Mathematical modelling of HIV/AIDS with recruitment of infecteds

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Abstract

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The influx of infecteds into a population plays a critical role in HIV transmission. These infecteds are known to migrate from one region to another, thereby having some interaction with a host population. This interactive mobility or migration causes serious public health problems. In a very insightful paper by Shedlin *et al.* [51], the authors discover risk factors but also beneficial factors with respect to fighting human immunodeficiency virus (HIV) transmission, in the lifestyles of immigrants from different cultural backgrounds. These associated behavioral factors with cross-cultural migrations have not received adequate theoretical attention. In this dissertation we use the compartmental model of Bhunu *et al.* [6] to form a new model of the HIV epidemic, to include the effect of infective immigrants in a given population.

In fact, we first produce a deterministic model and provide a detailed analysis. Thereafter we introduce stochastic perturbations on the new model and study sta-

bility of the disease-free equilibrium (DFE) state. We investigate theoretically and computationally how cross-cultural migrations and public health education impacts on the HIV transmission, and how best to intervene in order to minimize the spread of the disease. In order to understand the long-time progression of the disease, we calculate the threshold parameter, known as the basic reproduction number, $\mathcal{R}_0$. The basic reproduction number has the property that if $\mathcal{R}_0$ is sufficiently small, usually $\mathcal{R}_0 < 1$, then the disease eventually vanishes from the population, but if $\mathcal{R}_0 > 1$, the disease persists in the population.

We study the sensitivity of the basic reproduction number with respect to model parameters. In this regard, if $\mathcal{R}_0 < 1$, we show that the DFE is locally asymptotically stable. We also show global stability of the DFE using the Lyapunov method. We derive the endemic equilibrium points of our new model.

We intend to counteract the negative effect of the influx of infecteds into a population with educational campaigns as a control strategy. In doing so, we employ optimal control theory to find an optimal intervention on HIV infection using educational campaigns as a basic input targeting the host population. Our aim is to reduce the total number of infecteds while minimizing the cost associated with the use of educational campaign on $[0, T]$. We use Pontryagin's maximum principle to characterize the optimal level of the control. We investigate the optimal education campaign strategy required to achieve the set objective of the intervention. The resulting optimality system is solved numerically using the Runge-Kutta fourth order method. We present numerical results obtained by simulating the optimality system using ODE-solvers in MATLAB program.

We introduce randomness known as white noise into our newly formed model, and discuss the almost sure exponential stability of the disease-free equilibrium. Finally, we verify the analytical results through numerical simulations.

Keywords

Influx of infecteds

HIV transmission

Migration

Disease-free equilibrium

Basic reproduction number

Global stability

Lyapunov method

Pontryagin's maximum principle

Runge-Kutta fourth order method

Stochastic perturbations

Almost sure exponential stability

Declaration

I declare that this is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Thapelo Jacob Seatlhodi

Signed: .....

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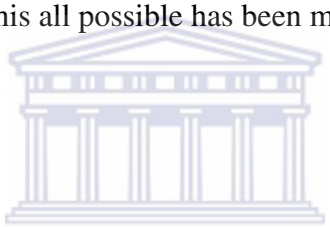


List of acronyms

Human Immunodeficiency Virus (HIV);

Acquired Immune Deficiency Syndrome (AIDS);

Cluster of Differentiation 4 (CD4);

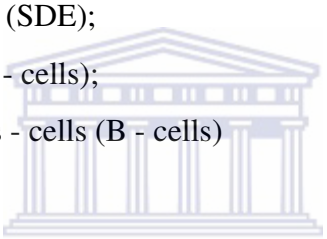
Highly Active Antiretroviral Therapy (HAART);

Ordinary Differential Equation (ODE);

Stochastic Differential Equation (SDE);

Thymus Lymphocytes - cells (T - cells);

Bursa of Fabricius Lymphocytes - cells (B - cells)



List of notation

L : Differential operator

$\mathcal{R}_0$: Basic reproduction number

$(\Omega, \mathcal{F}, \mathbb{P})$: Probability triple

$\{\mathcal{F}_n\}_{n \geq n_0}$, $\{\mathcal{F}_t\}_{t \geq t_0}$: Filtration

W : Brownian motion or Wiener process

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Chapter 1

General Introduction

1.1 Introduction to HIV/AIDS

Since its discoveries in the early 1980*s*, AIDS (Acquired immune deficiency syndrome or acquired immunodeficiency syndrome) and its cause, HIV (Human Immunodeficiency Virus) has had a great impact around the world both as a disease and as a source of stigma and discrimination. While HIV/AIDS can be considered a global pandemic, it is by any account overwhelmingly an African one, particularly in sub-Saharan Africa. HIV/AIDS continues to be the leading cause of death in Sub-Saharan Africa, with an estimated 24.1 million people living with the disease, over two thirds of the global total [26].

