MATHEMATICAL MODELING OF R5 and X4 HIV:*From within host dynamics to the epidemiology of HIV infection.*

Edna C. Manda

Submitted in fulfillment of a Master's Degree at University of KwaZuluNatal

Edna C. Manda

This dissertation is submitted to the School of Mathematics, Statistics and Computer Science at University of KwaZulu-Natal, Pietermaritzburg, in fulfillment of the requirements for the degree of Master in Science.

As the candidate's supervisor, I have approved this dissertation for submission.

Signed: Dr. F. Chirove .....

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Dedication

To the almighty God who brought me this far and gave me wisdom to pursue the turbulent routes of academics. To the love of my life George Bottie Manda, who has always been by my side. To my late parents Steve Mcheka Chilenje and Annie Manda Chilenje. I wish you were alive to see my successes, your still in my heart. I miss you.

Abstract

Most existing models have considered the immunological processes occurring within the host and the epidemiological processes occurring at population level as decoupled systems. We present a new model using continuous systems of non linear ordinary differential equations by directly linking the within host dynamics capturing the interactions between Langerhans cells, CD4+ T-Cells, R5 HIV and X4 HIV and the without host dynamics of a basic compartmental HIV/AIDS, susceptible, infected, AIDS model. The model captures the biological theories of the cells that take part in HIV transmission. The study incorporates in its analysis the differences in time scales of the fast within host dynamics and the slow without host dynamics. In the mathematical analysis, important thresholds, the reproduction numbers, were computed which are useful in predicting the progression of the infection both within the host and without the host. The study results showed that the model exhibits four within host equilibrium points inclusive of three endemic equilibria whose effects translate into different scenarios at the population level. All the endemic equilibria were shown to be globally stable using Lyapunov functions and this is an important result in linking the within host dynamics to the population dynamics, because the disease free equilibrium point ceases to exist. The linked models had no effect on the basic reproduction numbers of the within host dynamics but on the basic reproduction number of the population dynamics. The effects of linking were observed on the endemic equilibrium points of both the within host and population dynamics. Therefore, linking the two dynamics leads to the increase in the viral load within the host and increase in the epidemic levels in the population dynamics.

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List of Abbreviations

Abbreviation	Meaning
LC	Healthy Langerhans cells
L_T	Latently infected Langerhans cells
L_I	Infected Langerhans cells
C	Healthy $CD4^+$ T cells
C_I	Infected $CD4^+$ T cells
V_{R5}	R5 virus
V_{X4}	X4 virus
CCR5	Chemokine co-receptor type 5
CXCR4	Chemokine co-receptor type 4
S	Susceptible individuals
I	Infected individuals
A	AIDS individuals
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
DFE	Disease Free Equilibrium point
EE	Endemic Equilibrium Point

Chapter 1

INTRODUCTION

The dynamics of infectious diseases affect populations in many hierarchical levels which can be summarized as from omics to population dynamics. Understanding the dynamics of infection at these levels will definitely enhance the prognosis and diagnosis of infections as well as interventions. Therefore, we focus, in this study, on two of the hierarchical levels and investigate the effects of linking the infection dynamics between these two levels. The levels are (i) the immunological dynamics and (ii) the epidemiological dynamics. We study the interactions between different cells that take part in HIV transmission from the within host dynamics to the population dynamics and from the population dynamics to within the host dynamics because important relationships exist between what is happening in the host and what is occurring at the population level. The evidence of this existing relationship is that the study of patterns and disease conditions in defined populations are caused by parasites that either go into the host from the population or from within the host to the population to cause infections.

This study will focus on Langerhans cells and $CD4^+$ T-cells which are immune cells of the immune system. The immune system is a system of many biological structures and processes within an organism that protects an organism against diseases. To function properly, the immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissues.

1.1 Background Information

Langerhans cells are antigen-presenting immune cells of the skin and mucosa which contain large organelles called Birbeck granules. They are present in all layers of the epidermis, but most prominent in the *stratum spinosum*. They also occur in the papillary dermis, particulary around blood vessels, as well as in the mucosa of the mouth, foreskin and vagina [34].

Langerhans cells have two main functions. Firstly, they are an integral part of the body's total defense system [35] where they help protect the body by keeping dangerous microbes from entering it and defending the skin from infection through stimulating allergic reactions. Secondly, they act as a medium of infection for HIV transmission [36] where even if they capture antigens and degrade them they loose their antigen presenting property and pass on the HIV to the $CD4^+$ T-cells. Thus, during this process, Langerhans cells get infected and when they come in contact with the $CD4^+$ T-cells, they pass the virus to the $CD4^+$ T-cells.

The $CD4^+$ T-cells also called CD4 cells, T-helper cells or T4 cells are white blood cells that are an essential part of the immune system [12]. Millions of $CD4^+$ T-cells are produced by the body to assist with the immunity maintenance. The $CD4^+$ T-cells are called helper cells because one of their main roles is to send signals to activate the body's immune response when they detect "intruders" like viruses or bacteria to the other types of immune cells including CD8 killer cells which then destroys the infectious particles. $CD4^+$ T-cells do not have the ability to kill the infectious particle [12].

Human Immunodeficiency Virus (HIV) is the virus that causes Acquired Immunodeficiency Syndrome (AIDS). HIV as a retrovirus, kills or damages the cells of the body's immune system. Langerhans cells and $CD4^+$ T-cells are some of the target cells for HIV. A retrovirus is a single-stranded positive-sense RNA virus with a DNA intermediate and, as an obligate

parasite, targets a host cell. Once inside the host cell cytoplasm, the virus uses its own reverse transcriptase enzyme to produce DNA from its RNA genome, the reverse of the usual pattern, thus retro (backwards). This new DNA is then incorporated into the host cell genome by an integrase enzyme, at which point the retroviral DNA is referred to as a provirus. The host cell then treats the viral DNA as part of its own genome, translating and transcribing the viral genes along with the cell's own genes, producing the proteins required to assemble new copies of the virus. It is difficult to detect the virus until it has infected the host. At that point, the infection will persist indefinitely [37].

HIV is transmitted primarily by unprotected sexual intercourse with an infected person through certain bodily fluids like blood, semen, pre-seminal fluid , rectal fluids and vaginal fluids. It is also spread by contaminated blood transfusions and hypodermic needles. Women with HIV can transmit the virus to their babies during pregnancy, delivery or breastfeeding. HIV-infected people taking anti-retroviral therapy can still infect others through unprotected sex and needle sharing [13].

HIV has four stages of infection namely, the primary(acute) infection stage, clinically asymptomatic stage, symptomatic HIV infection stage and the progression to AIDS stage. Firstly, the primary phase lasts for 2 to 3 weeks and is often accompanied by short flu-like illnesses such as fever, headache, and rash. During this stage, there is a large amount of HIV in the peripheral blood and the immune system begins to respond to the virus by producing HIV antibodies and cytotoxic lymphocytes. The $CD4^+$ T-cells count at this stage is 500 per microliter. Secondly, the clinically asymptomatic stage lasts for an average of ten years and as its name suggests, is free from major symptoms although there may be swollen glands. The level of HIV in the peripheral blood drops to very low levels but individuals remain infectious and HIV antibodies are detectable in the blood. The $CD4^+$ T-cells count in this stage is 350 to 499 per microliter. Thirdly, the symptomatic HIV infection stage is when the immune system becomes severely damaged by HIV. This may be due to the lymph nodes and tissues getting burnt out because of the years of activity and also due to new mutants which are more pathogenic leading to more

T-helper cells destruction. The body in this phase fails to keep up with replacing the T-helper cells that are lost. Emergence of opportunistic infections is used as an identifier in this stage and the $CD4^+$ T-cells count is 200 to 349 per microliter. Lastly, the AIDS stage is when the immune system becomes more and more damaged that the individual develops increasingly severe opportunistic infections such as tuberculosis, pneumonia and cancers. Here, the number of $CD4^+$ T-cells lowers to 200 per microliter leading to an AIDS diagnosis [13, 12].

HIV uses several receptors to bind and infect host cells. We shall focus on two of the several cell surface chemokine receptors namely chemokine co-receptor type 5, CCR5 and chemokine co-receptor type 4, CXCR4 as co-receptors for HIV infection. These are known as R5 HIV and X4 HIV respectively. CCR5 is a protein on the surface of white blood cells that is involved in the immune system as it acts as a receptor for chemokine receptor that infects Langerhans cells and $CD4^+$ T-cells. R5 is a type of HIV that uses co-receptor CCR5 to bind and infect immune cells. Receptors are membrane proteins that take part in communication between the cell and the outside world. A chemokine co-receptor is a cell surface receptor that binds a signalling molecule in addition to a primary receptor in order to facilitate ligand recognition and initiate biological processes, such as entry of a pathogen into a host cell. CXCR4 referred to as X4 is a protein encoded by the CXCR4 gene in humans. CXCR4 is one of several chemokine receptors that HIV can use to infect $CD4^+$ T-cells and Langerhans cells. HIV uses CCR5 and CXCR4 to enter and infect both Langerhans cells and $CD4^+$ T-cells. The entry of HIV into its target cells is facilitated by the prior binding to the cell surface molecule CD4 and the secondary co-receptors, CCR5 and CXCR4. In early HIV infection, R5 viruses are mostly dominant while a receptor switch towards X4 viruses occurs in about 50% of the infected individuals. X4 viruses are associated with the progression of the disease [38].

Once HIV enters the body from the population, Langerhans cells as the initial targets of infection captures the virus and degrades it using Langerin that produces birbeck granules. When the Langerhans cells are overwhelmed by the virus, they present it to the naive T-cells and are responsible for the infection of $CD4^+$ T-cells. HIV then attaches itself to the protein CD4

present on the surface of $CD4^+$ T-cells using CXCR4 to enter into $CD4^+$ T-cells. HIV then duplicates itself increasing its potential to kill the $CD4^+$ T-cells and as a result the infected cells outnumber the healthy $CD4^+$ T-cells making them unavailable to immune defence. Therefore HIV weakens the immune system putting an individual at risk of developing opportunistic infections because of low $CD4^+$ T-cells and ultimately the individual develops AIDS which leads to death [35, 36].

Genetic research indicates that HIV originated in west-central Africa during the late 19th or early 20th century. AIDS was first recognized by the United States Centers for Disease Control and Prevention (CDC) in 1981 and its cause was identified in the early part of the decade. HIV/AIDS has had a great impact on society, as an illness [11].

HIV/AIDS epidemic is defined by the HIV prevalence in the general population. HIV prevalence is the percentage of the population living with HIV. In a population, the individuals at risk of getting the infection are those that are sexually active, ages $15 - 49$. HIV/AIDS is considered a pandemic, a disease outbreak which is present over a large area and is actively spreading [11]. At population level, HIV can be transmitted from infected or AIDS individuals to susceptible individuals.

The two mechanisms of HIV infection are cell-to-cell and cell-free infection. Cell-to-cell infection occurs when the virus is transmitted by a host from one cell to another through cell communication. Cell-free infection occurs when the free virus infects the host cells by penetrating into the cell. Therefore, for immunological and epidemiology dynamics, HIV is either spread through cell-to-cell or cell-free infection mechanisms.

1.2 Problem Statement

Most HIV/AIDS models showed that HIV states are based on $CD4^+$ T-cells cells as the target cells infected by HIV such that the analysis of Langerhans cells has not been given enough attention in as far as its contribution towards HIV progression is concerned during the primary phase of HIV infection. Further, they has been not much research on CXCR4 and CCR5. It is therefore worthy exploring the effects of these two types of cell surfaces that R5 HIV and X4 HIV uses to infect cells in a host. Again most existing models have considered within host dynamics models and population models as decoupled systems and do not link them explicitly.

We therefore develop a within host mathematical model to investigate the infections of Langerhans cells and $CD4^+$ T-cells with R5 HIV and X4 HIV. We also review a basic population model to investigate the population dynamics of HIV/AIDS. We shall connect the two models to develop an immuno-epidemiology model linking the within host dynamics to the population dynamics to investigate insights on how the two may affect each other. Mathematical theories will be used to abstract biological processes into mathematical formulas and analysis will be transferred back to the biological explanations.

1.3 Aim

The aim of the study is to use mathematical models to investigate the effects of the link between within host and the epidemiology of HIV infection through studying within host model dynamics of R5 HIV and X4 HIV and the population dynamics of HIV infection.

1.4 Objectives

The objectives of the study are:

1. To develop a within host mathematical model that captures the interactions between Langerhans cells, $CD4^+$ T-cells, R5 virus and X4 virus during the primary phase of HIV infection.

2. To review an epidemiological dynamics model for HIV infection.

3. To develop a model linking the within host dynamics to the epidemiological dynamics.

4. Analyze the mathematical models in objectives 1, 2 and 3 analytically and carry out numerical simulations using data from published literature.

1.5 Significance of the Study

The emergence of diseases combines two elements, the introduction of the pathogen into the human and its subsequent spread and maintenance within the population. The study and analysis of linking within host dynamics and without host dynamics in HIV infection may be used as a basis of understanding how the viral load and the CD4 count are affected in the course of HIV infection. It also helps us to understand the several pathways that the virus uses to invade and infect a host from the population to the within host and vice versa. Mathematical models based on underlying transmission mechanisms of HIV might help the medical and scientific community understand better how the disease spreads in the community. The outcome of this study may help the government, countries, public health sectors to establish policies and plans for administering treatment mechanisms as they will keep track of the emergence and spread of the virus.

1.6 Scope of the Study

This chapter has provided a general overview of biological theories of the interactions between different cells that take part in HIV transmission from the population level to within the host and viceversa. Chapter 2 contains a review of the studies that were done by other researchers and also some preliminary concepts which will be used for mathematical model analysis. In

chapter 3, a within host dynamics mathematical model will be formulated and analysed and a basic population dynamics mathematical model will be reviewed and analyzed in detail. In Chapter 4 we link the within host dynamics and the population dynamics and detailed analysis of the linked models are provided. Chapter 5 provides numerical simulations of our models and discuss the results from the simulations, give possible recommendations and conclusion based on the model results. Finally Chapter 6 will contain a detailed discussion of results, observations, conclusion, strength and weakness of the models and future work to be done.

Chapter 2

LITERATURE REVIEW AND PRELIMINARY CONCEPTS

2.1 Introduction

This chapter reviews published research conducted by different researchers to get the general information on within host models focusing on infection of Langerhans cells and $CD4^+$T-cells with the R5 HIV and X4 HIV. We also review models on population dynamics and immuno-epidemiological dynamics, where within host dynamics are explicitly linked to population dynamics. We shall select a few studies that we will review as building blocks to our study. In the preliminary concepts, definitions and major concepts that will be used in the mathematical analysis of the models will be defined and discussed in detail.

2.2 Literature Review

Sugaya et al [41] studied how HIV infected Langerhans cells preferentially transmit to proliferating autologous $CD4^+$T-cells memory T-cells located with Langerhans cell T-cell clusters experimentally. The purpose of their study was to examine the nature of the $CD4^+$T-cells that becomes infected by HIV-infected Langerhans cells. They infected human Langerhans cells with

tissue explants *ex vivo* and three days later cocultured HIV-infected Langerhans cells with different subsets of autologous $CD4^+$T-cells. Their results showed that HIV infected Langerhans cells infected $CD4^+$T-cells compared to naive $CD4^+$T-cells. The infected $CD4^+$T-cells were more frequently detected in conjugates of Langerhans cells and autologous $CD4^+$T-cells. Their results suggested that T-cells becomes activated and preferentially get infected though cluster formation with infected Langerhans cells rather than getting infected with free virus produced by single HIV-infected Langerhans cells or $CD4^+$T-cells. Their results highlighted that close interactions between Langerhans cells and $CD4^+$T-cells are important for optimal HIV replications within specific subsets of $CD4^+$T-cells. However they concentrated on experiments and no mathematical analysis was carried out to ensure validation of mathematical results to the biological set up of the infection process.

Mbongo et al [20] studied a stochastic model for Langerhans cells and HIV dynamics in *vivo*. In their study, they derived and analyzed a stochastic model explaining the dynamics of HIV, $CD4^+$ T-cells and Langerhans cells interactions under therapeutical interaction in *vivo*. Their model results showed that HIV states should not be based on $CD4^+$ T-cells as the target cells infected by HIV. The findings illustrated the role of Langerhans cells as a central hub of interaction and information exchange during HIV infection. Yet, they did not capture the degradation effects of HIV by Langerhans cells and did not specify the type of HIV that prefers infecting the Langerhans cells and the $CD4^+$ T-cells.

Culshaw et al [27] developed a delay differential equation model for HIV infection of $CD4^+$T-cells. Their study aimed to simplify the model by A.S Perelson et al and introduce a discrete time delay to the model to describe the time between infection of a $CD4^+$T-cells and the emission of viral particles on a cellular level. Their results suggested that intracellular delay can cause the cell and virus populations to fluctuate in the early stage of infection, in a longer term they will converge to the infected steady state values. However, they focused on $CD4^+$T-cells

being initial targets of HIV infection and ignored the contribution of other immune cells such as the Langerhans cells that contributes to HIV infection progression during early infection of the virus.

Kamp [38] investigated the HIV co-receptor switch from a dynamical perspective. He developed a model to investigate the conditions under which the receptor switch occurs. The model allowed him to investigate the evolution of viral strains within a probabilistic framework along the three stages of disease from primary, latent to the onset of AIDS with a sudden increase in viral load which goes with the impairment of the immune system. The model investigated the evolution of the viral quasi species in terms of R5 viruses and X4 viruses which directly translates into the composition of viral load and consequently the question of the co-receptor switch. The model results managed to explain the co-receptor switch as a result of a dynamical change in the underlying environmental conditions in the host. Still, they did not specify the type of HIV that prefer infecting the type of different host cells.

Zhilan et al [21] developed a mathematical model for coupling within and between host dynamics in an environmentally-driven infection disease. Their work presented a model for the linking of within and between host dynamics through their connection to a contaminated environment. Their model results provided new insights into the effects of each of the processes on the other and showed that new properties can emerge from the coupled system and more complex dynamics may be expected. But, their model is more appropriate for only environmentally driven infections with indirect links. In the case of HIV infection, direct links are required to capture the connections.

Gagira et al [25] investigated a mathematical model framework for linked within-host and between host dynamics for infections with free living pathogens in the environment. In their

study, they linked the within host dynamics and the between host dynamics by identifying the within host and between host variables and parameters associated with the environmental dynamics of the pathogen. The results in their study were significant for the current ongoing efforts to develop new theoretical modeling framework of the evolution of infectious diseases. Nevertheless, they did not identify a generalized framework for linking within host dynamics and population dynamics of infectious diseases.

Another study by Gil et al [24] introduced the evolution of virulence: Interdependence, constraints, and selection using nested models. In their study, they explicitly examined ideas and assumptions that studies which examine selection at both scales assume that between- and within-host selection are necessarily in conflict using a model of within-host viral dynamics nested within a model of between-host disease dynamics. Their approach allowed them to evaluate the direction of selection at the within and between-host levels and identify situations leading to conflict and accord between the two levels of selection. Their results indicated that the general assumptions that both virulence and transmission increase with parasite load do not necessarily lead to a conflict in selection at the between and within-host levels. They proposed the understanding of the within host dynamics and their link to the epidemiological level as being necessary steps towards a general theory of the evolution of parasite virulence. Again for HIV direct links are required.

Jen et al [26] studied an immuno-epidemiological model with threshold delay: a study of the effects of multiple exposures to a pathogen. Their model incorporated two main features: (i) the epidemiological model included within host pathogen dynamics for an infectious disease, (ii) the susceptible individuals to the infection experience a series of exposures via the pathogen before becoming infectious. Their results constituted an important step towards articulating an integrated and more refined epidemiological theories that can influence between host- pathogen interactions, epidemiological mixing, and disease spread.

Maia et al [23] developed the linking of immunological and epidemiological dynamics of HIV; a case of super infection. In their study, they aimed to formulate a two strain model that linked immunological and epidemiological dynamics across scales. They linked their models through the age-since-infection structure of the epidemiological variables. Their results showed that on within host scales, the two strains eliminate each other with the strain with the larger immunological basic reproduction number persisting. They found a possibility of superinfection on the population scale with the strain with larger immunological reproduction number super infecting the strain with the smaller immunological reproduction number. They also found that that the between host transmission and the disease induced death rate depended on the within host viral load. However,in their within host dynamics model, they only considered infection of $CD4^+$ T-Cells and ignored the contribution of Langerhans cells to HIV infection. They also did not specify the type of viral strains that they were studying.

A number of researchers , the likes of Johnson, Baryarama et al and Sani et al [28, 29, 30, 31] developed and analyzed compartmental SIA HIV/AIDS models. In their models, Johnson [28] studied an introduction to the mathematics of HIV/AIDS modeling. Their study presented a basic SI model of HIV transmission and discussed how the model could be improved to allow for greater accuracy in modeling of HIV transmission by introducing survival functions. Nonetheless, their model was not structured by age and therefore of limited use in long term population projections. Sani et al [29] formulated a stochastic model for the spread of HIV in a heterosexual mobile population, under the assumption of a constant and varying population sizes. In their model, they derived deterministic and diffusion analogues using convenient re scaling techniques to analyze the stability conditions and equilibrium behaviors. Again their model was not structured by age. Baryarama et al [30, 31] developed an HIV/AIDS model incorporating complacency for the adult population, in their model they assumed complacency as a function of the number of AIDS cases in a community with an inverse relation. Their model analysis showed that complacency resulting from dependence of HIV transmission on

the number of AIDS cases in a community leads to damped periodic oscillations in the number of infective with oscillations more marked at lower rates of progression to AIDS. Their study revealed that prolonged survival of AIDS cases may lower the endemic equilibrium level of HIV infection. Still, they did not specify the age of the adult population. In the other model, they developed an HIV/AIDS model with variable force of infection for the adult population. The main finding of their research was that in settings with high recruitment rates, the HIV epidemic reaches peak prevalence when the rate of new infections is still higher than the removal of those infected with HIV. All the models that we reviewed provided interesting results. We reviewed a basic SIA model in our study because for the linking purposes of the within host dynamics to the population dynamics, we wanted to start with a simple case and see the general overview of the effects of linking the within host to the population before we start adding some parameters to get more insights.

2.3 Preliminary Concepts

2.3.1 The Reproduction Number (R_0)

Van den Driessche and Watmough [1] defines the basic reproduction number (R_0) as the average number of second generation infections produced by a typical infective person in a totally susceptible population. In their approach, they assumed that there are n compartments of which m are infected, $\bar{x} = (x_1, x_2, \ldots, x_n)$, where $\bar{x}$ is the disease free equilibrium (DFE) point and x_i denotes the number of individuals in the i^{th} compartment. The matrix $\mathcal{F}_i(\bar{x})$ is defined to be the rate of new infections into compartment i and the transition matrix $\mathcal{V}_i(\bar{x}) = \mathcal{V}_i^-(\bar{x}) - \mathcal{V}_i^+(\bar{x})$, where $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means and $\mathcal{V}_i^-$ is the rate of transfer of individuals out of the compartment i. The next generation matrix is defined by FV^{-1} from the matrices of partial derivatives of $\mathcal{F}_i$, $\mathcal{V}_i$ evaluated at $\bar{x}$. $F = \left[\frac{\partial \mathcal{F}_i(\bar{x})}{\partial x_j}\right]$ and $V = \left[\frac{\partial \mathcal{V}_i(\bar{x})}{\partial x_j}\right]$, where $i, j = 1, \ldots, m$.

The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i times the average length of time an individual spends in a single visit to compartment j. R_0 therefore is given by the spectral radius(ρ),the largest eigenvalue of the matrix FV^{-1}. Thus $R_0 = \rho(FV^{-1})$.

2.3.2 The Jacobian Matrix and Characteristic Equation

A Jacobian matrix is a matrix of all first order partial derivatives of a vector-valued function [2]. Suppose $F : \mathbb{R}^n \to \mathbb{R}^m$ is a function, where F is given by m-real valued component functions $F_1(x_1, \ldots, x_n), \ldots, F_m(x_1, \ldots, x_n)$. The partial derivatives of all these functions with respect to the variables $x_1, \ldots, x_n$ (if they exist) can be organized in an $m \times m$ matrix. The Jacobian matrix J of F is given as follows:

$$J = \begin{pmatrix} \frac{\partial F_1}{\partial x_1} & \cdots & \frac{\partial F_1}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \frac{\partial F_m}{\partial x_1} & \cdots & \frac{\partial F_m}{\partial x_n} \end{pmatrix}$$

A characteristic equation of a matrix is the equation in one variable λ of the form $det(J-\lambda I) = 0$ where det is the determinant of a matrix, I is the $m \times m$ identity matrix and J is the Jacobian matrix. The solutions of the characteristic equation are precisely the eigenvalues of the matrix J.

2.3.3 The Routh Hurwitz Criterion [3, 39]

Routh Hurwitz stability criterion is a mathematical test that is a necessary and sufficient condition for the stability of a linearized system. The Routh Hurwitz matrices give necessary conditions for all roots of the characteristic polynomial to have negative real parts implying local stability.

