Modelling cancer that is HIV-related in the presence of treatment

by

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Abstract

In this study, a theoretical nonlinear mathematical model was revised to understand the interaction of HIV-related cancer cells dynamics with treatment. The work done is adopted from the paper by Lou et al. This work develops a mathematical model that combines healthy CD4+ cells, cancer cells, HIV-infected T cells, and cancer HIV-infected cells. The well-posedness of the model is established and discussed. The computation of reproduction numbers, equilibria, and stabilities are analyzed. Numerical simulations are carried out to determine the parameters that have a high impact on the spread of the disease and Matlab software was used for the numerical simulations. The numerical simulations for the model with no treatment show that the disease will persist. To curb this situation, we introduced the model that incorporated treatment, that is, HAART coupled with Chemotherapy to control the rate of infected T-cells with time. The results obtained are consistent with those obtained by Carvalho et al., Aogo et al., and Kaondera et al.

Preface

The work described in this dissertation was carried out under the supervision of Dr G. M. Moremedi, Department of Mathematical Sciences, University of South Africa.

This dissertation represents original work by the author and has not otherwise been submitted in any form for any degree or diploma to any other University. Where use has been made of the work of others, it is duly acknowledged in the text.

Signed :

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Contents

Chapter 1: Biological backgrounds of HIV and cancer

1.1 Introduction

Human immunodeficiency virus (HIV) is described as a retrovirus that infects cells of the human resistant system (such as CD4+ T-cells and macrophages—key components of the cellular immune system) and destroys their functions [59]. HIV infection has been identified as the leading cause of AIDS [59]. Acquired Immunodeficiency Syndrome (AIDS) was first acknowledged to exist in 1981 and within the period 1981-2020, more than $[55.9 - 110]$ million people have been infected and $[27.2 - 47.8]$ million died after contracting it [12, 59, 10]. The disease, known as AIDS, begins when the virus seriously damages the immune system, causing certain types of infections and other complications. For individuals infected with HIV, cancer remains a critical burden [10]. Individuals with AIDS are more likely to develop different types of cancer, including Kaposi's sarcoma, high-grade pathological type, and non-Hodgkin's lymphoma and, invasive cervical cancer with B cells or unknown immunological phenotype [40]. Insights into the underlying epidemiology and mechanisms of AIDS-related cancers may give us a better understanding of cancer immunity and viral oncogenesis [10, 37]. Numerous studies which focused on either tumor growth modeling or HIV dynamics in the bio-mathematical literature appear in [12]. In particular, the most common neoplasm that occurs in AIDS patients is Kaposi's sarcoma. It develops as a tumor on mucous membranes such as the skin and mouth, but it can also develop in other parts of the body, such as the lymph nodes, lungs, and digestive system [10].

1.2 Human immunodeficiency virus (HIV)

The human immunodeficiency virus (HIV1) has the major infectious nodes where classical cell-free infection and direct cell-to-cell transfer occur [10, 25]. HIV infection of CD4 + T cells causes their rapid decline, endangering the host's immune system and resulting in the death of infected patients due to infection or cancer[8, 44]. When HIV damages the immune system, individuals who are also infected with certain viruses (eg. Kaposi Sarcoma Herpesvirus) are more likely to develop Kaposi Sarcoma [7, 10]. Infected individuals show no symptoms, however, have proceeded with viral replications for certain years until an expansion in viral infection and the decrease of CD4+ T cells lead to AIDS and even death [32].

1.3 Cancer

The term cancer is used for diseases in which abnormal cells in the body begin to grow out of control. Normal cells grow, divide and die in an orderly fashion. Cancer cells are thus different

from normal cells in the way they grow. Cells become cancer cells because of damage to DNA. Cancer cells can move to other parts of the body, where they begin to grow and form new tissues that replace normal tissues [57]. This process is called metastasis and it happens when the cancer cells enter the bloodstream or lymph vessels [57].
A tumor is an abnormal growth of body tissues. It can be cancerous or non-cancerous. Cancer is known worldwide to be a disease that has a significant burden on HIV-infected individuals. HIV is the human immunodeficiency virus that causes AIDS disease. HIV is transmitted from one human to another by blood and bodily secretions. The majority of cancers affecting HIV-positive people are those established as AIDS-defining: Kaposi's sarcoma, Non-Hodgkin lymphoma, and Cervical cancer [30]. Today, over 60 million people worldwide have been infected with HIV, and more than 80% of them live in developing countries [1]. Researchers found no viral sequence in the DNA of the cancer cells and they included that HIV-1 particle can not by itself engender tumor in an HIV patient [27].

There are different types of cancers. Below we define the major ones.

- Kaposi's sarcoma (KS):
  It's a specific form of skin cancer. It grows in the tissue under the skin's surface or the mouth and nasal mucous membranes. Studies have unequivocally demonstrated significant declines in the incidence of KS following the introduction of HAART (Highly Active Antiretroviral Therapy) [37]. KS was the AIDS-defining disease that rate had increased to about 47 people per 1 million people of afflicted individuals in the early 1990s, a figure that later fell in recent years to about 6 cases per 1 million people because of more effective treatments for HIV/AIDS [57].

- Non-Hodgkin lymphoma (NHL) :
  It's a specific form of cancer of the lymph system. The lymphatic system is made up of small tubes that branch out to different areas of the body. After Kaposi's sarcoma, NHL is the second most common cancer associated with HIV/AIDS. It can affect the brain, the spine, and the lungs. High-grade B-cell lymphomas account for more than 80% of lymphomas in people with HIV/AIDS, while 10% to 15% of lymphomas in people without HIV/AIDS are of the same type [37]. The risk of developing NHL is substantially increased in HIV-infected individuals, with risks ranging from approximately 40 to 400 times that of the general population, depending on the specific study and the type of NHL, though most studies report rates of 100 to 200 fold [37].

- Cervical cancer:
  It grows in the lower part of a woman's uterus, the cervix. Cervical Intraepithelial Neoplasia is a common complication in HIV-positive women (CIN). High-grade CIN affects 11% to 29% of HIV-positive women and may be linked to human papillomavirus (HPV) infection [37]. Some less common types of cancers may develop as a result of HIV/AIDS.

1.3.1 Characteristics of cancer cells

Cancer cells can be differentiated from normal cells. Characteristics of cancers are as follows.

- They reproducing indefinitely.
- Cancer cells resist signals from other cells. [47]
- Cancer cells don't stick together.
- Cancer cells do not differentiate and remain immature.

- They can spread through blood vessels.

1.3.2 Symptoms

The following symptoms can appear in people with HIV/AIDS-related cancer:
Kaposi's sarcoma:

- Wounds in the mouth or throat.
- Lymphedema (Swelling occurs when the lymphatic system is clogged).
- Unexpected chest, cough, stomach, or intestinal pains.

Non-Hodgkin lymphoma:

- Enlarged liver.
- Sweating and chills.

Cervical cancer:

- Between or during menstrual cycles, there might be bloody spots or light bleeding.
- Various forms of examinations result in bleeding.

1.3.3 Cancer treatments

Staging is a way of identifying cancer, such as its location, if it has spread or not and it is not interfering with the functions of other organs in the body [57]. Identifying the level of stage help to decide what kind of treatment is effective to be considered by the practitioner [57]. Cancer treatment is determined by the cancer type in each individual. The high risk of infections caused by HIV reduces white blood cell count and immune function, which implies that cancer treatment in people with AIDS will be difficult [57]. There are four different types of treatment regimes namely: chemotherapy, immunotherapy, radiotherapy, and surgery.

- Radiotherapy works as a type of energy that shrinks tumors or eliminates cancer cells. Cancer cells are normally regarded to be sensitive to radiation and die when treated. Tumor cells are destroyed by high-powered radiation rays which stop the tumors from growing. Radiotherapy is often employed to destroy tumor tissue that cannot be removed surgically or to attack cancer cells that may survive surgery [57]. The implementation of 3D-imaging, can precisely aid practitioners to see the tumor mass before radiation and then target the radiation at a particular location [38].

- Chemotherapy is used to eliminate cancer and is given in the form of drugs. This type of treatment can cause side effects like loss of hair follicle cells. Questions can arise that need to be addressed regarding chemotherapy. How large or small should the dosage be? How long should the duration of the treatment be? How periodic should be the dosage? Drugs that operate on tumor cells can be classified into two types: those that target both proliferating and nonproliferating (quiescent) cells in various sections of the tumor mass, and those that only target dividing cells during particular phases of cell division [38].

- Immunotherapy is a form of treatment that helps to strengthen the immune system so that it can kill cancer cells [57]. It boosts, targets, or restores immune system function using substances produced by the body or in a laboratory [57].
  Surgery aims to eliminate as many tumor cells and surrounding normal tissue as possible. Curative surgery is the primary treatment for primary tumors that have not metastasized and requires the removal of tumors that are limited to a single region [57]. Unfortunately, many cancers, such as extreme types of brain tumors, are inoperable due to their location [38].

1.4 Co-infection between cancer and HIV

Co-infection is more than one disease co-existing within a single host [20]. Non-AIDS-defining cancers (NADCs) are typically defined in contrast to the three AIDS-defining cancers (ADCs) – Kaposi sarcoma, non-Hodgkin lymphoma (NHL), and cervical cancer [7]. Factors that may contribute to the increased risk of NADC include HIV viremia, coinfection with carcinogens, chronic immunosuppression, immune activation, and exposure to high levels of carcinogens increase [9]. Although they fall into the same general category, not all NADCs share the same pathogenesis and risk factors. The higher danger of certain cancers among HIV-Infected individuals is the higher prevalence of common cancer risk factors such as smoking, oncogenic virus coinfection, including human papillomavirus (HPV) or hepatitis B or C [49]. Theories have been proposed to explain the increased risk of NADC associated with these viruses,and this includes the high prevalence of co-infection with the virus in HIV-infected populations [9, 16, 49]. There are models which have been developed to model cancer in HIV-infected individuals, see for instance Straus and Kirschner [22, 53]. For example in the study by [10, 30, 40], a dynamical model of HIV-1 with AIDS-related cancer cells was investigated. The model has three compartments of; cancer cells, healthy CD4+ T lymphocytes, and infected CD4+ T lymphocytes. We re-look at this model in this project by including treatment, an aspect that was not included in the work in [30].
The model that was investigated is a cell to cell distribution of HIV-1 in combination with cancer cells in tissue cultures [30]. The immune system can distinguish between cancerous and non-cancerous cells. It surveys them before carrying out the killing operation. CD4+ T lymphocytes are used to represent the immune system which binds with the cancer cells and destroys them.

1.5 Research objectives

The primary goal of this research is to create mathematical models for co-infection that examine the dynamics of cancer and cancer-infected cells within the host. The specific objectives are:

- Re-develop and analyze the cancer model from Lou et al.[30].
- Extend the model by incorporating with treatment to analyze the effect on the co-infection model.

1.6 Outline of the Dissertation

- Chapter 1 depicts the biological background of HIV and cancer.
- Chapter 2 consists of the reviewed model by Lou et al. [30] to include the boundedness and positivity of the model. The stability equilibrium was analyzed and numerical simulations were carried out to further understand the impact of parameters in the model.
- In Chapter 3 we reformulate the cancer model to include the co-infection of cancer infected cells without treatment [30]. The basic reproduction number is used to determine the system's stability. To obtain a better understanding of the dynamics of the cancer model, some numerical simulations are run.
  The presence of treatment is considered, and the basic cancer model is expanded to examine the dynamics of co-infection of cancer and cancer HIV-infected cells. The intervention method in this model will be able to show the effect of HAART and chemotherapy drugs on the dynamics of cancer-infected cells.
- In Chapter 4 discussion of the results will be outlined and concluding remarks are made.

1.7 Conclusion of the chapter

The chapter summarises the different types of infections that as HIV infection, and cancer infection and it also outlines the objectives of the research. In the next chapter, we are reviewing the cancer model by Lou et al [30].

Chapter 2: Mathematical analysis of a reviewed cancer model

2.1 Introduction

In this chapter work done by Lou et al.,[30] is reviewed to give insight into cancer cells and healthy cells interacting with infected cells. The model presented is a nonlinear deterministic mathematical model proposed by [30]. In Duarte et al. [10], they still deal with the same systems as Lou et al., but their focus was to determine the dynamical behaviors of the system by observing two biological meaningful parameters: r_1 representing the proliferation rate of cancer cells and k_1 which represent the immune system's killing rate of the cancer cells. The maximum Lyapunov function was computed to identify the chaotic regimes [10]. In their conclusion, they revealed that the greatest observable variable is given in the population of cancer cells. The approach of constructing a chaotic attractor could be used to characterize the attractor governing coexistence among cancer cells, CD4+ T cells, and HIV-infected T-cells [10]. In our case, we use a compartmental modeling approach. This study is pursued further by looking at the well-posedness and equilibria of the model to allow us to analyze the interaction of the cells in this three-component model without treatment. Let $C(t)$, $T(t)$,and $I(t)$ be the concentration of cancer cells, healthy T-cells ,and infected T-cells, respectively. Considering a T cell, moreover called T lymphocyte, a sort of leukocyte (white blood cell) that's a fundamental portion of the resistant framework. T cells are one of two essential sorts of lymphocytes—B cells being the moment type—that decide the specificity of resistant reaction to antigens (foreign substances) within the body. In some works of literature Lou et al. and Duarte [30, 10] use healthy CD4+ T lymphocytes but in this study, we will use healthy CD4+ T-cells throughout the work.

2.2 Model formulation

The model reviewed considers cell-to-cell dynamics between the state variables in which there is interaction between healthy CD4+ T-cells, $T(t)$ with HIV-1 infected T-cells, $I(t)$ and the $T(t)$ cells also attacking and killing the cancer cells, $C(t)$. The following assumptions are made:

1. One cell causes cancer due to a gene mutation, and use the parameter r_1 as the uncontrolled proliferation rate. The cancer cells grow logistically according to $\frac{dT(t)}{dt} = r_1 T(t)\left(1 - \frac{C(t)+T(t)+I(t)}{M}\right)$, the total population is $C(t)+T(t)+I(t)$ and M is the carrying capacity.

2. The $CD4+$ lymphocyte represents the immune system in our model. The healthy CD4+ T-cells grow logistically as $\frac{dT(t)}{dt} = r_2 T(t)\left(1 - \frac{C(t)+T(t)+I(t)}{M}\right)$, where r_2 represent the rate

at which healthy CD4+ T-cells grow. Detecting harmful cells, k_1 reflect the rate at which cancer cells are killed by the immune system. In the process of killing cancer cells, there is a loss of the immune system which is represented by p due to the fact that it kills cancer cells, hence we have the term $-pk_1$.

3. The healthy CD4+ T-cells become infected by direct contact with the HIV infected T-cells, described by the mass action term $k_2T(t)I(t)$, where k_2 is the infection rate that accounts for HIV-1 reproduction's overall effects. The rate at which infected cells die is represented by μ_I. The constants, r_1 and r_2 are such that $r_1 > r_2$ [18].

Based on the biological assumptions stated above, the system of equations are given by:

$$\begin{aligned}
\frac{dC(t)}{dt} &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)}{M}\right)-k_1T(t)\right],\\
\frac{dT(t)}{dt} &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)}{M}\right)-pk_1C(t)-k_2I(t)\right], \qquad (2.1)\\
\frac{dI(t)}{dt} &= I(t)\left[k_2T(t)-\mu_I\right].
\end{aligned}$$

The initial conditions are assumed to be

$$C(0) \geq 0, T(0) \geq 0, I(0) \geq 0. \qquad (2.2)$$

The schematic diagram depicting all the considered dynamical variables is shown:

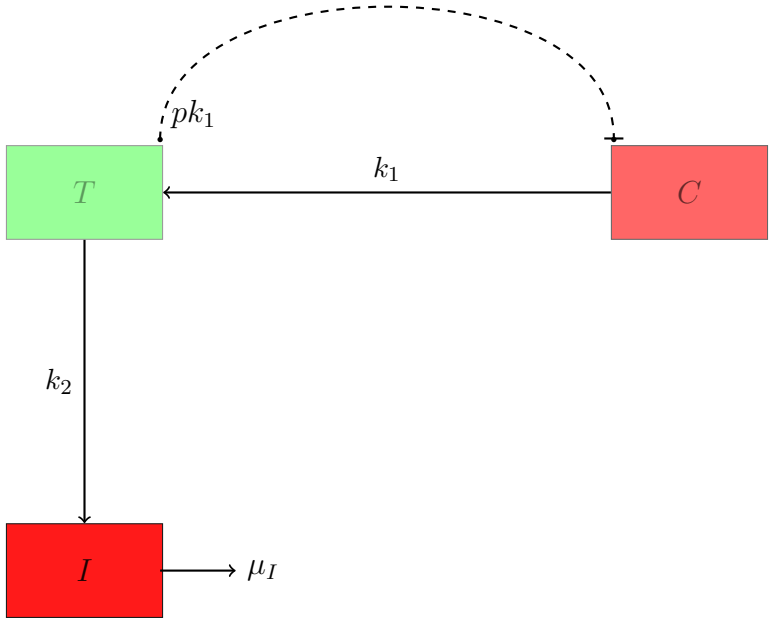


Figure 2.1: The model flow depicting the biological system for the model (2.1). Healthy T-cells become infected by interacting with productively infected T-cells (I). Cancer cells (C) develop due to gene mutation. Sharp arrows represent the production or activation of cancers cells or infected T-cells. The dashed line represents the loss of healthy CD4+ T-cells due to killing the cancer cells.

Table 2.1: State variables and units

State Variable	Description	Units
$C(t)$	concentration of cancer population	(cells mL^{-1})[Estimated]
$T(t)$	concentration of healthy CD4+ T-cells	(cells mL^{-1}) [Estimated]
$I(t)$	concentration of infected T-cells	(cells mL^{-1}) [Estimated]
k_1	rate of immune system killing cancer cells	(ml/day) [30]
r_1	maximal proliferation rate of cancer cells	(ml/day) [30]
r_2	intrinsic growth rate of healthy CD4+ T-cells	(ml/day)[30]
r_3	intrinsic growth rate of cancer infected T-cells	(ml/day) [Estimated]
p	rate of losing immune due to infection	(ml/day)[30]
k_2	rate of infection	(/ml/day) [30]
μ_I	death rate of infected T-cells	(/day) [30]
M	carrying capacity	(/ml) [30]

2.3 Basic properties

The classical definition of well-posedness given by [17], states that a mathematical model of a physical phenomenon is well-posed if it has the following properties:

i. A solution exists.

ii. The solution is unique.

iii. The solution's behavior changes continuously with the initial conditions.

The above properties are also applicable to the model (2.1) with initial conditions (2.2) as has been shown in other biological systems. So, we demonstrate that all state variables are non-negative for the study to be epidemiologically valid and well-posed, $\forall t \geq 0$.

2.3.1 The existence and uniqueness of solution

Theorem 1. *Let* $\Gamma = \{\big(C(t), T(t), I(t)\big) \in \mathbb{R}^3_+\}$ *denote the region defined by model system (2.1). Then, there exists a solution for model system (2.1) which is bounded in the region* Γ.

Proof. In order to prove the above theorem, the concept we derive is in [11].

$$\begin{aligned} f_1 &= C(t)\left[r_1\left(1-\tfrac{C(t)+T(t)+I(t)}{M}\right)-k_1T(t)\right], \\ f_2 &= T(t)\left[r_2\left(1-\tfrac{C(t)+T(t)+I(t)}{M}\right)-pk_1C(t)-k_2I(t)\right], \\ f_3 &= I(t)\left[k_2T(t)-\mu_I\right]. \end{aligned} \tag{2.3}$$

It suffices to show that $\frac{\partial f_1}{\partial C(t)}, \frac{\partial f_2}{\partial T(t)}, \frac{\partial f_3}{\partial I(t)}$ are continuous. The partial derivatives below are con-

sidered

$$\begin{aligned}
\left|\frac{\partial f_1}{\partial C(t)}\right| &= \left|r_1\left(1-\frac{2C(t)+T(t)+I(t)}{M}\right)-k_1T(t)\right|<\infty,\\
\left|\frac{\partial f_1}{\partial T(t)}\right| &= \left|-\frac{r_1C(t)}{M}-k_1C(t)\right|<\infty,\\
\left|\frac{\partial f_1}{\partial I(t)}\right| &= \left|-\frac{r_1C(t)}{M}\right|<\infty,\\
\left|\frac{\partial f_2}{\partial C(t)}\right| &= \left|-\frac{r_2T(t)}{M}-pk_1T(t)\right|<\infty,\\
\left|\frac{\partial f_2}{\partial T(t)}\right| &= \left|r_2\left(1-\frac{C(t)+2T(t)+I(t))}{M}\right)-pk_1C(t)-k_2I(t)\right|<\infty,\\
\left|\frac{\partial f_2}{\partial I(t)}\right| &= \left|-\frac{r_2T(t)}{M}-k_2T(t)\right|<\infty,\\
\left|\frac{\partial f_3}{\partial C(t)}\right| &= |0|<\infty,\\
\left|\frac{\partial f_3}{\partial T(t)}\right| &= \left|k_2I(t)\right|<\infty,\\
\left|\frac{\partial f_3}{\partial I(t)}\right| &= \left|k_2T(t)-\mu_I\right|<\infty.
\end{aligned}$$

All these partial derivates are continuous and bounded, hence there exists a unique solution of equations (2.3) in the region Γ. □

Theorem 2. *Assume the parameters of model (2.1) are nonnegative constants. A nonnegative solution of $C(0)$, $T(0)$ and $I(0)$ for model (2.1) exists for all state variables with nonnegative initial conditions $C(0)\geq 0, T(0)\geq 0, I(0)\geq 0$, $\forall t>0$.*

Proof. From the system (2.1), we have

$$\begin{aligned}
\frac{dC(t)}{dt} &= C(t)\left[r_1\left(1-\tfrac{C(t)+T(t)+I(t)}{M}\right)-k_1T(t)\right]\geq C(t)r_1\left(1-\frac{C(t)}{M}\right),\\
\frac{dT(t)}{dt} &= T(t)\left[r_2\left(1-\tfrac{C(t)+T(t)+I(t)}{M}\right)-pk_1C(t)-k_2I(t)\right]\geq T(t)r_2\left(1-\frac{T(t)}{M}\right),\\
\frac{dI(t)}{dt} &= I(t)\left[k_2T(t)-\mu_I\right]\geq -\mu_II(t).
\end{aligned}\tag{2.4}$$

The initial concentration of the state variables are assumed to be: $C(0)=C_0$, $T(0)=T_0$ and $I(0)=I_0$. They are assumed nonnegative so as to be biologically feasible.
Using the second equation of (2.4), and applying separation of variables yields

$$\frac{dT(t)}{T(t)\left(1-\frac{T(t)}{M}\right)} \geq r_2dt. \tag{2.5}$$

The left-hand side of the equation (2.5), is expressed in partial fractions and integrated which leads to

$$\frac{1}{M}\left[\int\frac{dT(t)}{T(t)}+\int\frac{dT(t)}{M-T(t)}\right] \geq \int r_2dt, \tag{2.6}$$

therefore

$$ln\left|T(t)\right| - ln\left|M - T(t)\right| \geq r_2 Mt + c, \tag{2.7}$$

multipying (2.7) with negative sign

$$ln\left|M - T(t)\right| - ln\left|T(t)\right| \geq -r_2 Mt - c, \tag{2.8}$$

then

$$\left|\frac{M - T(t)}{T(t)}\right| \geq e^{-c}e^{-r_2 Mt}. \tag{2.9}$$

We define $c_1 = e^{-c}$, then the equation becomes

$$\frac{M - T(t)}{T(t)} \geq c_1 e^{-r_2 Mt} \tag{2.10}$$

Simplifying the equation (2.10) to obtain $T(t)$, where $A = \dfrac{M - T_0}{T_0}$ as $t = 0$ and $T(0) = T_0$. yields

$$T(t) \geq \frac{M}{1 + Ae^{-r_2 Mt}}. \tag{2.11}$$

If the same approach is used in equation one of the systems (2.4), then we obtain

$$C(t) \geq \frac{M}{1 + Be^{-r_1 Mt}}, \tag{2.12}$$

where $B = \dfrac{M - C_0}{C_0}$ at $t = 0$ and $C(0) = C_0$.
Furthermore, the third equation of the system (2.4) becomes

$$I(t) \geq I(0)e^{-\int \mu_I dt} \geq 0. \tag{2.13}$$

This proves that $T(t)$, $C(t)$, and $I(t)$ remain positive for $\forall t > 0$. This completes the proof. □