As a disease, on one hand, it devastates and weakens the immune system leaving the immune system more vulnerable to infections and diseases. A person is prone to experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the infection spreads further, it interferes with functioning of the immune system, making the person more susceptible to common infections like tuberculosis (TB), as well as opportunistic infections. The late symptoms of the infection are referred to as AIDS which comprises the

defining conditions such as pneumocystis pneumonia, severe weight loss, a type of cancer known as Kaposi's sarcoma, or other AIDS-defining conditions.

Understanding the epidemiology of HIV provides an important foundation for public health authorities in recognizing risk behaviors associated with clinical manifestations suggestive of HIV infection in their patients. It is also vital to encourage acceptance of HIV testing and adoption of risk-reduction strategies to prevent further transmission, and treatment to prevent opportunistic illnesses and curb disease progression [6].

On the other hand, stigma and discrimination associated with HIV continue to undermine prevention, treatment and care of people living with the HIV and AIDS. The people living with the virus are still treated as different by those who are uninfected. This hinders those with the virus from telling their partners about their status as well as threatening their access to health care [6, 43, 51]. The isolation and lack of health care available to immigrant populations also impedes HIV testing, treatment, and prevention efforts. HIV-related restrictions for those visiting or immigrating to a country exacerbate these problems by discouraging individuals from seeking testing or treatment for fear of being denied entry or placed on deportation proceedings.

Since the work of Kermack and Mckendrick, mathematical models of epidemiological dynamics have been developed and utilized extensively. The book [9] of Brauer and van den Driessche gives a nice introduction to the subject. Such models are useful in predicting future scenarios, thereby informing policy and strategies for combating the disease(s) in question. Mathematical models have been developed throughout the past to control and predict the prevalence of infectious diseases [31]. The driving force behind the disease prevalence is closely linked

with an increasing population mobility and increasing mutual interaction between populations [39, 51, 62]. Population mobility and sexual intercourse are well-known to be major forces in the spread of sexually transmitted diseases (STDs) worldwide [39]. This mobility and mutual interaction between populations contribute to the HIV pandemic on a significant level. Inadequacy of health facilities in host regions to deal with mobile and immigrant populations, often make the immigrants vulnerable to social and public health risks, in particular, HIV. Insufficient attention has been paid in public health research to study the impact of cross-cultural migrations influencing the inflow of infected on the HIV/AIDS prevalence [44, 50, 51, 53].

Various studies on the vaccination, and possibly the eradication of the HIV disease, strongly suggest that educational programs regarding HIV/AIDS have a positive impact on the HIV/AIDS epidemic [6, 45, 18]. Furthermore, educating migrating people, those infected (and those around them) of the consequences of the disease transmission can in turn reduce HIV/AIDS infections. The theoretical model by Abiodun *et al.*, [1], provides insightful views around the advantages of parental care and screening control. Furthermore, studying the effect of public health education campaigns on HIV transmission dynamics include papers such as [6, 45, 18, 43].

There is a threshold parameter that might tell whether a population will increase or decrease or even die out or, whether an infectious disease will persist or die out within a population. This parameter is commonly known as the basic reproductive number and is denoted by $\mathcal{R}_0$. This, in epidemiology, is defined to be the number of secondary infections caused by a single infective introduced into a wholly susceptible population, over the course of the infection of this single infective.

Bhunu *et al.* [6] discusses the impact of public health education and abstinence on the transmission dynamics of HIV in Sub-Saharan Africa. In their model they derive the basic reproduction number which predicts whether the disease is persistent or not. In their analysis of reproduction numbers, they found that effective counseling and testing have a positive impact in dealing with HIV/AIDS epidemic. Furthermore, their analysis also shows how educational programs regarding HIV/AIDS may have a positive impact on the HIV/AIDS epidemic.

Mukandavire *et al.* [43] evaluated the impact of educational campaign as a possible control strategy for the spread of HIV/AIDS. Their model assumes sexual transmission with an explicit incubation period for HIV infectivity. Their analysis shows that public health education campaigns can effectively reduce the threshold parameter, $\mathcal{R}_0$, to values below unity as intended for disease control, and consequently can succeed in controlling the epidemic. On the contrary, their results also suggest that it is more imperative to educate the sexually immature and mature individuals concurrently than merely focussing public health campaign on sexually immature or mature individuals only.

Nyabadza *et al.* [45] presented a model system highlighting the impact of media campaigns on HIV transmission. Their findings, illustrated through numerical simulation results, show that an increase in media campaigns as well as withdrawal of a proportion of AIDS individuals from sexual activities leads to a reduction in the HIV transmission.