Given a characteristic polynomial $P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots a_{n-1}\lambda + a_n$ where the coefficients a_i are real constants, $i = 1, \ldots, n$. The n Hurwitz matrices of the characteristic polynomial are

given by

$$B_1 = \begin{vmatrix} a_1 \end{vmatrix}, \quad B_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix}, \quad B_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix}, \quad B_n = \begin{vmatrix} a_1 & 1 & 0 & 0 & \cdots 0 \\ a_3 & a_2 & a_1 & 1 & \cdots 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots \\ 0 & 0 & 0 & 0 & \cdots a_n \end{vmatrix}$$

where $a_j = 0$ if $j > n$. The roots of the characteristic polynomial $P(\lambda)$ are non positive or have non positive real parts if and only if all Hurwitz matrices are non-negative. $det(B_j) > 0$, $j = 1, 2 \ldots, n$.

Example 2.3.4. For n=2, the characteristic equation is $P(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0$ and the corresponding Hurwitz matrix is

$$B_2 = \begin{vmatrix} a_1 & 1 \\ 0 & a_2 \end{vmatrix},$$

$det(B_2) = a_1 a_2 > 0$. The Routh-Hurwitz conditions are $a_1 > 0$, $a_2 > 0$.

Example 2.3.5. For n=3, the characteristic equation is $P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ and the corresponding Hurwitz matrix is

$$B_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{vmatrix},$$

$det(B_3) = a_3(a_1 a_2 - a_3) > 0$. The Routh-Hurwitz conditions are $a_1 > 0$, $a_3 > 0$ and $a_1 a_2 > a_3$.

The Routh Hurwitz conditions, however, can sometimes be very difficult to apply if $n \geq 3$. Other methods for determining local stability like the Corollary of Gershgorin Circle Theorem can be easily applied for an $n \times n$ matrix.

2.3.6 Descartes Rule of Signs[39]

Considering the n^{th} polynomial

$$f(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots + a_n = 0 \tag{2.1}$$

and without loss of generality $a_n > 0$. Letting A be the number of sign changes in the sequence of coefficients $a_n, a_{n-1}, \ldots, a_0$ and ignoring the ones that are zeros. Descartes rule of signs states that there are at most A roots of the given polynomial (2.1) which are real and non-negative. Further, the rule states that there are $A - 2K$, $K \geq 0$ and $K \in \mathbb{Z}^k$ real positive roots. If we let $\omega = -\lambda$ and again applying the Descartes rule of signs we obtain $A - 2K$ real negative roots.

2.3.7 Equilibrium Points [3]

We consider an autonomous system of differential equations of the form

$$\frac{dx}{dt} = f(x), \quad x(t_0) = x_0 \tag{2.2}$$

where $x(x_1, x_2, \ldots, x_n)^T, f(x) = (f_1(x_1, x_2, \ldots, x_n), f_2(x_1, x_2, \ldots, x_n), \ldots f_n(x_1, x_2, \ldots, x_n))^T$ and f does not depend explicitly on t

An equilibrium point $x^* \in \mathbb{R}^n$ is called an equilibrium point of (2.2) if

$$f(x^*) = 0$$

Equilibrium points of dynamical systems represent constant solutions of the system and therefore give an indication of the long term behavior of the system. Intuitively, this means that the state of the system is not changing.

The Disease Free Equilibrium Point(DFE)

The DFE is defined as the point at which no disease is present in the population. It is the point where the infected population is zero [4].

The Endemic Equilibrium Point

The Endemic equilibrium point is defined as the point at which the disease is present in the population [4].

2.3.8 Stability Analysis

The stability theory in mathematics is used to analyze the stability of the solutions of differential equations and trajectories of dynamical systems under small perturbations of initial conditions. It helps us to understand what happens when we perturb a system. The analysis allows us to determine whether or not a system is stable, unstable or will be stable if perturbed [5].

Local Stability

An equilibrium point x^* of the system (2.2) is said to be locally stable provided that , if the initial values x_0 is sufficiently close to x^* then the solution $x(t)$ remains close to x^* for all $t \geq 0$.Thus an equilibrium point x^* is stable if for each $\epsilon > 0$ there exists a $\delta > 0$ such that

$$\| x_0 - x^* \| < \delta \Rightarrow \| x(t) - x^* \| < \epsilon$$

The critical point $x = x^*$ is called unstable if it is not stable [3]. Intuitively,we say that an equilibrium point is locally stable if all solutions which start near x^*, that is, the neighborhood of x^* remain close to x^* for all time.

Local Stability(Lyapunov Indirect Method)[3]

Theorem 2.3.1. *Let x^* be an equilibrium point of the system of differential equations*

$$\frac{dx}{dt} = f(x), \quad x(0) = x_0$$

where $f : D \to \mathbb{R}^n$ is continuously differentiable and D is a neighborhood of the x^*, Let the

Jacobian matrix at x^* be

$$A = \frac{\partial f}{\partial x} \mid_{x=x^*}$$

such that the linearized system is

$$\frac{du}{dt} = Au, \quad u = x - x^*$$

then

1. x^* is asymptotically stable if $Re\,(\lambda_i(A)) < 0$ for $i = 1, \ldots, n$.
2. x^* is unstable if $Re\,(\lambda_i(A)) > 0$ for at least one i.

$Re\,(\lambda_i(A))$ designates the real part of the i^{th} eigenvalues of A. Since A is only defined at x^*, stability determined by the indirect method is restricted to small neighborhood of x^*. For this reason, it is called local stability .

Global Stability and Lyapunov functions(Lyapunov's direct method)[3]

Definition 2.3.2. A continuously differentiable function $V : \mathbb{R}^n \longrightarrow \mathbb{R}_+$ is said to be

1. positive definite in a region U of R^n that contains the origin if
   (a) $V(0) = 0$,
   (b) $V(x) > 0$, for $x \in U$ and $x \neq 0$.
2. negative definite in a region U of R^n that contains the origin if
   (a) $V(0) = 0$,
   (b) $V(x) < 0$,
3. $V(x)$ is said to be
   (a) positive semi-definite if $V(x) \geq 0$ for $x \in U$ and $x \neq 0$.

(b) negative semi-definite if $V(x) \leq 0$ for $x \in U$ and $x \neq 0$.

Theorem 2.3.3. (Lyapunov Stability) let $x = 0$ be an equilibrium point for a system described by: $\dot{x} = f(x)$ where $U \longrightarrow \mathbb{R}^n$ is a locally Lipschitz and $U \subset \mathbb{R}^n$ a domain that contains the origin.
Let $V : U \longrightarrow \mathbb{R}$ be a continuously differentiable, positive function in U.

1. If $\dot{V}(x) = \left[\frac{\partial V}{\partial x}\right]^T f(x) \leq 0$, then $x = 0$ is a stable equilibrium point.
2. If $\dot{V}(x) < 0$, then $x = 0$ is an asymptotically stable equilibrium point.

In both cases V is called a Lyapunov function. If the conditions hold for all $x \in \mathbb{R}^n$ and $\| x \| \rightarrow \infty$ implies that $V(x) \rightarrow \infty$, then $x = 0$ is asymptotically stable in 3a and globally asymptotically stable in 3b.
According to [10], the most commonly used Lyapunov functions are:

1. Quadratic Functions:

$$V(x) = \frac{c_1}{2}(x_1 - x_1^*)^2 + \frac{c_2}{2}(x_2 - x_2^*)^2 + \ldots + \frac{c_n}{2}(x_n - x_n^*)^2$$

   where the equilibrium points are given by $x_1^*, x_2^*, \ldots, x_n^*$.

2. Voltera Functions:

$$V(x) = c_1\left(x_1 - x_1^* - x_1^* ln\left(\frac{x_1}{x_1^*}\right)\right) + c_2\left(x_2 - x_2^* - x_2^* ln\left(\frac{x_2}{x_2^*}\right)\right) + \ldots + c_n\left(x_n - x_n^* - x_n^* ln\left(\frac{x_n}{x_n^*}\right)\right).$$

3. Composite Functions:

$$V(x_1, x_2, \ldots, x_n) = \frac{c}{2}\left[\sum_{i=1}^{n}(x_i - x_i^*)\right]^2.$$

Intuitively, the global stability means that the system will come to the equilibrium point from any possible starting point (there is no "nearby" condition).

2.3.9 The Fixed Point Theorem

Let I be a set and let $f : I \longrightarrow I$ be a function that maps I into itself and such a function is often called, a transformation, or a transform on I. A fixed point of f is an element of I_i of I for which $f(I) = I_i$ [7]. We use the fixed point theory to obtain the existence of the endemic equilibria. We find their existence under some specific conditions, where $f(I_i)$ is the disease incidence for stage i, $i = 1, 2, \ldots, n$ and I_i is the infection class. The non-linear function f is assumed to satisfy the following assumptions:

1. $f(0) = 0$,
2. $f'(I_i) > 0$,
3. $f''(I_i) < 0$,
4. $\lim_{I \to +\infty} f(I_i) = C < +\infty$.

The function f is an increasing, bounded and convergent with no change of convexity on a finite interval [8]. Let y be the solution of $y = f(y)$,that is, y is a fixed point of f. Consider the dynamics of the distances $y^v - y$ between iterates y^v and a fixed point $y(v = 0, 1, 2, \ldots, n)$. If $y^{(v+1)} = f(y^{(v)})$ and $y = f(y)$, then

$$y^{(v+1)} - y = f(y^{(v)}) - y = \frac{\partial f(y)}{\partial y}\left(y^{(v)} - y\right) + \text{high order terms.}$$

The local stability is then governed by the liberalization (to high order terms)

$$y^{(v+1)} - y = L((y^{(v)} - y),$$

which implies

$$y^{(v)} - y = L^v((y^{(0)} - y),$$

L denotes the Jacobian matrix f_y of the n^2 first order partial derivatives of f, evaluated at y. Then there exists a set of n linearly independent eigenvectors w^k with eigenvalues μ_k such that the initial distance $\left(y^{(0)} - y\right)$ can be written as a linear combination, and $y^{(v)} - y = L^v((y^{(0)} - y)$ implies

$$y^{(v)} - y = L^v \sum_{k=1}^{n} c_k W^k = \sum_{k=1}^{n} c_k L^v W^k = \sum_{k=1}^{n} c_k \mu_k^v W^k,$$

which shows that convergence $y^{(v)} \longrightarrow y$ can only take place for $v \longrightarrow \infty$ when $\mid \mu_k \mid < 1$ for all $k = 1, 2, \ldots, n$ [9].

Theorem 2.3.4. *Assume that all eigenvalues μ_k of L lie inside the unit circle. i.e $\mid \mu_k \mid < 1$. Then, locally, the iterates $y^{(v)}$ converge towards y, which is a stable fixed point. If $\mid \mu_k \mid < 1$, the fixed point is stable. If $\mid \mu_k \mid > 1$, the fixed point is unstable and the iterates $y^{(v)}$ moves away from y or it diverges.*

Summary

In this chapter we reviewed different views that different researchers have on within host focusing on Langerhans cells, $CD4^+$ T cells, R5 HIV and X4 HIV and also reviews on population dynamics. Concepts that will be used in the model analysis have also been defined and a detailed explanation on how to calculate them has been provided. We use studies in this chapter as building blocks to the formulation of within host mathematical models with direct link to the population dynamics of HIV infection in the next chapters.

Chapter 3

THE IMMUNOLOGICAL AND EPIDEMIOLOGICAL DYNAMICS OF HIV INFECTION

Immunological dynamics are the dynamics that focus on the aspects of the immune system inside all living organisms. Epidemiological dynamics are the dynamics that deal with the incidence, distribution and control of a disease in a population. This chapter presents a within host mathematical model on immunological dynamics of HIV infection inside a host and a without host mathematical model on epidemiological dynamics of HIV infection outside the host.

3.1 THE IMMUNOLOGICAL DYNAMICS

3.1.1 Introduction

This section presents a basic co-infection within host mathematical model that captures the interactions between Langerhans cells, $CD4^+$ T-cells, R5 HIV and X4 HIV during the primary phase of HIV infection. Langerhans cells are initial targets for HIV following sexual exposure

to the virus. Langerhans cells provide an efficient means for HIV to gain access to lymph node T-cells. According to [13], HIV is spread easily in the early stages of infection because during this time, large amounts of the virus are being produced in the body leading to an increase in the viral load. The viral load is the amount of active HIV in the blood [12]. The higher the viral load, the more active HIV is present in the blood. During this stage, the Langerhans cells as the initial targets of infection, captures the virus and degrades it, but when they are overwhelmed they are infected and transmit the virus to the $CD4^+$ T-cells. The virus uses $CD4^+$ T-cells to replicate itself and this results in high levels of virus replication within the $CD4^+$ T-cells which leads to the destruction of the $CD4^+$ T-cells resulting in fast progression of HIV infection in the body. The increase in viral load over time eventually leads to more and more $CD4^+$ T-cells getting infected and eventually crippling the immune system to an extent that it fails to produce HIV antibodies and cytotoxic lymphocytes to defeat the virus. The effects of continued HIV infection leads to a decline in the CD4 count. The study in [12] defines a CD4 count as a test that measures the number of CD4 cells in a sample of blood, it is an important indicator of how well the immune system is working.

We shall formulate a basic within host model and analyze it by proving that the model is positively invariant and bounded in a feasible region, calculating the basic reproduction number and determining equilibrium points and their stability. We aim to answer the question: *What are the effects of combined infection of Langerhans cells and $CD4^+$ T-cells with R5 HIV and X4 HIV on the CD4 count and viral load during the primary phase of HIV infection*?

3.1.2 Model Formulation

The infection of Langerhans cells and $CD4^+$ T-cells by the R_5 HIV and X_4 HIV involves the following variables: healthy Langerhans cells L, latently infected Langerhans cells L_T, infected Langerhans cells L_I, healthy $CD4^+$ T-cells C, infected $CD4^+$ T-cells C_I and two HIV strains namely R5 HIV and X4 HIV.

The healthy Langerhans cells are the first line of immune defense against HIV since they are found on the surface of the skin and are ideally situated to efficiently capture pathogens that enter the body. Latently infected Langerhans cells are cells infected by HIV which cannot transmit nor produce the virus but act as a reservoir for the virus. Infected Langerhans cells are the cells that have the virus and have the ability to produce and transmit it to the healthy Langerhans cells and healthy $CD4^+$ T-cells. The heathy $CD4^+$ T-cells also are the command cells of the immune system. They are a type of white blood cells playing a major role in protecting the body from infection by sending signals to other types of immune cells which then destroy the foreign or infectious particle presented to them. Infectious $CD4^+$ T-cells , are infected $CD4^+$ T-cells by the virus that can produce the virus and transmit it to other cells in the body. CCR5 and CXCR4 are cell surfaces that HIV uses to penetrate and infect host cells.

The healthy Langerhans cells are produced from the bone marrow at a constant rate π and die naturally at a constant rate μ. The healthy Langerhans cells are removed from their class through infection by the R5 HIV, X4 HIV, infected Langerhans cells and infected $CD4^+$ T-cells with a force of infection $\lambda_1 = \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I)$ which is the rate at which a susceptible langerhans cell can be infected by an infected cell. β_1 is the probability that a contact between a healthy Langerhans cell and either the R5 HIV, X4 HIV, infected Langerhans cells or infected $CD4^+$ T-cells results in a successful infection. The rates of infection by these infectious classes differ due to the fact that during early infection, there are more R5 HIV cells in circulation with a few X4 HIV cells, infected $CD4^+$ T-cells and infected Langerhans cells. We account for the differences in infection by introducing the parameters η_1, η_2 and η_3 which are related by $0 < \eta_3 < \eta_2 < \eta_1 < 1$. To explain the derivation of this relationship, we apply inequalities and assume that the R5 virus is more abundant followed by infected Langerhans cells, followed by infected $CD4^+$ T-cells, followed by the X4 virus [18]. This assumption transfers to their contribution towards the rates of successful infection. The rate of successful infection for R5 virus is $\beta_1 > 0$ and the rate of successful infection by infected langerhans cells is $\beta_1\eta_1$. Thus, $\beta_1 > \beta_1\eta_1$ and implies that $\eta_1 < 1$. Similarly, the rate of successful infection

by infected CD4$^+$ T-cells is $\beta_1\eta_2$. Thus, $\beta_1 > \beta_1\eta_1 > \beta_1\eta_2$ and implies $\eta_2 < \eta_1 < 1$. The rate of successful infection by the X4 virus is $\beta_1\eta_3$. Thus, $\beta_1 > \beta_1\eta_1 > \beta_1\eta_2 > \beta_1\eta_3$ and implies $\eta_3 < \eta_2 < \eta_1 < 1$.

η_3 is the measure with which the probability of a successful infection of a healthy Langerhans cells by the X4 HIV is reduced due to the less abundance of X4 HIV compared to the R5 HIV, infected Langerhans cells and infected CD4$^+$ T-cells. η_2 is the measure with which the probability of a successful infection of a healthy Langerhans cells by the infected CD4$^+$ T-cells is reduced due to the abundance of the infected CD4$^+$ T-cells compared to the R5 HIV, infected Langerhans cells and X4 HIV. η_1 is the measure with which the probability of a successful infection of a healthy Langerhans cells by the infected Langerhans cells is reduced due to the abundance of infected Langerhans cells compared to the R5 HIV, infected CD4$^+$ T-cells and X4 HIV. We shall assume that the saturation of infection of Langerhans cells is due to the degradation of the virus by healthy Langerhans cells. We shall use the average saturation defined by the average value of the function $\frac{1}{A+L}$ given by $\omega = \frac{1}{T}\int_0^T \frac{1}{1+L}dt$ over a time interval $[0, T]$. This means that $0 \leq \omega < 1$.

When the healthy Langerhans cells are infected, they change their status to become latently infected Langerhans cells L_T. The latently infected Langerhans cells are not capable to transmit the virus to the healthy Langerhans cells because the virus lies dormant within them. They act as a reservoir for the virus and remain quiescent before they become infectious. The latently infected langerhans cells die naturally at a constant rate μ and get activated to an infectious mode when the virus begins to produce large amounts of viral particles inside the cell thus move to the infectious class L_I at a constant rate γ.

The virus first attaches itself and fuses with the Langerhans cells. Then the viral RNA is converted into DNA and the virus uses the hosts cells machinery to replicate itself during a process called reverse transcription. New copies of HIV are then formed and when they mature, the cause the host cell to burst releasing themselves into the blood. The virus leaves the

infected Langerhans cell through budding off or lysis killing the cell that produces them at a constant rate δ. During the production of viral cells by the infectious Langerhans cells, more R5 cells are produced with a proportion ϵ than X4 viral cells so that $0.5 < \epsilon \leq 1$, $\epsilon = 1$ means that all of the R5 viral particles are produced by the infected Langerhans cells. We assume that lysis killing is the dominant viral production mechanism since more viral cells are produced in this process than through budding off. During lysis killing, the virus particles burst out of the host cell into the extracellular space resulting in the death of the cell. Once the virus has escaped from the host cell, it is ready to enter a new healthy cell. The infectious Langerhans cells die naturally at a constant rate μ. We assume that each actively infectious Langerhans cell produces an average number of N viral particles. The new viral particles then circulate freely in the blood as a new source of infection and infect the healthy Langerhans cells and the healthy $CD4^+$ T-cells.

The $CD4^+$ T-cells are produced from thymus at a constant rate π_4 and die naturally at a constant rate μ_4 .The healthy $CD4^+$ T-cells leave their class through infection from the R5 HIV, X4 HIV, infected Langerhans cells and infected $CD4^+$ T-cells with a force of infection $\lambda_2 = \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I)$ where β_2 is the probability that a contact between a healthy $CD4^+$ T-cells and either R5 HIV, X4 HIV, infected Langerhans cells and infected $CD4^+$ T-cells results in a successful infection. The parameters σ_1 , σ_2 and σ_3 are related by $0 < \sigma_3 < \sigma_2 < \sigma_1 < 1$. The justification of the relationship of the σ's is similar to the one for η's in the Langerhans cells. σ_3 is the measure with which the probability of a successful infection of a healthy $CD4^+$ T-cells by the R5 HIV is reduced due to the abundance of the R5 HIV compared to the X4, infected Langerhans cells and infected $CD4^+$ T-cells. σ_2 is the measure with which the probability of a successful infection of a healthy $CD4^+$ T-cells by the infected $CD4^+$ T-cells is reduced due to the abundance of the infected $CD4^+$ T-cells compared to the R5 HIV, X4 HIV and infected Langerhans cells. σ_1 is the measure with which the probability of a successful infection of a healthy $CD4^+$ T-cells by the infected Langerhans cells is reduced due to the presence of infected Langerhans cells compared to the R5 HIV, X4 HIV and infected

$CD4^+$ T-cells. This means more infection is caused by the X4 HIV followed by the infected Langerhans cells, infected $CD4^+$ T-cells, and the R5 HIV.

When infected, the healthy $CD4^+$ T-cells either remain latent or progress to the actively infected $CD4^+$ T-cells. We only consider the actively infectious $CD4^+$ T-cells and accounting for the latently infected $CD4^+$ T-cells by assuming a proportion θ, $0 < \theta < 1$ become actively infectious. Thus the latent reservoir is accounted for by the proportion $1 - \theta$. This allows us to leave out the latently infected $CD4^+$ T-cells population and yet be able to account for them.

The viral particles multiply in the infectious $CD4^+$ T-cells class and force the cell to burst and die at a rate ρ producing an average number of M viral particles per each actively infectious cell. During the production of viral cells by the infectious $CD4^+$ T-cells, more X4 viral cells are produced with a proportion ϕ compared to the R5 viral cells, where $0.5 < \phi \leq 1$. The infectious $CD4^+$ T-cells also die naturally at a constant rate μ_4.

The R5 HIV population grows through the bursting of infectious Langerhans cells and infectious $CD4^+$ T-cells at rates $\delta\epsilon NL_I$ and $\rho(1-\phi)MC_I$ respectively. The X4 HIV population grows through the bursting of infectious $CD4^+$ T-cells and infectious Langerhans cells at a rate $\rho\phi MC_I$ and $\delta(1-\epsilon)NL_I$ respectively. The two viral strains have a natural life span where they die naturally at a constant rate μ_v. The R5 and X4 virus are also degraded by Langerin inside the healthy Langerhans cells at a rate α. Langerin causes the breakdown of HIV particles and blocks viral transmission. It is also able to scavenge viruses from the surrounding environment, thereby preventing infection. We assume that the degradation of the virus is saturated.

The forces of infection λ_1 and λ_2 incorporate two mechanisms of infection namely the cell-to-cell HIV infection where a healthy cell is infected by an infectious cell and the cell-free HIV infection where a free virus infects a healthy cell.

The model diagram for the dynamics of HIV infection is given in Figure 3.1.

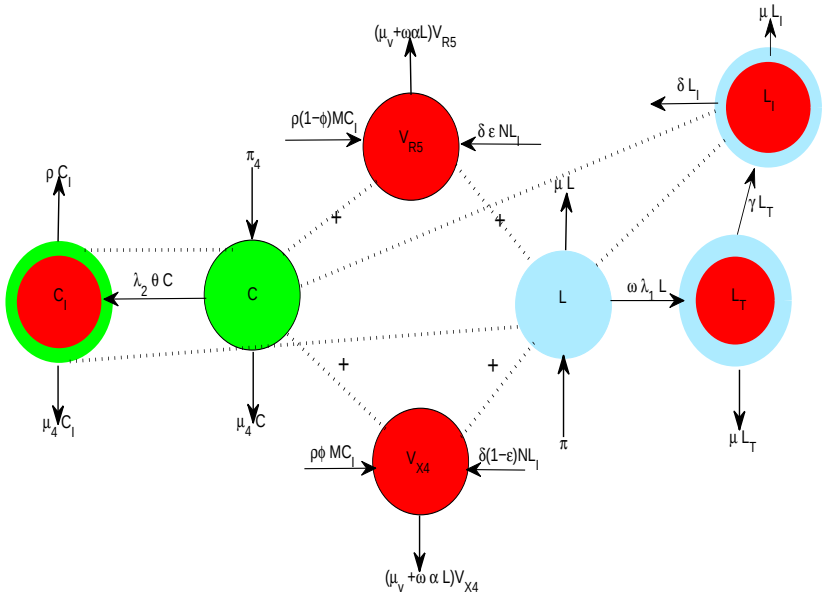

Figure 3.1: Model diagram for the within host dynamics

The mathematical model formulated using the guiding assumptions and model diagram 3.1 are given by the following system of non-linear ordinary differential equations:

$$\frac{dL}{dt} = \pi - (\omega\lambda_1 + \mu)L, \tag{3.1}$$

$$\frac{dL_T}{dt} = \omega\lambda_1 L - (\mu + \gamma)L_T, \tag{3.2}$$

$$\frac{dL_I}{dt} = \gamma L_T - (\mu + \delta)L_I, \tag{3.3}$$

$$\frac{dC}{dt} = \pi_4 - (\lambda_2 + \mu_4)C, \tag{3.4}$$

$$\frac{dC_I}{dt} = \theta\lambda_2 C - (\mu_4 + \rho)C_I, \tag{3.5}$$

$$\frac{dV_{R5}}{dt} = \delta\epsilon NL_I + \rho(1-\phi)MC_I - (\mu_v + \omega\alpha L)\,V_{R5}, \tag{3.6}$$

$$\frac{dV_{X4}}{dt} = \rho\phi MC_I + \delta(1-\epsilon)NL_I - (\mu_v + \omega\alpha L)\,V_{X4}, \tag{3.7}$$

where

$$\lambda_1 = \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I), \tag{3.8}$$

$$\lambda_2 = \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I). \tag{3.9}$$

3.1.3 Positivity and Boundedness of Solutions

For the system of differential equations, we need to prove that all the variables remain non-negative such that the solutions of the systems of equations with positive initial conditions remain positive for all time $t \geq 0$ and that all the solutions are bounded for all $t \geq 0$. The region is called the biologically feasible region where the model will be biologically meaningful. This means that the dynamics of the Langerhans cells, $CD4^+$ T-cells, R5 and X4 HIV populations should remain positive in all our analysis.

