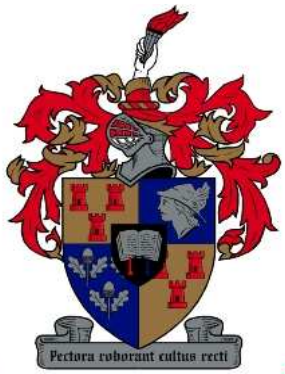


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# Mathematical Modelling of HIV/AIDS Transmission Under Treatment Structured by Age of Infection

by

Amsalework Ayele Ejigu

Thesis presented in partial fulfilment
of the requirements for the degree of
Master of Science
at Stellenbosch University

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# Declaration

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Amsalework Ayele Ejigu Date

# Abstract

This thesis takes into account the different levels of infectiousness of the human immunodeficiency virus (HIV) infected individuals throughout their period of infection. Infectiousness depends on the time since infection. It is high shortly after the infection occurs and then much lower for several years, and thereafter a higher plateau is reached before the acquired immunodeficiency syndrome (AIDS) phase sets in. In line with this, we formulated a mathematical model which is structured according to the age of infection. To understand the dynamics of the disease, we first discuss and analyse a simple model in which the age of infection is not considered, but progression of the HIV-AIDS transmission is taken into consideration by introducing three stages of infection. Analysis of these models tells us that the disease can be eradicated from the population only if on average one infected individual infects less than one person in his or her infectious period, otherwise the disease persists. To investigate the reduction of the number of infections caused by a single infectious individual to less than one, we introduce different treatment strategies for a model which depends on the age of infection, and we analyse it numerically. Current strategies amount to introducing treatment only at a late stage of infection when the infected individual has already lived through most of the infectious period. From our numerical results, this strategy does not result in eradication of the disease, even though it does reduce the burden for the individual. To eradicate the disease from the population, everyone would need to be HIV tested regularly and undergo immediate treatment if found positive.

# Opsomming

Hierdie tesis hou rekening met die verskillende aansteeklikheidsvlakke van die menslike immuniteitsgebreksvirus (MIV) deur besmette individue gedurende hulle aansteeklikheid-stydperk. Die graad van aansteeklikheid hang af van die tydperk sedert infeksie. Dit is hoog kort nadat die infeksie plaasvind en daarna heelwat laer vir etlike jare, en dan volg n hoer plato voordat uiteindelik die Verworwe-Immuniteitsgebreksindroom (VIGS) fase intree. In ooreenstemming hiermee, formuleer ons n wiskundige model van MIV-VIGS-oordrag met n struktureer waarin die tydperk sedert infeksie bevat is. Om die dinamika van die siekte te verstaan, bespreek en analiseer ons eers n eenvoudige model sonder inagneming van die tydperk sedert infeksie, terwyl die progressie van MIV-VIGS-oordrag egter wel in ag geneem word deur die beskouing van drie stadiums van infeksie. Analise van die modelle wys dat die siekte in die bevolking slegs uitgeroei kan word as elke besmette mens gemiddeld minder as een ander individu aansteek gedurende die tydperk waarin hy of sy self besmet is, anders sal die siekte voortduur. Vir die ondersoek oor hoe om die aantal infeksies per besmette individu tot onder die waarde van een te verlaag, beskou ons verskeie behandelingsstrategiee binne die model, wat afhang van die tydperk sedert infeksie, en ondersoek hulle numeries. Die huidige behandelingstrategiee kom neer op behandeling slegs gedurende die laat sta- dium van infeksie, wanneer die besmette individu reeds die grootste deel van die aansteeklikheidsperiode deurleef het. Ons numeriese resultate toon dat hierdie strategie nie lei tot uitroeiing van die siekte nie, alhoewel dit wel die las van die siekte vir die individu verminder. Om die siekte binne die bevolking uit te roei, sou elkeen gereeld vir MIV getoets moes word en indien positief gevind, dadelik met behandeling moes begin.

# Dedication

*To my husband*

# Acknowledgments

First of all, I would like to thank the almighty God who gave me strength during hard times beyond what I expect from myself. God you are always good. Special thanks for my supervisors Prof Fritz Hahne, who helped me from the beginning and Dr. Aziz Ouhinou for following up and working patiently with corrections. Thank you Dr. Senelani Dorothy Hove-Musekawa, Dr. Semu Mitiku, Prof. Ryszard Rudnicki, Prof. John Hargrove and Prof. Brian Williams for your helpful discussions and comments. I am also thankful for academic colleges and friends and all AIMS staffs. Lot thanks for Ms. Frances Aron and Mr. Jan Groenewald for the support throughout the writing of this thesis. I really thank my husband Mr. Melaku Tilahun. This work could not have been done with out his support during my stay away from home for long time. May God give us many years of togetherness . Thank you my parents and families for your prayers.

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# Chapter 1

# Introduction

## 1.1 Epidemiology of HIV/AIDS

The human immunodeficiency virus, HIV, infects cells in the immune system and the central nervous system. The T-helper lymphocytes are the main type of cell that HIV infects. The role of these cells in the immune system is to coordinate the actions of other immune system cells. A large reduction in the number of these cells results in weakening the immune system [12, 56]. HIV infects the T-helper cells because it has the protein called $CD4^+$ on its surface, which HIV uses to attach itself to cells before entering to them. That is why the T-helper cell is referred to as a $CD4^+$T lymphocyte. Once it attaches itself into a cell, HIV produces new copies which are capable of infecting other cells. When the age of infection increases[1], HIV infection leads to a severe reduction in the number of T-helper cells which are responsible to help fight diseases [56].

According to WHO[2] clinical staging of HIV/AIDS, HIV infection has four distinct stages: acute stage, asymptomatic stage, symptomatic stage and advanced AIDS stage [6, 24, 25, 50, 55]. The staging is based on clinical findings which gives implication for diagnosis, evaluation and management of HIV/AIDS. This staging system helps clinicians to decide whether the patient is eligible for treatment or not, especially in resource-constrained settings where $CD4^+$ count measurement or other diagnostic methods are not yet developed [25].

[1] Age of infection is a time since the person become infected.
[2] the World Health Organization

The acute stage can be represented by a period following HIV acquisition during which HIV RNA (HIV genetic material) and p24 antigen (a protein of HIV) can be detected when the usual screening tests for HIV antibodies are negative [48]. Since antibodies (HIV specific) have not yet developed, HIV continues to replicate and results in very high levels of the virus. In the first few weeks after being infected, infected individuals are highly infectious [6, 55]. At the acute stage there is a large amount of HIV in the peripheral blood (the blood in the circulating system not in the lymphatic system, bone marrow, liver or spleen), around $10^6$ copies of virus per $\mu l$ of blood [48]. Antibodies and cytotoxic lymphocytes start being produced as a response to the virus which is known as sero-conversion. At this stage, about 20% of people who are HIV positive show symptoms which are not mild. However, the diagnosis of HIV infection is missed at this stage [6].

The asymptomatic stage lasts for an average of eight years and can be characterized by a $CD4^+$ count around 500 cells per $\mu l$ [25]. This stage is free from major AIDS related diseases, although there may be swollen glands. The level of HIV in the peripheral blood settles down to a low level, even though infected individuals remain infectious. HIV antibodies are detectable in the blood and as a result antibody tests will show a positive result. A test which measures HIV RNA is referred to as the viral load test, and it has a crucial role to play in the treatment of HIV infection [6].

Infected individuals can progress to the symptomatic stage because of the lymph nodes and tissues become damaged due to the years of activity or HIV mutates and becomes more resistant or any other reasons. As a result, it leads to greater $CD4^+$ cell destruction and the immune system is not able to keep up with replacing the $CD4^+$ cells that are lost. As the immune system fails, symptoms start to develop. Initially many of the symptoms are mild, but as the immune system weakens, the symptoms increase. Symptomatic HIV infection is mainly caused by the emergence of opportunistic infections and cancers that the immune system is able to prevent and control in normal situations. This stage of HIV infection is often characterised by multi-system diseases and infections in almost all body systems. Treatment for the specific infection or cancer is often carried out, however the the main cause is the action of HIV as it attacks the immune system. Unless HIV itself can be slowed down, immune suppression will continue to be weaker [6].

AIDS is a condition diagnosed when there are a group of related symptoms that are caused

by severe HIV infection [6]. These infections are the cause of illness or death for HIV-positive individuals. On the other hand, progression to AIDS can be characterised by having a $CD4^+$ count of 200 per ml or below, while in the normal situation it is around 1000 per $ml$ [51]. At this stage, the infected individual is likely to develop opportunistic infections in their respiratory system, gastro-intestinal system, central nervous system and on the skin as well.

HIV is highly concentrated in the body fluids' such as, blood, fluids from reproductive organs and breast milk. Then an individual can contract HIV through untested blood transfusions, from infected sexual partners or from infected mothers during pregnancy, labour or delivery (vertical transmission), or through breast feeding. There are also other means for HIV transmission, like sharing sharp materials especially injecting drug users, [4]. In this work, we only consider the transmission from an infected partner through sexual intercourse.

## 1.2 Motivation

HIV is among the world's biggest health problem which increases morbidity and mortality of an infected individual. Millions died of AIDS and a large number of children became orphans because of AIDS deaths. According to the statistics from UNAIDS[3]/WHO in 2008, more than 25 million people have died of AIDS since the starting of the epidemic, 1981. In South Africa for instance, an estimated 5.2 million people were living with HIV and AIDS in 2008, more than in any other country in the world. It is estimated $250,000$ South Africans died of AIDS in the same year. Currently, the national prevalence is around 11% [6] (which is taken from antenatal clinic attendees).

Ever since the first observation of HIV, mathematical models have been developed to understand and explain the dynamics of the disease and suggest prevention in terms of education, counselling and also by providing anti-retroviral treatment (ART). Currently there are different kinds of ART. Among them, protease inhibitors and reverse transcriptase inhibitors are widely used. The former helps the immune system by opposing the replication of the virus and the latter inhibits the transcription of the viral single strand

[3]United States Agency for International Development

RNA into double strand DNA. As a result it interrupts the viral fusion to the host cell and further multiplication. Hence, it is believed that providing ART reduces the mortality and morbidity of already infected individuals and also reduces the rate of transmission of HIV by reducing the viral load up to an undetectable level [17].

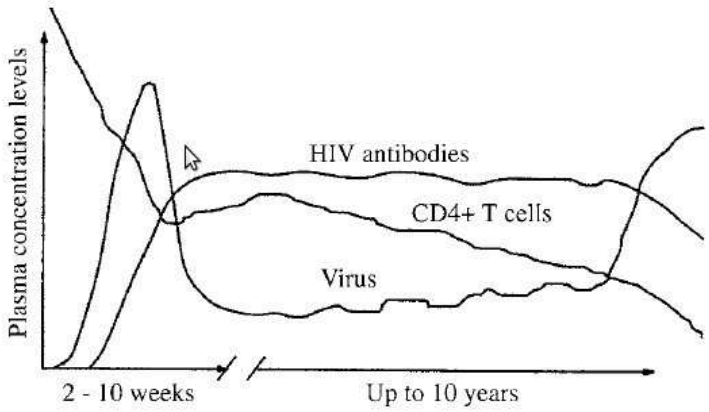


**Figure 1.1.** Source: [51], The viral load and CD4 count as a function of age of infection

In a newly infected individual, the number of $CD4^+$ cells starts decreasing since HIV affects them directly. At the same time, the viral load increases rapidly. This phenomenon continues up to three months on average. Because the number of $CD4^+$ cells is small and the number of viruses is large, the virus will not find free $CD4^+$ cells to infect, and hence their number starts decreasing, followed by a slight increase in the number of $CD4^+$ cells. The process is known as the prey-predator effect. The above diagram from [51] explains this effect. Then CD8 cells (sometimes called killer cells) kill infected $CD4^+$ cells on the process of fighting antigen (virus) [1]. As a result, the number of $CD4^+$ cells and viral load will remain lower for longer (about eight years) after the initial infection. When the immune system gets weaker and weaker, the viral load starts increasing and the number of $CD4^+$ cells decrease and the person is said to be in the final phase of HIV infection. Hence, one can say that the number of $CD4^+$ and viral particles are functions of age of infection.

As studies have suggested, infectiousness highly depends on the stage of infection of the infected individual [23, 24, 55]. Infected individuals in primary and late stages of infection are estimated to be 26 and 7 times, respectively, more infectious than those in the

asymptomatic stage [24].

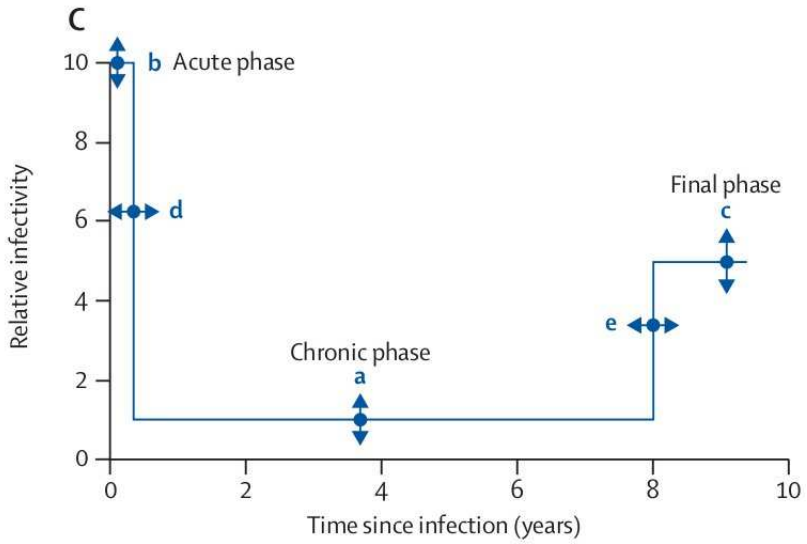


**Figure 1.2.** Source: [55], Infectiousness as a function of age of infection

## 1.3 Aim and Objectives

From Figure 1.2, as suggested by Reuben et al., infectiousness abruptly initially increases and drops down after the end of the acute stage. Then, it stays with the same probability of transmission for about ten years and starts to increase at the symptomatic stage [55]. Most epidemiological models of HIV consider one class of infected individuals by assuming that infected individuals have constant infectiousness throughout the infection period. But, it is observed that an HIV infected individual with different stages of infection has different viral load and different infectiousness as a result [24, 64, 55]. Considering a single class of infected individuals in a model means that an infected individual is assumed to have a constant viral load and infectiousness throughout the course of the infection. Thus, considering as many infectious classes as possible, is very important because it ends up considering uniform classes of infected individuals in a class. Hence age of infection of infected individuals is crucial in understanding the dynamics of the disease and provides interventions to counteract its effect.

Once we notice the variation of infectiousness when age of infection increases, it is important to consider it in the modelling of the transmission of the disease. Depending on the above fact, the aim of the thesis is:

- To investigate the effect of treatment on the transmission of HIV/AIDS in the population using the age of infection structured model.

To achieve our aim, we have the following objectives:

1. Implement the test and treat strategy using the age of infection structured HIV/AIDS model at different stages of the infection.
2. Investigate the effect of each stage of infection for the dynamics of the disease.
3. Compare results with the strategy presented by [55].

## 1.4 Methodology

According to Hollingsworth et al. and Reuben et al., the early and last stage of infection are responsible for the high rate of infectiousness [24, 55]. Even within one stage, there are different individuals with different infectiousness, [55]. If we consider the early stage, it lasts for about three months. Infected individuals with one month of infection and after three months of infection will have different viral loads and therefore different immune responses. In most compartmental HIV models infected individuals are assumed to have the same probabilities of infectiousness in every stage and the same rate of progression to the next stage (compartment). In our work, we will take into account that infected individuals in one class have different probability of infectiousness and rate of progression to AIDS depending on the age of infection.

In this research, the following points have been our methodologies to attain our objectives:

- Present a basic HIV/AIDS deterministic model by considering infected individuals to have the same effect for the dynamics of the disease throughout the course of the infection. This model gives a background of deterministic HIV/AIDS models.

- Formulate and analyse a staged progression HIV/AIDS model by dividing the infected class $I(t)$ into three further classes, $I_1(t)$, $I_2(t)$ and $I_3(t)$ depending on the age of infection.
- Formulate age of HIV infection structured model which generalises the above two deterministic models.
- Investigate the asymptotic behaviour of solutions and the stability analysis.
- Verify analytic solutions using numerical simulations.
- Introduce treatment for the model with age of infection at different stages of infection.
- Investigate how each stage of the infection affects the dynamics of the disease.

## 1.5 Thesis Organization

The rest of the thesis is organized as follows: In Chapter 2, we present an epidemiology model of HIV/AIDS by formulating and analysing two classic deterministic models. Chapter 3 presents an HIV/AIDS model structured by age of infection. It is a modification of the work done by [64]. In Chapter 4 we introduce antiretroviral treatment (ART) for the model presented in Chapter 3 and discuss results. Conclusions and recommendations for future work are presented in Chapter 5.

# Chapter 2

# Review of Deterministic HIV/AIDS Models

During the development of epidemiology in the population, deterministic (compartmental) models played a central role. Hamer used a deterministic model for measles in 1906 [19]. Such models divide the population into homogeneous sub-populations. Among them, models labelled by SI, SIS, SEIS, SIR and SEIR are mostly used where the sub-populations are Susceptible, Exposed, Infected and Recovered or Removed. In 1926, Kermack and McKendrick, while also using deterministic models, obtained the epidemic threshold result which shows that the density of susceptibles must exceed a critical value in order for a disease outbreak to occur [66]. In this Chapter, we discussed two SIR type models for HIV/AIDS transmission, where R is replaced by A to represent AIDS class.

## 2.1 Basic HIV Infection Model

In this standard model, the sexually matured population is divided into three classes, a class of susceptible individuals, a class of infected individuals and a class of AIDS progressed individuals, with population numbers in each class represented as functions of time by $S(t), I(t)$ and $A(t)$, respectively. Individuals $S(t)$ are those who are sexually active and had no exposure to the virus. Infectives $I(t)$ are those who are sexually active, infected and infectious for susceptible individuals. We consider $I(t)$ to be homogeneous with the same infection towards susceptible individuals and progress to AIDS class with the same

rate of progression. Individuals in the AIDS class, $A(t)$ are supposed to show AIDS-related symptoms and we assume that they do not involve much in sexual activities as a result of sickness [24].

### 2.1.1 Model Formulation

The number of susceptible individuals can increase due to newly recruited individuals, while the number can decrease due to new infection as a result of interaction with infected individuals in class $I(t)$ and also due to natural death. Infected individuals who joined the class $I(t)$ can progress into $A(t)$ or may die due to natural death. After progression to class $A(t)$, individuals are removed from this class due to natural or disease induced deaths.

The total sexually matured population at a given time is the sum of all individuals in all classes given by,

$$P(t) = S(t) + I(t) + A(t),$$

which varies with time since the disease induced death rate is far from negligible. Whereas, sexually active proportion is given by

$$N(t) = S(t) + I(t).$$

To express the dynamics mathematically, we considered $\Lambda$ the recruitment rate per unit of time into the susceptible class, $c$ the rate of sexual contact of an infected individual with susceptible individual per unit of time, $\beta$ is the probability of infecting per effective contact, $\mu$ the per capita natural death rate per unit of time (for individuals in each class), $\alpha$ the per-capita rate of progression of infected individuals to AIDS class per unit of time and $\nu$ the per-capita disease-induced death rate of individuals in AIDS class per unit of time.

The dynamics of the disease can be depicted in the following diagram:

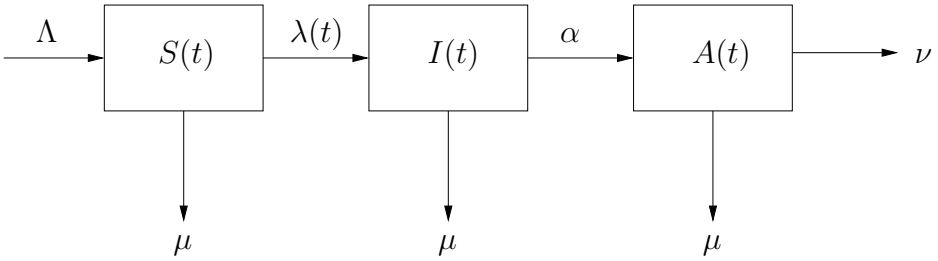


**Figure 2.1.** Diagrammatic representation of the basic HIV/AIDS model

where $\lambda(t) = \dfrac{c\beta I(t)}{N(t)}$ represents the standard incidence function.

Under the above assumptions and descriptions, the mathematical model of HIV transmission across $S$, $I$, $A$ compartments for $t \geqslant 0$ is given as follows:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \dfrac{c\beta S(t)I(t)}{N(t)} - \mu S(t), \\ \dfrac{dI(t)}{dt} = \dfrac{c\beta S(t)I(t)}{N(t)} - (\mu + \alpha)I(t), \\ \dfrac{dA(t)}{dt} = \alpha I(t) - (\mu + \nu)A(t), \end{cases} \tag{2.1}$$

with initial conditions,

$$S(0) = S_0 > 0, I(0) = I_0 > 0, A(0) = A_0 > 0.$$

### 2.1.2 Positivity of Solutions and the Invariant Region

The system in model (2.1) describes a human population, and hence we need to prove that the solutions $S(t), I(t), A(t)$ of the model (2.1) remain non-negative all the time. The model given (2.1) is studied in the following region for biological feasibility:

$$\mathfrak{D} = \Big\{(S, I, A) \in \mathbb{R}^3_+ : S + I + A \leqslant \frac{\Lambda}{\mu}\Big\}. \tag{2.2}$$

In other words, solutions of model (2.1) with given non negative initial data remain positive all the time and are bounded in region $\mathfrak{D}$ above.

