

# MATHEMATICAL ANALYSIS OF PRE-EXPOSURE PROPHYLAXIS ON HIV INFECTION

KOMI AFASSINOU



UNIVERSITY OF KwaZulu-Natal

KOMI AFASSINOU

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

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

Signed: Dr. F. Chirove  Signed: Prof. K. S. Govinder. 

# Abstract

We develop a mathematical model which seeks to assess the impact of HIV Pre-Exposure Prophylaxis (PrEP) on the prevalence and incidence of HIV infection. Mathematical analysis of the model is carried out to establish the threshold conditions that determine the stability of the steady states. Numerical simulations are performed to gain insight into the use and efficacy of PrEP. Results from our model reveal that the basic reproduction number is a function of the rate at which individuals use PrEP and the rate at which PrEP protects individuals from HIV infection. Furthermore, strategies where either PrEP awareness or PrEP efficacy was low show potential loop-holes that can lead to more complications than benefits. The best strategies revealed by our results is that a high level of awareness and high PrEP efficacy are needed.

## Declaration 1

I declare that the contents of this dissertation are original except where due reference has been made. It has not been submitted before for any degree to any other institution.

Komi Afassinou

A handwritten signature in black ink, appearing to read 'Komi Afassinou', written in a cursive style.

## Declaration 2 - Plagiarism

I, **Komi Afassinou**, declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
3. This thesis does not contain other persons data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
  - (a.) Their words have been re-written but the general information attributed to them has been referenced
  - (b.) Where their exact words have been used, then their writing has been placed in italics and inside quotation marks, and referenced.
5. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the references sections.

Signed 

## Acknowledgements

I give thanks to God the Father of the Saviour Jesus Christ for blessing me throughout my studies. My invaluable gratitude goes to my supervisor Dr Farai Chirove and my co-supervisor Prof Kesh Govinder who exposed me to this new field of mathematical biology and for their great assistance and suggestions for the achievement of this research work.

My sincere gratitude goes to AIMS (African Institute for Mathematical Sciences) for financial support. I am grateful to the College of Agriculture, Engineering and Science, to the Dean of the School of Mathematics, Statistics and Computer Science, Professor K S Govinder, for trusting my potential to enrol at UKZN and his financial support, and to all the staff members of the school, especially Ms Nonhlanhla Mkhwanazi, for the warm welcome and kind assistance in accessing facilities.

Finally, I would like to acknowledge my late mother for the education she gave to me and her prophesy on my life. I acknowledge my sister Mrs Agbolo Rose and her husband Mr Agbolo Leopold, and uncles Gavitse Herve and Gavitse Corneil who supported me throughout this studies. Thanks to my Professors Mr H. Quadjovie, Mr A. D'Almeida and Mr K. Assiamoua, my aunt Mrs Cathérine Sama, my grandmother Mrs Apéfavi Afassinou, my friends Roland Loufouma, Dr Kpanzou Tchilabalo Abozou, Mr Kumnandi Piqwa, Ms Alali Adelina, and my officemates for their support and their friendship throughout the year.

# Dedication

To the Almighty God, to the Holy Spirit and Saviour Jesus Christ.

To my late mother Edoh Tchefonagno.

# Contents

<b>Abstract</b>	<b>ii</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Literature review . . . . .	4
1.1.1 HIV infection . . . . .	4
1.1.2 HIV phases of infection progression . . . . .	4
1.2 Basic notions and definitions . . . . .	5
1.2.1 Equilibrium point of a system of equations . . . . .	5
1.2.2 Local and global stability of an equilibrium point . . . . .	5
1.2.3 Spectral radius of a matrix . . . . .	6
1.2.4 Basic reproduction number . . . . .	6
<b>2 REVIEW OF BASIC HIV MODEL</b>	<b>10</b>
2.1 Model description . . . . .	10
2.2 Case 1: Birth rate balanced by death rate with no AIDS deaths . . . . .	11
2.2.1 Nondimensionalization of the model . . . . .	13
2.2.2 Positivity and boundedness of solutions of the model . . . . .	13
2.3 Stability analysis of the equilibrium points . . . . .	15



2.3.1	Disease free equilibrium point (DFE) . . . . .	15
2.3.2	Basic reproduction number . . . . .	15
2.3.3	Stability analysis of the disease free equilibrium . . . . .	17
2.3.4	Endemic equilibrium point (EEP) . . . . .	18
2.3.5	Stability analysis of the endemic equilibrium point . . . . .	18
2.4	Case 2: Birth rate different from death rate with no AIDS deaths . . . . .	20
2.4.1	Comparison and observations . . . . .	22
2.5	Case 3: Birth rate different from death rate with deaths due to AIDS . . . . .	23
2.5.1	Basic reproduction number . . . . .	23
2.5.2	Disease free equilibrium point . . . . .	24
2.5.3	Stability analysis of the disease free equilibrium point . . . . .	24
2.5.4	The endemic equilibrium point . . . . .	25
2.5.5	Stability analysis of the endemic equilibrium point . . . . .	26
2.6	Remarks . . . . .	27
<b>3</b>	<b>PRE-EXPOSURE HIV PROPHYLAXIS MODEL</b>	<b>30</b>
3.1	Introduction . . . . .	30
3.1.1	Model description . . . . .	31
3.1.2	Positivity and boundedness of solutions of the model . . . . .	32
3.2	PrEP model analysis . . . . .	32
3.2.1	Disease free equilibrium point and basic reproduction number . . . . .	33
3.2.2	Influence of PrEP on $\mathcal{R}_0$ . . . . .	35
3.2.3	Mathematical observations and biological interpretation . . . . .	37
3.2.4	Local stability of the disease free equilibrium point . . . . .	40
3.2.5	Global stability of the disease free equilibrium point . . . . .	42

3.2.6	Endemic equilibrium point and its local stability . . . . .	44
<b>4</b>	<b>Numerical Simulations</b>	<b>58</b>
4.1	Introduction . . . . .	58
<b>5</b>	<b>Conclusion</b>	<b>68</b>
5.1	Observations . . . . .	68
5.2	Further Work . . . . .	70
	<b>Bibliography</b>	<b>71</b>

# Chapter 1

## Introduction

HIV infection has been one of the most dramatic pandemic that the world population has ever faced. Since the detection of HIV patients in 1981 [1], the virus invaded the world population and progressively grew to a global pandemic. According to UNAIDS, in 2011 approximately 34 million people were carriers of HIV infection and 1.8 million people died from AIDS [2]. Many preventive strategies including abstinence, reducing number of sexual partners, partner selection, use of male and female condoms, mutual monogamy practice with an HIV-negative partner, and needle hygiene were used by the health care authorities in various settings to reduce and prevent HIV infection [3]. Despite all these efforts, the strategies were shown to be insufficient and inadequate to curb the pandemic.

New preventive interventions are still being investigated in order to stop or to slow down the ongoing progression of the virus. Prophylactic drug administration such as HIV pre-exposure prophylaxis (PrEP) use seemed, recently, to be the most promising and ideal intervention to prevent HIV transmission via sexual intercourses. Prophylaxis is preventive medicine or preventive care consisting of measures taken to prevent the outbreak of some diseases rather than curing them or treating their symptoms [4]. Examples of prophylaxis include measles vaccine, influenza vaccine, birth control pills and antimalarials [4]. In the case of HIV, prophylaxis is administered orally in form of PrEP. Many clinical trials and other research on HIV transmission prevention proved fruitless as they failed to ascertain total safety of individual involved.

Recently, a cellulose sulphate (microbicide) test was stopped prematurely because the gel was ineffective and also exposed the population to a higher risk of infection [5].

However, antiretroviral (ARV) drugs consistently used by infected individuals show significant reduction of the likelihood risk of infecting uninfected individuals. Results from some trials proved that in serodiscordant couples, the infected individuals using ARVs reduces the risk of infecting the seronegative partners by 62% to 73% [6]. Furthermore, in the case of preventing mother-to-child transmission (PMTCT), ARV administration to HIV-infected mothers showed substantial reduction in perinatal HIV transmission [3]. These findings give a motivation to the hypothesis that transmission could be reduced further if treatment was delivered before any potential exposure to HIV infection using PrEP [7]. HIV PrEP consists of taking antiretroviral drugs as daily single doses by uninfected individuals in order to reduce the risk of HIV infection in high risk settings. PrEP awareness, PrEP efficacy and the acceptability of PrEP use are some of the various challenges that concerns the PrEP approach as a preventive measure [3]. Many trials based on PrEP drugs use and PrEP drugs efficacy for HIV prevention are underway across the world.

In 2004–2005, many clinical trials, in different regions of the world, were undertaken in order to evaluate the biological safety of the ARV Tenofovir disoproxil fumarate (TDF) in humans and to assess the acceptability of TDF for PrEP. In Botswana the studies focused on the (sexually active) young adults class, in Thailand (Bangkok) the studies targeted the injection drugs users (IDUs), in Ghana, Cameroon, Nigeria, and Cambodia, female sex workers, and in USA (San Fransisco and Atlanta), men having sex with men (MSM) settings [3]. PrEP use for HIV prevention has thus generated considerable interest in researchers to further explore its benefits.

Mathematical analyses have been carried out to assess the likely impacts of PrEP use as vaccines on HIV/AIDS incidence in various communities. A study by Vissers *et al.* [8] used a mathematical model to fit data collected from some countries which rolled out PrEP use in high risk populations only. The model captured a number of factors affecting PrEP use by categorizing populations through variables such as gender, level of risk, stage of infection and PrEP intake. Their results suggested that high risk behaviour reduced the impact of PrEP use.

However, the study concentrated on simulations and one cannot ascertain the well-posedness of the model used and no mathematical analysis was carried out to ensure validation of mathematical results to the biological set-up of the infection. Bhunu and Mushayabasa [9], formulated a model that highlighted PrEP use as vaccine on susceptible individuals and the existing antiretroviral as therapy for infected individuals in community. Their theoretical results showed, via the reproduction number obtained, that the combined strategies (vaccine + therapy) use in community have a great impact in reduction of HIV transmission rate. They carried out the model analysis validating the results by numerical simulations. However, the efficacy of pre-exposure vaccine that is a main factor affecting PrEP use was not highlighted.

In this study, we develop mathematical models which captures the population dynamics of HIV infection progression and assess the effects of PrEP on HIV incidence and HIV prevalence by incorporating PrEP. We focus and validate the model analysis on two of the factors affecting PrEP use i.e PrEP awareness and PrEP efficacy. We ensure well-posedness of our model in order to trust the validation of the results emanating from the models.

This thesis is divided into five chapters. In the remainder of this first chapter we give definitions of some basic concepts and analytical techniques that are very useful in our analysis. In the second chapter, we review the basic models developed by May and Anderson [10, 11] as a basis for discussing how mathematical models are developed and used to represent the dynamics of HIV. We use various techniques to ensure that the models developed are well-posed. In chapter 3, we incorporate pre-exposure HIV prophylaxis in the model including aspects that measure PrEP awareness and PrEP efficacy. We carry out the analysis of the model and focus on the important threshold parameter that is used as a measure of determining progression of HIV in a population using PrEP. In chapter 4, we carry out numerical simulations to gain more insight in the interpretations of model results and possible predictions. We present different strategies of PrEP use and efficacy and find the best possible strategies revealed by our model. In chapter 5, we discuss our results and give possible recommendations as revealed by our model results as well as limitations for our model.

## 1.1 Literature review

### 1.1.1 HIV infection

Human immunodeficiency virus (HIV) was diagnosed in the first patients in 1981 [1]. Its origin was revealed to be from animal species. HIV invaded the world population and progressively developed into a global pandemic. According to UNAIDS [2], about 34 million people are currently carriers of HIV infection, more than 2.7 million people newly infected of HIV and approximately 1.8 million people died from AIDS in 2011. HIV infection is transmitted through risky exposure to infected blood transfusion, sexual intercourse, mother-to-child during birth or breastfeeding, organ transplant, etc. The virus typically lives off the blood cells ( $CD4^+$  T-cells) which are the system's immune command center. In fact, a healthy individual's blood counts 800 to  $1,200/mm^3$   $CD4^+$  T-cells. An individual is declared HIV positive (or identified as developing AIDS) once the number of the  $CD4^+$  T-cells is less than  $200/mm^3$  [1].

### 1.1.2 HIV phases of infection progression

An individual infected by HIV generally can be asymptomatic or symptomatic as time progresses. These symptoms are manifested progressively and are grouped into distinct categories as follows [12]:

1. **Primary HIV infection stage:** This is a highly infectious stage. It lasts for a few weeks up to three months during which the individual can even be declared HIV-negative. Individuals in this stage are mostly asymptomatic.
2. **Chronic stage:** During this period individuals become symptomatic. This stage can last for a decade or more. The level of infection is low during this stage.
3. **Pre-AIDS stage:** Advanced symptoms such as diarrhoea, loss of weight, fever, cough, etc are observed. The immune system of the patient becomes extremely weak.
4. **AIDS:** This is the last stage of the infection before an individual dies. Severe symptoms

are observed. The individual is exposed to opportunistic infectious diseases such as TB, cholera and malaria amongst others.

## 1.2 Basic notions and definitions

Here we provide some concepts, theorems and definitions used in this thesis.

- **Susceptible individual:** Uninfected individual but who is at risk of HIV infection.
- **Infected individual:** An individual with HIV infection, infectious and capable of passing infection to other individuals.
- **AIDS individual:** HIV-positive individual with full blown AIDS.
- **Force of infection:** The force of infection refers to the rate at which susceptible individuals can be infected by an infected individual through sexual contact or other means such as blood transfusion and use of infected materials.

### 1.2.1 Equilibrium point of a system of equations

**Definition 1.2.1.** Consider the following initial value problem (IVP)

$$\begin{cases} \dot{x}(t) = F(x(t)), & x \in \mathbb{R}^n, \\ x(t_0) = x_0, \end{cases} \quad (1.1)$$

where  $F : \mathbb{R}^n \rightarrow \mathbb{R}^n$ . A point  $x_0^*$  is said to be a fixed point, stationary point, critical point, steady state or equilibrium point of system (1.1) if

$$F(x_0^*) = \mathbf{0}. \quad (1.2)$$

### 1.2.2 Local and global stability of an equilibrium point

The equilibrium point  $x_0^*$  of system (1.1) is said to be **locally stable** if all solutions of system (1.1), with given initial values in a neighbourhood of  $x_0^*$ , remain close to  $x_0^*$  for all time. The

equilibrium point  $x_0^*$  is **asymptotically stable** if it is stable and all solutions of system (1.1) starting near  $x_0^*$  converge to  $x_0^*$  as time goes to infinity. Asymptotic stability of  $x_0^*$  of the system (1.1) can also be inferred when all the eigenvalues of the Jacobian matrix of the system (1.1) are negative or have negative real parts. A point  $x_0^*$  is **globally stable** if its stability is independent of the given initial conditions. An equilibrium point that is not stable is said to be **unstable**.

### 1.2.3 Spectral radius of a matrix

Let  $A$  be an  $n \times n$  matrix and  $\lambda_i$  ( $1 \leq i \leq n$ ) be its eigenvalues. The spectral radius of the matrix  $A$  is the eigenvalue with the largest absolute value, i.e

$$\rho(A) = \max\{|\lambda_i|, i = 1, \dots, n\}.$$

### 1.2.4 Basic reproduction number

This dimensionless positive number is one of the most useful parameters in mathematical analysis of epidemiological models. It is often used to characterize or to describe the progression of an infection in a community. The role played by the reproduction number is to provide information about the spread and the possibilities of the eradication of the infection. This is because its expression is composed of key parameters on which the model assumptions were made.

**Definition 1.2.2.** A function  $h : x \mapsto h(x) \in \mathbb{R}^n$  defined for  $x \in \mathbb{R}^n$  is said to be homogeneous of degree  $\alpha > 0$ , if  $\forall x \in \mathbb{R}^n$ ,  $h$  satisfies [13]

$$h(\lambda x) = \lambda^\alpha h(x), \quad \lambda > 0. \tag{1.3}$$

In particular, for  $\alpha = 1$ ,  $h$  is said to be homogeneous of degree 1.

**Proposition 1.2.3.** *Any homogeneous function  $h$  of degree 1 satisfies the following property (Euler Identity)*

$$\sum_{i=1}^n \frac{\partial h(x)}{\partial x_i} x_i = h(x). \tag{1.4}$$



The homogeneity property of the function allows one to introduce a new variable [13].

**Corollary 1.2.4.** *In general, a system in  $\mathbb{R}^n$  defined as follows*

$$\dot{x} = h(x), \quad x \in \mathbb{R}^n, \quad (1.5)$$

*is said to be homogeneous of degree 1, if  $h$  is homogeneous of degree 1.*

**Proposition 1.2.5.** *Every homogeneous system  $\dot{x} = h(x)$  of dimension  $n$  can be projected onto a hyperplane (of dimension  $n - 1$ ) [13].*

*Proof.* Without loss generality, let us consider the system (1.5) as a biological model defined in a region  $\Omega$  such that  $\Omega$  is positively invariant. The system being homogeneous, we introduce a new variable  $y$  such that

$$y = \frac{x}{N}, \quad x \in \mathbb{R}_+^n,$$

where  $N = x_1 + x_2 + \dots + x_n$  can be the total population of individuals.  $N$  varies in time since  $x_i$  ( $1 \leq i \leq n$ ) varies in time. Then

$$\begin{aligned} \dot{y} &= \frac{\dot{x}}{N} - \frac{x}{N^2} \dot{N} \\ &= \frac{1}{N} h(x) - \frac{x}{N^2} \sum_{i=1}^n h_i(x) \\ &= h\left(\frac{x}{N}\right) - \frac{x}{N} \sum_{i=1}^n h_i\left(\frac{x}{N}\right) \quad \text{since } h \text{ is homogeneous} \\ &= h(y) - y \sum_{i=1}^n h_i(y). \end{aligned}$$

Thus we have

$$\dot{y} = h(y) - y \sum_{i=1}^n h_i(y), \quad (1.6)$$

and

$$\sum_{i=1}^n y_i = 1. \quad (1.7)$$

The system (1.6) is defined in the hyperplane  $\sum_{i=1}^n y_i = 1$ . Thus the system (1.5) is projected onto the hyperplane  $\sum_{i=1}^n y_i = 1$ . In other words, the system (1.6) is said to be the non-dimensionalized form of the system (1.5) [13].  $\square$

**Definition 1.2.6. (Prophylaxis)** The term prophylaxis is regarded as all preventive measures taken by high risk individuals in a community where an epidemic is revealed.

Prophylaxis is simply a way to stamp out an outbreak of a disease or minimize the symptoms of someone who has been exposed to the infection [4]. Two types of prophylaxis are known: pre-exposure prophylaxis and post-exposure prophylaxis. Pre-exposure prophylaxis is a measure taken by susceptible individuals in order to prevent themselves from getting infected while post-exposure prophylaxis refers to any procedures that help to prevent disease or infection immediately after exposure or to ease symptoms associated with the illness [4].

**Theorem 1.2.7.** *Let us consider the following system of ordinary differential equations with a parameter  $\varepsilon$  [14]*

$$\frac{dX}{dt} = f(X, \varepsilon), \quad (1.8)$$

where  $f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}^n$  and  $f \in \mathcal{C}^2(\mathbb{R}^n \times \mathbb{R})$ , so that  $X^* = \mathbf{0}$  is an equilibrium point of system of equations (1.8), that is  $f(0, \varepsilon) = 0$  for all  $\varepsilon$ . In addition, we assume

(i)  $A = Df_X(0, 0) = \frac{\partial f_i}{\partial x_j}(0, 0)$  is the linearization matrix of the system of equations (1.8) around the equilibrium point  $X^* = \mathbf{0}$ , with  $\varepsilon$  evaluated at 0. Zero is a simple eigenvalue of  $A$  and other eigenvalues of  $A$  have negative real parts.

(ii) Matrix  $A$  has a right eigenvector  $U = (u_i)$  ( $1 \leq i \leq n$ ) and a left eigenvector  $V = (v_j)$  ( $1 \leq j \leq n$ ) corresponding to the zero eigenvalue.

Let  $f_k$  be the  $k^{\text{th}}$  component of  $f$  such that

$$a = \sum v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \quad b = \sum v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \varepsilon}(0, 0). \quad (1.9)$$

The local stability of the equilibrium point  $X^* = \mathbf{0}$  is confirmed by the signs of  $a$  and  $b$ .

(I)  $a > 0, b > 0$ . When  $\varepsilon < 0$ , with  $|\varepsilon| \ll 1$ ,  $\mathbf{0}$  is locally asymptotically stable, and there exists a positive unstable equilibrium. When  $0 < \varepsilon \ll 1$ ,  $\mathbf{0}$  is unstable and there exists a negative and locally asymptotically stable equilibrium.

(II)  $a < 0, b < 0$ . When  $\varepsilon < 0$  with  $|\varepsilon| \ll 1$ ,  $\mathbf{0}$  is unstable. When  $0 < \varepsilon \ll 1$ ,  $\mathbf{0}$  is locally asymptotically stable, and there exists a positive unstable equilibrium.

(III)  $a > 0, b < 0$ . When  $\varepsilon < 0$ ,  $\mathbf{0}$  is unstable, and there exists a locally asymptotically stable negative equilibrium. When  $0 < \varepsilon \ll 1$ ,  $\mathbf{0}$  is stable, and a positive unstable equilibrium appears.

(IV)  $a < 0, b > 0$ . When  $\varepsilon$  changes from negative to positive,  $\mathbf{0}$  changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

**Theorem 1.2.8.** Consider an epidemic model [15]

$$\frac{dZ}{dt} = F(X, Y), \quad (1.10)$$

which is written in the form

$$\begin{aligned} \frac{dX}{dt} &= G(X, Y), \\ \frac{dY}{dt} &= H(X, Y), \quad H(X, 0) = 0, \end{aligned}$$

where the vector  $X \in \mathbb{R}^m$  (its components) denotes the number of uninfected individuals and the vector  $Y \in \mathbb{R}^n$  (its components) denotes the number of infected individuals and  $\varepsilon_0 = (X_0, 0)$  denotes the disease-free equilibrium of the system (1.10). If the following conditions are satisfied

- (i) For  $\frac{dX}{dt} = G(X, 0)$ ,  $X_0$  is globally asymptotically stable,
- (ii)  $H(X, Y) = BY - \hat{H}(X, Y)$ ,  $\hat{H}(X, Y) \geq 0$  for  $(X, Y) \in \Omega$ ,

where  $\Omega$  is the region where the model makes biological sense,  $B = D_X H(X_0, 0)$  is a matrix with off diagonal elements positive, then the disease-free equilibrium  $\varepsilon_0 = (X_0, 0)$  is a globally asymptotically stable equilibrium point of (1.10) provided the basic reproduction number of the model is less than one.

# Chapter 2

## REVIEW OF BASIC HIV MODEL

### 2.1 Model description

We consider a simple HIV/AIDS model (see Figure 2.1) governed by the system of non-linear equations below:

$$\begin{aligned}\dot{S} &= bN - \lambda S - \mu S, \\ \dot{I} &= \lambda S - (\rho_1 + \mu)I, \\ \dot{A} &= \rho_1 I - (\mu + \delta)A.\end{aligned}\tag{2.1}$$

We consider a population of size  $N$ , which is divided into susceptible individuals ( $S$ ), infected individuals ( $I$ ) and AIDS individuals ( $A$ ) so that

$$N = S + I + A.\tag{2.2}$$

We denote by  $\lambda$ , the force of infection. We assume that a proportion  $\lambda$  of susceptible individuals become infected by infectious individuals and AIDS individuals so that their number diminishes at the rate  $\lambda S$  while the number of infected individuals increases at the same rate. The force of infection is

$$\lambda = \frac{c(\eta_1 I + \eta_2 A)}{N}.\tag{2.3}$$

We consider recruitment of individuals,  $bN$ , as the source of susceptible individuals. The natural death rate is denoted by  $\mu$  and the natural birth rate by  $b$ . We assume that AIDS individuals

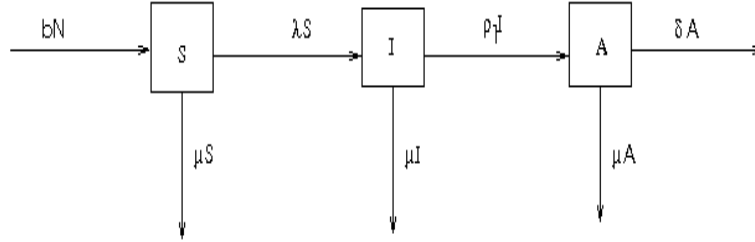


Figure 2.1: Flow diagram for the model

are dying either by natural death or from AIDS at the rate  $\delta$ . A proportion  $\rho_1$  of infected individuals progresses to the full blown AIDS class. The negative terms in the three equations of (2.1) indicate the movement of individuals out of a class while the positive terms denotes movement into a class.