Theorem 3.1.1. *All solutions of the system of differential equations are positive for all $t > 0$, and there exists a $Q > 0$ such that all positive solutions satisfy $L(t)$, $L_T(t)$, $L_I(t)$, $C(t)$, $C_I(t)$, $V_{R5}(t)$, $V_{X4}(t) < Q$ for all large t.*

To prove the positivity of solutions, we suppose by contradiction that t_i, $i = 1, 2, 3, 4, 5, 6, 7$ are the first times when $L(t)$, $L_T(t)$, $L_I(t)$, $C(t)$, $C_I(t)$, $V_{R5}(t)$, $V_{X4}(t)$ reach zero respectively and $t_0 = min\{t_i\}$.

Firstly, if $t_0 = t_1$, we assume $t_1 \neq t_2$, $t_1 \neq t_3$, $t_1 \neq t_4$, $t_1 \neq t_5$, $t_1 \neq t_6$, $t_1 \neq t_7$ and $L(t) < 0$ in $[0, t_1]$ and $L(t_1) = 0$, $L_T(t_1) > 0$, $L_I(t_1) > 0$, $C(t_1) > 0$, $C_I(t_1) > 0$, $V_{R5}(t_1) > 0$, $V_{X4}(t_1) > 0$ for all $t \in [0, t_1]$.
From (3.1)

$$\frac{dL}{dt} = \pi - (\omega\lambda_1 + \mu)L \geq -(\omega\lambda_1 + \mu)L,$$
$$L(t) \geq L(0)e^{\int_0^t -(\omega\lambda_1(s)+\mu)ds},$$

at $t = t_1$

$$L(t_1) \geq L(0)e^{\int_0^{t_1} -(\omega\lambda_1(s)+\mu)ds} > 0$$

This is a contradiction to the fact that $L(t_1) = 0$. Therefore $L(t) \not< 0$ in $[0, t_1]$ neither will $L(t_1) = 0$.
$\therefore L(t) > 0$

Secondly, if $t_0 = t_2$, we assume $t_2 \neq t_3$, $t_2 \neq t_4$, $t_2 \neq t_5$, $t_2 \neq t_6$, $t_2 \neq t_7$ and $L_T(t) < 0$ in $[0, t_2]$ and $L_T(t_2) = 0$, $L(t_2) > 0$, $L_I(t_2) > 0$, $C(t_2) > 0$, $C_I(t_2) > 0$, $V_{R5}(t_2) > 0$, $V_{X4}(t_2) > 0$ for all $t \in [0, t_2]$.
From (3.2)

$$\frac{dL_T}{dt} = \omega\lambda L - (\mu + \gamma)L_T \geq -(\mu + \gamma)L_T,$$
$$L_T(t) \geq L_T(0)e^{-(\mu+\gamma)t}$$

at $t = t_2$

$$L_T(t_2) \geq L_T(0)e^{-(\mu+\gamma)t_2} > 0$$

This is a contradiction to the fact that $L_T(t_2) = 0$. Therefore $L_T(t) \not< 0$ in $[0, t_2]$ neither will $L_T(t_2) = 0$.
$\therefore L_T(t) > 0$

Thirdly, if $t_0 = t_3$, we assume $t_3 \neq t_4$, $t_3 \neq t_1$, $t_3 \neq t_2$,$t_3 \neq t_5$, $t_3 \neq t_6$, $t_3 \neq t_7$ and $L_I(t) < 0$ in $[0, t_3]$ and $L_I(t_3) = 0$, $L(t_3) > 0$, $L_T(t_3) > 0$, $C(t_3) > 0$, $C_I(t_3) > 0$, $V_{R5}(t_3) > 0$, $V_{X4}(t_3) > 0$ for all $t \in [0, t_3]$.
From (3.3)

$$\frac{dL_I}{dt} = \gamma L_T - (\mu + \delta)L_I \geq -(\mu + \delta)L_I$$
$$L_I(t) \geq L_I(0)e^{-(\mu+\delta)t}$$

at $t = t_3$

$$L_I(t_3) \geq L_I(0)e^{-(\mu+\delta)t_3} > 0$$

This is a contradiction to the fact that $L_I(t_3) = 0$. Therefore $L_I(t) \not< 0$ in $[0, t_3]$ neither will $L_I(t_3) = 0$.
$\therefore L_I(t) > 0$

Fourthly, if $t_0 = t_4$, we assume $t_4 \neq t_5, t_6, t_7, t_3, t_2, t_1$ and $C(t) < 0$ in $[0, t_4]$ and $L(t_4) = 0$, $L_T(t_4) > 0$, $L_I(t_4) > 0$, $C_I(t_4) > 0$, $V_{R5}(t_4) > 0$, $V_{X4}(t_4) > 0$ for all $t \in [0, t_4]$.
From (3.4)

$$\frac{dC}{dt} = \pi_4 - (\lambda_2 + \mu_4)C \geq -(\lambda_2 + \mu_4)C$$
$$C(t) \geq C(0)e^{\int_0^t -(\lambda_2(s)+\mu_4)ds}$$

at $t = t_4$

$$C(t_4) \geq C(0)e^{\int_0^{t_4} -(\lambda_2(s)+\mu_4)ds} > 0$$

This is a contradiction to the fact that $C(t_4) = 0$. Therefore $C(t) \not< 0$ in $[0, t_4]$ neither will $C(t_4) = 0$.
$\therefore C(t) > 0$

Fifthly, if $t_0 = t_5$, we assume $t_5 \neq t_6, t_7, t_4, t_3, t_2, t_1$ and $C_I(t) < 0$ in $[0, t_5]$ and $C_I(t_5) = 0$, $L(t_5) > 0$, $L_T(t_5) > 0$, $C(t_5) > 0$, $L_I(t_5) > 0$, $V_{R5}(t_5) > 0$, $V_{X4}(t_5) > 0$ for all $t \in [0, t_5]$.
From (3.5)

$$\frac{dC_I}{dt} = \theta\lambda_2 C - (\mu_4 + \rho)C_I \geq -(\mu_4 + \rho)C_I$$
$$C_I(t) \geq C_I(0)e^{-(\mu_4+\rho)t}$$

at $t = t_5$

$$C_I(t_5) \geq C_I(0)e^{-(\mu_4+\rho)t_5} > 0$$

This is a contradiction to the fact that $C_I(t_5) = 0$. Therefore $C_I(t) \not< 0$ in $[0, t_5]$ neither will $C_I(t_5) = 0$.
$\therefore C_I(t) > 0$

Lastly, if $t_0 = t_6$ and $t_0 = t_7$, and $V_{R5}(t_6) < 0 \in [0, t_6]$ and $V_{X4}(t_7) < 0 \in [0, t_7]$, and $V_{R5}(t_6) = 0$ and $V_{X4}(t_6) = 0$ for all $t \in [0, t_6]$ and $t \in [0, t_7]$.
From (3.6) and (3.7) and at $t = t_6$ and $t = t_7$

$$\frac{dV_{R5}}{dt} \geq -\left(\omega\alpha L(t) + \mu_v\right) V_{R5} \geq V_{R5}(0)e^{-\int_0^{t_6}(\omega\alpha L(t)+\mu_v)t_6} > 0$$
$$\frac{dV_{X4}}{dt} \geq -\left(\omega\alpha L(t) + \mu_v\right) V_{X4} \geq V_{X4}(0)e^{-\int_0^{t_7}(\omega\alpha L(t)+\mu_v)t_7} > 0$$

A contradiction to the fact that $V_{R5}(t_6) = 0$ and $V_{X4}(t_7) = 0$. Therefore $V_{R5}(t)$ and $V_{X4}(t) \not< 0$ in $[0, t_6]$ and $[0, t_7]$ respectively. Neither will $V_{R5}(t_6) = 0$ and $V_{X4}(t_7) = 0$.
$\therefore V_{R5}(t) > 0$ and $V_{X4}(t) > 0$

The contradiction holds for t_1, t_2, t_3, t_4, t_5, t_6, $t_7 \to \infty$. All the cases have been considered and a contradiction has been found for each case. Therefore, there is no such t_i, $i = 1, 2, 3, 4, 5, 6, 7$. This means $L(t) > 0$, $L_T(t) \geq 0$, $L_I(t) \geq 0$, $C(t) > 0$, $C_I(t) \geq 0$, $V_{R5}(t) \geq 0$, $V_{X4}(t) \geq 0$, for all large $t \geq 0$.

We have proved that our solutions are restricted in a positive region and that the initial conditions that were chosen inside the region will always stay positive and our model will give positive projections.

To prove boundedness, having assured that we are dealing with positive solutions in a pos-

itive region, we now prove that the solutions are globally bounded meaning that they all have a common upper bound and that none of them can blow to infinity.

Using a Lyapunov function, we prove that L(t), $L_T(t)$, $L_I(t)$, $C(t)$, $C_I(t)$,$V_{R5}(t)$, $V_{X4}(t)$ are bounded.

$$\text{Let} \quad Y(t) = L(t) + L_T(t) + L_I(t) + C(t) + C_I(t) + V_{R5}(t) + V_{X4}(t) = L_{tot} + C_{tot} + V_{tot}$$

where

$$L_{tot} = \pi - \mu L_{tot} - \delta L_I, \quad C_{tot} = \pi_4 - \mu_4 C_{tot} - \lambda_2(1-\theta)C - \rho C_I$$
$$V_{tot} = \delta\epsilon N L_I + \rho(1-\phi)MC_I - (\alpha\omega L + \mu_v)\, V_{R5} + \rho\phi MC_I + \delta(1-\epsilon)NL_I - (\alpha\omega L + \mu_v)\, V_{X4}$$

and

$$L_{tot} \leq \frac{\pi}{\mu} = L^*_{tot}$$
$$C_{tot} \leq \frac{\pi_4}{\mu_4} = C^*_{tot}$$
$$V_{tot} \leq \frac{\delta N L^*_0 + \rho M C^*_0}{\alpha\omega L^*_0 + \mu_v} = V^*_{tot}$$

$$\dot{Y}(t) \leq \pi - \mu L_{tot} - \delta L_I + \pi_4 - \mu_4 C_{tot} - \lambda_2(1-\theta)C - \rho C_I + \delta\epsilon N L_I +$$
$$\rho(1-\phi)MC_I - (\alpha\omega L + \mu_v)\, V_{R5} + \rho\phi MC_I + \delta(1-\epsilon)NL_I - (\alpha\omega L + \mu_v)\, V_{X4}$$

set $\mu_{tot} = min\{\mu, \mu_4, \mu_v\}, \quad Y(t) = L_{tot} + C_{tot} + V_{tot}$

$$\begin{aligned}
Y(t) &\leq \pi + \pi_4 - \mu_{tot}Y(t) + \delta(N-1)L_I + \rho(M-1)C_I - \lambda_2(1-\theta)C \\
&\leq \pi + \pi_4 - \mu_{tot}Y(t) + \delta N L_{tot} + \rho M C_{tot}, \\
&\leq \pi + \pi_4 - \mu_{tot}Y(t) + \delta^*(L_{tot} + C_{tot}), \qquad \delta^* = max\{\delta N, \rho M\} \\
&\leq \pi + \pi_4 - \mu_{tot}Y(t) + \delta^* Y(t) - \delta V^*_{tot}, \\
&\leq \pi + \pi_4 - (\mu_{tot} - \delta^*)Y(t), \\
Y(t) &\leq \frac{\pi + \pi_4}{\mu_{tot} - \delta^*} + \left(Y(0) - \frac{\pi + \pi_4}{\mu_{tot} - \delta^*}\right) e^{-(\mu_{tot} - \delta^*)t} \\
\lim_{t\to\infty} \sup Y(t) &\leq \frac{\pi + \pi_4}{\mu_{tot} - \delta^*} \qquad \text{when} \qquad \mu_{tot} > \delta^*
\end{aligned}$$

Defining $Q = \frac{\pi+\pi_4}{\mu_{tot}-\delta^*}$, then $L_{tot} + C_{tot} + V_{tot} \leq Q \ \forall t \geq 0$.

Hence, we obtain a boundedness of Y(t), that is, there exists $Q > 0$ such that all the solutions satisfy $0 \leq L(t), L_T(t), L_I(t), C(t), C_I(t), V_{R5}(t), V_{X4}(t) \leq Q$ for all large t.

Remark 3.1.4. The concept of positive invariance ensures that positive solutions are preserved and bounded in that positive region both mathematically and biologically. Populations under consideration should always be positive or non-negative thus mathematical solutions from the model will have a biological meaning and predictions from the mathematical solutions can be biologically verified.

3.1.5 Disease Free Equilibrium Point

The disease free equilibrium point is the equilibrium point which occurs when there are no R5 viruses and X4 viruses, infected Langerhans cells and infected $CD4^+$ T-cells in an individual's body.

In our model, equating the right hand side of the system of differential equations (3.1)-(3.7) to zero and considering that $L^*_T = L^*_I = C^*_I = V^*_{R5} = V^*_{X4} = 0$ we solve for L^* and C^*, denoting

$L^* = L_0$ and $C^* = C_0$

$$L_0 = \frac{\pi}{\mu}, \qquad C_0 = \frac{\pi_4}{\mu_4}.$$

Thus, the disease free equilibrium point of the system of equations denoted E_0 is given by

$$E_0 = (L_0, 0, 0, C_0, 0, 0, 0)\,.$$

3.1.6 The Basic Reproduction Number (R_0)

One of the most important parameters that explains conditions under which the infection is cleared or persists in a population, is the basic reproduction number denoted as R_0. From our model it is defined as the expected number of secondary infections that result when either infected by Langerhans cells, infected $CD4^+$ T-cells , R5 HIV or X4 HIV are introduced in a completely susceptible cell population of Langerhans cells and $CD4^+$ T-cells. The calculation of the basic reproduction number helps us to analyze the existence and stability of the disease free equilibrium point and the endemic equilibrium point which depends on its values. The basic reproduction number will be computed using the next generation matrix used by Watmough and Van Den Drissche in [1].

We consider a matrix $\mathcal{F}_i$, the rate of appearances of new infections in compartment i,

$$\mathcal{F} = \begin{pmatrix} \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I)\omega L \\ 0 \\ \beta_2\theta(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I)C \\ 0 \\ 0 \end{pmatrix}.$$

The Jacobian matrix of $\mathcal{F}$, evaluated at the disease free equilibrium point E_0 gives rise to a matrix F given by

$$F = \begin{pmatrix} 0 & \beta_1\eta_1\omega L_0 & \beta_1\eta_2\omega L_0 & \beta_1\omega L_0 & \beta_1\eta_3\omega L_0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_2\theta\sigma_1 C_0 & \beta_2\theta\sigma_2 C_0 & \beta_2\theta\sigma_3 C_0 & \beta_2\theta C_0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

We consider the transition matrix $\mathcal{V}$,

$$\mathcal{V} = \begin{pmatrix} (\mu+\gamma)L_T \\ (\mu+\delta)L_I - \gamma L_T \\ (\mu_4+\rho)C_I \\ \omega\alpha V_{R5}L + \mu_v V_{R5} - \delta\epsilon N L_I - \rho(1-\phi)MC_I \\ \omega\alpha V_{X4}L + \mu_v V_{X4} - \rho\phi MC_I - \delta(1-\epsilon)NL_I \end{pmatrix}.$$

The Jacobian matrix of $\mathcal{V}$, evaluated at the disease free equilibrium point E_0 gives rise to a matrix V given by

$$V = \begin{pmatrix} (\mu+\gamma) & 0 & 0 & 0 & 0 \\ -\gamma & (\mu+\delta) & 0 & 0 & 0 \\ 0 & 0 & (\mu_4+\rho) & 0 & 0 \\ 0 & -\delta\epsilon N & -\rho(1-\phi)M & \omega\alpha L_0 + \mu_v & 0 \\ 0 & -\delta(1-\epsilon)N & -\rho\phi M & 0 & \omega\alpha L_0 + \mu_v \end{pmatrix}.$$

The inverse matrix of V, denoted V^{-1} is given as

$$V^{-1} = \begin{pmatrix} \frac{1}{(\mu+\gamma)} & 0 & 0 & 0 & 0 \\ \frac{\gamma}{(\mu+\gamma)(\mu+\delta)} & \frac{1}{(\mu+\delta)} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{(\mu_4+\rho)} & 0 & 0 \\ \frac{\gamma N\delta\epsilon}{(\mu+\gamma)(\mu+\delta)(\omega\alpha L_0+\mu_v)} & A & B & C & 0 \\ D & \frac{N\delta(1-\epsilon)}{(\mu+\delta)(\omega\alpha L_0+\mu_v)} & F & 0 & G \end{pmatrix},$$

where

$$\begin{aligned} A &= \frac{N\delta\epsilon}{(\mu+\delta)(\omega\alpha L_0+\mu_v)}, \qquad B = \frac{M\rho(1-\phi)}{(\mu_4+\rho)(\omega\alpha L_0+\mu_v)}, \\ C &= \frac{1}{(\omega\alpha L_0+\mu_v)}, \qquad D = \frac{N\delta\gamma(1-\epsilon)}{(\mu+\gamma)(\mu+\delta)(\omega\alpha L_0+\mu_v)}, \\ F &= \frac{M\phi\rho}{(\mu_4+\rho)(\omega\alpha L_0+\mu_v)}, \qquad G = \frac{1}{\omega\alpha L_0+\mu_v}. \end{aligned}$$

The next generation matrix denoted FV^{-1} is

$$FV^{-1} = \begin{pmatrix} a & b & c & d & e \\ 0 & 0 & 0 & 0 & 0 \\ f & g & h & i & j \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where

$$
\begin{aligned}
a &= \frac{\beta_1 \omega L_0 \gamma}{(\mu+\gamma)(\mu+\delta)}\left[\eta_1 + \frac{\delta\epsilon N}{\omega\alpha L_0+\mu_v} + \frac{\eta_3 N\delta(1-\epsilon)}{\omega\alpha L_0+\mu_v}\right], \\
b &= \frac{\beta_1 \omega L_0}{(\mu+\delta)}\left[\eta_1 + \frac{\delta\epsilon N}{\omega\alpha L_0+\mu_v} + \frac{\eta_3 N\delta(1-\epsilon)}{\omega\alpha L_0+\mu_v}\right], \\
c &= \frac{\beta_1 \omega L_0}{(\mu_4+\rho)}\left[\eta_2 + \frac{M\rho(1-\phi)}{\omega\alpha L_0+\mu_v} + \frac{\eta_3 M\rho\phi}{\omega\alpha L_0+\mu_v}\right], \\
d &= \frac{\beta_1 \omega L_0}{\omega\alpha L_0+\mu_v}, \quad e = \frac{\beta_1\eta_3\omega L_0}{\omega\alpha L_0+\mu_v}, \\
f &= \frac{\beta_2 \theta C_0 \gamma}{(\mu+\gamma)(\mu+\delta)}\left[\sigma_1 + \frac{\sigma_3 N\delta\epsilon}{\omega\alpha L_0+\mu_v} + \frac{N\delta(1-\epsilon)}{\omega\alpha L_0+\mu_v}\right], \\
g &= \frac{\beta_2 \theta C_0}{(\mu+\delta)}\left[\sigma_1 + \frac{\sigma_3 N\delta\epsilon}{\omega\alpha L_0+\mu_v} + \frac{N\delta(1-\epsilon)}{\omega\alpha L_0+\mu_v}\right], \\
h &= \frac{\beta_2 \theta C_0}{(\mu_4+\rho)}\left[\sigma_2 + \frac{\sigma_3 M\rho(1-\phi)}{\omega\alpha L_0+\mu_v} + \frac{M\rho\phi}{\omega\alpha L_0+\mu_v}\right], \\
i &= \frac{\beta_2 \theta \sigma_3 C_0}{\omega\alpha L_0+\mu_v}, \quad j = \frac{\beta_2\theta C_0}{\omega\alpha L_0+\mu_v}.
\end{aligned}
$$

From the next generation matrix, FV^{-1} , a is the number of secondary infections caused by one latently infected Langerhans cell to produce new latently infected Langerhans cells. b is the number of secondary latently infected Langerhans cells produced by actively infected Langerhans cells. c is the number of latent infected Langerhans cells produced by infected $CD4^+$ T-cells. d is the number of latent infected Langerhans cells produced by the R5 virus and e is the number of latent infected Langerhans cells produced by the X4 virus. f is the number of secondary infections caused by one infected $CD4^+$ T-cell to produce new Latent infected Langerhans cells. g is the number of secondary $CD4^+$ T-cell infections produced by infected Langerhans cells. h is the number of secondary infected $CD4^+$ T-cells infections produced by infected $CD4^+$ T-cells. i is the number of infected $CD4^+$ T-cells produced by the R5 virus and j is the number of infected $CD4^+$ T-cells produced by the X4 virus.

Therefore, the basic reproduction ratio which is the spectral radius of the next generation matrix, FV^{-1} is given by

$$\begin{aligned} R_0 &= \frac{1}{2}\left[(a+h)+\sqrt{a^2+4cf-2ah+h^2}\right], \\ &= \frac{1}{2}\left[(a+h)+\sqrt{(a-h)^2+4cf}\right]. \end{aligned}$$

Where

1. a is the local basic reproduction number of Langerhans cells due to infection emanating from infected Langerhans cells and the free virus produced by infected Langerhans cells.

2. h is the local basic reproduction number of $CD4^+$ T-cells due to infection propagated from infected $CD4^+$ T-cells and the free virus produced by infected $CD4^+$ T-cells.

3. c is the local basic reproduction number of Langerhans cells due to infection primarily from infected $CD4^+$ T-cells and the free virus produced from $CD4^+$ T-cells.

4. f is the local basic reproduction number of $CD4^+$ T-cells due to infection by infected Langerhans cells and the free virus produced by infected Langerhans cells.

3.1.7 Endemic Equilibrium Point

We calculate the endemic equilibrium points in terms of the forces of infection λ_1^* and λ_2^*. We set the right hand side of the equations of the model (3.1)-(3.7) to zero and
(3.1) becomes

$$\begin{aligned} \pi-(\omega\lambda_1^*+\mu)L^* &= 0 \\ L^* &= \frac{\pi}{(\omega\lambda_1^*+\mu)}. \end{aligned}$$

Similarly, setting equation (3.2)-(3.7) to zero yields

$$
\begin{aligned}
L_T^* &= \frac{\pi\lambda_1^*}{(\omega\lambda_1^*+\mu)(\mu+\gamma)}, \qquad L_I^* = \frac{\gamma\pi\lambda_1^*}{(\omega\lambda_1^*+\mu)(\mu+\gamma)(\mu+\delta)},\\
C^* &= \frac{\pi_4}{(\lambda_2^*+\mu_4)}, \qquad C_I^* = \frac{\theta\pi_4\lambda_2^*}{(\lambda_2^*+\mu_4)(\mu_4+\rho)},\\
V_{R5}^* &= \frac{\delta\epsilon N\pi\gamma\lambda_1^*}{(\mu+\gamma)(\mu+\delta)\left[\mu_v(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]} + \frac{\rho(1-\phi)M\lambda_2^*\theta\pi_4(\omega\lambda_1^*+\mu)}{(\lambda_2^*+\mu_4)(\mu_4+\rho)\left[\mu_v(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]},\\
V_{X4}^* &= \frac{\rho\phi M\theta\pi_4\lambda_2^*(\omega\lambda_1^*+\mu)}{(\lambda_2^*+\mu_4)(\mu_4+\rho)\left[\mu_v(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]} + \frac{\delta(1-\epsilon)N\gamma\pi\lambda_1^*}{(\mu+\gamma)(\mu+\delta)\left[\mu_v(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]}.
\end{aligned}
$$

and

$$
\begin{aligned}
\lambda_1^* &= \beta_1\left(V_{R5}^* + \eta_1 V_{X4}^* + \eta_2 C_I^* + \eta_3 L_I^*\right)\\
\lambda_2^* &= \beta_2\left(V_{X4}^* + \sigma_1 V_{R5}^* + \sigma_2 C_I^* + \sigma_1 L_I^*\right)
\end{aligned}
$$

Case 1. $\lambda_1^* = \lambda_2^* = 0$

This corresponds to the disease free equilibrium point, where there are no infected Langerhans cells, infected CD4$^+$ T-cells, R5 HIV and X4 HIV in an individual's body. Therefore $E_0 = (L_0^*, 0, 0, C_0^*, 0, 0, 0.)$

$$
L_0^* = \frac{\pi}{\mu}, \qquad C_0^* = \frac{\pi_4}{\mu_4}.
$$

Case 2. $\lambda_1^* = 0, \quad \lambda_2^* \neq 0$

This is where there are no infected Langerhans cells but infected CD4$^+$ T-cells and R5 viruses and X4 viruses produced by infected CD4$^+$ T-cells in an individual's body.

