Modelling Early Initiation of HAART to Forestall AIDS-related Lymphoma in South Africa: a Cost-Effectiveness Analysis

by

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Abstract

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The burden of cancer in low and middle income countries has been projected to shift from 59% (in 2012) to 65% (by 2030) of all cancer cases globally. Since the introduction of highly active antiretroviral therapy (HAART) in South Africa, there has been a marked decline in AIDS-related illnesses and premature death. However, this has not been the case with AIDS-related lymphoma which was observed to be on the rise despite the large HAART roll-out programme. It was discovered that 37% of all lymphoma cases diagnosed in 2009 in the Western Cape province, were HIV-related, indicating a remarkable increase from 5% in 2002. The ineffectiveness of HAART in reducing the incidence of lymphoma is largely attributed to late commencement of treatment. However, increasing HAART coverage is still a major challenge to many developing countries in Africa as well as South Africa due to limited resources. Therefore, increasing early HAART initiation has a cost implication that needs to be investigated in resource limited settings. In this study we used a deterministic compartmental model to investigate the potential impact of initiating HAART at

different CD4 cell count levels on the incidence of lymphoma in HIV-infected individuals. We also developed a linked transmission and health state transition (Markov) model in TreeAge Pro to determine the cost-effectiveness of early HAART initiation from the public healthcare payer perspective. The CD4 count driven transmission model predicted lymphoma incidence in HIV-infected adults (aged 15 to 80 years) over a period of ten years. The Markov model predicted the health outcomes and costs. Data on transmission, transition probabilities, CD4 count thresholds, life expectancy, effectiveness and costs were obtained from literature. We compared early initiation of HAART at a CD4 cell count of greater than 500 cells/μL to initiation at less than 500 cells/μL, the current standard of care. Our primary outcomes were Quality-adjusted life years (QALYs), expected costs, net monetary benefit and the incremental cost-effectiveness ratio (ICER). Health outcomes and costs were discounted at a rate of 5% per annum as recommended in Southern Africa. We also performed deterministic sensitivity analyses to assess parameter uncertainty.

Results indicated that early HAART initiation prevents lymphoma cases and related deaths, translating to 3.76 QALYs gained over the 10-year time horizon (6.47 vs. 2.71 expected QALYs with HAART initiation at greater than 500 cells/μL and less than 500 cells/μL, respectively). The incremental cost of early initiation was \$14,613 compared to the alternative. The net monetary benefit (NMB) of early initiation was \$90,581 and \$30,063 for the alternative. HAART initiation at greater than 500 cells/μL was therefore cost-effective with an ICER of \$3,890/QALY gained. Sensitivity analysis showed outcomes were sensitive to the effectiveness of HAART in preventing lymphoma, with early initiation being more sensitive than the base case. Therefore, early HAART initiation at CD4 greater than 500 cells/μL would not only be effective in forestalling AIDS-related lymphoma but also cost-effective in resource limited settings.

Uittreksel

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Die las van kanker in 'n lae en middel-inkomste lande is geprojekteer vanaf 59% (in 2012) te skuif na 65% (in 2030) van alle kankergevalle wêreldwyd. Sedert die bekendstelling van hoogs aktiewe antiretrovirale terapie in Suid-Afrika, daar was 'n merkbare afname in vigs - verwante siektes en voortydige dood. Maar dit is nog nie die geval met vigsverwante limfoom wat waargeneem om op te gewees die opkoms ten spyte van die groot HAART uitrol program. Daar is vasgestel dat 37% van al limfoom gevalle gediagnoseer in 2009 in Wes-Kaap was MIV-verwante wat dui op 'n merkwaardige toename van 5% in 2002. Die ondoeltreffendheid van HAART in die vermindering van die voorkoms van limfoom is grootliks toegeskryf word aan die laat aanvang behandeling. Maar, die verhoging van HAART dekking is nog steeds 'n groot uitdaging om baie ontwikkelende lande in Afrika, insluitend Suid-Afrika as gevolg van beperkte hulpbronne. Daarom, die verhoging van die vroeë HAART inisiasie het 'n koste-implikasie wat gevolg moet word ondersoek in hulpbron beperk instellings. Ons gebruik 'n deterministiese kompartementele model om die

potensiële impak van die inisiëring HAART op verskillende CD4-seltelling vlakke op die voorkoms van limfoom in MIV-geïnfekteerde individue te ondersoek. Ons het ook 'n gekoppelde transmissie en gesondheid toestand oorgang (Verborge) model in TreeAge Pro om die koste-effektiwiteit van die vroeë HAART inleiding bepaal uit die openbare gesondheidsorg betaler perspektief. Die CD4-telling gedryf transmissie model voorspel limfoom voorkoms van MIV-geïnfekteerde volwassenes (15-80 jaar oud) oor 'n tydperk van tien jaar. Die Markov model voorspel dat die gesondheid uitkomste en koste. Data oor die oordrag , oorgang waarskynlikhede, tel CD4 drempels, lewensverwagting, doeltreffendheid en koste is verkry uit die literatuur. Ons vergelyk vroeë aanvang van HAART op 'n CD4-seltelling van meer as 500 selle/μL na inisiasie teen minder as 500 selle/μL, die huidige standaard van sorg. Ons primêre uitkomste was lewe jaar Kwaliteit-aangepaste (QALYs), verwagte koste, netto monetêre voordeel en die inkrementele koste-effektiwiteit verhouding (ICER). Gesondheid uitkomste en koste word verdiskonteer teen 'n koers van 5% per jaar soos aanbeveel in Suider-Afrika. Ons het ook uitgevoer deterministiese sensitiwiteitsanalises om parameter onsekerheid te evalueer. Resultate het aangedui dat vroeë HAART inisiasie verhoed limfoom gevalle en verwante sterftes, vertaal na 3.76 QALYs wat oor die 10-jarige tydhorison (6,47 teen 2,71 verwag QALYs met HAART inleiding op groter as 500 selle/μL en teen minder as 500 selle/μL , onderskeidelik). Die inkrementele koste van vroeë aanvang was $14,613 in vergelyking met die alternatiewe . Die netto monetêre voordeel (NMB) van vroeë aanvang was $90,581 en $30,063 vir die alternatiewe . HAART inleiding op groter as 500 selle/μL was dus kostedoeltreffende met 'n ICER van $3,890/QALY opgedoen. Sensitiwiteitsanalise het uitkomste was sensitief vir die doeltreffendheid van HAART in die voorkoming van limfoom, met vroeë aanvang om meer sensitief as die basis geval. Daroom, vroeë HAART inleiding op CD4 groter as 500 selle/μL sou nie net effektief in forestalling vigsverwante limfoom, maar ook koste-effektief in beperkte hulpbronne instellings wees.

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Dedications

To Mum, Dad, Ankunda and Andinda.
You are my source of inspiration and motivation.

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Chapter 1

Introduction

1.1 HIV and AIDS-related Cancers

Sub-Saharan Africa carries the greatest burden of HIV with about two-thirds of HIV-infected people living in this region [82]. There has been a high HIV prevalence and increasing burden of HIV-associated malignancies in this resource-limited region. HIV is known to attack cells that are critical to the human immune system and destroys their ability to fight infections. The HIV virus targets the $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the immune system. Although HIV infects other immune cells, it mostly wreaks havoc on the $CD4^+$ T cells by causing their destruction and decline, thus decreasing the immune system's resistance to invaders. As a result, people who have developed AIDS are unable to fight off infections by other viruses or bacteria and can die from infections that are normally harmless because as the immune system weakens, the body is vulnerable to life-threatening infections and cancers [19, 78]. These are normally referred to as opportunistic infections.

In an HIV-infected individual, the viral load and CD4 cell count are determinants of disease progression. The extent to which the immune system of an HIV-infected individual is weakened, often depends on the viral load. The lower the viral load in an individual, the stronger the immune system and thus, the less likely the development of opportunistic infections and AIDS-associated malignancies. "However, it has been shown that CD4 cell count is a better predictor of disease progression than viral load" [81]. CD4 cell count levels are the best predictors of the risk of opportunistic infections because the HIV virus usually targets these cells and destroys them. A

healthy individual is said to normally have a CD4 cell count of (800 - 1200) cells/μL [5]. Thus, a CD4 cell count below 500 cells/μL is usually an indicator of immune suppression and vulnerability to opportunistic infections.

Several types of cancer that develop during states of immunodeficiency in HIV-infected individuals are rare cancers associated with viral infection. Specific types of cancer that have been found to appear mainly in people living with HIV are Kaposi sarcoma, Non-Hodgkin lymphoma and Cervical cancer [19]. These cancers are often called AIDS-defining conditions, meaning that if a person with HIV has one of these cancers it can signify the development of AIDS.

According to the South African national HIV prevalence, incidence and behaviour survey 2012 by the Human Sciences Research Council (HSRC), HIV prevalence in South Africa has increased substantially. It was estimated that in 2012 about 6.4 million people were HIV positive (12.2% of the population) as compared to 5.2 million in 2008 (10.6% of the population), an increment of 1.2 million people [73, 77]. With an increase in the number of people infected with HIV, there is most likely to be an increase in incidences of opportunistic infections and AIDS-related malignancies. Despite the various interventions (such as HAART initiation) put in place to reduce the spread of HIV in South Africa, the current prevailing situation is still of major concern as there is no noted decrease in the incidence of HIV. As a result, the effectiveness and impact of the control measures in place has to be re-evaluated and carefully analysed as there is a cost implication that could be a financial burden to the country.

1.2 AIDS-related Lymphoma

Lymphoma is a cancer of the lymphatic system that starts in lymphocytes which are a type of white blood cells made in the bone marrow, lymphatic tissue and also in the blood. The lymphatic system is a network of lymphatic vessels that carry lymph, a colorless fluid containing white blood cells, throughout the body. The lymphatic system consists of lymph nodes which are found in clusters located in the abdomen, groin, pelvis, underarms and neck. Other organs that are part of the lymphatic system include the spleen, which makes lymphocytes and filters blood; the thymus, an organ under the breastbone and the tonsils, located in the throat. The major role of the lymphatic system is to defend the body against infections and

disease [22, 57].

Lymphoma starts when normal cells in the lymphatic system change and grow uncontrollably, forming a mass called a tumour. A tumour can be benign (non-cancerous) or malignant (cancerous, meaning it can spread to other parts of the body). Although lymphomas are often confined to lymph nodes and other lymphatic tissue, they can spread to other types of tissue anywhere in the body (extranodal disease). In contrast to lymphomas that occur in immunocompetent individuals, AIDS-related lymphoma often occurs extranodally (such as in the primary central nervous system lymphoma (PCNSL), gut or bone marrow) and has an aggressive clinical course [16, 22].

There are mainly two types of lymphoma, namely; Hodgkin's lymphoma (previously known as Hodgkin's disease) and Non-Hodgkin's Lymphoma (NHL). The two lymphoma types are similar in appearance, with the same kind of symptoms and occur in the same places but their difference is eminent under microscopic examinations. Their difference is in the involvement of a specific type of lymphocyte known as the Reed-Sternberg cells. Hodgkin's lymphoma (HL) develops from abnormal B-cells which are the Reed-Sternberg cells and Non-Hodgkin's lymphoma does not involve the Reed-Sternberg cells. HL tends to spread in a more orderly way than NHL. Classification of lymphoma is complicated due to the multitude of subtypes. This largely depends on genetic characteristics of affected cells, lymph nodes areas of the body they originate in, and many other factors. Hodgkin's lymphoma has five subtypes and Non-Hodgkin's lymphoma has about sixty classified subtypes according to the World Health Organisation [22, 56, 57].

Non-Hodgkin's lymphoma subtypes are classified mainly into B-cell lymphoma, T-cell and natural killer (NK) cell lymphoma. The B-cell subtypes are the most common, accounting for over 80% of all lymphomas. Examples of B-cell lymphomas include; Diffuse large B-cell lymphoma, Primary effusion lymphoma, Burkitt's lymphoma, Intravascular large B-cell lymphoma, Follicular lymphoma, Small cell lymphocytic lymphoma, Mantle cell lymphoma, Mediastinal (thymic) large B-cell lymphoma, etc [21, 56, 57]. T-cell and NK cell lymphoma subtypes include; Anaplastic large cell lymphoma, Hepatosplenic lymphoma, Cutaneous T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, NK-cell lymphoma and Peripheral T-cell lymphomas which are not specified [22, 51, 57]. NHL subtypes are known to be either indolent (slow growing) or aggressive (fast growing). The aggressive lymphomas

are the most common with Diffuse large B-cell lymphoma being the most common subtype and Follicular lymphoma being the most common indolent subtype. However, it is not unusual to find some patients with intermediate grade disease which lies between indolent and aggressive. While in some cases indolent lymphoma may transform to aggressive NHL [16, 22, 56].

HIV-infected individuals were found to be at increased risk of developing AIDS-related lymphoma 60-200 times more than other individuals [1, 21]. Although both hodgkin lymphoma and Non-Hodgkin lymphoma have been diagnosed in HIV-infected people, the latter is more common. AIDS-related lymphoma can be divided into three main types which are; Systemic NHL, Primary central nervous system lymphoma and Primary effusion lymphoma (also known as "body cavity lymphoma"). Incidence of NHL has been observed to be higher in men than women in general.
The Tygerberg Lymphoma Study Group (TGLSG) in Western Cape, South Africa was established in 2007 to investigate the impact of the HIV epidemic and Antiretroviral treatment policy on the incidence of HIV-related lymphomas (HRL) in Western Cape, South Africa [1]. Their findings indicated that in contrast to developed countries, cases of HRL were on the rise in Western Cape, South Africa despite the ART roll out plan that commenced in 2004.

Lymphomas specifically occurring in HIV patients are closely linked to other viral diseases, thus, the HIV virus is not thought to be a direct cause of lymphoma, but rather, it weakens the body's defence system and increases susceptibility to infections like Epstein-Barr and HHV-8 viruses which are associated with these lymphoma types [43]. AIDS-related lymphoma is the second most common type of AIDS-related cancer in Sub-Saharan Africa. HIV is said to increase the risk of high grade lymphomas which are the aggressive types of lymphoma that are known to grow quickly. Most AIDS-related NHLs belong to one of three categories of high-grade B-cell lymphomas: Burkitt's lymphoma, centroblastic lymphoma, and immunoblastic lymphoma [23]. Burkitt's lymphoma is the most common type of high grade NHL in South Africa. Lymphoma is fatal if not treated early enough and remains a significant cause of morbidity and mortality in people living with HIV in Sub-Saharan Africa [3, 51].

1.2.1 Lymphoma Diagnosis and Treatment

The symptoms of AIDS-related lymphoma depend on the location of the tumor. Lymphoma can be asymptomatic or may present with symptoms such as fever, sudden weight loss, night sweats, itchy skin and chills. However, the most common early symptoms of lymphoma are painless swellings (swollen lymph nodes) in the neck, groin, chest, underarm or abdomen. In cases where lymphoma starts from a body organ, symptoms such as rashes, chest pain, cough, abdominal pain and lumps under the skin, may be present [22, 56, 57].

The diagnosis of AIDS-related non-Hodgkin lymphoma often involves a complete physical examination including the history of a patient's habits and previous illnesses. It also includes lymph node biopsy, which involves taking a sample of lymph node tissue by needle or surgery to determine the presence of lymphoma [22, 56, 57]. The biopsy performed may include one of the following procedures:

- Removal of an entire lymph node (excisional biopsy).
- Removal of part of the lymph node (incisional biopsy).
- Removal of lymph node tissue by use of a wide needle (core biopsy).
- Removal of lymph node tissue by use of a thin needle (fine-needle aspiration (FNA) biopsy).
- Removal of bone marrow, blood, and a small piece of bone through inserting a hollow needle into the hipbone or breastbone (bone marrow aspiration biopsy).

Certain lab tests are also carried out to confirm presence of the disease and whether it may have spread to other parts of the body. These tests often include; complete blood count (CBC), spinal tap/lumbar puncture, HIV test and blood chemistry analysis. A complete blood count test involves checking a blood sample for the proportion of red blood cells, white blood cells and platelets. The spinal tap involves extracting spinal fluid from the spine using a needle, then checking it for cancer cells. In blood chemistry analysis, blood is screened for chemicals that are known to indicate presence of the disease in certain organs.
Also Imaging tests are carried out to help identify the location and distribution of enlarged lymph nodes, large tumors and other affected body organs. Imaging

tests include X-rays, Computed tomography (CT) scan, Magnetic resonance imaging (MRI) scan and Positron emission tomography (PET) scan [22, 56, 57].

If the above tests confirm the presence of lymphoma, then further additional tests are carried out to determine the disease stage. Staging is important in order to identify the lymphoma type and subtypes so as to determine the appropriate treatment to use. Staging involves determining the extent to which the cancer has spread and its location [22, 56]. Non-Hodgkin lymphoma has four stages of disease: stage I (early disease) is when the cancer cells are in only one lymph node area of the body; Stage II (locally advanced disease) is when the cancer cells are in two or more lymph node areas above or below the diaphragm; Stage III (advanced disease) is when the cancer cells are on both sides of the diaphragm; Stage IV (widespread disease) is a situation where by lymphoma has spread extensively in the lymph nodes and other body organs which are not part of the lymphatic system such as the liver, lungs, cerebrospinal fluid and bone marrow [20, 27, 56]. AIDS-related lymphoma stages may also be classified in terms of "E" and "S", where E represents extranodal disease where by cancer is found in other areas of the body besides the lymph nodes or has spread to areas surrounding the lymph nodes, and S represents the spleen, meaning cancer cells are found in the spleen. Stage III disease can be further classified as IIIE, IIIS and IIIE+S depending on the extent to which the lymphoma has spread. If a patient is undergoing lymphoma treatment but the cancer keeps spreading out, this condition is known as progressive disease, also called refractory NHL. Once lymphoma has been treated and it reappears some time later on, it is said to be recurrent or relapsed NHL [20, 22, 27].

Treatment of AIDS-related Lymphoma (ARL) mainly involves three standard therapy types namely; chemotherapy, radion therapy and high dose chemotherapy with stem cell/bone marrow transplant. In treating ARL patients, lymphoma therapy is combined with AIDS treatment in most cases. ARL treatment also includes Immunotherapy, which is a type of biological therapy designed to boost the body's natural defense system to fight off cancer. However, in the early stages of disease, the doctors may chose to watch and wait especially if the patient has indolent or low-grade lymphoma without symptoms. During the watchful waiting period, patients have to under go active surveillance where patients are monitored for possibility of the cancer spreading [20, 56, 57]. Chemotherapy involves the use of anti-cancer drugs to kill the cancer cells or hinder their ability to divide. The most common

NHL treatment combination contains cyclophosphamide, doxorubicin, vincristine and prednisone, known as CHOP. In some cases rituximab is added to CHOP. Chemotherapy can always be used in combination with other treatments. Radiation therapy involves the use of x-rays or other high-energy rays to destroy cancer cells. Non-Hodgkin lymphoma is often treated with external beam radiation therapy, administered alongside chemotherapy. Stem cell/bone marrow transplantation involves replacing bone marrow the contains cancer with hematopoietic stem cells which develop into healthy bone marrow. Hematopoietic stem cells are stem cells that produce all other blood cells and are found in the blood stream and bone marrow. Stem cell transplantation consists of two types, that is, Allogeneic and Autologous, depending on the source of the stem cells used. Allogeneic involves the use of stem cells from a donor and autologous involves using the patient's own stem cells that have been extracted and stored before chemotherapy . Stem cell transplant is often used to treat patients with aggressive or recurrent lymphoma and is usually administered in combination with high-dose chemotherapy [20, 22, 57].