Theorem 3. *All solutions $C(t), T(t), I(t)$ of model (2.1) are bounded.*

Proof. We prove that the solutions of system (2.1) are uniformly bounded for $t > 0$, following Lou and Zhao [33]. We already showed in Theorem 1 that $C(t), T(t), I(t)$ remain positive for $\forall t > 0$. It then suffices to assume that $T(0) = T_0$, $C(0) = C_0$ and $I(0) = I_0$, an assumption already made above. It is known from Lou and Zhao [33], that the T-cell concentration stabilizes at a level T_0, where T_0 is the positive root of F(T) = 0. Adopting this view, we then have $F(T) = 0$). Hence, this implies that the other equations of system (2.1) becomes zero at level $T(0) > 0$, $C_0 = 0$, $I_0 = 0$, where T_0 is the positive root, from equation 2 of system (2.1), we have

$$T(t)\left[r_2\left(1 - \frac{T(t)}{M}\right)\right] = F(T) = 0, \tag{2.14}$$

$$F(T) = r_2 MT(t) - r_2 T^2(t), \tag{2.15}$$

thus

$$0 = MT_0 - T_0^2, \tag{2.16}$$

where $T_0 = 0$ or $T_0 = M$. By summing equations $T(t)$ and $I(t)$ of system (2.1), we obtain

$$\frac{d\left(T(t) + I(t)\right)}{dt} \leq r_2 T_0 - \mu I(t). \tag{2.17}$$

Hence

$$\lim sup_{t\to\infty}(T(t)+I(t)) \leq \frac{r_2 T_0}{\mu_I} := M_1. \tag{2.18}$$

It follows from the first equation of system (2.1) that

$$\frac{dC(t)}{dt} \leq r_1 C(t)\left(1-\frac{C(t)}{M}\right), \tag{2.19}$$

then the

$$\lim sup_{t\to\infty}(C(t)) \leq M := M_2. \tag{2.20}$$

All solutions of the system are bounded in the feasible region

$$\Gamma = \{\big(C(t),T(t),I(t)\big) \in \mathbb{R}^3_+ : 0 \leq C(t) \leq M_2, 0 < T(t) \leq T_0, 0 < T(t)+I(t) \leq M_1\}. \tag{2.21}$$

Thus Γ is positively inviariant with respect to system (2.1). □

2.4 The disease-free equilibria and their stabilities

Linear stability is a concept that is used to study the behavior of solutions that are similar to steady-state. A steady-state can be stable or unstable and thus can be determined by linear stability analysis. The trivial equilibrium $E_0 = (0,0,0)$ exists but it is not biologically feasible, because when we have a trivial state only then do individual cells are dead. Cancer in itself in this model is not viable to exist hence mutations have to occur, e.g cancer equilibrium. A state of no disease in the population is called the disease-free equilibrium (DFE) and is obtained by setting the system (2.1) to zero thus

$$\frac{dC(t)}{dt} = \frac{dT(t)}{dt} = \frac{dI(t)}{dt} = 0.$$

In the DFE point $C(t) = I(t) = 0$, hence we have

$$\begin{aligned} T(t)\left(1-\frac{T(t)}{M}\right) &= 0, \\ T(t) &= M, \end{aligned} \tag{2.22}$$

therefore the DFE labelled as $E_{01} = (0, M, 0)$.

2.4.1 Computation of the basic reproduction number

To investigate the equilibrium's stability, we must first introduce the basic reproduction number R_0. The R_0 in a fully susceptible population, is described as the estimated number of secondary infections caused by an index event [46]. The R_0 involves the product of infection rate and the duration of infection. The reproduction number acts as a predictor of disease outbreaks and aids in the development of control strategies. The analytical expression of R_0 indicates which element of the system can be controlled to reduce the outbreak of the disease [55].

We employ the next-generation matrix approach which is used to derive the basic reproduction number [55]. To calculate the system's next-generation matrix from the system (2.1), we will have to figure out how many different ways new diseases can spread and how many different ways individuals can switch between compartments. The infected variables are firstly ordered by rewriting the vectors in the form,

$$\frac{dI(t)}{dt} = I(t)\left[k_2 T(t) - \mu_I\right]. \tag{2.23}$$

We then obtain,

$$\mathcal{F} = \begin{pmatrix} k_2 I(t)T(t) \\ \\ 0 \end{pmatrix}, \tag{2.24}$$

and

$$\mathcal{V} = \begin{pmatrix} I(t)\mu_I \\ \\ -C(t)\left(1 - \frac{C(t)+T(t)+I(t)}{M}\right) + k_1 C(t)T(t) \end{pmatrix}, \tag{2.25}$$

where $\mathcal{F}$ represents the rate of appearance of new infection and $\mathcal{V}$ denotes the rate of transfer of individuals. Differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to $I(t)$, then substituting the disease free equilibrium $E_{01} = (0, M, 0)$ into the states $C(t), T(t), I(t)$, we obtain

$$F = \begin{pmatrix} k_2 M & 0 \\ \\ 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu_I & 0 \\ \\ 0 & k_1 M \end{pmatrix},$$

where

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_I} & 0 \\ \\ 0 & \frac{1}{k_1 M} \end{pmatrix}.$$

The next generation matrix for model (2.1) is given by FV^{-1}. It follows the spectral radius of matrix FV^{-1} is $\rho(FV^{-1}) = \dfrac{k_2 M}{\mu_I}$. The reproduction number R_0 is given as, the spectral radius of

$$\rho(FV^{-1}) = R_0 = \frac{k_2 M}{\mu_I}. \tag{2.26}$$

The R_0 represents the number of healthy CD4+ T-cells generated as a result of one infected cell. The goal for reducing the chance of cancer-related HIV outbreak is to reduce R_0, the R_0 can be managed by reducing the infected cell's density. If $R_0 < 1$ this means that $k_2 M < \mu_I$. Interpreting the result biologically for $R_0 < 1$ means that the individual will not get infected by HIV. Preventing individuals from getting infected with HIV leads to avoiding the infection of cancer that is related to HIV. When $R_0 > 1$ the outbreak will occur, which implies that there are high chances of cancer that is related to HIV.

2.4.2 The cancer cells and healthy CD4+ T-cells equilibrium

This equilibrium indicated by E_{02}, is found by setting $I(t) = 0$, such that the system reduces to

$$\begin{aligned} 0 &= r_1\left(1 - \tfrac{C(t)+T(t)}{M}\right) - k_1 T(t), \\ 0 &= r_2\left(1 - \tfrac{C(t)+T(t)}{M}\right) - pk_1 C(t). \end{aligned} \tag{2.27}$$

Using the first equation in (2.27), we obtain $C(t) = \dfrac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}$. Substituting $C(t)$ into the second equation of (2.27), we obtain

$$0 = r_2 M - r_2\left[\frac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}\right] - r_2 T(t) - Mpk_1\left[\frac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}\right]. \tag{2.28}$$

Rearranging the equation and making $T(t)$ the subject of the formula and labeling it as $\bar{T}$, we have

$$\bar{T} = \frac{r_1 pM}{r_2 + p\left(r_1 + Mk_1\right)}. \tag{2.29}$$

Substituting $\bar{T}$ into the first equation of (2.27) and rearranging by making $C(t)$ the subject of the formula and labeling it as $\bar{C}$ yeilds,

$$\bar{C} = \frac{r_2 M}{r_2 + p\left(r_1 + Mk_1\right)}. \tag{2.30}$$

The cancer cells and healthy T-cells equilibrium $E_{02} = \left(\bar{C}, \bar{T}, 0\right)$.

2.4.3 The healthy CD4+ T-cells and infected T-cells equilibrium

This equilibrium indicated by E_{03} where $C(t) = 0$, then we have the equations

$$\begin{aligned} 0 &= T(t)\left[r_2\left(1 - \tfrac{T(t)}{M}\right) - k_2 I(t)\right], \\ 0 &= I(t)\left[k_2 T(t) - \mu_I\right], \end{aligned} \tag{2.31}$$

where

$$T^* = \frac{\mu_I}{k_2}. \tag{2.32}$$

We substitute T^* in the first equation of (2.31), such that

$$0 = r_2 - \frac{r_2 \mu_I}{k_2 M} - \frac{r_2 I(t)}{M} - k_2 I(t), \tag{2.33}$$

then

$$I^* = \frac{r_2\left(k_2 M - \mu_I\right)}{k_2\left(r_2 + k_2 M\right)}, \tag{2.34}$$

therefore

$$I^* = \frac{r_2 \mu_I\left(R_0 - 1\right)}{k_2\left(r_2 + k_2 M\right)}. \tag{2.35}$$

This equilibrium $E_{03} = (0, T^*, I^*) = \left(0, \dfrac{\mu_I}{k_2}, \dfrac{r_2\mu_I\left(R_0-1\right)}{k_2\left(r_2+k_2M\right)}\right)$ exist when $R_0 > 1$. $R_0 < 1$ means that there will be more healthy T-cells. If $R_0 > 1$, there will be a decline in the healthy CD4+ T-cells and infected T-cells will increase and this leads to the endemic equilibrium. If $R_0 = 1$, then the equilibrium $E_{02} = E_{03}$.

2.4.4 Stability analysis of the disease-free equilibria

The Jacobian matrix of model system (2.1) is

$$J_E = \begin{pmatrix} r_1(1-q_1) - k_1T(t) & -\frac{r_1C(t)}{M} - k_1C(t) & -\frac{r_1C(t)}{M} \\ -\frac{r_2T(t)}{M} - pk_1T(t) & r_2\,(1-q_2) - pk_1C(t) - k_2I(t) & -\frac{r_2T(t)}{M} - k_2T(t) \\ 0 & k_2I(t) & k_2T(t) - \mu_I \end{pmatrix},$$

where $q_1 = \dfrac{2C(t) + T(t) + I(t)}{M}$ and $q_2 = \dfrac{C(t) + 2T(t) + I(t)}{M}$.

2.4.4.1 Stability analysis of the disease-free equilibrium points E_0, E_{01}, E_{02}, E_{03}

Theorem 4. *The trivial equilibrium point $E_0 = (0, 0, 0)$ of the system 2.1 is always unstable.*

Proof. The eigenvalues of the matrix J_E at the trivial steady state $E_0 = (0, 0, 0)$ are r_1, r_2 and $-\mu_I$. Two of the eigenvalues are positive and other one is negative. Therefore the trivial equilibrium is unstable. □

Theorem 5. *The system's state of disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The local stability of E_{01} is determined using the Jacobian matrix,

$$J_{E_{01}} = \begin{vmatrix} r_1 - k_1M & 0 & 0 \\ -r_2 - pk_1M & -r_2 & -r_2 - k_2M \\ 0 & 0 & k_2M - \mu_I \end{vmatrix}.$$

The eigenvalues of $J_{E_{01}}$ are

$$\begin{aligned} \lambda_1 &= r_1 - k_1M, \\ \lambda_2 &= -r_2, \\ \lambda_3 &= \mu_I(R_0 - 1). \end{aligned}$$

The eigenvalues of $J_{E_{01}}$ are negative when $R_0 < 1$, and $r_1 < k_1M$ then equilibrium will be local asymptotically stable otherwise when $R_0 > 1$ is unstable. Hence, we have the theorem proved. □

Remark: If $R_0 < 1$ then E_{01} is locally stable. The individual will not be infected by HIV. Since the immune system is strong to fight the infection, individuals will not develop cancer. If $R_0 > 1$ then E_{01} is unstable. The outbreak will occur. The healthy CD4+ T-cells will be infected with HIV, though cancer that is related to HIV will not develop.

2.4.4.2 The cancer cells and healthy CD4+ T-cells equilibrium

Theorem 6. *The equilibrium point E_{02} is unstable if one of the eigenvalues is positive or else it will be stable.*

Proof. The cancer cells and healthy CD4+ T-cells equilibrium $E_{02} = (\bar{C}, \bar{T}, 0)$, the Jacobian matrix of this equilibrium is

$$J_{E_{02}} = \begin{pmatrix} -\phi_{11} & -\phi_{12} & -\phi_{13} \\ -\phi_{21} & -\phi_{22} & -\phi_{23} \\ 0 & 0 & -\phi_{33} \end{pmatrix},$$

where

$$\begin{aligned}
\phi_{11} &= -r_1\left(1 - \frac{2\bar{C} + \bar{T}}{M}\right) + k_1\bar{T}, \phi_{12} = \left(\frac{r_1}{M} + k_1\right)\bar{C}, \phi_{13} = \frac{r_1}{M}\bar{C}, \\
\phi_{21} &= \left(\frac{r_2}{M} + pk_1\right)\bar{T}, \phi_{22} = -r_2\left(1 - \frac{\bar{C} + 2\bar{T}}{M}\right) + pk_1\bar{C}, \phi_{23} = \left(\frac{r_2}{M} + k_2\right)\bar{T}, \\
\phi_{31} &= 0, \phi_{32} = 0, \phi_{33} = -k_2\bar{T} + \mu_I, \bar{T} = \frac{r_1 pM}{r_2 + p\left(r_1 + Mk_1\right)}, \bar{C} = \frac{r_2 M}{r_2 + p\left(r_1 + Mk_1\right)}.
\end{aligned}$$

The characteristic equation of the Jacobian J associated with the equilibrium E_{02} is given by

$$\xi^3 + \widehat{\phi}_3\xi^2 + \widehat{\phi}_2\xi + \widehat{\phi}_1 = 0, \tag{2.36}$$

The eigenvalues of the characteristic equation 2.36 are

$$\begin{aligned}
\xi_1 &= \frac{1}{2}\left[\sqrt{\phi_{11}^2 - 2\phi_{11}\phi_{22} + 4\phi_{12}\phi_{21} + \phi_{22}^2} - \phi_{11} + \phi_{22}\right], \\
\xi_2 &= \frac{1}{2}\left[\sqrt{\phi_{11}^2 - 2\phi_{11}\phi_{22} + 4\phi 12\phi_{21} + \phi_{22}^2} + \phi_{11} + \phi_{22}\right], \\
\xi_3 &= \phi_{33}.
\end{aligned}$$

The equilibrium point E_{02} is unstable, because the eigenvalue ξ_3 will always be positive, hence the rate of infection is very small.

□

2.4.4.3 The healthy CD4+ T-cells and infected T-cells equilibruim

Theorem 7. *The equilibrium point E_{03} is unstable if one of the eigenvalues is positive or else it will be stable.*

Proof. To prove this statement where the healthy CD4+ T-cells and infected T-cells equilibrium $E_{03} = (0, T^*, I^*)$, the Jacobian matrix of this equilibrium is,

$$J_{E_{03}} = \begin{pmatrix} -\phi_{11} & 0 & 0 \\ -\phi_{21} & -\phi_{22} & -\phi_{23} \\ 0 & -\phi_{32} & -\phi_{33} \end{pmatrix},$$

where

$$\begin{aligned} \phi_{11} &= -r_1\left(1-\frac{2T^*+I^*}{M}\right)+k_1T^*, \phi_{12}=0, \phi_{13}=0, \\ \phi_{21} &= \left(\frac{r_2}{M}+pk_1\right)T^*, \phi_{22}=-r_2\left(1-\frac{2T^*+I^*}{M}\right)+k_2I^*, \phi_{23}=\left(\frac{r_2}{M}+k_2\right)T^*, \\ \phi_{31} &= 0, \phi_{32}=-k_2I^*, \phi_{33}=-k_2T^*+\mu_I. \end{aligned}$$

The characteristic equation of the Jacobian J associated with the equilibrium E_{03} given by

$$\xi^3+\widehat{\phi}_3\xi^2+\widehat{\phi}_2\xi+\widehat{\phi}_1=0, \tag{2.37}$$

The eigenvalues of the characteristic equation (2.37) are

$$\begin{aligned} \xi_1 &= -\mu_I, \\ \xi_2 &= \frac{r_2\left(k_2^2M^2+r_2\mu_I\right)}{k_2M\left(k_2M+r_2\right)}, \\ \xi_3 &= -\frac{r_1k_2^2M-\left(k_1k_2M\mu_I+r_1k_2\mu_I+r_2k_1\mu_I\right)}{k_2\left(k_2M+r_2\right)}. \end{aligned}$$

Then the healthy CD4+ T-cells and infected T-cells equilibrium point E_{03} is unstable, hence this eigenvalue ξ_2 will always be positive. □

2.5 The endemic equilibrium and its stability

2.5.1 Endemic equilibrium

The endemic equilibrium states $E_* = (C_*, T_*, I_*)$, then we have the following equations,

$$\begin{aligned} 0 &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)}{M}\right)-k_1T(t)\right], \\ 0 &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)}{M}\right)-pk_1C(t)-k_2I(t)\right], \\ 0 &= I(t)\left[k_2T(t)-\mu_I\right]. \end{aligned} \tag{2.38}$$

The steady state of C_*, T_*, I_* are solved, thus

$$T_* = \frac{\mu_I}{k_2}, \tag{2.39}$$

and

$$C_* = \frac{r_1k_2M-k_1M\mu_I-r_1\mu_I-r_1k_2I(t)}{r_1k_2}. \tag{2.40}$$

To find $I(t)$, we substitute equation (2.40) into equation two of (2.38), then simplifying the equation leads to

$$\begin{aligned}
r_1 M k_2 (pk_1 - k_2) I(t) &= M k_1 p r_1 k_2 M - r_2 k_1 M \mu_I - M k_1 p k_1 M \mu_I - M k_1 p r_1 \mu_I, \\
I_* &= \frac{M\left[k_1 p r_1 k_2 M - r_2 k_1 \mu_I - k_1 p k_1 M \mu_I - k_1 p r_1 \mu_I\right]}{r_1 M k_2 (pk_1 - k_2)}, \\
&= \frac{k_1\left[p r_1 k_2 M - (r_2 + k_1 p M + p r_1)\mu_I\right]}{r_1 k_2 (pk_1 - k_2)}, \\
&= \frac{r_1 p \mu_I \left(\frac{k_2 M}{\mu_I} - 1\right) - \mu_I (r_2 + k_2 M)}{r_1 k_2 (pk_1 - k_2)}, \\
&= \frac{\left[\frac{r_1 p (R_0 - 1)}{r_2 + M k_2} - 1\right](r_2 + M k_2)\mu_I}{r_1 k_2 (pk_1 - k_2)}, \\
&= \frac{[R_1 - 1](r_2 + M k_2)\mu_I}{r_1 k_2 (pk_1 - k_2)},
\end{aligned} \tag{2.41}$$

where $R_1 = \dfrac{r_1 p (R_0 - 1)}{r_2 + M k_2}$. Substituting equation (2.41) into equation (2.40), simplifying the equation then

$$\begin{aligned}
C_* &= M - \frac{\mu_I}{k_2} - \frac{k_1 M \mu_I}{k_2 r_1} + \frac{[k_1 p r_1 k_2 M - r_2 k_1 M \mu_I - k_1 p k_1 M \mu_I - k_1 p r_1 \mu_I]}{r_1 k_2 (k_2 - p k_1)}, \\
&= \frac{M k_2 r_1 k_2 - r_1 \mu_I k_2 - k_1 M \mu_I k_2 - r_2 \mu_I k_1}{r_1 k_2 (k_2 - p k_1)}, \\
&= \frac{M r_1 k_2^2 - (r_1 k_2 + k_1 M k_2 + r_2 k_1)\mu_I}{r_1 k_2 (k_2 - p k_1)}, \\
&= \frac{r_1 k_2 \mu_I \left(\frac{k_2 M}{\mu_I} - 1\right) - k_1 \mu_I (r_2 + k_2 M)}{r_1 k_2 (k_2 - p k_1)}, \\
&= \frac{\left[\frac{r_1}{k_1}\frac{k_2 (R_0 - 1)}{r_2 + M k_2} - 1\right](r_2 + M k_2) k_1 \mu_I}{r_1 k_2 (k_2 - p k_1)}, \\
&= \frac{[R_2 - 1](r_2 + M k_2) k_1 \mu_I}{r_1 k_2 (k_2 - p k_1)},
\end{aligned} \tag{2.42}$$

where $R_2 = \dfrac{r_1}{k_1}\dfrac{k_2 (R_0 - 1)}{r_2 + M k_2}$.
This equilibrium $E_* = (C_*, T_*, I_*)$ exist when $R_0 > 1$. To study the existence of the equilibruim, since $R_1, R_2 > 1$ which depends on $R_0 > 1$ and the positive equilibruim E_* exists.

2.5.2 Stability of endemic equilibrium

The linear stability of endemic equilibrium can be established by following the Descarte's rule of signs is used to find the roots of equations if and only if the conditions are satisfied.

Theorem 8. *The equilibrium point E_* is locally asymptotically stable, when $R_0 > 1$.*

Proof. To prove this statement where the endemic equilibrium $E_* = (C_*, T_*, I_*)$, the Jacobian matrix of this equilibrium is

$$J_{E_*} = \begin{pmatrix} -\phi_{11} & -\phi_{12} & -\phi_{13} \\ -\phi_{21} & -\phi_{22} & -\phi_{23} \\ 0 & -\phi_{32} & -\phi_{33} \end{pmatrix},$$

where

$$\begin{aligned}
\phi_{11} &= -r_1\left(1 - \frac{2C_* + T_* + I_*}{M}\right) + k_1 T_*, \phi_{12} = \left(\frac{r_1}{M} + k_1\right) C_*, \phi_{13} = \left(\frac{r_1}{M}\right) C_*, \\
\phi_{21} &= \left(\frac{r_2}{M} + pk_1\right) T_*, \phi_{22} = -r_2\left(1 - \frac{C_* + 2T_* + I_*}{M}\right) + pk_1 C_* + k_2 I_*, \\
\phi_{23} &= \left(\frac{r_2}{M} + k_2\right) T_*, \\
\phi_{31} &= 0, \phi_{32} = -k_2 I_*, \phi_{33} = -k_2 T_* + \mu_I.
\end{aligned}$$

The characteristic polynomial of the Jacobian J associated with the equilibrium E_* is given by

$$P(\xi) = \widehat{\phi}_0 \xi^3 + \widehat{\phi}_1 \xi^2 + \widehat{\phi}_2 \xi + \widehat{\phi}_3, \tag{2.43}$$

where the coefficient are equal to

$$\begin{aligned}
\widehat{\phi}_0 &= 1, \\
\widehat{\phi}_1 &= -\left[\phi_{11} + \phi_{22} + \phi_{33}\right], \\
\widehat{\phi}_2 &= \phi_{11}\phi_{22} + \phi_{11}\phi_{33} + \phi_{22}\phi_{33} - \left[\phi_{23}\phi_{32} + \phi_{12}\phi_{21}\right], \\
\widehat{\phi}_3 &= \phi_{11}\phi_{23}\phi_{32} + \phi_{12}\phi_{21}\phi_{33} - \left[\phi_{13}\phi_{21}\phi_{32} + \phi_{11}\phi_{22}\phi_{33}\right].
\end{aligned}$$

We analyze the nature of the polynomial to show that the endemic equilibrium is positive only when $R_0 > 1$.