$E_1 = (L^*, 0, 0, C^*, C_I^*, V_{R5}^*, V_{X4}^*.)$.

$$
\begin{aligned}
L^* &= \frac{\pi}{\mu}, \qquad L_T^* = L_I^* = 0,\\
C^* &= \frac{\pi_4}{(\lambda_2^*+\mu_4)}, \qquad C_I^* = \frac{\theta\pi_4\lambda_2^*}{(\lambda_2^*+\mu_4)(\mu_4+\rho)},\\
V_{R5}^* &= \frac{\rho(1-\phi)M\theta\pi_4\lambda_2^*\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}, \qquad V_{X4}^* = \frac{\rho\phi M\theta\pi_4\lambda_2^*\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}.
\end{aligned}
$$

Substituting the new expressions of $L^*, L_T^*, L_I^*, C^*, C_I^*, V_{R5}^*, V_{X4}^*$ into the force of infection $\lambda_2^* = \beta_2(V_{X4}^* + \sigma_3 V_{R5}^* + \sigma_2 C_I^*)$ yields

$$
\lambda_2^* = \beta_2\left(\frac{\rho\phi M\theta\pi_4\lambda_2^*\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)} + \frac{\sigma_3\rho(1-\phi)M\theta\pi_4\lambda_2^*\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)} + \frac{\sigma_2\theta\pi_4\lambda_2^*}{(\lambda_2^*+\mu_4)(\mu_4+\rho)}\right),
$$

which reduces to

$$\lambda_2^*\left(1-\frac{\rho\phi M\theta\pi_4\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}+\frac{\sigma_3\rho(1-\phi)M\theta\pi_4\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}+\frac{\sigma_2\theta\pi_4}{(\lambda_2^*+\mu_4)(\mu_4+\rho)}\right)=0.$$

Either

$$\lambda_2^*=0$$

which corresponds to the disease free equilibrium or

$$1-\frac{\rho\phi M\theta\pi_4\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}+\frac{\sigma_3\rho(1-\phi)M\theta\pi_4\mu}{(\lambda_2^*+\mu_4)(\mu_4+\rho)(\omega\alpha\pi+\mu_v\mu)}+\frac{\sigma_2\theta\pi_4}{(\lambda_2^*+\mu_4)(\mu_4+\rho)}=0$$

which then reduces to

$$\lambda_2^*=\mu_4\left[\frac{\beta_2\theta C_0^*}{\mu_4+\rho}\left(\sigma_2+\frac{\sigma_3M\rho(1-\phi)\mu}{\omega\alpha\pi+\mu_v\mu}+\frac{M\rho\phi\mu}{\omega\alpha\pi+\mu_v\mu}\right)-1\right]$$
$$\lambda_2^*=\mu_4\left[R_0^c-1\right],\quad R_0^c=h.$$

Where R_0^c is the local reproduction number of the $CD4^+$ T-cells

For existence of E_1, we require $R_0^c>1$.

Case 3. $\lambda_1^*\neq 0,\qquad \lambda_2^*=0$

This is where there are infected Langerhans cells, R5 viruses and X4 viruses produced by infected Langerhans cells but no infected $CD4^+$ T-cells in an individual's body.

$E_2=(L^*,L_T^*,L_I^*,C^*,0,V_{R5}^*,V_{X4}^*)$., where

$$L^*=\frac{\pi}{(\omega\lambda_1^*+\mu)},\quad L_T^*=\frac{\pi\lambda_1^*}{(\omega\lambda_1^*+\mu)(\mu+\gamma)},$$
$$L_I^*=\frac{\gamma\pi\lambda_1^*}{(\omega\lambda_1^*+\mu)(\mu+\gamma)(\mu+\delta)},\quad C^*=\frac{\pi_4}{(\mu_4)},\quad C_I^*=0,$$
$$V_{R5}^*=\frac{\delta\epsilon N\gamma\pi\lambda_1^*}{(\mu+\gamma)(\mu+\delta)\left[\mu_v\mu(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]},$$
$$V_{X4}^*=\frac{\delta(1-\epsilon)N\gamma\pi\lambda_1^*}{(\mu+\gamma)(\mu+\delta)\left[\mu_v\mu(\omega\lambda_1^*+\mu)+\omega\alpha\pi\right]}.$$

Substituting the new expressions of $L^*, L_T^*, L_I^*, C^*, C_I^*, V_{R5}^*, V_{X4}^*$ into the force of infection $\lambda_1^* = \omega\beta_1(V_{R5} + \eta_3 V_{X4} + \eta_1 L_I)$ yields

$$\lambda_1^* = \omega\beta_1 \left(\frac{\delta\epsilon N\gamma\pi\lambda_1^*}{Q} + \frac{\eta_3\delta(1-\epsilon)N\gamma\pi\lambda_1^*}{Q} + \frac{\eta_1\gamma\pi\lambda_1^*}{(\mu+\gamma)(\mu+\delta)(\omega\lambda_1^*+\mu)} \right),$$
$$\text{where} \quad Q = (\mu+\gamma)(\mu+\delta)\left[\mu_v\mu(\omega\lambda_1^*+\mu) + \omega\alpha\pi\right],$$

which reduces to

$$\lambda_1^*\left(1 - r_1 - r_2 - r_3\right) = 0,$$

where

$$r_1 = \frac{\omega\beta_1\delta\epsilon N\gamma\pi}{(\mu+\gamma)(\mu+\delta)\left[\mu_v\mu(\omega\lambda_1^*+\mu) + \omega\alpha\pi\right]}, \quad r_2 = \frac{\omega\beta_1\eta_3\delta(1-\epsilon)N\gamma\pi}{(\mu+\gamma)(\mu+\delta)\left[\mu_v\mu(\omega\lambda_1^*+\mu) + \omega\alpha\pi\right]},$$
$$r_3 = \frac{\omega\beta_1\eta_1\gamma\pi}{(\omega\lambda_1^*+\mu)(\mu+\gamma)(\mu+\delta)}.$$

Either

$$\lambda_1^* = 0 \quad \text{which corresponds to the disease free equilibrium point}$$

or

$$1 - r_1 - r_2 - r_3 = 0.$$

To find the other equilibrium points, we consider the expression $1 - r_1 - r_2 - r_3 = 0$ which when expressed in terms of λ_1^* gives

$$a_2\lambda_1^{*2} + a_1\lambda_1^* + a_0 = 0, \tag{3.11}$$

where

$$a_2 = \left[\omega^2\mu_v(\mu+\gamma)(\mu+\delta)\right],$$
$$a_1 = (\mu+\gamma)(\mu+\delta)\left[\omega\mu_v + \omega^2\alpha\pi + \omega\mu\mu_v\right]\left(1 - R_0^l\right) + \left(\omega^2\beta_1\gamma\pi\right),$$
$$a_0 = (\mu+\gamma)(\mu+\delta)\left[\mu^2\mu_v + \mu\omega\alpha\pi\right]\left(\omega^2\beta_1\eta_1\gamma\pi^2\alpha\right)\left(1 - R_0^l\right).$$

$R_0^l = a$.

Solving for λ_1^*, we have two roots

$$\lambda_{1a}^* = \frac{-a_1 + \sqrt{a_1^2 - 4a_2a_0}}{2a_2}, \qquad \lambda_{1b}^* = \frac{-a_1 - \sqrt{a_1^2 - 4a_2a_0}}{2a_2}$$

1. If $R_0^l = 1$ then $a_0 = 0$, $a_1 > 0$, $a_2 > 0$. Therefore $\lambda_{1a} = 0$, and $\lambda_{1b} = -\frac{a_1}{a_2}$ will present a non-feasible equilibrium point.

2. If $R_0^l < 1$ then $a_0 > 0$, $a_1 > 0$, $a_2 > 0$. Therefore, no positive equilibrium point because according to Descartes rule of signs, there is no sign change from the coefficients of (3.11).

3. If $R_0^l > 1$ then $a_0 < 0$, $a_1 > 0$, $a_2 > 0$. The co-efficient a_1 of (3.11) could be positive or negative when $R_0^l > 1$. In either case there is one sign change and one positive equilibrium point. Therefore, the positive equilibrium point is $\lambda_{1a} > 0$ and $\lambda_{1b} < 0$ will have a negative equilibrium point and according to Descartes rule of signs, there is only one sign change in the coefficients of (3.11).

Therefore for existence of the equilibrium point E_2, we require $R_0^l > 1$

Case 4. $\lambda_1^* \neq 0, \quad \lambda_2^* \neq 0$

This is where there are infected Langerhans cells , infected CD4$^+$ T-cells , R5 viruses and X4 viruses in an individuals body.

$E_3 = (L^*, L_T^*, L_I^*, C^*, C_I^*, V_{R5}^*, V_{X4}^*)$.

$$\begin{aligned}
L^* &= \frac{\pi}{\omega\lambda_1^* + \mu}, \quad L_T^* = \frac{\lambda_1^*}{\tau_1(\omega\lambda_1^* + \mu)}, \quad L_I^* = \frac{\lambda_1^*}{\tau_2(\omega\lambda_1^* + \mu)}, \\
C^* &= \frac{\pi_4}{(\lambda_2^* + \mu_4)}, \quad C_I^* = \frac{\lambda_2^*}{\tau_3(\lambda_2^* + \mu_4)}, \\
V_{R5}^* &= \frac{\lambda_1^*}{\tau_4(\lambda_1^* + \tau_8)} + \frac{\lambda_2^*(\omega\lambda_1^* + \mu)}{\tau_5(\lambda_2^* + \mu_4)(\lambda_1^* + \tau_8)}, \\
V_{X4}^* &= \frac{\lambda_2^*(\omega\lambda_1^* + \mu)}{\tau_6(\lambda_2^* + \mu_4)(\lambda_1^* + \tau_8)} + \frac{\lambda_1^*}{\tau_7(\lambda_1^* + \tau_8)}.
\end{aligned}$$

where

$$\tau_1 = \frac{(\mu+\gamma)}{\pi}, \quad \tau_2 = \frac{(\mu+\gamma)(\mu+\delta)}{\pi\gamma}, \quad \tau_3 = \frac{(\mu_4+\rho)}{\pi_4\theta},$$
$$\tau_4 = \frac{(\mu+\gamma)(\mu+\delta)}{\delta\epsilon N\gamma\pi}, \quad \tau_5 = \frac{(\mu_4+\rho)}{\rho(1-\phi)M\theta\pi_4}, \quad \tau_6 = \frac{(\mu_4+\rho)}{\rho\phi M\theta\pi_4},$$
$$\tau_7 = \frac{(\mu+\gamma)(\mu+\delta)}{\delta(1-\epsilon)N\gamma\pi}, \quad \tau_8 = \frac{\mu_v\mu+\omega\alpha\pi}{\mu_v\omega}, \quad \tau_9 = \frac{\omega\alpha\pi}{\mu_v}.$$

Substituting expressions $L^*, L_T^*, L_I^*, C^*, C_I^*, V_{R5}^*, V_{X4}^*$ into the two forces of infection λ_1^* and λ_2^*, we obtain

$$\begin{aligned}
\lambda_1 &= \beta_1\left(\frac{\lambda_1^*}{\tau_4(\lambda_1^*+\tau_8)} + \frac{\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_5(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\eta_3\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_6(\lambda_2+\mu_4)(\lambda_1+\tau_8)} + \frac{\eta_3\lambda_1^*}{\tau_7(\lambda_1^*+\tau_8)}\right) \\
&\quad + \beta_1\left(\frac{\eta_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)} + \frac{\eta_1\lambda_1^*}{\tau_2(\omega\lambda_1^*+\mu)}\right), \\
\lambda_2 &= \beta_2\left(\frac{\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_6(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\lambda_1^*}{\tau_7(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_1^*}{\tau_4(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_5(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)}\right) \\
&\quad + \beta_2\left(\frac{\sigma_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)} + \frac{\sigma_1\lambda_1^*}{\tau_2(\omega\lambda_1^*+\mu)}\right).
\end{aligned}$$

The equilibrium points of the model can be obtained by finding the fixed points of the equations $\kappa(\lambda_1,\lambda_2) = \begin{pmatrix}\kappa_1(\lambda_1,\lambda_2)\\ \kappa_2(\lambda_1,\lambda_2)\end{pmatrix}$ given by,

$$\begin{pmatrix}\kappa_1(\lambda_1,\lambda_2)\\ \kappa_2(\lambda_1,\lambda_2)\end{pmatrix} =$$

$$\begin{pmatrix}\beta_1\left(\frac{\lambda_1^*}{\tau_4(\lambda_1^*+\tau_8)} + \frac{\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_5(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\eta_3\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_6(\lambda_2+\mu_4)(\lambda_1+\tau_8)} + \frac{\eta_3\lambda_1^*}{\tau_7(\lambda_1^*+\tau_8)} + \frac{\eta_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)} + \frac{\eta_1\lambda_1^*}{\tau_2(\omega\lambda_1^*+\mu)}\right)\\ \beta_2\left(\frac{\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_6(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\lambda_1^*}{\tau_7(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_1^*}{\tau_4(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_5(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\sigma_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)} + \frac{\sigma_1\lambda_1^*}{\tau_2(\omega\lambda_1^*+\mu)}\right)\end{pmatrix}$$

clearly, $(\lambda_1^*,\lambda_2^*) = (0,0)$ is a fixed point which corresponds to the disease free equilibrium point.

Theorem 3.1.2. *There exists a unique fixed point* $(\lambda_1^*,\lambda_2^*)$, $\lambda_1^* > 0$, $\lambda_2^* > 0$ *satisfying* $\kappa(\lambda_1^*,\lambda_2^*) = \binom{\lambda_1^*}{\lambda_2^*}$ *corresponding to the endemic equilibrium point* E_3.

Proof. For each fixed $\lambda_1 > 0$, we consider real valued functions depending on λ_2:

$$\kappa_1^{\lambda_1}(\lambda_2) = \beta_1 \left(\frac{\lambda_1^*}{\tau_4(\lambda_1^* + \tau_8)} + \frac{\lambda_2^*(\omega\lambda_1^* + \mu)}{\tau_5(\lambda_2^* + \mu_4)(\lambda_1^* + \tau_8)} + \frac{\eta_3\lambda_2^*(\omega\lambda_1^* + \mu)}{\tau_6(\lambda_2 + \mu_4)(\lambda_1 + \tau_8)} + \frac{\eta_3\lambda_1^*}{\tau_7(\lambda_1^* + \tau_8)} \right).$$
$$+ \beta_1 \left(\frac{\eta_2\lambda_2^*}{\tau_3(\lambda_2^* + \mu_4)} + \frac{\eta_1\lambda_1^*}{\tau_2(\omega\lambda_1^* + \mu)} \right).$$

so that

$$\kappa_1^{\lambda_1}(0) = \beta_1 \left(\frac{\lambda_1}{\tau_4(\lambda_1 + \tau_8)} + \frac{\eta_3\lambda_1}{\tau_7(\lambda_1 + \tau_8)} + \frac{\eta_1\lambda_1}{\tau_2(\omega\lambda_1 + \mu)} \right) > 0.$$

and

$$\lim_{\lambda_2 \to \infty} \kappa_1^{\lambda_1}(\lambda_2) = \beta_1 \left(\frac{\lambda_1}{\tau_4(\lambda_1 + \tau_8)} + \frac{(\omega\lambda_1 + \mu)}{\tau_5(\lambda_1 + \tau_8)} + \frac{\eta_3(\omega\lambda_1 + \mu)}{\tau_6(\lambda_1 + \tau_8)} + \frac{\eta_3\lambda_1}{\tau_7(\lambda_1 + \tau_8)} \right)$$
$$+ \beta_1 \left(\frac{\eta_2}{\tau_3} + \frac{\eta_1\lambda_1}{\tau_2(\omega\lambda_1 + \mu)} \right) < \infty$$

Thus $0 < \kappa_1^{\lambda_1}(\lambda_2) < \infty$ so that the function $\kappa_1^{\lambda_1}(\lambda_2)$ is bounded for every fixed $\lambda_1 > 0$. The first derivative of $\kappa_1^{\lambda_1}(\lambda_2)$ with respect to λ_2 is given by

$$\frac{\partial \kappa_1^{\lambda_1}(\lambda_2)}{\partial \lambda_2} = \beta_1 \left(\frac{\mu_4(\omega\lambda_1 + \mu)}{\tau_5(\lambda_1 + \tau_8)(\lambda_2 + \mu_4)^2} + \frac{\eta_3\mu_4(\omega\lambda_1 + \mu)}{\tau_6(\lambda_1 + \tau_8)(\lambda_2 + \mu_4)^2} + \frac{\eta_2\mu_4}{\tau_3(\lambda_2 + \mu_4)^2} \right) > 0$$

The second derivative of $\kappa_1^{\lambda_1}(\lambda_2)$ with respect to λ_2 is

$$\frac{\partial^2 \kappa_1^{\lambda_1(\lambda_2)}}{\partial^2 \lambda_2} = -2\beta_1 \left(\frac{\mu_4(\omega\lambda_1 + \mu)}{\tau_5(\lambda_1 + \tau_8)(\lambda_2 + \mu_4)^4} + \frac{\eta_3\mu_4(\omega\lambda_1 + \mu)}{\tau_6(\lambda_1 + \tau_8)(\lambda_2 + \mu_4)^4} + \frac{\eta_2\mu_4}{\tau_3(\lambda_2 + \mu_4)^3} \right) < 0$$

Since $\dfrac{\partial \kappa_1^{\lambda_1}(\lambda_2)}{\partial \lambda_2} > 0$ and $\dfrac{\partial^2 \kappa_1^{\lambda_1}(\lambda_2)}{\partial^2 \lambda_2} < 0$, the function $\kappa_1^{\lambda_1}(\lambda_2)$ is an increasing concave down function which has no change in convexity in the bounded domain. This implies that there exists a unique point $\lambda_2^* > 0$ satisfying $\kappa_1^{\lambda_1}(\lambda_2^*) = \lambda_2^*$.

For λ_2^* we consider the following real-valued function depending on λ_1

$$\kappa_2^{\lambda_2^*}(\lambda_1) = \beta_2\left(\frac{\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_6(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)} + \frac{\lambda_1^*}{\tau_7(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_1^*}{\tau_4(\lambda_1^*+\tau_8)} + \frac{\sigma_3\lambda_2^*(\omega\lambda_1^*+\mu)}{\tau_5(\lambda_2^*+\mu_4)(\lambda_1^*+\tau_8)}\right) + \beta_2\left(\frac{\sigma_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)} + \frac{\sigma_1\lambda_1^*}{\tau_2(\omega\lambda_1^*+\mu)}\right),$$

$$\kappa_2^{\lambda_2^*}(0) = \beta_2\left(\frac{\lambda_2^*\mu}{\tau_6\tau_8(\lambda_2^*+\mu_4)} + \frac{\sigma_3\lambda_2^*\mu}{\tau_5\tau_8(\lambda_2^*+\mu_4)} + \frac{\sigma_2\lambda_2^*}{\tau_3(\lambda_2^*+\mu_4)}\right) > 0,$$

$$\lim_{\lambda_1\to\infty}\kappa_2^{\lambda_2^*}(\lambda_1) = \beta_2\left(\frac{\lambda_2\omega}{\tau_6(\lambda_2+\mu_4)} + \frac{1}{\tau_7} + \frac{\sigma_3}{\tau_4} + \frac{\sigma_3\lambda_2\omega}{\tau_5(\lambda_2+\mu_4)} + \frac{\sigma_2\lambda_2}{\tau_3(\lambda_2+\mu_4)} + \frac{\sigma_1}{\tau_2\omega}\right) < \infty$$

The real valued function is bounded for every fixed $\lambda_2^* > 0$.

Therefore,

$$\frac{\partial\kappa_2^{\lambda_2^*}(\lambda_1)}{\partial\lambda_1} = \beta_2\left(\frac{\lambda_2\tau_9}{\tau_6(\lambda_2+\mu_4)(\lambda_1+\tau_8)^2} + \frac{\tau_8}{\tau_7(\lambda_1+\tau_8)^2} + \frac{\sigma_3\tau_8}{\tau_4(\lambda_1+\tau_8)^2}\right) + \beta_2\left(\frac{\sigma_3\lambda_2\tau_9}{\tau_5(\lambda_2+\mu_4)(\lambda_1+\tau_8)^2} + \frac{\sigma_1\mu}{\tau_2(\omega\lambda_1+\mu)^2}\right) > 0$$

The second derivative of $\kappa_2^{\lambda_2^*}(\lambda_1)$ with respect to λ_1 is

$$\frac{\partial^2\kappa_2^{\lambda_2^*}(\lambda_1)}{\partial^2\lambda_1} = -2\beta_2\left(\frac{\lambda_2\tau_9}{\tau_6(\lambda_2+\mu_4)(\lambda_1+\tau_8)^3} + \frac{\tau_8}{\tau_7(\lambda_1+\tau_8)^4} + \frac{\sigma_3\tau_8}{\tau_4(\lambda_1+\tau_8)^4}\right) - 2\beta_2\left(\frac{\sigma_3\lambda_2\tau_9}{\tau_5(\lambda_2+\mu_4)(\lambda_1+\tau_8)^3} + \frac{\sigma_1\mu}{\tau_2(\omega\lambda_1+\mu)^4}\right) < 0.$$

which implies that the real valued function $\kappa_2^{\lambda_2^*}(\lambda_1)$ is an increasing concave down function which has no change in convexity in the positive domain. This means that there exists $\lambda_1^* > 0$ satisfying $\kappa_2^{\lambda_2^*}(\lambda_1^*) = \lambda_1^*$. Therefore, we have a unique fixed point $(\lambda_1^*, \lambda_2^*)$ corresponding to the endemic equilibrium point E_3. □

3.1.8 Global Stability Analysis of Equilibrium Points

Stability Analysis of the DFE (E_0)

We shall prove that the disease free equilibrium point is globally stable by means of Lyapunov functions.

Theorem 3.1.3. *The disease free equilibrium, E_0 is globally asymptotically stable in the positively invariant region Ω if $R_0 \leq 1$*

Proof. Define $H_0 : \{(L, L_T, L_I, C, C_I, V_{R5}, V_{X4}) \in \Omega : L > 0, C > 0\} \longrightarrow \mathbb{R}$ by
$H_0 = \left(L - L^* - L^* log\frac{L}{L^*}\right) + a_1 L_T + a_2 L_I + \left(C - C^* - C^* log\frac{C}{C^*}\right) + a_3 C_I + a_4 V_{R5} + a_5 V_{X4}$
The time derivative of H_0 computed along the solutions of the model is

$$
\begin{aligned}
\dot{H_0} &= \left(1 - \frac{L^*}{L}\right)\dot{L} + a_1\dot{L_T} + a_2\dot{L_I} + \left(1 - \frac{C^*}{C}\right)\dot{C} + a_3\dot{C_I} + a_4\dot{V_{R5}} + a_5\dot{V_{X4}}, \\
&= \left(1 - \frac{L^*}{L}\right)(\pi - \beta_1\omega(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I)L - \mu L) \\
&+ a_1(\beta_1\omega(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I)L - (\mu + \gamma)L_T) \\
&+ a_2(\gamma L_T - (\mu + \delta)L_I) \\
&+ \left(1 - \frac{C^*}{C}\right)(\pi_4 - \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I)C - \mu_4 C) \\
&+ a_3(\theta\beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I)C - (\mu_4 + \rho)C_I) \\
&+ a_4\left(\delta\epsilon N L_I + \rho(1-\phi)MC_I - \mu_v V_{R5} - \alpha\omega V_{R5} L\right) \\
&+ a_5\left(\rho\phi M C_I + \delta(1-\epsilon)N L_I - \mu v V_{X4} - \alpha\omega V_{X4} L\right).
\end{aligned}
$$

Collecting the linear terms of $L_T, L_I, C_I, V_{R5}, V_{X4}$ we obtain the following set of equations and solve for a_1, a_2, a_3, a_4 by setting the coefficients of $L_T, L_I, C_I, V_{R5}, V_{X4}$ to zero as

$$
\begin{aligned}
&-a_1(\mu+\gamma)+a_2\gamma=0,\\
&a_1\beta_1\omega\eta_1-a_2(\mu+\delta)+a_3\theta\beta_2\sigma_1+a_4\delta\epsilon N+a_5\delta(1-\epsilon)N=0,\\
&a_1\beta_1\omega\eta_2+a_3\theta\beta_2\sigma_2-a_3(\mu_4+\rho)+a_4\rho(1-\phi)M+a_5\rho\phi M=0,\\
&a_1\beta_1\omega+a_3\theta\beta_2\sigma_2-a_4\mu_v-a_4\alpha\omega V_{R5}L=0,\\
&a_1\beta_1\omega\eta_3+a_3\theta\beta_2-a_5\mu_v-a_5\alpha\omega V_{X4}L=0.
\end{aligned}
$$

This yields

$$
\begin{aligned}
a_4&=\frac{a_1\beta_1\omega+a_3\theta\beta_2\sigma_3}{\mu_v+\alpha\omega L},\quad a_5=\frac{a_1\beta_1\omega\eta_3+a_3\theta\beta_2}{\mu_v+\alpha\omega L},\\
a_3&=\frac{a_1\beta_1\omega\eta_2+a_3\theta\beta_2\sigma_2+a_4\rho(1-\phi)M+a_5\rho\phi M}{(\mu_4+\rho)},\\
a_2&=\frac{a_1\beta_1\omega\eta_2+a_3\theta\beta_2\sigma_1+a_4\delta\epsilon N+a_5\delta(1-\epsilon)N}{(\mu+\delta)},\\
a_1&=\frac{a_2\gamma}{(\mu+\gamma)}.
\end{aligned}
$$

Substituting the expressions a_1, a_2, a_3, a_4, a_5 in the equation of H_0 and simplifying, we obtain

$$
\begin{aligned}
\dot{H}_0&=\left(1-\frac{L^*}{L}\right)(\pi-\beta_1\omega(V_{R5}+\eta_3V_{X4}+\eta_2C_I+\eta_1L_I)L-\mu L)\\
&+\left(1-\frac{C^*}{C}\right)(\pi_4-\beta_2(V_{X4}+\sigma_3V_{R5}+\sigma_2C_I+\sigma_1L_I)C-\mu_4C)\\
&=-\frac{\mu}{L}(L-L^*)^2-\frac{\mu_4}{C}(C-C^*)^2<0
\end{aligned}
$$

$\dot{H}=0$ when $L=L^*$ and $C=C^*$ and all the infectious classes are zero at this point. This means that the DFE is the only equilibrium point E_0 that exists at that particular singleton and according to LaSalles invariant principle and the properties of the constructed Lyapunov function, the DFE is globally asymptotically stable.