**Lemma 2.1.1.** *All solutions of the system with positive initial conditions are non-negative for all time* $t \geq 0$.

*Proof.* Assume if $S(0) > 0, I(0) > 0$ and $A(0) > 0$, then for all $t \geq 0$, we have to prove that $S(t) > 0, I(t) > 0$ and $A(t) > 0$. We define:

$$T = \sup\{t > 0 | \forall s < t, S(s) > 0, I(s) > 0, A(s) > 0\} \tag{2.3}$$

From the continuity of $S(t), I(t)$ and $A(t)$, we deduce that $T > 0$. If T = $+\infty$, then the claim holds. But, if $0 < T < +\infty$,

$$S(T) = 0 \quad or \quad I(T) = 0 \quad or \quad A(T) = 0. \tag{2.4}$$

In the case when S(T) = 0,

$$\frac{dS(T)}{dt} = \lim_{t \to T^-} \frac{S(T) - S(t)}{T - t} \leqslant 0 \tag{2.5}$$

From the first equation of (2.1) we have,

$$\frac{dS(T)}{dt} = \Lambda > 0,$$

resulting in contradiction with (2.5). Hence,

$$S(T) \neq 0. \tag{2.6}$$

The second case is

$$I(T) = 0. \tag{2.7}$$

From the second equation of (2.1), if we denote

$$x(t) = \frac{c\beta S(t)}{N(t)} - (\mu + \alpha),$$

we have,

$$I(T) = I(0) \exp\Big( \int_0^T x(t)dt \Big) > 0. \tag{2.8}$$

which is contradiction with (2.7). Thus

$$I(T) \neq 0. \tag{2.9}$$

From (2.6) and (2.9), we necessarily have

$$A(T) = 0. \tag{2.10}$$

Then from the third equation of (2.1), using the variation of constant formula we have,

$$A(T) = A(0) \exp{(-\mu - \nu)T} + \alpha \int_0^T I(s) \exp{(-\mu - \nu)(T - s)ds} > 0.$$

Hence, also $A(T)$ could not be zero. Consequently $T = +\infty$. By this we have shown that all the solutions of (2.1) are in $\mathbb{R}^3_+$, provided that the initial conditions are positive. □

**Lemma 2.1.2.** *The region $\mathfrak{D}$ given by (2.2) is positively invariant and attracts all solutions in $\mathbb{R}^3_+$.*

*Proof.* Adding all equations of the system (2.1) gives us

$$P(t) \leqslant \frac{\Lambda}{\mu} + \exp(-\mu t)\left\{P_0 - \frac{\Lambda}{\mu}\right\}. \tag{2.11}$$

If we start inside the region $\mathfrak{D}$, that is $P_0 \leqslant \dfrac{\Lambda}{\mu}$, then,

$$P(t) \leqslant \frac{\Lambda}{\mu}.$$

So we stay inside the region $\mathfrak{D}$, hence $\mathfrak{D}$ is a positively invariant region. However, if $P_0 > \dfrac{\Lambda}{\mu}$ from equation (2.11), we get

$$\limsup_{t\to\infty} P(t) \leqslant \frac{\Lambda}{\mu}.$$

This implies that every solution of the system (2.1) either enters in the region $\mathfrak{D}$ or approaches asymptotically. □

### 2.1.3 Basic Reproduction Number and Equilibria

The analysis of the model includes finding equilibrium points (steady states) of the model, finding the threshold value, basic reproduction number $\mathcal{R}_0$ and investigate the stability of the equilibrium points (disease-free and endemic which will be characterized using the threshold value $\mathcal{R}_0$).

**Definition 2.1.3.** *Basic reproduction number, $\mathcal{R}_0$, is the average number of new cases of disease generated by a single infectious individual during the entire infectious period, in a totally susceptible population [14, 15] .*

If $\mathcal{R}_0 < 1$ the number of infected individuals will decrease from generation to the next and the disease dies out asymptotically. However, if $\mathcal{R}_0 > 1$ the number of infected individuals will increase from generation to the next with a ratio $\mathcal{R}_0 > 1$ and the disease will persist. The basic reproduction number $\mathcal{R}_0$ can be determined using the method of next-generation matrix as presented in [14, 15].

Taking the infectious compartment to be $I$, from the system (2.1) we have,

$$\mathcal{F} = \begin{bmatrix} \frac{c\beta S(t)I(t)}{N(t)} \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} (\alpha+\mu)I(t) \end{bmatrix},$$

where $\mathcal{F}$ and $\mathcal{V}$ are *transmission* and *transition* matrices, respectively, as presented in [14]. We need to differentiate both matrices $\mathcal{F}$ and $\mathcal{V}$ with respect to $I(t)$ to get $f$ and $v$ respectively, since $I(t)$ is the cause for further new infections. Then we substitute $S(t)$ by $N(t)$ in the expression of $f$, $\Big($when there is no disease in the population we have $S^* = N^* = \frac{\Lambda}{\mu}\Big)$. Hence,

$$f = \begin{bmatrix} c\beta \end{bmatrix},$$

and

$$v = \begin{bmatrix} \alpha+\mu \end{bmatrix}.$$

The next generation matrix is given by

$$K = fv^{-1}.$$

Then, the basic reproduction number $\mathcal{R}_0$, can be given by the spectral radius of the matrix $K$. That is,

$$\mathcal{R}_0 = \rho(K) = \frac{c\beta}{\mu+\alpha}.$$

The expression of $\mathcal{R}_0$ is a product of probability of infecting per effective contact $\beta$, rate of contact per unit of time $c$, and $\frac{1}{\mu+\alpha}$ the life expectancy of infected individuals in $I(t)$ before leaving the class by natural death or progression to AIDS.

**Definition 2.1.4.** *Given a system of differential equations* $\mathbf{x}'(t) = \mathbf{f}(t)$*, an equilibrium* $\mathbf{x}^*$ *of this system is a point in the state space for which* $\mathbf{x}(t) = \mathbf{x}^*$ *is a solution for all t. Th*

To find the equilibrium of the system (2.1), we equate the right-hand side to zero,

$$\begin{cases} 0 &= \Lambda - \frac{c\beta S^* I^*}{N^*} - \mu S^*, \\ 0 &= \frac{c\beta S^* I^*}{N^*} - (\mu+\alpha)I^*, \\ 0 &= \alpha I^* - (\mu+\nu)A^*. \end{cases} \tag{2.12}$$

Let

$$c\beta S^* I^*/N^* = \Gamma. \tag{2.13}$$

Substituting (2.13) into (2.12) gives,

$$S^* = \frac{\Lambda - \Gamma}{\mu}, \quad I^* = \frac{\Gamma}{(\alpha+\mu)}, \quad A^* = \frac{\alpha}{\mu+\nu}\frac{\Gamma}{\alpha+\mu}. \tag{2.14}$$

Substituting equation (2.14) into (2.12) results

$$\Gamma_0 = 0, \quad \text{or} \quad \Gamma^* = \frac{\Lambda(\mathcal{R}_0-1)(\mu+\alpha)}{(\mu+\alpha)(\mathcal{R}_0-1)+\mu}. \tag{2.15}$$

Substituting equation (2.15) into (2.14) gives

$$S_0 = \frac{\Lambda}{\mu}, \quad I_0 = 0, A_0 = 0,$$

or,

$$S^* = \frac{\Lambda}{(\mathcal{R}_0-1)(\mu+\alpha)+\mu}, I^* = \frac{\Lambda(\mathcal{R}_0-1)}{(\mathcal{R}_0-1)(\mu+\alpha)+\mu},$$
$$A^* = \frac{\Lambda\alpha(\mathcal{R}_0-1)}{(\mu+\gamma)\left((\mu+\alpha)(\mathcal{R}_0-1)+\mu\right)}.$$

Hence, the following theorem gives us the disease-free and endemic equilibrium.

**Theorem 2.1.5.** *The model given by the system* (2.1) *has a unique feasible disease-free equilibrium given by*

$$E_0 = (S_0, I_0, A_0) = \left(\frac{\Lambda}{\mu}, 0, 0\right).$$

*If* $\mathcal{R}_0 > 1$*, in addition to the disease-free equilibrium the model given by* (2.1) *has a unique endemic equilibrium point given by,*

$$E^* = (S^*, I^*, A^*) = \left(\frac{\Lambda}{(\mu+\alpha)(\mathcal{R}_0-1)+\mu}, \frac{\Lambda(\mathcal{R}_0-1)}{(\mu+\alpha)(\mathcal{R}_0-1)+\mu}, \frac{\Lambda(\mathcal{R}_0-1)\alpha}{(\mu+\nu)\left((\mu+\alpha)(\mathcal{R}_0-1)+\mu\right)}\right).$$

Hence the equilibrium with all states positive exists for $\mathcal{R}_0 > 1$.

### 2.1.4 Linear Stability of Equilibria

In the following section we show that the disease-free equilibrium of the model (2.1) is linearly (locally) stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

**Theorem 2.1.6.** *If $\mathcal{R}_0 < 1$, the disease-free equilibrium of the model given (2.1) is locally asymptotically stable.*

*Proof.* Substituting $N = S + I$ and linearising the system (2.1) gives the Jacobian matrix

$$J = \begin{bmatrix} -Q_1 - \mu & -Q_2 & 0 \\ Q_1 & Q_2 - (\mu + \alpha) & 0 \\ 0 & \alpha & -(\nu + \mu) \end{bmatrix},$$

where

$$Q_1 = \frac{c\beta I}{N}\left(1 - \frac{S}{N}\right) \quad \text{and} \quad Q_2 = \frac{c\beta S}{N}\left(1 - \frac{I}{N}\right).$$

Evaluating the above Jacobian matrix at the disease-free equilibrium gives

$$J_0 = \begin{bmatrix} -\mu & -c\beta & 0 \\ 0 & c\beta - (\mu + \alpha) & 0 \\ 0 & \alpha & -(\nu + \mu) \end{bmatrix},$$

where the characteristic polynomial of the Jacobian matrix is

$$(\mu + \lambda)(\mu + \nu + \lambda)(c\beta - (\mu + \alpha + \lambda)) = 0.$$

Solving the characteristic polynomial gives

$$\lambda_1 = -\mu, \quad \lambda_2 = -(\mu + \nu), \quad \lambda_3 = (\mu + \alpha)(\mathcal{R}_0 - 1). \tag{2.16}$$

Since for $\mathcal{R}_0 < 1$ all the eigenvalues are negative, which confirms that the disease-free equilibrium is linearly asymptotically stable.

□

**Theorem 2.1.7.** *If $\mathcal{R}_0 > 1$, the endemic equilibrium is locally asymptotically stable.*

*Proof.* By evaluating the Jacobian of the system (2.1) at the endemic equilibrium, we get

$$J_{E^*} = \begin{bmatrix} -Q_1^* - \mu & -Q_2^* & 0 \\ Q_1^* & Q_2^* - (\mu + \alpha) & 0 \\ 0 & \alpha & -(\nu + \mu) \end{bmatrix},$$

where

$$Q_1^* = \frac{c\beta I^*}{N^*}\Big(1 - \frac{S^*}{N^*}\Big) \quad \text{and} \quad Q_2^* = \frac{c\beta S^*}{N^*}\Big(1 - \frac{I^*}{N^*}\Big).$$

To get the eigenvalues, we need to find the roots of the characteristic polynomial

$$P(\lambda) = -(\nu+\mu+\lambda)\Big(\lambda^2 + \lambda(Q_1^* - Q_2^* + 2\mu + \alpha) + \mu(Q_1^* - Q_2^* + \mu + \alpha) + Q_1^*\alpha\Big) = 0, \quad (2.17)$$

which implies

$$-(\mu+\nu+\lambda) = 0 \quad \text{or} \quad \Big(\lambda^2 + \lambda(Q_1^* - Q_2^* + 2\mu + \alpha) + \mu(Q_1^* - Q_2^* + \mu + \alpha) + Q_1^*\alpha\Big) = 0.$$

It could be written as

$$(\mu+\nu+\lambda) = 0 \quad \text{or} \quad \lambda^2 + \lambda a_1 + a_2 = 0,$$

where

$$a_1 = Q_1^* - Q_2^* + 2\mu + \alpha, \quad a_2 = \mu(Q_1^* - Q_2^* + \mu + \alpha) + Q_1^*\alpha.$$

We can easily see that $Q_1^*$ and $Q_2^*$ are positive since the fractions $\frac{I^*}{N^*}$ and $\frac{S^*}{N^*}$ are less than unity.

From $Routh-Hurwitz$ criteria, we need to check the sign of $a_1$ and $a_2$: if they are positive, the endemic equilibrium is linearly stable. In other words we need to show

$$Q_1^* - Q_2^* + 2\mu + \alpha > 0 \quad \text{and} \quad \mu(Q_1^* - Q_2^* + \mu + \alpha) + Q_1^*\alpha > 0.$$

One can see that if

$$0 < (Q_1^* - Q_2^* + \mu + \alpha), \quad (2.18)$$

then $a_1 > 0$ and $a_2 > 0$. Substituting back the value of $Q_1$ and $Q_2$ into Equation (2.18) results,

$$\begin{aligned} -(\mu+\alpha) &< \frac{c\beta}{N^*}(I^* - S^*) \\ &< \frac{c\beta}{N^*}((\mathcal{R}_0 - 1)S^* - S^*) \\ &< \frac{c\beta}{\mathcal{R}_0}(\mathcal{R}_0 - 2) \\ &< (\mathcal{R}_0 - 2)(\mu+\alpha) \\ 1 &< \mathcal{R}_0. \end{aligned}$$

We have got that if $\mathcal{R}_0 > 1$, then the roots of characteristic polynomial given by equation (2.17) are with negative real parts. Consequently, the endemic equilibrium of the model (2.1) is linearly stable. □

### 2.1.5 Global Stability of Equilibria

For global stability of the disease-free equilibrium, we used *Lyapunov Function* as discussed in [59].

**Theorem 2.1.8.** *If $\mathcal{R}_0 \leqslant 1$, the disease-free equilibrium given by Theorem 2.1.5 is globally stable.*

*Proof.* Let V be a positive definite function given by

$$V(I(t)) = \frac{c\beta}{\mu+\alpha} I(t).$$

Hence,

$$\begin{aligned}
\frac{dV(I(t))}{dt} &= \frac{c\beta}{\mu+\alpha}\frac{dI(t)}{dt} \\
&= \frac{c\beta}{\mu+\alpha}\Big(\frac{c\beta S(t)I(t)}{N(t)} - (\mu+\alpha)I(t)\Big) \\
&= \frac{c\beta I(t)}{\mu+\alpha}\Big(\frac{c\beta S(t)}{N(t)} - (\mu+\alpha)\Big) \\
&= V(I(t))(\mathcal{R}(t)-1)(\mu+\alpha)
\end{aligned}$$

where

$$\mathcal{R}(t) = \frac{c\beta}{\mu+\alpha}\frac{S(t)}{N(t)}$$

is the reproduction function. The fact that $S(t) \leqslant N(t)$ implies, $\mathcal{R}(t) \leqslant \mathcal{R}_0$. Hence, $V' \leqslant 0$. As a result, $V'$ is negative definite and using La Salle principle, the disease-free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$. □

To discuss global stability of the endemic equilibrium given by Theorem 2.1.5, we use the *Duluc – Bendixson criterion*. *Duluc – Bendixson criterion* is stated for a system of two equations. Since the third equation in system (2.1) is decoupled, we can reduce the system to the first two equations and deduce the asymptotic behaviour of the third state variable from the above two. Hence, the invariant region for the reduced system is given by

$$\mathfrak{D}_1 = \left\{(S(t), I(t)) \in \mathbb{R}^2_+ : S(t) + I(t) \leqslant \frac{\Lambda}{\mu}\right\}.$$

**Lemma 2.1.9.** *Duluc-Bendixson criterion: Consider a dynamical system,*

$$\frac{dN_1(t)}{dt} = f_1\left(N_1(t), N_2(t)\right), \frac{N_2(t)}{dt} = f_2\left(N_1(t), N_2(t)\right), \tag{2.19}$$

*where $f_1$ and $f_2$ are continuously differentiable functions on some simply connected domain $\Omega \subset \mathbb{R}^2$ . If there is a function $\rho : \Omega \to \mathbb{R}$ such that,*

$$\frac{\partial\left(\rho f_1\right)\left(N_1, N_2\right)}{\partial N_1} + \frac{\partial\left(\rho f_2\right)\left(N_1, N_2\right)}{\partial N_2} > 0, \tag{2.20}$$

*then there will not be a closed orbit contained within $\Omega$.*

**Theorem 2.1.10.** *If $\mathcal{R}_0 > 1$, the endemic equilibrium $E^*$, given by Theorem 2.1.5, is globally stable.*

*Proof.* In our case, we have,

$$\begin{cases} \dfrac{dS(t)}{dt} = f_1(S(t), I(t)) = \Lambda - \dfrac{c\beta S(t)I(t)}{(I+S)} - \mu S(t), \\ \dfrac{dI(t)}{dt} = f_2(S(t), I(t)) = \dfrac{c\beta S(t)I(t)}{(I+S)} - (\mu+\alpha)I(t) \end{cases}$$

and

$$\Omega = \mathfrak{D}_1.$$

Define

$$\rho(S, I) = \frac{-1}{S(t)I(t)}.$$

Then we need to check whether (2.20) is satisfied or not, that means, we need to check if the following condition holds:

$$\frac{\partial}{\partial S}\left(\rho f_1\right) + \frac{\partial}{\partial I}\left(\rho f_2\right) > 0.$$

To this end, we have

$$\begin{aligned} \frac{\partial}{\partial S}(\rho f_1) + \frac{\partial}{\partial I}(\rho f_2) &= \frac{\partial}{\partial S}\left(\frac{\beta}{S+I} + \frac{\mu}{I} - \frac{\Lambda}{SI}\right) + \frac{\partial}{\partial I}\left(\frac{\mu+\alpha}{S} - \frac{\beta}{S+I}\right) \\ &= \frac{\Lambda}{IS^2} - \frac{\beta}{(S+I)^2} + \frac{\beta}{(S+I)^2} \\ &= \frac{\Lambda}{IS^2} > 0. \end{aligned}$$

By this we ensure that there will not be a closed orbit contained within $\Omega$. If there is no closed orbit, the solution should converge to one of the equilibrium points.

When $\mathcal{R}_0 > 1$, the system has two equilibrium points, the disease-free $E_0$ and endemic equilibrium $E^*$. Here the disease-free equilibrium is unstable from equation (2.16). Then the solution converges to the endemic equilibrium. In other words, the endemic equilibrium point is globally stable for $\mathcal{R}_0 > 1$. □

| Parameter | Description | Value | Reference |
|---|---|---|---|
| $\Lambda$ | Recruitment rate | 801403 | Estimated [52] |
| $\mu$ | Natural death rate | 1/34 | [65] |
| $c$ | Contact rate | 0.3 and 2.5 | Estimated |
| $\beta$ | Probability of infecting per contact | 0.12 | [65] |
| $\alpha$ | Progression rate | 0.125 | [9] |
| $\nu$ | Disease related death rate | 0.115 | [36] |

**Table 2.1.** Parameters used for the numerical simulations

### 2.1.6 Numerical Simulations

In the following section we illustrate the analytic results with numerical simulations. We use the *odesolver* package in Python. To determine the annual recruitment rate $\Lambda$, we used the method used by S. Kassa and A. Ouhinou [36]. The total population of South Africa in 1990 was $36,877,000$ with adult population of 56.3%. The annual rates of increase for adult population of South Africa were estimated to be 3.5% in the years $1990-1995$, 2.2% in the years $1995-2000$, and 0.8% in the years $2000-2005$ [52].

Average annual rate of increase becomes 2.16%. Whereas, annual rate of increase for adult population is the net increase which includes the death. However, $\Lambda$ is crude income to the population per year. Hence, we need to add individuals who were removed by natural death rate. We take the average life expectancy at birth to be 60 years. Therefore,

$$\Lambda = 36,877,000 \times 56\% \times (2.16\% + 1.7\%) = 801403.$$

The initial conditions are $S_0 = 36,877,000 \times 56\% = 20651120$ individuals, $I_0 = 144557$ individuals and $A_0 = 0$ individual. The parameter values used for the simulation are given in Table (2.1.6). The figure below, Fig.(2.2) is for $c = 0.3$. The corresponding value for the basic reproduction number is $\mathcal{R}_0 = 0.2$. The number of susceptible individuals increased and stabilised at the disease free equilibrium. Whereas the number of infected and AIDS progressed individuals goes to zero eventually, as we have obtained from mathematical discussion when $\mathcal{R}_0 < 1$.