Despite the improvement in prognosis and treatment of AIDS-related lymphoma, there are some complications that have been observed as a result of late treatment. Some HIV-positive individuals have been diagnosed with acute myeloid leukemia which is associated with chemotherapy and also secondary malignancy a few years after treatment which poses a challenge to the efficacy of the treatment used [12, 59]. However, there are continuous clinical trials being carried out currently to test several other types of treatment for NHL and hopefully a more effective type of therapy will be discovered soon.

1.3 HAART as Prevention of AIDS-related Lymphoma

Over the years, since the introduction of HAART, there has been a noted decrease in Kaposi Sarcoma incidence and other AIDS defining illnesses but this has not been the case with non-Hodgkin lymphoma which has been increasing [79]. South Africa has the largest Antiretroviral Therapy (ART) roll-out programme in the world. The current standard practice in South Africa is to commence antiretroviral therapy at CD4 cell count of less than 500 cells/μL but prior to 2014, the standard practice was to initiate treatment at CD4 less than 350 cells/μL which was implemented in

2011 and at CD4 less than 200 cells/μL before then. It was estimated that by mid 2012, over two million HIV-infected people in South Africa were on antiretroviral therapy, with the number of females in the programme surpassing the number of male patients. On average, it was estimated that 31.2% of the total number of HIV-positive people in South Africa were enrolled on ART in 2012 [73, 77].

The causes of most lymphomas are still unknown to clinicians and researchers, which makes prevention of the disease rather difficult. However, in order to address this kind of situation, one can take into consideration the risk factors related to developing lymphoma, such as immune deficiency. In the world today, HIV infection is one of the leading causes of immunodeficiency. Therefore, HIV prevention through antiretroviral therapy can be used as a strategy for improving the immunity of HIV-infected individuals, thus reducing the risk of immunodeficiency and AIDS-related malignancies such as non-Hodgkin lymphoma.

Currently, the standard antiretroviral therapy in use is Highly Active Antiretroviral Therapy (HAART) which consists of a combination of three drugs that suppress HIV replication, thus reducing immunosuppression. HAART, therefore improves the life expectancy of people living with HIV by reducing their chances of morbidity and mortality. In South Africa, HAART was introduced in 2004 and by 2008 it had an estimated coverage of approximately 371,731 patients [2, 28].

HAART has been highly effective in reducing the levels of human immunodeficiency virus, thus boosting immunity and increasing the chances of survival of HIV-infected people [24]. Improved immunity has led to a decline in incidences of life threatening illnesses such as AIDS-related malignancies in people living with HIV.

Since the introduction of HAART, there has been a decline in the incidence of non-Hodgkin lymphoma among HIV-infected individuals. However, in order to reduce the risk of developing non-Hodgkin lymphoma, early initiation of highly active antiretroviral therapy is advocated for. Studies have been carried out to show that low CD4 cell count increases the risk of several cancers after starting HIV therapy [89]. A study by Guiguet et al. [47] reported that the most predictive risk factor for all cancers, except anal cancer, is a patient's CD4 cell count and patients with a CD4 cell count of less than 200 cells/μL are most at risk of death. According to Biggar et al. [15], genetic errors of increased lymphocyte turnover could also increase the risk of developing non-Hodgkin lymphoma.

1.4 Health Interventions

A health intervention is a combination of strategies, policies or programs designed to improve the health status of individuals or an entire population, through shifting the whole distribution of health risk by addressing underlying social, economic and environmental conditions [49, 63]. A health intervention can also be seen as a deliberate activity aimed at improving the health of individuals by reducing risk, duration or severity of a health problem. Health interventions can be in the form of treatment to be administered, screening tests or even primary prevention techniques such as vaccination.

The importance of health interventions is to reduce disease incidences or complications that could cause accelerated morbidity and mortality in the population affected, hence improving quality of life and the life expectancy of individuals. The benefits of these interventions are known as health outcomes which can be in form of the number of deaths averted or improved years of life.

The effectiveness of a health intervention is determined by the improvements in health states and the resulting effects on life expectancy of individuals. In order to make a decision on the best choice of intervention, the efficiency of all available interventions is put into account. However, in order to maximise health benefits within a given budget, we need to know the cost per year of life saved and/or the cost per year of quality-life gained with that intervention. Therefore, for optimal use of resources available, we aim at minimizing the number of new infections in the population and thus maximizing the number of years lived in good health. It is thus imperative to carry out cost-effectiveness analysis of interventions put in place to prevent diseases in resource limited settings, in order to identify the strategies that offer the highest value for resources used.

1.4.1 QALYs and DALYs

Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QALYs) are standardized measures of the effects of a disease on the length of life and also take into consideration the negative effects of morbidity. Health programmes are geared towards averting DALYs and gaining QALYs.

QALYs can be seen as a measure of quality and quantity of life, that is a year of life lived in perfect health. QALYs are patient preferences of health states, where

by a year of life in one particular health state is more desirable than the other, for example, a year of life without lymphoma is more desirable than a year with lymphoma. The average number of QALYs we can expect to live at any given age is known as the Quality Adjusted Life Expectancy (QALE) which can be defined as the expected average number of years lived in perfect health. Health interventions aim to increase the QALYs of individuals in a given population thus offering the benefits of moving from a less desirable health state to a better one for a given period of time.

The DALYs are an indicator of how much people are disabled by their illness. The DALY is a quantitative measure of disease burden, that is, the number of years lost due to a certain disease or years of life lived in a certain disease state. DALYs can be used for direct comparison of disease burden and thus permit comparison of treated and untreated diseases. They also aid in comparison of different disease interventions such as treatment expansion versus prevention campaigns. DALYs comprise of mortality and morbidity. Mortality is a measure of life lost due to premature death and morbidity is a measure of all non-fatal chronic incidences such as illness episodes. The DALYs calculation is given by the overall sum of the number of years of life lost due to a disease and the number of years lived with a disability caused by the disease. Therefore;

DALYS = **Mortality** + **Morbidity**,

where mortality and morbidity are given by
Mortality = Life expectancy - Age at death
Morbidity = Disability weight $\times$ Duration of disability

The disability weight is a severity rating ranging from 0 to 1 given to each illness effect, with 1 implying fully disabled/dead and 0 standing for fully healthy/no disability. According to the global burden of disease 2013 study [68],the disability weights for symptomatic HIV, HIV/AIDS on ART and AIDS without ART are 0.274, 0.078 and 0.582 on average respectively. While for cancer with primary treatment the average disability weight is 0.288, metastatic cancer, 0.451 and when the cancer is in terminal phase, the disability weights on average are 0.54 with medication and 0.569 without medication.

1.5 Cost-Effectiveness Analysis

Cost-Effectiveness Analysis (CEA) in public health is used to asses health care interventions in terms of the benefits they provide. Reporting of results is usually in terms of resources needed to produce an extra unit of change in health effectiveness. CEA compares two or more health interventions in terms of their costs and effectiveness. The incremental cost-effectiveness ratio (ICER) is often used to express the results (a lower cost effectiveness ratio implies a higher degree of comparative value and vice versa). The main purpose of CEA therefore, is to examine efficiency of activities so as to ensure the best use of available resources and identify possibilities of reducing costs or extending benefits for the same costs.

In health evaluation, an intervention is regarded as cost-effective if;

- It is less costly but as effective as the competing alternative. The competing alternative is the intervention being compared with the intervention of interest.
- It is more effective and more costly but the added benefit is worth the additional cost.
- It is less effective and less costly, where the added benefits are not worth the additional costs.
- It is cost saving with an equal or better outcome.

Interventions that include multiple strategies are usually the most effective in giving rise to desired change.

According to the World Health Organisation, a health intervention is considered to be cost-effective if it costs less than three times the national annual gross domestic product (GDP) per capita, per disability adjusted life year (DALY) averted. Further, if an intervention costs less than once the national annual GDP per capita, it is considered highly cost-effective. The GDP of a country is a measure of the size of its economy. It represents the monetary value of all goods and services produced within a country's geographic borders over a specified period of time.

Cost-effectiveness analysis is used in forecasting the effects of one intervention strategy in comparison to another in terms of years of life lost, or years of life gained

and the related costs, as a result of the intervention and health care costs in order to estimate cost-effectiveness.

In order to determine the cost-effectiveness of the interventions under consideration, we review program financial and services records over a given period of time to quantify the resources used, associated costs and clients served.

1.6 Problem Statement

People living with HIV have been found to be at an increased risk of developing AIDS-related lymphoma 60-200 times more than other people. The human immunodeficiency virus (HIV) which causes AIDS is still a major public health challenge in the world today, mainly due to the rising incidences of cancers associated with HIV infection, despite the various prevention strategies put in place to prevent HIV progression. There is still an urgent need to curb HIV spread and prevent incidences of AIDS-related malignancies in Sub-Saharan Africa, although resources available for interventions are limited. This creates an increasing need to identify the best intervention option that gives the best value for available resources. Thus, the need for Cost-Effectiveness Analysis of prevention strategies in place and those under consideration.

1.7 Research Question

With the increase in lymphoma incidence, and given the challenges that surround treatment of lymphoma in HIV-infected individuals, there is need to examine the economic impact there of. It is therefore imperative to determine how the timing of HAART initiation could impact the incidence of AIDS-related lymphoma and the associated cost-effectiveness. Therefore the question is:
Would increased early initiation of highly active antiretroviral therapy (HAART) be effective and cost-effective in forestalling AIDS-related lymphoma in South Africa?

1.8 Aims/Goals

The goals of this study are as follows:

i. To show the impact of early initiation of HAART on the incidence of AIDS-related non-Hodgkin lymphoma and the associated cost-effectiveness.

ii. To guide the decision-making process of policy-makers regarding prevention and treatment of AIDS-related lymphoma in resource limited settings.

1.9 Objectives

The study objectives are as follows:

i. To examine the impact of early HAART initiation on Lymphoma incidence in people living with HIV.

ii. To asses the effectiveness of HAART in forestalling AIDS-related lymphoma.

iii. To examine the impact of antiretroviral therapy on the quality of life of HIV-infected individuals in South Africa.

iv. To determine the net costs and effectiveness of early therapy initiation in South Africa.

1.10 Significance of the Study

With the advent of highly active antiretroviral therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression (Palella et al. 1998 [66]). However, reports have shown that complete immune reconstitution may not be possible if the commencement of HAART is at a stage when the CD4 cell count of an infected person is very low [18, 89]. In our study therefore, we aim at showing the advantages of early therapy initiation to the immune system of HIV-infected individuals.

Although quite a number of studies have been carried out to determine the efficacy of HAART in reducing HIV infection, such as Granich et al. 2012, Auvert et al. 2004, Sterling et al. 2001, Opravil et al. 2002 [9, 46, 65, 81], limited attention has been given to early HAART initiation as prevention for AIDS-related malignancies. We thus assess the potential impact of early HAART initiation on the incidence AIDS-related lymphoma.

A search carried out by MEDLINE for articles published in 2007 relating to cost-effectiveness, cost utility or economic evaluation revealed that quite a small proportion of such publications were from developing countries despite limited health care resources. The search revealed that only 7% of the 564 articles were from developing countries and only eight were from Africa [74]. This is an indication of the gap in this area of research in Africa and therefore need for more studies in economic evaluation to inform health policy.

1.11 Key Terminology

HIV, HAART, CD4 cell count, Non-Hodgkin Lymphoma (NHL), AIDS-related lymphoma (ARL), Cancer, Malignancies, Cost, Cost-effectiveness Analysis (CEA), Incremental cost-effectiveness ratio (ICER), Disability-adjusted life year (DALY), Quality-adjusted life year (QALY).

1.12 Brief Chapter Overview

In chapter one we have looked at the background of HIV and AIDS-related Lymphoma and the motivation for our research. Going forth, in the next chapter we will review some of the previous studies that are related to our research problem in order to justify our approach and method used to address the research problem in question. In chapter three, we shall elaborate on the methods used for our research work, analysing the mathematical model formulated and decision tree created. In the final chapter, we then present and explain the results and give some recommendations for future research.

Chapter 2

Literature Review

Intoduction

In this chapter we review some of the studies related to HIV/AIDS prevention, the impact of HAART on HIV incidence and AIDS-associated malignancies in published literature. We also review some of the existing interventions for AIDS-related cancers and their cost-effectiveness.

2.1 Impact of HAART on HIV in Sub-Saharan Africa

A study by Auvert et al. 2004 [9] to determine the impact of HAART on HIV transmission and spread in South Africa revealed that HAART could reduce the annual risk of HIV transmission by approximately 11.9%. The cohort study was done on a random sample of about one thousand men and women between the ages of 15 - 49 years in a high HIV-1 prevalence township in Johannesburg. According to their findings, prevalence of HIV-1 was 21.8%, and 9.5% of these were eligible for HAART, while 6.3% would need to start treatment in each of the next three years. Only a small proportion of partnerships involved a spouse with a CD4 cell count below 200 cells/μL and would have benefited from HAART reducing transmission (by decreasing the plasma HIV-1 RNA load [81]). There was a significant improvement in the health status and life expectancy of HIV-infected patients enrolled on ART observed among the cohort. However, it was estimated that if the threshold for HAART intiation had been adjusted to less than 350 cells/μL at the time of the

study, the impact of HAART on the short term spread of HIV would have been greater. It was estimated that had the threshold of ART initiation been raised to less than 350 cells/μL at that time, 56.3% of HIV patients would be eligible to start ART and as a result the reduction in transmission of HIV of 50% for spousal and 59.3% for non-spousal relationships would benefit from the intervention. Also the annual risk of HIV transmission would be reduced by 71.8%. This study indicates the importance of HAART in reducing HIV infection and thus narrowing the possibility of increased incidence of AIDS-related malignancies. The less the number of people infected with HIV, the less the number of HIV-related cancers that will be expected.

A study by M. Badri et al. 2006 [11] to determine when to initiate highly active antiretroviral therapy in sub-Saharan Africa showed that there was an increase in clinical benefits of early HAART initiation in South Africa. The model used in this study had 7 health states defined by three CD4 cell count thresholds,that is, less than 200 cells/μL, $(200 - 350)$ cells/μL and greater than 350 cells/μL classified by two treatment alternatives of ART and No-ART. The study used a cohort of 10,000 patients which was run over 50 years so that almost all of the patients were dead when it terminated. Cost-effectiveness analysis was carried out using a markov state-transition model with Monte Carlo simulation in TreeAge Pro. It was observed that 295 patients died from the No-ART group which was very significant as compared to only 34 that died from the HAART group. The death rate of patients in the class of CD4 count less than 200 cells/μL was significantly greater than that of patients in the other two classes. Also the study related the decline in the incidence of AIDS, Tuberculosis and death to early initiation of treatment. The life expectancy of patients on HAART was found to be in the range of 18.8 to 23.3 years. Therapy initiation at a CD4 cell count of greater than 350 cells/μL was shown to be more cost-effective with an incremental cost-effectiveness ratio (ICER) compared to initiation at $(200 - 350)$ cells/μL, of US$1,137 per quality-adjusted life year (QALY), while initiation at $(200 - 350)$ cells/μL had an ICER of US$616 as compared to initiation at less than 200 cells/μL [11]. The study showed that for people living with HIV, HAART is reasonably cost-effective and most effective if initiated at a CD4 cell count level of greater than 350 cells/μL . This result indicates that initiating antiretroviral therapy at an early stage is beneficial in terms of costs and additional clinical benefits. However, given that the study period was only 22 months, this period is not sufficient enough to rely on the results indicating that CD4 cell count is a better predictor of HIV progression than HIV-RNA levels

in patients receiving HAART.

Leigh F. Johnson et al. 2011 [54] designed a model to determine the impact of antiretroviral treatment initiation policy on the rate of ART uptake using data from Masiphumelele settlement community in Cape Town. The study was driven by the uncertainty of the impact of the new ART initiation policy at the time on the number of patients that would get enrolled on ART. Future ART uptake projections were also limited by the uncertainty surrounding the rate at which patients who had previously stopped taking treatment restart ART. The data from Masiphumele community also helped to address the challenges encountered by several other similar studies as a result of loss to follow up. The rate of ART initiation was estimated using the number of patients starting ART in the community, stratified by gender, year of initiation, CD4 cell count and previous enrolment on ART. Results from the study indicated that despite the expansion of eligibility criteria for starting ART to include patients with CD4 cell count in the range $(200 - 349)$ cells/μL, the rate of ART initiation of patients within that category was considerably low especially among male HIV-infected individuals. Asymptomatic patients with CD4 cell count between 200 cells/μL and 350 cells/μL were less likely to know their status and thus less likely to start ART which explained the small increment in the number of patients enrolling on ART despite the increased eligibility threshold. The rate at which patients with CD4 cell count greater than 200 cells/μL enrolled on ART was largely dependent on the number of patients in that category that went for HIV testing and were thus aware of their status. The rate of ART initiation among treatment-naive patients with low CD4 cell count of less than 200 cells/μL was found to be higher than that of patients that had previously dropped out of the ART programme. From this study we see that despite the change in ART initiation threshold, the actual change in the number of patients enrolling on ART was not very significant. This implies that in order to increase ART initiation, several other strategies such as increasing awareness and HIV testing should be taken into account besides raising the eligibility threshold.

A study by Sterling et al. 2001 [81] to determine the clinical response to HAART of HIV-infected individuals was done by assessing disease progression according to the levels of HIV-1 RNA and CD4 cells in both the patients on treatment and those not receiving HAART. This study was done with a cohort from the John Hopkins hospital HIV clinic. The cohort comprised of 1014 HIV patients of whom 530 were on

HAART and the cohort was followed up for 22 months on average. It was observed that among the patients who had started HAART with CD4 cell count less than 200 cells/μL, there was a reduced risk of disease progression due to treatment in contrast to those who did not receive treatment. However, patients with CD4 cell count greater than 200 cells/μL prior to HAART initiation did not show any statistically significant effects of HAART on HIV disease progression. Patients on HAART with CD4 cell count less than 200 cells/μL were found to have the highest risk of disease progression regardless of their level of HIV-1 RNA. The study indicated that CD4 cell count was a better predictor of which patients would benefit more from HAART than their level of HIV-1 RNA.

2.2 Cost-Effectiveness Analysis of HAART and HIV Interventions in Africa

There have been several studies to determine the cost-effectiveness of HAART in resourse limited settings. In this section, we look at the research findings of some of these studies.

A review study by Creese et al. 2002 [30] to determine the cost-effectiveness of HIV/AIDS interventions in Africa indicated a big margin in the cost-effectiveness of different interventions. The study was carried out using expert consultations and databases with more than sixty reports identified that measured the cost (in US$) and effectiveness of HIV/AIDS interventions in Africa. Only 24 of these reports satisfied the criteria for inclusion and were used to determine the cost per HIV infection averted and QALY gained for 31 interventions in the year 2000. The results of this study revealed that HIV could be prevented with interventions like blood safety measures, condom distribution and treatment of sexually transmitted diseases at a cost of $11 and a QALY gained at $1. Interventions such as voluntary counselling and testing, mother-to-child prophylaxis and treatment of Tuberculosis had a cost less than $75 per QALY gained. Other interventions involving antiretroviral therapy and home-based care programmes were found to be much more expensive with home-based care costs ranging from $100 to $1000. This study highlights the importance of carrying out cost-effectiveness analysis in Africa for better management of available resources. However, this research report was rather confusing as they seemed to refer to DALYs as desired and yet in reality it is the QALYs that are

desired and thus gained while the years of life lost due to disability (DALYs) are undesired and therefore minimised.

