Modelling the Dynamics of HIV-Related Malignancies

by

Morenikeji Deborah Akinlotan

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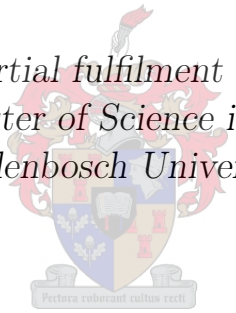

Department of Mathematical Sciences,
Mathematics Division,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Supervisor: Prof. F. Nyabadza

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Declaration

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Abstract

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M. D. Akinlotan

Department of Mathematical Sciences,
Mathematics Division,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

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In recent years, HIV-associated cancers have proven to be the bane of our time, since HIV is decimating humanity across the globe, even in the twilight of the last century. Cancer rates continue to rise in developing countries, where 95% of the world's HIV-infected population lives, yet less than 1% have access to antiretroviral therapy. HIV-infected individuals have a higher proclivity to develop cancers, mainly from immunosuppression. An understanding of the immunopathogenesis of HIV-related cancers (HRC) is therefore a major prerequisite for rationally developing and/or improving therapeutic strategies, developing immunotherapeutics and proplylatic vaccines. In this study, we explore the pathology of HIV-related cancer malignancies, taking into account the pathogenic mechanisms and their potential for improving the treatment of management of these malignancies especially in developing countries. We mathematically model the dynamics of malignant tumors in an HIV-free environment, investigate the impact of cancer malignancies on HIV-positive patients and explore the benefits of various therapeutic intervention strategies in the management of HIV-related cancers. We present two deterministic models of infectious diseases to implement these, and they were analysed. We use HIV-related lymphomas in the Western Cape of South Africa as a case study. We validated the proposed models using lymphoma incidence data from the Tygerberg Lymphoma Study Group (TLSG), Tygerberg Hospital, Western Cape, South Africa. We show that the increasing prevalence of HIV increases lymphoma cases, and thus, other HIV-related cancers. Our models also suggests that an increase in the roll-out of the HAART program can reduce the number of lymphoma cases in the nearest future, while it averts many deaths. Furthermore, the results indicate that a highly crucial factor to consider in the prognosis of the incidence of lymphoma (and other cancer types) in HIV-infected patients is their CD4 cell count, irrespective of whether the patient has developed an HRC or not.

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"Now to Him Who, by (in consequence of) the [action of His] power that is at work within us, is able to [carry out His purpose and] do superabundantly, far over and above all that we [dare] ask or think [infinetly beyond our highest prayers, desires, thoughts, hopes, or dreams], to Him be glory in the church and in Christ Jesus throughout all generations forever and ever. Amen (so be it)." - Ephesians 3:20 (Amplified version)

Dedications

This work is dedicated to the Lord God Almighty, the author and finisher of my faith in Christ Jesus.

Contents

Chapter 1

Introduction

1.1 Cancer

Cancer is a group of diseases typified by the uncontrolled growth, division and proliferation of abnormal cells [1; 2]. Cancerous cells are also referred to as malignant cells [3]. Cancerous cells develop when there is an uncontrollable proliferation of abnormal cells in the body. These abnormal cells are formed when there is a mutation (result of deoxyribonucleic acid (DNA) damage or errors) or transformation of normal cells, which after proliferation, starts to aggregate to form malignant tumours or lumps known as cancers. Every cancer type is attributed to the malfunction of the genes responsible for cell growth, division and death control [2].

The malignancy of these tumours causes them to overtake the space they are in, deprive other surrounding healthy cells of their space, nutrients and oxygen which causes them to malfunction. They eventually spread to, and invade other parts of the body, thereby causing destruction to invaded tissues [1; 4–6]. This spread of the tumour(s) can be facilitated by the entering of cancerous cells into the body's bloodstream or lymphatic vessels. These tumours eventually displace the normal tissues(s) originally located at the cancer sites. The process of this spread and displacement is called *metastatis* [1], and such tumours are caled metastatic tumours. They contain cancerous cells of the tumour(s) in the original (primary) site, and are thus named with respect to their site of origin [1; 7]. An example is a breast cancer that has spread to the liver, it is called metastatic breast cancer [1], or breast metastasis, or breast metastases if tht tumour is more than one. It is imperative to mention that not all tumours are malignant (cancerous). Such tumours are said to be *benign* (or non-malignant). They can grow very large but they do not spread to, or invade other tissues [1; 7].

There are so many different types of cancers. Cancers are usually classified

by the organs of their primary locations (site of origin) or by their tissue types. According to the National Cancer Institute (NCI), there are five main categories of cancers with respect to their tissue type, viz: carcinoma, sarcoma, leukemia, lymphoma and myeloma, and central nervous system cancers [7].

Carcinoma is a group of cancers that originates from the epithelia tissues (the layer of cells that line or cover internal organs and tubes). Sarcoma is the group of cancers that originates from the bone (sometimes termed osteosarcoma), cartilage, fat, blood vessels, or other connective or supportive tissues. Leukemia are cancers that originate from blood-forming tissues such as bone marrow and causes large number of abnormal blood cells to be produced and enter the blood. They are grouped under blood cancers and are sometimes referred to as "liquid cancers". Lymphoma and myeloma are cancers that originate from cells of the immune system. Lymphomas are cancers of the lymphatic system while myelomas specifically originate the plasma cells of the bone marrow. These two cancer types are also blood cancers, however, lymphomas are sometimes referred to as "solid cancers". Central nervous system cancers are cancers that originate from the tissues of the brain and the spinal cord [7; 8]. Note that cancers are also classified by the grade and by the stage in which the cancer is in.

Anybody can develop cancer, since some cancers have genetic factors that are not necessarily hereditary. Most genetic aberrants that predisposes an individual to cancer are antecedents of genetic mutations which may be a consequence of internal or external factors [2], such as the metabolism of cell nutrients [2], menopause hormone therapy (treatment to relieve women of repercussions of menopause by suing artificial hormones) and family history of cancer, for example, hereditary breast and/or ovarian cancer, which is a result of a deleterious BRCA1 or BRCA2 (human genes) mutation. Compromise in the body's immune system and/or viral infection is also an important cause of cancer. Examples of such viruses or bacteria are the human papillomaviruses (HPVs) (the leading cause of cervical cancer), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8), hepatitis B (HBV) and hepatitis C viruses (HCV), human T-cell leukemia/lymphoma virus (HTLV-1), and helicobacter pylori [7]. Old age, diet and body overweight are other causes of cancer [1]. Some external or environmental carcinogenic factors include tobacco smoking (including the inhaling of environmental tobacco smoke (ETS) or residual tobacco smoke), exposure to ionizing rediation (e.g. radon, X-rays, cosmic rays), exposure to ultraviolet (UV) radiation, excessive alcohol consumption, exposure to environmental chemicals or minerals such as asbestos, nickel, benzene, formaldehyde, vinyl chloride, cadmium, pesticides, fertilizers, etc [1; 7; 9]. Nevertheless, the causes of many cancers are still unidentified.

1.1.1 Cancer Types

Signs and symptoms of cancers are numerous and they vary with respect to their types and location, speed with which they grow, their spread mechanism and their sizes (some cancers give no sign or symptom until they are large) [10]. Some general and common signs and symptoms of cancer include local symptoms (e.g. lump, swelling, bleeding, ulcers or skin sore etc at the primary site of cancer), other metastatic lumps (e.g. swelling of the lymph nodes near the primary site of cancer), systemic symptoms such as unexplained weight loss, fever, fatigue, pain, poor appetite, depression, itchy skin or skin discolouration, excessive sweating at night, etc [8; 10]. Many other symptoms are specific to the site of origin of the cancer. These include symptoms related to the gastrointestinal respiratory and cardio-vascular systems. There are also many neurological. skin-related urological and genital symptoms [8].

In order to detect the presence of cancer in patients, physicians use several diagnostic procedures and tools. To detect the location or size of a tumour and the organs affected, several imaging techniques can be used. They include X-rays, ultrasound scans, PET scans, CT (computed tomography) scans, and MRI scans. Physicians also conduct an endoscopy to get a camera view of the affected area. The most common diagnostic procedure is *biopsy*, in which cells of the tumour are removed for pathological examination under a microscope. There are different types of biopsy. They include incisional biopsy (removal of a sample of tht tissue with a needle, which is either wide; core biopsy or fine tipped; fine needle aspiration) and surgical excisional biopsy (surgical removal of an entire lump, suspected tumour or suspicious area) [8; 11]. Some imaging techniques such as CT scan or ultrasound are also used in directing the physician to the affected site or organs during the biopsy.

Other diagnostic procedures include sentinel node biopsy (surgical excision and examination of nodes close to the primary site of cancer), endoscopy, bone marrow biopsy (in cases of leukemia or lymphoma), chest X-ray and other molecular diagnosis like blood test; complete blood count (CBC), pap test (also called pap smear or cervical smear), sputum analysis and bronchial washing analysis [3; 8].

1.1.2 Cancer Treatment

In treating cancer, several factors such as the cancer type, cancer stage (how much it has spread or grown), and age of the patient amidst other things are considered. Most cancers are treated with a combination of different therapies. Cancer therapies include surgery, radiation therapy, chemotherapy, biological therapy, hormone therapy, stem cell transplant (peripheral blood, bone mar-

row, and cord clood transplant), photodynamic therapy, and targeted therapy amidst other upcoming therapies.

As a treatment procedure, surgery, the oldest known cancer therapy, is usually used to treat (or probably cure) a patient with a cancer that has not metastasised by surgically removing tumours and identified cancerous tissues. Examples of non-metastasised cancers that surgery can likely cure are breast, skin, lung and colon cancers. Surgery cannot be used to treat cancers such as leukemia and lymphoma.

Radiation therapy is the use of high-energy radiation beams focused on cancerous regions, in order to destroy the cancerous cells, or to shrink a tumour. It does this by stopping the division of cancerous cells. It does have side effects (especially when relatively early) which include skin burns, fatigue, etc. It is often used along side some other cancer therapies [3; 8; 11; 12].

Chemotherapy is the use of cytotoxic chemicals or drugs to kill all malignant and/or proliferating cells in the body. Since the drugs do not discriminate among the fast-growing cells they destroy, they also interfere with rapidly growing normal cells such as the bone marrow cells, gastrointestinal tract lining cells, and hair follicle cells. Thus, some anticancer drugs have side effects such as bone marrow suppression, hairloss, fatigue, vomiting, and nausea. It is also often used in combination with other cancer therapies [8; 12].

Biological therapy, also known as immunotherapy, is the administration of immune cells to the cancer site (local immunotherapy) or the whole body (systemic immunotherapy), in order to incite and strengthen the immune system of the host body to fight, destroy and/or shrink tumours or malignant cells. Hormone therapies are used in cases where the cancer is directly linked to the body's hormones. This is done, e.g., by reducing the oestrogen level in a breast cancer patient, or testosterone in a prostate cancer patient, with the use of hormone altering or modulating drugs [8; 12].

Some cancers destroy the bone marrow (the body cell producer). Chemotherapy and radiation therapy, especially in a high dose, can also destroy the bone marrow. Hence, some patients, with blood cancers or patients who have had chemotherapy and/or radiation therapy may need a bone marrow transplant (stem cells transfusion) for the restoration of their damaged bone marrow. There are basically three types of bone marrow transplant (BMT), named with respect to the source of the stem cells used in the procedure. They are bone marrow transplant, peripheral blood stem cell transplant, and the cord blood transplant. Bone marrow transplant is that in which stems cells can be obtained from a healthy donor (allogenic BMT), patient pre-treatment (autologous transplant), or an identical twin of the patient (syngeneic transplant). Peripheral blood stem cell transplant is that in which stem cells are obtained from the peripheral blood (the flowing, circulating blood of the body). Cord

blood transplant is that in which stem cells are obtained from the umbilical cords and placenta of newborns [7; 8; 13].

Photodynamic therapy involves the use of drugs called photosensitising agents, used along with laser light to destroy cancer cells. Targeted therapy is used when cancer cells alone can be destroyed by specific procedures, without affecting the healthy cells. They are different from, and have less adverse effects than other anti-cancer drugs [8].

1.2 Lymphoma

Lymphoma can be simply defined as a cancer of the lymphatic system [14]. The lymphatic system is a part of the immune system of the human body. It is a complex network of vessels (the lymphatic vessels), glands (or lymph nodes) and other lymphoid tissues (which include the spleen, the thymus gland and the bone marrow [4]) that convey electrolytes (called lymph), mainly lymphocytes (a variety of white blood cell) throughout the body.

Lymph nodes are groups of lymph tissues (small swellings; referred to as 'swollen glands') located along the lymphatic system at intervals. They are small and bean-sized. They are the centre of production and storage of lymph [15]. They serve as filters for the lymph, thus, averting the entrance of foreign materials (such as viruses, bacteria, or other microbes) from entering the blood stream where they are processed [4; 14].

Lymphocytes are involved in immunity, as they help the human body to combat a variety of pathogens (infectious agents). They multiply in the local lymph node of an infection, when an infection occur in that area (the infection site), so as to fight such infections. Lymphocytes are of two major subtypes; *B lymphocytes* and *T lymphocytes* (also called B cells and T cells respectively).

B cells, which mature in the bone marrow [16], help to shield the body from pathogens by producing proteins called *antibodies*. These antibodies attach to the infectious organism and abnormal cells, while it alerts other immune system cells and certain blood proteins that can kill the pathogens.

T cells, which mature in the thymus [16; 17], play several roles (that concerns its many subtypes) in the mechanism of the immune system. Some of them, when activated kill pathogens directly, or destroy infected cells, or cells that have changed into cancer cells [4; 18]. Some T cells play a part in either boosting or slowing down the activity (prevention of underactivity or overactivity respectively) of other cells of the immune system [4; 15]. Some T cells also keep a memory of particular antigens that have previously attacked the body, so that they may provide a quick resolute response when such are recognised [17; 18].

Lymphoma cells are the malignant transformation of either of the B or T lymphocytes, or their subtypes [4; 15]. Since these malignant lymphocytes are transported between the lymphatic system and the circulatory system, the lymph is eventually returned to the bloodstream via the innominate veins, thus making lymphomas *blood-related cancers* [5; 15]. Thus, lymphoma cells are sometimes found in the blood, the lymph nodes (where they are often confined) and other lyphatic tissues. They can spread to almost any other organs or tissues outside the lymphatic tissue. Such lymphoma development is referred to as *extranodal disease*. Malignant lymphoma cells, after proliferating, tend to coagulate into tumours in the lymph system or in other remote organs through the lymphatic system.

Thus, lymphomas are particular cancers that originate only from the lymphocytes in either the lymph nodes or other lymphoid tissues. They can affect lymph nodes in all parts of the body and other organs involved in the immune system, which can afterward spread to other remote organs. Most lymphomas starts in the B cells [14; 15]. However, some other cancer types can spread to lymph tissues such as the lymph nodes. These are not referred to as lymphomas [15].

1.2.1 Lymphoma Types

There are two major types of lymphoma, namely Hodgkin lymphoma (also Hodgkin's disease/lymphoma) and Non-Hodgkin lymphoma (also Non-Hodgkin's disease/lymphoma).

Hodgkin lymphoma (HL) is a lymphoma that contains abnormal cells known as the *Reed-Sternberg cells* (visible under a microscope). This is its major defining characteristic which makes it different from Non-Hodgkin's lymphoma. HL spreads in predictable ways, by contiguity, from one lymph nodal chain to adjacent nodal sites. It is non-contagious. It is a result of the cancerous trasformation of B lymphocytes [6].

There are two subtypes of HL: Classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. The latter often develops more at an older age than those diagnosed for the classical HL. It is also usually diagnosed at its early stage and it grows at a slower rate than the classical HL. The two HL subtypes also have different forms of treaments [19].

The causes of Hodgkin lymphoma is generally unidentified. However, despite the fact that HL is considered a non-AIDS-defining cancer, HIV/AIDS patients have about 10-20 times proclivity to develop it in comparison with the general population [6]. A recent British report on the effect of highly active antiretroviral therapy (HAART) on the incidence of HL, suggests that there may be a relation between the HAART and the incidence of HL in HIV/AIDS

patients on the HAART [20]. In addition, viral infection with viruses such as Epstein-Barr virus (EBV) have also been observed to be a likely predisposing factor to deveoping HL. HL is more predominant in men than in women, and it can occur at any age. However, it occurs mostly in people between the ages of 15 and 35, or 55 and above [5; 14].

Non-Hodgkin lymphoma (NHL) is simply a general term for any other lymphoma that is not Hodgkin's, i.e its biopsy does not reveal any presence of Reed-Sternberg cells. There are over five dozens different types of NHL. Cases of NHLs are more common than HL and it comprise about 90% of all diagnosed lymphomas [5; 6]. Most NHL patients are people aged over 55, and NHLs are now the most common cancers in individuals aged 75 and above [5; 14].

The mode with which NHL invades the body is unpredictable. NHL is classified according to the rate of the growth of the cancerous cells. It is described as *high-grade* (aggressive) NHL or *low-grade* (indolent) NHL. The former describes a NHL with cells that seem to divide quickly, which is an indication that the particular diagnosed NHL is fast growing. These lymphomas are either B cell (more common) or T cell lymphomas. Low-grade NHLs describes a lymphoma with cells that seem to divide slowly, which implies that the particular NHL diagnosed is growing slowly [19].

The causes of NHL are also generally unknown. However, a compromised immune system; immunosuppression or immune deficiency is a definite risk factor for NHL. Transplant patients are at risk, as well as HIV/AIDS patients. It has also been observed that past cancer treatment (repercussion of chemotherapy), after several years can also cause one to be at risk of developing NHL. Several viral and bacterial infections also predisposes a person to NHL. Such viruses include the human T cell lymphoma virus 1 (HTLV1), Epstein Barr virus and hepatitis C virus [21].

Common symptoms of lymphoma include painless swelling (or lump in) the lymph nodes in the neck, under the arm or groin, unexplained weight loss, excessive night sweats, unexplained persistent fever, persistent itchy skin, and other malfunctions or pains in other parts or organs of the body affected by the lymphoma [4; 11; 13].

There is the need for the identification of the lymphoma subtype a patient has using biopsy, after which treatments are administered with respect to that patient's particular case. Lymphoma treatments include chemotherapy (most often drug administration), radiotherapy (targetted high energy X-ray exposure to destroy cancer cells), peripheral blood stem cell or bone marrow transplant (in very extreme cases and sometimes for relapsed diseases), monoclonal antibody therapy (a type of immunotherapy, sometimes used alongside chemotherapy), immunotherapy (also referred to as biological therapy or biotherapy), and radioimmunotherapy [11; 13].

If lymphoma is diagnosed at a very early stage, then there is a high chance of it being cured. Nevertheless, there is quite a lot of debate as to whether cancers can actually be cured. An effective treatment therapy can afford a patient the chance of being in remission. A cancer patient is said to be in lymphoma (or cancer) *remission* after lymphoma (or in general, cancer) treatment if the lymphoma (cancer) cells in the body are undetectable and cause no symptoms. The main aim of medical therapy in lymphoma (and other cancer) treatment is to achieve a *complete remission* in patients, that is, after the treatment of lymphoma (cancer), every sign of lymphoma (cancer) is gone [22; 23].

A patient is said to be in a *partial remission* if a part of the tumour shrinks after treatment, or if there is a partial response of the lymphoma (cancer) to any treatment therapy, in that there are still signs of that lymphoma subtype (cancer) in the patient. A patient that remains in remission for a long period of time, say for many years, is said to be in a *durable remission* [23].

Patients can be in remission for a long period of time, as well as for a short period of time. If lymphoma reoccurs after a patient has been in remission for sometimes, then the patient is said to have a *relapse* (of lymphoma), and there is said to be a lymphoma *recurrence*. Factors that determine if a patient will spend months, years, or even a lifetime in remission depends on the stage and grade of that patient's lymphoma subtype. The duration of a patient's remission can be used to determine how aggressive the lymphoma is [22; 23].

Chapter 2

HIV-Related Lymphoma (HRL)

2.1 Introduction

Despite the fact that some malignant neoplasms are defined as non-HIV-defining, they are profusely reported in HIV-positive patients. Such cancers include Hodgkin lymphoma (HL), multiple myeloma, lung cancer, invasive anal carcinoma, leukemia and those involving the oral cavity, liver, gastrointestinal tracts, lip, oesophagus, heart, pancreas, vulva, vigina, soft tissues (e.g. leiomyosarcoma in children), and the stomach [24]. In contrast, some common carcinomas found in the general population does not siginificantly occur in PLWHA. They include breast, prostate and colon/rectum carcinomas [24; 25].

People living with HIV/AIDS (PLWHA) have been observed to be at a higher proclivity of about 60-200 times of developing HIV-related lymphoma (HRL), in comparison with the general HIV-free population which include some immunosuppressed individuals such as organ transplant patients [26–28]. The overall prevalence of HRL remains significant, even after the introduction and wide implementation of the HAART. In addition, HRL is still one of the most frequent causes of mortality in HIV-positive patients [28].

In particular, the incidence of Non-Hodgkin lymphoma (NHL) is increased by almost 25- to 250-fold in individuals infected with HIV, especially in the advanced stage, compared to the general/HIV-free population. It is the second most common neoplasm that HIV-positive individuals develop [29–33]. This high risk of lymphoma development in PLWHA is most likely a direct implication of severe immune system dysfunction, cytokin dysregulation, prolonged HIV infection, old age, and opportunistic infections (OI) due to intense immunosuppression of the body from chronic HIV infection [31; 32]. Concormitant oncogenic viruses that are associated with many of the immunological dysfunctions, especially malignant lymphomas and other OI include Epstein-

Barr (EBV) (which plays a major role as it is found in 40-50% of HRL [25; 31]), human herpesvirus 8 (HHV-8) and human papilloma virus (HPV) [27; 30–32].

The World Health Organisation (WHO) has classified HRL subtypes into 3 major categories: lymphoma also ocurring in immunocompetent patients, lymphoma ocurring more specifically in HIV-positive patients, and lymphoma also ocurring in other immunodeficiency states [28; 30; 31]. According to this classification, lymphomas also ocurring expressly in HIV-positive patients include primary effusion lymphoma (PEL) (and its solid variants) and plasmablastic lymphoma (PBL) of the oral cavity type [31; 32]. Note that large B-cell lymphoma arising in Kaposi Sarcoma herpesvirus (KSHV)-associated multicentric Castleman disease (MCD) has also been defined as an HRL [27; 34].

Lymphoma also arising in immunocompetent patients include: Burkitt lymphoma (BL) and Burkitt-like lymphoma (BLL), diffuse large B-cell lymphoma (DLBCL); both centroblastic and immunoblastic (including primary central nervous system (CNS) lymphoma), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma - which is rare), peripheral T-cell lymphoma (also rare) and classical Hodgkin lymphoma. Lymphomas also arising in many other immunodeficiency states include polymorphic B-cell lymphoma, which is like the post-transplant lymphoproliferative disorder (PTLD) and it is rare [28; 31].

The most commonly reported cases of HRL are of the B-cell derivation; mostly represented by DLBCL with immunoblastic-plasmacytoid differentiation (also involving the CNS) and BL [24; 30–32; 34]. They are distinguished by clinical aggressiveness, advanced stage, and a high frequency of extranodal involvement [35].In most studies, DLBCL reportedly accounts for 60-80% of aggressive HRL cases, of which the median CD4 count on diagnosis is often about 130cells/μL and a CD4 count of $<$ 200cells/μL in about 30% of all DLBCL cases [31]. EBV is detected in about 50- to -70% of all DLBCL cases [25]. Extranodal sites common to DLBCL (especially in HIV-infected individuals) include lymph nodes, bone marrow, liver, gastrointestinal tract, and virtually any extranodal sites. The most common of this is the brain, with primary central nervous system lymphoma (PCNSL) (also known as *primary brain lymphoma*) accounting for about 15-30% of HIV-related Non-Hodgkin lymphoma (HIV-NHL) [30–32; 36].

BL and BLL (BL's morphological variant) accounts for about 35-50% of all HIV-NHL in several studies [30; 31; 37]. EBV is present in about 30% of all BL cases. Extranodal sites common to BL include the liver, spleen, bone marrow, gastrointestinal tract and meningeal involvement [31]. It is pertinent to note that while BL is common in HIV-infected patients, it has no other association with other kinds of immunosuppression [30].

PCNSL, also known as primary brain lymphoma is an immunoblastic (or high-grade) variant of DLBCL. It tends to occur only in PLWHA, especially those with severe HIV infection (advanced AIDS) [29–31]. It accounts for 15-30% of

all HIV-NHL. About two-third of PCNSL patients had AIDS-defining-illnesses (ADI) prior to developing PCNSL. HIV-related PCNSL (HIV-PCNSL) generally have a median survival of approximately 3 years [29]. Over 95% of PCNSL cases are closely associated with EBV [25]. PCNSL is associated with severe immunosuppression, even in people who are iatrogenically immunosuppressed. The median CD4 count on diagnosis is less that 50cells/μL [24; 29; 31; 32]. The neoplasm mostly occurs in the cerebrum as multiple lesions, but it can also involve nonhemispheric brain areas; cerebellum, brain stem or basal ganglia, periventricular. Extranodal sites frequently common to PCNSL include the liver, bone marrow, and gastrointestinal tract. PCNSL has a poor prognosis. Factors that affects this include old age (from 50 years and above), very low CD4 count, and the involvement of hemispheric brain areas [30]. It also has a poor median survival of about 4 months [32]. Radiation therapy is the most common treatment for both HIV-PCNSL and non-HIV-PCNSL [29].

Primary effusion lymphoma (PEL) is a distinct high-grade B-cell neoplasm that rarely occurs in HIV-negative patients. It comprises less than 5% of all HIV-NHL. It is consistently associated with infection by Kaposi sarcoma-associated herpesvirus (also known as HHV-8), with a frequent ($>$ 90%) coinfection with EBV [24; 34; 36; 38]. Most cases of PEL are reported to be in HIV-positive men, who are majorly homosexuals, and with a diminished CD4 count ($<$ 200cells/μL). The median of their ages is between the mid-30s and mid-40s, of which they commonly have an AIDS history [31; 35; 36].

PEL has two variants; the *classic PEL* (or "body cavity-based lymphoma") and a "solid variant", otherwise called *extracavity PEL*. PEL mostly develops as malignant serous (or lymphomatous) effusions. It is common for PEL to be metastatic [35; 36; 38]. The extracavity PEL most commonly involves the gastrointestinal tract or soft tissue, the skin, large bowel, lung and lymph nodes with similar immunophenotypic features. It is also associated with HHV-8 [24; 30; 31; 36]. Most PEL patients have pre-existing (or subsequent) HHV-8 related diseases, which include Kaposi sarcoma or multicentric Castleman disease (MCD). PEL patients are also mostly homosexuals [30; 35; 36].

Plasmablastic lymphoma (PBL) is a rare and distinct NHL subtype, as classified by the WHO [33], and it is formerly classified as a clinicopathological variant of immunoblastic DLBCL. It is characterised by blastoid morphology, plasmacytoid differentiation, a rare immunophenotype of plasma cells (PC), and a penchant for the oral cavity, especially the mucosa of the jaws of (predominantly) HIV-infected individuals [24; 30; 39; 40]. It is a HIV-related high-grade lymphoma that develops mostly in males. It has also been reported in immunocompetent patients [33; 39]. It is closely associated with latent EBV infection in most (70%) cases [38; 39; 41].

PBL accounts for 2.6%- to -30% of all HIV-NHL cases [33; 41]. Other extraoral sites common to PBL include the anal cavity, lung, gastrointestinal tract,

anorectal region, paranal sinuses, (cervical) lymph nodes, spermatic cord, skin, testicle, and bone [33; 38; 41]. PBL patients present with a depreciated CD4 count ($<$ 200cells/μL), and the median of their ages is usually between 38 and 48 years [37; 40]. PBL has a prominent propensity for the gastrointestinal tract and the central nervous system as extranodal (anatomic) sites. Reports also show that the most common intraoral sites are the gingiva (mostly localised there), the floor of mouth and the palate [33; 39]. PBL has a poor prognosis and poor response to therapy, even with polychemotherapy, with, or without combined radiography. PBL patients have an average survival time of 14 months[39; 41]. A recent study by Hansra *et al.* [41], suggests that PBL is a heterogenous group of NHLs with distinct clinicopathology, viral associations and outcomes. They reported that it has two unique clinical variant entities; *PBL of the oral mucosa* and the *extraoral PBL*.

2.2 HRL in the Post-HAART Era

The highly active antiretroviral therapy (HAART) was globally and publicly rolled out through expanded access programmes in late 1996 [30; 42]. In the pre-HAART era, the prognosis for HRL was very poor, and this is due to many reasons. These include HIV history, low CD4 count ($<$ 100cells/μL), injection drug use and old age (35 years or older). Complete remission was achieved in 30-60% and the median overall survival was (5-8) months [31]. Also, patients with DLBCL had significantly higher rates of HIV-related illnesses (HRI), coupled with lower CD4 counts, in comparison with BL patients at HRL diagnosis [32].

The advent of HAART have precipitously improved HIV-related mortality and morbidity, in that they have impressively declined. HAART has (generally) efficaciously reduced the pace at which HIV-infected patients progress to AIDS. Hence, it has declined the risk of developing some HIV-related cancers (HRC) in HIV-infected patients. This is strikingly evident in the incidence of KS and other opportunistic infections (OI) in the post-HAART era [25; 43]. When HAART regimens are effectively combined and adhered to, it avails HIV patients with immune restoration, thereby reducing the overall incidence of HRL. This effect has changed the epidemiological and clinical profile of HRC in general [24; 25; 30; 31; 35]. In addition, the incidence of most AIDS-defining illnesses (ADI) have dramatically declined [25; 32]. An effective HAART regimen leads to decreased cytokine stimulation or an improved immune function, fewer infectious complications, and a significant improvement in the survival of HIV-infected patients [24; 32].

Since the HAART roll out, there have been a particular decrease in the risk of lymphoma in people living HIV/AIDS (PLWHA). It has also improved

clinical outcomes [30]. This diminishing risk is seen to be associated with improved CD4 counts, which is a consequence of HAART in PLWHA using it. Thus, there is an improved prognosis in most HRL patients using HAART, and their survival approaches those of the HIV-negative lymphoma patients. This is also partly because of higher mean CD4 counts, which has given HRL patients more tolerance for chemotherapy [25; 44]. HAART has improved the overall outcome of NHL, as the overall incidence of HIV-NHL have declined [25; 35; 36]. HAART has also decreased the mortality rate of HIV-related Hodgkin lymphoma (HIV-HL) patients who use HAART, thereby changing the mortality rate at 3 years for HIV-HL patients without HAART, to 5.6 times of those on HAART. Thus, HAART is correlated with improved prognosis in HIV-HL cases [31]. We must note that non-AIDS defining cancers (NADC) are seen to be on the rise, even in the post-HAART era. However, it's been reported that early diagnosis and the effective use of HAART will also arrest this situation [43; 45].

2.2.1 Effects of HAART on Some Specific NHL Subtypes

A study by Diamond *et al.* [44], where the San Diego County registry data were linked with its AIDS registry data to identify some HIV-NHL patients, showed that the incidence of NHL from the pre- to -post-HAART era decreased dramatically (from 29.6 per 1000 person-years pre-HAART to 6.5 per 1000 person-years post-HAART). The proportion of high-grade NHL (which most study reports to be primarily high-grade immunoblastic DLBCL [31; 32]) also decreased from 38% to 19%, and that of PCNSL decreased from 28% to 17%. They also affirmed that immune reconstitution and diminished cytokine stimulation afforded by HAART, can result in a decrease in the frequency of herpesvirus-associated immunoblastic NHL.

HIV-related PCNSL (HIV-PCNSL) is reported to have improved significantly in the HAART era, as viral load is being decreased by ≥ 0.5 $\log_{10}$ plasma cells/mL, and CD4 count is increased by 50cells/μL or more [31]. There is also a very significant and dramatic decline in PCNSL cases in relation to other HRLs [24; 29; 32]. This is particularly reported to be the most significant impact of HAART [25; 36]. A significant delay in the development of PCNSL, and a steady decline in the histologies and sites of this immunoblastic lymphoma, in several HIV-infected PCNSL patients on HAART have also been observed [25; 32].

PEL is reported to have a poor prognosis even in the post-HAART era, with or without chemotherapy, and it has extremely minute number of long-term survivors [35; 36]. Nevertheless, there are a few exceptional reports of HAART-induced responses [35]. In a recent large multicenter retrospective study of 28

HIV-positive PEL patients, PEL is shown to have a 1 year overall survival (OS) rate of 39.3%, with a median survival time of 6.2 months [35]. Their result suggests that the two most predictive prognostic factors that are independently associated with a longer survival of patients are performance status and HAART use [30; 35].

PBL, which is often treated with chemotherapy has a poor response to treatment therapies. Despite this fact, survival with PBL may be improving in the HAART era. In the earlier AIDS epidemic, PBL survival was short, with an average survival time of 5.5 months [31; 41]. A study by Lester *et al.* [46] reports that PBL has an average survival duration of 14 months as a response to HAART in an HIV-infected patient of theirs, but relapsed after the patient failed to adhere to his HAART regimen for some months. However, the patient went on complete remission (CR) for 8 months from diagnosis of relapse, after another combination of chemotherapy. Another study reported that about 50% of HIV-infected PBL patients who used HAART regimens sometimes during their lymphoma treatment responded to it, of which most of them (about 90%) were still alive as at the time of publication of their result (about one year later) [37]. Lester *et al.* [46] also reported that HAART may afford PBL patients immunological restitution and virologic control, which may maintain CR. Prognostic factors for PBL include low CD4 count or viral load history, oral or gastrointestinal symptoms, or any other primary site of the malignancy, clinical stage, sex and EBV association [37; 46].

It is pertinent to note that the use of HAART during HIV progression may trigger the development of lymphoma. Pantanowitz *et al.* [47] reported an abrupt decline in the viral load, and a rise in the very low CD4 cell count of their highly deteriorated HIV-infected-EBV-related-PBL patient, who was treated with a full chemotherapy regimen with HAART. However, they observed an aggravation of their patient's case, of which HAART initiation was a transient cause, like in some other reports. This lymphoma aggravation is suggested to be a consequence of immune enhancement afforded by HAART, as opposed to lymphoma progression due to lack of response to HAART. This phenomenon was referred to as immune reconstitution inflammatory syndrome (IRIS). The risk factors for an IRIS include low CD4 cell count, presence of infection(s), and a robust virologic and immunologic response to HAART. Nevertheless, such aggravations can be eschewed if the optimal time for HAART initiation is recognised on a per-patient basis.

The study by Diamond *et al.* [44] also reports that the proportion of intermediate-grade lymphoma (primarily DLBCL) increased from 33% to 49%, that of BL increased from 4% to 9%, and the proportion of centroblastic DLBCL increased from 21% to 44% cases. The increase in some HRL in the post-HAART era, such as the centroblastic DLBCL and BL can be attributed to the relation of these HRL subtypes with the immunosuppression level in the patient. These

two subtypes occur in patients with normal or slightly depreciated CD4 counts [24; 30; 44].

A ridiculously low CD4 count ($<$ 100cells/μL) is obviously associated with worse outcomes in HRL. Even in the HAART era, CD4 counts less than 100cells/μL or 50cells/μL in HRL patients, have been shown to predict lower complete remission (CR) rates [31]. Since HIV patients on HAART regimens now live longer with chronic HIV infection, but with few OI, HIV-related malignancies are increasingly conspicuous causes of death in the later stages of AIDS [24; 32; 48].

2.3 Concormitant Treatment of HRL Patients with HAART and Chemotherapy

Several studies report that HRL patients treated with chemotherapy and HAART concormitantly have significant decrease in CD4 count during treatment, but a steady and significant increase in the median CD4 count after chemotherapy, while still simultaneously under some HAART regimen. Nevertheless, the assumption that CD4 counts depreciates with chemotherapy is safest, and it is advisable to use oppotunistic infection (OI) prophylaxis consequently [31].

As earlier stated, while some exceptional reports have it that there are HAART-induced improvement of some NHL cases like PEL [35], several reports also have it that prolonged remission have been achieved in PEL patients with the use of HAART alone. This suggests that immune reconstitution plays an important role in controlling high-grade (aggresive) lymphomas. Hence, it is suggested that a concormitant treatment with HAART (either by initiating it or continuing it if the patient is not HAART-naive) as a supportive therapy be recommended for HIV-positive PEL patients initiating PEL treatment [36].

It is important to note that antiretrovirals may interfere with cytotoxic drug metabolism, which means that the HAART and/or chemotherapy dosage may need to be adjusted on an individual patient basis. Zidovudine (AZT), in most cases causes myelosuppression effects and is hence not recommended to be used with chemotherapy.

With all these encouraging reports on the improvement of the health of HIV-HRL patients, by the use of lymphoma treatments (especially chemotherapy) and concormitant HAART, it is secure for HIV-HRL patients to be administered chemotherapies (and other treatment therapies when necessary) with curative intents, and without long-term immune suppression [25; 48]. However, it should be noted that such concormitant treatments should be prescribed on an individual patient basis, that is, with respect to individual cases [29].

2.4 HRL in South Africa: Western Cape province as a case study

In South Africa, there was an initiation of a national HAART roll-out program in 2004. This HAART program have been gaining more grounds over the years, and its coverage was about 31% as at 2009 [26; 27]. The incidence and pattern of HRL in the Western Cape (WC) province of South Africa (SA) was not previously documented prior to the year 2002. An on-going study by the Tygerberg Lymphoma Study Group (TLSG), in conjunction with some other institutions is shedding more light on how HIV is changing the incidence and pattern of HRL in the WC province of SA [27]. Their analysis of documented data shows that incidences of HRL keeps increasing in this geographical location despite the roll-out of the HAART program in 2004. There was an increase of HRL cases, from about 5% of all lymphoma cases in 2002, to 37% of all the lymphoma cases documented in 2009. This is contrary to the report of many related international studies, which often suggest remarkable reduction in the incidence of HRL in regions with effective HAART programs [24; 27].

During this period of data collection, the national HIV treatment policy as to when patients can receive HAART was that their CD4 cell counts must be $\leq$ 200 cells/μL. Nevertheless, most patients who present often do at a CD4 cell count of $<$ 100 cells/μL. This is an indicator of a degenarated immune system, which can hardly be reconstituted (that is, raising the CD4 cell count to more than 500 cells/μL) even when the patient in such situation is placed on HAART [27; 38; 49]. This clearly shows that patients often present late, and thus, usually have deteroriated immune systems which are mostly irremediable. Another consequence of this is that even when those who eventually get enrolled into the HAART program live longer than they would have, they will remain significantly immunosuppressed and challenged, thereby developing immune system-related conditions such as HRLs, as is the case in the WC province.

Burkitt lymphoma was previously a rare lymphoma subtype in the WC province of SA, but now, it is the commonest HRL. The next to it are diffuse large B-cell lymphoma subtypes. Plasmablastic lymphoma is also another new and unfolding lymphoma subtype in this population. These are pointers to the fact that HIV is drastically affecting the incidence and emergence of different subtypes of HRL in this population. Suggested reasons for these inauspicious developments include inadequate HAART coverage, late presentation of patients (and thus late commencement of HAART), inconsistent adherence to HAART regimen, increased age and inefficient viral suppression in patients on HAART [27; 38].

Chapter 3

HIV-Related Lymphoma Model

3.1 Introduction

While lot of coinfection mathematical models of HIV and cancer (at cell level [50–52]) and population level ([53]) have been proposed, none of them, to the best of our knowledge have explored the dynamics of HIV-related cancers (specifically lymphoma) on a population level, with the different stages of HIV and cancer coinfection incorporated. The HIV and lymphoma coinfection model proposed in this study investigates likely factors that are responsible for the reasons HIV is transforming the incidence, prognosis, and outcomes of lymphoma (and every other cancer subtypes in general) in HIV-infected individuals.

This study is a component of the Tygerberg Lymphoma Study Group, that looks at using expanded laboratory profiling in conjunction with clinical, imaging and demographic methodologies to improve the understanding of how HIV is transforming the incidence, pattern, prognosis and outcomes of lymphoproliferative disorders in the Tygerberg catchments area of the Western Cape province of South Africa.

The major premise of this study is to investigate and understand the asymptotic dynamics of HIV-related (or AIDS-defining) malignancies in the human population, taking the Western Cape province of South Africa as our case study.

3.2 Model Formulation

We construct a mathematical model that describes the different stages individuals can progress into during the course of developing lymphoma, or contracting HIV, or contracting HIV after lymphoma has developed in the body,

or developing lymphoma after having contracted HIV. This model conceptualises and demonstrates plausible features of what happens in an HIV and lymphoma co-infection setting. Since there is a lot of lymphoma cases among aged people, but less in children, HIV is more predominant among the sexually active population ($15-49$ years), and HIV and lymphoma co-infection occurs both in the sexually active population and the aging population, we consider a population $N(t)$, at time t, with ages ranging between $15-80^{+}$ years, which we refer to as adult population.

With respect to the infection and treatment stages, we subdivided the total population $N(t)$ into distinct (non-intersecting) population classes (compartments). Each compartment is characterised by a heterogenous mixing of individuals within it, while there is a homogenous interaction of individuals between the non-intersecting classes. Thus, each susceptible individual is assumed to have an equal chance of being infected by an infectious individual (i.e. population mixes homogenously). The compartments include; the susceptible population $S(t)$, which comprises of individuals that are predisposed to contracting HIV and developing lymphoma (every individual introduced into the population is assumed to be susceptible), lymphoma patients $I_L(t)$, HIV-infected patients $I_H(t)$, patients co-infected with both HIV and lymphoma I_{LH}, lymphoma patients who have been treated for lymphoma and then went into remission $I_{LR}(t)$, (who will be referred to as *Lymphoma patients in remission*), HIV-infected patients who are under a HAART regimen $I_{HT}(t)$, (who will be referred to as *HIV-positive patients under antiretroviral regimen(s)*), patients with both HIV and lymphoma, and who are in remission after some lymphoma treatment $I_{LHR}(t)$, (who will be referred to as *patients with both HIV and lymphoma, and in remission*), patients with both HIV and lymphoma, and are using a HAART regimen $I_{LHT}(t)$, patients with both HIV and lymphoma, who are in remission for lymphoma treatment, and who are using some HAART regimens $I_{LHTR}(t)$, and patients whose HIV have progressed to AIDS $A(t)$. The total sexually active population at any given time t, including the old age population is thus given by

$$N = S + I_L + I_H + I_{LH} + I_{LR} + I_{HT} + I_{LHR} + I_{LHT} + I_{LHTR} + A. \quad (3.2.1)$$

The recruitment of individuals into the class of susceptibles is proportional to the population, thus, the recruitment rate is given by bN, where b is the crude birth rate. We let $K = bN_0$, where N_0 is the initial population size. The mean lifetime of an individual is estimated as $1/\mu$, where μ is the natural mortality rate, which is common to all the compartments. The (HIV) disease-related death rate is given by δ. Observe that lymphoma related deaths are omitted because we assume that when lymphoma patients are not coinfected with HIV (which can relatively rapidly destroy their immune systems), they either die at

almost the natural death rate, or they are treated for lymphoma, or they get infected with HIV, which enables them to move into other population classes in the model, without necessarily leaving the population pool. The lymphoma development rate of susceptibles (which are generally HIV-negative individuals) is α_1. This model has 3 distinct classes described as being susceptible to HIV infection. They are S, I_L and I_{LR}. The model assumes a non-linear standard incidence function. The force of infection for class S, is λ_1, while the force of infection for those with lymphoma (classes I_L and I_{LR}) is λ_2. We assume different forces of infection for these two groups because individuals in class S are supposed to be more immunocompetent than those in I_L and I_{LR}, as their immune systems would have been challenged. The forces of infection $\lambda_i,\ i = 1, 2$, are given by:

$$\lambda_i = \frac{\beta_i}{N}\left[I_H + \eta_1 I_{HT} + \eta_2(I_{LH} + I_{LHR}) + \eta_3(I_{LHT} + I_{LHTR}) + \eta_4 A\right], \quad (3.2.2)$$

provided $\lambda_i(t)$ is redefined at the ϵ-neighbourhood of $N = 0$, for it to be finite at $t = 0$ and biologically plausible. The parameters β_1 and β_2 are the effective contact rates of HIV infection for susceptible individuals, and for lymphoma patients (either treated or not) respectively. β_i is a product of the number of contacts, effective or not, per unit time and the risk of infection (or probability that an infection will occur), also called transmission risk, given contact between a susceptible and an infectious individual. $\eta_i,\ i = 1, 2, 3, 4$, are the modification parameters (or adjustment factors), which measure the relative infectiousness of individuals in $I_{HT}, I_{LH}, I_{LHR}, I_{LHT}, I_{LHTR}$ and $A(t)$ to the infectiousness of those in I_H. Individuals with high viral loads (either in the acute infection stage; window period, or at the end-stage disease) are highly infectious [54]. Thus, the likelihood of HIV-infecteds to be infectious is directly proportional to their viral loads [55]. Hence, we consider $1 \leq \eta_i \leq 2$, for all $i \in \{1, 2, 3, 4\}$.

