of infected cells by HIV-1 specific effector cells. The infected cells are lysed at a rate of μ_{x_4} due to which new HIV-1 particles are produced. The efficacy function ζ_r represents the effect of reverse transcriptase inhibitors that are a component of HAART therapy.

HHV-8 specific effector cells dynamics:

$$\dot{x}_5 = s_{x_5} + r_{x_5} x_5 H_8(x_7, \gamma) - \mu_{x_5} x_5. \quad (4.5)$$

The HHV-8-specific effector cells are replenished at a constant rate s_{x_5} , undergo proliferation in the presence of HHV-8 and are lost due to natural death.

HIV-1 dynamics:

$$\dot{x}_6 = (1 - \zeta_p)N_{x_6}\mu_{x_4}x_4 - \mu_{x_6}x_6. \quad (4.6)$$

Following Perelson and Nelson [56], the HIV-1 dynamics are governed by two processes: the first term describes the release of new free viral particles due to lytic death of infected $CD4^+$ T-cells and the second term accounts to loss due to natural death. The efficacy function ζ_p represents the effect of protease inhibitors (PIs) that are a component of HAART therapy.

HHV-8 dynamics:

$$\dot{x}_7 = N_{x_7}\mu_{x_1}x_1(1 + \delta H_1(x_6, \beta)) - \mu_{x_7}x_7. \quad (4.7)$$

The first term describes the production of free HHV-8 virions due to lysis of infected B-cells and their enhancement by HIV-1 at a rate δ . The last term accounts for loss due to natural death.

In what follows, we will assume there is no cART therapy (e.g. $\eta_c = \zeta_p = \zeta_r = 0$) and the effect of cART will be investigated using optimal control in Chapter 5.

We now investigate how the infection characteristics are altered for the cases when $\gamma = \beta$ and when $\gamma \neq \beta$, where γ and β express the magnitude of proliferation. More specifically, we consider three cases when the infection parameters (γ, β) are zero, which represents constant source terms for the infected and effector cell dynamics. Secondly, we consider the case when one infection parameter (for HHV-8) is zero, that is $\gamma = 0$, but the infection parameter for HIV-1 is non-zero, that is $\beta = 1$. Lastly, we consider the case when both infection parameters γ and β are nonzero. These cases are summarised as follows: (i) $\gamma = \beta = 0$, (ii) $\gamma = 0$ and $\beta = 1$, (iii) $\gamma = \beta = 1$.

4.2 Weak viral source model with $H_1(x_6, \beta) = x_6^\beta$ and $H_8(x_7, \gamma) = x_7^\gamma$

In this section, we consider the model with weak viral source model. We assume that there is no treatment, that is, $\eta_c = \zeta_p = \zeta_r = 0$. The new system will be essentially the same as (4.1) – (4.7) except that $H_1(x_6, \beta) = x_6^\beta$ and $H_8(x_7, \gamma) = x_7^\gamma$. The source type was motivated by the clinical studies by Mahnke *et al.* [6] and Doyle [7] where we constructed

the growth terms for the immune cell populations by fitting the proliferation function to clinical data. The approach represents various phases of infection, that is low and high VL.

4.2.1 Positivity and boundedness of solutions

We denote by $\mathbb{R}_+^7$ the set of points $x_t = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)$ with positive coordinates and consider the system (4.1)–(4.7) with initial values $x^0 = (x_1^0, x_2^0, x_3^0, x_4^0, x_5^0, x_6^0, x_7^0)$. In this section, we prove the following theorem:

Theorem 4.1. *The system (4.1)–(4.7) can be written as a system of differential inequalities*

$$\frac{dx_i}{dt} \geq A_i x_i + \sum_j^7 B_{ij} x_j + \varepsilon \quad i = (1, \dots, 7), \quad (4.8)$$

where B_{ij} is a matrix and ε a constant satisfying the conditions

$$B_{ij} \geq 0, \quad \varepsilon \geq 0.$$

If $x_i(0) \geq \varepsilon$ for $1 \leq i \leq 7$, then $x_i(t) \geq 0$ for all $t > 0$ and $1 \leq i \leq 7$.

Without loss of generality we may assume that $\varepsilon > 0$, since the case $\varepsilon = 0$ follows by approximating the system with a sequence $\varepsilon = \varepsilon_k \downarrow 0$.

Proof. Suppose that the assertion $x_i(0) \geq \varepsilon > 0$, for $1 \leq i \leq 7$, is not true. Then there exists the smallest number $t_0 > 0$, such that

$$\begin{aligned} x_i(t) &> 0 \quad \text{for } 1 \leq i \leq 7, \quad 0 \leq t \leq t_0, \\ x_i(t_0) &= 0 \quad \text{for at least one } i, \text{ say } i = i_0. \end{aligned}$$

The x_{i_0} is a decreasing function at $t = t_0$, so that

$$\frac{dx_{i_0}}{dt}(t_0) \leq 0.$$

From the differential inequality 4.8 for $x_{i0}(t)$ we get

$$\frac{dx_{i0}}{dt}(t_0) \geq \sum_j^7 B_{ij}x_j + \varepsilon \geq \varepsilon > 0,$$

which is a contradiction.

For the state variables in our model, we always take

$$\begin{aligned} x_1(0) \geq 0, \quad x_2(0) \geq 0, \quad x_3(0) \geq 0, \quad x_4(0) \geq 0, \\ x_5(0) \geq 0, \quad x_6(0) \geq 0, \quad x_7(0) \geq 0. \end{aligned}$$

From Theorem 4.1 we conclude that

$$\begin{aligned} x_1(t) \geq 0, \quad x_2(t) \geq 0, \quad x_3(t) \geq 0, \quad x_4(t) \geq 0, \\ x_5(t) \geq 0, \quad x_6(t) \geq 0, \quad x_7(t) \geq 0. \end{aligned}$$

□

Thus, in the region $\mathbb{R}_+^7$ the model is epidemiologically and mathematically well posed and we can use it to study the dynamics of AIDS-KS.

4.2.2 Equilibria

In order to fully understand the dynamics, there is a need to first of determine values of equilibria of the model of Equations (4.1)–(4.7). Two important equilibria exist: (1) the virus free equilibrium; which means that the virus is eliminated from the body as $t \rightarrow \infty$ and (2) the virus persistent equilibrium; where as $t \rightarrow \infty$ the virus stays in the system. We consider the three special cases: (i) $\gamma = \beta = 0$, (ii) $\gamma = 0$ and $\beta = 1$, (iii) $\gamma = \beta = 1$. Here we will show local stability for (ii)-(iii) and global stability for (i)-(iii) of the equilibrium points and describe the parameter choices. Throughout this thesis it will be assumed that $\mu_{x_3} > r_{x_3}$ and $\mu_{x_5} > r_{x_5}$ and $i, j = 1 \dots 7$ will denote matrix entries of $\mathbf{M}$ defined in Appendix A.1.

4.2.2.1 Virus free equilibrium (VFE), $\mathcal{E}_0$

In the case when all cell populations have constant source terms, the virus free equilibrium for which

$$x_1 = x_2 = x_4 = x_6 = x_7 = 0 \implies r_{x_1} = r_{x_4} = 0 \quad (4.9)$$

is given by

$$\mathcal{E}_0 = (0, 0, x_3^*, 0, x_5^*, 0, 0),$$

where $x_3^* = \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} > 0$, $x_5^* = \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} > 0$, $\mu_{x_3} > r_{x_3}$ and $\mu_{x_5} > r_{x_5}$.

The biological interpretation of $\mathcal{E}_0$ is the case when an infection is removed from the body naturally after it exists for a short period of time, that is the virus does not persist.

4.2.2.2 Virus persistent equilibria

On the other hand, when $x_1 \neq 0$, $x_2 \neq 0$, $x_4 \neq 0$, $x_6 \neq 0$, $x_7 \neq 0$, the virus persistent equilibria is given by

$$\mathcal{E}_1 = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*, x_7^*).$$

This will be explored numerically due to the complexity of solving it analytically. Biologically, virus persistent equilibria is the case where the body is not able to clear the infection by itself, hence the virus persists.

4.2.3 Local stability analysis of VFE $\mathcal{E}_0$

A stability analysis of the system of equations (4.1)–(4.7) In order to gain an understanding into the type of behaviour that will be exhibited by enables a better understanding into the behavior that the system will exhibit. For the analysis of our system, we make use of the following theorems: Poincare-Perron, Routh-Hurwitz Criteria and Hartman-Grobman Theorem. This local stability analysis can provide the basis for the global stability analysis.

The stability properties for linear ODEs rely only on the eigenvalues of the system. Since our model is nonlinear, we need to rely on linearisation as well as the Hartman & Grobman Theorem to bring together the local behavior of the linear and nonlinear systems.

Linearising the system requires evaluating the Jacobian matrix at the equilibrium. Afterwards, we find the associated characteristic polynomial where the roots are the eigenvalues of the Jacobian matrix. For local stability, the requirement is that all the eigenvalues have negative real parts, else, the equilibrium is not locally stable. The reproduction number $\mathcal{R}_0$ which determines the stability of the system can be found from the threshold parameters of the roots of the characteristic polynomial. Viral extinction occurs when $\mathcal{R}_0 < 1$, otherwise viral persistence occurs as $t \rightarrow \infty$. In order to carry out the stability analysis, we consider the special cases:

(i) $\gamma = \beta = 0$

(ii) $\gamma = 0$ and $\beta = 1$

(iii) $\gamma = \beta$

We now determine the local stability of our system. For the case (i)-(iii), the system (4.1)–(4.7) can be rewritten in matrix form as

$$\dot{x} = \mathbf{A}x^\gamma + \mathbf{B}x \quad (4.10)$$

where the matrices $\mathbf{A}$ and $\mathbf{B}$ are given below:

$$\mathbf{A} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & M_{17} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & M_{36} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & M_{46} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & M_{57} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{B} = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ M_{21} & M_{22} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & M_{33} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & M_{44} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & M_{55} & 0 & 0 & 0 \\ 0 & 0 & 0 & M_{64} & 0 & M_{66} & 0 & 0 \\ \frac{M_{71}}{1+\delta} & 0 & 0 & 0 & 0 & 0 & 0 & M_{77} \end{pmatrix}$$

Stability analysis case (i)

Consider the case of HIV-1-dependent and HHV-8-independent proliferation terms ($\gamma = 0$ and $\beta = 0$). In this situation, infection is not spread.

Theorem 4.2. *For $\gamma = 0$ and $\beta = 0$, both HIV-1 and HHV-8 infection does not spread*

Stability analysis case (ii)

Consider the case of HIV-1-dependent and HHV-8-independent proliferation terms ($\gamma = 0$ and $\beta = 1$). The system (4.1)–(4.7) reduces to

$$\dot{x} = \mathbf{H}x \quad (4.11)$$

where $\mathbf{H}$ is given by

$$\mathbf{H} = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 & 0 & 0 \\ M_{21} & M_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & M_{33} & 0 & 0 & M_{36} & 0 \\ 0 & 0 & 0 & M_{44} & 0 & M_{46} & 0 \\ 0 & 0 & 0 & 0 & M_{55} & 0 & 0 \\ 0 & 0 & 0 & M_{64} & 0 & M_{66} & 0 \\ \frac{M_{71}}{1+\delta} & 0 & 0 & 0 & 0 & 0 & M_{77} \end{pmatrix}$$

The matrix $\mathbf{H}$ has five negative eigenvalues:

$$\lambda_1 = -\mu_{x_3}, \lambda_2 = -(\mu_{x_5} - r_{x_5}), \lambda_3 = -\kappa_3 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}, \lambda_4 = -\mu_{x_7}, \lambda_5 = -\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}\right).$$

The remaining two are obtained from the characteristic polynomial $P(\lambda) = \lambda^2 + a_1\lambda + a_2$, where

$$a_1 = \left[\left(\mu_{x_4} + \kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} \right) + \mu_{x_6} \right] > 0, \quad a_2 = \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} [\mu_{x_4}(\mu_{x_3} - r_{x_3}) + \kappa_4 s_{x_3}] \right] (1 - \mathcal{R}_0) > 0$$

for $\mathcal{R}_0 = \frac{r_{x_4} N_{x_6} \mu_{x_4} (\mu_{x_3} - r_{x_3})}{[\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})] \mu_{x_6}} < 1$. The stability results are summarised in the following theorem:

Theorem 4.3. *For $\gamma = 0$ and $\beta = 1$ the VFE, $\mathcal{E}_0$, for the system (4.1)–(4.7) is stable if $\mathcal{R}_0 < 1$.*

Remark 4.1. $\mathcal{R}_0 < 1$ implies that for an HIV-1 virus infection, each infected cell infects less than one healthy cell throughout its infectivity period. With an increase in time, the HIV-1 virus can be cleared. Otherwise infection persists.

Stability analysis case (iii)

Consider the case of HIV-1- and HHV-8-dependent proliferation terms ($\gamma = \beta = 1$.) Then system (4.1)–(4.7) can be written as $\dot{x} = \mathbf{C}x$, where $\mathbf{C} = \mathbf{A} + \mathbf{B}$ is given by

$$\mathbf{C} = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 & 0 & M_{17} \\ M_{21} & M_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & M_{33} & 0 & 0 & M_{63} & 0 \\ 0 & 0 & 0 & M_{44} & 0 & M_{64} & 0 \\ 0 & 0 & 0 & 0 & M_{55} & 0 & M_{57} \\ 0 & 0 & 0 & M_{64} & 0 & M_{66} & 0 \\ \frac{M_{71}}{1+\delta} & 0 & 0 & 0 & 0 & 0 & M_{77} \end{pmatrix} \quad (4.12)$$

Three of the eigenvalues of the matrix $\mathbf{C}$ are as follows: $\lambda_1 = -\mu_{x_3}$, $\lambda_2 = -\mu_{x_5}$ and $\lambda_3 = -\kappa_3 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}$. The other four eigenvalues are determined using the Routh-Hurwitz criterion from the characteristic polynomial $P(\lambda) = \lambda^4 + \sum_{j=1}^3 a_j \lambda^{4-j}$. Define

$$\mathcal{R}_{0x_6} = \frac{r_{x_4} N_{x_6} \mu_{x_4} (\mu_{x_3} - r_{x_3})}{[\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})] \mu_{x_6}}, \quad \mathcal{R}_{0x_7} = \frac{r_{x_1} N_{x_7} \mu_{x_1} (\mu_{x_5} - r_{x_5})}{[\kappa_1 s_{x_5} + \mu_{x_1} (\mu_{x_5} - r_{x_5})] \mu_{x_7}},$$

$$\mathcal{R}_{0x_i} = \text{Max}[\mathcal{R}_{0x_6}, \mathcal{R}_{0x_7}]$$

Then, if $\mathcal{R}_{0x_i} < 1$, it is easy to see that the coefficients of a_i for $i = 1, 2, 3, 4$ are all positive as shown in A.2. To conclude stability, it suffices to show that $a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$. It is shown in A.3 that this condition is satisfied provided $\mu_{x_1} > 2\mu_{x_6}$ and $\mathcal{R}_{0x_i} < 1$. Our result is summarised as follows:

Theorem 4.4. *For $\gamma = \beta = 1$ the VFE, $\mathcal{E}_0$, for the system (4.1)–(4.7) is stable if $\mathcal{R}_{0x_i} < 1$ and $\mu_{x_1} > 2\mu_{x_6}$.*

Remark 4.2. $\mathcal{R}_{0x_i} < 1$ implies that for both HIV-1 and HHV-8 viruses infection can be cleared. Otherwise infection persists.

4.2.4 Global asymptotic stability of VFE, $\mathcal{E}_0$

The global asymptotic stability (GAS) is established using the approach given in Castillo-Chavez *et al.* [104]. Define two classes: a class of non-infected states $W = (x_3, x_5)$ and a class of infected states $Z = (x_1, x_2, x_4, x_6, x_7)$. We rewrite the system (4.1)–(4.7) in the form of

$$\dot{W} = F(W, Z) \quad \text{and} \quad \dot{Z} = G(W, Z)$$

such that $G(W, \hat{0}) = \hat{0}$, $\hat{0} = (0, 0, 0, 0, 0)$, $W \in \mathbb{R}^2$ and $Z \in \mathbb{R}^5$. The functions $F(W, Z)$ and $G(W, Z)$ denote classes of non-infected and infected states, respectively, where

$$F(W, Z) = \begin{pmatrix} s_{x_3} + r_{x_3}x_3x_6^\gamma - \mu_{x_3}x_3 \\ s_{x_5} + r_{x_5}x_5x_7^\gamma - \mu_{x_5}x_5 \end{pmatrix}, \quad G(W, Z) = \begin{pmatrix} r_{x_1}x_7^\gamma - \mu_{x_1}x_1 - \kappa_1x_1x_5 \\ \alpha x_1 \left(1 - \frac{x_2}{\omega}\right) - \kappa_3x_2x_5 \\ r_{x_4}x_6^\beta - \kappa_4x_3x_4 - \mu_{x_4}x_4 \\ N_{x_6}\mu_{x_4}x_4 - \mu_{x_6}x_6 \\ N_{x_7}\mu_{x_1}(1 + \delta x_6^\beta)x_1 - \mu_{x_7}x_7 \end{pmatrix}$$

We redefine the virus-free equilibrium as $\bar{\mathcal{E}}_0 = (W^*, \hat{0})$, where $W^* = \left(\frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})}, \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right)$. This theorem on GAS is proved in Castillo-Chavez *et al.* [104].

Theorem 4.5. (a) The equilibrium point $\bar{\mathcal{E}}_0 = (W^*, \hat{0})$ is GAS for $\gamma = \beta = 0$

(b) The equilibrium point $\bar{\mathcal{E}}_0 = (W^*, \hat{0})$ is GAS for $\gamma = 0$ and $\beta = 1$ if $\mathcal{R}_0 < 1$.

(c) The equilibrium point $\bar{\mathcal{E}}_0 = (W^*, \hat{0})$ is GAS for $\gamma = \beta = 1$ if $\mathcal{R}_{0x_i} < 1$.

Proof. **3(a):** The case $\gamma = \beta = 0$. Setting the infection variables of $F(W, Z)$ to zero, we have

$$F(W, 0) = (s_{x_3} - (\mu_{x_3} - r_{x_3})x_3, s_{x_5} - (\mu_{x_5} - r_{x_5})x_5)^T.$$

Consider the system

$$\dot{W} = s_x - \mu_x W, \quad W = \begin{pmatrix} x_3 \\ x_5 \end{pmatrix}, \quad \mu_x = \begin{pmatrix} \mu_{x_3} - r_{x_3} \\ \mu_{x_5} - r_{x_5} \end{pmatrix}, \quad s_x = \begin{pmatrix} s_{x_3} \\ s_{x_5} \end{pmatrix} \quad (4.13)$$

Then, the solution is given by

$$W(t) = \left(W(0) - \frac{s_x}{\mu_x} \right) e^{-\mu_x t} + \frac{s_x}{\mu_x}$$

Since $F(W, \hat{0})$ is a limiting function of $\dot{W} = F(W, Z)$, that is $\lim_{t \rightarrow \infty} W(t) =$

$\left(\frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})}, \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right)^T = W^*$, then $F(W^*, \hat{0})$ is GAS.

Let $y_3 = s_{x_3} - (\mu_{x_3} - r_{x_3})x_3$ and $y_5 = s_{x_5} - (\mu_{x_5} - r_{x_5})x_5$. Then $F(W, \hat{0})$ can be written as

$$\begin{pmatrix} \dot{y}_3 \\ \dot{y}_5 \end{pmatrix} = \begin{pmatrix} -\frac{1}{(\mu_{x_3} - r_{x_3})} & 0 \\ 0 & -\frac{1}{(\mu_{x_5} - r_{x_5})} \end{pmatrix} \begin{pmatrix} y_3 \\ y_5 \end{pmatrix},$$

where the eigenvalues are $\lambda_3 = -\frac{1}{(\mu_{x_3} - r_{x_3})} < 0$ and $\lambda_5 = -\frac{1}{(\mu_{x_5} - r_{x_5})} < 0$. It follows that W^* is asymptotically stable. Now consider,

$$D_Z G(W^*, 0)Z - G(W, Z) = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 \\ M_{21} & M_{22} & 0 & 0 & 0 \\ 0 & 0 & M_{44} & 0 & 0 \\ 0 & 0 & M_{64} & M_{66} & 0 \\ M_{71} & 0 & 0 & 0 & M_{77} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_4 \\ x_6 \\ x_7 \end{pmatrix} - \begin{pmatrix} M_{17} + M_{11}x_1 \\ M_{21}\left(1 - \frac{x_2}{\omega}\right)x_1 + M_{22}x_2 \\ M_{46} + M_{44}x_4 \\ M_{64}x_4 + M_{66}x_6 \\ M_{71}x_1 + M_{77}x_7 \end{pmatrix}$$

$$= \begin{pmatrix} -r_{x_1} \\ \frac{\alpha x_1 x_2}{\omega} \\ -r_{x_4} \\ 0 \\ 0 \end{pmatrix} = \hat{0}^T$$

by (4.9). Hence, $\mathcal{E}_0$ is GAS.

Proof **3(b)**: For $\gamma = 0$ and $\beta = 1$, it can be shown that

$$\hat{G}(W, Z) = D_Z G(W^*, 0)Z - G(W, Z) = \left(-r_{x_1}, \frac{\alpha x_1 x_2}{\omega}, r_{x_4} - r_{x_4} x_6, 0, -N_{x_7} \mu_{x_1} \delta x_6 \right)^T = \hat{0}^T$$

by (4.9). Hence, $\hat{\mathcal{E}}_0$ is GAS.

Proof **3(c)**: The case $\gamma = \beta = 1$ is similar to **3(b)**. □

Immunologically, $\hat{\mathcal{E}}_0$ being globally asymptotically stable means that, perturbing the equilibrium point by introducing free virus particles, will always make the model solutions to converge to the virus free equilibrium whenever $\mathcal{R}_0 < 1$.

4.2.5 Model variables and parameters

The parameter values are as given in Table 4.2 where the estimated parameters are derived from the simulations. We consider the chronic phase of HIV-1 infection, that is two years post infection.

We consider $x_1(0) = 5 \times 10^2$ cells mL^{-1} and $x_7(0) = 6.4 \times 10^4$ virions mL^{-1} as in Hadinoto *et al.* [112]. Based on Bajaria [113], we take the initial HIV-1 specific effector cell population to be $x_3(0) = 5 \times 10^5$ cells mL^{-1} , the initial infected T cell population to be $x_4(0) = 10^2$ cells mL^{-1} and the initial HIV-1 population to be $x_6(0) = 2 \times 10^5$ virions mL^{-1} based on Boer *et al.* [114]. The estimated initial KS cell population is taken to be $x_2(0) = 2 \times 10^2$

cells mL^{-1} based on a study by Louzoun *et al.* [115] and we estimate $x_5(0) = 5 \times 10^2$ cells mL^{-1} in accordance with a study by Szomolay and Lungu.

Based on a study by Szomolay and Lungu [37], we take the range $s_{x_3} = 3 \times 10^2 - 9 \times 10^5$ cells mL^{-1} and we estimate the value of s_{x_5} to be 1.1×10^3 cells mL^{-1} .

The proliferation rate of HIV-1 specific effector cells are taken from studies by Gumel [116] and Stilianakis [117]. In these studies r_{x_3} is assumed to be $2 \times 10^{-6} \text{ day}^{-1}$. Due to absence of HHV-8 proliferation rates, we have estimated $r_{x_5} = 1.2 \times 10^{-8} \text{ day}^{-1}$. We estimate r_{x_1} and r_{x_4} to be in the range $2 - 12 \text{ day}^{-1}$, the range for δ is estimated to be in the region 3×10^{-8} to $3 \times 10^{-4} \text{ day}^{-1}$.

TABLE 4.2: Variables and parameter values.

Variables	Initial values		Units	Reference
x_1	$x_1(0) = 5 \times 10^2$		cells mL^{-1}	[112]
x_2	$x_2(0) = 2 \times 10^2$		cells mL^{-1}	Estimated
x_3	$x_3(0) = 5 \times 10^5$		cells mL^{-1}	[113]
x_4	$x_4(0) = 10^2$		cells mL^{-1}	[114]
x_5	$x_5(0) = 5 \times 10^2$		cells mL^{-1}	Estimated
x_6	$x_6(0) = 2 \times 10^5$		virions mL^{-1}	[114]
x_7	$x_7(0) = 6.4 \times 10^4$		virions mL^{-1}	[112]
Parameters	Range	Value	Units	Reference
<i>Death/ clearance rates</i>				
μ_{x_1}	[0.2, 0.5]	0.33	day^{-1}	[118, 119]
μ_{x_3}	[0.001, 0.04]	0.03	day^{-1}	[116]
μ_{x_4}	$[1.1 \times 10^{-4}, 2.5 \times 10^{-4}]$	1.87×10^{-4}	day^{-1}	[120, 121]
μ_{x_5}	[0.008, 0.4]	0.3	day^{-1}	[118, 119]
μ_{x_6}	[0.1, 5]	0.1	day^{-1}	[113, 116]
μ_{x_7}	[0.35, 0.69]	0.57	day^{-1}	[122]
<i>Source terms</i>				
s_{x_3}	$[3 \times 10^2, 9 \times 10^5]$	3×10^3	cells mL^{-1}	[37]
s_{x_5}	$[10^3, 2 \times 10^3]$	1.1×10^3	cells mL^{-1}	Estimated
<i>Proliferation rates</i>				
r_{x_1}	[1, 12]	5	day^{-1}	Estimated
r_{x_3}	$[2 \times 10^{-9}, 10^{-5}]$	2×10^{-6}	day^{-1}	[116, 117]
r_{x_4}	[1, 12]	3	day^{-1}	Estimated
r_{x_5}	$[10^{-9}, 10^{-6}]$	1.2×10^{-8}	day^{-1}	Estimated
δ	$[3 \times 10^{-9}, 3 \times 10^{-4}]$	3×10^{-8}	day^{-1}	Estimated
<i>Constants</i>				
γ	[0,1]	variable		
β	[0,1]	variable		
<i>Growth rates</i>				
α	[2, 6]	2	day^{-1}	Estimated
<i>Killing rates</i>				
κ_1	$[1.2 \times 10^{-4}, 10^{-2}]$	9.9×10^{-3}	$\text{mL cell}^{-1} \text{day}^{-1}$	[118, 119]
κ_3	$[8 \times 10^{-7}, 5 \times 10^{-4}]$	3×10^{-4}	$\text{mL cell}^{-1} \text{day}^{-1}$	[115]
κ_4	$[10^{-5}, 2 \times 10^{-4}]$	9×10^{-5}	$\text{mL cell}^{-1} \text{day}^{-1}$	[117]
<i>Maximum cell population</i>				
ω	$[1.2 \times 10^5, 5 \times 10^6]$	1.2×10^5	cells mL^{-1}	[37]
<i>Burst size</i>				
N_{x_6}	$[10^3, 5.4 \times 10^4]$	1000	virions cell^{-1}	[123]
N_{x_7}	$[2 \times 10^2, 10^3]$	900	virions cell^{-1}	[112]

We estimate the cancer growth rate α to be 2 day^{-1} and we have used the killing rate of infected B cells $\kappa_1 = 9.9 \times 10^{-3} \text{ mL cell}^{-1} \text{ day}^{-1}$. Based on Louzoun [115], the killing rate of KS cells is taken to be $\kappa_3 = 3 \times 10^{-4} \text{ mL cell}^{-1} \text{ day}^{-1}$. The killing rate of infected CD4^+ T cells is $\kappa_4 = 9 \times 10^{-5} \text{ mL cell}^{-1} \text{ day}^{-1}$ as in Stilianakis [117]. Following Szomolay and Lungu [37], we take $\omega = 1.2 \times 10^5 \text{ cells}$. We take the total burst size of infected CD4^+ T cells, N_{x_6} to be in the range $10^3 - 5 \times 10^4 \text{ virions day}^{-1}$ as in Boer [114]. The range for N_{x_7} is taken to be $2 \times 10^2 - 10^3 \text{ virions cell}^{-1}$ based on Hadinoto [112].

Huynh [118] and Shapiro *et al.* [119] took the death rate of infected B cells for the Epstein-Barr virus (EBV) infection to be $\mu_{x_1} = 0.33 \text{ day}^{-1}$. HHV-8 and EBV are different viruses but due to absence of a clinical value for this parameter, we used $\mu_{x_1} = 0.33 \text{ day}^{-1}$ (as in [118, 119]). We assume the death rates for HIV-1 and HHV-8 specific effector cells to be $\mu_{x_3} = 0.03 \text{ day}^{-1}$ as in Gumel *et al.* [116] and $\mu_{x_5} = 0.3 \text{ day}^{-1}$ as in [118, 119]. Based on the research by Mclean [120] and Weston [121], we took the lytic death rate of infected CD4^+ T cells to be $\mu_{x_4} = 1.87 \times 10^{-4} \text{ day}^{-1}$. The estimated clearance rate of HIV-1 virus, μ_{x_6} , is taken to be in the range $0.1 - 5 \text{ day}^{-1}$ based on a study by Bajaria and Gumel [113, 116]. Due to the absence of estimates for the virus half life of HHV-8, we will use the value in a study by Foglieni *et al.* [122] which is $\mu_{x_7} = 0.57 \text{ day}^{-1}$. We now show how μ_{x_4} was estimated.

Parameter estimation of μ_{x_4}

We estimate the infected T cell death rate by a combination of two methods: (1) plotting T cell count for an HIV-1 infected patient over a period of time without treatment, adapted from WHO [8] and (2) from research carried out by Mclean and Michie [120]. Figure 4.4 illustrates the T cell count for an HIV-1 infected patient. Due to the infection, the T cells become depleted.

From Figure 4.4, the equation for the tangentline is $y = -1.308x + 719.59$. So the death rate is $1.308 \text{ cells /}\mu\text{l per week}$ which would translate to $= 0.001308 \text{ cells/mL per week}$, hence we have death rate as $\mu_I = 0.0001869 \text{ day}^{-1}$ for an infected person. [120] carried out a research on the *in vivo* estimates of division and death rates of healthy human T lymphocytes. The best estimates for $\mu_H = 0.00014 \text{ day}^{-1}$ and 95% confidence interval of $0.00007 - 0.00021 \text{ day}^{-1}$ for a healthy person. From [8] and [120] we get: infected T cell death rate $\mu_I = 0.0001869$. On the other hand for a healthy person $\mu_H = 0.00014$ based on the study by [120], hence $\beta = \mu_I - \mu_H = 0.0000469$ from $\dot{T} = \Pi - \mu_H T - \beta TV$ which

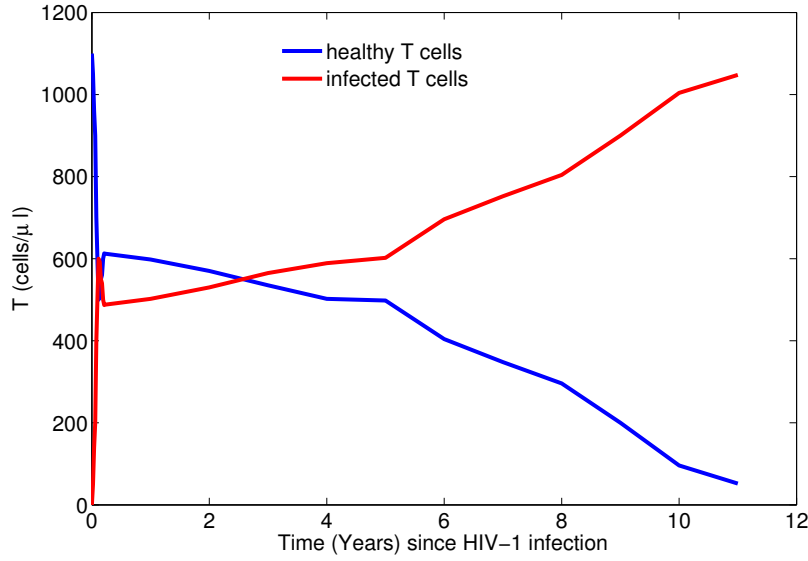


FIGURE 4.4: T cell count for an HIV-1 infected patient without treatment adapted from WHO [8].

represents the dynamics of healthy T cells in general. Hence we conclude that μ_{x_4} ranges from 1.1×10^{-4} to 2.5×10^{-4} .

4.2.6 Sensitivity and uncertainty analysis of $\mathcal{R}_{0x_6}$ and $\mathcal{R}_{0x_7}$

In determining how best to treat AIDS-KS infection, it is necessary to know the relative importance of the different factors responsible for its transmission. If $\mathcal{R}_{0x_i}$, for $i = 6, 7$, is very sensitive to a particular parameter, then an adjustment of the conditions that connect the dynamics to such a parameter may prove useful in identifying policies or intervention strategies that reduce KS prevalence.

We explore the parameter space by performing an uncertainty analysis using Latin Hypercube Sampling (LHS) method as described by Blower and Gomero [105, 106]. Coefficients (PRCC) are used to evaluate the contribution of vital parameters on the model dynamics, most specifically to establish the parameters that have significant influence on the HIV-related KS. MATLAB software was used for the PRCC analysis with a sampling size, $n = 1000$.