A cost-effectiveness analysis of expanding ART for prevention and treatment of HIV in South Africa was carried out by Granich et al. 2012 [46]. The study considered four CD4 cell count thresholds for eligibility of initiating antiretroviral therapy and a 90% coverage of HIV testing among the age group of 15 to 49 years with an assumption of ART reducing HIV transmission by 92%. Findings from this study indicated that increasing ART initiation at CD4 less than 350 cells/μL could potentially reduce new HIV infection by 265,000 and 1.4 million over 5 and 40 years respectively. Also the same strategy could reduce deaths by 200,000 and costs by $504 million in 5 years and approximately 15.7 million DALYs averted and 3.9 billion dollars saved over 40 years. Initiation at CD4 cell count less than 500 cells/μL was also found to potentially reduce mortality by 1.9 million and DALYs by 14.8 million in 40 years with cost reductions of about $100 million in 5 years and $5 billion in 40 years. While considering initiation at all CD4 cell count levels would further reduce infections by 3.3 million, deaths by 3.5 million and DALYs by 25.7 million with a cost saving of $10 billion in 40 years compared with initiation at CD4 count less than 350 cells/μL. Further more, it was also found that if ART could reduce transmission by 99%, savings could reach $17.5 billion with initiation at all CD4 cell count levels. This study showed the importance of ART initiation at a higher CD4 cell count threshold in controlling HIV spread and bringing about improved quality of life, reduced costs and more lives saved. We can therefore see that increased early ART initiation for HIV prevention and treatment in South Africa is cost-effective over time.

A study by Badri et al. 2005 [10] to asses the cost-effectiveness of HAART in South Africa indicated that use of HAART was cost-effective. The study compared the costs and utilisation of HIV-1 related services among patients on HAART and those not receiving antiretroviral therapy (but were accessing other HIV-related care services) in the Cape Town AIDS cohort. The cohort comprised of 1,630 patients of which 292 received HAART and the rest had not access to antiretroviral therapy throughout the study. Of those who received ART, 27 had AIDS and 235 of the no-ART patients also had AIDS. HAART initiation was stratified by CD4 cell count, WHO stage of AIDS, age and social-economic status. About a third of the patients in the matched non-AIDS group (with HAART and no-ART) had a CD4 cell count

of less than 200 cells/μL. Progression of disease was observed to be significantly lower among HAART patients with a median of 4.1 years than in the no-ART with median 3years in the non-AIDS cohort. On the other hand, in the AIDS group, 77% of the patients had CD4 count less than 200 cells/μL, median progression time was 3.1 years and 1.4 years among the HAART and no-ART groups respectively. The incremental cost per year of life gained for AIDS patients was cost saving for the two HAART price scenarios (US$730 per annum - scenario 1 and US$181 per annum - scenario 2) considered. The study results indicated that for the no-AIDS patients the mean number of in-patient days for individuals on HAART were significantly less than those in the no-ART group and the average service provision for the no-ART group was relatively higher than the HAART group under price scenario 2 but was considerably lower under price scenario 1. The incremental cost per year of life gained under HAART price scenario 1 was $1,622 and $675 for scenario 2. For patients with AIDS, the mean in-patient days for no-ART group were much higher than that of the HAART group but the mean out-patient visits were not very different for both groups. The average service provision was however found to be much higher among the no-ART group than in the HAART group regardless of the price scenario. The incremental cost per year of life gained here was cost-saving in both scenarios of HAART prices. From this study we can deduce that HAART is cost-effective in South Africa and is even more cost saving if the price of HAART is reduced to about $181 per annum. Therefore with the use of HAART as an intervention for prevention of HIV progression, there will be savings on hospital utilisation and end of life care for HIV-infected patients thus resulting in reduction of general health care costs. However, we note that from 1995 to December 2000 (the period in which this study was done), HAART was not yet available in the healthcare sector of South Africa that is publicly funded.

2.3 AIDS-related Lymphoma Progression and Interventions

There has not been much done on mathematical modelling of AIDS-related lymphoma in Africa. With regards to published studies, there is none on mathematical modelling of lymphoma yet.

However, in a study done by M.D Akinlotan and F. Nyabadza at Stellenbosch University, 2013 a mathematical model of CD4 cell count driven AIDS-related non-

Hodgkin lymphoma was developed and analysed [6]. According to their findings, patients with a CD4 cell count less than 200 cells/μL have a higher chance of developing AIDS and lymphoma therefore, as the incidence of lymphoma increased among this group. They also predicted that the increased effective use of HAART in the population, could significantly reduce the incidence of lymphoma in HIV-infected patients.

Existing reports on AIDS-related lymphoma interventions are mainly in the form of comparing treatment options e.g Best et al. 2005, De witt et al. 2013, Marti-Carvajal et al. 2009 [14, 35, 60]. Only a few studies have been done regarding lymphoma prevention in HIV patients and these are in relation to the timing of antiretroviral therapy initiation.

A study by Stebbing et al. 2004 [79] to determine the influence of HAART and immunologic factors on the risk of non-Hodgkin lymphoma revealed that the effective use of HAART could prevent NHL through maintaining CD4 and CD8 counts. The study investigated changes in innate and adaptive immune functions and confirmed that HAART leads to delays in cancer progression. It was observed that the protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) in HAART are equally effective in protecting against cancer. Also, it was noted that a decrease in immune parameters predisposes individuals to AIDS-related cancers. Of the 9,621 HIV-infected patients in the cohort study, 280 patients had developed lymphoma and of these, 206 had systemic non-Hodgkin lymphoma, 55 had primary celebral lymphoma and 19 had hodgkin's disease. It was observed that lower T-cell and natural killer cells significantly predisposed individuals to systemic NHL. The study also revealed that a low CD4 cell count, together with a CD8 count of greater than 846 cells/μL was sufficient enough to offer protection from NHL.

Crum-Cianflone et al. 2009 [31] carried out a cohort study to describe the trends in the incidence of cancers among HIV-infected people and the impact of antiretroviral therapy. This study was done on over 4 thousand HIV-infected U.S military beneficiaries with 33,486 person-years of follow-up for twenty years. The study revealed that 10 percent of the cohort developed cancer and the rate of AIDS-related cancers increased between the early (1984-1990) and late (1991-1995) pre-HAART eras and reduced significantly during the HAART era. It was also observed that low CD4 cell count, lack of HAART and AIDS diagnosis were predictors of AIDS-related cancers. The study indicated that HAART significantly reduces chances of developing AIDS

defining cancers and non-AIDS defining cancers in HIV-infected individuals. This study therefore highlights the importance of HAART in reducing the incidence of AIDS-related cancers.

Besson et al. 2001 [13] carried out a study using HIV-infected patients in the French Hospital Database on HIV to investigate the changes in AIDS-related lymphoma before and after the introduction of HAART. Their findings indicated a decrease in the incidence of AIDS-related lymphoma from 86 per 10000 person-years during the first period of 1993-1994 to 42.9 per 10000 person-years during the second period of 1997-1998. It was observed that patients with similar CD4 cell counts in the first and second period were at equal risk of developing AIDS-related lymphoma. Patients with CD4 count greater than 350 cells/μL were found to be at lower risk of developing lymphoma and those with a CD4 cell count less than 50 cells/μL had the highest risk of developing AIDS-related lymphoma. It was also observed that the number of patients at risk of developing lymphoma with a CD4 cell count less than 200 cells/μL decreased fron 49.5% to 24.5% between the two periods and during the second period 64% of the patients diagnosed with ARL had been on HAART. There was significant increase in survival of patients from about 6.3 months in the first period to about 21.2 months in the second period. This increase in survival was attributed to the change in proportion of patients on HAART from 40% to 100% between the two periods. The results of this study are indicative of the importance of HAART in reducing the risk of lymphoma among patients with low CD4. From this study we can also deduce that early therapy initiation is important in reducing the incidence of lymphoma in HIV-infected people.

A study by Achenbach et al.2011 [3] to evaluate the survival of patients after diagnosis of cancer revealed that there are several factors that contribute to mortality in HIV-infected individuals diagnosed with cancer. These factors include failure of ART to completely suppress HIV, the cancer stage at diagnosis and inaccessibility of cancer treatment. The study was carried out on a cohort of HIV-positive patients enrolled on ART for atleast six months before being diagnosed with cancer. The results of the study showed that on average, patients developed cancer after three years and only 92% of them were still on ART at the time of cancer diagnosis. Overall, more than 3% of the patients on ART developed cancer and the mortality rate of these patients was found to be 20.6 per 100 person-years and their overall two-year survival rate was at 58%. There was increased mortality among patients with low

CD4 cell count and most of the patients had low nadir CD4 count. This finding further stresses the point that early ART initiation is vital for immune reconstitution and prevention of HIV-associated malignancies.

A case-control study by Stein et al. 2008 [80] looked at the risk of HIV-1 associated cancers among the South African black population. The study confirmed the strong link between Kaposi sarcoma, non-Hodgkin lymphoma and HIV infection. An increased risk of developing NHL among the black HIV-infected patients that is consistent with other research studies done with different population groups in Africa was observed. There was an association between Hodgkin lymphoma and HIV observed as well as several other virus associated cancers. The risk of HIV-infected individuals developing cancer was higher than HIV-negative individuals, with the risk of Kaposi sarcoma about 50 times high, non-Hodgkin lymphoma 6 times high, and other cancers such as cervical cancer, squamous cell skin cancer, anogenital and Hodgkin lymphoma $(1.5 - 2.5)$ times high. Highly active antiretroviral therapy was not routinely available during the study period and thus the effects of treatment on cancer incidence could not be readily established. This study shows that the risk of HIV-related cancers among HIV-infected individuals in South Africa is the same as in other African countries and is slightly lower than that observed in developed countries. The significance of this study is to see the spectrum of HIV-related cancers in the South African HIV-positive population prior to initiation of HAART.

A review study, taking into account the epidemiology, diagnosis and treatment of AIDS-related non-Hodgkin Lymphoma in high prevalence resource poor setting was carried out by Ulrickson et al. 2012 [82]. The study examined several published literature on AIDS-related NHL comparing the findings of different studies from Africa and other developed nations in the pre-combination antiretroviral therapy (pre-cART) and post-cART eras. However, the true incidence of NHL in Africa was believed to be higher than that documented but limited by inefficiency in data collection and inaccessibility of medical care. It was found that in Africa on average, patients developed HIV-related complications at a higher CD4 count than those in developed countries. This study highlights the fact that access to cancer care is a major challenge in resource poor settings due to the high costs involved thus leading to difficulties in increasing accessibility to treatment for patients who are in need. Despite this, it was estimated that the cost of inaction was more significant to the situation in developing countries than the actual cost of accessing treatment and

care. Improvement in treatment of HIV-related lymphoma in developing countries was largely attributed to accessibility to antiretroviral therapy, early detection of the disease and effective management of other opportunistic infections. This study brings to attention the fact that cancer care and treatment is very costly and therefore much emphasis needs to be put on prevention and early detection rather than treatment of advanced disease. End stage cancer is much more expensive to take care of due to the intensive therapies required and the high risk of non-response to therapy.

2.4 Conclusion

In conclusion from the above studies, we can deduce that HAART is very instrumental in reducing the risk of HIV-related malignancies among people living with HIV in Sub-Saharan Africa. Where as it is important to increase HAART coverage for prevention of AIDS-related cancers, the timing of HAART initiation is crucial to this cause. We also observe that concurrent treatment of HIV and HIV-related opportunistic infections plus early diagnosis and treatment of these cancers will lead to increased overall survival among HIV-positive individuals. With these observations, the challenge still remains on what is the cost implication of increasing HAART initiation. Given the fact that we are looking at quite a large number of people living with HIV in South Africa and considering the budgetary constraints of the country. Although studies have shown that HAART is cost-effective for people living with HIV in South Africa, there has not been any study yet to determine if increased early HAART initiation would still be cost-effective in the prevention of AIDS-related malignancies. The fact that there is no known direct cause of malignancies makes it difficult for one to come up with optimal prevention strategies but knowing that for HIV-infected individuals, HAART has the ability to reduce the risk of developing HIV-related cancers, it is thus worthwhile to look into all possibilities of obtaining the maximum benefits that HAART could offer.

Chapter 3

Mathematical Model for AIDS-related Lymphoma

3.1 Intoduction

In this chapter, we formulate a mathematical model for lymphoma progression with HAART intervention at different CD4 cell count levels in resource limited settings. We start off with a fully susceptible population and model the dynamics of HIV with progression to AIDS-related lymphoma. We examine the potential impact of initiating treatment at a CD4 cell count level of greater than 500 cells/μL or less than 500 cells/μL to determine which option gives the best value for resources used.

We also develop and analyse a linked transmission and health state transition (Markov) decision analysis model incorporating lymphoma incidence projections from HIV-infected individuals with and without HAART, using TreeAge Pro 2015, healthcare decision analysis software (TreeAge Software, Williamstown, MA, USA). We use this model to determine the expected costs per quality of life gained (QALYs) with HAART initiation at the two CD4 count thresholds (that is, greater than 500 cells/μL and less than 500 cells/μL) over a period of ten years.

3.2 Model Formulation

We develop a mathematical model with intervention that projects the development of lymphoma from both HIV positive and negative individuals. Our total population $N(t)$, is taken to be the adult population in the range of 15 to 80 years of age. This

is due to the fact that we are considering the sexually active population from 15 to 49 years, that is more susceptible to HIV infection. The incidence of lymphoma and many other cancers is generally observed to be higher in individuals above the age of 60 than the younger population. Old age is a major risk factors for developing lymphoma and hence the choice of population age range 15 to 80.

We construct a compartmental model describing the movement of individuals from one health state to another, starting from the susceptible class (S). Individuals can either develop lymphoma or get infected with HIV, thus moving into the L class or I_{H} class respectively. At this stage, there is no intervention yet because the individuals are not yet aware of their status. A proportion of individuals in the lymphoma class then progress into the cancer therapy class (H_{L}) on discovering they have developed lymphoma (this may be through screening tests done or ill health that necessitates seeking medical attention), while others contract HIV and move into the class of HIV-infected with lymphoma (I_{HL}). Some individuals from the HIV-infected class (I_{H}) progress into the HIV-infected with lymphoma class (I_{HL}) and others go on to start HIV treatment (HAART). We classify the HIV-infected individuals who enrol into HAART into two classes which we will refer to as the a and c class depending on their CD4 cell count at the time of starting treatment. The I_{HT}^{c} class consists of those that start treatment with a CD4 cell count of less than 500 cells/μL and the I_{HT}^{a} class consists of those that start treatment with CD4 cell count of greater than 500 cells/μL. A certain proportion of individuals from the I_{HT}^{c} class progress to the I_{HT}^{a} class at a CD4 cell count upswing rate ξ. Some individuals from these two classes go on to develop lymphoma and move to the class of HIV-infected with lymphoma on HAART (I_{HLT}). Some individuals from the I_{HL} class also enrol into HAART and move into I_{HLT} class while others go on to receive cancer therapy without HAART, that is, move to the H_{HL} class. Individuals in the class of HIV-infected on HAART with lymphoma (I_{HLT}) are enrolled into cancer therapy at a rate ρ_3. The total population N at any time (t) is thus given by;

$$N = S + L + I_{H} + I_{HL} + I_{HT}^{a} + I_{HT}^{c} + I_{HLT} + H_{L} + H_{HL} + H_{HLT}. \tag{3.2.1}$$

The intervention considered here is the initiation of HAART, which is administered at different CD4 cell count levels to see which option is more effective in preventing the development of AIDS-related lymphoma.

We consider different classes for treatment of lymphoma, which are; lymphoma

therapy hospitalization for lymphoma only patients (H_{L}), lymphoma therapy hospitalization for patients with both HIV and lymphoma without antiretroviral therapy (H_{HL}) and lymphoma therapy hospitalization for lymphoma patients with HIV and on HAART (H_{HLT}). This is done in order to account for the differences in costs of treatment in the different categories depending on whether the patient has HIV and is enrolled in HAART or not. Lymphoma therapy requires hospitalization for treatment which cannot be otherwise administered at home.

In our model, there are two classes that are susceptible to HIV infection and these are the S and L classes. We assume the same force of infection for both classes. However, the effective contact rate of individuals in the S class will be different from that of individuals from the L class and the rates are: β_1 and β_2 respectively. The parameters β_i, $i = 1, 2, 3$, represent the transmission risk when an HIV-infected individual comes into contact with a susceptible person. It is the number of contacts per unit time or the probability of an infection occurring. We have $\eta_i, i = 1, 2, 3$ as the modification parameter that measures the relative infectiousness of individuals in classes $I_{HL}, I^a_{HT}, I^c_{HT}$ and I_{HLT} to those in the I_H class. The force of infection λ is therefore given by the following equation;

$$\lambda = \frac{\beta_i}{N}\left[I_H + \eta_1 I_{HL} + \eta_2(\, I^c_{HT} + I_{HLT}\,) + \eta_3 I^a_{HT}\right]. \tag{3.2.2}$$

provided $\lambda(t)$ is redefined at the ϵ-neighbourhood of $N = 0$, for it to be biologically plausible and finite at time, $t = 0$. The infectiousness of HIV-infected individuals is directly proportional to their viral load. We therefore consider $0 < \eta_i < 1$ for $i = 1, 2, 3$.

The individuals in the class of HIV-infected with lymphoma and not on HAART (I_{HL}) are assumed to have a higher viral load as compared to the other infected individuals in the other classes who are receiving HAART [26]. Also the individuals in the I^a_{HT} class are considered to have a lower viral load as compared to those in the I^c_{HT} and I_{HLT} classes because their CD4 cell count levels are reasonably higher than that of the individuals in the two classes, I^c_{HT} and I_{HLT}. It therefore follows that $0 < \eta_3 < \eta_2 < \eta_1 < 1$, meaning that individuals in the I_{HL} class are more infectious than those in I^c_{HT} and I_{HLT}, who are also more infectious than those in the I^a_{HT} class. This is due to the fact that the individuals in the I^a_{HT} class have a better immune system since their CD4 cell count is greater than 350 cells/μL and are able to achieve some level of virologic suppression as a result of antiretroviral therapy.

3.2.1 Model Assumptions

In our model we make the following assumptions to make it less complex and simple enough to analyse mathematically;

1. We consider a fully susceptible population with no prior intervention and that the population is large enough to be modelled deterministically.
2. We assume homogeneous mixing of individuals in the same compartment and heterogeneous mixing between compartments. This means that each susceptible individual has the same probability of being infected by an individual from an infectious class.
3. We assume that there is 80% coverage of HAART as stipulated by the South African HIV National Strategic Plan [77].
4. We assume there is disease induced death of individuals in all classes with HIV infection or lymphoma.
5. We assume that remission is only possible after treatment and that all patients who undergo lymphoma therapy without HAART from the class H_{HL} are immediately enrolled on HAART when they go into remission and thus move to the class of HIV-infected individuals with lymphoma on HAART (I_{HLT}).