We assume that $\eta_1 < 1$, because of the decrease in the viremia of individuals in class I_{HT}. We have also assumed that individuals with both HIV and lymphoma, and those with HIV and lymphoma, but in remission due to lymphoma treatment have a higher viremia in relation to individuals with HIV [56], but using some antiretroviral regimen, thus $\eta_2 > \eta_1$ and $\eta_2 > 1$. In like manner, we assumed that individuals co-infected with HIV and lymphoma, who are using HAART regimen, and that are either in remission for lymphoma treatment or not, are less infectious (because of lower, treatment-induced viremia) than individuals who are also co-infected, with lymphoma and HIV, whether in lymphoma remission or not, thus, $\eta_3 < \eta_2$ and $\eta_3 < 1$. Similar, individuals with both lymphoma and HIV, using HAART regimens, and either in remission for lymphoma treatment (or who are not on treatment) are considered

more infectious than individuals with HIV only, but on HAART regimens too. Thus, $\eta_3 > \eta_1$.

Individuals with AIDS are considered as the class with the highest level of viremia, and are thus the most infectious population group. Hence, $\eta_4 > \eta_1, \eta_2, \eta_3$, and $\eta_4 > 1$. Our model assumes that every epidemiological parameter is constant and positive. The lymphoma development rate of HIV-infected individuals, and the HIV-infectives using antiretroviral regimens is denoted by α_2 and α_3 respectively. The probability that a (lymphoma-free) HIV patient, a patient with both HIV and lymphoma, and a patient with both HIV, lymphoma, and in remission for lymphoma treatment are recruited into treatment is given by σ_1, σ_2, and σ_3 respectively. Table 3.1 outlines the description and symbols of state variables used in the model. Every other epidemiological parameters, with their symbols and description is outlined in Table 3.2.

The flow of individuals between the ten compartments is illustrated by the model diagram shown in Figure 3.1.

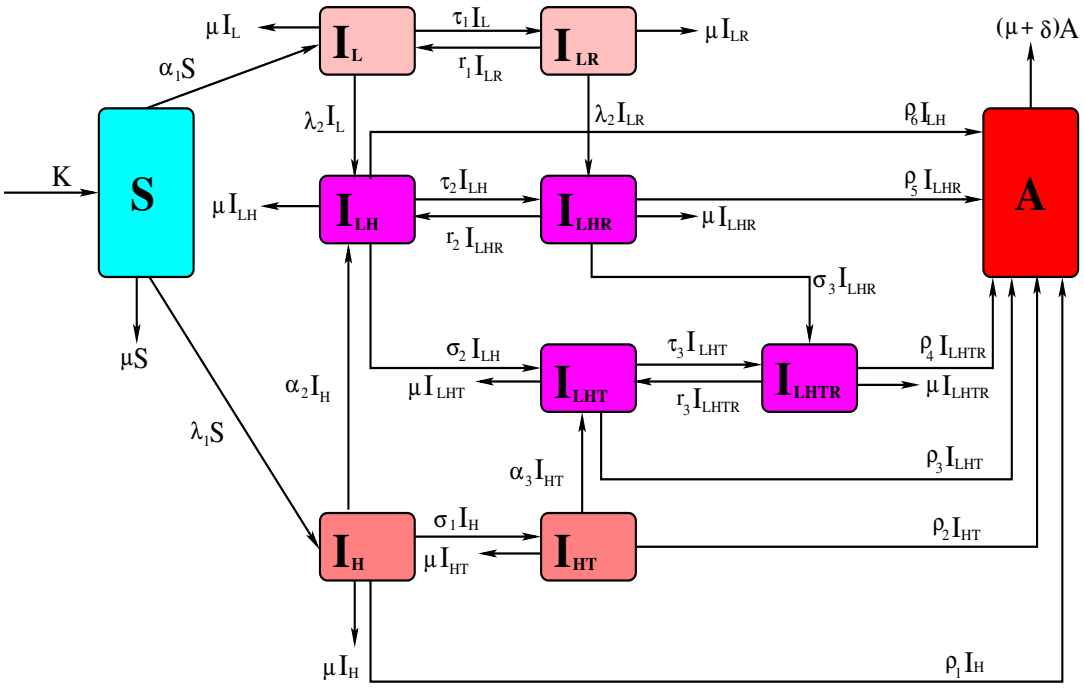

Figure 3.1: Diagrammatic Structure of the HIV-Lymphoma Model

3.2.1 Model Equations

The dynamical system described by Figure 3.1, our assumptions and parameters' description, is given by the following system of first order ordinary differential equations:

$$\frac{dS}{dt} = K - \lambda_1 S - (\mu + \alpha_1)S \tag{3.2.3a}$$
$$\frac{dI_L}{dt} = r_1 I_{LR} + \alpha_1 S - \lambda_2 I_L - (\mu + \tau_1)I_L \tag{3.2.3b}$$
$$\frac{dI_{LR}}{dt} = \tau_1 I_L - \lambda_2 I_{LR} - (\mu + r_1)I_{LR} \tag{3.2.3c}$$
$$\frac{dI_H}{dt} = \lambda_1 S - (\mu + \alpha_2 + \sigma_1 + \rho_1)I_H \tag{3.2.3d}$$
$$\frac{dI_{LH}}{dt} = \lambda_2 I_L + \alpha_2 I_H + r_2 I_{LHR} - (\mu + \tau_2 + \sigma_2 + \rho_6)I_{LH} \tag{3.2.3e}$$
$$\frac{dI_{HT}}{dt} = \sigma_1 I_H - (\mu + \alpha_3 + \rho_2)I_{HT} \tag{3.2.3f}$$
$$\frac{dI_{LHR}}{dt} = \lambda_2 I_{LR} + \tau_2 I_{LH} - (\mu + r_2 + \sigma_3 + \rho_5)I_{LHR} \tag{3.2.3g}$$
$$\frac{dI_{LHT}}{dt} = \sigma_2 I_{LH} + \alpha_3 I_{HT} + r_3 I_{LHTR} - (\mu + \tau_3 + \rho_3)I_{LHT} \tag{3.2.3h}$$
$$\frac{dI_{LHTR}}{dt} = \sigma_3 I_{LHR} + \tau_3 I_{LHT} - (\mu + r_3 + \rho_4)I_{LHTR} \tag{3.2.3i}$$
$$\frac{dA}{dt} = \rho_1 I_H + \rho_2 I_{HT} + \rho_3 I_{LHT} + \rho_4 I_{LHTR} + \rho_5 I_{LHR} + \rho_6 I_{LH} - (\mu + \delta)A, \tag{3.2.3j}$$

with initial conditions of the model system given by $S(0) = S^0$, $I_L(0) = I_L^0$, $I_H(0) = I_H^0$, $I_{LH}(0) = I_{LH}^0$, $I_{LR}(0) = I_{LR}^0$, $I_{HT}(0) = I_{HT}^0$, $I_{LHR}(0) = I_{LHR}^0$, $I_{LHT}(0) = I_{LHT}^0$, $I_{LHTR}(0) = I_{LHTR}^0$, $A(0) = A^0$.

Variables	Description
S	Susceptible individuals
I_L	Lymphoma patients
I_H	HIV-positive patients
I_{LH}	Patients with both HIV and lymphoma
I_{LR}	Lymphoma patients in remission
I_{HT}	HIV-positive patients under antiretroviral regimen(s)
I_{LHR}	Patients with both HIV and lymphoma, and in remission
I_{LHT}	Patients with both HIV and lymphoma, and under antiretroviral regimen(s)
I_{LHTR}	Patients with both HIV and lymphoma, under antiretroviral regimen(s) and in remission
A	Patients with full-blown AIDS
N	Total size of population

Table 3.1: Symbols and description of the variables used in the model

Parameters	Description
K	Recruitment rate for susceptibles
μ	Natural mortality rate
δ	Disease-induced mortality rate
λ_1	Force of (HIV) infection of susceptible individuals
λ_2	Force of (HIV) infection of lymphoma patients
β_1	Effective contact rate of HIV for susceptible individuals
β_2	Effective contact rate of HIV for lymphoma patients
α_1	Lymphoma development rate of susceptible individuals
α_2	Lymphoma development rate of HIV-positive patients
α_3	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s)
σ_1	HIV treatment rate of lymphoma-free HIV patients
σ_2	HIV treatment rate of patients with lymphoma and HIV
σ_3	HIV treatment rate of patients with lymphoma, HIV, and in remission
τ_1	Lymphoma treatment rate of lymphoma-only patients
τ_2	Lymphoma treatment rate of patients with lymphoma and HIV
τ_3	Lymphoma treatment rate of patients with lymphoma, HIV, and are under antiretroviral regimen(s)
r_1	Lymphoma relapse rate of lymphoma patients in remission
r_2	Lymphoma relapse rate of lymphoma patients with lymphoma and HIV in remission
r_3	Lymphoma relapse rate of lymphoma patients with lymphoma, HIV, in remission and under antiretroviral regimen(s)
ρ_1	Progression rate to full-blown AIDS in HIV patients
ρ_2	Progression rate to full-blown AIDS in HIV patients under antiretroviral regimen(s)
ρ_3	Progression rate to full-blown AIDS in patients with lymphoma, HIV, and under antiretroviral regimen(s)
ρ_4	Progression rate to full-blown AIDS in patients with lymphoma, HIV, under antiretroviral regimen(s), and in remission
ρ_5	Progression rate to full-blown AIDS in patients with lymphoma, HIV, and in remission
ρ_6	Progression rate to full-blown AIDS in patients with lymphoma and HIV

Table 3.2: Symbols and description of the parameters used in the model

3.3 Model Basic Properties

In this section, we investigate and establish some basic properties of the model system (3.2.3).

3.3.1 Invariant Region

The model studies variations in the human population under certain conditions. Hence, the state variables and parameters are assumed to be positive entities for all time values $t \geq 0$. We analyse the model system (3.2.3) in an apposite biologically feasible region Γ. We have the following results with respect to the feasible region Γ of the model system (3.2.3).

Lemma 3.3.1. *The biologically feasible region* Γ *defined by the compact set:*

$$\Gamma = \{(S, I_L, I_{LR}, I_H, I_{LH}, I_{HT}, I_{LHR}, I_{LHT}, I_{LHTR}, A) \in \mathbb{R}^{10}_{+} : N \leq \frac{K}{\mu}\}$$

with initial conditions $S(0)$, $I_L(0)$, $I_{LR}(0)$, $I_H(0)$, $I_{LH}(0)$, $I_{HT}(0)$, $I_{LHR}(0)$, $I_{LHT}(0)$, $I_{LHTR}(0)$, $A(0) > 0$, *is positively invariant and attracting with respect to the model system* (3.2.3) *for all* $t > 0$.

Proof. By summing up the equations of the model system (3.2.3), the total population size $N(t)$ is seen to be time variable with

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= K - \mu N - \delta A, \\ &\leq K - \mu N, \\ \implies \frac{dN}{dt} &+ \mu N \leq K. \end{aligned} \tag{3.3.1}$$

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

$$IF = \mathrm{e}^{\int \mu \mathrm{d}t},$$

equation (3.3.1) becomes

$$\begin{aligned} \frac{d(N\mathrm{e}^{\mu t})}{\mathrm{d}t} &\leq K\mathrm{e}^{\int \mu dt} \quad \text{(integrate both sides)}, \\ \implies N\mathrm{e}^{\mu t} &\leq \frac{K}{\mu}\mathrm{e}^{\mu t} + C, \\ \implies N(t) &\leq \frac{K}{\mu} + C\mathrm{e}^{-\mu t}. \end{aligned} \tag{3.3.2}$$

Applying the initial condition, at $t = 0$, let $N(0) = N_0$, where N_0 is the sum of the initial values of the variables of the model equation, we obtain

$$C = N_0 - \frac{K}{\mu}.$$

This implies that

$$\begin{aligned} N(t) &\leq \frac{K}{\mu} + \left(N_0 - \frac{K}{\mu}\right) \mathrm{e}^{-\mu t}, \\ &= N_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right). \end{aligned} \tag{3.3.3}$$

As $t \longrightarrow \infty$, we have: $\limsup_{t\to\infty} N(t) \leq \frac{K}{\mu}$.

If $N(0) \leq \frac{K}{\mu}$, then,

$$\begin{aligned} & N(t) \leq N_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right), \\ \Longrightarrow\ & N(t) \leq \frac{K}{\mu}\mathrm{e}^{-\mu t} + \frac{K}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right), \\ & N(t) \leq \frac{K}{\mu}. \end{aligned} \tag{3.3.4}$$

Thus every solution $N(t)$ of equation (3.3.1) satisfies the relation below;

$$0 \leq N(t) \leq N_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right), \tag{3.3.5}$$

where N_0 is the sum of all the initial conditions of the variables of the model system.

If $N_0 \leq \frac{K}{\mu}$, then, the non-negative solutions of equation (3.3.1) are increased monotonically and are bounded above by $\frac{K}{\mu}$. On the contrary, if $N_0 > \frac{K}{\mu}$, then, the non-negative solutions of equation (3.3.1) are monotone decreasing and bounded below by $\frac{K}{\mu}$. Nevertheless, in both cases, at limiting equilibrium, $\lim_{t\to\infty} N(t) = \frac{K}{\mu}$.

This implies that any solution $S(t), I_L(t), I_{LR}(t), I_H(t), I_{LH}(t), I_{HT}(t), I_{LHR}(t)$, $I_{LHT}(t), I_{LHTR}(t), A(t)$, at $t \geq 0$, of (3.2.3) that commences in the positive orthant $\mathbb{R}^{10}_+$, either remains confined in, enters or approaches Γ asymptotically. Hence, the region Γ is positively invariant and attracting with respect to the flow incited by the model system (3.2.3). This completes the proof. □

Thus, in Γ, the model (3.2.3) is mathematically and epidemiologically well-posed. Hence, it is sufficient to study the dynamics of the flow induced by the model system (3.2.3) in Γ.

3.3.2 Positivity of Solutions

Epidemiologically, it is absurd to have negative populations. Since the model system (3.2.3) describes the dynamics of human population, it is consequently essential to prove that all the state variables of the model system (3.2.3) remain non-negative. This is to ensure that the solutions of the system, when subjected to positive initial conditions, will remain positive for all $t > 0$. Consequently, we have the following lemma.

Lemma 3.3.2. *Given that the initial values of the state variables of the model system (3.2.3) are non-negative, the model equations (3.2.3a)-(3.2.3j) preserve positivity of solutions for all time $t > 0$.*

Proof. Suppose that

$$\hat{t} = \sup\{t > 0 : S, I_L, I_{LR}, I_H, I_{LH}, I_{HT}, I_{LHR}, I_{LHT}, I_{LHTR}, A > 0\} \in [0, t]$$

From equation (3.2.3a),

$$\begin{aligned} \frac{dS}{dt} &= K - (\lambda_1 + \mu + \alpha_1)S, \\ \frac{dS}{dt} &+ (\lambda_1 + \mu + \alpha_1)S = K. \end{aligned} \tag{3.3.6}$$

Using the integrating factor (IF) given by

$$IF = \exp\left\{\int_0^t (\mu + \alpha_1 + \lambda_1(\omega))\,\mathrm{d}\omega\right\} = \exp\left\{[(\mu + \alpha_1)t + \int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]\right\},$$

equation (3.3.6) becomes

$$\begin{aligned} & \frac{d}{dt}\left[S(t)\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\right] = K\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}, \\ \Longrightarrow \quad & \int_{S(0)}^{S(\hat{t})} d\left[S(t)\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\right] = K\int_0^{\hat{t}} \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\,dt, \\ \Longrightarrow \quad & S(\hat{t})\mathrm{e}^{[(\mu+\alpha_1)\hat{t}+\int_0^{\hat{t}} \lambda_1(\omega))\,\mathrm{d}\omega]} - S(0) = K\int_0^{\hat{t}} \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\,dt, \end{aligned} \tag{3.3.7}$$

$$\begin{aligned}
\implies \quad S(\hat{t}) &= \mathrm{e}^{-[(\mu+\alpha_1)\hat{t}+\int_0^{\hat{t}}\lambda_1(\omega))\,\mathrm{d}\omega]}\left[S(0)+K\int_0^{\hat{t}}\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t\lambda_1(\omega))\,\mathrm{d}\omega]}\,dt\right], \\
S(\hat{t}) &\geq K\mathrm{e}^{-[(\mu+\alpha_1)\hat{t}+\int_0^{\hat{t}}\lambda_1(\omega))\,\mathrm{d}\omega]}\int_0^{\hat{t}}\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t\lambda_1(\omega))\,\mathrm{d}\omega]}\,dt.
\end{aligned} \tag{3.3.8}$$

Since the exponential function is always positive, we have

$$S(\hat{t}) > 0, \quad \forall\ \hat{t} > 0. \tag{3.3.9}$$

From equation (3.2.3b),

$$\begin{aligned}
\frac{\mathrm{d}I_L}{\mathrm{d}t} &= \alpha_1 S + r_1 I_{LR} - (\lambda_2(t)+\tau_1+\mu)I_L, \\
&\geq -(\lambda_2(t)+\tau_1+\mu)I_L, \\
\implies \quad \frac{\mathrm{d}I_L}{\mathrm{d}t} &+ (\lambda_2(t)+\tau_1+\mu)I_L \geq 0.
\end{aligned} \tag{3.3.10}$$

Using the IF given by

$$IF = \mathrm{e}^{\int_0^t[(\mu+\tau_1)+\lambda_2(\omega)]\,\mathrm{d}\omega} = \mathrm{e}^{[(\mu+\tau_1)t+\int_0^t\lambda_2(\omega)\,\mathrm{d}\omega]},$$

equation (3.3.10) becomes

$$\begin{aligned}
&\int_{I_L(0)}^{I_L(\hat{t})}\mathrm{d}\left[I_L(t)\mathrm{e}^{[(\mu+\tau_1)t+\int_0^t\lambda_2(\omega)\,\mathrm{d}\omega]}\right] \geq 0, \\
\implies \quad & I_L(\hat{t})\mathrm{e}^{[(\mu+\tau_1)\hat{t}+\int_0^{\hat{t}}\lambda_2(\omega)\,\mathrm{d}\omega]} \geq I_L(0), \\
\implies \quad & I_L(\hat{t}) \geq I_L(0)\left(\mathrm{e}^{-[(\mu+\tau_1)\hat{t}+\int_0^{\hat{t}}\lambda_2(\omega)\,\mathrm{d}\omega]}\right), \\
\implies \quad & I_L(\hat{t}) > 0 \quad \forall\,\hat{t} > 0.
\end{aligned} \tag{3.3.11}$$

Using a similar procedure as above, from equation (3.2.3c),

$$\begin{aligned}
\frac{\mathrm{d}I_{LR}}{\mathrm{d}t} &\geq -(\lambda_2(t)+\mu+r_1)I_{LR}, \\
\implies \quad \frac{\mathrm{d}I_{LR}}{\mathrm{d}t} &+ (\lambda_2(t)+\mu+r_1)I_{LR} \geq 0. \\
\implies \quad \int_{I_{LR}(0)}^{I_{LR}(\hat{t})}&\mathrm{d}\left[I_{LR}(t)\mathrm{e}^{[(\mu+\tau_1)t+\int_0^t\lambda_2(\omega)\,\mathrm{d}\omega]}\right] \geq 0,
\end{aligned}$$

$$\begin{aligned} & I_{LR}(\hat{t}) \geq I_{LR}(0)\left(\mathrm{e}^{-[(\mu+\tau_1)t+\int_0^t \lambda_2(\omega)\,\mathrm{d}\omega]}\right), \\ \Longrightarrow \quad & I_{LR}(\hat{t}) > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.12}$$

In like manner, we obtain the following:

From equation (3.2.3d),

$$\begin{aligned} \frac{\mathrm{d}I_H}{\mathrm{d}t} &\geq (\mu+\alpha_2+\sigma_1+\rho_1)I_H, \\ \Rightarrow \int_{I_H(0)}^{I_H(\hat{t})} &\geq \int_0^{\hat{t}} -(\mu+\alpha_2+\sigma_1+\rho_1)\mathrm{d}t, \\ \Rightarrow \ln\left(\frac{I_H(\hat{t})}{I_H(0)}\right) &\geq -(\mu+\alpha_2+\sigma_1+\rho_1)\hat{t}, \\ \Rightarrow I_H(\hat{t}) &\geq I_H(0)\left(\mathrm{e}^{-(\mu+\alpha_2+\sigma_1+\rho_1)\hat{t}}\right). \\ \text{Hence,}\ \ I_H(\hat{t}) &> 0, \ \ \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.13}$$

From equation (3.2.3e),

$$\begin{aligned} \frac{\mathrm{d}I_{LH}}{\mathrm{d}t} &\geq (\mu+\tau_2+\sigma_2+\rho_6)I_{LH}, \\ \Rightarrow \int_{I_{LH}(0)}^{I_{LH}(\hat{t})} &\geq \int_0^{\hat{t}} -(\mu+\tau_2+\sigma_2+\rho_6)\mathrm{d}t, \\ \Rightarrow \ln\left(\frac{I_{LH}(\hat{t})}{I_{LH}(0)}\right) &\geq -(\mu+\tau_2+\sigma_2+\rho_6)\hat{t}, \\ \Rightarrow I_{LH}(\hat{t}) &\geq I_H(0)\left(\mathrm{e}^{-(\mu+\tau_2+\sigma_2+\rho_6)\hat{t}}\right). \\ \text{Hence,}\ \ I_{LH}(\hat{t}) &> 0, \ \ \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.14}$$

From equation (3.2.3f),

$$\begin{aligned} & \frac{\mathrm{d}I_{HT}}{\mathrm{d}t} + (\mu+\alpha_3+\rho_2)I_{HT} \geq 0, \\ \Longrightarrow \quad & I_{HT}(\hat{t}) \geq I_{HT}(0)\left(\mathrm{e}^{-(\mu+\alpha_3+\rho_2)\hat{t}}\right), \\ & > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.15}$$

From equation (3.2.3g),

$$\begin{aligned} & \frac{\mathrm{d}I_{LHR}}{\mathrm{d}t} + (\mu + r_2 + \sigma_3 + \rho_5)I_{LHR} \geq 0, \\ \implies \quad & I_{LHR}(\hat{t}) \geq I_{LHR}(0)\left(\mathrm{e}^{-(\mu+r_2+\sigma_3+\rho_5)\hat{t}}\right), \\ & > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.16}$$

From equation (3.2.3h),

$$\begin{aligned} & \frac{\mathrm{d}I_{LHT}}{\mathrm{d}t} \geq -(\mu + \tau_3 + \rho_3)I_{LHT}, \\ & \frac{\mathrm{d}I_{LHT}}{\mathrm{d}t} + (\mu + \tau_3 + \rho_3)I_{LHT} \geq 0, \\ \implies \quad & I_{LHT}(\hat{t}) \geq I_{LHT}(0)\left(\mathrm{e}^{-(\mu+\tau_3+\rho_3)\hat{t}}\right), \\ & > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.17}$$

From equation (3.2.3i),

$$\begin{aligned} & \frac{\mathrm{d}I_{LHTR}}{\mathrm{d}t} \geq -(\mu + r_3 + \rho_4)I_{LHTR}, \\ & \frac{\mathrm{d}I_{LHTR}}{\mathrm{d}t} + (\mu + r_3 + \rho_4)I_{LHTR} \geq 0, \\ \implies \quad & I_{LHTR}(\hat{t}) \geq I_{LHTR}(0)\left(\mathrm{e}^{-(\mu+r_3+\rho_4)\hat{t}}\right), \\ & > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.18}$$

From equation (3.2.3j),

$$\begin{aligned} & \frac{\mathrm{d}A}{\mathrm{d}t} \geq -(\mu + \delta)A, \\ & \frac{\mathrm{d}A}{\mathrm{d}t} + (\mu + \delta)A \geq 0, \\ \implies \quad & A(\hat{t}) \geq A(0)\left(\mathrm{e}^{-(\mu+\delta)\hat{t}}\right), \\ & > 0 \quad \forall\, \hat{t} > 0. \end{aligned} \tag{3.3.19}$$

Thus, we have shown, in (3.3.6) - (3.3.19), that every solution of the state variables of model system (3.2.3) will always be positive for all non-negative initial conditions, at any time $\hat{t} > 0$. This completes the proof. □

3.3.3 Existence and Uniqueness of Solutions

Theorem 3.3.3. *Solutions of the model system (3.2.3) exists, and is unique in Γ, for all time $t > 0$, and for every non-negative initial values of the model state variables that are non zero.*

Proof. Since the right hand side of the model system (3.2.3) is locally Lipschitz continuous, then local existence and uniqueness of solutions is ascertained. □

3.4 Model Equilibria Analysis and the Basic Reproduction Number

We derive and investigate an equilibrium E_0 of the model system (3.2.3), which we refer to as the HIV-free lymphoma steady state, and the model's endemic equilibria E_1. We investigate the stability of these steady states using the basic reproduction number $\mathcal{R}_0$.

3.4.1 HIV-free Lymphoma Steady State

For us to consider the model system (3.2.3) in the absence of HIV, every variable having the impact of HIV is set to zero, i.e. $I_H = I_{LH} = I_{HT} = I_{LHR} = I_{LHT} = I_{LHTR} = A = 0$. Hence, in the absence of HIV, the model has the HIV-free lymphoma equilibrium. This is obtained below, by setting the right-hand side (RHS) of the model system equations (3.2.3a) - (3.2.3j) to zero.

$$I_H = I_{LH} = I_{HT} = I_{LHR} = I_{LHT} = I_{LHTR} = A = 0 \implies \lambda_1 = \lambda_2 = 0.$$

We obtain

$$\begin{aligned} &K - q_1 S^* = 0, \quad \text{where } q_1 = \mu + \alpha_1, \\ \implies \quad &S^* = \frac{K}{q_1} = \frac{K}{\mu + \alpha_1}. \end{aligned} \tag{3.4.1}$$

$$\begin{aligned} &r_1 I^*_{LR} + \alpha_1 S^* - q_2 I^*_L = 0, \quad \text{where } q_2 = \mu + \tau_1, \\ \implies \quad &I^*_L = \frac{1}{q_2}\left[r_1 I^*_{LR} + \frac{\alpha_1 K}{q_1}\right]. \end{aligned} \tag{3.4.2}$$

$$\begin{aligned} \tau_1 I_L^* - q_5 I_{LR}^* = 0, \quad \text{where} \quad q_5 = \mu + r_1, \\ \implies \quad I_{LR}^* = \frac{\tau_1 I_L^*}{q_5}. \end{aligned} \tag{3.4.3}$$

Substituting for (3.4.3) in (3.4.2), we obtain:

$$\begin{aligned} I_L^* \left[1 - \frac{r_1\tau_1}{q_2 q_5}\right] &= \frac{\alpha_1 K}{q_1 q_2}, \\ I_L^* &= \frac{\alpha_1 K}{q_1 q_2[1-\phi_1]}, \\ \implies \quad I_{LR}^* &= \frac{\tau_1\alpha_1 K}{q_1 q_2 q_5[1-\phi_1]}, \end{aligned} \tag{3.4.4}$$

where

$$\phi_1 = \frac{r_1\tau_1}{q_2 q_5}, \implies \quad 1 - \phi_1 = \frac{\mu(\mu + r_1 + \tau_1)}{(\mu + \tau_1)(\mu + r_1)}.$$

Thus,

$$\begin{aligned} I_L^* &= \frac{\alpha_1 K(\mu + r_1)}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)}, \quad \text{and} \\ I_{LR}^* &= \frac{\tau_1\alpha_1 K}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)}. \end{aligned} \tag{3.4.5}$$

Hence, the model has an equilibrium (which we call the HIV-free lymphoma steady state) given by

$$E_0 = \left(\frac{K}{\mu + \alpha_1}, \frac{\alpha_1 K(\mu + r_1)}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)}, \frac{\tau_1\alpha_1 K}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)}, 0, 0, 0, 0, 0, 0, 0\right). \tag{3.4.6}$$

3.4.2 The Basic Reproduction Number

The basic reproduction number, symbolised by $\mathcal{R}_0$ is the *"expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during his entire period of infectiousness"* [57]. The $\mathcal{R}_0$ definition in the context of the proposed model is given later in this chapter.

The $\mathcal{R}_0$ is the most significant quantity in the epidemiology of infectious diseases and is widely used in epidemiological literatures [58]. It is a threshold parameter that plays a vital role in determining whether a disease can invade and persist in a (new host) population when one infected individual is introduced into the wholly susceptible population [59; 60]. The threshold criterion states that "*the disease can invade the population if* $\mathcal{R}_0 > 1$*, whereas, it cannot if* $\mathcal{R}_0 < 1$" [57]. This is because the threshold parameter has the property that if $\mathcal{R}_0 < 1$, the the disease-free equilibrium (DFE) is locally asymptotically stable and the disease cannot invade the population, but if $\mathcal{R}_0 > 1$, then, the DFE is unstable and the disease can always invade the population [59; 60]. However, a recent result by van Driessche *et al.* [60] suggests that a disease may persist even when the disease free equilibrium is locally stable.

In the computation of $\mathcal{R}_0$, the only states (or classes of individuals) considered are those that pertains to the infected individuals, in which new infections are differentiated from all other change in state among infected individuals [57; 58; 60]. The set of equations these states refer to are called the *infected subsystem*. It is important to note that $\mathcal{R}_0$ is obtained by first decomposing the linearised infected subsystem of the model. This linear system, which is described by the Jacobian of the non-linear infected subsystem is evaluated at the infection/disease-free equilibrium (which as a rule exists) [58; 60]. "Epidemiologically, the linearisation reflects that $\mathcal{R}_0$ characterises the potential for initial spread of an infectious agent when it is introduced into a fully susceptible population, and that we assume that the change in the susceptible population is negligible during the initial spread" [58].

For our model system (3.2.3), since we are considering two types of diseases, our infected subsystem is from equations (3.2.3d)-(3.2.3j). Following the procedure described in [60] (also see [58]), we shall compute $\mathcal{R}_0$ as the *spectral radius* (largest eigen-value) of the next generation matrix [57] FV^{-1} as we shall define shortly.

Note that development of lymphomas by HIV-negative patients, irrespective of what state they are in, are not considered to be new infections, since lymphoma is not an infectious disease. In general, movement of different states of individuals into any HIV-free lymphoma state (whether in remission or not) is not considered a transmission term.

Decomposing the infected subsystem (3.2.3d)-(3.2.3j) into the components $\mathscr{F}(x)$ and $\mathscr{V}(x)$ as in [60], where $\mathscr{F}(x)$ is the column matrix that represents the rate of appearance of new infections in each of the infected compartments, $\mathscr{V}^+(x)$ represents the rate of transfer of individuals into the infected compartments and $\mathscr{V}^-(x)$ represents the rate of transfer of individuals out of the infected compartments. $\mathscr{V}^-(x)$ is given by the relation

$$\mathscr{V}(x) = \mathscr{V}^-(x) - \mathscr{V}^+(x).$$

$$\mathscr{F}(x) = \begin{pmatrix} \lambda_1 S \\ \lambda_2 I_L \\ 0 \\ \lambda_2 I_{LR} \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$= \begin{pmatrix} \frac{\beta_1}{N}[I_H + \eta_1 I_{HT} + \eta_2(I_{LH} + I_{LHR}) + \eta_3(I_{LHT} + I_{LHTR}) + \eta_4 A]S \\ \frac{\beta_2}{N}[I_H + \eta_1 I_{HT} + \eta_2(I_{LH} + I_{LHR}) + \eta_3(I_{LHT} + I_{LHTR}) + \eta_4 A]I_L \\ 0 \\ \frac{\beta_2}{N}[I_H + \eta_1 I_{HT} + \eta_2(I_{LH} + I_{LHR}) + \eta_3(I_{LHT} + I_{LHTR}) + \eta_4 A]I_{LR} \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathscr{V}(x) = \begin{pmatrix} (\mu + \alpha_2 + \sigma_1 + \rho_1)I_H \\ (\mu + \tau_2 + \sigma_2 + \rho_6)I_{LH} - (\alpha_2 I_H + r_2 I_{LHR}) \\ (\mu + \alpha_3 + \rho_2)I_{HT} - \sigma_1 I_H \\ (\mu + r_2 + \sigma_3 + \rho_5)I_{LHR} - \tau_2 I_{LH} \\ (\mu + \tau_3 + \rho_3)I_{LHT} - (\sigma_2 I_H + \alpha_3 I_{HT} + r_3 I_{LHTR}) \\ (\mu + r_3 + \rho_4)I_{LHTR} - (\sigma_3 I_{LHR} + \tau_3 I_{LHT}) \\ (\mu + \delta)A - (\rho_1 I_H + \rho_2 I_{HT} + \rho_3 I_{LHT} + \rho_4 I_{LHTR} + \rho_5 I_{LHR} + \rho_6 I_{LH}) \end{pmatrix}.$$

Following [60] and [58], the matrices F and V for the *new infection* and *transition terms* (which includes other terms related with change in state/condition) respectively, are defined by

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(E_0)\right] \quad \text{and} \quad V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(E_0)\right], \tag{3.4.7}$$

where E_0 is the Disease-free equilibrium (i.e. our model's HIV-free lymphoma steady state) and $1 \leq i, j \leq 7, \quad i, j \in \mathbb{Z}^+$. Note that $F - V$ is the *Jacobian* of the infected subsystem at the HIV-free Lymphoma Steady State (HLSS). F is the *transmission part* of the system and it describes the production of new infections, while V is the *transition part* and it describes changes in states [58]. The matrices are shown below.

.

$$F = \begin{pmatrix} \frac{\beta_1}{N^*}S^* & \frac{\beta_1}{N^*}\eta_2 S^* & \frac{\beta_1}{N^*}\eta_1 S^* & \frac{\beta_1}{N^*}\eta_2 S^* & \frac{\beta_1}{N^*}\eta_3 S^* & \frac{\beta_1}{N^*}\eta_3 S^* & \frac{\beta_1}{N^*}\eta_4 S^* \\ \frac{\beta_2}{N^*}I_L^* & \frac{\beta_2}{N^*}\eta_2 I_L^* & \frac{\beta_2}{N^*}\eta_1 I_L^* & \frac{\beta_2}{N^*}\eta_2 I_L^* & \frac{\beta_2}{N^*}\eta_3 I_L^* & \frac{\beta_2}{N^*}\eta_3 I_L^* & \frac{\beta_2}{N^*}\eta_4 I_L^* \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_2}{N^*}I_{LR}^* & \frac{\beta_2}{N^*}\eta_2 I_{LR}^* & \frac{\beta_2}{N^*}\eta_1 I_{LR}^* & \frac{\beta_2}{N^*}\eta_2 I_{LR}^* & \frac{\beta_2}{N^*}\eta_3 I_{LR}^* & \frac{\beta_2}{N^*}\eta_3 I_{LR}^* & \frac{\beta_2}{N^*}\eta_4 I_{LR}^* \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} q_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_2 & q_4 & 0 & -r_2 & 0 & 0 & 0 \\ -\sigma_1 & 0 & q_6 & 0 & 0 & 0 & 0 \\ 0 & -\tau_2 & 0 & q_7 & 0 & 0 & 0 \\ 0 & -\sigma_2 & -\alpha_3 & 0 & q_8 & -r_3 & 0 \\ 0 & 0 & 0 & -\sigma_3 & -\tau_3 & q_9 & 0 \\ -\rho_1 & -\rho_6 & -\rho_2 & -\rho_5 & -\rho_3 & -\rho_4 & q_{10} \end{pmatrix},$$

where $q_1 = \mu + \alpha_1$, $q_2 = \mu + \tau_1$, $q_3 = \mu + \alpha_2 + \sigma_1 + \rho_1$, $q_4 = \mu + \tau_2 + \sigma_2 + \rho_6$, $q_5 = \mu + r_1$, $q_6 = \mu + \alpha_3 + \rho_2$, $q_7 = \mu + r_2 + \sigma_3 + \rho_5$, $q_8 = \mu + \tau_3 + \rho_3$, $q_9 = \mu + r_3 + \rho_4$ and $q_{10} = \mu + \delta$, $q_i \in \mathbb{R}^+$ (positive constants), $\forall\ i = 1, 2, \ldots, 10$.

The next generation matrix for the infected subsystem of model (3.2.3) is FV^{-1}, with the matrices as defined above. The *spectral radius* of $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = \rho(FV^{-1}). \tag{3.4.8}$$

The model's reproduction number $\mathcal{R}_0$ was obtained to be an aggregate of contributions from the infected compartments of the different stages of the model system. It is thus given by

$$\mathcal{R}_0 = \mathcal{R}_0^{I_H} + \mathcal{R}_0^{I_{HT}} + \mathcal{R}_0^{I_{LH}} + \mathcal{R}_0^{I_{LHR}} + \mathcal{R}_0^{I_{LHT}} + \mathcal{R}_0^{I_{LHTR}} + \mathcal{R}_0^{A}, \tag{3.4.9}$$

where

$$\mathcal{R}_0^{I_H} = \frac{C_S \beta_1}{q_3},$$

$$
\begin{aligned}
\mathcal{R}_0^{I_{HT}} &= \left(\frac{\sigma_1}{q_3}\right)\left(\frac{C_S\beta_1\eta_1}{q_6}\right),\\
\mathcal{R}_0^{I_{LH}} &= \bar{A}\left[\left(\frac{C_S\beta_1\eta_2}{q_4}\right)\left(\frac{\alpha_2}{q_3}\right)+\left(\frac{C_L\beta_2\eta_2}{q_4}\right)+\left(\frac{C_R\beta_2\eta_2}{q_4}\right)\right],\\
\mathcal{R}_0^{I_{LHR}} &= \bar{A}\left[\left(\frac{C_S\beta_1\eta_2}{q_7}\right)\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\tau_2}{q_4}\right)+\left(\frac{C_L\beta_2\eta_2}{q_7}\right)\left(\frac{\tau_2}{q_4}\right)+\left(\frac{C_R\beta_2\eta_2}{q_7}\right)\right],\\
\mathcal{R}_0^{I_{LHT}} &= \bar{A}B\left[\left(\frac{C_S\beta_1\eta_3}{q_8}\right)\left\{\left(\frac{\sigma_1}{q_3}\right)\left(\frac{\alpha_3}{q_6}\right)\left(\frac{1}{\bar{A}}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\sigma_2}{q_4}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\tau_2}{q_4}\right)\right.\right.\\
&\quad\left.\times\left(\frac{\sigma_3}{q_7}\right)\left(\frac{r_3}{q_9}\right)\right\}+\left(\frac{C_L\beta_2\eta_3}{q_8}\right)\left\{\left(\frac{\sigma_2}{q_4}\right)+\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)\left(\frac{r_3}{q_9}\right)\right\}\\
&\quad\left.+\left(\frac{C_R\beta_2\eta_3}{q_8}\right)\left\{\left(\frac{\sigma_2}{q_4}\right)\left(\frac{r_2}{q_7}\right)+\left(\frac{\sigma_3}{q_7}\right)\left(\frac{r_3}{q_9}\right)\right\}\right],\\
\mathcal{R}_0^{I_{LHTR}} &= \bar{A}B\left[\left(\frac{C_S\beta_1\eta_3}{q_9}\right)\left\{\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)+\left(\frac{\sigma_1}{q_3}\right)\left(\frac{\alpha_3}{q_6}\right)\left(\frac{\tau_3}{q_8}\right)\left(\frac{1}{A}\right)\right.\right.\\
&\quad\left.+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\sigma_2}{q_4}\right)\left(\frac{\tau_3}{q_8}\right)\right\}+\left(\frac{C_R\beta_2\eta_3}{q_9}\right)\left\{\left(\frac{\sigma_3}{q_7}\right)+\left(\frac{\sigma_2}{q_4}\right)\left(\frac{r_2}{q_7}\right)\left(\frac{\tau_3}{q_8}\right)\right\}\\
&\quad\left.+\left(\frac{C_L\beta_2\eta_3}{q_9}\right)\left\{\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)+\left(\frac{\sigma_2}{q_4}\right)\left(\frac{\tau_3}{q_8}\right)\right\}\right],\\
\mathcal{R}_0^{A} &= \bar{A}B\left[\left(\frac{C_S\beta_1\eta_4}{q_{10}}\right)\left\{\left(\frac{\rho_1}{q_3}\right)\left(\frac{1}{\bar{A}B}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\rho_6}{q_4}\right)\left(\frac{1}{B}\right)+\left(\frac{\sigma_1}{q_3}\right)\left(\frac{\rho_2}{q_6}\right)\right.\right.\\
&\quad\times\left(\frac{1}{\bar{A}B}\right)+\left(\frac{\sigma_1}{q_3}\right)\left(\frac{\alpha_3}{q_6}\right)\left(\frac{\rho_3}{q_8}\right)\left(\frac{1}{A}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\sigma_2}{q_4}\right)\left(\frac{\rho_3}{q_8}\right)+\left(\frac{\alpha_2}{q_3}\right)\\
&\quad\times\left(\frac{\tau_2}{q_4}\right)\left(\frac{\rho_5}{q_7}\right)\left(\frac{1}{B}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_3}{q_8}\right)\left(\frac{r_3}{q_9}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\tau_2}{q_4}\right)\\
&\quad\times\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_4}{q_9}\right)+\left(\frac{\alpha_2}{q_3}\right)\left(\frac{\sigma_2}{q_4}\right)\left(\frac{\tau_3}{q_8}\right)\left(\frac{\rho_4}{q_9}\right)+\left(\frac{\sigma_1}{q_3}\right)\left(\frac{\alpha_3}{q_6}\right)\left(\frac{\tau_3}{q_8}\right)\left(\frac{\rho_4}{q_9}\right)\\
&\quad\times\left(\frac{1}{\bar{A}}\right)\Big\}+\left(\frac{C_R\beta_2\eta_4}{q_{10}}\right)\left\{\left(\frac{\rho_5}{q_7}\right)\left(\frac{1}{B}\right)+\left(\frac{\rho_6}{q_4}\right)\left(\frac{r_2}{q_7}\right)\left(\frac{1}{B}\right)+\left(\frac{\sigma_2}{q_4}\right)\left(\frac{r_2}{q_7}\right)\right.\\
&\quad\times\left(\frac{\rho_3}{q_8}\right)+\left(\frac{\sigma_2}{q_4}\right)\left(\frac{r_2}{q_7}\right)\left(\frac{\tau_3}{q_8}\right)+\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_3}{q_8}\right)\left(\frac{r_3}{q_9}\right)+\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_4}{q_9}\right)+\left(\frac{\sigma_2}{q_4}\right)\\
&\quad\times\left(\frac{r_2}{q_7}\right)\left(\frac{\tau_3}{q_8}\right)\left(\frac{\rho_4}{q_9}\right)\Big\}+\left(\frac{C_L\beta_2\eta_4}{q_{10}}\right)\left\{\left(\frac{\rho_6}{q_4}\right)\left(\frac{1}{B}\right)+\left(\frac{\sigma_2}{q_4}\right)\left(\frac{\rho_3}{q_8}\right)+\left(\frac{\tau_2}{q_4}\right)\right.\\
&\quad\times\left(\frac{\rho_5}{q_7}\right)\left(\frac{1}{B}\right)+\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_3}{q_8}\right)\left(\frac{r_3}{q_9}\right)+\left(\frac{\tau_2}{q_4}\right)\left(\frac{\sigma_3}{q_7}\right)\left(\frac{\rho_4}{q_9}\right)+\left(\frac{\sigma_2}{q_4}\right)\\
&\quad\left.\left.\times\left(\frac{\tau_3}{q_8}\right)\left(\frac{\rho_4}{q_9}\right)\right\}\right],
\end{aligned}
$$

and the following psitive constants

$$\bar{A} = \frac{1}{1-\xi_1}, \quad B = \frac{1}{1-\xi_2}, \quad \xi_1 = \left(\frac{r_2}{q_7}\right)\left(\frac{\tau_2}{q_4}\right), \quad \xi_2 = \left(\frac{r_3}{q_9}\right)\left(\frac{\tau_3}{q_8}\right),$$
$$C_S = \frac{S^*}{N^*}, \quad C_L = \frac{I_L^*}{N^*}, \quad \text{and} \quad C_R = \frac{I_{LR}^*}{N^*}. \tag{3.4.10}$$

3.4.3 $\mathcal{R}_0$ Interpretation

$\mathcal{R}_0^{I_H} = \dfrac{C_s\beta_1}{\mu+\alpha_2+\sigma_1+\rho_1}$, is simply the product of the per capita rate of infection and the average duration of stay of an individual in class I_H. This reproductive rate is sometimes referred to as the *back of the napkin* [61]. It is the number of HIV-infection cases produced by a single untreated HIV-positive individual during his/her entire lifetime in class I_H, in a totally susceptible (naive) population.

$$\mathcal{R}_0^{I_{HT}} = \underbrace{\frac{\sigma_1}{(\mu+\alpha_2+\sigma_1+\rho_1)}}_{\text{P}} \times \underbrace{\frac{1}{(\mu+\alpha_3+\rho_2)}}_{\text{Q}} \times \underbrace{C_S\beta_1\eta_1}_{\text{R}}.$$

$\mathcal{R}_0^{I_{HT}}$ above, is the product of the fraction (or proportion) of HIV-only positive indivuals (I_H) surviving, at least, to the stage of being treated for HIV (I_{HT}), denoted by P, the average infectious period of an individual in class I_{HT}, denoted by Q, and the infectivity of individuals in class I_{HT}, denoted by R respectively. To determine what the $\mathcal{R}_0^i$ interpretation of the contributions of the other infectious compartments, $i \in \{I_H, I_{LH}, I_{LHR}, I_{LHT}, I_{LHTR}, A\}$, to the model's basic reproduction number $\mathcal{R}_0$ is, it is expedient that we describe the duration of infectivity of an individual introduced into either the I_{LHR} or the I_{LHTR} compartments. We illustrate this by considering an extraction of a subsection from our model. We shall represent the movement of individuals from I_{LH} to I_{LHR} in a diagrammatic form, as in Fig. 3.2.