Brauer *et al.* [9] developed an HIV model that includes immigration and demographic effects, and supports the view that HIV infection cannot be eliminated from the population when there is a constant flow of new infectives into the population. Thus suggesting that in order to minimize or eradicate the disease, it would

be necessary to isolate the fraction of arriving infectives into the population. In contrast to Brauer *et al.*, [9], recent studies by [39, 51, 62], have a differing statement that it is difficult to measure infected amongst migrants while visiting host regions, and that isolation phenomena leads to stigmatization. The work of Naresh *et al.*, [44], suggest that the spread of HIV infection can be slowed down if the recruitment of infected is thoroughly investigated and restricted into the population.

1.2 Aims and objectives

A vital focus of our work is the prevention of HIV/AIDS among mobile and immigrant groups who are referred as infecteds in our study. In such groups, we intend to counteract the negative effect of the influx of infecteds into a population through the use of educational campaigns as a control strategy. The research assumes that campaigns can eventually reduce the contact rate between the susceptible and the infected individuals. The research will investigate quantitatively how strategies of public health education campaigns can be rolled out effectively to deal with the global burden of HIV disease.

We begin by exploring the types of the mathematical epidemic models addressing infectious diseases and in particular, epidemiology of the HIV/AIDS. Our primary attention will be on the mathematical models that have a strong focus on the use of optimal control theory to combat the infectious diseases and in particular, the epidemiology of HIV/AIDS. We will then employ optimal control theory to find an optimal intervention on HIV infection using educational campaigns as a basic input targeting the host population. We use Pontryagin's maximum principle to characterize the optimal level of the control. We investigate the optimal education campaign strategy required to achieve the set objective of the intervention. The

resulting optimality system is solved numerically using the Runge-Kutta fourth order method. We present numerical results obtained by simulating the optimality system using ODE-solvers in MATLAB program. This will be followed by a discussion of the numerical results to illustrate how the roll-out changes with time.

We introduce randomness known as white noise into our newly formed model, and discuss the almost sure exponential stability of the disease-free equilibrium. Finally, we perform numerical simulations to illustrate and verify the analytical results.

1.3 Scope of this dissertation

This dissertation consists nine chapters which are outlined as follows.

Chapter 1 provides a brief background of HIV/AIDS. It discusses a brief overview of the mathematical models on the study of HIV/AIDS. The aims and objectives of the dissertation are laid out and the introductory chapter is concluded with a scope of the dissertation.

Chapter 2 presents the mathematical tools where all the relevant concepts from mathematical epidemiology are covered.

Chapter 3 provides a literature review on background to epidemiology and HIV/AIDS. This chapter comprises two main sections. The first section of the chapter briefly reviews HIV/AIDS and the immune system. Under this section the meaning behind HIV and how it affects the immune system is explained. The explanation is followed by a model of HIV showing gp120 binding to CD4 molecules and a flow chart of specific immune response. The second last section discusses the

epidemiology of HIV/AIDS showing the countries which are mostly affected by the disease such as South Africa. This section ends with the discussion on the role of migration on HIV/AIDS.

Chapter 4 provides an overview of mathematical modelling of infectious diseases. Types of mathematical epidemic models is discussed. This is followed by a discussion on the role of mathematical models on infectious diseases.

Chapter 5 presents a basic model of an HIV/AIDS epidemic for our current study. With the model of Bhunu *et al.* [6], as a basis, we form a new model of the HIV epidemic. The new model allows for an inflow of infecteds into the population. We study the existence and other basic properties of the solutions of the our model system. Global stability analysis of the disease-free equilibrium is studied. We also give endemic equilibrium solution followed by an example. We numerically analyze the effect of the rate of knowing ones HIV status through counseling and testing for our model system. Furthermore, we carry out sensitivity analysis of basic reproduction number on the basis of the model parameters.

Chapter 6 presents public health education for HIV/AIDS control for the model described in Chapter 5. We determine efficient roll-out of strategy for the control of HIV/AIDS in a population. We solve the control model analytically and run some numerical simulation to illustrate the behaviour of the solution over time.

Chapter 7 provides basic mathematical tools on stochastic differential equations which are essential for the following Chapter 8.

Chapter 8 constructs a stochastic version of the proposed model described in Chapter 5 by introducing the stochastic perturbations into the model. In making our model more realistic, the positivity of the solutions is studied. Almost sure

stability of the disease free equilibrium is showed through a Theorem. Finally, results are illustrated by means of numerical simulations to verify the stability of the Theorem in question.

We conclude and summarize the main results in Chapter 9.