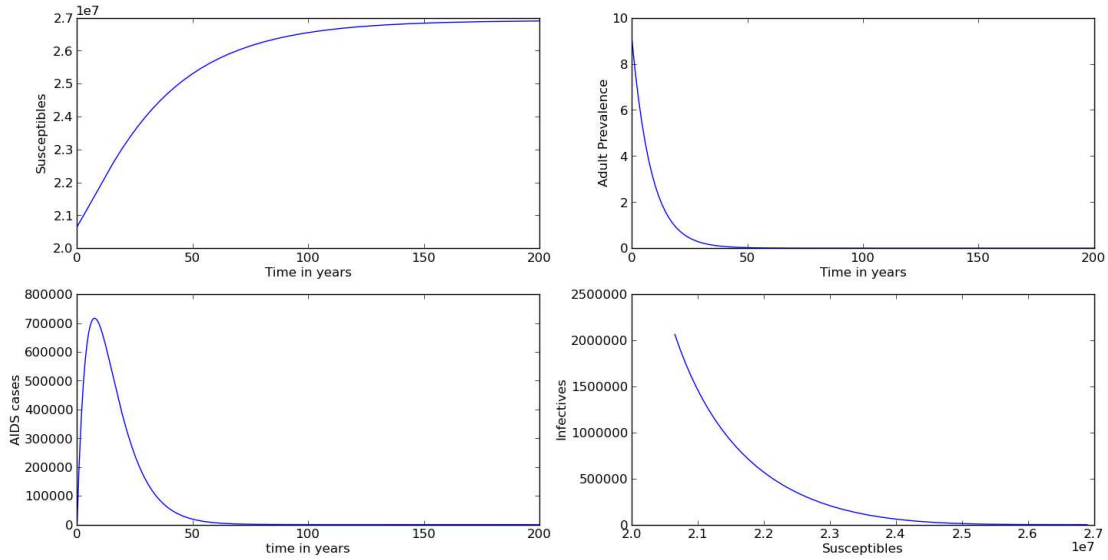


**Figure 2.2.** The dynamics of the disease when $\mathcal{R}_0 < 1$

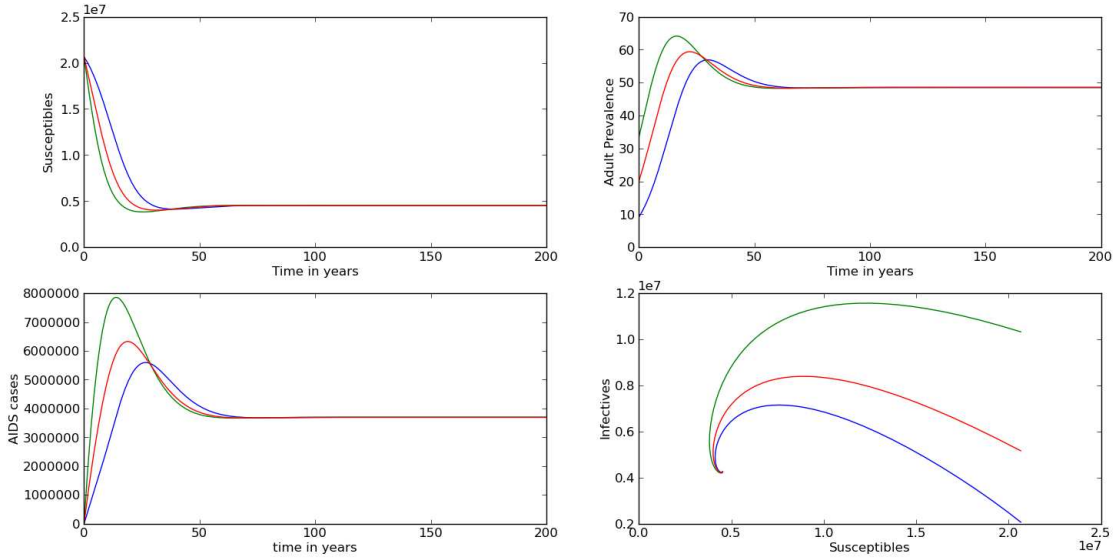


**Figure 2.3.** The dynamics of the disease when $\mathcal{R}_0 > 1$ with different $I_0$

Figure 2.3 represents the dynamics of the disease when $\mathcal{R}_0 = 1.9$ and $c = 2.5$. We observed that different initial conditions for infected individuals does not affect the stability. The

prevalence peaks with high value and the number of susceptible individuals decreases extremely, which is far from reality. To fit the model into data, we need to consider behaviour change as a result of mortality and morbidity of the disease. The simple model is widely used model for national projection of the disease prevalence. However, the projection is lower because the model disregards the initial epidemic growth phase [9]. Hence, we extend our work to staged progression model for better understanding of HIV/AIDS dynamics.

## 2.2 Staged Progression HIV Model

In this model, we take into account the different infection rates during the course of HIV infection. According to reports from WHO and many other resources, HIV positive individuals pass through three main stages of infection before progressing to full-blown AIDS [6, 9, 18, 64, 33]. Among these, the acute and symptomatic stages are responsible for a high rate of infection. According to Hollingsworth et.el. [24], the acute stage is 26 times more infectious than at the asymptomatic stage and the symptomatic (chronic) stage is 7 times more infectious as compared to the asymptomatic stage. In another study, Reuben et.al suggested that the acute stage is 10 times more infectious than the asymptomatic stage and the symptomatic stage is 5 times infectious than asymptomatic stage [55]. Nevertheless, the asymptomatic stage is by no means negligible due to its long life span. It lasts for an average of 8 - 12 years [50].

### 2.2.1 Model Formulation

In addition to the assumptions and descriptions of the basic model of Section 1, in this model the infected class is further divided into three classes according to the probability of infecting for susceptible individuals. Let $I_1(t), I_2(t)$ and $I_3(t)$ represent the number of infected individuals at the acute, asymptomatic and chronic stage, respectively. If susceptible individuals make sufficient contact with individuals in one of the stages, new infections will result, and all the newly infected individuals will join the acute stage. Once infected individuals join the acute stage, they will stay there until they either will be progressed to second and then third classes or they may die due to natural causes at each stage.

The parameters used in this model are, $\Lambda$ the recruitment rate of sexually matured individuals into a susceptible class, $c$ the contact rate of susceptible individuals with infected individuals, $\mu$ the per-capita natural death rate of individuals in all classes, irrespective of being susceptible or infected. Furthermore, $\beta_1, \beta_2$ and $\beta_3$ represent the transmission probability per effective contact of susceptibles with $I_1(t), I_2(t)$ and $I_3(t)$, respectively, $\alpha_1, \alpha_2$ and $\alpha_3$ are progression rates of infected individuals from classes $I_1(t)$, $I_2(t)$ and $I_3(t)$ to $I_2(t), I_3(t)$ and $A(t)$ respectively, whereas $\nu$ represents the per-capita disease-induced death rate per unit time.

The flow diagram of the infection will be summarized as follows:

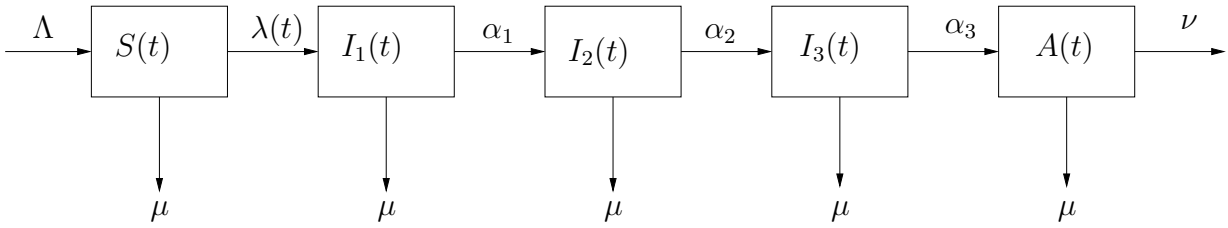


**Figure 2.4.** Diagrammatic representation of staged progression HIV/AIDS model

where $\lambda(t) = \dfrac{c}{N(t)}\Big(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3\Big)$ is the standard incidence function.

The resulting system of equations is given by:

$$\begin{cases} \dfrac{dS(t)}{dt} &= \Lambda - \dfrac{cS(t)}{N(t)}\Big(\beta_1 I_1(t) + \beta_2 I_2(t) + \beta_3 I_3(t)\Big) - \mu S(t), \\ \dfrac{dI_1(t)}{dt} &= \dfrac{cS(t)}{N(t)}\Big(\beta_1 I_1(t) + \beta_2 I_2(t) + \beta_3 I_3(t)\Big) - (\mu + \alpha_1) I_1(t), \\ \dfrac{dI_2(t)}{dt} &= \alpha_1 I_1(t) - (\mu + \alpha_2) I_2(t), \\ \dfrac{dI_3(t)}{dt} &= \alpha_2 I_2(t) - (\mu + \alpha_3) I_3(t), \\ \dfrac{dA(t)}{dt} &= \alpha_3 I_3(t) - (\mu + \nu) A(t), \end{cases} \tag{2.21}$$

where $N(t)$ represents the sexually active proportion of the population given by

$$N(t) = S(t) + I_1(t) + I_2(t) + I_3(t). \tag{2.22}$$

Total adult population is given by

$$P(t) = N(t) + A(t).$$

Since it could be done in the same way as the basic model, we left some of the details of the model described by system (2.21).

### 2.2.2 Basic Reproduction Number

By the method used in the previous section, the basic reproduction number of model (2.21) is given by

$$\mathcal{R}_0 = \mathcal{R}_1 + \mathcal{R}_2 + \mathcal{R}_3, \tag{2.23}$$

where

$$\mathcal{R}_1 = \frac{c\beta_1}{\mu+\alpha_1}, \mathcal{R}_2 = \frac{c\beta_2}{(\mu+\alpha_2)}\frac{\alpha_1}{(\mu+\alpha_1)}, \mathcal{R}_3 = \frac{c\beta_3}{(\mu+\alpha_3)}\frac{\alpha_1\alpha_2}{(\mu+\alpha_2)(\mu+\alpha_1)}, \tag{2.24}$$

which represents the average number of infected individuals as a contribution of each class $I_1(t), I_2(t)$ and $I_3(t)$ respectively.

The expression of $\mathcal{R}_0$ meets the discussion given by [15] for the staged progression model. The term $\frac{c\beta_1}{\mu+\alpha_1}$ represents the new infections resulted by infected individuals in the first stage $I_1$ where $\frac{1}{\mu+\alpha_1}$ is the average time that infected individuals spend in the first stage before progressing to the second stage or before dying due to natural causes.

From the second term of $\mathcal{R}_0$, $\frac{\alpha_1}{\mu+\alpha_1}$ represents the fraction of individuals who progressed from stage one and $\frac{c\beta_2}{\mu+\alpha_2}$ represents the new infections caused by the infected individuals in the second stage.

The last term, $\frac{c\beta_3}{\mu+\alpha_3}$, represents the number of new infections from infected individuals at the third stage, $\frac{\alpha_1\alpha_2}{(\mu+\alpha_1)(\mu+\alpha_2)}$ is a proportion of individuals progress to the third stage and $\frac{1}{\mu+\alpha_3}$ the average time an infected individual will stay in the third stage.

As a generalization in the staged progression models, the $i^{th}$ term in $\mathcal{R}_0$ is the product of the infection of individuals in stage $i$, the fraction of initially infected individuals surviving at least to stage $i$ and the average infectious period of an individual in stage $i$.

### 2.2.3 Equilibria

To find the steady states, we equate all the derivatives in the model in (2.21) to zero and we solve the following system for the state variables:

$$\begin{cases} 0 &= \Lambda - \dfrac{cS^*}{N^*}\Big(\beta_1 {I_1}^* + \beta_2 {I_2}^* + \beta_3 {I_3}^*\Big) - \mu S^*, \\ 0 &= \dfrac{cS^*}{N^*}\Big(\beta_1 {I_1}^* + \beta_2 {I_2}^* + \beta_3 {I_3}^*\Big) - (\mu+\alpha_1){I_1}^*, \\ 0 &= \alpha_1 {I_1}^* - (\mu+\alpha_2){I_2}^*, \\ 0 &= \alpha_2 {I_2}^* - (\mu+\alpha_3){I_3}^*, \\ 0 &= \alpha_3 {I_3}^* - (\mu+\nu)A^*, \end{cases} \tag{2.25}$$

and

$$N^* = S^* + {I_1}^* + {I_2}^* + {I_3}^*. \tag{2.26}$$

Adding the first two equations of (2.25) gives

$$S^* = \frac{\Lambda - (\mu+\alpha_1){I_1}^*}{\mu}. \tag{2.27}$$

From the third equation in system (2.25), we have

$${I_2}^* = \frac{\alpha_1}{(\mu+\alpha_2)}{I_1}^*. \tag{2.28}$$

Substituting equation (2.28) into the fourth equation in system (2.25) gives us

$${I_3}^* = \frac{\alpha_1\alpha_2}{(\mu+\alpha_2)(\mu+\alpha_3)}{I_1}^* \tag{2.29}$$

Substituting equation (2.29) into the fifth equation in system (2.25) gives

$$A^* = \frac{\alpha_1\alpha_2\alpha_3}{(\mu+\nu)(\mu+\alpha_2)(\mu+\alpha_3)}{I_1}^*. \tag{2.30}$$

From equation (2.26), we have

$$N^* = \frac{\Lambda}{\mu} - \frac{\alpha_1\alpha_2\alpha_3 I_1^*}{\mu(\mu+\alpha_2)(\mu+\alpha_3)}. \tag{2.31}$$

Substituting equations (2.27) up to (2.31) into the second equation in system (2.25) gives

$$I_1 = 0 \quad \text{or} \quad {I_1}^* = \frac{\Lambda(\mathcal{R}_0 - 1)}{(\mu+\alpha_1)\,(\mathcal{R}_0 - k)}, \tag{2.32}$$

where

$$k = \frac{\alpha_1\alpha_2\alpha_3}{(\mu+\alpha_1)(\mu+\alpha_2)(\mu+\alpha_3)}.$$

By substituting equation (2.32) into equation(2.27) up to equation (2.31) we have

$$E_0 = (S_0, I_1, I_2, I_3, A_0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right) \quad \text{or} \quad E^* = (S^*, {I_1}^*, {I_2}^*, {I_3}^*, A^*)$$

where

$$\begin{cases} S^* &= \dfrac{\Lambda(1-k)}{\mu(\mathcal{R}_0-k)}, \\ {I_1}^* &= \dfrac{\Lambda(\mathcal{R}_0-1)}{(\mu+\alpha_1)}, \\ {I_2}^* &= \dfrac{\Lambda\alpha_1(\mathcal{R}_0-1)}{(\mathcal{R}_0-k)(\mu+\alpha_1)(\mu+\alpha_2)}, \\ {I_3}^* &= \dfrac{\Lambda(\mathcal{R}_0-1)k}{(\mathcal{R}_0-k)\alpha_3}, \\ A^* &= \dfrac{\Lambda(\mathcal{R}_0-1)k}{(\mathcal{R}_0-k)(\mu+\nu)}. \end{cases} \tag{2.33}$$

Then we have the following result:

**Theorem 2.2.1.** *i) If $\mathcal{R}_0 < 1$, the model given by the system (2.21) has a unique feasible disease-free-equilibrium given by,*

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right).$$

*ii) If $\mathcal{R}_0 > 1$, in addition to the disease-free equilibrium the model given (2.21) has a unique endemic equilibrium point given by $E^* = (S^*, {I_1}^*, {I_2}^*, {I_3}^*, A^*)$, given by (2.33).*

### 2.2.4 Local Stability of Equilibria

By linearising the model (2.21) around the disease-free equilibrium given by Theorem 2.2.1, we have the following Jacobian matrix:

$$J_{E_0} = \begin{bmatrix} -\mu & -c\beta_1 & -c\beta_2 & -c\beta_3 & 0 \\ 0 & c\beta_1-(\mu+\alpha_1) & c\beta_2 & c\beta_3 & 0 \\ 0 & \alpha_1 & -(\mu+\alpha_2) & 0 & 0 \\ 0 & 0 & \alpha_2 & -(\mu+\alpha_3) & 0 \\ 0 & 0 & 0 & \alpha_3 & -(\mu+\nu) \end{bmatrix}$$

The corresponding eigenvalues are

$$\lambda = -\mu, \lambda = -(\mu + \nu),$$

and

$(c\beta_1 - (\mu + \alpha_1 + \lambda))\,(\mu + \alpha_2 + \lambda)(\mu + \alpha_3 + \lambda) + \alpha_1\,(c\beta_2(\mu + \alpha_3 + \lambda) + c\beta_3\alpha_2) = 0$, where as $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$,

where

$$\begin{aligned}
a_1 &= (\mu + \alpha_1) + (\mu + \alpha_2) + (\mu + \alpha_3) - c\beta_1, \\
a_2 &= (\mu + \alpha_2)(\mu + \alpha_3))\,((\mu + \alpha_1) - c\beta_1) + c\alpha_1\beta_2 + (\mu + \alpha_2)(\mu + \alpha_3), \\
a_3 &= \alpha_1 c\beta_2(\mu + \alpha_3) - \alpha_1\alpha_2 c\beta_3 - (\mu + \alpha_3)(\mu + \alpha_2)\,((\mu + \alpha_1) - c\beta_1)\,.
\end{aligned}$$

From $Routh - Hurwitz\ criteria$ of third order polynomials, we need to check that $a_1 > 0, a_3 > 0$ and $a_1 a_2 > a_3$ so that all eigenvalues will have negative real parts.

$$\begin{aligned}
&a_1 > 0 \Rightarrow \\
&(\mu + \alpha_1) + (\mu + \alpha_2) + (\mu + \alpha_3) - c\beta_1 > 0 \Rightarrow \\
&(\mu + \alpha_2) + (\mu + \alpha_3) > c\beta_1 - (\mu + \alpha_1), \\
&(\mu + \alpha_2) + (\mu + \alpha_3) > (\mu + \alpha_1)(\mathcal{R}_1 - 1).
\end{aligned}$$

Since at the disease-free equilibrium $\mathcal{R}_0 < 1$, $\mathcal{R}_1 < 1$. Hence, the inequality

$$(\mu + \alpha_2) + (\mu + \alpha_3) > (\mu + \alpha_1)(\mathcal{R}_1 - 1)$$

holds.

Therefore $a_1 > 0$.

$$\begin{aligned}
&a_3 > 0 \Rightarrow \\
&\alpha_1 c\beta_2(\mu + \alpha_3) - \alpha_1\alpha_2 c\beta_3 - (\mu + \alpha_3)(\mu + \alpha_2)\Big((\mu + \alpha_1) - c\beta_1\Big) > 0 \Rightarrow \\
&(1 - \mathcal{R}_1) - \mathcal{R}_2 + \mathcal{R}_3 > 0, \\
&(1 - \mathcal{R}_1) > \mathcal{R}_2 - \mathcal{R}_3.
\end{aligned}$$

Whereas, from the fact that at the disease-free equilibrium $\mathcal{R}_0 < 1$,

$$\begin{aligned} \mathcal{R}_0 &= \mathcal{R}_1 + \mathcal{R}_2 + \mathcal{R}_3 < 1, \\ & \mathcal{R}_2 + \mathcal{R}_3 < 1 - \mathcal{R}_1, \\ & 1 - \mathcal{R}_1 > \mathcal{R}_2 + \mathcal{R}_3. \end{aligned}$$

Therefore

$$(1 - \mathcal{R}_1) > \mathcal{R}_2 - \mathcal{R}_3$$

holds and as a result, $a_3 > 0$. We still need the condition $a_1 a_2 > a_3$ so that the disease-free equilibrium to be locally stable which is not easy to show from the above expression. The numerical simulation will help to asses the linear stability of the disease-free equilibrium in the following section.

To investigate the local stability of the endemic equilibrium, the linearised system of the model (2.21) around the endemic equilibrium given by Theorem 2.2.1 results in

$$J_{E^*} = \begin{bmatrix} -E_1 - \mu & -E_2 & -E_3 & -E_4 & 0 \\ E_1 & E_2 - (\mu + \alpha_1) & E_3 & E_4 & 0 \\ 0 & \alpha_1 & -(\mu + \alpha_2) & 0 & 0 \\ 0 & 0 & \alpha_2 & -(\mu + \alpha_3) & 0 \\ 0 & 0 & 0 & \alpha_3 & -(\mu + \nu) \end{bmatrix}$$

where

$$\begin{aligned} E_1 = \lambda^*(1 - \frac{S^*}{N^*}), \lambda^* &= \frac{{I_1}^*}{N^*}(\mathcal{R}_0(\mu + \alpha_1)), E_2 = c\beta_1 \frac{S^*}{N^*}(1 - \frac{I_1^*}{N^*}), \\ & E_3 = c\beta_2 \frac{S^*}{N^*}(1 - \frac{I_2^*}{N^*}), E_4 = c\beta_3 \frac{S^*}{N^*}(1 - \frac{I_3^*}{N^*}) \end{aligned}$$

We can see that the expressions $\lambda^*, E_1, E_2, E_3$ and $E_4$ are all positive. To find the eigenvalues of the Jacobian matrix we need to determine $\lambda$ from the expression

$$-(\mu + \nu + \lambda)\Big( - (E_1 + \mu + \lambda)\det(A_1) - E_1 \det(A_2)\Big) = 0,$$

where

$$A_1 = \begin{bmatrix} E_2 - \lambda & E_3 & E_4 \\ E_2 - (\mu + \alpha_1) & -(\mu + \alpha_2 + \lambda) & 0 \\ 0 & \alpha_2 & -(\mu + \alpha_3 + \lambda) \end{bmatrix}$$

and

$$A_2 = \begin{bmatrix} -E_2 & -E_3 & -E_4 \\ E_2 - (\mu + \alpha_1) & -(\mu + \alpha_2 + \lambda) & 0 \\ 0 & \alpha_2 & -(\mu + \alpha_3 + \lambda) \end{bmatrix}.$$

This yields

$$-(\mu + \nu + \lambda)(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4) = 0,$$

where

$$\begin{aligned}
a_1 &= E_1 + E_2 + 3\mu + \alpha_2 + \alpha_3, \\
a_2 &= (E_1 + E_2 + \mu)(\alpha_2 + 2\mu + \alpha_3) + E_3(E_2 - (\mu + \alpha_1)) + \mu(\alpha_2 + \alpha_3 + \mu) + E_2\mu + \alpha_2\alpha_3, \\
a_3 &= E_1(\mu(\alpha_2 + \alpha_2 + \mu) + \alpha_2\alpha_3) + E_3(E_2 - (\mu + \alpha_1))(2\mu + \alpha_3) \\
&\quad + \mu\Big(E_2(\alpha_2 + \mu + \alpha_3) + 1 + (E_2 + \mu)(\alpha_2 + \alpha_3)\Big) + \alpha_2\alpha_3 - E_4\alpha_2(E_2 - (\mu + \alpha_1)) \\
a_4 &= E_2\mu^3 + E_2\mu\alpha_2\alpha_3 + E_2\mu^2(\alpha_2 + \alpha_3) + E_3\mu(E_2 - (\mu + \alpha_1))(\mu + \alpha_3) - \\
&\quad E_4\mu\alpha_2(E_2 - (\mu + \alpha_1))
\end{aligned}$$

One of the eigenvalues is given by $\lambda = -(\mu + \nu)$.