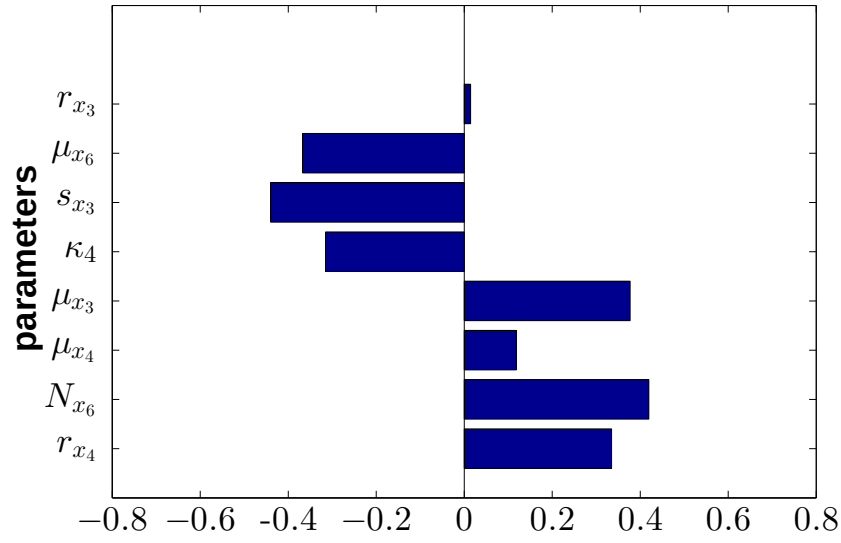
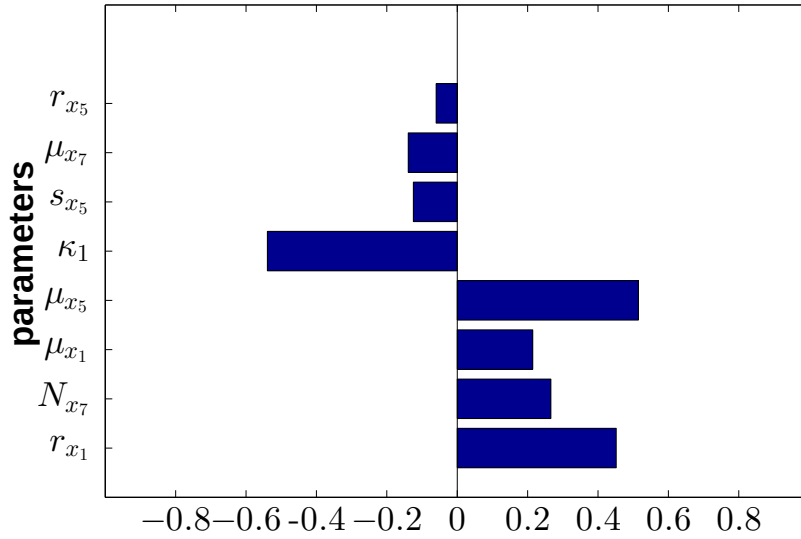
(a) PRCC values for $\mathcal{R}_{0x_6}$ (b) PRCC values for $\mathcal{R}_{0x_7}$

FIGURE 4.5: Partial Rank Correlation Coefficients (PRCCs) of the model parameters with respect to (a) $\mathcal{R}_{0x_6}$ and (b) $\mathcal{R}_{0x_7}$. This analysis was adopted from Blower and Gomero [105, 106]. Model parameters were sampled 1000 times where the values and ranges are given in Table 4.2.

PRCC is the tool we use to evaluate the impact of changes of each parameter on $\mathcal{R}_{0x_6}$ and $\mathcal{R}_{0x_7}$. It is informative on what parameters to target in order to achieve specific goals

for example how to effectively reduce VL and KS. Figure 4.5(a) shows the PRCC results which illustrate the dependence of $\mathcal{R}_{0x_6}$ on each parameter. The positive signs of their PRCCs indicate that if the parameters are increased, the value of $\mathcal{R}_{0x_6}$ increases and vice versa. The following parameters have a statistically significant PRCC value and a negative influence on $\mathcal{R}_{0x_6}$: κ_4 , s_{x_3} and μ_{x_6} while the the opposite is true for r_{x_4} , N_{x_6} , μ_{x_4} , r_{x_3} and μ_{x_3} . Predominantly, s_{x_3} has the greatest influence on $\mathcal{R}_{0x_6}$. Figure 4.5(b) shows the PRCC results which illustrate the dependence of $\mathcal{R}_{0x_7}$ on each parameter. The following HHV-8 associated parameters have a statistically significant PRCC value and have the potential to positively influence infection: r_{x_1} , N_{x_7} , μ_{x_1} and μ_{x_5} and the opposite is true for κ_1 , s_{x_5} , r_{x_5} and μ_{x_7} . The most significant control parameter for $\mathcal{R}_{0x_7}$ is κ_1 .

The significance of the PRCC for each parameter is determined by calculating a p -value for each using the methods described by Marino *et al.* [124]. The PRCC values with a p -value less than 0.01 are considered statistically significant. From Tables 4.3 and 4.5, it can be seen that r_{x_3} and r_{x_5} are not statistically significant.

In order to test for independence between the parameters which affect the reproduction numbers, we apply the Fisher transformation to the PRCC as described by Fieller *et al.* [125]. We use R software is to test for independence. We corrected the resulting p -values for false discovery using the false discovery rate (FDR) method of Benjamini and Hochberg [126]. Using the parameters whose PRCC values were found to be significant, we performed pairwise comparisons with Fisher transformed values [125], hence produces the results given in Table 4.4 and Table 4.6. A red TRUE indicates independence between two parameters a black FALSE indicates the opposite. The independence test indicates that s_{x_3} may be influenced by μ_{x_6} as illustrated in Table 4.4.

TABLE 4.3: PRCC for $\mathcal{R}_{0x_6}$ and p-values resulting from the sensitivity analysis.

Variable	PRCC	p – value
r_{x_4}	0.3350	0.000
N_{x_6}	0.4195	0.000
μ_{x_4}	0.1183	1.842×10^{-4}
μ_{x_3}	0.3771	0.000
κ_4	-0.31534	0.000
s_{x_3}	-0.4399	0.000
μ_{x_6}	-0.3673	0.000
r_{x_3}	0.0145	6.482×10^{-1}

TABLE 4.4: Pairwise comparisons for $\mathcal{R}_{0x_6}$ parameters.

	N_{x_6}	μ_{x_4}	μ_{x_3}	κ_4	s_{x_3}	μ_{x_6}
r_{x_4}	TRUE	TRUE	FALSE	TRUE	TRUE	TRUE
N_{x_6}		TRUE	FALSE	TRUE	TRUE	TRUE
μ_{x_4}			TRUE	TRUE	TRUE	TRUE
μ_{x_3}				TRUE	TRUE	TRUE
κ_4					TRUE	FALSE
s_{x_3}						FALSE

TABLE 4.5: PRCC for $\mathcal{R}_{0x_7}$ and p-values resulting from the sensitivity analysis.

Variable	PRCC	p – value
r_{x_1}	0.3944	0.000
N_{x_7}	0.2890	0.000
μ_{x_1}	0.1771	1.784×10^{-8}
μ_{x_5}	0.4705	0.000
κ_1	-0.5217	0.000
s_{x_5}	-0.1035	1.082×10^{-3}
μ_{x_7}	-0.1552	8.521×10^{-7}
r_{x_5}	-0.0320	3.138×10^{-1}

TABLE 4.6: Pairwise comparisons for $\mathcal{R}_{0x_7}$ parameters.

	N_{x_7}	μ_{x_1}	μ_{x_5}	κ_1	s_{x_5}	μ_{x_7}
r_{x_1}	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
N_{x_7}		TRUE	TRUE	TRUE	TRUE	TRUE
μ_{x_1}			TRUE	TRUE	TRUE	TRUE
μ_{x_5}				TRUE	TRUE	TRUE
κ_1					TRUE	TRUE
s_{x_5}						FALSE

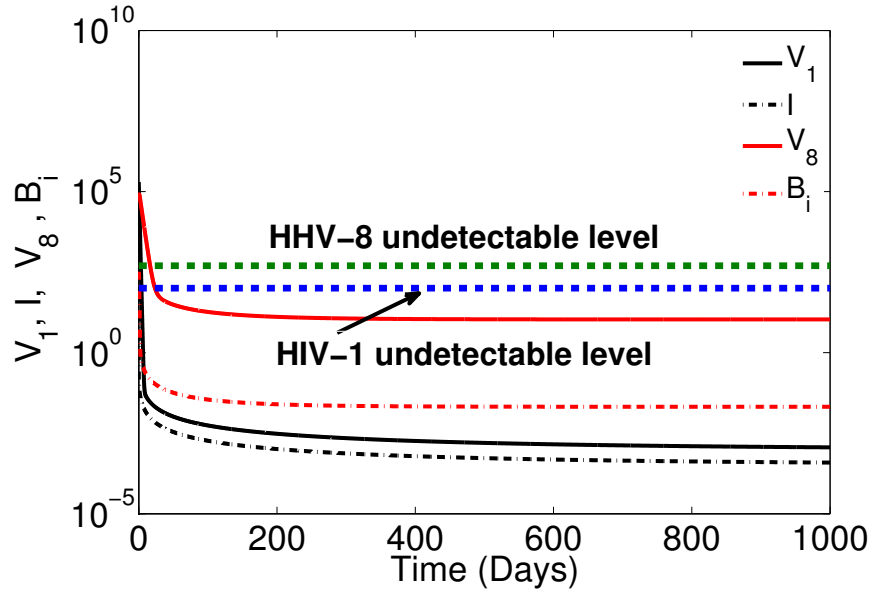
4.2.7 Numerical simulations for the weak viral source model without optimal control

The numerical simulations are implemented in MATLAB. In order to examine the progression of the infection, we consider the following scenarios: (i) $\gamma = \beta = 0$, (ii) $\gamma = 0$ and $\beta = 1$ and (iii) $\gamma = \beta = 1$. Figure 4.6 shows the prognosis of the infection for $\gamma = \beta = 0$. This case demonstrates a scenario when both infected T and B cells divide at a constant rate (Cho *et al.* [127]). Figure 4.6(a) shows that after reaching a peak during

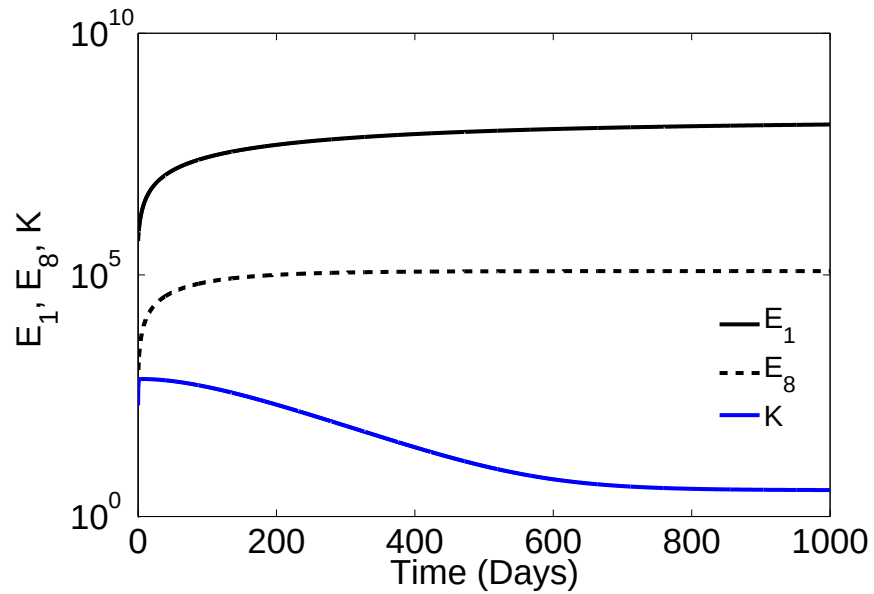
the primary stage, the HIV-1 viral load, x_6 , decays below a detectable level of 40 virions per microliter of blood [61]. A similar pattern is observed for HHV-8, x_7 . In response, both HIV-1 and HHV-8 specific effector cells, x_3 and x_5 , respectively increase to a peak and remain constant throughout the chronic stage (4.6(b)). Figure 4.6(a) shows that the infected B and T cells, x_1 and x_4 , respectively decrease due to lysing by the increasing populations of respective effector cells. Figure 4.6(b) shows that the population of Kaposi sarcoma cells declines. KS cannot develop into a clinical condition for $\gamma = \beta = 0$. The WHO guidelines are not available for us to conclude whether this steady state, below 100 copies/mL, is detectable or undetectable for KS.

Figure 4.7 illustrates the case when the infected B cells are dividing slowly and the infected T cells are dividing rapidly. We demonstrate the case for $\gamma = 0$ and $\beta = 1$. We can see that HIV-1 viral load is high but HHV-8 viral load is low. The infected T cell population is also high but the infected B cell population is low. The prognosis for the KS is low suggesting that cell division for infected B cells plays a very important role. The high population of HHV-8 specific effector cells, x_5 , suggests a high rate of lysing of KS cells.

Figure 4.8 describes disease progression for $\gamma = \beta = 1$. This case represents a scenario when both infected T and B cells divide rapidly. Figure 4.8(a) shows prolonged and severe viremia for both HIV-1 and HHV-8. The viral loads remain detectable throughout the chronic stage. Figure 4.8(a) shows a high population level for infected T cells. The HIV-1 and HHV-8 specific effector cell populations remain high throughout and consequently the KS cells population remains high improving the chances of KS development. (Figure 4.8(b)). With a low cancer burden representing only 0.001% of maximum carrying capacity of KS cells, the HHV-8 load will reach equilibrium that is either below the level of detection ($\gamma = 0$ and $\beta \geq 0$), or above ($\gamma = \beta = 1$). In the latter case, over 3000-fold increase in HHV-8 load is obtained compared to the level off detection and the KS load increases to 2.7% of the maximum carrying capacity (Figure 4.9).

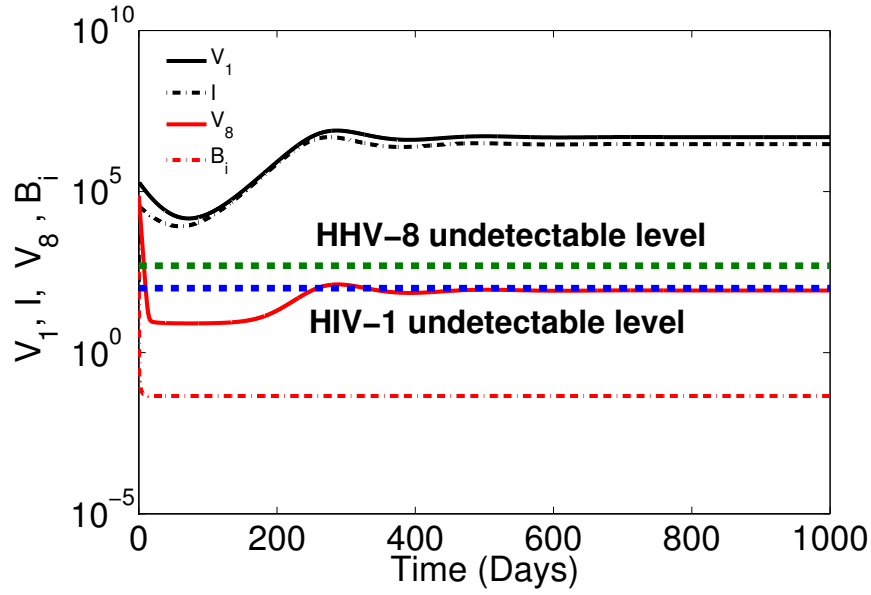


(a)

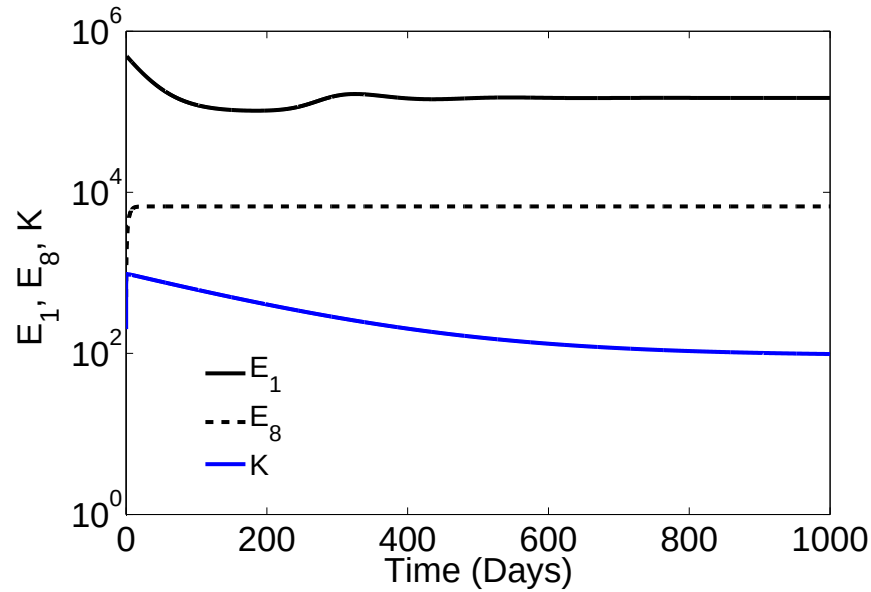


(b)

FIGURE 4.6: Model predictions for the weak viral source model without treatment for the case $\gamma = \beta = 0$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .

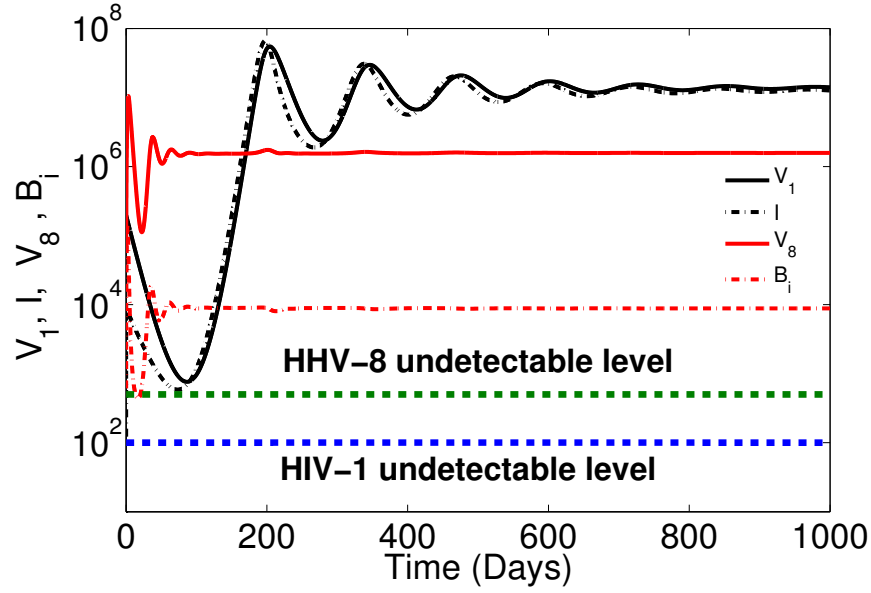


(a)

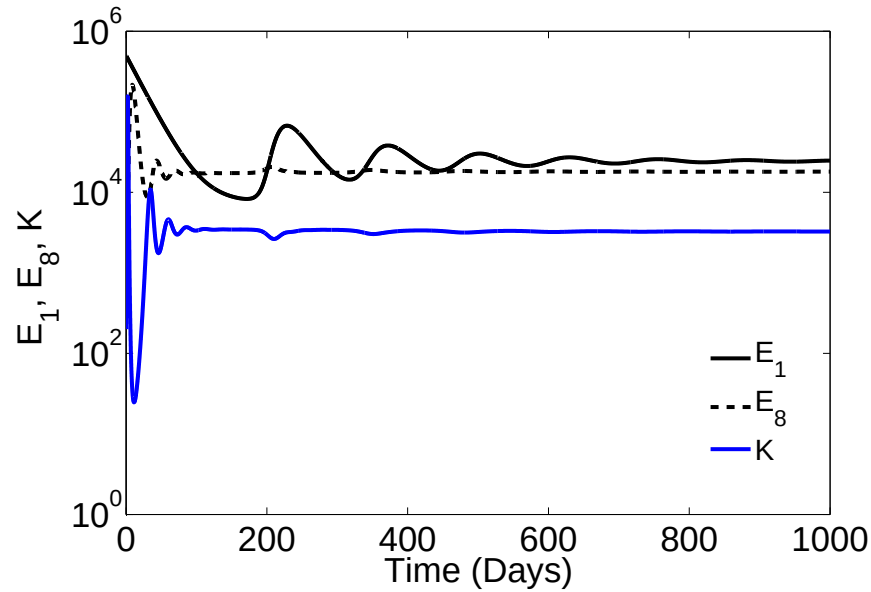


(b)

FIGURE 4.7: Model predictions for the weak viral source model without treatment for the case $\gamma = 0$ and $\beta = 1$ with $\mathcal{R}_0 > 1$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .



(a)



(b)

FIGURE 4.8: Model predictions for the weak viral source model without treatment for the case $\gamma = \beta = 1$ with $\mathcal{R}_{0x_i} > 1$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .

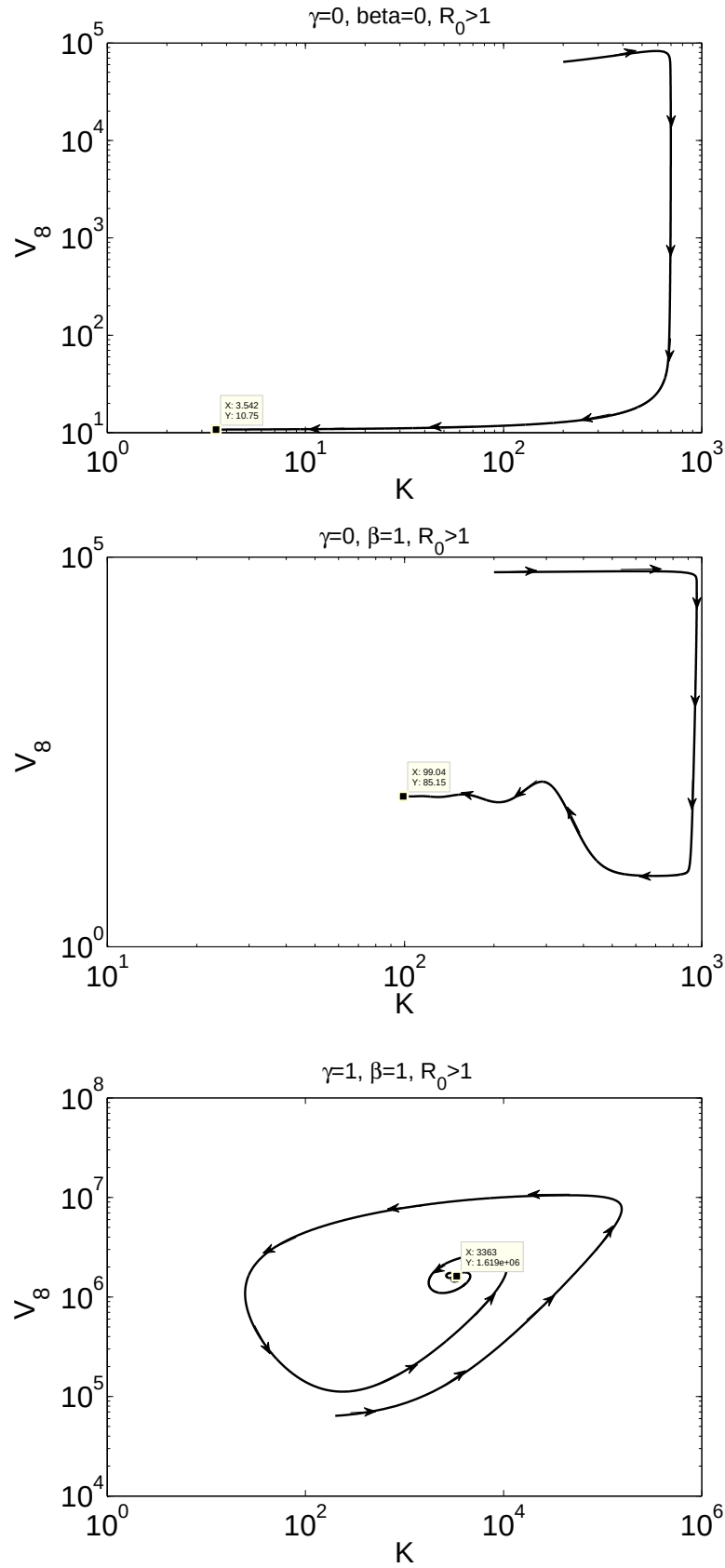


FIGURE 4.9: The trajectory between viral population, HHV-8 (V_8) and cancer cells, K for the weak viral source model. This is for the three cases, $\gamma = \beta = 0$ (top plot), $\gamma = 0$ and $\beta = 1$ (middle plot) and $\gamma = \beta = 1$ (bottom plot).

4.3 Strong viral source model with $H_1(x_6, \beta) = x_6^\beta + x_6$ and $H_8(x_7, \gamma) = x_7^\gamma + x_7$

In this section, we consider the model with strong viral source that may be caused by many factors such as non-adherence to treatment. Adherence to HAART helps maintain low to undetectable VL. However, non-adherence leads to higher number of infected cells and consequently to an increase in the VL [128, 129]. The new system (4.1)*–(4.7)* will be essentially the same as (4.1) – (4.7) except that $H_1(x_6, \beta) = x_6^\beta + x_6$ and $H_8(x_7, \gamma) = x_7^\gamma + x_7$. We note that (4.1)*–(4.7)* can be rewritten as $\dot{x} = \mathbf{A}x^\gamma + \mathbf{C}x$, where matrix $\mathbf{A}$ is defined in (4.2.3) and matrix $\mathbf{C}$ is defined in (4.12). We consider the cases (i)–(iii) as in Section 4.2.

4.3.1 Stability Analysis Case (i)

Consider the case $\gamma = \beta = 0$. The system (4.1)*–(4.7)* reduces to $\dot{x} = \mathbf{M}x$, where the matrix $\mathbf{M}$ is given in A.1. The coefficients of the characteristic polynomial $P(\lambda) = \lambda^4 + \sum_{j=1}^4 a_j \lambda^{4-j}$, associated with $\mathbf{M}$, are given by a_1, a_2, a_3 , and a_4 (shown in A.2). In this case the term $(1 - \mathcal{R}_{0x_i})$ is replaced by $(1 - \mathcal{R}_{0x_i}^*)$ with $\mathcal{R}_{0x_i}^* = \text{Max}[\mathcal{R}_{0x_6}^*, \mathcal{R}_{0x_7}^*]$, where $\mathcal{R}_{0x_6}^* = \mathcal{R}_{0x_6}$ and $\mathcal{R}_{0x_7}^* = (1 + \delta)\mathcal{R}_{0x_7}$.

Theorem 4.6. *For $\gamma = \beta = 0$ the VFE, $\mathcal{E}_0$, is stable if $\mathcal{R}_{0x_i}^* < 1$, otherwise it is unstable.*

Remark 4.3. In this case the reproduction number is not zero as in Section 4.2.2.

4.3.2 Stability Analysis Case (ii)

When $\gamma = 0$ and $\beta = 1$, the system (4.1)*–(4.7)* becomes $\dot{x} = \mathbf{N}x$, where

$$\mathbf{N} = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 & 0 & M_{17} \\ M_{21} & M_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & M_{33} & 0 & 0 & 2M_{36} & 0 \\ 0 & 0 & 0 & M_{44} & 0 & 2M_{46} & 0 \\ 0 & 0 & 0 & 0 & M_{55} & 0 & M_{57} \\ 0 & 0 & 0 & M_{64} & 0 & M_{66} & 0 \\ \frac{M_{71}}{1+\delta} & 0 & 0 & 0 & 0 & 0 & M_{77} \end{pmatrix}$$

The term $(1 - \mathcal{R}_{0x_i})$ in the coefficients of the characteristic polynomial given in A.2, is replaced by $(1 - \bar{\mathcal{R}}_{0x_i})$. We have $\bar{\mathcal{R}}_{0x_i} = \text{Max}[\bar{\mathcal{R}}_{0x_6}, \bar{\mathcal{R}}_{0x_7}]$ where $\bar{\mathcal{R}}_{0x_6} = 2\mathcal{R}_{0x_6}$ and $\bar{\mathcal{R}}_{0x_7} = \mathcal{R}_{0x_7}$.

Theorem 4.7. *For $\gamma = 0$ and $\beta = 1$ the VFE, $\mathcal{E}_0$, is stable if $\bar{\mathcal{R}}_{0x_i} < 1$, otherwise it is unstable.*

4.3.3 Stability Analysis Case (iii)

When $\gamma = \beta = 1$, the system (4.1)*–(4.7)* can be written as $\dot{x} = \mathbf{D}x$, where $\mathbf{D} = \mathbf{A} + \mathbf{C}$ and matrix $\mathbf{A}$ is defined in (4.2.3) and matrix $\mathbf{C}$ is defined in (4.12). The term $(1 - \mathcal{R}_{0x_i})$ in the coefficients of the characteristic polynomial given in A.2, is replaced by $(1 - \bar{\mathcal{R}}_{0x_i})$, where $\hat{\mathcal{R}}_{0x_i} = 2\mathcal{R}_{0x_i}$.

Remark 4.4. The case $\gamma = \beta = 1$ leads to doubling of the reproduction number. Non-adherence to treatment results in increased reproduction number and can complicate treatment. Nachega et al. [130] has pointed out that adherence to HAART suppresses viral replication and leads to slow cell division.

Remark 4.5. Generally some patients are immunologically susceptible to high VL production. Such patients should be identified through screening (regular checkups) and made to start their treatment early.

4.3.4 Numerical simulations for the strong viral source model without optimal control

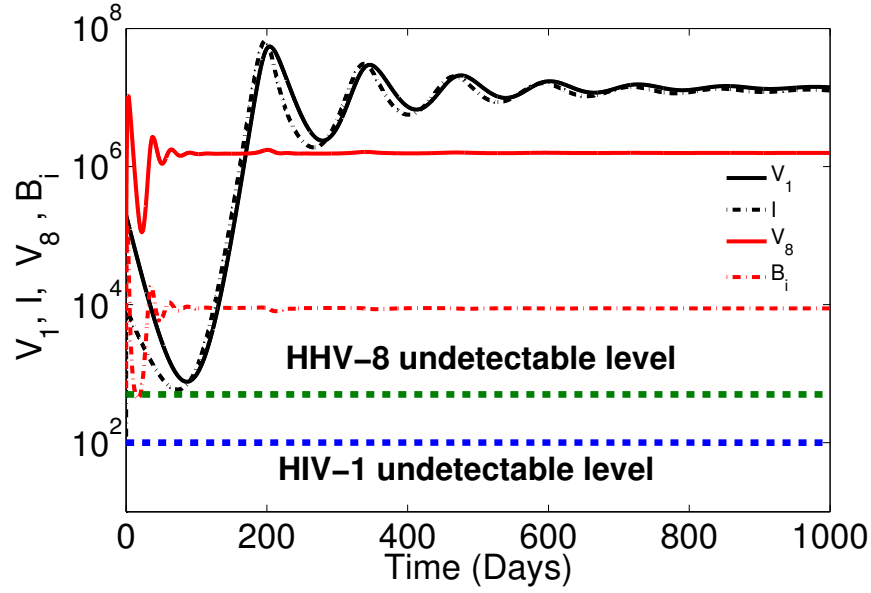
Figure 4.10 depicts the population dynamics of virions and cell population when the viral load is high for the case when $\gamma = \beta = 0$. HIV-1 and HHV-8 viral loads remain high throughout the chronic stage, consequently, high levels of infected T and B cells are observed in Figure 4.10(a). This results in high levels of KS as shown in Figure 4.10(b). The immune response remains high due to the high levels of infected T and B cells (Figure 4.10(b)). The pattern observed here is similar to that observed in Figure 4.8 for the low viral load model when $\gamma = \beta = 1$.

Figure 4.11 illustrates the case when $\gamma = 0$ and $\beta = 1$. HIV-1 and HHV-8 viral loads remain above detectable levels throughout the infection as seen in Figure 4.11(a). Due to high levels of HIV-1 and HHV-8 viral loads, the infected T and B cell populations remain high as shown in Figure 4.11(a). Consequently (as seen in Figure 4.11(b)), the

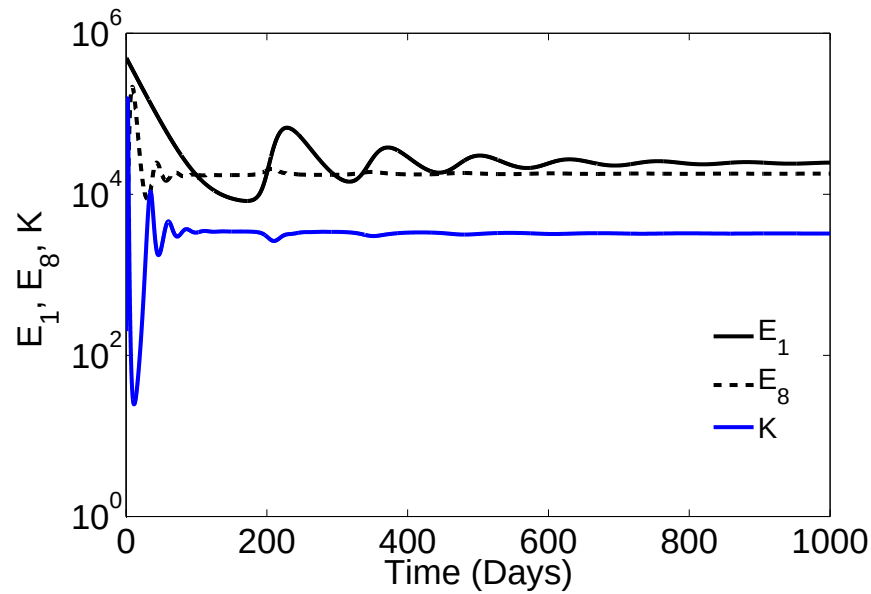
KS population remains high due to high levels of HHV-8. In response, the HIV-1 and HHV-8 specific effector cell populations remain high as illustrated in Figure 4.11(b). The cell levels in Figure 4.11 are significantly higher than those in Figure 4.10.