□

Stability Analysis of the Endemic Equilibrium E_1

We shall prove that the endemic equilibrium point E_1 is globally stable by means of Lyapunov functions.

Theorem 3.1.4. *The endemic equilibrium, E_1 is globally asymptotically stable in the positive region Ω if $R_0 > 1$.*

Proof. Using the same method as in Theorem 3.1.3, we define $H_1 : \{(C, C_I, V_{R5}, V_{X4}) \in \Omega : C > 0, C_I > 0, V_{R5} > 0, V_{X4} > 0\} \longrightarrow \mathbb{R}$ by
$H_1 = \left(C - C^* - C^* log\frac{C}{C^*}\right) + \left(C_I - C_I^* - C_I^* log\frac{C_I}{C_I^*}\right) b_2$
$+ \left(V_{R5} - V_{R5}^* - V_{R5}^* log\frac{V_{R5}}{V_{R5}^*}\right) b_3 + \left(V_{X4} - V_{X4}^* - V_{X4}^* log\frac{V_{X4}}{V_{X4}^*}\right) b_4,$
where

$$b_2 = \frac{b_3\rho(1-\phi)M + b_4\rho\phi M}{((\mu+\rho) - \beta_2\theta\sigma_2)}, \quad b_3 = \frac{b_2\beta_2\theta\sigma_3}{\mu_v + \alpha\omega L}, \quad b_4 = \frac{b_2\beta_2\theta}{\mu_v + \alpha\omega L},$$

and

$$\dot{H}_1 = -\frac{\mu_4}{C}(C - C^*)^2 + \frac{b_2}{C_I}(C_I - C_I^*) + \frac{b_3}{V_{R5}}(V_{R5} - V_{R5}^*) + \frac{b_4}{V_{X4}}(V_{X4} - V_{X4}^*) \leq 0$$
$$\text{If} \quad C_I \leq C_I^*, \quad V_{R5} \leq V_{R5}^*, \quad V_{X4} \leq V_{X4}^*.$$

Hence global stability of the endemic equilibrium point, E_1 is proved. □

Stability Analysis of the Endemic Equilibrium E_2

Theorem 3.1.5. *The endemic equilibrium, E_2 is globally asymptotically stable in the positive region Ω if $R_0 > 1$*

Proof. Similarly as in proof of Theorem 3.1.3, we define $H_2 : \{(L, L_T, L_I, V_{R5}, V_{X4}) \in \Omega : L > 0, L_I > 0, L_T > 0, V_{R5} > 0, V_{X4} > 0\} \longrightarrow \mathbb{R}$ by
$H_2 = \left(L - L^* - L^* log\frac{L}{L^*}\right) + \left(L_T - L_T^* - L_T^* log\frac{L_T}{L_T^*}\right) d_2$

$$+\left(L_I - L_I^* - L_I^* log\frac{L_I}{L_I^*}\right) d_3 + \left(V_{R5} - V_{R5}^* - V_{R5}^* log\frac{V_{R5}}{V_{R5}^*}\right) d_4 + \left(V_{X4} - V_{X4}^* - V_{X4}^* log\frac{V_{X4}}{V_{X4}^*}\right) d_5$$

where

$$d_2 = \frac{d_3\gamma}{(\mu+\gamma)}, \quad d_3 = \frac{d_2\beta_1\omega\eta_1 + d_4\delta\epsilon N + d_5\delta(1-\epsilon)N}{\mu+\delta},$$
$$d_4 = \frac{d_2\beta_1\omega}{\mu_v + \alpha\omega L}, \quad d_5 = \frac{d_2\beta_1\omega\eta_3}{\mu_v + \alpha\omega L},$$

so that

$$\dot{H}_2 = -\frac{\mu}{L}(L - L^*)^2 + \frac{d_2}{L_T}(L_T - L_T^*) + \frac{d_3}{L_I}(L_I - L_I^*)$$
$$+ \frac{d_4}{V_{R5}}(V_{R5} - V_{R5}^*) + \frac{d_5}{V_{X4}}(V_{X4} - V_{X4}^*) \leq 0$$
$$\text{If} \quad L \leq L^*, L_T \leq L_T^*, \quad L_I \leq L_I^*, \quad V_{R5} \leq V_{R5}^*, \quad V_{X4} \leq V_{X4}^*.$$

Thus, global stability of the endemic equilibrium point, E_2. □

Stability Analysis of the EE, E_3

We shall prove the global Stability of endemic equilibrium point E_3.

Theorem 3.1.6. *If $R_0 > 1$ then the unique endemic equilibrium E_3^* of the system of differential equations (3.1) -(3.7) is globally asymptotically stable in the feasible region Ω.*

Proof. Define $H_3 : \{(L, L_T, L_I, C, C_I, V_{R5}, V_{X4}) \in \Omega : L > 0, L_T > 0, L_I > 0, C > 0, C_I > 0, V_{R5} > 0, V_{X4} > 0\} \longrightarrow \mathbb{R}$ by

$V = \left[L - L^* - L^* \ln\left(\frac{L}{L^*}\right)\right] + c_2\left[L_T - L_T^* - L_T^* \ln\left(\frac{L_T}{L_T^*}\right)\right] + c_3\left[L_I - L_I^* - L_I^* \ln\left(\frac{L_I}{L_I^*}\right)\right]$
$+ \left[C - C^* - C^* \ln\left(\frac{C}{C^*}\right)\right] + c_5\left[C_I - C_I^* - C_I^* \ln\left(\frac{C_I}{C_I^*}\right)\right] + c_6\left[V_{R5} - V_{R5}^* - V_{R5}^* \ln\left(\frac{V_{R5}}{V_{R5}^*}\right)\right]$
$+ c_7\left[V_{X4} - V_{X4}^* - V_{X4}^* \ln\left(\frac{V_{X4}}{V_{X4}^*}\right)\right],$

with

$$
\begin{aligned}
c_2 &= \frac{\gamma c_3}{\mu+\gamma},\\
c_3 &= \frac{c_2\beta_1\omega\eta_1 + c_5\beta_2\theta\sigma_2 + c_6\delta\epsilon N + c_7\delta(1-\epsilon)N}{(\mu+\delta)},\\
c_5 &= \frac{c_2\beta_1\omega\eta_2 + c_6\rho(1-\phi)M + c_7\rho\phi M}{((\mu_4+\rho)-\beta_2\theta\sigma_2)},\\
c_6 &= \frac{c_2\beta_1\omega + c_5\beta_2\theta\sigma_3}{\mu_v+\alpha\omega L} \quad c_7 = \frac{c_2\beta_1\omega\eta_3 + c_5\beta_2\theta}{\mu_v+\alpha\omega L}.
\end{aligned}
$$

so that

$$
\begin{aligned}
\dot{H}_3 &= -\frac{\mu}{L}(L-L^*)^2 + \frac{c_2}{L_T}(L_T-L_T^*) + \frac{c_3}{L_I}(L_I-L_I^*) - \frac{\mu_4}{C}(C-C^*)^2\\
&\quad + \frac{c_5}{C_I}(C_I-C_I^*) + \frac{c_6}{V_{R5}}(V_{R5}-V_{R5}^*) + \frac{c_7}{V_{X4}}(V_{X4}-V_{X4}^*) \le 0\\
\dot{H}_3 &< 0 \quad \text{If} \quad L_T \le L_T^*, \quad L_I \le L_I^*, \quad C_I \le C_I^*, \quad V_{R5} \le V_{R5}^*, \quad V_{X4} \le V_{X4}^*, \quad L \le L^*, \quad C \le C^*.
\end{aligned}
$$

Therefore, global stability of the endemic equilibrium point E_3 is ensured. □

Remark 3.1.9. Our model revealed four scenarios,

1. The disease free case where they are no infected Langerhans cells and no infected $CD4^+$ T-cells in the body.
2. An endemic case where they are infected Langerhans cells and no infected $CD4^+$ T-cells.
3. An endemic case where they are infected $CD4^+$ T-cells cells and no infected Langerhans cells.
4. An endemic case where they are infected Langerhans cells and infected $CD4^+$ T-cells.

3.2 THE EPIDEMIOLOGICAL DYNAMICS

3.2.1 Introduction

This section presents a basic compartmental SIA population model that captures the interactions between sexually active individuals. We review one of the basic models developed by May and Anderson [16] as a basis for discussing how mathematical models are developed and used to represent the dynamics of HIV. We formulate a model, prove its positivity and boundedness, calculate the reproduction number (R_0^p) and determine the equilibrium points and their stability. We aim to *investigate the population dynamics of HIV/AIDS that is mostly spread through sexual contacts targeting the risk group* $15-49$ *years of age.*

3.2.2 Model Formulation

The SIA model involves the following variables, Susceptible individuals (S), Infected individuals (I) and AIDS individual (A). We consider a sexually active population of size N_p divided into susceptible individuals, infected individuals and AIDS individuals. Susceptible individuals are members of the population who are at risk of becoming infected. Infected Individuals are the people who have been infected, have the HIV virus and can infect others. At this stage, the viral load begins to rise and the CD 4 count begins to decline in the body of such individuals. The AIDS individuals are the ones that their HIV status has developed to AIDS and this is the advanced stage of HIV infection. This is the stage that occurs when the immune system cannot fight against infections and one becomes vulnerable to infections and infection related cancers called opportunistic infections. At this stage, the CD 4 count is less than 200 [13].

We assume the force of infection, λ_0, which is the rate at which susceptible individuals become infected by infected individuals and AIDS individuals so that their number decreases at a rate $\lambda_0 S$ while the number of infected increases at the same rate. Individuals are recruited due to sexual activity at a rate Λ_0 as a source of susceptible individuals. The natural death rate is denoted by d_0 in all the populations and the disease induced death is denoted by δ_0. We assume

that AIDS individuals die naturally or from the disease. γ_0 is the progression rate of infected individuals to the AIDS class, It can take many years for people with the virus to develop AIDS. η_0 is the contact rate of AIDS individuals and susceptible individuals where $\eta_0 > 1$. The model diagram for the population dynamics is given in Figure 3.2.

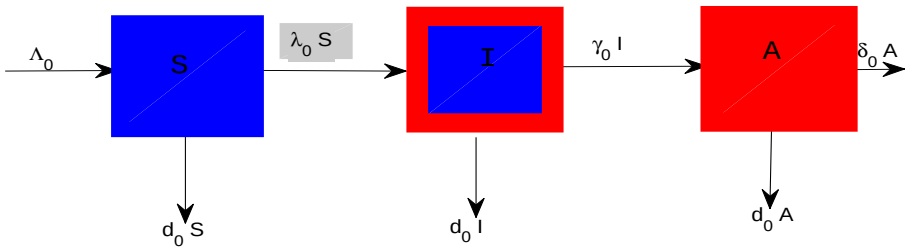

Figure 3.2: Model diagram for the Population Dynamics

The model equations that describe the assumptions are given as a system of non linear ordinary differential equations below:

$$\frac{dS}{dt} = \Lambda_0 - \lambda_0 S - d_0 S, \tag{3.12}$$

$$\frac{dI}{dt} = \lambda_0 S - (d_0 + \gamma_0) I, \tag{3.13}$$

$$\frac{dA}{dt} = \gamma_0 I - (d_0 + \delta_0) A, \tag{3.14}$$

where

$$\lambda_0 = \frac{\beta_0 (I + \eta_0 A)}{N_p}$$

and

$$N_p = S + I + A.$$

3.2.3 Positivity and Boundedness of Solutions

Theorem 3.2.1. *Let $S(0) > 0$, $I(0) \geq 0$, $A(0) \geq 0$. The solutions of $S(t)$, $I(t)$, $A(t)$ are positively invariant for all $t \geq 0$ in the region $\Omega = \{(S, I, A) \in \mathbb{R}^3_+ | 0 \leq S, I, A \leq \frac{\Lambda_0}{d_0}\}$*

for $t \geq 0$ equation (3.12) becomes

$$\frac{dS}{dt} + (\lambda_0 + d_0)S = \Lambda_0,$$

whose solution is

$$S(t) = S(0)e^{(-(d_0 t + \int_0^t \lambda_0(s)ds))} + e^{(-(d_0 t + \int_0^t \lambda_0(s)ds))} \left[\int_0^t \Lambda_0 e^{(ds + \int_0^s \lambda_0(r)dr)ds} \right] > 0.$$

From equation (3.13) and (3.14), we obtain;

$$\frac{dI}{dt} \geq -(d_0 + \gamma_0)I \quad and \quad \frac{dA}{dt} \geq -(d_0 + \delta_0)A,$$

which becomes

$$I(t) \geq I(0)e^{-(d_0+\gamma_0)t} \geq 0 \quad and \quad A(t) \geq A(0) \geq e^{-(d_0+\delta_0)t} \geq 0.$$

Therefore, all state variables are non-negative. To prove boundedness of solutions, we consider the total number of HIV/AIDS population of the people as $S + I + A = N_{ptot}$ by adding the right hand sides of equations (3.12) to (3.14) such that;

$$\frac{dN_{ptot}}{dt} = \Lambda_0 - d_0 N - \delta_0 A \leq \Lambda_0 - d_0 N. \tag{3.15}$$

Solving (3.15) we have

$$N_p \leq \left(N_p(0) - \frac{\Lambda_0}{d_0} \right) e^{d_0 t} + \frac{\Lambda_0}{d_0}.$$

Taking the limit supremum of N_p as $t \longrightarrow \infty$

$$\lim_{t\to\infty} \sup N_p \leq \frac{\Lambda_0}{d_0} = S_0$$

This means that

$$S(t) \leq S_0, \quad I(t) \leq S_0, \quad A(t) \leq S_0.$$

Since $0 \leq S \leq S_0$, $0 \leq I \leq S_0$, $0 \leq A \leq S_0$, we have $S, I, A \leq S_0$. Thus all state variables are bounded above by $\frac{\Lambda_0}{d_0}$. Since all state variables are positive and bounded in $\mathbb{R}^3_+$, then the region Ω is positively invariant.

3.2.4 The Reproduction Number (R_0^p)

In this model, R_0^p is defined as the expected number of second generation infections caused by the infected individuals and AIDS individuals in a totally susceptible population. Using the next generation method [1] , the reproduction number for the model is

$$R_0^p = \frac{\beta_0(d_0 + \delta_0 + \gamma_0\eta_0)}{(d_0 + \gamma_0)(d_0 + \delta_0)}$$

3.2.5 Disease Free Equilibrium Point

The disease free equilibrium point occurs when there is no infection in the body of susceptibles and is obtained by setting the infectious classes $I^* = A^* = 0$ and is given by

$$E_0 = (S_0, 0, 0), \quad S_0 = \frac{\Lambda_0}{d_0}$$

3.2.6 Local Stability of the DFE

The Jacobian matrix of the system (3.12) to (3.14) evaluated at the DFE is given by;

$$JE_0 = \begin{pmatrix} -d_0 & -\beta_0 & -\beta_0\eta_0 \\ 0 & \beta_0 - (d_0 + \gamma_0) & \beta_0\eta_0 \\ 0 & \gamma_0 & -(d_0 + \delta_0) \end{pmatrix}.$$

One of the eigenvalues of the Jacobian matrix JE_0 is $\lambda_1 = -d_0 < 0$. The other two are solutions of the characteristic equation

$$\lambda^2 + a_1\lambda + a_0 = 0$$

where $a_1 = 2d_0 + \delta_0 + \gamma_0 - \beta_0$ and $a_2 = (1 - R_0^p)$

The solutions of the characteristic equation are

$$\lambda_{2,3} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_0}}{2}.$$

Therefore all eigenvalues have negative real parts when $a_0 > 0$ and that is when $R_0^p < 1$.

The disease free equilibrium point E_0 of the system of equations (3.12) to (3.14) is locally stable when $R_0^p < 1$

3.2.7 Endemic Equilibrium Point

To determine the endemic equilibrium point of the system, we solve the system of equations S^*, I^*, A^* by setting the RHS of (3.12) to (3.14) to zero to obtain

$$E_1^* = \left(\frac{\Lambda_0(d_0 + \gamma_0 + \delta_0)(R_0^p - 1)}{\Psi}, \frac{\Lambda_0(d_0 + \delta_0)(R_0^p - 1)}{\Psi}, \frac{\gamma\Lambda_0(R_0^p - 1)}{\Psi} \right)$$

where $\Psi = d_0(d_0 + \gamma_0 + \delta_0)R_0^p + \delta_0\gamma_0(R_0^p - 1)$

Therefore, the solutions of S^*,I^* and A^* are positive when $R_0^p > 1$.

Theorem 3.2.2. *The endemic equilibrium point E_1^* of the system (3.12) to (3.14) exists only when $R_0^p > 1$*

3.2.8 Local Stability of the Endemic Equilibrium Point

Theorem 3.2.3. *The Endemic Equilibrium Point of the system (3.12) to (3.14) is locally asymptotically stable when* $R_0^p > 1$.

Proof. Let $J(E_1^*)$ be the Jacobian matrix of the system of equations (3.12) to (3.14) evaluated at endemic equilibrium point

$$J(E_1^*) = \begin{pmatrix} -\frac{(\gamma_0+d_0)I^*(R_0^p-1)}{S^*R_0^p} - d_0 & \frac{(\gamma_0+d_0)I^*}{N^*} - \frac{\beta_0}{R_0^p} & \frac{(\gamma_0+d_0)I^*}{N^*} - \frac{\beta_0\eta_0}{R_0^p} \\ \frac{(\gamma_0+d_0)I^*(R_0^p-1)}{S^*R_0^p} & -\frac{(\gamma_0+d_0)I^*}{N^*} + \frac{\beta_0}{R_0^p} - (\gamma_0+d_0) & -\frac{(\gamma_0+d_0)I^*}{N^*} + \frac{\beta_0\eta_0}{R_0^p} \\ 0 & \gamma_0 & -(d_0+\delta_0) \end{pmatrix}.$$

The characteristic equation of the Jacobian matrix is given by

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$$

where

$$\begin{aligned} a_2 &= A_2 + \frac{(\gamma_0+d_0)(d_0+\delta_0)(R_0^p-1)}{d_0+\gamma_0+\delta_0} \\ a_1 &= A_1 + \frac{(\gamma_0+d_0)(d_0+\delta_0)(2d_0+\delta_0+\gamma_0)(R_0^p-1)}{d_0+\gamma_0+\delta_0} \\ a_0 &= \frac{(\gamma_0+d_0)^2(d_0+\delta)^2(R_0^p-1)^2}{R_0^p(\gamma_0+d_0+\delta_0)} + \frac{d_0(\gamma_0+d_0)(d_0+\delta)(R_0^p-1)}{R_0^p} \end{aligned}$$

and;

$$A_1 = d_0(d_0+\delta) + \frac{\beta_0 d_0\eta_0\gamma_0}{(d_0+\delta)R_0^p} \qquad A_2 = 2d_0 + \delta_0 + \frac{\beta_0\eta_0\gamma_0}{(d_0+\delta_0)R_0^p}$$

Using the Routh-Hurwitz criterion, to determine conditions for $Re(\lambda) < 0$ we require; $a_0 > 0$, $a_2 > 0$ and $a_0a_1 - a_2 > 0$.

Clearly, $a_0 > 0$, $a_2 > 0$ if $R_0^p > 1$, and

$$a_0a_1 - a_2 = A_1A_2 + \frac{A_1(d_0+\gamma_0)(d_0+\delta_0)(R_0^p-1)}{(d_0+\gamma_0+\delta_0)} + A_3 + A_4 > 0$$

and;

$$A_3 = d_0 + (d_0 + \gamma_0 + \delta_0)(R_0^p - 1))\frac{(\gamma_0 + d_0)^2(d_0 + \delta_0)^2(R_0^p - 1)^2}{(d_0 + \gamma_0 + \delta_0)^2 R_0^p}$$

$$A_4 = A_2 d_0 R_0^p + (d_0 + \gamma_0 + \delta_0)\left(d_0(R_0^p - 1) + (d_0 + \delta_0)R_0^p + \frac{\beta_0\eta_0\gamma_0}{d_0 + \delta_0}\right)\frac{(\gamma_0 + d_0)(\delta_0 + d_0)(R_0^p - 1)}{(d_0 + \gamma_0 + \delta_0)R_0^p}$$

Therefore $a_0a_1 - a_2 > 0$ if $R_0^p > 1$.

Since all conditions for the Routh-Hurwitz are satisfied, therefore all eigenvalues are negative or have negative real parts and the endemic equilibrium point is locally asymptotically stable when $R_0^p > 1$. This result suggests that the virus will remain in the population if the reproduction number is greater than one and all the infected individuals will produce more than one new infected individual. □

Summary

In section 3.1, we formulated and analyzed a within host dynamics mathematical model that captured the interactions between Langerhans Cells, $CD4^+$ T-cells, R5 virus and X4 virus in the early stages of HIV infection. We proved that the model had a positive region and that all solutions were positive and bounded in that region. The basic reproduction number was calculated and we noticed that the model revealed four sub local basic reproduction numbers (i) from the Langerhans cells due to the infection emanating from infected Langerhans cells and the free virus. (ii) From the $CD4^+$ T-cells due to infection from infected $CD4^+$ T-cells and the free virus. (iii) From the Langerhans cells due to the infection coming from the infected $CD4^+$ T-cells and the free virus produced from the infected $CD4^+$ T-cells. (iv) And from the $CD4^+$ T-cells due to infection caused by infected Langerhans cells and the free virus produced by the infected Langerhans cells. Equilibrium points which help us tell the behavior of the solutions were calculated and we found out that the model had four equilibrium points, one was the disease free equilibrium point E_0 and three were endemic equilibrium points. The first endemic equilibrium point E_1 represented a case where a person had only infected $CD4^+$ T-cells

in the body. The second endemic equilibrium point E_2 showed a case where a person had only infected Langerhans cells in the body. The last endemic equilibrium point E_3 represented a person that had both infected $CD4^+$ T-cells and Langerhans cells in the body. The existence of E_0, E_1, E_2 depended on the value of the basic reproduction number while the existence of E_3 was dependent on a fixed point using the fixed point theorem. Global stability analysis using Lyapunov functions was proved and the model showed that all the endemic equilibrium points were globally asymptotically stable. The importance of global stability is that it helps us to link the immunological dynamics to the epidemiological dynamics in a way that the fast immunological dynamics are already at equilibrium when linking them to the slow epidemiological dynamics.

In section 3.2, we reviewed a basic compartmental SIA HIV/AIDS model that captured the dynamics of a basic population model. We proved that the region Ω was biologically feasible. The basic reproduction number that explains conditions under which the infection is cleared or persists in a population was calculated and we observed that when $R_0^p < 1$ meant that the virus will reduce in the population and when $R_0^p > 1$ showed that the virus will persist in the population. The model showed that it had two equilibrium points, the disease free and the endemic equilibrium points. Both equilibrium points were proved to be locally stable. We used the Routh Hurwitz criterion to prove that the endemic equilibrium point was locally asymptotically stable.