To determine the sign of the other eigenvalues by using $Routh - Hurwitz$ criteria, we need to check the condition $a_1 > 0, a_3 > 0, a_4 > 0$ and $a_1a_2a_3 > a_2 + a_2a_4$.

But it is not obvious. For that reason we use the numerical simulations to show the local stability of the endemic equilibrium in the following subsection.

### 2.2.5 Numerical Simulations

The *Odesolver* package is used in Python for the numerical simulations. The parameter values are given in Table (2.3). The initial conditions for our numerical solutions are $S_0 = 20651120$, $I_{1,0} = 144557, I_{2,0} = 0, I_{3,0} = 0$ and $A_0 = 0$.

| Parameter | Description |
|---|---|
| $\Lambda$ | Recruitment rate |
| $\mu$ | Natural death rate |
| $c$ | contact rate |
| $\beta_1$ | Probability of infecting per contact in $I_1$ |
| $\beta_2$ | Probability of infecting per contact in $I_2$ |
| $\beta_3$ | Probability of infecting per contact in $I_3$ |
| $\alpha_1$ | Rate of progression to $I_2$ |
| $\alpha_2$ | Rate of progression to $I_3$ |
| $\alpha_3$ | Rate of progression to $A$ |
| $\nu$ | Disease related death rate |

**Table 2.2.** Description of parameters used in the model

M. Reuben et.al. suggested the relation among $\beta_1, \beta_2$ and $\beta_3$ as, $\beta_1 = 10\beta_2$ and $\beta_3 = 5\beta_2$ [55], whereas a study by Hollingsworth et.al. give $\beta_2 = 0.1$, [24]. By combining the two we get the values of $\beta_1$ and $\beta_3$ as given in Table 2.3.

| Parameter | Value | Reference |
|---|---|---|
| $\Lambda$ | 801403 | Estimated from [52] |
| $\mu$ | 1/34 | [65] |
| $c$ | c=0.3 and 2.5 | Fitted |
| $\beta_1$ | 1.0 | [24, 55] |
| $\beta_2$ | 0.1 | [24] |
| $\beta_3$ | 0.5 | [24, 55] |
| $\alpha_1$ | 8.7 | [9] |
| $\alpha_2$ | 0.167 | [9] |
| $\alpha_3$ | 0.5 | [9] |
| $\nu$ | 0.115 | [36] |

**Table 2.3.** Parameter values used for the simulation

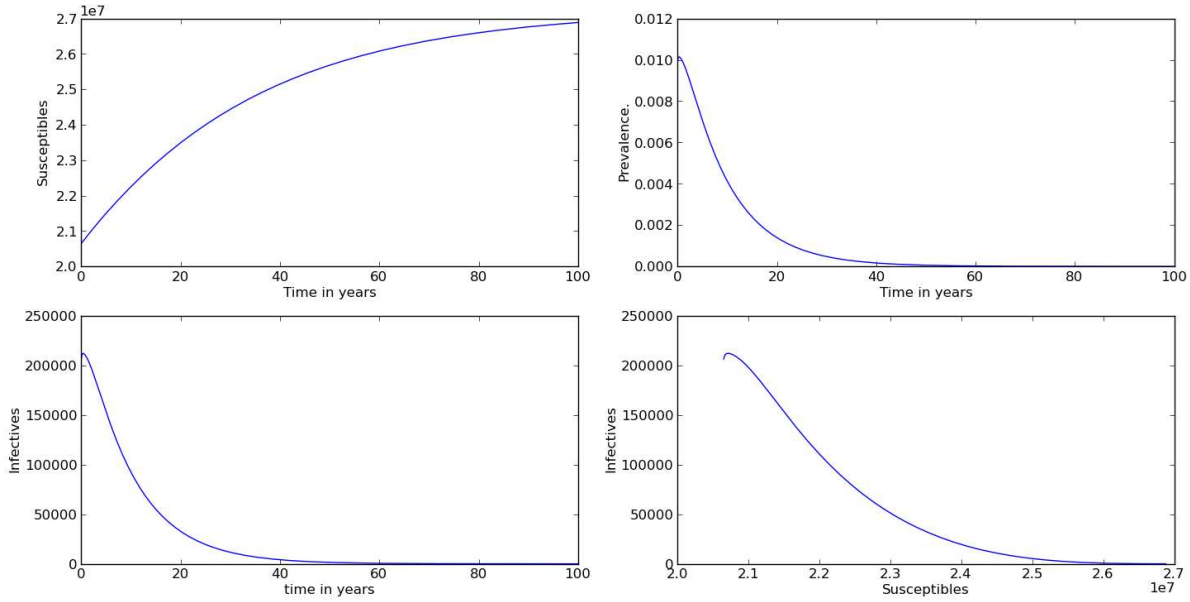


**Figure 2.5.** The dynamics of the disease when $\mathcal{R}_0 < 1$

Figure 2.5 depicts the dynamics of the disease with $c = 0.3$, $\mathcal{R}_0 = 0.6$ and other parameters as given in Table 2.3.

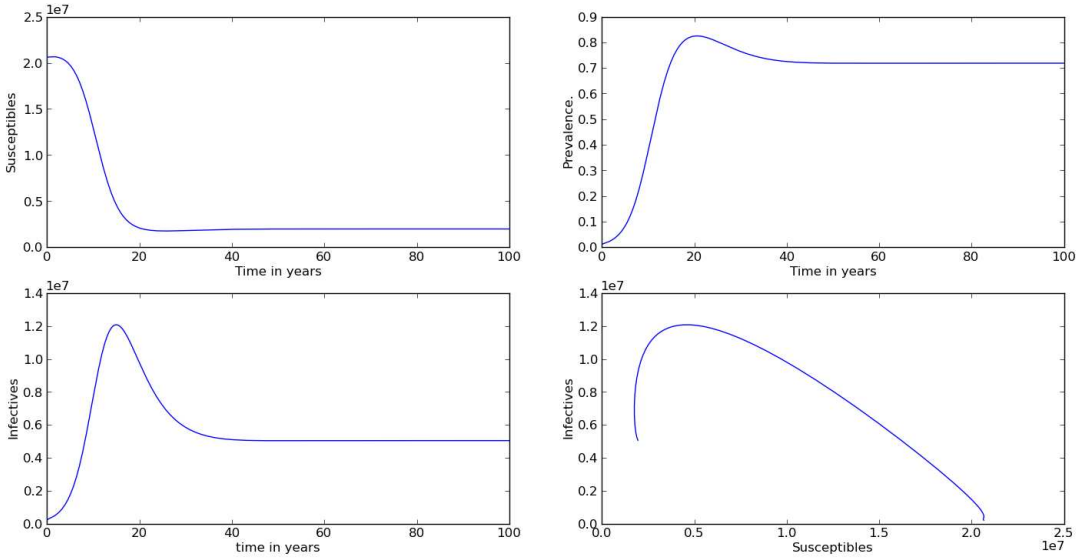


**Figure 2.6.** The dynamics of the disease when $\mathcal{R}_0 > 1$

Figure 2.6 shows the dynamics of the disease with $c = 2$ and $\mathcal{R}_0 = 4.8$. The prevalence peak and the time of the peak are not exactly the same as the national prevalence since we considered that there is no change of behaviour as a result of hazards due to the disease.

## 2.3 Summary

In this chapter we have seen two HIV compartmental models as a background. The first model is a classical model which assumes the infected class is homogeneous throughout the course of the infection. The second model considers three classes of infected individuals, having different probability of infecting and rate of progression to the next stage. Numerical results gave us that high peak of the early infection does not affect the stability of the system, rather it changes the speed with which the disease spreads. Stability analysis and numerical simulations are presented for both models.

The staged progression model presented in (2.21) is better than the simple model (2.1) by considering different infection for the three stages of infection. However, it considers that infection is constant in each stages, which is not the case. In addition, infected individuals

are supposed to pass through all the three infectious stages before progressing to AIDS. In reality, infected individuals may progress to AIDS from one of the three classes, not necessarily from the third stage. For these and other reasons (which we explain in the next chapter), we considered a mathematical model of HIV/AIDS dynamics structured by age of infection.

# Chapter 3

# Model of HIV/AIDS Transmission Structured by age of infection

Research shows that infecting varies as age of HIV infection increases [18, 21, 64]. In addition to the assumptions and descriptions of the above two models, in this chapter $I(t)$ is divided into infinitely many classes according to the probability of infecting per effective contact. In the model (2.21), infected individuals are assumed to progress to each class of infection before progressing to AIDS. In actual fact, infected individuals may progress to AIDS at any time after infection, and not necessarily only after passing through all the stages of infection. For that reason this model allows fast progression of infected individuals into the AIDS class at any time of infection with a specific progression rate.

## 3.1 Model Formulation

Let $i(t, a)$ be an integrable function which represents the age-density function of infected individuals at time $t$ and age of infection $a \in [0, a^+]$ where $a^+$ is the maximum time infected individuals will spend in the infectious class before they die or progress to AIDS. We will be using $a \in [0, \infty)$ for convenience of a mathematical description, knowing that $i(t, a) \simeq 0$ for $a > a^+$ since $a^+$ is the maximum time infected individuals can survive in the infectious class. The total number of infected individuals at a given time $t$, $I(t)$, is the sum of all infected individuals in the infectious class with different ages of infection. Mathematically,

it can be written as

$$I(t) = \int_0^\infty i(t,a)da. \tag{3.1}$$

Let the probability of infecting per effective contact with infected individuals with age of infection $a$ be $\beta(a)$. The infecting of infected individuals is highly connected to the viral load in their blood [48]. Thus, in average the infecting of an infected individual follows the same slope as the viral dynamics in the plasma, see Figure (1.1). The functional value of $\beta(a)$ quickly increases after few days of infection to reach its maximum. After a couple of weeks, it decreases sharply to a lower level from which it starts increasing slightly for 8-10 years in average. Then this phase is followed by a late plateau before AIDS symptoms develop (see Fig.(1.2) from [55] and [24, 32, 51]). In what follows we assume that $\beta(a)$ is a bounded function and we take

$$\hat{\beta} := \sup_{a \geqslant 0} \beta(a). \tag{3.2}$$

Interaction between infected individuals in class $I(t)$ and susceptible individuals in class $S(t)$ with sufficient contact per unit time will result new infections, which is in-flow for class $I(t)$. The number of new infections at time $t$ who will be removed from susceptible class, which is represented in our model by infected individuals with age of infection equals to zero, is given by:

$$i(t,0) = \frac{cS(t)}{N(t)} \int_0^\infty \beta(a) i(t,a) da, \tag{3.3}$$

where $c$ is the contact rate and $N(t)$ is the sexually active proportion of the population. From the expression (3.3), we separate the following quantity

$$\lambda(t) = \frac{c}{N(t)} \int_0^\infty \beta(a) i(t,a) da \tag{3.4}$$

which is known as the force of infection. As a result, the number of susceptible individuals can vary according to the following scenario

$$\frac{dS(t)}{dt} = \Lambda - \frac{cS(t)}{N(t)} \int_0^\infty \beta(a) i(t,a) da - \mu S(t),$$

where $\Lambda$ and $\mu$ are as described in the above two models. Infected individuals who have survived $a$ units of time after infection will progress to the AIDS class with a rate of

progression $\alpha(a)$. As $a$ increases, $\alpha(a)$ also increases because of the increment in the viral load and weakness of the immune system [32]. The number of individuals who progress to AIDS class at time $t$ is given by $\int_0^\infty \alpha(a)i(t,a)da$.

Whereas the number of deaths at time $t$ in the class of infected individuals $I(t)$ is given by

$$\int_0^\infty \mu i(t,a)da = \mu I(t). \tag{3.5}$$

The following diagram summarizes the dynamics of the disease, where $\lambda(t)$ is as given in equation (3.4).

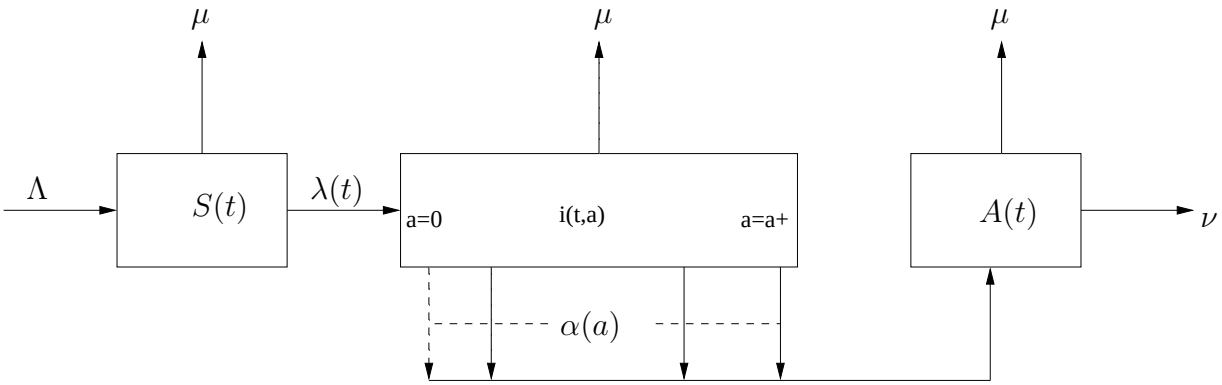


**Figure 3.1.** Diagrammatic representation of HIV model structured by age of infection

As the above diagram shows, the out-flow of infected individuals from the infected class is either due to natural death or due to the progression to AIDS.

Hence, the variation of infected individuals with age of infection $a$ at time $t$ is given by:

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) i(t,a) = -(\mu + \alpha(a))i(t,a).$$

The number of individuals who progress to AIDS, who are in class $A(t)$, are those who are removed from class $I(t)$ with rate of progression $\alpha(a)$. Individuals in class $A(t)$ will leave

the class due to both natural and AIDS related deaths. Hence, the number of individuals in class $A(t)$ varies as follows:

$$\frac{dA(t)}{dt} = \int_0^\infty \alpha(a)i(t,a)da - (\mu+\nu)A(t).$$

Then, the age of infection structured mathematical model for HIV/AIDS dynamics is given by the following system of ordinary differential equations mixed with partial differential equation having non-local boundary condition:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \dfrac{cS(t)}{N(t)}\displaystyle\int_0^\infty \beta(a)i(t,a)da - \mu S(t), \\ \Big(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\Big)i(t,a) = -(\mu+\alpha(a))i(t,a), \\ i(t,0) = \dfrac{cS(t)}{N(t)}\displaystyle\int_0^\infty \beta(a)i(t,a)da, \\ \dfrac{dA(t)}{dt} = \displaystyle\int_0^\infty \alpha(a)i(t,a)da - (\mu+\nu)A(t), \end{cases} \tag{3.6}$$

with initial conditions, $S(0) \geqslant 0, i(0,a) = \phi(a) \geqslant 0$ for $a \geqslant 0$ and $A(0) \geqslant 0$.

## 3.2 Solutions Along Characteristic Lines

Here, we use the characteristic method to solve the $PDE$ as $ODE$, as presented in [12].

Define $\tilde{i}(h) = i(t_0+h, a_0+h)$, for constant values of $t_0 > 0$ and $a_0 > 0$. Hence, the second equation of (3.6) can be written as,

$$\frac{d\tilde{i}(h)}{dh} = -\left(\mu + \alpha(a_0+h)\right)\tilde{i}(h). \tag{3.7}$$

Solving (3.7) explicitly, we get

$$\tilde{i}(h) = \tilde{i}(0)\exp\left(-\mu h - \int_0^h \alpha(r)dr\right),$$
$$i(t_0+h, a_0+h) = i(t_0,a_0)\exp\left(-\mu h - \int_0^h \alpha(r)dr\right).$$

For $a \leqslant t$, setting $(t_0, a_0) = (t-a, 0)$ and $h = a$, gives the following expression:

$$i(t,a) = i(t-a,0)\exp\left(-\mu a - \int_0^a \alpha(r)dr\right).$$

For $a > t$, setting $(t_0, a_0) = (0, a - t)$ and $h = t$, we get

$$i(t,a) = i(0,a-t)\exp\left(-\mu t - \int_{a-t}^{a}\alpha(r)dr\right).$$

Hence, we obtained the following solution for the second equation of system (3.6) along characteristic lines,

$$i(t,a) = \begin{cases} i(0,a-t)\exp\left(-\mu t - \int_{a-t}^{a}\alpha(r)dr\right), & 0 < t < a, \\ i(t-a,0)\exp\left(-\mu a - \int_{0}^{a}\alpha(r)dr\right), & t \geqslant a > 0. \end{cases} \tag{3.8}$$

We denote $\pi(a) = \exp\left(-\mu a - \int_0^a \alpha(r)dr\right)$, which gives the survival probability of infected individuals up to $a$ units of time after infection before progressing to the AIDS class. For simplicity of notation, let $B(t) := i(t,0)$, and $\phi(a) := i(0,a)$. Hence, (3.8) can be rewritten as:

$$i(t,a) = \begin{cases} \phi(a-t)\dfrac{\pi(a)}{\pi(a-t)}, & 0 \leqslant t \leqslant a, \\ B(t-a)\pi(a), & t \geqslant a \geqslant 0. \end{cases} \tag{3.9}$$

## 3.3 The Model with Particular Cases

In this section, we discuss the model (3.6) with some restricted assumptions. Under different assumptions, the model could be written as the basic model (2.1), staged progression model (2.21) with a discrete delay and also as a system of differential equations with a distributed delay.

### 3.3.1 When Infected Class is Homogeneous

The objective of this subsection is to derive the basic model presented (2.1) from the age of infection structured model (3.6) under the assumptions: $\beta(a) = \beta$ (infected individuals have a constant infecting) and $\alpha(a) = \alpha$ (uniform progression to AIDS).

**Proposition 3.3.1.** *If the probability of infecting $\beta(a)$ and the rate of progression $\alpha(a)$ are constants, then the model presented (3.6) can be written as the basic model (2.1).*

*Proof.* Using the above assumptions, the third equation can be written as

$$\begin{aligned} i(t,0) &= \frac{cS(t)}{N(t)} \int_0^\infty \beta i(t,a)da \\ &= \frac{c\beta S(t)}{N(t)} I(t). \end{aligned}$$

Hence, the first equation of (3.6) becomes

$$\frac{dS(t)}{dt} = \Lambda - \frac{c\beta S(t)}{N(t)} I(t) - \mu S(t). \tag{3.10}$$

Differentiating (3.1) and substituting the second equation of (3.6) and equation (3.5) into equation (3.1) gives

$$\begin{aligned} \frac{dI(t)}{dt} &= \frac{d}{dt}\int_0^\infty i(t,a)da = \int_0^\infty \frac{\partial}{\partial t} i(t,a)da \\ &= -\int_0^\infty \left(\frac{\partial}{\partial a} + \mu + \alpha\right) i(t,a)da \\ &= i(t,0) - \int_0^\infty (\alpha+\mu) i(t,a)da \\ &= \frac{c\beta S(t) I(t)}{N(t)} - (\mu+\alpha) I(t). \end{aligned} \tag{3.11}$$

To get the expression for the variation of the number of individuals in the AIDS class, we consider the fourth equation of (3.6),

$$\frac{dA(t)}{dt} = \int_0^\infty \alpha(a) i(t,a)da - (\mu+\nu)A(t) = \alpha I(t) - (\mu+\nu)A(t). \tag{3.12}$$

From the expressions (3.10), (3.11) and (3.12), we get the system of ordinary differential equations given in (2.1). □

### 3.3.2 Model with Three Stages of Infection

In this subsection, we suppose that the class of infected individuals is further divided into three classes $I_1, I_2$ and $I_3$, corresponding to the three stages of infection, see [55]. Individuals in each class have corresponding probabilities of infecting and progression rates to AIDS class. The assumptions of this subsection are summarised in Table (3.1).

| Class | Age of infection | infection | Progression rate to AIDS |
|---|---|---|---|
| $I_1$ | between 0 and $a_1$ | $\beta_1$ | $\alpha_1$ |
| $I_2$ | between $a_1$ and $a_2$ | $\beta_2$ | $\alpha_2$ |
| $I_3$ | between $a_2$ and $a^+$ | $\beta_3$ | $\alpha_3$ |

**Table 3.1.** Assumptions of a three-staged model

Using assumptions of Table (3.1), the total number of infected individuals at time $t$ in each infectious class is:

$$I_1(t) = \int_0^{a_1} i(t,a)da, I_2(t) = \int_{a_1}^{a_2} i(t,a)da, I_3(t) = \int_{a_2}^{\infty} i(t,a)da. \tag{3.13}$$

The force of infection given in equation (3.4) can be rewritten as

$$\begin{aligned}
\lambda(t) &= \frac{c}{N(t)} \int_0^{\infty} \beta(a) i(t,a) da \\
&= \frac{c}{N(t)} \left( \int_0^{a_1} \beta(a) i(t,a) da + \int_{a_1}^{a_2} \beta(a) i(t,a) da + \int_{a_2}^{\infty} \beta(a) i(t,a) da \right) \\
&= \frac{c}{N(t)} \left( \beta_1 \int_0^{a_1} i(t,a) da + \beta_2 \int_{a_1}^{a_2} i(t,a) da + \beta_3 \int_{a_2}^{\infty} i(t,a) da \right) \\
&= \frac{c}{N(t)} \left( \beta_1 I_1(t) + \beta_2 I_2(t) + \beta_3 I_3(t) \right).
\end{aligned}$$

Hence, the first equation of (3.6) becomes

$$\frac{dS(t)}{dt} = \Lambda - \lambda(t) S(t) - \mu S(t). \tag{3.14}$$

From equation (3.13) and the second equation of (3.6), we have

$$\begin{aligned}
\frac{dI_1(t)}{dt} &= \frac{d}{dt} \int_0^{a_1} i(t,a) da = \int_0^{a_1} \frac{\partial}{\partial t} i(t,a) da \\
&= -\int_0^{a_1} \Big( \frac{\partial}{\partial a} + \mu + \alpha(a) \Big) i(t,a) da \\
&= -\int_0^{a_1} \frac{\partial}{\partial a} i(t,a) da - \int_0^{a_1} (\mu + \alpha(a)) i(t,a) da \\
&= i(t,0) - i(t,a_1) - (\mu + \alpha_1) I_1(t).
\end{aligned}$$

Using solutions along characteristic lines for large values of $t$ ($t > a$), one can get

$$\frac{dI_1(t)}{dt} = \lambda(t) S(t) - \lambda(t-a_1) S(t-a_1) \pi_1 - (\mu + \alpha_1) I_1(t), \tag{3.15}$$

where $\pi_1 = \exp -(\mu + \alpha_1)\, a_1$ is the survival probability of infected individuals up to $a_1$ units of time in class $I_1(t)$ before progressing to AIDS.