The model flow diagram for the progression of lymphoma from HIV-infected and other susceptible individuals is as shown in Figure 3.1 below and the description of variables and parameters used in the diagram is as given in Tables 3.1 and 3.2 that follow respectively.

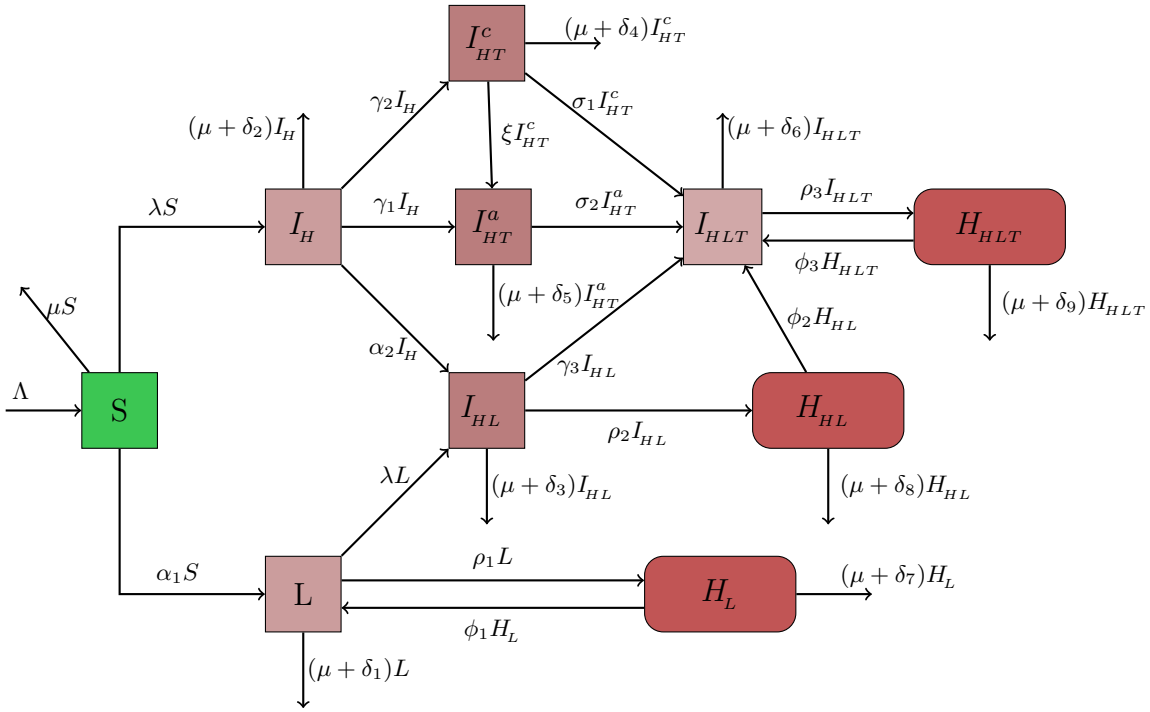


Figure 3.1: Schematic diagram for Non-hodgkin Lymphoma progression

3.2.2 Model Equations

The dynamical system represented in figure 3.1, our assumptions, variables and parameters are described by the following system of first order non-linear differential equations;

$$\left.\begin{aligned}
\dot{S} &= \Lambda - (\mu+\lambda+\alpha_1)S,\\
\dot{L} &= \alpha_1 S + \phi_1 H_L - (\lambda+q1)L,\\
\dot{I}_H &= \lambda S - (\mu+\delta_2)I_H - (\gamma_1+\gamma_2-\alpha_2)I_H,\\
\dot{I}_{HL} &= \lambda L + \alpha_2 I_H - (\gamma_3+\mu+\delta_3+\rho_2)I_{HL},\\
\dot{I}^c_{HT} &= \gamma_2 I_H - (\sigma_1+\mu+\delta_4)I^c_{HT} - \xi I^c_{HT},\\
\dot{I}^a_{HT} &= \gamma_1 I_H + \xi I^c_{HT} - (\sigma_2+\mu+\delta_5)I^a_{HT},\\
\dot{I}_{HLT} &= \gamma_3 I_{HL} + \sigma_2 I^a_{HT} + \sigma_1 I^c_{HT} + \phi_2 H_{HL} + \phi_3 H_{HLT} - (\mu+\delta_6+\rho_3)I_{HLT},\\
\dot{H}_{HLT} &= \rho_3 I_{HLT} - \phi_3 H_{HLT} - (\mu+\delta_9)H_{HLT},\\
\dot{H}_{HL} &= \rho_2 I_{HL} - \phi_2 H_{HL} - (\mu+\delta_8)H_{HL},\\
\dot{H}_L &= \rho_1 L - (\mu+\delta_7)H_L - \phi_1 H_L.
\end{aligned}\right\} \tag{3.2.3}$$

The initial conditions of the model are;

$S(0)=S^0,\quad L(0)=L^0,\quad I_H(0)=I^0_H,\quad I_{HL}(0)=I^0_{HL},\quad I^c_{HT}(0)=I^{c0}_{HT},$
$I^a_{HT}(0)=I^{a0}_{HT},\quad I_{HLT}(0)=I^0_{HLT},\quad H_{HLT}(0)=H^0_{HLT},\quad H_{HL}(0)=H^0_{HL},$

$H_L(0) = H_L^0$.

Table 3.1: Variables used in the Model

Variable	Description
$S(t)$	Susceptible individuals.
$I_H(t)$	HIV-infected individuals without HAART.
$L(t)$	HIV-negative individuals that develop lymphoma.
I_{HL}	HIV-infected individuals with lymphoma.
I_{HT}^a	HIV-infected individuals that start HAART at CD4 $>$ 500 cells/μL.
I_{HT}^c	HIV-infected individuals that start HAART at CD4 $<$ 500 cells/μL.
I_{HLT}	HIV-infected individuals with lymphoma on HAART.
H_L	HIV-negative individuals hospitalized for lymphoma therapy.
H_{HL}	HIV-infected individuals hospitalized for lymphoma therapy.
H_{HLT}	HIV-infected individuals hospitalized for lymphoma therapy with HAART.

Table 3.2: Description of parameters and symbols used in the Model

Parameter	Description
Λ	Recruitment rate of susceptibles.
μ	Natural death rate.
β_1	Effective transmission contact rate for S class.
β_2	Effective transmission contact rate for L class.
α_1	Rate of developing lymphoma by Susceptibles.
α_2	Rate of developing lymphoma by I_H.
λ	Force of infection with HIV.
γ_1	Rate of HAART initiation at $>$ 500 CD4 cells/μL.
γ_2	Rate of HAART initiation at $<$ 500 CD4 cells/μL.
ξ	Rate of CD4 cell count increase to $>$ 500 cells/μL.
σ_1	Rate of I_{HT}^c developing lymphoma.
σ_2	Rate of I_{HT}^a developing lymphoma.
ρ_1	Rate of seeking care and treatment for lymphoma by class L.
ρ_2	Rate of seeking care and treatment for lymphoma by class I_{HL}.
ρ_3	Rate of seeking care and treatment for lymphoma by class I_{HLT}.
ϕ_1	Rate at which individuals in H_L go into remission.
ϕ_2	Rate at which individuals in H_{HL} go into remission.
ϕ_3	Rate at which individuals in H_{HLT} go into remission.
$\delta_i (i = 1, \ldots, 9)$	Disease induced death.

3.3 Epidemiological Measures

Epidemiological measures are concerned with the frequency of health-related events so as to better understand and contain health risks. The link between frequency of occurrence of an event and the various risk factors surrounding it are put into consideration. This is the association measure which is determined by the difference in the rate of occurrence of a disease and the relative risk surrounding it. Here, the frequency measure of the health event which is given by the incidence and prevalence rate is calculated. The incidence of an event is given by the number of new cases during a given period of time and the prevalence of an event is given by the total number of existing cases at a given point in time. In our case disease incidence will be determined by the basic reproduction number R_0 at the HIV-disease-free equilibrium. R_0 is defined as the average number of secondary infections caused by one infectious individual in a fully susceptible population.

3.4 Model Steady State Analysis

We analyse the model to determine the conditions necessary for the existence of an equilibrium/steady state which we will refer to as the HIV-free lymphoma steady state. This is the equilibrium at which the population remains in the absence of HIV infection. In order to find this steady state, we set all terms which contain HIV infection to zero, that is, $I_{H} = I_{HL} = I^{a}_{HT} = I^{c}_{HT} = I_{HLT} = H_{HLT} = H_{HL} = 0$. This implies that the force of infection, $\lambda = 0$.

To obtain the steady state solution of the system, we set the right hand side of the equations in system (3.2.3) to zero. Let the HIV-free lymphoma steady state be denoted by E^*, this will be given by;

$$E^* = (S^*, L^*, I^*_{H}, I^*_{HL}, I^{a*}_{HT}, I^{c*}_{HT}, I^*_{HLT}, H^*_{HLT}, H^*_{HL}, H^*_{L}).$$

then we have;

$$\Lambda - (\mu + \lambda + \alpha_1)S = 0, \qquad \lambda = 0,$$
$$\implies S^* = \frac{\Lambda}{\alpha_1 + \mu}.$$

Consequently,
letting $k = \alpha_1 S^*, \quad q_1 = \rho_1 + \mu + \delta_1, \quad q_2 = \phi_1 + \mu + \delta_7,$ we then have,

$$H_L^* = \frac{\rho_1 k q_1}{q_1^2 q_2 - \rho_1 \phi_1} = \rho_1 k \left[\frac{q_1}{q_1^2 q_2 - \rho_1 \phi_1} \right];$$
$$\implies H_L^* = \frac{\rho_1 \alpha_1 \Lambda}{\alpha_1 + \mu} \left[\frac{\rho_1 + \mu + \delta_1}{(\rho_1 + \mu + \delta_1)^2(\phi_1 + \mu + \delta_7) - \rho_1 \phi_1} \right].$$

$$L^* = \frac{k}{q_1} \left[1 + \frac{\phi_1 \rho_1 q_1}{q_1^2 q_2 - \rho_1 \phi_1} \right];$$
$$\implies L^* = \frac{\alpha_1 \Lambda}{(\alpha_1 + \mu)(\rho_1 + \mu + \delta_1)} \left[1 + \frac{\phi_1 \rho_1 (\rho_1 + \mu + \delta_1)}{(\rho_1 + \mu + \delta_1)^2(\phi_1 + \mu + \delta_7) - \rho_1 \phi_1} \right].$$

Therefore the model has an HIV-free lymphoma steady state, E^* as given below

$$E^* = (S^*, L^*, 0, 0, 0, 0, 0, 0, 0, H_L^*);$$
$$E^* = \left(\frac{\Lambda}{\alpha_1 + \mu}, \frac{k}{q_1} \left[1 + \frac{\phi_1 \rho_1 q_1}{q_1^2 q_2 - \rho_1 \phi_1} \right], 0, 0, 0, 0, 0, 0, 0, \rho_1 k \left[\frac{q_1}{q_1^2 q_2 - \rho_1 \phi_1} \right] \right)$$

3.4.1 The Basic Reproduction Number

The basic reproduction number, R_0 is a threshold parameter that determines whether the disease-free equilibrium (DFE) is stable or otherwise. If $R_0 < 1$, then the DFE is locally asymptotically stable, which means that the disease will eventually die out because there is not enough new cases generated to keep the infection in the population. While, if $R_0 > 1$, the DFE is unstable, which means that there is a likelihood that an epidemic will occur in the population since each infectious individual is able to produce more than one secondary case of infection in the population [36, 38]. However, a disease may persist even though the DFE is locally stable [38]. In the presence of an intervention, we have R_e, which is known as the effective reproduction number.

The effective reproduction number of our model is calculated using the next generation matrix method (Watmough and Van den Driessche [38]). We first find the matrix representing new infections, F and the matrix representing progression of infection, V, from our system of equations (3.2.3).

In this model, we assume that all individuals under lymphoma therapy are hospitalised. Therefore lymphoma patients who are HIV$^+$ are not able to transmit the

disease to other people because of the restricted contact and care they are given in hospital.

Let

$$q = \frac{S^*}{N^*},$$
$$w = \frac{L^*}{N^*}$$

we have;

$$F = \begin{pmatrix} \beta q & \beta\eta_1 q & \beta\eta_2 q & \beta\eta_3 q & \beta\eta_2 q \\ \beta w & \beta\eta_1 w & \beta\eta_2 w & \beta\eta_3 w & \beta\eta_2 w \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.4.1}$$

$$V = \begin{pmatrix} g_1 & 0 & 0 & 0 & 0 \\ -\alpha_2 & g_2 & 0 & 0 & 0 \\ -\gamma_2 & 0 & g_3 & 0 & 0 \\ -\gamma_1 & 0 & -\xi & g_4 & 0 \\ 0 & -\gamma_3 & -\sigma_1 & -\sigma_2 & g_5 \end{pmatrix} \tag{3.4.2}$$

where , $g_1 = \gamma_1 + \gamma_2 + \alpha_2 + \mu + \delta_2$, $g_2 = \gamma_3 + \rho_2 + \mu + \delta_3$, $g_3 = \sigma_1 + \xi + \mu + \delta_4$, $g_4 = \sigma_2 + \mu + \delta_5$, $g_5 = \rho_3 + \mu + \delta_6$.

The next generation matrix for the infected subsystem of the model system (3.2.3) is given by the product FV^{-1}, calculated at the disease free equilibrium and thus the spectral radius of R_0 is given by;

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

The model reproduction number , R_e (effective reproduction number due to presence of treatment as an intervention) was found to be a combination of contributions from the different infected classes in the model and is the sum of the reproduction numbers at each infectious stage. When we put all the intervention terms to zero, that is; $\gamma_i = \rho$

$$R_e = R_e^{I_H} + R_e^{I_{HL}} + R_e^{I_{HT}^c} + R_e^{I_{HT}^a} + R_e^{I_{HLT}}; \tag{3.4.3}$$

where,

$$\left.\begin{aligned} R_e^{I_H} &= \tfrac{q\beta}{g_1}, \\ R_e^{I_{HT}^c} &= \tfrac{q\beta\eta_2\gamma_2}{g_1 g_3}, \\ R_e^{I_{HL}} &= \tfrac{\beta\eta_1}{g_2}\left[\tfrac{q\alpha_2}{g_1} + w\right], \\ R_e^{I_{HT}^a} &= \tfrac{q\beta\eta_3}{g_1 g_4}\left[\tfrac{\gamma_2\xi}{g_3} + \gamma_1\right], \\ R_e^{I_{HLT}} &= \tfrac{\beta\eta_2 q}{g_1 g_5}\left[\tfrac{\gamma_1\sigma_2}{g_4} + \tfrac{\alpha_2\gamma_3}{g_2} + \tfrac{\gamma_2\sigma_1}{g_3} + \tfrac{\gamma_2\sigma_2\xi}{g_3 g_4}\right] + \tfrac{\beta\eta_2\gamma_3 w}{g_2 g_5}. \end{aligned}\right\} \tag{3.4.4}$$

Interpretation of R_0

The reproduction number, $R_e^{I_H} = \frac{q\beta}{g_1}$ is a product of the rate of progression of individuals into the I_H class and their average duration of stay in that class. $R_e^{I_H}$ is therefore the average number of new infections caused by a single infectious individual during their stay in the I_H class, in a fully susceptible population.
On the other hand, the reproduction number $R_e^{I_{HL}}$ is a sum of two terms which represent the different ways in which individuals that come to that class contribute to that reproduction number as explained below.

$$R_e^{I_{HL}} = \underbrace{\frac{1}{g_2}}_{X} \times \left[\underbrace{\frac{q\beta\eta_1\alpha_2}{g_1}}_{Y} + \underbrace{w\beta\eta_1}_{Z}\right]$$

The term denoted by X represents the average duration of infectivity of individuals in the $R_e^{I_{HL}}$ class, the term denoted by Y represents the contribution to $R_e^{I_{HL}}$ by HIV-infected individuals from the I_H class that develop lymphoma and progress to the I_{HL} class, while the term denoted by Z represents the contribution to $R_e^{I_{HL}}$ by individuals originally with lymphoma from the L class who get infected with HIV and progress to the I_{HL} class. The same logical explanation follows for all the other reproduction number cases presented in (3.4.4) above.

A more specific definition of R_e in the context of our model is the number of new secondary cases of infection produced by an HIV-infected individual (regardless of whether he/she has developed lymphoma and is under antiretroviral therapy or not) when they are introduced in a wholly susceptible population.

However, the basic reproduction number (R_0) for our model can be obtained by setting the treatment parameters $(\gamma_1, \gamma_2, \gamma_3, \rho_2, \rho_3)$ to zero. This will imply that $R_e^{I_{HT}^c}, R_e^{I_{HT}^a}$ and $R_e^{I_{HLT}}$ will all go to zero because they are from the classes of individuals receiving antiretroviral therapy as an intervention. Therefore our R_0 will be

given by;

$$R_0 = R_0^{I_H} + R_0^{I_{HL}}; \tag{3.4.5}$$

where,

$$R_0^{I_H} = \frac{q\beta}{(\alpha_2 + \mu + \delta_2)},$$
$$R_0^{I_{HL}} = \frac{\beta\eta_1}{(\mu + \delta_3)}\left[\frac{q\alpha_2}{(\alpha_2 + \mu + \delta_2)} + w\right].$$

3.4.1.1 Comparison of the Reproduction Numbers

We compare the reproduction numbers of the model using Matlab to determine how each reproduction number varies as the transmission contact rate (β) changes.

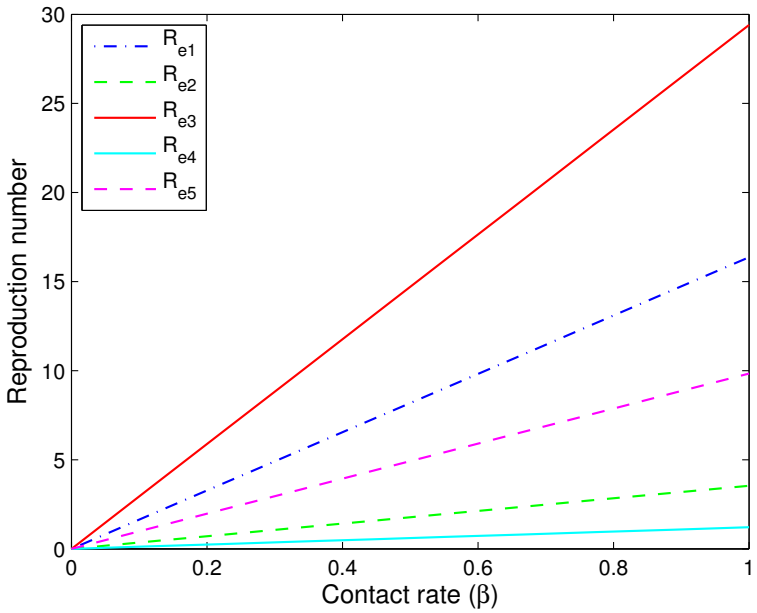


Figure 3.2: The correlation between the effective reproduction numbers and contact rate (β).