Figure 4.12 shows the case when $\gamma = \beta = 1$, that is when both infected T and infected B cells divide faster. A similar behavior to that in Figure 4.11 is observed. From Figures 4.11 and 4.12, we conclude that the higher the proliferation of HHV-8 due to enhancement by HIV-1 has more impact on the development of KS than the increase in the infected B cell population.

Although the equilibria for the strong viral source model when $\gamma = 0$ and $\beta \geq 0$ do not change substantially, there is a profound impact on KS and HHV-8 burden when $\gamma = \beta = 1$. In the latter case the KS load increases to over 80% of the maximum carrying capacity of KS cells and the HHV-8 load over 200000-fold above the level of HHV-8 detection, surpassing even the HIV-1 load (Figure 4.13).



(a)



(b)

FIGURE 4.10: Model predictions for the strong viral source model without treatment for the case $\gamma = \beta = 0$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .

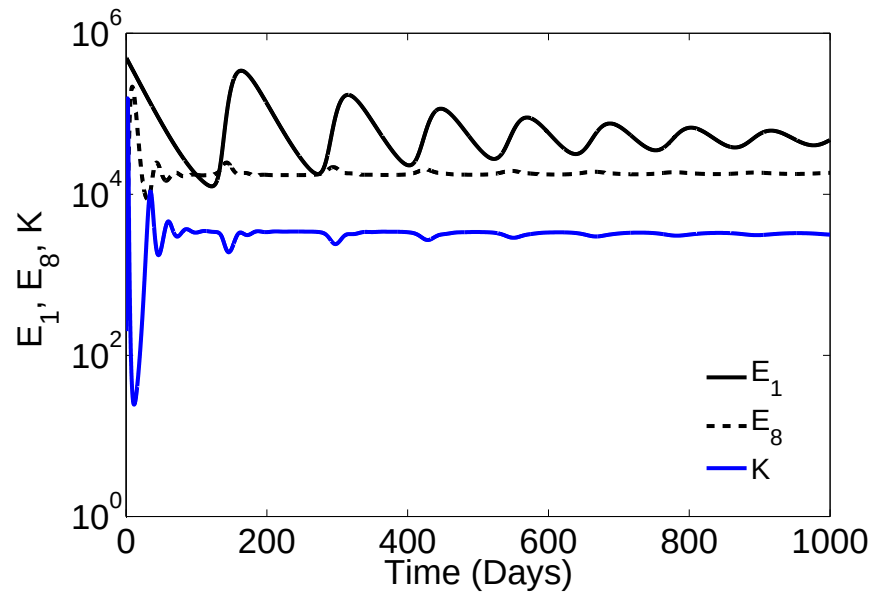
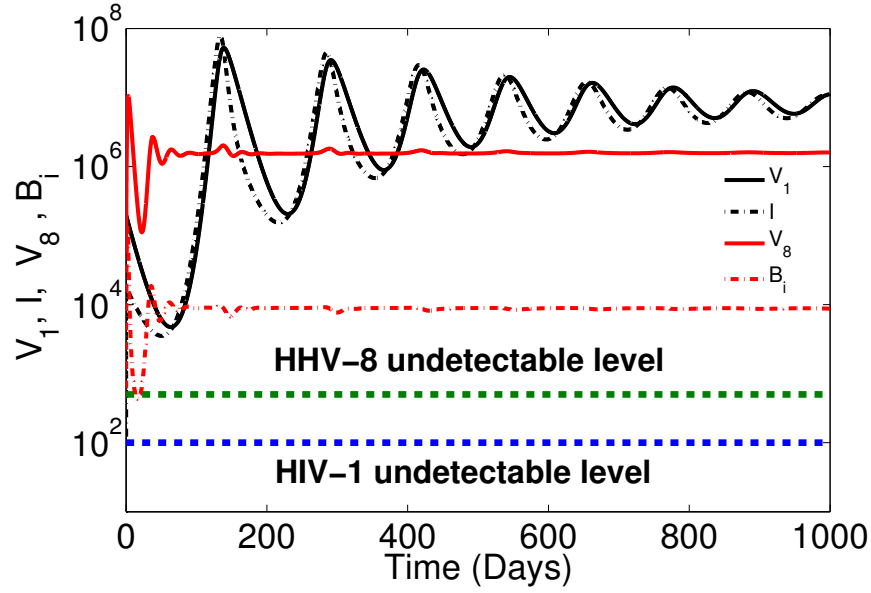
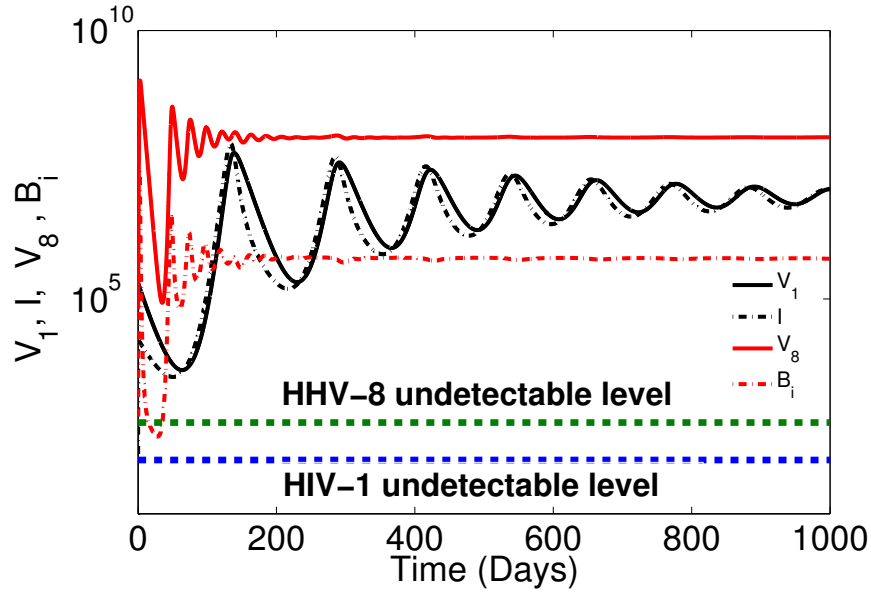
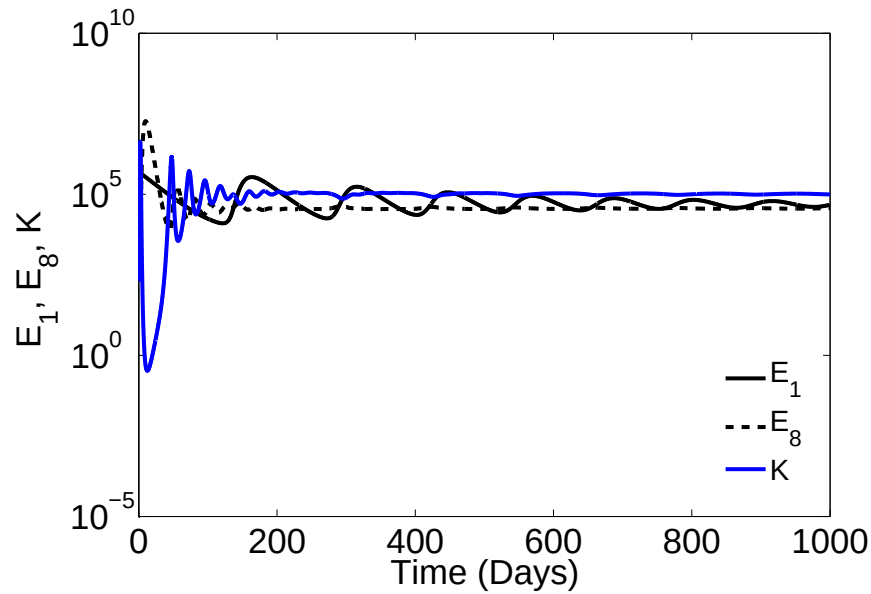


FIGURE 4.11: Model predictions for the strong viral source model without treatment for the case $\gamma = 0$ and $\beta = 1$ with $\mathcal{R}_0 > 1$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .



(a)



(b)

FIGURE 4.12: Model predictions for the strong viral source model without treatment for the case $\gamma = \beta = 1$ with $\mathcal{R}_{0x_i} > 1$. The parameter values and ranges are given in Table 4.2. The figures illustrate the dynamics of (a) the viruses (virions/mL), that is, HIV-1 (V_1), HHV-8 (V_8) and infected cells (cells/mL), that is, infected B cells (B_i), infected T cells (I), (b) the effector cells (cells/mL), that is, HIV-1 specific effector cells (E_1), HHV-8 specific effector cells (E_8) and the cancer (cells/mL), K .

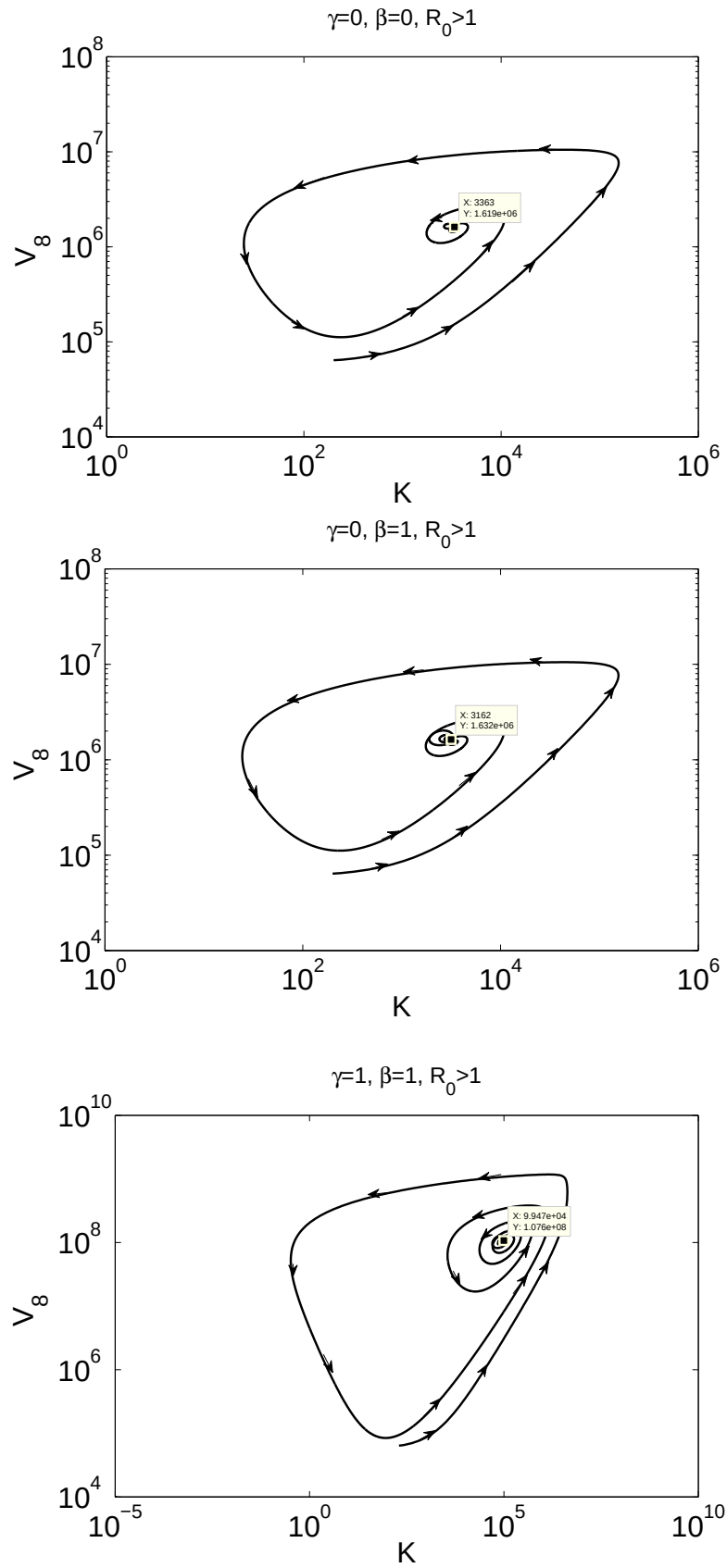


FIGURE 4.13: The trajectory between viral population, HHV-8 (V_8) and cancer cells, K for the strong viral source model. This is for the three cases, $\gamma = \beta = 0$ (top plot), $\gamma = 0$ and $\beta = 1$ (middle plot) and $\gamma = \beta = 1$ (bottom plot).

Optimal control of AIDS-KS

Regulation of HIV-1/HHV-8 viral load (VL) and viral reservoir cells is crucial for restoring a patient to an asymptomatic stage. Therefore, to devise an optimal treatment plan, we apply the optimal control theory to both the weak and strong viral source models. We find the optimal dosage scheme for combined antiretroviral therapy (cART) comprising of HAART and KS therapy that minimizes the infected T-cell count, KS tumor burden and drug toxicity. HAART involves the usage of multiple forms of antiretroviral agents, typically reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), whose efficacy is denoted by ζ_r and ζ_p , respectively. The RTIs are inhibiting the HIV virions from successfully infecting the cell and the PIs prevent the already infected cells from producing mature infectious virions as highlighted by Perelson [131]. The KS therapy can involve chemotherapy or interferon therapy and its efficacy is expressed by η_c .

5.1 Optimal control problem for the weak viral source model

5.1.1 Optimal control problem formulation

In this section, we apply optimal control strategies to the system (4.1) – (4.7), that is $\eta_c \neq 0$, $\zeta_p \neq 0$ and $\zeta_r \neq 0$. We formulate an optimal control problem (OCP) by considering cART to minimise the number of infected T-cells, KS cells and the cost of treatment (e.g. drug toxicity, cytokine storm) over a given time interval $[0, t_f]$.

5.1.2 Objective functional

Our goal is to determine the efficacy functions $0 \leq \zeta_r, \zeta_p, \eta_c \leq 1$ that minimise the objective functional given by

$$J(\zeta_r, \zeta_p, \eta_c) = \int_0^{t_f} (A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2) dt, \quad (5.1)$$

where x_2, x_4 are solutions of the system (4.1)–(4.7) with $H_1(x_6, \beta) = x_6^\beta$ and $H_8(x_7, \gamma) = x_7^\gamma$. The efficacy functions ζ_r, ζ_p, η_c are bounded and Lebesgue integrable as was indicated by Lenhart and Workman [5]. The case $\zeta_r = \zeta_p = \eta_c = 1$ represents total efficacy for the RTIs, PIs and KS therapy, respectively, and $\zeta_r = \zeta_p = \eta_c = 0$ represents no treatment. As studied in Holash *et al.* [132], the delivery time for anti-angiogenic treatment is two to three weeks. This study specifies treatment time to be 20 days to compare with to previous clinical trials and allows for an easy transition from the current practice to the proposed dosing regimen.

The coefficients A_i where $i = 1, 2, 3, 4, 5$ are positive weights to balance the factors and the term $A_1 x_4$ and $A_2 x_2$ are cost of infection while $A_3 \zeta_r^2$, $A_4 \zeta_p^2$ and $A_5 \eta_c^2$ are the cost associated with controls. The quadratic control in the treatment terms has the advantage of keeping both small and large infections in check, see for example, Kirschner *et al.* [133] and Pillis *et al.* [134]. In addition, the quadratic control allows the system to keep the burden on KS tumors low while minimising toxicity with optimal treatment. Note that the parameters ζ_r^2 , ζ_p^2 and η_c^2 of the integrand of the Equation (5.1) indicate the so-called continuous optimal control. Continuous optimal control guarantees that the medications are being applied continuously over the entire treatment period and ensure that there is no biological drug clearance from the patient's system. This study was motivated by the study by Szomolay and Lungu [37] which demonstrated that good adherence to treatment plays a crucial role of controlling the spread of AIDS-KS in patients. Hence adherence to treatment requires continuous optimal control.

We seek efficacy functions ζ_r, ζ_p and η_c such that

$$J(\zeta_r^*, \zeta_p^*, \eta_c^*) = \min\{J(\zeta_r, \zeta_p, \eta_c) : \zeta_r, \zeta_p, \eta_c \in U\},$$

where U is the control set defined by

$$U = \{(\zeta_r, \zeta_p, \eta_c) : \zeta_r, \zeta_p, \eta_c \text{ is Lebesgue measurable}, 0 \leq \zeta_r, \zeta_p, \eta_c \leq 1, t \in [0, t_f]\}. \quad (5.2)$$

5.1.3 Existence and uniqueness of optimal control

Theorem 5.1. *There exists an optimal control $u^* = (\zeta_r^*, \zeta_p^*, \eta_c^*)$ such that $\min_{\zeta_r, \zeta_p, \eta_c \in U} J(\zeta_r, \zeta_p, \eta_c) = J(\zeta_r^*, \zeta_p^*, \eta_c^*)$ subject to the OCP (4.1)–(4.7) with (5.1) and non-negative initial conditions.*

Proof. In order to prove the existence of optimal control, the following conditions should be satisfied:

1. The set of controls and the corresponding state variables is nonempty.
2. The control set U is convex and closed.
3. The right hand side of the state system is bounded by a linear function in the state and control variables.
4. The integrand in the functional (5.1), $A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2$ is convex on the control set U . There exist a constant $\rho > 1$ and positive numbers ϵ_1 and ϵ_2 such that $J(\zeta_r, \zeta_p, \eta_c) \geq -\epsilon_2 + \epsilon_1(|\zeta_r|^2 + |\zeta_p|^2 + |\eta_c|^2)^{\rho/2}$.

Condition 1 proof:

To prove that the set of controls and the corresponding state variables is nonempty. Let $\dot{x}_1 = F_{x_1}(t; x_1, x_2, \dots, x_7)$, $\dot{x}_2 = F_{x_2}(t; x_1, x_2, \dots, x_7)$, $\dots$, $\dot{x}_7 = F_{x_7}(t; x_1, x_2, \dots, x_7)$ where $F_{x_1}, \dots, F_{x_7}$ form the right hand side of the system (4.1)–(4.7). Since all parameters are constants and $x_1, \dots, x_7$ are also continuous, then the partial derivatives $\frac{\partial F_{x_1}}{\partial x_1}, \dots, \frac{\partial F_{x_1}}{\partial x_7}$, $\frac{\partial F_{x_2}}{\partial x_1}, \dots, \frac{\partial F_{x_2}}{\partial x_7}, \dots, \frac{\partial F_{x_7}}{\partial x_1}, \dots, \frac{\partial F_{x_7}}{\partial x_7}$ are all continuous. Therefore, there exists a unique solution $(x_1, x_2, \dots, x_7)$ that satisfies the initial conditions. Therefore, the set of controls and the corresponding state variables is nonempty and condition 1 is satisfied.

Condition 2 proof:

By definition, U is closed. Take any controls $u, v \in U$ and $\lambda \in [0, 1]$. Then $0 \leq \lambda u + (1 - \lambda)v$. Additionally, we observe that $\lambda u \leq \lambda$ and $(1 - \lambda)v \leq (1 - \lambda)$, then $\lambda u + (1 - \lambda)v \leq \lambda + (1 - \lambda) = 1$. Hence,

$0 \leq \lambda u + (1 - \lambda)v \leq 1$ for all $u, v \in U$ and $\lambda \in [0, 1]$.

Therefore, U is convex and condition 2 is satisfied.

Condition 3 proof:

From the system (4.1)–(4.7) all solutions are bounded, hence condition 3 is satisfied.

Condition 4 proof:

The integrand in the objective functional (5.1) is convex on U . We need to show that there exist a constant $\rho > 1$ and positive numbers ϵ_1 and ϵ_2 such that $J(\zeta_r, \zeta_p, \eta_c) \geq -\epsilon_2 + \epsilon_1(|\zeta_r|^2 + |\zeta_p|^2 + |\eta_c|^2)^{\rho/2}$.

This implies that

$$A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2 \geq -\epsilon_2 + \epsilon_1(|\zeta_r|^2 + |\zeta_p|^2 + |\eta_c|^2)^{\rho/2}$$

where ϵ_2 depends on the upper bound on x_2 and x_4 and $\epsilon_1 > 0$ since $A_3 > 0$, $A_4 > 0$ and $A_5 > 0$. We impose a bound on the length of time interval in order to guarantee the uniqueness of the optimality system. Since all the four conditions are met, we have proved the existence and uniqueness of the control. □

5.1.4 Necessary conditions for the existence of optimal control

In order to find the optimal solutions, we first trace the Lagrangian and Hamiltonian for the OCP (4.1)–(4.7) with (5.1). The Lagrangian of the OCP is given by:

$$L(x_1, x_2, x_3, x_4, x_5, x_6, x_7, \zeta_r, \zeta_p, \eta_c) = A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2 \quad (5.3)$$

Pontryagin's Maximum Principle (see Lenhart and Workman [5]) is applied to determine the conditions for effective control. This principle converts the system (4.1)–(4.7) with (5.1)–(5.2) into a problem of minimising a Hamiltonian pointwisely with respect to ζ_r, ζ_p and η_c . We define the Hamiltonian, H , for the OCP:

$$H = L(x_1, x_2, x_3, x_4, x_5, x_6, x_7, \zeta_r, \zeta_p, \eta_c) + \sum_{i=1}^7 \lambda_i f_i$$

where L is the Lagrangian function (5.3), λ_i , $i = 1, 2, \dots, 7$ are the adjoints variables (co-state variables) for the states $x_1, x_2, x_3, x_4, x_5, x_6, x_7$ and f_i is the right hand side of the differential equation of i -th state variable. Our aim is to seek an optimal control pair (u^*, X^*) where $u^* = (\zeta_r^*, \zeta_p^*, \eta_c^*)$ and $X^* = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*, x_7^*)$, that minimizes the Hamiltonian of the system given by:

$$\begin{aligned} H = & A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2 + \lambda_1 [r_{x_1} x_7^\gamma - \mu_{x_1} x_1 - \kappa_1 x_1 x_5] \\ & + \lambda_2 [(1 - \eta_c) \alpha x_1 \left(1 - \frac{x_2}{\omega}\right) - \kappa_3 x_2 x_5] + \lambda_3 [s_{x_3} + r_{x_3} x_3 x_6^\beta - \mu_{x_3} x_3] \\ & + \lambda_4 [(1 - \zeta_r) r_{x_4} x_6^\beta - \kappa_4 x_3 x_4 - \mu_{x_4} x_4] + \lambda_5 [s_{x_5} + r_{x_5} x_5 x_7^\gamma - \mu_{x_5} x_5] \\ & + \lambda_6 [(1 - \zeta_p) N_{x_6} \mu_{x_4} x_4 - \mu_{x_6} x_6] + \lambda_7 [N_{x_7} \mu_{x_1} x_1 (1 + \delta x_6^\beta) - \mu_{x_7} x_7] \end{aligned}$$

Pontryagin's Maximum Principle gives the necessary conditions for the existence of an optimal solution. The results of applying Pontryagin's Maximum Principle lead to the following theorem:

Theorem 5.2. (Optimal Control for the weak viral source model). *There exists an optimal control $\zeta_r^*, \zeta_p^*, \eta_c^*$ and the corresponding solutions $(x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*, x_7^*)$ that minimizes $J(\zeta_r, \zeta_p, \eta_c)$ over U . Furthermore, there exists adjoint variables λ_i , $i = 1, 2, \dots, 7$ which satisfy*

$$\begin{aligned} \dot{\lambda}_1 &= \lambda_1 (\mu_{x_1} + \kappa_1 x_5) - \lambda_2 \alpha (1 - \eta_c) \left(1 - \frac{x_2}{\omega}\right) - \lambda_7 N_{x_7} \mu_{x_1} (1 + \delta x_6^\beta), \\ \dot{\lambda}_2 &= \lambda_2 [(1 - \eta_c) \alpha \frac{x_1}{\omega} + \kappa_3 x_5] - A_2, \\ \dot{\lambda}_3 &= \lambda_4 \kappa_4 x_4 - \lambda_3 (r_{x_3} x_6^\beta - \mu_{x_3}), \\ \dot{\lambda}_4 &= \lambda_4 (\kappa_4 x_3 + \mu_{x_4}) - \lambda_6 (1 - \zeta_p) N_{x_6} \mu_{x_4} - A_1, \\ \dot{\lambda}_5 &= \lambda_1 \kappa_1 x_1 + \lambda_2 \kappa_3 x_2 - \lambda_5 (r_{x_5} x_7^\gamma - \mu_{x_5}), \\ \dot{\lambda}_6 &= \lambda_6 \mu_{x_6} - \lambda_3 r_{x_3} \beta x_3 x_6^{\beta-1} - \lambda_4 (1 - \zeta_r) r_{x_4} \beta x_6^{\beta-1} - \lambda_7 N_{x_7} \mu_{x_1} \delta \beta x_1 x_6^{\beta-1}, \\ \dot{\lambda}_7 &= \lambda_7 \mu_{x_7} - \lambda_1 r_{x_1} \gamma x_7^{\gamma-1} - \lambda_5 r_{x_5} \gamma x_5 x_7^{\gamma-1}. \end{aligned}$$

with transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, 2, \dots, 7$. The optimal control is given by

$$\zeta_r^* = \max \left\{ 0, \min \left(\frac{\lambda_4 r_{x_4} x_6^{\beta*}}{2A_3}, 1 \right) \right\}, \quad \zeta_p^* = \max \left\{ 0, \min \left(\frac{\lambda_6 N_{x_6} \mu_{x_4} x_4^*}{2A_4}, 1 \right) \right\}, \quad (5.4)$$

$$\eta_c^* = \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega} \right) \right), 1 \right) \right\}. \quad (5.5)$$

Proof. Due to the convexity of the integrand of J in equation (5.1), a priori boundedness of the state solutions and the Lipschitz property of the state system with respect to the state variables, the adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that $\dot{\lambda}_i = -\frac{\partial H}{\partial x_i}$, with transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, 2, \dots, 7$. The characterisation of the optimal control obtained by solving the optimality condition $\frac{\partial H}{\partial \zeta_r} = \frac{\partial H}{\partial \zeta_p} = \frac{\partial H}{\partial \eta_c} = 0$ gives the following characterisations of the controls:

$$\begin{aligned}\frac{\partial H}{\partial \zeta_r} &= 2A_3\zeta_r^* - \lambda_4 r_{x_4} x_6^{\beta*} = 0, \\ \frac{\partial H}{\partial \zeta_p} &= 2A_4\zeta_p^* - \lambda_6 N_{x_6} \mu_{x_4} x_4^* = 0, \\ \frac{\partial H}{\partial \eta_c} &= 2A_5\eta_c^* - \lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega}\right) = 0.\end{aligned}\tag{5.6}$$

Solving (5.6) gives

$$\zeta_r^* = \frac{\lambda_4 r_{x_4} x_6^{\beta*}}{2A_3}, \quad \zeta_p^* = \frac{\lambda_6 N_{x_6} \mu_{x_4} x_4^*}{2A_4} \quad \text{and} \quad \eta_c^* = \frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega}\right) \right).$$

The standard control arguments on the controls are such that

$$\zeta_r^* = \begin{cases} 0 & \text{if } m_1^* \leq 0 \\ m_1^* & 0 < m_1^* < 1 \\ 1 & m_1^* \geq 1 \end{cases} \quad \text{where } m_1^* = \frac{\lambda_4 r_{x_4} x_6^{\beta*}}{2A_3}, \tag{5.7}$$

$$\zeta_p^* = \begin{cases} 0 & \text{if } m_2^* \leq 0 \\ m_2^* & 0 < m_2^* < 1 \\ 1 & m_2^* \geq 1 \end{cases} \quad \text{where } m_2^* = \frac{\lambda_6 N_{x_6} \mu_{x_4} x_4^*}{2A_4}, \tag{5.8}$$

$$\zeta_r^* = \begin{cases} 0 & \text{if } m_3^* \leq 0 \\ m_3^* & 0 < m_3^* < 1 \\ 1 & m_3^* \geq 1 \end{cases} \quad \text{where } m_3^* = \frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega}\right) \right). \tag{5.9}$$

Equations (5.7), (5.8) and (5.9) can be written in compact form as in Equations (5.4)-(5.5).

□

5.1.5 The optimality system

The optimality system (5.10) consists of a system of states and adjoint which includes the characterisation of the optimal control (5.6), initial conditions and transversality conditions. We have the following optimality system which characterises the optimal control:

$$\begin{aligned}
\dot{x}_1 &= r_{x_1} x_7^\gamma - \mu_{x_1} x_1 - \kappa_1 x_1 x_5 \\
\dot{x}_2 &= \left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega} \right) \right), 1 \right) \right\} \right) \alpha x_1 \left(1 - \frac{x_2}{\omega} \right) - \kappa_3 x_2 x_5 \\
\dot{x}_3 &= s_{x_3} + r_{x_3} x_3 x_6^\beta - \mu_{x_3} x_3 \\
\dot{x}_4 &= \left(1 - \max \left\{ 0, \min \left(\frac{\lambda_4 r_{x_4} x_6^{\beta*}}{2A_3}, 1 \right) \right\} \right) r_{x_4} x_6^\beta - \kappa_4 x_3 x_4 - \mu_{x_4} x_4 \\
\dot{x}_5 &= s_{x_5} + r_{x_5} x_5 x_7^\gamma - \mu_{x_5} x_5 \\
\dot{x}_6 &= \left(1 - \max \left\{ 0, \min \left(\frac{\lambda_6 N_{x_6} \mu_{x_4} x_4^*}{2A_4}, 1 \right) \right\} \right) N_{x_6} \mu_{x_4} x_4 - \mu_{x_6} x_6 \\
\dot{x}_7 &= N_{x_7} \mu_{x_1} x_1 (1 + \delta x_6^\beta) - \mu_{x_7} x_7 \\
\dot{\lambda}_1 &= \lambda_1 (\mu_{x_1} + \kappa_1 x_5) - \lambda_2 \alpha \left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega} \right) \right), 1 \right) \right\} \right) \left(1 - \frac{x_2}{\omega} \right) \\
&\quad - \lambda_7 N_{x_7} \mu_{x_1} (1 + \delta x_6^\beta), \\
\dot{\lambda}_2 &= \lambda_2 \left[\left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\lambda_2 \alpha x_1^* \left(1 - \frac{x_2^*}{\omega} \right) \right), 1 \right) \right\} \right) \alpha \frac{x_1}{\omega} + \kappa_3 x_5 \right] - A_2, \\
\dot{\lambda}_3 &= \lambda_4 \kappa_4 x_4 - \lambda_3 (r_{x_3} x_6^\beta - \mu_{x_3}), \\
\dot{\lambda}_4 &= \lambda_4 (\kappa_4 x_3 + \mu_{x_4}) - \lambda_6 \left(1 - \max \left\{ 0, \min \left(\frac{\lambda_6 N_{x_6} \mu_{x_4} x_4^*}{2A_4}, 1 \right) \right\} \right) N_{x_6} \mu_{x_4} - A_1, \\
\dot{\lambda}_5 &= \lambda_1 \kappa_1 x_1 + \lambda_2 \kappa_3 x_2 - \lambda_5 (r_{x_5} x_7^\gamma - \mu_{x_5}), \\
\dot{\lambda}_6 &= \lambda_6 \mu_{x_6} - \lambda_3 r_{x_3} \beta x_3 x_6^{\beta-1} - \lambda_4 \left(1 - \max \left\{ 0, \min \left(\frac{\lambda_4 r_{x_4} x_6^{\beta*}}{2A_3}, 1 \right) \right\} \right) r_{x_4} \beta x_6^{\beta-1} \\
&\quad - \lambda_7 N_{x_7} \mu_{x_1} \delta \beta x_1 x_6^{\beta-1}, \\
\dot{\lambda}_7 &= \lambda_7 \mu_{x_7} - \lambda_1 r_{x_1} \gamma x_7^{\gamma-1} - \lambda_5 r_{x_5} \gamma x_5 x_7^{\gamma-1}
\end{aligned} \tag{5.10}$$

with initial conditions $x_1(0) \geq 0$, $x_2(0) \geq 0$, $x_3(0) \geq 0$, $x_4(0) \geq 0$, $x_5(0) \geq 0$, $x_6(0) \geq 0$, $x_7(0) \geq 0$ and transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, \dots, 7$.

5.1.6 Uniqueness of the optimality system

To ascertain the uniqueness of the optimality system, the bounds of the state and adjoint solutions must be used. We note that from the bounds for the state equations, we see that the adjoint system has bounded coefficients and is linear in each adjoint variable. Hence, the solutions of the adjoint system are bounded on a finite time interval. For the small time interval, we shall use the following lemma while proving the uniqueness of solutions of the optimality system .

Lemma 5.1. *The function $u^*(s) = \max(a, \min(s, b))$ is Lipschitz continuous in s , where $a < b$ are some fixed positive constants.*

Proof. Consider s_1, s_2 as real numbers and a, b as fixed positive constants. We will show the Lipschitz continuity holds in all possible cases for $\min(s, b)$. Similar arguments hold for $\max(a, \min(s, b))$ as well.