Having analyzed the within host and without host dynamics of HIV infection in the early stages, we introduce the linked models. We shall use direct linking method which is more appropriate for models involving HIV transmission.

Chapter 4

LINKING WITHIN HOST DYNAMICS TO POPULATION DYNAMICS

4.1 Introduction

We present in this chapter a model linking the within host dynamics and the population dynamics of HIV/AIDS infection. We make use of a direct linking of the epidemiological and immunological dynamics with the assumption that hosts acquire infection by direct sexual contact with infected individuals. Thus, if the number of contacts with the infected individuals are high, then the spread of infection in the population is also high. We also make use of the global stability of the endemic equilibrium points of the within host dynamics since by introducing the linked dynamics, the within host dynamics disease free equilibrium point ceases to exist.

We use linear functions as linking functions because in the early infection stages of HIV, the viral load grows proportionally to the number of infected cells available but we acknowledge that for long term dynamics, linking functions should be saturation functions since the viral load is relatively constant in the chronic phase of HIV. We seek to investigate *how the within-*

host infection can affect the population level of infection and how the infection in the population can affect the within host level of infection.

4.2 Linking Functions

In this paper, we used linear functions because we were modeling the early stages of HIV infection. We reckon that one can use any type of functions convenient to what is being modeled. Examples of linking functions can be found in the studies in [21, 22, 23, 25].

4.2.1 Properties of Linking Functions from within host dynamics to population dynamics

The linking functions used in this study satisfy the following conditions and the explanation thereof is given in remark 4.2.2.

1. $\beta_3(0,0) = 0\ , \qquad \beta_3(V_{X4}, V_{R5}) > 0, \qquad \beta_3(0, V_{R5}) > 0, \qquad \beta_3(V_{X4}, 0) > 0.$
2. $\beta_3'(V_{X4}, V_{R5}) > 0, \quad \beta_3'(0, V_{R5}) > 0, \quad \beta_3'(V_{X4}, 0) > 0.$
3. $\beta_3''(V_{X4}, V_{R5}) \leq 0, \quad \beta_3''(0, V_{R5}) \leq 0, \quad \beta_3''(V_{X4}, 0) \leq 0.$

Remark 4.2.2.

1. $\beta_3(0,0) = 0.$ shows that when there are no viruses in the body then we cannot have infected individuals, thus no viral load and no infection in both the within host and no infection is transmitted to the population. $\beta_3(V_{X4}, V_{R5}) > 0$ shows that the rate of transmission of HIV in the population is an increasing function of both the V_{X4} virus and the V_{R5} virus from within host dynamics. The infection comes from both viruses. $\beta_3(0, V_{R5}) > 0$ shows that if an individual transmits only V_{R5} virus, the rates of this transmission is an increasing function of V_{R5} and the infection progresses in the population because of V_{R5} virus transmission. $\beta_3(V_{X4}, 0) > 0$ shows that if an individual transmits

only V_{X4} virus, the rates of this transmission is an increasing function of V_{X4} and the infection progresses in the population because of V_{X4} virus transmission.

2. $\beta_3'(V_{X4}, V_{R5}) > 0$, shows that the rate of HIV transmission to the population is an increasing function of both the V_{X4} virus and the V_{R5} virus. $\beta_3'(0, V_{R5}) > 0$ and $\beta_3'(V_{X4}, 0) > 0$ shows the increasing functions for the rate of HIV transmission of the R5 virus and X4 virus respectively.

3. $\beta_3''(V_{X4}, V_{R5}) \leq 0$, $\beta_3''(0, V_{R5}) \leq 0$, $\beta_3''(V_{X4}, 0) \leq 0$ shows an increasing rate of transmission with a concave down function, thus infection of the V_{X4} virus and the V_{R5} virus increases to a global maximum point and cannot go beyond the bounded region.

4.2.3 Properties of Linking Functions from the population dynamics to the within host dynamics

Linking population dynamics affects the viral load where we assume that the rate of shedding of the virus is proportional to the number of infected individuals sexually active in the population. The functions we use are $f_{pi}(I, A) = f(I + \eta_0 A)$ where f is a constant of proportionality.

In the case of Langerhans cells dominated dynamics, $f = \zeta_l p$ and $f = (1 - \zeta_l)p$. In the case of the CD4$^+$T-cells dominated dynamics, $f = \zeta_c p$ and $f = (1 - \zeta_c)p$. In the case of the combined infection for the Langerhans cells and the CD4$^+$T-cells dynamics, $f = 1 - (\zeta_c + \zeta_l)p$ and $f = (\zeta_c + \zeta_l)p$. The absence of the V_{R5} virus transmission to the population shows that the contact rate by the infected individuals is $\zeta_l = 0$ in the Langerhans cells and $\zeta_c = 1$ in the CD4$^+$T-cells. For both the Langerhans cells and the CD4$^+$T-cells, the contact rate by infected individuals is $\zeta_l + \zeta_c = 1$ where $0 \leq \zeta_c + \zeta_l \leq 1$. On the other hand, the absence of the V_{X4} virus in the population entails that the contact rate made by the infected individuals is $\zeta_l = 1$ in the Langerhans cells and $\zeta_c = 0$ in the CD4$^+$T-cells. For both the Langerhans cells and the CD4$^+$T-cells, $\zeta_l + \zeta_c = 0$ where $0 \leq -(\zeta_c + \zeta_l) \leq 0$.

4.2.4 Implementing Linking Functions in the Model

From the linking functions the within host dynamics to the population dynamics will affect the force of infection. We explain all the scenarios of linking these dynamics.

Langerhans Cells and Population Dynamics

We assume that the rate of infection of each individual at population level depends linearly on the density of both V_{X4} and V_{R5} viruses. Thus β is transformed to be a linear function of V_{X4} and V_{R5} yielding $\frac{\beta(V_{X4}+V_{R5})}{V_{max}}$, $\eta_{oi} > 1$, η_{oi} is the measure with which the probability of a successful infection of a susceptible individual by an AIDS individual is reduced due to less abundance of AIDS individuals compared to infected individuals. We shall denote $\beta_3 = \frac{\beta}{V_{max}}$, the carrying capacity of the virus. Therefore, the linking function is $\beta_3(V_{X4} + V_{R5})$. Thus if the individual has virus predominantly from Langerhans cell dynamics, then the force of infection at the population level is given by $\lambda_{0l} = \frac{\beta_3(V_{X4}+\eta_{oi}V_{R5})(I+\eta_0 A)}{N_0}$. For the Langerhans cells, the population can be linked to the within host dynamics by $\zeta_l p_l(I + \eta_0 A)$, where ζ_l is the rate at which contact is made and p_l is the probability of successful introduction of the virus into the host by the infected individual with the R5 virus per coital acts. For the X4 virus, the population can be linked by the remaining proportion to yield $(1 - \zeta_l)p_l(I + \eta_0 A)$.

CD 4^+ T cells to Population Dynamics

To link the within host CD 4^+ T cells dynamics to the population dynamics, we modify the force of infection, λ_{0c} to $\lambda_{oi.} = \frac{\beta_3(\eta_{oi}.V_{X4}+V_{R5})(I+\eta_0 A)}{N_0}$. The force of infection shows that an infected individual can either transmit V_{X4} or V_{R5} virus with V_{X4} being dominant since the $CD4^+T$ cells are mostly infected by the X4 virus. We assume that every contact will result in shedding of the viruses back into the individual at a rate proportional to the available infectious population and AIDS population with ζ_c as a constant of proportionality and p_c the probability of successful shedding per coital acts. In the population, the virus can be linked to the within host by $\zeta_c p_c(I + \eta_0 A)$, which captures the introduction of the virus into the host by the infected individual with the X4 virus and $(1 - \zeta_c)p_c(I + \eta_0 A)$, is the introduction of the virus into the

host by the infected individual with R5 virus.

Linking Within Host Cells to Population Dynamics

The linking function for the within host dynamics of Langerhans cells and the CD 4^+ T cells to the population is $\lambda_{0a} = \frac{\beta_3(\eta_b V_{X4}+(1-\eta_b)V_{R5})(I+\eta_0 A)}{N_0}$, η_b is the measure of the probability of successful infection of the susceptible population by the infected individuals. In this case,an infected person can either transmit V_{X4} or V_{R5} virus into the body. The amount depends on the cells that the virus is targeting at that moment that becomes dominant to infection than the other. The linking functions from the population to both Langerhans cells and CD 4^+ T cells are $(1-(\zeta_c+\zeta_l))p_l(I+\eta_0 A)$ for the V_{R5} and $(\zeta_c+\zeta_l)p_c(I+\eta_0 A)$ for the V_{X4} so that $0 \leq \zeta_c + \zeta_l \leq 1$.

4.3 Model Formulation

We shall present the linked model informed by the three endemic equilibrium states E_1, E_2, E_3 from the within host dynamics namely: the Langerhans cells dominating, $CD4^+$T-cells dominating and combined Langerhans cells and $CD4^+$T-cells at equilibrium. These will lead to the cases of the effects thereof. We will determine the impact of these cases in the forthcoming subsections.

The full model for the linking Langerhans cells, CD4$^+$T-cells and the population is

$$\begin{aligned}
\frac{dL}{dt} &= \pi - (\omega\lambda_{12} + \mu)L, \\
\frac{dL_T}{dt} &= \omega\lambda_{12}L - (\mu + \gamma)L_T, \\
\frac{dL_I}{dt} &= \gamma L_T - (\mu + \delta)L_I, \\
\frac{dC}{dt} &= \pi_4 - (\lambda_{21} + \mu_4)C, \\
\frac{dC_I}{dt} &= \theta\lambda_{21}C - (\mu_4 + \rho)C_I, \\
\frac{dV_{R5}}{dt} &= (1 - (\zeta_c + \zeta_l))p_l(I + \eta_0 A) + \rho(1 - \phi)MC_I + \delta\epsilon NL_I - (\mu_v + \omega\alpha L)V_{R5}, \\
\frac{dV_{X4}}{dt} &= (\zeta_c + \zeta_l)p_c(I + \eta_0 A) + \rho\phi MC_I + \delta(1 - \epsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}, \\
\frac{dS}{dt} &= \Lambda_{0a} - \lambda_0 S - d_0 S, \\
\frac{dI}{dt} &= \lambda_{0a}S - (d_0 + \gamma_0)I, \\
\frac{dA}{dt} &= \gamma_0 I - (d_0 + \delta_0)A,
\end{aligned}$$

where

$$\begin{aligned}
\lambda_{12} &= \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I), \\
\lambda_{21} &= \beta_2(V_{X4} + \sigma_3 V_{X4} + \sigma_2 C_I + \sigma_1 L_I), \\
\lambda_{0a} &= \frac{\beta_3(\eta_b V_{R5} + (1 - \eta_b)V_{X4})(I + \eta io A)}{N_0}
\end{aligned}$$

4.4 Submodels

Case 5. *Langerhans Cells and Population dynamics*

$$\begin{aligned}
\frac{dL}{dt} &= \pi - (\omega\lambda_{11} + \mu)L, \\
\frac{dL_T}{dt} &= \omega\lambda_{11}L - (\mu + \gamma)L_T, \\
\frac{dL_I}{dt} &= \gamma L_T - (\mu + \delta)L_I, \\
\frac{dV_{R5}}{dt} &= \zeta_l p_l(I + \eta_0 A) + \delta\epsilon N L_I - (\mu_v + \omega\alpha L)V_{R5}, \\
\frac{dV_{X4}}{dt} &= (1 - \zeta_l)p_l(I + \eta_0 A) + \delta(1 - \epsilon)N L_I - (\mu_v + \omega\alpha L)V_{X4}, \\
\frac{dS}{dt} &= \Lambda_{0l} - \lambda_{0l}S - d_0 S, \\
\frac{dI}{dt} &= \lambda_0 S - (d_0 + \gamma_0)I, \\
\frac{dA}{dt} &= \gamma_0 I - (d_0 + \delta_0)A,
\end{aligned}$$

where

$$\begin{aligned}
\lambda_{11} &= \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_1 L_I), \\
\lambda_{0l} &= \frac{\beta_3(V_{X4} + \eta_{io} V_{R5})(I + \eta io A)}{N_0}.
\end{aligned}$$

Case 6. *CD4$^+$ T-cells and Population dynamics*

$$\begin{aligned}
\frac{dC}{dt} &= \pi_4 - (\lambda_{22} + \mu_4)C, \\
\frac{dC_I}{dt} &= \theta\lambda_{22}C - (\mu_4 + \rho)C_I, \\
\frac{dV_{R5}}{dt} &= (1 - \zeta_c p_c)(I + \eta_0 A) + \rho(1 - \phi)M C_I - (\mu_v + \omega\alpha L)V_{R5}, \\
\frac{dV_{X4}}{dt} &= \zeta_c p_c(I + \eta_0 A) + \rho\phi M C_I - (\mu_v + \omega\alpha L)V_{X4}, \\
\frac{dS}{dt} &= \Lambda_0 - \lambda_{0c}S - d_0 S, \\
\frac{dI}{dt} &= \lambda_{0c}S - (d_0 + \gamma_0)I, \\
\frac{dA}{dt} &= \gamma_0 I - (d_0 + \delta_0)A,
\end{aligned}$$

where

$$\lambda_{22} = \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I),$$
$$\lambda_{0c} = \frac{\beta_3(V_{R5} + \eta_{io} V_{X4})(I + \eta ioA)}{N_0}$$

4.5 Model Analysis

A common approach to analyzing linked systems is to take advantage of the different time scales of the processes being modeled. An important biological feature of the coupled system is that the within-host dynamics occurs on a faster time scale while the population dynamics occurs on a slow time scale. For analysis of the coupled model, we follow the same approach as in [22] and assume that the within host dynamics are fast compared to the dynamics of the population which allows us to analyze the within host dynamics while treating the population dynamics as constants. Thus our analysis will entail computing the positive endemic equilibrium points of the within host system combining Langerhans cells and $CD4^+$T-cells dynamics with the linking functions being treated as constants, and substituting the equilibrium points into the population dynamics. To balance the time scales, we introduce a slow time variable $\tau_b = \epsilon_b t$ where $0 < \epsilon_b \ll 1$. We consider the parameters associated with the dynamics at the population level to be small based on the assumption that the population dynamics occur on a slower time scale than the within host dynamics.
We denote $'.' = \frac{d}{dt}$ and $'\prime' = \frac{d}{d\tau_b}$ and let $\Lambda_0 = \epsilon_b \tilde{\Lambda_0}$, $\beta_i = \epsilon_b \tilde{\beta_i}$, $d_0 = \epsilon_b \tilde{d_0}$, $\gamma_0 = \epsilon_b \tilde{\gamma_0}$ $N_0 = \epsilon_b \tilde{N_0}$ $\delta = \epsilon_b \tilde{\delta}$.

4.5.1 The balanced time scales dynamics

Case 7. The subsystem for the within host dynamics of the Langerhans cells and $CD4^+$T-cells of the full model which corresponds to the Endemic equilibrium point E_3 in the within host dynamics is a fast system with equations

Table 4.1: Balanced time scales for within host dynamics and population dynamics

Equations with respect to fast dynamics	Equations with respect to slower time τ_b
$\dot{L} = \pi - (\omega\lambda_{12} + \mu)L$	$\epsilon_b L' = \pi - (\omega\lambda_{12} + \mu)L$
$\dot{L_T} = \lambda_{12}L - (\mu + \gamma)L_T$	$\epsilon_b L'_T = \lambda_{12}L - (\mu + \gamma)L_T$
$\dot{L_I} = \gamma L_T - (\mu + \delta)L_I$	$\epsilon_b L'_I = \gamma L_T - (\mu + \delta)L_I$
$\dot{C} = \pi_4 - (\lambda_{21} + \mu_4)C$	$\epsilon_b C' = \pi_4 - (\lambda_{21} + \mu_4)C$
$\dot{C_I} = \theta\lambda_{21}C - (\mu_4 + \rho)C_I$	$\epsilon_b C'_I = \theta\lambda_{21}C - (\mu_4 + \rho)C_I$
$\dot{V_{R5}} = \epsilon_b(1-(\zeta_c+\zeta_l))p(I+\eta_0 A)+\rho(1-\phi)MC_I+$ $\delta\epsilon NL_I - (\mu_v + \omega\alpha L)V_{R5}$	$\epsilon_b V'_{R5} = (1-(\zeta_c+\zeta_l))p(I+\eta_0 A)+\rho(1-\phi)MC_I+$ $\delta\epsilon NL_I - (\mu_v + \omega\alpha L)V_{R5}$
$\dot{V_{X4}} = \epsilon_b(\zeta_c + \zeta_l)p(I + \eta_0 A) + \rho\phi MC_I + \delta(1 -$ $\epsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}$	$\epsilon_b V'_{X4} = (\zeta_c + \zeta_l)p(I + \eta_0 A) + \rho\phi MC_I + \delta(1 -$ $\epsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}$
$\dot{S} = \epsilon_b \left(\tilde{\Lambda_0} - \tilde{\lambda_{0a}}S - \tilde{d_0}S\right)$	$S' = \tilde{\Lambda_0} - \tilde{\lambda_{0a}}S - \tilde{d_0}S$
$\dot{I} = \epsilon_b \left(\tilde{\lambda_{0a}}S - (\tilde{d_0} + \tilde{\gamma_0})I\right)$	$I' = \tilde{\lambda_{0a}}S - (\tilde{d_0} + \tilde{\gamma_0})I$
$\dot{A} = \epsilon_b \left(\tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A\right)$	$A' = \tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A$

Case 8. The subsystem for the within host dynamics Langerhans cells in case (5) which corresponds to the Endemic equilibrium point E_2 in the within host dynamics can be considered as a fast system with equations

Table 4.2: Balanced time scales for within host Langerhans cells dynamics and population dynamics

Equations with respect to fast dynamics	Equations with respect to slower time τ_b
$\dot{L} = \pi - (\omega\lambda_{11} + \mu)L$	$\epsilon_b L' = \pi - (\omega\lambda_{11} + \mu)L$
$\dot{L_T} = \omega\lambda_{11}L - (\mu + \gamma)L_T$	$\epsilon_b L'_T = \omega\lambda_{11}L - (\mu + \gamma)L_T$
$\dot{L_I} = \gamma L_T - (\mu + \delta)L_I$	$\epsilon_b L'_I = \gamma L_T - (\mu + \delta)L_I$
$\dot{V_{R5}} = \epsilon_b\zeta_l p_l(I + \eta_0 A) + \delta\epsilon N L_I - (\mu_v + \omega\alpha L)V_{R5}$	$\epsilon_b V'_{R5} = \zeta_l p_l(I + \eta_0 A) + \delta\epsilon N L_I - (\mu_v + \omega\alpha L)V_{R5}$
$\dot{V_{X4}} = \epsilon_b(1-\zeta_l)p_l(I+\eta_0 A)+\delta(1-\epsilon)NL_I-(\mu_v+\omega\alpha L)V_{X4}$	$\epsilon_b V'_{X4} = (1-\zeta_l)p_l(I+\eta_0 A)+\delta(1-\epsilon)NL_I-(\mu_v+\omega\alpha L)V_{X4}$
$\dot{S} = \epsilon_b\left(\tilde{\Lambda_0} - \tilde{\lambda_{0l}}S - \tilde{d_0}S\right)$	$S' = \tilde{\Lambda_0} - \tilde{\lambda_{0l}}S - \tilde{d_0}S$
$\dot{I} = \epsilon_b\left(\tilde{\lambda_{0l}}S - (\tilde{d_0} + \tilde{\gamma_0})I\right)$	$I' = \tilde{\lambda_{0l}}S - (\tilde{d_0} + \tilde{\gamma_0})I$
$\dot{A} = \epsilon_b\left(\tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A\right)$	$A' = \tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A$

Case 9. The subsystem for the within host dynamics of the CD4$^+$T-cells in (6) which corresponds to the endemic equilibrium point E_1 in the within host dynamics can also be considered as a fast system with equations

Table 4.3: Balanced time scales for within host CD4$^+$T-cells dynamics and population dynamics

Equations with respect to fast dynamics	Equations with respect to slower time τ_b
$\dot{C} = \pi_4 - (\lambda_{22} + \mu_4)C$	$\epsilon_b C' = \pi_4 - (\lambda_{22} + \mu_4)C$
$\dot{C_I} = \theta\lambda_{22}C - (\mu_4 + \rho)C_I$	$\epsilon_b C'_I = \theta\lambda_{22}C - (\mu_4 + \rho)C_I$
$\dot{V_{R5}} = \epsilon_b(1 - \zeta_c p_c)(I + \eta_0 A) + \rho(1 - \phi)MC_I - (\mu_v + \omega\alpha L)V_{R5}$	$\epsilon_b V'_{R5} = (1 - \zeta_c p_c)(I + \eta_0 A) + \rho(1 - \phi)MC_I - (\mu_v + \omega\alpha L)V_{R5}$
$\dot{V_{X4}} = \epsilon_b\zeta_c p_c(I+\eta_0 A)+\rho\phi MC_I-(\mu_v+\omega\alpha L)V_{X4}$	$\epsilon_b V'_{X4} = \zeta_c p_c(I+\eta_0 A)+\rho\phi MC_I-(\mu_v+\omega\alpha L)V_{X4}$
$\dot{S} = \epsilon_b\left(\tilde{\Lambda_0} - \tilde{\lambda_0}S - \tilde{d_0}S\right)$	$S' = \tilde{\Lambda_0} - \tilde{\lambda_{0c}}S - \tilde{d_0}S$
$\dot{I} = \epsilon_b\left(\tilde{\lambda_{0c}}S - (\tilde{d_0} + \tilde{\gamma_0})I\right)$	$I' = \tilde{\lambda_{0c}}S - (\tilde{d_0} + \tilde{\gamma_0})I$
$\dot{A} = \epsilon_b\left(\tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A\right)$	$A' = \tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A$

To analyze the fast system dynamics, we let $\epsilon_b = 0$ and the population dynamics become $\dot{S} = 0$, $\dot{I} = 0$ and $\dot{A} = 0$. Which implies that S, I and A are constants. We denote these constant

populations as $S = S_0$, $I = I_0$ and $A = A_0$. Therefore, our within host system from Table 4.1 will be

$$\begin{aligned}
\dot{L} &= \pi - (\omega\lambda_{12} + \mu)L \\
\dot{L_T} &= \omega\lambda_{12}L - (\mu + \gamma)L_T \\
\dot{L_I} &= \gamma L_T - (\mu + \delta)L_I \\
\dot{C} &= \pi_4 - (\lambda_{21} + \mu_4)C \\
\dot{C_I} &= \theta\lambda_{21}C - (\mu_4 + \rho)C_I \\
\dot{V_{R5}} &= (1 - (\zeta_c + \zeta_l))p(I + \eta_0 A) + \rho(1 - \phi)MC_I + \delta\epsilon NL_I - (\mu_v + \omega\alpha L)V_{R5} \\
\dot{V_{X4}} &= (\zeta_c + \zeta_l)p(I + \eta_0 A) + \rho\phi MC_I + \delta(1 - \epsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}.
\end{aligned}$$

To analyze the population dynamics, we let $\epsilon_b = 0$ and the within host dynamics parameters become constants. Therefore, the equations for our system will be

$$\begin{aligned}
S' &= \tilde{\Lambda_0} - \tilde{\lambda_{0a}}S - \tilde{d_0}S \\
I' &= \tilde{\lambda_{0a}}S - (\tilde{d_0} + \tilde{\gamma_0})I \\
A' &= \tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A
\end{aligned}$$

The same analysis can be done for the two sub-models of the Langerhans cells and the $CD4^+$T-cells in Table 4.2 and Table 4.3 respectively. We have analysed a scenario where $\epsilon_b = 0$, on the other hand, if $\epsilon_b > 0$, the rules for singular perturbation theory may be applied.

Remark 4.5.2.