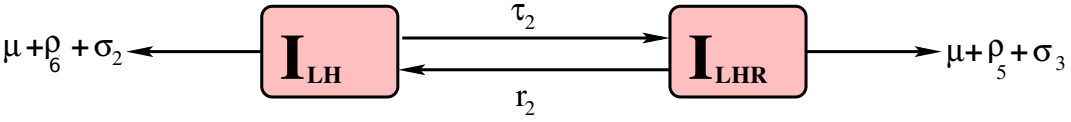

Figure 3.2: Progression diagram for the movement of individuals (of (3.2.3e) and (3.2.3g)) from I_{LH} to I_{LHR}

Let

$$m_1 = \frac{\tau_2}{\mu + \tau_2 + \sigma_2 + \rho_6}, \quad \text{and} \quad m_2 = \frac{r_2}{\mu + r_2 + \sigma_3 + \rho_5}. \tag{3.4.11}$$

A fraction m_1 of HIV-positive lymphoma patients will progress to the class I_{LHR}, of those in remission after receiving (or being on) lymphoma treatment. A fraction m_2 of HIV-positive lymphoma patients, who are on remission will relapse and re-enter compartment I_{LH}. This implies that a fraction m_1 of HIV-positive lymphoma patients must have passed through I_{LHR} at least once. A fraction $m_1^2 m_2$ must have passed through I_{LHR} at least twice. In a similar fashion, if the cycle continues, a fraction $m_1^i m_2^{i-1}$ must have passed through I_{LHR} at least i times, and the average duration of stay in compartment I_{LHR}, on each pass is $\omega_1 = 1/q_7$ (where $q_7 = \mu + r_2 + \sigma_3 + \rho_5$ and $q_4 = \mu + \tau_2 + \sigma_2 + \rho_6$). This implies that an individual who moves into class I_{LHR} spends an average of $\omega_1(m_1 + m_1^2 m_2 + m_1^3 m_2^2 + \cdots)$ time units in I_{LHR}.

$$\omega_1(m_1 + m_1^2 m_2 + m_1^3 m_2^2 + \cdots) = \omega_1 m_1 \sum_{i=0}^{\infty} (m_1 m_2)^i. \tag{3.4.12}$$

Equation (3.4.12) is a simple infinite series known as the Geometric series. For this series to converge, the common ration $r = m_1 m_2$ of the series must be absolutely less than one.

$$\begin{aligned} \mid m_1 m_2 \mid &= \left| \left(\frac{\tau_2}{\mu + \tau_2 + \sigma_2 + \rho_6} \right) \left(\frac{r_2}{\mu + r_2 + \sigma_3 + \rho_5} \right) \right|, \\ &= \left| \left(\frac{\tau_2}{q_4} \right) \left(\frac{r_2}{q_7} \right) \right|. \end{aligned} \tag{3.4.13}$$

But $\tau_2 < q_4$ and $r_2 < q_7$, which implies that $\frac{\tau_2}{q_4} < 1$ and $\frac{r_2}{q_7} < 1$ respectively. Using the direct proof technique, that for $a, b, c, d > 0$, if $a < b$ and $c < d$, then, $ac < bd$, we have it that

$$\frac{\tau_2}{q_4}\frac{r_2}{q_7} < 1 \quad \Longrightarrow \quad \left| \frac{\tau_2}{q_4}\frac{r_2}{q_7} \right| < 1. \tag{3.4.14}$$

Since equation (3.4.14) is valid, then the geometric series

$$\sum_{i=0}^{\infty} (m_1 m_2)^i$$

converges to $\dfrac{1}{1 - m_1 m_2}$. Hence, an individual who moves from the I_{LH} compartment into the I_{LHR} compartment will spend an average time unit of

$$\frac{\omega_1 m_1}{1 - m_1 m_2}$$

over his/her lifetime. Similar evaluation process can be repeated to estimate the average lifetime duration of an individual in the I_{LR} and I_{LHTR} compartments. Note that

$$\begin{aligned}\frac{\omega_1 m_1}{1-m_1 m_2} &= \left(\frac{\tau_2}{q_4 q_7}\right)\left(\frac{1}{1-\xi_1}\right), \\ &= \bar{A}\left(\frac{\tau_2}{q_4}\frac{1}{q_7}\right).\end{aligned} \tag{3.4.15}$$

The infectivity of individuals in compartment I_{LHR}, and who are in this compartment as a consequence of having being treated for lymphoma (that is, they moved from I_{LH} to I_{LHR}), is $C_L\beta_2\eta_2$. If we multiply this infectivity with the expression in 3.4.15, we shall obtain

$$\bar{A}\left(\frac{\tau_2}{q_4}\right)\left(\frac{C_L\beta_2\eta_2}{q_7}\right),$$

which is the $\mathcal{R}_0^{I_{LHR}}$ contribution of individuals who passed through compartment I_{LHR}, by going through the I_L and I_{LH} compartments.

Using *Theorem* 2 of van den Driessche and Watmough [60], the following result is established.

Theorem 3.4.1. *The HIV-free lymphoma steady state (HLSS) E_0, which is our model system (3.2.3)'s disease-free equilibrium (DFE), exists and is locally asymptotically stable if $\mathcal{R}_0 < 1$, otherwise, it is unstable.*

In the context of our model, a more general definition for the basic reproduction number is the number of secondary cases or new infections generated by an infectious HIV-positive patient, irrespective of whether the patient has developed lymphoma or not, irrespective of whether the patient is under a treatment regimen for HIV only or HIV and lymphoma, when such patient is introduced into a wholly susceptible host population at the DFE [60]. Since the presence of the HIV in the human body gives it a higher proclivity for developing lymphoma and other AIDS defining conditions (ADC), then it is expected that the eradication of the HIV from the population under study is expected to significantly reduce the number of lymphoma cases. Hence, epidemiologically, Theorem 3.4.1 implies that HIV can be eliminated from the population under study whenever $\mathcal{R}_0 < 1$ (which in turn reduces lymphoma cases) and HIV will invade the population (which in turn increases lymphoma cases) whenever $\mathcal{R}_0 > 1$. This is always true, provided the initial sizes of the sub-populations are within the confines of attraction of E_0. In order to establish the stability of this steady state, it is expedient that we show that the DFE is globally stable.

Theorem 3.4.2. *The disease-free equilibrium E_0, of the model system (3.2.3) is globally asymptotically stable, provided $\mathcal{R}_0 < 1$.*

Proof. Following Castillo-Chavez *et al.* [62], we first write the system (3.2.3) in the form

$$\begin{aligned} \dot{X} &= F(X, Y), \\ \dot{Y} &= G(X, Y), \quad G(X, \mathbf{0}) = \mathbf{0}, \end{aligned} \tag{3.4.16}$$

where $X = (S, I_L, I_{LR})$ and $Y = (I_H, I_{LH}, I_{HT}, I_{LHR}, I_{LHT}, I_{LHTR}, A)$. Here, $X \in \mathbb{R}^3_+$ (its components) denotes the number of individuals that are not infected with HIV, but may have developed lymphoma, and $Y \in \mathbb{R}^7_+$ (its components) denotes the number of individuals that are infected with HIV, irrespective of whether they have developed lymphoma or not. We thus denote the disease-free equilibrium of this system (3.4.16) by $\hat{E}_0 = (X^*, \mathbf{0})$, where $X^* = (S^*, I_L^*, I_{LR}^*)$.

We have to prove that the following conditions C1 and C2 below are satisfied.

(C1) For $\dot{X}(t) = F(X, \mathbf{0})$, X^* is globally asymptotically stable.

(C2) $G(X, Y) = AY - \hat{G}(X, Y)$, $\hat{G}(X, Y) \geq 0$ for $(X, Y) \in \Gamma$,

where Γ is a positively invariant attracting domain (where the model makes biological sense), and $A = \mathcal{D}_Y G(X^*, \mathbf{0})$ is an M-matrix (the off-diagonal elements of A are non-negative).

Let

$$F(X, Y) = \begin{pmatrix} K - \lambda_1 S - (\mu + \alpha_1) S \\ r_1 I_{LR} + \alpha_1 S - \lambda_2 I_L - (\mu + \tau_1) I_L \\ \tau_1 I_L - \lambda_2 I_{LR} - (\mu + r_1) I_{LR} \end{pmatrix}, \tag{3.4.17}$$

$$\implies F(X, \mathbf{0}) = \begin{pmatrix} K - (\mu + \alpha_1) S \\ r_1 I_{LR} + \alpha_1 S - (\mu + \tau_1) I_L \\ \tau_1 I_L - (\mu + r_1) I_{LR} \end{pmatrix} = \dot{X}(t). \tag{3.4.18}$$

Note that when $Y = \mathbf{0}$, $\lambda_1 = \lambda_2 = 0$. The equilibrium point of this subsystem (3.4.18) is given by

$$X^* = \left(\frac{K}{\mu + \alpha_1}, \frac{\alpha_1 K (\mu + r_1)}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)}, \frac{\tau_1 \alpha_1 K}{\mu(\mu + \alpha_1)(\mu + r_1 + \tau_1)} \right). \tag{3.4.19}$$

Lemma 3.4.3. *The biolgically feasible region* Ω *defined by the compact set*

$$\hat{\Omega} = \{(S, I_L, I_{LR}) \in \mathbb{R}^3_+ : \hat{N} \leq \frac{K}{\mu}\},$$

with initial conditions $S(0), I_L(0), I_{LR}(0) > 0$ *, is positively invariant and attracting with respect to the model subsystem* (3.4.18) *for all* $t > 0$, $(\hat{N} = S + I_L + I_{LR})$.

Proof. By summing up the equations of the model system (3.4.18), the total population size $\hat{N}(t)$ is seen to be time variable with

$$\begin{aligned} \frac{\mathrm{d}\hat{N}}{\mathrm{d}t} &= K - \mu\hat{N}, \\ \Longrightarrow \frac{d\hat{N}}{dt} &+ \mu\hat{N} = K. \end{aligned} \tag{3.4.20}$$

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

$$IF = \mathrm{e}^{\int \mu \mathrm{d}t},$$

equation (3.4.20) becomes

$$\begin{aligned} \frac{d(\hat{N}\mathrm{e}^{\mu t})}{\mathrm{d}t} &= K\mathrm{e}^{\int \mu dt}. \\ \text{We thus have} \quad \hat{N}(t) &= \frac{K}{\mu} + C\mathrm{e}^{-\mu t}. \end{aligned} \tag{3.4.21}$$

Applying the initial condition, at $t = 0$, let $\hat{N}(0) = \hat{N}_0$, where $\hat{N}_0$ is the sum of the initial values of the variables of the model equation, we obtain

$$C = \hat{N}_0 - \frac{K}{\mu}$$

$$\begin{aligned} \Longrightarrow \hat{N}(t) &\leq \frac{K}{\mu} + (\hat{N}_0 - \frac{K}{\mu})\mathrm{e}^{-\mu t} \\ &= \hat{N}_0\mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}) \end{aligned} \tag{3.4.22}$$

As $t \longrightarrow \infty$, we have: $\limsup_{t\to\infty} \hat{N}(t) \leq \dfrac{K}{\mu}$.

If $\hat{N}(0) \leq \dfrac{K}{\mu}$, then,

$$\begin{aligned} \hat{N}(t) &\leq \hat{N}_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}) \\ \Longrightarrow \hat{N}(t) &\leq \frac{K}{\mu} \end{aligned} \tag{3.4.23}$$

Thus every solution $\hat{N}(t)$ of equation (3.3.1) satisfies the relation below.

$$0 \leq \hat{N}(t) \leq \hat{N}_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}), \tag{3.4.24}$$

where $\hat{N}_0$ is the sum of all the initial conditions of the variables of the model system.

If $\hat{N}_0 \leq \frac{K}{\mu}$, then, non-negative solutions of equation (3.4.20) are monotone increasing and are bounded above by $\frac{K}{\mu}$. On the contrary, if $\hat{N}_0 > \frac{K}{\mu}$, then, non-negative solutions of equation (3.4.20) are monotone decreasing and bounded below by $\frac{K}{\mu}$. Nevertheless, in both cases, at limiting equilibrium, $\lim_{t\to\infty} \hat{N}(t) = \frac{K}{\mu}$.

This implies that any solution $S(t), I_L(t), I_{LR}(t)$, at $t \geq 0$, of (3.4.18) that commences in the positive orthant $\mathbb{R}^3_+$, either remains confined in, enters or approaches $\hat{\Omega}$ asymptotically. Hence, the region $\hat{\Omega}$ is positively invariant and attracting with respect to the flow incited by the model system (3.4.18). This completes the proof. □

We now show that condition (C1) is satisfied. To show the preclusion of periodic solutions in the system (3.4.18), we use the Bendixson criterion for autonomous system as described in [63]. We first need to show that the autonomous system (3.4.18) is an invariant linear subspace. By the definition of an invariant linear subspace (see Definition A.0.3), we show that the system (3.4.18) satisfies the conditions [H1] and [H2].

The Jacobian matrix $\mathcal{J}(S, I_L, I_{LR})$ of the system (3.4.18) is

$$\begin{aligned} \mathcal{J} &= \begin{pmatrix} -(\mu + \alpha_1) & 0 & 0 \\ \alpha_1 & -(\mu + \tau_1) & r_1 \\ 0 & \tau_1 & -(\mu + r_1) \end{pmatrix} \\ &= -\mu I + \hat{A}, \end{aligned} \tag{3.4.25}$$

where I is a 3×3 identity matrix and $\hat{A}(S, I_L, I_{LR})$ is a matrix-valued function given by

$$\hat{A} = \begin{pmatrix} -\alpha_1 & 0 & 0 \\ \alpha_1 & -\tau_1 & r_1 \\ 0 & \tau_1 & -r_1 \end{pmatrix}. \tag{3.4.26}$$

Let $\hat{B} = (1, 1, 1)$ be a constant 1×3 row matrix. The rank of the matrix $\hat{B}$ is $r = 1$. Then, $\hat{B}\hat{A} = 0$ for all $(S, I_L, I_{LR}) > 0$. Hence, conditions [H1] and [H2] are satisfied, with $n = 3$, $r = 1, \Omega = \mathbb{R}^3_+, \nu = \mu$ (see Definition A.0.3). Thus, the model subsystem (3.4.18) is an invariant linear subspace.

We employ *Theorem* 3.3 of [63] here. To implement this theorem, we construct the $(r+2)-th$ additive compound matrix $\mathcal{J}^{[r+2]}$ (see Definition A.0.8) of the Jacobian matrix $\mathcal{J}(S, I_L, I_{LR})$. Since $r + 2 = 3 = n$, where the matrix $\mathcal{J}$ is actually an $n \times n$ matrix, then, the special property that $\mathcal{J}^{[3]} = \text{tr}(\mathcal{J})$ is valid in this case.

$$\text{tr}(\mathcal{J}) = -(3\mu + \alpha_1 + \tau_1 + r_1) < -\mu. \tag{3.4.27}$$

Since (3.4.27) is valid, then, by Theorem 3.3 of [63], the subsystem (3.4.18) has neither periodic solutions, nor homoclinic orbits, nor heteroclinic cycles, for all values of its parameters. Since the system 3.4.18 satisfies the properties [H1] and [H2], and $\hat{B}$ is a constant matrix, then, $\hat{\Omega}$ is a global invariant 2-dimensional affine manifold. Furthermore, since the system 3.4.18 has only one unique critical point X^*, and the fact that Theorem 3.3.1 is valid, then, by a simple application of the Generalised Poincaré-Bendixson Theorem (see Definition A.0.7), it suffices to show that the distinct steady state X^* is globally asymptotically stable.

We now go on to prove that condition (C2) is also satisfied.

.

$$G(X, Y) = \begin{pmatrix} \lambda_1 S - (\mu+\alpha_2+\sigma_1+\rho_1) I_H \\ \lambda_2 I_L + \alpha_2 I_H + r_2 I_{LHR} - (\mu+\tau_2+\sigma_2+\rho_6) I_{LH} \\ \sigma_1 I_H - (\mu+\alpha_3+\rho_2) I_{HT} \\ \lambda_2 I_{LR} + \tau_2 I_{LH} - (\mu+r_2+\sigma_3+\rho_5) I_{LHR} \\ \sigma_2 I_{LH} + \alpha_3 I_{HT} + r_3 I_{LHTR} - (\mu+\tau_3+\rho_3) I_{LHT} \\ \sigma_3 I_{LHR} + \tau_3 I_{LHT} - (\mu+r_3+\rho_4) I_{LHTR} \\ \rho_1 I_H + \rho_2 I_{HT} + \rho_3 I_{LHT} + \rho_4 I_{LHTR} + \rho_5 I_{LHR} + \rho_6 I_{LH} - (\mu+\delta) A \end{pmatrix}. \tag{3.4.28}$$

Clearly, $G(X, \mathbf{0}) = \mathbf{0}$. We shall construct the matrix $A = \mathcal{D}_Y G(X^*, \mathbf{0})$. The matrix $\mathcal{D}_Y G(X, Y)$ is given by

.

$$\mathcal{D}_Y G(X,Y) =$$

$$\begin{pmatrix}
\frac{\beta_1 S}{N} - q_3 & \frac{\beta_1\eta_2 S}{N} & \frac{\beta_1\eta_1 S}{N} & \frac{\beta_1\eta_2 S}{N} & \frac{\beta_1\eta_3 S}{N} & \frac{\beta_1\eta_3 S}{N} & \frac{\beta_1\eta_4 S}{N} \\
\frac{\beta_2 I_L}{N} + \alpha_2 & \frac{\beta_2\eta_2 I_L}{N} - q_4 & \frac{\beta_2\eta_1 I_L}{N} & \frac{\beta_2\eta_2 I_L}{N} + r_2 & \frac{\beta_2\eta_3 I_L}{N} & \frac{\beta_2\eta_3 I_L}{N} & \frac{\beta_2\eta_4 I_L}{N} \\
\sigma_1 & 0 & -q_6 & 0 & 0 & 0 & 0 \\
\frac{\beta_2 I_{LR}}{N} & \frac{\beta_2\eta_2 I_{LR}}{N} + \tau_2 & \frac{\beta_2\eta_1 I_{LR}}{N} & \frac{\beta_2\eta_2 I_{LR}}{N} - q_7 & \frac{\beta_2\eta_3 I_{LR}}{N} & \frac{\beta_2\eta_3 I_{LR}}{N} & \frac{\beta_2\eta_4 I_{LR}}{N} \\
0 & \sigma_2 & \alpha_3 & 0 & -q_8 & r_3 & 0 \\
0 & 0 & 0 & \sigma_3 & \tau_3 & -q_9 & 0 \\
\rho_1 & \rho_6 & \rho_2 & \rho_5 & \rho_3 & \rho_4 & -q_{10}
\end{pmatrix}. \tag{3.4.29}$$

$X^* = (S^*, I_L^*, I_{LR}^*)$, where

$$S^* = \frac{K}{q_1},\ I_L^* = \frac{\alpha_1 K q_5}{\mu q_1(q_5+\tau_1)},\ I_{LR}^* = \frac{\tau_1\alpha_1 K}{\mu q_1(q_5+\tau_1)}.\ \text{Thus, } N^* = \frac{K}{\mu}.$$

We obtain

$$\begin{aligned} A &= \mathcal{D}_Y G(X^*, \mathbf{0}) \\ &= \begin{pmatrix} \Psi_1 & \Psi_2 \\ \Psi_3 & \Psi_4 \end{pmatrix}, \end{aligned} \tag{3.4.30}$$

where

$$\Psi_1 = \begin{pmatrix}
\frac{\beta_1\mu}{q_1} - q_3 & \frac{\beta_1\eta_2\mu}{q_1} & \frac{\beta_1\eta_1\mu}{q_1} \\
\frac{\beta_2\alpha_1 q_5}{q_1(q_5+\tau_1)} + \alpha_2 & \frac{\beta_2\eta_2\alpha_1 q_5}{q_1(q_5+\tau_1)} - q_4 & \frac{\beta_2\eta_1\alpha_1 q_5}{q_1(q_5+\tau_1)} \\
\sigma_1 & 0 & -q_6
\end{pmatrix},$$

$$\Psi_2 = \begin{pmatrix}
\frac{\beta_1\eta_2\mu}{q_1} & \frac{\beta_1\eta_3\mu}{q_1} & \frac{\beta_1\eta_3\mu}{q_1} & \frac{\beta_1\eta_4\mu}{q_1} \\
\frac{\beta_2\eta_2\alpha_1 q_5}{q_1(q_5+\tau_1)} + r_2 & \frac{\beta_2\eta_3\alpha_1 q_5}{q_1(q_5+\tau_1)} & \frac{\beta_2\eta_3\alpha_1 q_5}{q_1(q_5+\tau_1)} & \frac{\beta_2\eta_4\alpha_1 q_5}{q_1(q_5+\tau_1)} \\
0 & 0 & 0 & 0
\end{pmatrix},$$

$$\Psi_3 = \begin{pmatrix} \frac{\beta_2\tau_1\alpha_1}{q_1(q_5+\tau_1)} & \frac{\beta_2\eta_2\tau_1\alpha_1}{q_1(q_5+\tau_1)} + \tau_2 & \frac{\beta_2\eta_1\tau_1\alpha_1}{q_1(q_5+\tau_1)} \\ 0 & \sigma_2 & \alpha_3 \\ 0 & 0 & 0 \\ \rho_1 & \rho_6 & \rho_2 \end{pmatrix},$$

$$\Psi_4 = \begin{pmatrix} \frac{\beta_2\eta_2\tau_1\alpha_1}{q_1(q_5+\tau_1)} - q_7 & \frac{\beta_2\eta_3\tau_1\alpha_1}{q_1(q_5+\tau_1)} & \frac{\beta_2\eta_3\tau_1\alpha_1}{q_1(q_5+\tau_1)} & \frac{\beta_2\eta_4\tau_1\alpha_1}{q_1(q_5+\tau_1)} \\ 0 & -q_8 & r_3 & 0 \\ \sigma_3 & \tau_3 & -q_9 & 0 \\ \rho_5 & \rho_3 & \rho_4 & -q_{10} \end{pmatrix}.$$

Using the definition $G(X,Y) = AY - \hat{G}(X,Y)$ to obtain $\hat{G}(X,Y)$, we have

.

$$\begin{aligned} \hat{G}(X,Y) &= \begin{pmatrix} \hat{G}_1(X,Y) \\ \hat{G}_2(X,Y) \\ \hat{G}_3(X,Y) \\ \hat{G}_4(X,Y) \\ \hat{G}_5(X,Y) \\ \hat{G}_6(X,Y) \\ \hat{G}_7(X,Y) \end{pmatrix}, \\ &= \begin{pmatrix} \beta_1\left[I_H+\eta_1 I_{HT}+\eta_2(I_{LH}+I_{LHR})+\eta_3(I_{LHT}+I_{LHTR})+\eta_4 A\right]\Pi_1 \\ \beta_2\left[I_H+\eta_1 I_{HT}+\eta_2(I_{LH}+I_{LHR})+\eta_3(I_{LHT}+I_{LHTR})+\eta_4 A\right]\Pi_2 \\ 0 \\ \beta_2\left[I_H+\eta_1 I_{HT}+\eta_2(I_{LH}+I_{LHR})+\eta_3(I_{LHT}+I_{LHTR})+\eta_4 A\right]\Pi_3 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \end{aligned} \tag{3.4.31}$$

where

$$\begin{aligned} \Pi_1 &= \left(\frac{\mu}{q_1} - \frac{S}{N}\right), \\ \Pi_2 &= \left(\frac{\alpha_1 q_5}{q_1(q_5+\tau_1)} - \frac{I_L}{N}\right), \\ \Pi_3 &= \left(\frac{\alpha_1\tau_1}{q_1(q_5+\tau_1)} - \frac{I_{LR}}{N}\right). \end{aligned}$$

We now show that $\hat{G}(X,Y) \geq 0$ for $(X,Y) \in \Gamma$, which implies that we must show that $\hat{G}_1(X,Y)$, $\hat{G}_2(X,Y)$, $\hat{G}_4(X,Y)$, ≥ 0. It suffices to show that:

(i) $\dfrac{\mu}{q_1} - \dfrac{S}{N} \geq 0,$

(ii) $\dfrac{\alpha_1 q_5}{q_1(q_5+\tau_1)} - \dfrac{I_L}{N} \geq 0,$

(iii) $\dfrac{\alpha_1 \tau_1}{q_1(q_5+\tau_1)} - \dfrac{I_{LR}}{N} \geq 0.$

We prove these relations by contradiction. Suppose that

$$\begin{aligned} \frac{\mu}{q_1} &< \frac{S}{N}, \\ \frac{\alpha_1 q_5}{q_1(q_5+\tau_1)} &< \frac{I_L}{N}, \\ \frac{\alpha_1 \tau_1}{q_1(q_5+\tau_1)} &< \frac{I_{LR}}{N}. \end{aligned} \tag{3.4.32}$$

Using the direct proof technique, that for positive constants $a, b, c, d > 0$, if $a < b$ and $c < d$, then, $a + c < b + d$, we sum the three relations above to obtain,

$$\begin{aligned} \frac{\mu}{q_1} + \frac{\alpha_1 q_5}{q_1(q_5+\tau_1)} + \frac{\alpha_1 \tau_1}{q_1(q_5+\tau_1)} &< \frac{S + I_L + I_{LR}}{N}, \\ \implies \frac{(\mu+\alpha_1)(q_5+\tau_1)}{q_1(q_5+\tau_1)} = 1 &< \frac{S + I_L + I_{LR}}{N}. \end{aligned} \tag{3.4.33}$$

However, since $N = S + I_L + I_{LR} + I_H + I_{LH} + I_{HT} + I_{LHR} + I_{LHT} + I_{LHTR} + A$, then by definition, we have the relation

$$0 < S + I_L + I_{LR} < N, \implies \frac{S + I_L + I_{LR}}{N} < 1. \tag{3.4.34}$$

Relations (3.4.33) and (3.4.34) implies that

$$1 < \frac{S + I_L + I_{LR}}{N} < 1, \implies 1 < 1.$$

This is a contradiction. Hence, the converse of the relations in (3.4.32) is true. This implies that relations (i)-(iii) are valid. Hence $\hat{G}(X, Y) \geq 0$ for $(X, Y) \in \Gamma$. This completes the proof. □

Remark 3.4.4. Note that in a later Theorem in this chapter (*Theorem* 3.4.5), it will be seen that the disease-free equilibrium E_0 is truly globally asymptotically stable if $\mathcal{R}_0 < 1$, but that is valid only if $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, where $\mathcal{R}_0^c$ is a threshold called the *critical reproduction number*.

3.4.4 Existence of the Endemic Steady States

In order to compute the endemic equilibria of the model system (3.2.3), where at least one of the infected compartments is not null, we set the right hand side of the system (3.2.3) to zero, and solve for all its state variables. In this process, we express the state variables in terms of the forces of infection λ_1^* and λ_2^*, where

$$\lambda_1^* = \frac{\beta_1}{N^*}[I_H^* + \eta_1 I_{HT}^* + \eta_2(I_{LH}^* + I_{LHR}^*) + \eta_3(I_{LHT}^* + I_{LHTR}^*) + \eta_4 A^*], \tag{3.4.35}$$

$$\lambda_2^* = \frac{\beta_2}{N^*}[I_H^* + \eta_1 I_{HT}^* + \eta_2(I_{LH}^* + I_{LHR}^*) + \eta_3(I_{LHT}^* + I_{LHTR}^*) + \eta_4 A^*], \tag{3.4.36}$$

$$N^* = S^* + I_L^* + I_H^* + I_{LH}^* + I_{LR}^* + I_{HT}^* + I_{LHR}^* + I_{LHT}^* + I_{LHTR}^* + A^*. \tag{3.4.37}$$

Observe that

$$\lambda_2 = \frac{\beta_2\,\lambda_1}{\beta_1}. \tag{3.4.38}$$

This implies that λ_2 is simply a (positive) constant multiple of λ_1. Thus any qualitative inference(s) made from investigating the polynomial arising from λ_1 also applies to the polynomial equation that ought to arise from λ_2.

Thus, the endemic equilibria of the model (3.2.3) are given by

$$E_1 = (S^*, I_L^*, I_H^*, I_{LH}^*, I_{LR}^*, I_{HT}^*, I_{LHR}^*, I_{LHT}^*, I_{LHTR}^*, A^*), \tag{3.4.39}$$

where

.

$$S^* = \frac{K}{q_1+\lambda_1^*}, \tag{3.4.40a}$$

$$I_L^* = \frac{K\,\alpha_1\,(q_5+\lambda_2^*)}{(q_1+\lambda_1^*)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}, \tag{3.4.40b}$$

$$I_{LR}^* = \frac{K\,\alpha_1\,\tau_1}{(q_1+\lambda_1^*)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}, \tag{3.4.40c}$$

$$I_H^* = \frac{K\,\lambda_1^*}{q_3\,(q_1+\lambda_1^*)}, \tag{3.4.40d}$$

$$I_{LH}^* = \frac{K\,\alpha_1\,\lambda_2^*\,(q_7\,(q_5+\lambda_2^*)+r_2\,\tau_1)}{q_4\,q_7\,(q_1+\lambda_1^*)\,(1-\xi_1)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$

$$+\frac{K\,\alpha_2\,\lambda_1^*}{q_3\,q_4\,(q_1+\lambda_1^*)\,(1-\xi_1)}, \tag{3.4.40e}$$

$$I_{HT}^* = \frac{K\,\lambda_1^*\,\sigma_1}{q_3\,q_6\,(q_1+\lambda_1^*)}, \tag{3.4.40f}$$

$$I_{LHR}^* = \frac{1}{q_7\,(1-\xi_1)}\left[\frac{K\,q_4\,\alpha_1\,\lambda_2^*\,\tau_1+K\,\alpha_1\,\lambda_2^*\,(q_5+\lambda_2^*)\,\tau_2}{q_4\,(q_1+\lambda_1^*)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}\right.$$
$$\left.+\frac{K\,\alpha_2\,\tau_2\,\lambda_1^*}{q_3\,q_4\,(q_1+\lambda_1^*)}\right], \tag{3.4.40g}$$

$$I_{LHT}^* = \frac{K\,\alpha_1\,\lambda_2^*\,(q_9\,\sigma_2\,(q_7\,(q_5+\lambda_2^*)+r_2\,\tau_1)+r_3\,\sigma_3\,(q_4\,\tau_1+(q_5+\lambda_2^*)\,\tau_2))}{q_4\,q_7\,q_8\,q_9\,(q_1+\lambda_1^*)\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$+\frac{K\,\lambda_1^*\,(q_4\,q_7\,q_9\,\alpha_3\,(1-\xi_1)\,\xi_2\,\sigma_1+q_6\,q_7\,q_9\,\alpha_2\,\sigma_2+q_6\,r_3\,\alpha_2\,\sigma_3\,\tau_2)}{q_3\,q_4\,q_6\,q_7\,q_8\,q_9\,(q_1+\lambda_1^*)\,(1-\xi_1)\,(1-\xi_2)}$$
$$+\frac{K\,\alpha_3\,\lambda_1^*\,\sigma_1}{q_3\,q_6\,q_8\,(q_1+\lambda_1^*)}, \tag{3.4.40h}$$

$$I_{LHTR}^* = \frac{K\,\alpha_3\,\lambda_1^*\,\sigma_1\,\tau_3}{q_3\,q_6\,q_8\,q_9\,(q_1+\lambda_1^*)\,(1-\xi_2)}+\frac{K\,\alpha_2\,\lambda_1^*\,(q_8\,\sigma_3\,\tau_2+q_7\,\sigma_2\,\tau_3)}{q_3\,q_4\,q_7\,q_8\,q_9\,(q_1+\lambda_1^*)\,(1-\xi_1)\,(1-\xi_2)}$$
$$+\frac{K\,\alpha_1\,\lambda_2^*\,(q_4\,q_8\,\sigma_3\,\tau_1+q_8\,(q_5+\lambda_2^*)\,\sigma_3\,\tau_2+\sigma_2\,(q_7\,(q_5+\lambda_2^*)+r_2\,\tau_1)\,\tau_3)}{q_4\,q_7\,q_8\,q_9\,(q_1+\lambda_1^*)\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}, \tag{3.4.40i}$$

$$A^* = \frac{K}{q_{10}\,(q_1+\lambda_1^*)}\left(\frac{\lambda_1^*\,\rho_1}{q_3}+\frac{\lambda_1^*\,\rho_2\,\sigma_1}{q_3\,q_6}\right.$$
$$+\frac{\rho_6\,(q_7\,(q_5+\lambda_2^*)\,(q_3\,\alpha_1\,\lambda_2^*+\alpha_2\,\lambda_1^*\,(q_2+\lambda_2^*))-(q_7\,r_1\,\alpha_2\,\lambda_1^*-q_3\,r_2\,\alpha_1\,\lambda_2^*)\,\tau_1)}{q_3\,q_4\,q_7\,(1-\xi_1)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$+\frac{\rho_5\,(\alpha_2\,\tau_2\,\lambda_1^*\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3)))}{q_3\,q_4\,q_7\,(1-\xi_1)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$+\frac{\rho_5\,(q_3\,\alpha_1\,\lambda_2^*\,(q_4\,\tau_1+(q_5+\lambda_2^*)\,\tau_2))}{q_3\,q_4\,q_7\,(1-\xi_1)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$+\rho_3\left(\frac{\alpha_1\,\lambda_2^*\,(q_5\,q_7\,q_9\,\sigma_2+q_7\,q_9\,\lambda_2^*\,\sigma_2+q_9\,r_2\,\sigma_2\,\tau_1)}{q_4\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}\right.$$
$$+\frac{\alpha_1\,\lambda_2^*\,(q_4\,r_3\,\sigma_3\,\tau_1+r_3\,(q_5+\lambda_2^*)\,\sigma_3\,\tau_2)}{q_4\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$\left.+\frac{\lambda_1^*\,(q_4\,q_7\,q_9\,\alpha_3\,\sigma_1-q_9\,r_2\,\alpha_3\,\sigma_1\,\tau_2+q_6\,\alpha_2\,(q_7\,q_9\,\sigma_2+r_3\,\sigma_3\,\tau_2))}{q_3\,q_4\,q_6\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)}\right)$$
$$+\frac{\rho_4\,(q_3\,q_6\,\alpha_1\,\lambda_2^*\,(q_8\,\sigma_3\,(q_4\,\tau_1+(q_5+\lambda_2^*)\,\tau_2)+\sigma_2\,(q_7\,(q_5+\lambda_2^*)+r_2\,\tau_1)\,\tau_3))}{q_3\,q_4\,q_6\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$
$$+\frac{\rho_4\,(\lambda_1^*\,((q_2+\lambda_2^*)\,(q_5+\lambda_2^*)-r_1\,\tau_1)\,(q_4\,q_7\,\alpha_3\,(1-\xi_1)\,\sigma_1\,\tau_3))}{q_3\,q_4\,q_6\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\,(1-\xi_3))}$$

$$+\frac{\rho_4\ (\lambda_1^*\ ((q_2+\lambda_2^*)\ (q_5+\lambda_2^*)-r_1\,\tau_1)\ (q_6\,\alpha_2\ (q_8\,\sigma_3\,\tau_2+q_7\,\sigma_2\,\tau_3)))}{q_3\,q_4\,q_6\,q_7\,q_8\,q_9\ (1-\xi_1)\ (1-\xi_2)\ (q_2\,\lambda_2^*+q_5\,\lambda_2^*+(\lambda_2^*)^2+q_2\,q_5\ (1-\xi_3))}\Bigg). \tag{3.4.40j}$$