Lemma 1. *The polynomial $P(\xi)$ has exactly one positive real root.*

Proof. We will first start by showing that the polynomial has at least one positive real root. The polynomial $P(\xi)$ is of the form

$$P(\xi) = \widehat{\phi}_0 \xi^3 + \widehat{\phi}_1 \xi^2 + \widehat{\phi}_2 \xi + \widehat{\phi}_3, \xi \in \mathbb{R}$$

To show that we have exactly one positive root, we will apply Descartes's Rule of signs. The theorem states that the number of positive real roots of a polynomial is equal to either the number of times or less than that by some even number [60]. For example, if a polynomial has coefficients that change sign three times, the number of positive real roots is either 3 or 1. We consider another example, if another polynomial has coefficients that change sign four times, the number of positive real roots is either $4, 2$ or 0. In our case, if we examine the coefficients of the polynomial $P(\xi)$, we see that $\widehat{\phi}_0 > 0$, $\widehat{\phi}_1 < 0$ and the coefficients of $\widehat{\phi}_2, \widehat{\phi}_3$ maybe either positive or negative depending on the value of the parameters.
We consider the cases:

- **Case 1**: If $\widehat{\phi}_2 > 0, \widehat{\phi}_3 > 0$, We will only have two sign changes.
- **Case 2**: If $\widehat{\phi}_2 < 0, \widehat{\phi}_3 < 0$, We will only have one sign change.

- **Case 3**: If $\widehat{\phi}_2 > 0, \widehat{\phi}_3 < 0$, We will only have three sign changes, which implies that we have one positive real root.
- **Case 4**: If $\widehat{\phi}_2 < 0, \widehat{\phi}_3 > 0$, We will only have two sign changes.

Therefore when case 3 is satisfied, the endemic equilibrium point E_* of the model 2.1 is locally asymptotically stable whenever $R_0 > 1$. □

□

Remark: Epidemiologically this means that if a few infected individuals are introduced into a susceptible population, each infected individual will produce on average more than one infected individual in the entire period of infectivity. This implies that when $R_0 > 1$, the disease will persist in the population.

2.6 Numerical Simulation

Investigating the behavior of the system (2.1), numerically using Matlab variable step Runge-Kutta method of order four. The parameters that were used were taken from the study by Lou et al [30, 33]. Table (2.2) shows the parameter values used in the simulations.

Table 2.2: Numerical values of parameters used in the simulations

Parameter and variables	Values
$C(0)$ initial cancer population	100 (cells mL^{-1})[Estimated]
$T(0)$ initial healthy CD4+ T-cells	250(cells mL^{-1}) [Estimated]
$I(0)$ initial infected T-cells	100(cells mL^{-1}) [Estimated]
k_1 rate of immune system killing cancer cells	$10^{-5} \sim 10^{-3}$ (ml/day) [30]
r_1 maximal proliferation rate of cancer cells	0.02 : 0.5 (ml/day) [30]
r_2 intrinsic growth rate of healthy CD4+ T-cells	$0.05 \sim 0.5$ (ml/day)[30]
p rate of losing immune due to infection	0.1 (ml/day)[30]
k_2 rate of infection	0.00005 : 0.0005 (/ml/day) [30]
μ_I death rate of infected T-cells	0.3 (/day) [30]
M carrying capacity	M=750 : 3000(/ml) [30]

The simulation results obtained, depicted in Figure (2.2), shown when $R_0 = 0.5$. We note that in Figure 2.2(a) the numerical results show that the number of healthy CD4+ T-cells increases. Figure (2.2) (b)-(c) represents the population of cancer cells and infected cells decreasing. Figure (2.2) (d)-(e) shows the interaction of cancer cells with healthy CD4+ T-cells and infected cells with healthy CD4+ T-cells. In Figure (2.3) give approximate solutions of our model when the reproduction satisfies $R_0 > 1$. These figures show that more than two years of periodic solutions are obtained from our simulation and the disease persists in the population. Existence of periodic solutions with different periods that epidemics can occur repeatedly when $R_0 > 1$. The simulation results obtained, depicted in Figure (2.4), show different values of R_0. We note that in Figure (2.4)(a)-(e) the numerical results show that the number of healthy CD4+ T-cells decrease as the rate of infection increase and cancer cells increases. Figure (2.5) (a), (b) and (c) shows the varying of the cancer and healthy CD4+ T-cells growth, where the proliferation rate is assumed to be $r_1 = 0.02 : 0.05$ and the immune systems killing rate is $k_1 = 0.0001$. It shows that when the proliferation rate is low the is less increase in cancer cells and the increase of healthy CD4+ T-cells, hence the killing rate of cancer cells by the healthy CD4+

T-cells is strong. Figure (2.5) (d), (e) and (f) Proliferation rate from $r_1 = 0.2 : 0.5$ where $k_1 = 0.00001$. In Figures (2.6),(a), (b) and (c) Varying the cancer cells and healthy CD4+ T-cells growth where the proliferation rate is $r_1 = 0.02 : 0.05$ and the immune systems killing rate is $k_1 = 0.00001$. It shows that when the proliferation rate is low there is a sliding increase in cancer cells and a reduction of healthy CD4+ T-cells, hence the killing rate of cancer cells by the healthy CD4+ T-cells is strong. Figure (2.6) (d), (e), and (f) when the proliferation rate is between $r_1 = 0.2 : 0.5$ and $k_1 = 0.0001$, It shows that when the proliferation rate is high there is an increase in cancer cells and a reduction of healthy CD4+ T-cells, hence the killing rate of cancer cells by the healthy CD4+ T-cells is weak.

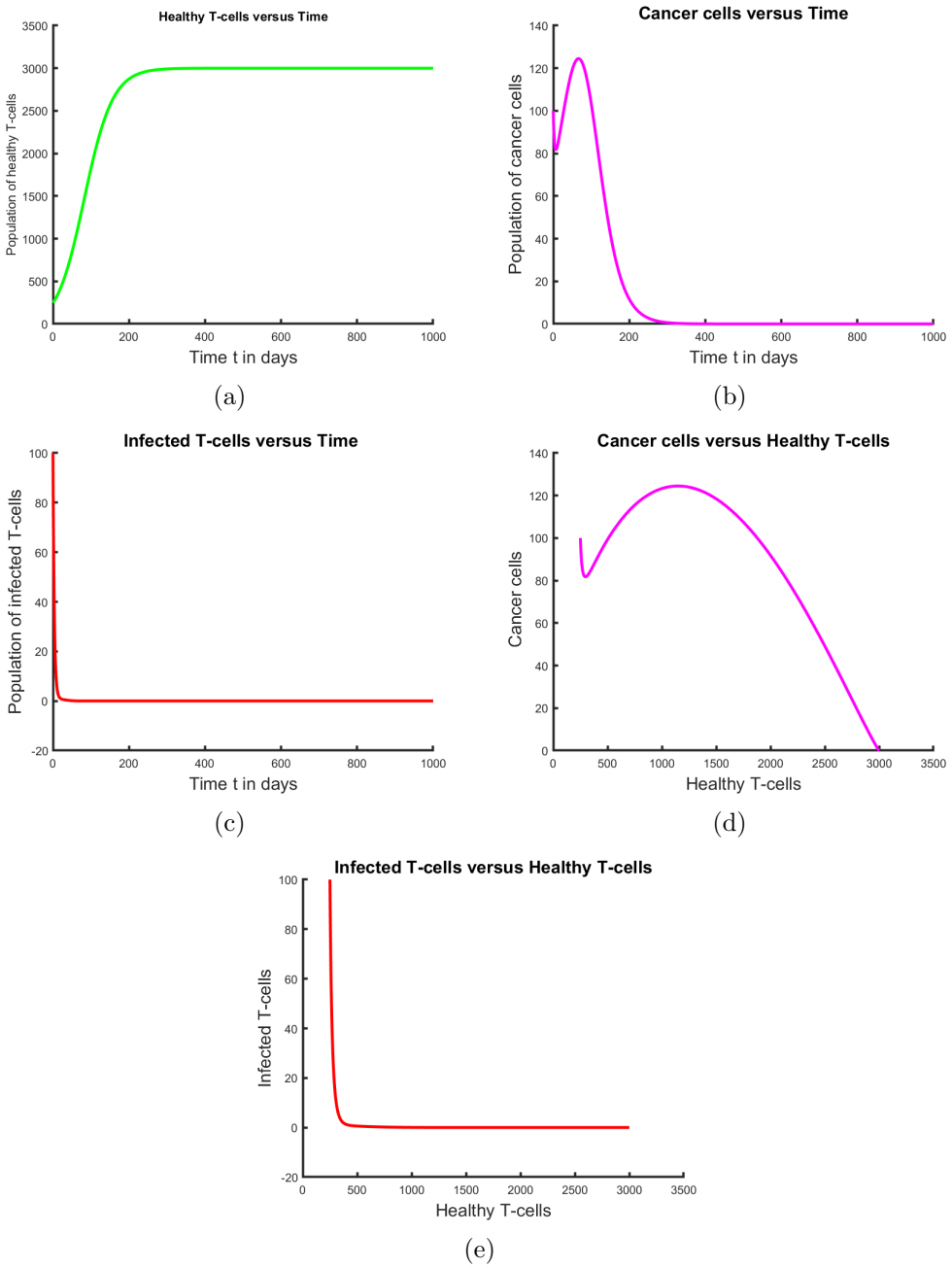
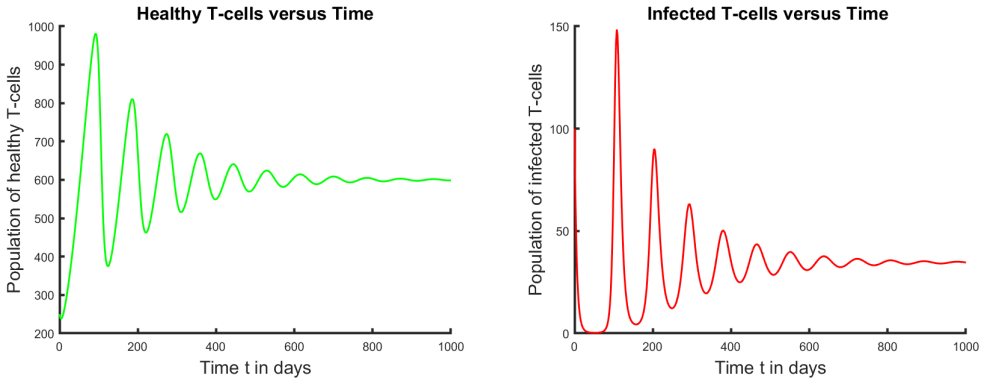
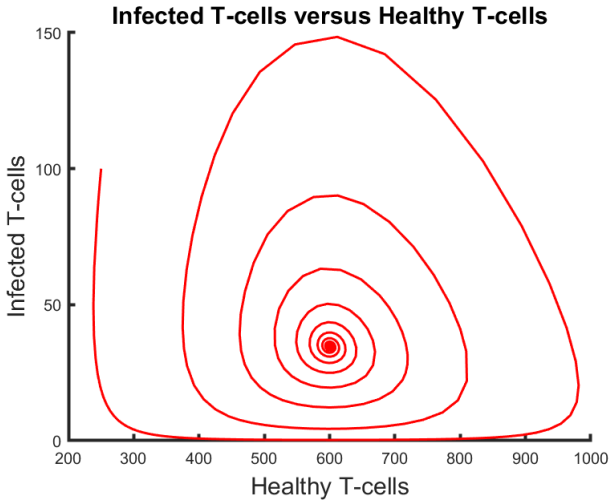


Figure 2.2: Variation of the cancer model related with HIV when $R_0 = 0.5$, where $r_1 = 0.03$, $k_2 = 0.00005$ and $M = 3000$, no cancer cells.



(a)

(b)



(c)

Figure 2.3: Variation of the cancer model related with HIV when $R_0 = 2.5$, where $r_1 = 0.03$, $k_2 = 0.0005$ and $M = 1500$.

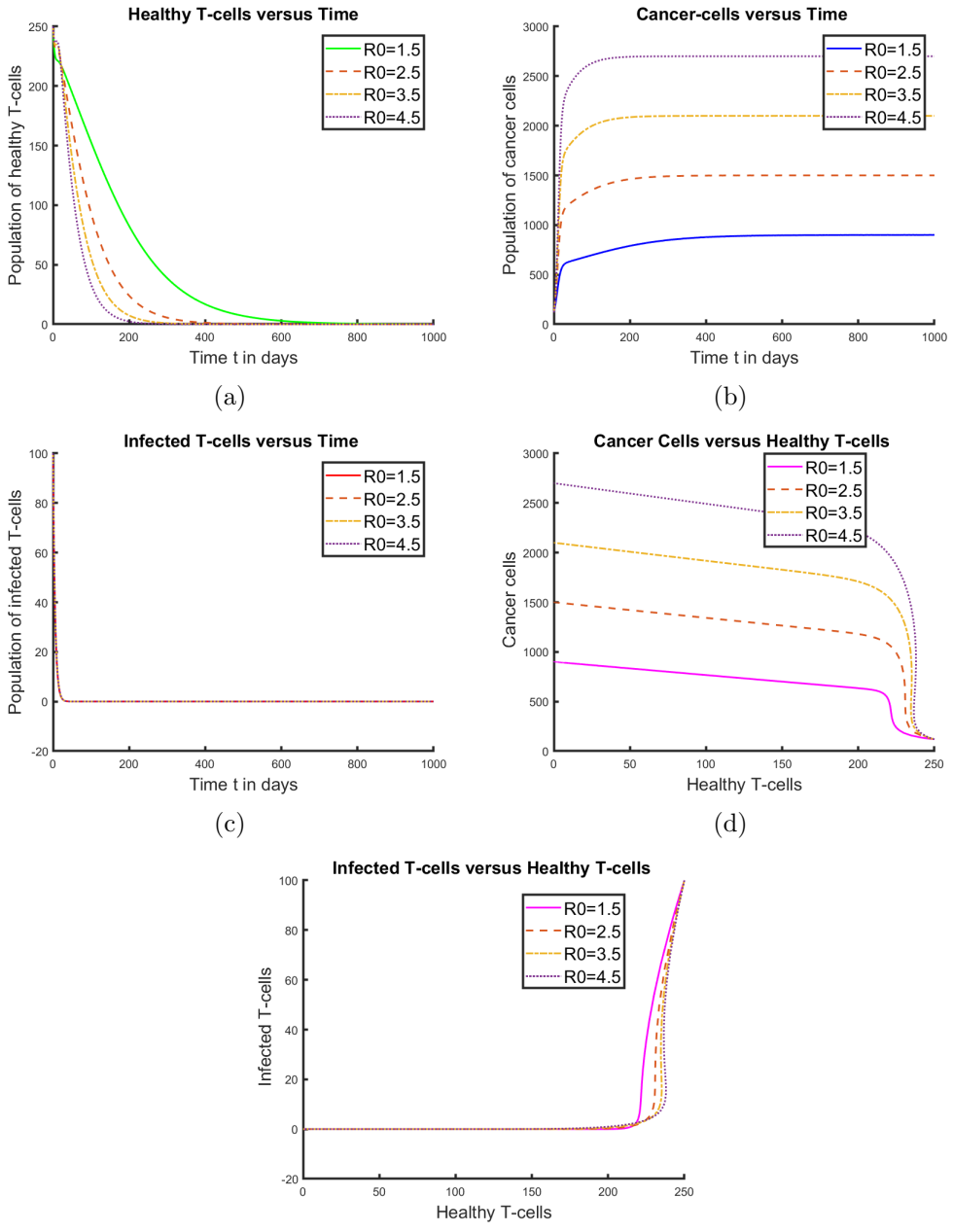


Figure 2.4: Variation of the endemic state showing different values of the reproduction, $R_0 = 1.5, 2.5, 3.5, 4.5$ where $r_1 = 0.5$, $k_2 = 0.0005$, $M = 900$,1500,2100,2700.

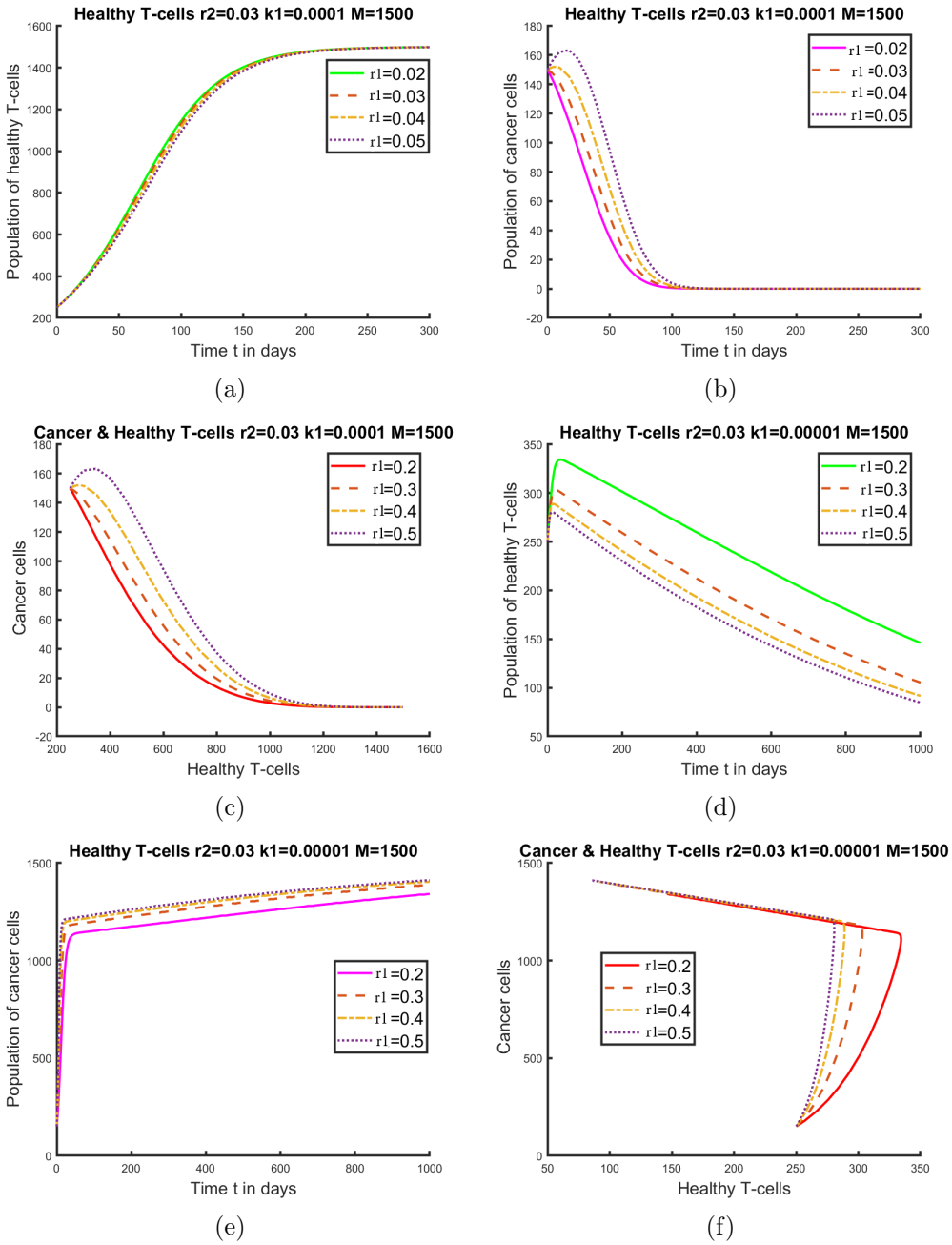


Figure 2.5: In (a), (b) and (c) we vary the cancer and healthy T-cells where $M = 1500$, $r_1 = 0.02 : 0.05$ and $k_1 = 0.0001$. Figure (2.5) (d), (e) and (f) $r_1 = 0.2 : 0.5$ where $k_1 = 0.00001$.

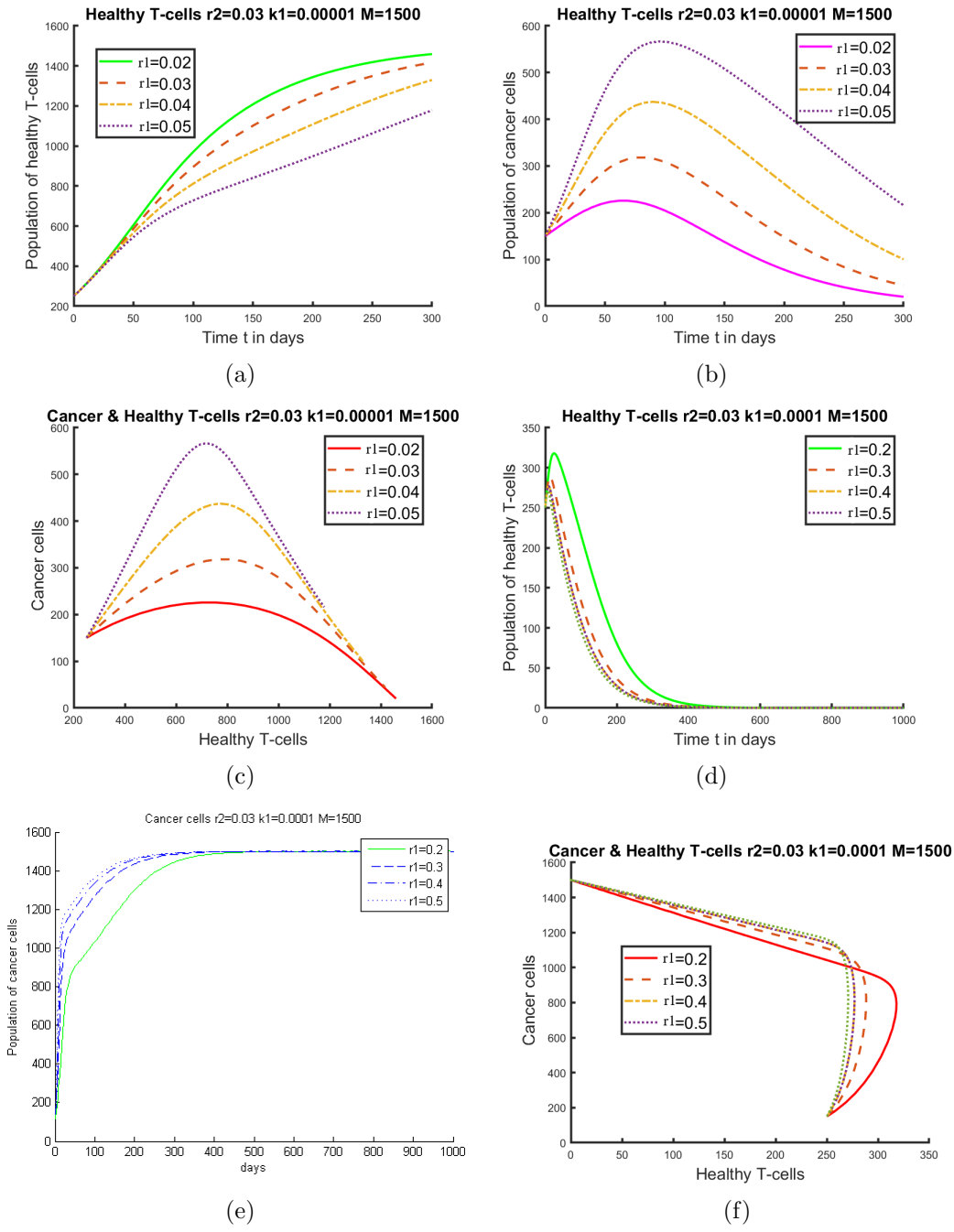


Figure 2.6: In (a), (b) and (c) we vary the cancer cells and healthy CD4+ T-cells where $M = 1500$, $r_1 = 0.02 : 0.05$ and $k_1 = 0.00001$. Figure (2.6) (d), (e) and (f) $r_1 = 0.2 : 0.5$ where $k_1 = 0.0001$.