Similarly,

$$\begin{aligned}\frac{dI_2(t)}{dt} &= \frac{d}{dt}\int_{a_1}^{a_2} i(t,a)da = \int_{a_1}^{a_2}\frac{\partial}{\partial t}i(t,a)da \\ &= -\int_{a_1}^{a_2}\Big(\frac{\partial}{\partial a}+\mu+\alpha(a)\Big)i(t,a)da \\ &= -\int_{a_1}^{a_2}\frac{\partial}{\partial a}i(t,a)da - \int_{a_1}^{a_2}\Big(\mu+\alpha(a)\Big)i(t,a)da \\ &= i(t,a_1) - i(t,a_2) - (\mu+\alpha_2)I_2(t).\end{aligned}$$

From the solutions along characteristic lines for large $t$ ($t > a_2$), we have

$$\frac{dI_2(t)}{dt} = \lambda(t-a_1)S(t-a_1)\pi_1 - \lambda(t-a_2)S(t-a_2)\pi_1\pi_2 - (\mu+\alpha_2)I_2(t), \tag{3.16}$$

where $\pi_2 = \exp -(\mu+\alpha_2)(a_2-a_1)$ is the survival probability of infected individuals up to age of infection $a_2$ after progressing to $I_2(t)$ having age of infection $a_1$. A similar procedure gives us

$$\frac{dI_3(t)}{dt} = \lambda(t-a_2)S(t-a_2)\pi_1\pi_2 - (\mu+\alpha_3)I_3(t). \tag{3.17}$$

Furthermore, applying assumptions of Table 3.1 for the fourth equation of (3.6) gives

$$\begin{aligned}\frac{dA(t)}{dt} &= \int_0^{\infty}\alpha(a)i(t,a)da - (\mu+\nu)A(t), \\ &= \int_0^{a_1}\alpha(a)i(t,a)da + \int_{a_1}^{a_2}\alpha(a)i(t,a)da + \int_{a_2}^{\infty}\alpha(a)i(t,a)da - (\mu+\nu)A(t), \\ &= \alpha_1 I_1(t) + \alpha_2 I_2(t) + \alpha_3 I(3) - (\mu+\nu)A(t).\end{aligned} \tag{3.18}$$

From equations (3.14 - 3.18), the following result holds.

**Proposition 3.3.2.** *Under the assumption in Table 3.1 the model* (2.21) *is equivalent to the following staged progression model with fast-AIDS progression:*

$$\begin{cases} \frac{dS(t)}{dt} &= \Lambda - \lambda(t)S(t) - \mu S(t), \\ \frac{dI_1(t)}{dt} &= \lambda(t)S(t) - \lambda(t-a_1)S(t-a_1)\pi_1 - (\mu+\alpha_1)I_1(t), \\ \frac{dI_2(t)}{dt} &= \lambda(t-a_1)S(t-a_1)\pi_1 - \lambda(t-a_2)S(t-a_2)\pi_1\pi_2 - (\mu+\alpha_2)I_2(t), \\ \frac{dI_3(t)}{dt} &= \lambda(t-a_2)S(t-a_2)\pi_1\pi_2 - (\mu+\alpha_3)I_3(t), \\ \frac{dA(t)}{dt} &= \alpha_1 I_1(t) + \alpha_2 I_2(t) + \alpha_3 I(3) - (\mu+\nu)A(t). \end{cases} \tag{3.19}$$

The expression $\lambda(t-a_1)S(t-a_1)\pi_1$ represents the number of infected individuals who were infected before $a_1$ units of time and survived with a survival probability $\pi_1 = e^{-(\mu+\alpha_1)a_1}$ who withstood the natural death and progression to AIDS. Since they stayed up to a maximum time in the first stage, $a_1$, they progressed to the second compartment $I_2$. Whereas $\lambda(t-a_2)S(t-a_2)\pi_1\pi_2$ represents the number of infected individuals who were infected $a_2$ units of time ago, in the first class for $a_1$ units of time with probability $\pi_1$ and survived $a_2 - a_1$ units of time within the second class with probability $\pi_2$, before progressing to the third stage (since $a_2$ is the infection age at which infected individuals spend before progressing to the third stage). The model presented (2.21) is different from the model given (3.19) in that the model given in (2.21) assumes infected individuals pass through all the infection stages before progression to AIDS, but in (3.19), infected individuals may progress to AIDS from all of the stages (fast progression). If we take $\alpha_1 = \alpha_2 = 0$ we will get the staged progression model (2.21) with discrete delays. In reality, an infected individual may die of HIV infection quickly after infection, at any time $a$ after infection not necessarily after passing through all the stages of infection. The model presented (3.6) considers this fact by taking the rate of progression to AIDS, $\alpha(a)$, as a function of age of infection $a$ .

### 3.3.3 Uniform infection with Fast Progression

Here we assume that the infecting of infected individuals to be $\beta$ irrespective of their age of infection. However, they are expected to progress to the AIDS class with varying rate at different ages of infection, $\alpha(a)$. Using this assumption, the first equation of system (3.6) can be written as,

$$\frac{dS(t)}{dt} = \frac{c\beta S(t)I(t)}{N(t)} - \mu S(t). \tag{3.20}$$

Using solutions along characteristic lines (3.8), we have

$$\begin{aligned} I(t) &= \int_0^\infty i(t,a)da \\ &= \int_0^t i(t,a)da + \int_t^\infty i(t,a)da \\ &= \int_0^t i(t-a,0)\exp\left(-\mu a - \int_0^a \alpha(r)dr\right)da + \int_t^\infty i(0,a-t)\exp\left(-\mu t - \int_{a-t}^a \alpha(r)dr\right)da \\ &= \int_0^t i(t-a,0)\exp\left(-\mu a - \int_0^a \alpha(r)dr\right)da + \exp -\mu t \int_t^\infty \phi(a-t)\exp\left(-\int_{a-t}^t \alpha(r)dr\right)da. \end{aligned} \tag{3.21}$$

From the third equation of (3.6), we have

$$i(t,0) = \frac{\beta c S(t)}{N(t)}\int_0^\infty i(t,a)da = \frac{\beta c S(t)}{N(t)} I(t),$$

from which follows

$$i(t-a,0) = \frac{\beta c S(t-a)}{N(t-a)} I(t-a). \tag{3.22}$$

Therefore, substituting (3.22) into (3.21) gives

$$\begin{aligned} I(t) = \beta c \int_0^t \frac{S(t-a)}{N(t-a)} I(t-a)\exp -\left(\mu a + \int_0^a \alpha(r)dr\right)da \\ + \exp(-\mu t)\int_t^\infty \phi(a-t)\exp -\left(\int_{a-t}^a \alpha(r)dr\right)da. \end{aligned}$$

Using the change of variable $t-a=\sigma$, we have

$$\begin{aligned} I(t) = \beta c \int_0^t \frac{S(\sigma)}{N(\sigma)} I(\sigma)\exp -\left(\mu(t-\sigma) + \int_0^{t-\sigma} \alpha(r)dr\right)da \\ + \exp(-\mu t)\int_{-\infty}^0 \phi(-\sigma)\exp -\left(\int_\sigma^{t-\sigma} \alpha(r)dr\right)d\sigma. \end{aligned}$$

We observe that, the second term on the right hand side goes to zero exponentially and therefore it can be neglected for large values of $t$, where the term $\int_{-\infty}^0 \phi(-\sigma)\exp -\left(\int_\sigma^{t-\sigma}\alpha(r)dr\right)d\sigma$ represents infected individuals who were infected at $t=-\sigma$ and survived up to $t=0$. That means all individuals who were initially infected will die as time passes. Therefore, for large value of $t$ we have

$$I(t) = \beta c \int_0^t \frac{S(\sigma)}{N(\sigma)} I(\sigma)\exp\left(-\mu(t-\sigma) - \int_0^{t-\sigma}\alpha(r)dr\right)da. \tag{3.23}$$

By differentiating (3.23) and substituting back $\sigma = t - a$, we have

$$\frac{dI(t)}{dt} = \frac{c\beta S(t)I(t)}{N(t)} - c\beta \int_0^t \frac{\alpha(a)S(t-a)}{N(t-a)} I(t-a)\pi(a)da - \mu I(t). \tag{3.24}$$

Following the same procedure for the fourth equation of (3.6) yields

$$\frac{dA(t)}{dt} = c\beta \int_0^t \frac{\alpha(a)S(t-a)}{N(t-a)} I(t-a)\pi(a)da - (\mu+\nu)A(t). \tag{3.25}$$

Hence, from equations (3.20), (3.24) and (3.25) we arrive at the following proposition.

**Proposition 3.3.3.** *The mathematical model* (3.6) *for constant infecting* $\beta$ *can be written as a system of differential equations with distributed delay*

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \dfrac{c\beta S(t)I(t)}{N(t} - \mu S(t), \\ \dfrac{dI(t)}{dt} = \dfrac{c\beta S(t)I(t)}{N(t)} - c\beta \displaystyle\int_0^t \frac{\alpha(a)S(t-a)}{N(t-a)} I(t-a)\pi(a)da - \mu I(t), \\ \dfrac{dA(t)}{dt} = c\beta \displaystyle\int_0^t \frac{\alpha(a)S(t-a)}{N(t-a)} I(t-a)\pi(a)da - (\mu+\nu)A(t). \end{cases}$$

The expression $\dfrac{\alpha(a)S(t-a)}{N(t-a)} I(t-a)\pi(a)$ represents the number of infected individuals who were infected at time $t = t - a$ and survived with probability $\pi(a)$ and progress to the AIDS class at time $t$.

We have seen that the model (3.6) generalizes the models given by (2.1), (2.21) and also (**??**). In the rest of this chapter, we focus on the analysis of the general model (3.6).

## 3.4 Positivity of Solutions

The mathematical model structured by age of infection (3.6) represents human population. As a result, we need to show that all the solutions are non-negative at any time $t$ for a given positive initial value. Existence and boundedness of solutions are adopted from [64, 63, 67].

**Proposition 3.4.1.** *All solutions of the system (3.6) are positive for all time* $t \geqslant 0$ *provided that the initial conditions are positive.*

*Proof.* Claim that if $S(0) > 0, i(0,a) > 0$ and $A(0) > 0$, then for all $t > 0$, we need to show that $S(t) > 0, i(t,a) > 0$ and $A(t) > 0$.

$$\text{Define}: T_0 = \sup\{t > 0 | \forall\, r < t, S(r) > 0, i(r,a) > 0 \text{for } a \geqslant 0, A(r) > 0\}. \tag{3.26}$$

If $T_0 = +\infty$, then the claim holds. On the contradiction, suppose that $0 < T_0 < +\infty$. From the definition of (3.26), it follows that,

$$S(T_0) = 0 \text{ or } i(T_0, a_0) = 0 \text{ for some } a_0 > 0, \text{ or } A(T_0) = 0. \tag{3.27}$$

In the case where

$$\begin{aligned} &S(T_0) = 0, \\ &\frac{dS(T_0)}{dt} = \lim_{t \to T_0^-} \frac{S(T_0) - S(t)}{T_0 - t} \leqslant 0. \end{aligned} \tag{3.28}$$

However, from the first equation of (3.6), we have

$$\frac{dS(T_0)}{dt} = \Lambda > 0, \tag{3.29}$$

which contradicts (3.28). This implies that $S(T_0)$ could not be zero.

Consider the case

$$i(T_0, a_0) = 0 \text{ for some } a_0 \geqslant 0, \tag{3.30}$$

from (3.9) we have

$$i(T_0, a_0) = \begin{cases} \phi(a_0 - T_0)\dfrac{\pi(a_0)}{\pi(a_0 - T_0)}, & T_0 < a_0, \\ i(T_0 - a_0, 0)\pi(a_0), & T_0 \geqslant a_0. \end{cases}$$

If $T_0 < a_0$, then $\phi(a_0 - T_0) > 0$ since it is a value of the initial condition. Hence,

$$i(T_0, a_0) > 0 \text{for} \quad T_0 \leqslant a_0. \tag{3.31}$$

When $T_0 \geqslant a_0$, from the boundary condition of system (3.6) one gets

$$i(T_0 - a_0, 0) = \frac{cS(T_0 - a_0)}{N(T_0 - a_0)} \int_0^\infty \beta(a) i(T_0 - a_0, a) da.$$

The term $i(T_0 - a_0, a) > 0$ for $a \geqslant 0$ (from the definition of $T_0$, since $T_0 - a < T_0$). This gives that

$$i(T_0, a) > 0 \text{ for all } a_0 \leqslant T_0. \tag{3.32}$$

Therefore, from equations (3.31) and (3.32) $i(T_0, a) \neq 0$ for all $a \geqslant 0$ which contradicts (3.30). Then, $A(T_0)$ has to be zero. However, from the fourth equation of system (3.6), we have

$$A(T_0) = A_0 \exp\left(-(\mu + \nu)T_0\right) + \int_0^{T_0} \alpha(a) i(t, a) \exp\left(-(\mu + \nu)(T_0 - t)\right) dt > 0, \tag{3.33}$$

which is a contradiction. Consequently, $T_0 = +\infty$. This ends the proof. □

## 3.5 Equilibria and Basic Reproduction Number

For the mathematical analysis we consider the model given in system (3.6). To derive the basic reproduction number, we consider a condition for which the endemic equilibrium exists and is biologically meaningful. At the equilibrium, we denote time independent solutions of system (3.6) by

$$S(t) = S^*, i(t,a) = i^*(a), \quad \text{and} \quad A(t) = A^*.$$

Then, the model presented by system (3.6) can be written as

$$\begin{cases} 0 = \Lambda - \dfrac{cS^*}{N^*}\displaystyle\int_0^\infty \beta(a)i^*(a)da - \mu S^*, \\ \dfrac{d}{da}i^*(a) = -\Big(\mu + \alpha(a)\Big)i^*(a), \\ B^* = \dfrac{cS^*}{N^*}\displaystyle\int_0^\infty \beta(a)i^*(a)da, \\ 0 = \displaystyle\int_0^\infty \alpha(a)i^*(a)da - (\mu+\nu)A^*, \end{cases} \tag{3.34}$$

and

$$I^* = \int_0^\infty i^*(a)da, N^* = S^* + I^*. \tag{3.35}$$

From the first and third equation of (3.34) we have,

$$\begin{aligned} \Lambda - \mu S^* = \frac{cS^*}{N^*}\int_0^\infty \beta(a)i^*(a)da = B^*, \\ S^* = \frac{\Lambda - B^*}{\mu}. \end{aligned} \tag{3.36}$$

Integrating the second equation of system (3.34) gives

$$\begin{aligned} i^*(a) &= B^* \exp\left(-\mu a - \int_0^a \alpha(r)dr\right) \\ &= B^*\pi(a), \end{aligned} \tag{3.37}$$

where $B^*$ is the new infections at the equilibrium. Substituting $N^* = S^* + I^*$ and equation (3.37) into the third equation of system (3.34) results in

$$B^* = \frac{cS^*B^*}{S^* + I^*}\int_0^\infty \beta(a)\pi(a)da.$$

Hence,

$$B^* = 0 \quad \text{or} \quad \frac{cS^*}{S^* + I^*} \int_0^\infty \beta(a)\pi(a)da = 1. \tag{3.38}$$

By substituting $B^* = 0$ into system (3.34), we get a disease-free equilibrium given by

$$E_0 = (S_0, i_0(a), A_0) = \Big(\frac{\Lambda}{\mu}, 0, 0\Big). \tag{3.39}$$

When $B^* \neq 0$, from equation (3.38) it follows that

$$cS^* \int_0^\infty \beta(a)\pi(a)da = S^* + I^*.$$

Then,

$$I^* = S^*\Big(c\int_0^\infty \beta(a)\pi(a)da - 1\Big). \tag{3.40}$$

For the endemic equilibrium to be biologically meaningful, the number of infected individuals should be non-negative. Then we have the condition that

$$c\int_0^\infty \beta(a)\pi(a)da > 1$$

is needed for the endemic equilibrium (if it exists) to be biologically meaningful. Then we suggest the basic reproduction number, $\mathcal{R}_0$, to be

$$\mathcal{R}_0 = c\int_0^\infty \beta(a)\pi(a)da. \tag{3.41}$$

While a newly infected individual is surviving in the compartment $I$ with probability $\pi(a)$, s/he infects susceptible individuals with rate $c\beta(a)$, which depends on the age of infection too. Then, $\mathcal{R}_0$ is the number of secondary cases which is the sum among all possible infections that occur during his/her stay in $I$ class of infected individuals given by (3.41).

Hence, we conclude that the term

$$\mathcal{R}_0 = c\int_0^\infty \beta(a)\pi(a)da$$

is the basic reproduction number of model (3.6). Then, using the above notation, equation (3.40) can be written as

$$I^* = S^*(\mathcal{R}_0 - 1) \quad \text{and} \quad S^* = \frac{I^*}{\mathcal{R}_0 - 1}. \tag{3.42}$$

Substituting equation (3.37) into equation (3.35) gives

$$I^* = B^* \int_0^\infty \pi(a)da. \tag{3.43}$$

Substituting equation (3.43) into equation (3.42) gives

$$S^* = \frac{B^* \int_0^\infty \pi(a)da)}{\mathcal{R}_0 - 1}. \tag{3.44}$$

Equating equations (3.36) and (3.44) gives

$$\frac{B^* \int_0^\infty \pi(a)da}{\mathcal{R}_0 - 1} = \frac{\Lambda - B^*}{\mu}.$$

Then we solve for $B^*$, the new infections with age of infection equal to zero at the endemic equilibrium as

$$B^* = \frac{\Lambda(\mathcal{R}_0 - 1)}{\mu \int_0^\infty \pi(a)da + (\mathcal{R}_0 - 1)}. \tag{3.45}$$

From the fourth equation of system (3.34), we have

$$A^* = \frac{B^* \int_0^\infty \alpha(a)\pi(a)da}{\mu + \nu}.$$

Hence the following theorem gives us the equilibria of the system (3.6).

**Theorem 3.5.1.** *i) If $\mathcal{R}_0 < 1$, the model* (3.6) *has a unique biologically feasible equilibrium $E_0 = (S_0, i_0(a), A_0) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$, which is a disease-free equilibrium.*
*ii) If $\mathcal{R}_0 > 1$, in addition to a disease-free equilibrium the model given by system* (3.6) *has a unique endemic equilibrium given by*

$$E^* = (S^*, i^*(a), A^*) = \left(\frac{\Lambda - B^*}{\mu}, B^*\pi(a), \frac{B^* \int_0^\infty \alpha(a)\pi(a)da}{\mu + \nu}\right),$$

*where $B^*$ represents the number of new infections at the endemic equilibrium given in* (3.45).

## 3.6 Stability Analysis of Equilibria

By using the results in [64], we analyse the stability of the disease-free equilibrium.