We analyse the model (2.1) by computing the basic reproduction number of the model using van den Driessche and Watmough's approach [16] and study the (local) stability of its equilibrium points. Firstly, we simplify the model by considering the case  $\delta = 0$  and  $\mu = b$ , carry out the model analysis and relax these assumptions subsequently. We assume that  $S(t)$ ,  $I(t)$ , and  $A(t)$  are positive functions for all  $t \geq 0$ , continuous, at least twice differentiable and that all the parameters defined are positive. In Table 2.1, we define each variable and each parameter in the system (2.1).

## 2.2 Case 1: Birth rate balanced by death rate with no AIDS deaths

In this case, we assume that the full blown AIDS individuals are not dying from AIDS ( $\delta = 0$ ) and all deaths are due to natural causes and that the natural birth rate is equal to the natural death rate ( $b = \mu$ ). The system (2.1) becomes

Table 2.1: Parameters and variables used in the model.

Variables	Description
$S$	Number of susceptible individuals.
$I$	Number of infected individuals.
$A$	Number of individuals suffering from AIDS.
$N$	Total size of population considered.
Parameters	Description
$b$	Natural birth rate.
$\mu$	Natural death rate.
$\delta$	Death rate due to AIDS.
$\rho_1$	Progression rate from infected class to AIDS class.
$\eta_1$	Contact rate of infected person and susceptible person.
$\eta_2$	Contact rate of AIDS person and susceptible person.
$c$	Average number of new sexual partners acquired per unit time.
$\lambda$	Force of infection.

$$\begin{aligned}
 \dot{S} &= \mu N - \frac{c(\eta_1 I + \eta_2 A)}{N} S - \mu S, \\
 \dot{I} &= \frac{c(\eta_1 I + \eta_2 A)}{N} S - (\rho_1 + \mu) I, \\
 \dot{A} &= \rho_1 I - \mu A.
 \end{aligned} \tag{2.4}$$

Adding the three equations of system (2.4) we have

$$\dot{N} = \dot{S} + \dot{I} + \dot{A} = \mu N - \mu(S + I + A) = 0. \tag{2.5}$$

The total population  $N$  considered is therefore constant.

### 2.2.1 Nondimensionalization of the model

From system (2.4) we pose

$$h(S, I, A) = (\dot{S}, \dot{I}, \dot{A}). \quad (2.6)$$

Since for  $\lambda > 0$ , we have

$$\begin{aligned} h(\lambda S, \lambda I, \lambda A) &= \left( \mu\lambda N - \frac{c(\eta_1\lambda I + \eta_2\lambda A)}{\lambda N} \lambda S - \mu\lambda S, \frac{c(\eta_1\lambda I + \eta_2\lambda A)}{\lambda N} \lambda S - (\rho_1 + \mu)\lambda I, \rho_1\lambda I - \mu\lambda A \right) \\ &= \lambda \left( \mu N - \frac{c(\eta_1 I + \eta_2 A)}{N} S - \mu S, \frac{c(\eta_1 I + \eta_2 A)}{N} S - (\rho_1 + \mu)I, \rho_1 I - \mu A \right) \\ &= \lambda h(S, I, A), \end{aligned}$$

$h(S, I, A)$  is homogeneous of degree 1.

Therefore we nondimensionalize the system (2.4) by setting

$$s = \frac{S}{N}, \quad i = \frac{I}{N}, \quad a = \frac{A}{N}, \quad \dot{s} = \frac{\dot{S}}{N}, \quad \dot{i} = \frac{\dot{I}}{N}, \quad \dot{a} = \frac{\dot{A}}{N}. \quad (2.7)$$

Substituting (2.7) into the system of equations (2.4) we have

$$\begin{aligned} \dot{s} &= \mu - c(\eta_1 i + \eta_2 a)s - \mu s, \\ \dot{i} &= c(\eta_1 i + \eta_2 a)s - (\rho_1 + \mu)i, \\ \dot{a} &= \rho_1 i - \mu a, \end{aligned} \quad (2.8)$$

with

$$s + i + a = 1. \quad (2.9)$$

### 2.2.2 Positivity and boundedness of solutions of the model

We define the feasible region (region with positive solutions) of model (2.8) to be

$$\Omega = \{(s, i, a) \in \mathbb{R}_+^3 \mid s \geq 0, i \geq 0, a \geq 0, s + i + a = 1\}. \quad (2.10)$$

We proceed to prove that  $\Omega$  is positively invariant and solutions in  $\Omega$  are bounded in the following theorem.

**Theorem 2.2.1.**  $\Omega$  is positively invariant for the system (2.8) and there exists a constant  $\mathcal{M} > 0$  such that all solutions starting in  $\Omega$  satisfy  $s, i, a \leq \mathcal{M}$  for all large  $t$ .

*Proof.* We assume that  $s(0) > 0$ ,  $i(0) > 0$  and  $a(0) > 0$ . Considering the first equation of (2.8), we obtain the integrating factor

$$\varphi(t) = e^{\int_0^t (c\eta_1 i(\tau) + c\eta_2 a(\tau) + \mu) d\tau}. \quad (2.11)$$

$$\begin{aligned} \frac{d}{dt}(\varphi(t)s(t)) &= \dot{\varphi}(t)s(t) + \varphi(t)\dot{s}(t) \\ &= (c\eta_1 i(t) + c\eta_2 a(t) + \mu)\varphi(t)s(t) - (c\eta_1 i(t) + c\eta_2 a + \mu)\varphi(t)s(t) + \mu\varphi(t) \\ &= \mu\varphi(t). \end{aligned}$$

Integrating both sides we have

$$\begin{aligned} \varphi(t)s(t) &= s(0) + \mu \int_0^t \varphi(\tau) d\tau, \\ &> 0 \quad \text{for all } t \geq 0. \end{aligned} \quad (2.12)$$

Similarly, let us consider the equation

$$\dot{a}(t) = \rho_1 i(t) - \mu a(t) \quad (2.13)$$

$$= \rho_1(1 - s(t) - a(t)) - \mu a(t) \quad (2.14)$$

$$= \rho_1(1 - s(t)) - (\rho_1 + \mu)a(t). \quad (2.15)$$

We obtain the integrating factor

$$\Phi(t) = e^{\int_0^t (\mu + \rho_1) d\tau} = e^{(\mu + \rho_1)t}. \quad (2.16)$$

We have

$$\frac{d}{dt}(\Phi(t)a(t)) = \dot{\Phi}(t)a(t) + \Phi(t)\dot{a}(t) \quad (2.17)$$

$$= (\rho_1 + \mu)a(t)\Phi(t) - (\rho_1 + \mu)a(t)\Phi(t) + \rho_1(1 - s(t))\Phi(t) \quad (2.18)$$

$$= \rho_1(1 - s(t))\Phi(t). \quad (2.19)$$



Integrating both sides of equation (2.19), we obtain

$$\Phi(t)a(t) = a(0) + \rho_1 \int_0^t (1 - s(\tau))\Phi(\tau)d\tau, \quad (2.20)$$

$$> 0 \quad \text{since} \quad 0 < s(t) \leq 1 \quad \text{for all} \quad t \geq 0. \quad (2.21)$$

Since  $s(t) + i(t) + a(t) = 1$ ,  $i(t) = 1 - s(t) - a(t) > 0$  for all  $t \geq 0$ . Thus the region  $\Omega$  is positively invariant.

We know that  $0 < s(t) \leq 1$ ,  $0 < i(t) \leq 1$ ,  $0 < a(t) \leq 1$  and  $s(t) + i(t) + a(t) = 1$ . Choosing  $\mathcal{M} = 1$ , gives  $0 < s(t) \leq \mathcal{M}$ ,  $0 < i(t) \leq \mathcal{M}$ ,  $0 < a(t) \leq \mathcal{M}$ , for all large  $t$ . Therefore all solutions of the system of equation (2.4) starting in the region  $\Omega$  are bounded. This completes the proof of the theorem.  $\square$

## 2.3 Stability analysis of the equilibrium points

### 2.3.1 Disease free equilibrium point (DFE)

The disease free equilibrium point of the model is a solution of the system when there is no infection in the population. We calculate the DFE of the system of equations (2.8) for  $s$ ,  $i$ , and  $a$  by setting  $\dot{s} = 0$ ,  $\dot{i} = 0$ , and  $\dot{a} = 0$ , with  $i = 0$  and  $a = 0$  to yield,

$$s = 1. \quad (2.22)$$

The disease free equilibrium point of the system of equations (2.8) is

$$E_0 = (1, 0, 0). \quad (2.23)$$

### 2.3.2 Basic reproduction number

The basic reproduction number, denoted by  $\mathcal{R}_0$ , is defined as the expected number of secondary infections that result from introducing a single infected individual into a purely susceptible population. For a simple model where there is only one infected compartment,  $\mathcal{R}_0$  is simply the product of the infection rate and the mean duration of the infection [16]. However, for a

model with more than one infected compartments, we compute  $\mathcal{R}_0$  by using the next generation matrix approach used by Watmough and Van Den Driessche [16]. According to Watmough and van den Driessche, the basic reproduction number  $\mathcal{R}_0$  is defined by

$$\mathcal{R}_0 = \rho(FV^{-1}), \quad (2.24)$$

where

- $F = (f_{ij})$  is a matrix for which the entry  $(i, j)$  is the rate at which infected individuals in compartment  $j$  produce new infections in compartment  $i$ .
- $V^{-1} = (v_{jk})$  is a matrix for which the entry  $(j, k)$  is the average duration of the infected individuals in compartment  $j$ .
- $\rho(FV^{-1})$  is the spectral radius of the next generation matrix  $FV^{-1}$ .

Considering the infected compartments ( $i$  and  $a$ ) in model (2.8) and using the same notation as used in [16], the matrix of rate of appearance of new infection,  $\mathcal{F}$ , and the matrix of rate of transfer individuals  $\mathcal{V}$  are given by

$$\mathcal{F} = \begin{bmatrix} c(\eta_1 i + \eta_2 a)s \\ 0 \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} (\rho_1 + \mu)i \\ -\rho_1 i + \mu a \end{bmatrix}. \quad (2.25)$$

Evaluating the Jacobian matrices of  $\mathcal{F}$  and  $\mathcal{V}$  at  $E_0$  we have

$$F = \left[ \frac{\partial \mathcal{F}_i}{\partial x_j}(E_0) \right] = \begin{bmatrix} c\eta_1 s & c\eta_2 s \\ 0 & 0 \end{bmatrix}, \quad V = \left[ \frac{\partial \mathcal{V}_i}{\partial x_j}(E_0) \right] = \begin{bmatrix} (\rho_1 + \mu) & 0 \\ -\rho_1 & \mu \end{bmatrix}. \quad (2.26)$$

It follows that

$$V^{-1} = \begin{bmatrix} \frac{1}{\rho_1 + \mu} & 0 \\ \frac{\rho_1}{\mu(\rho_1 + \mu)} & \frac{1}{\mu} \end{bmatrix}. \quad (2.27)$$

Thus the next generation matrix of the system of equations (2.8) is given by

$$FV^{-1} = \begin{bmatrix} \frac{c\eta_1 \mu + c\eta_2 \rho_1}{\mu(\rho_1 + \mu)} & \frac{c\eta_2}{\mu} \\ 0 & 0 \end{bmatrix}. \quad (2.28)$$

The next generation matrix  $FV^{-1}$  has only one non-zero eigenvalue. The basic reproduction number of the system of equations (2.8) is

$$\mathcal{R}_0 = \frac{c(\eta_1\mu + \eta_2\rho_1)}{\mu(\rho_1 + \mu)}. \quad (2.29)$$

Moreover,  $\mathcal{R}_0$  can be written in the form

$$\mathcal{R}_0 = \frac{c\eta_1}{\rho_1 + \mu} + \frac{c\eta_2\rho_1}{\mu(\mu + \rho_1)}, \quad (2.30)$$

where the first term is a contribution of infected individuals in the infected class and the second term is that of AIDS individuals in contact with susceptible individuals.

### 2.3.3 Stability analysis of the disease free equilibrium

To analyse the stability of the DFE, we evaluate the Jacobian matrix of the system of equations (2.8) at  $E_0$ . We have

$$J_{E_0} = \begin{bmatrix} -\mu & -c\eta_1 & -c\eta_2 \\ 0 & c\eta_1 - (\rho_1 + \mu) & c\eta_2 \\ 0 & \rho_1 & -\mu \end{bmatrix}, \quad (2.31)$$

with characteristic equation given by

$$\det(J_{E_0} - \lambda I) = 0. \quad (2.32)$$

This gives

$$(\mu + \lambda)(\lambda^2 + b_1\lambda + b_0) = 0, \quad (2.33)$$

with  $b_1 = 2\mu + \rho_1 - c\eta_1$ ,  $b_0 = \mu(\mu + \rho_1)(1 - \mathcal{R}_0)$ .

The disease free equilibrium point  $E_0$  is locally asymptotically stable if all the eigenvalues of the Jacobian matrix  $J_{E_0}$  are negative or have negative real parts and unstable if at least one eigenvalue is positive or has a positive real part.

The characteristic equation (2.33) has at most three solutions. The first is  $\lambda_1 = -\mu < 0$ . The other two eigenvalues are roots of the quadratic equation  $\lambda^2 + b_1\lambda + b_0 = 0$ , with solution

$$\lambda_{2,3} = \frac{-b_1}{2} \pm \sqrt{\left(\frac{b_1}{2}\right)^2 - b_0}. \quad (2.34)$$

In order to have eigenvalues with negative real parts, it is sufficient that  $b_0 > 0$ . This is achieved when  $\mathcal{R}_0 < 1$ . We summarize the result into the following theorem.

**Theorem 2.3.1.** *The disease free equilibrium point  $E_0$  is locally asymptotically stable when  $\mathcal{R}_0 < 1$  and unstable when  $\mathcal{R}_0 > 1$ .*

### 2.3.4 Endemic equilibrium point (EEP)

We compute the endemic equilibrium point when  $i \neq 0$  and  $a \neq 0$ , that is when the infection persists.

Solving the system (2.8) for  $s^*$ ,  $i^*$ , and  $a^*$ , the last equation yields

$$a^* = \frac{\rho_1}{\mu} i^*. \quad (2.35)$$

Adding the first and the second equations of the system (2.8) yields

$$s^* = 1 - \left(1 + \frac{\rho_1}{\mu}\right) i^*. \quad (2.36)$$

Substituting (2.36) into the first equation of the system (2.8), we obtain

$$i^* = \frac{\mu(\mathcal{R}_0 - 1)}{(\rho_1 + \mu)\mathcal{R}_0}. \quad (2.37)$$

Manipulating (2.35), (2.36) and (2.37) we obtain the endemic equilibrium point given by

$$E_1 = \left( \frac{1}{\mathcal{R}_0}, \frac{\mu(\mathcal{R}_0 - 1)}{(\rho_1 + \mu)\mathcal{R}_0}, \frac{\rho_1(\mathcal{R}_0 - 1)}{(\rho_1 + \mu)\mathcal{R}_0} \right). \quad (2.38)$$

The endemic equilibrium  $E_1$  exists when  $\mathcal{R}_0 > 1$ .

### 2.3.5 Stability analysis of the endemic equilibrium point

We analyse the stability of the endemic equilibrium point of the system of equations (2.8) by proving the following theorem:

**Theorem 2.3.2.** *The endemic equilibrium of the system (2.8) is locally asymptotically stable when  $\mathcal{R}_0 > 1$ .*

*Proof.* The Jacobian matrix of system (2.8) evaluated at the endemic equilibrium point  $E_1$  is given by

$$J_{E_1} = \begin{bmatrix} -\mu - c(\eta_1 i^* + \eta_2 a^*) & -c\eta_1 s^* & -c\eta_2 s^* \\ c(\eta_1 i^* + \eta_2 a^*) & c\eta_1 s^* - (\rho_1 + \mu) & c\eta_2 s^* \\ 0 & \rho_1 & -\mu \end{bmatrix}. \quad (2.39)$$

Substituting  $s^*$ ,  $i^*$  and  $a^*$  into  $J_{E_1}$ , we obtain

$$J_{E_1} = \begin{bmatrix} -\mu\mathcal{R}_0 & -\frac{c\eta_1}{\mathcal{R}_0} & -\frac{c\eta_2}{\mathcal{R}_0} \\ \mu(\mathcal{R}_0 - 1) & \frac{c\eta_1}{\mathcal{R}_0} - (\rho_1 + \mu) & \frac{c\eta_2}{\mathcal{R}_0} \\ 0 & \rho_1 & -\mu \end{bmatrix}. \quad (2.40)$$

The characteristic equation of the matrix (2.40) is given by

$$\det(J_{E_1} - \lambda I) = \begin{vmatrix} -\mu\mathcal{R}_0 - \lambda & -\frac{c\eta_1}{\mathcal{R}_0} & -\frac{c\eta_2}{\mathcal{R}_0} \\ \mu(\mathcal{R}_0 - 1) & \frac{c\eta_1}{\mathcal{R}_0} - (\rho_1 + \mu) - \lambda & \frac{c\eta_2}{\mathcal{R}_0} \\ 0 & \rho_1 & -\mu - \lambda \end{vmatrix} = 0. \quad (2.41)$$

Expanding the determinant in equation (2.41) along the third row, we have

$$(\lambda + \mu)(\lambda^2 + a_1\lambda + a_0) = 0, \quad (2.42)$$

where  $a_1 = \mu\mathcal{R}_0 + \rho_1 + \mu - \frac{c\eta_1}{\mathcal{R}_0}$ ,  $a_0 = \mu(\rho_1 + \mu)(\mathcal{R}_0 - 1)$ .

The solutions of the characteristic equation (2.42) are  $\lambda_1 = -\mu < 0$  and the other two are solutions of the quadratic equation  $\lambda^2 + a_1\lambda + a_0 = 0$  which are

$$\lambda_{2,3} = -\frac{a_1}{2} \pm \sqrt{\left(\frac{a_1}{2}\right)^2 - a_0}.$$

The eigenvalues  $\lambda_{2,3}$  have negative real parts when  $a_0 > 0$ , that is  $\mathcal{R}_0 > 1$ . This completes the proof of the theorem.  $\square$

**Remark 2.3.3.**

1. For  $0 < \mathcal{R}_0 < 1$ , the disease free equilibrium point  $E_0 = (1, 0, 0)$  is the only equilibrium that exists and it is locally asymptotically stable in  $\Omega$ . This means, when  $\mathcal{R}_0$  is less than unity, an infected individual produces less than one new infected individual and the epidemic dies out.

2. For  $\mathcal{R}_0=1$ , the DFE and EEP coalesce. A phenomenon known as supercritical bifurcation occurs. There is exchange of stability between the DFE and EEP.
3. For  $\mathcal{R}_0 > 1$ , the DFE  $E_0$  becomes unstable and a new equilibrium point, the endemic equilibrium point (EEP) exists and it is locally asymptotically stable in  $\Omega$ . In this case, all solutions starting inside  $\Omega$  converge to the EEP. Each infected individual produces more than one new infected individuals and the epidemic persists in the population.

## 2.4 Case 2: Birth rate different from death rate with no AIDS deaths

In this case, we consider the fact that the birth rate is different from the natural death rate, i.e  $b \neq \mu$  and there are no deaths due to AIDS.

$$\begin{aligned}
\dot{S} &= bN - \frac{c(\eta_1 I + \eta_2 A)}{N} S - \mu S, \\
\dot{I} &= \frac{c(\eta_1 I + \eta_2 A)}{N} S - (\rho_1 + \mu) I, \\
\dot{A} &= \rho_1 I - \mu A.
\end{aligned} \tag{2.43}$$

Adding the three equations of the system (2.43), we have

$$\dot{N} = \dot{S} + \dot{I} + \dot{A} = (b - \mu)N. \tag{2.44}$$

Since  $b \neq \mu$ , then  $\dot{N}(t) \neq 0$ . This means that  $N(t)$  varies in time, and from (2.44) we obtain

$$N(t) = N_0 e^{(b-\mu)t}, \tag{2.45}$$

where  $N = N_0$  at  $t = 0$ .

From (2.45), we note that if  $b > \mu$ , that is when the natural birth rate is greater than the natural death rate,  $N(t) \rightarrow \infty$  as  $t \rightarrow \infty$  and if  $b < \mu$ , that is when the natural death rate goes above the natural birth rate,  $N(t) \rightarrow 0$  (extinction) as  $t \rightarrow \infty$ .

We non-dimensionalize the system of equation (2.43) by setting

$$s = \frac{S}{N}, \quad i = \frac{I}{N}, \quad a = \frac{A}{N}. \tag{2.46}$$

Then

$$\begin{aligned}
\dot{s} &= \frac{\dot{S}}{N} - \frac{S}{N^2}\dot{N} \\
&= \frac{1}{N} \left( bN - \frac{c(\eta_1 I + \eta_2 A)}{N} S - \mu S \right) - \frac{S}{N^2}(b - \mu)N \\
&= b - c(\eta_1 i + \eta_2 a)s - \mu s - (b - \mu)s \\
&= b - (c\eta_1 i + c\eta_2 a)s - bs.
\end{aligned}$$

$$\begin{aligned}
\dot{i} &= \frac{\dot{I}}{N} - \frac{I}{N^2}\dot{N} \\
&= c(\eta_1 i + \eta_2 a)s - (\rho_1 + \mu)i - (b - \mu)i \\
&= c(\eta_1 i + \eta_2 a)s - (\rho_1 + b)i.
\end{aligned}$$

Similarly, we obtain  $\dot{a} = \rho_1 i - ba$ .

The non-dimensionlazed system of (2.43) becomes

$$\begin{aligned}
\dot{s} &= b - c(\eta_1 i + \eta_2 a)s - bs, \\
\dot{i} &= c(\eta_1 i + \eta_2 a)s - (\rho_1 + b)i, \\
\dot{a} &= \rho_1 i - ba.
\end{aligned} \tag{2.47}$$

with

$$s + i + a = 1. \tag{2.48}$$

Note that the system of equations (2.47) has the same form as the system of equations (2.8), except that we have  $b$  in the dynamics and not  $\mu$ . Therefore we can apply the same techniques as in section 2.2 for stability analysis of the model.

We thus consider the region  $\Omega$  defined as follows, as the biologically feasible region of the system (2.47):

$$\Omega = \{(s, i, a) \in \mathbb{R}_+^3 \mid s \geq 0, i \geq 0, a \geq 0, s + i + a = 1\}. \tag{2.49}$$

As proved in section 2.2,  $\Omega$  is positively invariant and attracting. The DFE point is the same as that in section 2.2 and the basic reproduction number depending on  $b$  is given by

$$\mathcal{R}_b = \frac{c(\eta_1 b + \eta_2 \rho_1)}{b(\rho_1 + b)}. \tag{2.50}$$

**Theorem 2.4.1.** *The disease free equilibrium point  $E_b$  of the system (2.47) is locally asymptotically stable when  $\mathcal{R}_b < 1$  and unstable when  $\mathcal{R}_b > 1$ .*

The proof of this theorem is similar to that of theorem 2.3.1.

The endemic equilibrium point is given by

$$E_b^* = \left( \frac{1}{\mathcal{R}_b}, \frac{b(\mathcal{R}_b - 1)}{(\rho_1 + b)\mathcal{R}_b}, \frac{\rho_1(\mathcal{R}_b - 1)}{(\rho_1 + b)\mathcal{R}_b} \right), \quad (2.51)$$

and the existence of stability conditions are summarized in the following theorem:

**Theorem 2.4.2.** *The endemic equilibrium point of the system of equations (2.47) exists and is locally asymptotically stable when  $\mathcal{R}_b > 1$ .*

### 2.4.1 Comparison and observations

We compare the basic reproduction number found in the cases  $b = \mu$  and  $b \neq \mu$ .