2.7 Conclusion

In Chapter 2, the relationship between cancer cells, healthy CD4+ T-cells, and infected T-cells was studied using a proposed model that included cancer cells, healthy CD4+ T-cells, and infected T-cells. The disease-free and endemic equilibria were established, and stabilities were investigated. The disease-free equilibrium was found to be locally asymptotically stable, implying that the disease will inevitably vanish after some time. The model showed that the endemic free equilibrium is locally asymptotically stable when $R_0 > 1$, which implies that the infection rate is high. Employing Descartes's rule of signs to analyze the cancer cells and healthy CD4+ T-cells; healthy CD4+ T-cells and infected T-cells; and endemic equilibrium, the equilibria are stable by Descarte's rule of signs, otherwise, they are not stable. In this Chapter, the effects of certain parameters were investigated using numerical simulations. The variations of experimenting by computations were simulated to investigate the influence of parameters in the dynamical populations of cells. When $R_0 < 1$, we note that the effect of the immune system is strong, which implies that the proliferation rate of cancer growth is delayed and the HIV infected cells are weak to invade the system. The impact of $R_0 > 1$, shows the chaotic behavior of the dynamical system through some oscillations. To control the infection rate by blocking the replication of infected T-cells, the growth of cancer cells will be minimal. The parameters were varied to compare how the dynamics of cancer would grow in the model as the proliferation rate of cancer cells was investigated. In the simulations, it is observed that the lesser the proliferation rate the stronger the immune system, then the higher the proliferation rate the weaker the immune system, and the higher the cancer cells. In Chapter 3, the model will be investigated with the inclusion of cancer-infected T-cells which occurs as $R_0 > 1$.

Chapter 3: Impact of treatment in an HIV-Cancer co-infection model

3.1 Introduction

The theoretical study of cancer-related to HIV has a long history, a good summary can be found in Lou, Ruggeri, and Tebaldi [22, 30, 33]. We attempt to add to the existing literature by exploring the role of HIV cancer co-infection in the disease dynamics as well as addressing the impact of the optimal control. Several mathematical models have been designed and used to study the effect of both HIV and cancer related to HIV (e.g Kaposi Sarcoma) on the progression of incorporating the chemotherapy and HAART [5, 23]. Therefore, an optimal control strategy is mostly given by combining the cART (combine Antiretroviral Treatment) [20]. This chapter aims to depict the theoretical assessment of the impact of treatment in an HIV cancer co-infection model. The proposed model will be divided into two sections: The first section will consider the model without treatment and the second part will be a model incorporated with treatment.

3.2 Model formulation

The model that will be presented is an extension of the model by Lou et al [30]. Our model from theirs is differentiated by assumptions. The distinguished proposed assumption is the incorporation of the compartment with cancer HIV infected T-cells. Cancer cells are assumed to be created by a gene mutation. A summary of the model is managed in this manner, where there are four different cells: cancer cells, healthy CD4+ T-cells which represent the immune system, HIV-infected T-cells, and cancer HIV-infected T-cells.

Let $C(t)$ be the concentration of cancer cells, $T(t)$ the concentration of healthy CD4+ T-cells, $I(t)$ the concentration of HIV infected T-cells and $C_I(t)$ the concentration of cancer infected T-cells with HIV which is assumed to be infectious at time t. Cancer cells are formed through the abnormal growth of cells. The growth of cancer cells is given by

$$C(t)r_1\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)$$

which is the logistic growth function. The uncontrolled proliferation rate of the cancer cells is represented by r_1. The main objective is to identify at what rate will cancer cells grow. The system's carrying capacity is M. The immune system eliminates the cancer cells, where k_1 is the rate at which cancer cells are killed by the immune system. The rate of losing cancer cells due to infection is represented by k_3. The rate at which cancer cells with HIV-infected T-cells die out is represented by k_4. The rate of change of cancer cells is given by:

$$\frac{dC(t)}{dt} = C(t)\left[r_1\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - k_1 T(t) - (k_3+k_4)\, I(t)\right]. \tag{3.1}$$

The growth of healthy CD4+ T-cells is given by the term

$$T(t) r_2 \left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)$$

which is the logistic growth function for the healthy T-cells. The constant term r_2, is the intrinsic growth rate. The process of losing the immune system due to killing the cancer cells is given by $k_1 p T(t) C(t)$, where p is the rate of losing the immune system due to its killing of the cancer cells. The healthy CD4+ T-cells get infected at a rate of k_2, which is the infection rate that accounts for the overall effects of HIV-1 reproduction. The rate of co-infection (cancer infected T-cells) is represented by k_5. The proportion rate of healthy CD4+ T-cells killing the cancer infected T-cells is represent by β, then we have the term $(1-\beta)k_5 C_I(t)T(t)$, where $0 < \beta < 1$ [24]. The rate of change of healthy T-cells is given by:

$$\frac{dT(t)}{dt} = T(t)\left[r_2\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - p k_1 C(t) - k_2 I(t) - (1-\beta)\, k_5 C_I(t)\right]. \tag{3.2}$$

The infection process leads to the growth of infected cells and is modeled by the term $k_2 T(t) I(t)$. The death rate of the HIV-infected T-cells is μ_I. The rate of change of infected cells is given by:

$$\frac{dI(t)}{dt} = I(t)\left[k_2 T(t) + k_4 C(t) - \mu_I\right] + k_5 C_I(t) T(t). \tag{3.3}$$

The growth of cancer HIV-infected T-cells is given by the term

$$C_I(t) r_3 \left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)$$

which is the logistic growth function of the cancer HIV-infected T-cells. In the process of cancer and HIV-infected T-cells interaction, the cancer infected T-cells emerge, which is represented by $k_3 C(t) I(t)$ [57]. The constant term r_3 is the growth rate. The rate of change of cancer infected T-cells is given by:

$$\frac{dC_I(t)}{dt} = C_I(t)\left[r_3\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] + k_3 C(t) I(t) - \beta k_5 C_I T(t). \tag{3.4}$$

The above equations (3.1)-(3.4) result in the following system of equations:

$$\begin{aligned}
\frac{dC(t)}{dt} &= C(t)\left[r_1\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - k_1 T(t) - (k_3+k_4)\, I(t)\right],\\
\frac{dT(t)}{dt} &= T(t)\left[r_2\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - p k_1 C(t) - k_2 I(t) - (1-\beta)\, k_5 C_I(t)\right],\\
\frac{dI(t)}{dt} &= I(t)\left[k_2 T(t) + k_4 C(t) - \mu_I\right] + k_5 C_I(t) T(t),\\
\frac{dC_I(t)}{dt} &= C_I(t)\left[r_3\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] + k_3 C(t) I(t) - \beta k_5 C_I T(t).
\end{aligned} \tag{3.5}$$

The initial conditions are assumed to be

$$C(0) \geq 0, T(0) \geq 0, I(0) \geq 0, C_I(0) \geq 0. \tag{3.6}$$

3.3 Theoretical results

3.3.1 Basic properties

So, we demonstrate that all state variables are non-negative in order for the study to be epidemiologically valid and well-posed, $\forall t \geq 0$.

3.3.2 The existence and uniqueness of solution

Theorem 9. *Let* $\Gamma = \{\big(C(t), T(t), I(t), C_(t)_I\big) \in \mathbb{R}^4_+\}$ *denote the region defined by model system (3.5). Then, there exists a solution for model system (3.5) which is bounded in the region* Γ.

Proof. In order to prove the above theorem, the concept we derive is in [11]. Let

$$\begin{aligned}
f_1 &= C(t)\left[r_1\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - k_1 T(t) - (k_3 + k_4)\, I(t)\right], \\
f_2 &= T(t)\left[r_2\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - pk_1 C(t) - k_2 I(t) - (1-\beta)\, k_5 C_I(t)\right], \\
f_3 &= I(t)\left[k_2 T(t) + k_4 C(t) - \mu_I\right] + k_5 C_I(t) T(t), \\
f_4 &= C_I(t)\left[r_3\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] + k_3 C(t) I(t) - \beta k_5 C_I T(t).
\end{aligned} \tag{3.7}$$

It suffices to show that $\frac{\partial f_1}{\partial C(t)}, \frac{\partial f_2}{\partial T(t)}, \frac{\partial f_3}{\partial I(t)}$ and $\frac{\partial f_4}{\partial C_I(t)}$ are continuous. The partial deriva-

tives below are considered

$$\left|\frac{\partial f_1}{\partial C(t)}\right| = \left|r_1\left(1-\frac{2C(t)+T(t)+I(t)+C_I(t)}{M}\right)-k_1T(t)-(k_3+k_4)\,I(t)\right|<\infty,$$

$$\left|\frac{\partial f_1}{\partial T(t)}\right| = \left|-\frac{r_1C(t)}{M}-k_1C(t)\right|<\infty,$$

$$\left|\frac{\partial f_1}{\partial I(t)}\right| = \left|-\frac{r_1C(t)}{M}-(k_3+k_4)\,C(t)\right|<\infty,$$

$$\left|\frac{\partial f_1}{\partial C_I(t)}\right| = \left|-\frac{r_1C(t)}{M}\right|<\infty,$$

$$\left|\frac{\partial f_2}{\partial C(t)}\right| = \left|-\frac{r_2T(t)}{M}-pk_1T(t)\right|<\infty,$$

$$\left|\frac{\partial f_2}{\partial T(t)}\right| = \left|r_2\left(1-\frac{C(t)+2T(t)+I(t)+C_I(t)}{M}\right)-pk_1C(t)-k_2I(t)-(1-\beta)\,k_5C_I(t)\right|<\infty,$$

$$\left|\frac{\partial f_2}{\partial I(t)}\right| = \left|-\frac{r_2T(t)}{M}-k_2T(t)\right|<\infty,$$

$$\left|\frac{\partial f_2}{\partial C_I(t)}\right| = \left|-\frac{r_1T(t)}{M}-(1-\beta)\,k_5T(t)\right|<\infty,$$

$$\left|\frac{\partial f_3}{\partial C(t)}\right| = \left|k_4I(t)\right|<\infty,$$

$$\left|\frac{\partial f_3}{\partial T(t)}\right| = \left|k_2I(t)+k_5C_I(t)\right|<\infty,$$

$$\left|\frac{\partial f_3}{\partial I(t)}\right| = \left|k_2T(t)+k_4C(t)-\mu_I\right|<\infty,$$

$$\left|\frac{\partial f_3}{\partial C_I(t)}\right| = \left|k_5T(t)\right|<\infty,$$

$$\left|\frac{\partial f_4}{\partial C(t)}\right| = \left|-\frac{r_3C_I(t)}{M}+k_3I(t)\right|<\infty,$$

$$\left|\frac{\partial f_4}{\partial T(t)}\right| = \left|-\frac{r_3C_I(t)}{M}-\beta k_5C_I(t)\right|<\infty,$$

$$\left|\frac{\partial f_4}{\partial I(t)}\right| = \left|-\frac{r_3C_I(t)}{M}+k_3C(t)\right|<\infty,$$

$$\left|\frac{\partial f_4}{\partial C_I(t)}\right| = \left|r_3\left(1-\frac{C(t)+T(t)+I(t)+2C_I(t)}{M}\right)-\beta k_5T(t)\right|<\infty.$$

All these partial derivates are continuous and bounded, hence there exists a unique solution of equations (3.7). □

Theorem 10. *Assume the parameters of model (3.5) are nonnegative constants. A nonnegative solution of $C(0)$, $T(0)$, $I(0)$ and $C_I(0)$ for model (2.1) exists for all state variables with*

nonnegative initial conditions $C(0) \geq 0, T(0) \geq 0, I(0) \geq 0, C_I(0) \geq 0\ \forall t > 0$.

Proof. From the system (3.5), we have

$$\begin{aligned}
\frac{dC(t)}{dt} &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)-k_1T(t)-(k_3+k_4)\,I(t)\right]\\
&\geq C(t)r_1\left(1-\frac{C(t)}{M}\right),\\
\frac{dT(t)}{dt} &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)-pk_1C(t)-k_2I(t)-(1-\beta)\,k_5C_I(t)\right]\\
&\geq T(t)r_2\left(1-\frac{T(t)}{M}\right),\\
\frac{dI(t)}{dt} &= I(t)\left[k_2T(t)+k_4C(t)-\mu_I\right]+k_5C_I(t)T(t) \geq -\mu_I I(t),\\
\frac{dC_I(t)}{dt} &= C_I(t)\left[r_3\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right]+k_3C(t)I(t)-\beta k_5C_IT(t)\\
&\geq C_I(t)r_1\left(1-\frac{C_I(t)}{M}\right).
\end{aligned} \tag{3.8}$$

The initial concentration of the state variables are assumed to be: $C(0) = C_0$, $T(0) = T_0$, $I(0) = I_0$ and $C_I(0) = C_{I_0}$. They are assumed nonnegative so as to be biologically feasible. Using the second equation of (3.8), and applying separation of variables yields

$$\frac{dT(t)}{T(t)\left(1-\frac{T(t)}{M}\right)} \geq r_2dt. \tag{3.9}$$

The left-hand side of the equation (3.9), is expressed in partial fractions and integrated which leads to

$$\int \frac{dT(t)}{T(t)} + \int \frac{dT(t)}{M-T(t)} \geq \int r_2dt, \tag{3.10}$$

therefore

$$ln\left|T(t)\right| - ln\left|M-T(t)\right| \geq r_2t+c, \tag{3.11}$$

multipying (3.11) with negative sign

$$ln\left|M-T(t)\right| - ln\left|T(t)\right| \geq -r_2t-c, \tag{3.12}$$

then

$$\left|\frac{M-T(t)}{T(t)}\right| \geq e^{-c}e^{-r_2t}. \tag{3.13}$$

We define $c_1 = e^{-c}$, then the equation becomes

$$\frac{M-T(t)}{T(t)} \geq c_1e^{-r_2t} \tag{3.14}$$

Simplifying the equation (3.14) to obtain $T(t)$, where $A = \dfrac{M-T_0}{T_0}$ as $t = 0$ and $T(0) = T_0$. yields

$$T(t) \geq \frac{M}{1+Ae^{-r_2t}}. \tag{3.15}$$

If the same approach is used in equation one of the systems (3.9), then we obtain

$$C(t) \geq \frac{M}{1+Be^{-r_1 t}}, \tag{3.16}$$

where $B = \dfrac{M - C_0}{C_0}$ at $t = 0$ and $C(0) = C_0$.
Furthermore, the third equation of the system (3.9) becomes

$$I(t) \geq I(0)e^{-\int \mu_I dt} \geq 0. \tag{3.17}$$

If the same approach is used in equation four of the system (3.9), then we obtain

$$C_I(t) \geq \frac{M}{1+Pe^{-r_3 t}}, \tag{3.18}$$

where $P = \dfrac{M - C_{I_0}}{C_{I_0}}$ at $t = 0$ and $C_I(0) = C_{I_0}$.
This proves that $T(t)$, $C(t)$, $I(t)$ and $C_I(t)$ remain positive for $\forall t > 0$. This completes the proof. □

Theorem 11. *All solutions $C(t), T(t), I(t), C_I(t)$ of model (3.5) are bounded.*

Proof. We prove that the solutions of system (3.5) are uniformly bounded for $t > 0$, following Lou and Zhao [33]. We already showed in Theorem 1 that $C(t), T(t), I(t)$ and $C_I(t)$ remain positive for $\forall t > 0$. It then suffices to assume that $T(0) = T_0$, $C(0) = C_0$, $I(0) = I_0$ and $C_I(0) = C_{I_0}$, an assumption already made above. It is known from Lou and Zhao [33], that the T-cell concentration stabilizes at a level T_0, where T_0 is the positive root of F(T) = 0. Adopting this view, we then have $F(T) = 0$. Hence, this implies that the other equations of system (3.5) becomes zero at level $T(0) > 0$, $C_0 = 0$, $I_0 = 0$, $C_I(0) = 0$, where T_0 is the positive root, from equation 2 of system (3.5), we have

$$T(t)\left[r_2\left(1 - \frac{T(t)}{M}\right)\right] = F(T) = 0,$$

$$F(T) = r_2 M T(t) - r_2 T^2(t), \tag{3.19}$$

thus

$$0 = MT_0 - T_0^2, \tag{3.20}$$

where $T_0 = 0$ or $T_0 = M$. By summing equations $T(t)$ and $I(t)$ of system (3.5), we obtain

$$\frac{d\left(T(t) + I(t)\right)}{dt} \leq r_2 T_0 - \mu I(t). \tag{3.21}$$

Hence

$$\lim sup_{t\to\infty}(T(t) + I(t)) \leq \frac{r_2 T_0}{\mu_I} := M_1. \tag{3.22}$$

It follows from the first equation of the model system (3.5) that

$$\frac{dC(t)}{dt} \leq r_1 C(t)\left(1 - \frac{C(t)}{M}\right), \tag{3.23}$$

then the

$$\lim sup_{t\to\infty}(C(t)) \leq M := M_2. \tag{3.24}$$

It follows from the fourth equation of model system (3.5) that

$$\frac{dC_I(t)}{dt} \leq r_3 C_I(t)\left(1-\frac{C_I(t)}{M}\right), \tag{3.25}$$

hence the

$$\lim sup_{t\to\infty}(C_I(t)) \leq M := M_3. \tag{3.26}$$

All solutions of the system are bounded in the feasible region

$$\begin{aligned}\Gamma &= \{\big(C(t),T(t),I(t),C_I(t)\big) \in \mathbb{R}^3_+ : 0 \leq C_I(t) \leq M_3, 0 \leq C(t) \leq M_2,\\ &\quad 0 < T(t) \leq T_0, 0 < T(t)+I(t) \leq M_1\}.\end{aligned} \tag{3.27}$$

Thus Γ is positively invariant with respect to system (3.5). □

3.3.3 The disease-free equilibria and their stabilities

Linear stability is used to study the action of solutions that are similar to steady state. Linear stability analysis can determine if a steady state is stable or unstable.
Steady states are obtained by setting the right hand side of model (3.5) to zero, thus

$$\frac{dC(t)}{dt} = \frac{dT(t)}{dt} = \frac{dI(t)}{dt} = \frac{dC_I(t)}{dt} = 0.$$

The systems yields,

$$\begin{aligned}
0 &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - k_1 T(t) - (k_3+k_4)\, I(t)\right],\\
0 &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right) - pk_1 C(t) - k_2 I(t) - (1-\beta)\, k_5 C_I(t)\right],\\
0 &= I(t)\left[k_2 T(t) + k_4 C(t) - \mu_I\right] + k_5 C_I(t) T(t),\\
0 &= C_I(t)\left[r_3\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] + k_3 C(t) I(t) - \beta k_5 C_I(t) T(t).
\end{aligned} \tag{3.28}$$

3.3.4 Disease-free equilibrium

The term "disease-free equilibrium" (DFE) refers to a population that is free of disease and is obtained by setting system (3.5) to zero thus

$$\frac{dC(t)}{dt} = \frac{dT(t)}{dt} = \frac{dI(t)}{dt} = \frac{dC_I(t)}{dt} = 0.$$

In the DFE point $C(t) = I(t) = C_I(t) = 0$, when substituting into system (3.5), then we have

$$\begin{aligned}
T\left(1-\frac{T(t)}{M}\right) &= 0,\\
T(t) &= M,
\end{aligned} \tag{3.29}$$

therefore the DFE labelled as $E_1 = (0, M, 0, 0)$.

3.3.5 Computation of the basic reproduction number

To investigate the equilibrium's stability, we must first introduce the basic reproduction number R_0. The R_0 in a fully susceptible population, is described as the estimated number of secondary infections caused by an index event [46]. The R_0 involves the product of infection rate and the duration of infection. The reproduction number acts as a predictor of disease outbreaks and aids in the development of control strategies. The analytical expression of R_0 indicates which element of the system can be controlled to reduce the outbreak of the disease [55].
To calculate the next-generation matrix of the system (3.5), we will have to determine how many different ways can new diseases spread and how many different ways individuals can switch between compartments. The infected variables are firstly ordered by rewritting the vectors in the form,

$$\begin{aligned} \frac{dI(t)}{dt} &= I(t)\left[k_2T(t) + k_4C(t) - \mu_I\right] + k_5C_I(t)T(t), \\ \frac{dC_I(t)}{dt} &= C_I(t)\left[r_3\left(1 - \frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] + k_3C(t)I(t) - \beta k_5 C_I T(t). \end{aligned} \tag{3.30}$$

We then obtain,

$$\mathcal{F} = \begin{pmatrix} k_2I(t)T(t) + k_4C(t)I(t) + k_5C_I(t)T(t) \\ \\ 0 \end{pmatrix}, \tag{3.31}$$

and

$$\mathcal{V} = \begin{pmatrix} I(t)\mu_I \\ \\ -C_I(t)\left[r_3\left(1 - \dfrac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right] - k_3C(t)I(t) + \beta k_5 C_I T(t) \end{pmatrix}, \tag{3.32}$$

where $\mathcal{F}$ represents the rate of appearance of new infection and $\mathcal{V}$ denotes the rate of transfer of individuals. Differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to $I(t)$ and $C_I(t)$, then substituting the disease free equilibrium $E_1 = (0, M, 0, 0)$ into the states $C(t), T(t), I(t), C_I(t)$, we obtain

$$F = \begin{pmatrix} k_2M & k_5M \\ \\ 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu_I & 0 \\ \\ 0 & \beta k_5 M \end{pmatrix},$$

where

$$V^{-1} = \begin{pmatrix} \dfrac{1}{\mu_I} & 0 \\ \\ 0 & \dfrac{1}{\beta k_5 M} \end{pmatrix}.$$

The next-generation matrix for model (3.5) is given by FV^{-1}. It follows the spectral radius of matrix FV^{-1} which is $\rho(FV^{-1}) = \dfrac{k_2 M}{\mu_I} + \dfrac{1}{\beta}$. The reproduction number R_I is given as the spectral radius of

$$\rho(FV^{-1}) = R_I = \frac{k_2 M}{\mu_I} + \frac{1}{\beta}, \tag{3.33}$$

where

$$R_I = R_0 + R_0^{CoInfection},$$

in simple form

$$R_I = R_0 + R_0^{CoInf}. \tag{3.34}$$

The R_I represents the number of healthy CD4+ T-cells generated as a result of one infected T-cell. The goal for reducing the chance of cancer-related HIV outbreak is to reduce R_I, the R_I can be managed by reducing the infected T-cells density. Interpreting the result biologically, for $R_I < 1$, it means that the individual will not get infected by HIV. Preventing individuals from getting infected with HIV helps to avoid the infection of cancer that is related to HIV. When $R_I > 1$ the outbreak will occur, which implies that there are high chances of cancer that is related to HIV.