**Theorem 3.6.1.** *Suppose that $\mathcal{R}_0 < 1$. Then, the disease-free equilibrium is globally attractive:*

$$\lim_{t\to\infty} I(t) = 0 \quad \text{and} \quad \lim_{t\to\infty} S(t) = \frac{\Lambda}{\mu}.$$

*Proof.* Using the expression (3.1),

$$\begin{aligned} I(t) &= \int_0^\infty i(t,a)da = \int_0^t i(t,a)da + \int_t^\infty i(t,a)da \\ &= \int_0^t i(t-a,0)\exp\left(-\mu a - \int_0^a \alpha(r)dr\right)da + \int_t^\infty i(0,a-t)\exp\left(-\mu t - \int_{a-t}^a \alpha(r)dr\right)da \\ &= \int_0^t B(t-a)\pi(a)da + \int_t^\infty i(0,a-t)\exp\left(-\mu t - \int_{a-t}^a \alpha(r)dr\right)da. \end{aligned}$$

Considering the second term on the right-hand side, we have

$$\limsup_{t\to\infty} \int_t^\infty i(0,a-t)\exp\left(-\mu t - \int_{a-t}^a \alpha(r)dr\right)da = 0, \tag{3.46}$$

since $\alpha(a)$ is a positive and increasing function which is the rate of progression to the AIDS class. Hence

$$\limsup_{t\to\infty} I(t) = \limsup_{t\to\infty} \int_0^t B(t-a)\pi(a)da. \tag{3.47}$$

We extend the function $B$ on $\mathbb{R}$ by

$$\tilde{B}(t) = \begin{cases} 0, & t < 0, \\ B(t), & t \geqslant 0. \end{cases} \tag{3.48}$$

Hence, (3.47) can be written as,

$$\limsup_{t\to\infty} I(t) = \limsup_{t\to\infty} \int_0^\infty \tilde{B}(t-a)\pi(a)da. \tag{3.49}$$

Applying *Reverse Fatou's Lemma* to (3.49) results in

$$\begin{aligned} \limsup_{t\to\infty} I(t) &\leqslant \int_0^\infty \limsup_{t\to\infty} \tilde{B}(t-a)\pi(a)da = \int_0^\infty \limsup_{t\to\infty} B(t)\pi(a)da \\ &\leqslant \limsup_{t\to\infty} B(t) \int_0^\infty \pi(a)da. \end{aligned} \tag{3.50}$$

From the boundary condition, we have

$$\begin{aligned} B(t) &= \frac{cS(t)}{N(t)} \int_0^\infty \beta(a) i(t,a) da \\ &\leqslant c \int_0^\infty \beta(a) i(t,a) da \\ &\leqslant c \int_0^t \beta(a) i(t,a) da + c \int_t^\infty \beta(a) i(t,a) da \\ &\leqslant c \int_0^t \beta(a) B(t-a) \pi(a) da + c \int_t^\infty \beta(a) i(0, a-t) \exp\left(-\mu t - \int_{a-t}^a \alpha(r) dr\right) da. \end{aligned}$$

The second term on the right hand-side goes to zero. In fact

$$\begin{aligned} c \int_t^\infty \beta(a) i(0, a-t) \exp\left(-\mu t - \int_{a-t}^a \alpha(r) dr\right) da \\ \leqslant c\hat{\beta} \exp(-\mu t) \int_t^\infty i(0, a-t) da = c\hat{\beta} I(0) \exp(-\mu t), \end{aligned} \tag{3.51}$$

where $\hat{\beta}$ is as defined in (3.2). Hence

$$\limsup_{t\to\infty} B(t) \leqslant \limsup_{t\to\infty} c \int_0^t \beta(a) B(t-a) \pi(a) da. \tag{3.52}$$

Using equation (3.48), equation (3.52) becomes

$$\limsup_{t\to\infty} B(t) \leqslant \limsup_{t\to\infty} c \int_0^\infty \beta(a) \tilde{B}(t-a) \pi(a) da. \tag{3.53}$$

Applying *Reverse Fatou's lemma* to equation (3.53) gives us

$$\begin{aligned} \limsup_{t\to\infty} B(t) &\leqslant \limsup_{t\to\infty} \tilde{B}(t) c \int_0^\infty \beta(a) \pi(a) da = \limsup_{t\to\infty} B(t) c \int_0^\infty \beta(a) \pi(a) da \\ &\leqslant \mathcal{R}_0 \limsup_{t\to\infty} B(t). \end{aligned}$$

Since $\mathcal{R}_0 < 1$, we necessarily have $\limsup_{t\to\infty} B(t) = 0$.

From equation (3.50), it follows that $\limsup_{t\to\infty} I(t) = 0$. Since we have shown that all solutions $I(t)$ are positive, $\lim_{t\to\infty} I(t) = 0$.

From the first equation of system (3.6), we get

$$S(t) = S(0) \exp(-\mu t) + \frac{\Lambda}{\mu} - \int_0^t B(s) \exp(-\mu(t-s)) ds.$$

Since

$$\limsup_{t\to\infty}\int_0^t B(s)\exp\left(-\mu(t-s)\right)ds \leqslant \limsup_{t\to\infty}\int_0^\infty \tilde{B}(t-s)\exp\left(-\mu s\right)ds$$
$$\leqslant \limsup \tilde{B}(t)\int_0^\infty \exp\left(-\mu s\right)ds = 0,$$

which follows that

$$\lim_{t\to\infty} S(t) = \frac{\Lambda}{\mu}.$$

Therefore, for $\mathcal{R}_0 < 1$, the disease-free equilibrium of the model (3.6) is globally stable. □

Next, we investigate the linear stability of the endemic equilibrium of the model (3.6) which is given by Theorem 3.5.1.

In [64, 67], the authors developed some techniques to approach the linear stability of an infinite dimension abstract model for infectious diseases structured by age of infection. Individuals in the AIDS class are supposed to develop AIDS related symptoms and do not involve in sexual activities. As a result, they do not contribute to the transmission of the disease. Asymptotic behaviour of $A(t)$ can be deduced from the asymptotic behaviours of $S(t)$ and $i(t,a)$. Hence, we consider the class of susceptible and infected individuals only for the stability analysis. Consider a small perturbations $s(t)$ and $u(t,a)$ from the endemic equilibrium of system (3.6), and let

$$s(t) = S(t) - S^*, u(t,a) = i(t,a) - i^*(a).$$

As a result, $N(t) = N^* + (s(t) + v(t))$ and $I(t) = I^* + v(t)$, where $v(t) = \int_0^\infty u(t,a)da$.

By using Tylor expansion and ignoring the higher-order terms, the linearised system of (3.6) around the endemic equilibrium gives:

$$\begin{cases} \dfrac{ds(t)}{dt} = -u(t,0) - \mu s(t), \\ \Big(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\Big)u(t,a) = -(\alpha(a)+\mu)u(t,a), \\ u(t,0) = \dfrac{c}{N^*}W^* s(t) - \dfrac{c}{N^{*2}}(s(t)+v(t))S^*W^* + \dfrac{c}{N^*}S^* w(t), \end{cases} \tag{3.54}$$

where $W^* = \int_0^\infty \beta(a)i^*(a)da, w(t) = \displaystyle\int_0^\infty \beta(a)u(t,a)da.$

To find eigenvalues of the resulting linear system (3.54), consider the exponential solutions as follows,

$$s(t) = \tilde{s}\exp(zt), u(t,a) = \tilde{u}(a)\exp(zt), \tag{3.55}$$

where $z$ is a complex number and $(\tilde{s}, \tilde{u}) \neq (0,0)$.

The endemic equilibrium will be locally asymptotically stable if all solutions of the form (3.55) of system (3.54) have $z$ non-positive real parts, but it will be unstable if there is a solution with $z$ having positive real part.

Substituting the expressions (3.55) of $s(t)$ and $u(t,a)$ into (3.54) gives

$$\begin{cases} (\mu+z)\tilde{s} = -\tilde{u}(0), \\ z\tilde{u}(a) + \dfrac{d\tilde{u}(a)}{da} = -(\alpha(a)+\mu)\tilde{u}(a), \\ \tilde{u}(0) = \dfrac{c}{N^*}\tilde{s}W^* - \dfrac{c}{N^{*2}}(\tilde{s}+\tilde{v})S^*W^* + \dfrac{c}{N^*}S^*\tilde{w}, \end{cases} \tag{3.56}$$

where

$$\tilde{v} = \int_0^\infty \tilde{u}(a)da, \tilde{w} = \int_0^\infty \beta(a)\tilde{u}(a)da. \tag{3.57}$$

From the first equation of system (3.56),

$$\tilde{s} = -\frac{\tilde{u}(0)}{\mu+z}. \tag{3.58}$$

The second equation of system (3.56) is solved as

$$\tilde{u}(a) = \tilde{u}(0)\exp\left(-\int_0^a (\alpha(s)+\mu+z)ds\right) = \tilde{u}(0)\pi(a)\exp -za. \tag{3.59}$$

Substituting equation (3.59) into equation (3.57), we get

$$\tilde{v} = \tilde{u}(0)\hat{\pi}(z), \tag{3.60}$$

$$\tilde{w} = \tilde{u}(0)\hat{Q}(z), \tag{3.61}$$

where $\hat{\pi}(z)$ and $\hat{Q}(z)$ represent the *Laplace transforms* of $\pi(a)$ and $Q(a)$, respectively, given by

$$\hat{\pi}(z) = \int_0^\infty \pi(a)\exp(-za)da, \hat{Q}(z) = \int_0^\infty Q(a)\exp(-za)da \tag{3.62}$$

and

$$Q(a) = \beta(a)\pi(a).$$

Substituting equations (3.58), (3.60) and (3.61) into the third equation of system (3.56) and dividing by $\tilde{u}(0) \neq 0$, we end with the characteristic equation,

$$-\frac{W^*}{\mu + z}\Big(\frac{c}{N^*} - S^*\frac{c}{N^{*2}}\Big) + S^*\frac{c}{N^{*2}}\hat{\pi}(z)W^* + S^*\frac{c}{N^*}\hat{Q}(z) = 1. \tag{3.63}$$

Hence, we arrive at the relation between the asymptotic stability of the endemic equilibrium and the roots of the characteristic equation in (3.63).

**Proposition 3.6.2.** *[64] The endemic equilibrium of system* (3.6) *is linearly stable if all the roots $z$ of the characteristic equation (3.63) have strictly negative real part.*

This thesis does not contain proof of Proposition 3.6.2. Instead, we analyse the characteristic equation (3.63) by applying the techniques used in [64]. Analysing the characteristic equation given (3.63) is not obvious. As in [64], we normalise the system for mathematical simplicity. Let

$$\xi = \frac{I^*}{N^*}, \quad \text{then} \quad \frac{S^*}{N^*} = (1 - \xi). \tag{3.64}$$

Hence, $0 < \xi < 1$ since $N(t) = S(t) + I(t)$.

From the third equation of (3.34) and (3.64), we have

$$\frac{c}{N^*}W^* = \frac{B^*}{S^*} = \frac{I^*}{S^*}\frac{1}{\hat{\pi}(0)} = \frac{I^*}{N^*}\frac{N^*}{S^*}\frac{1}{\hat{\pi}(0)} = \frac{\xi}{1-\xi}\frac{1}{\hat{\pi}(0)}.$$

$$S^*W^* = \frac{N^*}{c}B^* = \frac{N^*}{c}\frac{I^*}{\hat{\pi}(0)} = \frac{N^{*2}}{c}\frac{I}{N^*}\frac{1}{\hat{\pi}(0)} = \frac{N^{*2}}{c}\frac{\xi}{\hat{\pi}(0)}.$$

$$\frac{cS^*}{N^*} = \frac{1}{\hat{Q}(0)}.$$

Hence, the characteristic equation (3.63) can be written as

$$-\frac{1}{\mu + z}\frac{\xi}{\hat{\pi}(0)}\Big(\frac{1}{1-\xi} - 1\Big) - \xi\frac{\hat{\pi}(z)}{\hat{\pi}(0)} + \frac{\hat{Q}(z)}{\hat{Q}(0)} = 1. \tag{3.65}$$

Define

$$p(s) = \frac{\pi(s)}{\hat{\pi}(0)}, \quad q(s) = \frac{Q(s)}{\hat{Q}(0)}, \tag{3.66}$$

where

$$\pi(a) = \exp\left(-\mu a - \int_0^a \alpha(r)dr\right).$$

Thus

$$p(0) = \frac{\pi(0)}{\hat{\pi}(0)} = \frac{1}{\hat{\pi}(0)}. \tag{3.67}$$

Hence, the expression (3.65) can be simplified as

$$-\frac{p(0)\xi}{\mu + z}\left(\frac{1}{1-\xi} - 1\right) - \xi\hat{p}(z) + \hat{q}(z) = 1. \tag{3.68}$$

Recall that $0 < \xi < 1$, the fraction of infected individuals over the sexually active population. In order to analyse the sign of the eigenvalues, we substitute $z = x + iy$,

$$-\frac{p(0)\xi}{\mu + (x+iy)}\Big(\frac{1}{1-\xi} - 1\Big) - \xi\left(\int_0^\infty p(s)e^{-(x+iy)s}ds\right) + \int_0^\infty q(s)e^{-(x+iy)s}ds = 1.$$

Using *Euler's Formula* and then separating the real and complex part results in

$$1 - \int_0^\infty e^{-(xs)}\cos(sy)q(s)ds = -\frac{(\mu+x)p(0)\xi}{(\mu+x)^2 + y^2}\left(\frac{1}{1-\xi} - 1\right) - \xi\int_0^\infty e^{-xs}\cos(sy)p(s)ds \tag{3.69}$$

$$\int_0^\infty e^{-(xs)}\sin(sy)q(s)ds = \frac{yp(0)\xi}{(\mu+x)^2 + y^2}\left(\frac{1}{1-\xi} - 1\right) + \xi\int_0^\infty e^{-xs}\sin(sy)p(s)ds. \tag{3.70}$$

Multiplying (3.69) by $y$ and (3.70) by $\mu + x$, adding the two equations and solving for $\xi$ as,

$$\xi = \frac{y\left(1 - \int_0^\infty e^{-(xs)}\cos(sy)q(s)ds\right) + (\mu+x)\int_0^\infty e^{-(xs)}\sin(sy)q(s)ds}{\left((\mu+x)\int_0^\infty e^{-xs}\sin(sy)p(s)ds - y\int_0^\infty e^{-xs}\cos(sy)p(s)ds\right)}. \tag{3.71}$$

For $0 < \xi < 1$ and $x = 0, y > 0$, (3.69) and (3.70) become,

$$\int_0^\infty \cos(sy)q(s)ds - \frac{\mu p(0)\xi}{\mu^2 + y^2}\left(\frac{1}{1-\xi} - 1\right) - \xi\int_0^\infty \cos(sy)p(s)ds = 1. \tag{3.72}$$

$$\frac{yp(0)\xi}{\mu^2 + y^2}\Big(\frac{1}{1-\xi} - 1\Big) + \xi\int_0^\infty \sin(sy)p(s)ds - \int_0^\infty \sin(sy)q(s)ds = 0. \tag{3.73}$$

Using (3.72) and (3.73), we obtain

$$\xi = \frac{y\Big(1 - \int_0^\infty \cos(sy)q(s)ds\Big) + \mu \int_0^\infty \sin(sy)q(s)ds}{\Big(\mu \int_0^\infty \sin(sy)p(s)ds - y \int_0^\infty \cos(sy)p(s)ds\Big)}.$$

We arrive at the following proposition, which gives conditions for the eigenvalues to have negative real parts, which is proven by H. R. Thieme and C. Castillo-Chavez [64].

**Theorem 3.6.3.** *[64] Let $\mathcal{R}_0 > 1$, then there are no roots of (3.69) and (3.70) with $x \geqslant 0$ if one of the following holds:*

i) $\xi$ is sufficiently close to 0 or 1;

ii) $p(0)$ is sufficiently large;

iii) There is no $y > 0$ satisfying the following simultaneously:

$$\int_0^\infty \cos(sy)q(s)ds > 0, \int_0^\infty \sin(sy)q(s)ds > 0, \int_0^\infty \cos(sy)p(s)ds < 0,$$
$$0 < y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds$$
$$< \gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right).$$

In the first condition, from equation (3.64), $\xi$ close to one or zero means the proportion of infected individuals at the endemic equilibrium is very large or very small. $\xi$ close to zero is equivalent to saying that $\mathcal{R}_0$ is greater than one but is very close to one, whereas $\xi$ close to one means that $\mathcal{R}_0$ is large enough. As a condition, there is a switch of stability for the disease-free equilibrium from stable to unstable when $\mathcal{R}_0$ crosses one from the left to the right. The endemic equilibrium exists when $\mathcal{R}_0 > 1$, and is linearly stable for $\mathcal{R}_0$ close to one or large enough. Theorem 3.6.3 does not conclude about the stability of endemic equilibrium for all $\mathcal{R}_0 > 1$.

From equations (3.62) and (3.67), the second condition in Theorem 3.6.3 states that endemic equilibrium will be stable if $\mathcal{R}_0 > 1$ with $p(0)$ is sufficiently large or equivalently, $\hat{\pi}(0)$ is small. This means infected individuals survive for short time in the infectious class and the basic reproduction number slightly bigger than one and we conclude from the previous discussion when $\xi$ is close to zero.

## 3.7 Numerical Simulation

### 3.7.1 Numerical Scheme

For the numerical simulation, we use finite difference approximation. To approximate the integral, we use the Trapezium method. The time steps are, $dt = h$ and $da = k$. If we divide the interval $[0, a_{max}]$ into $D$ points, $kD = M$. Define a grid in the $(t, a)$ plane, given by the points $(t_n, a_m) = (nh, mk)$ for arbitrary integers $n$ and $m$ while $mk < a_{max}$ and $nh \geqslant 0$. The notations $i_m^n$ represents the value of $i$ at the grid point $(t_n, a_m)$, which is $i(t_n, a_m)$. Similarly, $S^n, I^n$ and $A^n$ represent the functional values of $S, I$ and $A$ at the point $t_n = nh$.

Using the Trapezium method, we have

$$I^n \simeq \int_0^M i(t,a)da = \frac{k}{2}\left(i_0^n + 2\sum_{m=1}^{D-1} i_m^n + i_D^n\right)$$

and

$$\int_0^M \beta(a)i(t,a)da \simeq \frac{k}{2}\left(\beta_0 i_0^n + 2\sum_{m=1}^{D-1}\beta_m i_m^n + \beta_D i_D^n\right).$$

To approximate $S(t)$, we use the forward time scheme as given by J. C. Strikwerda [62]. Thus,

$$\frac{S^{n+1} - S^n}{h} \simeq \Lambda - \frac{cS^n}{N^n}\frac{k}{2}\left(\beta_0 i_0^n + 2\sum_{m=1}^{D-1}\beta_m i_m^n + \beta_D i_D^n\right) - \mu S^n.$$

By collecting the like terms and some arrangements, we get the following formula:

$$S^{n+1} \simeq \Lambda h - S^n\left(\frac{ch}{N^n}\frac{k}{2}\left(\beta_0 i_0^n + 2\sum_{m=1}^{D-1}\beta_m i_m^n + \beta_D i_D^n\right) + h\mu - 1\right).$$

By using the backward-time backward-age of infection scheme, the second equation of system (3.6) becomes,

$$\frac{i_m^n - i_m^{n-1}}{h} + \frac{i_m^n - i_{m-1}^n}{k} \simeq -(\mu + \alpha_m)i_m^n,$$
$$i_m^n \simeq \frac{hi_{m-1}^n + i_m^{n-1}}{\frac{h}{k}(\mu + \alpha_m) + h + k}.$$

| Parameter | Description | Value | Reference |
|---|---|---|---|
| $\Lambda$ | Recruitment rate | 801403 | Estimated [52] |
| $\mu$ | Natural death rate | 1/34 | [65] |
| $c$ | Contact rate | 0.3, 2.5 | Fitted |
| $\beta(a)$ | Probability of infecting per contact | Function | Estimated [24, 32, 55] |
| $\alpha(a)$ | Rate of progression | Function | Estimated [32] |
| $\nu$ | Disease induced death rate | 0.115 | [36] |

**Table 3.2.** Parameters used for the simulations

The boundary condition is approximated as follows:

$$i_0^n \simeq \frac{S^n c}{N^n}\frac{k}{2}\left(\beta(0)i_0^{n-1} + 2\sum_{m=1}^{D-1}\beta_m i_m^{n-1} + \beta(D)i_D^{n-1}\right).$$

Before writing the finite difference approximation for class $A(t)$, we first need to use the Trapezium method for the integral inside.

$$\int_0^M \alpha(a)i(t,a)da \simeq \frac{k}{2}\left(\alpha_0 i_0^n + 2\sum_{m=1}^{D-1}\alpha_m i_m^n + \alpha_D i_D^n\right).$$

Hence, the forward time scheme gives us

$$A^{n+1} \simeq \frac{hk}{2}\left(\alpha_0 i_0^n + 2\sum_{m=1}^{D-1}\alpha_m i_m^n + \alpha_D i_D^n\right) + A^n\left(1 - h(\mu+\nu)\right).$$

Initial conditions are $S^0 = S(0), i_m^0 = \phi(m)$ and $A^0 = A(0)$.