In Figure 3.2, the variables $R_{e1}, R_{e2}, R_{e3}, R_{e4}$ and R_{e5} represent the reproduction numbers $R_e^{I_H}, R_e^{I_{HL}}, R_e^{I_{HT}^c}, R_e^{I_{HT}^a}$ and $R_e^{I_{HLT}}$ respectively. The figure provides a comparison of the different effective reproduction numbers with respect to the contact rate (β) as it varies between 0 and 1. We observe that as β increases the following relationship with the reproduction numbers holds;

$$R_e^{I_{HL}} > R_e^{I_H} > R_e^{I_{HT}^c} > R_e^{I_{HLT}} > R_e^{I_{HT}^a}$$

This means that the infectiousness of individuals in the classes without intervention is much higher than that of individuals in the classes with intervention as their contact rate increases. From this observation we can deduce that intervention at a CD4 cell count greater than 500 cells/μL is more effective at reducing HIV infection and therefore reducing the prospect of developing AIDS-related malignancies.

We conclude therefore that the transmission contact rate has a substantial effect on the reproduction numbers. With the presence of interventions, the incidence of HIV infection is reduced but early intervention at a CD4 cell count of greater than 500 cells/μL is more effective in reducing the reproduction number as compared to intervention at a CD4 cell count level of less than 500 cells/μL.

3.5 Incidence and Mortality

The incidence of lymphoma in HIV positive individuals is largely due to a severely suppressed immune system. The survival rate of people with non-Hodgkin lymphoma (NHL) varies widely and depends on the number of risk factors affecting the individual such as age (60^+) at time of onset of the disease, extra-nodal sites of the disease, an arbor stage III/IV, Lactate dehydrogenase (LDH) greater than the normal upper limit, among others [4]. Individuals with more than three risk factors have a higher mortality rate than those with one or less risk factors. According to the American cancer society, the relative survival rate for patients with NHL is 67% for 5 years and 55% for 10 years [4].

3.5.1 Lymphoma Incidence

The incidence of lymphoma in our model is determined by the CD4 cell count of individuals at the time of treatment initiation. The individuals that enrol into treatment at an early stage have less chances of developing lymphoma. Therefore lymphoma incidence depends on the parameters $\alpha_1, \alpha_2, \sigma_1, \sigma_2$ and γ_1, the rate at which individuals start treatment at CD4 cell count greater than 500 cells/μL.

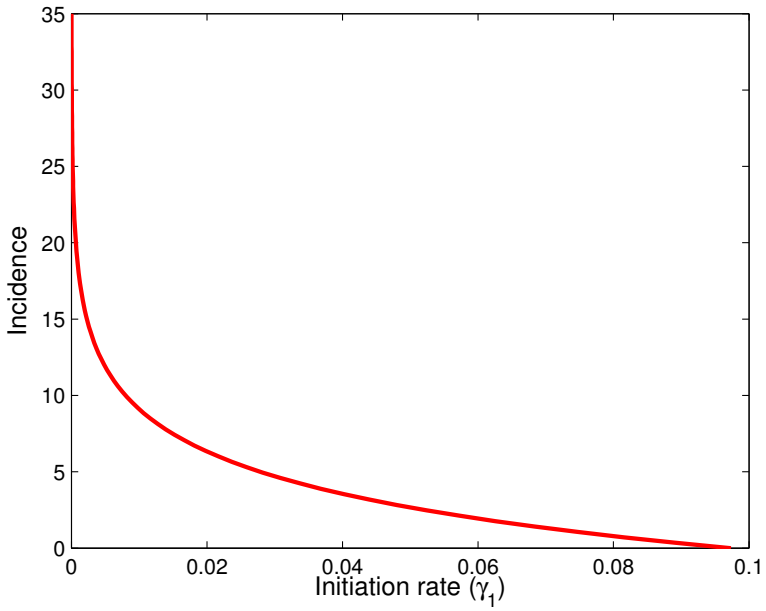
The population considered to be at risk of developing lymphoma according to our model are the Susceptibles (S), HIV-infected individuals not on HAART (I_H) , individuals enrolling on HAART at CD4 count greater than 500 cells/μL (I^a_{HT}) and individuals that enrol on HAART at CD4 count less than 500 cells/μL (I^c_{HT}). The

incidence of lymphoma will therefore be given by the following function;

$$\text{Incidence} = \frac{(\alpha_1 + \alpha_2 + \sigma_1 + \sigma_2)e^{-(\gamma_1 I_H)}}{S + I_H + I^a_{HT} + I^c_{HT}}, \tag{3.5.1}$$

where α_1, α_2, σ_1 and σ_2 are the rates at which individuals in the S, I_H, I^c_{HT} and I^a_{HT} classes respectively, develop lymphoma. We use γ_1 as the preferred initiation rate since the recommendation for reducing lymphoma incidence is a higher CD4 count threshold.

Figure 3.3: Correlation between lymphoma incidence and HAART initiation rate (γ_1).



In plotting the incidence function against the rate of HAART initiation γ_1, we see that as initiation increases, the incidence of lymphoma decreases. We also observe that it would be possible to eliminate lymphoma through increasing HAART initiation at CD4 count greater than 500 cells/μL to above 80% coverage. This would meet the requirement for elimination of HIV transmission according to the South African HIV National Strategic Plan 2012 [77]. Therefore, increasing early therapy initiation would not only reduce the transmission and incidence of HIV but also prevent AIDS-related lymphoma.

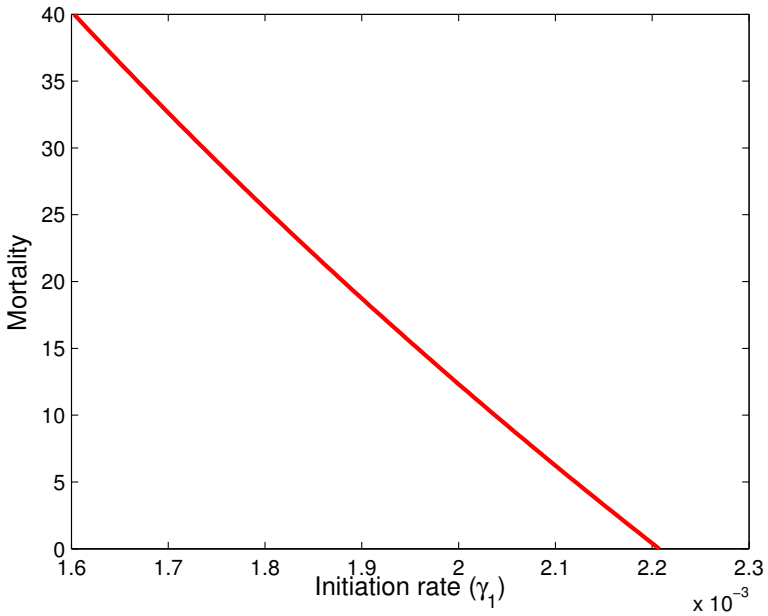
3.5.2 Mortality

The mortality rate due to lymphoma in our model will depend on the total number of deaths due to lymphoma in the ten-year period under consideration and the population at risk of death due to lymphoma which are the individuals in the classes that have lymphoma. Mortality rate will therefore be given by the following function;

$$\text{Mortality} = \frac{\delta_1 L + \delta_3 I_{HL} + \delta_6 I_{HLT} + \delta_9 H_{HLT} + \delta_8 H_{HL} + \delta_7 H_L}{L + I_{HL} + I_{HLT} + H_{HLT} + H_{HL} + H_L} \tag{3.5.2}$$

Plotting mortality against early HAART initiation rate, γ_1, in Figure 3.4, we see that as the rate of early initiation increases, mortality rate decreases. This result indicates that early HAART initiation could be effective in reducing lymphoma-related deaths.

Figure 3.4: Correlation between mortality rate and early initiation rate (γ_1).



3.6 Economic Measures

3.6.1 Cost Measurement

We measure the costs associated with each intervention strategy by reviewing the program's financial and services records in order to quantify the resources used,

associated costs and clients served. We then compare the costs for every alternative. Individuals accumulate costs as they move through the model cycles and these costs are associated with the event and outcomes at each stage. These costs comprise of direct medical costs which include screening costs, diagnostic tests and costs for lymphoma therapy. Costs for HIV care and treatment are informed by literature and include both inpatient and outpatient care.
In South Africa, the costs of lymphoma treatment and diagnosis are very high and are mainly subsidised by medical insurance and the government. However, data on lymphoma healthcare costs is not readily available, therefore we use estimates derived from similar studies and costs of HAART are informed by previous studies carried out in Southern Africa [8, 46].

We assume that screening for HIV is done twice a year and screening for lymphoma is done once a year for HIV-infected individuals. Screening costs are associated with the fraction of susceptible individuals who choose to go for HIV testing and individuals from the HIV class that get screened for lymphoma, then also lymphoma only patients from the L class that go for HIV screening. We denote the cost of screening for HIV and lymphoma by C_{s1} and C_{s2} respectively (also includes costs of delivering screening tests). The annual cost of initiating HAART at CD4 count greater than 500 cells/μL denoted by C_a is associated with the proportion of individuals in the I^a_{HT} class from the I_H class whose CD4 cell count is greater than 500 cells/μL at the time of enrolling on HAART. The annual costs of initiating HAART at CD4 count less than 500 cells/μL denoted by C_c are associated with the proportion of HIV-infected individuals in the I^c_{HT} class from I_H that enrol onto HAART with a CD4 cell count of less than 500 cells/μL. C_c also includes costs of treating opportunistic infections that arise with low CD4 cell count due to immunosuppression. The cost of increasing HAART coverage denoted by C_p is proportional to the number of people that enrol on HAART irrespective of their CD4 cell count. The cost of enrolling lymphoma patients who get infected with HIV on HAART denoted by C_l is associated with the proportion of individuals from the I_{HL} class who enrol on HAART and are in the I_{HLT} class. C_h denotes the costs that are associated with treatment, care and hospitalization for patients who have developed lymphoma and are receiving lymphoma therapy. C_f denotes the costs of follow up which are associated with individuals in the classes I_{HLT} and L who are in remission after lymphoma therapy. C_f also includes costs on follow-up tests and doctors' visits.
The costs indicated here are representative of healthcare expenditure on individuals

in a particular disease stage measured annually. Therefore, the overall cost rate function in US dollars denoted by $C(t)$ at time t, is given by the following equation.

$$\begin{aligned}\mathbf{C(t)} =& C_{s1}\left[S(t)+L\right]+C_{s2}\left[I_{H}+I_{HT}^{a}+I_{HT}^{c}\right]+C_{f}\left[I_{HLT}+L\right]+C_{a}I_{HT}^{a}+C_{c}I_{HT}^{c}\\&+C_{l}\left[\gamma_{3}I_{HL}\right]+C_{h}\left[H_{HLT}+H_{HL}+H_{L}\right]+C_{p}\left[I_{HT}^{a}+I_{HT}^{c}+I_{HLT}\right].\end{aligned}$$

The total costs accumulated over 10 years are calculated by summing up all costs incurred in each health state over the entire period of time.

3.6.2 Discounting

In cost-effectiveness analysis, it is important to discount all costs in order to account for all future costs in terms of the net present-day value [63, 72]. Costs and health benefits accrued in future are worth less than those accrued at present. Discounting is usually done to account for inflation that will affect accuracy in measuring future costs. All costs and health events are discounted to the year 2015 at a rate (r) of 5% per annum, which is consistent with that used in previous studies done in Southern Africa [52]. We use cumulative costs to calculate average costs per annum for the entire period of study. Therefore, the total discounted costs over 10 years per individual in any given health state of our model will be given by the following function;

$$C_{cum}=\int_{0}^{10}C(t)e^{-rt}dt.$$

3.7 Decision Analysis

Decision analysis is the process of making informed and objective decisions in the presence of a complex situation. This process involves decision structuring techniques, assessment of alternatives, quantifying uncertainties and evaluating options in order to determine the best alternative under the given circumstances. Decision analysis is facilitated by statistical tools such as decision trees, multivariate analysis and probabilistic forecasting which are applied to mathematical models of real-life situations in order to determine the course of action that best suits the situation giving the best value for resources used.

With the increasing costs of healthcare today, it has become inevitable for policy-makers, clinicians and researchers to use decision-analysis modelling in addressing this challenge. Decision analysis involves making a decision in uncertain circumstances. In the case of our model, we need to decide on whether it is more beneficial

to initiate HAART at CD4 count less than 500 cells/μL or greater than 500 cells/μL. We want to determine the costs of each intervention option in relation to its effectiveness in preventing lymphoma. In this regard, we carry out cost-effectiveness analysis of initiating HAART at the different CD4 cell count thresholds. We construct a decision tree in TreeAge Pro in order to estimate the expected costs and health benefits (life years gained) of initiating HAART at the two CD4 cell count thresholds and the impact of each alternative on the incidence of lymphoma. In this study, our base case is; determining when to initiate HAART and the decision lies between initiating treatment at CD4 count less than 500 cells/μL or at CD4 count greater than 500 cells/μL as illustrated in Figure 3.5 below. The nodes marked m1 and m2 are markov nodes.

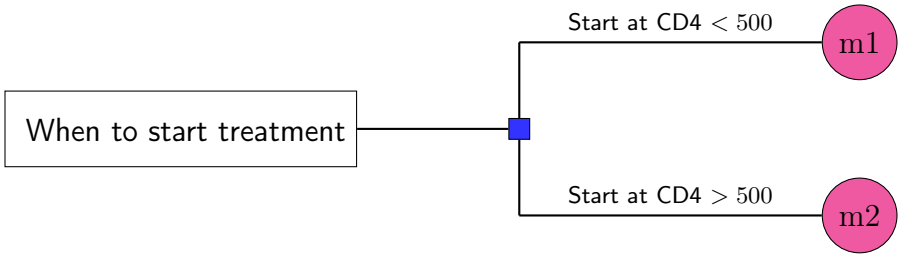


Figure 3.5: The base case and decision

Markov nodes and the cycle sub-trees that follow represent markov processes. We take the length of each cycle in the markov model to be one year. In a markov process it is assumed that the behaviour of individuals in the system only depends on their current health state and transition probabilities. We use markov modelling here because of the continuous risk of re-occurrence of lymphoma over time. When lymphoma patients undergo first-line treatment and recover, there is a likelihood that they could relapse later on and have to take second-line treatment. This scenario is common in patients who are initially diagnosed with indolent (low-grade) lymphoma because its chances of being completely eliminated are low. Patients with advanced low-grade lymphoma are likely to have a relapse more than once in their lifetime. The recurrence of lymphoma is likely to take place in the same area of the body as previously affected or it could recur in another place [56, 57].

Figure 3.6 is a representation of the markov processes in our model for the No-HAART and HAART scenarios. The model is comprised of six health states, each of which incorporates the natural history of HIV, AIDS-related lymphoma with and without antiretroviral therapy. It is assumed that patients with lymphoma

are given lymphoma therapy before going into remission and those with HIV and lymphoma without HAART could either first enrol into HAART or first receive lymphoma therapy before enrolling into antiretroviral therapy. It is also assumed that all patients in remission are enrolled into HAART.

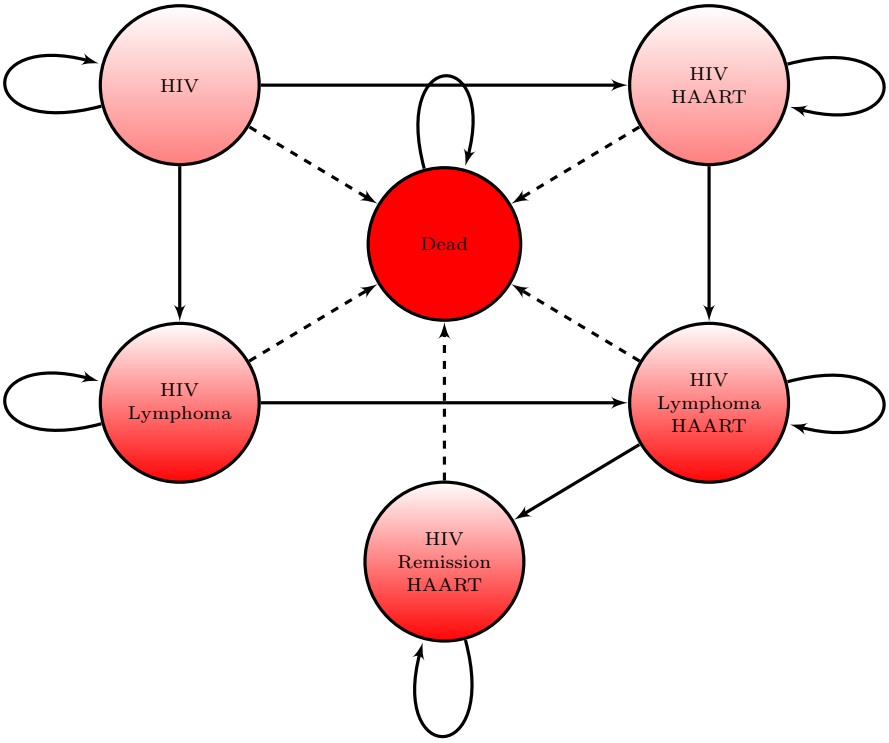


Figure 3.6: Markov state transition diagram

The decision tree in Figure 3.7 illustrates the modelling process involved in decision analysis of initiating HAART at two different CD4 cell count levels (The full decision tree build up is as shown in Figure 4.1). In the diagram, RX and No RX represent treatment and no treatment respectively. The model structure is a collection of nodes which are chronologically arranged to relay decisions and events from the original decision to all possible scenarios for each option taken. We start with patients who are HIV-positive and use CD4 cell count as a threshold to determine the proportion of individuals who can start treatment as stratified by the current policy in place, then we follow all individuals through a markov process to developing lymphoma, then end up in a certain health state or die. We use transition probabilities for individuals to move from one stage to another and conditional statements for logical decisions at the logic node (the initiation policy determines the proportion of individuals taking each path at this node, there is no free will for individuals to

make a choice). We attach costs and utilities at each stage in order to be able to determine effectiveness at each path and compare the different options.