Chapter 2

Mathematical tools

2.1 Introduction

This chapter presents some definitions, theorems, lemmas and prepositions required to analyze model systems in this dissertation. We present phenomena and tools such as compartmental modelling, Runge-Kutta fourth order method, optimal control technique, Lyapunov stability function, optimal control technique, basic reproduction number and sensitivity analysis. Just to give a snapshot on some of these sections. The first of these sections focuses on the compartmental modelling which provides a brief background on mathematical modelling within the history of epidemiology. The third last section, an algorithm for computing the basic reproduction number is provided. Finally, the last of these sections is on the sensitivity analysis of the threshold parameter $\mathcal{R}_0$. The references are provided for the proofs of the results.

2.2 Compartmental modelling

The spread of infectious diseases is a complex phenomenon with many interacting factors. Efficient preventive and control measures of the spread of a life-threatening pathogen depends on understanding of the mechanisms of that pathogen [41]. Mathematical epidemiology serves as a tool to model the establishment and spread of pathogens. A standard procedure is to use the notion of dividing the population into compartments under certain assumptions, which represent their health status with respect to the pathogen in the system. A tremendous foundation in this method was done by Kermack and McKendrick in the year 1927 [8]. This method is known as compartmental models in epidemiology, and they serve as a basic mathematical framework for understanding the complex dynamics of the system, with an intention to model the main characteristics of the system. In the simplest case, the population is stratified into two health states: susceptible to the infection of the pathogen (often denoted by S); and infected by the pathogen (denoted by the symbol I). The way that these compartments interact is often based upon key assumptions. These models are usually investigated through ordinary differential equations which are either deterministic or stochastic in nature.

The compartments usually considered are primarily the following

- Susceptible compartment (S) - A group of individuals in a population are called susceptibles if they are not infected and however still at risk of being infected.

- Infected compartment (I) is a group of individuals who are infected with the disease and are capable of spreading the disease to those in the susceptible category.

- Recovered or Removed compartment (R) represents the individuals who have been infected then recover from the disease and acquire either temporary or permanent immunity through immunization or death. Those in this compartment are not able to be infected again or to transmit the infection to others.

Compartmental models have provided valuable insights into the epidemiology of many infectious diseases which includes Tuberculosis, Malaria, Measles, and HIV/AIDS, to mention but a few. Some examples on the use of compartmental modelling can be found in [1, 7, 6, 15, 23], etc. There are types of infectious diseases which confer immunity and those that do not, and each type has a particular terminology or description. We proceed by highlighting them as follows

- The classical SIR model: describes the infectious disease which confer immunity, the individuals move from susceptible (S), to the infective (I) and then move to the removed compartment (R).

- The SIS model: describes the individuals who recovers with no immunity to the disease, that is, individuals are immediately susceptible once they have recovered.

- The SIRS model: this model allows members of the recovered class to be free of infection for some time and at some point rejoin the susceptible class.

- The SEIR model: This model takes into account only those diseases which cause an individual not to be able to infect others immediately upon their infection. Many diseases have what is termed a latent or exposed phase "E", during which the individual is said to be infected but not infectious.

- The SEIS model: In this model an infection does not leave any immunity. Thus individuals that have recovered return to being susceptible (S) again immediately.

The magnitude of each compartment at time t are represented by $S(t)$, $I(t)$, $R(t)$, and $N(t)$ represents the total population. Also, the force of infection, denoted by symbol λ, is the rate at which susceptible individuals acquire an infectious disease.

2.3 Optimal control method

Optimal control refers to the process of determining controls and the state trajectories for a dynamic system over a period of time to maximize or minimize a performance index. The state variables, x_i, for $i = 1,2,...,n$, depend on the controls u_k, for $k = 1,2,...,m$. The primary objective is to alter u to either minimize or maximize a performance index described by an objective functional $J(t,x_1(t),...,x_n(t),u_1(t),...,u_m(t))$, that attains the anticipated objective while keeping the required cost to attaining it as low as possible. The optimal control can be derived using Pontryagin's maximum principle or solving the Hamilton-Jacobi-Bellman equation, see Lenhart and Workman [31]. We shall be concerned only with the following type of optimal control problem, which is a special case of the problem as presented in [31].

The control problem:

Find the maximum of the integral as indicated,

$$\max_{u_1,...,u_m} \int_{t_0}^{t_1} f(t,x_1(t),...,x_n(t),u_1(t),...,u_m(t))dt \tag{2.1}$$

subject to

$$x'_i(t) = g_i(t, x_1(t), ..., x_n(t), u_1(t), ..., u_m(t)),$$

$$x_i(t_0) = x_{i0} \text{ for } i = 1, 2, ..., n,$$

where the functions f, g_i are continuously differentiable in all variables.