3.3.6 The cancer cells and healthy CD4+ T-cells equilibrium

The cancer cells and healthy T-cells equilibrium E_2, where $I(t) = 0$, the system reduces to

$$\begin{aligned} 0 &= r_1 \left(1 - \frac{C(t) + T(t)}{M}\right) - k_1 T(t), \\ 0 &= r_2 \left(1 - \frac{C(t) + T(t)}{M}\right) - p k_1 C(t). \end{aligned} \tag{3.35}$$

Rearranging the first equation of (3.35) such that $C(t) = \frac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}$, we then substitute $C(t)$ into the second equation of (3.35), then

$$0 = r_2 M - r_2 \left[\frac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}\right] - r_2 T(t) - M p k_1 \left[\frac{r_1 M - r_1 T(t) - M k_1 T(t)}{r_1}\right]. \tag{3.36}$$

Rearranging the equation and making $T(t)$ the subject and labeling it as $\bar{T}$, we have

$$\bar{T} = \frac{r_1 p M}{r_2 + p\,(r_1 + M k_1)}. \tag{3.37}$$

Substituting $\bar{T}$ into the second equation of (3.35) and rearranging by making $C(t)$ the subject of the formula and labeling it as $\bar{C}$ yeilds,

$$\bar{C} = \frac{r_2 M}{r_2 + p\,(r_1 + M k_1)}. \tag{3.38}$$

The cancer cells and healthy CD4+ T-cells equilibrium $E_2 = \left(\bar{C}, \bar{T}, 0, 0\right)$.

3.3.7 The healthy CD4+ T-cells and infected T-cells equilibrium

The healthy T-cells and infected T-cells equilibrium states E_3 where $C(t) = 0$ and $C_I(t) = 0$, then we have the following equations,

$$\begin{aligned} 0 &= T(t)\left[r_2\left(1-\tfrac{T(t)+I(t)}{M}\right)-k_2 I(t)\right], \\ 0 &= I(t)\left[k_2 T(t)-\mu_I\right], \end{aligned} \tag{3.39}$$

where $T(t)$ is written as T^* and $I(t)$ as I^*

$$T^* = \frac{\mu_I}{k_2}. \tag{3.40}$$

We substitute T^* in the first equation of (3.39),

$$0 = r_2 - \frac{r_2\mu_I}{k_2 M} - \frac{r_2 I(t)}{M} - k_2 I(t),$$

then

$$I^* = \frac{r_2\left(k_2 M-\mu_I\right)}{k_2\left(r_2+k_2 M\right)},$$

therefore

$$I^* = \frac{r_2\mu_I\left(R_0-1\right)}{k_2\left(r_2+k_2 M\right)}. \tag{3.41}$$

This equilibrium $E_3 = (0, \frac{\mu_I}{k_2}, \frac{r_2\mu_I\left(R_0-1\right)}{k_2\left(r_2+k_2 M\right)}, 0)$ exist when $R_0 > 1$. When R_0 is increasing, the number of CD4+ T-cells declines and the number of infected T-cells rises.

3.3.8 The cancer cells, healthy T-cells and infected T-cells equilibrium

The cancer cells, healthy CD4+ T-cells and infected T-cells equilibrium states E_4 where $C_I(t) = 0$, then we have the following equations,

$$\begin{aligned} 0 &= C(t)\left[r_1\left(1-\tfrac{C(t)+T(t)+I(t)}{M}\right)-k_1 T(t)-\left(k_3+k_4\right)I(t)\right], \\ 0 &= T(t)\left[r_2\left(1-\tfrac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)-pk_1 C(t)-k_2 I(t)\right], \\ 0 &= I(t)\left[k_2 T(t)+k_4 C(t)-\mu_I\right]. \end{aligned} \tag{3.42}$$

4 Using mathematica to solve the unknowns $C(t), T(t), I(t)$, then we have C^{**}, T^{**} and I^{**} as

$$
\begin{aligned}
C^{**} &= \frac{\mu_I k_1 \left[Mk_2 + r_2 - p\left(M\left(k_3+k_4\right)+r_1\right)\right] + \mu_I\left(1-R_0\right)\left(k_2 r_1 - r_2\left(k_3+k_4\right)\right)}{k_1 k_4 \left[Mk_2 + r_2 - p\left(M\left(k_3+k_4\right)+r_1\right)\right] + \left(k_4-k_2\right)\left(k_2 r_1 - r_2\left(k_3+k_4\right)\right)}, \\
T^{**} &= \frac{\left(\mu_I - Mk_4\right)\left(r_2\left(k_3+k_4\right) - k_2 r_1\right)}{k_1 k_4 \left[Mk_2 + r_2 - p\left(M\left(k_3+k_4\right)+r_1\right)\right] + \left(k_4-k_2\right)\left(k_2 r_1 - r_2\left(k_3+k_4\right)\right)}, \qquad (3.43) \\
I^{**} &= \frac{k_1\left(\mu_I - Mk_4\right)\left(pr_1 - r_2\right)}{k_1 k_4 \left[Mk_2 + r_2 - p\left(M\left(k_3+k_4\right)+r_1\right)\right] + \left(k_4-k_2\right)\left(k_2 r_1 - r_2\left(k_3+k_4\right)\right)}.
\end{aligned}
$$

These cancer cells, healthy CD4+ T-cells and infected T-cells equilibrium, $E_4 = (C^{**}, T^{**}, I^{**}, 0)$ exist when,

$$
\begin{array}{ll}
Mk_2 + r_2 & > p\left(M\left(k_3+k_4\right)+r_1\right), \\
k_2 r_1 & > r_2\left(k_3+k_4\right), \\
Mk_2 + r_2 & > p\left(M\left(k_3+k_4\right)+r_1\right), \\
k_1 k_4 \left[Mk_2 + r_2 - p\left(M\left(k_3+k_4\right)+r_1\right)\right] & > \left(k_4-k_2\right)\left(k_2 r_1 - r_2\left(k_3+k_4\right)\right), \\
\mu_I & > Mk_4, \\
pr_1 & > r_2.
\end{array} \qquad (3.44)
$$

3.4 Stability analysis of the disease-free equilibria

The stability of each system equilibrium is discussed in this section (3.5). Let $E(\bar{C}, \bar{T}, \bar{I}, \bar{C}_I)$ to be any arbitrary equilibrium of (3.5). The system's Jacobian matrix is given by

$$
J_E = \begin{pmatrix}
X & -\left(\frac{r_1}{M}+k_1\right)\bar{C} & -\left(\frac{r_1}{M}+(k_3+k_4)\right)\bar{C} & -\frac{r_1\bar{C}}{M} \\
-\left(\frac{r_2}{M}+pk_1\right)\bar{T} & Y & -\left(\frac{r_2}{M}+k_2\right)\bar{T} & -\left(\frac{r_2}{M}+(1-\beta)\,k_5\right)\bar{T} \\
k_4\bar{I} & k_2\bar{I}+k_5\bar{C}_I & k_2\bar{T}+k_4\bar{C}-\mu_I & k_5\bar{T} \\
-\frac{r_3\bar{C}_I}{M}+k_3\bar{I} & -\frac{r_3\bar{C}_I}{M} & -\frac{r_3\bar{C}_I}{M}+k_3\bar{C} & Z
\end{pmatrix},
$$

where

$$
\begin{aligned}
X &= r_1\left(1-\frac{2\bar{C}+\bar{T}+\bar{I}+\bar{C}_I}{M}\right) - k_1\bar{T} - \left(k_3+k_4\right)\bar{I}, \\
Y &= r_2\left(1-\frac{\bar{C}+2\bar{T}+\bar{I}+\bar{C}_I}{M}\right) - pk_1\bar{C} - k_2\bar{I} - \left(1-\beta\right)k_5\bar{C}_I, \\
Z &= r_3\left(1-\frac{\bar{C}+\bar{T}+\bar{I}+2\bar{C}_I}{M}\right) - \beta k_5\bar{T}.
\end{aligned}
$$

3.4.1 Stability of disease-free equilibrium

Theorem 12. *The equilibrium point E_1 is stable if and only if $R_0 < 1$.*

Proof. The Jacobian matrix at $E_1 = (0, M, 0, 0)$ is given by

$$J_{E_1} = \begin{bmatrix} -k_1M - \lambda_1 & 0 & 0 & 0 \\ -r_2 - pk_1M & -r_2 - \lambda_2 & -r_2 - k_2M & -r_2 - (1-\beta)\,k_5M \\ 0 & 0 & k_2M - \mu_I - \lambda_3 & k_5M \\ 0 & 0 & 0 & -\beta k_5 - \lambda_4 \end{bmatrix}.$$

The eigenvalues of J_{E_1} are

$$\begin{aligned} \lambda_1 &= -k_1M, \\ \lambda_2 &= -r_2, \\ \lambda_3 &= \mu_I(R_0 - 1), \\ \lambda_4 &= -\beta k_5. \end{aligned}$$

The eigenvalues of J_{E_1} are negative when $R_0 < 1$, the equilibrium will be stable otherwise is unstable. □

Remark: For us to have a stable equilibrium in which only the healthy CD4+ T-cells are present (no HIV and cancer). The rate at which cancer cells are generated must be less than the rate at which cancer cells are cleared by the immune system.

3.4.2 The cancer cells and healthy CD4+ T-cells equilibrium

Theorem 13. *The equilibrium point E_2 is stable when applying case 1, which is $a_1 > 0, b_1 > 0, a_0 > 0, b_0 > 0$, otherwise it is unstable.*

Proof. For the equilibrium solution $E_2 = (\bar{C}, \bar{T}, 0, 0)$, the Jacobian matrix is

$$J_{E_2} = \begin{pmatrix} q_{11} & -\left(\frac{r_1}{M} + k_1\right)\bar{C} & -\left(\frac{r_1}{M} + (k_3 + k_4)\right)\bar{C} & -\frac{r_1\bar{C}}{M} \\ -\left(\frac{r_2}{M} + pk_1\right)\bar{T} & q_{22} & -\left(\frac{r_2}{M} + k_2\right)\bar{T} & -\left(\frac{r_2}{M} + (1-\beta)\,k_5\right)\bar{T} \\ 0 & 0 & q_{33} & k_5\bar{T} \\ 0 & 0 & k_3\bar{C} & q_{44} \end{pmatrix},$$

where $q_{11} = r_1\left(1 - \dfrac{2\bar{C} + \bar{T}}{M}\right) - k_1\bar{T}$,$q_{22} = r_2\left(1 - \dfrac{\bar{C} + 2\bar{T}}{M}\right) - pk_1\bar{C}$, $q_{33} = k_2\bar{T} + k_4\bar{C} - \mu_I$ and $q_{44} = r_3\left(1 - \dfrac{\bar{C} + \bar{T}}{M}\right) - \beta k_5\bar{T}$. The eigenvalues will be given by the determinant below,

$$\begin{vmatrix} r_1\left(1 - \dfrac{2\bar{C} + \bar{T}}{M}\right) - k_1\bar{T} - \lambda & -\left(\frac{r_1}{M} + k_1\right)\bar{C} & -\left(\frac{r_1}{M} + (k_3 + k_4)\right)\bar{C} & -\dfrac{r_1\bar{C}}{M} \\ -\left(\frac{r_2}{M} + pk_1\right)\bar{T} & A^1* & -\left(\frac{r_2}{M} + k_2\right)\bar{T} & -\left(\dfrac{r_2}{M} + (1-\beta)\,k_5\right)\bar{T} \\ 0 & 0 & k_2\bar{T} + k_4\bar{C} - \mu_I - \lambda & k_5\bar{T} \\ 0 & 0 & k_3\bar{C} & r_3\left(1 - \frac{\bar{C}+\bar{T}}{M}\right) - \beta k_5\bar{T} - \lambda \end{vmatrix} = 0.$$

Where $A^1* = r_2\left(1-\frac{\bar{C}+2\bar{T}}{M}\right) - pk_1\bar{C} - \lambda$, then we have

$$\left[r_1\left(1-\frac{2\bar{C}+\bar{T}}{M}\right)-k_1\bar{T}-\lambda\right]\begin{vmatrix} A^1* & -\left(\frac{r_2}{M}+k_2\right)\bar{T} & -\left(\frac{r_2}{M}+(1-\beta)\,k_5\right)\bar{T} \\ 0 & k_2\bar{T}+k_4\bar{C}-\mu_I-\lambda & k_5\bar{T} \\ 0 & k_3\bar{C} & r_3\left(1-\frac{\bar{C}+\bar{T}}{M}\right)-\beta k_5\bar{T}-\lambda \end{vmatrix}$$

$$-\left[\left(\frac{r_2}{M}+pk_1\right)\bar{T}\right]\begin{vmatrix} -\left(\frac{r_1}{M}+k_1\right)\bar{C} & -\left(\frac{r_1}{M}+(k_3+k_4)\right)\bar{C} & -\frac{r_1\bar{C}}{M} \\ 0 & k_2\bar{T}+k_4\bar{C}-\mu_I-\lambda & k_5\bar{T} \\ 0 & k_3\bar{C} & r_3\left(1-\frac{\bar{C}+\bar{T}}{M}\right)-\beta k_5\bar{T}-\lambda \end{vmatrix} = 0.$$

The characteristic polynomial will be obtained from the equation below

$$\left[\left(r_1\left(1-\frac{2\bar{C}+\bar{T}}{M}\right)-k_1\bar{T}-\lambda\right)\left(r_2\left(1-\frac{\bar{C}+2\bar{T}}{M}\right)-pk_1\bar{C}-\lambda\right)-\left(\frac{r_2}{M}+pk_1\right)\left(\frac{r_1}{M}+k_1\right)\bar{T}\bar{C}\right]$$
$$\left[\left(k_2\bar{T}+k_4\bar{C}-\mu_I-\lambda\right)\left(r_3\left(1-\frac{\bar{C}+\bar{T}}{M}\right)-\beta k_5\bar{T}-\lambda\right)-k_3k_5\bar{T}\bar{C}\right]=0. \tag{3.45}$$

The following characteristic equations are given as:

$$\lambda^2 + a_1\lambda + a_0 = 0, \tag{3.46}$$

or

$$\lambda^2 + b_1\lambda + b_0 = 0, \tag{3.47}$$

where

$$\begin{aligned} a_1 &= -\left[r_1\left(1-\frac{2\bar{C}+\bar{T}}{M}\right)-k_1\bar{T}+r_2\left(1-\frac{\bar{C}+2\bar{T}}{M}\right)-pk_1\bar{C}\right], \\ a_0 &= \left[r_1\left(1-\frac{2\bar{C}+\bar{T}}{M}\right)-k_1\bar{T}\right]\left[r_2\left(1-\frac{\bar{C}+2\bar{T}}{M}\right)-pk_1\bar{C}\right]-\left(\frac{r_2}{M}+pk_1\right)\left(\frac{r_1}{M}+k_1\right)\bar{T}\bar{C}, \\ b_1 &= -\left[k_2\bar{T}+k_4\bar{C}-\mu_I+r_3\left(1-\frac{\bar{C}+\bar{T}}{M}\right)-\beta k_5\bar{T}\right], \\ b_0 &= \left[k_2\bar{T}+k_4\bar{C}-\mu_I\right]\left[r_3\left(1-\frac{\bar{C}+\bar{T}}{M}\right)-\beta k_5\bar{T}\right]-k_3k_5\bar{T}\bar{C}. \end{aligned} \tag{3.48}$$

The trace and determinant are obtained from this equation, where a_1 and b_1 is the trace, a_0 and b_0 is the determinant. Then recalling equations (3.38) and (3.37), which is $\bar{T}$ and $\bar{C}$ we substitute in the equations of (3.48). Mathematica software was employed to simplify all the equations to the simplest form which will be given below

$$\begin{aligned}
a_1 &= \frac{pr_1^2 + Mk_1r_2 + r_1k_1Mp^2 + r^2 - k_1Mp\left(r_1 + r_2\right)}{r_2 + p\left(r_1 + Mk_1\right)},\\
a_0 &= \frac{Mk_1\left[r_1r_2p\left(r_1^2r_2 + r_1p + 1\right) + r_2^2\left(r_1 + r_2\right) - \left(3r_1r_2p\left(r_1 + r_2\right) + p\left(r_1^2p^2 + r_2^2\right)\right)\right]}{\left[r_2 + p\left(r_1 + Mk_1\right)\right]^2},\\
b_1 &= \frac{\mu_Ip\left(r_1 + Mk_1\right) + r_2\left(\mu_I\left[1 - R_0\right] + \beta Mk_5\right) - Mp\left(r_1k_4 + r_3k_1\right)}{r_2 + p\left(r_1 + Mk_1\right)},\\
b_0 &= \frac{r_2Mk_5\left[Mpk_1\left(\beta\mu_I + r_1Mpk_4\right) + \beta r_1p\mu_I + r_2\beta\left(1 - R_0\right)\right] - Mpk_1\left[Mp\left(\mu_Ik_1 + r_1r_2Mk_5\left(k_3 + \beta k_4\right)\right.\right.}{\left[r_2 + p\left(r_1 + Mk_1\right)\right]^2}
\end{aligned} \tag{3.49}$$

In this equilibrium point $R_0 < 1$, assuming these cases apply
Case 1: If $a_1 > 0, b_1 > 0, a_0 > 0, b_0 > 0$ then all the eigenvalues are negative.
Case 2: If one of either the trace or determinant is positive then this emplies that one eigenvalue will be positive.

□

3.4.3 The healthy CD4+ T-cells and infected T-cells equilibrium

Theorem 14. *The equilibrium point E_3 is unstable, when $\lambda_2 > 0$ and exists if and only if $R_0 > 1$.*

Proof. For the equilibrium solution $E_3 = (0, \frac{\mu_I}{k_2}, \frac{r_2\mu_I\left(R_0 - 1\right)}{k_2\left(r_2 + k_2M\right)}, 0)$, the Jacobian matrix is

$$J_{E_3} = \begin{pmatrix}
Q_{11} & 0 & 0 & 0\\
-\left(\frac{r_2}{M} + pk_1\right)T^* & Q_{22} & -\left(\frac{r_2}{M} + k_2\right)T^* & -\left(\frac{r_2}{M} + \left(1 - \beta\right)k_5\right)T^*\\
k_4I^* & k_2I^* & k_2T^* - \mu_I & k_5T^*\\
k_3I^* & 0 & 0 & Q_{44}
\end{pmatrix},$$

where $Q_{11} = r_1\left(1 - \frac{T^* + I^*}{M}\right) - k_1T^* - \left(k_3 + k_4\right)I^*$, $Q_{22} = r_2\left(1 - \frac{2T^* + I^*}{M}\right) - k_2I^*$, $Q_{44} = r_3\left(1 - \frac{T^* + I^*}{M}\right) - \beta k_5T^*$. The eigenvalues will be obtained from the determinant

$$a_1\begin{vmatrix}
r_2\left(1 - \frac{2T^* + \bar{I}}{M}\right) - k_2I^* - \lambda & -\left(\frac{r_2}{M} + k_2\right)T^* & -\left(\frac{r_2}{M} + \left(1 - \beta\right)k_5\right)T^*\\
k_2I^* & k_2T^* - \mu_I - \lambda & k_5T^*\\
0 & 0 & a_2
\end{vmatrix} = 0,$$

where

$$a_1 = r_1\left(1-\frac{T^*+I^*}{M}\right)-k_1T^*-(k_3+k_4)\,I^*-\lambda, \tag{3.50}$$

$$a_2 = r_3\left(1-\frac{T^*+I^*}{M}\right)-\beta k_5T^*-\lambda. \tag{3.51}$$

The determinant gives the following characteristic equation as:

$$a_1a_2\left[\left(r_2\left(1-\frac{2T^*+I^*}{M}\right)-k_2I^*-\lambda\right)(k_2T^*-\mu_I-\lambda)+\left(\frac{r_2}{M}+k_2\right)T^*k_2I^*\right]=0, \tag{3.52}$$

which leads to the following equations, where $a_1=0$ and $a_2=0$ then

$$\begin{aligned}
0 &= r_1\left(1-\tfrac{T^*+I^*}{M}\right)-k_1T^*-(k_3+k_4)\,I^*-\lambda_1,\\
0 &= r_3\left(1-\tfrac{T^*+I^*}{M}\right)-\beta k_5T^*-\lambda_2,\\
0 &= \left(r_2\left(1-\tfrac{2T^*+I^*}{M}\right)-k_2I^*-\lambda_3\right)(k_2T^*-\mu_I-\lambda_3)+\left(\tfrac{r_2}{M}+k_2\right)T^*k_2I^*.
\end{aligned} \tag{3.53}$$

The eigenvalue of equations in the system (3.53) are presented where the equations of $\bar{T}$ and $\bar{I}$ are recalled as (3.43) and (3.41) then this leads to

$$\begin{aligned}
\lambda_1 &= \frac{\mu_I\left[k_1\left(Mk_2+r_2\right)-\left[\left(R_0-1\right)\left(r_1k_2-r_2\left(k_2+k_4\right)\right)\right]\right]}{k_2\left(Mk_2+r_2\right)},\\
\lambda_2 &= -\frac{\beta\mu_Ik_5}{k_2}+\frac{r_2\mu_I\left(R_0-1\right)}{r_2+Mk_2}.
\end{aligned} \tag{3.54}$$

The following conditions follows:
Eigenvalue $\lambda_1<0$, since $k_1\left(Mk_2+r_2\right)<\left(R_0-1\right)\left(r_1k_2-r_2\left(k_2+k_4\right)\right)$.
Eigenvalue $\lambda_2>0$, since $\dfrac{r_2\mu_I\left(R_0-1\right)}{r_2+Mk_2}>\dfrac{\beta\mu_Ik_5}{k_2}$.

Finding the other eigenvalues leads to

$$\left(r_2\left(1-\frac{2T^*+I^*}{M}\right)-k_2I^*-\lambda_3\right)(k_2T^*-\mu_I-\lambda_3)+\left(\frac{r_2}{M}+k_2\right)T^*k_2I^*=0. \tag{3.55}$$

Applying the product and simplifying the equation yields

$$\lambda_3^2+\left[\mu_I+k_2I^*-k_2T^*-r_2\left(1-\frac{2T^*+I^*}{M}\right)\right]\lambda_3+\left[r_2\left(1-\frac{2T^*+I^*}{M}\right)-k_2I^*\right][k_2T^*-\mu_I]$$
$$+\left(\frac{r_2}{M}+k_2\right)k_2T^*I^*=0.$$

Let the equations be defined as

$$\begin{aligned}
b_0 &= \mu_I+k_2I^*+r_2\left(\tfrac{2T^*+I^*}{M}\right)-\left(k_2T^*+r_2\right),\\
b_1 &= \left[r_2\left(1-\tfrac{2T^*+I^*}{M}\right)-k_2I^*\right][k_2T^*-\mu_I]+\left(\tfrac{r_2}{M}+k_2\right)k_2T^*I^*,
\end{aligned} \tag{3.56}$$

then

$$\lambda_3^2 + b_0\lambda_3 + b_1 = 0. \tag{3.57}$$

Substituting T^* and I^* into (3.56) and simplifying the equation leads to

$$\begin{aligned} b_0 &= \frac{\mu_I r_2}{M k_2}, \\ b_1 &= \frac{\mu_I^2 r_2}{M k_2}\left(R_0 - 1\right). \end{aligned} \tag{3.58}$$

The characteristic equation $\lambda^2 + b_0\lambda + b_1 = 0$ will always have negative eigenvalues.

□

Remarks: Since HIV's infectiousness is too high to infect healthy CD4+ T-cells, the requirement for local stability can be interpreted to indicate that the person will be infected with HIV. Another factor may be the immune system's inability to combat the infection. However, the immune system's ability to destroy cancer cells if k_1 is high, or the rate at which cancer cells are generated if r_1 is too small.