Setting  $\mathcal{R} = \mathcal{R}_b - \mathcal{R}_0$ , then

$$\begin{aligned} \mathcal{R} &= \frac{c(\eta_1 b + \eta_2 \rho_1)}{b(\rho_1 + b)} - \frac{c(\eta_1 \mu + \eta_2 \rho_1)}{\mu(\rho_1 + \mu)} \\ &= \frac{c\eta_1}{(b + \rho_1)} + \frac{c\eta_2 \rho_1}{b(\rho_1 + b)} - \frac{c\eta_1}{(\mu + \rho_1)} - \frac{c\eta_2 \rho_1}{\mu(\rho_1 + \mu)} \\ &= \frac{c\eta_1}{(b + \rho_1)} - \frac{c\eta_1}{(\mu + \rho_1)} + \frac{c\eta_2 \rho_1}{b(\rho_1 + b)} - \frac{c\eta_2 \rho_1}{\mu(\rho_1 + \mu)} \\ &= \frac{c\eta_1(\mu - b)}{(\rho_1 + \mu)(\rho_1 + b)} + \frac{c\eta_2 \rho_1(\mu - b)(b + \mu)}{b\mu(\rho_1 + \mu)(\rho_1 + b)} + \frac{c\eta_2 \rho_1^2(\mu - b)}{b\mu(\rho_1 + \mu)(\rho_1 + b)} \\ &= (\mu - b) \left[ \frac{c\eta_1}{(\rho_1 + \mu)(\rho_1 + b)} + \frac{c\eta_2 \rho_1(b + \mu)}{b\mu(\rho_1 + \mu)(\rho_1 + b)} + \frac{c\eta_2 \rho_1^2}{b\mu(\rho_1 + \mu)(\rho_1 + b)} \right] \\ &= (\mu - b) \left[ \frac{cb\eta_1 \mu + c\eta_2(b + \mu)\rho_1 + c\eta_2 \rho_1^2}{b\mu(\rho_1 + \mu)(\rho_1 + b)} \right]. \end{aligned}$$

The sign of  $\mathcal{R}$  depends on the sign of  $\mu - b$ , thus

- (i) For  $b < \mu$ ,  $\mathcal{R}_0 < \mathcal{R}_b$ , the scenario leading to extinction.
- (ii) For  $b = \mu$ ,  $\mathcal{R}_b = \mathcal{R}_0$ , the scenario in section 2.2 with a constant population.
- (iii) For  $b > \mu$ ,  $\mathcal{R}_0 > \mathcal{R}_b$ , the case with exponential growth.



## 2.5 Case 3: Birth rate different from death rate with deaths due to AIDS

We incorporate the death rate due to AIDS and assume that the recruitment rate is constant and denoted by  $\pi$  instead of  $bN$ . We thus obtain the modified system (2.52).

$$\begin{aligned}\dot{S} &= \pi - \frac{c(\eta_1 I + \eta_2 A)}{N} S - \mu S, \\ \dot{I} &= \frac{c(\eta_1 I + \eta_2 A)}{N} S - (\rho_1 + \mu) I, \\ \dot{A} &= \rho_1 I - (\mu + \delta) A.\end{aligned}\tag{2.52}$$

Adding the three equations in (2.52), we have

$$\dot{N} = \pi - \mu N - \delta A\tag{2.53}$$

$$\leq \pi - \mu N.\tag{2.54}$$

This means the right hand side of (2.54) is bounded by  $\pi - \mu N$  for which using initial condition  $N = N_0$  at  $t = 0$ , we have

$$N(t) \leq \frac{\pi}{\mu}(1 - e^{-\mu t}) + N_0 e^{-\mu t}.\tag{2.55}$$

Thus  $N(t) \leq \frac{\pi}{\mu}$  if  $N_0 \leq \frac{\pi}{\mu}$ .

If  $N(t) > \frac{\pi}{\mu}$ ,  $\dot{N} < 0$  then  $(S, I, A)$  enters or approaches asymptotically inside the positive region  $\Omega_\delta$ . From equation (2.55) it is seen that as  $t \rightarrow \infty$ ,  $N(t)$  is bounded above by  $\frac{\pi}{\mu}$ . As a result, we define the set  $\Omega_\delta$  as

$$\Omega_\delta = \left\{ (S, I, A) \in \mathbb{R}_+^3 \mid S + I + A \leq \frac{\pi}{\mu} \right\},\tag{2.56}$$

as the biologically feasible region of the system (2.52). It is clear that all solutions of the system of equations (2.52) are bounded and  $\Omega_\delta$  is attracting.

### 2.5.1 Basic reproduction number

The basic reproduction number  $\mathcal{R}_\delta$  of the system of equations (2.52) is computed using the technique of the next generation matrix approach as used in our previous cases.

We obtain

$$\mathcal{R}_\delta = \frac{c(\eta_1(\mu + \delta) + \eta_2\rho_1)}{(\mu + \delta)(\rho_1 + \mu)}. \quad (2.57)$$

**Remark 2.5.1.**

It can be seen that for  $\delta = 0$ ,  $\mathcal{R}_\delta = \mathcal{R}_0$  whilst for  $\delta \neq 0$ ,  $\mathcal{R}_\delta < \mathcal{R}_0$ .

Indeed,

$$\begin{aligned} \mathcal{R}_\delta - \mathcal{R}_0 &= \frac{c\eta_1(\mu + \delta) + \eta_2\rho_1}{(\mu + \delta)(\rho_1 + \mu)} - \frac{c\eta_1\mu + c\eta_2\rho_1}{\mu(\rho_1 + \mu)} \\ &= \frac{c\eta_1}{\mu + \rho_1} + \frac{c\eta_2\rho_1}{(\delta + \mu)(\mu + \rho_1)} - \frac{c\eta_1}{\mu + \rho_1} - \frac{c\eta_2\rho_1}{\mu(\mu + \rho_1)} \\ &= \frac{c\eta_2\rho_1}{(\delta + \mu)(\mu + \rho_1)} - \frac{c\eta_2\rho_1}{\mu(\mu + \rho_1)} \\ &= -\frac{c\eta_2\rho_1\delta}{\mu(\mu + \delta)(\mu + \rho_1)} < 0. \end{aligned}$$

## 2.5.2 Disease free equilibrium point

Equating the right side of the system of equations (2.52) to zero with the conditions  $I = 0$ ,  $A = 0$ , and solving for  $S$ ,  $I$ , and  $A$ , we obtain

$$S = \frac{\pi}{\mu}. \quad (2.58)$$

Thus, the DFE of the system of equations (2.52) is given by

$$E_\delta = \left( \frac{\pi}{\mu}, 0, 0 \right). \quad (2.59)$$

## 2.5.3 Stability analysis of the disease free equilibrium point

The Jacobian matrix of the system of equations (2.52) evaluated at DFE is given by

$$J_{E_\delta} = \begin{bmatrix} -\mu & -c\eta_1 & -c\eta_2 \\ 0 & c\eta_1 - (\rho_1 + \mu) & c\eta_2 \\ 0 & \rho_1 & -(\mu + \delta) \end{bmatrix}. \quad (2.60)$$

One of the eigenvalues of the Jacobian matrix  $J_{E_\delta}$  is  $\lambda_1 = -\mu < 0$ . The other two are solutions of the characteristic equation

$$\lambda^2 + a_1\lambda + a_0 = 0, \quad (2.61)$$

where  $a_1 = (2\mu + \rho_1 - c\eta_1 + \delta)$ ,  $a_0 = (\mu + \delta)(1 - \mathcal{R}_\delta)$ .

The solutions of (2.61) are given by

$$\lambda_{2,3} = -\frac{a_1}{2} \pm \sqrt{\left(\frac{a_1}{2}\right)^2 - a_0}. \quad (2.62)$$

We can see that all the eigenvalues have negative real parts when  $a_0 > 0$ , that is when  $\mathcal{R}_\delta < 1$ .

**Theorem 2.5.2.** *The disease free equilibrium point  $E_\delta$  of the system of equations (2.52) is locally asymptotically stable when  $\mathcal{R}_\delta < 1$  and unstable when  $\mathcal{R}_\delta > 1$ .*

## 2.5.4 The endemic equilibrium point

To determine the endemic equilibrium point of the system (2.52), we solve the system of equations (2.63)–(2.65) for  $S^*$ ,  $I^*$ , and  $A^*$  as follows

$$\pi - \frac{c(\eta_1 I^* + \eta_2 A^*)}{N^*} S^* - \mu S^* = 0, \quad (2.63)$$

$$\frac{c(\eta_1 I^* + \eta_2 A^*)}{N^*} S^* - (\rho_1 + \mu) I^* = 0, \quad (2.64)$$

$$\rho_1 I^* - (\mu + \delta) A^* = 0. \quad (2.65)$$

Equation (2.65) yields

$$A^* = \frac{\rho_1}{\mu + \delta} I^*. \quad (2.66)$$

Adding equations (2.63) and (2.64) we obtain

$$S^* = \frac{\pi}{\mu} - \left( \frac{\rho_1 + \mu}{\mu} \right) I^*. \quad (2.67)$$

Substituting (2.66) and (2.67) into equation (2.64) we have

$$I^* = \frac{\pi(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mu(\mu + \rho_1 + \delta)\mathcal{R}_\delta + \delta\rho_1(\mathcal{R}_\delta - 1)}. \quad (2.68)$$

Substituting (2.68) into (2.66) and (2.67) we have

$$S^* = \frac{\pi(\mu + \rho_1 + \delta)}{\mu(\mu + \rho_1 + \delta)\mathcal{R}_\delta + \delta\rho_1(\mathcal{R}_\delta - 1)}, \quad A^* = \frac{\pi\rho_1(\mathcal{R}_\delta - 1)}{\mu(\mu + \rho_1 + \delta)\mathcal{R}_\delta + \delta\rho_1(\mathcal{R}_\delta - 1)}. \quad (2.69)$$

The EEP of the system of equations (2.52) is given by

$$E_\delta^* = \left( \frac{\pi(\mu + \rho_1 + \delta)}{\Phi + \delta\rho_1(\mathcal{R}_\delta - 1)}, \frac{\pi(\mu + \delta)(\mathcal{R}_\delta - 1)}{\Phi + \delta\rho_1(\mathcal{R}_\delta - 1)}, \frac{\pi\rho_1(\mathcal{R}_\delta - 1)}{\Phi + \delta\rho_1(\mathcal{R}_\delta - 1)} \right), \quad (2.70)$$

where  $\Phi = \mu(\mu + \rho_1 + \delta)\mathcal{R}_\delta$ .

Solutions  $S^*$ ,  $I^*$ , and  $A^*$  are positive when  $\mathcal{R}_\delta > 1$ . This leads to the following theorem:

**Theorem 2.5.3.** *The endemic equilibrium point  $E_\delta^*$  of the system of equations (2.52) exists only when  $\mathcal{R}_\delta > 1$ .*

### 2.5.5 Stability analysis of the endemic equilibrium point

We show the stability of the EEP of the system of equations (2.52) by proving the following theorem:

**Theorem 2.5.4.** *The EEP of the system of equations (2.52) is locally asymptotically stable when  $\mathcal{R}_\delta > 1$ .*

*Proof.* Let  $J_{E_\delta^*}$  be the Jacobian matrix of the system of equations (2.52) evaluated at EEP,

$$J_{E_\delta^*} = \begin{bmatrix} -\frac{(\rho_1 + \mu)I^*(\mathcal{R}_\delta - 1)}{S^*\mathcal{R}_\delta} - \mu & \frac{(\rho_1 + \mu)I^*}{N^*} - \frac{c\eta_1}{\mathcal{R}_\delta} & \frac{(\rho_1 + \mu)I^*}{N^*} - \frac{c\eta_2}{\mathcal{R}_\delta} \\ \frac{(\rho_1 + \mu)I^*(\mathcal{R}_\delta - 1)}{S^*\mathcal{R}_\delta} & -\frac{(\rho_1 + \mu)I^*}{N^*} + \frac{c\eta_1}{\mathcal{R}_\delta} - (\rho_1 + \mu) & -\frac{(\rho_1 + \mu)I^*}{N^*} + \frac{c\eta_2}{\mathcal{R}_\delta} \\ 0 & \rho_1 & -(\mu + \delta) \end{bmatrix}.$$

The characteristic equation of the Jacobian matrix is given by

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0, \quad (2.71)$$

where

$$\begin{aligned} a_2 &= A_2 + \frac{(\rho_1 + \mu)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta}, \\ a_1 &= A_1 + \frac{(\rho_1 + \mu)(\mu + \delta)(2\mu + \delta + \rho_1)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta}, \\ a_0 &= \frac{(\rho_1 + \mu)^2(\mu + \delta)^2(\mathcal{R}_\delta - 1)^2}{\mathcal{R}_\delta(\rho_1 + \mu + \delta)} + \frac{\mu(\rho_1 + \mu)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mathcal{R}_\delta}, \end{aligned}$$

$$A_1 = \mu(\mu + \delta) + \frac{c\mu\eta_2\rho_1}{(\mu + \delta)\mathcal{R}_\delta}, \quad A_2 = 2\mu + \delta + \frac{c\eta_2\rho_1}{(\mu + \delta)\mathcal{R}_\delta}.$$

Clearly,  $a_0$ ,  $a_1$ , and  $a_2 > 0$  when  $\mathcal{R}_\delta > 1$  and

$$\begin{aligned}
a_2 a_1 - a_0 &= \left( A_2 + \frac{(\rho_1 + \mu)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} \right) \left( A_1 + \frac{(\rho_1 + \mu)(\mu + \delta)(2\mu + \delta + \rho_1)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} \right) \\
&\quad - \frac{(\delta + \mu)^2(\rho_1 + \mu)^2(\mathcal{R}_\delta - 1)^2}{\mathcal{R}_\delta(\mu + \rho_1 + \delta)} - \frac{\mu(\mu + \rho_1)(\delta + \mu)(\mathcal{R}_\delta - 1)}{\mathcal{R}_\delta} \\
&= \frac{(\rho_1 + \mu)^2(\mu + \delta)^2(2\mu + \rho_1 + \delta)(\mathcal{R}_\delta - 1)^2}{(\mu + \rho_1 + \delta)^2} + \frac{A_2(\mu + \delta)(\rho_1 + \mu)(2\mu + \delta + \rho_1)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} \\
&\quad + \frac{A_1(\mu + \rho_1)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} - \frac{(\rho_1 + \mu)^2(\mu + \delta)^2(\mathcal{R}_\delta - 1)^2}{\mathcal{R}_\delta(\mu + \rho_1 + \delta)} - \frac{\mu(\mu + \rho_1)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mathcal{R}_\delta} \\
&\quad + A_1 A_2 \\
&= A_1 A_2 + \frac{A_1(\mu + \rho_1)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} + B_1 + B_2 > 0, \quad \text{when } \mathcal{R}_\delta > 1,
\end{aligned}$$

where

$$\begin{aligned}
B_1 &= \frac{(\mu + \delta)^2(\rho_1 + \mu)^2(2\mu + \rho_1 + \delta)(\mathcal{R}_\delta - 1)^2}{(\mu + \rho_1 + \delta)^2} - \frac{(\delta + \mu)^2(\rho_1 + \mu)^2(\mathcal{R}_\delta - 1)^2}{\mathcal{R}_\delta(\mu + \rho_1 + \delta)} \\
&= [\mu + (\mu + \rho_1 + \delta)(\mathcal{R}_\delta - 1)] \frac{(\rho_1 + \mu)^2(\mu + \delta)^2(\mathcal{R}_\delta - 1)^2}{(\mu + \rho_1 + \delta)^2 \mathcal{R}_\delta}, \\
B_2 &= \frac{A_2(\mu + \delta)(\rho_1 + \mu)(2\mu + \delta + \rho_1)(\mathcal{R}_\delta - 1)}{\mu + \rho_1 + \delta} - \frac{\mu(\mu + \rho_1)(\mu + \delta)(\mathcal{R}_\delta - 1)}{\mathcal{R}_\delta} \\
&= \left[ A_2 \mu \mathcal{R}_\delta + (\mu + \rho_1 + \delta) \left( \mu(\mathcal{R}_\delta - 1) + (\mu + \delta)\mathcal{R}_\delta + \frac{c\eta_2 \rho_1}{\mu + \delta} \right) \right] \frac{(\rho_1 + \mu)(\delta + \mu)(\mathcal{R}_\delta - 1)}{(\mu + \rho_1 + \delta)(\mathcal{R}_\delta)}.
\end{aligned}$$

All the Routh–Hurwitz conditions are satisfied when  $\mathcal{R}_\delta > 1$ . Therefore, by the Routh–Hurwitz criterion for stability [17], all the eigenvalues of  $J_{E_\delta^*}$  are negative or have negative real parts.

The endemic equilibrium point  $E_\delta^*$  is thus locally asymptotically stable when  $\mathcal{R}_\delta > 1$ .  $\square$

## 2.6 Remarks

(I) If we consider the expression of  $I^*$  in equation (2.68), we have

$$I_{sat}^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} I^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} \frac{\pi(\mu + \delta)(\mathcal{R}_\delta - 1)}{(\mu + \rho_1)(\mu + \delta)\mathcal{R}_\delta - \delta\rho_1} = \frac{\pi}{\mu + \rho_1}. \quad (2.72)$$

Similarly, the AIDS individuals attains its saturation  $A_{sat}^*$ , that is

$$A_{sat}^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} A^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} \frac{\pi\rho_1(\mathcal{R}_\delta - 1)}{(\mu + \rho_1)(\mu + \delta)\mathcal{R}_\delta - \delta\rho_1} = \frac{\pi\rho_1}{(\mu + \rho_1)(\mu + \delta)}, \quad (2.73)$$

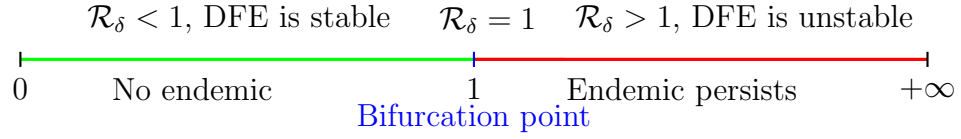


Figure 2.2: Graphical representation of the endemic as function of  $\mathcal{R}_\delta$

and

$$S_{sat}^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} S^* = \lim_{\mathcal{R}_\delta \rightarrow \infty} \frac{\pi(\mu + \rho_1 + \delta)}{(\mu + \rho_1)(\mu + \delta)\mathcal{R}_\delta - \delta\rho_1} = 0. \quad (2.74)$$

The biological meaning of equations (2.72)–(2.74) is that when there is no HIV intervention, that is no use of condoms, counselling, HIV education or pre-exposure HIV prophylaxis, the number of infected people increases exponentially and attains the saturation  $I_{sat}^*$ . In this situation the number of susceptible individuals progressively diminishes and tends to zero whereas the number of AIDS individuals converges to the saturation  $A_{sat}^*$ . Hence, if the infection is not controlled every individual will end up being a carrier of HIV or having full blown AIDS. However, some susceptible individuals aware of the high risk of HIV infection, due to various awareness interventions mentioned earlier, may decide to take the pre-exposure HIV prophylaxis. Taking this fact into account, we modify our model and look for the impact of including pre-exposure HIV prophylaxis in our findings in the previous sections.

- (II) Furthermore, for  $0 < \mathcal{R}_\delta < 1$ , the number of susceptible individuals is equal to  $\frac{\pi}{\mu}$ , while the number of infected and that of AIDS individuals are equal to zero. In that situation, it is clear that the DFE is the only equilibrium point that exists and it is locally asymptotically stable. An infected individual produces less than one infected individual. Hence, no epidemic will develop.

For  $\mathcal{R}_\delta = 1$ , an exchange of stability occurred (supercritical bifurcation) between the DFE and the EEP (See Figures 2.2 and 2.3).

For  $\mathcal{R}_\delta > 1$ , the EEP exists and it is locally asymptotically stable. The DFE becomes unstable. Each infected individual infects more than one (susceptible) individual per unit time. The infection develops into a stable endemic.

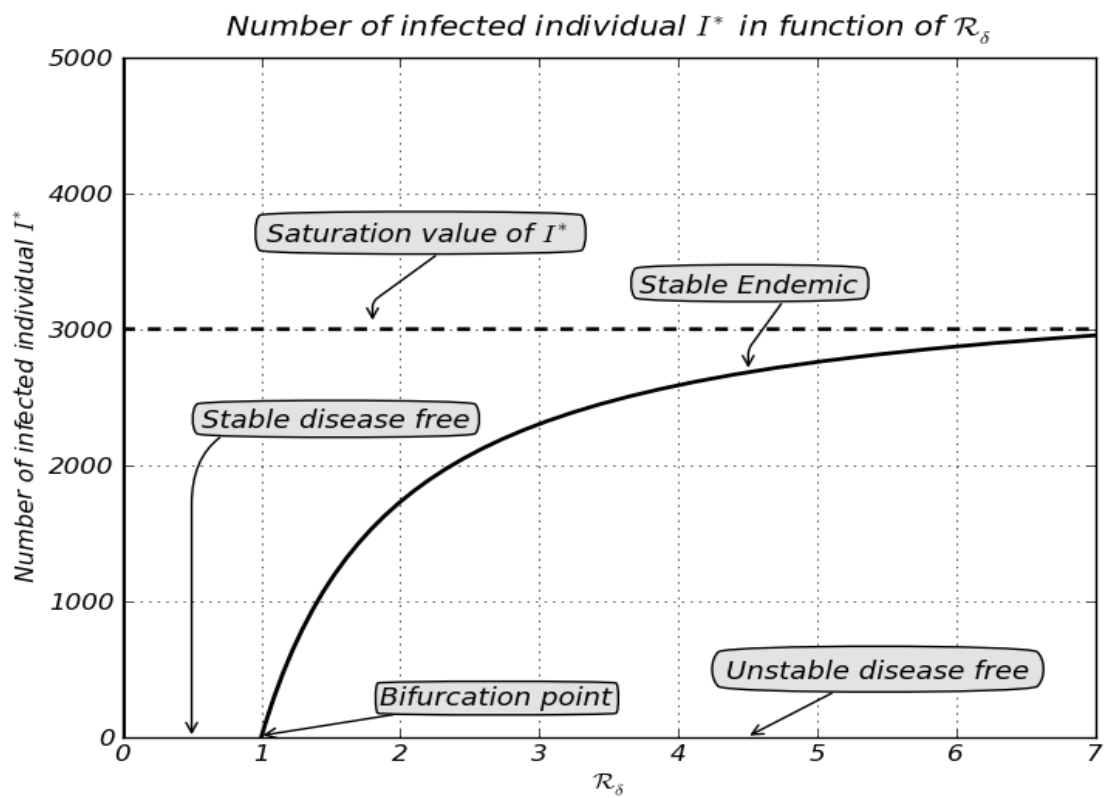


Figure 2.3: The bifurcation diagram and evolution of the infection by  $\mathcal{R}_\delta$  with estimated values of the parameters  $\pi = 10^5$ ,  $\rho_1 = 0.6$ ,  $\mu = 0.03$ , and  $\delta = 0.04$  [21].

# Chapter 3

## PRE-EXPOSURE HIV PROPHYLAXIS MODEL

### 3.1 Introduction

HIV infection prevention by means of abstinence or mutual monogamy practice with an HIV-negative partner remains the first line of defence against the virus. Although the method is more effective, one notices that, it is not fully practised by many individuals in different communities. The antiretroviral drugs use and correct use of condoms before any sexual activity has been demonstrated to be a highly potent and fundamental strategy against HIV infection. These health precaution measures taken by uninfected individuals, before being exposed to a risk of HIV infection, are defined as pre-exposure HIV prophylaxis (PrEP). Two recent studies showed that PrEP using antiretroviral drugs (Tenofovir and Truvada) substantially reduced the risk of acquiring HIV infection [18]. The efficacy and the use of PrEP medication remain a big challenge in PrEP intervention. In this section, we investigate how PrEP use and its efficacy can impact the prevalence and the incidence of HIV infection in our community. We thus set up some hypotheses for convenient scenarios in communities which lead to a model for analysis.



### 3.1.1 Model description

We consider that some susceptible individuals who are at high risk of HIV infection take PrEP but some do not. We assume that a proportion  $\gamma$  of susceptible individuals is on PrEP and the remaining proportion  $(1 - \gamma)S$  is not on prophylaxis ( $\gamma$  can be regarded as the measure of awareness on the use of PrEP, so that  $0 \leq \gamma \leq 1$ ). We denote the number of susceptible individuals using the PrEP by  $S_p$ . However, only a proportion  $\sigma$  of  $S_p$  is protected from the PrEP ( $\sigma$  is the measure of effectiveness of the drugs that are used as PrEP, with  $0 \leq \sigma \leq 1$ ). As a result  $(1 - \sigma)S_p$  are exposed to the risk of HIV infection due to PrEP failure. The individuals who become infected due to PrEP failure move to a new infected class  $I_p$  while those who do not take PrEP and become infected move to the infected class  $I$ . Individuals from the  $I$  and  $I_p$  classes progress to the AIDS class, denoted by  $A$ , at constant rates  $\rho_1$  and  $\rho_2$  respectively. The total population  $N$  considered is the sum of all these individuals:

$$N = S + S_p + I + I_p + A. \quad (3.1)$$

We assume that recruited individuals into the population  $N$  are susceptible individuals so that the compartment  $S$  increases with constant recruitment rate  $\pi$ . The resultant system of differential equations is given by

$$\begin{aligned} \dot{S} &= \pi - \gamma S - (1 - \gamma)\lambda S - \mu S, \\ \dot{S}_p &= \gamma S - (1 - \sigma)\lambda S_p - \mu S_p, \\ \dot{I} &= (1 - \gamma)\lambda S - (\rho_1 + \mu)I, \\ \dot{I}_p &= (1 - \sigma)\lambda S_p - (\rho_2 + \mu)I_p, \\ \dot{A} &= \rho_1 I + \rho_2 I_p - (\mu + \delta)A. \end{aligned} \quad (3.2)$$

with

$$N = S + S_p + I + I_p + A.$$

We consider the force of infection to be

$$\lambda = \frac{c(\eta_1 I + \eta_2 I_p + \eta_3 A)}{N}. \quad (3.3)$$

The flow diagram of model (3.2) is represented in Figure 3.1. All the variables and parameters are defined in Table 3.1.