Necessary conditions for a solution

Define the Hamiltonian:

$$\mathcal{H}(t, x, u, \lambda) = f(t, x, u) + \lambda(t) \cdot g(t, x, u),$$

where $\cdot$ is the dot product of vectors and $\lambda(t)$ is a Lagrange multiplier or *co-state variable*. Necessary conditions for $u = u^*$, $x = x^*$, and $\lambda = \lambda^*$, to be an optimal solution, are the following:

(i) $x'_i(t) = \dfrac{\partial \mathcal{H}}{\partial \lambda_i} = g_i(t, x, u), \;\; x_i(t_0) = x_{i0} \text{ for } i = 1, 2, ...n,$

(ii) $-\lambda'_j(t) = \dfrac{\partial \mathcal{H}}{\partial x_j}, \text{ for } j = 1, 2, ...n,$

(iii) The control u^* must maximize $\mathcal{H}$. So, if the necessary partial derivatives exist, then we must have

$$\left.\frac{\partial \mathcal{H}}{\partial u_k}\right|_{u^*} = 0, \text{ for all } k = 1, 2, ..., m.$$

(iv) Certain so-called transitivity conditions must hold, see Lenhart and Workman [31].

2.4 Runge-Kutta fourth order method

The fourth order Runge-Kutta method is a numerical approach used to solve ordinary differential equation of the form (see J. C. Butcher [10])

$$\frac{dy}{dx} = f(x,y), \;\; y(0) = y_0. \tag{2.2}$$

The fourth order Runge Kutta method is based on the following general equation

$$y_{(i+1)} = y_i + (a_1k_1 + a_2k_2 + a_3k_3 + a_4k_4)h \tag{2.3}$$

where from knowing the value of $y = y_i$ at the point x_i, we can find the value of $y = y_{(i+1)}$ at the point x_{i+1}, and $h = x_{i+1} - x_i$ is the step size.

The equation (2.3) is the representation of the first five terms of the Taylor series:

$$y_{i+1} = y_i + f(x_i,y_i)h + \frac{1}{2!}f'(x_i,y_i)h^2 + \frac{1}{3!}f''(x_i,y_i)h^3 + \frac{1}{4!}f'''(x_i,y_i)h^4 \tag{2.4}$$

Based on the equation (2.4), one of the common solutions used is given as

$$y_{(i+1)} = y_i + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4) \tag{2.5}$$

where

$$\begin{aligned}
\mathrm{k}_1 &= f(x_i,y_i) \\
k_2 &= f(x_i + \tfrac{1}{2}, y_i + \tfrac{1}{2}k_1h) \\
k_3 &= f(x_i + \tfrac{1}{2}, y_i + \tfrac{1}{2}k_2h) \\
k_4 &= f(x_i + \tfrac{1}{2}, y_i + k_3h).
\end{aligned}$$

2.5 Lyapunov stability function

In this section we review Lyapunov stability function. This function will be used in chapter five to analyze the stability of the disease free equilibrium for our basic model system. We present the function's definitions, and a theorem that we shall need in the sequel, with no proof. The interested reader should consult a standard text, such as Linda and Allen [3].

The function is demonstrated for the following two dimensional autonomous system:

$$\frac{dx}{dt} = f(x,y) \quad \text{and} \quad \frac{dy}{dt} = g(x,y). \tag{2.6}$$

Definition 2.1 Let U be an open subset of $\mathbb{R}^2$ containing the origin. A real-valued $C^1(U)$ function V, $V : U \to \mathbb{R}, [(x,y) \in U, V(x,y) \in \mathbb{R}]$ is said to be positive definite on the set U if the following two conditions hold:

(i) $V(0,0) = 0$.

(ii) $V(x,y) > 0$ for all $(x,y) \in U$ with $(x,y) \neq (0,0)$.

The function V is said to be negative definite if $-V$ is positive definite.

Definition 2.2 A positive definite function V in an open neighborhood of the origin is said to be a *Lyapunov function* for the autonomous differential system (2.6)

If $\dfrac{dV(x,y)}{dt} \leq 0$ for all $(x,y) \in U - (0,0)$.

If $\dfrac{dV(x,y)}{dt} < 0$ for all $(x,y) \in U - (0,0)$, the function V is called a strict Lyapunov function.

Theorem 2.3 *Let $(0,0)$ be an equilibrium of the autonomous system (2.6) and let V be a positive definite C^1 function in a neighborhood U of the origin.*

(i) If $\dfrac{dV(x,y)}{dt} \leq 0$ for $(x,y) \in U - (0,0)$, then $(0,0)$ is stable.

(ii) If $\dfrac{dV(x,y)}{dt} < 0$ for $(x,y) \in U - (0,0)$, then $(0,0)$ is asymptotically stable.

(iii) If $\dfrac{dV(x,y)}{dt} > 0$ for $(x,y) \in U - (0,0)$, then $(0,0)$ is unstable.