1. $s_1 \leq b, s_2 \leq b.$

$$|\min(s_1, b) - \min(s_2, b)| = |s_1 - s_2|$$

2. $s_1 \leq b, s_2 \geq b.$

$$|\min(s_1, b) - \min(s_2, b)| = |s_1 - b| \leq |s_1 - s_2|$$

3. $s_1 \geq b, s_2 \leq b.$

$$|\min(s_1, b) - \min(s_2, b)| = |b - s_2| \leq |s_1 - s_2|$$

4. $s_1 \geq b, s_2 \geq b.$

$$|\min(s_1, b) - \min(s_2, b)| = |b - b| = 0 \leq |s_1 - s_2|$$

Hence $|\min(s_1, b) - \min(s_2, b)| \leq |s_1 - s_2|$ and we have Lipschitz continuity of m^* in s $\square$

Theorem 5.3. *For $t \in [0, t_f]$, the bounded solutions to the optimality system is unique.*

Proof. Proof of the theorem is shown in Appendix A.4 $\square$

Remark 5.1. The optimal controls, ζ_r , ζ_p and η_c can be characterised in terms of the unique solution of the optimality system (5.10). The above optimal controls give an optimal treatment strategy for the patient who is dually infected with HIV-1 and HHV-8 under the scenario of RTIs , PIs and KS therapy.

5.1.7 Optimal control simulations for the weak viral source model

Here we show the numerical results of the OCP and we will assume that $\gamma = \beta = 1$ since the simulations remain largely unaffected by the other cases. The algorithm for simulating the system using the forward-backward sweep method is adopted from Lenhart and Workman [5]. The state system with an initial guess is solved forward in time and then the adjoint system is solved backward in time. The controls are updated at the end of each iteration using the formula for optimal controls. The iterations continue until convergence is achieved.

We take $t_f = 20$ days which represents the time in which treatment is stopped. The values of the weight function are taken as $A_1 = 10$, $A_2 = 0.01$, $A_3 = 200$, $A_4 = 100$ and $A_5 = 1000$. It should be pointed out that the weights used in the simulations are not clinically determined but are used to illustrate the control strategies proposed for this study. The costs correspond to the case of very cheap to very expensive control strategies. The higher the value, the more expensive the treatment. The initial variables and parameter values are taken from Table 4.2. The initial values are chosen such that they reflect a patient during chronic infection since the WHO recommendations stipulate that all people living with the HIV be put on HAART irrespective of their CD4⁺ T cell counts [135]. The reproduction number in the absence of treatment is $R_{0x_i} = \max[1.44, 6.14] = 6.14$ which was obtained from using the parameter values in Table 4.2.

The results of the system (4.1)–(4.7) with and without controls are depicted in Figures (5.1) – (5.8). Figure 5.1 shows the HIV-1 virus population level with and without controls. We can see that the VL when the treatment is not optimal can result in very high levels. When optimal treatment is administered the VL remains low. As demonstrated by Figure 5.2, the HHV-8 population starts to decline slowly after day 2. We see from Figure 5.3 that when there is no control the infected T cell population rises and settles at some steady state level. With optimal treatment the infected T cell population declines and remains significantly lower than the population without controls. The infected B cell population on the other hand starts to decline slowly after day 2 when treatment is optimal (Figure 5.4). Figure 5.5 and Figure 5.6 shows that when treatment is optimal, the HIV-1 and HHV-8 specific effector cells are not affected by treatment as expected. Figure 5.7 demonstrates how the optimal treatment affects the KS development. Without treatment the KS cell population grows very fast, but when there is optimal treatment the KS cell population remains constant for most of the treatment period.

Figure 5.8 illustrates the control profiles where control η_c is at upper bound in the drug level 10 before gradually declining to the final time. The control ζ_r is at upper bound in the drug level till day 11 and before gradually declining to minimum dosage at day 20, a level it maintains to the final time. The control ζ_p is at minimum dosage before rising to its upper bound at day 7, a level it maintains until the end of the intervention. Administration of the drugs will be determined by the medical practitioner.

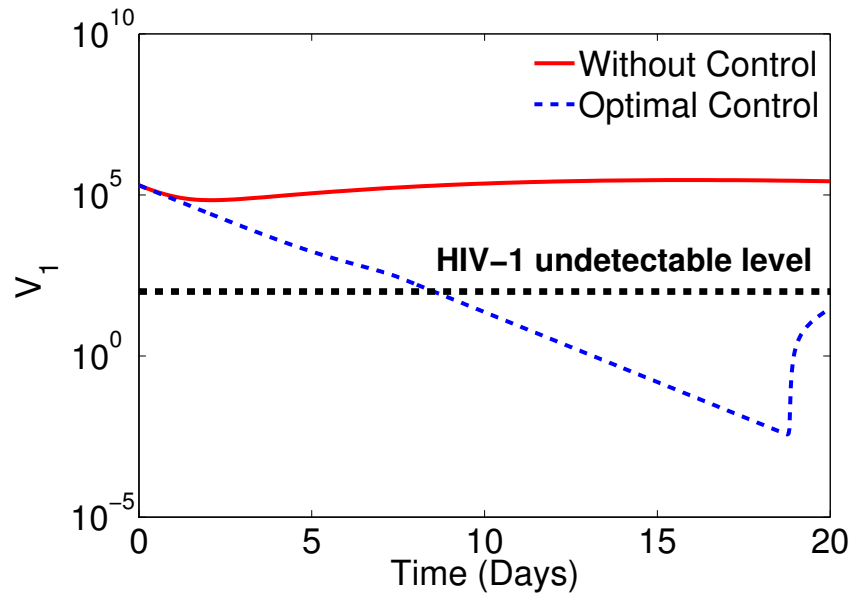


FIGURE 5.1: HIV-1 virions, (V_1) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

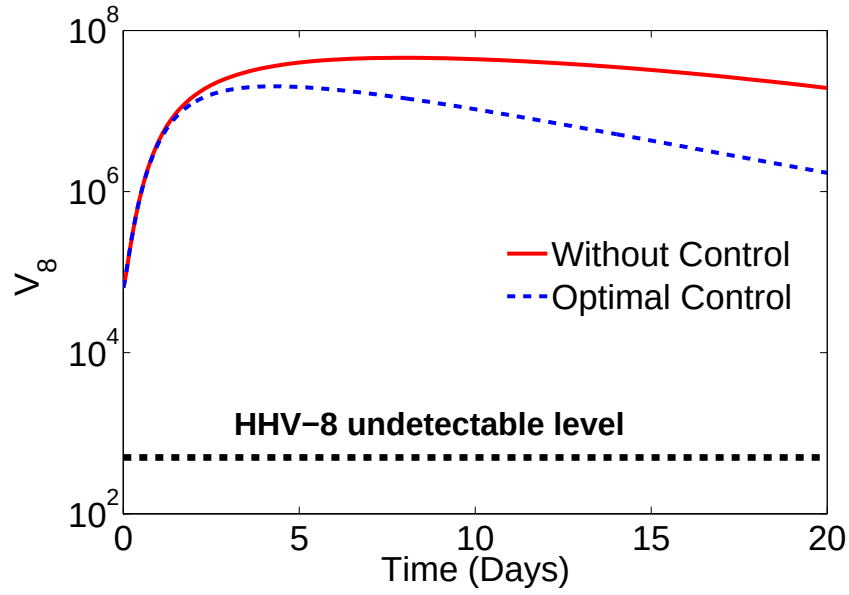


FIGURE 5.2: HHV-8 virions, (V_8) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

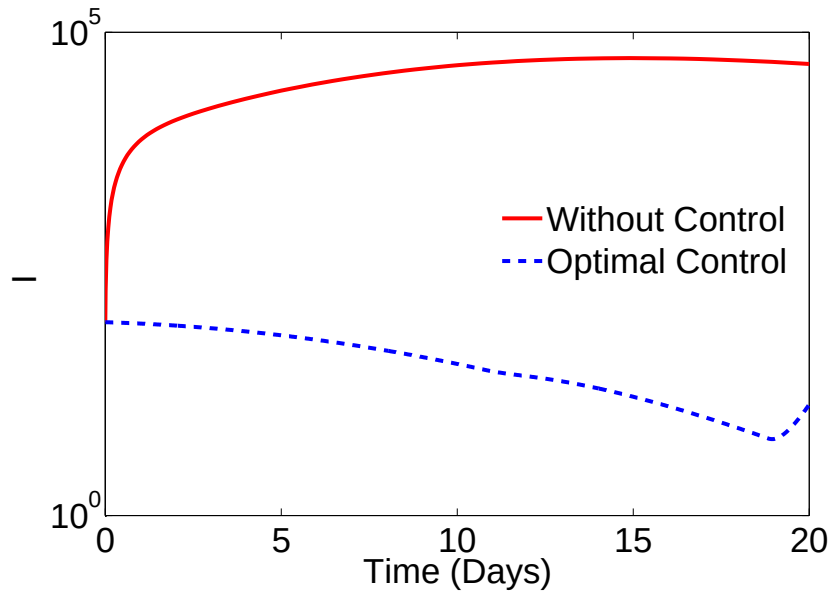


FIGURE 5.3: Infected T cells, (I) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

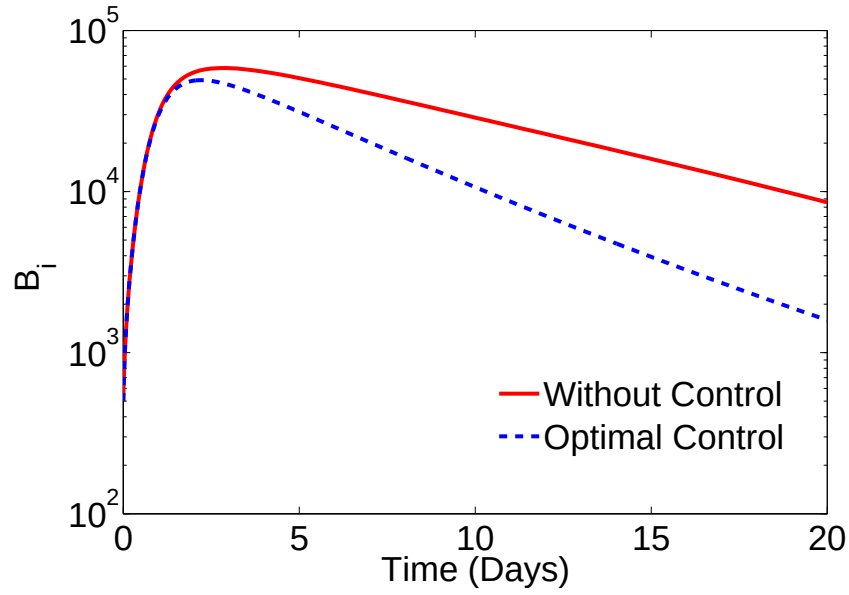


FIGURE 5.4: Infected B cells, (B_i) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

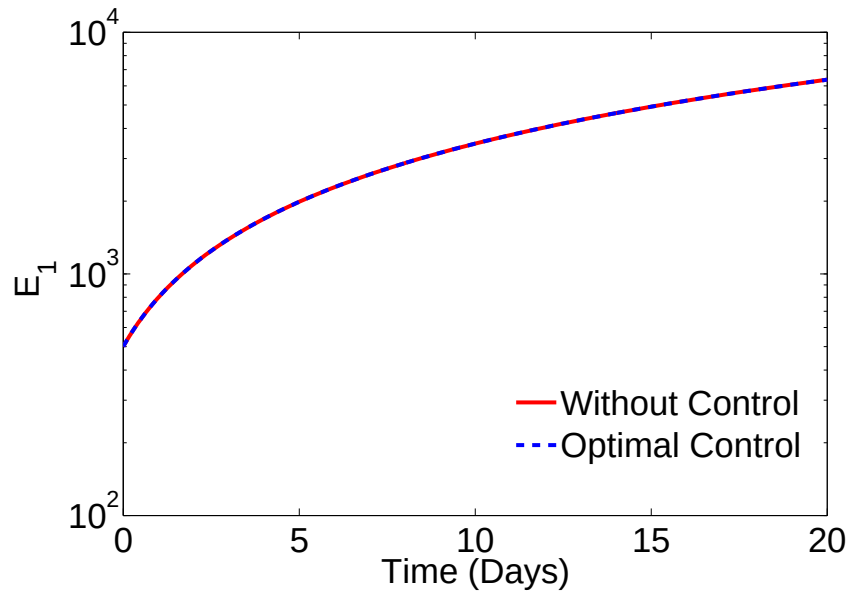


FIGURE 5.5: HIV-1 specific effector cells, (E_1) without control (solid line) and with optimal control (dashed line) for the weak viral source model. The parameter values and ranges are given in Table 4.2. $R_{0x_i} = 6.14$.

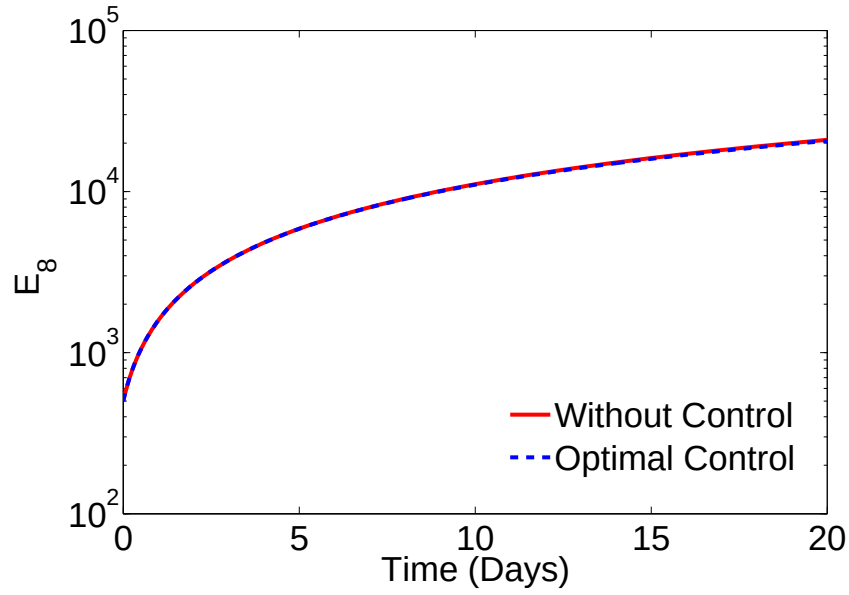


FIGURE 5.6: HIV-8 specific effector cells, (E_8) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

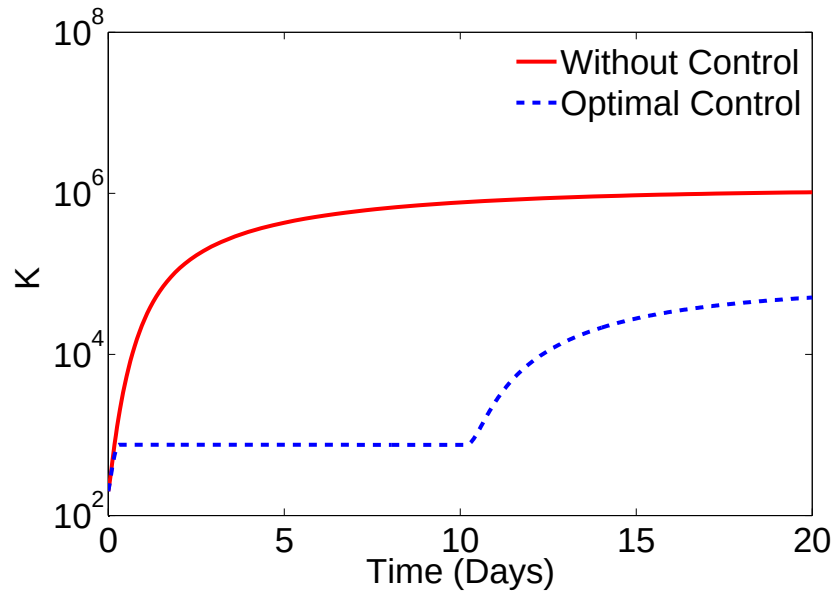


FIGURE 5.7: KS cells, (K) without control (solid line) and with optimal control (dashed line) for the weak viral source model. $R_{0x_i} = 6.14$. The parameter values and ranges are given in Table 4.2.

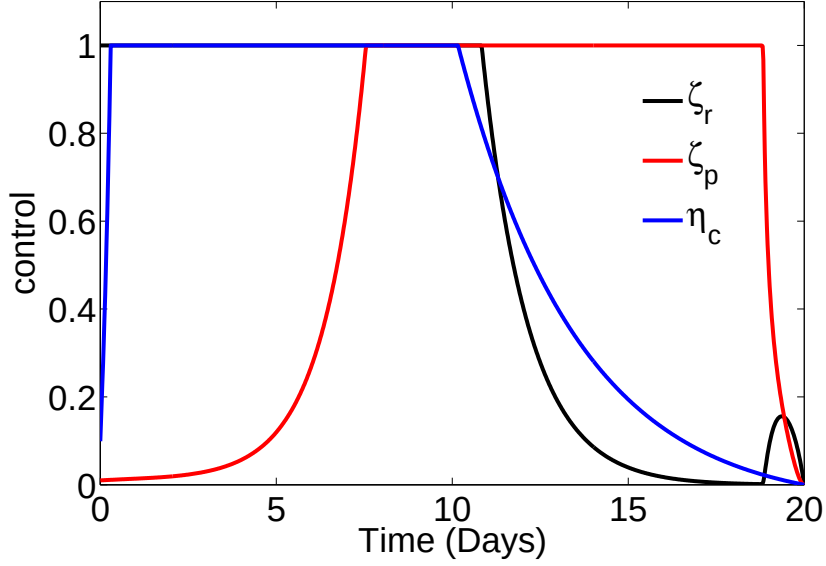


FIGURE 5.8: Control profiles of reverse transcriptase inhibitors (ζ_r), protease inhibitors (ζ_p) and KS therapy (η_c) for the weak viral source model.

5.2 Optimal control problem for the strong viral source model

Like in the weak viral source model, we want to minimise the objective functional 5.1 of the the system (4.1)–(4.7) with $H_1(x_6, \beta) = x_6^\beta + x_6$ and $H_8(x_7, \gamma) = x_7^\gamma + x_7$.

To this end, the Hamiltonian is given as:

$$\begin{aligned}
 H = & A_1 x_4 + A_2 x_2 + A_3 \zeta_r^2 + A_4 \zeta_p^2 + A_5 \eta_c^2 + \lambda_1 [r_{x_1} (x_7^\gamma + x_7) - \mu_{x_1} x_1 - \kappa_1 x_1 x_5] \\
 & + \lambda_2 [(1 - \eta_c) \alpha x_1 \left(1 - \frac{x_2}{\omega}\right) - \kappa_3 x_2 x_5] + \lambda_3 [s_{x_3} + r_{x_3} x_3 (x_6^\beta + x_6) - \mu_{x_3} x_3] \\
 & + \lambda_4 [(1 - \zeta_r) r_{x_4} (x_6^\beta + x_6) - \kappa_4 x_3 x_4 - \mu_{x_4} x_4] + \lambda_5 [s_{x_5} + r_{x_5} x_5 (x_7^\gamma + x_7) - \mu_{x_5} x_5] \\
 & + \lambda_6 [(1 - \zeta_p) N_{x_6} \mu_{x_4} x_4 - \mu_{x_6} x_6] + \lambda_7 [N_{x_7} \mu_{x_1} x_1 [1 + \delta (x_6^\beta + x_6)] - \mu_{x_7} x_7]
 \end{aligned}$$

By applying the Pontryagin's Maximum Principle, we obtain the following theorem:

Theorem 5.4. (Optimal control for the strong viral source model). *There exists an optimal control $\hat{\zeta}_r, \hat{\zeta}_p, \hat{\eta}_c$ and the corresponding solutions $(\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6, \hat{x}_7)$ that minimises $J(\zeta_r, \zeta_p, \eta_c)$ over U . Furthermore, there exists adjoint variables $\lambda_i, i = 1, 2, \dots, 7$ which satisfy the equations*

$$\begin{aligned}
\dot{\lambda}_1 &= \lambda_1(\mu_{x_1} + \kappa_1 x_5) - \lambda_2 \alpha (1 - \eta_c) \left(1 - \frac{x_2}{\omega}\right) - \lambda_7 N_{x_7} \mu_{x_1} \left[1 + \delta(x_6^\beta + x_6)\right], \\
\dot{\lambda}_2 &= \lambda_2 \left[(1 - \eta_c) \alpha \frac{x_1}{\omega} + \kappa_3 x_5\right] - A_2, \\
\dot{\lambda}_3 &= \lambda_4 \kappa_4 x_4 - \lambda_3 \left[r_{x_3}(x_6^\beta + x_6) - \mu_{x_3}\right], \\
\dot{\lambda}_4 &= \lambda_4(\kappa_4 x_3 + \mu_{x_4}) - \lambda_6(1 - \zeta_p) N_{x_6} \mu_{x_4} - A_1, \\
\dot{\lambda}_5 &= \lambda_1 \kappa_1 x_1 + \lambda_2 \kappa_3 x_2 - \lambda_5 \left[r_{x_5}(x_7^\gamma + x_7) - \mu_{x_5}\right], \\
\dot{\lambda}_6 &= \lambda_6 \mu_{x_6} - \lambda_3 r_{x_3} x_3 (\beta x_6^{\beta-1} + 1) - \lambda_4 (1 - \zeta_r) r_{x_4} (\beta x_6^{\beta-1} + 1) - \lambda_7 N_{x_7} \mu_{x_1} \delta(\beta x_6^{\beta-1} + 1), \\
\dot{\lambda}_7 &= \lambda_7 \mu_{x_7} - \lambda_1 r_{x_1} (\gamma x_7^{\gamma-1} + 1) - \lambda_5 r_{x_5} x_5 (\gamma x_7^{\gamma-1} + 1)
\end{aligned}$$

with transversality conditions: $\lambda_i(t_f) = 0$, $i = 1, 2, \dots, 7$.

Furthermore, the control variables satisfy:

$$\hat{\zeta}_r = \max \left\{ 0, \min \left(\frac{\lambda_4 r_{x_4} (x_6^{\hat{\beta}} + \hat{x}_6)}{2A_3}, 1 \right) \right\}, \quad (5.11)$$

$$\hat{\zeta}_p = \max \left\{ 0, \min \left(\frac{\lambda_6 N_{x_6} \mu_{x_4} \hat{x}_4}{2A_4}, 1 \right) \right\}, \quad (5.12)$$

$$\hat{\eta}_c = \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\lambda_2 \alpha \hat{x}_1 \left(1 - \frac{\hat{x}_2}{\omega} \right) \right), 1 \right) \right\}. \quad (5.13)$$

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

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial H}{\partial x_1}, & \dot{\lambda}_2 &= -\frac{\partial H}{\partial x_2}, & \dot{\lambda}_3 &= -\frac{\partial H}{\partial x_3}, & \dot{\lambda}_4 &= -\frac{\partial H}{\partial x_4}, \\
\dot{\lambda}_5 &= -\frac{\partial H}{\partial x_5}, & \dot{\lambda}_6 &= -\frac{\partial H}{\partial x_6}, & \dot{\lambda}_7 &= -\frac{\partial H}{\partial x_7}.
\end{aligned}$$

with transversality conditions: $\lambda_i(t_f) = 0$, $i = 1, 2, \dots, 7$.

The optimal control $\hat{\zeta}_r$, $\hat{\zeta}_p$ and $\hat{\eta}_c$ can be solved from the optimality conditions,

$$\frac{\partial H}{\partial \zeta_r} = 0, \frac{\partial H}{\partial \zeta_p} = 0 \text{ and } \frac{\partial H}{\partial \eta_c} = 0.$$

By the bounds in U of the controls, we obtain ζ_r , ζ_p and η_c in the form of (5.11), (5.12) and (5.13) respectively. $\square$

The state system, the adjoint system and the characterisation of the control given by Equations (5.11)–(5.13) form the optimality system.

5.2.1 Uniqueness of the optimality system

For the small time interval, the uniqueness of solutions of the optimality system can be obtained due to the priori boundedness of the state, adjoint functions and the resulting Lipschitz structure of the ODEs. Hence the following theorem:

Theorem 5.5. *For $t \in [0, t_f]$, the bounded solutions to the optimality system is unique.*

Proof. The above theorem is proved in a similar manner as in Theorem (5.3). $\square$

5.2.2 Optimal control simulations for the strong viral source model

Numerical investigations were implemented using the Forward Backward Sweep Method to solve the system. We use $t_f = 20$ days which represents the time in which treatment is stopped. The values of the weight function are taken as $A_1 = 1$, $A_2 = 1$, $A_3 = 10$, $A_4 = 10$ and $A_5 = 10$ where the costs correspond to the case of very cheap to very expensive control strategies. $R_{0x_i} = \max[1.63, 1.14] = 1.63$ in the absence of treatment and this was obtained from using the parameter values in Table 4.2.

The optimal control numerical results with and without controls are depicted in Figures (5.9) – (5.16). Figure 5.9 shows the HIV-1 virus population level with and without controls. As illustrated, without control, this results in very high viral load. On the other hand, when optimal treatment is administered the viral load remains low. As demonstrated by Figure 5.10, with optimal control, we see a slow decrease in the HHV-8 population after approximately day 10. We see from Figure 5.11 that when there is no control the infected T cell population is high. With optimal treatment the infected T cell population declines and remains significantly lower than the population without controls. The infected B cell population on the other hand starts to decline slowly after day 2 when treatment is optimal (Figure 5.12). Figure 5.13 shows that with optimal control, there is a decrease in

the HIV-1 effector cells and Figure 5.14 shows that when treatment is optimal, the HHV-8 specific effector cells are not having quite the expected effect by the treatment as expected. Moreover, it is also observed that in Figure 5.15, optimal control can effectively reduce the volume of the tumor compared with the model without control.

Figure 5.16 illustrates the control profiles where control η_c is administered at maximum dosage throughout the treatment period. The control ζ_r is at upper bound in the drug level till day 17 and before gradually declining to minimum dosage at the end of the treatment period. The control ζ_p is at minimum dosage a level it maintains until the end of the intervention.

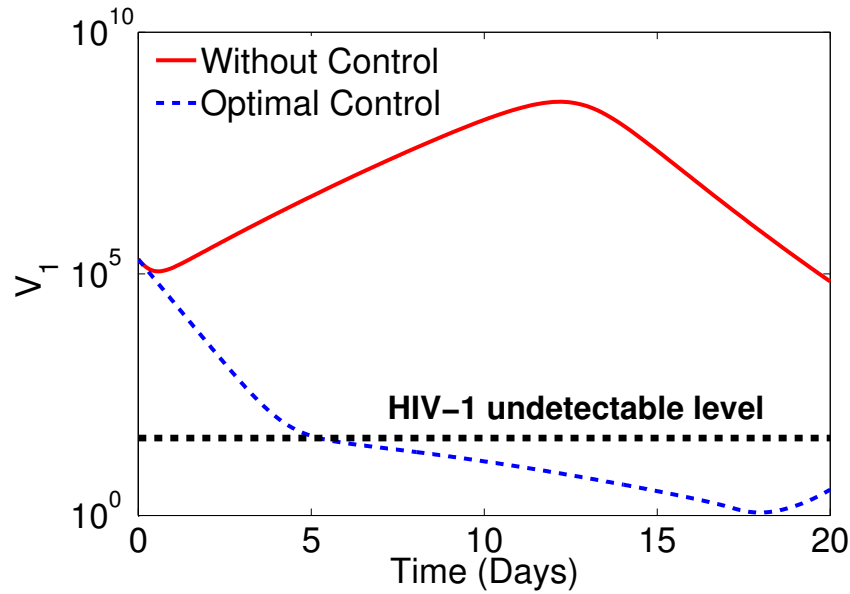


FIGURE 5.9: HIV-1 virions, (V_1) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

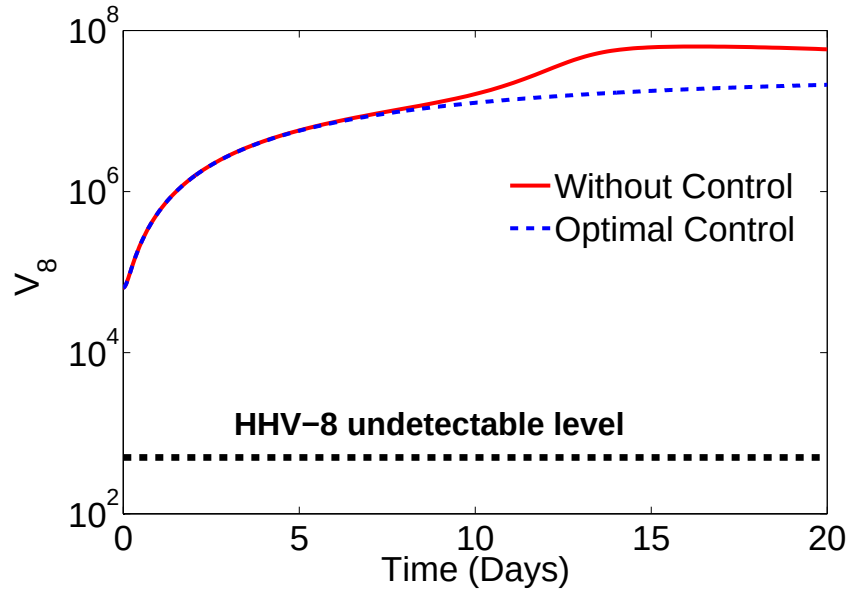


FIGURE 5.10: HHV-8 virions, (V_8) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

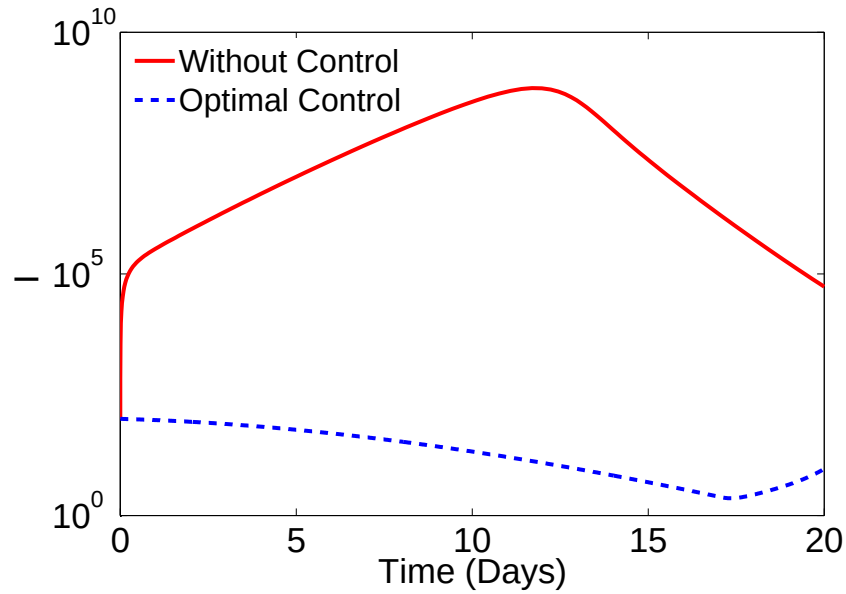


FIGURE 5.11: Infected T cells, (I) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

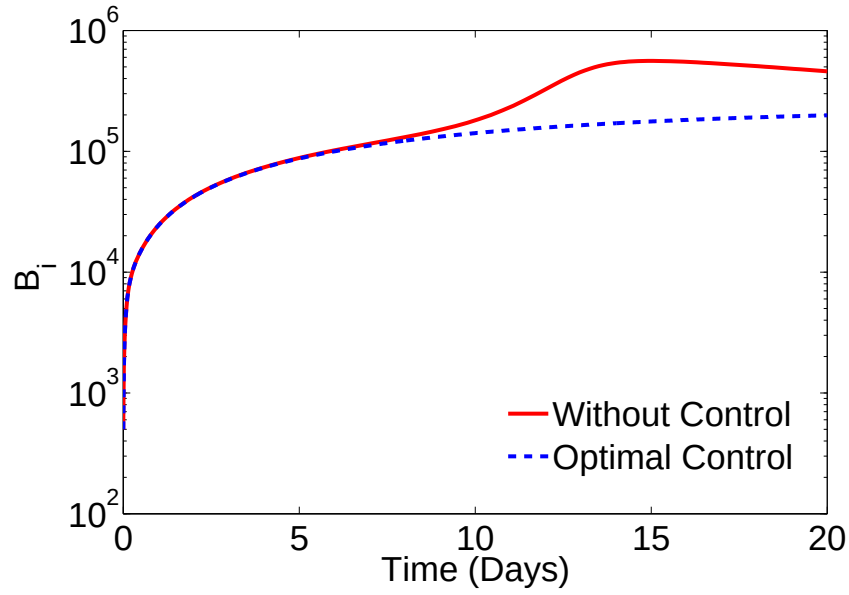


FIGURE 5.12: Infected B cells, (B_i) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

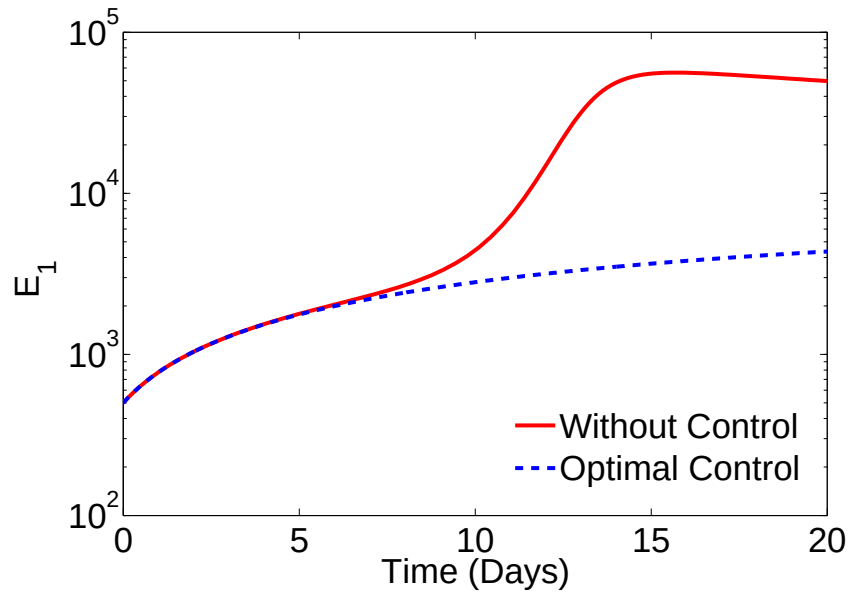


FIGURE 5.13: HIV-1 specific effector cells, (E_1) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

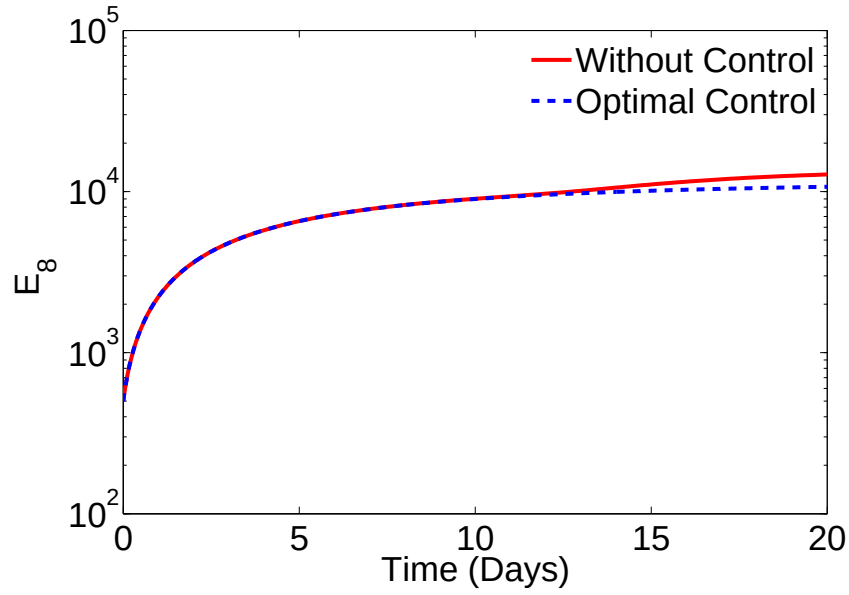


FIGURE 5.14: HIV-8 specific effector cells, (E_8) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

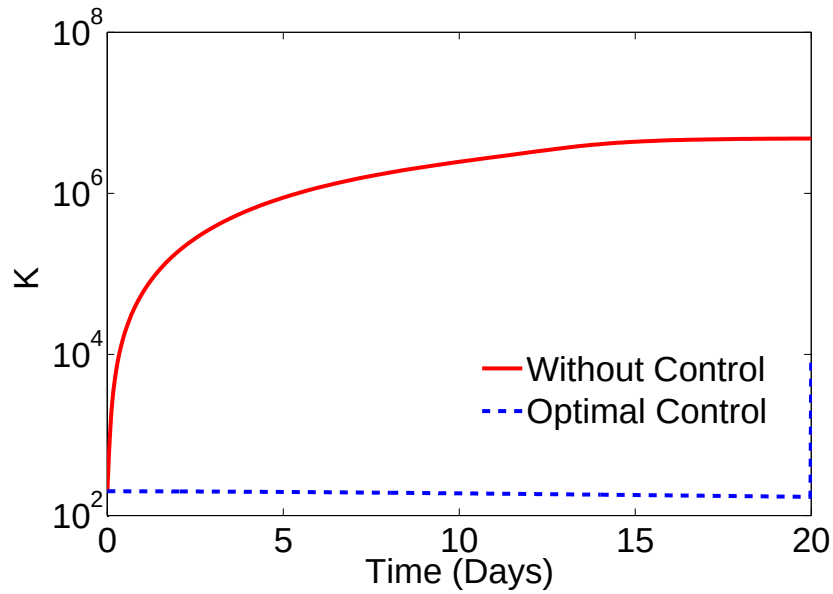


FIGURE 5.15: KS cells, (K) without control (solid line) and with optimal control (dashed line) for the strong viral source model. $R_{0x_i} = 1.63$. The parameter values and ranges are given in Table 4.2.