### 3.7.2 Implementation

The probability of infecting $\beta(a)$ and the rate of progression to AIDS $\alpha(a)$ are approximated from [24, 32, 55]. The initial conditions are $S_0 = 20651120$ individuals, $I_0 = 144557$ individuals and $A_0 = 0$ individual. Parameter values used for the simulation are given in Table (3.2). We implement the numerical scheme in Python and get the following simulation results:

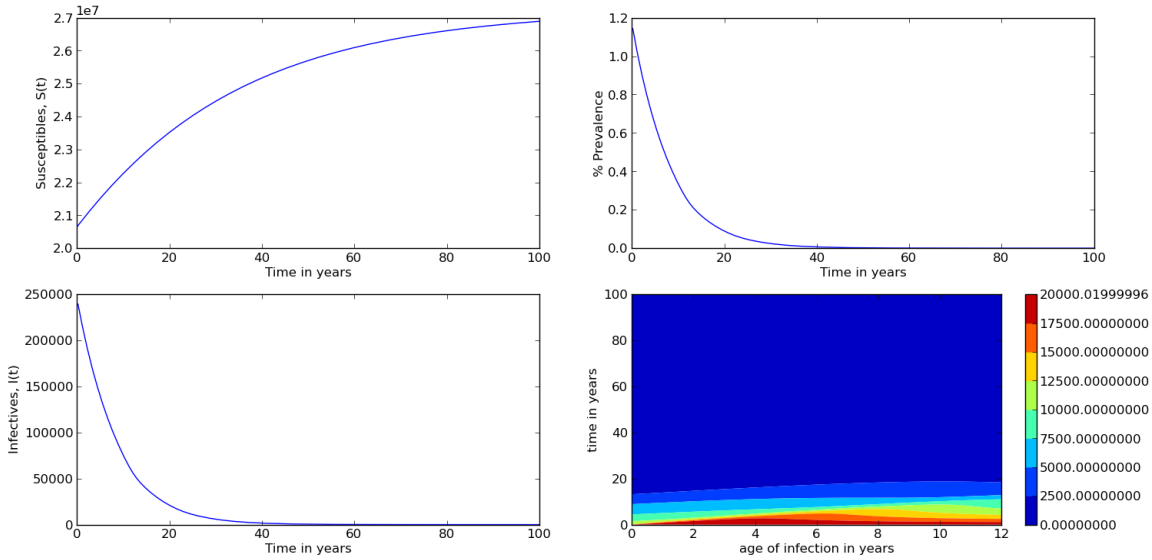


**Figure 3.2.** The dynamics of the disease when $\mathcal{R}_0 < 1$

Figure 3.2 shows the dynamics of the disease when $c = 0.3$ and the basic reproduction number $\mathcal{R}_0 = 0.3$. The contour plot shows the distribution profile of infected individuals. The number of infected individuals $i(t, a)$ eventually decreases vertically and horizontally (with time and age of infection) respectively. Finally, the whole area is covered by the dark blue, which shows the non-existence of infected individuals and the eradication of the disease.

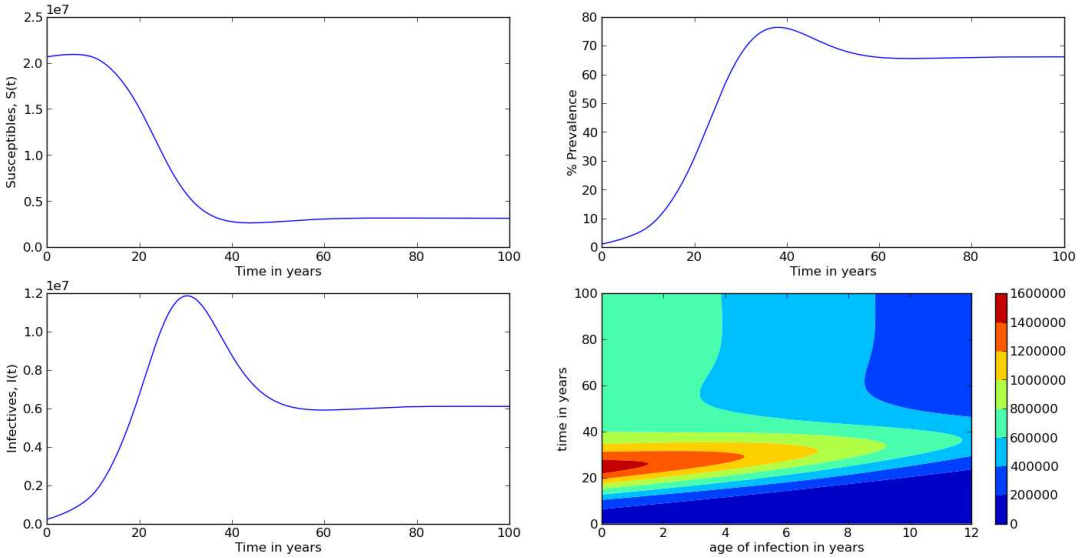


**Figure 3.3.** The dynamics of the disease when $\mathcal{R}_0 > 1$

Figure 3.3 shows the dynamics of the disease with $c = 2.5$ and $\mathcal{R}_0 = 2.9$. The dark blue indicates the low density of infected individuals at the start of the disease. We observe an increase of the infectious population (shown by the other colours) before it settles to a uniform distribution of infected individuals with respect to time. We say that the solution reaches an equilibrium which is endemic as shown in Theorem 3.5.1. The horizontal decrease of the concentration of infected individuals is due to the removal of infected individuals by natural death and progression to AIDS.

## 3.8 Summary

In this chapter, we formulated and analysed an age of infection-structured HIV/AIDS model by considering varying infecting with respect to age of infection. We have shown that model (3.6) generalises some of the mathematical models used to model HIV transmission including (2.1) and (2.21) given in Chapter (2). The basic reproduction number $\mathcal{R}_0$ is given for the model (3.6) and equilibria are found in terms of $\mathcal{R}_0$. We checked the global stability of the disease-free equilibrium and we verified the linear stability of the

endemic equilibrium. Numerical simulations are generated and confirm the theoretical results obtained earlier.

# Chapter 4

# Model of HIV/AIDS Transmission Under Treatment Structured by Age of Infection

This model introduces antiretroviral treatment (ART) for individuals in the infected class to the model discussed in Chapter 3. Infected individuals are assumed either to progress directly to AIDS with rate of progression $\alpha(a)$ or start ART and progress to the compartment of infected individuals under treatment $T$ with rate $\rho(a)$. Infected individuals who are under treatment also progress to AIDS with a lower rate $\bar{\alpha}$. They are able to transmit the HIV to susceptible individuals, but biological evidence showed that their infectiousness is very small compared to the infectiousness of infected individuals who are not under treatment [48]. The reason for this is the reduction of viral load in the blood stream for patients under treatment [27, 60]. Taking ART will reduce viral load up to an undetectable level after a few months [58], typical numbers being from $10^6$ to 10 if there is full drug adherence [48, 55].

For an HIV positive individual to receive ART, s/he first needs to be tested and identified as HIV positive and also as being within the eligible group for treatment. Without compulsion, HIV infected individuals only go for HIV testing when they have symptoms of AIDS. This is typically the case in resource-limited countries. First the symptoms may be seen already in 2-3 years (approximately 10% of patients) but it may take up to 8 - 10 years since infection for symptoms to appear [55, 54]. AIDS-related symptoms occur due to a reduced

number (less than 200 per $\mu l$) $CD4^+$ cells and thus the immune system is too weak to fight the opportunistic diseases [51]. From the above arguments, it is expected that about 10% of HIV infected individuals will have a $CD4^+$ count of less than 200 within 2 or 3 years of infection while for the rest it occurs later. However, there is no fix relation between $CD4^+$ count and time after HIV infection. As Reuben et al. shows, even HIV negative persons might have a $CD4^+$ count less than 100, Figure (1a) [55] where the authors showed the distribution of $CD4^+$ cells in HIV negative men in South Africa. Hence, using a $CD4^+$ count to estimate the age of infection is not straight forward and definite. But, it can provide some insight into the study.

## 4.1 Model Formulation

For an HIV infected individual, the probability of being tested $\delta(a)$ is very small up to 2 or 3 years and starts increasing slightly as a result of symptoms [55, 54]. It is likely that at the late stage of infection (between $8-10$ years of infection), the probability of being tested HIV positive is close to one due to accumulated AIDS-related symptoms. Therefore, the Hill function can be a good approximation for the probability of being tested due to the plateau-like structure at a late stage of infection.

Hence, the probability of being tested can be given by,

$$\delta(a) = \frac{a^n}{a^n + a^{*n}},$$

where $a^*$ is the age of infection of an infected individual at which the probability of being tested increases quickly and is the inflection point of the Hill function and $n$ is a Hill coefficient which determines the slope of the function $\delta(a)$. For large value of $n$, the age of infection $a^*$ becomes the frequency at which people go for testing.

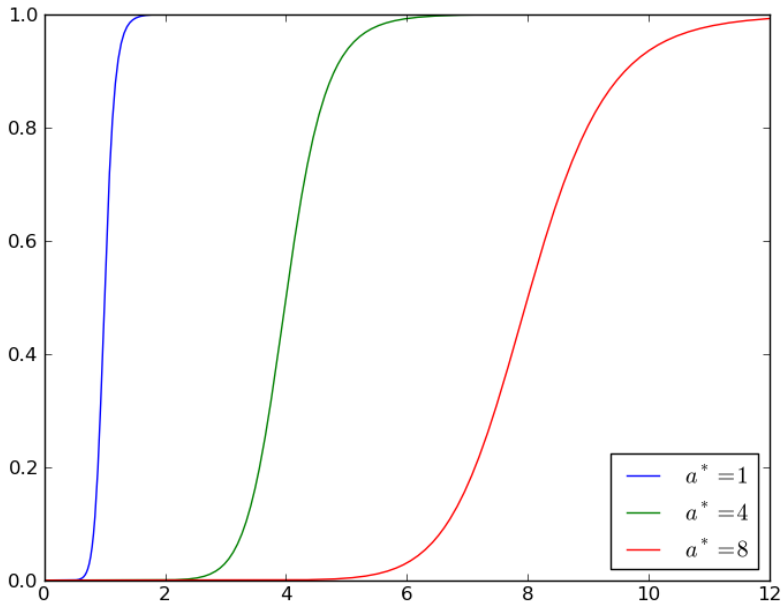


**Figure 4.1.** Probabilities of being tested

Figure (4.1) depicts the probability of being tested $\delta(a)$ versus age of infection $a$ for $n = 12$. We use this graph for our numerical simulations below. The rate of treatment coverage per year, $\rho_0(a)$ can differ in different countries. In developed countries infected individuals who are HIV positive are considered to be under treatment without restriction and almost 100% of those eligible infected individuals are getting treatment. In this case since every infected individual is eligible for the treatment, $\rho_0(a)$ is one. In developing countries, South Africa for instance, not all HIV positive individuals are eligible for treatment. HIV positive children (irrespective of their $CD4^+$), HIV positive individuals who are co-infected with TB, and pregnant women are eligible for treatment if the $CD4^+$ count is less than 350 per $\mu l$. For others, a $CD4^+$ count less than 200 per $\mu l$ is the criteria for HIV infected individuals to be recruited under treatment. Here, the main aim of the treatment is to reduce mortality and mother-to-child transmission. Among those who are eligible for treatment, currently around 70% are under treatment, and by June 2011, 80% of them are expected to be under treatment [3]. The rate of being under treatment, $\rho(a)$, is determined by the probability of being tested $\delta(a)$ and treatment coverage per year if one has tested HIV positive, $\rho_0(a)$. Then the rate at which infected individuals with age of infection $a$ recruited to the class

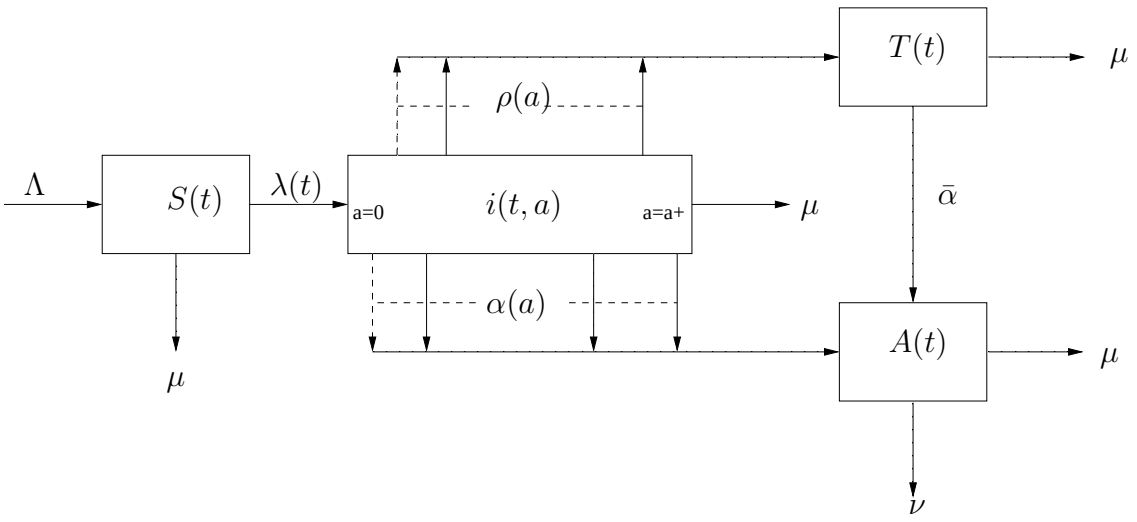


**Figure 4.2.** Diagrammatic representation of age of infection HIV model with treatment

of treatment is given by:

$$\rho(a) = \rho_0(a)\delta(a).$$

A susceptible individual can get an infection due to contact with infected individuals in class $I$ or with infected individuals who are under treatment in class $T$. Let $\bar{\beta}$ be the probability of infecting of infected individuals under treatment. Hence

$$\lambda_1(t) = \frac{c}{N(t)} \int_0^\infty \beta(a) i(t,a) da \quad \text{and} \quad \lambda_2(t) = \frac{c\bar{\beta} T(t)}{N(t)}$$

represents the force of infections resulting due to the interaction of susceptible individuals with infected individuals in class $I$ and with individuals under treatment respectively. Then the total force of infection is given by:

$$\lambda(t) = \lambda_1(t) + \lambda_2(t).$$

Figure (4.2) depicts diagrammatic representation of the dynamics of HIV/AIDS infection with treatment.

The total number of infected individuals who are recruited into treatment at time $t$ is given by $\int_0^\infty \rho(a) i(t,a) da$. Let $\bar{\alpha}$ be the rate of progression of treated individuals to AIDS. The change of the number of treated individuals at a given time $t$ is given by,

$$\frac{dT(t)}{dt} = \int_0^\infty \rho(a) i(t,a) da - (\mu + \bar{\alpha}) T(t).$$

In addition to natural mortality and progression to AIDS, there is an outflow of infected individuals from class $I(t)$ due to treatment with a recruitment rate $\rho(a)$ where $a$ is age of infection. Hence we have,

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right) i(t,a) = -\left(\mu+\alpha(a)+\rho(a)\right) i(t,a).$$

The resulting model equations are,

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \left(\dfrac{c}{N(t)}\displaystyle\int_0^\infty \beta(a)i(t,a)da + \dfrac{c\bar{\beta}T(t)}{N(t)}\right) S(t) - \mu S(t), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right) i(t,a) = -(\mu+\alpha(a)+\rho(a))i(t,a), \\ B(t) = \left(\dfrac{c}{N(t)}\displaystyle\int_0^\infty \beta(a)i(t,a)da + \dfrac{c\bar{\beta}T(t)}{N(t)}\right) S(t), \\ \dfrac{dT(t)}{dt} = \displaystyle\int_0^\infty \rho(a)i(t,a)da - (\mu+\bar{\alpha})T(t), \\ \dfrac{dA(t)}{dt} = \displaystyle\int_0^\infty \alpha(a)i(t,a)da + \bar{\alpha}T(t) - (\mu+\nu)A(t), \end{cases} \tag{4.1}$$

where the total number of infected individuals at time $t$ is given by

$$I(t) = \int_0^\infty i(t,a)da \tag{4.2}$$

and $N(t)$ the sexually active proportion of the population is given by,

$$N(t) = S(t) + I(t) + T(t).$$

Parameters description is summarised in the following Table:

| Parameter | Description |
|---|---|
| $\Lambda$ | Recruitment rate |
| $\mu$ | Natural death rate |
| $c$ | Contact rate |
| $\beta(a)$ | Probability of infecting per contact |
| $\alpha(a)$ | Rate of progression |
| $\bar{\beta}$ | Probability of infecting under treatment |
| $\bar{\alpha}$ | Rate of progression under treatment |
| $\nu$ | Disease induced death rate |

**Table 4.1.** Description of parameters used in the model

## 4.2 Equilibria and Reproduction Number

In this section we investigate the time-independent solutions (equilibrium points) of the model with treatment given (4.1).

At the steady state, system (4.1) can be written as:

$$\begin{cases} 0 = \Lambda - B^* - \mu S^*, \\ \dfrac{di^*(a)}{da} = -\left(\mu + \alpha(a) + \rho(a)\right) i^*(a), \\ B^* = \left(\dfrac{c}{N^*}\displaystyle\int_0^\infty \beta(a) i^*(t) da + \dfrac{c\bar{\beta} T^*}{N^*}\right) S^*, \\ 0 = \displaystyle\int_0^\infty \rho(a) i^*(a) da - (\mu + \bar{\alpha}) T^*, \\ 0 = \displaystyle\int_0^\infty \alpha(a) i(t,a) da + \bar{\alpha} T(t) - (\mu + \nu) A(t), \end{cases} \tag{4.3}$$

and

$$I^* = \int_0^\infty i^*(a) da. \tag{4.4}$$

The first equation of (4.3) gives us:

$$S^* = \frac{\Lambda - B^*}{\mu}. \tag{4.5}$$

The second equation of (4.3) implies that

$$i^*(a) = B^* \exp\left(-\mu a - \int_0^a (\alpha(s) + \rho(s)) ds\right). \tag{4.6}$$

To simplify the notation let

$$\Pi(a) = \exp\left(-\mu a - \int_0^a (\alpha(s) + \rho(s)) ds\right), \tag{4.7}$$

which is the probability of surviving up to $a$ unit of time being HIV infected in class $I(t)$. Hence,

$$i^*(a) = B^* \Pi(a). \tag{4.8}$$

The fourth equation of (4.3) and (4.8) give us

$$T^* = \frac{B^* \int_0^\infty \rho(a) \Pi(a) da}{\mu + \bar{\alpha}}. \tag{4.9}$$

The third equation of (4.3) results in

$$B^* = \frac{cS^*}{N^*}\left(\int_0^\infty \beta(a)i^*(a)da + \bar{\beta}T^*\right). \tag{4.10}$$

Substituting equations (4.8) and (4.9) into (4.10) gives us

$$B^* = 0, \quad \text{or} \tag{4.11}$$

$$\frac{cS^*}{N^*}\Big(\int_0^\infty \beta(a)\Pi(a)da + \frac{\bar{\beta}}{\mu+\bar{\alpha}}\int_0^\infty \rho(a)\Pi(a)da\Big) - 1 = 0. \tag{4.12}$$

By substituting $N^* = S^* + I^* + T^*$ into (4.12) we get

$$I^* + T^* = (\mathcal{R}_e - 1)S^*, \tag{4.13}$$

where

$$\mathcal{R}_e = c\int_0^\infty \beta(a)\Pi(a)da + \frac{c\bar{\beta}}{\mu+\bar{\alpha}}\int_0^\infty \rho(a)\Pi(a)da. \tag{4.14}$$

Here $\mathcal{R}_e$ should be greater than unity for $I^* + T^*$ to be biologically meaningful. The expression $\mathcal{R}_e$ meets the threshold criteria for the existence of endemic equilibrium. We show that the threshold parameter is indeed the reproduction number of the model given (4.1). In fact from its expression, the first term represents new infections due to the interaction of an infected individual in class $I$ with susceptible individuals, and the second term represents new infections as a result of interaction between the infected individual under treatment and susceptible individuals. The term $\int_0^\infty \rho(a)\Pi(a)da$ represents the probability of being recruited for treatment and survived in class $T$. If the person did not start treatment, the second term becomes zero and we get exactly the same expression for the basic reproduction number we find in Chapter (3). The reproduction number that we deduce is an effective reproduction number $\mathcal{R}_e$, not basic since the model incorporates treatment as an intervention to control the hazards due to the disease. As a result, we arrived at the following proposition.

**Proposition 4.2.1.** *The expression $\mathcal{R}_e$ is an effective reproduction number of the model with treatment given (4.1).*

Next, we make use of the effective reproduction number in order to discuss the equilibria. Furthermore, substituting equation (4.5) into equation (4.13) gives

$$I^* + T^* = \frac{\Lambda - B^*}{\mu}(\mathcal{R}_e - 1). \tag{4.15}$$

From equation (4.2) and equation (4.8), we get

$$I^* = B^* \int_0^\infty \Pi(a)da. \tag{4.16}$$

Substituting equations (4.9) and (4.16) into (4.15) yields,

$$B^* = \frac{\Lambda(\mathcal{R}_e - 1)(\mu + \bar{\alpha})}{(\mu + \bar{\alpha})\Big(\mu \int_0^\infty \Pi(a)da + \mathcal{R}_e - 1\Big) + \mu \int_0^\infty \rho(a)\Pi(a)da}, \tag{4.17}$$

which represents the new cases at the endemic equilibrium. Whereas, from the fifth equation of (4.3) and (4.17) one can get

$$A^* = \frac{B^* \int_0^\infty \alpha(a)\Pi(a)da + \bar{\alpha}T^*}{\mu + \nu}. \tag{4.18}$$

Hence, we conclude the following result which connects reproduction number and equilibria.

**Theorem 4.2.2.**

*If $\mathcal{R}_e < 1$, the model given (4.1) has a disease free-equilibrium only given as*

$$E_0 = (S_0, i_0(a), T_0, A_0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right).$$

*If $\mathcal{R}_e > 1$, the model has a unique endemic equilibrium given by*

$$E^* = (S^*, i^*(a), T^*, A^*),$$

$$S^* = \frac{\Lambda - B^*}{\mu}, i^*(a) = B^*\Pi(a), T^* = \frac{B^* \int_0^\infty \rho(a)\Pi(a)da}{\mu + \bar{\alpha}}, A^* \ = \frac{B^* \int_0^\infty \alpha(a)\Pi(a)da + \bar{\alpha}T^*}{\mu + \nu}$$

*and $B^*$ is as given in equation* (4.17).