Substituting for the steady states above in (3.4.35), we obtain the quartic polynomial in λ_1^* given by

$$C_{14}(\lambda_1^*)^4+C_{13}(\lambda_1^*)^3+C_{12}(\lambda_1^*)^2+C_{11}\lambda_1^*=0, \tag{3.4.41}$$

where

$$\begin{aligned}
C_{14} &= -\left(\frac{\beta_2}{\beta_2}\right)^2[(q_4\,q_7\,q_8\,q_9\ (1-\xi_1)\ (1-\xi_2)\ (q_6\ (q_{10}+\rho_1)+(q_{10}+\rho_2)\ \sigma_1))\\
&\quad +q_6\,\alpha_2\ (r_3\ (q_{10}+\rho_3)+q_8\ (q_{10}+\rho_4))\ \sigma_3\,\tau_2+q_6\,q_8\,q_9\,\alpha_2\ (1-\xi_2)\ (q_7\ (q_{10}+\rho_6)\\
&\quad +(q_{10}+\rho_5)\ \tau_2)+q_4\,q_7\,\alpha_3\ (1-\xi_1)\ \sigma_1\ (q_9\ (q_{10}+\rho_3)+(q_{10}+\rho_4)\ \tau_3)\\
&\quad +q_6\,q_7\,\alpha_2\,\sigma_2\ (q_9\ (q_{10}+\rho_3)+(q_{10}+\rho_4)\ \tau_3)],\\
C_{13} &= \frac{\beta_2}{\beta_2}\left[\left(\frac{\beta_2}{\beta_2}\right)(-(q_3\,q_6\ (q_4\,q_7\,q_8\,q_9\,q_{10}\ (1-\xi_1)\ (1-\xi_2)+\alpha_1\ ((r_3\ (q_{10}+\rho_3)\ \sigma_3\right.\\
&\quad +q_8\ (q_9\ (1-\xi_2)\ (q_{10}+\rho_5)+(q_{10}+\rho_4)\ \sigma_3))\ \tau_2+q_7\ (q_8\,q_9\ (1-\xi_2)\ (q_{10}+\rho_6)\\
&\quad \left.+\sigma_2\ (q_9\ (q_{10}+\rho_3)+(q_{10}+\rho_4)\ \tau_3))))))-[(q_4\,q_7\,q_8\,q_9\ (1-\xi_1)\ (1-\xi_2)\\
&\quad \times(-(q_6\,q_{10}\,\beta_2)+(q_2+q_5)\ (q_6\ (q_{10}+\rho_1)+(q_{10}+\rho_2)\ \sigma_1)))+q_5\,q_6\,q_{10}\ (q_8+r_3)\\
&\quad \times\alpha_2\,\sigma_3\,\tau_2+q_5\,q_6\,\alpha_2\ (r_3\,\rho_3+q_8\,\rho_4)\ \sigma_3\,\tau_2+(q_2+q_5)\ q_6\,q_8\,q_9\,\alpha_2\ (1-\xi_2)\\
&\quad \times\ (q_7\ (q_{10}+\rho_6)+(q_{10}+\rho_5)\ \tau_2)+q_2\,q_6\,\alpha_2\ (q_{10}+\rho_3)\ (q_7\,q_9\,\sigma_2+r_3\,\sigma_3\,\tau_2)\\
&\quad +q_5\,q_6\,q_7\,q_{10}\,\alpha_2\,\sigma_2\ (q_9+\tau_3)+q_5\,q_6\,q_7\,\alpha_2\,\sigma_2\ (q_9\,\rho_3+\rho_4\,\tau_3)+q_4\ (q_2+q_5)\ q_7\,\alpha_3\\
&\quad \times(1-\xi_1)\ \sigma_1\ (q_9\ (q_{10}+\rho_3)+(q_{10}+\rho_4)\ \tau_3)+q_2\,q_6\,\alpha_2\ (q_{10}+\rho_4)\ (q_8\,\sigma_3\,\tau_2\\
&\quad +q_7\,\sigma_2\,\tau_3)]+[q_4\,q_7\,q_8\,q_9\,q_{10}\,\beta_2\,\eta_1\ (1-\xi_1)\ (1-\xi_2)\ \sigma_1+q_6\,q_8\,q_9\,q_{10}\,\alpha_2\,\beta_2\,\eta_2\\
&\quad \times(1-\xi_2)\ (q_7+\tau_2)+q_{10}\,\beta_2\,\eta_3\ (q_6\ (q_8+r_3)\ \alpha_2\,\sigma_3\,\tau_2+q_4\,q_7\,\alpha_3\ (1-\xi_1)\ \sigma_1\\
&\quad \times(q_9+\tau_3)+q_6\,q_7\,\alpha_2\,\sigma_2\ (q_9+\tau_3))+\eta_4\ (q_4\,q_7\,q_8\,q_9\,\beta_2\ (1-\xi_1)\ (1-\xi_2)\\
&\quad \times(q_6\,\rho_1+\rho_2\,\sigma_1)+q_6\,q_8\,q_9\,\alpha_2\,\beta_2\ (1-\xi_2)\ (q_7\,\rho_6+\rho_5\,\tau_2)+q_4\,q_7\,\alpha_3\,\beta_2\ (1-\xi_1)\\
&\quad \times\sigma_1\ (q_9\,\rho_3+\rho_4\,\tau_3)+q_6\,\alpha_2\,\beta_2\ ((r_3\,\rho_3+q_8\,\rho_4)\ \sigma_3\,\tau_2+q_7\,\sigma_2\ (q_9\,\rho_3+\rho_4\,\tau_3)))]],\\
C_{12} &= q_4\,q_6\,q_7\,q_8\,q_9\,q_{10}\,\beta_2\ (q_2+q_5)\ (1-\xi_1)\ (1-\xi_2)-D_1+D_2+D_3,
\end{aligned} \tag{3.4.42}$$

and

$$
\begin{aligned}
D_1 = &[q_2\,q_4\,q_5\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(1-\xi_3)\,(q_6\,(q_{10}+\rho_1)+(q_{10}+\rho_2)\,\sigma_1)\\
&+q_2\,q_5\,q_6\,q_8\,q_9\,\alpha_2\,(1-\xi_2)\,(1-\xi_3)\,(q_7\,q_{10}+(q_{10}+\rho_5)\,\tau_2)+(1-\xi_3)\,(q_7\,\rho_6\\
&+q_2\,q_5\,q_6\,\alpha_2\,(q_7\,q_9\,(q_{10}+\rho_3)\,\sigma_2+(r_3\,(q_{10}+\rho_3)+q_8\,(q_{10}+\rho_4))\,\sigma_3\,\tau_2)\\
&+q_6\,q_7\,\alpha_2\,(q_2\,q_5\,q_{10}+\rho_4)\,\sigma_2\,\tau_3)+\alpha_3\,(1-\xi_1)\,(1-\xi_3)\,\sigma_1\,(q_2\,q_5\,q_9\,\rho_3\\
&+q_4\,q_7\,(\rho_4\,\tau_3+q_2\,q_5\,q_{10}\,(q_9+\tau_3)))],\\
D_2 = &[q_4\,(q_2+q_5)\,q_7\,q_8\,q_9\,q_{10}\,\beta_2\,\eta_1\,(1-\xi_1)\,(1-\xi_2)\,\sigma_1+(q_2+q_5)\,q_6\,q_8\,q_9\,q_{10}\,\alpha_2\\
&\times\beta_2\,\eta_2\,(1-\xi_2)\,(q_7+\tau_2)+(q_2+q_5)\,\beta_2\,\eta_3\,(q_4\,q_7\,q_{10}\,\alpha_3\,(1-\xi_1)\,\sigma_1\,(q_9+\tau_3)\\
&+q_6\,q_{10}\,\alpha_2\,((q_8+r_3)\,\sigma_3\,\tau_2+q_7\,\sigma_2\,(q_9+\tau_3)))+\beta_2\,\eta_4\,(q_2\,q_6\,\alpha_2\,(r_3\,\rho_3+q_8\,\rho_4)\\
&\times\sigma_3\,\tau_2+q_5\,q_6\,\alpha_2\,(r_3\,\rho_3+q_8\,\rho_4)\,\sigma_3\,\tau_2+q_2\,q_6\,q_7\,\alpha_2\,\sigma_2\,(q_9\,\rho_3+\rho_4\,\tau_3)+q_5\,q_6\,q_7\\
&\times\alpha_2\,\sigma_2\,(q_9\,\rho_3+\rho_4\,\tau_3)+(q_2+q_5)\,(q_4\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(q_6\,\rho_1+\rho_2\,\sigma_1)\\
&+q_6\,q_8\,q_9\,\alpha_2\,(1-\xi_2)\,(q_7\,\rho_6+\rho_5\,\tau_2)+q_4\,q_7\,\alpha_3\,(1-\xi_1)\,\sigma_1\,(q_9\,\rho_3+\rho_4\,\tau_3)))],
\end{aligned}
$$

$$
\begin{aligned}
D_3 = &\frac{\beta_2}{\beta_1}[-[(q_3\,q_4\,q_6\,q_7\,q_8\,q_9\,q_{10}\,(q_2+q_5+\alpha_1)\,(1-\xi_1)\,(1-\xi_2))+q_3\,q_6\,q_8\,q_9\,\alpha_1\\
&\times(1-\xi_2)\,((q_{10}+\rho_6)\,(q_5\,q_7+r_2\,\tau_1)+(q_{10}+\rho_5)\,(q_4\,\tau_1+q_5\,\tau_2))+q_3\,q_6\,\alpha_1\\
&\times(q_9\,(q_{10}+\rho_3)\,\sigma_2\,(q_5\,q_7+r_2\,\tau_1)+q_{10}\,(q_8+r_3)\,\sigma_3\,(q_4\,\tau_1+q_5\,\tau_2)+(r_3\,\rho_3\\
&+q_8\,\rho_4)\,\sigma_3\,(q_4\,\tau_1+q_5\,\tau_2)+(q_{10}+\rho_4)\,\sigma_2\,(q_5\,q_7+r_2\,\tau_1)\,\tau_3)]+q_3\,q_6\,q_8\,q_9\,q_{10}\\
&\times\alpha_1\,\beta_2\,\eta_2\,(1-\xi_2)\,(q_7+\tau_2)+q_3\,q_6\,q_{10}\,\alpha_1\,\beta_2\,\eta_3\,((q_8+r_3)\,\sigma_3\,\tau_2+q_7\,\sigma_2\\
&\times(q_9+\tau_3))+q_3\,q_6\,\alpha_1\,\beta_2\,\eta_4\,((r_3\,\rho_3+q_8\,\rho_4)\,\sigma_3\,\tau_2+q_8\,q_9\,(1-\xi_2)\,(q_7\,\rho_6+\rho_5\,\tau_2)\\
&+q_7\,\sigma_2\,(q_9\,\rho_3+\rho_4\,\tau_3))],
\end{aligned}
$$

$$
\begin{aligned}
C_{11} = &-[(q_2\,q_4\,q_5\,q_6\,q_7\,q_8\,q_9\,q_{10}\,(q_3-\beta_1)\,(1-\xi_1)\,(1-\xi_2)\,(1-\xi_3))+q_3\,q_4\,q_6\,q_7\\
&\times q_8\,q_9\,q_{10}\,\alpha_1\,(1-\xi_1)\,(1-\xi_2)\,(q_5+\tau_1)]+q_2\,q_4\,q_5\,q_7\,q_8\,q_9\,q_{10}\,\beta_1\,\eta_1\,(1-\xi_1)\\
&\times(1-\xi_2)\,(1-\xi_3)\,\sigma_1+\eta_2\,(q_2\,q_5\,q_6\,q_8\,q_9\,q_{10}\,\alpha_2\,\beta_1\,(1-\xi_2)\,(1-\xi_3)\,(q_7+\tau_2)\\
&+q_3\,q_6\,q_8\,q_9\,q_{10}\,\alpha_1\,\beta_2\,(1-\xi_2)\,((q_4+r_2)\,\tau_1+q_5\,(q_7+\tau_2)))+\eta_3\,(q_3\,q_6\,q_{10}\,\alpha_1\\
&\times\beta_2\,((q_8+r_3)\,\sigma_3\,(q_4\,\tau_1+q_5\,\tau_2)+\sigma_2\,(q_5\,q_7+r_2\,\tau_1)\,(q_9+\tau_3))+q_2\,q_5\,q_{10}\,\beta_1\\
&\times(1-\xi_3)\,(q_4\,q_7\,\alpha_3\,(1-\xi_1)\,\sigma_1\,(q_9+\tau_3)+q_6\,\alpha_2\,((q_8+r_3)\,\sigma_3\,\tau_2+q_7\,\sigma_2\\
&\times(1+\tau_3))))+\eta_4\,(q_3\,q_6\,q_8\,q_9\,\alpha_1\,\beta_2\,(q_3\,q_6\,(r_3\,\rho_3+q_8\,\rho_4)\,\sigma_3\,(q_4\,\tau_1+q_5\,\tau_2)\\
&+(1-\xi_2)\,(\rho_6\,(q_5\,q_7+r_2\,\tau_1)+\rho_5\,(q_4\,\tau_1+q_5\,\tau_2))+q_3\,q_6\,\sigma_2\,(q_5\,q_7+r_2\,\tau_1)\\
&\times(q_9\,\rho_3+\rho_4\,\tau_3))+\beta_1\,(q_2\,q_4\,q_5\,q_7\,q_8\,q_9\,(1-\xi_1)\,(1-\xi_2)\,(1-\xi_3)\,(q_6\,\rho_1\\
&+\rho_2\,\sigma_1)+q_2\,q_5\,q_6\,q_8\,q_9\,\alpha_2\,(1-\xi_2)\,(1-\xi_3)\,(q_7\,\rho_6+\rho_5\,\tau_2)+q_2\,q_4\,q_5\,q_7\,\alpha_3\\
&\times(1-\xi_1)\,(1-\xi_3)\,\sigma_1\,(q_9\,\rho_3+\rho_4\,\tau_3)+q_2\,q_5\,q_6\,\alpha_2\,(1-\xi_3)\,((r_3\,\rho_3+q_8\,\rho_4)\\
&\times\sigma_3\,\tau_2+q_7\,\sigma_2\,(q_9\,\rho_3+\rho_4\,\tau_3)))).
\end{aligned}
\tag{3.4.43}
$$

λ_1^* can be factored out to give

$$\lambda_1^* \left[C_{14}(\lambda_1^*)^3 + C_{13}(\lambda_1^*)^2 + C_{12}\lambda_1^* + C_{11} \right] = 0, \tag{3.4.44}$$

which has two solutions, that is, $\lambda_1^* = 0$ (which is the disease free equilibrium) or $C_{14}(\lambda_1^*)^3 + C_{13}(\lambda_1^*)^2 + C_{12}\lambda_1^* + C_{11} = 0$. Since we are not currently estimating the DFE (that's been dealt with), then $\lambda_1 \neq 0$. This implies that the polynomial (3.4.41) reduces to a cubic polynomial given by

$$H(\lambda_1^*) = C_{14}(\lambda_1^*)^3 + C_{13}(\lambda_1^*)^2 + C_{12}\lambda_1^* + C_{11} = 0. \tag{3.4.45}$$

The new constant term in this cubic polynomial is C_{11}. C_{11} expressed in terms of $\mathcal{R}_0$ is given by

$$C_{11} = -q_1 q_3 q_4 q_6 q_7 q_8 q_9 q_{10}(q_5 + \tau_1)\left[1 - \mathcal{R}_0\right]. \tag{3.4.46}$$

The existence, and number of endemic equilibria for the model system (3.2.3) is determined by the existence of, and number of positive roots of the cubic equation (3.4.45). We investigate and characterise the solutions (roots) of the cubic polynomial (3.4.45) by using the signs of its coefficients C_{14}, C_{13}, C_{12} and C_{11}. Since $r_2 < q_7$ and $\tau_2 < q_4$, then, by direct proof, $r_2\tau_2 < q_4 q_7$. This implies that $\xi_1 = \frac{r_2\tau_2}{q_4 q_7} < 1$. Thus, $1 - \xi_1 > 0$. In like manner, $1 - \xi_2, 1 - \xi_3, > 0$. Clearly, $C_{14} < 0$. If $\mathcal{R}_0 < 1$, then $C_{11} < 0$. Also, if $\mathcal{R}_0 > 1$, then $C_{11} > 0$.

In order to determine whether the model (3.2.3) has a unique endemic equilibrium or multiple endemic equilibria when $\mathcal{R}_0 > 1$, we determine the turning points of the polynomial equation (3.4.45). We do this by evaluating the first order derivative of $H(\lambda_1^*)$ and equate it to zero. This gives

$$H'(\lambda_1^*) = 3C_{14}(\lambda_1^*)^2 + 2C_{13}\lambda_1^* + C_{12} = 0. \tag{3.4.47}$$

The turning points of equation (3.4.45) (using the quadratic formula to evaluate the roots of (3.4.47)) are given by

$$(\lambda_1^*)_{1,2} = \frac{-C_{13} \pm \sqrt{C_{13}^2 - 3C_{12}C_{14}}}{3C_{14}}. \tag{3.4.48}$$

The discriminant of solutions (3.4.48) is $\triangle = C_{13}^2 - 3C_{12}C_{14}$. We investigate the nature of the roots (3.4.48) by analysing possible signs of the discriminant $\triangle$. If $\triangle < 0$, then $H(\lambda_1^*)$ has no real turning points, which implies that $H(\lambda_1^*)$ is a strictly monotonic function. We investigate the monotonicity of $H(\lambda_1^*)$ by examining the sign of $H'(\lambda_1^*)$ (equation (3.4.47)). We use completing the squares method to convert $H'(\lambda_1^*)$ into the sum of a square and a constant term. We obtain

$$H'(\lambda_1^*) = 3C_{14}\left[\left(\lambda_1^* + \frac{C_{13}}{3C_{14}}\right)^2 + \frac{1}{9C_{14}^2}(3C_{12}C_{14} - C_{13}^2)\right]. \tag{3.4.49}$$

If $\triangle < 0$, then $3C_{12}C_{14} - C_{13}^2 > 0$. Since $C_{14} < 0$, then $H'(\lambda_1^*) < 0$. This implies that the polynomial function $H(\lambda_1^*)$ in (3.4.45) is strictly monotone decreasing. Note that $H(0) = C_{11} > 0$ if $\mathcal{R}_0 > 1$. Hence, $H(\lambda_1^*)$ has only one positive real root, and consequently only one endemic equilibrium.

If $\triangle = 0$, then $H'(\lambda_1^*)$ has only one real root with multiplicity two. This implies that $(\lambda_1^*)_1 = (\lambda_1^*)_2 = -\frac{C_{13}}{3C_{14}}$. $\triangle = 0$ implies that $3C_{12}C_{14} - C_{13}^2 = 0$, which also implies that $H'(\lambda_1^*) < 0$. This indicates that $H(\lambda_1^*)$ is a decreasing funtion. $H'(\lambda_1^*)$ has only one root which is $-\frac{C_{13}}{3C_{14}}$, and it has multiplicity two. $H''(\lambda_1^*) = 6C_{14}\lambda_1^* + 2C_{13}$. We observe that $H''(-\frac{C_{13}}{3C_{14}}) = 0$. This means that the turning point $(\lambda_1^*)_1 = (\lambda_1^*)_2 = -\frac{C_{13}}{3C_{14}}$ is a point of inflexion for $H(\lambda_1^*)$. Since the only stationary point of $H(\lambda_1^*)$ in this case is a point of inflexion, $H(0) = C_{11} > 0$ for $\mathcal{R}_0 > 1$, and $H(\lambda_1^*)$ is a decreasing function, then, $H(\lambda_1^*)$ has only one positive real root, and consequently only one endemic equilibrium.

For $\triangle > 0$, we consider two cases; $C_{12} < 0$ and $C_{12} > 0$. If $C_{12} < 0$, then $C_{12}C_{14} > 0$. This means that $\sqrt{\triangle} < C_{13}$. Irrespective of the sign of C_{13}, $H'(\lambda_1^*)$ has two real positive and distinct roots. This implies that $H(\lambda_1^*)$ has two positive turning points. Since $H(0) = C_{11} > 0$ for $\mathcal{R}_0 > 1$, then, $H(\lambda_1^*)$ has at least one positive real root, and consequently at least one endemic equilibrium.

If $C_{12} > 0$, then $C_{12}C_{14} < 0$, which implies that $\sqrt{\triangle} > C_{13}$. For $C_{13} > 0$, $H'(\lambda_1^*)$ has two real roots of opposite signs. Since $H(0) = C_{11} > 0$ for $\mathcal{R}_0 > 1$, then, $H(\lambda_1^*)$ has one positive root. For $C_{13} < 0$, $H'(\lambda_1^*)$ has two negative real roots. Since $H(0) = C_{11} > 0$ for $\mathcal{R}_0 > 1$, then, $H(\lambda_1^*)$ has only one positive real root, and consequently only one endemic equilibrium.

Furthermore, we use the *Descartes' Rule of Signs* [64] to explore the existence of endemic equilibrium (or equilibria) for $\mathcal{R}_0 < 1$, and investigate the possibility of a backward bifurcation (that is a likelihood of the system (3.2.3) to be bistable with both its DFE and endemic equilibrium/equilibria coinciding at $\mathcal{R}_0 < 1$). $C_{14} < 0$ and $C_{11} < 0$ when $\mathcal{R}_0 < 1$. If $C_{13} > 0$ and $C_{12} < 0$, then, equation (3.4.45) can be expressed as

$$H(\lambda_1^*) = -C_{14}(\lambda_1^*)^3 + C_{13}(\lambda_1^*)^2 - C_{12}\lambda_1^* - C_{11} = 0. \tag{3.4.50}$$

There are only two sign changes in equation (3.4.50), which implies that (3.4.50) can only have two positive roots. This means that equation (3.4.45) has two endemic equilibria.

If $C_{13} > 0$ and $C_{12} > 0$, then, equation (3.4.45) can be expressed as

$$H(\lambda_1^*) = -C_{14}(\lambda_1^*)^3 + C_{13}(\lambda_1^*)^2 + C_{12}\lambda_1^* - C_{11} = 0. \tag{3.4.51}$$

There are only two sign changes in equation (3.4.51), which implies that (3.4.51) has two positive roots. This means that equation (3.4.45) has two endemic equilibria.

If $C_{13} < 0$ and $C_{12} < 0$, then, equation (3.4.45) can be expressed as

$$H(\lambda_1^*) = -C_{14}(\lambda_1^*)^3 - C_{13}(\lambda_1^*)^2 - C_{12}\lambda_1^* - C_{11} = 0. \tag{3.4.52}$$

There are are no sign changes in (3.4.52), whic implies that (3.4.51) will have no positive root.

If $C_{13} < 0$ and $C_{12} > 0$, then, equation (3.4.45) can be expressed as

$$H(\lambda_1^*) = -C_{14}(\lambda_1^*)^3 - C_{13}(\lambda_1^*)^2 + C_{12}\lambda_1^* - C_{11} = 0. \tag{3.4.53}$$

There are two sign changes in equation (3.4.53), which implies that (3.4.53) has two positive roots. This means that equation (3.4.45) has two endemic equilibria.

The theorem below summarises the existence of endemic equilibria of the model system (3.2.3).

Theorem 3.4.5. *The model system* (3.2.3)

(i) has no endemic equilibrium if $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, *where* $\mathcal{R}_0^c$ *is a threshold called the critical* $\mathcal{R}_0$.

(ii) has at least one endemic equilibrium in Γ, *if* $\mathcal{R}_0 > 1$.

(iii) has two endemic equilibria for some parameter values of $\mathcal{R}_0$ *within the range* $\mathcal{R}_0^c < \mathcal{R}_0 < 1$. *Within this range, one endemic equilibrium and the DFE are locally stable.*

(iv) has no endemic equilibrium otherwise.

Remark 3.4.6. Since the system possesses two endemic equilibria when $\mathcal{R}_0^c < \mathcal{R}_0 < 1$, then, the DFE E_0 is not globally asymptotically stable for $\mathcal{R}_0 < 1$, except if $\mathcal{R}_0 < \mathcal{R}_0^c$.

Proposition 3.4.7. *The model system (3.2.3) exhibits backward bifurcation for* $\mathcal{R}_0 < 1$.

Remark 3.4.8. The consequence of Proposition 3.4.7 is that bringing $\mathcal{R}_0$ below unity is not sufficient to eradicate the disease when introduced into a wholly susceptible population. If this must be achieved, then, $\mathcal{R}_0$ must be brought below the critical value $\mathcal{R}_0^c$, or $\mathcal{R}_0^c$ must be raised. The critical value $\mathcal{R}_0^c$ is a threshold after both the DFE and the endemic equilibrium(s) co-exist. Note that because the DFE is locally asymptotically stable, the disease will not return if it is eradicated.

We give a description of the critical value $\mathcal{R}_0^c$ by investigating the possible roots (3.4.48) of the quadratic turning point 3.4.47, of equation (3.4.45). As earlier stated, the roots of equation (3.4.47) (using the quadratic formula) are given by equation (3.4.48).

Let

$$\begin{aligned}(\lambda_1^*)_1 &= \frac{-C_{13} + \sqrt{C_{13}^2 - 3C_{12}C_{14}}}{3C_{14}},\\ (\lambda_1^*)_2 &= \frac{-C_{13} - \sqrt{C_{13}^2 - 3C_{12}C_{14}}}{3C_{14}}.\end{aligned} \tag{3.4.54}$$

Let $(\lambda_1^*)_c$ be the root that corresponds to the critical $\mathcal{R}_0$. The discriminant of roots (3.4.48) is $\triangle = C_{13}^2 - 3C_{12}C_{14}$. Remember that $C_{14} < 0$. If $\triangle < 0$, then, we cannot estimate the (real) roots of the turning points $H'(\lambda_1^*)$.

Consider $\triangle < 0$. If $C_{12} > 0$, then $\sqrt{\triangle} > C_{13}$. If in addition $C_{13} > 0$, then, $(\lambda_1^*)_1, (\lambda_1^*)_2 < 0$. This case is invalid as we are only interested in the positive root(s) $H'(\lambda_1^*)$. On the other hand, if $C_{13} < 0$, then, $(\lambda_1^*)_1 < 0$ and $(\lambda_1^*)_2 > 0$. This summarily implies that if $\triangle < 0, C_{12} > 0$, and $C_{13} < 0$, then, $(\lambda_1^*)_c = (\lambda_1^*)_2$.

If $C_{12} < 0$, then $\sqrt{\triangle} < C_{13}$. If in addition $C_{13} > 0$, then, $(\lambda_1^*)_1, (\lambda_1^*)_2 > 0$. This implies that the turning points of $H(\lambda_1^*)$ are in the positive (first) quadrant of the $\lambda_1^* - H(\lambda_1^*)$ plane. This suggests that there can be three endemic equilibria (when a vertical line is drawn across the $\lambda_1^* - H(\lambda_1^*)$ plane). We do not consider this case as there are only two endemic equilibria when $\mathcal{R}_0^c < \mathcal{R}_0 < 1$. On the contrary, if $C_{13} < 0$, then $(\lambda_1^*)_1 > 0$ and $(\lambda_1^*)_2 < 0$. Thus, for $\triangle < 0, C_{12} < 0$, and $C_{13} < 0$, $(\lambda_1^*)_c = (\lambda_1^*)_1$.

Consider $\triangle = 0$. $H'(\lambda_1^*)$ will have only one root with multiplicity two, given by

$$(\lambda_1^*)_1 = (\lambda_1^*)_2 = -\frac{C_{13}}{3C_{14}}. \tag{3.4.55}$$

If $C_{13} > 0$, then, $(\lambda_1^*)_1 > 0$. On the other hand, if $C_{13} < 0$, then, $(\lambda_1^*)_1 < 0$. Thus, for $\triangle = 0$ and $C_{13} > 0$, $(\lambda_1^*)_c = (\lambda_1^*)_1 = (\lambda_1^*)_2$.

Below is a summary of the only plausible conditions for $(\lambda_1^*)_c$, such that $H(\lambda_1^*)_c = \mathcal{R}_0^c$;

(i) $(\lambda_1^*)_c = (\lambda_1^*)_2$, for $C_{12} > 0, C_{13} < 0$, and $C_{13}^2 - 3C_{12}C_{14} > 0$.

(ii) $(\lambda_1^*)_c = (\lambda_1^*)_1$, for $C_{12} < 0, C_{13} < 0$, and $C_{13}^2 - 3C_{12}C_{14} > 0$.

(iii) $(\lambda_1^*)_c = (\lambda_1^*)_1 = (\lambda_1^*)_2$, for $C_{13} > 0$, and $C_{13}^2 - 3C_{12}C_{14} = 0$.

3.5 Numerical Simulations

In order to illustrate the theoretical results of the preceding analysis, and to study the dynamics of the model system (3.2.3), even the effects of its various parameters, we integrate the system (3.2.3), using the fourth order Runge-Kutta method. Table 3.3 displays the lymphoma data obtained by the TLSG, which we used to fit the model. We do not have adequate information on the annual proportion of HIV patients on HAART, lymphoma patients in remission or their age range for this particular data. The parameter values used in the numerical simulations are given in the Table 3.4. Lymphoma incidence data (for both HIV-infected and HIV-free patients) for the years 2002-2012, were obtained from the Tygerberg Lymphoma Study Group (TLSG) of the Tygerberg Hospital (TH), Stellenbosch University, Western Cape province, South Africa.

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
HIV +ve	2	15	17	16	35	43	43	48	32	53	55
HIV -ve	33	106	95	62	147	133	150	131	150	185	144
Total	35	111	112	78	182	176	193	179	182	238	194

Table 3.3: The number of lymphoma cases per year for HIV positive (HIV^+) and HIV negative (HIV^-) individuals, data obtained from the TLSG, [27].

Many of the parameter values used have not been clinically or experimentally estimated. In the estimation of our parameters, we aim at obtaining the most suitable parameters that will ensure coherence between numerically obtained data, and clinically observed data. To do this, the unknown parameters can be obtained by an iterative method (which may not be efficient), or by fitting the model to real data, through the use of scientific packages. These packages aim at (statistically) finding parameters that give the best fit. An example of such

packages is the *least suqare curve fit routine (lsqcurvefit)*, built into Matlab. One can write a code (e.g a Matlab code) which takes a range of paramaters values (lower and upper bounds of parameters), from which paramaters values that fit the model best can be sampled and optimised by the least suqare curve fit routine, with respect to the model system, and the set of observed data.

Thus, in order to facilitate the illustration of the dynamics of the model, we simulate the model using several assumed parameters, within realistic biological and epidemiological ranges. Some of the assumed parameters obtained coincide with the parameter estimates of the least-square curve fit scheme, which were used to fit the model to data. While many of these parameters could also be applicable in other HIV-related malignancy setting, and in other regions of the world, we restrict our simulation to the particular incidence of HIV-related lymphoma in the Western Cape province of South Africa, for which some parameters are know. Known model parameters include demp-graphic parameters: μ,b (birth rate), and δ.

3.5.1 Parameter Estimation

The 2013 mid-year population estimate by Statistics South Africa (StatsSA) [65], reports that the average life expectancy of the people of Western Cape, South Africa, from 2001-2006 was 56.6 and 63.7 years (average is 60.15 years), from 2006-2011 was 60.6 and 66.1 years (average is 63.35 years), and from 2011-2016 was 64.2 and 70.1 years (average is 67.15 years) for males and females respectively. The corresponding mortality rates for each year sections are 0.01663yr^{-1}, 0.01579yr^{-1} and 0.01489yr^{-1} respectively. Hence, the mortality rate we used for the model was sampled from the range (0.014-0.017), of which the sampled value that fits our model is 0.017. In like manner, the (crude) birth rate of the people of the Western Cape of South Africa from 2001-2006 is about 21.7 childbirths per 1000 people per year, i.e. (0.0217yr^{-1}), from 2006-2011, it is about 20.7 childbirths per 1000 people per year, i.e. (0.0207yr^{-1}), and from 2011-2016, it is about 19.0 childbirths per 1000 people per year, i.e. (0.0190yr^{-1}) [65]. Thus, the birth rate (b) used in the model simulation was sampled from the range (0.020-0.025). We estimate the recruitment rate $K = bN_0$.

In the estimation of the effective contact rates β_1 and β_2, we supposed that lymphoma patients have lesser effective contacts with HIV-infected individuals, in comparison with susceptibles ($\beta_1 > \beta_2$). This is because lymphoma patients are (assumed) sick and immunocompromised. Since HIV-positive patients have a higher proclivity to developing lymphoma, we assumed that their lymphoma development rates α_2 and α_3, irrespective of whether they are on treatment, are higher than that of HIV-negative patients α_1, that is $\alpha_2, \alpha_3 > \alpha_1$. Several studies have reported that treatment of HIV with HAART have caused a

decline in the incidence of some lymphoma subtypes, such as HIV-PCNSL and DLBCL (see 2.2.1), while it has caused an increase in the incidence of some lymphoma subtypes (that occurs mostly in patients with normal or slightly depreciated CD4 counts), such as BL and centroblastic DLBCL. Due to this fact, we could not definitely assume which is greater of α_2 and α_3. However, our model fit to data suggests that $\alpha_3 > \alpha_2$, which could imply that many of the patients, in the population under study, develops lymphoma after their initiation of HAART. This could be attributed to very late presentation of cases (when lyphoma is worse and CD4 count is dangerously low; many present at a CD4 count of $< 100\text{cells}/\mu\text{L}$) and lack of adherence to HAART treaments. Parameter values for these assumptions were obtained during our fitting of model to data.

Furthermore, we assumed that the viral infection of patients with HIV, and those co-infected with HIV and lymphoma progresses to AIDS, at a faster rate, than every other patients in such classes but in one kind of treatment or the other, that is, $\rho_1, \rho_6 > \rho_2, \rho_3, \rho_4, \rho_5$. We also assumed that the rate at which the viral infection of patients co-infected with HIV and lymphoma, and using HAART, and those co-infected with HIV and lymphoma, but in remission after being treated for lymphoma, advance to the AIDS stage, are about the same, and faster than the rate at which patients co-infected with HIV and lymphoma, but using HAART and in remission progresses to AIDS, that is, $\rho_3, \rho_5 > \rho_4$. However, theoretically, we suppose that patients who have been co-infected with HIV and lymphoma (and in treatment for both illnesses), have been more immunocompromised than patients infected with HIV alone and using HAART, we assumed that the rate at which the viral infection of the former progresses to AIDS is faster than the rate at which the latter progresses to AIDS, that is, $\rho_4 > \rho_2$. Parameter values for these assumptions, and every other unknown parameters were obtained during our fitting of model to data. All the parameter values used, with their ranges and description, for our model simulation and validation are displayed in Table 3.4.

The population we fitted to our model is that of Western Cape. However, the clinical data we are fitting to our model is from Tygerberg Hospital, which covers about half the population of Western Cape. Our source of data for the population under consideration is from StatsSA. For coherence of data, we halved the population of the adult population (15^+) to get the total number of susceptibles for the purpose of our data fit to model. The susceptible population used to set the initial conditions of the model, for the year 2002-2012 can be found in [65–75].

Table 3.4: Parameter values and ranges used in numerical simulation

Parameters	Description	Range	Point value	Source
K	Recruitment rate for susceptibles	(43000-44000)	$43049yr^{-1}$	Demo
μ	Natural mortality rate	(0.015-0.017)	$0.017yr^{-1}$	Demo
δ	Disease-induced mortality rate	(0.0015-0.0025)	$0.002yr^{-1}$	Demo
β_1	Effective contact rate of HIV for susceptible individuals	(0.0088-0.0093)	$0.009yr^{-1}$	Estimated
β_2	Effective contact rate of HIV for lymphoma patients	(0.0018-0.0022)	$0.002yr^{-1}$	Estimated
α_1	Lymphoma development rate of HIV-negative patients	(0.000080-0.0000885)	$0.000082yr^{-1}$	Estimated
α_2	Lymphoma development rate of HIV-positive patients	(0.000134-0.000136)	$0.000135yr^{-1}$	Estimated
α_3	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s)	(0.078-0.082)	$0.08yr^{-1}$	Estimated
σ_1	HIV treatment rate of lymphoma-free HIV patients	(0.031-0.035)	$0.034yr^{-1}$	Estimated
σ_2	HIV treatment rate of patients with lymphoma and HIV	(0.00067-0.00072)	$0.0007yr^{-1}$	Estimated
σ_3	HIV treatment rate of patients with lymphoma and HIV, and in remission	(0.00078-0.00083)	$0.0008yr^{-1}$	Estimated
τ_1	Lymphoma treatment rate of lymphoma-only patients	(0.990-0.995)	$0.99yr^{-1}$	Estimated
τ_2	Lymphoma treatment rate of patients with lymphoma and HIV	(0.118-0.125)	$0.122yr^{-1}$	Estimated
τ_3	Lymphoma treatment rate of patients with lymphoma and HIV, and are under antiretroviral regimen(s)	(0.77-0.80)	$0.78yr^{-1}$	Estimated
r_1	Lymphoma relapse rate of lymphoma patients in remission	(0.0018-0.0022)	$0.002yr^{-1}$	Estimated
r_2	Lymphoma relapse rate of lymphoma patients with lymphoma and HIV in remission	(0.050-0.057)	$0.055yr^{-1}$	Estimated
r_3	Lymphoma relapse rate of lymphoma patients with lymphoma and HIV, in remission and under antiretroviral regimen(s)	(0.38-0.42)	$0.4yr^{-1}$	Estimated
ρ_1	Progression rate to full-blown AIDS in HIV patients	(0.009-0.011)	$0.01yr^{-1}$	Estimated
ρ_2	Progression rate to full-blown AIDS in HIV patients under antiretroviral regimen(s)	(0.001-0.0012)	$0.001yr^{-1}$	Estimated
ρ_3	Progression rate to full-blown AIDS in patients with lymphoma and HIV, and under antiretroviral regimen(s)	(0.0068-0.0072)	$0.007yr^{-1}$	Estimated
ρ_4	Progression rate to full-blown AIDS in patients with lymphoma and HIV, under antiretroviral regimen(s) and in remission	(0.0049-0.0053)	$0.005yr^{-1}$	Estimated
ρ_5	Progression rate to full-blown AIDS in patients with lymphoma and HIV, and in remission	(0.0068-0.0071)	$0.007yr^{-1}$	Estimated
ρ_6	Progression rate to full-blown AIDS in patients with lymphoma and HIV	(0.0098-0.0099)	$0.01yr^{-1}$	Estimated
η_1	Modification parameter for class I_{HT}	(0.50-0.52)	0.5	Estimated
η_2	Modification parameter for classes I_{LH} and I_{LHR}	(1.30-1.32)	1.3	Estimated
η_3	Modification parameter for classes I_{LHT} and I_{LHTR}	(0.7-0.72)	0.7	Estimated
η_4	Modification parameter for class A	(1.59-1.62)	1.6	Estimated

3.5.2 Sensitivity Analysis

Using the Latin Hypercube Sampling (LHS) technique, we investigate and quantify the uncertainties and sensitivity of the response of the model system 3.2.3, to a range of 1000 samples each of varying input parameter values, as described in Table 3.4. To excute this, we observe the response of $\mathcal{R}_0$ to the variation of the predictors (input model parameters). The LHS is a stratified Monte Carlo sampling scheme, which is efficient for simultaneously obtaining unprejudiced sampling of all predictors, in a multi-dimensional parameter space, for the purpose of executing an uncertainty analysis [76; 77]. Uncertainty analysis is a method that can be used to evaluate the variability (prediction imprecision) in the response ($\mathcal{R}_0$ of our model system), which is a consequence of the uncertainty in estimating our predictor variables. Sensitivity analysis is a method that can extend an uncertainty analysis, by demonstrating which predictors makes important contribution to the prediction imprecision of the response, and consequently, the model system [76; 77].

Sensitivity analysis can be performed by calculating the Partial Rank Correlation Coefficients (PRCCs) for each predictor obtained by LHS, and the response variable, in order to rank the input parameters with respect to their contribution to the uncertainty of the response variable. The use of PRCCs aids the assessment of the statistical relationship between the predictors and response(s), as it demonstrates the degree of monotonicity between particular predictors and outcome [76; 77]. The sign of the PRCC of an input parameter depicts the particular kind of qualitative affiliation it has with the outcome variable. When a predictor has a positive PRCC value, it simply implies that when it is increased, the outcome variable will increase and when it is decreased, the outcome variable will also decrease. Input parameter values that have the largest (absolutely) valued (either being originally positive or negative) PRCCs are the parameters in which the uncertainty in estimating them are most critical, in affecting the variability of the outcome variable [77].

In this model, the used data was not analysed for statistical independency of its input parameters, hence, we must report that this model is being used as a thought experiment to examine the independent effects of each predictor on the response ($\mathcal{R}_0$) of the HIV infection) [77]. The input parameters may be interdependent, however, the independent effects of the input parameters on the response is very paramount in this analysis as it determines how important the uncertainty in estimating each input parameters is, in contribution to the variability of the response. PRCC measures this independent effects, irrespective of whether any correlations exist between any of the input parameters [77]. In this analysis, PRCC was used to distinguish and measure this statistical influence, importantly the monotonicity of the predictors on the response. We must note that if the model's input parameters are statistically independent, the LHS would consequently use a marginal distribution,

which will ensure that our uncertainty analysis' outcome will not competently exhibit the prediction imprecision of the model. To conduct sensitivity and uncertainty analysis on our model, the sampling and sensitivity analysis methods used in SaSAT (Sampling and Sensitivity Analysis Tools) were implemented [76]. It is worthy of note that if there is colinearity between the input parameters, the robustness of the model results may not be compromised because the sampling and sensitivity analysis methods used in SaSAT [76] incorporate statistical dependencies (see [76–79]).

Figure 3.6 is the tornado plot of the PRCC of all the predictors of our model system as described in Table 3.4. It connotes the importance of the uncertainty of individual predictor, with respect to their contribution to the variability in the basic reproduction number $\mathcal{R}_0$ of the HIV infection, as described by the model system 3.2.3. Tornado plots are used for illustrating the results of sensitivity analysis [76]. Input parameter with positive PRCCs are depicted by bar plots to the right, and with positive calibration on the horizontal axis, while input parameter with negative PRCCs are depicted by bar plots to the left, and with negative calibration on the horizontal axis. In order to evaluate the monotonicity between chosen predictors, those with high (absolute) value of PRCC, and the response $\mathcal{R}_0$, we plot the scatter plot of their PRCCs, and examine the plot. For our analysis, we displayed predictors with significant monotonic (statistical) relationship with the response $\mathcal{R}_0$; those whose varying PRCCs are either monotone increasing or decreasing.

Figures 3.3 and 3.4 display the Monte Carlo simulations of a range of 1000 samples for three input parameters with the highest absolute PRCC values. Figure 3.3 is the scatter plot of the natural mortality rate μ, in relation to $\mathcal{R}_0$. It depicts that $\mathcal{R}_0$ is monotone decreasing with an increasing natural mortality rate μ. μ has the strongest correlation with $\mathcal{R}_0$. Figure 3.4 is the scatter plot of , in relation to $\mathcal{R}_0$. It shows that $\mathcal{R}_0$ is monotone increasing with increasing values of the effective contact rate of HIV for susceptible individuals, β_1. It implies that if the effective contact rate, which breeds the transmission of HIV infection between susceptibles and HIV infecteds, is drastically reduced, HIV infection will go into extinction.

Figure 3.5 is the boxplot of $\mathcal{R}_0$, which graphically depicts some of its statistical measures, such as its median. The boxplot shows that the overall median of $\mathcal{R}_0 > 1$. This suggets that the current epidemic of the incidence of cancers in HIV-infected individuals may not always be restrained or eradicated.

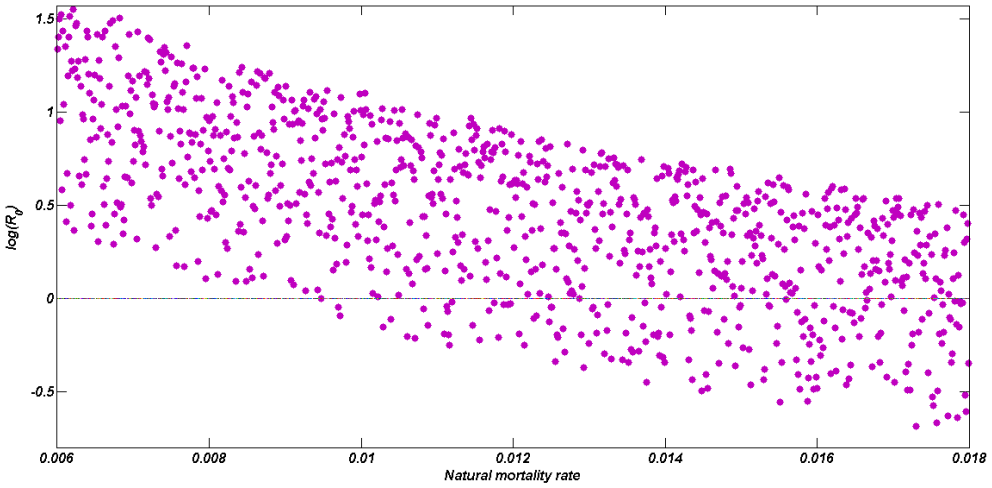

Figure 3.3: Scatter plot of the natural mortality rate, μ, in relation to $\mathcal{R}_0$.

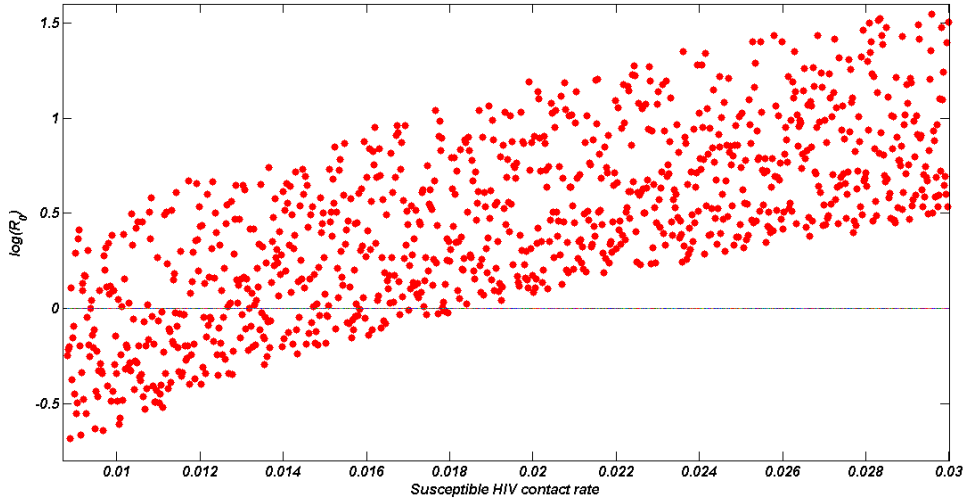

Figure 3.4: Scatter plot of the effective contact rate of HIV for susceptible individuals, β_1, in relation to $\mathcal{R}_0$.

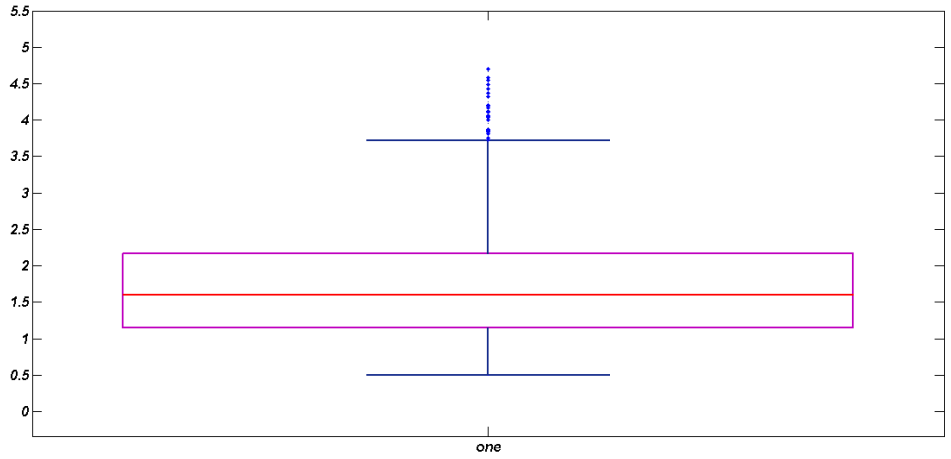

Figure 3.5: Boxplot of $\mathcal{R}_0$.