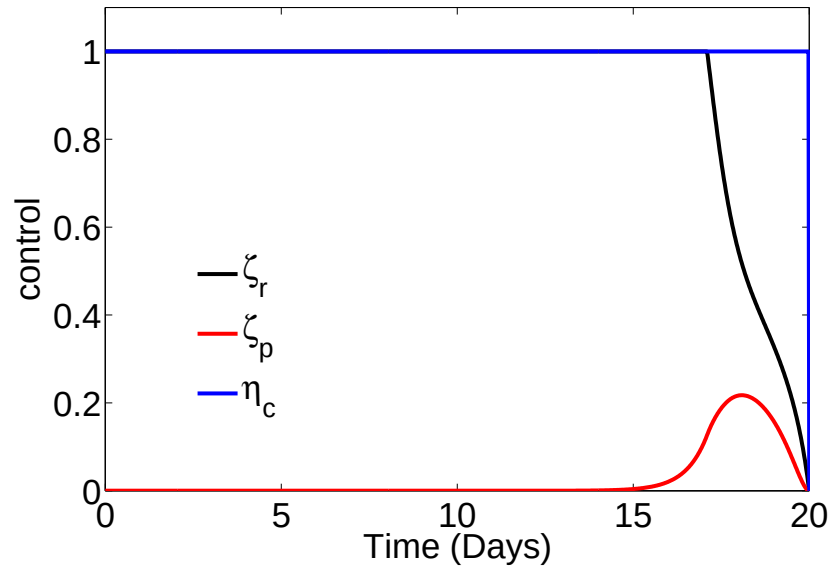


FIGURE 5.16: Control profiles of reverse transcriptase inhibitors (ζ_r), protease inhibitors (ζ_p) and KS therapy (η_c) for the strong viral source model.

Public health education intervention: modelling Ebola virus disease outbreaks in Sudan

Education targeted at specific populations and sub-populations through practical health information is essential to controlling Ebola virus disease (EVD). The work presented in this chapter forms part of a jointly-authored publication in *Infectious Disease Modelling* [136]. We formulate a model for the case with an educated class and an uneducated class. The parameters are estimated separately for each class using the reduced version of our model. The parameters governing the uneducated class are obtained using the 1976 Sudan epidemic data and the educated class parameters are estimated using the 1979 Sudan epidemic data and then numerical simulations are carried out. The numerical results include varying key parameters such as education rates for future EVD epidemics in Sudan.

6.1 Model formulation

We formulate a model with the susceptible class partitioned into two groups. We utilise the subscript “*edu*” to mean the class that avoids potential risk during an EVD outbreak because of public health education. There are two susceptible classes (S_{edu} and S), which contain the quantity of people in each group. Correspondingly, there are two classes (I_{edu} and I) that contain the number of infected people that exist in the network. Both I_{edu}

and I can move into a second infected class we consider to be the number of individuals in a health care setting (H), where people are being cared for by trained experts. Note that we consider the medical care experts themselves to be in S_{edu} . In societies and healthcare facilities, infection occurs in both settings. The model additionally incorporates a recovered class (R) and class of dead bodies (D), the two of which likewise have units of quantities of people. Finally, there is the environmental class (B), which represents the Ebola environment. Recovered people no longer experience intense indications of Ebola and are resistant to reinfection as we will be just taking into account a brief timeframe outline. The class of the dead is required on the grounds that it is regular practice in West Africa for relatives to interact with deceased family members, which makes this transmission course for Ebola especially one of a kind and fascinating. The environment class represents all conceivable pollution in the overall network including the presence of bodily fluids, grimy cloths and any potential creatures which might be a source of contamination. Table 6.1 presents a complete list and description of all parameters in the model. A flow diagram characterising the full model is depicted in Figure 6.1.

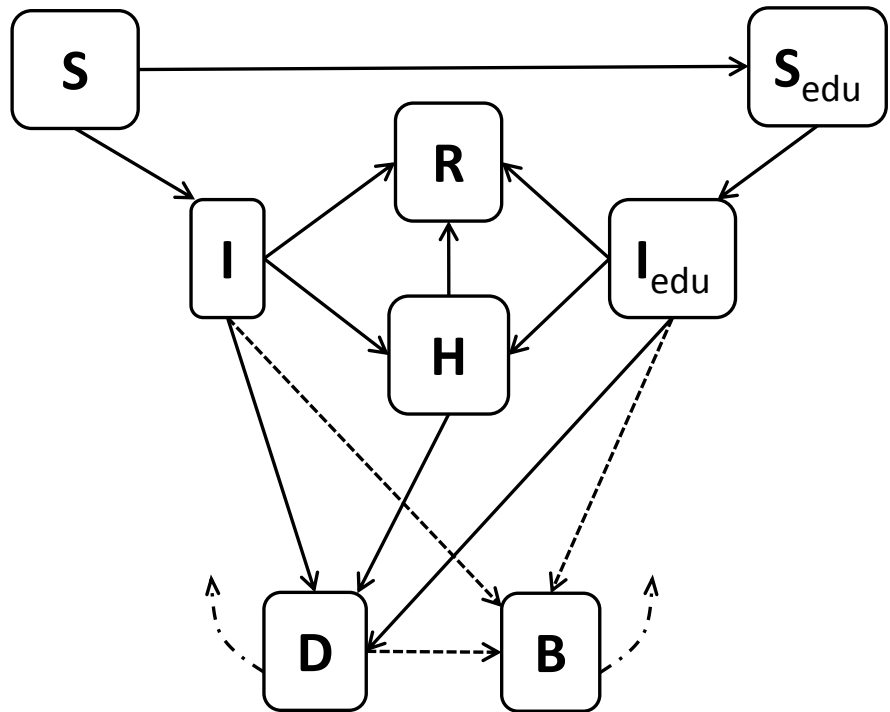


FIGURE 6.1: Flow diagram for the full Ebola model. Solid lines represent flow between compartments, the dashed lines represent the infected classes contaminating the environment and the curved dashed lines represent new infections coming from interaction of susceptibles with the environment.

The full model is given below:

$$\begin{aligned}
S' &= \pi - \mu S - \theta S - (\beta_{0a}B + \beta_{1a}I + \beta_{3a}I_{edu} + \beta_{4a}D + \beta_{2a}H)S \\
S'_{edu} &= \theta S - \mu S_{edu} - (\beta_{0b}B + \beta_{1b}I + \beta_{3b}I_{edu} + \beta_{4b}D + \beta_{2b}H)S_{edu} \\
I' &= (\beta_{0a}B + \beta_{1a}I + \beta_{3a}I'_{edu} + \beta_{4a}D + \beta_{2a}H)S - \gamma(\alpha_{1a}, \alpha_{2a}, H_{total})I - \phi_1 I - \delta_1 I \\
I'_{edu} &= (\beta_{0b}B + \beta_{1b}I + \beta_{3b}I_{edu} + \beta_{4b}D + \beta_{2b}H)S_{edu} - \gamma(\alpha_{1b}, \alpha_{2b}, H_{total})I_{edu} - \phi_2 I_{edu} - \delta_2 I_{edu} \\
H' &= \gamma(\alpha_{1b}, \alpha_{2b}, H_{total})I_{edu} + \gamma(\alpha_{1a}, \alpha_{2a}, H_{total})I - \delta_3 H - \phi_3 H \\
R' &= \phi_1 I + \phi_2 I_{edu} + \phi_3 H - \mu R \\
D' &= \delta_1 I + \delta_2 I_{edu} + \delta_3 H - \omega D \\
B' &= \xi(I + I_{edu} + H + D) - dB
\end{aligned} \tag{6.1}$$

where

$$\gamma(\alpha_{1i}, \alpha_{2i}, H) = \frac{1 - e^{\frac{-H}{\alpha_{1i}}}}{1 + \alpha_{2i}e^{\frac{-H}{\alpha_{1i}}}}.$$

Recall that it is normal in West African nations for unwell people to forgo seeing a medical doctor and as an alternative be cared for at home, particularly on account of a minor sickness. Because EVD initially presents with flu-like symptoms, the number of people looking for care toward the start of an episode is particularly low. In any case, as more instances of an outbreak are distinguished, the familiarity with the ailment increments in the network through the media, government and even informal. Expanded mindfulness brings about individuals looking for help sooner and consequently an expanded pace of move to medical care settings. We capture this characteristic with the sigmoidal shaped function γ , which ranges from 0 (no one goes to the hospital) to 1 (maximum rate of medical consultation). The parameter α_2 defines the point at which its rapid growth begins and α_1 determines the slope of the growth. Since γ is a function of H , as hospital admissions increase, general awareness of infectious diseases increases and the rate of people seeking treatment in a medical clinic will increment. There are two distinct arrangements of α values for the educated and uneducated populations on the grounds that educated people will be bound to understand the importance of an outbreak and the implications of neglecting to look for treatment contrasted and the uneducated population. We have additionally included distinctive death rates ($\delta_1, \delta_2, \delta_3$) and recovery rates (ϕ_1, ϕ_2, ϕ_3) to recognise rates for the individuals who play it safe versus the individuals who do not, as

TABLE 6.1: Parameters found in the model.

Parameter	Description
β_{0a}	Transmission rate from uneducated interaction with the environment
β_{1a}	Transmission rate from uneducated interaction with uneducated infected
β_{2a}	Transmission rate from uneducated in hospitals
β_{3a}	Transmission rate from uneducated interaction with educated infected
β_{4a}	Transmission rate from uneducated interaction with dead bodies
β_{0b}	Transmission rate from educated interaction with the environment
β_{1b}	Transmission rate from educated interaction with uneducated infected
β_{2b}	Transmission rate from educated in hospitals
β_{3b}	Transmission rate from educated interaction with educated infected
β_{4b}	Transmission rate from educated interaction with dead bodies
α_{1a}	Sigmoidal constant that governs uneducated infected movement into hospital
α_{2a}	Sigmoidal constant that governs uneducated infected movement into hospital
α_{1b}	Sigmoidal constant that governs educated infected movement into hospitals
α_{2b}	Sigmoidal constant that governs educated infected movement into hospitals
ϕ_1	Recovery rate for infected uneducated individuals in the community
ϕ_2	Recovery rate for infected educated individuals in the community
ϕ_3	Recovery rate for infected individuals in hospitals
δ_1	Death rate for uneducated infected individuals in the community
δ_2	Death rate for educated infected individuals in the community
δ_3	Death rate for infected individuals in hospitals
ω	Burial rate of dead bodies
ξ	Environmental contamination rate
d	rate of decay of ebola in the environment
π	Growth of uneducated susceptible
μ	Natural death rate
γ	Sigmoidal constant governing the rate of transfer to hospital
θ	Rate of education

well as individuals in the community versus those in the hospital. We likewise incorporate a rate of burial ω and environmental contamination rate ξ so we can appropriately show these transmission courses.

The transmission coefficients ($\beta_{i,j}$) are distinctive for educated individuals than those for uneducated to mirror the way that individuals who are taught about the ailment will avoid potential risk instead of the individuals who are most certainly not. Differences in behaviour exhibited by educated individuals are expected to reduce interaction with infected individuals, corpses and pollution, bringing about decreased transmission when contrasted with individuals who do not play it safe. We additionally permit the flow from the uneducated susceptible class to the educated susceptible class by means of the parameter θ to symbolize behavioral changes which might result from expanded

mindfulness of the epidemic through media scope, word of mouth, and/or dispersal of data by healthcare organisations.

6.2 Parameter Estimation

So as to gauge the transmission coefficients, we use information from Sudan where an outbreak happened in similar area at two separate occurrences. The underlying outbreak happened in 1976 and was the primary recorded episode of Ebola [39, 74]; the subsequent outbreak happened in 1979 in a similar general area [73, 39]. We take the initial 1976 episode to be a population completely uneducated about the infection as it was the starting archived event of Ebola within the world. As a result of media scope and public health education, we assume that in the three years following the preliminary outbreak the remaining population got to be mindful of EVD and how to maintain a strategic distance from it. Therefore, we take the subsequent outbreak to be a population of people who conduct contrastingly because of different types of public health education. Our assumptions are upheld by the way that, under almost indistinguishable transmission conditions, there were essentially more cases in preliminary outbreak contrasted with the second (see Tables 6.2 and 6.3). Also, there were a lot more contaminations that occurred in emergency clinics in the 1976 outbreak. To estimate parameters for these contrasting behaviors, the model is reduced to a single population and use a least squared optimisation approach to find the set of parameters that best match the data.

In each reduced model we just consider a single population- one either educated around the EVD or uneducated about the infection. Since we are simulating an epidemic scenario that happens during a brief timeframe outline, we take the natural death rate (μ) and birth rate (π) to be zero. This yields the following system that portrays the 1976 episode:

$$\begin{aligned}
 S' &= -(\beta_{0a}B + \beta_{1a}I + \beta_{4a}D)S - \beta_{2a}SH \\
 I' &= (\beta_{0a}B + \beta_{1a}I + \beta_{4a}D)S + \beta_{2a}SH - \gamma(\alpha_{1a}, \alpha_{2a}, H)I - \phi_1I - \delta_1I \\
 H' &= \gamma(\alpha_{1a}, \alpha_{2a}, H)I - \delta_2H - \phi_2H \\
 R' &= \phi_1I + \phi_2H \\
 D' &= \delta_1I + \delta_2H - \omega D \\
 B' &= \xi(I + H + D) - dB.
 \end{aligned}$$

TABLE 6.2: Data from the 1976 outbreak of Ebola in Sudan.

	July	August	September	October	November
Cumulative Cases	8	38	176	260	280
Cumulative Recovered	4	17	90	121	133
Cumulative Deaths	4	21	86	139	147
New Cases	8	30	138	84	20
New Recovered	4	13	73	31	12
New Deaths	4	17	65	53	8

% infections that occurred in the community	% infections that occurred in the hospital
38.5%	61.5%

TABLE 6.3: Data from the 1979 outbreak of Ebola in Sudan.

	End July & August	September	October
Cumulative Cases	16	33	34
Cumulative Recovered	2	11	12
Cumulative Deaths	13	20	22
New Cases	16	17	1
New Recovered	2	9	1
New Deaths	13	7	2

% infections that occurred in the community	% infections that occurred in the hospital
85%	15%

In the primary scenario, we consider Sudan 1976 outbreak that occurred in the towns of Nzara and Maridi, which had a consolidated population adding up to 35,000 [74]. The outbreak started when labourers of a cotton production line in Nzara turned out to be sick on June 27, 1976 and went on until the end of November. The disease spread to Maridi in the beginning of August when an infected patient infected in Nzara was admitted to a hospital in Maridi. Most of the cases occurred in Maridi with the hospital referred to as an enhancement factor [74]. The main worldwide reaction occurred on October 29, 1976 when the WHO despatched an emergency response crew to research and help with the new ailment [74]. At this point the outbreak was almost over as the quantity of new cases had been declining for longer than a month [74].

The 1976 epidemic exemplified the introduction of EVD into a system in which the entire population was not educated about Ebola and subsequently does not play it safe against the spread of the disease. This incorporates not following accepted healthcare protocols, which is reflected in the huge number of new cases that occurred in medical services settings. In this manner we will utilise information from the 1976 outbreak to gauge parameters identified with a population that is uneducated about EVD and a medical

care setting completely ill-equipped to deal with the virus. The WHO's report from this episode incorporates the information found in Table 6.2 [74].

In the subsequent situation, we consider the 1979 Sudan outbreak [73]. This EVD outbreak occurred in the cities of Nzara and Yambio, much like the outbreak in 1976. The report from this episode incorporates the information shown in the Table 6.3 [73]. The outbreak commenced on July 31 1979 in Nzara and afterward spread through family individuals to the adjacent town of Yambio [73]. The infection was dynamic from the last few days of July through to the first week of October. Since the 1979 episode occurred within the same area as the past outbreak and as it was just three years after, the population is composed of for the most part the same people as the 1976 outbreak. We subsequently expect the population was more taught approximately the disease, that individuals took safeguards against contracting the virus and sick people were seeking medical help more often. Be that as it may, in spite of having as of late managed with EVD, the medical care centers were not set up to manage another episode. The health care facilities were understaffed, did not have an isolate strategy and the staff was not prepared on proper disinfecting and sterilisation strategies [73]. Accordingly, 15% of new cases occurred in a medical services setting. It was only after the WHO mediated on September 22 when appropriate convention was set up, which quenched the outbreak [73]. Since the subsequent episode occurred just 3 years after, we will take the population size to be the equivalent to 1976.

To gauge parameters utilising the reduced model, we look for the set of values that best matched the data by making a minimisation scheme that relates model yield to information from the outbreak. We utilise the MultiStart calculation and `fmincon` from the optimisation tool kit in MATLAB to implement all optimisation schemes. The `fmincon` algorithm accepts an unknown parameter as an input with a $(J(x))$ scalar value minimised by applying an inequality constraint. Since `fmincon` is a local solver, the Multistart algorithm creates many starting points to test. This ensures that the global minimum is found. All parameter estimation simulations use a population size of 35,000 and start with infected individuals within the community and in the healthcare environment. It is assumed that the recovered, corpses and the initial value of the environment class are zero. This is because these compartments are not populated until Ebola is present in the population.

To help comprehend proper limits to force on the parameters, we to begin with essentially minimising the difference between the number of new cases in the data and the number of new cases produced by the model:

$$\underset{x}{\text{Minimize}} \quad J(x) = \|NC - NC^*\|_2,$$

where NC represents the 1×5 vector of new cases generated every month, NC^* represents the 1×5 vector of new cases from each month in the data, and x represents the unknown parameters.

After figuring out suitable appropriate bounds to force on the parameters, in order to constrain the search region, we run the scheme once more, but this time according to the number of new cases and the percentage of infections that came from the community or health care:

$$\underset{x}{\text{Minimize}} \quad J(x) = \|NC - NC^*\|_2 + \|100 * (PC - PC^*)\|_2 + \|100 * (PH - PH^*)\|_2,$$

where PC represents the the proportion of recent cases springing up in the community and PH represents the percent of recent cases springing up in health care settings. We multiply by 100 in order to weight the values as it should be.

This allows us to further refine the parameter range. We then fit the percentage of new cases, new deaths, new recoveries, infections from the community and the percent of infections that came from the community and hospital:

$$\underset{x}{\text{Minimize}} J(x) = \|NC - NC^*\|_2 + \|100 * (PC - PC^*)\|_2 + \|100 * (PH - PH^*)\|_2 \\ + \|100 * (NR - NR^*)\|_2 + \|100 * (ND - ND^*)\|_2,$$

where NR represents the 1×5 vector of new monthly recoveries and ND represents the 1×5 vector of new monthly deaths.

To begin with, the step-wise strategy depicted above was utilised with the information from the 1976 Sudan episode to gauge the parameters associated with individuals who do not take safety measures against contracting and spreading EVD. Estimated parameter values are shown in Table 6.4.

By adopting a step-by-step approach to fitting the parameters, we were able to fit the records from the 1976 outbreak as depicted in Figure 6.2. Since those who are not aware of the risks associated with Ebola are much more likely to be treated at home,

TABLE 6.4: Parameter estimation results obtained by fitting 1976 Sudan data to the reduced model.

Parameter	Description	Value
β_{0a}	Transmission rate from uneducated interaction with the environment	9.90×10^{-08}
β_{1a}	Transmission rate from uneducated interaction with uneducated infected	4.40×10^{-06}
β_{2a}	Transmission rate from uneducated in hospitals	.012
β_{4a}	Transmission rate from uneducated interaction with dead bodies	1.84×10^{-07}
α_{1a}	Sigmoidal constant that governs uneducated infected movement into hospitals	18.8
α_{2a}	Sigmoidal constant that governs uneducated infected movement into hospitals	15
ϕ_1	Recovery rate for infected uneducated individuals in the community	0.04
ϕ_3	Recovery rate for infected uneducated individuals in hospitals	0.011
δ_1	Death rate for uneducated infected individuals in the community	0.077
δ_3	Death rate for uneducated infected individuals in hospitals	0.07
ω	Burial rate of dead bodies	0.07
ξ	Environmental contamination rate	0.43
d	rate of decay of Ebola in the environment	0.87

initially, the number of infections in the community increases faster than in hospitals. Once enough people had been admitted to hospitals an epidemic is announced and information is disseminated to the general public, which will increase widespread recognition of the sickness resulting in greater people seeking medical attention. Two different peaks in the graph depicting infected people reflect this effect. The quantity of infections in the community is growing much faster than the number of infections in hospitals, until the threshold of awareness is reached at which people start visiting hospitals more often, which eventually leads to the suppression of the outbreak.

Now, attention is drawn to the model for 1979 Sudan outbreak:

$$\begin{aligned}
S'_{edu} &= -(\beta_{0b}B + \beta_{1b}I_{edu} + \beta_{4b}D)S_{edu} - \beta_{2b}S_{edu}H \\
I'_{edu} &= (\beta_{0b}B + \beta_{1b}I_{edu} + \beta_{4b}D)S_{edu} + \beta_{2b}S_{edu}H - \gamma(\alpha_{1b}, \alpha_{2b}, H)I_{edu} - \phi_1I_{edu} - \delta_1I_{edu} \\
H' &= \gamma(\alpha_{1b}, \alpha_{2b}, H)I_{edu} - \delta_2H - \phi_2H \\
R' &= \phi_1I_{edu} + \phi_2H \\
D' &= \delta_1I_{edu} + \delta_2H - \omega D \\
B' &= \xi(I + H + D) - dB
\end{aligned}$$

We once more utilise the same optimisation tools and approach to gauge parameters related to those who take safeguards against contracting and spreading EVD. By taking the already portrayed step-by-step approach to fitting the parameters we were able to fit the information from the 1979 Sudan outbreak. Results from this procedure are shown in Table 6.5 and model output is illustrated in Figure 6.3. Since there has been a far shorter outbreak with far fewer cases the information is extra coarsely fit, but we have

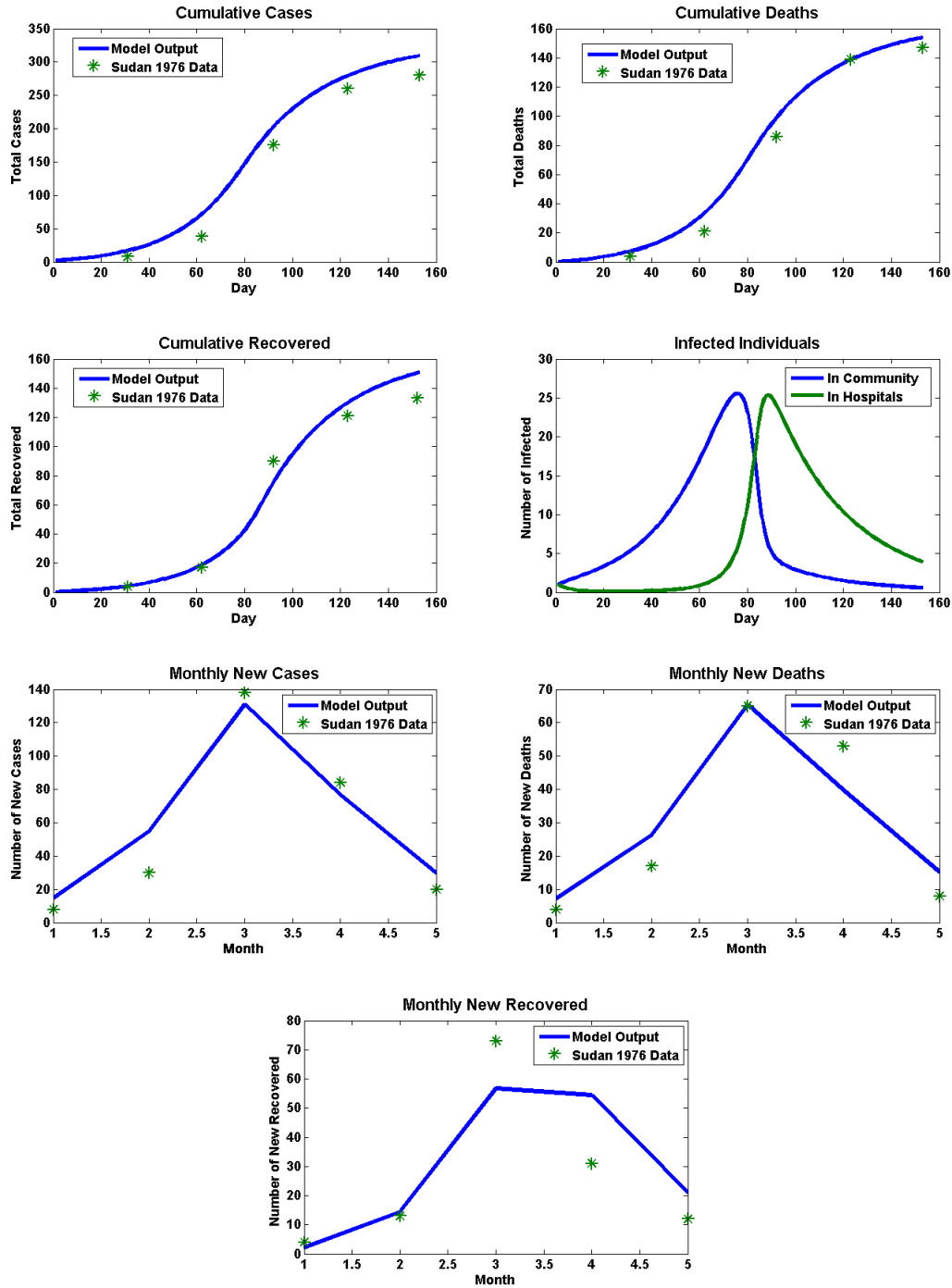


FIGURE 6.2: Results from fitting the reduced model to the 1976 Sudan data.

been nonetheless able to capture the dynamics observed in the data. Take note that since this population seeks medical treatment at a higher rate, exceptionally few infections are present within the community at a given time. Instead, people search for expert medical attention almost straight away.

TABLE 6.5: Parameter estimation results obtained by fitting 1979 Sudan data to the reduced model.

Parameter	Description	Value
β_{0b}	Transmission rate from educated interaction with the environment	1.96×10^{-18}
β_{2b}	Transmission rate from educated in hospitals	2.07×10^{-06}
β_{3b}	Transmission rate from educated interaction with educated infected	2.23×10^{-06}
β_{4b}	Transmission rate from educated interaction with dead bodies	3.77×10^{-13}
α_{1b}	Sigmoidal constant that governs educated infected movement into hospitals	4
α_{2b}	Sigmoidal constant that governs educated infected movement into hospitals	3
ϕ_2	Recovery rate for infected educated individuals in the community	0.02
ϕ_3	Recovery rate for infected educated individuals in hospitals	0.02
δ_2	Death rate for educated infected individuals in the community	0.02
δ_3	Death rate for infected educated individuals in hospitals	0.02
ω	Burial rate of dead bodies	0.09
ξ	Environmental contamination rate	0.2
d	rate of decay of Ebola in the environment	0.8

Table 6.6 presents the list of parameters which could not be estimated from the two single-population information sets, including transmission rates that administer the connection between those educated about EVD and the individuals who are definitely not. We assume that the association between susceptible uneducated and infected educated would be the same as susceptible uneducated and infected uneducated. We consequently anticipate that $\beta_{3,a} = \beta_{1,a}$ and $\beta_{1,b} = \beta_{3,b}$ will best represent the behavior being modelled in each class. The rate of education, θ , is an unknown parameter that controls flow from the S class into the S_{edu} class. By changing this rate, we can examine the significance of mediations, for example, public health education as well as general public education about EVD in forestalling or decreasing an outbreak.

TABLE 6.6: Parameters that could not be estimated from the data.

Parameter	Description	Value
β_{3a}	Transmission rate from uneducated interaction with educated infected	$\beta_{3,a} = \beta_{1,a}$
β_{1b}	Transmission rate from educated interaction with uneducated infected	$\beta_{1,b} = \beta_{3,b}$
θ	Rate of education	

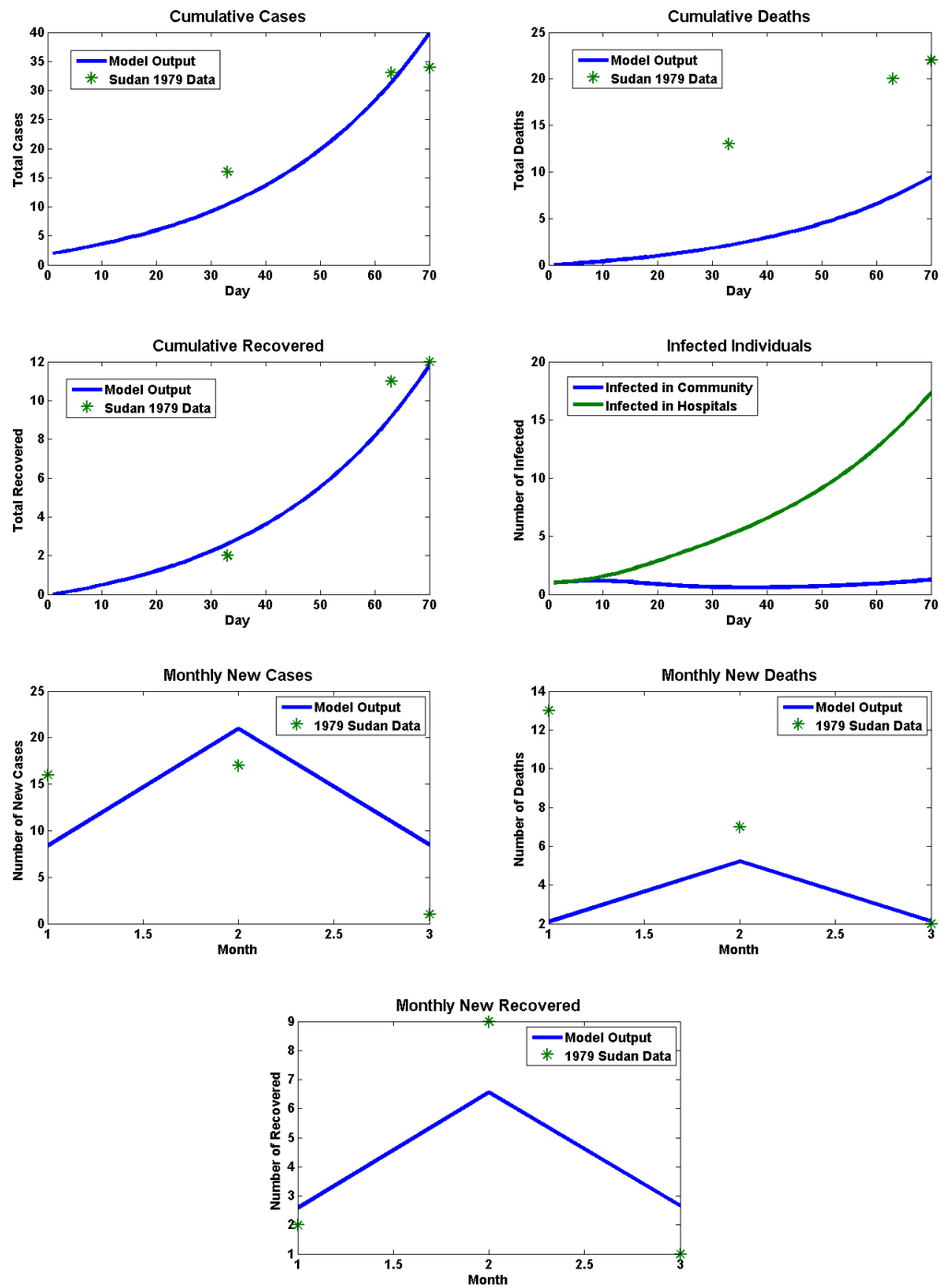


FIGURE 6.3: Results from fitting the reduced model to the 1979 Sudan data.