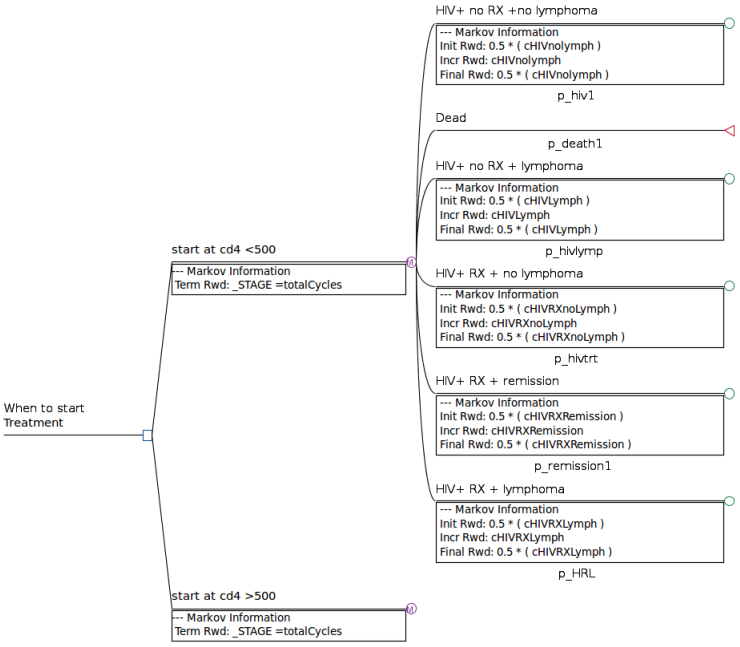


Figure 3.7: Example of Decision Tree model diagram

Each of the nodes in the decision tree represents a different course of action that has to be taken voluntarily or involuntarily.
The decision node (with a square shape) indicates a choice that is under the control of individuals that make decisions such as policy makers. The chance node (circular in shape) represents events that may occur beyond the control of decision makers and are associated with the probability of subsequent events. The terminal nodes which are triangular in shape represent the end point/terminal point of a process and these are normally assigned payoff values. Each terminal node represents the entire path from the root node to that terminal node. The branches from each node represent possible events that follow consequently. Hence, branches from decision nodes represent the actions/strategies under consideration, these may not be mutually exclusive. The branches from chance nodes represent probable outcomes from that event, these should be mutually exclusive and exhaustive with a probability sum of one. A Markov node on the other hand normally has several branches orig-

inating from it, representing each of the health states involved in the process and each branch connects to a cycle tree/sub-tree which reflects all the events that occur during that cycle. The probability at each markov branch represents the initial proportion of individuals in each health state. Attached to each markov branch is an incremental utility that represents one cycle's value of being in that state. The terminal nodes in markov models are set to one of the markov states and are also called "jump states". These jump states indicate what state to go to in the next cycle. Unlike in other decision trees, in markov models outcomes are not defined at the terminal node due to the fact that they are jump states. The dead state however, is an absorbing state and thus has no branches emerging from it.

In this tree analysis, we want to investigate the cost impact of initiating HAART at different CD4 cell count levels on lymphoma incidence and the quality of life of individuals. We start off with a population of HIV-infected individuals. The decision to be made initially is on when to start antiretroviral therapy. There are two options to choose from, which include, starting treatment at a CD4 count less than 500 cells/μL or at CD4 count greater than 500 cells/μL. Therefore all individuals diagnosed with HIV have to be classified according to their CD4 cell count (which is usually done by flow cytometry) in order to determine whether they meet the criteria for starting antiretroviral therapy at that node. Depending on the policy in place, the decision will lead to one of the two branches of scenarios for starting treatment. This initial position (the decision) for all cases in the model cannot be repeated. Once the decision has been established we follow the patients through a markov modelling process. It is important to note that the sub-tree and consequently the order of events in the markov clone at the node "start at CD4 $>$ 500" is an exact replica of the markov sub-tree at the node "start at CD4 $<$ 500" and the difference between the two is the probability at which events occur and the effectiveness of treatment at each health state. These variables are defined at each of the markov nodes for each of the markov processes. We assume that the CD4 count of all patients that start treatment increases by 50 cells/μL in the next stage and reduces by 50 cells/μL with no treatment in the subsequent stages. Therefore we use the functions;

$$CD4 = CD4_0 + stage \times 50 \qquad \text{for increasing } CD4 \text{ count,}$$
$$CD4 = CD4_0 - stage \times 50 \qquad \text{for declining } CD4 \text{ count,}$$

where, $CD4_0$ represents the CD4 count at the previous stage.

At the logic node we enter a condition that is tested before proceeding to either of the branches. In our analysis we used the following conditional statement which is an if function;

- if (condition; true value; false value):
  where, the condition is threshold for treatment initiation, and the true value is the probability of starting treatment at either one of the two markov nodes.

Results and Findings

From the model analysis in Treeage, the cumulative discounted costs at CD4 less than 500 for a period of tens years were as indicated in Figure 3.8 and the discounted cumulative effectiveness for the same period was as indicated in Figure 3.9 below.

From the figures, we see that there is a rapid increase in costs associated with

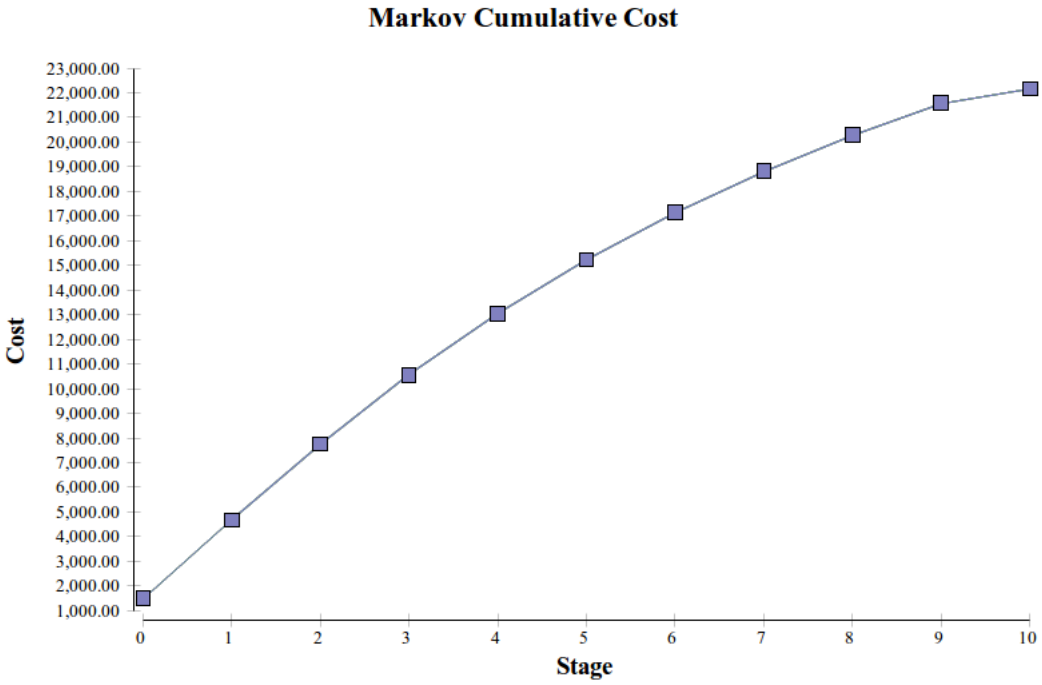


Figure 3.8: Cumulative costs at CD4 less than 500**.**

initiating HAART at CD4 count less than 500cells/μL. Cumulative costs rise from nearly \$2,000 at the beginning to about \$24,200 at the termination stage of the model. Cumulative effectiveness on the other hand increases from about 0.3 at the start to about 2.7 at the end of the 10 years. This implies that the cost per unit of effectiveness would be approximately \$9,250 which is quite high and not desirable.

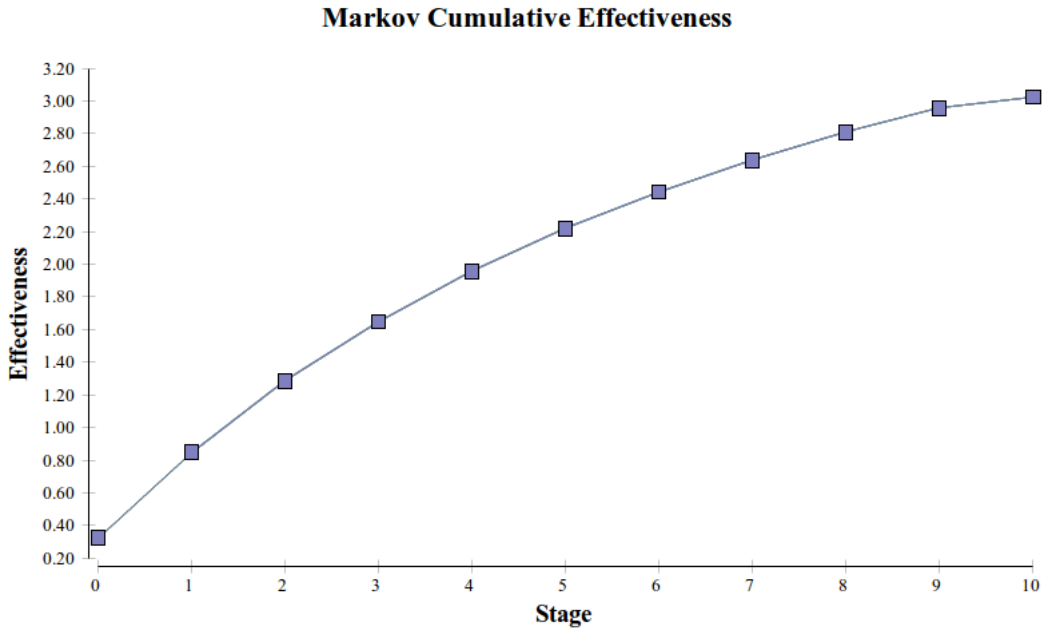


Figure 3.9: Cumulative Effectiveness at CD4 less than 500**.**

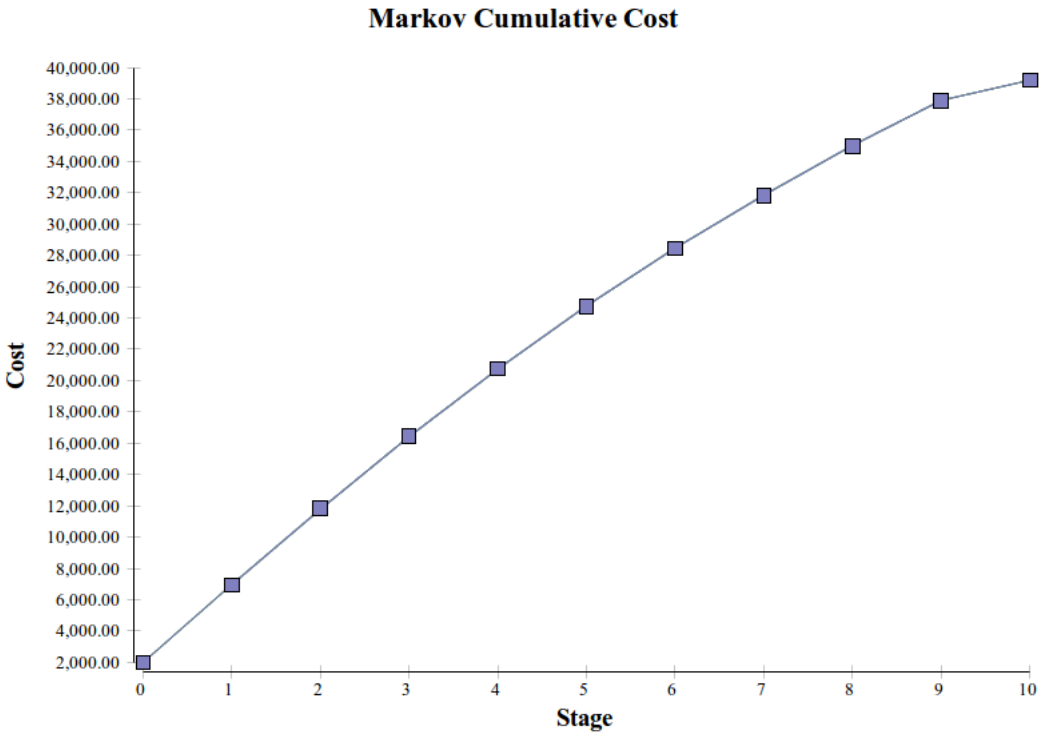


Figure 3.10: Cumulative Costs at CD4 greater than 500**.**

Figure 3.10 and 3.11 show that with HAART initiation at CD4 count greater than 500 cells/μL, cumulative costs will increase from \$2,000 to about \$38,800 and cumulative effectiveness will also increase from about 0.3 to about 6.4. Although there is a higher increase in cost in this strategy than the alternative, the resulting increase

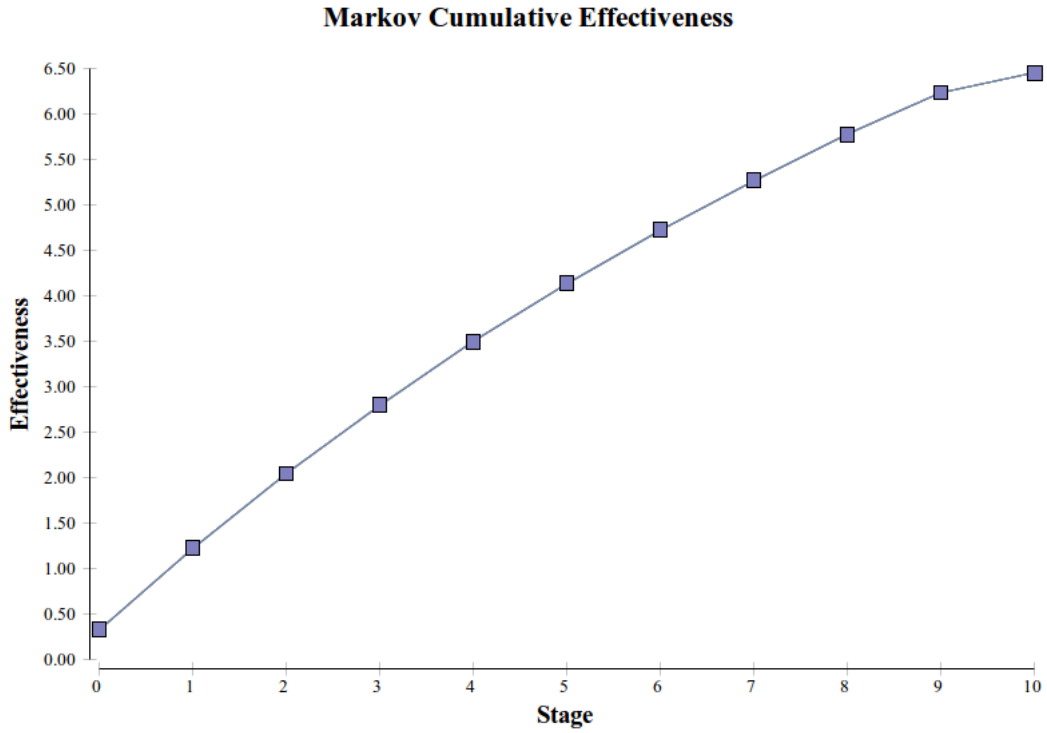


Figure 3.11: Cumulative effectiveness at CD4 greater than 500**.**

in effectiveness is more than twice as much as that of the alternative and would thus be a more desirable outcome. Further, looking at the cost-effectiveness analysis of each strategy we see that both strategies lead to increased effectiveness in terms of life years gained, but there is a remarkable increase in the costs as well. Therefore, neither of the two strategies is dominated but one exceeds the other in terms of the resulting health outcomes and thus makes it more favourable. An intervention can be taken to be cost-effective if it more costly and more effective at the same time, which is what we see in this case.

The graph of cost-effectiveness results Figure 3.12 clearly shows the difference between the two strategies. The costs and effectiveness of initiating HAART at CD4 count greater than 500 cells/μL are much higher than initiation at CD4 count less than 500 cells/μL the base case. This indicates that the former is more cost-effective than the base case since it is more efficient in improving health resulting in more life years gained.

The results of Markov modelling are as displayed in the Figures 3.13 and 3.14 representing HAART initation at CD4 less than 500 cells/μL and at CD4 greater than 500 cells/μL respectively. We considered six possible health states and the entire cohort is HIV-infected initially. The health states that follow are the possible states in

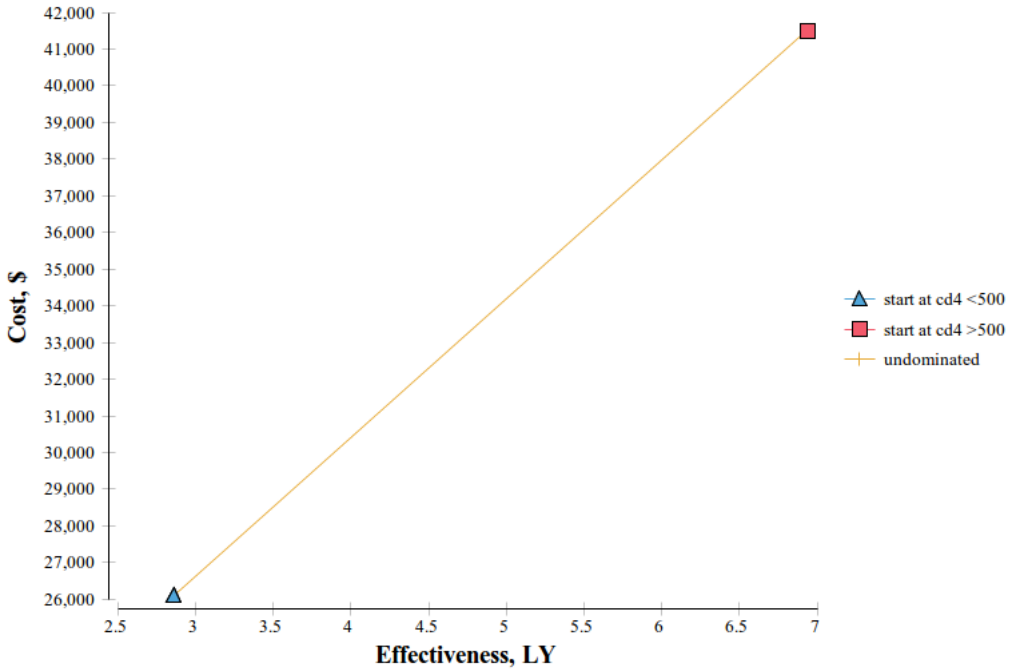


Figure 3.12: Cost-effectiveness results graph.

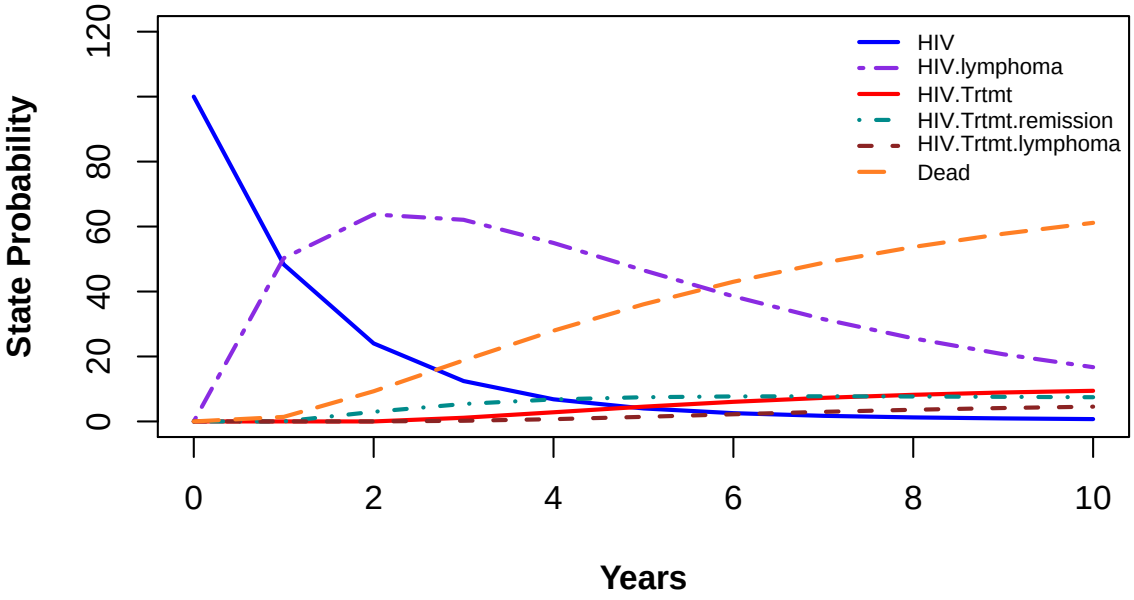


Figure 3.13: Markov state probability at CD4 less than 500 cells/μL

which individuals could be with time as some of them progress to developing AIDS-related lymphoma. Costs and utilities are attached to these health states in order to calculate the cost-effectiveness of each strategy. The health states considered are as described in Table 3.3.