1. The reproduction number of the fast system of the within host Langerhans cells is

$$R_0^{lf} = \frac{\beta_1\omega L_0\gamma}{(\mu + \gamma)(\mu + \delta)}\left[\eta_1 + \frac{\delta\epsilon N}{(\omega\alpha L_0 + \mu_v)} + \frac{\eta_3 N\delta(1 - \epsilon)}{(\omega\alpha L_0 + \mu_v)}\right].$$

We note that the coupled system with the external virus from infected individuals as new

infections and without external virus from infected individuals as new infections has the same reproduction number with the isolated Langerhans cells system. The system has a no disease free and one endemic equilibrium point $E_{1f} = (L^*, L_T^*, L_I^*, V_{R5}^*, V_{X4}^*)$. Thus setting the right hand side of the equations to zero and calculating in terms of the force of infection λ_{11}. Using a similar approach from chapter 3, we get

$$\begin{aligned}
L^* &= \frac{\pi}{(\omega\lambda_{11}^* + \mu)} \\
L_T^* &= \frac{\pi\lambda_{11}^*}{(\omega\lambda_{11}^* + \mu)(\mu + \gamma)}, \qquad L_I^* = \frac{\gamma\pi\lambda_{11}^*}{(\omega\lambda_{11}^* + \mu)(\mu + \gamma)(\mu + \delta)}, \\
V_{R5}^* &= \frac{\zeta_l p_l(I_0 + \eta_0 A_0) + \delta\epsilon N\pi\gamma\lambda_{11}^*}{(\mu + \gamma)(\mu + \delta)\left[\mu_v(\omega\lambda_{11}^* + \mu) + \omega\alpha\pi\right]} \\
V_{X4}^* &= \frac{(1 - \zeta_l)p_l(I_0 + \eta_0 A_0) + \delta(1 - \epsilon)N\gamma\pi\lambda_{11}^*}{(\mu + \gamma)(\mu + \delta)\left[\mu_v(\omega\lambda_{11}^* + \mu) + \omega\alpha\pi\right]}
\end{aligned}$$

When we substitute the new expressions of $L^*, L_T^*, L_I^*, V_{R5}^*, V_{X4}^*$ into λ_{11}, we get

$$\lambda_{11}^{*2} = \frac{-u_1 + \sqrt{u_1^2 - 4u_2u_0}}{2u_2}$$

and

$$\begin{aligned}
u_2 &= \left[\omega^2\mu_v(\mu + \gamma)(\mu + \delta)\right], \\
u_1 &= (\mu + \gamma)(\mu + \delta)\left[\omega\mu_v + \omega^2\alpha\pi + \omega\mu\mu_v\right]\left(1 - R_0^{lf}\right) + \left(\omega^2\beta_1\gamma\pi\right), \\
u_0 &= (\mu + \gamma)(\mu + \delta)\left[\mu^2\mu_v + \mu\omega\alpha\pi\right]\left(\omega^2\beta_1\eta_1\gamma\pi^2\alpha\right)\left(1 - R_0^{lf}\right).
\end{aligned}$$

$$R_0^{lf*} = \frac{\beta_1\omega L_0\gamma}{(\mu + \gamma)(\mu + \delta)}\left[\eta_1 + \frac{(\zeta_l p_l(I_0 + \eta_0 A_0) + \delta\epsilon N)}{\omega\alpha L_0 + \mu_v} + \frac{\eta_3((1 - \zeta_l)p_l(I_0 + \eta_0 A_0) + N\delta(1 - \epsilon))}{\omega\alpha L_0 + \mu_v}\right],$$

For existence of E_{lf}, we require that $R_0^{lf*} > 1$. And we observe that $R_0^{lf*} > R_0^l$.

2. The reproduction number of the fast system of the CD4$^+$T-cells is

$$R_0^{cf} = \frac{\beta_2 \theta C_0}{(\mu_4 + \rho)} \left[\sigma_2 + \frac{\sigma_3 \rho (1-\phi) M}{(\omega \alpha L + \mu_v)} + \frac{\rho M \phi}{(\omega \alpha L + \mu_v)} \right].$$

We notice that the linked system with the external virus from infected individuals as new infections and without external virus from infected individuals as new infections has the same reproduction number with the unlinked CD4$^+$T-cells system.

Again, the system has a no disease free case and an endemic equilibrium point $E_{1c} = (C^*, C_I^*, V_{R5}^*, V_{X4}^*)$. Using a similar approach from chapter 3, we set right hand side of the equations to zero and calculate in terms of the force of infection λ_{22} and get

$$\begin{aligned}
C^* &= \frac{\pi_4}{(\lambda_{22}^* + \mu_4)} \qquad C_I^* = \frac{\theta \pi_4 \lambda_{22}^*}{(\mu_4 + \lambda_{22}^*)(\mu_4 + \rho)}, \\
V_{R5}^* &= \frac{(1-\zeta_c) p_c (I_0 + \eta_0 A_0) + \rho (1-\phi) M \theta \pi_4 \lambda_{22}^* \mu}{(\lambda_{22}^* + \mu_4)(\mu_4 + \rho)(\omega \alpha \pi + \mu_v)} \\
V_{X4}^* &= \frac{\zeta_c p_c (I_0 + \eta_0 A_0) + \rho \phi M \theta \pi_4 \lambda_{22}^* \mu}{(\lambda_{22}^* + \mu_4)(\mu_4 + \rho)(\omega \alpha \pi + \mu_v)}
\end{aligned}$$

The equilibrium point E_{1c} exists when there are infected CD4$^+$T-cells and substituting the new expressions of $C^*, C_I^*, V_{R5}^*, V_{X4}^*$ in the force of infection λ_{22}, we get

$$\lambda_{22}^* = \beta_2 \left(V_{X4}^* + \sigma_3 V_{R5}^* + \sigma_2 C_I^* \right),$$

which reduces to

$$\lambda_{22}^* = \mu_4 C_0^* \left[R_0^{cf} - 1 \right],$$

and

$$R_0^{cf} = \frac{\beta_2\theta}{\mu_4+\rho}\left(\sigma_2 + \frac{\sigma_3(1-\zeta_c)p_c(I_0+\eta_0 A_0)+M\rho(1-\phi)\mu}{\omega\alpha\pi+\mu_v\mu} + \frac{\zeta_c p_c(I_0+\eta_0 A_0)+M\rho\phi\mu}{\omega\alpha\pi+\mu_v\mu}\right),$$

where R_0^{cf} is the local reproduction number of the linked model of CD4$^+$T-cells to the population. For existence of E_{lc}, we require $R_0^{cf} > 1$. We also notice that $R_0^{cf*} > R_0^c$

3. The reproduction number of the fast system of both the Langerhans cells and CD4$^+$T-cells linked to the population is

$$R_0^b = \frac{1}{2}\left[(R_0^{lf} + R_0^{cf}) + \sqrt{(R_0^{lf} - R_0^{cf})^2 + 4cf}\right]$$

where

   (a) R_0^{lf} is the local reproduction number of the linked fast model of the Langerhans cells

   (b) R_0^{cf} is the local reproduction number of the linked fast model of the CD4$^+$ T-cells

   (c) c is the local reproduction number of linked Langerhans cells due to infection primarily from infected CD4$^+$ T-cells and the free virus produced from CD4$^+$ T-cells.

   (d) f is the local reproduction number of linked CD4$^+$ T-cells due to infection by infected Langerhans cells and the free virus produced by infected Langerhans cells.

Again, for the endemic equilibrium point $E_{lfc} = L^*, L_T^*, L_I^*, C^*, C_I^*, V_{R5}^*, V_{X4}^*$, we set the right hand side of the equations to zero and calculate in terms of the forces of infection $\lambda_{12} = \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I)$ and $\lambda_{21} = \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I)$. Using the fixed point theorem approach in chapter 3, we have a unique fixed point $(\lambda_{12}^*, \lambda_{21}^*)$ corresponding to the endemic equilibrium point E_{lfc}

4. The reproduction number of the slow system associated with the combined infection of Langerhans cells and CD4$^+$T-cells is

$$R_0^s = \frac{\beta_0(d_0 + \delta_0 + \gamma_0\eta_0)(\eta_b V_{X40} + (1-\eta_b)V_{R50})}{(d_0+\gamma_0)(d_0+\delta_0)}$$

The reproduction number of the slow system associated with the infection of Langerhans cells only is

$$R_0^{sl} = \frac{\beta_0(d_0 + \delta_0 + \gamma_0\eta_0)(V_{X40} + \eta_{io} V_{R50})}{(d_0+\gamma_0)(d_0+\delta_0)}$$

The reproduction number of the slow system associated with the infection of CD4$^+$T-cells is

$$R_0^{sc} = \frac{\beta_0(d_0 + \delta_0 + \gamma_0\eta_0)(\eta_{io} V_{X40} + V_{R50})}{(d_0+\gamma_0)(d_0+\delta_0)}$$

From the reproduction numbers, the within host dynamics are independent of the population dynamics while as the population dynamics is dependent on the V_{R5} viruses and V_{X4} viruses from the within host. The endemic equilibrium point is

$$E_p^{s*} = \left(\frac{\Lambda_0(d_0+\gamma_0+\delta_0)(R_0^s-1)}{\Psi}, \frac{\Lambda_0(d_0+\delta_0)(R_0^s-1)}{\Psi}, \frac{\gamma\Lambda(R_0^s-1)}{\Psi} \right)$$

where $\Psi = d_0(d_0+\gamma_0+\delta_0)R_0^s + \delta_0\gamma_0(R_0^s-1)$ and E_p^{s*} of the system exists only when $R_0^s > 1$. Again here we observe that $R_0^s > R_0^p$. Using the same analysis, the endemic equilibrium point associated with infection from Langerhans cells only, E_p^{sl*} of the system exists only when $R_0^{sl} > 1$ and the endemic equilibrium point associated with infection from CD4$^+$ T-cells only E_p^{sc*} of the system exists only when $R_0^{sc} > 1$.

4.6 Summary

This chapter analyzed how linking the within host dynamics affect the population dynamics and viceversa. We linked Langerhans cells HIV dynamics to the population dynamics, CD4$^+$ T-cells

HIV dynamics to the population dynamics and both Langerhans cells and $CD4^+$ T-cells HIV dynamics to the population dynamics. We introduced linking functions that showed how the within host dynamics affected the population dynamics and also how the population dynamics affected the within host dynamics. The linked dynamics showed that if there is no virus in the within host means that there is no virus transferred to the population level, and the presence of viruses in the within host means the presence of viruses in the population dynamics. The within host dynamics are considered to be fast systems while the population dynamics are slow systems. We introduced separation of time scales and changed the time scales which allowed the within host dynamics processes and the population dynamics processes to occur at the same time scales. The basic reproduction numbers were calculated and we found out that for the within host dynamics, the basic reproduction numbers were the same for the isolated models and linked models. For the population model the basic reproduction number for the linked model was greater than the one of the decoupled system, in the population dynamics, the value of the basic reproduction number had additional parameters associated with the fast system. The fast dynamics were already at equilibrium such that when introducing the linking dynamics, the disease free equilibrium point ceased to exist and the linked within host systems were always at the endemic equilibrium point. The equilibrium points of the fast system dynamics had new parameters associated with the slow system dynamics , also the equilibrium points of the slow system dynamics had other parameters associated with the fast system dynamics. In both within host dynamics and population dynamics, the endemic equilibrium levels we increased due to the effects of linking. The linking functions in our model express the fact that an increase in sexual contact rate also increases the viral load of the individual.

Chapter 5

Numerical Simulations

5.1 Introduction

This chapter presents numerical simulations to enhance the understanding of the predictions of the analytical results. The data was obtained from published literature and some parameter values were estimated, guided by biological principles used in model formulation, because some are not known due to lack of data and difficulty to measure the values. Real data required to test the model predictions is not easy to obtain due to the nature of the study that requires data from human subjects therefore prediction are purely theoretical in nature. Numerical results will help to draw important conclusions and to also give an understanding of linking the within host dynamics to the without host dynamics. We illustrate the simulation results using graphs plotted from $MATLAB$ which shows the trends of the variables over a period of time.

5.2 Parameter Estimation for Within-host Dynamics

This section presents the parameter values for the within-host dynamics of the Langerhans cells, $CD4^+$ T-cells, R5 HIV and X4 HIV. The parameter values and units are explained in detail in Tables 5.1.

Table 5.1: Within Host Model Parameters for LC and CD4$^+$ T-cells HIV dynamics

parameter	Values	Units	References
π	1.5	$cells/day^{-1}$	estimated
μ	0.002	day^{-1}	[20]
β_1	0.00001	day^{-1}	[20]
η_3	$0 < \eta_3 < \eta_2 < \eta_1 < 1$	day^{-1}	see text
η_2	$0 < \eta_2 < \eta_1 < 1$	day^{-1}	see text
η_1	$0 < \eta_1 < 1$	day^{-1}	see text
ω	$0 < \omega < 1$	day^{-1}	see text
γ	0.035	day^{-1}	assumed
δ	0.025	day^{-1}	assumed
ϵ	$0.5 < \epsilon \leq 1$	virions/cell	see text
M	[200,1000]	virions/cell	[17]
π_4	20	$cells/day^{-1}$	[27].
μ_4	[0.02,0.24]	day^{-1}	[15]
β_2	0.000024	day^{-1}	[17]
σ_3	$0 < \sigma_3 < \sigma_2 < \sigma_1 < 1$	day^{-1}	see text
σ_2	$0 < \sigma_2 < \sigma_1 < 1$	day^{-1}	see text
σ_1	$0 < \sigma_1 < 1$	day^{-1}	see text
θ	$0 < \theta < 1$	day^{-1}	see text
ρ	0.239	day^{-1}	[17]
N	500	virion/cell	[20]
ϕ	$0.5 < \phi \leq 1$	day^{-1}	see text
α	[2,9]	day^{-1}	[32]
μ_v	2.4	day^{-1}	[33]

For the within host model, the initial conditions were assumed to be $1000 cells/mm^{-3}$ healthy Langerhans cells, $1000 cells/mm^{-3}$ healthy CD 4$^+$T cells , no latently infected Langerhans cells, $3 cells/mm^{-3}$ of infected Langerhans cells and $2 cells/mm^{-3}$ of infected CD 4$^+$T cells. We also assumed a population of $0.001 mm^{-3}$ of the R_5 virus and $0.001 mm^{-3}$ of the X_4 virus meaning one virus of each strain was introduced in a population of $1000 cells/mm^{-3}$ healthy Langerhans

cells and healthy CD 4^{+}T cells [17].

5.3 Parameter Estimation for Without-host Dynamics

We shall use parameter estimates guided by the data for South Africa and acknowledge that the same analysis can be performed for any other country using the data available for that country. We consider the population of sexually active individuals which will be from $15-49$ years. We shall extract data for this age group and estimate the initial conditions and some parameters associated with this group. The South Africa Statistical release P0302 [14], estimates the mid-year total population of 2015 as 54,960,000. The total number for HIV positive sexually active adults aged $15-49$ years was estimated to be 16.6% of the sexually active population.

We shall estimate the total population N_0 from the age groups $15-49$ that is sexually active. According to [14], the mid year population estimated by population age group, $15-20$ was 5124373, $20-24$ was 5302246, $25-29$ was 5232254, $30-34$ was 4307693, $35-39$ was 3774921, $40-44$ was 3204952 and $45-49$ was 273858. Therefore, the total number of the $15-49$ age group was 29,705,039=N_0. The total number of people living with HIV in 2015 was estimated at approximately 6.19 million. For adults aged $15-49$ years, an estimated 16.6% of the population was HIV. Therefore $I+A=\frac{16.6}{100}\times 6.19=1,027,540$. There is no separation of Infected individuals and AIDS individuals from the data. For our model, I_0=$1,027,540$ and A_0=0. The initial conditions were assumed to be $28,677,494$ for the susceptible individuals (S_0) and was calculated with the assumption that $S+I+A=N$, therefore, $S=N-(I+A)$, $S=29,705,039-1,027,540$ and $S=28,677,494$.

The life expectancy at birth was 60.6 years for males and 64.3 years for females. To estimate the death rate, we shall assume that the life expectancy of the population is the average of 60.6 and 64.3 which is 62.45. Thus death rate is estimated as the reciprocal of the average life expectancy. Therefore d_0=$\frac{1}{62.45}$=0.01601. The percentage of AIDS deaths in 2015 was 30.5%,

this gives the estimate of deaths due to AIDS as δ_0=$\frac{30.5}{100}$=0.305. The median time from HIV infection to death was 10.5 years for men and 11.5 years for women. Therefore the average progression rate from HIV to death for both populations is 11 years. Thus, the progression rate $\gamma_0 = \frac{1}{11}$ yields 0.0911. The transmission rate β_0 is estimated between 0 and 1. To estimate the recruitment rate, we note that at the disease free equilibrium point, $S_0 = \frac{\Lambda_0}{d_0}$, so that $S_0 \times d_0 = \Lambda_0$. Since $S_0 = 28,677,494$ and $d_0 = 0.1601$, then $\Lambda_0 = 459,126.6309$.

Table 5.2 shows the parameters of the without host dynamics

Table 5.2: Without Host Model Parameters

Parameter	Value	Units	References
Λ_0	459,126.6309	pop $year^{-1}$	[14]
d_0	0.01601	$year^{-1}$	[14]
δ_0	0.305	$year^{-1}$	[14]
γ_0	0.0911	$year^{-1}$	[14]
η_0	$\eta_0 > 1$	$year^{-1}$	see text
β_0	$[0, 1]$	$year^{-1}$	estimated

5.4 Parameter Estimation for Linking Functions

The linking functions parameters, meaning and their values are given in Table 5.3. We assume the introduction of the R_5 virus and X_4 virus from the population to the within as $0 \leq \zeta_c+\zeta_l \leq 1$.

Table 5.3: Linking Functions Parameters

parameter	Meaning	Value	References
ζ_l	successful introduction of R_5 from the population to within	[0,1]	estimated
ζ_c	successful introduction of X_4 to within from the population	[0,1]	estimated
p_l	probability of successful infection of R_5	[0,1]	estimated
p_c	probability of successful infection of X_4	[0,1]	estimated

5.5 Simulations - The Ideal Scenario

5.5.1 Within Host Dynamics

We want to observe the impact of R_5 HIV and X_4 HIV infection on the Langerhans cells and $CD4^+$T-cells within the host during early HIV infection. In Figure 5.1, we observe that the healthy Langerhans cells initially decrease possibly due to infection of R_5 HIV and X_4 HIV. The decrease in the healthy Langerhans cells causes the increase of the latently infected Langerhans cells and later followed by the increase of the infected Langerhans cells. In Figure 5.2 R_5 viruses increase to higher levels than the X_4 viruses because during early HIV infection, R_5 viruses are the ones that prefer infecting the Langerhans cells. The decrease of the virus due to death or degradation and other infectious classes causes a slight growth of the healthy Langerhans cells at a later stage of the infection. The results suggest that a decrease of the healthy Langerhans cells and a resultant increase in the infected Langerhans cells may lead to the enhanced infection of healthy $CD4^+$ T-cells. This is most likely to happen during the antigen presentation process.

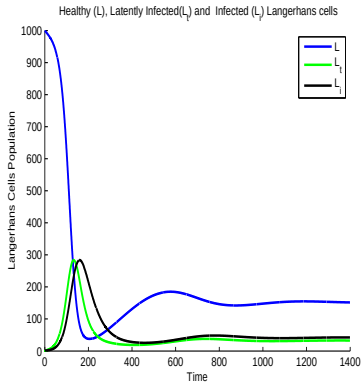

Figure 5.1: HIV Langerhans cells population dynamics

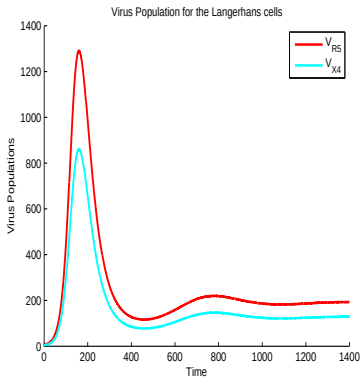

Figure 5.2: Virus population for the Langerhans cells

In Figure 5.3, we observe that $CD4^+$ T-cells population will start decreasing possibly with infection by R_5 HIV and X_4 HIV. As the number of the healthy $CD4^+$ T-cells decreases, the number of the infected $CD4^+$ T-cells increases and this result is in agreement with the literature to say the infection causes virus replication in the $CD4^+$ T-cells and this leads to the fast progression of HIV infection towards the development of AIDS as the CD4 count decreases below 500, below this level one requires intervention. In Figure 5.4, we observe an increase in the R5 virus and X4 virus, X4 virus being dominant as it is the one that prefers to infect the $CD4^+$ T-cells.

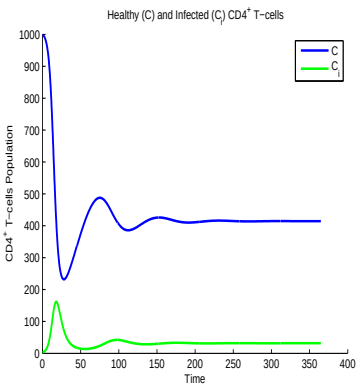

Figure 5.3: HIV $CD4^+$ T-Cells population dynamics

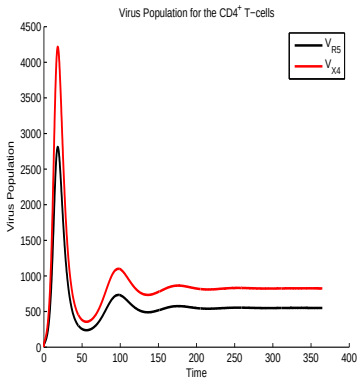

Figure 5.4: Virus population for the $CD4^+$ T-cells population

In Figures 5.5 and 5.6 we observe the dynamics of combined effects of Langerhans cells and $CD4^+$ T-cells with R_5 and X_4 HIV. In Figure 5.5, we observe that after possible infection by any of the two virus strains, the healthy Langerhans cells start to decrease causing an increase of the latent infected Langerhans cells and infected Langerhans cells which later affects the $CD4^+$ T-cells leading to their decrease and an increase of the infected $CD4^+$ T-cells. Figure 5.6 shows the increase of the virus populations to high peaks before settling at equilibrium levels. The increase of the virus populations is associated with the decrease of Langerhans cells and decrease of $CD4^+$ T-cells in Figure 5.5. The eventual decrease in the virus population is associated with a corresponding increase of the healthy Langerhans cells population till they reach their equilibrium values. The viral population initially grows in a switching dominant manner but eventually settles at equilibrium, the X_4 virus remained dominant over the R_5 virus. Therefore, we note that, in the combined infection scenarios, X_4 viruses dominate the R_5 viruses.

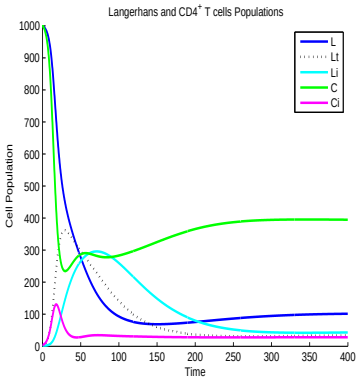

Figure 5.5: Langerhans and $CD4^+$ T-Cells population

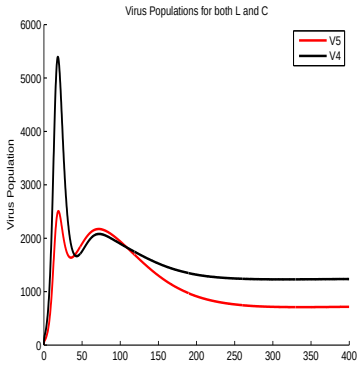

Figure 5.6: Virus population for Langerhans & $CD4^+$ T-Cells population

5.5.2 Population Dynamics

This section presents the dynamics of the SIA population model. In Figure 5.7 we observe that the susceptible population begins to decrease at a lower equilibrium. The decrease in the susceptible population leads to an increase in the infected population and after some time, an increase in of the infected individuals leads to an increase of the population in the AIDS stage.

The scenario is expected in a situation where there is no intervention.

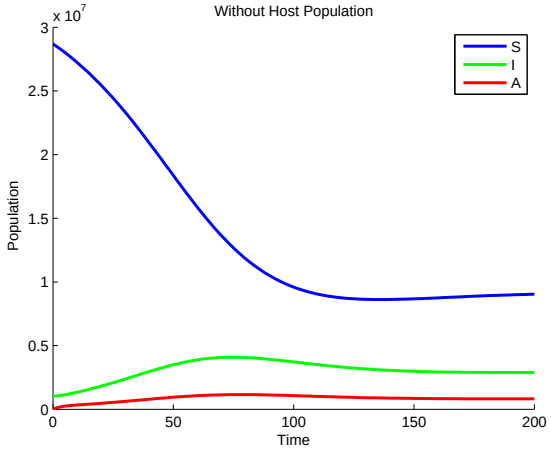

Figure 5.7: SIA population

5.6 Simulations- The Linking Scenario

5.6.1 Linking Population to in-host dynamics at equilibrium

Having observed the trends of the ideal situations of the within host dynamics and the population dynamics separately, we also investigated the effects that linking the within host dynamics at equilibrium has to the population dynamics.

Within host CD4$^+$ T-cells dynamics to Population dynamics

In Figure 5.8, the within host CD4$^+$ T-cells dynamics were linked to the population dynamics. From the graphs, we observed a decrease in the susceptible populations and an increase of the infectious populations. The linked susceptible graph was much lower than the unlinked one and also the linked infectious and AIDS graphs were higher than the unlinked ones. The results suggest that linking the CD4$^+$ T-cells dynamics to Population dynamics leads to an increase in infection dominantly by the X_4 viruses because the CD4$^+$ T-cells are associated with infection

by the X_4 virus.