2.6 Basic reproduction number

The basic reproduction number or basic reproduction ratio, sometimes referred to as the threshold parameter, is a very important metric in epidemiology. This concept is fundamental to the study of epidemiology as it helps determine whether or not an infectious disease can spread through a population. This ratio was originally developed for the study of demographics, independently studied for vector-borne diseases such as malaria and other human infections. Currently it is widely used in the study of infectious diseases and in-host population dynamics, see [16]. As a general epidemiological definition, the basic reproduction ratio, which is denoted by $\mathcal{R}_0$, is defined as the number of secondary cases which one case would produce in a completely susceptible population. Basically, $\mathcal{R}_0$ can be thought of as the average number of people who will catch a disease from one contagious person. The interpretation of the word *secondary*, however, depends on the context. For instance, in demographics and ecology, $\mathcal{R}_0$ is taken to be the lifetime reproductiveness of a typical member of a species. For in-host population dynamics, $\mathcal{R}_0$ is taken as the number of newly infected cells produced by one infected cell during its lifetime assuming that all other cells are susceptible.

In epidemiology, $\mathcal{R}_0$ is taken to mean the number of persons affected by a single person during their entire infectious period, in a population that is entirely susceptible or disease-free. When $\mathcal{R}_0 < 1$, the infection will die out in the long run, which means each infected person produces, on average, less than one new infected person. Also there exist only one equilibrium, the disease-free equilibrium, and it is locally asymptotically stable. Alternatively, when $\mathcal{R}_0 > 1$, the infection will be able to spread in a susceptible population. This type of threshold behavior is the fundamental and useful aspect of the $\mathcal{R}_0$ concept. For a larger value of $\mathcal{R}_0$,

that is the endemic infection, we can determine which control measures, and at what size, would be most effective in reducing $\mathcal{R}_0$ below unity, to prevent sustained spread of the infection, thus providing important guidance for public health initiatives. The following section presents the complete algorithm to compute the basic reproduction number in mathematical epidemiological modelling, using the Van den Driessche and J. Watmough setting, [61]. We demonstrate this setting by way of a computational example using a non-linear deterministic mathematical model.

2.7 The next generation matrix

This section presents an algorithm for obtaining $\mathcal{R}_0$ for a general compartmental ordinary differential equations model of disease transmission. The term *disease* referred in this text includes asymptomatic stages of infection as well as symptomatic. The next generation matrix method introduced by Van den Driessche and J. Watmough [61], is a general method for deriving $\mathcal{R}_0$, or an equivalent threshold parameter, when more than one class of infectives are involved, in which the population is divided into discrete, dis-joined compartments. The next generation operator can thus be used for models with age structure or spatial structure. Continuous variables within the population are approximated by a number of discrete compartments. In the next generation method, $\mathcal{R}_0$ emerges as the spectral radius, or equivalently, the supremum among absolute eigenvalues in a spectrum, of the next generation operator. The formation of the operator involves determining the compartments that are infected and non-infected, from the model.

We outline the steps needed to find the next generation operator in matrix notation. Suppose we have a heterogeneous population whose individuals are differentiable

by characteristic behavior, age, spatial position, or stage of the disease, but can be categorized into n homogenous compartments of which m are infected, see Van den Driessche and J. Watmough [61].

X_s is defined to be the set of all disease free states:

$$X_s = \{x \geq 0 \mid x_i = 0, \ i = 1, ..., m\}.$$

First of all new infections must be distinguished from all other changes in population before calculating $\mathcal{R}_0$.

Let

- $F_i(x)$: rate of appearance of new infections in compartment i,
- $V_i^+(x)$: rate of transfer of individuals into compartment i by all other means,
- $V_i^-(x)$: rate of of transfer of individuals out of compartment i.

Each of the above functions ($F_i(x), V_i^+(x)$ and $V_i^-(x)$) is assumed to be at least twice continuously differentiable.

The disease transmission model consists of non-negative initial conditions coupled with the following system of equations:

$$\dot{x_i} = f_i(x) = F_i(x) - V_i(x), \ \ i = 1, ..., n, \tag{2.7}$$

where $V_i^-(x) - V_i^+(x)$ and the functions satisfy assumptions one to five below:

Assumption one: If $x \geq 0$, then $F_i(x) \geq 0$, $V_i^+(x) \geq 0$, $V_i^-(x) \geq 0$ for $i = 1, ..., n$. If a compartment is empty, then it means no transfer of individuals between compartments. Thus,

Assumption two: If $x = 0$, then $V_i^-(x) = 0$. In particular, if $x \in X_s$ then $V_i^-(x) = 0$, for $i = 1, ..., m$. The next condition arises from the simple fact that the incidence of infection for uninfected compartment is zero.