The probability that an HIV-infected individual will be in any of the six health states at a given time within the ten-year time period is displayed in Figures 3.13

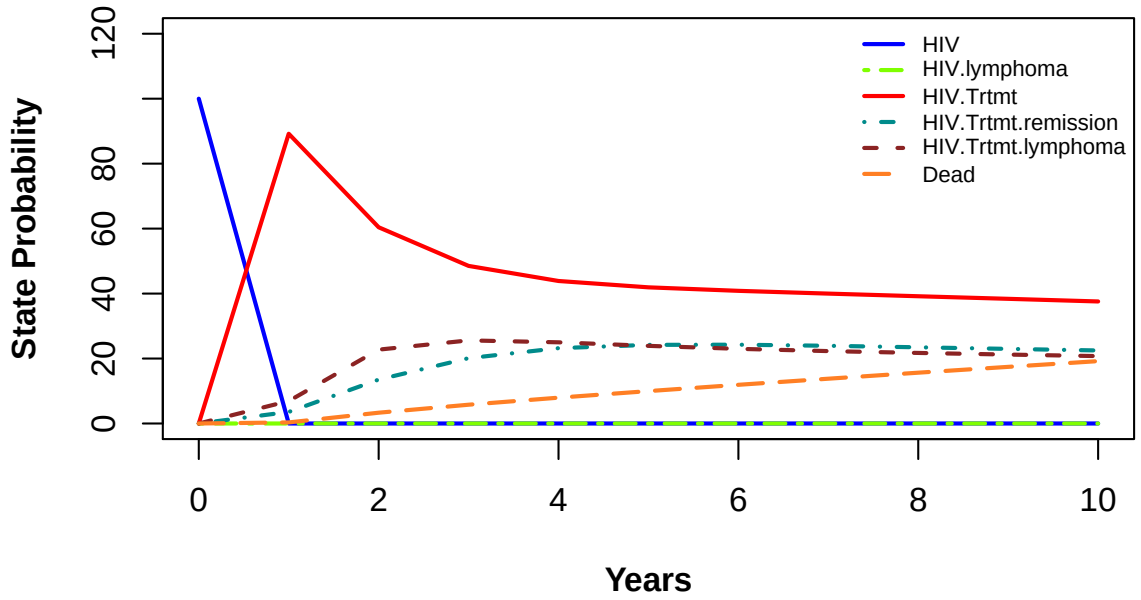


Figure 3.14: Markov state probability at CD4 greater than 500 cells/μL

Table 3.3: Markov health states

State	Definition
HIV	state with HIV, no HAART and no lymphoma.
HIV.Trtmt	state with HIV, HAART and no lymphoma.
HIV.lymphoma	state with HIV, lymphoma and no HAART.
HIV.Trtmt.lymphoma	state with HIV, HAART and lymphoma.
HIV.Trtmt.remission	state with HIV, HAART and in remission.
Dead	the death state.

and 3.14 depending on their CD4 count at the time of HAART initiation. The peaks in the figures indicate the time when individuals in the cohort are at the highest risk of being in that state. In Figure 3.13, we see that halfway through the process, individuals who are to start antiretroviral therapy at a lower CD4 count are more likely to have developed lymphoma or be dead. At the end of the process we see that there are higher chances of an individual having lymphoma without treatment and also with treatment as compared to the probability of reaching the final stage without having lymphoma. With time as CD4 count depreciates, individuals will be eligible to start HAART and therefore progress to a state with treatment. However, we see that the proportion of those that develop lymphoma without treatment is still slightly greater than that of individuals that develop lymphoma with treatment. In Figure 3.14, we observe that the state probability of HIV.Trtmt stands out, indicating that initiating HAART at CD4 count greater than 500 cells/μL is highly effective. From the figure, we can also see that there is a greater chance of an

individual in our cohort existing in the above mentioned health state than in any of the other states due to early antiretroviral treatment initiation. It is also imperative to note the low rate of deaths and individuals that have lymphoma or are in remission with early HAART initiation. Also in Figure 3.14, we see that the two health states with no treatment (HIV and HIV.lymphoma) go to and remain at zero probability before the second year. This can be explained by the fact that the condition for initiating treatment will ensure that all individuals enrol into treatment early enough before their CD4 count depreciates. This leads to an increased (or stable) CD4 count above the threshold that always meets the criteria for treatment initiation throughout the entire period of 10 years considered in the model.

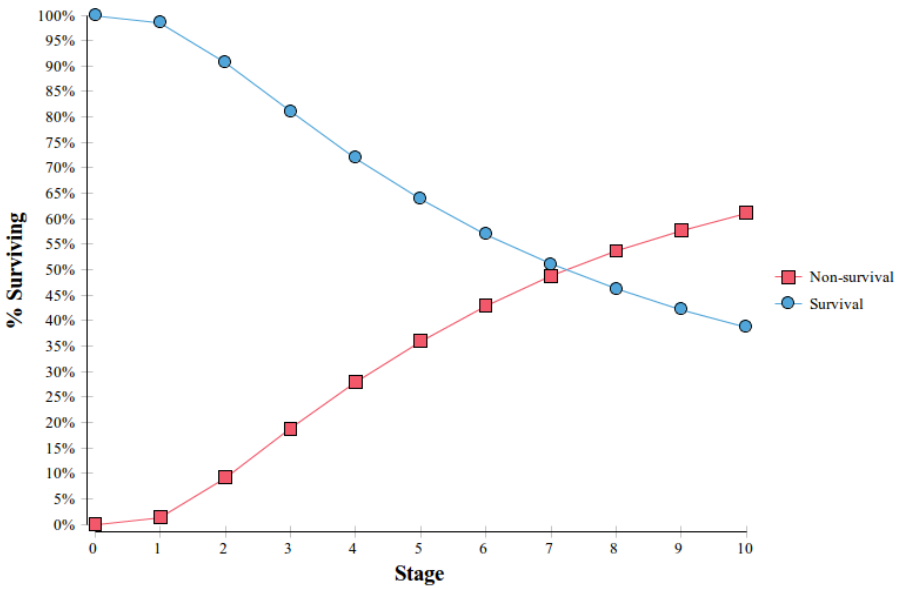


Figure 3.15: Survival/non-survival at CD4 less than 500 **cells/**μL

The survival and non-survival curves in Figure 3.15 indicate that the probability of an individual who started HAART treatment at CD4 less than 500 cells/μL will die in 10 years is higher than the probability that they will survive. Therefore, this strategy may not be effective in improving the health and livelihood of individuals. On the other hand, the curves in Figure 3.16 indicate a big gap between survival and non-survival of individuals that start HAART treatment at CD4 count greater than 500 cells/μL. The probability of surviving with early initiation is much higher, at a rate of approximately 80%, than the probability of dying approximated at 20%. Therefore individuals that start treatment early are more likely to live longer than the ones that start later. Figure 3.17 clearly shows the distinction in survival between the two initiation strategies. From the above results, we can conclude that early

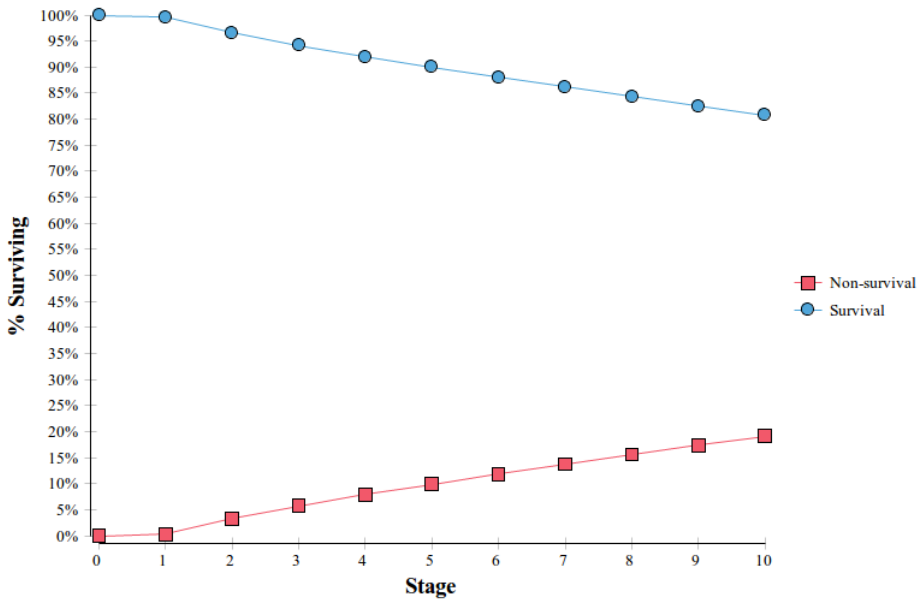


Figure 3.16: Survival/non-survival at CD4 greater than 500 cells/μL

HAART treatment initiation has a higher survival rate than the alternative and is therefore effectiveness in reducing the mortality rate of HIV-infected individuals and promoting quality of life.

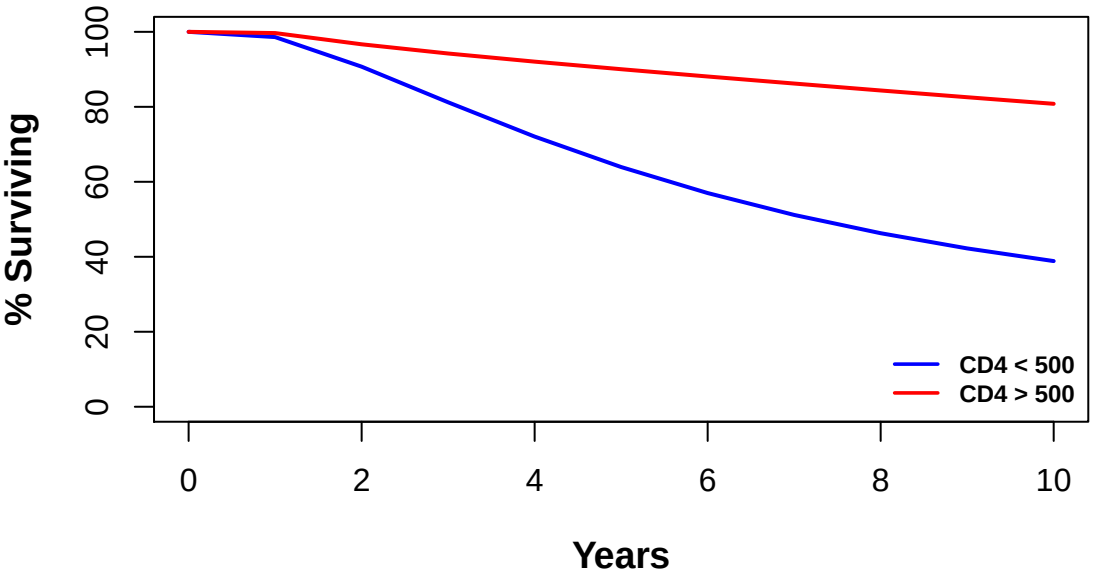


Figure 3.17: Survival at CD4 greater than 500 cells/μL vs. survival at CD4 less than 500 cells/μL

Costs used for modelling are mainly inferred from existing literature and all future costs are discounted to the year 2015/2016. All costs are presented in US dollars ($). Health care costs were attached to health states from the public health care perspective. In most cases patients are seen by a general practitioner at primary

Table 3.4: Clinical event parameters used in Decision Analysis

Variable	Value (%)	Range (%)	Reference
Probability of starting HAART at CD4 < 500	40	10 - 60	assumed.
Probability of starting HAART at CD4 > 500	65	40 - 80	assumed.
Probability of developing NHL without HAART	56	10 - 80	[18]
Probability of developing NHL with HAART at CD4 < 500	41	10 - 60	[18]
Probability of developing NHL with HAART at CD4 > 500	33	10 - 50	[18]
Probability of remission with HAART	50	10 - 60	assumed.
Probability of remission without HAART	30	01 - 40	assumed.
Probability of relapse without HAART	95	40 - 100	assumed.
Probability of relapse with HAART	45	01 - 50	assumed.
Probability of HIV death while on HAART	0.1	0.01 - 0.4	assumed.
Probability of lymphoma death without HAART	0.2	0.01 - 0.4	assumed.
Probability of lymphoma death with HAART	0.1	0.01 - 0.4	assumed.
Probability of HIV death without HAART	0.2	0.01 - 0.6	assumed.
Probability lymphoma persists with HAART	15	02 - 25	assumed.
Probability lymphoma persists without HAART	76	50 - 99	assumed.
Probability of death in remission	0.3	0.1 - 1.0	assumed.
HIV prevalence	17.9	17.2 - 18.2	[8]
Total cycles	10	10	assumed.

care level before going to a secondary level hospital for treatment according to the public health system. Some of the costs used in the analysis were inferred from the Western Cape public hospital tariff schedule [86]. Medical services costs are also included in healthcare cost calculation because they represent the monetary value of patient care.

Table 3.5: Health care cost estimates

Costs	Value (US$)	Reference
Cost of GP visit	32	[86]
Annual cost of HIV screening per person	22	[46, 52]
Annual cost of Lymphoma screening	105	[44]
HIV care costs at CD4 < 500	14,000	[46]
HIV care costs at CD4 > 500	14,600	[46]
Lifetime medical care costs for HIV	8,000	[55]
Cost of diagnostic biopsy	105	[44]
Cost of patient follow up per annum	69	[44]
Annual cost of lymphoma therapy	6,000	estimated.
Annual Cost of HAART per patient	113	[83]
Discount rate	5%	[52]

A summary of the cost-effectiveness results is as shown in the Table 3.6 below;

Table 3.6: Cost-effectiveness results table

Strategy	Total Cost ($)	Total Eff. (LY)	Incr. Cost ($)	Incr. Eff.	NMB ($)	ICER ($)
HAART at CD4 < 500	24,219	2.71	-	-	30,063	-
HAART at CD4 > 500	38,832	6.47	14,613	3.76	90,581	3,890

3.7.1 Sensitivity Analysis

In order to determine the ICER variations with key parameter changes, sensitivity analysis was carried out. One-way sensitivity analysis was done on event probabilities, costs and utilities to determine the impact of their uncertainty on the final results of cost-effectiveness analysis. The tornado plot in Figure 3.18 shows results of one-way sensitivity analysis, indicating how the outcomes are affected by some of the model input parameters. The tornado plot is stacked according to decreasing width with parameter inputs at the top displaying the greatest influence on outcomes and changes in parameter inputs close to the bottom exhibiting less influence on the outcomes. Sensitivity analysis results showed that outcomes were most sensitive to the effectiveness of HAART in preventing lymphoma incidence, with early initiation at CD4 count greater than 500 cells/μL, exerting the greatest influence on net benefits and the ICER outcomes than the base case. Most of the parameters, except for the ones indicated in the tornado plot with a certain degree of uncertainty, did not have notable influence on cost-effectiveness analysis results and are thus considered to be neither value nor decision sensitive. More information pertaining to the parameters indicated in the sensitivity analysis tornado plot is required in order to ascertain their actual impact on the results of cost-effectiveness analysis. The effectiveness of HAART, in the absence of lymphoma, displayed the widest range of uncertainty and therefore there is more information required on this utility than the other parameters displayed therein for further clarification on the results of the model analysis. From the tornado plot results, we can also deduce that a higher value of HAART without lymphoma utility could lead to increased net benefits.

3.8 Conclusion

In this chapter, we developed a health state transmission model to predict the incidence of AIDS-related lymphoma in a population of age range 15 to 80 years and also a decision analysis Markov state transition model to determine the cost-effectiveness of early HAART initiation. The model described the progression of individuals from health states with HIV and incorporated HAART initiation at different CD4 counts of greater than 500 cells/μL and less than 500 cells/μL. The results of the model analysis indicated that HAART initiation at a higher CD4 count is more effective in reducing the incidence of HIV (as shown by comparison of the effective reproduction

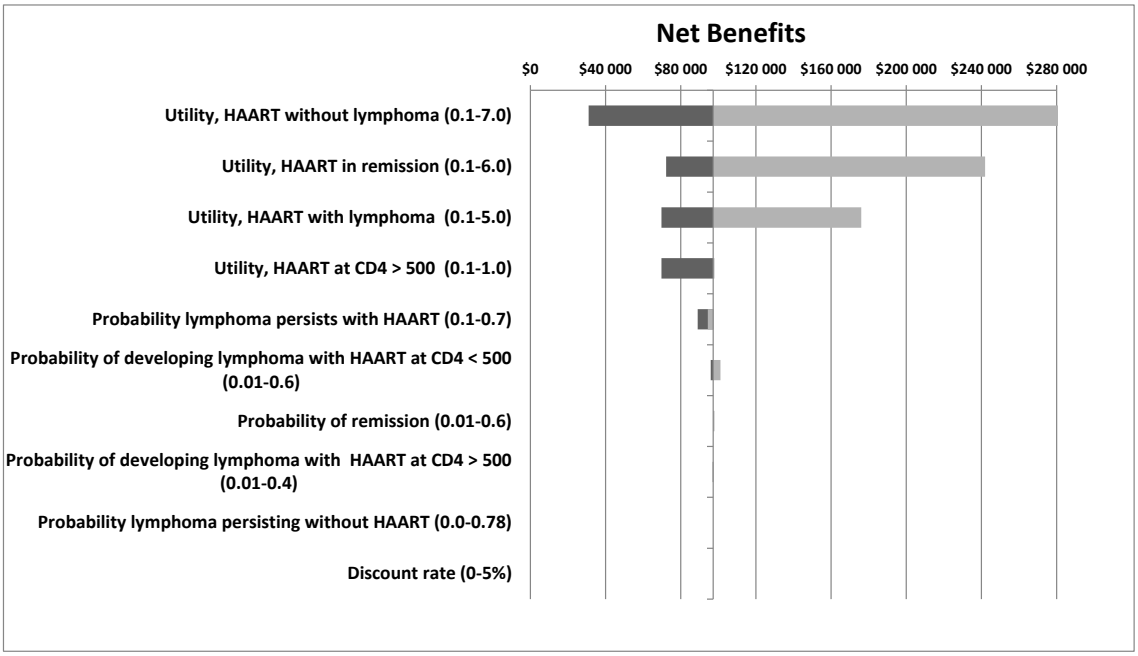


Figure 3.18: Tornado plot of one-way sensitivity analysis

numbers in Figure 3.2), and thereby preventing the incidence of AIDS-related lymphoma. This implies that preventing further spread of HIV, the greatest risk factor for AIDS-related malignancies, leads to prevention of AIDS-related lymphoma. Results also indicated that the rate of HAART initiation has an effect on the incidence of AIDS-related lymphoma (Figure 3.3). The incidence of lymphoma decreases with increase in the rate of HAART initiation, and increasing the rate of initiation to above 80% could potentially lead to no lymphoma incidence at all. With the decision analysis model, we were able to determine and compare the expected costs, net monetary benefits and quality of life gained with HAART initiation at CD4 count greater than 500 cells/μL and at CD4 count less than 500 cells/μL, the current standard of care. The model is run over a 10-year time horizon and the outcomes are discounted at a rate of 5% as recommended in Southern Africa. Results from this analysis indicated that the costs of HAART initiation at CD4 count greater than 500 cells/μL would be higher than the costs of initiation at CD4 count less than 500 cells/μL by approximately $14,613 over 10 years. The net monetary benefit of early initiation as compared to the alternative would be $60,518 and the QALYs gained with early initiation would be 6.47 as compared to 2.71 for the alternative. From the results we can deduce that early HAART initiation at CD4 count greater than 500 cells/μL is more cost-effective than the alternative with an incremental cost-effectiveness ratio of $3,890 per QALY gained. Sensitivity analysis carried out on the model parameters indicated that the results were highly sensitive to the ef-

fectiveness of HAART in preventing lymphoma, and the effectiveness at CD4 count greater than 500 cells/μL was more sensitive than the alternative. Therefore, increased early initiation of HAART is not only effective but also cost-effective in preventing AIDS-related lymphoma in resource limited settings.