3.4.4 The cancer cells, healthy T-cells, and infected T-cells equilibrium

Theorem 15. *The equilibrium point E_4 is stable, if $R_0 > 1$.*

Proof. For the equilibrium $E_4 = (C^{**}, T^{**}, I^{**}, 0)$, the Jacobian matrix of this equilibrium is

$$J_{E_4} = \begin{pmatrix} -A_{11} & -A_{12} & -A_{13} & -A_{14} \\ -A_{21} & A_{22} & -A_{23} & -A_{24} \\ A_{31} & A_{32} & A_{33} & A_{34} \\ A_{41} & A_{42} & A_{43} & -A_{44} \end{pmatrix},$$

where

$$\begin{aligned} A_{11} &= -r_1\left(1 - \frac{2C^{**} + T^{**} + I^{**}}{M}\right) + k_1 T^{**} + \left(k_3 + k_4\right) I^{**}, A_{12} = \left(\frac{r_1}{M} + k_1\right) C^{**}, \\ A_{13} &= \left(\frac{r_1}{M} + \left(k_3 + k_4\right)\right) C^{**}, A_{14} = \frac{r_1 C^{**}}{M}, \\ A_{21} &= \left(\frac{r_2}{M} + p k_1\right) T^{**}, A_{22} = r_2\left(\frac{C^{**} + 2T^{**} + I^{**}}{M}\right) + p k_1 C^{**} + k_2 \bar{I} - r_2, A_{23} = \left(\frac{r_2}{M} + k_2\right) T^{**}, \\ A_{24} &= \left(\frac{r_2}{M} + \left(1 - \beta\right) k_5\right) T^{**}, \\ A_{31} &= k_4 I^{**}, A_{32} = k_2 I^{**}, A_{33} = k_2 T^{**} + k_4 C^{**} - \mu_I, A_{34} = k_5 T^{**}, \\ A_{41} &= k_3 I^{**}, A_{42} = 0, A_{43} = k_3 C^{**}, A_{44} = -r_3\left(1 - \frac{C^{**} + T^{**} + I^{**}}{M}\right) + \beta k_5 T^{**}. \end{aligned}$$

The associated characteristic equation is given by

$$P(\xi) = \widehat{A}_0\xi^4 + \widehat{A}_1\xi^3 + \widehat{A}_2\xi^2 + \widehat{A}_3\xi + \widehat{A}_4, \tag{3.59}$$

where

$$\begin{aligned}
\widehat{A}_0 &= 1,\\
\widehat{A}_1 &= A_{11} + A_{12} + A_{14} - A_{13},\\
\widehat{A}_2 &= A_{11}A_{22} + A_{13}A_{31} + A_{23}A_{32} + A_{14}A_{41} + A_{24}A_{42} + A_{11}A_{44} + A_{22}A_{44} -\\
&\quad [A_{12}A_{21} + A_{11}A_{33} + A_{22}A_{33} + A_{34}A_{43} + A_{33}A_{44}],\\
\widehat{A}_3 &= A_{13}A_{22}A_{31} + A_{11}A_{23}A_{32} + A_{12}A_{21}A_{33} + A_{14}A_{22}A_{41} + A_{13}A_{34}A_{41} + A_{11}A_{24}A_{42} + A_{23}A_{34}A_{42} +\\
&\quad A_{14}A_{31}A_{43} + A_{24}A_{32}A_{43} + A_{11}A_{22}A_{44} + A_{13}A_{31}A_{44} + A_{23}A_{32}A_{44} - \Big[A_{12}A_{23}A_{31} + A_{13}A_{21}A_{32}\\
&\quad + A_{11}A_{22}A_{33} + A_{12}A_{24}A_{41} + A_{14}A_{33}A_{41} + A_{14}A_{21}A_{42} + A_{24}A_{33}A_{42} + A_{11}A_{34}A_{43} + A_{22}A_{34}A_{43}\\
&\quad + A_{12}A_{21}A_{44} + A_{11}A_{33}A_{44} + A_{22}A_{33}A_{44}\Big],\\
\widehat{A}_4 &= A_{14}A_{23}A_{32}A_{41} + A_{12}A_{24}A_{33}A_{41} + A_{13}A_{22}A_{34}A_{41} + A_{13}A_{24}A_{31}A_{42} + A_{14}A_{21}A_{33}A_{42} +\\
&\quad A_{11}A_{23}A_{34}A_{42} + A_{14}A_{22}A_{31}A_{43} + A_{11}A_{24}A_{32}A_{43} + A_{12}A_{21}A_{34}A_{43} + A_{13}A_{22}A_{31}A_{44} +\\
&\quad A_{11}A_{23}A_{32}A_{44} + A_{12}A_{21}A_{33}A_{44} - \Big[A_{13}A_{24}A_{32}A_{41} + A_{14}A_{22}A_{33}A_{41} + A_{12}A_{23}A_{34}A_{41} +\\
&\quad A_{14}A_{23}A_{31}A_{42} + A_{11}A_{24}A_{33}A_{42} + A_{13}A_{21}A_{34}A_{42} + A_{12}A_{24}A_{31}A_{43} + A_{14}A_{21}A_{32}A_{43} +\\
&\quad A_{11}A_{22}A_{34}A_{43} + A_{12}A_{23}A_{31}A_{44} + A_{13}A_{21}A_{32}A_{44} + A_{11}A_{22}A_{33}A_{44}\Big].
\end{aligned}$$

It can be seen that $\widehat{A}_0$ and $\widehat{A}_3$ are always positive since all the parameters are non-negative and $R_0 > 1$. Thus, the number of possible positive real roots the polynomial (3.59) can have depends on the sign of $\widehat{A}_1$,$\widehat{A}_2$ and $\widehat{A}_4$. The signs of $\widehat{A}_1$, $\widehat{A}_2$ and $\widehat{A}_4$ are examined and then follow the possibilities of their signs:

i. $\widehat{A}_1 > 0$, $\widehat{A}_2 > 0$, $\widehat{A}_4 > 0$;

ii. $\widehat{A}_1 < 0$, $\widehat{A}_2 < 0$, $\widehat{A}_4 < 0$;

iii. $\widehat{A}_1 > 0$, $\widehat{A}_2 < 0$, $\widehat{A}_4 < 0$;

iv. $\widehat{A}_1 > 0$, $\widehat{A}_2 > 0$, $\widehat{A}_4 < 0$;

v. $\widehat{A}_1 < 0$, $\widehat{A}_2 > 0$, $\widehat{A}_4 < 0$;

vi. $\widehat{A}_1 < 0$, $\widehat{A}_2 < 0$, $\widehat{A}_4 > 0$;

vii. $\widehat{A}_1 > 0$, $\widehat{A}_2 < 0$, $\widehat{A}_4 < 0$;

viii. $\widehat{A}_1 < 0$, $\widehat{A}_2 > 0$, $\widehat{A}_4 > 0$.

Hence, by Descartes' Rule of Signs equation (3.59) will have either a unique positive real root or three positive roots when $R_0 > 1$ or equation (3.59) will have either zero, two or four positive roots when $R_0 > 1$. Hence, the system may undergo backward bifurcation [14, 30].

□

3.5 The endemic equilibrium and its stability

3.5.1 Endemic equilibrium

The Co-infected endemic equilibrium $E_{**} = (C_{**}, T_{**}, I_{**}, C_{**I})$, where $N_{**} = C_{**} + T_{**} + I_{**} + C_{**I}$. Therefore the system (3.28) becomes

$$\begin{aligned} 0 &= r_1\left(1-\tfrac{N_{**}}{M}\right) - k_1 T_{**} - (k_3+k_4) I_{**}, \\ 0 &= r_2\left(1-\tfrac{N_{**}}{M}\right) - pk_1 C_{**} - k_2 I_{**} - (1-\beta) k_5 C_{**I}, \\ 0 &= k_2 T_{**} I_{**} + k_4 C_{**} I_{**} - \mu_I I_{**} + k_5 C_{**I} T_{**}, \\ 0 &= r_3 C_{**I}\left(1-\tfrac{N_{**}}{M}\right) + k_3 C_{**} I_{**} - \beta k_5 C_{**I} T_{**}. \end{aligned} \tag{3.60}$$

Equation number three of (3.60) becomes,

$$T_{**} = \frac{(\mu_I - k_4 C_{**})\, I_{**}}{k_2 I_{**} + k_5 C_{**I}}, \tag{3.61}$$

for T_{**} to exist then $\mu_I > k_4 C_{**}$. By rearranging equation number four of (3.60), we obtain

$$C_{**I} = \frac{k_3 C_{**} I_{**}}{\beta k_5 T_{**} + \frac{r_3 N_{**}}{M} - r_3}, \tag{3.62}$$

for C_{**I} to exist then $\beta k_5 T_{**} + \frac{r_3 N_{**}}{M} > r_3$.
Substituting C_{**I} into equation number two of (3.60) and grouping in terms of C_{**}, then

$$\begin{aligned} 0 &= r_2\left(1-\tfrac{N_{**}}{M}\right) - k_2 I_{**}\left[pk_1 + \frac{(1-\beta)k_3 k_5 I_{**}}{\beta k_3 T_{**} + \dfrac{r_3 N_{**}}{M} - r_3}\right] C_{**}, \\ C_{**} &= \frac{r_2\left(1-\frac{N_{**}}{M}\right) - k_2 I_{**}}{\left[pk_1\left(\beta k_3 T_{**} + \frac{r_3 N_{**}}{M} - r_3\right) + (1-\beta) k_3 k_5 I_{**}\right]\left[\beta k_3 T_{**} + \frac{r_3 N_{**}}{M} - r_3\right]}. \end{aligned}$$

Since $r_2\left(1-\frac{N_{**}}{M}\right) > k_2 I_{**}$ and this implies that C_{**} exist. Recalling equation (3.61) and

substituting T_{**} in equation one of (3.60), the equation becomes

$$\begin{aligned}
0 &= r_1\left(1-\tfrac{N_{**}}{M}\right)-k_1\tfrac{(\mu_I-k_4C_{**})I_{**}}{k_2I_{**}+k_5C_{**I}}-(k_3+k_4)\,I_{**},\\
0 &= r_1M\,(k_2I_{**}+k_5C_{**I})-r_1N_{**}\,(k_2I_{**}+k_5C_{**I})-k_1M\,(\mu_II_{**}-k_4C_{**})-(k_3+k_4)\,(k_2I_{**}+k_5C_{**I})\,M\\
0 &= k_2M\,(k_3+k_4)\,I_{**}2+\left(k_2k_5M\,(k_3+k_4)\,C_{**I}+r_1k_2N_{**}+k_1\mu_IM-r_1k_2M\right)\\
&\quad-\left((r_1k_5M+k_1k_4MC_{**})-r_1k_5N_{**}C_{**I}\right).
\end{aligned}\tag{3.63}$$

Simplifying the equation further leads to

$$0 = b_1I_{**}^2+b_2I_{**}-b_3,\tag{3.64}$$

where

$$\begin{aligned}
b_1 &= k_2M\,(k_3+k_4)\,,\\
b_2 &= k_2k_5M\,(k_3+k_4)\,C_{**I}+r_1k_2N_{**}+k_1\mu_IM-r_1k_2M,\\
b_3 &= r_1k_5N^*C_{**I}-(r_1k_5M+k_1k_4MC_{**})\,.
\end{aligned}\tag{3.65}$$

By the use of quadratic formula then,

$$I_{**} = \frac{-b_2\pm\sqrt{b_2^2+4b_1b_3}}{2b_1}.\tag{3.66}$$

In this case we consider that,

$$I_{**1} = \frac{-b_2-\sqrt{b_2^2+4b_1b_3}}{2b_1},\tag{3.67}$$

$$I_{**2} = \frac{-b_2+\sqrt{b_2^2+4b_1b_3}}{2b_1}.\tag{3.68}$$

Case 1: If $b_2>0$, it follows that I_{**1}, I_{**2} are both less than zero. There are no sign changes and hence by Descarte's rule of signs, all their roots are negative.
Case 2: If $b_2<0$, it follows that I_{**1} can be either positive or negative and I_{**2} will be positive. There are sign changes and hence by Descarte's rule of signs, the roots I_{**2} is positive, therefore only the positive part will be considered

$$I_{**2} = \frac{-b_2+\sqrt{b_2^2+4b_1b_3}}{2b_1},\ \ b_2>0.\tag{3.69}$$

The Co-infected endemic equilibrium exists when $T_{**}>0$, $C_{**}>0$, $I_{**}>0$ and $C_{**I}>0$. This equilibrium implies that cancer-infected T-cells invade the whole system. The healthy CD4+ T-cells T^* still fight cancer-infected T-cells. If the rate of cancer infection increases, the individual will develop cancer that is HIV-related. Since the killing ability of the immune system is too weak.

3.5.2 Stability of endemic equilibrium

Theorem 16. *The equilibrium point E_{**} is locally stable if $R_0>1$.*

Proof. For the equilibrium $E_{**} = (C_{**}, T_{**}, I_{**}, C_{**I})$, the Jacobian matrix of this equilibrium is

$$J_{E^*} = \begin{pmatrix} -J_{11} & -J_{12} & -J_{13} & -J_{14} \\ -J_{21} & J_{22} & -J_{23} & -J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & -J_{42} & J_{43} & -J_{44} \end{pmatrix},$$

where

$$\begin{aligned}
J_{11} &= -r_1\left(1 - \frac{2C_{**} + T_{**} + I_{**} + C_{**I}}{M}\right) + k_1 T_{**} + (k_3 + k_4) I_{**}, J_{12} = \left(\frac{r_1}{M} + k_1\right) C_{**}, \\
J_{13} &= \left(\frac{r_1}{M} + (k_3 + k_4)\right) C_{**}, J_{14} = \frac{r_1 C_{**}}{M}, \\
J_{21} &= \left(\frac{r_2}{M} + pk_1\right) T_{**}, J_{22} = -r_2\left(1 - \frac{C_{**} + 2T_{**} + I_{**} + C_{**I}}{M}\right) + pk_1 C_{**} + k_2 I_{**} + (1-\beta) k_5 C_{**I}, \\
J_{24} &= \left(\frac{r_2}{M} + (1-\beta) k_5\right) T_{**}, \\
J_{31} &= k_4 \bar{I}, J_{32} = k_2 I_{**} + k_5 C_{**I}, J_{33} = k_2 T_{**} + k_4 C_{**} - \mu_I, J_{34} = -\frac{r_3 C_{**I}}{M} + k_5 T_{**}, \\
J_{41} &= -\frac{r_3 C_{**I}}{M} + k_3 I_{**}, J_{42} = -\frac{r_3 C_{**I}}{M}, J_{43} = -\frac{r_3 C_{**I}}{M} + k_3 C_{**}, \\
J_{44} &= -r_3\left(1 - \frac{C_{**} + T_{**} + I_{**} + 2C_{**I}}{M}\right) + \beta k_5 T_{**}.
\end{aligned}$$

The characteristic equation of the Jacobian J associated with the equilibrium E^* is given by

$$\xi^4 + \widehat{J}_1 \xi^3 + \widehat{J}_2 \xi^2 + \widehat{J}_3 \xi + \widehat{J}_4 = 0, \tag{3.70}$$

where

$$\begin{aligned}
\widehat{J}_1 &= J_{11} + J_{12} + J_{14} - J_{13}, \\
\widehat{J}_2 &= J_{11}J_{22} + J_{13}J_{31} + J_{23}J_{32} + J_{14}J_{41} + J_{11}J_{44} + J_{22}J_{44} - \\
&\quad [J_{12}J_{21} + J_{11}J_{33} + J_{22}J_{33} + J_{24}J_{42} + J_{34}J_{43} + J_{33}J_{44}], \\
\widehat{J}_3 &= J_{13}J_{22}J_{31} + J_{11}J_{23}J_{32} + J_{12}J_{21}J_{33} + J_{14}J_{22}J_{41} + J_{13}J_{34}J_{41} + J_{14}J_{31}J_{43} + J_{24}J_{32}J_{43} + J_{11}J_{22}J_{44} + \\
&\quad J_{13}J_{31}J_{44} + J_{14}J_{21}J_{42} + J_{24}J_{33}J_{42} + J_{23}J_{32}J_{44} - \Big[J_{12}J_{23}J_{31} + J_{13}J_{21}J_{32} + J_{11}J_{22}J_{33} + J_{12}J_{24}J_{41} + \\
&\quad J_{14}J_{33}J_{41} + J_{11}J_{34}J_{43} + J_{11}J_{24}J_{42} + J_{23}J_{34}J_{42} + J_{22}J_{34}J_{43} + J_{12}J_{21}J_{44} + J_{11}J_{33}J_{44} + J_{22}J_{33}J_{44}\Big], \\
\widehat{J}_4 &= J_{14}J_{23}J_{32}J_{41} + J_{12}J_{24}J_{33}J_{41} + J_{13}J_{22}J_{34}J_{41} + J_{14}J_{23}J_{31}J_{42} + J_{11}J_{24}J_{33}J_{42} + J_{13}J_{21}J_{34}J_{42} + \\
&\quad J_{14}J_{22}J_{31}J_{43} + J_{11}J_{24}J_{32}J_{43} + J_{12}J_{21}J_{34}J_{43} + J_{13}J_{22}J_{31}J_{44} + J_{11}J_{23}J_{32}J_{44} + J_{12}J_{21}J_{33}J_{44} - \\
&\quad \Big[J_{13}J_{24}J_{32}J_{41} + J_{14}J_{22}J_{33}J_{41} + J_{12}J_{23}J_{34}J_{41} + J_{13}J_{24}J_{31}J_{42} + J_{14}J_{21}J_{33}J_{42} + J_{11}J_{23}J_{34}J_{42} + \\
&\quad J_{12}J_{24}J_{31}J_{43} + J_{14}J_{21}J_{32}J_{43} + J_{11}J_{22}J_{34}J_{43} + J_{12}J_{23}J_{31}J_{44} + J_{13}J_{21}J_{32}J_{44} + J_{11}J_{22}J_{33}J_{44}\Big].
\end{aligned}$$

Due to the complexity involved in obtaining roots of ξ, the signs of the eigenvalues associated with the Jacobian matrix at E^*, are equally difficult to obtain. It can be shown that $\widehat{A}_0$ and $\widehat{A}_4$ are always positive since all the parameters are non-negative and $R_0 > 1$. Thus, the number of possible positive real roots the polynomial (3.70) can have depends on the sign of $\widehat{A}_1$,$\widehat{A}_2$ and $\widehat{A}_3$. The signs of $\widehat{A}_1$, $\widehat{A}_2$ and $\widehat{A}_3$ are examined and then follow the possibilities of their signs:

i. $\widehat{A}_1 > 0$, $\widehat{A}_2 > 0$, $\widehat{A}_3 > 0$;

ii. $\widehat{A}_1 < 0$, $\widehat{A}_2 < 0$, $\widehat{A}_3 < 0$;

iii. $\widehat{A}_1 > 0$, $\widehat{A}_2 < 0$, $\widehat{A}_3 < 0$;

iv. $\widehat{A}_1 > 0$, $\widehat{A}_2 > 0$, $\widehat{A}_3 < 0$;

v. $\widehat{A}_1 < 0$, $\widehat{A}_2 > 0$, $\widehat{A}_3 < 0$;

vi. $\widehat{A}_1 < 0$, $\widehat{A}_2 < 0$, $\widehat{A}_3 > 0$;

vii. $\widehat{A}_1 > 0$, $\widehat{A}_2 < 0$, $\widehat{A}_3 < 0$;

viii. $\widehat{A}_1 < 0$, $\widehat{A}_2 > 0$, $\widehat{A}_3 > 0$.

Hence, by Descartes' Rule of Signs equation (3.70) will have either a unique positive real root or three positive roots when $R_0 > 1$ or equation (3.70) will have either zero, two or four positive roots when $R_0 > 1$. The phenomenon of backward bifurcation is characterized by the stable endemic equilibrium when the associated reproduction number of the model is greater than one. Hence, the system may undergo backward bifurcation [14, 30]. The presence of this phenomenon in this model is not explored.

□

3.6 Numerical simulations

In the previous section, we presented the analytical methods proposed and demonstrated how to apply them to a qualitative study of the system, yielding some results about the system's dynamics. In this section, simulations are carried out for the system (3.5). Table (3.1) shows the parameter values used in the simulations.

In this section we first consider the system of equations (3.5). We analyze the system by considering the effect of reproduction number R_I in the development of cancer cells infected with HIV. There are parameters which are fixed throughout our simulations, where $k_1 = 0.00001$, $r_1 = 0.3$, $r_2 = 0.03$, $r_3 = 0.05$, $r_4 = 0.05$, $p = 0.1$, $\mu_I = 0.3$ are fixed parameters and these

Table 3.1: Numerical values of parameters used in the simulations

Parameter and variables	Values
$C(0)$ initial cancer population	100 (cells mL^{-1})[Estimated]
$T(0)$ initial healthy CD4+ T-cells	250(cells mL^{-1}) [Estimated]
$I(0)$ initial infected T-cells	100(cells mL^{-1}) [Estimated]
$C_I(0)$ initial cancer infected cells	100 (cells mL^{-1})[Estimated]
k_1 rate of immune system killing cancer cells	$10^{-5} \sim 10^{-3}$ (ml/day) [30]
r_1 maximal proliferation rate of cancer cells	$0.05 \sim 0.5$ (ml/day) [30]
r_2 intrinsic growth rate of healthy CD4+ T-cells	$0.05 \sim 0.5$ (ml/day)[30]
r_3 intrinsic growth rate of cancer infected T-cells	0.05 [Estimated]
p rate of losing immune due to infection	0.1 (ml/day)[30]
β rate of healthy CD4+ T-cells killing cancer infected T-cells	$0.297 \sim 18$ (ml/day) [33]
k_2 rate of infection	$5 * 10^{-5} \sim 5 * 10^{-4}$ (/ml/day) [30]
k_3 rate of cancer cells converting to cancer infected cells	0.0005 [Estimated]
k_4 rate of cancer cells with infected T-cells dying out	0.0005 [Estimated]
k_5 rate of co-infection	0.00005 [Estimated]
μ_I death rate of infected T-cells	0.3 (/day) [30]
M carrying capacity	1500(/ml) [30]

parameters M, k_2, β are varied to satisfy the analytical results. The case where $R_I < 1$ is considered and Matlab (2017) will be used to perform the simulations.
In figure (3.1) we considered the case where $R_I = 0.5$ and $\beta = 4$ the clearance rate of cancer infected T-cells by healthy CD4+ T-cells (a) and (b) show the healthy T-cells and cancer cells at the size of their carrying capacity fixed to $M = 1500$, where the rate of infection is a low scale $k_2 = 0.00005$. In figure (3.1) (c) and (d) when infection rate is very low, infected T-cells decline to zero. Figure (3.1) (e) shows the interaction of the healthy T-cells and cancer cells when the rate of the immune system is strong. Figure (3.1) (f) shows that cancer-infected disease can't persist and the healthy T-cells get strong and this is the case of the free disease equilibrium. In figure (3.2) we considered the case where $R_I = 2.75$ and $\beta = 4$, the clearance rate of cancer infected T-cells by healthy CD4+ T-cells, and the value of $k_2 = 0.00005$ increasing the carrying capacity $M = 15000$. Figure (3.2) (a) and (b) converge to the steady state. Figure (3.2) (c) shows there is an orbitally asmptotically stable periodic solution. In figure (3.3) we considered the case where $R_I = 2.75$, with cancer cells, cancer infected T-cells present, the value of $k_2 = 0.00005$, and $\beta = 0.4$. Figure (3.3) (a) and (c) shows decline of healthy T-cells and infected T-cells. Figure (3.3) (b) Cancer cells increase as healthy CD4+ T-cells decline. Figure (3.3) (d) The existence of the cancer infected T-cells. In figure (3.4) (a)-(c) The carrying capacity is increased to 15000 and $k_2 = 0.0005$, thus $R_I = 28.33$ no cancer cells and cancer infected T-cells, and $\beta = 0.3$. Figure (3.4) (a) and (b) shows the limit cycles of healthy CD4+ T-cells and infected T-cells. Figure (3.4) (c) show the orbitally asymptotically stable solution. In figure (3.5) (a)-(d) The carrying capacity of healthy CD4+ T-cells and cancer cells and cancer infected T-cells are increased to 20000 and $k_2 = 0.0005$, thus $R_I = 36.7$ and $\beta = 0.3$ the clearance rate of cancer infected cells by healthy T-cells [33]. Figure (3.5) (a) and (c) shows the decline of healthy CD4+ T-cells and infected T-cells. Figure (3.5) (b) and (d) shows the co-infected endemic equilibrium exist as R_I increases rapidly.