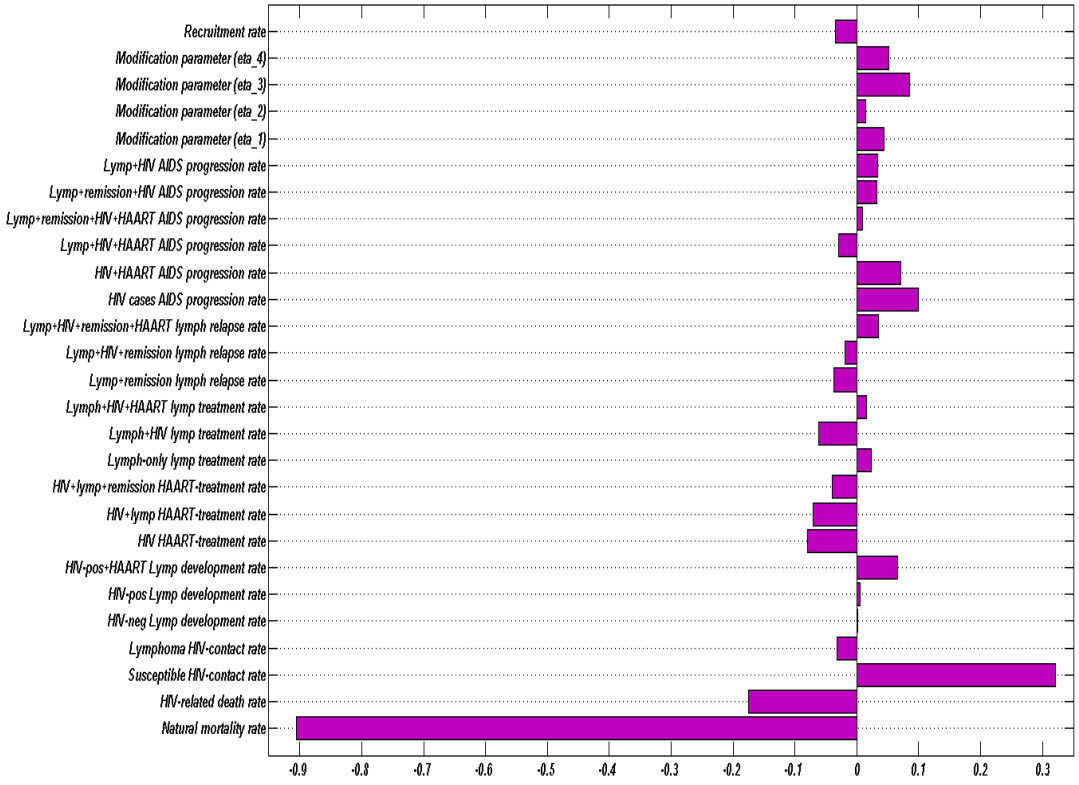

Figure 3.6: Tornado plot of the PRCC of the input parameters of our model system as described in Table 3.4

3.5.3 Results

We now exhibit the general dynamics of lymphoma (representing all HIV-related malignancies) in the HIV-infected and HIV-free population, using the fit of our model to the TLSG data. Fig. 3.7 is a graphical representation that shows the yearly incidence of lymphoma in individuals who are not infected with HIV from 2002-2012. It depicts that the incidence of lymphoma cases in HIV-negative patients increased significantly between 2002 and 2006, after which it increases only slightly significantly. The relatively low (declining) incidence of lymphoma in 2004 and 2005 as shown by the actual data, could be attributed to inadequate access to lymphoma data (in those years) by the TLSG.

Fig. 3.8 shows that the incidence of lymphoma cases in patients co-infected with lymphoma and HIV steadily increased from 2002-2012. The decrease in its incidence between 2004 and 2005, is also attributed to the lack of sufficient access to data by the TLSG. Fig. 3.9 demonstrates that the cummulative incidence of all lymphoma cases steadily increased from 2002-2006, after which the incidence slowly increases.

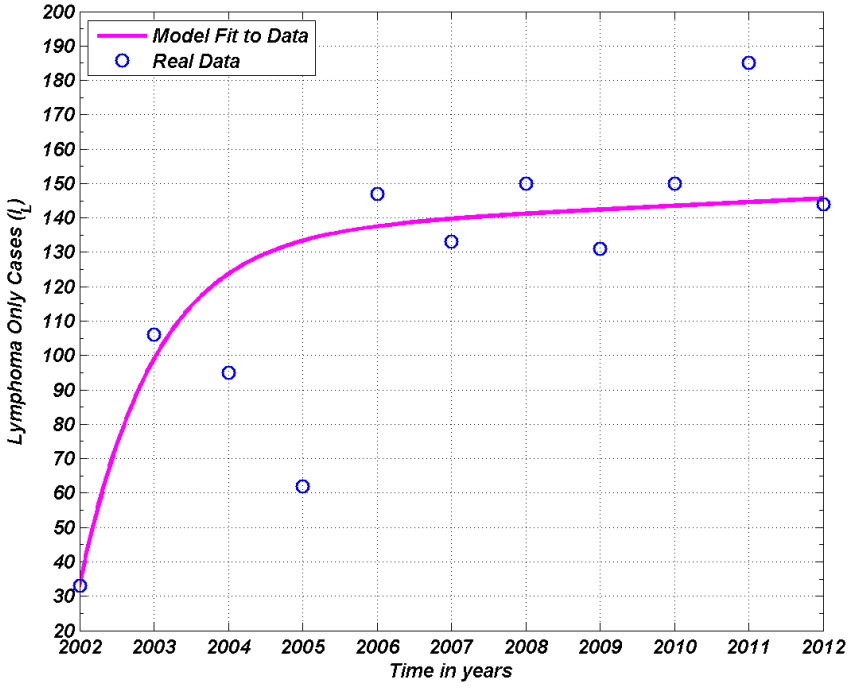

Figure 3.7: Incidence of lymphoma-only cases

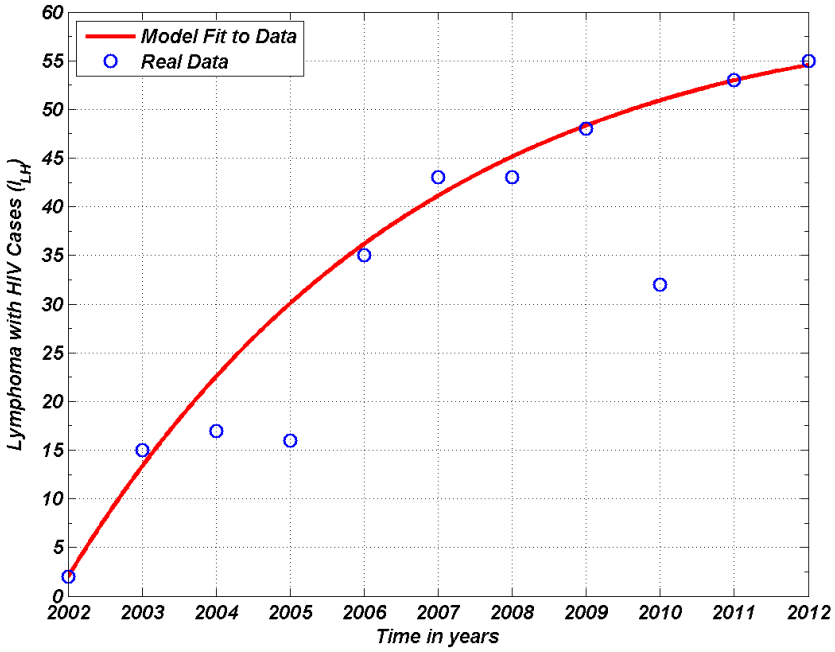

Figure 3.8: Incidence of lymphoma in HIV-infected individuals

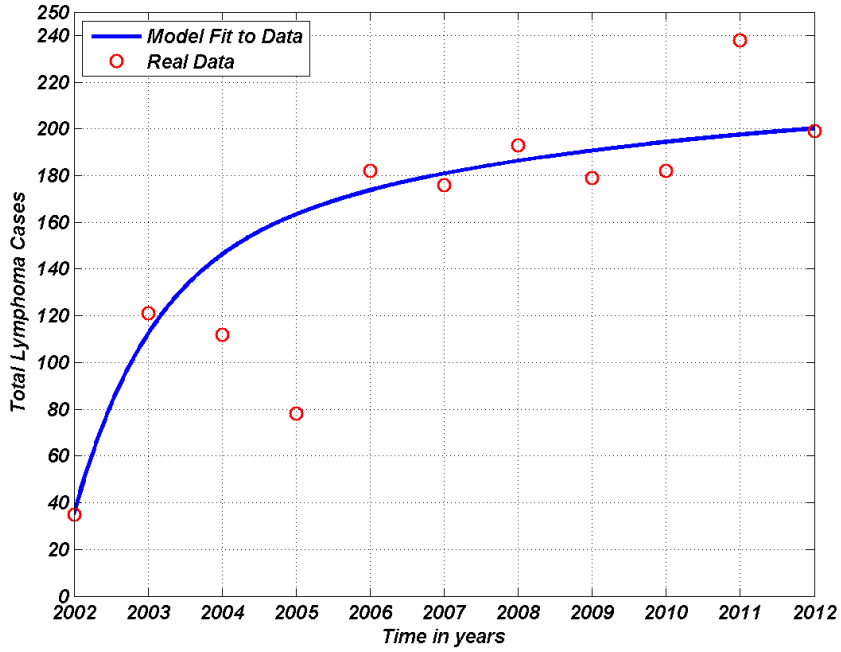

Figure 3.9: Incidence of lymphoma in both HIV-infected and HIV-negative individuals (Total Lymphoma Cases = $I_L + I_{LH}$, as shown in Table 3.3)

Our model can be used as a predictive tool. We can thus make projection on the future of the epidemic, assuming that the status quo remains the same, that is, no policy shift occurs, human behaviour remains constant, etc. Fig. 3.10 depicts the projected changes in the incidence of lymphoma only cases, up to year 2020. It shows that the incidence will continue to increase if the current status quo (every factor affecting the development of lymphoma, such as environmental hazards, immunocompression, old age, iatrogenic causes, etc) remains the same. Fig. 3.11 depicts the projected changes in the incidence of lymphoma in HIV-infected patients, up till 2020. It shows that the number of cases will continue to rise, though not exponentially. Fig. 3.12 demonstrates projected change in the incidence of all lymphoma cases, up to year 2020. It also predicts an increase in lymphoma cases.

Note that the fact that there are some treatments incorporated into the model, such as the HAART regimen, and other lymphoma treatment, does not necessarily cause a decline in the incidence of lymphoma in HIV-infected individuals. This is because our model flow allows individuals under treament to be infectious, which is biologically relevant. Also, lymphoma-only patients, who have been treated are also allowed to have relapses with some probability (as depicted by some of the model's parameter values). In addition, since HAART, HIV-infected patients live longer, and the incidence infection is still on the rise.

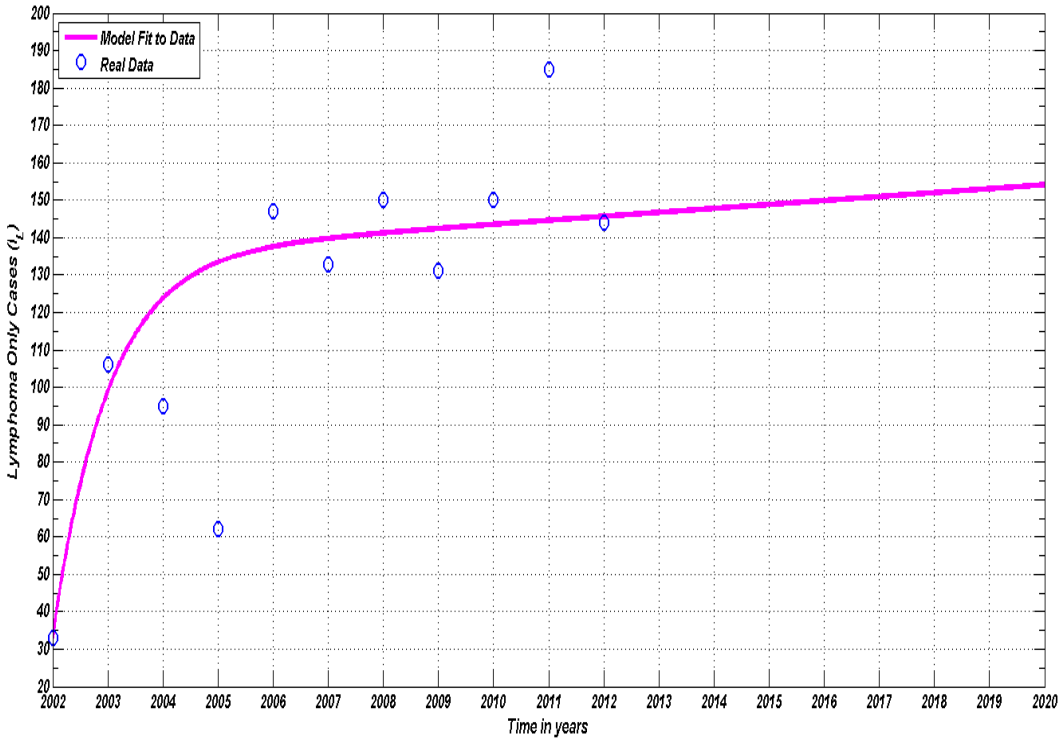

Figure 3.10: A Projection of the incidence of lymphoma-only cases

Hence, the pool of individuals with HIV, and that are developing lymphoma (as a consequence of immune suppression and dysfunction) are also on the rise.

The effective coverage of HAART, as at 2011, in the Western Cape province of South Africa, is about 31% [27]. In order to estimate the effect of increasing the effective coverage of HAART, as an intervention strategy in controlling the incidence of lymphoma in HIV-infected individuals, we consider scenarios in which the effective HAART coverage of all HIV-patients eligible for HAART is 30%, and increases to 60%, 80% and 100%. One reason for this is because several studies (as reviewed in Chapter 2) have reported that HAART use may alter or even correct the development of some lymphoma subtypes (and some other HIV-related malignancies). Using projections, Fig. 3.13 depicts the four scenarios generated for the incidence of lymphoma in patients co-infected with HIV and lymphoma. Fig. 3.14 depicts the four scenarios generated for the incidence of all lymphoma cases.

To effectively discuss the observed pattern in Figures 3.13 and 3.14, we show only the projected parts of the graphs. In Fig. 3.15 and Fig. 3.16, we magnify the scenarios in Figures 3.13 and 3.14 respectively, in order to see the effect of the four scenarios closely. For instance, the '60% HAART Coverage' in Fig. 3.15 shows that about a 30% projected increase in the effective delivery of

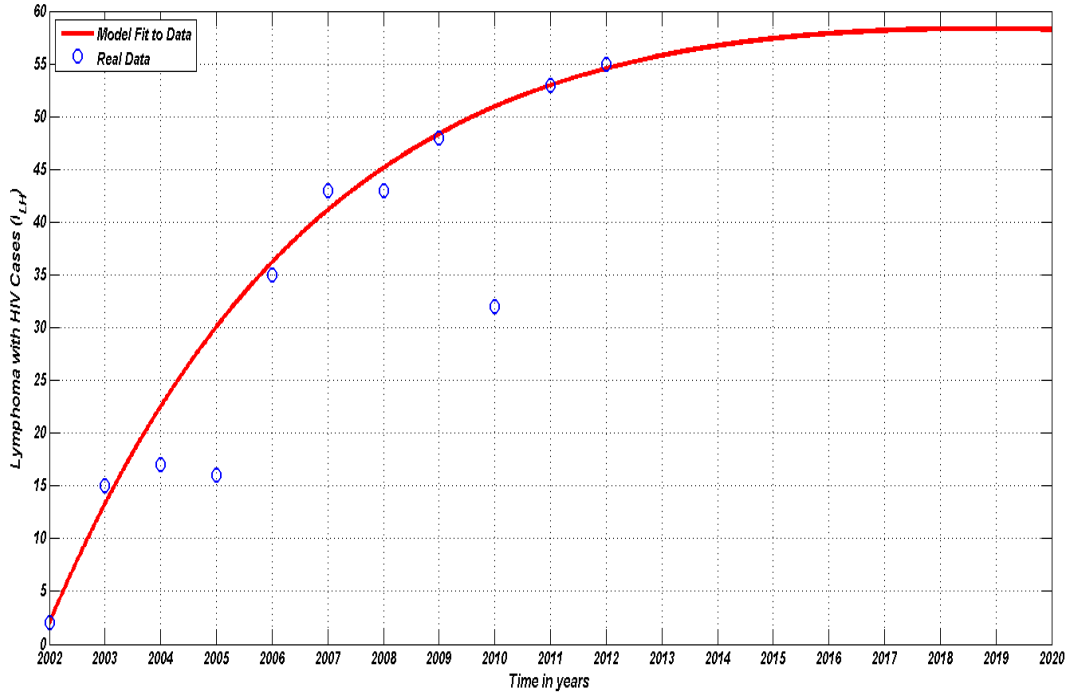

Figure 3.11: A Projection of the incidence of lymphoma in HIV-infected individuals

antiretroviral drugs to those eligible for them by 2014, will cause a 5% decline in the incidence of lymphoma (in HIV-infectives) by the year 2020. The two other scenarios (80% and 100% effective HAART delivery) even show a more significant projected derease in the incidence of lymphoma, with the 100% effective HAART coverage predicting a more rapid decline of about 8% in the incidence of lymphoma (in HIV-infectives) by 2020. In like manner, interpretation of the scenario illustrated by Fig. 3.16, which is for all lymphoma cases, can also be made.

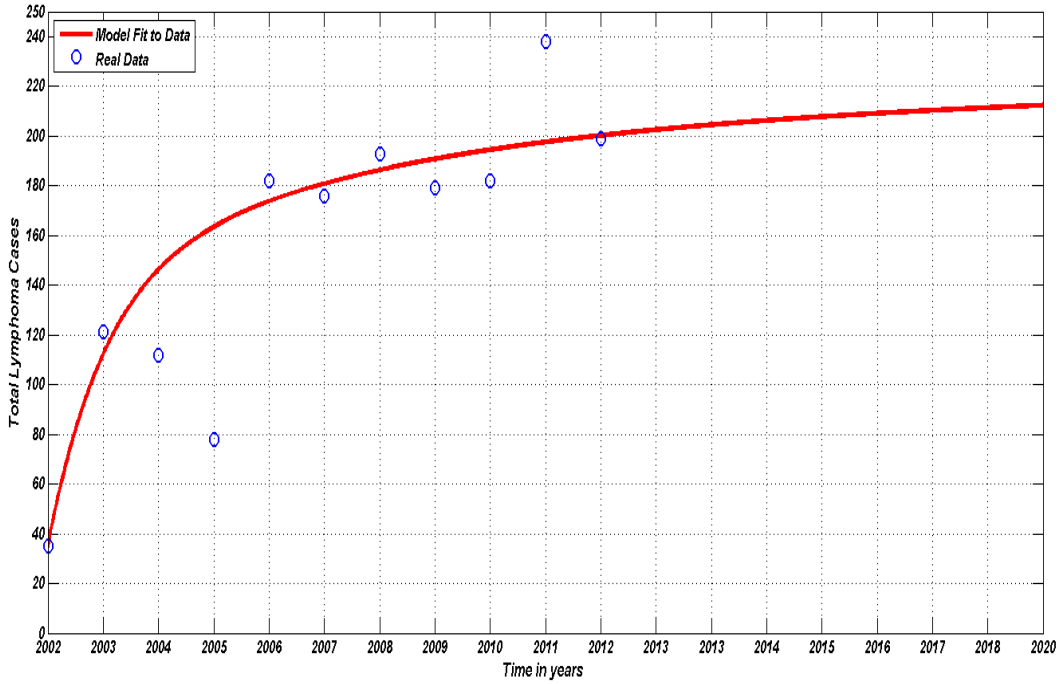

Figure 3.12: A Projection of the incidence of lymphoma in both HIV-infected and HIV-negative individuals (Total Lymphoma Cases $= I_L + I_{LH}$, as shown in Table 3.3)

3.5.4 Discussion

In this study, we present a mathematical model that explains the dynamics of HIV-related malignancies, with a closer look at the incidence of lymphoma in the Western Cape province of South Africa. We analysed the model qualitatively using its reproduction number $\mathcal{R}_0$. The model has an HIV-free lymphoma steady state which is locally stable when $\mathcal{R}_0 < 1$ and globally stable when $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, where $\mathcal{R}_0^c$ is the critical $\mathcal{R}_0$. When $\mathcal{R}_0 < 1$, the model has multiple endemic equilibria, which makes it to exhibit a backward bifurcation, and it has at least one endemic equilibrium when $\mathcal{R}_0 > 1$. We observed that when $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, HIV can be eradicated from the population under study. If HIV is eradicated from the population, then the incidence of the development of lymphoma in HIV patients is drastically reduced, and perhaps eradicated too.

We performed numerical simulations for the model. We fitted the model to lymphoma data, with the aim of making use of the model parameters that gives the best fit of our model to the data, in order to obtain lymphoma incidence curves. In order to determine which parameters have the most significant impact on the prediction imprecision of our model's $\mathcal{R}_0$, and to evaluate

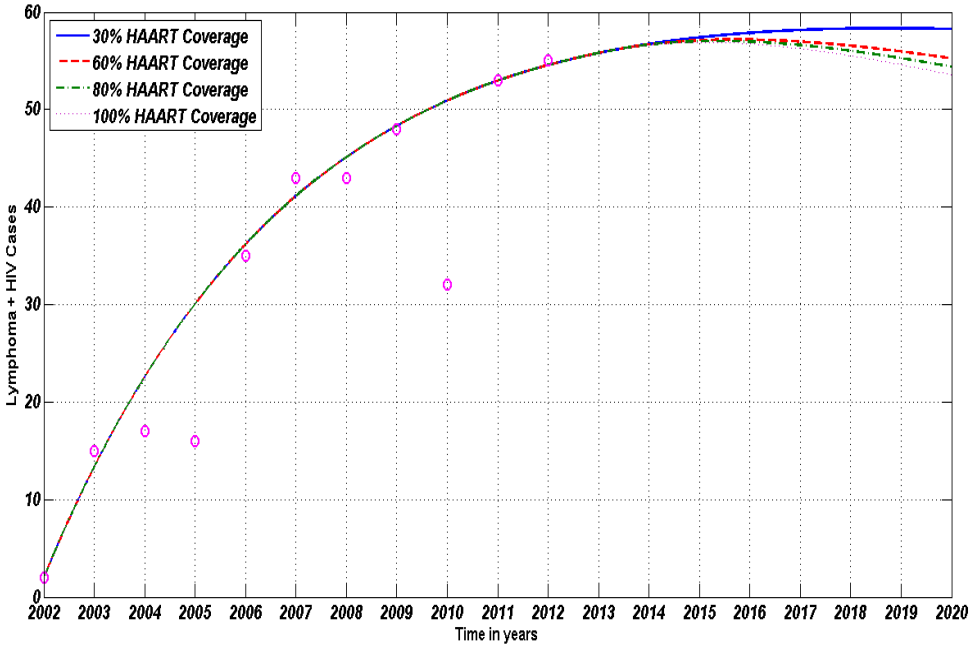

Figure 3.13: A scenario analysis of the incidence of lymphoma, for four different effective HAART coverage of HIV-infected individuals who has lymphoma (I_{LH}).

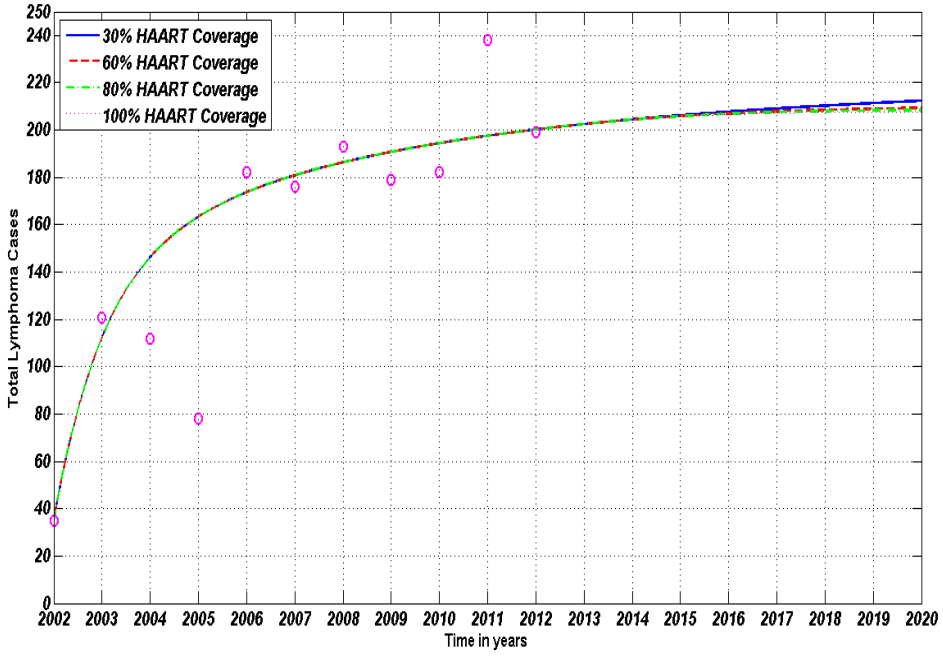

Figure 3.14: A diagrammatic illustration of the incidence of all lymphoma cases (Total Lymphoma Cases = $I_L + I_{LH}$, as shown in Table 3.3), for four different effective HAART coverage of HIV-infected individuals who has lymphoma.

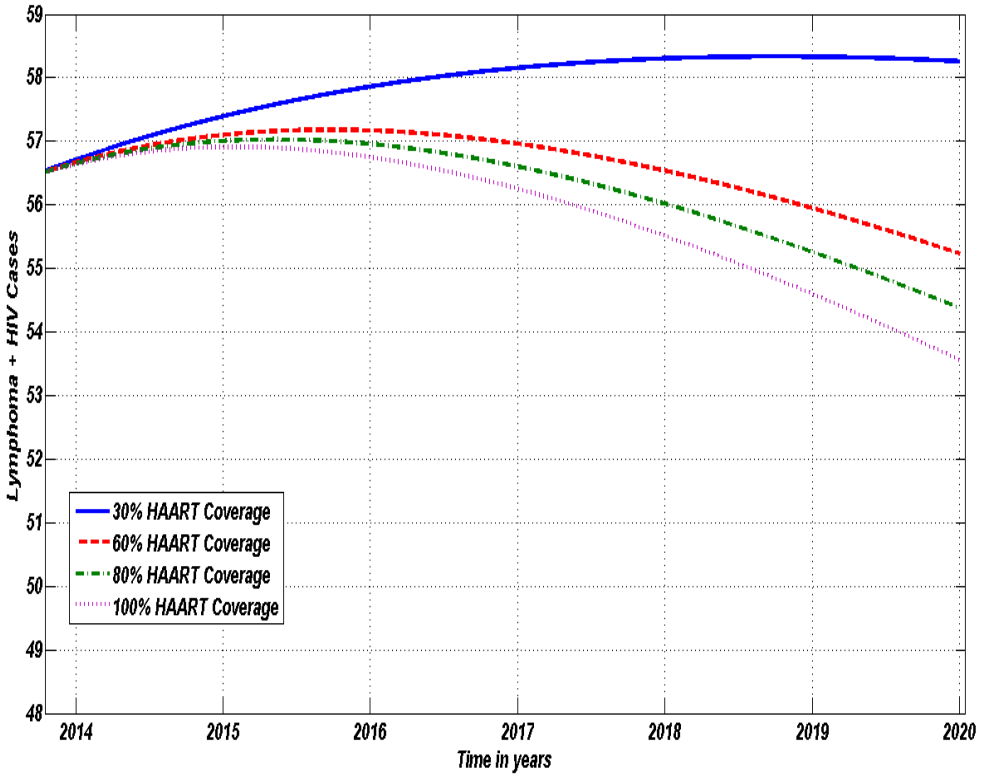

Figure 3.15: A magnified scenario analysis of the incidence of lymphoma, for four different effective HAART coverage of HIV-infected individuals who has lymphoma (I_{LH}).

the variability in $\mathcal{R}_0$ as those parameters varies, we carried out a sensitivity analysis using the Latin Hypercube Sampling (LHS) technique. This analysis demonstrates that the two parameters which are of the greatest impact on $\mathcal{R}_0$ are μ, the natural mortality rate (most negatively sensitive to $\mathcal{R}_0$), and β_1, the effective contact rate of HIV for susceptible individuals (most positively sensitive to $\mathcal{R}_0$). An increase in β_1 increases the value of $\mathcal{R}_0$. This suggests that some social intervention programs, beside HAART roll-out can be used to control the epidemic. Such programs may include increasing of the awareness of the public and educational campaigns on HIV and its significant relation to the development of malignant tumours, which even often times kills faster and in a shorter time than the HIV infection alone.

Since our model can be used as a predictive tool, we did a projection of the incidences of lymphoma in four scenarios. The scenario analysis present some probable trends the epidemic will take from 2014-2020, based on different percentage increase in the roll-out and uptake of effective of HAART coverage (as an intervention strategy) in the Western Cape province of South Africa.

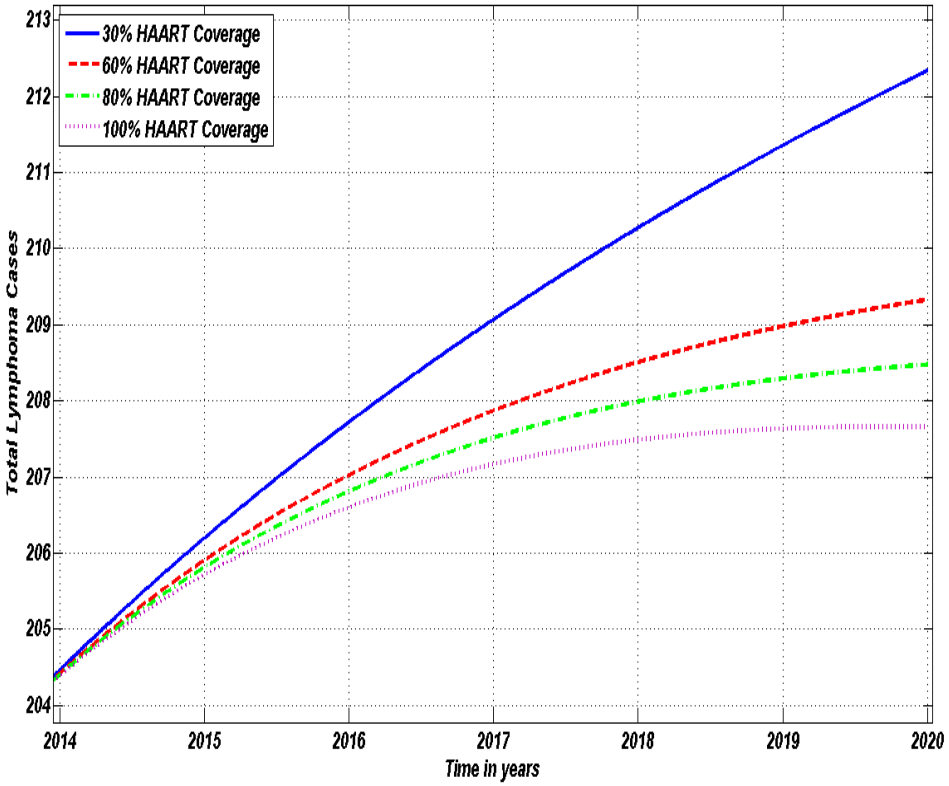

Figure 3.16: A magnified diagrammatic illustration of the incidence of all lymphoma cases (Total Lymphoma Cases $= I_L + I_{LH}$, as shown in Table 3.3), for four different effective HAART coverage of HIV-infected individuals who has lymphoma.

In 2011, the effective HAART coverage of the Western Cape province of South Africa was about 31% [27]. We discovered that an increase in the roll-out and effective use of HAART has a significant effect on the future of the epidemic, as a steady decline was observed in the incidence of lymphoma in HIV-infected individuals, which in turn caused a decline in the total lymphoma incidence. A 30% increase (that is a 60% effective HAART coverage) in the current roll-out of HAART in 2014 will cause a 5% decrease in the incidence of HRL by 2020, while a 70% increase will cause an 8% decrease in the incidence of HRL by 2020.

Furthermore, in the validation of this model, we had much predictors in comparison with the number of data points fitted. Despite the fact that we have done some statistical analysis on the basic reproduction number of the model, we must note that our efforts to ensure that the complex model explain the peculiarities of the limited lymphoma data fitted could result in overfitting. However, overfitting has been mitigated to a certain degree by the parameter sensitivity test. We may not be able to excuse the lymphoma data used from having some noise and/or slight inaccuracies, thus, it could have imposed some

errors (perhaps very little) on our model results, and thus (slightly) reduce the strength of the future demographic predictions presented in the model results.

In conclusions, it is pertinent to note that an age structured population model could have been appropriate for this population growth process. However, considering the complexity of the model, splitting the population into several age divisions will only complicate the model more and make its analysis unfeasible. Nevertheless, we must also note that tracking the population with respect to age may facilitate the incorporation of some crucial attributes of the growth process being modelled, which will in turn make the model more realistic. It may also make the model one that better explores future demographics [80; 81].

Chapter 4

CD4 Cell Count Driven HIV-Lymphoma Model

4.1 Introduction

The viral load of an HIV infected individual's body is often a predictor of how badly damaged the immune system is. It is expected that the lower the viral load, the lower the effectiveness of the HIV in depleting the immune system of the body, and thus, the lower the chances of developing any HIV-related cancer. Sathekge *et al.* [82] showed that there is an inverse correlation between the CD4 cell count and the viral load (also see [83]). This suggests that in order to decrease the viramea of an HIV infected individual, it may suffice to lower the viral load to an undetectable level, which in turn boosts the immune system and as a consequence increases the CD4 cell count.

Reports have shown that there may not be complete immune reconstitution if HAART is commenced when a patient's CD4 cell count is highly depreciated [49]. A close relationship between a low CD4 cell count and the risk of death has been established [84]. A study by Guiguet *et al* [85] reports that the most predictive risk factor for all cancers, with anal cancer as an exception, is a patient's CD4 cell count. They also reported that despite the fact that many of their patients were under combination antiretroviral therapy (cART), their patients' immunodeficiency prior to treatment was a great determinant of their immunological recovery. Patients most at risk of death were those with CD4 cell count of < 200 cells $/\mu L$. Consequently, we look at the HIV and lymphoma scenario with a special consideration for the categorisation of individuals with respect to their CD4 cell counts.

The aim of the study in this chapter is to examine the dynamic of the incidence of lymphoma in HIV patients, with respect to their CD4 cell counts. We investigate factors that the CD4 cell count level of an HIV patient affects,

and by how much it affects them. Such factors include the rate at which the patients will be treated for lymphoma and HIV, and the rate at which lymphoma develops in HIV patients. We also see how the CD4 cell count of patients infected with HIV, and of those who have developed lymphoma after HIV infection, affects the number of days they spend in the hospital. This implies that factors that can be influenced, in order to increase the number of HIV infected patients with high CD4 cell counts > 350 cells/μL, and thus cause a decline in the number of HIV infected patients with low CD4 cell counts < 350 cells/μL should be investigated.

The number of days a patient spends in the hospital and the patient's particular condition are some of the determinants of the cost of treating a patient. A South African study by Badri *et al.* [86] shows that patients with an increased severity of the HIV infection (AIDS patients) incur a more expensive hospital treatment cost in comparison with their more immunocompetent counterparts. This, they report, is likely related to AIDS-related conditions. They also report that the use of HAART is a very cost-effective intervention in the management of the HIV in the South African population, and perhaps in other sub-Saharan African populations. It is expedient that we conduct this study as it can affect governmental health policies, as to whether it is more cost effective to treat HIV infected patients at an earlier stage (with higher CD4 cell counts) than that which the current national policy has. An example is the national policy in South Africa, which only allows patients to be treated antiretrovirally when their CD4 cell count is < 350 cells/μL [87; 88]. It also shows how the CD4 cell count of HIV infected individuals affects the number of reported cases of lymphoma incidence, especially in the Western Cape of South Africa, which is our population of study.

4.2 Model Formulation

We construct a mathematical model that describes the different stages in which individuals are and can progress into, giving particular attention to individuals who are HIV infected, irrespective of whether they have developed lymphoma or not, or whether they are in any kind of treatment or not. We do this by classifying them into different categories with respect to their CD4 cell counts (and invariably their viral load). We classified every HIV infected patient's CD4 cell counts into three categories viz; patients with CD4 cell count > 350 cells/μL (which we call the class one (1) individuals), patients with CD4 cell counts that are within the closed set $[200, 350]$ cells/μL (which we call the class two (2) individuals), and patients with CD4 cell count < 200 cells/μL (which we call the class three (3) individuals). This model conceptualises and clearly exhibits the feasible scenario that can be seen in an HIV and lymphoma co-infection setting.

We consider a population $N(t)$, at time t, with ages ranging between 15 and 80 years, which we refer to as adult population. This is because lymphoma cases are much more predominant in the adult population than in the children population, with ages ranging between $0-14$ years. We also consider an adult population because HIV is more predominant among the sexually active population whose ages ranges from $15-49$ years, and because HIV and lymphoma co-infection occurs mostly in both the sexually active population and the aging population.

We subdivide this adult population $N(t)$, into ten distinct population classes, putting their infection and treatment stages into consideration. The model assumes a heterogenous mixing of individuals within the same compartment, but a homogenous mixing of individuals between non-intersecting classes. This implies that each susceptible individual is assumed to have an equal chance of being infected by an infectious individual (i.e. population mixes homogenously). The model also assumes that relapse after lymphoma treatment is negligible, which implies that individuals move out of the lymphoma-related classes with some probability after they must have been treated for their lymphoma subtypes. In addition, in order not to complicate the already complex model, the class of individuals infected with HIV only (I_H) was not categorised into different CD4 cell count classes.

The compartments the model is subdivided into include; the susceptible population $S(t)$, which comprises of individuals that are predisposed to contracting HIV and developing lymphoma (every individual introduced into the population is assumed to be susceptible), lymphoma patients $I_L(t)$, HIV-infected patients $I_H(t)$, HIV-infected patients who are under a HAART regimen $I_{HT}(t)$, (who will be referred to as HIV-positive patients under antiretroviral regimen(s)), patients co-infected with both HIV and lymphoma, and classified into either of classes one, two, or three, which we denote by $I^a_{LH}, I^b_{LH}, I^c_{LH}$ respectively, and patients co-infected with both HIV and lymphoma, under some antiretroviral regimen, and classified into either of classes one, two, or three, which we denote by I^a_{LHT}, I^b_{LHT} and I^c_{LHT} respectively. The total adult population is thus given by

$$N = S + I_L + I_H + I_{HT} + I^a_{LH} + I^b_{LH} + I^c_{LH} + I^a_{LHT} + I^b_{LHT} + I^c_{LHT}. \quad (4.2.1)$$

The recruitment of individuals into the class of susceptibles is proportional to the population, thus, the recruitment rate K is given by bN, where b is the crude birth rate (this differs from the superscript b). We thus let $K = bN_0$, where N_0 is the initial total population size. The mean lifetime of an individual is estimated as $1/\mu$, where μ is the natural mortality rate, which is common to all the compartments. The (HIV) disease-related death rates are given

by δ_1 and δ_2. The lymphoma development rate of susceptibles (which are generally HIV-negative individuals) is α_1. This model has 2 non-intersecting classes described as being susceptible to HIV infection. They are the S and I_L compartments. The model assumes a non-linear standard incidence function. The force of infection for class S, is λ_1, while the force of infection for class I_L is λ_2. We assume different forces of infection for these two groups because individuals in class S are assumed to be more immunocompetent than those in I_L, as the latter has a compromised immune system. The forces of infection $\lambda_i,\ i = 1, 2$, are given by:

$$\lambda_i = \frac{\beta_i}{N}[I_H+\eta_1(I^a_{LH}+I^b_{LH})+\eta_2(I^c_{LH}+I^c_{LHT})+\eta_3(I^a_{LHT}+I^b_{LHT})+\eta_4 I_{HT}], \quad (4.2.2)$$

provided $\lambda_i(t)$ is redefined at the ϵ-neighbourhood of $N = 0$, for it to be finite at $t = 0$ and biologically plausible. β_1 and β_2 are the effective contact rates of HIV for susceptible individuals, and for lymphoma patients respectively. β_i is a product of the number of contacts, effective or not, per unit time and the risk of infection (or probability that an infection will occur), also called transmission risk, given contact between a susceptible and an infectious individual. $\eta_i,\ i = 1, 2, 3, 4$, are the modification parameters (or adjustment factors), which measures the relative infectiousness of individuals in $I_{HT}, I^a_{LH}, I^b_{LH}, I^c_{LH}, I^a_{LHT}, I^b_{LHT}$ and I^c_{LHT} to the infectiousness of those in I_H. Individuals with high viral loads (either in the acute infection stage; window period, or at the end-stage disease) are highly infectious [54]. Thus, the likelihood of HIV-infecteds to be infectious is directly proportional to their viral loads [55]. Hence, we consider $1 \leq \eta_i \leq 2$, for all $i \in \{1, 2, 3, 4\}$.

Since the CD4 cell count is inversely proportional to the viral load of an HIV infected patient, then, the model reasonably assumes that patients with lower CD4 cell counts have higher viremia and thus a higher infectiousness than other HIV infected individuals with higher CD4 cell counts, who consequently have lower viremia and thus a lower infectiousness. As a result of this, we made additional feasible assumptions. Individuals co-infected with HIV and lymphoma, and in either of classes one or two, are assumed to have more viremia (they are neither treated for HIV or lymphoma) than individuals co-infected with HIV and lymphoma who are also in either of class one or two, but on antiretroviral treatment for HIV. Thus, $\eta_1 > \eta_4$, and η_4.

Similarly, we assumed that $\eta_3 > \eta_4$, since patients co-infected with HIV and lymphoma, in classes one or two, and under antiretroviral treatment are assumed to be more immunocompromised than individuals who are infected with HIV alone, and under some antiretroviral treatment. Furthermore, individuals co-infected with HIV and lymphoma and in class three (whether on antiretroviral treatment or not) are considered the most immunocompromised

individuals of all the classes (they have the highest level of viremia), for which reason they are assumed to be the most infectious of all the classes. Thus, $\eta_2 > 1, \eta_1, \eta_3$, and η_4. Outlined in Table 4.1 are the descriptions and symbols of state variables used in the model. Table 4.2 also outlines other epidemiological parameters, with their symbols and descriptions.

The schematic flow of individuals between the ten compartments is illustrated by the model diagram shown in Figure 4.1.