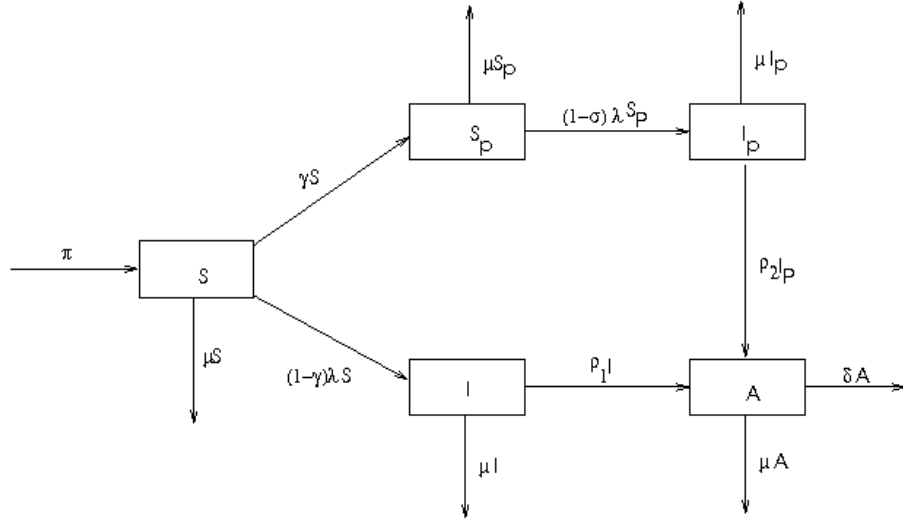


Figure 3.1: Flow diagram for the PrEP model.

### 3.1.2 Positivity and boundedness of solutions of the model

Since we know that the variables  $S(t)$ ,  $S_p(t)$ ,  $I(t)$ ,  $I_p(t)$ , and  $A(t)$  represent human population data, it is important to show that all solutions of the system of equations (3.2) are positive and bounded. To prove that, we add the right hand side and left hand side of the system to yield

$$\dot{N} = \pi - \mu N - \delta A. \quad (3.4)$$

It can be seen that equation (3.4) is the same as equation (2.53) and the analysis follows that of section 2.5. Thus, all solutions of the system of equations (3.2) are positive and bounded in  $\Omega_p$  defined by

$$\Omega_p = \left\{ (S, S_p, I, I_p, A) \in \mathbb{R}_+^5 \mid S + I + S_p + I_p + A \leq \frac{\pi}{\mu} \right\}. \quad (3.5)$$

## 3.2 PrEP model analysis

In this section, we investigate the local and the global stability of the equilibrium points of the model (3.2) using the basic reproduction number for our analysis. As before we make use of the van den Driessche and Watmough approach to calculate the basic reproduction number and we use centre manifold theory [15] for the local stability analysis of the EEP. We investigate the

Table 3.1: Parameters and variables used in the PrEP model .

Variables	Description
$S$	Number of susceptible individuals not on prophylaxis.
$I$	Number of infected individuals from $S$ compartment.
$S_p$	Number of susceptible individuals on PrEP.
$I_p$	Number of infected individuals from $S_p$ compartment.
$A$	Number of individuals suffering from AIDS.
$N$	Total population individuals considered.
Parameters	Description
$\pi$	Recruitment rate.
$\mu$	Natural death rate.
$\delta$	Death rate due to AIDS.
$\sigma$	Efficacy of the PrEP.
$\rho_1$	Progression rate from infected compartment $I$ to AIDS compartment.
$\rho_2$	Progression rate from infected compartment $I_p$ to AIDS compartment.
$\eta_1$	Contact rate of infected individuals from $I$ class and susceptible individual ( $S$ ).
$\eta_2$	Contact rate of infected individuals from $I_p$ class and susceptible individual ( $S_p$ ).
$\eta_3$	Contact rate of AIDS individuals and susceptible individual.
$c$	Average number of new sexual partners acquired per unit time.
$\lambda$	The force of infection.

impact of PrEP awareness and its efficacy on the progression of HIV infection in a population. In particular, we investigate its effects on HIV prevalence and incidence.

### 3.2.1 Disease free equilibrium point and basic reproduction number

The disease free equilibrium point of model (3.2) is obtained by setting the left hand side of the system (3.2) to zero with conditions  $I = 0$ ,  $I_p = 0$ , and  $A = 0$  and solving for  $S^o$  and  $S_p^o$ .

We obtain

$$E_p^o = (S^o, S_p^o, I^o, I_p^o, A^o) = \left( \frac{\pi}{\mu + \gamma}, \frac{\pi\gamma}{\mu(\mu + \gamma)}, 0, 0, 0 \right). \quad (3.6)$$

Following van den Driessche and Watmough [16], the Jacobian matrices of infected compartments,  $D_x\mathcal{F}(x)$  and  $D_x\mathcal{V}(x)$ , evaluated at DFE  $E_p^o$  are

$$F = \begin{bmatrix} \frac{c\mu(1-\gamma)\eta_1}{c\gamma(1-\sigma)\eta_1} & \frac{c\mu(1-\gamma)\eta_2}{c\gamma(1-\sigma)\eta_2} & \frac{c\mu(1-\gamma)\eta_3}{c\gamma(1-\sigma)\eta_3} \\ \frac{\mu + \gamma}{\mu + \gamma} & \frac{\mu + \gamma}{\mu + \gamma} & \frac{\mu + \gamma}{\mu + \gamma} \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \rho_1 + \mu & 0 & 0 \\ 0 & \rho_2 + \mu & 0 \\ -\rho_1 & -\rho_2 & (\mu + \delta) \end{bmatrix}. \quad (3.7)$$

It follows that

$$V^{-1} = \begin{bmatrix} \frac{1}{\rho_1 + \mu} & 0 & 0 \\ 0 & \frac{1}{\rho_2 + \mu} & 0 \\ \frac{\rho_1}{(\rho_1 + \mu)(\delta + \mu)} & \frac{\rho_2}{(\rho_2 + \mu)(\delta + \mu)} & \frac{1}{\mu + \delta} \end{bmatrix}. \quad (3.8)$$

The next generation matrix  $FV^{-1}$  of the system (3.2) is given by

$$FV^{-1} = \begin{bmatrix} \frac{c\mu(1-\gamma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\gamma + \mu)(\mu + \rho_1)(\mu + \delta)} & \frac{c\mu(1-\gamma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(\gamma + \mu)(\mu + \rho_2)(\mu + \delta)} & \frac{c\mu(1-\gamma)\eta_3}{(\gamma + \mu)(\mu + \delta)} \\ \frac{c\gamma(1-\sigma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\gamma + \mu)(\mu + \rho_1)(\mu + \delta)} & \frac{c\gamma(1-\sigma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(\gamma + \mu)(\mu + \rho_2)(\mu + \delta)} & \frac{c\gamma(1-\sigma)\eta_3}{(\gamma + \mu)(\mu + \delta)} \\ 0 & 0 & 0 \end{bmatrix}. \quad (3.9)$$

The characteristic equation is given by

$$\lambda(\lambda^2 - \text{tr}(A)\lambda + \det(A)) = 0. \quad (3.10)$$

The solutions of equation (3.10) are  $\lambda = 0$  and the solutions of the quadratic equation

$$\lambda^2 - \text{tr}(A)\lambda + \det(A) = 0. \quad (3.11)$$

The equation (3.11) is the characteristic equation of the matrix

$$A = \begin{bmatrix} \frac{c\mu(1-\gamma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\gamma + \mu)(\mu + \rho_1)(\mu + \delta)} & \frac{c\mu(1-\gamma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(\gamma + \mu)(\mu + \rho_2)(\mu + \delta)} \\ \frac{c\gamma(1-\sigma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\gamma + \mu)(\mu + \rho_1)(\mu + \delta)} & \frac{c\gamma(1-\sigma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(\gamma + \mu)(\mu + \rho_2)(\mu + \delta)} \end{bmatrix}. \quad (3.12)$$

Solving equation (3.11) we obtain

$$\lambda_1 = 0, \quad \lambda_2 = \text{tr}(A) = \frac{c\mu(1-\gamma)(\eta_1(\mu+\delta) + \rho_1\eta_3)}{(\gamma+\mu)(\mu+\rho_1)(\mu+\delta)} + \frac{c\gamma(1-\sigma)(\eta_2(\mu+\delta) + \rho_2\eta_3)}{(\gamma+\mu)(\mu+\rho_2)(\mu+\delta)}.$$

It follows that  $\rho(FV^{-1}) = \text{tr}(A)$ . Therefore the basic reproduction number of the model (3.2) is given by

$$\mathcal{R}_0 = \frac{c\mu(1-\gamma)(\eta_1(\mu+\delta) + \rho_1\eta_3)}{(\gamma+\mu)(\mu+\rho_1)(\mu+\delta)} + \frac{c\gamma(1-\sigma)(\eta_2(\mu+\delta) + \rho_2\eta_3)}{(\gamma+\mu)(\mu+\rho_2)(\mu+\delta)}. \quad (3.13)$$

### 3.2.2 Influence of PrEP on $\mathcal{R}_0$

We investigate the effects of the efficacy of PrEP on  $\mathcal{R}_0$  by computing the partial derivative of  $\mathcal{R}_0$  with respect to  $\sigma$ , that is

$$\frac{\partial \mathcal{R}_0}{\partial \sigma} = -\frac{c\gamma}{\gamma+\mu} \frac{\eta_2(\mu+\delta) + \rho_2\eta_3}{(\mu+\rho_2)(\mu+\delta)} < 0. \quad (3.14)$$

We note from equation (3.14) that  $\mathcal{R}_0$  is a decreasing function of  $\sigma$ . This means that the increase in the efficacy of PrEP results in the decline of the basic reproduction number due to infection from reduced PrEP failure. Thus the PrEP slows down the progression of HIV infection. Awareness of the PrEP protection in the community is also important for the control of the progression of HIV infection.

We can rewrite  $\mathcal{R}_0$  in the form

$$\mathcal{R}_0 = \frac{1-\gamma}{\gamma+\mu} R_n + \frac{\gamma}{\gamma+\mu} R_p, \quad (3.15)$$

where

$$R_n = \frac{c\mu(\eta_1(\mu+\delta) + \rho_1\eta_3)}{(\mu+\rho_1)(\mu+\delta)} \quad (3.16)$$

and

$$R_p = \frac{c(1-\sigma)(\eta_2(\mu+\delta) + \rho_2\eta_3)}{(\mu+\rho_2)(\mu+\delta)}. \quad (3.17)$$

We have

$$\frac{\partial \mathcal{R}_0}{\partial \gamma} = -\frac{\mu+1}{(\gamma+\mu)^2} [R_n - R_n^*], \quad (3.18)$$

where

$$R_n^* = \frac{\mu}{\mu + 1} R_p. \quad (3.19)$$

From equation (3.18), we make the following observations:

- (i) If  $R_n^* \geq R_n$ ,  $\frac{\partial \mathcal{R}_0}{\partial \gamma} \geq 0$ .
- (ii) If  $R_n^* < R_n$ ,  $\frac{\partial \mathcal{R}_0}{\partial \gamma} < 0$ .

We notice that when  $R_n$  is less than its threshold value  $R_n^*$ , the PrEP administration to individuals in the community may have no impact on the infection rate. When  $R_n$  is above the threshold value  $R_n^*$ , then the PrEP decreases the basic reproduction number. The analysis in (i) and (ii) reveals that raising awareness on prophylaxis alone as a strategy may not always work. Efforts should be made to consider the efficacy of PrEP as well.

We also note that

$$\lim_{(\sigma, \gamma) \rightarrow (\sigma, 1)} \mathcal{R}_0 = \frac{c(1 - \sigma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(1 + \mu)(\mu + \rho_2)(\mu + \delta)} = \frac{1}{\mu + 1} R_p, \quad (3.20)$$

$$\lim_{(\sigma, \gamma) \rightarrow (1, 1)} \mathcal{R}_0 = 0, \quad (3.21)$$

$$\lim_{(\sigma, \gamma) \rightarrow (1, \gamma)} \mathcal{R}_0 = \frac{c\mu(1 - \gamma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\gamma + \mu)(\mu + \rho_1)(\mu + \delta)} = \frac{1 - \gamma}{\mu + \gamma} R_n. \quad (3.22)$$

It can be seen that when protection from the PrEP improves, that is when  $\sigma$  goes to unity, only the second term of  $\mathcal{R}_0$  goes to zero. This means that increasing the efficacy of PrEP in community does not guarantee the total eradication of the infection but will certainly reduce the infection rate. When the response to PrEP awareness increases, that is when  $\gamma$  goes to unity, the infection is not eradicated either. However, when both of  $\sigma$  and  $\gamma$  tend simultaneously to unity, the number of secondary infections diminishes and tends to zero with increasing time. This means that a combined strategy regarding PrEP awareness and efficacy, when effectively implemented, may lead to effective control of HIV infection. However, the control status is unstable as drugs wane with time and individuals may respond to the awareness at different rates. For maximum benefits, care must be taken to ensure strict adherence to the use of PrEP and combine PrEP use with other strategies of HIV control.

### 3.2.3 Mathematical observations and biological interpretation

The basic reproduction number  $\mathcal{R}_0$  of the system of equations (3.2) can be regarded as a linear combination of two basic reproduction numbers,  $\mathcal{R}_1$  and  $\mathcal{R}_2$ , of two system of equations,  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$ , which are respectively governed by the triplets  $(S, I, A)$  and  $(S_p, I_p, A)$ . To show that, we consider the following two models generated by model (3.2)

$$\begin{aligned}
 \dot{S} &= \pi - (1 - \gamma) \frac{c(\eta_1 I + \eta_3 A)}{N_1} S - (\mu + \gamma) S, \\
 (\mathcal{S}_1) : \quad \dot{I} &= (1 - \gamma) \frac{c(\eta_1 I + \eta_3 A)}{N_1} S - (\rho_1 + \mu) I, \\
 \dot{A} &= \rho_1 I - (\mu + \delta) A,
 \end{aligned} \tag{3.23}$$

with

$$N_1 = S + I + A. \tag{3.24}$$

$$\begin{aligned}
 \dot{S}_p &= \gamma S - (1 - \sigma) \frac{c(\eta_2 I_p + \eta_3 A)}{N_2} S_p - \mu S_p, \\
 (\mathcal{S}_2) : \quad \dot{I}_p &= (1 - \sigma) \frac{c(\eta_2 I_p + \eta_3 A)}{N_2} S_p - (\rho_2 + \mu) I_p, \\
 \dot{A} &= \rho_2 I_p - (\mu + \delta) A,
 \end{aligned} \tag{3.25}$$

with

$$N_2 = S_p + I_p + A. \tag{3.26}$$

The system of equations  $(\mathcal{S}_1)$  describes interactions and progression dynamics of individuals not on PrEP, while the system of equations  $(\mathcal{S}_2)$  deals with interactions and progression dynamics of individuals on PrEP. We analyse the dynamics of both systems of equations.

#### (a) Positivity and boundedness of solutions

Adding both sides of system of equations  $(\mathcal{S}_1)$  and both sides of system of equations  $(\mathcal{S}_2)$ , we have respectively

$$\dot{N}_1 = \pi - \gamma S - \mu N_1 - \delta A \tag{3.27}$$

and

$$\dot{N}_2 = \gamma S - \mu N_2 - \delta A, \quad (3.28)$$

which respectively imply

$$\dot{N}_1 \leq \pi - \mu N_1 \quad (3.29)$$

and

$$\dot{N}_2 \leq \gamma S - \mu N_2. \quad (3.30)$$

From (3.29), we have

$$N_1 \leq \frac{\pi}{\mu} - N_1^0 e^{-\mu t}, \quad \text{where } N_1^0 = N_1(0), \quad (3.31)$$

$$\implies N_1 \leq \frac{\pi}{\mu}, \quad \forall t \geq 0. \quad (3.32)$$

Since,  $S < N_1 \leq \frac{\pi}{\mu}$ , then from (3.30) we obtain

$$\dot{N}_2 \leq \frac{\gamma\pi}{\mu} - \mu N_2, \quad (3.33)$$

which yields

$$N_2 \leq \frac{\gamma\pi}{\mu^2} - N_2^0 e^{-\mu t}, \quad (3.34)$$

where  $N_2^0 = N_2(0)$ .

Following the same analysis as that of equation (3.4), we define the feasible region of systems  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$  to be

$$\Omega_1 = \left\{ (S, I, A) \in \mathbb{R}_+^3 \mid S + I + A \leq \frac{\pi}{\mu} \right\} \subseteq \Omega_p \quad (3.35)$$

and

$$\Omega_2 = \left\{ (S_p, I_p, A) \in \mathbb{R}_+^3 \mid S_p + I_p + A \leq \frac{\gamma\pi}{\mu^2} \right\} \subseteq \Omega_p, \quad (3.36)$$

respectively.

From what precedes in section 2.2.2, one can state that the regions  $\Omega_1$  and  $\Omega_2$  are positively invariant and attracting. Moreover, it is seen that

$$N \leq N_1 + N_2 \leq \frac{\pi}{\mu} \left( 1 + \frac{\gamma}{\mu} \right). \quad (3.37)$$

Then every solution in  $\Omega_1$  or  $\Omega_2$  belongs to  $\Omega_p$ , this implies that  $\Omega_1 \cup \Omega_2 \subset \Omega_p$ .



(b) **Basic reproduction numbers**

The disease free equilibrium points of the system of equations  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$  are respectively

$$E_0^1 = \left( \frac{\pi}{\gamma + \mu}, 0, 0 \right), \quad (3.38)$$

and

$$E_0^2 = \left( \frac{\pi\gamma}{\mu(\gamma + \mu)}, 0, 0 \right). \quad (3.39)$$

The basic reproduction number of systems  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$  computed using van den Driessche and Watmough's techniques [16], leads to

$$\mathcal{R}_1 = \frac{c(1 - \gamma)(\eta_1(\mu + \delta) + \rho_1\eta_3)}{(\mu + \rho_1)(\mu + \delta)}, \quad (3.40)$$

and

$$\mathcal{R}_2 = \frac{c(1 - \sigma)(\eta_2(\mu + \delta) + \rho_2\eta_3)}{(\mu + \rho_2)(\mu + \delta)}. \quad (3.41)$$

It is clear that

$$\mathcal{R}_0 = \frac{\mu}{\gamma + \mu}\mathcal{R}_1 + \left(1 - \frac{\mu}{\gamma + \mu}\right)\mathcal{R}_2. \quad (3.42)$$

This confirms that the basic reproduction number of the main model (3.2),  $\mathcal{R}_0$ , is a linear combination of  $\mathcal{R}_1$  and  $\mathcal{R}_2$  that are reproduction numbers of models  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$ . We can see that the main model (3.2) is partitioned into two models  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$  and it follows that its basic reproduction number is a linear combination of each of both models  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$ . Such a model is said to be a parameter connected. This leads to the following definitions

**Definition 3.2.1.** An epidemiological model

$$(\mathcal{S}) : \dot{x} = f(x), \quad x \in \mathbb{R}_+^n \quad (3.43)$$

is said to be a **parameter connected model**, if there exists a partition of that model into two sub-models  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$  such that the basic reproduction number of the model  $(\mathcal{S})$  connected by a parameter  $\kappa$ , is linear combination of basic reproduction numbers,  $\mathcal{R}_1$  and  $\mathcal{R}_2$ , of the sub-models  $(\mathcal{S}_1)$  and  $(\mathcal{S}_2)$ , that is

$$\mathcal{R} = \kappa\mathcal{R}_1 + (1 - \kappa)\mathcal{R}_2. \quad (3.44)$$

We call  $\min\{\kappa\mathcal{R}_1, (1 - \kappa)\mathcal{R}_2\}$  the slow basic reproduction number and  $\max\{\kappa\mathcal{R}_1, (1 - \kappa)\mathcal{R}_2\}$  the fast basic reproduction number. Thus the parameter  $\kappa$  ( $0 < \kappa \leq 1$ ) is called the **slow-fast parameter** of the parameter connected model. From that definition, the model (3.2) is a parameter connected model with

$$\kappa = \frac{\mu}{\gamma + \mu}. \quad (3.45)$$

We note that the slow-fast parameter depends on the level of PrEP awareness. Increasing  $\gamma$  reduces the value of the  $\kappa$  whilst reducing  $\gamma$  increases the value of  $\kappa$ .

If the basic reproduction number cannot be disaggregated as in (3.44), we call the model a **compact model**. Thus the basic HIV model analysed in section 2.1 is a compact model. Even though some compact models present the required linear combination property they cannot always be partitioned into two sub-models.

The analysis of the parameter connected model for an epidemiological disease is important in the sense that it reveals that the control of infection in a community may need a balance in more than one intervention strategy. Thus in our case, the control will be done by simultaneously monitoring both the fast basic reproduction number and the slow basic reproduction number to levels where the epidemic can be managed effectively. The parameter connected model allows us to determine the group of individuals in a community who are more susceptible to infection. To eradicate the infection calls for measures to provide more PrEP education to individuals presenting the fast basic reproduction number and administering a more effective PrEP drug.

### 3.2.4 Local stability of the disease free equilibrium point

To analyze the local stability of the DFE, we compute the Jacobian matrix of the system of equations (3.2) and evaluate it at the DFE  $E_p^o$ . We have

$$J(E_p^o) = \begin{bmatrix} -\mu - \gamma & 0 & -\frac{c\mu(1-\gamma)\eta_1}{\mu + \gamma} & -\frac{c\mu(1-\gamma)\eta_2}{\mu + \gamma} & -\frac{c\mu(1-\gamma)\eta_3}{\mu + \gamma} \\ \gamma & -\mu & -\frac{c\gamma(1-\sigma)\eta_1}{\mu + \gamma} & -\frac{c\gamma(1-\sigma)\eta_2}{\mu + \gamma} & -\frac{c\gamma(1-\sigma)\eta_3}{\mu + \gamma} \\ 0 & 0 & \frac{c\mu(1-\gamma)\eta_1}{\mu + \gamma} - \rho_1 - \mu & \frac{c\mu(1-\gamma)\eta_2}{\mu + \gamma} & \frac{c\mu(1-\gamma)\eta_3}{\mu + \gamma} \\ 0 & 0 & \frac{c\gamma(1-\sigma)\eta_1}{\mu + \gamma} & \frac{c\gamma(1-\sigma)\eta_2}{\mu + \gamma} - \rho_2 - \mu & \frac{c\gamma(1-\sigma)\eta_3}{\mu + \gamma} \\ 0 & 0 & \rho_1 & \rho_2 & -(\mu + \delta) \end{bmatrix}. \quad (3.46)$$

The characteristic equation of  $J(E_p^o)$  is given by

$$\det(J(E_p^o)) = (\lambda + \mu)(\lambda + \gamma + \mu)P(\lambda) = 0, \quad (3.47)$$

where

$$P(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0, \quad (3.48)$$

and

$$\begin{aligned} a_2 &= (\delta + \mu) + (\rho_1 + 2\mu + \rho_2)(1 - \mathcal{R}_0) + \frac{(\rho_1 + \mu)\gamma\mathcal{R}_2 + (\rho_2 + \mu)\mu\mathcal{R}_1}{\mu + \gamma} + \frac{\eta_3(\mu\rho_1 + \gamma\rho_2)}{(\mu + \delta)(\mu + \gamma)}, \\ a_1 &= (\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0) + (\mu + \delta)(\rho_1 + \rho_2 + 2\mu)(1 - \mathcal{R}_0) + (\mu + \delta)(\mu + \rho_1)\frac{\gamma\mathcal{R}_2}{\mu + \gamma} \\ &\quad + (\mu + \delta)(\mu + \rho_2)\frac{\mu\mathcal{R}_1}{\mu + \gamma} + \frac{c\mu(1-\gamma)\rho_1\eta_3(\rho_2 + \mu)}{(\mu + \gamma)(\mu + \delta)} + \frac{c\gamma(1-\sigma)\rho_2\eta_3(\rho_1 + \mu)}{(\mu + \gamma)(\mu + \delta)}, \\ a_0 &= (\mu + \delta)(\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0). \end{aligned}$$

The first two eigenvalues of the matrix  $J(E_p^o)$  are  $\lambda_1 = -\mu < 0$  and  $\lambda_2 = -(\gamma + \mu) < 0$ . The other three are solutions of  $P(\lambda) = 0$ .