6.3 Sensitivity Analysis

We performed a sensitivity analysis on the full model utilising the total number of infections as the outcome of interest. The parameter values to be tested were sampled using Latin hypercube sampling (LHS) and Partial Rank Correlation Coefficients (PRCC) were used to assess how sensitive the total number of infections is to modifications in each parameter [105, 124]. We incorporated all the parameters from Table 6.9, except for β_{3a} , β_{1b} , ϕ_1 , δ_1 , δ_2 , β_{0b} , and β_{4b} as these inputs are either dependent on other parameters or their estimated values are less than 1.0×10^{-10} . We additionally treated the percentage of the initial population that begins in the uneducated susceptible class as a parameter, denoted as S_0 . To construct the interval for the LHS scan, we decided to select from values 50% above and below the baseline values given in Table 6.9 with uniform probability distributions used for each interim. We utilised the proposed number of draws given in [137], which brought about $N > 4K/3$ draws of the LHS design, where K is the number of input parameters and N is the number of LHS draws. For our situation, $K = 18$ and $N = 50$.

PRCC is a tool with which we can assess the effect of modifications in every parameter on the outcome of interest, even if when the relationship is non-linear. Note that we can apply the Fisher transformation to the PRCC as described in [125, 138]. To decide the importance of the PRCC for each parameter, we calculated a p -value for each utilising the strategies portrayed in [124]. Since we are performing $K = 18$ hypothesis tests, we amended the resulting p -values for false discovery using the FDR method of [126].

PRCC values with an adjusted p -value less than 0.01 are considered essentially distinctive from 0. The results of the sensitivity analysis are displayed in Table 6.7, where statistically significant PRCC values appear in red.

Based on the adjusted p -value, six of the PRCC values are regarded not noteworthy including β_{0a} , β_{1a} , β_{2a} , β_{4a} , α_{2a} , and ξ . All other PRCC values are deemed statistically significant, with positive values demonstrating a positive relationship between the parameter and total number of infections and a negative value shows a negative relationship. The following parameters therefore have a statistically significant PRCC value and a positive influence on the number of infections: β_{3b} , β_{2b} , α_{1b} , ω , and S_0 . Each of these values makes sense based on their role in the system. The following parameters have a statistically significant PRCC value and a negative influence on the number of infections: α_{1a} , α_{2b} , ϕ_2 , ϕ_3 , δ_3 , d , and θ .

TABLE 6.7: Model parameters and the corresponding PRCC p-values resulting from the sensitivity analysis.

Variable	PRCC	p-value
β_{0a}	-0.086030	7.162e-01
β_{1a}	0.282820	1.431e-01
β_{2a}	0.035981	8.437e-01
β_{4a}	0.322470	9.279e-02
β_{3b}	0.884460	1.878e-13
β_{2b}	0.917910	0.000e+00
α_{1a}	-0.387030	3.799e-02
α_{2a}	-0.063951	7.685e-01
α_{1b}	0.525560	3.550e-03
α_{2b}	-0.443820	1.618e-02
ϕ_2	-0.712940	4.494e-06
ϕ_3	-0.655080	6.291e-05
δ_3	-0.840170	1.323e-10
ω	0.467430	1.102e-02
ξ	-0.088059	7.162e-01
d	-0.414850	2.554e-02
θ	-0.587120	6.792e-04
S_0	0.489260	7.607e-03

Utilising the twelve parameters whose PRCC values were found to be significant, pairwise comparisons with Fisher transformed values [125] produces the outcomes given in Table 6.8. A red Y indicates the p -value is significant ($p < 0.01$) and a black N indicates the p -value is not significant. There is a significant difference between β_{3b} and β_{2b} with each of the remaining parameters, which stands out the most in these results. These two parameters represent transmission rates among the educated class and have the strongest PRCC values as seen in Table 6.7. In essence, β_{3b} and β_{2b} reflect the strength of behavior change in reducing an outbreak of EVD. If the educated portion of the populations does not take precautions against spreading the disease (ie, high β_{3b} and β_{2b} values), then a significant number of cases will be produced. Since the pairwise comparison between β_{3b} and β_{2b} was not significant, it is not clear which parameter is more influential. Additional proof for this point is given by the fact that the percent of the population that starts in the uneducated class (S_0) is also significantly different than most other parameters and is negatively correlated with the total number of infections. While recovery rates ϕ_2 and ϕ_3 as

well as death rate δ_3 were both negatively associated with the outcome in a significant way as individual parameters, the pairwise comparison of each was non-significant rendering the relative importance of each inconclusive.

TABLE 6.8: Pairwise comparisons for the model parameters.

	β_{2b}	α_{1a}	α_{1b}	α_{2b}	ϕ_2	ϕ_3	δ_3	ω	d	θ	S_0
β_{3b}	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
β_{2b}		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
α_{1a}			Y	N	N	N	Y	Y	N	N	Y
α_{1b}				Y	Y	Y	Y	N	Y	Y	N
α_{2b}					N	N	Y	Y	N	N	Y
ϕ_2						N	N	Y	N	N	Y
ϕ_3							N	Y	N	N	Y
δ_3								Y	Y	N	Y
ω									Y	Y	N
d										N	Y
θ											Y

6.4 Numerical Simulations

Considering the two separate populations, each of which influences the dynamics of transmission in its own way, we are in a position to simulate EVD epidemic in Sudan in the future. Parameters estimated from Sudan's 1976 data indicate transmission movements in a population that has no education about EVD and thus few precautions to deal with the disease in a community environment as well as inadequate protocol in medical services settings. Coefficients from 1979 Sudan data capture dynamics in an environment where the general population is familiar with Ebola and people take preventive measures against transmission, which represents our educated population. Be that as it may, since medical care staff were as yet not appropriately prepared to deal with EVD, transmission rates remained generally high in this setting. By consolidating estimated parameters in the full model while changing others, we can analyse the relevance of individual behaviour, cultural practices and appropriate medical care protocols to reduce or prevent an EVD outbreak.

In the following situations we model an outbreak of EVD in present day towns of Nzara, Maridi, and Yambio utilising the full model shown in system 6.1. The latest population estimates for these towns are 73,800 (Nzara), 18,000 (Maridi) and 40,382 (Yambio) for a total of 132,182 [139, 140, 141]. See Table 6.9 for an outline of all parameters utilised within the following simulations. In all simulations we begin with one uneducated infected

in the community, one educated infected in the community and one infected in the hospital. All remaining individuals will begin in one of the susceptible classes. All other individuals will start in one of the susceptible classes. We shall assume an initial value of zero for the recovered, dead body and environment classes. We use most of the estimated transmission rates $(\beta_{1a}, \beta_{3a}, \beta_{4a}, \beta_{1b}, \beta_{3b}, \beta_{4b})$ and all sigmoidal constants $(\alpha_{1a}, \alpha_{2a}, \alpha_{1b}, \alpha_{2b})$ shown in Tables Table 6.4, 6.5, and 6.6 in our simulations. The transmission rate in the medical services setting (β_{2a}, β_{2b}) will rely upon how EVD outbreak facilities are organised for an outbreak. Since EVD has been established in Africa for over 40 years, we can assume that in healthcare facility, the transmission rate will not be worse than the Sudanese outbreak of 1979. For the environmental contamination rate (ξ) and decay rate (d) , we took the average of the two estimated rates found in Tables 6.4 and 6.5. For the burial rate of dead bodies (ω) , we used the estimate from the 1979 outbreak, which is a faster burial rate compared to the 1976 outbreak. Simulating is done over a short time frame, hence, we take the growth rate (π) and death rate (μ) to be 0.

TABLE 6.9: Parameters values used in the simulations.

Parameter	Description	Source	Value Used
β_{0a}	Transmission rate from uneducated interaction with the environment	Sudan 1976	9.90×10^{-08}
β_{1a}	Transmission rate from uneducated interaction with uneducated infected	Sudan 1976	4.40×10^{-06}
β_{2a}	Transmission rate from uneducated in hospitals	$\leq \beta_{2b}$	$\leq 2.07 \times 10^{-06}$
β_{3a}	Transmission rate from uneducated interaction with educated infected	$= \beta_{1a}$	4.40×10^{-06}
β_{4a}	Transmission rate from uneducated interaction with dead bodies	Sudan 1976	1.84×10^{-07}
β_{0b}	Transmission rate from educated interaction with the environment	Sudan 1979	1.96×10^{-18}
β_{1b}	Transmission rate from educated interaction with uneducated infected	$= \beta_{3b}$	2.23×10^{-06}
β_{2b}	Transmission rate from educated in hospitals	Sudan 1979	$\leq 2.07 \times 10^{-06}$
β_{3b}	Transmission rate from educated interaction with educated infected	Sudan 1979	2.23×10^{-06}
β_{4b}	Transmission rate from educated interaction with dead bodies	Sudan 1979	3.77×10^{-13}
α_{1a}	Sigmoidal constant that governs uneducated infected movement into hospitals	Sudan 1976	18.8
α_{2a}	Sigmoidal constant that governs uneducated infected movement into hospitals	Sudan 1976	15
α_{1b}	Sigmoidal constant that governs educated infected movement into hospitals	Sudan 1979	4
α_{2b}	Sigmoidal constant that governs educated infected movement into hospitals	Sudan 1979	3
ϕ_3	Recovery rate for infected individuals in hospitals	Historic Average [142]	0.12 – 0.20
ϕ_1	Recovery rate for infected uneducated individuals in the community	Based on ϕ_3	$= 0.5\phi_3$
ϕ_2	Recovery rate for infected educated individuals in the community	Based on ϕ_3	$= 0.5\phi_3$
δ_3	Death rate for infected individuals in hospitals	Historic Average [143]	0.09 – 0.14
δ_1	Death rate for uneducated infected individuals in the community	Based on δ_3	$= 2\delta_3$
δ_2	Death rate for educated infected individuals in the community	Based on δ_3	$= 2\delta_3$
ω	Burial rate of dead bodies	Sudan 1979	0.09
ξ	Environmental contamination rate	Sudan 1976 & 1979	$0.5(0.43 + 0.2)$
d	rate of decay of EVD in the environment	Sudan 1976 & 1979	$0.5(0.87 + 0.08)$
θ	Rate of education	Will Vary	0 – 0.2

We start with a comparison of how different proportions of educated and uneducated people lead to different infection rates. Specifically, how they affect the duration of the outbreak and the number of people infected. To account for this, we compare the percentage of the total population infected in the two simulations of historical outbreaks in Sudan with the total percentage of the population infected in a simulation of an outbreak in current Sudan with a mixed population. In previous outbreak simulations in Sudan, we assumed that the population is either fully educated or not educated at all. In the current

Sudan simulation, we assume that 50% of the population will receive an education and 50% of the population will receive no education. We will use the hospital recovery and mortality rates of $\phi_3 = 0.16$ and $\delta_3 = 0.09$ as these values ensure that all death and recovery rates are within the historical average [142, 143]. The results of these simulations are shown in Figure 6.4. The totally uneducated population has the highest number of infected people due to the greater number of infected people who do not seek medical attention and instead remain in the community. On the other hand, the fully educated population is transitioning to hospital very rapidly, which extinguishes the outbreak. Current Sudan simulation is between the other two simulations because take only 50% of the population for training. This simulation shows the earliest initial increase in infected individuals due to the significantly larger population size. However, individuals are being hospitalised faster than the uneducated population as a whole, which quenches the episode.

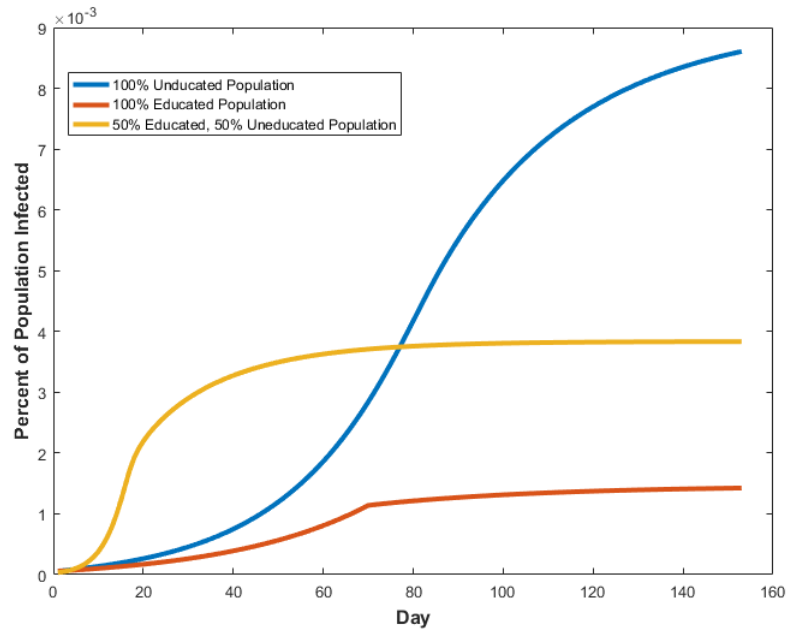


FIGURE 6.4: Various levels of education lead to different percent of total population infected.

Different strains of EVD will bring about fluctuating recovery and death rates. EVD's past average mortality was 6 to 16 days [143] and past average recovery time was 7-14 days [142]. Because certain EVD specific strains play an important role in certain recovery and death rates in future occurrences, we will consider a scope of the two values in our full model simulations that range the estimations of the historic rates. In addition, we assume that the death rate in the community is twice death rate in a health care settings ($\delta_1 = \delta_2 = 2\delta_3$) and that the recovery rate in the community is half the recovery rate

in a health care setting ($\phi_1 = \phi_2 = 0.5\phi_3$). Other unknown inputs of the full model are the education rate (θ) and the healthcare transmission rate (β_{2b}) and the proportion of initial susceptible population, educated or uneducated about preventing the spread of EVD. These inputs are especially important to explain the need to train healthcare professionals for the correct EVD protocol and to educate the general public about EVD before and during the outbreaks. The outbreak of Sudan in 1976 infected 0.008% of the total population [74] and the outbreak of EVD in West Africa in 2014 infected 0.001% of the total population [43]. For comparison in the current simulations, 0.008% of the total population of 132,182 would be 1,058 cases and 0.001% of the total population is 185 cases.

Utilising a proportion of uneducated:educated susceptibles of 1:3, a θ estimation of 0 and the health care transmission coefficient estimated from the Sudan 1979 information, we simulate an EVD outbreak using a 365-day period. In this situation, an unprecedented outbreak takes place for most values of ϕ_3 and δ_3 as seen in the top two plots in Figure 6.5, where most total case tallies were well above 1,000. This simulation represents a scenario with a relatively high percentage of educated people in the community, but there is no public health education ($\theta = 0$). Using the healthcare transfer coefficient from the 1979 outbreak, this simulation also represents a case in which healthcare workers are not appropriately trained on proper EVD protocol. This results in high incidence rates of low death and recovery rates as people begin to fill health facilities as the outbreak progresses, which is volatile in this setting. Even when the entire population is educated for the first time, a high transmission rate in health care settings still results in a massive outbreak takes place for most recovery and death rate values (ϕ_3 and δ_3), as seen in the top two plots in Figure 6.5. However, if the values of β_{2a} and β_{2b} are reduced by 0.5, the total number of cases is reduced to a reasonable level, as seen in the bottom plot in Figure 6.5. These simulations illustrate the fact that reducing transmission in a health care setting and/or educating individuals about EVD prior to an outbreak can significantly reduce the total cases during an epidemic.

To help communicate the interventions used to mitigate the impact of a future epidemic, we aim to capture the dynamics of public health education and associated behavior change in our model. We capture this dynamic with the θ parameter, which controls the flow from uneducated susceptible compartment into the educated susceptible compartment. The higher the value of θ , the faster the behavior change. We can also analyse the importance of timing for public health education by adjusting when θ becomes non-zero. Note that the delay between a public health campaign and a large-scale behaviour change will depend on many factors, including the specific methods used to get the message out. In this study, we

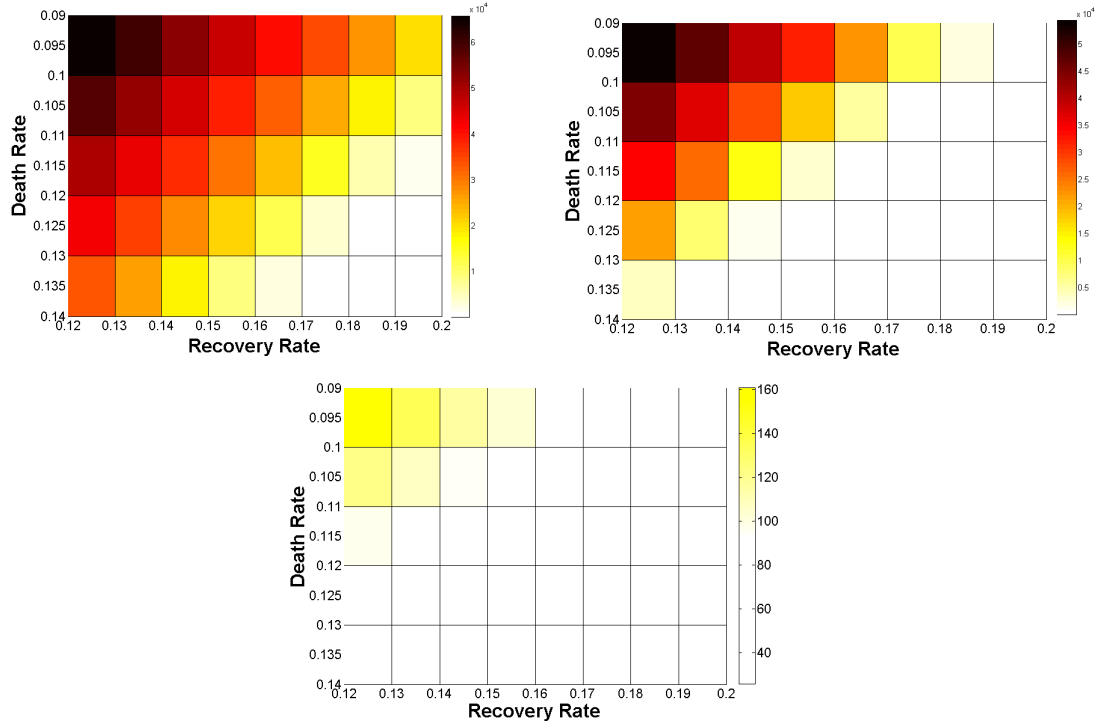


FIGURE 6.5: Results of a potential outbreak in Sudan for various recovery and death rates with a rate of education θ of 0 in all simulations. The color bar gives the total number of infections. The top left plot has a ratio of uneducated:educated susceptibles of 1:3 and the transmission rate in health care settings is high. The top right plot has 100% of the population educated and the transmission rate in health care settings is high. The bottom plot has a ratio of uneducated:educated susceptibles of 1:3 and the transmission rate in health care settings is reduced by 0.5.

only want to simulate how the behavior change itself can affect the outbreak. Therefore, we believe that activating θ to represent the moment when large-scale behavior change begins to occur, rather than the start of health education. While considering a hypothetical future EVD outbreak in Sudan, we assume that in hospital settings the transmission rate will be reduced by 75% compared to an estimated outbreak in 1979 and we simulate our model for one year. We use the original ratio of 3: 1 uneducated: educated susceptibles, which will change over time depending on the value of θ used.

Figure 6.6 shows results when no intervention happens, which implies that $\theta = 0$ in all simulations. For this situation, the outbreak peaks somewhere in the range of 40 and 50 days, with new cases showing up to 5 months after the initial case. In total, 350-650 EVD cases were reported, or 0.0026-0.0049 % of the total number of infected.

Figure 6.7 shows results when the intervention was started 60 days after the beginning of the outbreak. There were a total of 347-628 EVD cases, or 0.0026-0.0048 % of the total

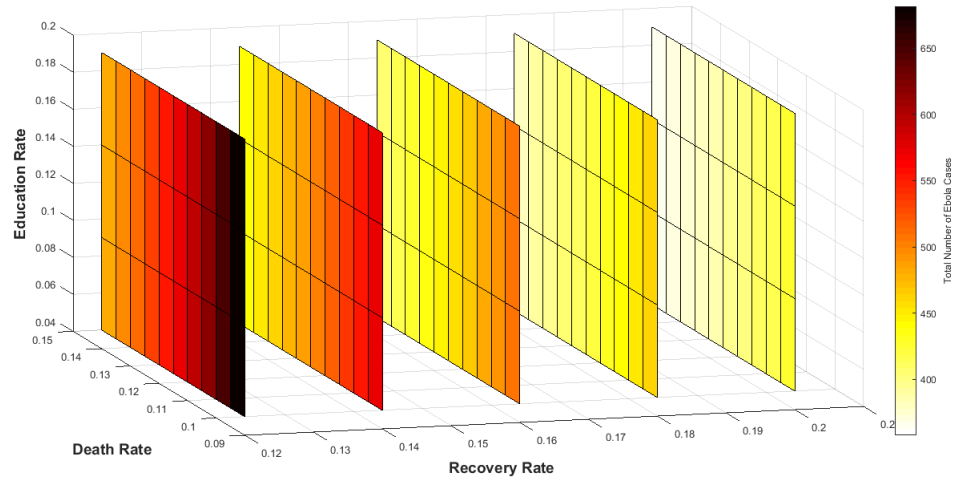


FIGURE 6.6: Results of a simulated outbreak in Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect the absence of public health education as $\theta = 0$ in all cases.

number of infected. In this situation, since the outbreak had just peaked, there was just a slight decrease in the total number of EVD cases.

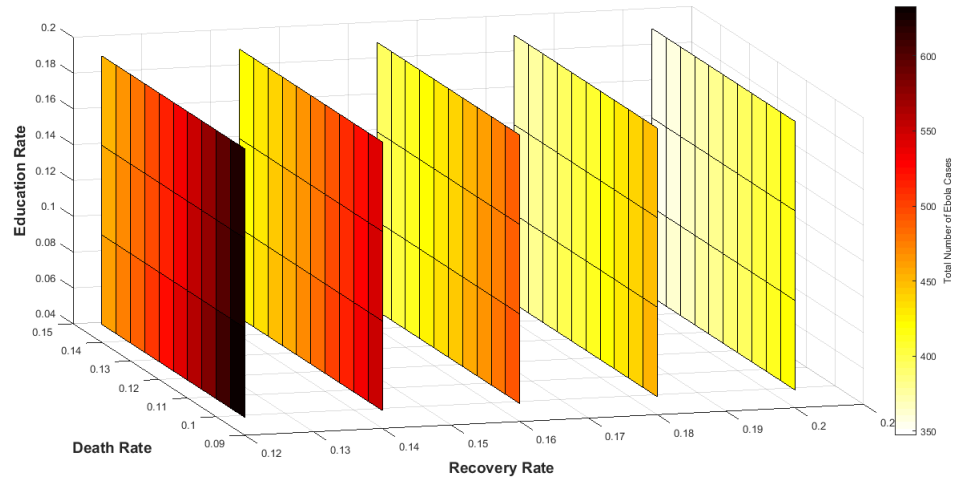


FIGURE 6.7: Results of a simulated outbreak in present day Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect public health education starting 60 days after the initial case, which is past the peak of the outbreak.

Figure 6.8 results when the intervention begins 30 days after the onset of the outbreak. Since the awareness campaign was launched before the total number of infections peaked, we see a more significant reduction in the total number of cases: 295-538 from EVD cases or 0.0022-0.0041% of the total number of infected.

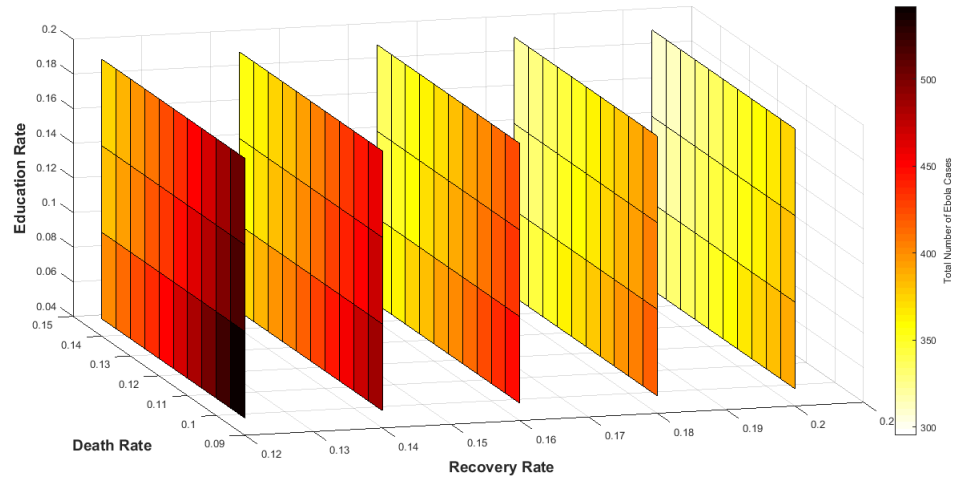


FIGURE 6.8: Results of a simulated outbreak in present day Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect public health education starting 30 days after the initial case, which is immediately prior to the peak of the outbreak.

Figure 6.9 shows results when the intervention begins 14 days after the outbreak, that is, before the peak of the outbreak. Thus, 107–420 EVD cases were reported, or 0.0008–0.0032% of the total number of infected.

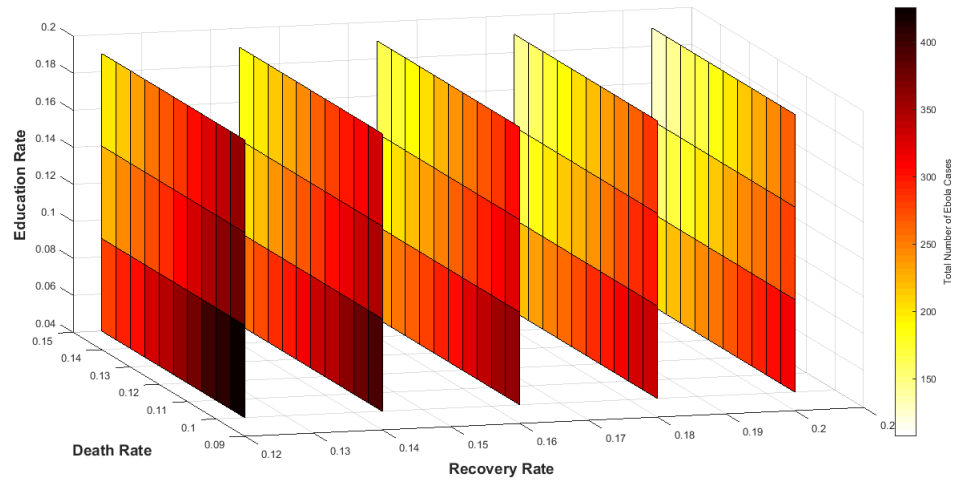


FIGURE 6.9: Results of a simulated outbreak in present day Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect public health education starting 14 days after the initial case, which is well prior to the peak of the outbreak.

Figure 6.10 shows results when the θ value is nonzero from the beginning of the outbreak. This simulation presents the most ideal situation in which public health education begins as

soon as the first EVD case is detected. For this situation there were 16-143 EVD cases, or 0.0001-0.0011% of the total number of infected. These outcomes clearly illustrate not just the significance of public health education that lead to conduct change, yet additionally timing of awareness campaigns.

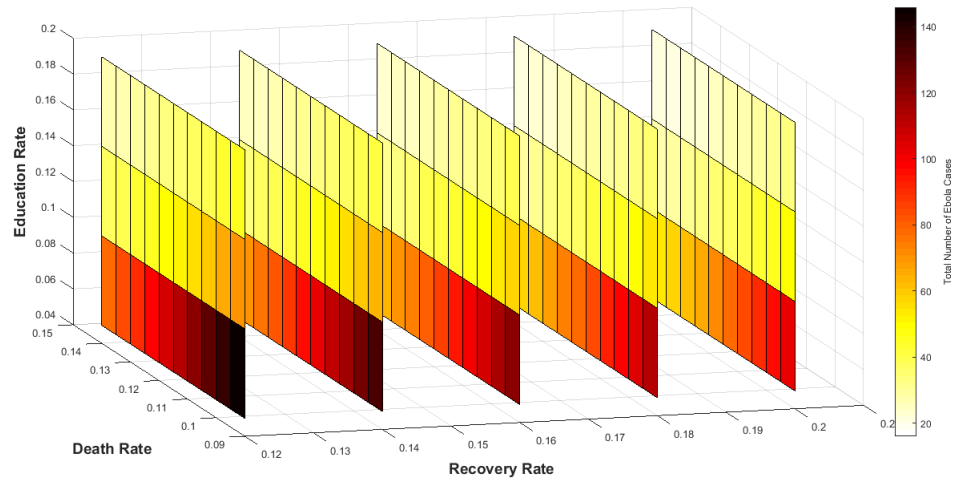


FIGURE 6.10: Results of a simulated outbreak in Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect public health education starting immediately after the initial case.

The earlier behaviour change starts to happen because of public health education, the more more lives that can be saved. To outline this, we consider the situation where the population is educated about EVD preceding an outbreak, so the initial proportion of uneducated:educated susceptibles is modified to 1:3 and no public health education is executed. The results of this simulation appear in Figure 6.11. In this situation, the quantity of cases ranges from 20-66 absolute cases or 0.0002-0.0005% of the complete populace, which is a critical decrease from all previous simulations.

The histogram in Figure 6.12 shows the total number of EVD cases from numerical simulations in Figures 6.6 through 6.11. The histogram plainly shows that the timing of public health education is important in reducing the number of EVD cases. In particular, the earlier an educational campaign is executed, the less cases that outcome. Organising an educational campaign during an outbreak can be difficult, as resources are already restricted. Thus, ongoing education of the population will not just result in less cases, but it is the most sensible methodology.

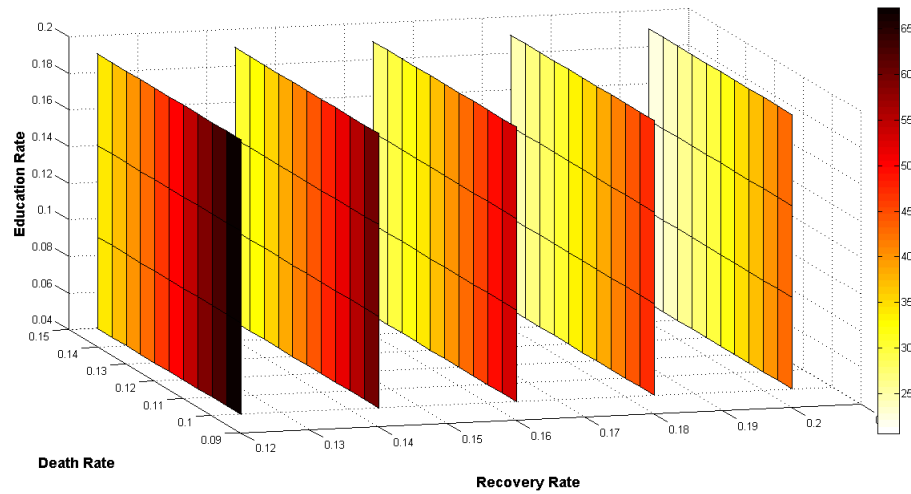


FIGURE 6.11: Results of a simulated outbreak in Sudan displaying the total cases of EVD for various recovery, death, and education rates. These figures reflect an initial ratio of uneducated:educated susceptibles of 1:3 and no public health education ($\theta = 0$). These figures illustrate how educating the population prior to a case of EVD can prevent an outbreak from occurring.