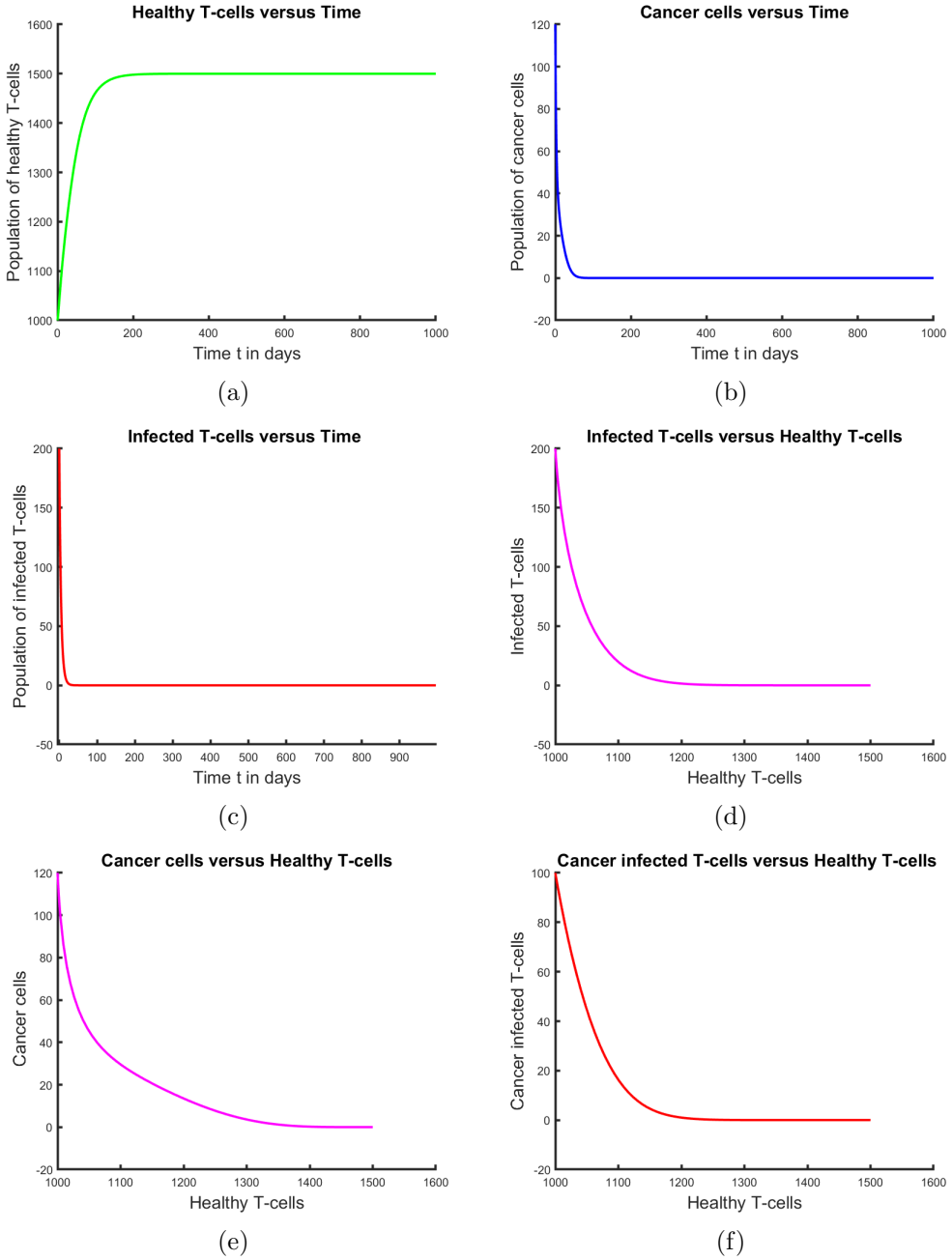
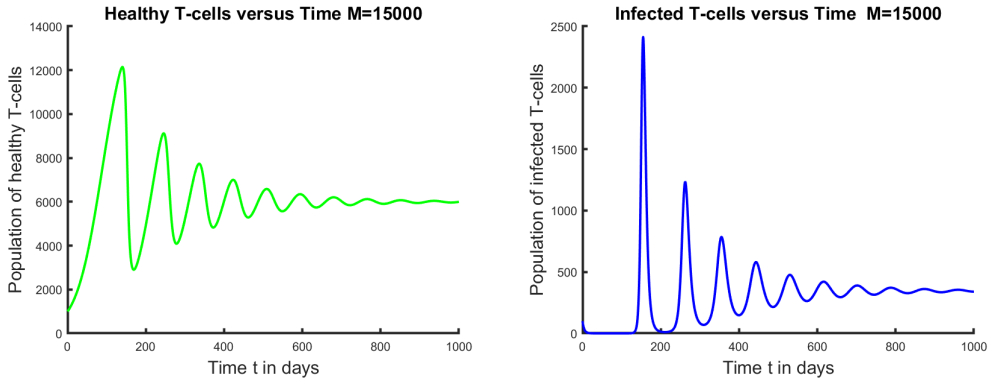
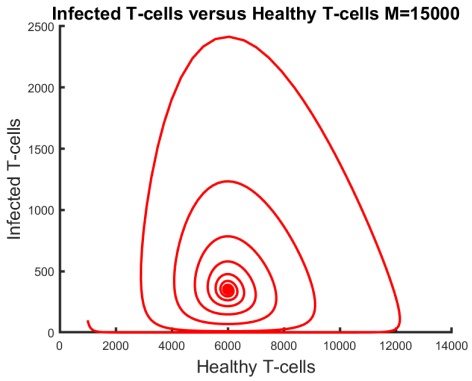


Figure 3.1: Variation of the HIV-cancer co-infection model where $R_I = 0.5$, $\beta = 4$, $M = 1500$, $k_2 = 0.00005$.



(a)

(b)



(c)

Figure 3.2: Variation of the HIV-cancer co-infection model where $R_I = 2.75$, $\beta = 4$, $k_2 = 0.0005$, $M = 1500$, no cancer cells.

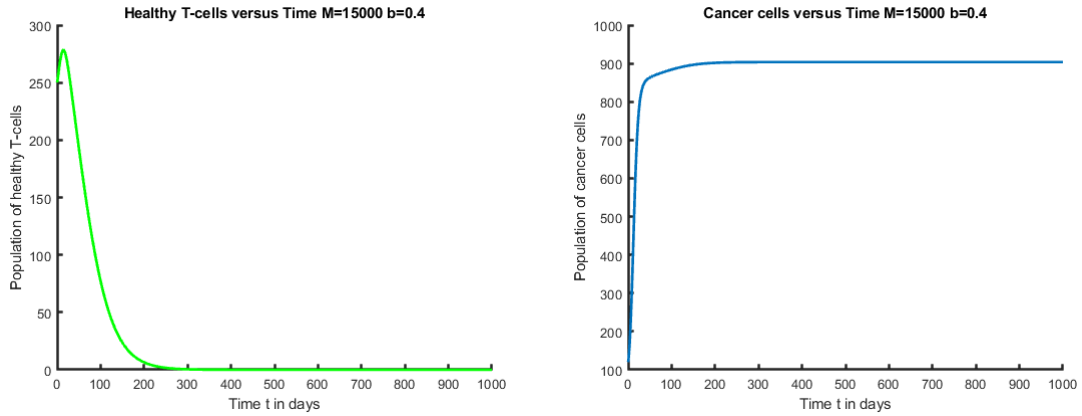
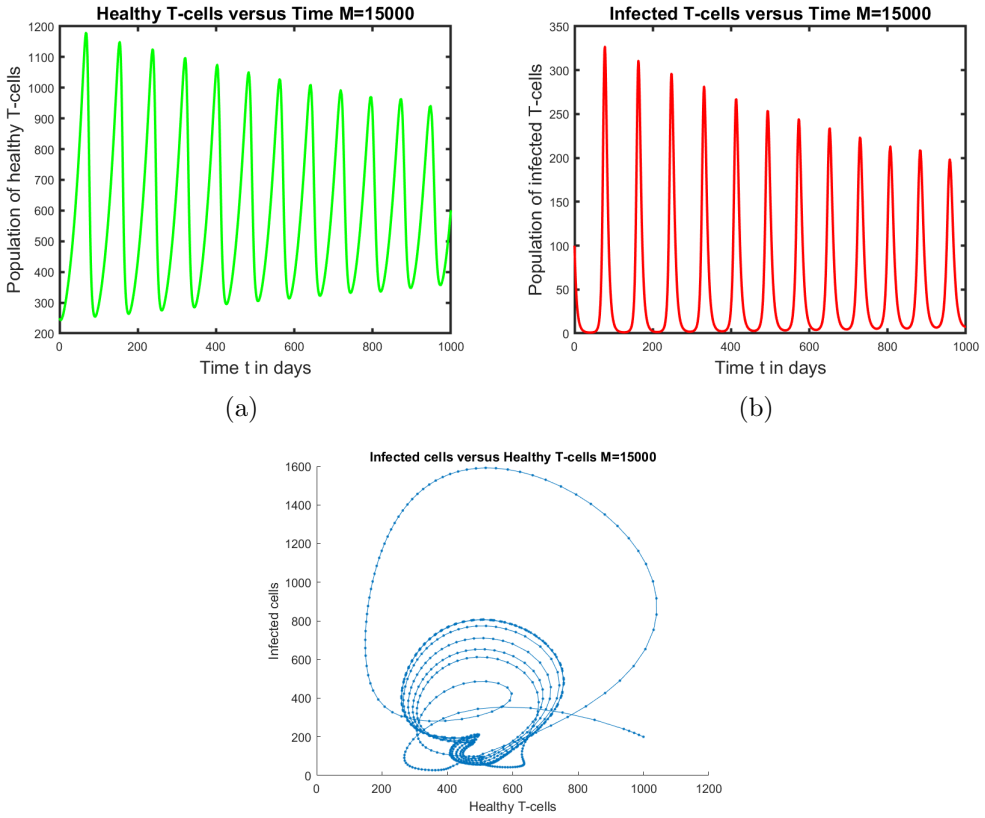


Figure 3.3: Variation of the HIV-cancer co-infection model where $M = 15000$, $R_I = 2.75$, $k_2 = 0.0005$, $\beta = 4$.



(a) (b)

(c)

Figure 3.4: Variation of the HIV-cancer co-infection model where (3.4) (a)-(c) $M = 15000$ and $k_2 = 0.0005$, thus $R_I = 28.33$, no cancer cells and cancer infected T-cells and $\beta = 0.3$

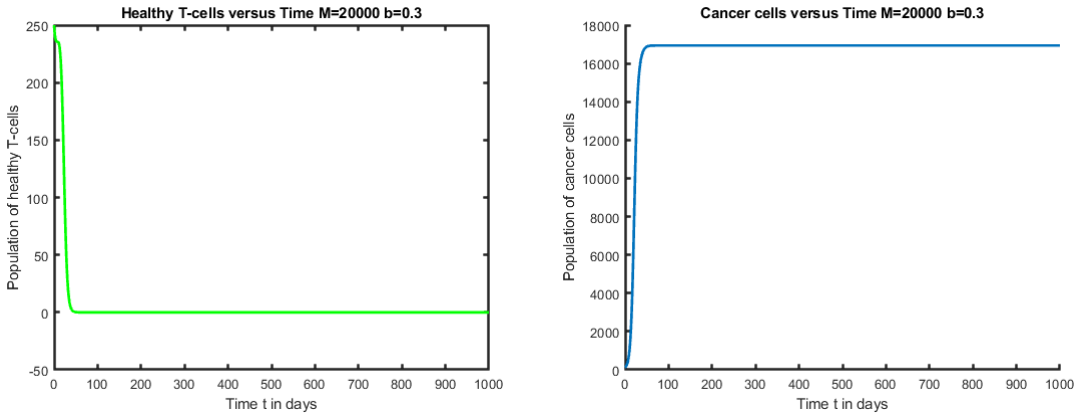


Figure 3.5: Deterministic trajectories of the HIV-cancer co-infection model $M = 20000$, $k_2 = 0.0005$, $R_I = 36.7$ and $\beta = 0.3$.

3.7 Conclusion for model without treatment

Here we studied a cancer model without treatment. When $C_I(t) = 0$ then the system (3.5) is reduced to a three system equation, which is related to the model in Lou et al [30], in their case the system had five steady states. In our model $C_I(t) \neq 0$ and there are five equilibria points considered excluding the trivial one, if $R_I < 1$ then the equilibria are stable. If $R_I > 1$, the endemic equilibrium is stable, this means that an infected T-cell introduced into a population of healthy CD4+ T-cells will produce more than one new infected T-cell, and the cancer-infected cells will survive because the immune system is unable to kill the infected T-cells. We noticed that the cancer equilibrium becomes stable if the intrinsic growth rate of the healthy CD4+ T-cells is less than the rate at which cancer cells are cleared. In [30] it has been obtained that when the uncontrolled proliferation rate of cancer cells is small, then cancer can't persist and only the HIV infected T-cells persist. Since the immune system breaks down in our model it is observed that the cancer HIV infected T-cells can coexist at the same time as [30] predicted in their paper. A study on the dynamic behavior of the system with treatment and its effect will be obtained in the next chapter.

3.8 Impact of HAART and chemotherapy drug on the dynamics of cancer infected cells

The model described by the system (3.5) was studied without treatment. We will introduce the treatment of HIV in combination with cancer treatment, the goal is to establish the effect of HAART which is a combination of drugs that inhibit reverse transcriptase and protease [42]. Individuals with HIV who develop cancer should be treated also for cancer growth. We will consider cancer treatment administered to patients with HIV related to cancer, more precisely Kaposi Sarcoma which depends on the HAART [20, 34, 56]. Antiretroviral treatment (ART) for HIV/AIDS is commonly used first, before all other treatment methods, to treat tumors and reduce patient mortality [57]. Its disadvantage is that it can worsen the infection and the Kaposi Sarcoma [57]. In our study, HAART will be given in combination with chemotherapy. The following are the main treatment types:

- Protease inhibitors (PIs) are metabolized by enzymes in the liver and can affect the way other drugs are processed in the body by speeding up or slowing it down [13]. PI's prevents HIV protease from separating polyprotein into functional units, which causes non-infectious virus particles to be produced by infected T-cells [58].

- Reverse transcriptase inhibitors (RTI's) HIV uses RTIs to convert its RNA to DNA, HIV is prevented from replicating by blocking reverse transcriptase and reverse transcription [13]. RTIs can block infection of target T-cells by infectious virus [58].

- Chemotherapy is a type of treatment that include a drug or combination of drugs to treat cancer[57]. Chemotherapy has more effect on cancer cells, as it keeps them from growing, dividing, and making more cells. These drugs are powerful and can be also destructive or cause damage to healthy cells [57].

3.9 Model formulation with Treatment

Mentioned therapies are considered for the treatment of HIV and cancer, we will focus on both the treatment. Our model formulation described in chapter 3, will include the therapy treatment parameters. Considering the effects of exposing the cancer cells population to a specific drug as in chemotherapy at a concentration $C(t)$ represented by δ where $0 < \delta < 1$, then the drug will eventually be equally toxic to proliferating cells. A killing cell term will be attached to the term $k_1C(t)T(t)$ to represent the effect of the drug on the cancer growth [54]. Protease inhibitors and reverse transcriptase inhibitors are applied to cells shortly after transfection and before infection, respectively [13]. The parameters η_{PI} and η_{RTI} represent the efficacy of anti-HIV treatment, which is usually a combination of drugs made by reverse transcriptase η_{RTI} and protease inhibitors η_{PI} [42, 46].
The model with the HAART and chemotherapy is as follows

$$
\begin{aligned}
\frac{dC(t)}{dt} &= C(t)\left[r_1\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)-k_1\delta T(t)-(1-\eta_{PI})\delta\left(k_3+k_4\right)I(t)\right],\\
\frac{dT(t)}{dt} &= T(t)\left[r_2\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)-pk_1\delta C(t)-(1-\eta_{PI})k_2I(t)-(1-\beta)\,\delta\,(1-\eta_{PI})\right.\\
\frac{dI(t)}{dt} &= (1-\eta_{RTI})k_2T(t)I(t)+(1-\eta_{PI})\delta k_4C(t)I(t)-\mu_II(t)+(1-\eta_{RTI})\delta k_5T(t)C_I(t),\\
\frac{dC_I(t)}{dt} &= C_I(t)\left[r_3\left(1-\frac{C(t)+T(t)+I(t)+C_I(t)}{M}\right)\right]+(1-\eta_{PI})\delta k_3C(t)I(t)\\
&\quad -(1-\eta_{PI})\delta\beta k_5T(t)C_I(t).
\end{aligned}
\tag{3.71}
$$

3.9.1 Comparison of the effective and the basic reproduction numbers

3.10 Control Reproduction number

The control reproduction number R_c is employed to represent the system with control (treatment of cancer and HIV-infected T-cells). The control program is considered which reduces either the length of time that an infection lasts by chemotherapy or the HAART. The repetition of computing the control reproduction number will be avoided, thus the chemotherapy and the transcriptase inhibitors induced reproduction number R_c is given by

$$
R_c = (1-\eta_{RTI})\,\delta\left[\frac{k_2M}{\mu_I}+\frac{1}{\beta}\right], \tag{3.72}
$$

where

$$
R_I = R_0 + R_c^{coinf} \tag{3.73}
$$

The threshold quantity R_c in the presence of treatment, the average number of infected people created by one infected person introduced into a naive population of cells as shown above. In the absence of treatment of HIV we have control reproduction given by

$$
R_{cc} = \delta\left[\frac{k_2M}{\mu_I}+\frac{1}{\beta}\right]. \tag{3.74}
$$

In the absense of chemotherapy interaction where $\delta = 1$ and only the HAART is involved the control reproduction number becomes

$$
R_{ch} = (1-\eta_{RTI})\left[\frac{k_2M}{\mu_I}+\frac{1}{\beta}\right]. \tag{3.75}
$$

In the absense of any interaction where $\delta = 1$ and $\eta_{RTI} = 0$, the reproduction number emerges as

$$
R_I = \frac{k_2M}{\mu_I}+\frac{1}{\beta}. \tag{3.76}
$$

Remarks: Noting from (3.72) that by using both the chemotherapy and the HAART treatments control to reduce the value of R_c, and at the same time the effects of both the interventions on R_c are not the addition of two independent effects, rather they multiply together to improve overall effects of population-level independently.

3.10.1 Comparison of the model with and without treatment at the endemic level

3.10.2 Results with no chemotherapy drug

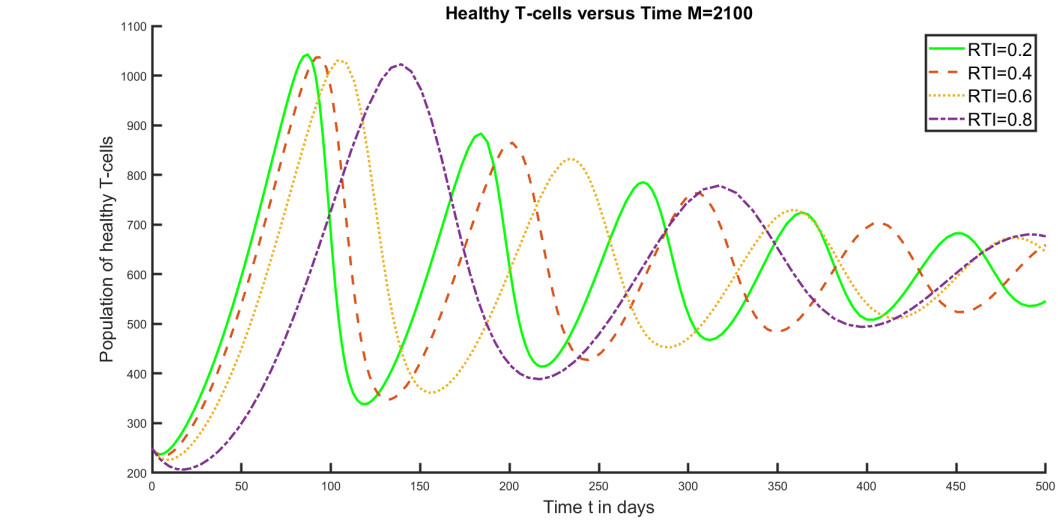
In this section, we carry out numerical simulation by Matlab ODE45 Solver which uses Runge kutta schemes to investigate the dynamical behaviour of the system (3.71) in the presence of controls using parameters:

$$\eta_{PI} = 0 : 0.8, \eta_{RTI} = 0 : 0.8, \delta = 0.2 : 1. \tag{3.77}$$

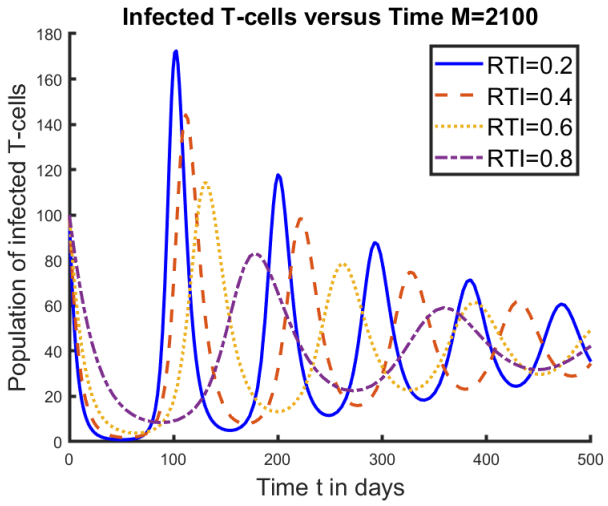
Unless stated otherwise, parameters are stated in Table (3.1).

3.10.2.1 Control of new infections by Reverse transcriptase inhibitors

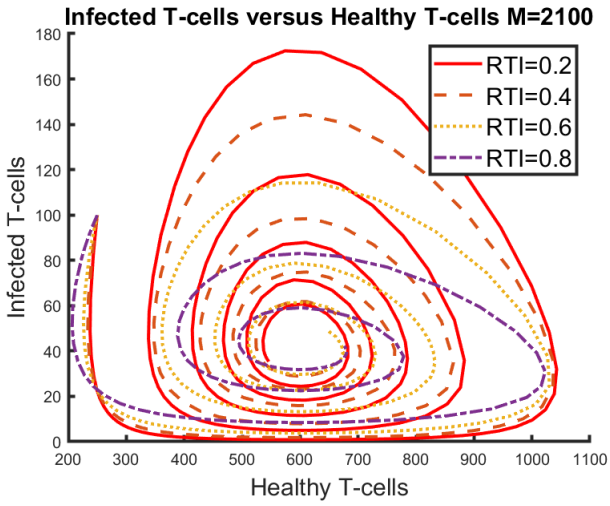
In this strategy, we set $\eta_{PI} = 0$ with no variation, and $\eta_{RTI} = 0.2 : 0.8$ vary the parameter related to the protection of healthy CD4+ T-cells from infection, Figure (3.6) shows that the increase of the individual protection level, reduces the disease prevalence. This result implies that this reduction is significant if the level of protection is kept high over a long period.