## 4.3 Numerical Scheme

Using the same techniques we used in Chapter (3), we get the following algorithm for our numerical simulations:

$$
\begin{aligned}
S^{n+1} &= \Lambda h - S^n \left( \frac{ch}{N^n} \frac{k}{2} \left( \beta_0 i_0^n + 2 \sum_{m=1}^{D-1} \beta_m i_m^n + \beta_D i_D^n \right) + h\mu + \frac{\bar{\beta} h c T^n}{N^n} - 1 \right), \\
i_m^n &= \frac{h i_{m-1}^n + i_m^{n-1}}{\frac{h}{k}(\mu + \alpha_m + \rho_m) + h + k}, \\
i_0^n &= \frac{S^n c}{N^n} \frac{k}{2} \left( \beta(0) i_0^{n-1} + 2 \sum_{m=1}^{D-1} \beta_m i_m^{n-1} + \beta(D) i_D^{n-1} \right) + \frac{\bar{\beta} c T^n}{N^n}, \\
I^n &= \frac{k}{2} \left( i_0^n + 2 \sum_{m=1}^{D-1} i_m^n + i_D^n \right), \\
T^{n+1} &= \frac{k}{2} \left( \rho_0 i_0^n + 2 \sum_{m=1}^{D-1} \alpha_m i_m^n + \alpha_D i_D^n \right) + T^n \left( 1 - h(\mu + \bar{\alpha}) \right), \\
A^{n+1} &= \frac{hk}{2} \left( \alpha_0 i_0^n + 2 \sum_{m=1}^{D-1} \alpha_m i_m^n + \alpha_D i_D^n \right) + A^n \left( 1 - h(\mu + \nu) \right) + h\bar{\alpha} T^n.
\end{aligned}
$$

Initial conditions are given by $S^0 = S(0), i_m^0 = \phi(m), T^0 = T(0)$ and $A^0 = A(0)$.

## 4.4 Simulation Results and Discussions

The numerical simulation is done to assess the effect of treatment on the transmission of the disease in the population with different treatment strategies.

### 4.4.1 Self-Motivated HIV Testing Scenario

Here, infected individuals are assumed to go for testing as a response of AIDS-related symptoms. This is more realistic in resource-limited areas especially. Around 80% of adults who are HIV infected are unaware of their HIV status and more than 90% adults in sub-Saharan Africa do not know whether their partners are infected with HIV or not [29].

| Parameter | Value | Reference |
|---|---|---|
| $\Lambda$ | 801403 | Estimated from [52] |
| $\mu$ | 1/34 | [65] |
| $c$ | 2.5 | Fitted |
| $\beta(a)$ | Function | Estimated [24, 32, 55] |
| $\alpha(a)$ | Function | Estimated [32] |
| $\bar{\beta}$ | $12\times10^{-4}$ | Estimated from [48, 65, 55, 51] |
| $\bar{\alpha}$ | 0.055 | Estimated from [8] |
| $\nu$ | 0.115 | [36] |

**Table 4.2.** Parameter values used for the simulation

It can also be called "disease motivated HIV testing scenario" since they go for testing due to the disease. Since they wait until they see AIDS-related symptoms, the number of $CD4^+$ cells is more likely to be less than 200 per $\mu$ $l$ of blood. As a result, all the known HIV positive individuals will be eligible for the treatment. That means, $\rho_0(a) = 100\%$ according to this assumption. Figure (4.3) gives us the numerical simulation for the dynamics of the disease with the above assumption.

To determine the values of $\bar{\beta}$, we use the fact that treatment reduces the viral load to the order of six [48]. The viral load is directly proportional to the probability of transmission, Figures (1.1) and (1.2). As a result, the Probability of infecting while an infected individual is under treatment decreases up to 1% compared to the infectiousness without treatment [55]. Hence, we take $\bar{\beta} = \frac{1}{100}\beta_1 = 12 \times 10^{-4}$. To estimate $\bar{\alpha}$, we take the average survival time under treatment to be 18 years [8]. Hence $\bar{\alpha} = \frac{1}{18} = 0.055y^{-1}$. The initial conditions are $S_0 = 20651120$, $I_0 = 144557, T_0 = 0$ and $A_0 = 0$.

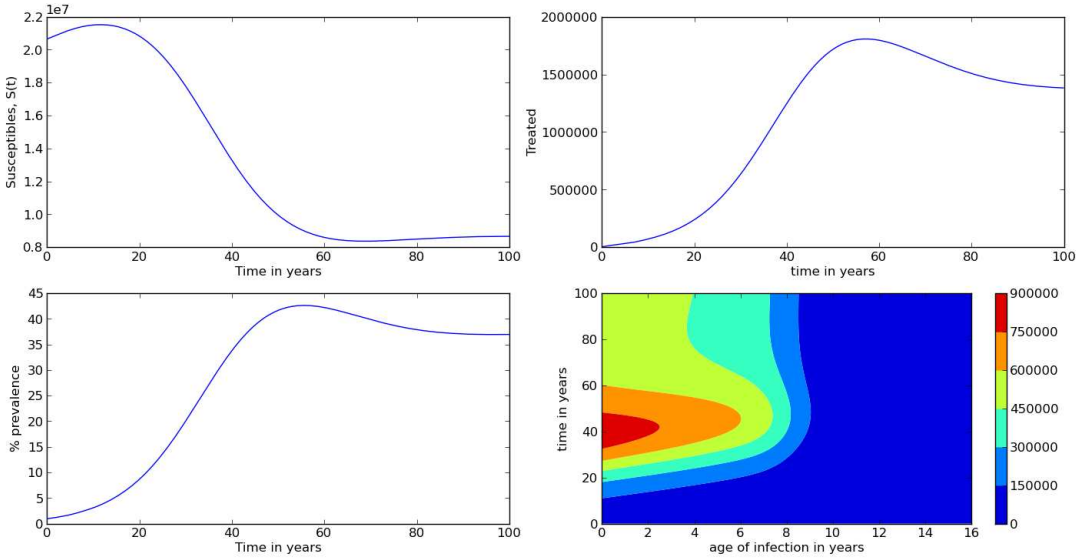


**Figure 4.3.** The dynamics of the disease with late-started treatment

Figure 4.3 shows the dynamics of the disease with $c = 2.5, a^* = 8, n = 12$ and $\mathcal{R}_0 = 1.6$. The contour plot shows that, infected individuals stay longer before they start treatment. The number of susceptible individuals decreases extremely and the prevalence continues increasing. The disease still remains endemic in the population at a high prevalence since infected individuals are starting treatment late, after they infect more than one susceptible.

### 4.4.2 Campaign Aided HIV Testing Strategy

In this section, we consider the universal voluntary test and immediate treatment with ART as suggested by Reuben et al. for the eradication of the disease from the population. According to them, eradication is defined as less than one case per thousand population [55]. It could be achieved through the help of campaigns in creating awareness among the population about the disease. International organizations like USAID and WHO and local governments are trying to increase the understanding of people about HIV/AIDS, providing ART and training how to use as well.

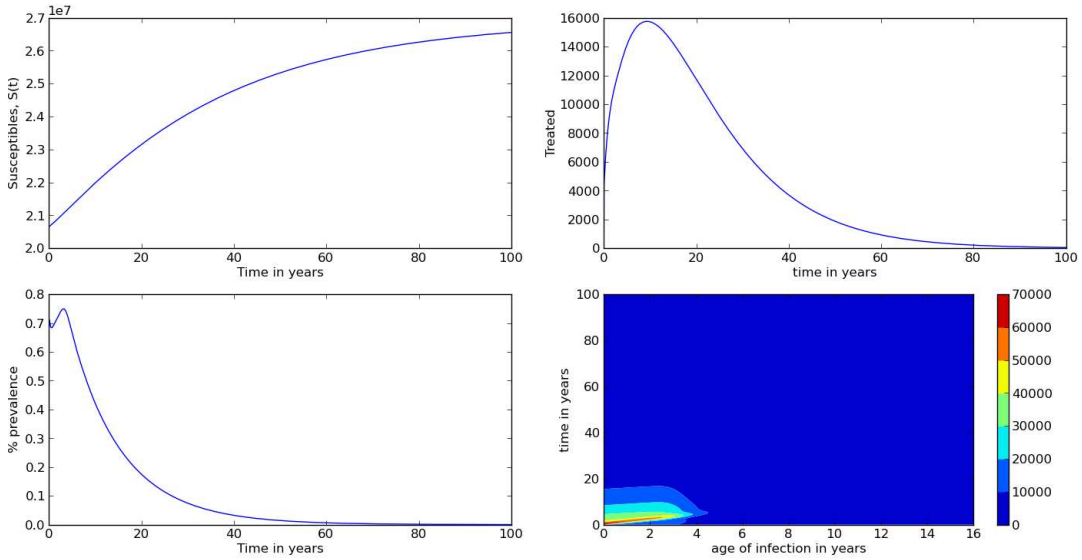


**Figure 4.4.** The dynamics of the disease with early-started treatment

Figure 4.4 represents the dynamics of the disease with parameters $c = 2.5, a^* = 3, n = 12$ and $\mathcal{R} = 0.87$.

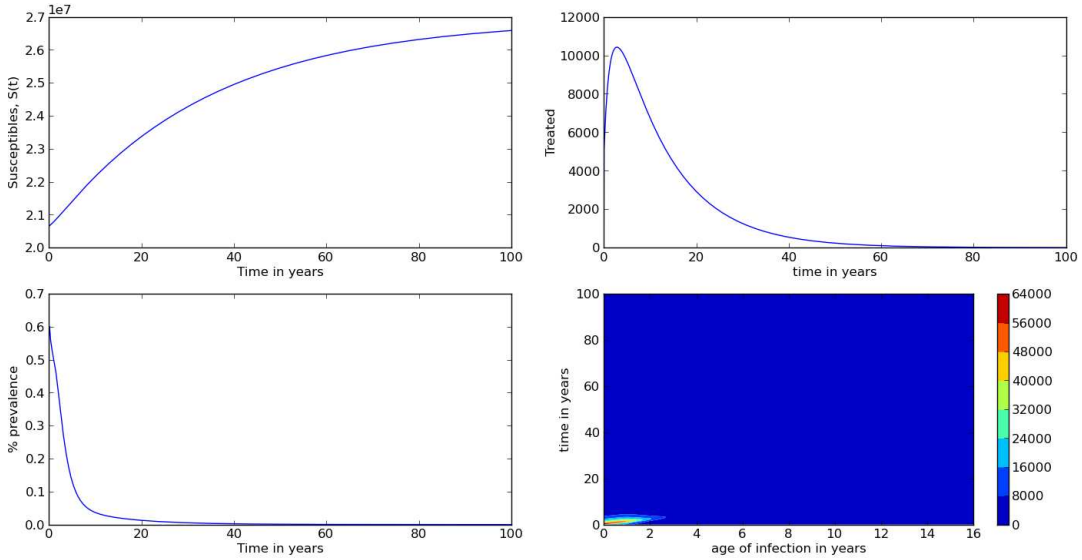


**Figure 4.5.** The dynamics of the disease with early-started treatment

Figure 4.5 represents the dynamics of the disease when $c = 2.5, a^* = 1, n = 12$ and $\mathcal{R}_0 = 0.6$. Here, the number of infected and treated individuals reaches to zero by testing and treating every infected individual every year. Since the early stage of infection is related to high infectiousness, including this stage in the treatment gives a better reduction of new infections. Indeed, early-started treatment highly reduces the infectiousness of infected individuals compared to those who are not under treatment. Interventions considering treatment at early stage of infection will inhibit new infections, as a result will reduce the effective reproduction number bellow one, which leads the disease to extinction. On the other hand, early-started treatment may cause drug resistance and resistant strains of HIV as a result. However, there is no concluding result about drug resistance for early-started treatment compared to late-started treatment. It needs further research in the future.

Comparing Figures 4.4 and 4.5, in both cases the disease dies out. But, in the first case, it takes longer time compared to the second.

### 4.4.3 Dependence of $\mathcal{R}_e$ on $a^*$

In this subsection, we discuss the effect of the average age of infection at which infected individuals go for testing and start treatment $a^*$ on the effective reproduction number $\mathcal{R}_e$.

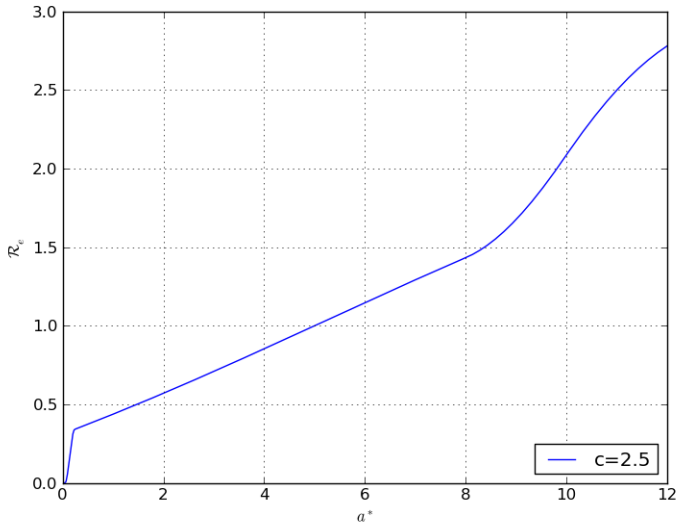


**Figure 4.6.** The dependence of $\mathcal{R}_e$ on $a^*$

Figure 4.6 shows $\mathcal{R}_e$ as a function of $a^*$ for $c = 2.5$ and $n = 12$. The graph has a rapid increase for small values of $a^*$. It correspond to the acute stage of infection which is related to high infectiousness. The slight increase is as a contribution of the asymptomatic stage of infection. Finally, it increases quickly again, as a result of increased infectiousness in the symptomatic stage of infection.

When $a^* = 4$, $\mathcal{R}_e$ is less than one but close to one. Hence, the dynamics takes longer to reach an equilibrium, as shown by Figure Figure 4.4. When $a^*$ decreases, the corresponding value of $\mathcal{R}_e$ also decreases which makes the eradication of the disease earlier, as shown by Figure 4.5. From Figure 4.6, if treatment is not initiated up to age of infection 12 then a single infected individual will infect around 3 susceptible individuals.

The doubling time for $HIV\text{-}AIDS$ epidemic in South Africa is 1.25 years [55]. Whereas, another study shows that the doubling time is 1.5 years [44] in 1990. In a total infectious period of 10 years , an infected individual can infect around 7 susceptible individuals, which we consider as the reproduction number without any intervention (without treatment, behaviour change, ...). In the context of our model 3.6, this corresponds to the effective reproduction number when $a^* = 12$.

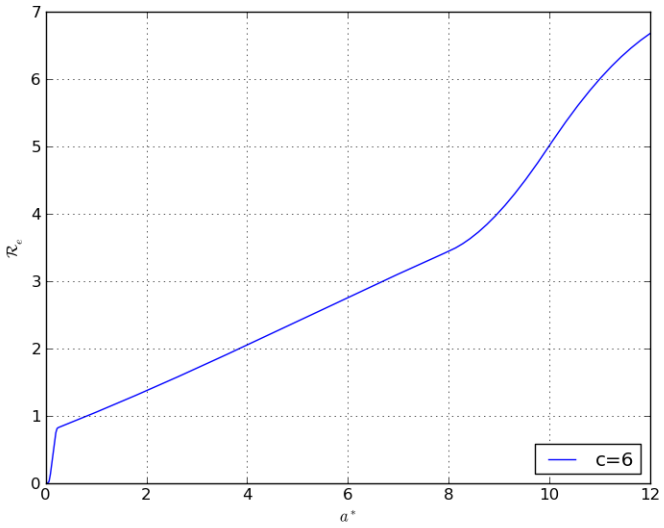


**Figure 4.7.** The dependence of $\mathcal{R}_e$ on $a^*$

Figure 4.7 shows the dependence of the effective reproduction number $\mathcal{R}_e$ on the age of infection at which treatment initiated with $c = 6$ and $n = 12$. We chooses these values in such a way that an infected individual infects 7 susceptible individuals in average throughout his or her infectious period. From the figure, early stage contributes around 10% of the total infection caused by a single individual. It is lower compared to the result given by [24], which is mention between 15% to 20%. The value of the effective reproduction number,$\mathcal{R}_e$ decreases when $a^*$ decreases, but to get the value of $\mathcal{R}_e$ less than one, $a^*$ should also be less than one. Which implies that, to eradicate the disease from the population, all the HIV positive individuals should be treated within one year after infection or earlier. This result is in agreement with the result given by Figure (3) [55].

As we observe from Figure 4.7, the value of the effective reproduction number is already near to one at the very early age of the infection. It is very difficult to reduce the value less than one, since HIV test takes around three months to be detected. To eradicate the disease, other aspects of intervention also need to be considered. For instance, behaviour change which brings reduction of the contact number will help to achieve the eradication of the disease easily (as we have seen in Figures 4.4 and 4.5 ).

## 4.5 Summary

In this chapter, we have seen different treatment scenarios for HIV infected individuals. In the first case we considered that infected individuals go for the test only when there are AIDS-related diseases. This assumption is reliable in resource-limited countries where health care facilities are inadequate and an understanding about HIV/AIDS is limited.

As a result of campaigns support, infected individuals go for the test and know their HIV status before they develop AIDS-related sicknesses which helps them to take action in advance to protect themselves and others also. In this case, we considered a campaign-aided scenario in which infected individuals go for testing earlier, before progressing to AIDS.

Reuben et.al. [55] suggest that a universal volunteer test and treat strategy will lead to an eradication of the disease if all infected individuals would know their HIV status at least once every year; see Figure 3 of [55]. Our numerical simulations also support that, such strategies are needed to eradicate the disease from the population.

# Chapter 5

# Conclusions and Recommendations

## 5.1 Conclusions and Remarks

In this thesis we formulate a mathematical model which is structured according to the age of infection. To understand the dynamics of the disease, we first discuss and analyse a simple model in which the age of infection is not considered, but progression of the HIV/AIDS transmission is taken into consideration by introducing three stages of infection.

Analysis of these models tells us that the disease can be eradicated from the population only if, on average, one infected individual infects less than one person in his or her infectious period, otherwise the disease will persist. To investigate the reduction of the number of infections caused by a single infectious individual to less than one, we introduce different treatment strategies for a model which depends on the age of infection, and we analyse it numerically.

In the first strategy, infected individuals go for testing as a response to AIDS-related diseases. Up to that time, they mix homogeneously with susceptible individuals and as a result they are capable of infecting more than one susceptible individual, which makes the reproduction number more than one and keeps the disease at an endemic level. This strategy only helps infected individuals at the late stage of infection to live longer, but not to eradicate the disease from the population.

Instead of waiting for disease-related symptoms, creating awareness in the population

through campaigns (campaign aided testing strategy) about the disease is necessary for individuals to get tested early and know their HIV status. Depending on how much effort is invested and how the population responds to the information, campaigns help early testing. Once knowing their HIV status, the starting time of the treatment is decided by the countries policy on treatment. In our theoretical strategy, every HIV positive individual is eligible for treatment irrespective of the age of infection, in other words irrespective of the $CD4^+$ count.

Introducing treatment at different ages of infection before developing AIDS-related diseases affects the dynamics to reduce the effective reproduction number even though it is greater than one and the disease remains endemic in the population. To eradicate the disease, testing every individual and treating all the known HIV positive individuals as early as possible is necessary. For contact rate $c = 2.5$, numerical results shows that testing every individual once in four years and treating all the known HIV positive individuals can lead to the eradication of the disease after a long time. But, if every individual gets tested and all those who are identified as positive enter the life-long treatment programme within one year after infection, disease eradication can be attained after 60 years of implementation of the strategy. The newly infected individuals who are in the acute stage (referred to as high infectiousness) get a chance to be under treatment before infecting others. As a result, eradication of the disease could be achieved more quickly. However, for $c = 6$ Figure (4.7) shows that testing everyone every year and immediate treatment for all HIV positive cases is needed to control the disease.

Among the difficulties of the mathematical model of HIV/AIDS under treatment structured by age of infection, is estimating age of infection-dependent parameters. Literature says infectiousness is high in the acute stage, low during the asymptomatic stage and again increases during the symptomatic stage [55, 24]. However, there is no tangible value for the infectiousness corresponding to the age of infection besides the comparison of the stages. To alleviate this, we take data points and interpolate the probability of infectiousness as a function of age of infection. Further study is necessary to get realistic parameter values. Having those challenges in mind, this thesis recommends early treatment for all HIV infected individuals for the eradication of the disease.

## 5.2 Limitations and Future Work

In this thesis work, there are some aspects of HIV/AIDS dynamics which we do not consider when formulating our mathematical models. The reason was to reduce the complexities which would otherwise arise in the mathematical analysis and in estimation of parameters for the numerical simulations. Modification and extension of the models can address the following points:

- TB is one of the most common opportunistic diseases for HIV positive individuals. Especially high TB prevalence areas such as South Africa, considering the co-infection of HIV and TB will help us to better understand the disease transmission, to suggest treatment strategies and make other decisions related to the prevention of the disease.
- To consider more accurate HIV/AIDS models, the age of the infected individual at the time of infection should be considered. This is due to the difference of the response in the immune system for different age groups.
- From the previous studies we reviewed, around 8% of infected individuals who are under treatment stop taking the treatment soon after starting treatment due to drug resistance and other reasons [55]. Including this fact in the modelling will provide us a better insight and good estimate for the projection of the disease dynamics.
- Behavioural change is mostly related to the prevalence of the disease. Hence, including behaviour change is an important factor to validate the model with data. This will give us more realistic values for the parameters in the models.

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