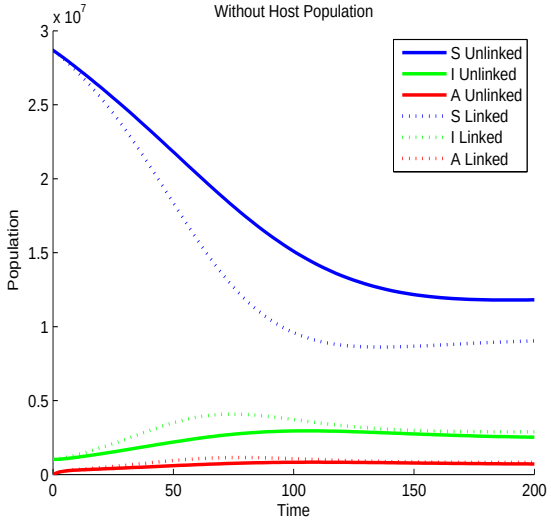

Figure 5.8: Population dynamics linked to $CD4^+$ T-Cells dynamics

Within host Langerhans Cells dynamics to population dynamics

In Figure 5.9, the trends are similar to the graph trends observed in Figure 5.8. However, in Figure 5.9, the results suggest that linking Langerhans cells dynamics to the population dynamics may lead to an increase in infection mostly by the R_5 virus because Langerhans cells are associated with infection dominantly from the R_5 viruses.

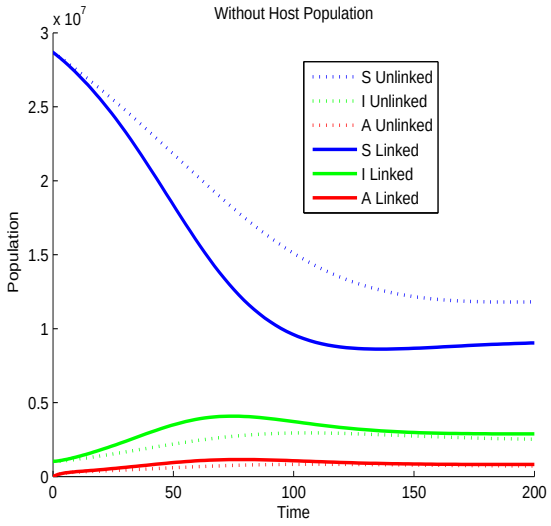

Figure 5.9: Population dynamics linked to Langerhans

Within host Langerhans & CD4$^+$ T-cells dynamics to population dynamics

In Figure 5.10, we observed the link between within host Langerhans cells and CD4$^+$ T-Cells dynamics to the population dynamics. The observation of the trends in graphs was similar to that in Figure 5.9 and Figure 5.8 , were they was a decrease in susceptible population and later an increase in the infectious populations. We notice that linking combined within host Langerhans cells and CD4$^+$ T-cells dynamics to the population dynamics leads to the populations reaching their peaks within the earliest times compared to when the within host cells (Langerhans cells and CD4$^+$ T-cells) dynamics are linked to population separately. This result may occur because the infected individual at this stage, is transmitting both the R_5 and X_4 viruses.

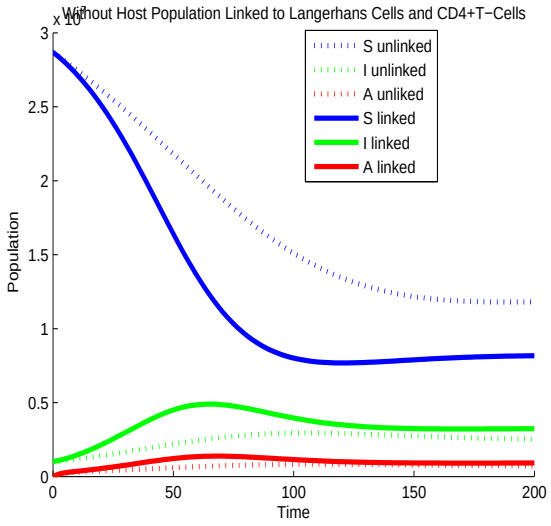

Figure 5.10: Population dynamics linked to Langerhans cells and $CD4^{+}$T-Cells

Graph for all scenarios

Figure 5.11 shows a summary for the linking of the within host Langerhans and $CD4^{+}$ T-cells dynamics to the population dynamics. The graphs reveals that the combined effects of the Langerhans cells and $CD4^{+}$ T-cells dynamics contributes more in increasing the infectious and AIDS stage individuals, followed by the contribution effects of the infected $CD4^{+}$ T-cells cell dynamics and the least contribution comes from the the infected Langerhans cells dynamics.

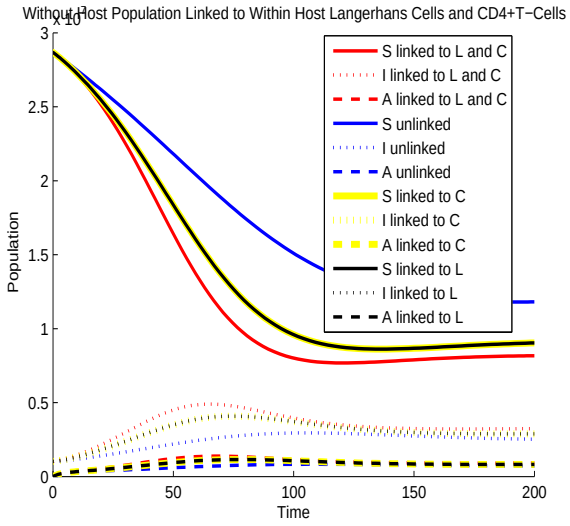

Figure 5.11: Population dynamics linked to Langerhans cells and $CD4^{+}$T-Cells

5.6.2 Linking Within Host Cell Dynamics and Population Dynamics Evolving with Time

Within host Langerhans Cells dynamics

We study the effects of linking Langerhans cells dynamics to the population in Figures 5.12, Figure 5.13 and Figure 5.14. In Figure 5.12, we notice that with time, as the population dynamics are infected with the viruses, we have more infections but later as the virus population in Figure 5.14 decreases, it triggers a slight growth in the susceptible population in Figure 5.12 at a later stage. Again as the individual transmits viruses to the within host dynamics, Figure 5.13 shows that the external virus from the population will increase infection of the cells, hence more infected cells.

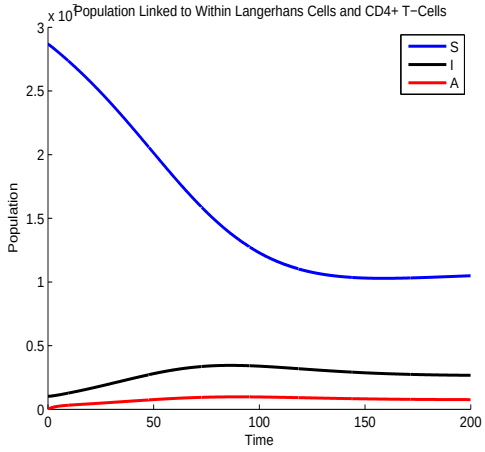

Figure 5.12: Population dynamics linked to Langerhans cells

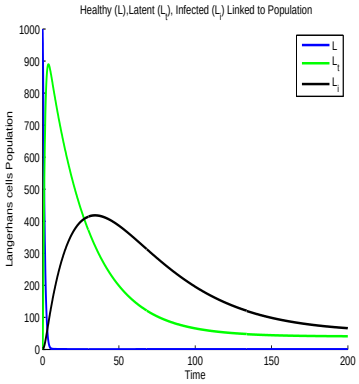

Figure 5.13: Langerhans cells linked to population dynamics

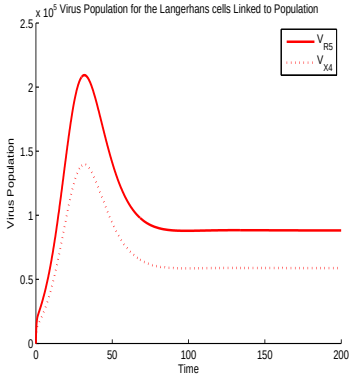

Figure 5.14: Virus of Langerhans linked to population dynamics

Within host CD4$^+$ T-Cells dynamics

Here, the analysis is similar with the Langerhans cells such that when the CD4$^+$ T-Cells are linked to the population dynamics, more X_4 viruses are going to the population and inside the host more CD4$^+$ T-Cells get infected as shown in Figure 5.16. For the virus population in Figure 5.17, it increases in the early stages and at a later stage settles down to an equilibrium value. We observe that V_{X4} virus is dominant because it is type of virus strain that prefers to infect the CD4$^+$ T-Cells. In Figure 5.15, the susceptible population decreases due to infection

from both the external virus from the population dynamics and the internal virus from the within host dynamics. Their decrease leads to an increase in the infected populations and AIDS populations.

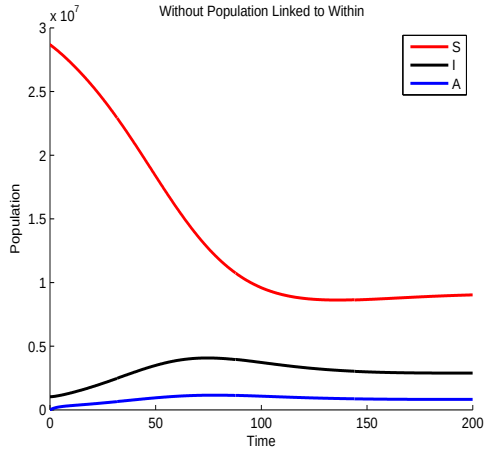

Figure 5.15: Population dynamics linked to CD4$^+$ T-Cells

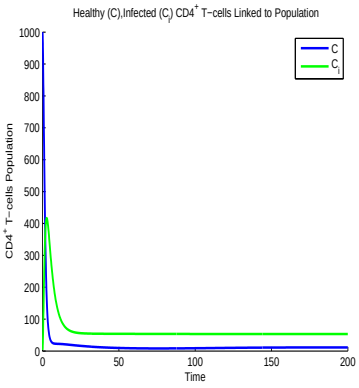

Figure 5.16: CD4$^+$ T-Cells linked to population dynamics

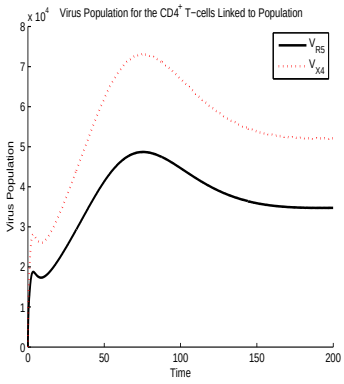

Figure 5.17: Virus for CD4$^+$ T-Cells linked to population dynamics

Within host Langerhans and CD4$^+$ T-Cells dynamics Combined

Linking both the within host cells dynamics to the population dynamics, in Figure 5.19, we notice that V_{X4} virus is dominant when we combine within host dynamics Langerhans cells and CD4$^+$ T-Cells. This proves that V_{X4} virus, is associated with the progression of HIV

infection. Figure 5.18 shows that the increase in infected populations and AIDS populations due to infection by R_5 virus and X_4 virus decreases the susceptible populations.

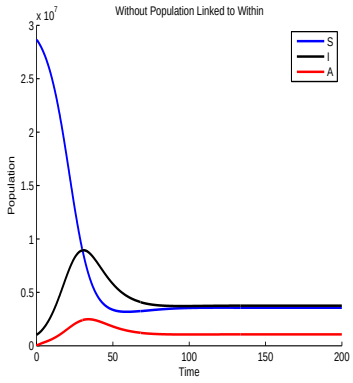

Figure 5.18: Population dynamics linked to CD4$^+$ T-Cells and Langerhans

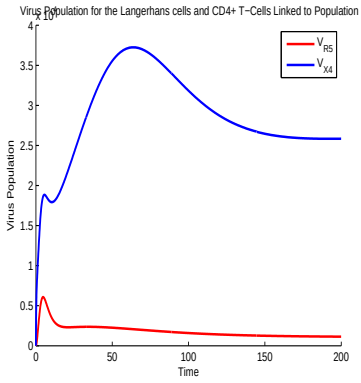

Figure 5.19: Virus for within host cells linked to population dynamics

5.7 Summary

This chapter provided insights on the prediction of the analytical results. The numerical simulation results were presented by graphs that showed trends of the within host dynamics and the population dynamics over a period of time. The population dynamics were linked to the to within host dynamics at equilibrium. The within host dynamics were also linked to population with time. The results obtained here helped us to draw conclusions towards the understanding of the linking of the within host dynamics to the population dynamics. From the graphs, we observed that the linked graphs showed immediate effects on the infection progression than the unlinked graphs. We also observed that linking both Langerhans cells and CD4$^+$ T-cells to the population increased infection compared to when the within host cells were linked to the population dynamics separately. The graphs showed that the combined effects of linking within host Langerhans cells and CD4$^+$ T-cells contribute to an increase in infection, followed by the effects of the infection by the CD4$^+$ T-cells and the infection by Langerhans cells showed to be the least in contributing to infection. The results suggests that linking the two dynamics leads to an increase in viral load thus increasing infection in both the within host and the population.

Chapter 6

Discussion of Results and Conclusion

6.1 Discussion of Results

We developed and analyzed mathematical models for within host dynamics and reviewed a without host mathematical model. We introduced linking dynamics to develop and analyze a model linking within host dynamics to population dynamics. In the within host dynamics, the interaction between different cells that take part in HIV transmission that is Langerhans cells and $CD4^+$ T-cells from the within host to the population were analyzed. In the population dynamics, a basic HIV/AIDS compartmental model was reviewed.

In the first model, we formulated a basic co-infection within host mathematical model that captured the interactions between Langerhans cells, $CD4^+$ T-cells, CCR5 HIV and CXCR4 HIV during the early stages of HIV infection. We aimed to find out the effects of combined infection of Langerhans cells and $CD4^+$ T-Cells with CCR5 HIV and CXCR4 HIV on the CD4 count and the viral load during the primary phase of HIV infection. We first proved that the state variables of the model were positive and bounded in the positive region to make sure that the region in which our model was analyzed was biologically feasible. We calculated the basic reproduction number and observed that it was dominated by the second generation infections from infected Langerhans cells, infected $CD4^+$ T-Cells, CCR5 HIV and CXCR4 HIV. The basic reproduction number had four sub-local reproduction numbers; the first one was

for the Langerhans cells with infection emanating from the infected Langerhans cells and the free virus produced from the infected Langerhans cells. The second was for the $CD4^+$ T-cells with infection originating from the infected $CD4^+$ T-cells and the free virus produced from the infected $CD4^+$ T-cells. The third was for the Langerhans cells with infection emerging from the infected $CD4^+$ T-Cells and the free virus from the $CD4^+$ T-cells. The last was for the $CD4^+$ T-cells with infection rising from the infected Langerhans cells and the free virus produced by the infected Langerhans cells. From the model, we had two forces of infection. One showed the rate at which Langerhans cells were infected by infected Langerhans cells, infected $CD4^+$ T-cells, CCR5 HIV and CXCR4 HIV. The other force of infection showed the rate at which $CD4^+$ T-cells get infected by CCR5 HIV, CXCR4 HIV, infected Langerhans cells and infected $CD4^+$ T-cells.

From the basic reproduction numbers, we observed that if we switch off infection from both the infected Langerhans cells, the infected $CD4^+$ T-Cells, CCR5 HIV and CXCR4 HIV, then we have a disease free case. If we have infection from infected Langerhans cells, infected $CD4^+$ T-Cells, CCR5 HIV and CXCR4 HIV, then the basic reproduction number depends on effects of all the infectious classes. If we switch off infection from the infected Langerhans cells only, then the basic reproduction number only depends on the contribution from the infected $CD4^+$ T-Cells and the virus produced by the infected $CD4^+$ T-cells. Switching off infection from the infected $CD4^+$ T-Cells, then the basic reproduction number only depends on the contribution of the infected Langerhans cells and the virus produced by the infected Langerhans cells.

The model had four equilibrium points, the disease free equilibrium point E_0 and three endemic equilibrium points points E_1, E_2, E_3. E_1 was associated with infection from the infected $CD4^+$ T-cells only, E_2 was connected with infection from the infected Langerhans cells only and E_3 was coupled with infection from both the infected Langerhans cells and infected $CD4^+$ T-cells. The existence and stability of the equilibrium points depended on the values of the basic reproduction numbers. The disease free equilibrium point existed for all values of the basic reproduction number and was stable when the basic reproduction number was less the unity

and unstable when the basic reproduction number was more than one. The endemic equilibrium point E_1, related to infection by $CD4^+$ T-cells only, was stable when the sub-local reproduction number associated with infection by infected $CD4^+$ T-cells and the virus produced from the infected $CD4^+$ T-cells was greater than one. The endemic equilibrium point E_2, affiliated to infection by Langerhans cells-HIV infection, was stable when the sub-local reproduction number associated with infection from Langerhans cells and the virus produced from the infected Langerhans cells was greater than one. The last endemic equilibrium point E_3, with combined infection of Langerhans cells and $CD4^+$ T-cells was proved to be an increasing concave down function that had no change in convexity in the feasible region. This showed that there was a unique fixed point corresponding to the endemic equilibrium point E_3 that was stable.

Threshold conditions for stability of the equilibrium points were established using Lyapunov functions. We constructed a logarithmic Lyapunov function and proved that the time derivatives computed along the solutions of the model were less than zero for the disease free equilibrium point and less than or equal to zero for the endemic equilibrium point. Therefore we found that the disease free equilibrium point and the three endemic equilibrium points were globally asymptotically stable in the feasible region.

Our within host model revealed four scenarios, a disease free case where they were no infected Langerhans cells, infected $CD4^+$ T-Cells , CCR5 HIV and CXCR4 viruses in the body. An endemic case where there were infected $CD4^+$ T-cells, CCR5 viruses and CXCR4 viruses only in the body, an endemic case where there were only infected Langerhans cells, CCR5 HIV and CXCR4 viruses only in the body, and an endemic case where they were both infected Langerhans cells and infected $CD4^+$ T-cells in the body.

In the second model, we reviewed and analyzed a basic compartmental susceptible, infected, AIDS model. This model captured the interactions between susceptible individuals, infected individuals and AIDS individuals of a sexually active population targeting the risk group 15-49 years of age. We choose to review a basic population model to get the general overview of

the effects of linking the within host dynamics to the population dynamics. All state variables were proved to be non-negative and bounded in the non-negative region. The feasible region was shown to be positively invariant. We computed the basic reproduction number and showed that it depended on parameters associated with HIV infected and AIDS individuals. The mathematical analysis carried out showed the existence of a disease free equilibrium point and an endemic equilibrium point. Conditions for stability were established through the basic reproduction number. It was shown that the disease free equilibrium point existed for all values of the basic reproduction number and was stable for values of the basic reproduction number less than unity. The endemic equilibrium point was locally asymptotically stable when the reproduction number was greater than one.

Then we investigated the effects of directly linking the within host dynamics to the population dynamics. Global stability of the within host dynamics was an important aspect that helped us to link the two systems together because the within host disease free equilibrium point ceases to exist when the linked dynamics are introduced. The within host dynamics are already at equilibrium at this point. We used direct linking since HIV infection is spread directly between individuals through sexual contacts. We used linear functions because in the early stages of HIV infection, the viral load grows proportionally to the number of cells available. We introduced linking functions that showed the impact of the virus both at the population level and the immunological level. The properties that we used for our linked model satisfied biological assumptions that is, if there is no virus, then there is no infection and infection offset when at least one of the viruses or both were present.

We formulated three linked sub-models. Firstly, we linked Langerhans cells HIV within host dynamics to the population dynamics. Secondly, we linked $CD4^+$ T-cells HIV within host dynamics to the population dynamics and lastly, we combined Langerhans cells and $CD4^+$ T-cells HIV within host dynamics and linked them to the population dynamics. The linking of within host dynamics and population dynamics has the consequences of using different time scales. Within host dynamics occur at a faster time scale and the population dynamics occur at a slow time scale. We adjusted the time scales by introducing a scaling factor in both dynamics

so that both the within host dynamics and the population dynamics occur at the same time scale. The subsystems of the linked sub-models corresponded to the three endemic equilibrium scenarios of the within host dynamics. The basic reproduction numbers for the linked model dynamics were calculated. We observed that the subsystem of the linked within host dynamics models had the same reproduction numbers as the decoupled systems of the unlinked within host dynamics. The basic reproduction number of the linked population model was modified by parameters from the within host dynamics. The result was that the basic reproduction number of the linked population dynamics model was greater than the basic reproduction number of the basic population model dynamics. This suggests that ignoring within host dynamics may underestimate the effects that they have on the population dynamics.

The linked sub-models had no disease free equilibrium point because when introducing linking dynamics, the fast dynamics are already at equilibrium such that the disease free equilibrium point ceases to exist thus the linked systems are always at the endemic equilibrium point. We found the endemic equilibrium points of the linked systems and observed that the existence of the endemic equilibrium points depended on the values of the local basic reproduction numbers associated with the linked models of the Langerhans cells to population dynamics, $CD4^+$ T-cells to population dynamics and both Langerhans cells and $CD4^+$ T-cells to population dynamics. The endemic equilibrium points of the linked within host model dynamics had additional terms from the population dynamics. The linked sub-model of Langerhans cells to the population dynamics was stable when the sub-local basic reproduction number associated with infection of Langerhans cells, infection from the population dynamics and the virus produced from the infected Langerhans cells was greater than one. The linked sub model of the $CD4^+$ T-cells to the population dynamics was stable when the sub local basic reproduction number associated with infection of $CD4^+$ T-cells, infection from the population dynamics and the virus produced from the infected $CD4^+$ T-cells was greater than one. Further, the linked sub-model of the combined infection of Langerhans cells and $CD4^+$ T-cells had a unique fixed point that corresponded to the equilibrium point and was stable.

The linked model had effects on both the endemic equilibrium points of the within host dynamics and the endemic equilibrium points of the population dynamics such that the within host dynamics had additional terms from the population dynamics in their equilibrium values and the population dynamics endemic equilibrium point had additional terms from the within host dynamics in its equilibrium values.

Numerical simulations were carried out to enhance the predictions of theoretical results and we observed the patterns of the ideal situations of the within host dynamics and the population dynamics. We observed the patterns of the linked within host dynamics of the Langerhans cells to the population dynamics, the $CD4^+$ T-cells to the population dynamics and both Langerhans cells and $CD4^+$ T-cells to the population dynamics. From the ideal situations, we observed that the healthy populations started to decrease because of the infection by the both the CCR5 HIV and CXCR4 HIV in both the Langerhans and $CD4^+$ T-cells populations, the decrease of the healthy populations led to an increase in the latent populations and later an increase in the infectious populations. In the Langerhans cells populations, we observed that the CCR5 virus was dominant and the CXCR4 virus was the one that was dominant in the $CD4^+$ T-cells population. When we combined the Langerhans and $CD4^+$ T-cells populations, the CXCR4 virus was the one that was dominant suggesting that it is the $CD4^+$ T-cells that are associated with the progression of HIV infection. There was an increase in infection when the infected Langerhans cells dynamics and infected $CD4^+$ T-cells dynamics were combined, followed by the the infection by the $CD4^+$ T-cells only and then infection by the Langerhans cells only. This result suggests that even though Langerhans cells are the initial targets of HIV infection, they are the least in contributing infection, $CD4^+$ T-cells contribute infections more than the Langerhans cells, however, a combination of both is deadly.

From the linked dynamics simulations, we observed that the linked dynamics model brings more CCR5 HIV and CXCR4 HIV in the individuals thus increasing infection. From the within host dynamics, apart from the internal virus that is there, there is an external virus coming from the population and in the population dynamics, there is an additional infection coming from

the within host dynamics. The linked model dynamics reached their peaks earlier compared to the unlinked models.

A number of studies in [21, 23, 25] have investigated the connection between within host dynamics and population dynamics. Our study is similar to the studies done in [21, 23, 25] because we both considered linking of the within host dynamics and the population dynamics. Nevertheless our study was different from the others in a way that we directly linked the within host dynamics to the population dynamics because HIV can be transmitted directly from one person to another. The direct linking can also be used for all infectious diseases that can be transmitted directly. In particular the studies in, [21] used a contaminated environment to link the within host dynamics to the population dynamics such that their model can only be appropriate for environmentally driven infections, thus indirect links. The study in [23] used the age-since-infection structure of the population dynamics variables to link the within host dynamics to the population dynamics. The Study in [25] also linked within host dynamics to population dynamics with a free living pathogen in the environment but they did not generalize a framework for the linking.

6.2 Conclusion

Our result suggest that linking the within host dynamics to the population dynamics has the potential to increase the viral load whilst decreasing the CD4 count within the host. At the population level only members of infected and AIDS individuals increase. Even though the actual data needed for the models might not be accurate or even available, such modeling is still vital in investigating how changes in the various assumptions and parameters affect the course of the epidemic.

6.3 Strengths and Weaknesses

Our model has provided insights in coupling dynamics with different timescales. We managed to directly link the within host dynamics to the population dynamics using the global stability of the within host dynamics. However, we were unable to obtain real data for the within dynamics to test the model. Some parameter values are not found in literature and were estimated, thus their effects need to be checked using sensitivity analysis.

6.4 Future Work

We acknowledge that more work can be done to improve the predictions of the model for instance using saturation functions for linking the dynamics in chronic stages of infection. The work can be developed further to include real data if it can be obtained. We can also include stochasticity since the infection dynamics during early infection are random. We can also include intervention methods. We can also incorporate multi-strain environment models and their effects of linking coupled with co-infection with other diseases such as malaria and tuberculosis. Omics to population dynamics can also be included. Further, we can use HIV infection data to fit the models and predict future outcomes of interventions and suggest policy statements guided by the findings of the project.

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