Assumption three: $F_i(x) = 0$ if $i > m$. To ensure that the disease-free subspace is invariant, it is assumed that if the population is free of the disease then the population will remain disease free. That is, there is no influx of infectives.

Assumption four: $x \in X_s$, then $F_i(x) = 0$, $V_i^+(x) = 0$ for $i = 1, \ldots, m$. The remaining condition is based on the derivatives of f near a disease-free equilibrium (DFE). DFE of (2.7) is defined to be a (locally asymptotically) stable equilibrium solution of the disease-free model, i.e., (2.7) restricted to X_s. An important note is that the model is assumed to have a unique DFE. Consider a population near the DFE x_0. If the population remains near the DFE, i.e., if the introduction of a few infective individuals does not result in an epidemic, then the population will return to the DFE according to the linearized system

$$\dot{x} = Df(x_0)(x - x_0), \tag{2.8}$$

where $Df(x_0)$ is the derivative $[\frac{\partial f_i}{\partial x_j}]$ evaluated at the DFE, x_0 (i.e., the Jacobian matrix). Here, and in what follows, some derivatives are one sided, since x_0 is on the domain boundary. The attention is restricted to systems in which the DFE is stable in the absence of new infection. That is,

Assumption five: If $F(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

These conditions make it possible to partition the matrix $Df(x_0)$ as shown by the following lemma.

Lemma 2.4 *P. van den Driessche and J. Watmough [61]. If x_0 is a disease-free equilibrium of system (2.7) and f_i satisfies assumptions 1 - 5 above, then the derivatives $DF(x_0)$ and $DV(x_0)$ are partitioned as*

$$DF(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad DV(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial F_i}{\partial x_j}(x_0)\right], \quad V = \left[\frac{\partial V_i}{\partial x_j}(x_0)\right],$$

with $1 \leq i, j \leq m$.

Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.

On the basis of the above assumptions, we can form the next generation matrix FV^{-1} from matrices of partial derivatives of F_i and V_i as shown in Lemma 2.4, where, $i, j = 1, ..., m$ and x_0 is a DFE. The (i, j) entry of F is the rate at which new infections are produced in compartment i by infected individuals in compartment j. The (j,k) entry of V^{-1} is the mean duration time the infected individual that is introduced into compartment k spends in compartment j in its life span. The entries of FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment j.

So we set,

$$\mathcal{R}_0 = \rho(FV^{-1}), \tag{2.9}$$

where ρ denotes the spectral radius (dominant eigenvalue) of the next generation matrix (FV^{-1}).

2.8 Sensitivity analysis

Sensitivity analysis technique in the context of deterministic dynamical model system refers to how sensitive a model is to changes in the values of its parameters. By deterministic model, the output of the model is strictly determined by the input parameters and the structure of the model system. That is, the same input produce the same output if the model is simulated multiple times. In contrast, its counterpart stochastic model does not produce the same output when repeated with the same inputs merely because of inherent randomness in the behavior of the system.

The aim of sensitivity analysis to identify critical inputs of a model quantifying how input uncertainty impacts model outcome. Many parameters used in the model system usually represent quantities that are often very difficult, or even impossible to compute accurately. Therefore, these parameter values are often estimated to match up with the level of accuracy necessary for a parameter to make a model system sufficiently useful and valid. When executed, the system behaves as expected from the real world observations. It provides some indication that the parameter values reflect, at least in some part, the real world.

In mathematical epidemiology, sensitivity analysis is naturally performed to study the disease transmission by computing the sensitivity indices of the basic reproduction number $\mathcal{R}_0$. Sensitivity analysis provides information as to how reactive each parameter is to disease transmission and somewhat tries to discover parameters that have a high impact on $\mathcal{R}_0$ and should be targeted by intervention strategies. Sensitivity analysis is usually carried out by a technique called the normalized forward sensitivity index of a variable with respect to a parameter, which is

the ratio of the relative change in the variable to the relative change in the parameter. The sensitivity index may be alternatively defined using partial derivatives, when the variable is a differentiable function of the parameter.

Definition 2.5 The normalized forward sensitivity index of $\mathcal{R}_0$, that depends differentiably on a parameter p, is defined by

$$\Upsilon_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}.$$

Chapter 3

Background to Epidemiology and HIV/AIDS

3.1 HIV/AIDS and the immune system

3.1.1 What is HIV/AIDS?

Human immunodeficiency virus (HIV) types, derived from primate lentiviruses, are the etiologic agents of AIDS. HIV is a retrovirus, a member of the Lentivirus genus, and exhibits many of the physicochemical features typical of the family [27]. Since HIV-1 was isolated in 1983, AIDS has become a worldwide epidemic, expanding in scope and magnitude as HIV infections have affected different populations and geographic regions [66]. Millions are now infected worldwide. Once infected, individuals remain infected for life. AIDS is one of the most important public health problems worldwide at the start of the 21*st* century. The development of highly active antiretroviral therapy (HAART) for chronic suppression of HIV replication and prevention of AIDS has been a major achievement in HIV medicine [27].