Clearly  $a_2$ ,  $a_1$ , and  $a_0$  are positive when  $\mathcal{R}_0 < 1$ , and

$$\begin{aligned} a_1a_2 - a_0 &= (\mu + \delta + C_2)(C_1 + (\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0)) - (\mu + \delta)(\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0) \\ &= (\mu + \delta)C_1 + C_2C_1 + C_2(\mu + \rho_1)(\mu + \rho_2)(1 - \mathcal{R}_0) \\ &> 0 \quad \text{when } \mathcal{R}_0 < 1, \end{aligned}$$

where

$$C_2 = (\rho_1 + \rho_2 + 2\mu)(1 - \mathcal{R}_0) + \frac{(\rho_1 + \mu)\gamma\mathcal{R}_2 + (\rho_2 + \mu)\mu\mathcal{R}_1}{\mu + \gamma} + \frac{\eta_3(\mu\rho_1 + \gamma\rho_2)}{(\mu + \delta)(\mu + \gamma)}.$$

$$C_1 = (\mu + \delta)(\rho_1 + \rho_2 + 2\mu)(1 - \mathcal{R}_0) + (\mu + \delta)(\rho_1 + \mu)\frac{\gamma\mathcal{R}_2}{\mu + \gamma} + (\mu + \delta)(\rho_2 + \mu)\frac{\mu\mathcal{R}_1}{\mu + \gamma}$$

$$+ \frac{c\mu(1 - \gamma)\rho_1\eta_3(\rho_2 + \mu)}{(\mu + \gamma)(\mu + \delta)} + \frac{c\gamma(1 - \sigma)\rho_2\eta_3(\rho_1 + \mu)}{(\mu + \gamma)(\mu + \delta)}.$$

The Routh–Hurwitz criterion for stability [17] is satisfied when  $\mathcal{R}_0 < 1$ , therefore all the eigenvalues of  $J(E_p^o)$  have a negative real part when  $\mathcal{R}_0 < 1$ . We summarize the results in the following theorem:

**Theorem 3.2.2.** *The disease free equilibrium point  $E_p^o$  of the system of equations (3.2) is locally asymptotically stable if  $\mathcal{R}_0 < 1$  and unstable when  $\mathcal{R}_0 > 1$ .*

Theorem 3.2.2 suggests that HIV infection can be eradicated from the population when the basic reproduction number  $\mathcal{R}_0$  is less than unity. This is a necessary condition for stability but one needs to take care when using this result for biological interpretation. This is because one of  $\mathcal{R}_1$  or  $\mathcal{R}_2$  may be greater than unity when  $\mathcal{R}_0 < 1$ . We proceed to test for global stability of the DFE.

### 3.2.5 Global stability of the disease free equilibrium point

We follow the Castillo-Chavez *et al.* [15] approach to prove the global stability of the DFE. In order to use Theorem 1.2.8, we write the system (3.2) in the form

$$\begin{aligned} \dot{X} &= F(X, Y), \\ \dot{Y} &= H(X, Y), \quad H(X, 0) = 0, \end{aligned} \tag{3.49}$$

where the components of the vector  $X = (S, S_p) \in \mathbb{R}_+^2$  denote the number of uninfected individuals and the components of vector  $Y = (I, I_p, A) \in \mathbb{R}_+^3$  denote the number of infected individuals. Thus the DFE becomes  $E_p^o = (X^o, 0)$  where

$$X^o = \left( \frac{\pi}{\gamma + \mu}, \frac{\pi\gamma}{\mu(\gamma + \mu)} \right). \tag{3.50}$$

The global stability property of the DFE is achieved when the following two conditions are satisfied:

$\mathcal{H}_1$ : For  $\dot{X} = F(X, 0)$ ,  $X^o$  is globally asymptotically stable (GAS).

$\mathcal{H}_2$ :  $H(X, Y) = BY - \hat{H}(X, Y)$ ,  $\hat{H}(X, Y) \geq 0$  for  $(X, Y) \in \Omega_p$ .

From equation (3.2), it follows that

$$F(X, 0) = \begin{bmatrix} \pi - (\mu + \gamma)S \\ \gamma S - \mu S_p \end{bmatrix}, \quad \hat{H}(X, Y) = \begin{bmatrix} \hat{H}_1 \\ \hat{H}_2 \\ \hat{H}_3 \end{bmatrix} = \begin{bmatrix} c(1 - \gamma)(\eta_1 I + \eta_2 I_p + \eta_3 A) \left( \frac{\mu}{\mu + \gamma} - \frac{S}{N} \right) \\ c(1 - \sigma)(\eta_1 I + \eta_2 I_p + \eta_3 A) \left( \frac{\gamma}{\mu + \gamma} - \frac{S_p}{N} \right) \\ 0 \end{bmatrix} \quad (3.51)$$

and

$$B = \begin{bmatrix} \frac{c\mu(1 - \gamma)\eta_1}{\mu + \gamma} - \rho_1 - \mu & \frac{c\mu(1 - \gamma)\eta_2}{\mu + \gamma} & \frac{c\mu(1 - \gamma)\eta_3}{\mu + \gamma} \\ \frac{c\gamma(1 - \sigma)\eta_1}{\mu + \gamma} & \frac{c\gamma(1 - \sigma)\eta_2}{\mu + \gamma} - \rho_2 - \mu & \frac{c\gamma(1 - \sigma)\eta_3}{\mu + \gamma} \\ \rho_1 & \rho_2 & -(\mu + \delta) \end{bmatrix}. \quad (3.52)$$

The first condition ( $\mathcal{H}_1$ ) is satisfied when  $X^o$  is a GAS equilibrium point of the system

$$\begin{aligned} \dot{S} &= \pi - (\mu + \gamma)S, \\ \dot{S}_p &= \gamma S - \mu S_p. \end{aligned} \quad (3.53)$$

To prove that, we solve system (3.53) for  $S$  and  $S_p$  and we obtain

$$X(t) = (S(t), S_p(t)) = \left( \frac{\pi}{\mu + \gamma} - c_0 e^{-(\mu + \gamma)t}, \frac{\gamma\pi}{\mu(\gamma + \mu)} + c_1 e^{-\mu t} + c_2 e^{-(\mu + \gamma)t} \right), \quad (3.54)$$

where  $c_0, c_1$ , and  $c_2 \in \mathbb{R}$ .

It is clear that

$$\lim_{t \rightarrow \infty} X(t) = X^o. \quad (3.55)$$

This implies that independently of the initial conditions values, all solutions of the system (3.53) converge to the equilibrium point  $X^o$ . Thus,  $X^o$  is GAS equilibrium point of (3.53).

To prove condition ( $\mathcal{H}_2$ ) that required  $\hat{H}(X, Y) \geq 0$ , which implies  $\hat{H}_1 \geq 0$  and  $\hat{H}_2 \geq 0$ , we proceed by contradiction.

We assume that  $\hat{H}_1 < 0$  and  $\hat{H}_2 < 0$ , which respectively implies that

$$\frac{\mu}{\mu + \gamma} < \frac{S}{N} \quad \text{and} \quad \frac{\gamma}{\mu + \gamma} < \frac{S_p}{N}. \quad (3.56)$$

Adding both inequalities in (3.56), we obtain

$$1 < \frac{S + S_p}{N} \quad \text{that is} \quad N < S + S_p, \quad (3.57)$$

which is a contradiction. Therefore  $\hat{H}_1 \geq 0$  and  $\hat{H}_2 \geq 0$ . This completes the proof to the two conditions.

As a result, we have therefore proved the global stability of the DFE  $E_p^o$  of system (3.2) that we summarized in the theorem as follows:

**Theorem 3.2.3.** *The DFE  $E_p^o$  of the system of equations (3.2) is globally asymptotically stable when  $\mathcal{R}_0 < 1$  and unstable  $\mathcal{R}_0 > 1$ .*

Theorem 3.2.3 confirms that when  $\mathcal{R}_0 < 1$ , we can take control of the spread of HIV infection independently of the initial conditions of the infection as long as we can keep the basic reproduction number below 1.

### 3.2.6 Endemic equilibrium point and its local stability

The coordinates of the endemic equilibrium point  $E_p^* = (S^*, S_p^*, I^*, I_p^*, A^*)$  of the system of equations (3.2) are obtained, using the approach of Lungu *et al.* [19] via

$$\pi - (\gamma + (1 - \gamma)\lambda^* + \mu)S^* = 0, \quad (3.58)$$

$$\gamma S^* - (\mu + (1 - \sigma)\lambda^*)S_p^* = 0, \quad (3.59)$$

$$(1 - \gamma)\lambda^* S - (\rho_1 + \mu)I^* = 0, \quad (3.60)$$

$$(1 - \sigma)\lambda^* S_p^* - (\rho_2 + \mu)I_p^* = 0, \quad (3.61)$$

$$\rho_1 I^* + \rho_2 I_p^* - (\mu + \delta)A^* = 0. \quad (3.62)$$

From equation (3.58) we have

$$S^* = \frac{\pi}{\gamma + (1 - \gamma)\lambda^* + \mu}. \quad (3.63)$$

Substituting equation (3.63) into equation (3.59) we obtain

$$S_p^* = \frac{\gamma\pi}{(\mu + (1 - \sigma)\lambda^*)(\gamma + (1 - \gamma)\lambda^* + \mu)}. \quad (3.64)$$

Equation (3.63) and equation (3.60) yield

$$I^* = \frac{(1 - \gamma)\lambda^*\pi}{(\rho_1 + \mu)(\gamma + (1 - \gamma)\lambda^* + \mu)}. \quad (3.65)$$

Substituting equation (3.64) into equation (3.61) we obtain

$$I_p^* = \frac{(1 - \sigma)\lambda^*\gamma\pi}{(\rho_2 + \mu)(\gamma + (1 - \gamma)\lambda^* + \mu)(\mu + (1 - \sigma)\lambda^*)}. \quad (3.66)$$

From equation (3.62) we have

$$A^* = \frac{\lambda^*\pi}{(\gamma + (1 - \gamma)\lambda^* + \mu)(\mu + \delta)} \left[ \frac{\rho_1(1 - \gamma)}{(\rho_1 + \mu)} + \frac{\rho_2\gamma(1 - \sigma)}{(\rho_2 + \mu)(\mu + (1 - \sigma)\lambda^*)} \right]. \quad (3.67)$$

Substituting the expressions for  $I^*$ ,  $I_p^*$ , and  $A^*$  into

$$\lambda^* = c \frac{\eta_1 I^* + \eta_2 I_p^* + \eta_3 A^*}{N^*}, \quad (3.68)$$

we obtain

$$\begin{aligned} \lambda^* N^* = & \frac{(c\eta_1(\mu + \delta) + \eta_3\rho_1)(1 - \gamma)(\mu + (1 - \sigma)\lambda^*)}{(\rho_1 + \mu)(\mu + \delta)(\gamma + (1 - \gamma)\lambda^* + \mu)(\mu + (1 - \sigma)\lambda^*)} \lambda^* \\ & + \frac{(c\eta_2(\mu + \delta) + \eta_3\rho_2)(1 - \sigma)\gamma}{(\mu + \delta)(\rho_2 + \mu)(\gamma + (1 - \gamma)\lambda^* + \mu)(\mu + (1 - \sigma)\lambda^*)} \lambda^*. \end{aligned} \quad (3.69)$$

Equation (3.69) has a trivial solution  $\lambda_1^* = 0$  or two non-zero solutions  $\lambda_{2,3}^* \neq 0$ . Clearly, when  $\lambda_1^* = 0$ ,

$$S^* = \frac{\pi}{\mu + \gamma}, \quad S_p^* = \frac{\pi\gamma}{\mu(\gamma + \mu)}, \quad I^* = 0, \quad I_p^* = 0, \quad A^* = 0. \quad (3.70)$$

Then  $\lambda_1^* = 0$  corresponds to the disease free equilibrium point and one of the non-zero solutions (the positive one) of equation (3.69), which are obtained via solutions to the following quadratic equation obtained from equation (3.69)

$$\lambda^{*2} - e_1\lambda^* + e_0 = 0, \quad (3.71)$$

where

$$e_1 = \frac{\delta\rho_1\mu(1 - \gamma) + \rho_2\delta(\rho_1 + \mu)}{(\mu + \rho_1 + \delta)} + \frac{\mathcal{R}_1(\rho_1 + \mu)(\mu + \delta)(1 - \sigma)}{(1 - \gamma)(\mu + \rho_1 + \delta)},$$

and

$$e_0 = \frac{(1 - \mathcal{R}_0)(\mu + \gamma)(\mu + \delta)(\rho_1 + \mu)}{(1 - \gamma)(1 - \sigma)(\mu + \rho_1 + \delta)},$$

would therefore correspond to the endemic equilibrium point.

The quadratic equation (3.71) has a real solution when its discriminant  $\Delta = (-e_1)^2 - 4e_0 > 0$ , i.e when  $e_0 < 0$ . This is possible when  $\mathcal{R}_0 > 1$ . From that we have

$$\lambda_2^* = \frac{e_1}{2} - \sqrt{\left(\frac{e_1}{2}\right)^2 - e_0} \quad \text{and} \quad \lambda_3^* = \frac{e_1}{2} + \sqrt{\left(\frac{e_1}{2}\right)^2 - e_0}.$$

Since for  $\mathcal{R}_0 > 1$ ,  $e_0 < 0$ , we have  $\left(\frac{e_1}{2}\right)^2 - e_0 > \left(\frac{e_1}{2}\right)^2$ . Thus,  $\lambda_2^* < 0$  and  $\lambda_3^* > 0$ .  $\lambda_3^* > 0$  is therefore the unique positive solution that corresponds to the EEP.

**Theorem 3.2.4.** *The PrEP model (3.2) has a unique endemic equilibrium point (EEP) when  $\mathcal{R}_0 > 1$ .*

To analyse the local stability of the endemic point of the model (3.2), we use centre manifold theory [14]. The centre manifold theory states that the stability of a steady state under the initial system is determined by its stability under the restriction of the system to the centre manifold [20]. To use the method, we introduce the new variables  $S = x_1$ ,  $S_p = x_2$ ,  $I = x_3$ ,  $I_p = x_4$ ,  $A = x_5$  and  $\dot{x}_1 = f_1$ ,  $\dot{x}_2 = f_2$ ,  $\dot{x}_3 = f_3$ ,  $\dot{x}_4 = f_4$ ,  $\dot{x}_5 = f_5$ . The total population  $N$  becomes  $N = x_1 + x_2 + x_3 + x_4 + x_5$ . The system (3.2) becomes

$$\begin{aligned} \dot{x}_1 = f_1 &= \pi - \gamma x_1 - (1 - \gamma) \frac{c(\eta_1 x_3 + \eta_2 x_4 + \eta_3 x_5)x_1}{x_1 + x_2 + x_3 + x_4 + x_5} - \mu x_1, \\ \dot{x}_2 = f_2 &= \gamma x_1 - (1 - \sigma) \frac{c(\eta_1 x_3 + \eta_2 x_4 + \eta_3 x_5)x_2}{x_1 + x_2 + x_3 + x_4 + x_5} - \mu x_2, \\ \dot{x}_3 = f_3 &= (1 - \gamma) \frac{c(\eta_1 x_3 + \eta_2 x_4 + \eta_3 x_5)x_1}{x_1 + x_2 + x_3 + x_4 + x_5} - (\rho_1 + \mu)x_3, \\ \dot{x}_4 = f_4 &= (1 - \sigma) \frac{c(\eta_1 x_3 + \eta_2 x_4 + \eta_3 x_5)x_2}{x_1 + x_2 + x_3 + x_4 + x_5} - (\rho_2 + \mu)x_4, \\ \dot{x}_5 = f_5 &= \rho_1 x_3 + \rho_2 x_4 - (\mu + \delta)x_5. \end{aligned} \tag{3.72}$$

The disease free equilibrium point of (3.72) is

$$E_0^p = \left( \frac{\pi}{\gamma + \mu}, \frac{\pi\gamma}{\mu(\gamma + \mu)}, 0, 0, 0 \right), \tag{3.73}$$



and the basic reproduction number of model (3.72) is given by

$$\mathcal{R}_0 = \frac{c\mu(1-\gamma)(\eta_1(\mu+\delta) + \eta_3\rho_1)(\mu+\rho_2) + c\gamma(1-\sigma)(\eta_2(\mu+\delta) + \eta_3\rho_2)(\mu+\rho_1)}{(\mu+\gamma)(\mu+\delta)(\rho_2+\mu)(\rho_1+\mu)}. \quad (3.74)$$

Let us consider  $c$  as bifurcation parameter. Setting  $\mathcal{R}_0 = 1$  and solving for  $c$  we obtain

$$c = c^* = \frac{(\mu+\gamma)(\mu+\delta)(\rho_2+\mu)(\rho_1+\mu)}{\mu(1-\gamma)(\eta_1(\mu+\delta) + \eta_3\rho_1)(\mu+\rho_2) + \gamma(1-\sigma)(\eta_2(\mu+\delta) + \eta_3\rho_2)(\mu+\rho_1)}. \quad (3.75)$$

The Jacobian matrix of (3.72) evaluated at the DFE  $E_0^p$  with  $c = c^*$  is

$$D_x f(E_0^p) = \begin{bmatrix} -\mu - \gamma & 0 & -\frac{c^*\mu(1-\gamma)\eta_1}{\mu+\gamma} & -\frac{c^*\mu(1-\gamma)\eta_2}{\mu+\gamma} & -\frac{c^*\mu(1-\gamma)\eta_3}{\mu+\gamma} \\ \gamma & -\mu & -\frac{c^*\gamma(1-\sigma)\eta_1}{\mu+\gamma} & -\frac{c^*\gamma(1-\sigma)\eta_2}{\mu+\gamma} & -\frac{c^*\gamma(1-\sigma)\eta_3}{\mu+\gamma} \\ 0 & 0 & \frac{c^*\mu(1-\gamma)\eta_1}{\mu+\gamma} - \rho_1 - \mu & \frac{c^*\mu(1-\gamma)\eta_2}{\mu+\gamma} & \frac{c^*\mu(1-\gamma)\eta_3}{\mu+\gamma} \\ 0 & 0 & \frac{c^*\gamma(1-\sigma)\eta_1}{\mu+\gamma} & \frac{c^*\gamma(1-\sigma)\eta_2}{\mu+\gamma} - \rho_2 - \mu & \frac{c^*\gamma(1-\sigma)\eta_3}{\mu+\gamma} \\ 0 & 0 & \rho_1 & \rho_2 & -(\mu+\delta) \end{bmatrix}. \quad (3.76)$$

The eigenvalues of the matrix  $D_x f(E_0^p)$  are solutions of

$$\lambda(\lambda + \mu)(\lambda + \mu + \gamma)(\lambda^2 + d_1\lambda + d_0) = 0. \quad (3.77)$$

where

$$\begin{aligned} d_1 &= (\delta + \mu) + (\rho_1 + \mu) \left(1 - \frac{c^*\mu(1-\gamma)\eta_1}{(\mu+\gamma)(\rho_1+\mu)}\right) + (\rho_2 + \mu) \left(1 - \frac{c^*\gamma(1-\sigma)\eta_2}{(\mu+\gamma)(\rho_2+\mu)}\right), \\ d_0 &= (\mu + \delta) \left[ (\mu + \rho_1) \left(1 - \frac{\mu\mathcal{R}_1}{\mu+\gamma}\right) + (\mu + \rho_2) \left(1 - \frac{\gamma\mathcal{R}_2}{\mu+\gamma}\right) \right] + \frac{c^*\mu(1-\gamma)\rho_1\eta_3(\rho_2+\mu)}{(\mu+\gamma)(\mu+\delta)} \\ &\quad + \frac{c^*\gamma(1-\sigma)\rho_2\eta_3(\rho_1+\mu)}{(\mu+\gamma)(\mu+\delta)}. \end{aligned}$$

The characteristic equation (3.77) has at most five solutions. The first three are  $\lambda_1 = 0$ ,  $\lambda_2 = -\mu < 0$ , and  $\lambda_3 = -(\mu + \gamma) < 0$ . The other two are roots of the quadratic equation

$$\lambda^2 + d_1\lambda + d_0 = 0, \quad (3.78)$$

whose solution is

$$\lambda_{2,3} = \frac{-d_1}{2} \pm \sqrt{\left(\frac{d_1}{2}\right)^2 - d_0}. \quad (3.79)$$

To have eigenvalues with negative real parts, it is sufficient that  $d_0 > 0$ , that is when

$$0 < \frac{\mu\mathcal{R}_1}{\mu + \gamma} \leq 1 \quad \text{and} \quad 0 < \frac{\gamma\mathcal{R}_2}{\mu + \gamma} \leq 1. \quad (3.80)$$

This is achieved since

$$\frac{\mu\mathcal{R}_1}{\mu + \gamma} + \frac{\gamma\mathcal{R}_2}{\mu + \gamma} = \mathcal{R}_0 = 1. \quad (3.81)$$

Since 0 is a simple eigenvalue of matrix  $D_x f(E_0^p)$ , we can apply centre manifold theory to determine the local stability of the endemic equilibrium point  $E_p^*$ .