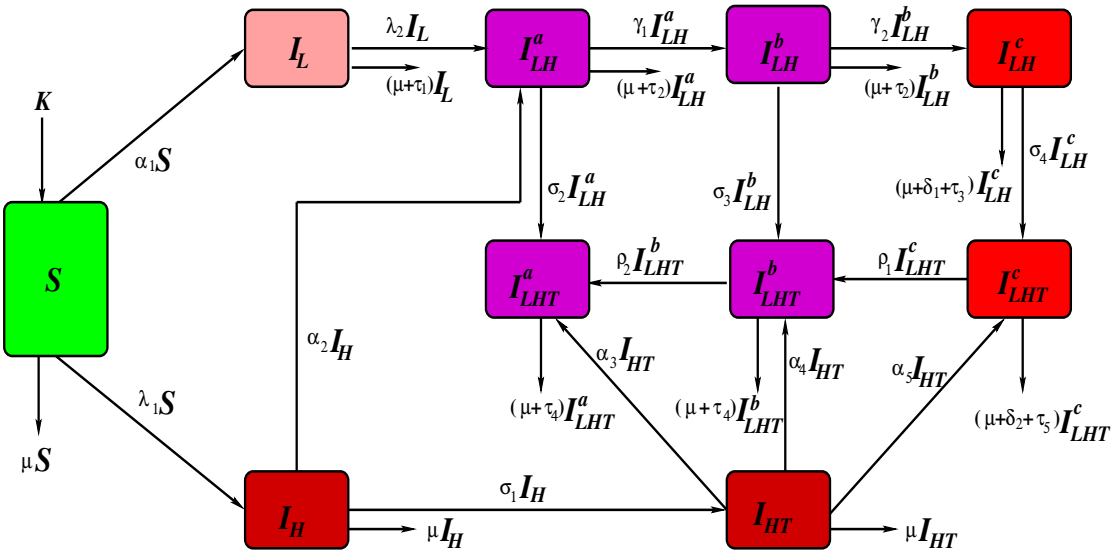

Figure 4.1: Diagrammatic structure of the HIV-Lymphoma cum CD4 cell count driven model system

Variables	Description
S	Susceptible individuals
I_L	Lymphoma patients
I_H	HIV-positive patients
I_{HT}	HIV-positive patients under antiretroviral regimen(s)
I_{LH}^a	Patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells/μL
I_{LH}^b	Patients with both HIV and lymphoma and whose CD4 cell count ranges between $[200, 350]$ cells/μL
I_{LH}^c	Patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells/μL
I_{LHT}^a	Patients with both HIV and lymphoma, under antiretroviral regimen(s), and with CD4 cell count that is > 350 cells/μL
I_{LHT}^b	Patients with both HIV and lymphoma, under antiretroviral regimen(s), and with CD4 cell count that ranges between $[200, 350]$ cells/μL
I_{LHT}^c	Patients with both HIV and lymphoma, under antiretroviral regimen(s), and with CD4 cell count that is < 200 cells/μL
N	Total size of (adult) population

Table 4.1: Symbols and description of the variables used in the model

Parameters	Description
K	Recruitment rate for susceptibles
μ	Natural mortality rate
δ_1	Disease and low CD4 cell count induced mortality rate (for individuals in class I^c_{LH})
δ_2	Disease and low CD4 cell count induced mortality rate (for individuals in class I^c_{LHT})
λ_1	Force of (HIV) infection of susceptible individuals
λ_2	Force of (HIV) infection of lymphoma patients
β_1	Effective contact rate of HIV for susceptible individuals
β_2	Effective contact rate of HIV for lymphoma patients
α_1	Lymphoma development rate of susceptible individuals
α_2	Lymphoma development rate of HIV-positive patients (into class I^a_{LH})
α_3	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^a_{LHT})
α_4	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^b_{LHT})
α_5	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^c_{LHT})
σ_1	HIV treatment rate of lymphoma-free HIV patients
σ_2	HIV treatment rate of patients with lymphoma and HIV and in class I^a_{LH}
σ_3	HIV treatment rate of patients with lymphoma and HIV and in class I^b_{LH}
σ_4	HIV treatment rate of patients with lymphoma and HIV and in class I^c_{LH}
τ_1	Lymphoma treatment rate of lymphoma-only patients
τ_2	Lymphoma treatment rate of patients with lymphoma and HIV and in either class I^a_{LH} or I^b_{LH}
τ_3	Lymphoma treatment rate of patients with lymphoma and HIV and in class I^c_{LH}
τ_4	Lymphoma treatment rate of patients with lymphoma, HIV, under antiretroviral regimen(s) and in class I^a_{LHT} or I^b_{LHT}
τ_5	Lymphoma treatment rate of patients with lymphoma, HIV, under antiretroviral regimen(s) and in class I^c_{LHT}
γ_1	CD4 cell count declination rate (rate of immune system deteroriation) of individuals in class I^a_{LH}
γ_2	CD4 cell count declination rate (rate of immune system deteroriation) of individuals in class I^b_{LH}
ρ_1	CD4 cell count upswing rate (rate of immune system amelioration) of individuals in class I^c_{LHT}
ρ_2	CD4 cell count upswing rate (rate of immune system amelioration) of individuals in class I^b_{LHT}

Table 4.2: Symbols and description of the parameters used in the model

4.2.1 Model Equations

The dynamical system described by the schematic diagram , Figure 4.1, our assumptions and parameters' description, is given by the following system of ordinary differential equations:

$$\frac{dS}{dt} = K - \lambda_1 S - (\mu + \alpha_1)S, \tag{4.2.3a}$$
$$\frac{dI_L}{dt} = \alpha_1 S - \lambda_2 I_L - (\mu + \tau_1)I_L, \tag{4.2.3b}$$
$$\frac{dI_H}{dt} = \lambda_1 S - (\mu + \sigma_1 + \alpha_2)I_H, \tag{4.2.3c}$$
$$\frac{dI_{HT}}{dt} = \sigma_1 I_H - (\mu + \alpha_3 + \alpha_4 + \alpha_5)I_{HT}, \tag{4.2.3d}$$
$$\frac{dI^a_{LH}}{dt} = \lambda_2 I_L + \alpha_2 I_H - (\mu + \tau_2 + \sigma_2 + \gamma_1)I^a_{LH}, \tag{4.2.3e}$$
$$\frac{dI^b_{LH}}{dt} = \gamma_1 I^a_{LH} - (\mu + \tau_2 + \sigma_3 + \gamma_2)I^b_{LH}, \tag{4.2.3f}$$
$$\frac{dI^c_{LH}}{dt} = \gamma_2 I^b_{LH} - (\mu + \delta_1 + \tau_3 + \sigma_4)I^c_{LH}, \tag{4.2.3g}$$
$$\frac{dI^a_{LHT}}{dt} = \sigma_2 I^a_{LH} + \alpha_3 I_{HT} + \rho_2 I^b_{LHT} - (\mu + \tau_4)I^a_{LHT}, \tag{4.2.3h}$$
$$\frac{dI^b_{LHT}}{dt} = \sigma_3 I^b_{LH} + \alpha_4 I_{HT} + \rho_1 I^c_{LHT} - (\mu + \tau_4 + \rho_2)I^b_{LHT} \tag{4.2.3i}$$
$$\frac{dI^c_{LHT}}{dt} = \sigma_4 I^c_{LH} + \alpha_5 I_{HT} - (\mu + \delta_2 + \tau_5 + \rho_1)I^c_{LHT}, \tag{4.2.3j}$$

with initial conditions of the model system given by $S(0) = S_0, I_L(0) = I_{L0}, I_H(0) = I_{H0}, I^a_{LH}(0) = (I^a_{LH})_0, I^b_{LH}(0) = (I^b_{LH})_0, I^c_{LH}(0) = (I^c_{LH})_0, I^a_{LHT}(0) = (I^a_{LHT})_0, I^b_{LHT}(0) = (I^b_{LHT})_0$ and $I^c_{LHT}(0) = (I^c_{LHT})_0$, all positive constants.

4.3 Basic Properties of the Model

4.3.1 Invariant Region

The model system (4.2.3) studies human population variations under certain conditions of biological and mathematical interest. State variables and parameters are thereby assumed to be positive, since their negativity makes no biological sense. We analyse the model system (4.2.3) in an apposite biologically feasible region Ω. We show that the system is dissipative, in that every viable solution is uniformly bounded in a proper subset Ω of $\mathbb{R}^{10}_+$. Hence the following lemma.

Lemma 4.3.1. *The biologically feasible region* Ω *defined by the compact set:*

$$\Omega = \{(S, I_L, I_H, I_{HT}, I^a_{LH}, I^b_{LH}, I^c_{LH}, I^a_{LHT}, I^b_{LHT}, I^c_{LHT}) \in \mathbb{R}^{10}_+ : N \leq \frac{K}{\mu}\}$$

with initial conditions $S(0), I_L(0), I_H(0), I_{HT}(0), I^a_{LH}(0), I^b_{LH}(0), I^c_{LH}(0), I^a_{LHT}(0), I^b_{LHT}(0), I^c_{LHT}(0) > 0$*, is positively invariant and attracting with respect to the model system* (4.2.3) *for all* $t > 0$.

Proof. We sum up the equations of the model (4.2.3), and the total adult population $N(t)$ is time variable with

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= K - \mu N - \tau_1 I_L - \tau_2 I^a_{LH} - \tau_2 I^b_{LH} - (\delta_1 + \tau_3) I^c_{LH} - \tau_4 I^a_{LHT} - \tau_4 I^b_{LHT} \\
&\quad - (\delta_2 + \tau_5) I^c_{LHT}, \\
&\leq K - \mu N, \\
&\implies \frac{dN}{dt} + \mu N \leq K.
\end{aligned} \tag{4.3.1}$$

Using the integrating factor $\mathrm{e}^{\int \mu \mathrm{d}t}$,

equation (4.3.1) becomes

$$\begin{aligned}
&\frac{d(N\mathrm{e}^{\mu t})}{\mathrm{d}t} \leq K\mathrm{e}^{\int \mu dt} \quad \text{(integrate both sides)}, \\
&\implies N\mathrm{e}^{\mu t} \leq \frac{K}{\mu}\mathrm{e}^{\mu t} + C, \\
&\implies N(t) \leq \frac{K}{\mu} + C\mathrm{e}^{-\mu t}.
\end{aligned} \tag{4.3.2}$$

When $t = 0$, $N(0) = N_0$ (the sum of all the initial values of the state variables of the model), we obtain

$$C = N_0 - \frac{K}{\mu}.$$

$$\begin{aligned}
\implies N(t) &\leq \frac{K}{\mu} + (N_0 - \frac{K}{\mu})\mathrm{e}^{-\mu t}, \\
&= N_0\mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}).
\end{aligned} \tag{4.3.3}$$

As $t \longrightarrow \infty$, we have: $\limsup_{t\to\infty} N(t) \leq \dfrac{K}{\mu}$.

Whenever $N(0) \leq \dfrac{K}{\mu}$,

$$\begin{aligned} N(t) &\leq N_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}), \\ \Longrightarrow N(t) &\leq \frac{K}{\mu}. \end{aligned} \tag{4.3.4}$$

Hence, every solution $N(t)$ of equation (4.3.1) satisfies the relation below;

$$0 \leq N(t) \leq N_0 \mathrm{e}^{-\mu t} + \frac{K}{\mu}(1 - \mathrm{e}^{-\mu t}), \tag{4.3.5}$$

where N_0 is the sum of all the initial conditions of the variables of the model system.

Whenever $N_0 \leq \frac{K}{\mu}$, positive solutions of equation (4.3.1) are increasingly monotonically and are bounded above by $\frac{K}{\mu}$. On the other hand, whenever $N_0 > \frac{K}{\mu}$, non-negative solutions of equation (4.3.1) are monotone decreasing and bounded below by $\frac{K}{\mu}$. Nevertheless, in both cases, at limiting equilibrium, $\lim_{t\to\infty} N(t) = \frac{K}{\mu}$.

Consequently, any solution

$$S(t), I_L(t), I_H(t), I_{HT}(t), I^a_{LH}(t), I^b_{LH}(t), I^c_{LH}(t), I^a_{LHT}(t), I^b_{LHT}(t), I^c_{LHT}(t),$$

at $t \geq 0$, of (4.2.3) that starts in the positive orthant $\mathbb{R}^{10}_+$, either remains confined in, enters or asymptotically approaches Ω. Therefore, the region Ω is positively invariant and attracting with respect to the flow incited by the model system (4.2.3). This completes the proof. □

Hence, in Ω, the model (4.2.3) is mathematically and epidemiologically well-posed. Thus, it is sufficient to study the dynamics of the flow induced by the model system (4.2.3) in Ω.

4.3.2 Positivity of Solutions

It is salient we prove that all the state variables of the model system (4.2.3) remain non-negative for all time $t > 0$. This is to certify that the model system is biologically meaningful, and to ensure that solutions of the system, when subjected to positive initial conditions, will remain positive for all $t > 0$. Hence the following lemma.

Lemma 4.3.2. *Given that the initial values of the state variables of the model system (4.2.3) are non-negative, the model equations (4.2.3a) - (4.2.3j) preserve positivity of solutions for all time $t > 0$.*

Proof. Assume that

$$\hat{t} = \sup\{t > 0 : S, I_L, I_H, I_{HT}, I^a_{LH}, I^b_{LH}, I^c_{LH}, I^a_{LHT}, I^b_{LHT}, I^c_{LHT} > 0\} \in [0, t]$$

From equation (4.2.3a),

$$\begin{aligned} \frac{dS}{dt} &= K - (\lambda_1 + \mu + \alpha_1)S, \\ \frac{dS}{dt} &+ (\lambda_1 + \mu + \alpha_1)S = K. \end{aligned} \tag{4.3.6}$$

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

$$IF = \mathrm{e}^{\int_0^t (\mu+\alpha_1+\lambda_1(\omega))\,\mathrm{d}\omega} = \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]},$$

is a suitable IF.

Equation (4.3.6) becomes

$$\begin{aligned} & \frac{d}{dt}\left[S(t)\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\right] = K\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]} \\ \Longrightarrow \quad & \int_{S(0)}^{S(\hat{t})} d\left[S(t)\mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\right] = K\int_0^{\hat{t}} \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\,dt \end{aligned} \tag{4.3.7}$$

$$\begin{aligned} \Longrightarrow \quad & S(\hat{t}) = \mathrm{e}^{-[(\mu+\alpha_1)\hat{t}+\int_0^{\hat{t}} \lambda_1(\omega))\,\mathrm{d}\omega]}\left[S(0) + K\int_0^{\hat{t}} \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\,dt\right] \\ & S(\hat{t}) \geq \mathrm{e}^{-[(\mu+\alpha_1)\hat{t}+\int_0^{\hat{t}} \lambda_1(\omega))\,\mathrm{d}\omega]}\int_0^{\hat{t}} \mathrm{e}^{[(\mu+\alpha_1)t+\int_0^t \lambda_1(\omega))\,\mathrm{d}\omega]}\,dt \\ & S(\hat{t}) > 0, \quad \forall\ \hat{t} > 0. \end{aligned} \tag{4.3.8}$$

From equation (4.2.3b),

$$\begin{aligned} \frac{\mathrm{d}I_L}{\mathrm{d}t} &= \alpha_1 S - (\lambda_2(t) + \tau_1 + \mu)I_L, \\ &\geq -(\lambda_2(t) + \tau_1 + \mu)I_L, \\ \Longrightarrow \quad \frac{\mathrm{d}I_L}{\mathrm{d}t} &+ (\lambda_2(t) + \tau_1 + \mu)I_L \geq 0. \end{aligned} \tag{4.3.9}$$

Using the IF given by

$$IF = \mathrm{e}^{\int_0^t [(\mu+\tau_1)+\lambda_2(\omega)]\,\mathrm{d}\omega} = \mathrm{e}^{[(\mu+\tau_1)t+\int_0^t \lambda_2(\omega)\,\mathrm{d}\omega]},$$

equation (4.3.9) becomes

$$\begin{aligned}
&\int_{I_L(0)}^{I_L(\hat{t})} \mathrm{d}\left[I_L(t)\mathrm{e}^{[(\mu+\tau_1)t+\int_0^t \lambda_2(\omega)\,\mathrm{d}\omega]}\right] \geq 0,\\
&\implies I_L(\hat{t})\mathrm{e}^{[(\mu+\tau_1)\hat{t}+\int_0^{\hat{t}} \lambda_2(\omega)\,\mathrm{d}\omega]} \geq I_L(0),\\
&\implies I_L(\hat{t}) \geq I_L(0)\left(\mathrm{e}^{-[(\mu+\tau_1)\hat{t}+\int_0^{\hat{t}} \lambda_2(\omega)\,\mathrm{d}\omega]}\right),\\
&\implies I_L(\hat{t}) > 0 \quad \forall\, \hat{t} > 0.
\end{aligned} \tag{4.3.10}$$

From equation (4.2.3c),

$$\begin{aligned}
\frac{\mathrm{d}I_H}{\mathrm{d}t} &\geq (\mu+\sigma_1+\alpha_2)I_H,\\
\Rightarrow \int_{I_H(0)}^{I_H(\hat{t})} &\geq \int_0^{\hat{t}} -(\mu+\sigma_1+\alpha_2)\mathrm{d}t,\\
\Rightarrow \ln\left(\frac{I_H(\hat{t})}{I_H(0)}\right) &\geq -(\mu+\sigma_1+\alpha_2)\hat{t},\\
\Rightarrow I_H(\hat{t}) &\geq I_H(0)\mathrm{e}^{-(\mu+\sigma_1+\alpha_2)\hat{t}}.\\
\text{Hence, } I_H(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0.
\end{aligned} \tag{4.3.11}$$

From equation (4.2.3d),

$$\begin{aligned}
\frac{\mathrm{d}I_{HT}}{\mathrm{d}t} &\geq (\mu+\alpha_3+\alpha_4+\alpha_5)I_{HT},\\
\Rightarrow \int_{I_{HT}(0)}^{I_{HT}(\hat{t})} &\geq \int_0^{\hat{t}} -(\mu+\alpha_3+\alpha_4+\alpha_5)\mathrm{d}t,\\
\Rightarrow \ln\left(\frac{I_{HT}(\hat{t})}{I_{HT}(0)}\right) &\geq -(\mu+\alpha_3+\alpha_4+\alpha_5)\hat{t},\\
\Rightarrow I_{HT}(\hat{t}) &\geq I_{HT}(0)\mathrm{e}^{-(\mu+\alpha_3+\alpha_4+\alpha_5)\hat{t}}.\\
\text{Hence, } I_{HT}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0.
\end{aligned} \tag{4.3.12}$$

Similarly, from equation (4.2.3e),

$$\begin{aligned} \frac{\mathrm{d}I^a_{LH}}{\mathrm{d}t} &\geq (\mu+\tau_2+\gamma_1+\sigma_2)I^a_{LH}, \\ \Rightarrow\ I^a_{LH}(\hat{t}) &\geq I^a_{LH}(0)\mathrm{e}^{-(\mu+\tau_2+\gamma_1+\sigma_2)\hat{t}}. \\ \text{Hence,}\ \ I^a_{LH}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.13}$$

From equation (4.2.3f),

$$\begin{aligned} \frac{\mathrm{d}I^b_{LH}}{\mathrm{d}t} &\geq (\mu+\tau_2+\gamma_2+\sigma_3)I^b_{LH}, \\ \Rightarrow\ I^b_{LH}(\hat{t}) &\geq I^b_{LH}(0)\mathrm{e}^{-(\mu+\tau_2+\gamma_2+\sigma_3)\hat{t}}. \\ \text{Hence,}\ \ I^b_{LH}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.14}$$

From equation (4.2.3g),

$$\begin{aligned} \frac{\mathrm{d}I^c_{LH}}{\mathrm{d}t} &\geq (\mu+\delta_1+\tau_3+\sigma_4)I^c_{LH}, \\ \Rightarrow\ I^c_{LH}(\hat{t}) &\geq I^c_{LH}(0)\mathrm{e}^{-(\mu+\delta_1+\tau_3+\sigma_4)\hat{t}}. \\ \text{Hence,}\ \ I^c_{LH}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.15}$$

From equation (4.2.3h),

$$\begin{aligned} \frac{\mathrm{d}I^a_{LHT}}{\mathrm{d}t} &\geq (\mu+\tau_4)I^a_{LHT}, \\ \Rightarrow\ I^a_{LHT}(\hat{t}) &\geq I^a_{LHT}(0)\mathrm{e}^{-(\mu+\tau_4)\hat{t}}. \\ \text{Hence,}\ \ I^a_{LHT}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.16}$$

From equation (4.2.3i),

$$\begin{aligned} \frac{\mathrm{d}I^b_{LHT}}{\mathrm{d}t} &\geq (\mu+\tau_4+\rho_2)I^b_{LHT}, \\ \Rightarrow\ I^b_{LHT}(\hat{t}) &\geq I^b_{LHT}(0)\mathrm{e}^{-(\mu+\tau_4+\rho_2)\hat{t}}. \\ \text{Hence,}\ \ I^b_{LHT}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.17}$$

From equation (4.2.3j),

$$\begin{aligned} \frac{\mathrm{d}I^c_{LHT}}{\mathrm{d}t} &\geq (\mu + \delta_2 + \tau_5 + \rho_1) I^c_{LHT}, \\ \Rightarrow\ I^c_{LHT}(\hat{t}) &\geq I^c_{LHT}(0)\mathrm{e}^{-(\mu+\delta_2+\tau_5+\rho_1)\hat{t}}. \\ \text{Hence,}\ \ I^c_{LHT}(\hat{t}) &> 0, \quad \forall\, \hat{t} > 0. \end{aligned} \tag{4.3.18}$$

Thus, equations (4.3.8)-(4.3.18) shows that every solution of the state variables of model system (4.2.3) will always be positive for all non-negative initial conditions, at any time $\hat{t} > 0$. This completes the proof.

□

4.3.3 Existence and Uniqueness of Solutions

Theorem 4.3.3. *Solutions of the model system (4.2.3) exists, and is unique in Ω, for all time $t > 0$, and for every non-negative and non-zero initial values of the state variables of the model.*

Proof. Since the right hand side of the model system (4.2.3) is locally Lipschitz continuous, then local existence and uniqueness of solutions is ascertained. □

4.4 Equilibria Analysis of the Model

In this section, analytic results of the model system (4.2.3) are displayed. We analyse the system by finding the model equilibria and investigate their stability analyses using the basic reproduction number $\hat{\mathcal{R}}_0$.

4.4.1 CD4-HIV-free Lymphoma Steady State (CHLSS)

In the absence of the HIV in our model system, that is, setting $I_H = I_{HT} = I^a_{LH} = I^b_{LH} = I^c_{LH} = I^a_{LHT} = I^b_{LHT} = I^c_{LHT} = 0$, we first obtain an equilibrium point which we refer to as the CD4 Count-Categorised System HIV-free Lymphoma Steady State. For the purpose of brevity, we will refer to this as the CD4-HIV-free Lymphoma Steady State (CHLSS), and it is denoted by $\hat{E}_0$. This was obtained by setting the right hand side of the system (4.2.3) to zero and we determined the state variables.

Note that

$$I_H = I_{HT} = I^a_{LH} = I^b_{LH} = I^c_{LH} = I^a_{LHT} = I^b_{LHT} = I^c_{LHT} = 0 \quad \Longrightarrow \lambda_1 = \lambda_2 = 0.$$

We have

$$\begin{aligned} K - p_1 S^{**} &= 0, \quad \text{where } p_1 = \mu + \alpha_1 \\ \implies \quad S^{**} &= \frac{K}{p_1} = \frac{K}{\mu + \alpha_1} \end{aligned} \tag{4.4.1}$$

$$\begin{aligned} \alpha_1 S^{**} - p_2 I_L^{**} &= 0, \quad \text{where } p_2 = \mu + \tau_1 \\ \implies \quad I_L^{**} &= \frac{\alpha_1 K}{p_1 p_2} = \frac{\alpha_1 K}{(\mu + \alpha_1)(\mu + \tau_1)} \end{aligned} \tag{4.4.2}$$

Hence, the model system (4.2.3) has an equilibrium point, the CD4-HIV-free Lymphoma Steady State $\hat{E}_0$, and it is given by

$$\hat{E}_0 = \left(\frac{K}{\mu + \alpha_1}, \frac{\alpha_1 K}{(\mu + \alpha_1)(\mu + \tau_1)}, 0, 0, 0, 0, 0, 0, 0, 0 \right). \tag{4.4.3}$$

Note that

$$N^{**} = \frac{K(\mu + \tau_1 + \alpha_1)}{(\mu + \alpha_1)(\mu + \tau_1)}. \tag{4.4.4}$$

4.4.2 Model Basic Reproduction Number

Using the same procedure as in *Subsection* 3.4.2, we obtain the reproduction number $\hat{\mathcal{R}}_0$ of the model system (4.2.3).

Let

$$\begin{aligned} \hat{C}_S &= \frac{S^{**}}{N^{**}}, \\ \hat{C}_L &= \frac{I_L^{**}}{N^{**}}. \end{aligned}$$

The matrices $\hat{F}$ and $\hat{V}$, which represent the *transmission part* and *transition part* respectively, of the infected subsystem (4.2.3c) - (4.2.3j) are given by

$$\hat{F} = \begin{pmatrix} \hat{C}_S\beta_1 & \hat{C}_S\beta_1\eta_4 & \hat{C}_S\beta_1\eta_1 & \hat{C}_S\beta_1\eta_1 & \hat{C}_S\beta_1\eta_2 & \hat{C}_S\beta_1\eta_3 & \hat{C}_S\beta_1\eta_3 & \hat{C}_S\beta_1\eta_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hat{C}_L\beta_2 & \hat{C}_L\beta_2\eta_4 & \hat{C}_L\beta_2\eta_1 & \hat{C}_L\beta_2\eta_1 & \hat{C}_L\beta_2\eta_2 & \hat{C}_L\beta_2\eta_3 & \hat{C}_L\beta_2\eta_3 & \hat{C}_L\beta_2\eta_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{4.4.5}$$

and

$$\hat{V} = \begin{pmatrix} p_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_1 & p_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_2 & 0 & p_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma_1 & p_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\gamma_2 & p_7 & 0 & 0 & 0 \\ 0 & -\alpha_3 & -\sigma_2 & 0 & 0 & p_8 & -\rho_2 & 0 \\ 0 & -\alpha_4 & 0 & -\sigma_3 & 0 & 0 & p_9 & -\rho_1 \\ 0 & -\alpha_5 & 0 & 0 & -\sigma_4 & 0 & 0 & p_{10} \end{pmatrix}, \tag{4.4.6}$$

where $p_1 = \mu + \alpha_1,\ p_2 = \mu + \tau_1,\ p_3 = \mu + \sigma_1 + \alpha_2,\ p_4 = \mu + \alpha_3 + \alpha_4 + \alpha_5,\ p_5 = \mu + \tau_2 + \sigma_2 + \gamma_1, p_6 = \mu + \tau_2 + \sigma_3 + \gamma_2,\ p_7 = \mu + \delta_1 + \tau_3 + \sigma_4,\ p_8 = \mu + \tau_4,\ p_9 = \mu + \tau_4 + \rho_2,\ p_{10} = \mu + \delta_2 + \tau_5 + \rho_1,\ p_i \in \mathbb{R}^+$ (positive constants), $\forall\ i = 1, 2, \cdots, 10$.

The next generation matrix for the infected subsystem of model (4.2.3) is $\hat{F}\hat{V}^{-1}$, with the matrices as defined above and the *spectral radius* of $\hat{\mathcal{R}}_0$ is given by

$$\hat{\mathcal{R}}_0 = \rho(FV^{-1}). \tag{4.4.7}$$

The reproduction number $\hat{\mathcal{R}}_0$ of the model (4.2.3) was obtained to be an aggregate of contributions from the infected compartments of the different stages of the model system. It is given by

$$\hat{\mathcal{R}}_0 = \hat{\mathcal{R}}_0^{I_H} + \hat{\mathcal{R}}_0^{I_{HT}} + \hat{\mathcal{R}}_0^{I_{LH}^a} + \hat{\mathcal{R}}_0^{I_{LH}^b} + \hat{\mathcal{R}}_0^{I_{LH}^c} + \hat{\mathcal{R}}_0^{I_{LHT}^a} + \hat{\mathcal{R}}_0^{I_{LHT}^b} + \hat{\mathcal{R}}_0^{I_{LHT}^c}, \tag{4.4.8}$$

where

$$\hat{\mathcal{R}}_0^{I_H} = \frac{\hat{C}_S\,\beta_1}{p_3},$$

$$
\begin{aligned}
\hat{\mathcal{R}}_0^{I_{HT}} &= \frac{\hat{C}_S\,\beta_1\,\eta_4\,\sigma_1}{p_3\,p_4},\\
\hat{\mathcal{R}}_0^{I^a_{LH}} &= \frac{1}{p_5}\left[\frac{\hat{C}_S\,\alpha_2\,\beta_1\,\eta_1}{p_3} + \hat{C}_L\,\beta_2\,\eta_1\right],\\
\hat{\mathcal{R}}_0^{I^b_{LH}} &= \frac{1}{p_6}\left[\frac{\hat{C}_S\,\alpha_2\,\beta_1\,\gamma_1\,\eta_1}{p_3\,p_5} + \frac{\hat{C}_L\,\beta_2\,\gamma_1\,\eta_1}{p_5}\right],\\
\hat{\mathcal{R}}_0^{I^c_{LH}} &= \frac{1}{p_7}\left[\frac{\hat{C}_S\,\alpha_2\,\beta_1\,\gamma_1\,\gamma_2\,\eta_2}{p_3\,p_5\,p_6} + \frac{\hat{C}_L\,\beta_2\,\gamma_1\,\gamma_2\,\eta_2}{p_5\,p_6}\right],\\
\hat{\mathcal{R}}_0^{I^a_{LHT}} &= \frac{1}{p_8}\left[\hat{C}_L\,\beta_2\,\eta_3\left(\frac{\sigma_2}{p_5} + \frac{\gamma_1\,\rho_2\,\sigma_3}{p_5\,p_6\,p_9} + \frac{\gamma_1\,\gamma_2\,\rho_1\,\rho_2\,\sigma_4}{p_5\,p_6\,p_7\,p_9\,p_{10}}\right) + \hat{C}_S\,\beta_1\,\eta_3\left(\frac{\alpha_3\,\sigma_1}{p_3\,p_4}\right.\right.\\
&\quad \left.\left. + \frac{\alpha_4\,\rho_2\,\sigma_1}{p_3\,p_4\,p_9} + \frac{\alpha_5\,\rho_1\,\rho_2\,\sigma_1}{p_3\,p_4\,p_9\,p_{10}} + \frac{\alpha_2\,\sigma_2}{p_3\,p_5} + \frac{\alpha_2\,\gamma_1\,\rho_2\,\sigma_3}{p_3\,p_5\,p_6\,p_9} + \frac{\alpha_2\,\gamma_1\,\gamma_2\,\rho_1\,\rho_2\,\sigma_4}{p_3\,p_5\,p_6\,p_7\,p_9\,p_{10}}\right)\right],\\
\hat{\mathcal{R}}_0^{I^b_{LHT}} &= \frac{1}{p_9}\left[\hat{C}_L\,\beta_2\,\eta_3\left(\frac{\gamma_1\,\sigma_3}{p_5\,p_6} + \frac{\gamma_1\,\gamma_2\,\rho_1\,\sigma_4}{p_5\,p_6\,p_7\,p_{10}}\right) + \hat{C}_S\,\beta_1\,\eta_3\left(\frac{\alpha_4\,\sigma_1}{p_3\,p_4} + \frac{\alpha_5\,\rho_1\,\sigma_1}{p_3\,p_4\,p_{10}}\right.\right.\\
&\quad \left.\left. + \frac{\alpha_2\,\gamma_1\,\sigma_3}{p_3\,p_5\,p_6} + \frac{\alpha_2\,\gamma_1\,\gamma_2\,\rho_1\,\sigma_4}{p_3\,p_5\,p_6\,p_7\,p_{10}}\right)\right],\\
\hat{\mathcal{R}}_0^{I^c_{LHT}} &= \frac{1}{p_{10}}\left[\frac{\hat{C}_L\,\beta_2\,\gamma_1\,\gamma_2\,\eta_2\,\sigma_4}{p_5\,p_6\,p_7} + \hat{C}_S\,\beta_1\,\eta_2\left(\frac{\alpha_5\,\sigma_1}{p_3\,p_4} + \frac{\alpha_2\,\gamma_1\,\gamma_2\,\sigma_4}{p_3\,p_5\,p_6\,p_7}\right)\right].
\end{aligned}
$$

4.4.3 $\hat{\mathcal{R}}_0$ Interpretation

$\hat{\mathcal{R}}_0^{I_H} = \dfrac{\hat{C}_S\,\beta_1}{\mu+\sigma_1+\alpha_2}$, is simply the product of the per capita rate of infection and the average duration of stay of an individual in class I_H. This reproductive rate is sometimes referred to as the *back of the napkin* [61]. It is the number of HIV-infection cases produced by a single untreated HIV-positive individual during his/her entire lifetime in class I_H, in a wholly susceptible population.

$$
\hat{\mathcal{R}}_0^{I^a_{LH}} = \underbrace{\frac{1}{\mu+\tau_2+\sigma_2+\gamma_1}}_{\mathbf{i}} \times \left[\underbrace{\hat{C}_S\,\beta_1\,\eta_1}_{\mathbf{j}} \times \underbrace{\frac{\alpha_2}{\mu+\sigma_1+\alpha_2}}_{\mathbf{k}} + \underbrace{\hat{C}_L\,\beta_2\,\eta_1}_{\mathbf{l}}\right].
$$

$\hat{\mathcal{R}}_0^{I^a_{LH}}$ above is the sum of two terms. We explain each summand of this term with respect to the letters they are represented with. The terms denoted by i,j and k are the average infectious period of an individual in compartment I^a_{LH}, the infectivity of individuals in class I^a_{LH} (who developed lymphoma after they became infected with HIV), and the proportion of HIV-infected indivuals

who developed lymphoma and progressed to class I^a_{LH} respectively. The term denoted by l is the infectivity of individuals in class I^a_{LH}, who actually had lymphoma before they got infected with the HIV, and thus have passed through class I_L.

Implementing *Theorem* 2 of van den Driessche and Watmough [60], the following result is established.

Theorem 4.4.1. *The CD4-HIV-free Lymphoma Steady State (CHLSS)* $\hat{E}_0$*, of the model system* (4.2.3) *is globally asymptotically stable, provided* $\hat{\mathcal{R}}_0 < 1$.

Proof. Still following Castillo-Chavez *et al.* [62], we first write the system (4.2.3) in the form:

$$\begin{aligned} \hat{X}' &= F(\hat{X}, \hat{Y}) \\ \hat{Y}' &= G(\hat{X}, \hat{Y}), \quad G(\hat{X}, \mathbf{0}) = \mathbf{0}, \end{aligned} \tag{4.4.9}$$

where $\hat{X} = (S, I_L)$ and $\hat{Y} = (I_H, I_{HT}, I^a_{LH}, I^b_{LH}, I^c_{LH}, I^a_{LHT}, I^b_{LHT}, I^c_{LHT})$. Here, $\hat{X} \in \mathbb{R}^2_+$ (its components) denotes the number of individuals that are not infected with HIV, but may have developed lymphoma, and $\hat{Y} \in \mathbb{R}^8_+$ (its components) denotes the number of individuals that are infected with HIV, irrespective of whether they have developed lymphoma or not, or are on antiretroviral treatment or not, or of their CD4-count category. We thus denote the disease-free equilibrium of this system by $\check{E}_0 = (\hat{X}^*, \mathbf{0})$, where $\hat{X}^* = (S^{**}, I^{**}_L)$.

To ascertain the asymptotic global stability of the endemic state $\hat{E}_0$, we have to show that the following conditions C1 and C2 below are satisfied.

(C1) For $\hat{X}'(t) = F(\hat{X}, \mathbf{0})$, $\hat{X}^*$ is globally asymptotically stable.

(C2) $G(\hat{X}, \hat{Y}) = A\hat{Y} - \hat{G}(\hat{X}, \hat{Y})$, $\hat{G}(\hat{X}, \hat{Y}) \geq 0$ for $(\hat{X}, \hat{Y}) \in \hat{\Gamma}$,

where $\hat{\Gamma}$ is a positively invariant attracting domain (where the model makes biological sense), and $A = \mathcal{D}_Y G(X^*, \mathbf{0})$ is an M-matrix (the off-diagonal elements of A are non-negative).

Let

$$F(\hat{X}, \hat{Y}) = \begin{pmatrix} K - \lambda_1 S - (\mu + \alpha_1)S \\ \alpha_1 S - \lambda_2 I_L - (\mu + \tau_1) I_L \end{pmatrix}, \tag{4.4.10}$$

$$\implies F(\hat{X}, \mathbf{0}) = \begin{pmatrix} K - (\mu + \alpha_1)S \\ \alpha_1 S - (\mu + \tau_1) I_L \end{pmatrix} = \hat{X}'(t). \tag{4.4.11}$$

Observe that $\hat{Y} = \mathbf{0}$ when $\lambda_1 = \lambda_2 = 0$. The unique equilibrium point of this subsystem (4.4.11) is given by:

$$\hat{X}^* = \left(\frac{K}{\mu + \alpha_1}, \frac{\alpha_1 K}{(\mu + \alpha_1)(\mu + \tau_1)} \right). \tag{4.4.12}$$

The biologically feasible region for the new system $\hat{X}'(t) = F(\hat{X}, \mathbf{0})$ is the positively invariant, attracting, and compact set

$$\hat{\Gamma} = \{(S, I_L) \in \mathbb{R}^2_+ : \check{N} \leq \frac{K}{\mu}, \ \check{N} = S + I_L\}.$$

The prove of this is exactly similar to that of Lemma 3.4.3.

In order to prove condition (C1), we first establish the fact the the steady state $\hat{X}^*$ is locally asymptotically stable. We use the Jacobian $J(S, I_L)$ of the subsystem 4.4.11, at $\hat{X}^*$. It is given by

$$J = \begin{pmatrix} -(\mu + \alpha_1) & 0 \\ \alpha_1 & -(\mu + \tau_1) \end{pmatrix}. \tag{4.4.13}$$

We observe that $J = J(\hat{X}^*)$, since it is a constant matrix. J is a triangular matrix, and the eigenvalues of a triangular matrix are its main diagonal entries. Thus, the eigenvalues of J are $\lambda_1 = -(\mu + \alpha_1)$ $\lambda_2 = -(\mu + \tau_1)$, $\lambda_1, \lambda_2 < 0$. This implies that the steady state $\hat{X}^*$ is locally asymptotically stable.

To show that this unique steady state $\hat{X}^*$ is globally asymptotically stable, we prove that the existence of periodic solutions are precluded from the subsystem 4.4.11. We rule out these periodic orbits in $\hat{\Gamma}$ using the Dulac's criteria (see Definition A.0.6)

Let

$$M(S, I_L) = K - (\mu + \alpha_1)S, \tag{4.4.14}$$
$$N(S, I_L) = \alpha_1 S - (\mu + \tau_1)I_L. \tag{4.4.15}$$

Let

$$\Theta(S, I_L) = \frac{1}{SI_L}, \quad S > 0, I_L > 0 \tag{4.4.16}$$

be a Dulac function.

We define another function Φ below. We see that

$$\Phi = \frac{\partial(M\Theta)}{\partial S} + \frac{\partial(N\Theta)}{\partial I_L}$$

$$= -\left(\frac{K}{S^2 I_L} + \frac{\alpha_1}{I_L^2}\right) < 0, \ \forall \ S > 0, I_L > 0. \tag{4.4.17}$$

This shows that the system (4.4.11) has no periodic solutions (or limit cycles) in the compact set $\hat{\Gamma}$. Since we have shown that the unique steady state $\hat{X}^*$ is locally asymptotically stable, then, by a simple application of Poincaré-Bendixson Theorem, it suffices to show that the unique steady state $\hat{X}^*$ of the subsystem 4.4.11 is globally asymptotically stable.

We now prove that the condition (C2) is also satisfied.

$$G(\hat{X}, \hat{Y}) = \begin{pmatrix} \lambda_1 S - (\mu + \sigma_1 + \alpha_2) I_H \\ \sigma_1 I_H - (\mu + \alpha_3 + \alpha_4 + \alpha_5) I_{HT} \\ \lambda_2 I_L + \alpha_2 I_H - (\mu + \tau_2 + \sigma_2 + \gamma_1) I_{LH}^a \\ \gamma_1 I_{LH}^a - (\mu + \tau_2 + \sigma_3 + \gamma_2) I_{LH}^b \\ \gamma_2 I_{LH}^b - (\mu + \delta_1 + \tau_3 + \sigma_4) I_{LH}^c \\ \sigma_2 I_{LH}^a + \alpha_3 I_{HT} + \rho_2 I_{LHT}^b - (\mu + \tau_4) I_{LHT}^a \\ \sigma_3 I_{LH}^b + \alpha_4 I_{HT} + \rho_1 I_{LHT}^c - (\mu + \tau_4 + \rho_2) I_{LHT}^b \\ \sigma_4 I_{LH}^c + \alpha_5 I_{HT} - (\mu + \delta_2 + \tau_5 + \rho_1) I_{LHT}^c \end{pmatrix}. \tag{4.4.18}$$

Since every element of the matrix $G(\hat{X}, \hat{Y})$ contains some HIV component, clearly, $G(\hat{X}, \mathbf{0}) = \mathbf{0}$. Next, we construct the matrix $A = \mathcal{D}_{\hat{Y}} G(\hat{X}^*, \mathbf{0})$. The matrix $\mathcal{D}_{\hat{Y}} G(\hat{X}, \hat{Y})$ is given by

.

$$\mathcal{D}_{\hat{Y}} G(\hat{X}, \hat{Y}) =$$

$$\begin{pmatrix} \frac{\beta_1 S}{N} - p_3 & \frac{\beta_1 \eta_4 S}{N} & \frac{\beta_1 \eta_1 S}{N} & \frac{\beta_1 \eta_1 S}{N} & \frac{\beta_1 \eta_2 S}{N} & \frac{\beta_1 \eta_3 S}{N} & \frac{\beta_1 \eta_3 S}{N} & \frac{\beta_1 \eta_2 S}{N} \\ \sigma_1 & -p_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_2 I_L}{N} + \alpha_2 & \frac{\beta_2 \eta_4 I_L}{N} & \frac{\beta_2 \eta_1 I_L}{N} - p_5 & \frac{\beta_2 \eta_1 I_L}{N} & \frac{\beta_2 \eta_2 I_L}{N} & \frac{\beta_2 \eta_3 I_L}{N} & \frac{\beta_2 \eta_3 I_L}{N} & \frac{\beta_2 \eta_2 I_L}{N} \\ 0 & 0 & \gamma_1 & -p_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma_2 & -p_7 & 0 & 0 & 0 \\ 0 & \alpha_3 & \sigma_2 & 0 & 0 & -p_8 & \rho_2 & 0 \\ 0 & \alpha_4 & 0 & \sigma_3 & 0 & 0 & -p_9 & \rho_1 \\ 0 & \alpha_5 & 0 & 0 & \sigma_4 & 0 & 0 & -p_{10} \end{pmatrix}. \tag{4.4.19}$$

$\hat{X}^* = (S^{**}, I_L^{**})$, where

$$S^{**} = \frac{K}{p_1}, \ I_L^{**} = \frac{\alpha_1 K}{p_1 p_2}. \ \text{Thus, } N^{**} = \frac{K(\alpha_1 + p_2)}{p_1 p_2}.$$

We obtain

$$\begin{aligned} A &= \mathcal{D}_{\hat{Y}} G(\hat{X}^*, \mathbf{0}) \\ &= \begin{pmatrix} \hat{\Psi}_1 & \hat{\Psi}_2 \\ \hat{\Psi}_3 & \hat{\Psi}_4 \end{pmatrix}, \end{aligned} \tag{4.4.20}$$

where

$$\hat{\Psi}_1 = \begin{pmatrix} \frac{\beta_1 p_2}{(\alpha_1+p_2)} - p_3 & \frac{\beta_1 p_2 \eta_4}{(\alpha_1+p_2)} & \frac{\beta_1 p_2 \eta_1}{(\alpha_1+p_2)} & \frac{\beta_1 p_2 \eta_1}{(\alpha_1+p_2)} \\ \sigma_1 & -p_4 & 0 & 0 \\ \frac{\beta_2 \alpha_1}{(\alpha_1+p_2)} + \alpha_2 & \frac{\beta_2 \alpha_1 \eta_4}{(\alpha_1+p_2)} & \frac{\beta_2 \alpha_1 \eta_1}{(\alpha_1+p_2)} - p_5 & \frac{\beta_2 \alpha_1 \eta_1}{(\alpha_1+p_2)} \\ 0 & 0 & \gamma_1 & -p_6 \end{pmatrix},$$

$$\hat{\Psi}_2 = \begin{pmatrix} \frac{\beta_1 p_2 \eta_2}{(\alpha_1+p_2)} & \frac{\beta_1 p_2 \eta_3}{(\alpha_1+p_2)} & \frac{\beta_1 p_2 \eta_3}{(\alpha_1+p_2)} & \frac{\beta_1 p_2 \eta_2}{(\alpha_1+p_2)} \\ 0 & 0 & 0 & 0 \\ \frac{\beta_2 \alpha_1 \eta_2}{(\alpha_1+p_2)} & \frac{\beta_2 \alpha_1 \eta_3}{(\alpha_1+p_2)} & \frac{\beta_2 \alpha_1 \eta_3}{(\alpha_1+p_2)} & \frac{\beta_2 \alpha_1 \eta_2}{(\alpha_1+p_2)} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\hat{\Psi}_3 = \begin{pmatrix} 0 & 0 & 0 & \gamma_2 \\ 0 & \alpha_3 & \sigma_2 & 0 \\ 0 & \alpha_4 & 0 & \sigma_3 \\ 0 & \alpha_5 & 0 & 0 \end{pmatrix},$$

$$\hat{\Psi}_4 = \begin{pmatrix} -p_7 & 0 & 0 & 0 \\ 0 & -p_8 & \rho_2 & 0 \\ 0 & 0 & -p_9 & \rho_1 \\ \sigma_4 & 0 & 0 & -p_{10} \end{pmatrix}.$$

Using the definition $G(\hat{X}, \hat{Y}) = A\hat{Y} - \hat{G}(\hat{X}, \hat{Y})$ to obtain $\hat{G}(\hat{X}, \hat{Y})$, we have:

.

$$\hat{G}(\hat{X},\hat{Y}) = \begin{pmatrix} \hat{G}_1(\hat{X},\hat{Y}) \\ \hat{G}_2(\hat{X},\hat{Y}) \\ \hat{G}_3(\hat{X},\hat{Y}) \\ \hat{G}_4(\hat{X},\hat{Y}) \\ \hat{G}_5(\hat{X},\hat{Y}) \\ \hat{G}_6(\hat{X},\hat{Y}) \\ \hat{G}_7(\hat{X},\hat{Y}) \\ \hat{G}_8(\hat{X},\hat{Y}) \end{pmatrix},$$

$$= \begin{pmatrix} \beta_1 \left[I_H + \eta_1(I^a_{LH} + I^b_{LH}) + \eta_2(I^c_{LH} + I^c_{LHT}) + \eta_3(I^a_{LHT} + I^b_{LHT}) + \eta_4 I_{HT}\right] \hat{\Pi}_1 \\ 0 \\ \beta_2 \left[I_H + \eta_1(I^a_{LH} + I^b_{LH}) + \eta_2(I^c_{LH} + I^c_{LHT}) + \eta_3(I^a_{LHT} + I^b_{LHT}) + \eta_4 I_{HT}\right] \hat{\Pi}_2 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{4.4.21}$$

where

$$\hat{\Pi}_1 = \left(\frac{p_2}{(\alpha_1 + p_2)} - \frac{S}{N}\right),$$
$$\hat{\Pi}_2 = \left(\frac{\alpha_1}{(\alpha_1 + p_2)} - \frac{I_L}{N}\right).$$

We now show that $\hat{G}(\hat{X},\hat{Y}) \geq 0$ for $(\hat{X},\hat{Y}) \in \hat{\Gamma}$, which implies that we must show that $\hat{G}_1(\hat{X},\hat{Y})$, $\hat{G}_3(\hat{X},\hat{Y})$, ≥ 0. It suffices to show that:

(i) $\dfrac{p_2}{(\alpha_1 + p_2)} - \dfrac{S}{N} \geq 0$,

(ii) $\dfrac{\alpha_1}{(\alpha_1 + p_2)} - \dfrac{I_L}{N} \geq 0.$

We prove these relations by contradiction. Suppose that:

$$\begin{aligned} \frac{p_2}{(\alpha_1 + p_2)} &< \frac{S}{N}, \\ \frac{\alpha_1}{(\alpha_1 + p_2)} &< \frac{I_L}{N}. \end{aligned} \tag{4.4.22}$$

Using the *direct proof* technique, that for $a, b, c, d > 0$, if $a < b$ and $c < d$, then, $a + c < b + d$, we sum the three relations above to obtain,

$$\begin{aligned} &\frac{p_2}{(\alpha_1 + p_2)} \frac{\alpha_1}{(\alpha_1 + p_2)} < \frac{S + I_L}{N}, \\ \Longrightarrow\ &\frac{(\alpha_1 + p_2)}{(\alpha_1 + p_2)} = 1 < \frac{S + I_L}{N}. \end{aligned} \tag{4.4.23}$$

However, since $N = S + I_L$, then by definition, we have it that

$$\Longrightarrow \frac{S + I_L}{N} = 1. \tag{4.4.24}$$

Relations (4.4.23) and (4.4.24) implies that

$$1 < 1.$$

This is a contradiction. Hence, the converse of the relations in (4.4.22) is true. This implies that relations (i) and (ii) are valid. Hence $\hat{G}(X, Y) \geq 0$ for $(\hat{X}, \hat{Y}) \in \hat{\Gamma}$. This completes the proof. □

4.4.4 Existence of the Endemic Equilibria

In order to compute the endemic equilibria of the model system (4.2.3), , where at least one of the infected compartments is non-zero, we set the right hand side of the system (3.2.3) to zero, and solve for all its state variables. The state variables are expressed in terms of the forces of infection λ_1^{**} and λ_2^{**}, where

$$\lambda_1^{**} = \frac{\beta_1}{N^{**}}[I_H^{**} + \eta_1((I_{LH}^a)^{**} + (I_{LH}^b)^{**}) + \eta_2((I_{LH}^c)^{**} + (I_{LHT}^c)^{**}) \tag{4.4.25}$$

$$+ \eta_3((I_{LHT}^a)^{**} + (I_{LHT}^b)^{**}) + \eta_4 I_{HT}^{**}], \tag{4.4.26}$$

$$\lambda_2^{**} = \frac{\beta_2}{N^{**}}[I_H^{**} + \eta_1((I_{LH}^a)^{**} + (I_{LH}^b)^{**}) + \eta_2((I_{LH}^c)^{**} + (I_{LHT}^c)^{**}) \tag{4.4.27}$$

$$+ \eta_3((I_{LHT}^a)^{**} + (I_{LHT}^b)^{**}) + \eta_4 I_{HT}^{**}], \tag{4.4.28}$$

$$N^{**} = S^{**} + I_L^{**} + I_H^{**} + I_{HT}^{**} + (I_{LH}^a)^{**} + (I_{LH}^b)^{**} + (I_{LH}^c)^{**} \tag{4.4.29}$$

$$+ (I_{LHT}^a)^{**} + (I_{LHT}^b)^{**} + (I_{LHT}^c)^{**}. \tag{4.4.30}$$

Note that

$$\lambda_2 = \frac{\beta_2 \lambda_1}{\beta_1}. \tag{4.4.31}$$

This implies that λ_2 is simply a (positive) constant multiple of λ_1. Thus any qualitative inference(s) made from investigating the polynomial arising from λ_1 also applies to the polynomial equation that ought to arise from λ_2.