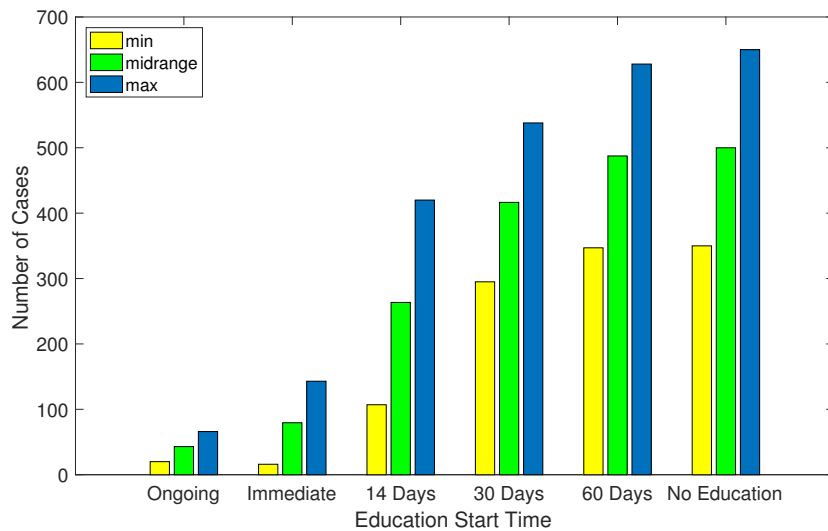


FIGURE 6.12: This histogram summarizes the simulated future outbreaks in Sudan. Specifically, it displays the maximum, minimum, and midrange of the total number of cases of EVD from the numerical simulations in Figures 6.6 through 6.11. Each simulation considered implementing public health education at a different time and the education rates, death rates, and recovery rates were varied in each case.

Discussion

Neglected tropical diseases (NTDs) are a health crisis that is ignored by the developed world and only starts getting attention when there is an outbreak that kills a large population [9]. AIDS-KS and Ebola virus disease (EVD) are NTDs which are caused by viral infections. In this thesis we have presented a within-host model for AIDS-KS and an epidemiologic model for Ebola.

The fact that AIDS-KS continues to be diagnosed in HIV infected patients despite the introduction of HAART, may be an indication that the first-line and second-line antiretroviral regimens as recommended by WHO are not working effectively for all patients to prevent HIV-1 related infections. In this study we have formulated weak and strong viral source mathematical models based on viremia levels for both HIV-1 and HHV-8 to study the prognosis of KS and to make recommendations on optimal dosage regimen for HIV-1 that would clear the viral infections (both HIV-1 and HHV-8), prevent tumor growth and minimise drug toxicity.

The AIDS-KS models are based on viral load (VL) where the effect of low and high VL was included in the proliferation terms of the infected cells and virus-specific effector cells. The viral sources are of the type $H_1(x_6, \beta) = x_6^\beta$, $H_8(x_7, \gamma) = x_7^\gamma$ and $H_1(x_6, \beta) = x_6^\beta + x_6$, $H_8(x_7, \gamma) = x_7^\gamma + x_7$ for the weak viral source model and strong viral source model respectively. Three special cases were considered, that is, (i) $\gamma = \beta = 0$, (ii) $\gamma = 0$, $\beta = 1$ and (iii) $\gamma = \beta = 1$ where $0 \leq \beta \leq 1$ and $0 \leq \gamma \leq 1$.

Through a sensitivity analysis of the reproduction numbers, we observed that the source of HIV-1 specific effector cells, s_{x_3} and the lysis of infected B cells, κ_1 have the greatest influence on the reproduction numbers, $\mathcal{R}_{0x_6}$ and $\mathcal{R}_{0x_7}$ respectively. Independent

testing between the parameters which affect the reproduction numbers showed that κ_1 is independent of the other parameters. However, s_{x_3} may be influenced by μ_{x_6} , the clearance of HIV-1 virions, hence the significance of each parameter can only be established by varying them and measuring how they alter the disease prognosis.

For the weak viral source model, we have found that for constant infected T-cell and B-cell sources (both from infection and proliferation) that is $\gamma = \beta = 0$, both HIV-1 and HHV-8 infections, measured by viral and infected cell levels, decline to below detectable levels. This result is true even for high constant initial infected T-cell and B-cell sources (large r_{x_1} and r_{x_4}). For constant infected T-cell and B-cell sources the respective effector cells (E_1 and E_8) are able to proliferate to levels that dominate and overcome the viral replenishment.

If the source for infected B-cells is constant ($\gamma = 0$) but the source for infected T-cells is strong ($\beta = 1$) then KS fails to develop since the HHV-8 VL which is responsible for KS development declines to below a detectable level even for a high constant initial source of infected B-cells. This is the case describing a scenario when HIV-1 infected individuals never suffer from KS throughout the period of their HIV-1 infection.

When both sources for infected T-cells and B-cells are strong ($\gamma = \beta = 1$) both HIV-1 and HHV-8 levels are detectable. The KS level is also high and the development of clinical KS is now possible. This result is true even when the proliferation rates for infected T-cells and B-cells r_{x_1} and r_{x_4} are low.

On the other hand, for the strong viral source model (for all the three cases), both HIV-1 and HHV-8 levels are detectable. Consequently, KS levels are also high and the development of KS is possible.

From the three special cases considered above, that is, $\gamma = \beta = 0$, $\gamma = 0, \beta = 1$, $\gamma = \beta = 1$ (before controlled treatment is administered) and the other cases $0 < \gamma < 1$ and $0 < \beta < 1$ (not shown in the thesis as it is inferred in the special cases), it can be deduced that the success of viral invasion of the host hinges on viral production from variable infected T and B cell sources being continuously variable. The variability of viral production is a necessary condition to ensure that the immune effector cells are unable to mount a sufficient response to overcome the viral replication.

For the strong viral sources $\gamma = 1, \beta = 1$ discussed above, we have shown that when treatment control parameters ζ_r , ζ_p and η_c representing efficacies for reverse transcriptase inhibitors, protease inhibitors and KS therapy, respectively are introduced, it is possible

to find optimal treatment levels ζ_r^* , ζ_p^* , η_c^* and $\hat{\zeta}_r$, $\hat{\zeta}_p$, $\hat{\eta}_c$ above which the HIV-1 infection declines to below detectable level resulting in the clearance of HHV-8 for the weak viral source model and strong viral source model respectively.

We simulated the case $\gamma = \beta = 1$ in Figure 4.8 above which yielded high VLs and a possibility of clinical KS. The conclusion when $\zeta_r \geq \zeta_r^*$, $\zeta_p \geq \zeta_p^*$, $\eta_c \geq \eta_c^*$ and when $\zeta_r \geq \hat{\zeta}_r$, $\zeta_p \geq \hat{\zeta}_p$, $\eta_c \geq \hat{\eta}_c$ yielded a different outcome as in this case the VL for both HIV-1 and HHV-8 declined to undetectable levels for any source of infected T-cells and B-cells.

Our work is important in that it supports the recommendation for early treatment for HIV-1 patients as a means to maintain low VLs and to prevent HIV-1 related infections. It also informs HIV-1 infected individuals about the importance of adhering to treatment to maintain low VLs as this would help to maintain the same treatment regimens and acceptable toxic levels.

In the future, AIDS-KS virus persistent equilibria could be explored using numerical root finding or bifurcation analysis software. The optimal treatment could be pursued further by considering the bang bang optimal control to cater for non-adherence. In reality it is challenging for patients to adhere to treatment for various reasons such as forgetfulness, travel for work or social activities and stigma.

Ebola is now endemic to most areas of sub-Saharan Africa. Understanding how this infection spreads and whether individuals learn from one outbreak and use their experience in a subsequent outbreak is important.

Unnecessary interactions with infected people and poor healthcare protocols play a significant role in the duration and spatial spread of an Ebola virus disease (EVD) outbreak [40, 45, 47, 50]. A portion of these causes result from cultural practices, while others are due to lack of awareness about EVD. Such behaviour is most evident in the 1976 outbreak of EVD in Sudan, as the initial documented outbreak of Ebola lasted five months, infected the majority of the population and led to many new infections in the health care system. Consequently, we have estimated the uneducated population parameters utilising information from the 1976 outbreak [74].

We then utilised the Sudan 1979 data to estimate the parameters of the educated population, as we assume that the outbreak included people who were more educated about EVD. This is a reasonable assumption as the outbreak went on for a shorter time, brought about fewer cases and medical care experts had an improved clinical understanding of the ailment. Given these facts about the outbreak of EVD in Sudan in 1979, our model

represented fewer cases due to having more educated susceptibles with respect to medically appropriate interactions with the infected. The knowledge of the general public as well as healthcare workers brought about lower estimated transmission rates.

In the past, public health education has been used to change the epidemic by increasing public understanding of the disease [95, 96, 144, 145]. We modelled the impact of these behavioural changes on an outbreak by considering the two subpopulations and estimating the relevant parameters identified with each independently before examining the interactions between the two groups in our full model. In a full model simulation, the initial proportions of educated or uneducated susceptibles and the timing of behavioural changes play an important role in reducing the extent of the outbreak. In particular, the sooner changes in behaviour happen and the more educated susceptibles that exist, the fewer the cases that result. This model is exceptionally sensitive to various inputs such as transmission rates, recovery rates and death rates as shown in simulation and sensitivity analysis. Our model shows that the severity of future outbreaks depends on the readiness of medical facilities and the particular strain of EVD.

Our conclusions echo the 2014 EVD outbreak in West Africa: the severity of the outbreak is directly related to the level of prior knowledge and education of the general population and the preparedness of healthcare facilities. For example, a higher proportion of people with education leads to far lower incidence levels of EVD. Education in this context involves breaking some of the cultural practices that are believed to contribute essentially to the spread of the infection. The study also identified the timing of behaviour change to be one of the deciding variables in the achievement of a control strategy. Late adherence can lead to the establishment of an infectious disease, which can lead to complications to reduce the burden of disease. Another key takeaway is the requirement for ongoing education in public health. This fact is supported by this work as having a higher percent of educated people brings about a far lower percent of the population getting infected. This was evident in the 2014 outbreak in West Africa, as by the time the public health campaigns were dispatched, the number of incidents had already reached a record level, making it difficult to reduce the epidemic. The simulation and sensitivity results show that the outcome of the epidemic is highly sensitive to various rates. Therefore, the seriousness of the future EVD outbreak is governed by the level of education of the population and the readiness of health care facilities. The ability to deal with huge numbers of hospitalisations because of education response rates, trust in health care systems and well-trained health professionals will contribute significantly to the reduction in the burden of the Ebola disease.

References

- [1] G. Pantaleo, C. Graziosi, A. S. Fauci, The immunopathogenesis of human immunodeficiency virus infection, *New England Journal of Medicine* 328(5) (1993) 327–335.
- [2] AIDSinfo, The stages of HIV infection, 2019. URL: <https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets>, (Date accessed: 11 October 2020).
- [3] E. R. Knowlton, L. M. Lepone, J. Li, G. Rappocciolo, F. J. Jenkins, C. R. Rinaldo, Professional antigen presenting cells in human herpesvirus 8 infection, *Frontiers in Immunology* 3 (2013) 427.
- [4] K. Foreman, Kaposi’s sarcoma: The role of HHV-8 and HIV-1 in pathogenesis, *Expert Reviews in Molecular Medicine* 3(9) (2001) 1–7.
- [5] S. Lenhart, J. T. Workman, *Optimal Control Applied to Biological Models*, CRC Press, Taylor and Francis Group, London, 2007.
- [6] Y. D. Mahnke, J. H. Greenwald, R. DerSimonian, G. Roby, L. R. Antonelli, A. Sher, M. Roederer, I. Sereti, Selective expansion of polyfunctional pathogen-specific CD4+ T cells in HIV-1-infected patients with immune reconstitution inflammatory syndrome, *Blood* 119(13) (2012) 3105–3112.
- [7] T. Doyle, Sudden viral load increase as an indicator of HIV-1 superinfection in HAART-naïve HIV-infected patients, 8th European HIV Drug Resistance Workshop, March 17-19, Sorrento, Italy, 2010.
- [8] World Health Organisation (WHO), Module 1: Overview of HIV infection, 2005. URL: https://www.who.int/diagnostics_laboratory/documents/guidance/pm_module1.pdf, (Date accessed: 11 October 2020).

- [9] World Health Organisation (WHO), Neglected tropical diseases, 2020. URL: https://www.who.int/neglected_diseases/diseases/en/, (Date accessed: 11 October 2020).
- [10] World Health Organization (WHO), Neglected tropical diseases, hidden successes, emerging opportunities, World Health Organization, Geneva, Switzerland, 2009.
- [11] C. M. Morel, Neglected diseases: under-funded research and inadequate health interventions: Can we change this reality?, *EMBO reports* 4(S1) (2003) S35–S38.
- [12] Centers for Disease Control and Prevention (CDC), Neglected tropical diseases, 2020. URL: https://www.cdc.gov/globalhealth/ntd/resources/ntd_factsheet_2020.pdf, (Date accessed: 11 October 2020).
- [13] Celgene Global Health (CGH), Neglected tropical diseases, 2020. URL: <https://www.celgene.com/responsibility/global-health/neglected-tropical-diseases/>, (Date accessed: 11 October 2020).
- [14] S. Uldrick, D. Whitby, Update on KSHV-epidemiology, Kaposi sarcoma pathogenesis, and treatment of Kaposi sarcoma, *Cancer Lett.* 305(2) (2011) 150–162.
- [15] M. C. Cheung, L. Pantanowitz, B. J. Dezube, AIDS-related malignancies: Emerging challenges in the era of highly active antiretroviral therapy, *The Oncologist* 10 (2005) 412–426.
- [16] National Cancer Institute, HIV infection and cancer risk, 2017. URL: <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hiv-fact-sheet>, (Date accessed: 11 October 2020).
- [17] J. L. Ziegler, E. Katongole-Mbidde, Kaposi’s sarcoma in childhood: an analysis of 100 cases from Uganda and relationship to HIV infection, *Int J Cancer* 65(2) (1996) 200–203.
- [18] D. C. Stefan, Patterns of distribution of childhood cancer in Africa, *J Trop Pediatr.* 61(3) (2015) 165–173.
- [19] K. Antman, Y. Chang, Kaposi’s sarcoma, *N Engl J Med* 342 (2000) 1027–1038.
- [20] E. A. Mesri, E. Cesarman, C. Boshoff, Kaposi’s sarcoma herpesvirus/ human herpesvirus-8 (KSHV/HHV8), and the oncogenesis of Kaposi’s sarcoma, *Nature Reviews Cancer* 310(10) (2010) 707–719.

- [21] American Cancer Society, Kaposi's sarcoma, 2018. URL: <http://www.cancer.org/cancer/kaposi-sarcoma.html>, (Date accessed: 11 October 2020).
- [22] Avert, Symptoms and stages of HIV infection, 2020. URL: <https://www.avert.org/about-hiv-aids/symptoms-stages?>, (Date accessed: 11 October 2020).
- [23] HIV.gov, HIV basics., 2017. URL: <https://www.hiv.gov>, (Date accessed: 11 October 2020).
- [24] UNAIDS, Global HIV and AIDS statistics — 2020 fact sheet, 2020. URL: <https://www.unaids.org/en/resources/fact-sheet>, (Date accessed: 11 October 2020).
- [25] A. E. Grulich, Y. Li, A. M. McDonald, P. K. Correll, M. G. Law, J. M. Kaldor, Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination anti-retroviral therapy, *Aids* 15(5) (2001) 629–633.
- [26] S. Franceschi, L. Dal Maso, M. Rickenbach, J. Polesel, B. Hirschel, M. Cavassini, A. Bordoni, L. Elzi, S. Ess, G. Jundt, et al., Kaposi sarcoma incidence in the swiss HIV cohort study before and after highly active antiretroviral therapy, *British journal of cancer* 99(5) (2008) 800–804.
- [27] E. Freeman, A. Semeere, M. Wenger, M. Bwana, F. C. Asirwa, N. Busakhala, E. Oga, E. Jedy-Agba, V. Kwaghe, K. Iregbu, et al., Pitfalls of practicing cancer epidemiology in resource-limited settings: the case of survival and loss to follow-up after a diagnosis of Kaposi's sarcoma in five countries across sub-Saharan Africa, *BMC cancer* 16(1) (2016) 1–7.
- [28] T. B. Campbell, M. Borok, I. E. White, I. Gudza, B. Ndemera, A. Taziwa, A. Weinberg, L. Gwanzura, Relationship of Kaposi sarcoma (KS)–associated herpesvirus viremia and KS disease in Zimbabwe, *Clinical Infectious Diseases* 36(9) (2003) 1144–1151.
- [29] F. Bihl, A. Mosam, L. N. Henry, J. V. Chisholm III, S. Dollard, P. Gumbi, E. Cassol, T. Page, N. Mueller, P. Kiepiela, et al., Kaposi's sarcoma-associated herpesvirus-specific immune reconstitution and antiviral effect of combined HAART/chemotherapy in HIV clade C-infected individuals with Kaposi's sarcoma, *AIDS* 21(10) (2007) 1245–1252.
- [30] S. E. Krown, C. B. Moser, P. MacPhail, R. M. Matining, C. Godfrey, S. R. Caruso, M. C. Hosseinipour, W. Samaneka, M. Nyirenda, N. W. Busakhala, et al., Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings:

- a three-arm, open-label, randomised, non-inferiority trial, *The Lancet* 395 (2020) 1195–207.
- [31] A. Mosam, F. Shaik, T. S. Uldrick, T. Esterhuizen, G. H. Friedland, D. T. Scadden, J. Aboobaker, H. M. Coovadia, A randomized controlled trial of HAART versus HAART and chemotherapy in therapy-naïve patients with HIV-associated Kaposi sarcoma in South Africa, *Journal of Acquired Immune Deficiency Syndromes* 60(2) (2012) 150.
- [32] World Health Organisation (WHO), What's new in treatment monitoring: Viral load and CD4 testing, 2017. URL: <https://www.who.int/hiv/pub/arv/treatment-monitoring-info-2017/en/>, (Date accessed: 11 October 2020).
- [33] T. Glass, L. Myer, M. Lesosky, The role of HIV viral load in mathematical models of HIV transmission and treatment: a review, *BMJ Global Health* 5(1) (2020) e001800.
- [34] C. Shoko, D. Chikobvu, A superiority of viral load over CD4 cell count when predicting mortality in HIV patients on therapy, *BMC Infectious Diseases* 19(1) (2019) 169.
- [35] F. Nani, M. Jin, Dynamics of HIV-1 associated Kaposi sarcoma during HAART therapy, *International Conference on Bioinformatics and Computational Biology* 11 (2011) 783–786.
- [36] F. Nani, M. Jin, Analysis of dynamics of HIV-1 associated kaposi sarcoma during HAART and ACI, *British Journal of Mathematics and Computer Science* 19(1) (2016) 1–22.
- [37] B. Szomolay, E. Lungu, A mathematical model for the treatment of AIDS-related Kaposi's sarcoma, *Journal of Biological Systems* 22 (2014) 495–522.
- [38] S. R. J. Moghadam, N. Omid, S. Bayrami, S. Moghadam, S. J. and SeyedAlinaghi, Ebola viral disease: a review literature, *Asian Pacific Journal of Tropical Biomedicine* 5(4) (2015) 260–267.
- [39] Centers for Disease Control and Prevention (CDC), Outbreaks chronology: Ebola virus disease, 2015. URL: <http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>, (Date accessed: 26 November 2015).
- [40] P. M. Dietz, A. Jambai, J. T. Paweska, Z. Yoti, T. G. Ksaizek, Epidemiology and risk factors for Ebola virus disease in Sierra Leone—23 May 2014 to 31 January 2015, *Clinical Infectious Diseases* 61(11) (2015) 1648–1654.

- [41] K. J. Olival, D. T. Hayman, Filoviruses in bats: current knowledge and future directions, *Viruses* 6(4) (2014) 1759–1788.
- [42] World Health Organization, Ebola virus disease: Fact sheet no. 103, 2015. URL: <http://www.who.int/mediacentre/factsheets/fs103/en/>, (Date accessed: 26 November 2015).
- [43] World Health Organization Ebola Response, Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections, *New England Journal of Medicine* 371(2014) (2014) 1481–1495.
- [44] G. Fitzpatrick, F. Vogt, O. Moi Gbabai, B. Black, M. Santantonio, E. Folkesson, T. Decroo, M. Van Herp, Describing readmissions to an Ebola case management centre (CMC), Sierra Leone, 2014, *Euro surveillance: bulletin Européen sur les maladies transmissibles= European communicable disease bulletin* 19(40) (2014) 20924.
- [45] B. W. Cook, T. A. Cutts, A. M. Nikiforuk, P. G. Poliquin, J. E. Strong, S. S. Theriault, Evaluating environmental persistence and disinfection of the ebola virus makona variant, *Viruses* 7(4) (2015) 1975–1986.
- [46] O. Olu, B. Kargbo, S. Kamara, A. H. Wurie, J. Amone, L. Ganda, B. Ntsama, A. Poy, F. Kuti-George, E. Engedashet, N. Worku, Epidemiology of Ebola virus disease transmission among health care workers in Sierra Leone, May to December 2014: a retrospective descriptive study, *BMC Infectious Diseases* 15(1) (2015) 1.
- [47] J. Brainard, L. Hooper, K. Pond, K. Edmunds, P. R. Hunter, Risk factors for transmission of eEbola or Marburg virus disease: a systematic review and meta-analysis, *International Journal of Epidemiology* 45(1) (2016) 102–116.
- [48] M. I. Meltzer, C. Y. Atkins, S. Santibanez, B. Knust, B. W. Petersen, E. D. Ervin, S. Nichol, I. Damon, M. L. Washington, Estimating the future number of cases in the Ebola epidemic—Eiberia and Sierra Seone, 2014–2015, *MMWR Surveill Summ* 63(suppl 3) (2014) 1–14.
- [49] World Health Organization, Statement on the 1st meeting of the ihr emergency committee on the 2014 ebola outbreak in west africa, 2014. URL: <http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/>, (Date accessed: 26 November 2015).

- [50] G. Chowell, L. Simonsen, C. Viboud, Y. Kuang, Is West Africa approaching a catastrophic phase or is the 2014 ebola epidemic slowing down? different models yield different answers for Liberia, *PLoS Currents Outbreaks* 6 (2014) 1.
- [51] D. Wodarz, *Killer Cell Dynamics Mathematical and Computational Approaches to Immunology*, Springer, California, 2005.
- [52] S. McComb, A. Thiriot, L. Krishnan, F. Stark, Introduction to the immune systems, *Methods in Molecular Biology* 1061 (2013) 0.
- [53] M. A. Nowak, R. M. May, Mathematical biology of HIV infections: antigenic variation and diversity threshold, *Mathematical biosciences* 106(1) (1991) 1–21.
- [54] J. N. Weber, R. A. Weiss, HIV infection, *Scientific American* 259(4) (1988) 100–109.
- [55] R. V. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of $CD4^+$ T-cells, *Mathematical Biosciences* 165 (2000) 27–39.
- [56] A. S. Perelson, P. W. Nelson, Mathematical analysis of HIV-1: Dynamics in vivo, *Society for Industrial and Applied Mathematics* 41 (1999) 3–44.
- [57] C. B. Wilen, J. C. Tilton, R. W. Doms, HIV: Cell binding and entry, *Cold Spring Harb Perspect Med* 2(8 (2012) a006866.
- [58] P. Mohammadi, S. Desfarges, I. Bartha, B. Joos, N. Zangger, M. Munoz, H. F. Günthard, N. Beerenwinkel, A. Telenti, A. Ciuffi, 24 hours in the life of HIV-1 in a T cell line, *PLoS Pathog* 9(1) (2013) e1003161.
- [59] A. Engelman, P. Cherepanov, The structural biology of HIV-1: mechanistic and therapeutic insights, *Nat Rev Microbiol.* 10(4) (2013) 279–290.
- [60] H. Jonckheere, J. Anne, E. D. Clercq, The HIV-1 reverse transcription (RT) process as target for RT inhibitors, *Med Res Rev* 20(2 (2000) 129–154.
- [61] Avert, What does undetectable mean?, 2020. URL: <https://www.avert.org/living-with-hiv/antiretroviral-treatment/what-does-undetectable-mean>, (Date accessed: 11 October 2020).
- [62] A. J. McMichael, P. Borrow, G. D. Tomaras, N. Goonetilleke, B. F. Haynes, The immune response during acute HIV-1 infection: clues for vaccine development, *Nature Reviews Immunology* 10(1) (2010) 11–23.

- [63] Y. Chang, E. Cesarman, M. S. Pessin, F. Lee, J. Culpepper, D. M. Knowles, P. S. Moore, Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma, *Science* 266(5192) (1994) 1865–1869.
- [64] P. Purushothaman, T. Uppal, S. C. Verma, Molecular biology of KSHV lytic reactivation, *Viruses* 7 (2015) 116–153.
- [65] L. Butler, T. Neilands, A. Mosam, S. Mzolo, J. Martin, A population-based study of how children are exposed to saliva in KwaZulu-Natal Province, South Africa: implications for the spread of saliva-borne pathogens to children, *Tropical Medicine & International Health* 15 (2010) 442–453.
- [66] C. Boshoff, Y. Chang, Kaposi's sarcoma-associated herpesvirus: A new DNA tumor virus, *Annual Review of Medicine* 52 (2001) 453–470.
- [67] S. Gantt, C. Casper, Professional antigen presenting cells in human herpesvirus 8 infection, *Current Opinion in Infectious Diseases* 24(4) (2011) 295–301.
- [68] F. Ye, X. Lei, S. Gao, Mechanisms of Kaposi's sarcoma-associated herpesvirus latency and reactivation, *Advances in Virology* 2011 (2011) 19.
- [69] A. Chiereghin, P. Barozzi, E. Petrisli, G. Piccirilli, L. Gabrielli, G. Riva, L. Potenza, G. Cappelli, N. De Ruvo, I. Libri, et al., Multicenter prospective study for laboratory diagnosis of HHV8 infection in solid organ donors and transplant recipients and evaluation of the clinical impact after transplantation, *Transplantation* 101(8) (2017) 1935–1944.
- [70] D. Canning, Priority setting and the 'neglected' tropical diseases, *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100(6) (2006) 499–504.
- [71] World Health Organization, Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults, World Health Organization, Switzerland, 2014.
- [72] S. Mannheimer, G. Friedland, J. Matts, C. Child, M. Chesney, et al., The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus—infected persons in clinical trials, *Clinical infectious diseases* 34(8) (2002) 1115–1121.
- [73] R. C. Baron, J. B. McCormick, O. A. Zubeir, Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread, *Bulletin of the World Health Organization* 6(61) (1993) 97.

-
- [74] WHO, Report of a who/international study team. (1978). ebola haemorrhagic fever in sudan, 1976, Bulletin of the World Health Organization 56(2) (1978) 247.
- [75] E. Lungu, T. J. Massaro, E. Ndelwa, N. Ainea, S. Chibaya, N. J. Malunguza, Mathematical modelling of the HIV Kaposi's sarcoma coinfection dynamics in areas of high HIV prevalence, Computational and Mathematical Methods in Medicine 2013 (2013) 12.
- [76] A. Mosam, H. Carrara, F. Shaik, T. Uldrick, A. Berkman, J. Aboobaker, H. Coovadia, Increasing incidence of Kaposi's sarcoma in black South Africans in Kwazulu-Natal, South Africa (1983–2006), International Journal of STD and AIDS 20 (2009) 553–556.
- [77] A. Facciola, E. Venanzi Rullo, M. Ceccarelli, F. D'aleo, M. Di Rosa, M. Pinzone, F. Condorelli, G. Visalli, I. Picerno, R. Fisichella, et al., Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals, European Review for Medical and Pharmacological Sciences 21(24) (2017) 5868–5879.
- [78] S. M. Fast, S. Mekaru, J. S. Brownstein, N. Postlethwaite, T. A. and Markuzon, The role of social mobilization in controlling Ebola virus in Lofa county, liberia, PLOS Currents Outbreaks 7 (2015) 1.
- [79] M. Shen, Y. Xiao, L. Rong, Modeling the effect of comprehensive interventions on ebola virus transmission, Scientific reports 5 (2015) 1.
- [80] J. J. Li, Y. Q. Huang, C. J. Cockerell, A. E. Friedman-Kien, Localization of human herpes-like virus type 8 in vascular endothelial cells and perivascular spindle-shaped cells of Kaposi's sarcoma lesions by in situ hybridization, The American Journal of Pathology 148(6) (1996) 1996.
- [81] Y. O. Huang and J. J. Li and W. Zhang *et al.*, Transcription of human herpesvirus-like agent (HHV-8) in Kaposi's sarcoma, The Journal of Clinical Investigation 97(12) (1996) 2803–2806.
- [82] K. E. Foreman, P. E. Bacon, E. D. Hsi, B. J. Nickoloff, In situ polymerase chain reaction-based localization studies support role of human herpesvirus-8 as the cause of two aids-related neoplasms: Kaposi's sarcoma and body cavity lymphoma, The Journal of Clinical Investigation 99(12) (1997) 2971–2978.
- [83] D. A. Davis, R. W. Humphrey, F. M. Newcomb, T. R. O'Brien, J. J. Goedert, S. E. Straus, R. Yarchoan, Detection of serum antibodies to a Kaposi's

- sarcoma—associated herpesvirus-specific peptide, *Journal of Infectious Diseases* 175(5) (1997) 1071–1079.
- [84] M. Kennedy, K. Cooper, D. Howells, S. Picton, S. Biddolph, S. Lucas, J. McGee, J. O’leary, Identification of HHV8 in early Kaposi’s sarcoma: implications for Kaposi’s sarcoma pathogenesis, *Molecular Pathology* 51(1) (1998) 14.
- [85] W. Harrington Jr, L. Sieczkowski, C. Sosa, S. Chan-a Sue, J. P. Cai, L. Cabral, C. Wood, Activation of HHV-8 by HIV-1 tat, *The Lancet* 309(9054) (1997) 774–775.
- [86] V. Fiorelli, G. Barillari, E. Toschi, C. Sgadari, P. Monini, M. Stürzl, B. Ensoli, Ifn- γ induces endothelial cells to proliferate and to invade the extracellular matrix in response to the HIV-1 tat protein: implications for AIDS-Kaposi’s sarcoma pathogenesis, *The Journal of Immunology* 162(2) (1999) 1165–1170.
- [87] P. Monini, S. Colombini, M. Sturzl, D. Goletti, A. Cafaro, C. Sgadari, S. Butto, M. Franco, P. Leone, S. Fais, et al., Reactivation and persistence of human herpesvirus-8 infection in B cells and monocytes by Th-1 cytokines increased in Kaposi’s sarcoma, *Blood, The Journal of the American Society of Hematology* 93(12) (1999) 4044–4058.
- [88] J. Chang, R. Renne, D. Dittmer, D. Ganem, Inflammatory cytokines and the reactivation of Kaposi’s sarcoma-associated herpesvirus lytic replication, *Virology* 266(1) (2000) 17–25.
- [89] Y. Aoki, G. Tosato, HIV-1 tat enhances kaposi sarcoma-associated herpesvirus (KSHV) infectivity, *Blood* 104(3) (2004) 810–814.
- [90] J. Estill, C. Aubriere, M. Egger, L. Johnson, R. Wood, D. Garone, T. Gsponer, G. Wandeler, A. Boulle, M.-A. Davies, et al., Viral load monitoring of antiretroviral therapy, cohort viral load and HIV transmission in Southern Africa: a mathematical modelling analysis, *AIDS (London, England)* 26(11) (2012) 1403–1413.
- [91] J. Estill, M. Egger, L. F. Johnson, T. Gsponer, G. Wandeler, M.-A. Davies, A. Boulle, R. Wood, D. Garone, J. S. Stringer, et al., Monitoring of antiretroviral therapy and mortality in HIV programmes in Malawi, South Africa and Zambia: mathematical modelling study, *PloS one* 8(2) (2013) e57611.
- [92] L. Salazar-Vizcaya, O. Keiser, K. Technau, M.-A. Davies, A. D. Haas, N. Blaser, V. Cox, B. Eley, H. Rabie, H. Moultrie, et al., Viral load versus CD4 monitoring and 5-year outcomes of ART in HIV-positive children in Southern Africa: cohort-based modelling study, *AIDS (London, England)* 28(16) (2014) 2451–2460.

-
- [93] M. Lesosky, T. Glass, E. Mukonda, N.-Y. Hsiao, E. J. Abrams, L. Myer, Optimal timing of viral load monitoring during pregnancy to predict viraemia at delivery in HIV-infected women initiating ART in South Africa: a simulation study, *Journal of the International AIDS Society* 20 (2017) e25000.
- [94] K. Perica, J. Varela, M. Oelke, J. Schneck, Adoptive t cell immunotherapy for cancer, *Rambam Maimonides Medical Journal* 6(1) (2015) e0004.
- [95] C. Bhunu, S. Mushayabasa, H. Kojouharov, J. Tchuente, Mathematical analysis of an HIV/AIDS model: impact of educational programs and abstinence in Sub-Saharan Africa, *Journal of Mathematical Modelling and Algorithms* 10(1) (2010) 31–55.
- [96] S. Del Valle, H. Hethcote, J. M. Hyman, C. Castillo-Chavez, Effects of behavioral changes in a smallpox attack model, *Mathematical Biosciences* 195(2) (2005) 228–251.
- [97] Z. Mukandavire, W. Garira, J. M. Tchuente, Modelling effects of public health educational campaigns on HIV/AIDS transmission dynamics, *Applied Mathematical Modelling* 33(4) (2009) 2084–2095.
- [98] H. Xiang, N. N. Song, H. F. Huo, Modelling effects of public health educational campaigns on drinking dynamics, *Journal of Biological Dynamics* 10(1) (2016) 164–178.
- [99] S. Mushayabasa, C. P. Bhunu, Assessing the impact of educational campaigns on controlling HCV among women in prison settings, *Communications in Nonlinear Science and Numerical Simulation* 17(4) (2012) 1714–1724.
- [100] L. Perko, *Differential Equations and Dynamical Systems* 3rd ed., Springer-Verlag, New York, 2001.
- [101] O. Diekmann, J. A. P. Heesterbeek, J. A. J. Metz, On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *Journal of Mathematical Biology* 28(4) (1990) 365–382.
- [102] F. Brauer, C. Castillo-Chavez, *Mathematical models in population biology and epidemiology*, Springer, 2012.
- [103] J. J. Anagnost, C. A. Desoer, An elementary proof of the Routh-Hurwitz stability criterion, *Circuits, systems and signal processing* 10(1) (1991) 101–114.