The right eigenvector  $Y = [y_1, y_2, y_3, y_4, y_5]^T$  associated with the zero eigenvalue is obtained by solving

$$D_x f(E_0^p) \cdot Y = \begin{bmatrix} -\mu - \gamma & 0 & -A\eta_1 & -A\eta_2 & -A\eta_3 \\ \gamma & -\mu & -B\eta_1 & -B\eta_2 & -B\eta_3 \\ 0 & 0 & A\eta_1 - \rho_1 - \mu & A\eta_2 & A\eta_3 \\ 0 & 0 & B\eta_1 & B\eta_2 - \rho_2 - \mu & B\eta_3 \\ 0 & 0 & \rho_1 & \rho_2 & -(\mu + \delta) \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \end{bmatrix} = \mathbf{0}, \quad (3.82)$$

where

$$A = \frac{c^*\mu(1 - \gamma)}{\mu + \gamma}, \quad B = \frac{c^*\gamma(1 - \sigma)}{\mu + \gamma}.$$

System (3.82) can be rewritten as

$$-(\mu + \gamma)y_1 - A\eta_1 y_3 - A\eta_2 y_4 - A\eta_3 y_5 = 0, \quad (3.83)$$

$$\gamma y_1 - \mu y_2 - B\eta_1 y_3 - B\eta_2 y_4 - B\eta_3 y_5 = 0, \quad (3.84)$$

$$(A\eta_1 - \rho_1 - \mu)y_3 + A\eta_2 y_4 - A\eta_3 y_5 = 0, \quad (3.85)$$

$$B\eta_1 y_3 + (B\eta_2 - \rho_2 - \mu)y_4 + B\eta_3 y_5 = 0, \quad (3.86)$$

$$\rho_1 y_3 + \rho_2 y_4 - (\delta + \mu)y_5 = 0. \quad (3.87)$$

Adding equation (3.83) to (3.85) and equation (3.84) to (3.86) and subsequently substituting

equation (3.87) into equations (3.85) and (3.86), the system (3.83)–(3.87) becomes

$$-(\mu + \gamma)y_1 + (\rho_1 + \mu)y_3 = 0, \quad (3.88)$$

$$\gamma y_1 - (\rho_2 + \mu)y_4 - \mu y_2 = 0, \quad (3.89)$$

$$\left( A \frac{\eta_1(\mu + \delta) + \rho_1 \eta_3}{\mu + \delta} - (\rho_1 + \mu) \right) y_3 + A \left( \frac{\eta_2(\delta + \mu) + \eta_2 \rho_3}{\delta + \mu} \right) y_4 = 0, \quad (3.90)$$

$$B \left( \frac{\eta_1(\delta + \mu) + \eta_1 \rho_3}{\delta + \mu} \right) y_3 + \left( B \frac{\eta_2(\mu + \delta) + \rho_2 \eta_3}{\mu + \delta} - (\rho_2 + \mu) \right) y_4 = 0, \quad (3.91)$$

$$\rho_1 y_3 + \rho_2 y_4 - (\delta + \mu)y_5 = 0, \quad (3.92)$$

Equation (3.88) gives

$$y_1 = -\frac{\rho_1 + \mu}{\mu + \gamma} y_3. \quad (3.93)$$

Substituting (3.93) into (3.89) we have

$$y_2 = -\frac{\gamma(\rho_1 + \mu)}{\mu(\mu + \gamma)} y_3 - \frac{(\rho_2 + \mu)}{\mu} y_4. \quad (3.94)$$

Substituting the expressions for  $A$  and  $B$  into equation (3.90), we obtain

$$y_4 = \frac{\gamma(1 - \sigma)}{\mu(1 - \gamma)} \left[ \begin{array}{c} 1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1 \\ \frac{\gamma}{\mu + \gamma} \mathcal{R}_2 \end{array} \right] y_3. \quad (3.95)$$

Substituting equation (3.95) into equation (3.92) we obtain

$$y_5 = \left( \frac{\rho_1}{\mu + \delta} + \frac{\gamma(1 - \sigma)\rho_2}{\mu(1 - \gamma)(\mu + \delta)} \left[ \begin{array}{c} 1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1 \\ \frac{\gamma}{\mu + \gamma} \mathcal{R}_2 \end{array} \right] \right) y_3. \quad (3.96)$$

To find  $y_3$ , we replace  $y_4$  in equation (3.91) to yield

$$\begin{aligned} \frac{\gamma}{\mu + \gamma} \frac{\mu}{\mu + \gamma} \mathcal{R}_2 \mathcal{R}_1 y_3 - \left( \frac{\gamma}{\mu + \gamma} \mathcal{R}_2 - 1 \right) \left( \frac{\mu}{\mu + \gamma} \mathcal{R}_1 - 1 \right) y_3 &= \frac{\gamma}{\mu + \gamma} \frac{\mu}{\mu + \gamma} \mathcal{R}_2 \mathcal{R}_1 y_3 - \\ \frac{\gamma}{\mu + \gamma} \frac{\mu}{\mu + \gamma} \mathcal{R}_2 \mathcal{R}_1 y_3 + \left( \frac{\mu}{\mu + \gamma} \mathcal{R}_1 + \frac{\gamma}{\mu + \gamma} \mathcal{R}_2 - 1 \right) y_3 &= 0, \end{aligned} \quad (3.97)$$

and so

$$(\mathcal{R}_0 - 1)y_3 = 0. \quad (3.98)$$

Since  $\mathcal{R}_0 = 1$ ,  $y_3$  is a non-zero arbitrary solution. Thus choosing  $y_3 = 1$ , we have

$$y_1 = -\frac{\rho_1 + \mu}{\mu + \gamma}, \quad (3.99)$$

$$y_2 = -\frac{\gamma(\rho_1 + \mu)}{\mu(\mu + \gamma)} - \frac{(\rho_2 + \mu)}{\mu} \frac{\gamma(1 - \sigma)}{\mu(1 - \gamma)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right], \quad (3.100)$$

$$y_3 = 1, \quad (3.101)$$

$$y_4 = \frac{\gamma(1 - \sigma)}{\mu(1 - \gamma)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right], \quad (3.102)$$

$$y_5 = \frac{\rho_1}{\mu + \delta} + \frac{\gamma(1 - \sigma)\rho_2}{\mu(1 - \gamma)(\mu + \delta)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right]. \quad (3.103)$$

The left eigenvector  $Z = [z_1, z_2, z_3, z_4, z_5]^T$  is obtained by solving the system of equations

$$(z_1, z_2, z_3, z_4, z_5) \cdot \begin{bmatrix} -\mu - \gamma & 0 & -A\eta_1 & -A\eta_2 & -A\eta_3 \\ \gamma & -\mu & -B\eta_1 & -B\eta_2 & -B\eta_3 \\ 0 & 0 & A\eta_1 - \rho_1 - \mu & A\eta_2 & A\eta_3 \\ 0 & 0 & B\eta_1 & B\eta_2 - \rho_2 - \mu & B\eta_3 \\ 0 & 0 & \rho_1 & \rho_2 & -(\mu + \delta) \end{bmatrix} = \mathbf{0}, \quad (3.104)$$

which gives

$$-(\mu + \gamma)z_1 + \gamma z_2 = 0, \quad (3.105)$$

$$\mu z_2 = 0, \quad (3.106)$$

$$-A\eta_1 z_1 - B\eta_1 z_2 + (A\eta_1 - \rho_1 - \mu)z_3 + B\eta_1 z_4 + \rho_1 z_5 = 0, \quad (3.107)$$

$$-A\eta_2 z_1 - B\eta_2 z_2 + A\eta_2 z_3 + (B\eta_2 - \rho_2 - \mu)z_4 + \rho_2 z_5 = 0, \quad (3.108)$$

$$-A\eta_1 z_1 - B\eta_1 z_2 + A\eta_3 z_3 + B\eta_3 z_4 - (\mu + \delta)z_5 = 0. \quad (3.109)$$

Equation (3.106) gives

$$z_2 = 0. \quad (3.110)$$

Substituting equation (3.110) into equation (3.105) we have

$$z_1 = 0. \quad (3.111)$$

From equation (3.109) we deduce

$$z_5 = \frac{A\eta_3}{\mu + \delta}z_3 + \frac{B\eta_3}{\mu + \delta}z_4. \quad (3.112)$$

Replacing  $z_5$  in equation (3.107) we obtain

$$A \frac{(\eta_1(\mu + \delta) + \rho_1\eta_3)}{\mu + \delta}z_4 + \left( B \frac{(\eta_1(\mu + \delta) + \rho_1\eta_3)}{\mu + \delta} - (\rho_1 + \mu) \right) z_3 = 0, \quad (3.113)$$

while substituting  $z_5$  into equation (3.108) we obtain

$$A \frac{(\eta_2(\mu + \delta) + \rho_2\eta_3)}{\mu + \delta}z_3 + \left( B \frac{(\eta_2(\mu + \delta) + \rho_2\eta_3)}{\mu + \delta} - (\rho_2 + \mu) \right) z_4 = 0. \quad (3.114)$$

Manipulating equation (3.113) and equation (3.112) with the expressions for  $A$  and  $B$ , we obtain

$$z_1 = 0, \quad (3.115)$$

$$z_2 = 0, \quad (3.116)$$

$$z_4 = \frac{\mu(1 - \gamma)}{\gamma(1 - \sigma)} \left[ \frac{\frac{\gamma}{\mu + \gamma}\mathcal{R}_2}{1 - \frac{\gamma}{\mu + \gamma}\mathcal{R}_2} \right] z_3, \quad (3.117)$$

$$z_5 = \frac{c\mu(1 - \gamma)\eta_3}{(\gamma + \mu)(\mu + \delta)} \left[ \frac{1}{1 - \frac{\gamma}{\mu + \gamma}\mathcal{R}_2} \right] z_3. \quad (3.118)$$

To find  $z_3$ , we substitute the expression for  $z_4$  into equation (3.114) and using the same manipulation as carried out in the right eigenvector's case, we obtain

$$(\mathcal{R}_0 - 1)z_3 = 0. \quad (3.119)$$

Again, since  $\mathcal{R}_0 = 1$  and setting  $z_3 = 1$ , we obtain

$$z_1 = 0, \quad (3.120)$$

$$z_2 = 0, \quad (3.121)$$

$$z_4 = \frac{\mu(1 - \gamma)}{\gamma(1 - \sigma)} \left[ \frac{\frac{\gamma}{\mu + \gamma}\mathcal{R}_2}{1 - \frac{\gamma}{\mu + \gamma}\mathcal{R}_2} \right], \quad (3.122)$$

$$z_5 = \frac{c\mu(1 - \gamma)\eta_3}{(\gamma + \mu)(\mu + \delta)} \left[ \frac{1}{1 - \frac{\gamma}{\mu + \gamma}\mathcal{R}_2} \right]. \quad (3.123)$$

We note that the non-zero components of the left eigenvector are positive. This is obvious since

$$0 < \frac{\gamma}{\mu + \gamma} \mathcal{R}_2 < \mathcal{R}_0 = 1. \quad (3.124)$$

In order to fully apply the method we need to compute  $a$  and  $b$  as defined in (1.9). We calculate all non-zero partial derivatives  $\frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_o^p, c^*)$  and  $\frac{\partial^2 f_k}{\partial x_i \partial c}(E_o^p, c^*)$  where  $(1 \leq i, j, k \leq 5)$ .

For  $a$ , we require:

- For  $k = 1$ , we have

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_1^2} &= 0, & \frac{\partial^2 f_1}{\partial x_1 \partial x_2} &= 0, & \frac{\partial^2 f_1}{\partial x_1 \partial x_3} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_1 \partial x_4} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_1 \partial x_5} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_2 \partial x_1} &= 0, & \frac{\partial^2 f_1}{\partial x_2^2} &= 0, & \frac{\partial^2 f_1}{\partial x_2 \partial x_3} &= \frac{\mu^2 c^*(1-\gamma)\eta_1}{\pi(\gamma+\mu)}, \\ \frac{\partial^2 f_1}{\partial x_2 \partial x_4} &= \frac{\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_2 \partial x_5} &= \frac{\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_3 \partial x_1} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_3 \partial x_2} &= \frac{\mu^2 c^*(1-\gamma)\eta_1}{\pi(\gamma+\mu)}, & \frac{\partial^2 f_1}{\partial x_3^2} &= \frac{2\mu^2 c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_3 \partial x_4} &= \frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_3 \partial x_5} &= \frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_4 \partial x_1} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_4 \partial x_2} &= \frac{\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_4 \partial x_3} &= \frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_4^2} &= \frac{2\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_4 \partial x_5} &= \frac{\mu^2 c^*(1-\gamma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_5 \partial x_1} &= -\frac{\mu\gamma c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_5 \partial x_2} &= \frac{\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_5 \partial x_3} &= \frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_1}{\partial x_4 \partial x_5} &= \frac{\mu^2 c^*(1-\gamma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_1}{\partial x_5^2} &= \frac{2\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}. \end{aligned}$$

- For  $k = 2$ , we have

$$\begin{aligned} \frac{\partial^2 f_2}{\partial x_1^2} &= 0, & \frac{\partial^2 f_2}{\partial x_1 \partial x_2} &= 0, & \frac{\partial^2 f_2}{\partial x_1 \partial x_3} &= \frac{\mu\gamma c^*(1-\sigma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_1 \partial x_4} &= \frac{\mu\gamma c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, \\ \frac{\partial^2 f_2}{\partial x_1 \partial x_5} &= \frac{\mu\gamma c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_2 \partial x_1} &= \frac{\partial^2 f_2}{\partial x_2^2} = 0, & \frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= -\frac{\mu^2 c^*(1-\sigma)\eta_1}{\pi(\gamma+\mu)}, \\ \frac{\partial^2 f_2}{\partial x_2 \partial x_4} &= -\frac{\mu^2 c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_2 \partial x_5} &= -\frac{\mu^2 c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_3 \partial x_1} &= \frac{\mu\gamma c^*(1-\sigma)\eta_1}{\pi(\mu+\gamma)}, \end{aligned}$$

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_3 \partial x_2} &= -\frac{\mu^2 c^*(1-\sigma)\eta_1}{\pi(\gamma+\mu)}, & \frac{\partial^2 f_2}{\partial x_3^2} &= \frac{2\mu\gamma c^*(1-\sigma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_3 \partial x_4} &= \frac{\mu\gamma c^*(1-\sigma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_2}{\partial x_3 \partial x_5} &= \frac{\mu\gamma c^*(1-\gamma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_4 \partial x_1} &= \frac{\mu\gamma c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_4 \partial x_2} &= -\frac{\mu^2 c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_2}{\partial x_4 \partial x_3} &= \frac{\mu\gamma c^*(1-\sigma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_4^2} &= \frac{2\mu\gamma c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_4 \partial x_5} &= \frac{\mu\gamma c^*(1-\sigma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_2}{\partial x_5 \partial x_1} &= \frac{\mu\gamma c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_5 \partial x_2} &= -\frac{\mu^2 c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_5 \partial x_3} &= \frac{\mu\gamma c^*(1-\sigma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_2}{\partial x_4 \partial x_5} &= \frac{\mu\gamma c^*(1-\sigma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_2}{\partial x_5^2} &= -\frac{2\mu\gamma c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}.
\end{aligned}$$

• For  $k = 3$ , we have

$$\begin{aligned}
\frac{\partial^2 f_3}{\partial x_1^2} &= 0, & \frac{\partial^2 f_3}{\partial x_1 \partial x_2} &= 0, & \frac{\partial^2 f_3}{\partial x_1 \partial x_3} &= \frac{\mu\gamma c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_1 \partial x_4} &= \frac{\mu\gamma c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_1 \partial x_5} &= \frac{\mu\gamma c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_2 \partial x_1} &= 0, & \frac{\partial^2 f_3}{\partial x_2^2} &= 0, & \frac{\partial^2 f_3}{\partial x_2 \partial x_3} &= -\frac{\mu^2 c^*(1-\gamma)\eta_1}{\pi(\gamma+\mu)}, \\
\frac{\partial^2 f_3}{\partial x_2 \partial x_4} &= -\frac{\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_2 \partial x_5} &= -\frac{\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_3 \partial x_1} &= \frac{\mu\gamma c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_3 \partial x_2} &= -\frac{\mu^2 c^*(1-\gamma)\eta_1}{\pi(\gamma+\mu)}, & \frac{\partial^2 f_3}{\partial x_3^2} &= -\frac{2\mu^2 c^*(1-\gamma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_3 \partial x_4} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_3 \partial x_5} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_4 \partial x_1} &= \frac{\mu\gamma c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_4 \partial x_2} &= -\frac{\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_4 \partial x_3} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_2)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_4^2} &= -\frac{2\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_4 \partial x_5} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_5 \partial x_1} &= \frac{\mu\gamma c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_5 \partial x_2} &= -\frac{\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_5 \partial x_3} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_1+\eta_3)}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_3}{\partial x_4 \partial x_5} &= -\frac{\mu^2 c^*(1-\gamma)(\eta_2+\eta_3)}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_3}{\partial x_5^2} &= -\frac{2\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)}.
\end{aligned}$$

• For  $k = 4$ , we have

$$\begin{aligned}
\frac{\partial^2 f_4}{\partial x_1^2} &= 0, & \frac{\partial^2 f_4}{\partial x_1 \partial x_2} &= 0, & \frac{\partial^2 f_4}{\partial x_1 \partial x_3} &= -\frac{\mu\gamma c^*(1-\sigma)\eta_1}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_4}{\partial x_1 \partial x_4} &= -\frac{\mu\gamma c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, \\
\frac{\partial^2 f_4}{\partial x_1 \partial x_5} &= -\frac{\mu\gamma c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_4}{\partial x_2 \partial x_1} &= 0, & \frac{\partial^2 f_4}{\partial x_2^2} &= 0, & \frac{\partial^2 f_4}{\partial x_2 \partial x_3} &= \frac{\mu^2 c^*(1-\sigma)\eta_1}{\pi(\gamma+\mu)}, \\
\frac{\partial^2 f_4}{\partial x_2 \partial x_4} &= -\frac{\mu^2 c^*(1-\sigma)\eta_2}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_4}{\partial x_2 \partial x_5} &= \frac{\mu^2 c^*(1-\sigma)\eta_3}{\pi(\mu+\gamma)}, & \frac{\partial^2 f_4}{\partial x_3 \partial x_1} &= -\frac{\mu\gamma c^*(1-\sigma)\eta_1}{\pi(\mu+\gamma)},
\end{aligned}$$

$$\begin{aligned}
\frac{\partial^2 f_4}{\partial x_3 \partial x_2} &= \frac{\mu^2 c^* (1 - \sigma) \eta_1}{\pi(\gamma + \mu)}, & \frac{\partial^2 f_4}{\partial x_3^2} &= -\frac{2\mu\gamma c^* (1 - \sigma) \eta_1}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_3 \partial x_4} &= -\frac{\mu\gamma c^* (1 - \sigma) (\eta_1 + \eta_2)}{\pi(\mu + \gamma)}, \\
\frac{\partial^2 f_4}{\partial x_3 \partial x_5} &= -\frac{\mu\gamma c^* (1 - \gamma) (\eta_1 + \eta_3)}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_4 \partial x_1} &= -\frac{\mu\gamma c^* (1 - \sigma) \eta_2}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_4 \partial x_2} &= \frac{\mu^2 c^* (1 - \sigma) \eta_2}{\pi(\mu + \gamma)}, \\
\frac{\partial^2 f_4}{\partial x_4 \partial x_3} &= -\frac{\mu\gamma c^* (1 - \sigma) (\eta_1 + \eta_2)}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_4^2} &= -\frac{2\mu\gamma c^* (1 - \sigma) \eta_2}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_4 \partial x_5} &= -\frac{\mu\gamma c^* (1 - \sigma) (\eta_2 + \eta_3)}{\pi(\mu + \gamma)}, \\
\frac{\partial^2 f_4}{\partial x_5 \partial x_1} &= -\frac{\mu\gamma c^* (1 - \sigma) \eta_3}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_5 \partial x_2} &= \frac{\mu^2 c^* (1 - \sigma) \eta_3}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_5 \partial x_3} &= -\frac{\mu\gamma c^* (1 - \sigma) (\eta_1 + \eta_3)}{\pi(\mu + \gamma)}, \\
\frac{\partial^2 f_4}{\partial x_4 \partial x_5} &= -\frac{\mu\gamma c^* (1 - \sigma) (\eta_2 + \eta_3)}{\pi(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_5^2} &= -\frac{2\mu\gamma c^* (1 - \sigma) \eta_3}{\pi(\mu + \gamma)}.
\end{aligned}$$

- For  $k = 5$ , we have

$$\frac{\partial^2 f_5}{\partial x_i \partial x_j} = 0, \quad 1 \leq i, j \leq 5.$$

For  $b$  we require:

- For  $k = 1$ ,

$$\begin{aligned}
\frac{\partial^2 f_1}{\partial x_1 \partial c^*} &= 0, & \frac{\partial^2 f_1}{\partial x_2 \partial c^*} &= 0, & \frac{\partial^2 f_1}{\partial x_3 \partial c^*} &= -\frac{\mu(1 - \gamma) \eta_1}{(\mu + \gamma)}, \\
\frac{\partial^2 f_1}{\partial x_4 \partial c^*} &= -\frac{\mu(1 - \gamma) \eta_2}{(\mu + \gamma)}, & \frac{\partial^2 f_1}{\partial x_5 \partial c^*} &= -\frac{\mu(1 - \gamma) \eta_3}{(\mu + \gamma)}.
\end{aligned}$$

- For  $k = 2$ ,

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_1 \partial c^*} &= 0, & \frac{\partial^2 f_2}{\partial x_2 \partial c^*} &= 0, & \frac{\partial^2 f_2}{\partial x_3 \partial c^*} &= -\frac{\gamma(1 - \sigma) \eta_1}{(\mu + \gamma)}, \\
\frac{\partial^2 f_2}{\partial x_4 \partial c^*} &= -\frac{\gamma(1 - \sigma) \eta_2}{(\mu + \gamma)}, & \frac{\partial^2 f_2}{\partial x_5 \partial c^*} &= -\frac{\gamma(1 - \sigma) \eta_3}{(\mu + \gamma)}.
\end{aligned}$$

- For  $k = 3$ ,

$$\begin{aligned}
\frac{\partial^2 f_3}{\partial x_1 \partial c^*} &= 0, & \frac{\partial^2 f_3}{\partial x_2 \partial c^*} &= 0, & \frac{\partial^2 f_3}{\partial x_3 \partial c^*} &= \frac{\mu(1 - \gamma) \eta_1}{(\mu + \gamma)}, \\
\frac{\partial^2 f_3}{\partial x_4 \partial c^*} &= \frac{\mu(1 - \gamma) \eta_2}{(\mu + \gamma)}, & \frac{\partial^2 f_3}{\partial x_5 \partial c^*} &= \frac{\mu(1 - \gamma) \eta_3}{(\mu + \gamma)}.
\end{aligned}$$

- For  $k = 4$ ,

$$\begin{aligned}
\frac{\partial^2 f_4}{\partial x_1 \partial c^*} &= 0, & \frac{\partial^2 f_4}{\partial x_2 \partial c^*} &= 0, & \frac{\partial^2 f_4}{\partial x_3 \partial c^*} &= \frac{\gamma(1 - \sigma) \eta_1}{(\mu + \gamma)}, \\
\frac{\partial^2 f_4}{\partial x_4 \partial c^*} &= \frac{\gamma(1 - \sigma) \eta_2}{(\mu + \gamma)}, & \frac{\partial^2 f_4}{\partial x_5 \partial c^*} &= \frac{\gamma(1 - \sigma) \eta_3}{(\mu + \gamma)}.
\end{aligned}$$



- For  $k = 5$ ,

$$\frac{\partial^2 f_5}{\partial x_i \partial c^*} = 0, \quad 1 \leq i \leq 5.$$

Putting it all together we obtain

$$\begin{aligned} a &= \sum_{i,j,k=1}^5 z_k y_i y_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} \\ &= \sum_{i,j=1}^5 z_1 y_i y_j \frac{\partial^2 f_1}{\partial x_i \partial x_j} + \sum_{i,j=1}^5 z_2 y_i y_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + \sum_{i,j=1}^5 z_3 y_i y_j \frac{\partial^2 f_3}{\partial x_i \partial x_j} + \sum_{i,j=1}^5 z_4 y_i y_j \frac{\partial^2 f_4}{\partial x_i \partial x_j} \\ &= \sum_{i,j=3}^5 z_3 y_i y_j \frac{\partial^2 f_3}{\partial x_i \partial x_j} + \sum_{i,j=3}^5 z_4 y_i y_j \frac{\partial^2 f_4}{\partial x_i \partial x_j} \\ &= z_3 \left( y_3 y_3 \frac{\partial^2 f_3}{\partial x_3^2} + 2y_3 y_4 \frac{\partial^2 f_3}{\partial x_3 \partial x_4} + 2y_3 y_5 \frac{\partial^2 f_3}{\partial x_3 \partial x_5} + 2y_4 y_5 \frac{\partial^2 f_3}{\partial x_4 \partial x_5} + y_4 y_4 \frac{\partial^2 f_3}{\partial x_4^2} + y_5 y_5 \frac{\partial^2 f_3}{\partial x_5^2} \right) + \\ &\quad z_4 \left( y_3 y_3 \frac{\partial^2 f_4}{\partial x_3^2} + 2y_3 y_4 \frac{\partial^2 f_4}{\partial x_3 \partial x_4} + 2y_3 y_5 \frac{\partial^2 f_4}{\partial x_3 \partial x_5} + 2y_4 y_5 \frac{\partial^2 f_4}{\partial x_4 \partial x_5} + y_4 y_4 \frac{\partial^2 f_4}{\partial x_4^2} + y_5 y_5 \frac{\partial^2 f_4}{\partial x_5^2} \right) \\ &= z_3 (\vartheta_{33}^3 + 2\vartheta_{34}^3 + 2\vartheta_{35}^3 + \vartheta_{44}^3 + 2\vartheta_{45}^3 + \vartheta_{55}^3) + z_4 (\vartheta_{33}^4 + 2\vartheta_{34}^4 + 2\vartheta_{35}^4 + \vartheta_{44}^4 + 2\vartheta_{45}^4 + \vartheta_{55}^4), \end{aligned}$$

where

$$\begin{aligned} \vartheta_{33}^3 &= y_3 y_3 \frac{\partial^2 f_3}{\partial x_3^2} = -2 \frac{\mu^2 c^* (1 - \gamma) \eta_1}{\pi(\mu + \gamma)}, \\ \vartheta_{34}^3 &= y_3 y_4 \frac{\partial^2 f_3}{\partial x_3 \partial x_4} = -\frac{\mu c^* \gamma (1 - \sigma) (\eta_1 + \eta_2)}{\pi(\mu + \gamma)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right], \\ \vartheta_{35}^3 &= y_3 y_5 \frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -\frac{\mu^2 c^* (1 - \gamma) (\eta_1 + \eta_3)}{\pi(\mu + \gamma)} \left( \frac{\rho_1}{\mu + \delta} + \frac{\gamma (1 - \sigma) \rho_2}{\mu (1 - \gamma) (\mu + \delta)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right] \right), \\ \vartheta_{44}^3 &= y_4 y_4 \frac{\partial^2 f_3}{\partial x_4^2} = -\frac{2\mu \gamma c^* (1 - \sigma) \eta_2}{\pi(\mu + \gamma)} \left( \frac{\gamma (1 - \sigma)}{\mu (1 - \gamma)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right] \right)^2, \\ \vartheta_{45}^3 &= y_4 y_5 \frac{\partial^2 f_3}{\partial x_4 \partial x_5} = -y_5 \frac{\mu^2 c^* (1 - \gamma) (\eta_2 + \eta_3)}{\pi(\mu + \gamma)} \left( \frac{\gamma (1 - \sigma)}{\mu (1 - \gamma)} \left[ \frac{1 - \frac{\mu}{\mu + \gamma} \mathcal{R}_1}{\frac{\gamma}{\mu + \gamma} \mathcal{R}_2} \right] \right), \end{aligned}$$

$$\begin{aligned}
\vartheta_{55}^3 &= y_5 y_5 \frac{\partial^2 f_3}{\partial x_5^2} = -\frac{2\mu^2 c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)} \left( \frac{\rho_1}{\mu+\delta} + \frac{\gamma(1-\sigma)\rho_2}{\mu(1-\gamma)(\mu+\delta)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right)^2, \\
\vartheta_{44}^4 &= y_4 y_4 \frac{\partial^2 f_4}{\partial x_4^2} = -2\frac{\mu^2 c^*(1-\gamma)\eta_2}{\pi(\mu+\gamma)} \left( \frac{\gamma(1-\sigma)}{\mu(1-\gamma)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right)^2, \\
\vartheta_{34}^4 &= y_3 y_4 \frac{\partial^2 f_4}{\partial x_3 \partial x_4} = -\frac{\mu\gamma c^*(1-\sigma)(\eta_1 + \eta_2)}{\pi(\mu+\gamma)} \left( \frac{\gamma(1-\sigma)}{\mu(1-\gamma)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right), \\
\vartheta_{35}^4 &= y_3 y_5 \frac{\partial^2 f_4}{\partial x_3 \partial x_5} = -\frac{\mu\gamma c^*(1-\sigma)(\eta_1 + \eta_3)}{\pi(\mu+\gamma)} \left( \frac{\rho_1}{\mu+\delta} + \frac{\gamma(1-\sigma)\rho_2}{\mu(1-\gamma)(\mu+\delta)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right), \\
\vartheta_{45}^4 &= y_4 y_5 \frac{\partial^2 f_4}{\partial x_4 \partial x_5} = -y_5 \frac{\mu\gamma c^*(1-\sigma)(\eta_2 + \eta_3)}{\pi(\mu+\gamma)} \left( \frac{\gamma(1-\sigma)}{\mu(1-\gamma)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right), \\
\vartheta_{55}^4 &= y_5 y_5 \frac{\partial^2 f_4}{\partial x_5^2} = -\frac{2\mu\gamma c^*(1-\gamma)\eta_3}{\pi(\mu+\gamma)} \left( \frac{\rho_1}{\mu+\delta} + \frac{\gamma(1-\sigma)\rho_2}{\mu(1-\gamma)(\mu+\delta)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma}\mathcal{R}_1}{\frac{\gamma}{\mu+\gamma}\mathcal{R}_2} \right] \right)^2.
\end{aligned}$$