Chapter 4

Discussion and Conclusion

This study, to the best of our knowledge, is the first attempt at modelling HAART initiation as prevention of AIDS-related lymphoma and its associated cost-effectiveness in South Africa. We have assessed the effectiveness and cost-effectiveness of initiating HAART at two CD4 cell count thresholds. Using a mathematical model for the dynamics of HIV progression with treatment initiation at two CD4 cell count levels, we were able to assess the impact of early antiretroviral therapy on the progression of HIV and development of lymphoma. We used a system of ordinary differential equations to analyse and understand the dynamics of disease progression among individuals in the different compartments. We found that early initiation of HAART at CD4 count greater than 500 cells/μL was more effective in preventing HIV progression and hence the development of lymphoma in HIV-infected individuals. The analysis of the basic reproduction number, R_0 showed that individuals that started treatment at a lower CD4 cell count and those with lymphoma were more likely to increase the spread of HIV than those that started treatment early.

We analysed the cost-effectiveness of HAART initiation at CD4 count greater than 500 cells/μL and at less than 500 cells/μL using a decision tree with markov processes in Treeage pro. The model was run over a time period of 10 years with a hypothetical cohort. From the analysis we found that early HAART initiation in HIV-infected individuals would provide greater value than the alternative and would be cost-saving in the long run with monetary benefits of $90,581 as compared with $30,063 of the alternative. Sensitivity analysis results showed that our model was sensitive to the effectiveness of HAART in preventing lymphoma and especially the effectiveness of early treatment initiation. There were more benefits in terms of qual-

ity of life gained with early initiation than the alternative (6.47 QALYs expected for initiation at CD4 count greater than 500 cells/μL versus 2.71 QALYs for initiation at CD4 count less than 500 cells/μL). From our model we could deduce that treatment initiation at CD4 count greater than 500 cells/μL could lead to improved quality of life translating to 3.76 QALYs in 10 years. The cost of early initiation increased by $14,613 in comparison to the alternative. Therefore early initiation of HAART at CD4 count greater than 500 cells/μL was cost-effective with an incremental cost-effectiveness ratio (ICER) of $3,890 per QALY gained. This analysis showed that there's more to gain by increasing early HAART initiation for all people infected with HIV in terms of costs and improved quality of life. However, the long-term impact of highly active antiretroviral therapy on AIDS-related lymphoma incidence still remains unknown and further research needs to be done in order to ascertain this. TreeAge Pro software (particulary the Healthcare module) has been a very helpful tool in the modelling and analysis of our model. The use of TreeAge pro in cost-effectiveness analysis is highly recommended as the software helps one easily build decision trees for better understanding of the stages and processes of analysis bringing to light more factors that go into the process of decision analysis.

As reported by other studies on the effectiveness and cost-effectiveness of HAART [11, 25, 46, 48, 65], our study also showed that early treatment initiation is effective in preventing further HIV progression and possibly forestalling AIDS-related lymphoma. Given that maximum coverage of early HAART initiation and complete adherence to treatment by all HIV-infected individuals is achieved, HIV and AIDS-related lymphoma would significantly reduce thus leading to savings on costs that would have been incurred on treatment of new cases and advanced disease stage that are more costly. This deduction however, needs to be verified by a clinical study with actual figures for all variables used in the model to ascertain the real implication of increasing HAART initiation to CD4 count greater than 500 cells/μL on lymphoma incidence and the associated cost-effectiveness. The late commencement of antiretroviral therapy is largely attributed to low rates of HAART coverage and initiation policy decisions that do not favour early commencement of treatment by all HIV-infected individuals. With a revised initiation policy in place, we should be able to see a notable decline in incidences of HIV and AIDS-related lymphoma in South Africa. This would also mean an improvement in the quality of life of people living with HIV and a reduced burden on the government economy as HIV and its related illness have been greatly affecting South Africa's economic growth. However,

there are several challenges of adherence to treatment that need to be addressed in order to achieve maximum benefits from a given treatment initiation strategy.

Limitations

The main limitation to CD4-count driven modelling of AIDS-related lymphoma is the lack of patient records on CD4 count history prior to lymphoma diagnosis. Records only show CD4 count measurements taken at the time of lymphoma diagnosis. The only data available to us currently is that of incidence and prevalence of HIV-related lymphoma in South Africa from 2002 to 2012 [1, 6] shown in Table 4.1.

Table 4.1: Number of lymphoma cases per year as recorded by TLSG

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

Although we were able to construct a model for cost-effectiveness analysis, we were unable to find comprehensive records on the costs of lymphoma diagnosis, treatment and care in HIV patients because such records are not readily available and therefore the parameter values used for evaluation in this study are estimates from similar studies.

Conclusion

As it stands, the cause of lymphoma is not yet established and therefore prevention of lymphoma largely depends upon reducing conditions that lead to the increased risk of developing malignancies such as immune suppression in HIV-infected individuals [13**?**]. Given the level of complexity of cancer epidemiology, it is difficult to determine the actual extent to which HAART could actually prevent AIDS-related lymphoma. However, the cost of cancer treatment and end of life care is much higher than the cost of increasing HAART initiation. Therefore, with the increasing burden of HIV and cancer in South Africa, our analyses suggest that early HAART initiation, increased coverage, routine screening for cancer and reduction in risky behaviours should be emphasised in order to prevent lymphoma in HIV-infected individuals.

4.1 Future Research Recommendations

This model can be extended to include demographic factors such as age, sex, race, geographical location (rural or urban settings) and income status of individuals. A cost-benefit analysis (CBA) could be carried out to asses whether the benefits of the intervention exceed its costs. However, it is important to note that in carrying out a CBA, expressing healthcare benefits in terms of their monetary value can be rather difficult and the process can be very complex and expensive to undertake. There are concerns with treatment resistance in some patients and this can also be considered in modelling the effectiveness of HAART in prevention of lymphoma [58].

Appendices

Appendix i

Decision Analysis Tools

In this section we present the breakdown of the decision tree model constructed in TreeAge Pro 2015 (TreeAge Software, Williamstown, MA) which was used to evaluate the cost-effectiveness of HAART initiation at two CD4 cell count levels.

Figures 4.2, 4.3, 4.4, 4.5 and 4.6 below show a breaking down of the sub-trees at each of the markov states indicated in fig 3.7 for a clear view of the processes that follow from each health state.

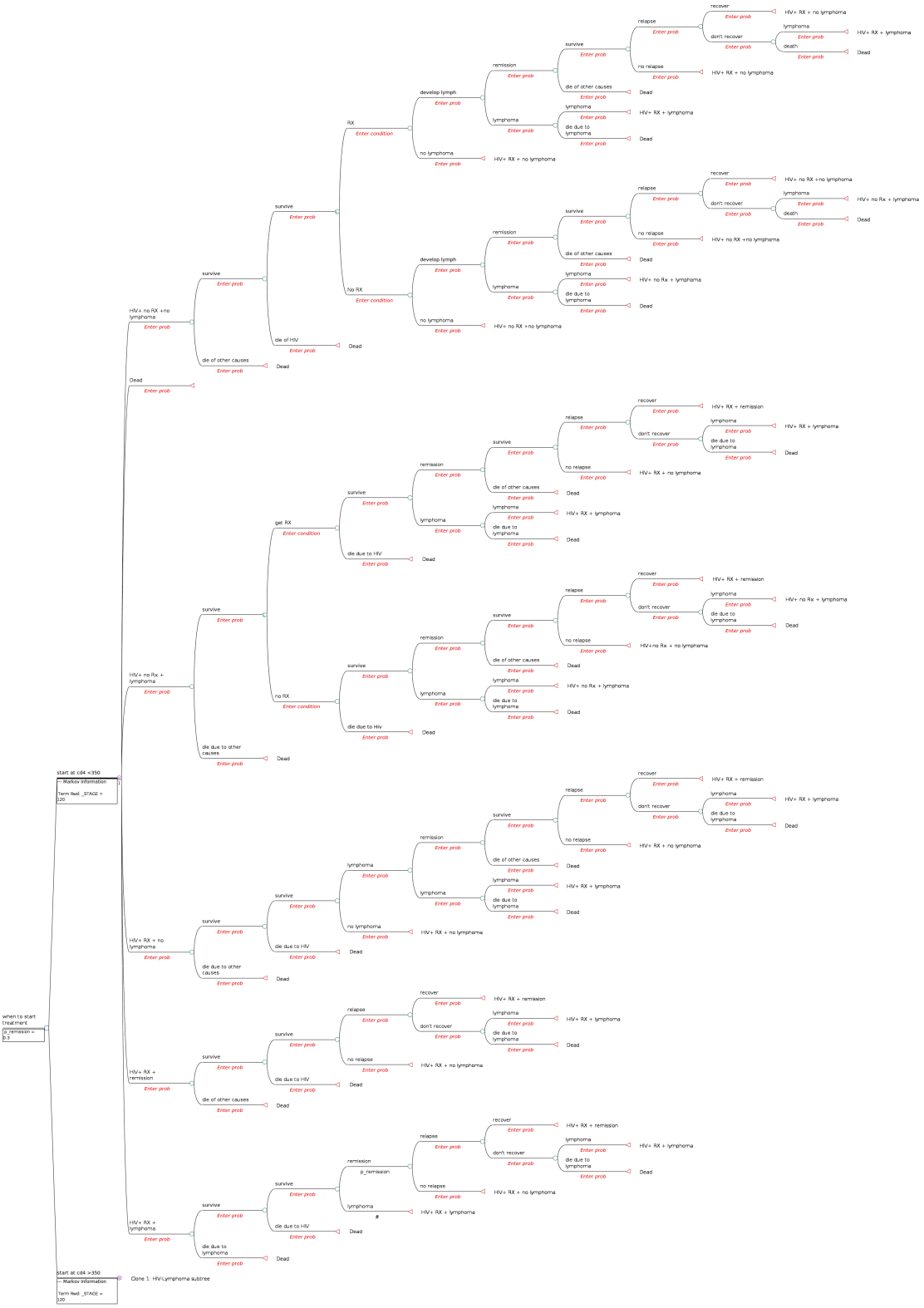


Figure 4.1: Complete Decision Tree diagram

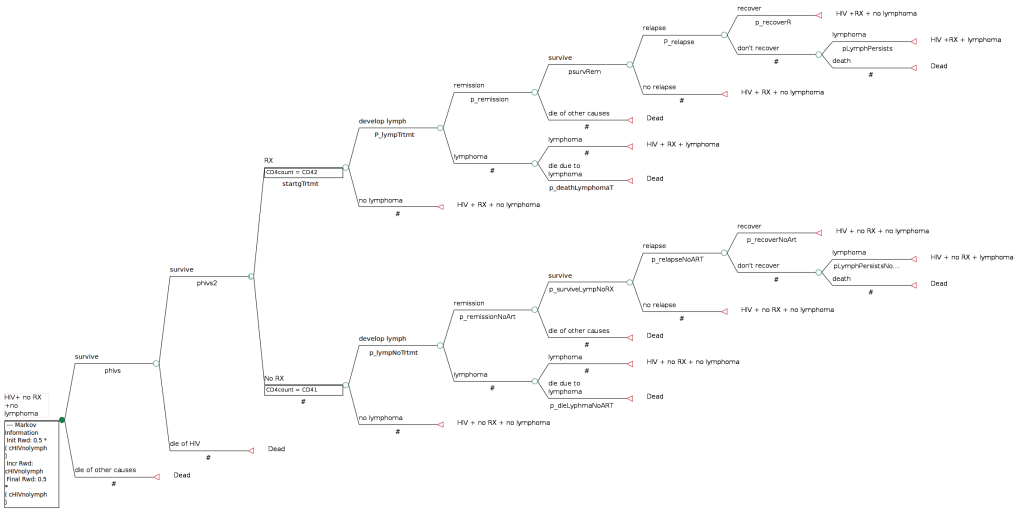


Figure 4.2: Sub-tree at Markov state HIV+no RX+no lymphoma

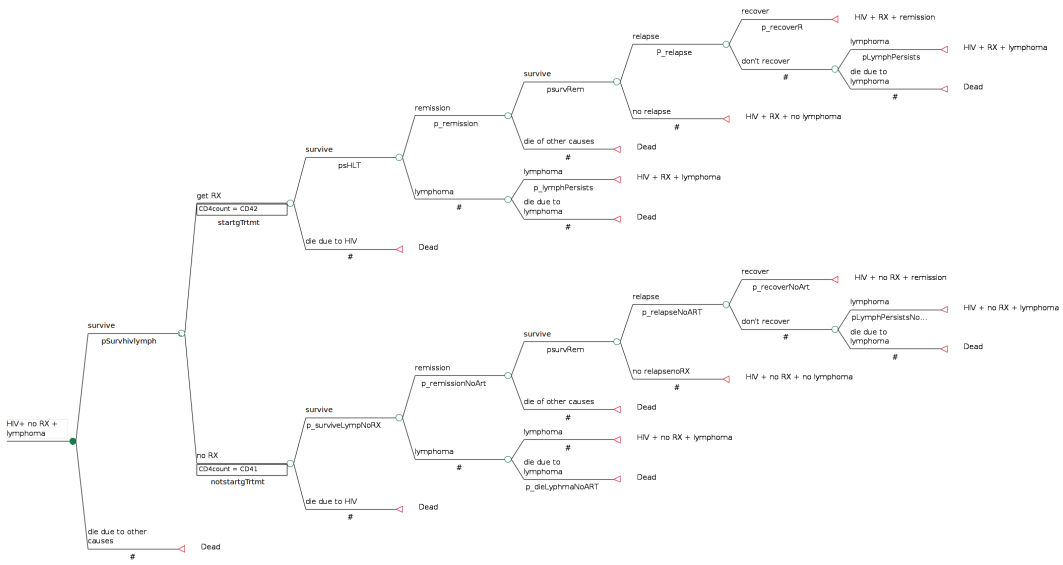


Figure 4.3: Sub-tree at Markov state HIV+no RX+lymphoma

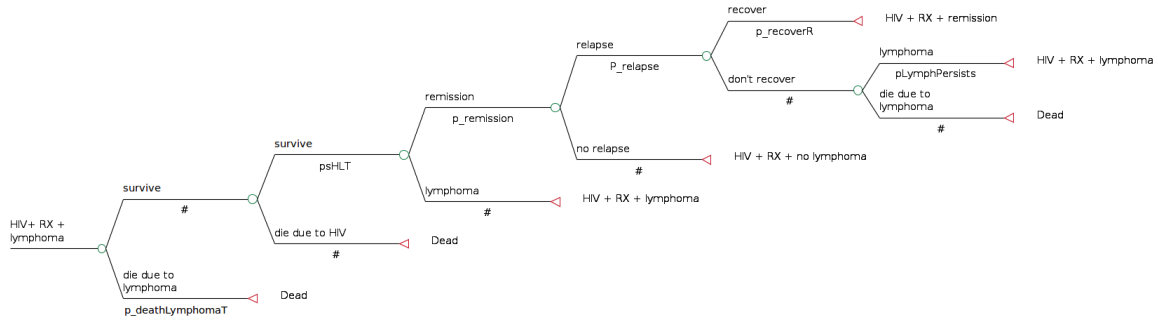


Figure 4.4: Sub-tree at Markov state HIV+RX+lymphoma

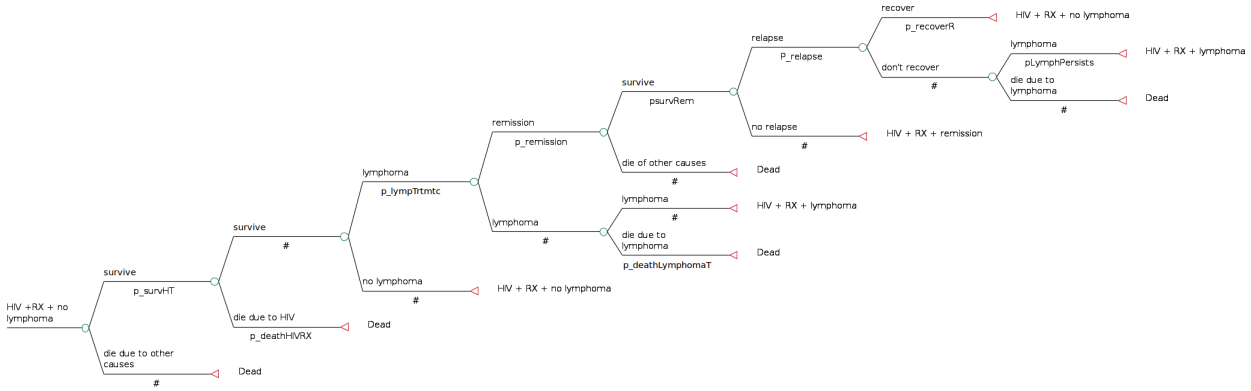


Figure 4.5: Sub-tree at Markov state HIV+RX+nolymphoma

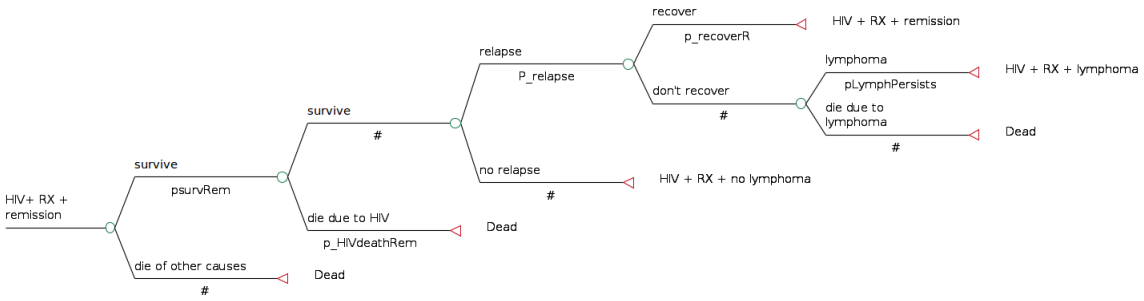


Figure 4.6: Sub-tree at Markov state HIV+RX+remission

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