-
- [104] C. Castillo-Chavez, Z. Feng, W. Huang, On the computation of R_0 and its role in global stability, *Institute for Mathematics and Its Applications* 125 (2002) 229.
- [105] S. M. Blower, H. Dowlatabadi, Sensitivity and uncertainty analysis of complex models of disease transmission: An HIV model, as an example, *International Statistical Review / Revue Internationale de Statistique* 62(2) (1994) 229–243.
- [106] B. Gomero, Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem, Master’s thesis, University of Tennessee, Knoxville, 2012.
- [107] F. H. Clarke, *Optimization and nonsmooth analysis*, Siam, New York, 1990.
- [108] M. I. Kamien, N. L. Schwartz, *Dynamic optimization: the calculus of variations and optimal control in economics and management*, Courier Corporation, New York, 2012.
- [109] K. R. Fister, S. Lenhart, J. S. McNally, Optimizing chemotherapy in an HIV model, *Electronic Journal of Differential Equations* 1998 (1998) 12.
- [110] G. B. West, J. H. Brown, B. J. Enquist, A general model for ontogenetic growth, *Nature* 413 (2001) 628–631.
- [111] C. Guiot, P. P. Delsanto, A. Carpinteri, N. Pugno, Y. Mansury, T. S. Deisboeck, The dynamic evolution of the power exponent in a universal growth model of tumors, *Journal of Theoretical Biology* 240 (2006) 459–463.
- [112] V. Hadinoto, M. Shapiro, C. C. Sun, D. A. Thorley-Lawson, The dynamics of EBV shedding implicate a central role for epithelial cells in amplifying viral output, *PLoS Pathog* 5(7) (2009) e1000496.
- [113] S. H. Bajaria, D. Kirschner, *CTL Action During HIV-1 Is Determined Via Interactions With Multiple Cell Types*, World Scientific, Singapore and New Jersey, 2005.
- [114] R. D. Boer, R. M. Ribeiro, A. S. Perelson, Current estimates for HIV-1 production imply rapid viral clearance in lymphoid tissues, *PLoS Comput Biol* 6(9) (2010) e1000906.
- [115] Y. Louzoun, C. Xue, G. B. Lesinski, A. Friedman, A mathematical model for pancreatic cancer growth and treatments, *Journal of Theoretical Biology* 351 (2014) 74–82.

-
- [116] A. Gumel, X.-W. Zhang, P. Shivakumar, M. Garba, B. Sahai, A new mathematical model for assessing therapeutic strategies for HIV infection, *Journal of Theoretical Medicine* 4(2) (2002) 147–155.
- [117] N. Stilianakis, D. Schenzle, On the intra-host dynamics of HIV-1 infections, *Mathematical Biosciences* 199(2006) (2005) 1–25.
- [118] G. T. Huynh, F. R. Adler, Mathematical modelling the age dependence of Epstein-Barr virus associated infectious mononucleosis, *Mathematical Medicine and Biology : a Journal of the IMA* 29(3) (2012) 245–61.
- [119] M. Shapiro, K. Duca, K. Lee, E. Delgado-Eckert, J. Hawkins, A. Jarrah, R. Laubenbacher, N. Polys, V. Hadinoto, D. Thorley-Lawson, A virtual look at Epstein–Barr virus infection: Simulation mechanism, *Journal of Theoretical Biology* 252(4) (2008) 633–648.
- [120] A. R. Mclean, C. A. Michie, In vivo estimates of division and death rates of human T lymphocytes, *Immunology* 92 (1995) 3707–3711.
- [121] R. Weston, B. Marett, HIV infection pathology and disease progression, *Clinical Pharmacist* 1 (2009) 387–392.
- [122] C. Foglieni, S. Scabini, D. Belloni, F. Broccolo, P. Lusso, M. Malnati, E. Ferrero, Productive infection of HUVEC by HHV-8 is associated with changes compatible with angiogenic transformation, *European Journal of Histochemistry* 49(3) (2005) 273–284.
- [123] R. D. Hockett, J. Michael Kilby, C. A. Derdeyn, M. S. Saag, M. Sillers, K. Squires, S. Chiz, M. A. Nowak, G. M. Shaw, R. P. Bucy, Constant mean viral copy number per infected cell in tissues regardless of high, low, or undetectable plasma HIV RNA, *Journal of Experimental Medicine* 189(10) (1999) 1545–1554.
- [124] S. Marino, I. B. Hogue, C. J. Ray, D. E. Kirschner, A methodology for performing global uncertainty and sensitivity analysis in systems biology, *Journal of Theoretical Biology* 254(1) (2008) 198–196.
- [125] E. C. Fieller, H. O. Hartley, E. S. Pearson, Tests for rank correlation coefficients. I, *Biometrika* 44 (1957) 480–481.
- [126] Y. Benjamini, Y. Hochberg, Controlling the false discovery rate: A practical and powerful approach to multiple testing, *Journal of the Royal Statistical Society. Series B (Methodological)* 57(1) (1995) 289–300.

- [127] B. K. Cho, V. P. Rao, Q. Ge, H. N. Eisen, J. Chen, Homeostasis-stimulated proliferation drives naive T cells to differentiate directly into memory T cells, *The Journal of experimental medicine* 192(4) (2000) 549–556.
- [128] B. J. Turner, Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients, *The Journal of Infectious Diseases* 185(2) (2002) S143–51.
- [129] World Health Organisation, Adherence to longterm therapies: Evidence for action, 2010. URL: http://www.who.int/chp/knowledge/publications/adherence_report/en/, (Date accessed: 11 October 2020).
- [130] J. B Nachega, V. C Marconi, G. U van Zyl, E. M Gardner, W. Preiser, S. Y Hong, E. J Mills, R. Gross, HIV treatment adherence, drug resistance, virologic failure: Evolving concepts, *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders)* 11(2) (2011) 167–174.
- [131] A. Perelson, Modelling viral and immune system dynamics, *Nature Reviews* 2 (2002) 28–36.
- [132] J. Holash, S. Davis, N. Papadopoulos, S. D. Croll, L. Ho, M. Russell, P. Boland, R. Leidich, D. Hylton, E. Burova, et al., VEGF-Trap: A VEGF blocker with potent antitumor effects, *Proceedings of the National Academy of Sciences* 99(17) (2002) 11393–11398.
- [133] D. Kirschner, S. Lenhart, S. Serbin, Optimal control of the chemotherapy of HIV, *J. Math. Biol.* 35 (1997) 775–792.
- [134] L. G. de Pillis, W. Gu, K. R. Fister, T. Head, K. Maples, A. Murugan, T. Neal, K. Yoshida, Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, *Mathematical Biosciences* 209(1) (2007) 292–315.
- [135] WHO, Consolidated delines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, World Health Organisation, Switzerland, 2016.
- [136] B. Levy, E. Christina, O. Gaoue, R. Kaondera-Shava, M. Kgosimore, S. Lenhart, B. Lephodisa, E. Lungu, T. Marijani, F. Nyabadza, Modeling the role of public health education in Ebola virus disease outbreaks in Sudan, *Infectious Disease Modelling* 2(3) (2017) 323–340.

- [137] M. D. McKay, R. J. Beckman, W. J. Conover, A comparison of three methods for selecting values of input variables in the analysis of output from a computer code, *Technometrics* 21 (1979) 239–245.
- [138] J. T. Macklin, An investigation of the properties of double radio sources using the spearman partial rank correlation coefficient, *Monthly Notices of the Royal Astronomical Society* 199(4) (1982) 1119–1136.
- [139] South Sudan National Bureau of Statistics, Population estimate for Maridi, 2011. URL: https://www.citypopulation.de/en/southsudan/admin/western_equatoria/9107__maridi/, (Date accessed: 26 November 2015).
- [140] South Sudan National Bureau of Statistics, Population estimate for Yambio, 2011. URL: <http://www.geonames.org/363656/yambio.html>, (Date accessed: 26 November 2015).
- [141] South Sudan National Bureau of Statistics, Population estimate for Nzara, 2014. URL: <http://www.citypopulation.de/php/southsudan-admin.php?adm2id=9103>, (Date accessed: 26 November 2015).
- [142] A. J. Magill, D. R. Hill, T. Solomon, E. T. Ryan, *Hunter’s Tropical Medicine and Emerging Infectious Disease* (9th ed.), Saunders, New York, 2013.
- [143] S. K. Singh, D. E. Ruzek, *Viral Hemorrhagic Fevers*, CRC Press, New York, 2013.
- [144] H. Joshi, S. Lenhart, K. Albright, K. Gipson, Modeling the effect of information campaigns on the HIV epidemic in Uganda, *Mathematical Biosciences and Engineering: MBE* 5(4) (2008) 757–770.
- [145] H. Joshi, S. Lenhart, S. Hota, F. Agosto, Optimal control of an SIR model with changing behavior through an education campaign, *Electronic Journal of Differential Equations* 2015(50) (2015) 1–14.

Appendix

A.1 Matrix $\mathbf{M}$

Entries from the following matrix $\mathbf{M}$ from Section 4.2 is used throughout this paper to abbreviate other matrices:

$$\mathbf{M} = \begin{pmatrix} M_{11} & 0 & 0 & 0 & 0 & 0 & M_{17} \\ M_{21} & M_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & M_{33} & 0 & 0 & M_{36} & 0 \\ 0 & 0 & 0 & M_{44} & 0 & M_{46} & 0 \\ 0 & 0 & 0 & 0 & M_{55} & 0 & M_{57} \\ 0 & 0 & 0 & M_{64} & 0 & M_{66} & 0 \\ M_{71} & 0 & 0 & 0 & 0 & 0 & M_{77} \end{pmatrix},$$

where $M_{11} = -\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}\right)$, $M_{17} = r_{x_1}$, $M_{21} = \alpha$, $M_{22} = -\kappa_3 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}$, $M_{33} = -(\mu_{x_3} - r_{x_3})$, $M_{36} = r_{x_3} \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})}$, $M_{44} = -\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4}\right)$, $M_{46} = r_{x_4}$, $M_{55} = -(\mu_{x_5} - r_{x_5})$, $M_{57} = r_{x_5} \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})}$, $M_{64} = N_{x_6} \mu_{x_4}$, $M_{66} = -\mu_{x_6}$, $M_{71} = N_{x_7} \mu_{x_1} (1 + \delta)$, $M_{77} = -\mu_{x_7}$.

A.2 Coefficients of the Characteristic Polynomial

These results are for the coefficients of the characteristic polynomial of the $\gamma = \beta = 1$ case for weak viral source model and all cases for the strong viral source model.

$$\begin{aligned}
a_1 &= \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] + \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_5} - r_{x_5})} + \mu_{x_4} \right) + \mu_{x_6} \right] > 0 \\
a_2 &= \left\{ \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) \right] + \left[\frac{\mu_{x_6}}{(\mu_{x_5} - r_{x_5}) - r_{x_3}} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_5} - r_{x_5}) - r_{x_3}) \right] \right\} \\
&\times (1 - \mathcal{R}_{0x_i}) + \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_5} - r_{x_5})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
&> \left\{ \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) \right] + \left[\frac{\mu_{x_6}}{(\mu_{x_5} - r_{x_5})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_5} - r_{x_5})) \right] \right\} \times (1 - \mathcal{R}_{0x_i}) > 0, \\
a_3 &= \left\{ \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) \right] \right. \\
&+ \left. \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \right\} (1 - \mathcal{R}_{0x_i}) > 0, \\
a_4 &= \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) \frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) (1 - \mathcal{R}_{0x_i})^2 > 0.
\end{aligned}$$

since all parameters are positive.

A.3 Proof of Local Stability when $\gamma = \beta = 1$ for the Weak Viral Source Model

We are going to show that $a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$. Hence, we have

$$\begin{aligned}
a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 &= \\
&\left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) (1 - \mathcal{R}_{0x_7}) \right] \\
&\times \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) (1 - \mathcal{R}_{0x_7}) \right] \\
&+ \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
&\times \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
&+ \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
&\times \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) (1 - \mathcal{R}_{0x_7}) \right]
\end{aligned}$$

$$\begin{aligned}
& + \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \right] \\
& \times \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
& + \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
& \times \left[\frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \right] \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \\
& + \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \\
& \times \left[\frac{\mu_{x_7}}{(\mu_{x_5} - r_{x_5})} (\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) (1 - \mathcal{R}_{0x_7}) \right] \\
& \times \left\{ \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \right. \\
& \left. - 2 \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \right\}
\end{aligned}$$

It suffices to show that

$$\begin{aligned}
& \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \\
& - 2 \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) > 0
\end{aligned}$$

Now,

$$\begin{aligned}
& \left[\left(\mu_{x_1} + \kappa_1 \frac{s_{x_5}}{(\mu_{x_5} - r_{x_5})} \right) + \mu_{x_7} \right] \left[\left(\kappa_4 \frac{s_{x_3}}{(\mu_{x_3} - r_{x_3})} + \mu_{x_4} \right) + \mu_{x_6} \right] \\
& - 2 \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \\
& = \frac{1}{(\mu_{x_5} - r_{x_5})} \left[(\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5}) + \mu_{x_7} (\mu_{x_5} - r_{x_5}) \right] \\
& \times \frac{1}{(\mu_{x_3} - r_{x_3})} \left[(\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \right] \\
& - 2 \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \\
& = \frac{1}{(\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5})} \left[\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5} + \mu_{x_7} (\mu_{x_5} - r_{x_5}) \right] \\
& \times [\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3}) + \mu_{x_6} (\mu_{x_3} - r_{x_3})] \\
& - 2 \frac{\mu_{x_6}}{(\mu_{x_3} - r_{x_3})} (\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3})) (1 - \mathcal{R}_{0x_6}) \\
& = \frac{1}{(\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5})} \left[\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5} + \mu_{x_7} (\mu_{x_5} - r_{x_5}) \right] \\
& \times [\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3}) + \mu_{x_6} (\mu_{x_3} - r_{x_3})]
\end{aligned}$$

$$\begin{aligned}
& - \frac{2}{(\mu_{x_3} - r_{x_3})(\mu_{x_5} - r_{x_5})} (\kappa_4 s_{x_3} (\mu_{x_5} - r_{x_5}) \mu_{x_6} + \mu_{x_4} (\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5}) \mu_{x_6}) (1 - \mathcal{R}_{0x_6}) \\
& = [\mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_1 s_{x_5} + \mu_{x_7} (\mu_{x_5} - r_{x_5})] [\kappa_4 s_{x_3} + \mu_{x_4} (\mu_{x_3} - r_{x_3}) + \mu_{x_6} (\mu_{x_3} - r_{x_3})] \\
& - 2(\kappa_4 s_{x_3} (\mu_{x_5} - r_{x_5}) \mu_{x_6} + \mu_{x_4} (\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5}) \mu_{x_6}) (1 - \mathcal{R}_{0x_6}) \\
& = \kappa_4 s_{x_3} \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_4 s_{x_3} \kappa_1 s_{x_5} \\
& + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \kappa_1 s_{x_5} + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \kappa_1 s_{x_5} + \kappa_4 s_{x_3} \mu_{x_7} (\mu_{x_5} - r_{x_5}) + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \mu_{x_7} (\mu_{x_5} - r_{x_5}) \\
& + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \mu_{x_7} (\mu_{x_5} - r_{x_5}) - (2\kappa_4 s_{x_3} (\mu_{x_5} - r_{x_5}) \mu_{x_6} + 2\mu_{x_4} (\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5}) \mu_{x_6}) (1 - \mathcal{R}_{0x_6})
\end{aligned}$$

We can show that for $\mathcal{R}_{0x_6} < 1$ the following holds

$$\begin{aligned}
& \kappa_4 s_{x_3} \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \mu_{x_1} (\mu_{x_5} - r_{x_5}) + \kappa_4 s_{x_3} \kappa_1 s_{x_5} \\
& + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \kappa_1 s_{x_5} + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \kappa_1 s_{x_5} + \kappa_4 s_{x_3} \mu_{x_7} (\mu_{x_5} - r_{x_5}) + \mu_{x_4} (\mu_{x_3} - r_{x_3}) \mu_{x_7} (\mu_{x_5} - r_{x_5}) \\
& + \mu_{x_6} (\mu_{x_3} - r_{x_3}) \mu_{x_7} (\mu_{x_5} - r_{x_5}) - 2\kappa_4 s_{x_3} (\mu_{x_5} - r_{x_5}) \mu_{x_6} - 2\mu_{x_4} (\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5}) \mu_{x_6} > 0 \\
& \implies \kappa_4 s_{x_3} (\mu_{x_5} - r_{x_5}) (\mu_{x_1} - 2\mu_{x_6}) + \mu_{x_4} (\mu_{x_3} - r_{x_3}) (\mu_{x_5} - r_{x_5}) (\mu_{x_1} - 2\mu_{x_6}) > 0 \\
& \implies \mu_{x_1} - 2\mu_{x_6} > 0 \implies \frac{\mu_{x_1}}{\mu_{x_6}} > 2
\end{aligned}$$

Hence, $a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$ on condition that $\frac{\mu_{x_1}}{\mu_{x_6}} > 2$.

A.4 Proof for uniqueness of optimality system

Theorem A.1. *For $t \in [0, t_f]$, the bounded solutions to the optimality system is unique.*

Proof. We suppose $(x_1, x_2, \dots, x_7, \lambda_1, \lambda_2, \dots, \lambda_7)$ and $(\bar{x}_1, \bar{x}_2, \dots, \bar{x}_7, \bar{\lambda}_1, \bar{\lambda}_2, \dots, \bar{\lambda}_7)$ are two distinct solutions to the optimality system. Let $x_1 = e^{\lambda t} p_1$, $x_2 = e^{\lambda t} p_2$, $\dots$, $x_7 = e^{\lambda t} p_7$, $\lambda_1 = e^{-\lambda t} q_1$, $\lambda_2 = e^{-\lambda t} q_2$, $\dots$, $\lambda_7 = e^{-\lambda t} q_7$ and $\bar{x}_1 = e^{\lambda t} \bar{p}_1$, $\bar{x}_2 = e^{\lambda t} \bar{p}_2$, $\dots$, $\bar{x}_7 = e^{\lambda t} \bar{p}_7$, $\bar{\lambda}_1 = e^{-\lambda t} \bar{q}_1$, $\bar{\lambda}_2 = e^{-\lambda t} \bar{q}_2$, $\dots$, $\bar{\lambda}_7 = e^{-\lambda t} \bar{q}_7$, where $\lambda > 0$ is to be chosen. Further we let

$$\zeta_r^* = \max \left\{ 0, \min \left(\frac{r_{x_4} p_6 q_4 e^{\lambda t (\beta - 1)}}{2A_3}, 1 \right) \right\}$$

$$\zeta_p^* = \max \left\{ 0, \min \left(\frac{N_{x_6} \mu_{x_4} p_4 q_6}{2A_4}, 1 \right) \right\}$$

$$\eta_c^* = \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\alpha p_1 q_2 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) \right), 1 \right) \right\}$$

and

$$\bar{\zeta}_r^* = \max \left\{ 0, \min \left(\frac{r_{x_4} \bar{p}_6 \bar{q}_4 e^{\lambda t(\beta-1)}}{2A_3}, 1 \right) \right\}$$

$$\bar{\zeta}_p^* = \max \left\{ 0, \min \left(\frac{N_{x_6} \mu_{x_4} \bar{p}_4 \bar{q}_6}{2A_4}, 1 \right) \right\}$$

$$\bar{\eta}_c^* = \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\alpha \bar{p}_1 \bar{q}_2 \left(1 - \frac{e^{\lambda t} \bar{p}_2}{\omega} \right) \right), 1 \right) \right\}$$

Now we substitute $x_1 = e^{\lambda t} p_1$ into the first ODE of (5.10) and we get

$$\begin{aligned} e^{\lambda t} (\dot{p}_1 + \lambda p_1) &= r_{x_1} e^{\gamma \lambda t} p_7 - \mu_{x_1} e^{\lambda t} p_1 - \kappa_1 p_1 p_5 e^{2\lambda t} \\ \dot{p}_1 + \lambda p_1 &= r_{x_1} e^{\lambda t(\gamma-1)} p_7 - \mu_{x_1} p_1 - \kappa_1 p_1 p_5 e^{\lambda t}. \end{aligned}$$

Similarly, for $x_2 = e^{\lambda t} p_2$, $x_3 = e^{\lambda t} p_3 \dots$, $x_7 = e^{\lambda t} p_7$, $\lambda_1 = e^{-\lambda t} q_1$, $\lambda_2 = e^{-\lambda t} q_2$, $\dots$, $\lambda_7 = e^{-\lambda t} q_7$ we obtain

$$\begin{aligned} \dot{p}_2 + \lambda p_2 &= \left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\alpha p_1 q_2 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) \right), 1 \right) \right\} \alpha p_1 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) - \kappa_3 p_2 p_5 e^{\lambda t}, \right. \\ \dot{p}_3 + \lambda p_3 &= s_{x_3} e^{-\lambda t} + r_{x_3} p_3 p_6 e^{\beta \lambda t} - \mu_{x_3} p_3, \\ \dot{p}_4 + \lambda p_4 &= \left(1 - \max \left\{ 0, \min \left(\frac{r_{x_4} p_6 q_4 e^{\lambda t(\beta-1)}}{2A_3}, 1 \right) \right\} r_{x_4} e^{\lambda t(\beta-1)} p_6 - \kappa_4 p_3 p_4 e^{\lambda t} - \mu_{x_4} p_4, \right. \\ \dot{p}_5 + \lambda p_5 &= s_{x_5} e^{-\lambda t} + r_{x_5} p_5 p_7 e^{\gamma \lambda t} - \mu_{x_5} p_5, \\ \dot{p}_6 + \lambda p_6 &= \left(1 - \max \left\{ 0, \min \left(\frac{N_{x_6} \mu_{x_4} p_4 q_6}{2A_4}, 1 \right) \right\} \right) N_{x_6} \mu_{x_4} p_4 - \mu_{x_6} p_6, \\ \dot{p}_7 + \lambda p_7 &= N_{x_7} \mu_{x_1} p_1 (1 + \delta e^{\beta \lambda t} p_6) - \mu_{x_7} p_7, \\ -\dot{q}_1 + \lambda q_1 &= q_1 (\mu_{x_1} + \kappa_1 e^{\lambda t} p_5) - q_7 N_{x_7} \mu_{x_1} (1 + \delta e^{\beta \lambda t} p_6) \\ &\quad - q_2 \alpha \left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\alpha p_1 q_2 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) \right), 1 \right) \right\} \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right), \right. \\ -\dot{q}_2 + \lambda q_2 &= -q_2 e^{\lambda t} \left[\left(1 - \max \left\{ 0, \min \left(\frac{1}{2A_5} \left(\alpha p_1 q_2 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) \right), 1 \right) \right\} \right) \alpha \frac{p_1}{\omega} + \kappa_3 p_5 \right] + A_2 e^{\lambda t}, \\ -\dot{q}_3 + \lambda q_3 &= -q_4 \kappa_4 e^{\lambda t} p_4 + q_3 (r_{x_3} e^{\beta \lambda t} p_6 - \mu_{x_3}), \\ -\dot{q}_4 + \lambda q_4 &= -q_4 (\kappa_4 e^{\lambda t} p_3 + \mu_{x_4}) + q_6 \left(1 - \max \left\{ 0, \min \left(\frac{N_{x_6} \mu_{x_4} p_4 q_6}{2A_4}, 1 \right) \right\} \right) N_{x_6} \mu_{x_4} + A_1 e^{\lambda t}, \end{aligned}$$

$$\begin{aligned}
-\dot{q}_5 + \lambda q_5 &= -q_1 \kappa_1 e^{\lambda t} p_1 - q_2 \kappa_3 e^{\lambda t} p_2 + q_5 (r_{x_5} e^{\gamma \lambda t} p_7 - \mu_{x_5}), \\
-\dot{q}_6 + \lambda q_6 &= -q_6 \mu_{x_6} + p_3 p_6 q_3 r_{x_3} \beta x_3 e^{\beta \lambda t} + p_1 p_6 q_7 N_{x_7} \mu_{x_1} \delta \beta e^{\beta \lambda t} \\
&\quad + p_6 q_4 \left(1 - \max \left\{ 0, \min \left(\frac{r_{x_4} p_6 q_4 e^{\lambda t (\beta-1)}}{2A_3}, 1 \right) \right\} \right) r_{x_4} \beta e^{\lambda t (\beta-1)}, \\
-\dot{q}_7 + \lambda q_7 &= -q_7 \mu_{x_7} + p_7 q_1 r_{x_1} \gamma e^{\lambda t (\gamma-1)} + p_5 p_7 q_5 r_{x_5} \gamma e^{\gamma \lambda t}
\end{aligned}$$

Now we subtract the equations for x_1 and $\bar{x}_1$, x_2 and $\bar{x}_2$, $\dots$, x_7 and $\bar{x}_7$, λ_1 and $\bar{\lambda}_1$, λ_2 and $\bar{\lambda}_2$, $\dots$, λ_7 and $\bar{\lambda}_7$. Afterwards, we multiply each equation by an appropriate difference of functions and integrate from 0 to t_f . Next we add all fourteen integral equations are combined, and estimates are utilised to obtain uniqueness. The estimate is obtained by using the Cauchy's inequality in order to separate the linear terms into quadratic terms.

For illustration purposes, some of the integral equations are listed below. Using Lemma (5.1) we have

$$\begin{aligned}
|\zeta_r^* - \bar{\zeta}_r^*| &\leq \left| \frac{r_{x_4} p_6 q_4 e^{\lambda t (\beta-1)}}{2A_3} - \frac{r_{x_4} \bar{p}_6 \bar{q}_4 e^{\lambda t (\beta-1)}}{2A_3} \right| \\
&\leq \frac{1}{2A_3} \left| r_{x_4} e^{\lambda t (\beta-1)} (p_6 q_4 - \bar{p}_6 \bar{q}_4) \right|,
\end{aligned}$$

also,

$$\begin{aligned}
|\zeta_p^* - \bar{\zeta}_p^*| &\leq \left| \frac{N_{x_6} \mu_{x_4} p_4 q_6}{2A_4} - \frac{N_{x_6} \mu_{x_4} \bar{p}_4 \bar{q}_6}{2A_4} \right| \\
&\leq \frac{1}{2A_4} \left| N_{x_6} \mu_{x_4} (p_4 q_6 - \bar{p}_4 \bar{q}_6) \right|
\end{aligned}$$

and

$$\begin{aligned}
|\eta_c^* - \bar{\eta}_c^*| &\leq \left| \frac{1}{2A_5} \left(\alpha p_1 q_2 \left(1 - \frac{e^{\lambda t} p_2}{\omega} \right) \right) - \frac{1}{2A_5} \left(\alpha \bar{p}_1 \bar{q}_2 \left(1 - \frac{e^{\lambda t} \bar{p}_2}{\omega} \right) \right) \right| \\
&\leq \frac{1}{2A_5} \left| \alpha (p_1 q_2 - \bar{p}_1 \bar{q}_2) \left(\frac{e^{\lambda t} (\bar{p}_2 - p_2)}{\omega} \right) \right|
\end{aligned}$$

Then we obtain

$$\begin{aligned}
\frac{1}{2}(p_1 - \bar{p}_1)^2 + \lambda \int_0^{t_f} (p_1 - \bar{p}_1)^2 dt &\leq r_{x_1} \int_0^{t_f} e^{\lambda t(\gamma-1)} |p_7 - \bar{p}_7| |p_1 - \bar{p}_1| dt + \int_0^{t_f} \mu_{x_1} |p_1 - \bar{p}_1|^2 \\
&\quad + \int_0^{t_f} \kappa_1 e^{\lambda t} |p_1 p_5 - \bar{p}_1 \bar{p}_5| |p_1 - \bar{p}_1| dt \\
&\leq C_1 \int_0^{t_f} |p_1 - \bar{p}_1|^2 dt + C_2 e^{\lambda t_f(\gamma-1)} \int_0^{t_f} |p_7 - \bar{p}_7|^2 |p_1 - \bar{p}_1|^2 dt \\
&\quad + C_3 e^{\lambda t_f} \int_0^{t_f} (|p_1 - \bar{p}_1|^2 + |p_5 - \bar{p}_5|^2) dt
\end{aligned}$$

$$\begin{aligned}
\frac{1}{2}(p_2 - \bar{p}_2)^2 + \lambda \int_0^{t_f} (p_2 - \bar{p}_2)^2 dt &\leq \int_0^{t_f} \left| \alpha(1 - \eta_c^*) p_1 \left(1 - \frac{e^{\lambda t} p_2}{\omega}\right) - \alpha(1 - \bar{\eta}_c^*) \bar{p}_1 \left(1 - \frac{e^{\lambda t} \bar{p}_2}{\omega}\right) \right| \\
&\quad \times |p_2 - \bar{p}_2| dt - \int_0^{t_f} \kappa_3 e^{\lambda t} |p_2 p_5 - \bar{p}_2 \bar{p}_5| |p_2 - \bar{p}_2| dt \\
&\leq C_4 \int_0^{t_f} (|p_1 - \bar{p}_1|^2 + |p_2 - \bar{p}_2|^2) dt \\
&\quad + C_5 e^{\lambda t_f} \int_0^{t_f} (|p_2 - \bar{p}_2|^2 + |p_5 - \bar{p}_5|^2) dt
\end{aligned}$$

The remaining equations are estimated in a similar fashion. To show uniqueness, the integral equations are combined. Adding all the fourteen estimates gives:

$$\begin{aligned}
&\frac{1}{2}(p_1 - \bar{p}_1)^2(t_f) + \frac{1}{2}(p_2 - \bar{p}_2)^2(t_f) + \frac{1}{2}(p_3 - \bar{p}_3)^2(t_f) + \frac{1}{2}(p_4 - \bar{p}_4)^2(t_f) + \frac{1}{2}(p_5 - \bar{p}_5)^2(t_f) \\
&\quad + \frac{1}{2}(p_6 - \bar{p}_6)^2(t_f) + \frac{1}{2}(p_7 - \bar{p}_7)^2(t_f) + \frac{1}{2}(q_1 - \bar{q}_1)^2(0) + \frac{1}{2}(q_2 - \bar{q}_2)^2(0) + \frac{1}{2}(q_3 - \bar{q}_3)^2(0) \\
&\quad + \frac{1}{2}(q_4 - \bar{q}_4)^2(0) + \frac{1}{2}(q_5 - \bar{q}_5)^2(0) + \frac{1}{2}(q_6 - \bar{q}_6)^2(0) + \frac{1}{2}(q_7 - \bar{q}_7)^2(0) \\
&\quad + \lambda \int_0^{t_f} \left[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 + (p_6 - \bar{p}_6)^2 \right. \\
&\quad \left. + (p_7 - \bar{p}_7)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2 \right. \\
&\quad \left. + (q_6 - \bar{q}_6)^2 + (q_7 - \bar{q}_7)^2 \right] dt \\
&\leq \left(\tilde{C}_1 + \tilde{C}_2 e^{2\lambda t_f} \right) \int_0^{t_f} \left[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 \right. \\
&\quad \left. + (p_6 - \bar{p}_6)^2 + (p_7 - \bar{p}_7)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2 \right. \\
&\quad \left. + (q_6 - \bar{q}_6)^2 + (q_7 - \bar{q}_7)^2 \right] dt.
\end{aligned}$$

Using the nonnegativity of the variable expressions evaluated at the initial and the final time and simplifying, the inequality is reduced to the following:

$$\begin{aligned} & \left(\lambda - \tilde{C}_1 - \tilde{C}_2 e^{2\lambda t_f} \right) \int_0^{t_f} \left[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 \right. \\ & + (p_6 - \bar{p}_6)^2 + (p_7 - \bar{p}_7)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2 \\ & \left. + (q_6 - \bar{q}_6)^2 + (q_7 - \bar{q}_7)^2 \right] dt \leq 0 \end{aligned}$$

where $\tilde{C}_1, \tilde{C}_2$ depend on the coefficients and the bounds on $p_1, p_2, \dots, p_7, q_1, q_2, \dots, q_7$. If λ is chosen such that $\lambda > \tilde{C}_1 + \tilde{C}_2$ thus, $\lambda - \tilde{C}_1 - \tilde{C}_2 e^{2\lambda t_f} > 0$. The natural logarithm is an increasing function, hence

$$\ln \left(\frac{\lambda - \tilde{C}_1}{\tilde{C}_2} \right) > 2\lambda t_f$$

which would give us $t_f < \frac{1}{2\lambda} \ln \left(\frac{\lambda - \tilde{C}_1}{\tilde{C}_2} \right)$. The choice of λ and t_f , has each of the squared terms in the integral terms being zero. Thus, $p_1 = \bar{p}_1, p_2 = \bar{p}_2, \dots, p_7 = \bar{p}_7, q_1 = \bar{q}_1, q_2 = \bar{q}_2, \dots, q_7 = \bar{q}_7$. Hence the solution is unique for small time. $\square$