Since  $0 < \frac{\mu}{\mu+\gamma}\mathcal{R}_1 < 1$  and  $0 < \frac{\gamma}{\mu+\gamma}\mathcal{R}_2 < 1$ ,  $z_3 > 0$ ,  $z_4 > 0$ , then all the terms  $\vartheta_{ij}^k$  for  $(3 \leq i, j \leq 5, k = 3 = 4)$  are negative. Hence,

$$a = z_3(\vartheta_{33}^3 + 2\vartheta_{34}^3 + 2\vartheta_{35}^3 + \vartheta_{44}^3 + 2\vartheta_{45}^3 + \vartheta_{55}^3) + z_4(\vartheta_{33}^4 + 2\vartheta_{34}^4 + 2\vartheta_{35}^4 + \vartheta_{44}^4 + 2\vartheta_{45}^4 + \vartheta_{55}^4) < 0 \quad (3.125)$$

and

$$\begin{aligned}
b &= \sum_{i,k=1}^5 z_k y_i \frac{\partial^2 f_k}{\partial x_i \partial c^*} \\
&= \sum_{i=1}^5 z_1 y_i \frac{\partial^2 f_1}{\partial x_i \partial c^*} + \sum_{i=1}^5 z_2 y_i \frac{\partial^2 f_2}{\partial x_i \partial c^*} + \sum_{i=1}^5 z_3 y_i \frac{\partial^2 f_3}{\partial x_i \partial c^*} + \sum_{i=1}^5 z_4 y_i \frac{\partial^2 f_4}{\partial x_i \partial c^*} + \sum_{i=1}^5 z_5 y_i \frac{\partial^2 f_5}{\partial x_i \partial c^*} \\
&= \sum_{i=1}^5 z_3 y_i \frac{\partial^2 f_3}{\partial x_i \partial c^*} + \sum_{i=1}^5 z_4 y_i \frac{\partial^2 f_4}{\partial x_i \partial c^*} \\
&= z_3 \left( y_3 \frac{\partial^2 f_3}{\partial x_3 \partial c^*} + y_4 \frac{\partial^2 f_3}{\partial x_4 \partial c^*} + y_5 \frac{\partial^2 f_3}{\partial x_5 \partial c^*} \right) + z_4 \left( y_3 \frac{\partial^2 f_4}{\partial x_3 \partial c^*} + y_4 \frac{\partial^2 f_4}{\partial x_4 \partial c^*} + y_5 \frac{\partial^2 f_4}{\partial x_5 \partial c^*} \right) \\
&= z_3(\omega_3^3 + \omega_4^3 + \omega_5^3) + z_4(\omega_3^4 + \omega_4^4 + \omega_5^4),
\end{aligned}$$

where

$$\begin{aligned}
\omega_3^3 &= y_3 \frac{\partial^2 f_3}{\partial x_3 \partial c^*} = \frac{\mu(1-\gamma)\eta_1}{(\mu+\gamma)}, \\
\omega_4^3 &= y_4 \frac{\partial^2 f_3}{\partial x_4 \partial c^*} = \frac{\eta_2 \gamma (1-\sigma)}{(\mu+\gamma)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma} \mathcal{R}_1}{\frac{\gamma}{\mu+\gamma} \mathcal{R}_2} \right], \\
\omega_5^3 &= y_5 \frac{\partial^2 f_3}{\partial x_5 \partial c^*} = \frac{\mu(1-\gamma)\eta_3}{(\mu+\gamma)} \left( \frac{\rho_1}{\mu+\delta} + \frac{\gamma(1-\sigma)\rho_2}{\mu(1-\gamma)(\mu+\delta)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma} \mathcal{R}_1}{\frac{\gamma}{\mu+\gamma} \mathcal{R}_2} \right] \right), \\
\omega_3^4 &= y_3 \frac{\partial^2 f_4}{\partial x_3 \partial c^*} = \frac{\gamma(1-\sigma)\eta_1}{(\mu+\gamma)}, \\
\omega_4^4 &= y_4 \frac{\partial^2 f_4}{\partial x_4 \partial c^*} = \frac{\gamma^2 \eta_2 (1-\sigma)^2}{\mu(\mu+\gamma)(1-\gamma)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma} \mathcal{R}_1}{\frac{\gamma}{\mu+\gamma} \mathcal{R}_2} \right], \\
\omega_5^4 &= y_5 \frac{\partial^2 f_4}{\partial x_5 \partial c^*} = \frac{\gamma(1-\sigma)\eta_3}{(\mu+\gamma)} \left( \frac{\rho_1}{\mu+\delta} + \frac{\gamma(1-\sigma)\rho_2}{\mu(1-\gamma)(\mu+\delta)} \left[ \frac{1 - \frac{\mu}{\mu+\gamma} \mathcal{R}_1}{\frac{\gamma}{\mu+\gamma} \mathcal{R}_2} \right] \right).
\end{aligned}$$

It follows that all the terms  $\omega_i^k$  for  $(3 \leq i \leq 5, k = 3 = 4)$  are positive. This is achieved since

$$0 < \frac{\mu}{\mu+\gamma} \mathcal{R}_1 < 1 \quad \text{and} \quad 0 < \frac{\gamma}{\mu+\gamma} \mathcal{R}_2 < 1,$$

and, moreover,  $z_3$  and  $z_4$  are also positive. Therefore

$$b = z_3(\omega_3^3 + \omega_4^3 + \omega_5^3) + z_4(\omega_3^4 + \omega_4^4 + \omega_5^4) > 0. \quad (3.126)$$

Thus we have  $a < 0$  and  $b > 0$  that corresponds to condition (iv) of Theorem 1.2.7. This leads to the following result:

**Theorem 3.2.5.** *The PrEP model (3.2) has a unique endemic equilibrium point  $E_p^*$  and it is locally asymptotically stable when  $\mathcal{R}_0 > 1$  but close to 1.*

Since  $a < 0$ ,  $b > 0$ , there is an exchange of stability between the DFE and EEP when  $\mathcal{R}_0 = 1$ . This means the system undergoes a supercritical bifurcation.

# Chapter 4

## Numerical Simulations

### 4.1 Introduction

Analytical results for the PrEP model (3.2) gave an insight of the conditions under which PrEP can be effective and those for which PrEP may fail. To quantitatively represent the evolution of the dynamics of PrEP use, we resort to the use of parameter values that can best represent possible hypothetical scenarios emanating from our analytical analysis to carry out the numerical simulations. We use such results to draw conclusions and have a better understanding of different strategies that can and cannot be used for effective PrEP administration. We use parameter values chosen from [21] and we summarize the threshold parameters values obtained using those parameters (see Table 4.1).

The assumptions made on the parameters  $\pi$ ,  $c$ ,  $\mu$ ,  $\delta$  in our study are the same as considered in [21]. We assume that  $\eta_1 < \eta_2$  to mean that probability of successful transmission of infection is higher in non-PrEP infectives than PrEP users infectives. Similarly,  $\eta_2 < \eta_3$  means that probability of successful transmission of HIV infection is AIDS individuals than the PrEP users'. We also assume that the progression of infected individuals from  $I_p$  to the AIDS class  $A$  is lower than the progression of infected individuals from  $I$  class to the AIDS class ( $A$ ), that is  $\rho_2 < \rho_1$ .

We use the Python programming language (Odeint) for our simulations. We focus our analysis

Table 4.1: Parameter values considered

$\pi$	$c$	$\mu$	$\delta$	$\rho_1$	$\rho_2$	$\eta_1$	$\eta_2$	$\eta_3$
$10^4$	4	0.02	0.04	0.7	0.6	0.4	0.04	0.3

on the effects of PrEP awareness ( $\gamma$ ) and its efficacy ( $\sigma$ ) on the HIV incidence function and HIV prevalence. We do this by investigating how increasing or decreasing  $\gamma$  and  $\sigma$  can affect the spread of HIV infection. We then give a biological interpretation of the numerical results obtained. We explore the effects of PrEP based on the following hypothetical scenarios on  $\gamma$  and  $\sigma$ :

- (i) No PrEP use, i.e  $\gamma = \sigma = 0$ .
- (ii) Low PrEP awareness and low PrEP efficacy.
- (iii) Low PrEP awareness and high PrEP efficacy.
- (iv) High PrEP awareness and low PrEP efficacy.
- (v) High PrEP awareness and high PrEP efficacy.

For illustrative purposes, we use representative proportions for PrEP awareness and PrEP efficacy as indicated Table 4.1. Representative figures (see Figures 4.1 to 4.5) are produced based on the values in Table 4.1 and the hypothetical values and the interpretations thereof. In all simulations,  $S(0) = 5 \times 10^5$ ,  $S_p(0) = 0$ ,  $I_p(0) = 0.1 \times 10^4$ ,  $I(0) = 1$ , and  $A(0) = 0$ .

(i) We take  $\gamma = \sigma = 0$  to mean there is no PrEP use. Figure 4.1 shows that when there is no PrEP use, the susceptible population is reduced significantly and the incidence of infection rises. This means that the majority of the individuals are either infected or have developed AIDS.

(ii) We take 35% to indicate low PrEP awareness for susceptible individuals and 35% to indicate low efficacy of PrEP drugs. The fast reproduction number is associated with individuals not taking PrEP whilst the slow reproduction number is for individuals on PrEP, even though

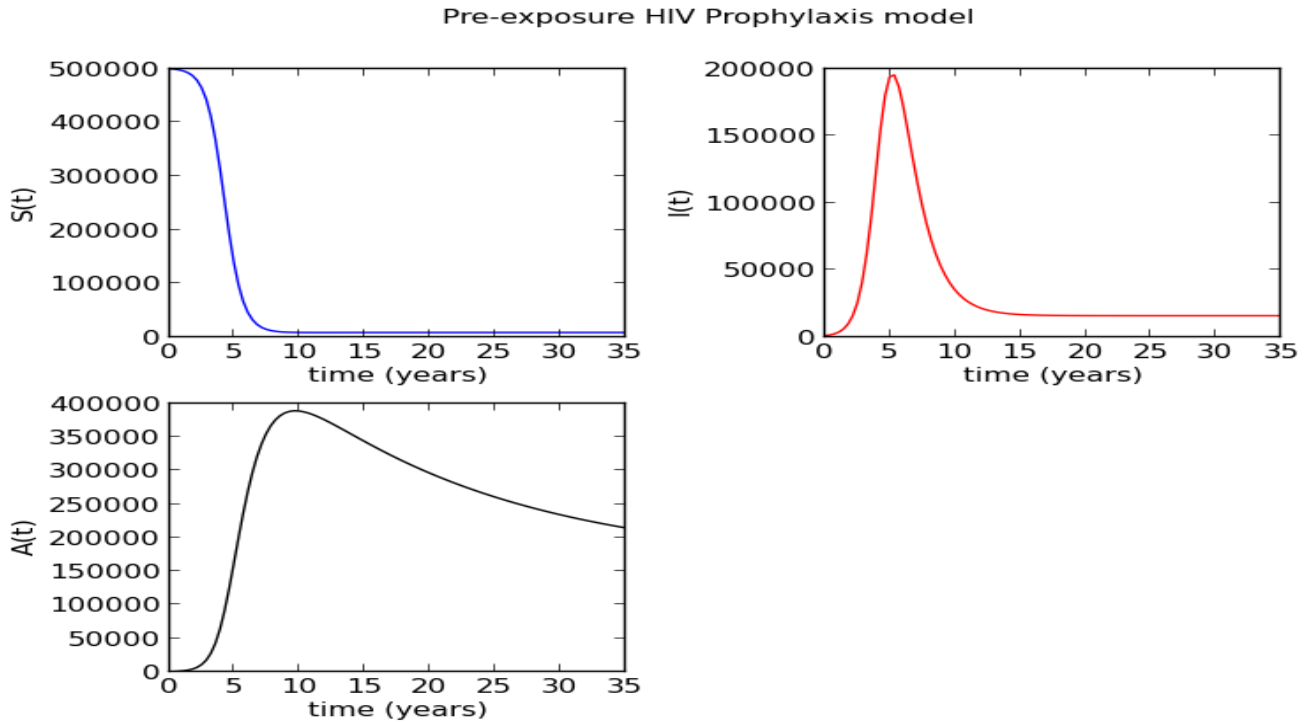


Figure 4.1: Profiles of each class of the population with  $\sigma = 0$ ,  $\gamma = 0$ ,  $\mathcal{R}_1 = 5.34$ ,  $\mathcal{R}_2 = 3.22$ ,  $\kappa = 1.00$ ,  $\mathcal{R}_0 = 5.34$ .

$\mathcal{R}_o$  is reduced compared to case (i). This strategy also reduces the incidence of the infection. However, it is not capable of suppressing the infection completely.

(iii) We now investigate the strategy of keeping the awareness level low (35%) whilst increasing the efficacy of drugs (to 85%). The fast reproduction number still remains associated with the non-PrEP group but the basic reproduction number reduces to below unity. Figure 4.3 shows a reduction in non-PrEP infected individuals and AIDS individuals associated with a slight increase in susceptible PrEP individuals. The incidence is reduced. Due care must be taken when using this strategy since much of the contribution to the infection still comes from the non-PrEP infected individuals. Our analytical results showed that the disease-free steady state is globally asymptotically stable when the reproduction number is less than unity. This therefore implies that the strategy of high PrEP drug efficacy may be successful in controlling HIV in the community. However, due care must be taken to ensure strict adherence to PrEP drug use to maintain the effectiveness of the strategy. The challenge that comes with this

Pre-exposure HIV Prophylaxis model

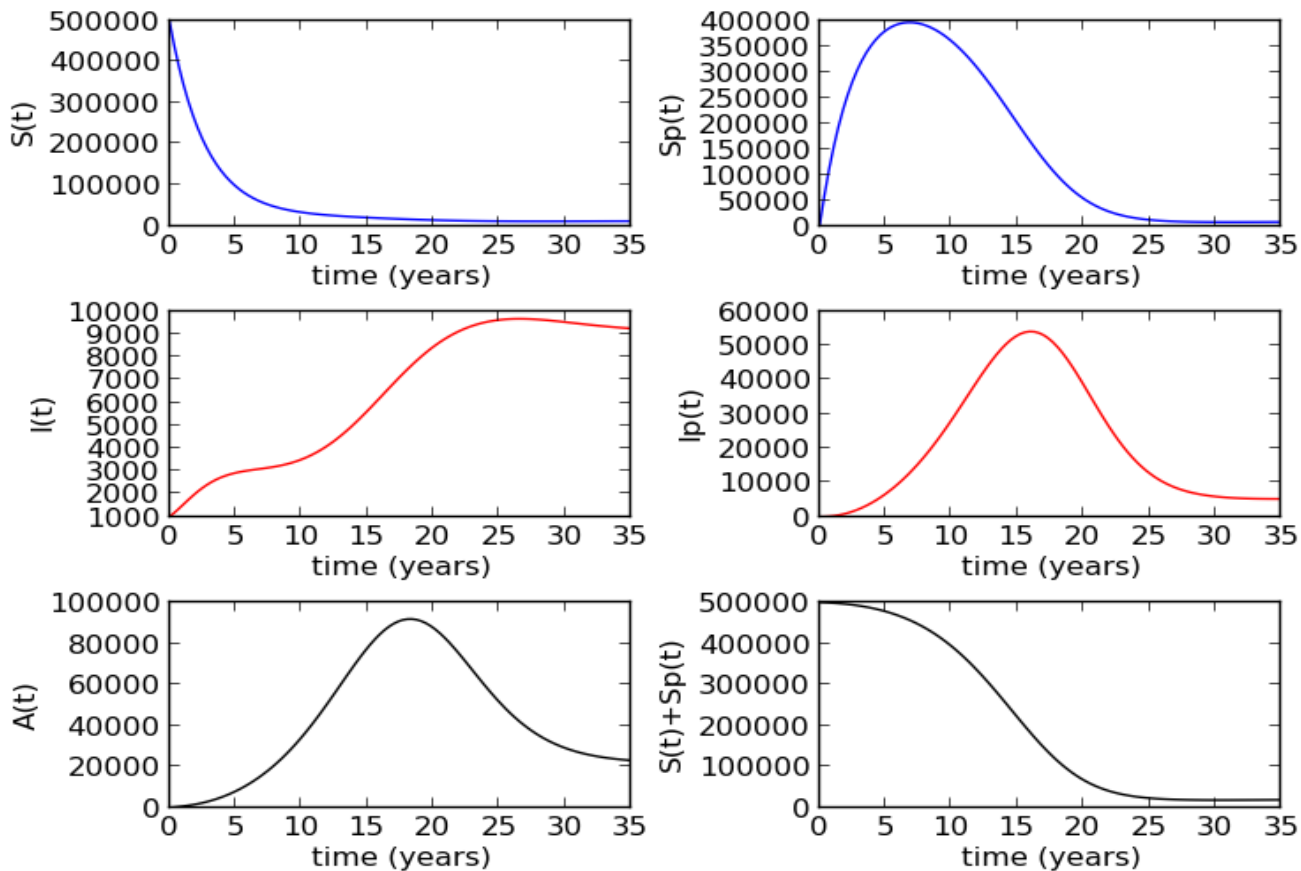


Figure 4.2: Profiles for state variable dynamics with  $\sigma = 0.35$ ,  $\gamma = 0.35$ ,  $\mathcal{R}_1 = 3.47$ ,  $\mathcal{R}_2 = 1.97$ ,  $\kappa = 0.054$ ,  $\mathcal{R}_0 = 2.63$ .

strategy is that the high efficacy of PrEP drugs may not be affordable in poorly resourced settings.

(iv) The next strategy is where the awareness is increased to 85% but with low efficacy of anti-HIV drugs (35%). In this case, there is a switch of the fast reproduction number from the non-PrEP group to the PrEP group. The basic reproduction number is also above unity. Figure 4.4 shows that a number of individuals escape infection due to PrEP use. We also observe an increase in the incidence of infection. Since the fast reproduction is above unity this strategy may not be reliable to use especially if the drugs used are of low efficacy and are prone to development of resistance.

Pre-exposure HIV Prophylaxis model

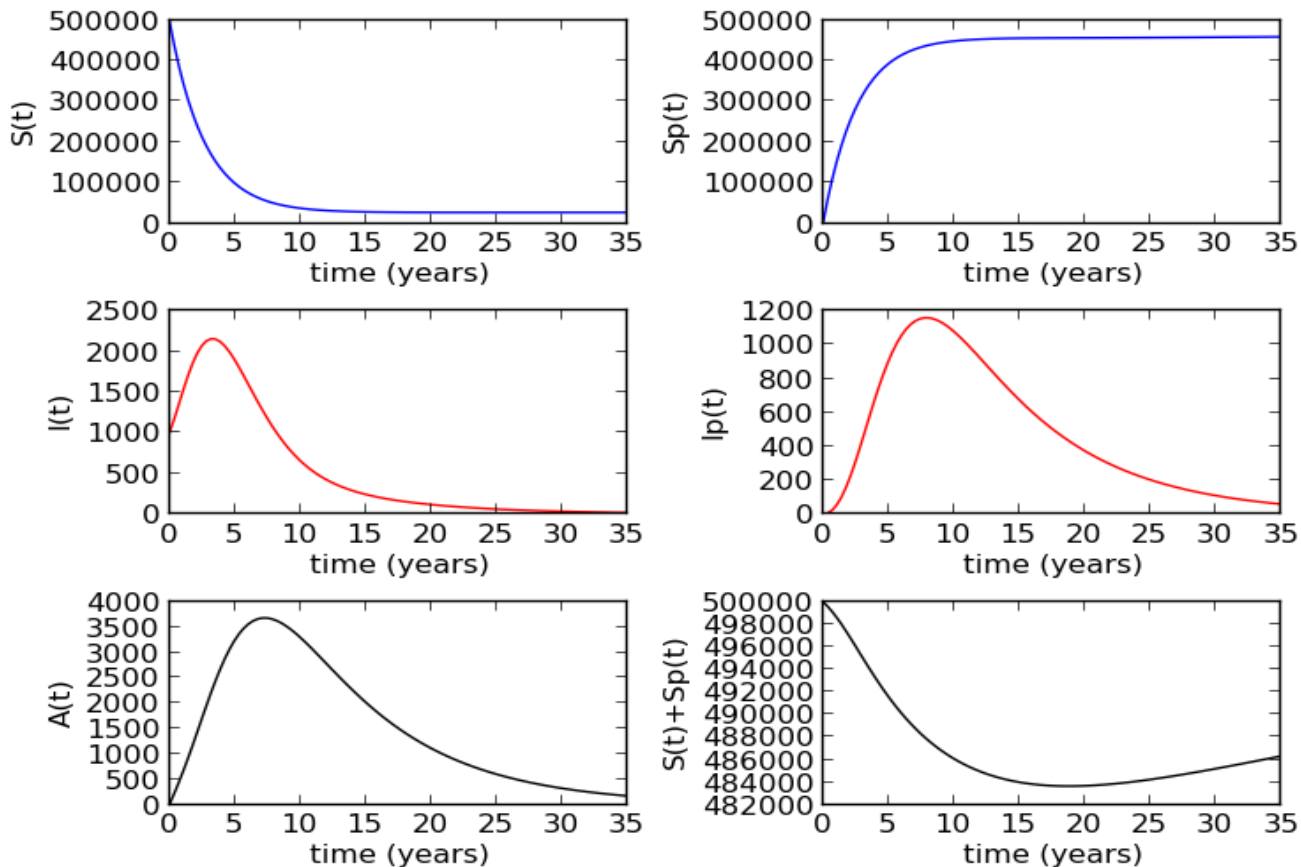


Figure 4.3: Profiles for state variable dynamics with  $\sigma = 0.85$ ,  $\gamma = 0.35$ ,  $\mathcal{R}_1 = 3.47$ ,  $\mathcal{R}_2 = 0.45$ ,  $\kappa = 0.054$ ,  $\mathcal{R}_0 = 0.61$ .

(v) We finally investigate the case where both awareness and efficacy are high, i.e.  $\gamma = 85\%$  and  $\sigma = 85\%$ . Figure 4.5 shows a significant decrease of the incidence function as well as the number of infected individuals ( $I$  and  $I_p$ ). The number of full blow AIDS individuals and infected individuals decreases progressively with time. The number of susceptible individuals on PrEP use increases compared to those who do not. The basic reproduction number  $\mathcal{R}_o$  obtained is less than one. Both slow and fast reproduction numbers are below unity. Clearly, this strategy of PrEP use and its efficacy is a viable preventive control measure against HIV transmission in the community. However, increasing  $\gamma = 85\%$  and efficacy  $\sigma = 85\%$  remains a big challenge since this involves strict adherence of individuals to drug uptake and effective



monitoring efforts on individuals' appropriate and proper utilization of PrEP education.