Hence, the endemic equilibria of the model (4.2.3) are given by

$$\hat{E}_1 = (S^{**}, I_L^{**}, I_H^{**}, I_{HT}^{**}, (I_{LH}^a)^{**}, (I_{LH}^b)^{**}, (I_{LH}^c)^{**}, (I_{LHT}^a)^{**}, (I_{LHT}^b)^{**}, (I_{LHT}^c)^{**}), \tag{4.4.32}$$

where

$$S^{**} = \frac{K}{p_1 + \lambda_1^{**}}, \tag{4.4.33}$$

$$I_L^{**} = \frac{K\,\alpha_1}{(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})}, \tag{4.4.34}$$

$$I_H^{**} = \frac{K\,\lambda_1^{**}}{p_3\,(p_1 + \lambda_1^{**})}, \tag{4.4.35}$$

$$I_{HT}^{**} = \frac{K\,\lambda_1^{**}\,\sigma_1}{p_3\,p_4\,(p_1 + \lambda_1^{**})}, \tag{4.4.36}$$

$$(I_{LH}^a)^{**} = \frac{K\,(p_3\,\alpha_1\,\lambda_2^{**} + \alpha_2\,\lambda_1^{**}\,(p_2 + \lambda_2^{**}))}{p_3\,p_5\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})}, \tag{4.4.37}$$

$$(I_{LH}^b)^{**} = \frac{K\,\gamma_1\,(p_3\,\alpha_1\,\lambda_2^{**} + \alpha_2\,\lambda_1^{**}\,(p_2 + \lambda_2^{**}))}{p_3\,p_5\,p_6\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})}, \tag{4.4.38}$$

$$(I_{LH}^c)^{**} = \frac{K\,\gamma_1\,\gamma_2\,(p_3\,\alpha_1\,\lambda_2^{**} + \alpha_2\,\lambda_1^{**}\,(p_2 + \lambda_2^{**}))}{p_3\,p_5\,p_6\,p_7\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})}, \tag{4.4.39}$$

$$\begin{aligned}(I_{LHT}^a)^{**} = K\,\lambda_1^{**} &\left(\frac{(p_9\,\alpha_3 + \alpha_4\,\rho_2)\,\sigma_1}{p_3\,p_4\,p_8\,p_9\,(p_1 + \lambda_1^{**})} + \frac{\alpha_2\,(p_6\,p_9\,\sigma_2 + \gamma_1\,\rho_2\,\sigma_3)}{p_3\,p_5\,p_6\,p_8\,p_9\,(p_1 + \lambda_1^{**})}\right. \\ &\left. + \frac{\rho_1\,\rho_2\,(p_5\,p_6\,p_7\,\alpha_5\,\sigma_1 + p_4\,\alpha_2\,\gamma_1\,\gamma_2\,\sigma_4)}{p_3\,p_4\,p_5\,p_6\,p_7\,p_8\,p_9\,p_{10}\,(p_1 + \lambda_1^{**})}\right) \\ &+ \frac{K\,\alpha_1\,\lambda_2^{**}\,(p_6\,p_7\,p_9\,p_{10}\,\sigma_2 + \gamma_1\,\rho_2\,(p_7\,p_{10}\,\sigma_3 + \gamma_2\,\rho_1\,\sigma_4))}{p_5\,p_6\,p_7\,p_8\,p_9\,p_{10}\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})},\end{aligned} \tag{4.4.40}$$

$$\begin{aligned}(I_{LHT}^b)^{**} = &\frac{K\,\alpha_1\,\gamma_1\,\lambda_2^{**}\,(p_7\,p_{10}\,\sigma_3 + \gamma_2\,\rho_1\,\sigma_4)}{p_5\,p_6\,p_7\,p_9\,p_{10}\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})} \\ &+ \frac{K\,\lambda_1^{**}\,(p_5\,p_6\,p_7\,(p_{10}\,\alpha_4 + \alpha_5\,\rho_1)\,\sigma_1 + p_4\,\alpha_2\,\gamma_1\,(p_7\,p_{10}\,\sigma_3 + \gamma_2\,\rho_1\,\sigma_4))}{p_3\,p_4\,p_5\,p_6\,p_7\,p_9\,p_{10}\,(p_1 + \lambda_1^{**})},\end{aligned} \tag{4.4.41}$$

$$\begin{aligned}(I_{LHT}^c)^{**} = &\frac{K\,p_5\,p_6\,p_7\,\alpha_5\,\lambda_1^{**}\,(p_2 + \lambda_2^{**})\,\sigma_1}{p_3\,p_4\,p_5\,p_6\,p_7\,p_{10}\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})} \\ &+ \frac{K\,p_4\,\gamma_1\,\gamma_2\,(p_3\,\alpha_1\,\lambda_2^{**} + \alpha_2\,\lambda_1^{**}\,(p_2 + \lambda_2^{**}))\,\sigma_4}{p_3\,p_4\,p_5\,p_6\,p_7\,p_{10}\,(p_1 + \lambda_1^{**})\,(p_2 + \lambda_2^{**})}.\end{aligned} \tag{4.4.42}$$

Substituting for the steady states above in (4.4.26), we obtain the quadratic polynomial

$$A(\lambda_1^{**})^2 + B(\lambda_1^{**}) + C = 0, \tag{4.4.43}$$

where

$$
\begin{aligned}
A &= \beta_2\ (p_5\,p_6\,p_7\ (p_9\,p_{10}\,\alpha_3 + p_8\ (p_{10}\,\alpha_4 + p_9\ (p_{10} + \alpha_5) + \alpha_5\,\rho_1)\\
&\quad + (p_{10}\,\alpha_4 + \alpha_5\,\rho_1)\ \rho_2)\ \sigma_1 + p_4\ (p_{10}\ (p_9\ (p_5\,p_6\,p_7\,p_8 + \alpha_2\ (p_8\,\gamma_1\ (p_7 + \gamma_2)\\
&\quad + p_6\,p_7\ (p_8 + \sigma_2))) + p_7\,\alpha_2\,\gamma_1\ (p_8 + \rho_2)\ \sigma_3) + \alpha_2\,\gamma_1\,\gamma_2\ (p_8\ (p_9 + \rho_1)\\
&\quad + \rho_1\,\rho_2)\ \sigma_4))\,,\\
B &= p_2\,\beta_1\ (p_5\,p_6\,p_7\ (p_9\,p_{10}\,\alpha_3 + p_8\ (p_{10}\,\alpha_4 + p_9\ (p_{10} + \alpha_5) + \alpha_5\,\rho_1)\\
&\quad + (p_{10}\,\alpha_4 + \alpha_5\,\rho_1)\ \rho_2)\ \sigma_1 + p_4\ (p_{10}\ (p_9\ (p_5\,p_6\,p_7\,p_8 + \alpha_2\ (p_8\,\gamma_1\ (p_7 + \gamma_2)\\
&\quad + p_6\,p_7\ (p_8 + \sigma_2))) + p_7\,\alpha_2\,\gamma_1\ (p_8 + \rho_2)\ \sigma_3) + \alpha_2\,\gamma_1\,\gamma_2\ (p_8\ (p_9 + \rho_1)\\
&\quad + \rho_1\,\rho_2)\ \sigma_4)) + \beta_2\ (p_3\,p_4\ (p_{10}\ (p_9\ (p_5\,p_6\,p_7\,p_8 + \alpha_1\ (p_8\,\gamma_1\ (p_7 + \gamma_2)\\
&\quad + p_6\,p_7\ (p_8 + \sigma_2))) + p_7\,\alpha_1\,\gamma_1\ (p_8 + \rho_2)\ \sigma_3) + \alpha_1\,\gamma_1\,\gamma_2\ (p_8\ (p_9 + \rho_1)\\
&\quad + \rho_1\,\rho_2)\ \sigma_4) - \beta_1\ (p_5\,p_6\,p_7\ (p_8\ (p_9\ (\alpha_5\,\eta_2 + p_{10}\,\eta_4) + \eta_3\ (p_{10}\,\alpha_4 + \alpha_5\,\rho_1))\\
&\quad + \eta_3\ (p_9\,p_{10}\,\alpha_3 + (p_{10}\,\alpha_4 + \alpha_5\,\rho_1)\ \rho_2))\ \sigma_1 + p_4\ (p_{10}\ (p_5\,p_6\,p_7\,p_8\,p_9\\
&\quad + \alpha_2\ (p_9\ (p_8\ (p_7\ (p_6 + \gamma_1)\ \eta_1 + \gamma_1\,\gamma_2\,\eta_2) + p_6\,p_7\,\eta_3\,\sigma_2) + p_7\,\gamma_1\,\eta_3\\
&\quad \times (p_8 + \rho_2)\ \sigma_3)) + \alpha_2\,\gamma_1\,\gamma_2\ (p_8\ (p_9\,\eta_2 + \eta_3\,\rho_1) + \eta_3\,\rho_1\,\rho_2)\ \sigma_4)))\,,\\
C &= -\,(\beta_1\ (-\,(p_2\,p_3\,p_4\,p_5\,p_6\,p_7\,p_8\,p_9\,p_{10}) + p_2\,p_5\,p_6\,p_7\,\beta_1\ (p_8\ (p_9\ (\alpha_5\,\eta_2\\
&\quad + p_{10}\,\eta_4) + \eta_3\ (p_{10}\,\alpha_4 + \alpha_5\,\rho_1)) + \eta_3\ (p_9\,p_{10}\,\alpha_3 + (p_{10}\,\alpha_4 + \alpha_5\,\rho_1)\ \rho_2))\ \sigma_1\\
&\quad + p_2\,p_4\,p_{10}\,\beta_1\ (p_5\,p_6\,p_7\,p_8\,p_9 + \alpha_2\ (p_9\ (p_8\ (p_7\ (p_6 + \gamma_1)\ \eta_1 + \gamma_1\,\gamma_2\,\eta_2)\\
&\quad + p_6\,p_7\,\eta_3\,\sigma_2) + p_7\,\gamma_1\,\eta_3\ (p_8 + \rho_2)\ \sigma_3)) + p_3\,p_4\,p_{10}\,\alpha_1\ (-\,(p_5\,p_6\,p_7\,p_8\,p_9)\\
&\quad + \beta_2\ (p_9\ (p_8\ (p_7\ (p_6 + \gamma_1)\ \eta_1 + \gamma_1\,\gamma_2\,\eta_2) + p_6\,p_7\,\eta_3\,\sigma_2) + p_7\,\gamma_1\,\eta_3\ (p_8 + \rho_2)\ \sigma_3))\\
&\quad + p_4\ (p_2\,\alpha_2\,\beta_1 + p_3\,\alpha_1\,\beta_2)\ \gamma_1\,\gamma_2\ (p_8\ (p_9\,\eta_2 + \eta_3\,\rho_1) + \eta_3\,\rho_1\,\rho_2)\ \sigma_4))\,.
\end{aligned}
\tag{4.4.44}
$$

The existence, and number of endemic equilibria for the model system (4.2.3) is determined by the existence of, and number of positive roots of the quadratic equation (4.4.43). We investigate and characterise the solutions (roots) of the quadratic polynomial (4.4.43) by using the quadratic formula to get its roots, and analyse them under different conditions. The roots of equation (4.4.43) are given by

$$
(\lambda_1^{**})_{1,2} = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}. \tag{4.4.45}
$$

The constant term C can be expressed in terms of $\hat{\mathcal{R}}_0$, and it is given by

$$
C = \beta_1 p_3 p_4 p_5 p_6 p_7 p_8 p_9 p_{10}(p_2 + \alpha_1)\left[1 - \hat{\mathcal{R}}_0\right]. \tag{4.4.46}
$$

From equation (4.4.46), if $\hat{\mathcal{R}}_0 > 1$, then $C < 0$. On the other hand, if $\hat{\mathcal{R}}_0 < 1$, then $C > 0$. We consider three cases of the discriminant Θ of equation (4.4.45), where $\Theta = B^2 - 4AC$.

We consider the existence of endemic equilibria for $\hat{\mathcal{R}}_0 > 1, C < 0$ and $A > 0$.

If $\Theta = 0$, then, $\lambda_1^{**})_1, (\lambda_1^{**})_2 = \dfrac{-B}{2A}$. If $B < 0$, then $(\lambda_1^{**})_1, (\lambda_1^{**})_2 > 0$. This implies that equation (4.4.43) has exactly one positive root with multiplicity two (a double root). If $B > 0$, then $(\lambda_1^{**})_1, (\lambda_1^{**})_2 < 0$, that is equation (4.4.43) has exactly one negative root with multiplicity two. Hence, if $\hat{\mathcal{R}}_0 > 1, C < 0, A > 0, \Theta = 0$ and $B < 0$, then the model system (4.2.3) has only one endemic equilibrium.

Consider $\Theta > 0$. If $B > 0$, then, $(\lambda_1^{**})_1 > 0$ and $(\lambda_1^{**})_2 < 0$. This implies that the quadratic equation (4.4.43) has two distinct roots of opposite signs. Thus, for $\hat{\mathcal{R}}_0 > 1, C < 0, A > 0, \Theta > 0$ and $B > 0$, the model system (4.2.3) has only one endemic equilibrium.

If $B < 0$, then, $(\lambda_1^{**})_1 > 0, (\lambda_1^{**})_2 > 0$. This implies that the quadratic equation (4.4.43) has two distinct positive roots. Thus, for $\hat{\mathcal{R}}_0 > 1, C < 0, A > 0, \Theta > 0$ and $B < 0$, the model system (4.2.3) has two endemic equilibria.

If $\Theta > 0$, then the quadratic equation (4.4.43) has no real solutions. This is of no interest to us.

We investigate the existence of endemic equilibria when $\hat{\mathcal{R}}_0 < 1$.

When $\Theta > 0$, then, $\sqrt{\Theta} < B$ since $AC > 0$. If $B > 0$, then the quadratic equation (4.4.43) has two distinct negative roots. However, If $B < 0$, it has two distinct roots of opposite signs. This implies if $\hat{\mathcal{R}}_0 < 1, C > 0, A > 0$, and $B < 0$, then the model system (4.2.3) has exactly one endemic equilibrium. Obviously, equation (4.4.43) has no real solution if $\Theta < 0$.

The theorem below summarises the existence of endemic equilibria of the model system (4.2.3).

Theorem 4.4.2. *The model system* (4.2.3)

(i) has no endemic equilibrium if $\hat{\mathcal{R}}_0 < \hat{\mathcal{R}}_0^c < 1$, *where* $\hat{\mathcal{R}}_0^c$ *is a threshold called the critical* $\hat{\mathcal{R}}_0$.

(ii) has at most two endemic equilibria in Ω, *if* $\hat{\mathcal{R}}_0 > 1$.

(iii) has a unique endemic equilibrium in Ω, *for some parameter values of* $\hat{\mathcal{R}}_0$ *within the range* $\hat{\mathcal{R}}_0^c < \hat{\mathcal{R}}_0 < 1$.

(iv) has no endemic equilibrium otherwise.

Proposition 4.4.3. *The model system* (4.2.3) *exhibits backward bifurcation for* $\hat{\mathcal{R}}_0 < 1$.

Remark 4.4.4. Proposition 4.4.3 implies that bringing $\hat{\mathcal{R}}_0$ below unity is does not suffice for the eradication of the incidence of lymphoma (cancers in general) in HIV-infected individuals when HIV is introduced into a wholly susceptible population. In order to achieve this main goal of epidemiology (bringing the disease into extinction), $\hat{\mathcal{R}}_0$ must be brought below the critical value $\hat{\mathcal{R}}_0^c$, or $\hat{\mathcal{R}}_0^c$ must be raised. The critical value $\hat{\mathcal{R}}_0^c$ is a threshold after both the DFE and the endemic equilibrium(s) co-exist.

To estimate the critical value $\hat{\mathcal{R}}_0^c$, we set the discriminant Θ of the polynomial (4.4.43) to zero, and make $\hat{\mathcal{R}}_0$ the subject of the relation. This new term is the critical value $\hat{\mathcal{R}}_0^c$ of the system (4.2.3), and it is given by

$$\hat{\mathcal{R}}_0^c = 1 - \frac{B^2}{4A\beta_1 p_3 p_4 p_5 p_6 p_7 p_8 p_9 p_{10}(p_2 + \alpha_1)}. \tag{4.4.47}$$

4.5 Numerical Simulations

In this section, we present the results of the numerical simulations for the model (4.2.3). These numerical simulations, which are being used to demonstrate the theoretical concepts of our model, were carried out using the fourth order Runge-Kutta scheme in Matlab. Using lymphoma incidence data of the Western Cape province of South Africa, which was obtained from the Tygerberg Lymphoma Study Group (TLSG), we fit our model to the available data. Table 4.3 displays lymphoma data classified according to CD4 cell count for population classes I_{LH}^a and I_{LH}^c. Table 4.4 shows the parameter values used in these simulations. Many of these parameters values are assumed values, obtained through iterative methods, in such a way that the values presented are those which best fit our lymphoma data. Nevertheless, the parameters used are those which are epidemiologically relevant.

4.5.1 Parameter Estimation

Using the 2001-2006, 2006-2011 and 2011-2016 mid-year population estimates by Statistics South Africa (StatsSA), we obtain the average life-expectancy of the population of the Western Cape province, and they are 60.15, 63.35, and 67.15 years (for the three year sections) respectively. We thus evaluate the mortality rates that corresponds to these three averages, and we obtain 0.01663, 0.01579 and 0.01489 years respectively. We thus sampled the natural mortality rate from the range (0.014-0.017), for which 0.017 best fits our model

[65]. In like manner, we obtain the crude birth rate b, of the Western Cape province population as a sample from the range (0.020-0.025).

Since PBL has also been reported in immunocompetent patients and HAART has improved its prognosis, in that the survival rate as increased by 2.5 [31; 41; 46]. Thus, we assumed that the HIV treatment rate of patients with lymphoma, HIV, and in class I^a_{LH} is 2.5 times that of those in class I^c_{LH}, that is $\alpha_2 = 2.5\alpha_4$.

The report by Diamond *et al* [44] show that the incidence of some HRL has almost doubled in the post-HAART era (see Subsection 2.2.1). Thus, we assumed that the lymphoma development rate of HIV positive patients under antiretroviral treatment (into class I^a_{LHT}) is twice the lymphoma development rate of HIV-positive patients (into class I^a_{LH}), that is $\alpha_3 = 2\alpha_2$. Consequently, we also assumed that $\alpha_4, \alpha_5 > \alpha_2$.

We obtained lymphoma incidence data from the Tygerberg Lymphoma Study Group (TLSG), Tygerberg Hospital, Western Cape (WC) province of South Africa (SA). The population under study is that of the WC province of SA, of which the Tygerberg Hospital covers about half of them.

Table 4.3: Lymphoma Data Classified According to CD4 Cell Count for Classes I^a_{LH} and I^c_{LH}

Population Class	**2007**	**2008**	**2009**	**2010**	**2011**
I^a_{LH}	4	6	15	8	9
I^c_{LH}	8	13	29	15	15

Table 4.4: Parameter values and ranges used in numerical simulation

Parameters	Description	Range	Point value	Source
K	Recruitment rate for susceptibles	(43000-44000)	$43049yr^{-1}$	Demo
μ	Natural mortality rate	(0.006-2)	$0.017yr^{-1}$	Demo
δ_1	Disease and low-CD4 cell count induced mortality rate (for I^c_{LH})	(0.0015-0.003)	$0.002yr^{-1}$	Demo
δ_2	Disease and low-CD4 cell count induced mortality rate (for I^c_{LH})	(0.0015-0.0025)	$0.0015yr^{-1}$	Demo
β_1	Effective contact rate of HIV for susceptible individuals	(0.001-0.003)	$0.002yr^{-1}$	Estimated
β_2	Effective contact rate of HIV for lymphoma patients	(0.005-0.01)	$0.009yr^{-1}$	Estimated
α_1	Lymphoma development rate for susceptible individuals	(0.00006-0.0001)	$0.0000974yr^{-1}$	Estimated
α_2	Lymphoma development rate of HIV-positive patients (into class I^a_{LH})	(0.00002-0.00004)	$0.00003315yr^{-1}$	Estimated
α_3	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^a_{LHT})	(0.00005-0.00008)	$0.0000663yr^{-1}$	Estimated
α_4	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^b_{LHT})	(0.00004-0.00007)	$0.00005yr^{-1}$	Estimated
α_5	Lymphoma development rate of HIV-positive patients under antiretroviral regimen(s) (into class I^c_{LHT})	(0.00008-0.0002)	$0.0001yr^{-1}$	Estimated
σ_1	HIV treatment rate of lymphoma-free HIV patients	(0.031-0.035)	$0.034yr^{-1}$	Estimated
σ_2	HIV treatment rate of patients with lymphoma, HIV, and in class I^a_{LH}	(0.001-0.003)	$0.002yr^{-1}$	Estimated
σ_3	HIV treatment rate of patients with lymphoma, HIV, and in class I^b_{LH}	(0.0006-0.00083)	$0.0007yr^{-1}$	Estimated
σ_4	HIV treatment rate of patients with lymphoma, HIV, and in class I^c_{LH}	(0.00078-0.00083)	$0.0008yr^{-1}$	Estimated
τ_1	Lymphoma treatment rate of lymphoma-only patients	(0.99-1.5)	$1.09yr^{-1}$	Estimated
τ_2	Lymphoma treatment rate of patients with lymphoma, HIV, and in either class I^a_{LH} or I^b_{LH}	(0-4)	$0.23yr^{-1}$	Estimated
τ_3	Lymphoma treatment rate of patients with lymphoma, HIV, and in class I^c_{LH}	(0.0004-0.0007)	$0.0005yr^{-1}$	Estimated
τ_4	Lymphoma treatment rate of patients with lymphoma, HIV, under antiretroviral regimen(s) and in class I^a_{LHT} or I^b_{LHT}	(0.9-1.5)	$1.12yr^{-1}$	Estimated
τ_5	Lymphoma treatment rate of patients with lymphoma, HIV, under antiretroviral regimen(s) and in class I^c_{LHT}	(0.004-0.007)	$0.005yr^{-1}$	Estimated
γ_1	CD4 cell count declinataion rate of patients in class I^a_{LH}	(0.08-0.2)	$0.1yr^{-1}$	Estimated
γ_2	CD4 cell count declinataion rate of patients in class I^b_{LH}	(8-9)	$9yr^{-1}$	Estimated
ρ_1	CD4 cell count upswing rate of patients in class I^c_{LHT}	(0.08-0.2)	$0.1yr^{-1}$	Estimated
ρ_2	CD4 cell count upswing rate of patients in class I^b_{LHT}	(1.0-1.5)	$1.2yr^{-1}$	Estimated
η_1	Modification parameter for classes I^a_{LH} and I^b_{LH}	(0.6-0.8)	0.7	Estimated
η_2	Modification parameter for classes I^c_{LH} and I^c_{LHT}	(1.30-1.32)	1.3	Estimated
η_3	Modification parameter for classes I^a_{LHT} and I^b_{LHT}	(0.5-0.72)	0.6	Estimated
η_4	Modification parameter for class I_{HT}	(0.4-0.6)	1.6	Estimated

4.5.2 Sensitivity Analysis

Using the same assumptions and procedure as in Subsection 3.5.2, we conduct sensitivity analysis on the model system (4.2.3). Figure 4.5 is a tornado plot of the Partial Rank Correlation Coefficient (PRCC) of the input parameters of our model system, as described in Table 4.4. It illustrates the results of the sensitivity analysis done on our model system [76]. It shows that the model's input parameter with the most negative PRCC is the natural mortality rate μ, while that with the most positive PRCC is the modification parameter η_4. We plotted scatter plots of the significant PRCC's. However, we have only displayed those ones which exhibit significant statistical relationships with $\hat{\mathcal{R}}_0$ as they vary.

Figures 4.2 and 4.3 are scatter plots obtained from the Monte Carlo simulations of 1000 samples, of the natural mortality rate μ, and the lymphoma treatment rate of patients with HIV and lymphoma (who are in class I^a_{LH} or I^b_{LH}). The figures shows how the variation of the aformentioned parameters affect the response $\hat{\mathcal{R}}_0$. Figure 4.2 shows that $\hat{\mathcal{R}}_0$ is monotone decreasing as μ increases. Figure 4.3 also shows that $\hat{\mathcal{R}}_0$ is monotone decreasing as the lymphoma treatment rate of patients with HIV, lymphoma, and in either of classes I^a_{LH} or I^b_{LH}) increases. This implies that a decrease in the number of patients who have both HIV and lymphoma, but not on any antiretroviral treatment (but rather on lymphoma treatment only) will cause a decrease in $\hat{\mathcal{R}}_0$ value, which in turn could lead to a control of the epidemic.

Figure 4.4 displays the statistical measures of $\hat{\mathcal{R}}_0$ on a boxplot. It shows that the median of $\hat{\mathcal{R}}_0 < 1$ for this run. However, the median of $\hat{\mathcal{R}}_0 > 1$ for many other simulations. This means that the epidemic will always remain (uneradicated) in the population under study.

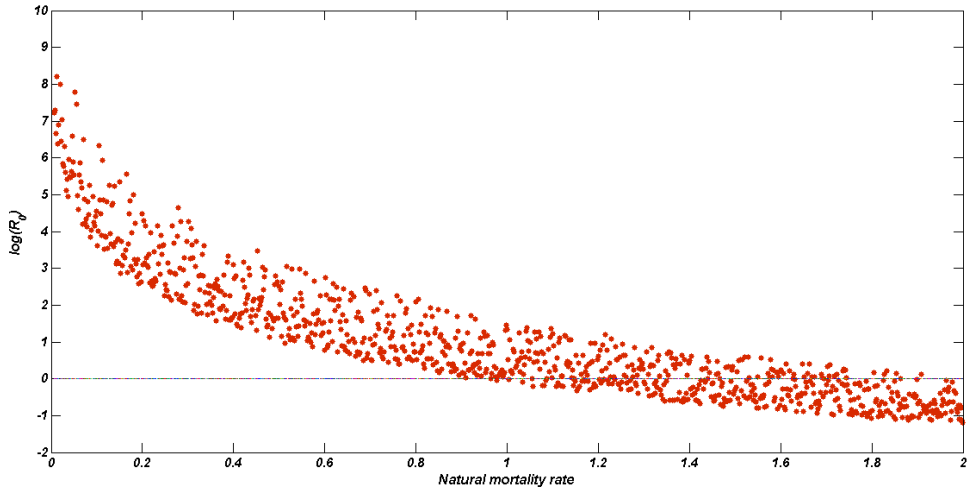

Figure 4.2: A scatter plot of the natural mortality rate, μ, as it relates to $\hat{\mathcal{R}}_0$. Note that $\hat{\mathcal{R}}_0 = \mathcal{R}_0$ in this diagram.

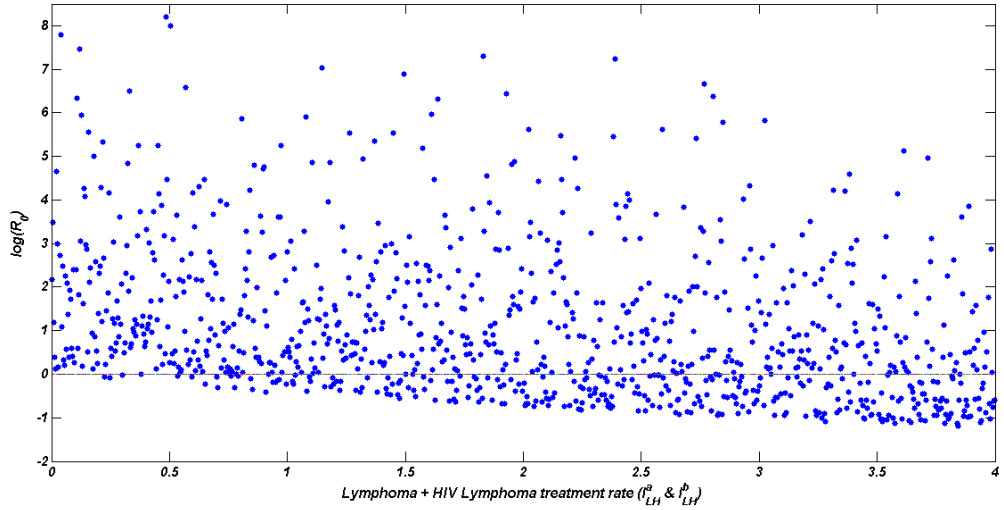

Figure 4.3: A scatter plot of the lymphoma treatment rate of patients with HIV and lymphoma (who are in class I^a_{LH} or I^b_{LH}), as it relates to $\hat{\mathcal{R}}_0$. Note that $\hat{\mathcal{R}}_0 = \mathcal{R}_0$ in this diagram.

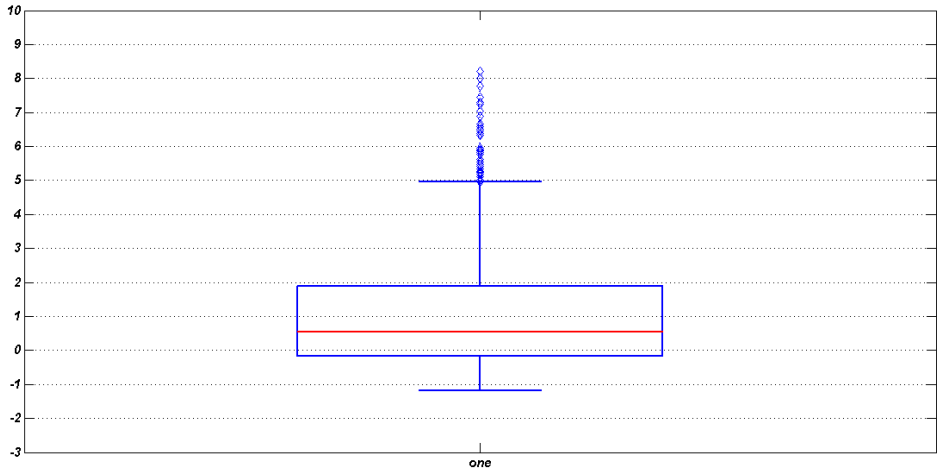

Figure 4.4: A boxplot of $\hat{\mathcal{R}}_0$.

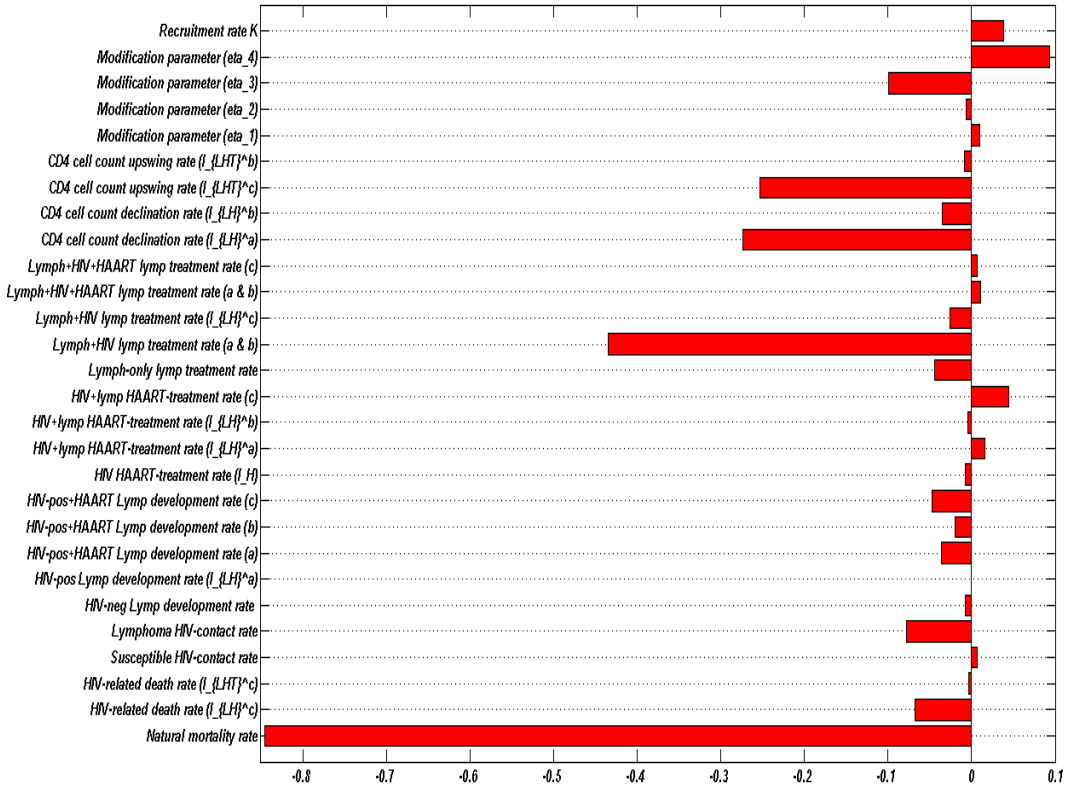

Figure 4.5: Tornado plot of the PRCC of the input parameters of our model system as described in Table 4.4

4.5.3 Results

We show the dynamics of lymphoma (and other HIV-related cancers) in the HIV-infected and uninfected population, using the fit of our model to the TLSG data. Figure 4.6 demonstrates that there is a steady increase in the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells $/\mu L$, from 2007-2011. It shows that a relatively high number of cases were recorded in the year 2009, thus making the data point of that year an outlier, in comparison with other data points. This is a consequence of a high access of the TLSG to clinical lymphoma data in 2009.

Figure 4.7 depicts a rapid increase in the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, from 2007-2008, after which it steadily increases from 2008-2011. The 2009 data point is also observed to be an outlier due to high access to clinical data by the TLSG. Figure 4.8 is a graphical comparison of the incidence of lymphoma in patients with HIV, lymphoma, and whose CD4 cell count is < 200 cells $/\mu L$, with those patients whose CD4 cell count is > 350 cells $/\mu L$. It shows that more patients with depreciated CD4 cell count (< 200 cells $/\mu L$) develop lymphoma in comparison with patients with higher CD4 cell count (> 350 cells $/\mu L$), from 2007-2011. This trend is consistent over the 5 years simulated period.

Figure 4.9 demonstrates that there is a steady increase in the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is > 350 cells $/\mu L$, from 2007-2011. This simulation has no data points because of the inavailability of lymphoma incidence data for this incidence, as the TLSG could not obtain adequate patient information with respect to this. This in actual fact has been clinically proven as several lymphoma subtypes develop only after the commencement of HAART. This is a result of several prognostic factors, such as the immunosuppression level in patients and immune reconstitution inflammatory syndrome (IRIS) (see Subsection 2.2.1).

Figure 4.10 demonstrates that there is a steady and non-trivial rise in the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$. Figure 4.11 compares the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$, with that of those patients whose CD4 cell counts are > 350 cells $/\mu L$. It shows that despite being on HAART regimen, much more patients with depreciated CD4 cell counts (< 200 cells $/\mu L$) develop lymphoma, in comparison to those patients with slightly normal or high CD4 cell counts (> 350 cells $/\mu L$). The increase in the number of patients in the former category was rapid between 2007-2011, while the number of patients in the latter

category only increased slowly and by a little amount over the 5 years period. This is an indicator that a low CD4 cell count is highly crucial in the prognosis of the incidence of lymphoma (and other cancer types) in HIV-infected patients.