(a)



(b)

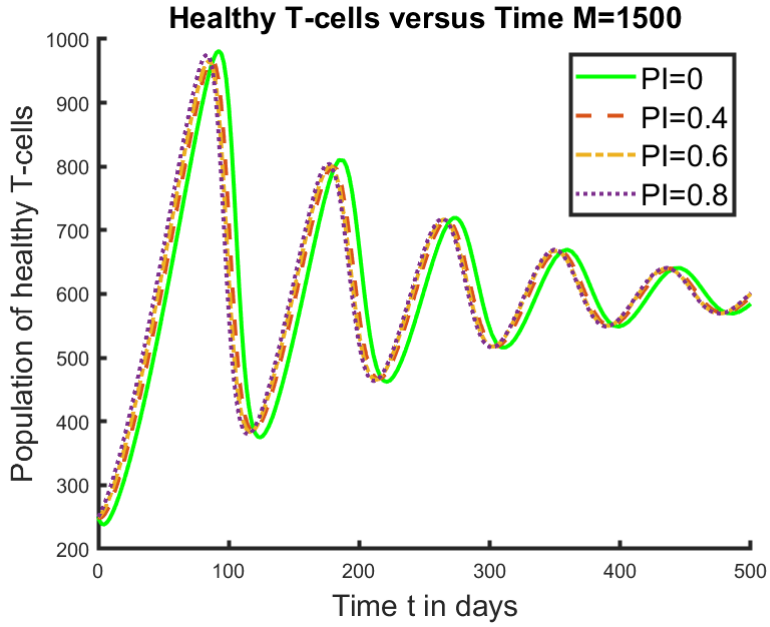


(c)

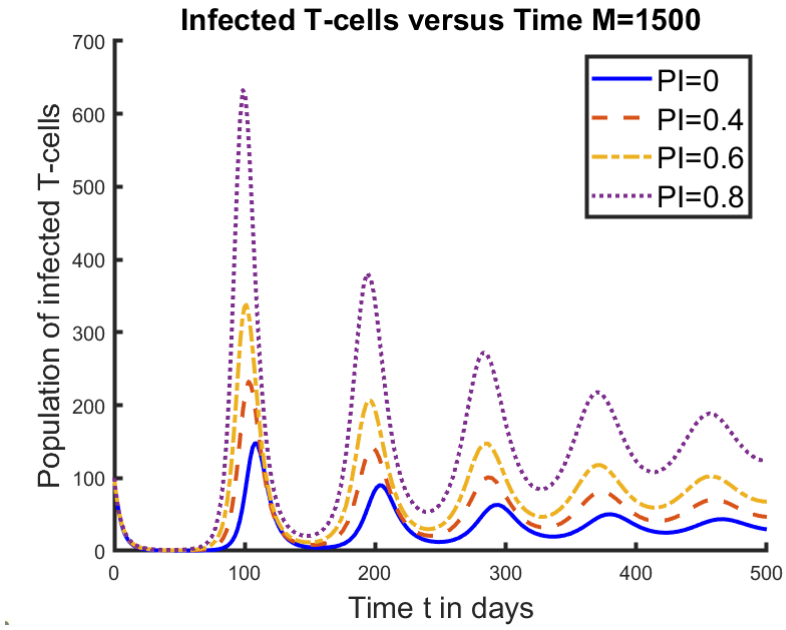
Figure 3.6: Simulation result showing the population dynamics of healthy CD4+ T-cells and Infected T-cells in the presence of reverse transcriptase inhibitors where $C(t) = C_I(t) = 0$.

3.10.2.2 Control of new infections by Protease inhibitors treatment

We set $\eta_{RTI} = 0$ with no variation, and $\eta_{PI} = 0 : 0.8$. The enrollment or detection of newly infected cells into HAART treatment depends on the diagnosis of HIV. Figures (3.7) show that increasing the number of infected T-cells treated has an important effect on lowering disease prevalence. However, this decrease in prevalence doesn't wipe out the infected cells and new individuals of healthy CD4+ T-cells are not protected from new infection.



(a)

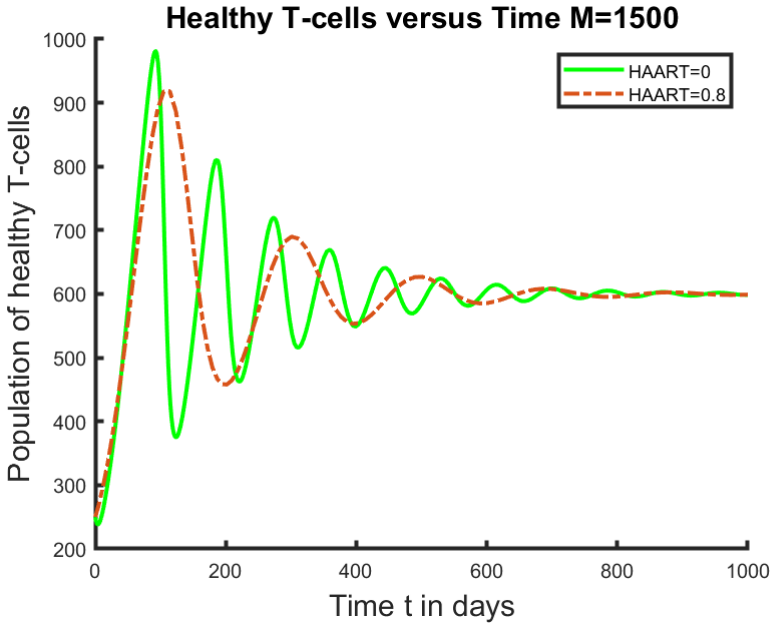


(b)

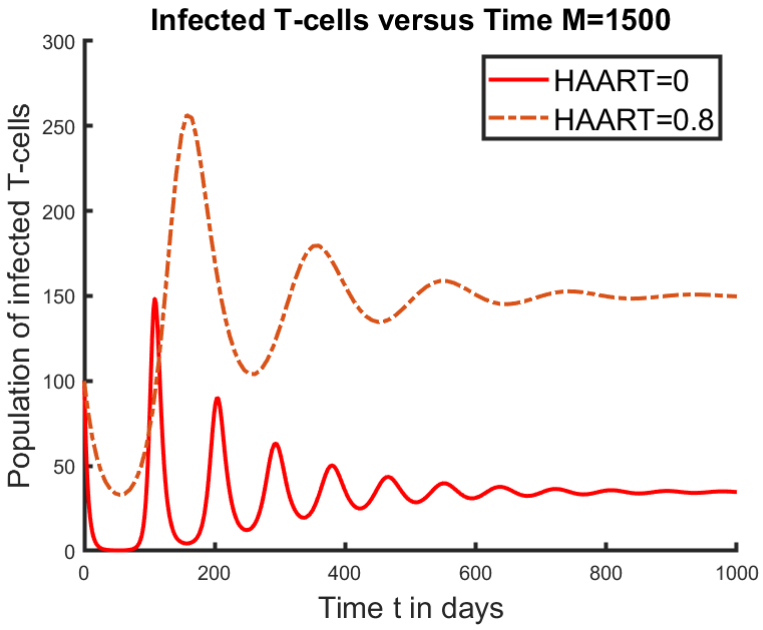
Figure 3.7: Simulation results showing the population dynamics of healthy CD4+ T-cells and infected T-cells in the presence of protease inhibitors where $C(t) = C_I(t) = 0$.

3.10.2.3 Control of new infections and infectious with HAART treatment

The result in Figure (3.8) show that the combination of the two control strategies results into positive impact in the control of HIV where $R_{ch} = 2.75$ reduces to $R_{ch} = 0.55$. The results show that if the control measures are held at approximately between 70% and 90%, then it will be easy to halt the replication or spread of the infection in the cells.



(a)



(b)

Figure 3.8: Population dynamics of the system with no chemotherapy

3.10.3 Results with chemotherapy drug

3.10.3.1 Control of cancer combined with HAART treatment

We are investigating the effects of chemotherapy on the decay rate of cancer and the depletion rate of cancer-infected T-cells. In this strategy, we set the $\eta_{PI} = \eta_{RTI} = 0:8$ and vary the parameter related to control of cancer from proliferating. In Figure (3.9), hence one observes that at $M = 1500$ a slight decrease or increase of population cells is observed from 50 days to 200 days due to the intervention. The effect of combining HIV therapy on cancer is explored. Hence one type of drug η_{RTI} reduces only the replication of infected cells with HIV, though another control strategy of drug η_{PI} reduces the rate of infected cells. In figure (3.9) the

dynamics of cancer and cancer infected T-cells are studied where the HAART is kept constant and the strategy is to vary the efficacy of the chemotherapy. It is seen that when the dosage of δ is increased, the population of cancers cells decreases rapidly and cancer-infected T-cells decrease slightly with time.

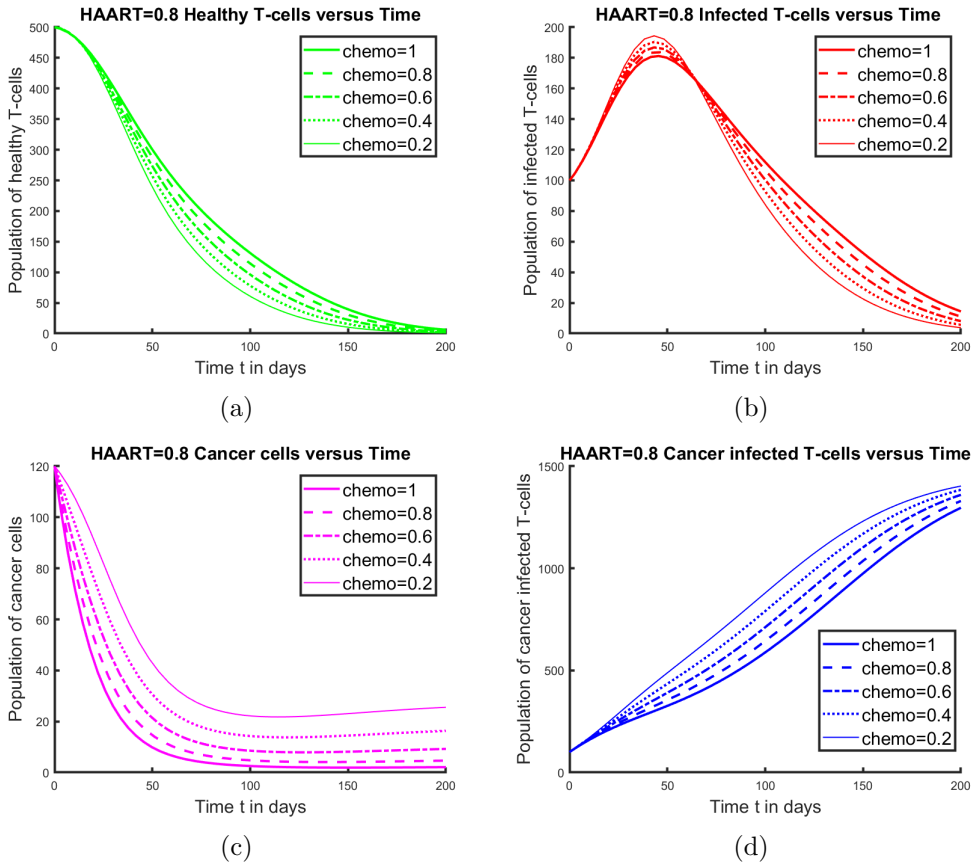


Figure 3.9: Chemotherapy treatment variation of cancer and cancer infected T-cells

3.10.3.2 Control with Chemotherapeutic drug at 0.25 combined with HAART treatment

Figure (3.10) shows that combining the two drugs lead to a significant decrease on the cancer infected cells. Varying the efficacy of η_{RTI} shows that the rate of infected T-cells decrease and healthy CD4+ T-cells increase, which implies the decrease in cancer cells rapidly and cancer infected T-cells slightly. The same results as chemotherapeutic drug dosage is fixed at 0.25 show a significance in declining the cancer cells in [5]. In Figure (3.11) the carrying capacity is increased M=1500:15000, and $\eta_{PI} = 0$, shows that with the variations of the HAART and Chemotherapy treatment as the RTI is increased, we observe the decline of cancer cells, infected T-cells and cancer infected T-cells with time. In our analyses it is observed that a dose of 90% effective η_{RTI} drugs with as low as 10% effective η_{PI} drugs which reduce the proliferation rate of cancer cells and same applies for 90% effective η_{PI} drugs which predicts the same result as in [5].

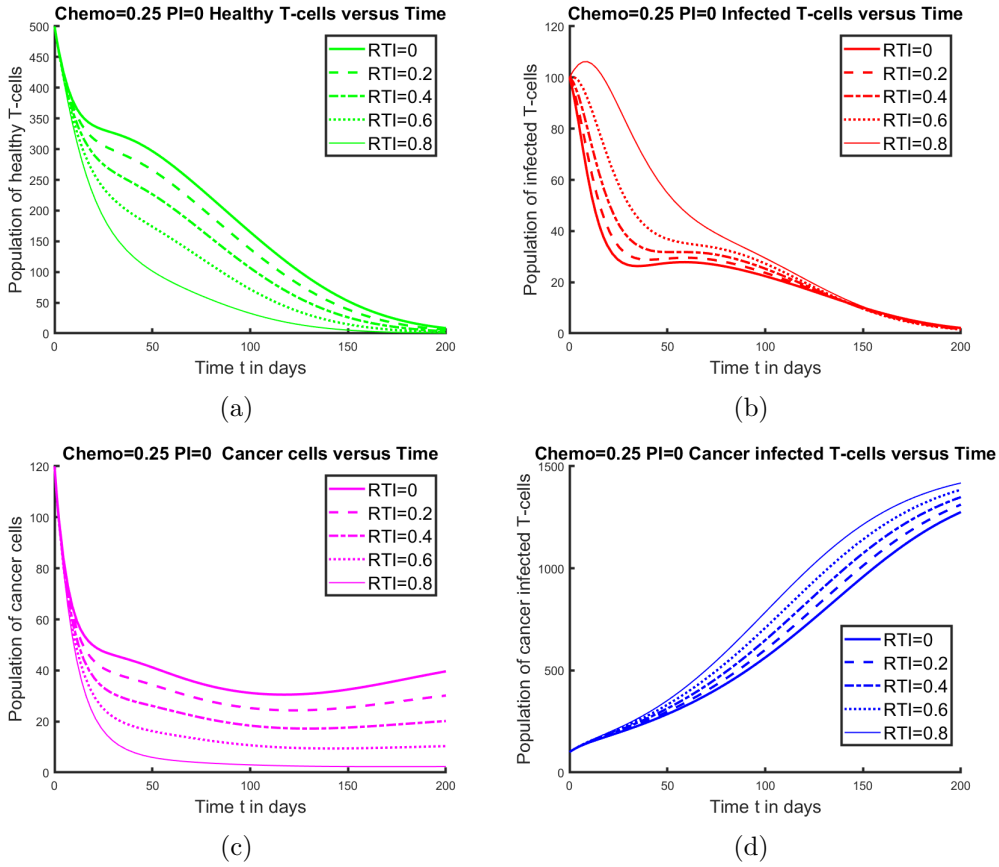


Figure 3.10: Chemotherapy treatment fixed at 0.25, and varying the RTI.

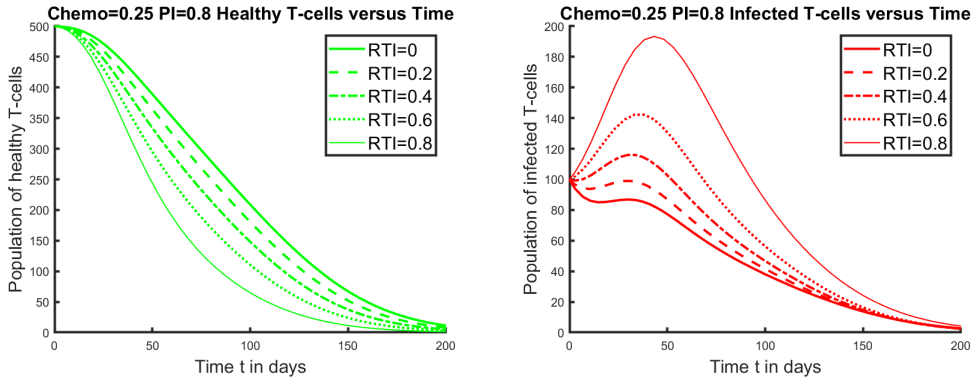


Figure 3.11: Chemotherapy treatment fixed at 0.25 and PI at 0.8, and varying the RTI.

3.11 Conclusion

In this chapter, we suggested a model that takes into account the impact of HIV treatment and chemotherapy on HIV-related cancer. The model developed in Chapter 3 was extended to investigate the dynamics of the intervention.

We observed that in the absence of cancer cells, with the variation of the combined RTI and PI drugs there is a reduction of the HIV cells load. The strategy employed where only the replication of infected cells will be targeted showed again in the loss of infection as the efficacy of the RTI approximated at 70% to 90% drives the system to a decline. The combination of RTI and PI would be effective if the efficacy is approximated at 90% which presents the best treatment option. Since HAART may be given alone to treat patients with cancer related to HIV, we, therefore, investigated effective PI and the results showed a slight decline [57]. However, it is not possible to eradicate cancer even with the response of the immune and treatment of HIV with the reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) drugs of a higher percentage.
The results of combining the HAART with chemotherapy in the presence of cancer infected cells show a significant impact on understanding the obstacle in most cancer-infected cells relating to complications. Increasing the treatment rate, the result will be more favorable to predict the efficacy. Providing treatment to HIV individuals, regardless of their cancer status, can offer a significant reduction in the overall number of full-blown cancer-related HIV.

Chapter 4: Discussions and Conclusions

Reviewed a model by Lou et al. [30], in Chapter 2 the study was employed to gain insight into understanding the interaction of the dynamical system of cancer cells, healthy CD4+ T-cells, and HIV infected T-cells. Boundedness, Positivity, Existence, and Uniqueness were established. The bifurcation appears which is the same as the one found by Lou et al in their work. The bifurcation issue was not pursued as this work was not intended to look into that. Stability analyses and numerical analyses were carried out. Thereafter, we extended a model formulated in [30] to study the effect of treatment on the dynamics of cancer cells. We first considered a model without treatment. The disease-free and endemic equilibrium levels were determined, and the stability of each was investigated. The model predicts that cancer cells persist if the intrinsic growth rate of healthy CD4+ T-cells is less than the rate at which cancer cells are cleared. In this dynamic, the key role is played by the reproduction number R_0. Considering the results obtained in chapter 3, the system has five equilibrium points. The system was found to be stable when $R_0 < 1$, which is a locally stable equilibrium in the healthy CD4+ T-cells. The equilibrium points with healthy CD4+ T-cells and infected T-cells are unstable when $R_0 > 1$. Due to mathematical complexity, it was not easy to express the endemic states in terms of the model parameters, although by using Descarte's rule of signs the equilibrium points were found to be stable. When the proliferation rate is low there is less increase in cancer cells and an increase in healthy CD4+ T-cells. This means that the killing rate of cancer cells by the healthy CD4+ T-cells is strong. We found that for higher values of the force of infection, the system is oscillatory around the endemic equilibrium since the oscillation is around the coexistence. In other literature it is shown in their dynamical system of HIV models interacting with cancer, that there is oscillation and chaotic fluctuations [8, 30].

In Chapter 3 we considered the model combined with HAART and chemotherapy. The treatment as varied proved to show a significant and effective impact on the investigation of the dynamical model in the presence of control measures. Our results suggest that cancer response depends on the therapy that kills proliferating cancer cells, not the infection rate. The effect of HIV therapy combined with chemotherapy optimizes the efficacy of treating cancer, HIV infected T-cells, with no damage to the healthy CD4+ T-cells while reducing the cancer growth. Showing that if treatment is offered regardless of either cancer status is known can offer an effective reduction in the persistence of cancer infected T-cells [50]. The model predicts that, for cancer-infected T-cells to persist in the presence of treatment, the treatment rate must be less than the production of cancer-infected T-cells. To be stable the treatment rate must be more than the production of cancer-infected T-cells. The results predict that for the low rate of infection, cancer cells will persist even when there is treatment. It was found from numerical simulations that the response of the immune system cannot eliminate the cancer cells at an early stage.

Numerical simulations of the model also showed that by first considering the case where the infection rate is low, the model predicts that for the low rate of treatment, cancer cells will

increase repetitively. By increasing the treatment rate from 0.4 to 0.7 the cancer cells reduce exponentially. In the case where $R_0 > 1$, by starting the treatment from 0.3, dampened oscillations appear. Cancer cells are cleared when the treatment rate is between 0.7 and 0.9. By starting the treatment early enough, the cancer cells can be controlled. The results show that early detection of cancer HIV infected T-cells when HAART treatment is taken can reduce the infection which leads to less chance of cancer-related HIV progressing. The model in this dissertation is extended from J. Lou with the coexistence of cancer and cancer HIV infected T-cells, it is still a simple description of a complicated biological interaction of healthy CD4+ T-cells. The model isn't meant to be used as a predictor, but rather as a way to organize thoughts about cancer, cancer-infected T-cells, and HIV infections so that more accurate models can be created. Regardless of how long the HIV endemic has been suppressed the reason is to work towards better models.

4.1 Future Work

In future work, we will propose a latent mathematical model that incorporates HIV viral load compartment. A model for viral infection and spread that includes two modes: diffusion-limited free virus transmission and direct viral particle movement from cell to cell.

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Appendix A

Statement of Theorem

Consider the system of equations below

$$\left.\begin{array}{l} x_1^{'} = f_1(t, x_1, x_2, ..., x_n), x_1(t_0) = x_{10}, \\ x_2^{'} = f_1(t, x_1, x_2, ..., x_n), x_2(t_0) = x_{20}, \\ \quad \vdots \\ x_n^{'} = f_1(t, x_1, x_2, ..., x_n), x_n(t_0) = x_{n0}. \end{array}\right\} \tag{4.1}$$

In this case we can write the equation (4.1) in the form

$$X^{'} = f(t, X), X(t_0) = x_0. \tag{4.2}$$

Theorem 17. *Suppose the region is denoted by* Γ *where*

$$|t - t_0| \leq a, \|x - x_0\| \leq b, x = (x_1, x_2, ..., x_n), x_0 = (x_{10}, x_{20}, ..., x_{n0}). \tag{4.3}$$

and suppose that $f(t, X)$ *satisfies the Lipschitz condition*

$$\left\| f(t, x_1) - f(t, x_2) \right\| \leq K \|x_1 - x_2\| . \tag{4.4}$$

for all (t, x_1), $(t, x_2) \in \Gamma$, *where* K *is a positive constant (Lipschitz Constant). Then, there is a constant* $\delta > 0$ *such that there exists a unique continuous vector solution* $\underline{X}(t)$ *of the system (4.2) in the interval* $|t - t_0| \leq \delta$. *It is crucial to note that the condition (4.4) is satisfied by the requirement that* $\frac{\partial f_i}{\partial x_j}, i, j = 1, 2, ..., n$ *be continuous and bounded in* Γ *[11].*

Appendix B

The value of R_0 of system can be estimated by using the next generation matrix method. We consider matrix G of order m which is composed of two matrices; matrix F (non-negative) and matrix V^{-1} (non-singular) such that

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j} \right]$$

where

$$1 \leq i, j \leq m.$$

F_i are the new infections, V_i are the transfers of infections from one compartment to another while x_0 is the drug free steady state. R_0 for our model is obtained by computing the spectral radius of $G = FV^1$.