(vi) Figure 4.6 depicts the evolution of the force of infection in time with the different strategies considering. It is interesting to note that considering strategy of high PrEP efficacy and low PrEP use has more benefits of decline the force of infection that the strategy of low PrEP efficacy and high PrEP use. Overall, it can see that strategy of high PrEP use and high PrEP efficacy significantly reduce the force of infection.

(vii) The contour plot in figure 4.7 shows how the different combined strategies of awareness and efficacy affects the basic reproduction number. It is clear that increasing both awareness and efficacy has a profound effect of reducing the basic reproduction number. Hence, any policy regarding the use of PrEP should focus on continuous improvement of both PrEP awareness and PrEP efficacy to achieve a significant control level of HIV infection.

Pre-exposure HIV Prophylaxis model

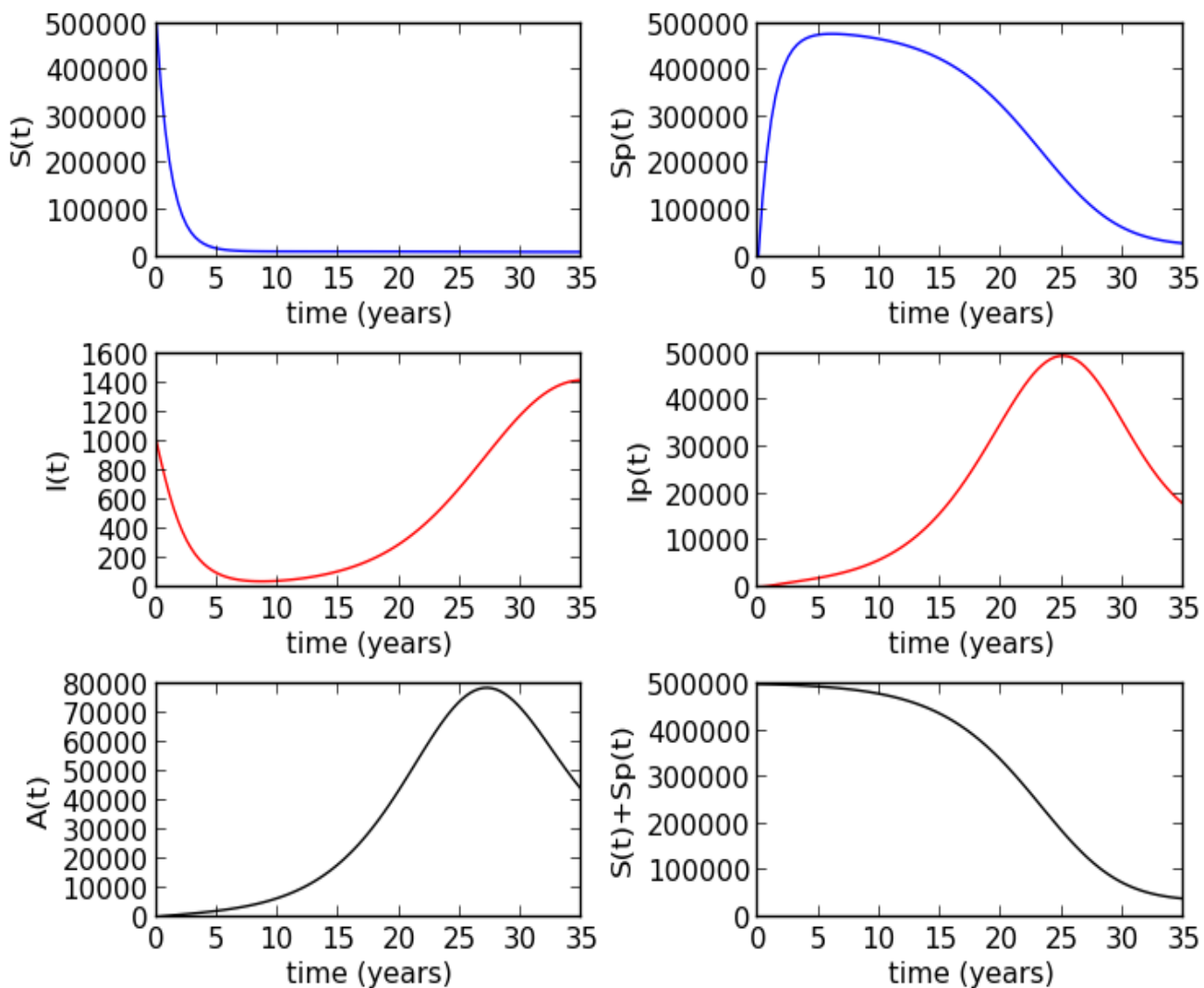


Figure 4.4: Profiles for state variable dynamics with  $\sigma = 0.35$ ,  $\gamma = 0.85$ ,  $\mathcal{R}_1 = 0.80$ ,  $\mathcal{R}_2 = 1.95$ ,  $\kappa = 0.022$ ,  $\mathcal{R}_0 = 1.93$ .

Pre-exposure HIV Prophylaxis model

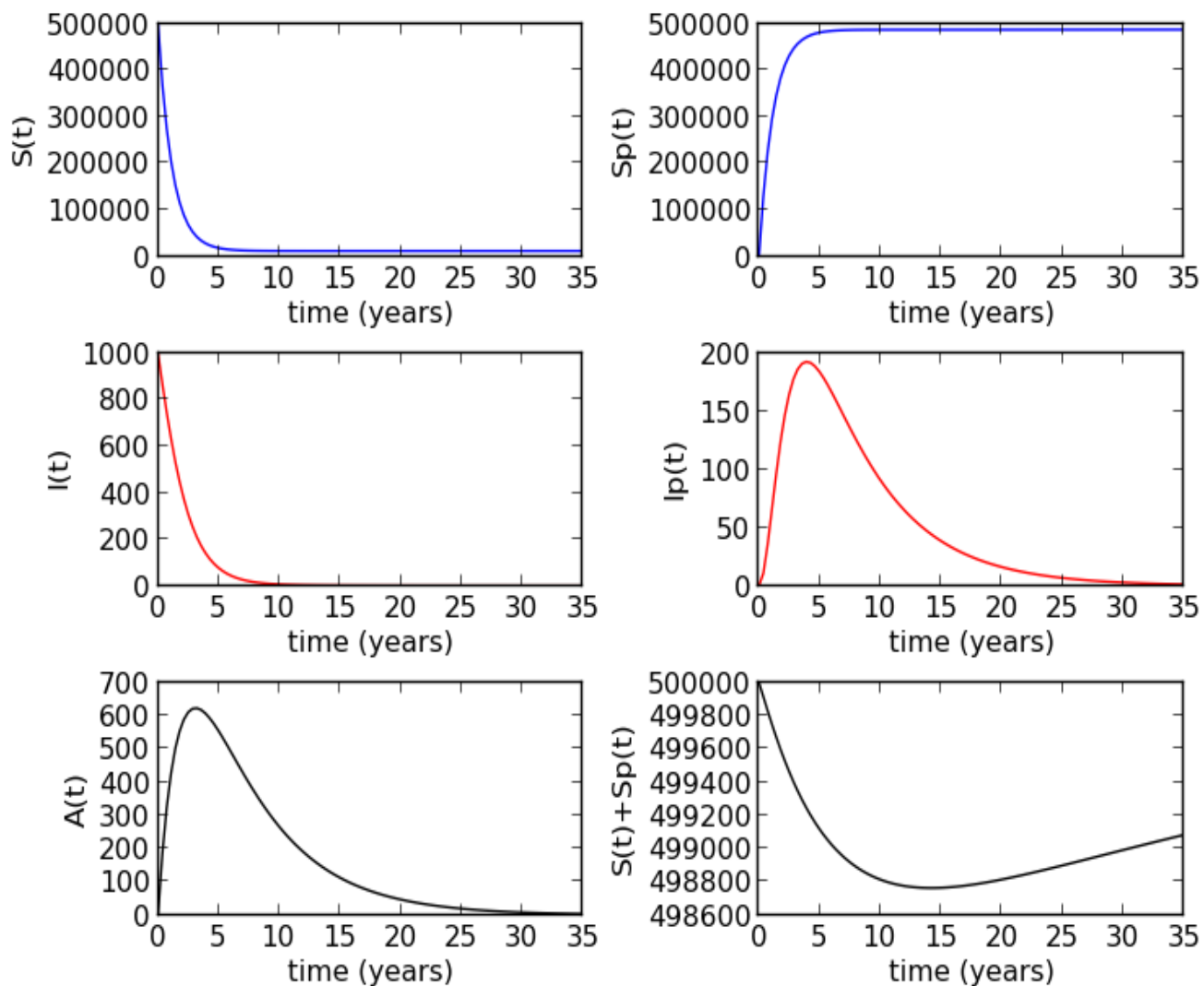


Figure 4.5: Profiles for state variable dynamics with  $\sigma = 0.85$ ,  $\gamma = 0.85$ ,  $\mathcal{R}_1 = 0.80$ ,  $\mathcal{R}_2 = 0.45$ ,  $\kappa = 0.022$ ,  $\mathcal{R}_0 = 0.46$ .

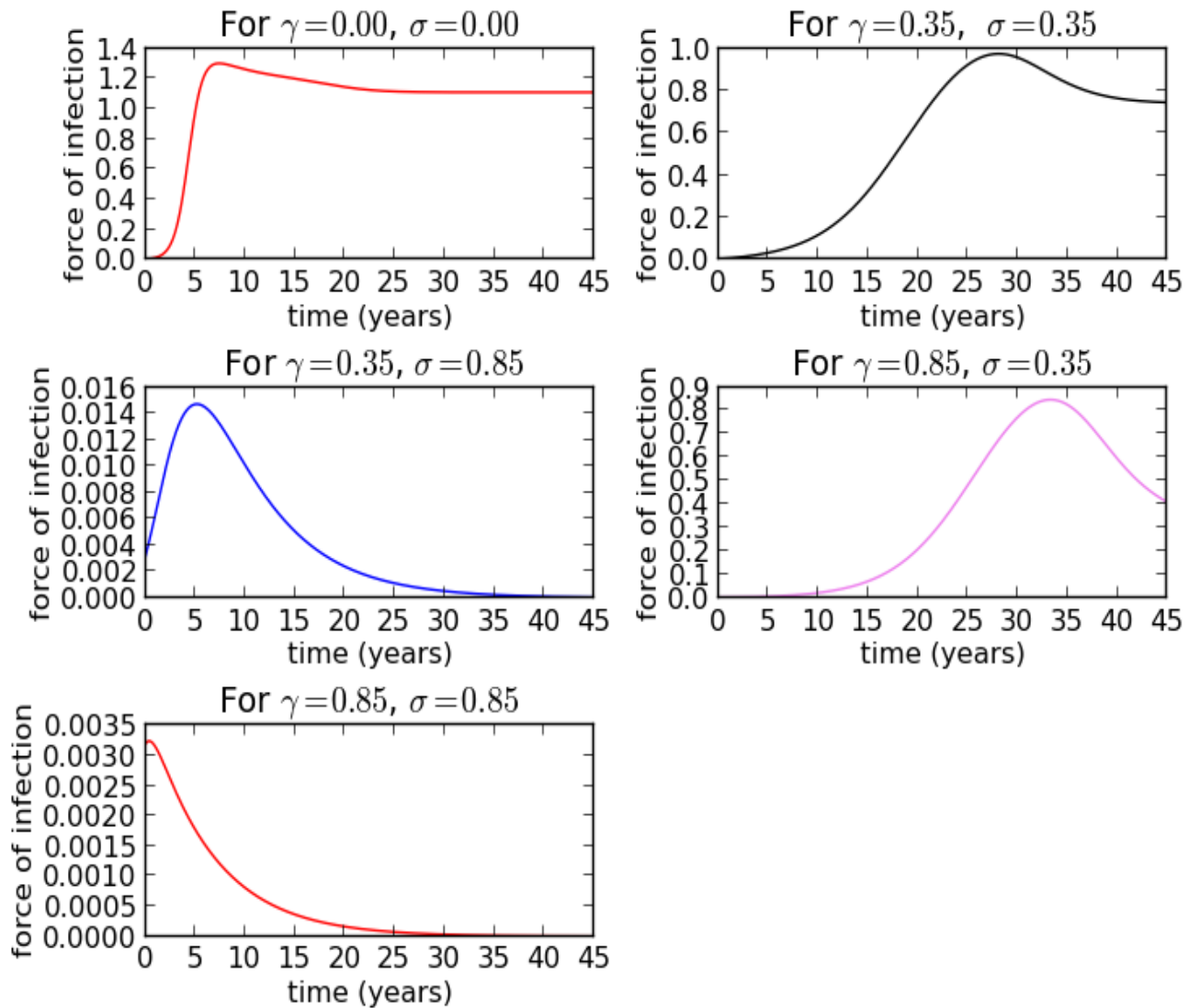


Figure 4.6: The incidence function  $\lambda(t) = \frac{c\eta_1 I(t) + c\eta_2 I_p(t) + c\eta_3 A(t)}{N(t)}$  with different values of  $\sigma$  and  $\gamma$ .

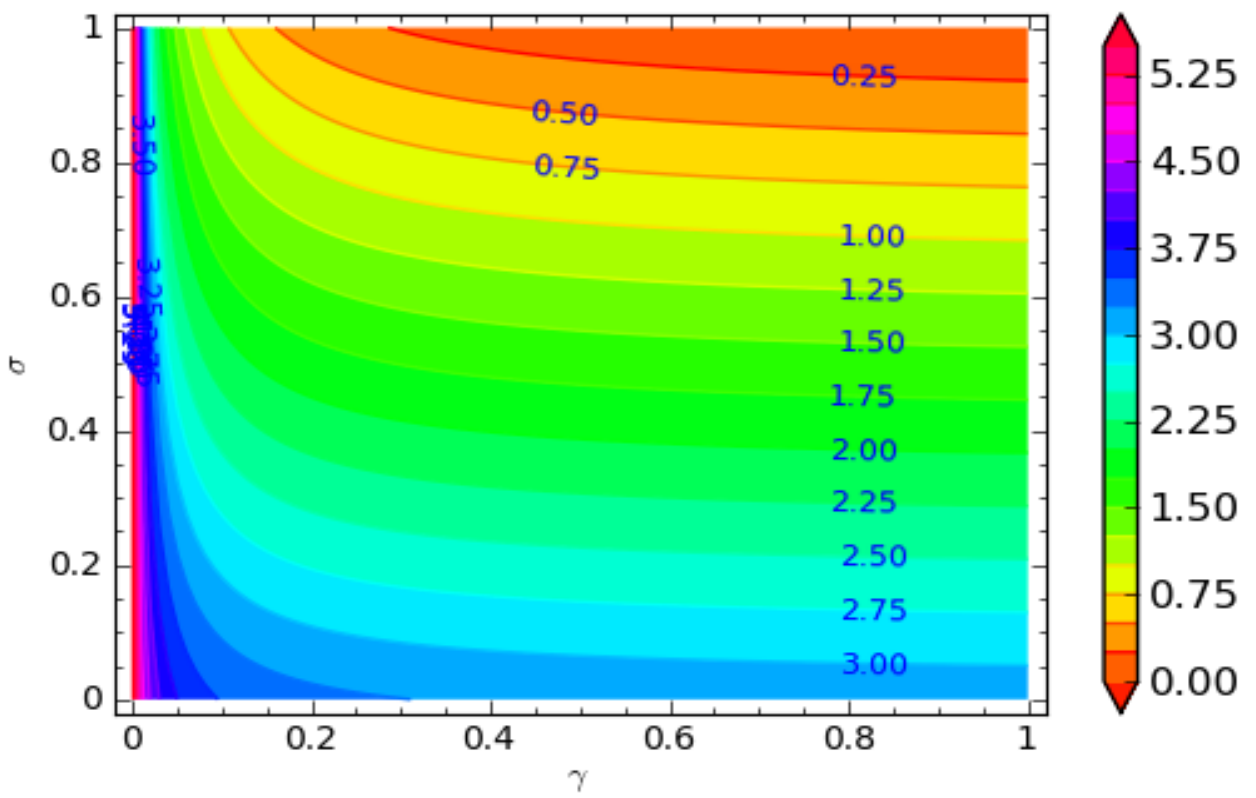


Figure 4.7: Contour plot on PrEP awareness ( $\gamma$ ) and its efficacy ( $\sigma$ ) vs  $\mathcal{R}_0$ .

# Chapter 5

## Conclusion

### 5.1 Observations

Pre-exposure prophylaxis (PrEP) used to prevent HIV infection has recently generated considerable interests [3]. In trying to investigate how PrEP use may affect HIV infection progression in the community, we developed an HIV/AIDS model and carried out analysis of the various steady states of the model. The model had two steady states: the disease free equilibrium point and the endemic equilibrium point. Threshold conditions for the stability of steady states were established through the use of the basic reproduction number. Stability analysis of both equilibrium points showed that when the basic reproduction number is less than one, the disease free equilibrium (DFE) point is locally asymptotically stable and when the basic reproduction number is greater than one, the DFE point becomes unstable while the endemic equilibrium is stable. Numerical simulations were carried out to support the theoretical results. The simulations suggest that in the absence of interventions, a large proportion of the population will end up being infected or developing full blown AIDS.

The basic reproduction number of the PrEP model depends on the rate at which individuals use PrEP (PrEP awareness) and the rate at which PrEP protects individuals (PrEP efficacy). The stability analysis of the steady states of the model was performed. The DFE point was locally asymptotically stable when the basic reproduction number is less than unity and unstable

otherwise. We used Centre Manifold theory to establish the stability of the endemic equilibrium point. Centre Manifold theory was used to prove that the endemic equilibrium point is locally asymptotically stable when the basic reproduction number is greater than one. Numerical simulations of the model on the influence of the PrEP awareness and PrEP efficacy revealed the following:

- In absence of preventive control measures the majority of individuals progress to the infected status or develop AIDS. This is an ideal case for HIV infection progression without intervention.
- PrEP intervention with low PrEP use and low PrEP efficacy reduces the progression rate but remains an ineffective strategy for the eradication of the infection.
- Large responses to PrEP use (by susceptible individuals) with low efficacy of PrEP drugs does not guarantee eradication of HIV infection in communities.
- Low PrEP awareness associated with high PrEP efficacy strategy reduces significantly the incidence of HIV infection. This reduction however, is dependent on a strict adherence to a suitable drug regimen and the maintenance of high awareness of PrEP use in the community.
- High PrEP use and awareness reduces the HIV infection more significantly than any other strategy considered.

One of the challenges associated with a high PrEP campaign and an effective PrEP implementation is that in resource-poor settings, funds are not enough to cater for expensive PrEP drugs and campaigns. For instance, the expected yearly per-case cost for TDF (Tenofovir Disoproxil Fumarate) is \$6,292/yr for 30 tablets in a month [3] and Truvada (Tenofovir + emtricitabine) costs \$869 for 30 days [7]. This high cost of PrEP remains an impeding factor in all efforts for effective PrEP intervention in countries which are unable to finance the PrEP program implementation. In an effort for successful PrEP program in high risk settings, governments should strive to ensure that they subsidize the price of high efficacy PrEP drugs. In addition expert advice is required to recommend drugs with little or no side effects, stage strategic awareness

campaigns to increase the knowledge and increase usage of PrEP, promote strict adherence of individuals on PrEP to reduce the occurrence of drug resistance, introduce screening facilities to any individual keen on using PrEP drugs, and establish regulations against illegal and unlicensed PrEP distribution to avoid provision of fake drugs. Care must be taken for individuals not to consider PrEP as the only way of prevention but to use it in combination with other intervention strategies such as condoms use, provision of good nutrition, counselling etc.

## 5.2 Further Work

In this study, we managed to expose the potential that PrEP use has in a bid to control HIV infection. This is a basic step towards more inclusive and deep studies on various intervention strategies. To improve the results of our model, possible extensions may include, incorporation of vertical transmission of HIV infection in the PrEP model dynamics, introduction of ARV treatment to individuals who become infected and those infected due to PrEP failure, use of data to validate the prediction of our PrEP model, and using PrEP with other intervention strategies such as condoms use, home based care etc.



# Bibliography

- [1] L. Cai, X. Li, M. Ghosh, and B. Guo, Stability analysis of an HIV/AIDS epidemic model with treatment, *Journal of Computational and Applied Mathematics*, 229 (2009), 313–323.
- [2] UNAIDS/WHO/UNICEF: Global/HIV/AIDS reponse: Epidemic update and health sector progress towards universal access, (progress report). Technical report, 2011. [http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20111130\\_Report\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20111130_Report_en.pdf).
- [3] G. Szekeres, T. J. Coates, S. Frost, A. Leibowitz, and S. Shoptaw, Anticipating the efficacy of HIV pre-exposure prophylaxis (PrEP) and the needs of at-risk Californians, *CHIPTS*, 2004, Technical report. [http://www.aidspartnership.ca.org/assets/documents/PrEP\\_report\\_final\\_11\\_1\\_04.pdf](http://www.aidspartnership.ca.org/assets/documents/PrEP_report_final_11_1_04.pdf).
- [4] WiseGEEK, What is prophylaxis?, 2012. Technical Report. <http://www.wisegeek.com/what-is-prophylaxis.htm>.
- [5] G. Ramjee, R. Govinden, N. S. Morar, and A. Mbwu, South Africa’s experience of the closure of the cellulose sulphate microbicide trial, *Journal of PLoS Med*, 4 (2007), 235.
- [6] IAS 2011 Conference: summary, HIV and AIDS treatment in practice, 2011. Technical Report. <http://www.aidsmap.com/ias2011>.
- [7] L. A. Paxton, T. Hope, and H. W. Jaffe, Pre-exposure prophylaxis for HIV infection: what if it works?, *Lancet*, 370 (2007), 89–93.

- [8] D. C. J. Vissers, H. A. C. M. Voeten, N. J. D. Nagelkerke, J. D. F. Habbema, and S. J. de Vlas, The impact of Pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: A simulation study, *Journal of PLoS ONE*, 3 (2008), 2077.
- [9] C. P. Bhunu and S. Mushayabaza, Assessing the impact of using antiretroviral drugs as pre-exposure vaccines, *Journal of HIV and AIDS Review*, 11 (2012), 42–48.
- [10] R. M. Anderson, The role of mathematical models in the study of HIV transmission and epidemiology of AIDS, *Journal of Acquired Immune Deficiency Syndromes*, 1 (1988), 241–256.
- [11] R. M. May and R. M. Anderson, Transmission of dynamics of HIV infection, *Journal of Nature*, 320 (1987), 137–142.
- [12] J. Robertson, WHO Clinical staging for HIV infection, *Suite101*, 2009. Technical Report. [suite101.com/article/who-clinical-staging-for-hiv-infection-a88683](http://suite101.com/article/who-clinical-staging-for-hiv-infection-a88683).
- [13] M. Y. Li, Mathematical Analysis of Epidemic Models: Five Classic Examples, current Lecture note. <http://www.math.ualberta.ca/mli/courses/current/664/chapter2.pdf>.
- [14] C. Castillo-Chavez and B. Song, Dynamical Models of Tuberculosis and their Applications, *Journal of Mathematical Biosciences and Engineering*, 1 (2004), 361–404.
- [15] C. Castillo-Chavez, Z. Feng, and W. Huang, On the Computation of  $\mathcal{R}_0$  and its role on global stability. Preprint: [math.la.asu.edu/chavez/2002/JB276.pdf](http://math.la.asu.edu/chavez/2002/JB276.pdf).
- [16] P. van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Journal of Mathematical Biosciences*, 180 (2002), 29–48.
- [17] F. Brauer and J. A. Nohel, The qualitative theory of ordinary differential equations: An introduction, *Dover*, New York, 1989.
- [18] K. Alcorn, Treatment is Prevention!, *HIV and AIDS Treatment in Practice*, (2011), 3–6. Technical Report. <http://www.aidsmap.com/ias2011>.

- [19] E. M. Lungu, M. Kgosimore and F. Nyabadza, Models for the Spread of HIV/AIDS: Trends in Southern Africa, *Journal of American Mathematical Society*, 410 (2006), 259–277.
- [20] B. Boldin, Introducing a population into a steady community: The critical case, the center manifold, and the direction of bifurcation, *SIAM Journal of Applied Mathematics*, 66 (2006), 1424–1453.
- [21] F. Nyabadza, On the Complexities of Modelling HIV/AIDS in South Africa, *Journal of Mathematical Modelling and Analysis*, 13 (2008), 539–552.