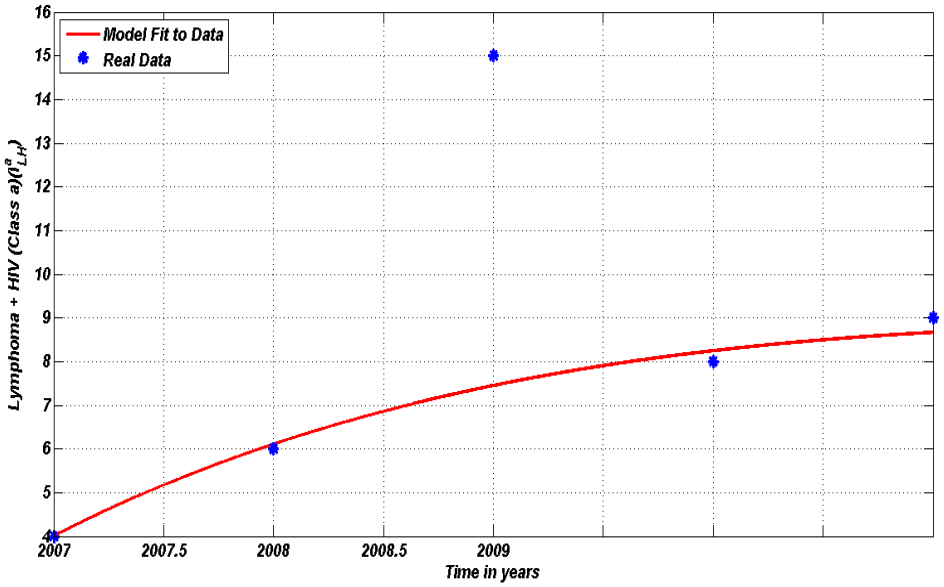

Figure 4.6: Incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells $/\mu L$

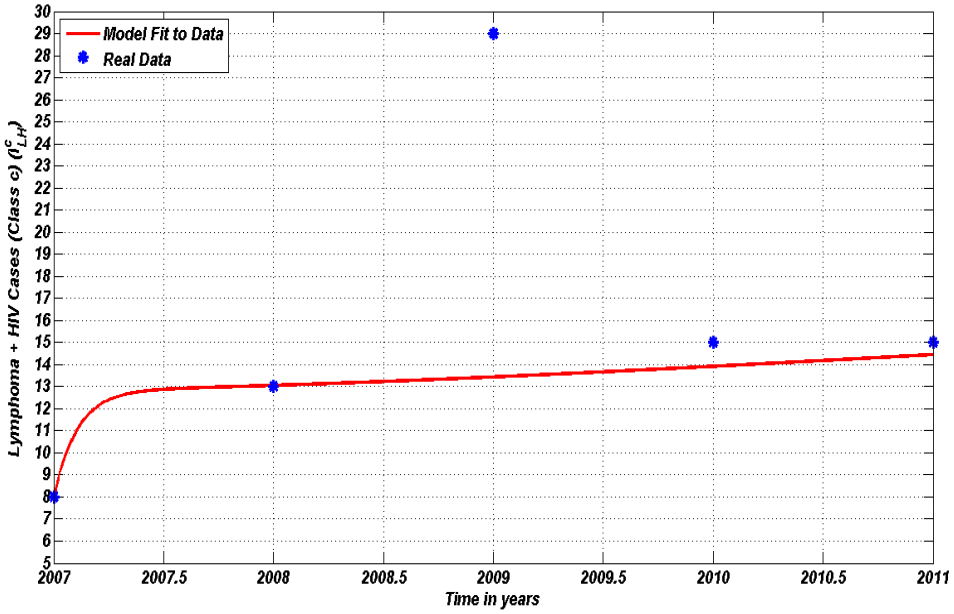

Figure 4.7: Incidence of lymphoma in patients with HIV and lymphoma, and whose CD4 cell count is < 200 cells $/\mu L$

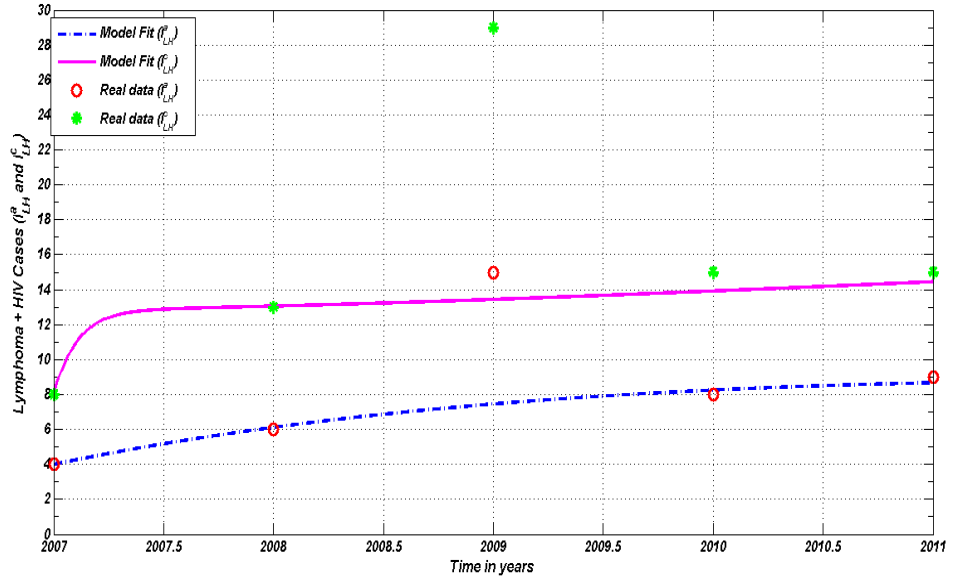

Figure 4.8: Incidence of lymphoma in patients with HIV, lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, and of those whose CD4 cell count is > 350 cells $/\mu L$

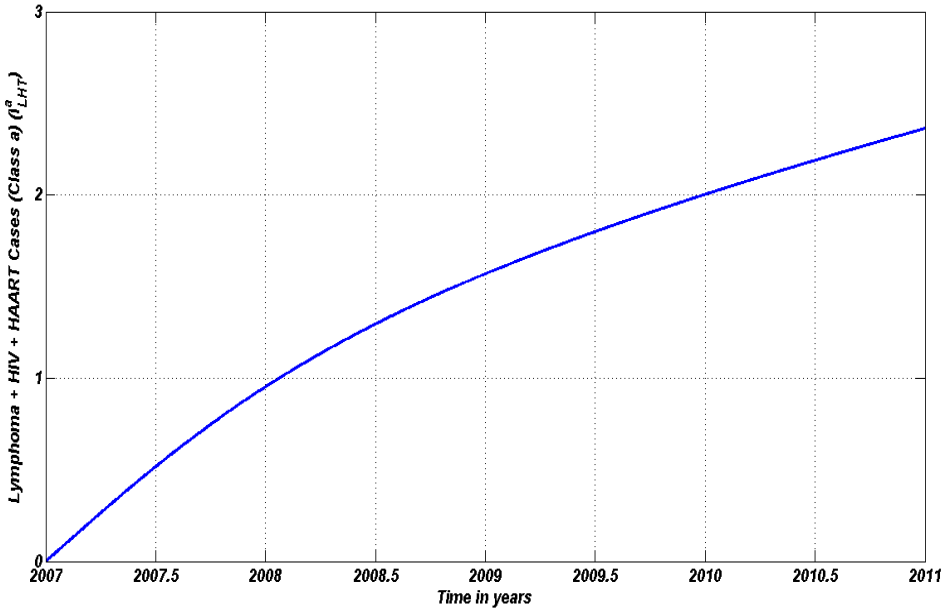

Figure 4.9: Incidence of lymphoma in patients with HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is > 350 cells $/\mu L$

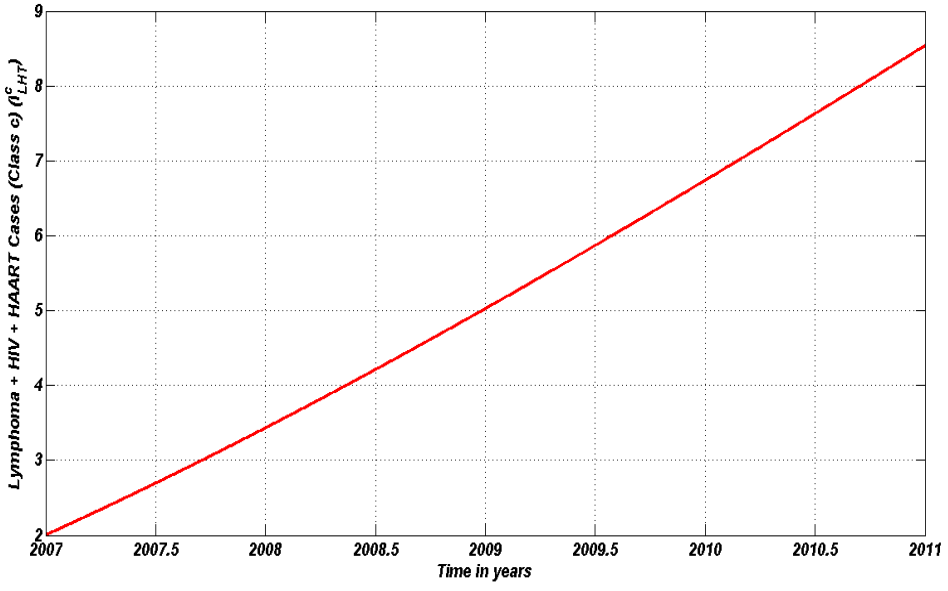

Figure 4.10: Incidence of lymphoma in patients with HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$

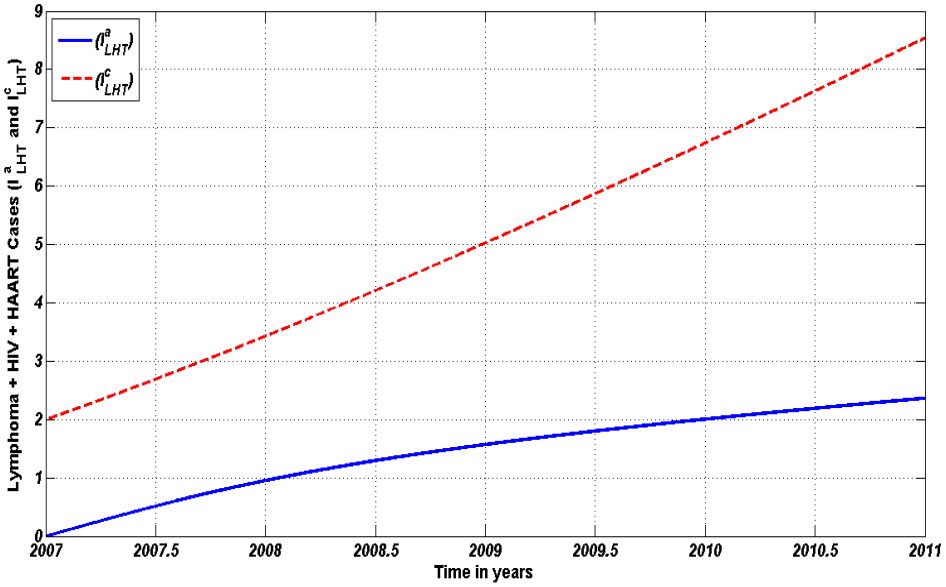

Figure 4.11: Incidence of lymphoma in patients with HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$, and those whose CD4 cell count is > 350 cells $/\mu L$

Since the use of HAART has been reported to decrease the incidence of some lymphoma subtypes, we use our model as a predictive tool, by considering different scenarios created by different percentage coverages of the rollout of HAART. The first scenario considered is the 30% effective HAART rollout, which is about the effective HAART coverage in the Western Cape province of South Africa as at 2011 [27]. We also considered three other scenarios that has to do with some increase in the effective HAART coverage of the Western Cape province of South Africa, viz 30%, 50% and 70% increase.

Figure 4.12 displays the projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage. Figure 4.13 displays the projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$ for various effective HAART coverage. For us to clearly observe and discuss the effects of the increase in the effective HAART coverage as seen in Figures 4.12 and 4.13, we display magnified views of the patterns shown in Figures 4.12 and 4.13 in Figures 4.14 and 4.15 respectively.

Figure 4.16 depicts the projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, and of those whose CD4 cell count is > 350 cells

$/\mu L$ for various effective HAART coverage. It shows that the incidence of cases of the former group is higher than that of the latter. Figure 4.17 is an accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, and of those whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage.

Figure 4.18 is a projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is > 350 cells $/\mu L$ for various effective HAART coverage. Figure 4.20 is a magnified version of it. It shows that an increase in effective HAART coverage, will increase the number of HIV cum lymphoma patients with a CD4 cell count that is > 350 cells $/\mu L$, that will be enrolled in the HAART treatment. Figure 4.19 is a projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$ for various effective HAART coverage. Figure 4.21 is its accentuated version. It also shows that when there is an increase in HAART roll-out, more lymphoma patients with a CD4 cell count of < 200 cells $/\mu L$ will be enrolled in HAART treatment.

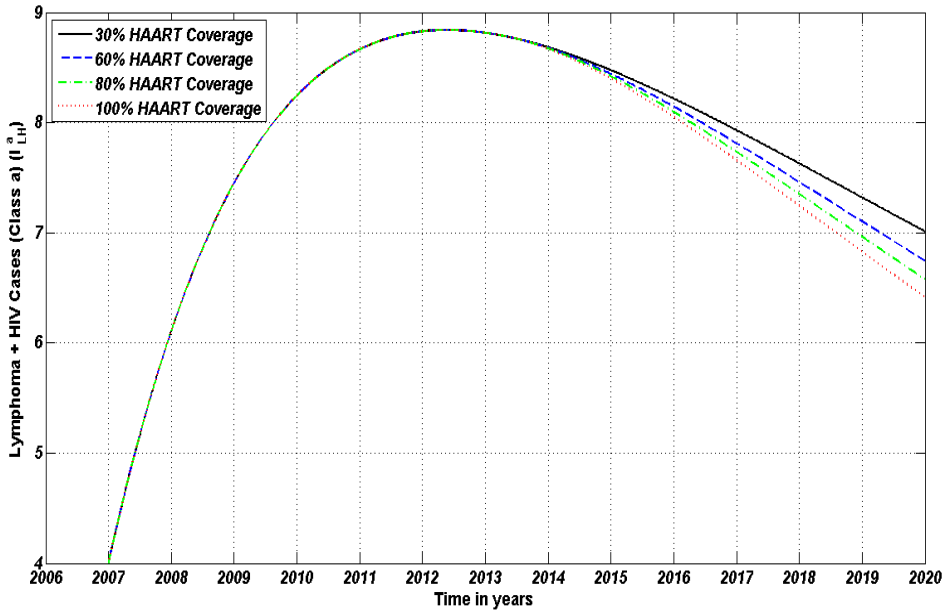

Figure 4.12: A projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage.

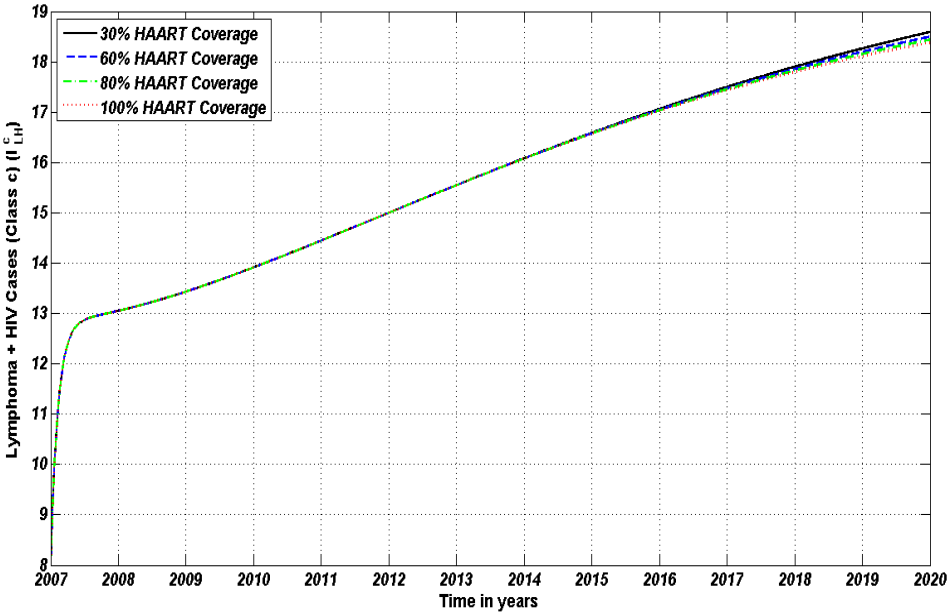

Figure 4.13: A projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$ for various effective HAART coverage.

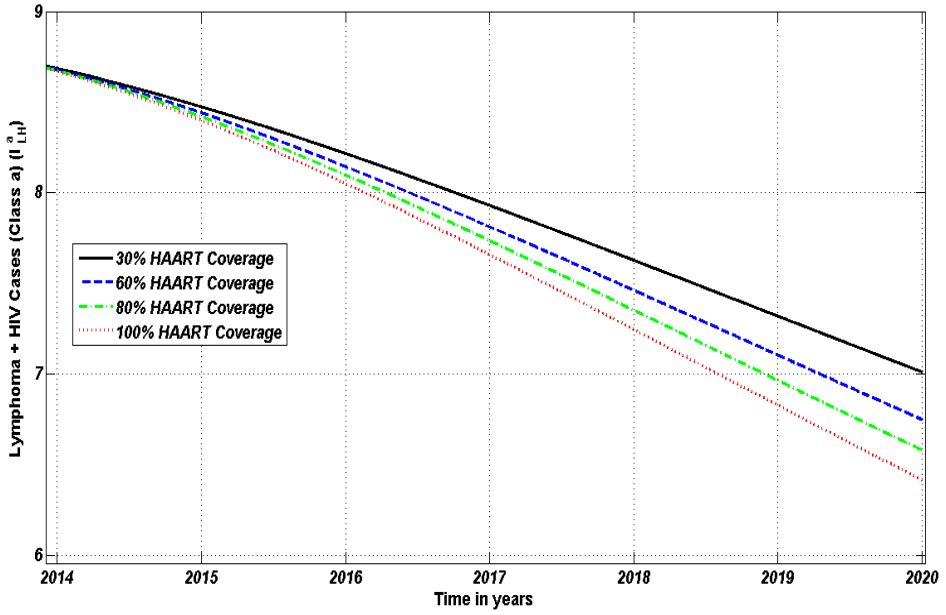

Figure 4.14: An accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage.

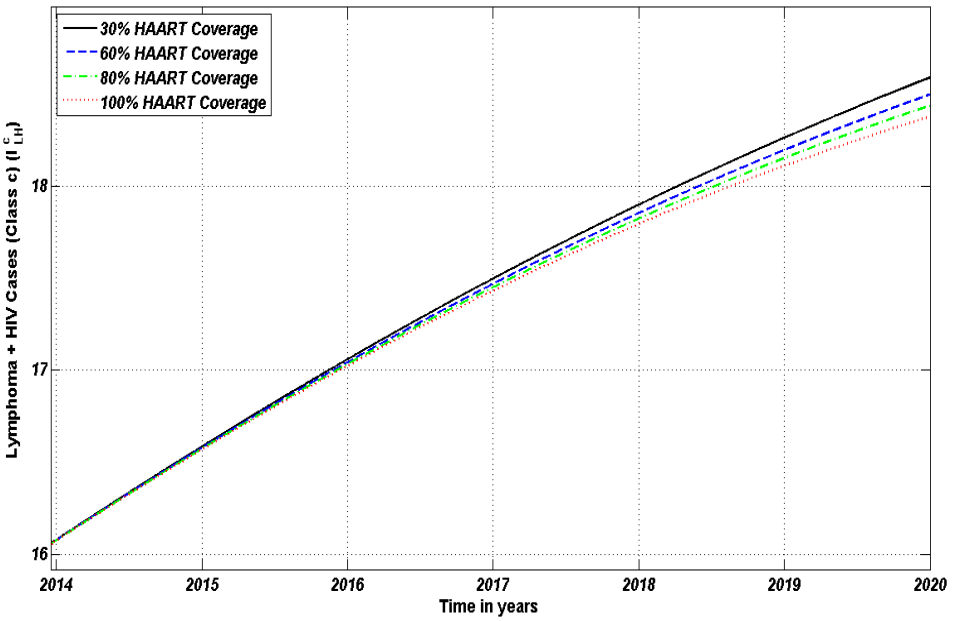

Figure 4.15: An accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$ for various effective HAART coverage.

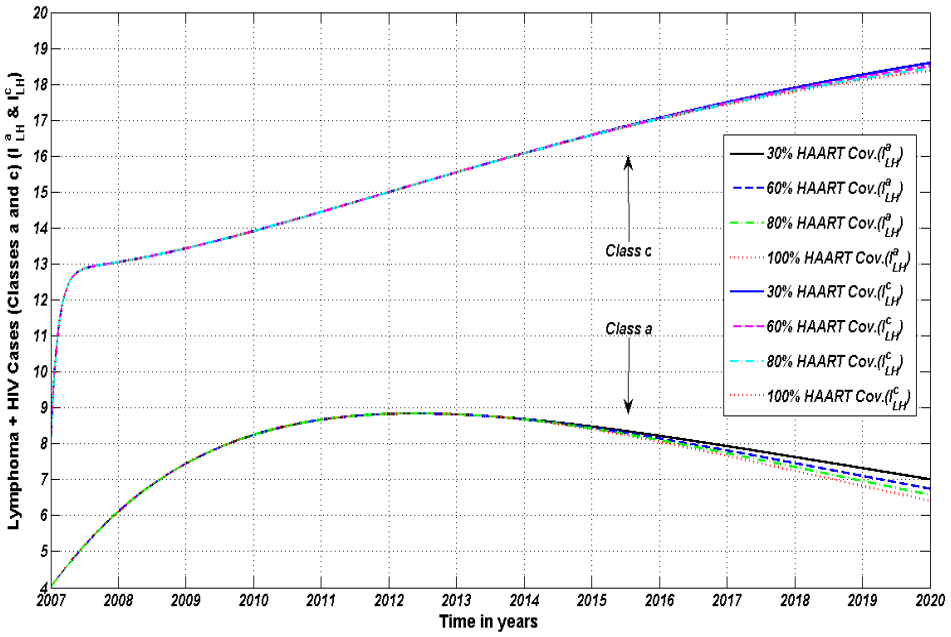

Figure 4.16: A projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, and of those whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage.

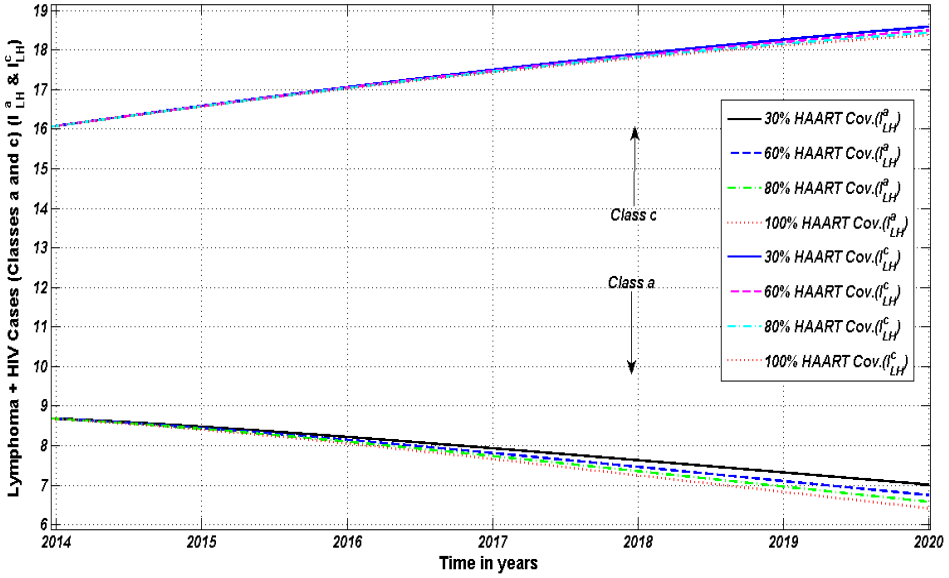

Figure 4.17: An accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma and whose CD4 cell count is < 200 cells $/\mu L$, and of those whose CD4 cell count is > 350 cells $/\mu L$ for various effective HAART coverage.

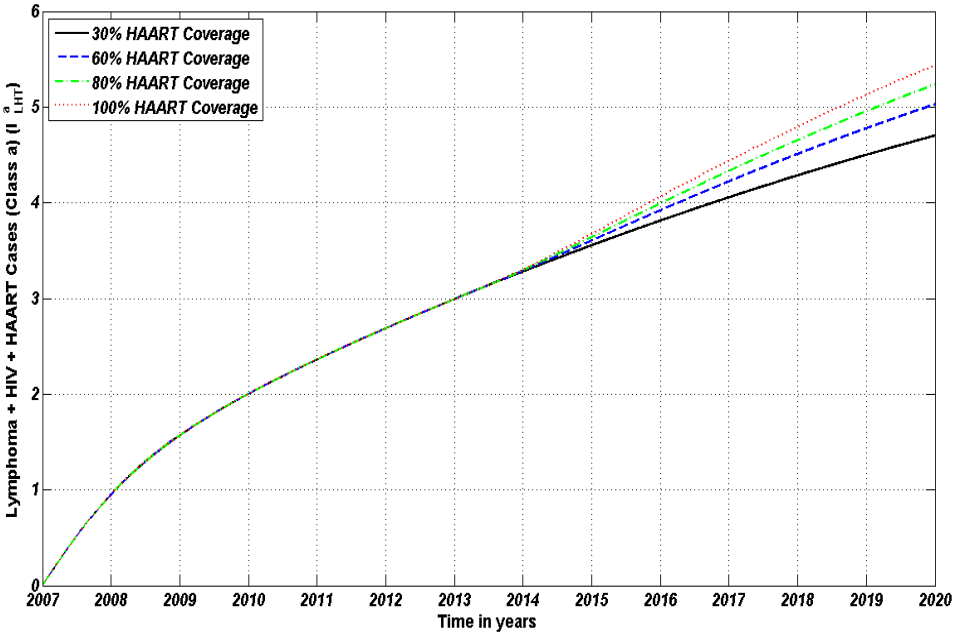

Figure 4.18: A projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is > 350 cells $/\mu L$ for various effective HAART coverage.

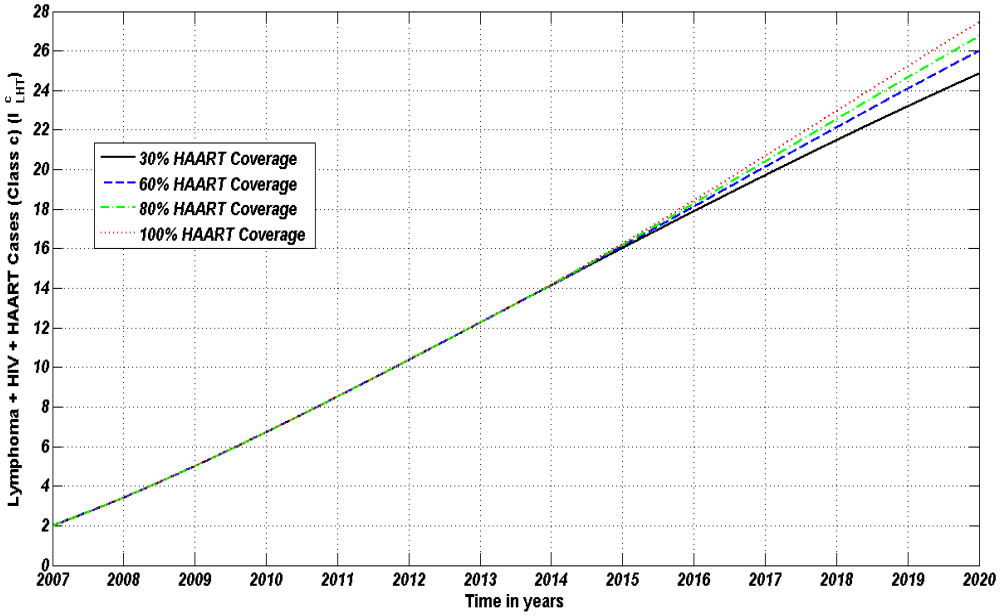

Figure 4.19: A projection and scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$ for various effective HAART coverage.

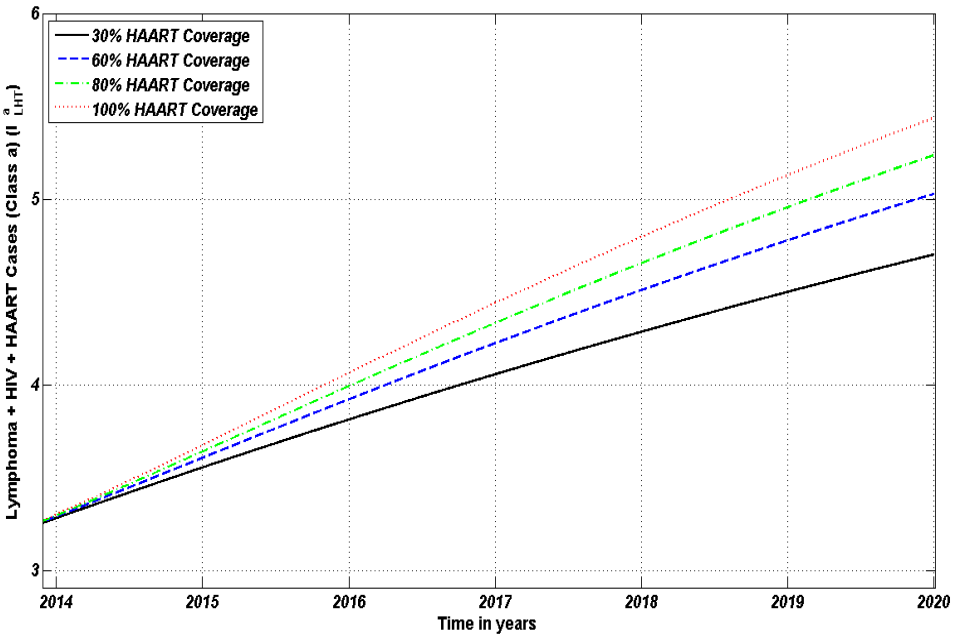

Figure 4.20: An accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is > 350 cells $/\mu L$ for various effective HAART coverage.

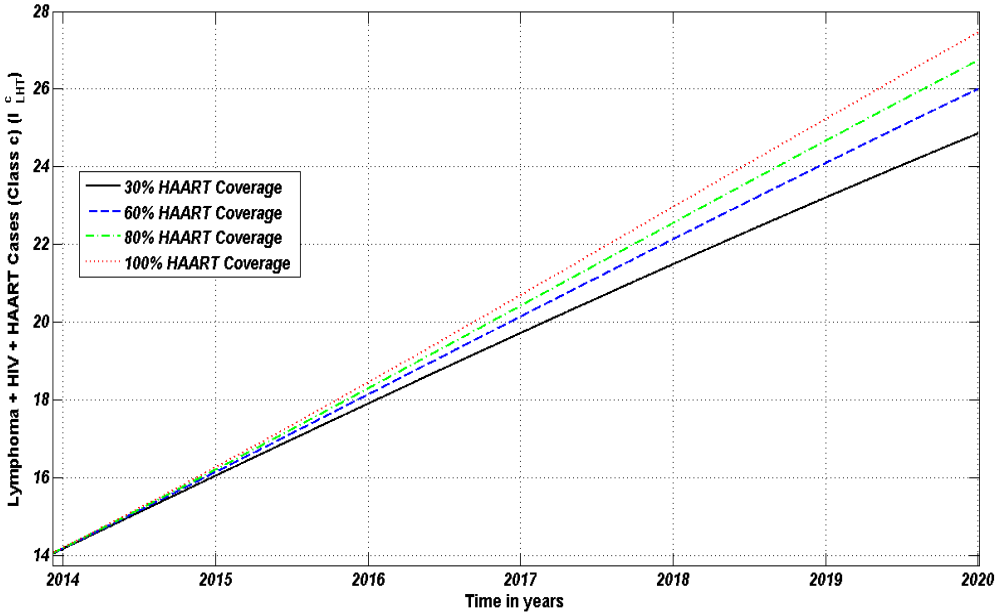

Figure 4.21: An accentuated scenario analysis of the incidence of lymphoma in patients with both HIV and lymphoma, under antiretroval regimen(s), and with CD4 cell count that is < 200 cells $/\mu L$ for various effective HAART coverage.

4.5.3.1 Discussion

In this chapter, we formulated a mathematical model that describes the dynamics of HIV-related cancers, whereby special consideration was given to the different classes of CD4 cell count levels an HIV-infected patient can fall into. Qualitative analysis of the model was done using its $\hat{\mathcal{R}}_0$ and $\hat{\mathcal{R}}_0^c$ thresholds, which are the basic reproduction number and the critical reproduction number respectively. We observed that the model's CD4-HIV-free lymphoma steady state is globally stable only if $\hat{\mathcal{R}}_0 < \hat{\mathcal{R}}_0^c$. In addition, we saw that when $\hat{\mathcal{R}}_0 < 1$, the model exhibits a backward bifurcation since the model has a unique endemic equilibrium, for some parameter values of $\hat{\mathcal{R}}_0$ within the range $\hat{\mathcal{R}}_0^c < \hat{\mathcal{R}}_0 < 1$. When $\hat{\mathcal{R}}_0 < \hat{\mathcal{R}}_0^c < 1$, HIV can be eradicated from the studied population.

Numerical simulations were also carried out for the model. Lymphoma data from the TLSG were fitted to the model to obtain lymphoma incidence curves. We observed that the incidence of lymphoma in patients with highly depreciated CD4 cell count is upswinging at an alarming rate, and earlier HAART administration is recommended. We also carried out sensitivity analysis of the model parameters. The implementation of Latin hypercube sampling which makes use of Partial rank correlation coefficients (PRCC) shows that the two parameters that have the most negative effect on the value of $\hat{\mathcal{R}}_0$, when varied, are μ, the natural mortality rate and τ_2, the lymphoma treatment rate of patients with HIV and lymphoma (who are in class I_{LH}^a or I_{LH}^b).

Similar to the projections of Subsection 3.5.3 (Chapter 3), we used the model as a predictive tool by projecting the incidences of lymphoma in four different scenarios. Similarly, the results shows that an increase in the roll-out and effective use of HAART has a significant declination effect on the incidence of the epidemic in the nearest future.

Our model results buttresses the fact that patients with low CD4 cell counts have a higher risk of developing AIDS or death [89–91]. Using the model, it has been shown that more patients with very low CD4 cell count (< 200 cells $/\mu L$) developed lymphoma between 2007 and 2011, in comparison with those who have a slightly normal to high CD4 cell count (> 350 cells $/\mu L$). Two major factors that should be considered when an ART decision is being made for a patient are the patient's viral load and CD4 cell count [92]. Our model shows that more incidences of lymphoma development will occur if patients are being treated at a CD4 cell count of < 200 cells $/\mu L$, as opposed to a CD4 cell count of > 350 cells $/\mu L$. However, the current problem of the increasing rise in the incidence of HRL is not just that of the CD4 cell count-related national antiretroviral commencement policy, but that of late presentation. The average CD4 cell count on presentation, of a South African HIV-infected individual is about 85 cells $/\mu L$ [93].

This implies that if patients continue to present late, more lymphoma cases will develop and may actually escalate at an uncontrollable rate. Thus, we suggest that more awareness programmes be rolled out to educate the general populace on the importance of HIV-infected individuals presenting their cases early, and the likely risks of developing a disastrous cancer that they could incur if they fail to do so. The control of this epidemic in the Western Cape province of South Africa may be pivotal on this. We also suggest that it will yield better results, and will in the long run cost less, if patients are being treated at a CD4 cell count of > 350 cells $/\mu L$, as fewer serious cases will be treated, which will reduce the cost of paying for longer days and more serious cases in the hospital.

Chapter 5

Discussion and Conclusions

The use of HAART have been seen to be effective in the continuous declination of the rate at which HIV-infected patients develop cancer [43; 45]. This could imply that if every patient eligible for the HAART is getting it, faithfully adhering to it, and actually commencing their HAART treatment before they become immunosuppressed (often a result of low CD4 cell count), then, the incidence of HRL, and HRC in general will drastically decline, and perhaps go into extinction (that is the patients live the normal average life-time of HIV-negative individuals without developing an HRC). Nancy *et al.* [45] reports that factors that determine if an HIV-infected patient will develop an AIDS defining cancer (ADC) include a low CD4 cell count, and the non-use of HAART.

A study by a UK Collaborative HIV Cohort (UK CHIC) [89; 90] reports that patients with low CD4 cell counts have a higher risk of developing AIDS or death. They reported this with some confidence interval, and with different CD4 cell counts category. They particularly discovered that for patients with a CD4 cell count > 350 cells $/\mu L$, each additional increase of 100 CD4 cells $/\mu L$ significantly reduces the chance of the development of AIDS (and consequently ADC) in the HIV-infected patients. This implies that patients with CD4 cell count > 350 cells $/\mu L$ have a better prognosis, than those whose CD4 cell count < 350 cells $/\mu L$. The worst prognosis expectedly was observed in patients with CD4 cell count < 200 cells $/\mu L$, as they have a high risk of developing AIDS (consequently ADC) or even death. Their report suggests that the use of antiretroviral therapy, which can afford patients immune reconstitution and thus CD4 cell count upswing, can be used to cause a decline in the risk of developing AIDS, AIDS-defining illnesses (such as ADC), and even death amongst HIV-infected individuals.

Another study by a large North American AIDS Cohort Collaboration on Research and Design [91], which involved over $8,000$ HIV-infected individuals, reports that HIV-infected patients who commence antiretroviral treatment at

high CD4 cell counts, between 350 and 500 cells $/\mu L$ have a significant lower risk of death than those whose CD4 cell count is $<$ 350 cells $/\mu L$ before antiretroviral therapy was commenced. They thus suggests that antiretroviral therapy be commenced at a CD4 cell count of $351-500$ cells $/\mu L$, as opposed to the current recommendation of $<$ 350 cells $/\mu L$.

In this study, we present two mathematical models on the dynamics of HIV-related malignancies. We implemented the use of ordinary differential equations in the comprehension of these dynamics. The first model, which was presented in Chapter 3 explain the dynamics of HIV-related malignancies by describing the different stages individuals can progress into during the course of lymphoma development and treatment in an HIV setting. The second model, which was presented in Chapter 4, describes the dynamics of HIV-related cancers, by giving specific deliberation to the different classes of CD4 cell count levels an HIV-infected patient can fall into.

Qualitative analyses and numerical simulations of both models were done by using their reproduction numbers $\mathcal{R}_0$ (for the first model), $\hat{\mathcal{R}}_0$ and $\hat{\mathcal{R}}_0^c$ (for the second model). The first model has a locally stable HIV-free lymphoma steady state when $\mathcal{R}_0 < 1$ and is globally stable when $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, where $\mathcal{R}_0^c$ is the critical $\mathcal{R}_0$. The second model has a globally stable HIV-free lymphoma steady state only if $\hat{\mathcal{R}}_0 < \hat{\mathcal{R}}_0^c$. Both models exhibit backward bifurcation when their reproduction numbers are less than one, that is, $\mathcal{R}_0, \hat{\mathcal{R}}_0 < 1$. The existence of backward bifurcation implies that there is the co-existece of a stable disease-free and endemic equilibrium(s) when the models' reproduction numbers are less than one. In the first model, HIV can be eradicated from the population under study if $\mathcal{R}_0 < \mathcal{R}_0^c < 1$, and also in the second model if $\hat{\mathcal{R}}_0 < \hat{\mathcal{R}}_0^c < 1$.

To obtain lymphoma incidence curves, lymphoma data from the TLSG were fitted to the two models. We also carried out sensitivity analyses using the Latin Hypercube Sampling (LHS) technique which makes use of Partial rank correlation coefficients (PRCC). The purpose of this implementation is to determine which parameters have the most significant impact on the prediction imprecision of the models' reproduction numbers, and to evaluate the variability in the reproduction numbers as those parameters varies. In both models, the most negatively sensitive parameter is the natural mortality rate μ. Another highly sensitive parameter in the first model is β_1, the effective contact rate of HIV for susceptible individuals (most positively sensitive to $\mathcal{R}_0$). Another highly sensitive parameter in the second model is τ_2, the lymphoma treatment rate of patients with HIV and lymphoma (who are in class I_{LH}^a or I_{LH}^b).

In order to use the models as predictive tools, we did projections of the incidences of lymphoma in four scenarios. The scenario analysis present some probable trends the epidemic will take from 2014-2020, based on different percentage increase in the roll-out and uptake of effective of HAART coverage (as

an intervention strategy) in the Western Cape province of South Africa. In both models, the results show that an increase in the roll-out and effective use of HAART has a significant declination effect on the incidence of lymphoma in HIV-infected individuals, which will in turn result in a decline in the total lymphoma incidence in the nearest future. It will also increase the number of HIV and lymphoma patients who will get enrolled into the HAART program. Specifically, the second model shows that the incidence of lymphoma in patients with highly depreciated CD4 cell count is upswinging at an alarming rate, and earlier HAART administration is recommended.

The models presented in this study suggest that some social intervention programs, beside HAART roll-out can be used to control the epidemic. Such programs may include an increase in the awareness of the public to, and educational campaigns on HIV and its significant relation to the development of cancers. The second model particularly shows that patients with low CD4 cell counts have a higher risk of developing AIDS (and AIDS-related cancers consequently) or death. It also suggests that there will be an upswing in the incidences of lymphoma development if patients are being treated at a CD4 cell count of < 200 cells $/\mu L$ (which is often the case, due to late presentation of cases), as opposed to a CD4 cell count of > 350 cells $/\mu L$.

In conclusion, we suggest that more awareness programs be rolled out to educate the general populace on the importance of HIV-infected individuals presenting their cases early, and the likely risks of developing a disastrous cancer that they could incur if they fail to do so. This will assist in alleviating the governmental financial burden brought by the treatment of HIV-related malignancies, by reducing the cost of treating patients with HIV, and the few who may unavoidably develop some HRCs. The control of this epidemic in the Western Cape province of South Africa may be pivotal on this. We also suggest that it will yield better prognosis of HRL if patients are being treated at a CD4 cell count of > 350 cells $/\mu L$.

Appendices

Appendix A

Mathematical Tools

We give some exposition on the mathematical tools used in the qualitative analyses of the models presented in this work.

Definition A.0.1. (*Lozinskiĭ Measure* $\mu(X)$) Let X be an $n \times n$ square matrix and be an induced matrix norm. The associated logarithm norm μ of X is defined as

$$\mu(X) = \lim_{h \to 0^+} \frac{\|I + hX\| - 1}{h}, \tag{A.0.1}$$

where I is an $n \times n$ identity matrix, and $h \in \mathbb{R}^+$. The Lozinskiĭ measure is otherwise known as the *logarithmic norm*. (A.0.1) is sometimes expressed as the right-hand derivative

$$\mu(X) = D_+ |I + hX|_{h=0}. \tag{A.0.2}$$

The value of $\mu(X)$ depends on the matrix norm it induces. $\|\cdot\|$ denotes any norm in $\mathbb{R}^n$ [94].

The Lozinskiĭ measure $\mu(X)$ satisfies the following properties [95]:

1. $\mu(X) \leq \|X\|$.

2. $\mu(\gamma X) = \gamma \mu(X)$, for $\gamma \geq 0$.

3. $\mu(X + Y) = \mu(X) + \mu(Y)$, where Y is a matrix of the same dimension as X.

Definition A.0.2. (*Convex Set*) Let $\mathbf{F}$ be a vector space over the real numbers. A set $D \subset \mathbf{F}$ is said to be convex if, for all x and y in D, and all $t \in [0,1]$, the point

$$(1-t)x + ty$$

is in D. Geometrically, this means that every point on the line segment connecting x and y is in D.

Definition A.0.3. Let $\Omega \subset \mathbf{R}^n$ be a convex open set, and $x \longmapsto f(x) \in \mathbf{R}^n$ a $\mathcal{C}^1$ function defined in Ω. We consider the autonomous system (of differential equations) in $\mathbf{R}^n$

$$x' = f(x) \tag{A.0.3}$$

under the following assumptions:

(H1) The Jacobian matrix $\partial f/\partial x$ of the vector field f of (A.0.3) can be written as

$$\frac{\partial f}{\partial x}(x) = -\nu I + A(x) \quad \text{for all } x \in \Omega, \tag{A.0.4}$$

where ν is a constant and $x \longmapsto A(x)$ is an $n \times n$ matrix-valued function.

(H2) There exists a constant matrix B with rank $B = r$ such that

$$BA(x) = 0 \quad \text{for all } x \in \Omega. \tag{A.0.5}$$

The non-linear system (A.0.3) satisfying (H1) and (H2) is called an *invariant linear subspace* [63; 96].

Definition A.0.4. (*Simply Connected Set*) A simply connected set $D \subset \mathbf{R}^2$ is a connected set having the property that every simple closed curve in D cannot continuously shrink (within D) to a point. Geometrically, a simply connected set D is one without any holes.

Definition A.0.5. (*Bendixson's Criterion*) Suppose D is a simple connected open set of $\mathbf{R}^2$. We define a two-dimensional autonomous system

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ \frac{dy}{dt} &= g(x,y) \end{aligned} \tag{A.0.6}$$

If the expression $div(f,g) \equiv \partial f/\partial x + \partial g/\partial y$ is not identically zero and does not change sign in D, then, there are no periodic orbits of the autonomous system (A.0.6) (or its closed orbit lying entirely) in D.

Definition A.0.6. (Dulac's Criterion) Suppose D is a simple connected open set of $\mathbf{R}^2$ and $B(x, y)$ is a real-valued $\mathcal{C}^1$ function in D. If the expression

$$div(Bf, Bg) = \frac{\partial(Bf)}{\partial x} + \frac{\partial(Bg)}{\partial y} \tag{A.0.7}$$

is not identically zero and does not change sign in D, then there are no periodic solutions of the autonomous system (A.0.6) in D.

The function $B(x, y)$ is called a *Dulac function*. Dulac's criterion is a generalisation of Bendixson's Criterion, in the special case where $B(x, y) = 1$.

Definition A.0.7. (*Generalised Poincaré-Bendixson theorem*) Suppose a trajectory Γ of a planar system is forward invariant in a compact set K that contains a finite number of critical points, i.e. $\Gamma^+ \subset K$. Then $\omega(\Gamma)$ is either

- a critical point
- a periodic orbit
- a finite number of critical points $p_1, p_2, \ldots, p_k$ and a countable number of limit orbits (heteroclinics and/or homoclinics) whose α and ω limit sets belong to $\{p_1, p_2, \ldots, p_k\}$ [97].

This theorem is also known as the *Poincaré-Bendixson Trichotomy*.

Definition A.0.8. (*Additive Compound Matrix*) Let M be an $n \times n$ matrix, integer $1 \leq k \leq n$, and $M^{[k]}$ denote the *k-th additive compound matrix* of M. This is an $L \times L$ matrix, $L = \binom{n}{k}$, defined by

$$M^{[k]} = D_+(I + hX)^{(k)}|_{h=0}, \tag{A.0.8}$$

where $B^{(k)}$ is the k-th exterior power of an $n \times n$ matrix B, and D_+ is the right-hand derivative with respect to h. In the special cases $k = 1, k = n$, we find

$$M^{[1]} = M, \quad M^{[k]} = \mathrm{Tr}(M), \tag{A.0.9}$$

where $\mathrm{Tr}(M)$ signifies the trace of the matrix M. The term *additive* is used since

$$(M + N)^{[k]} = M^{[k]} + N^{[k]},$$

and the map $M \to M^{[k]}$ is linear [94; 98].

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