Many studies had claimed that HIV in humans originated from cross-species infections by simian viruses in rural Kinshasa (now Democratic Republic of Congo), Central Africa, probably due to direct human contact with infected primates (monkeys) blood [66]. Current evidence is that the primate counterparts of HIV-1 and HIV-2 were transmitted to humans on multiple different occasions. Sequence evolution analysis place the introduction of simian immunodeficiency virus (SIV) into humans that gave rise to HIV-1 group M at about the 1930s [27]. Presumably, such transmissions occurred repeatedly over the ages, but particular social, economic, and behavioral changes that occurred in the mid-20th century provided circumstances that allowed these virus infections to expand, become well-established in humans, and reach epidemic proportions [27, 66].

3.1.2 The immune system

The function of the immune system requires antigen-specific lymphocytes of two major types (T- and B-cells) and cytokines. T-cells are thymus-derived lymphocytes and B-cells are bone marrow-derived lymphocytes. Cytokines are secreted polypeptides that modulate the functions of cells. Those produced by mononuclear cells (i.e. lymphocytes and mononuclear phagocytic cells) are called interleukins. These regulate the growth and differentiation of lymphocytes and hematopoietic stem cells and the interactions among T-cells, B-cells, and monocytes in the elaboration of an immune response. B-cells are responsible for the humoral immune response [54].

T-cells are responsible for:

- The initiation and modulation of immune responses (including B-cell responses)

- Cell-mediated immune processes that involve direct damage to antigen-bearing tissue or blood cells (e.g. HIV infected host cells)

- Stimulation and enhancement of the nonspecific immune functions of the host (e.g. the inflammatory reaction and antimicrobial activity of phagocytes)

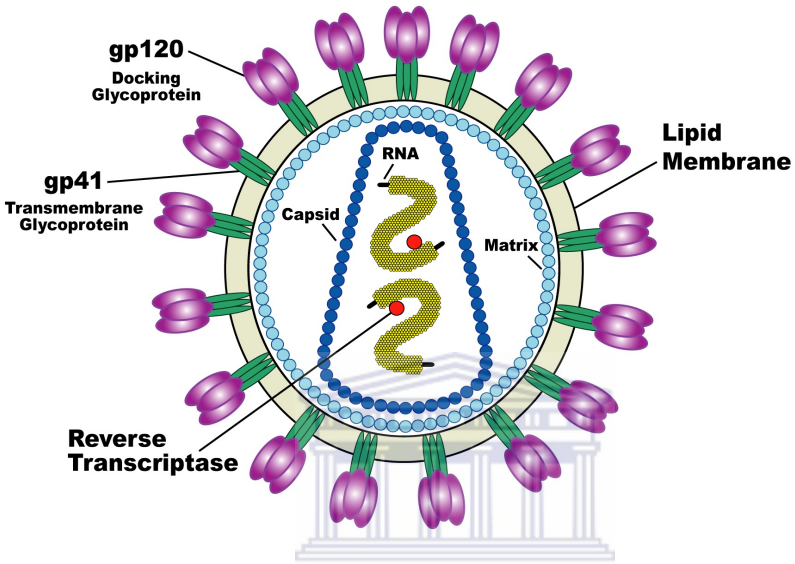

Figure 3.1: A model of HIV showing gp120 binding to CD4 molecules [54].

T-cells are classified by the presence of the surface molecules called CD4 and CD8, which in turn are related to functional activities classified as helper, suppressor, or cytotoxic. The immune response is a complex but precisely regulated defense system in which specific recognition is imparted by antibodies, B-cell immunoglobulin receptors, and T-cell receptors, and activation and differentiation are dependent on a regulatory cascade of cell-cell communication molecules.

The critical significance of CD4+ helper cells to the body is shown by the catastrophic effects of acquired immunodeficiency syndrome (AIDS), in which the hu-

man immunodeficiency virus (HIV-gp120) binds to the CD4 molecule, enters the cell, and interferes with its function or destroys it. As a result, the body becomes susceptible to a wide variety of bacterial, viral, protozoal, and fungal infections, both through loss of preexisting immunity and through failure to mount an effective immune response to newly acquired pathogens [54]. A flow chart depicting the aforementioned events and interactions surrounding the specific immune response is shown in Figure 3.2. The cell-mediated response begins at the top left and the humoral response begins at the top center. Fig. 3.1 below shows how the two responses interact.

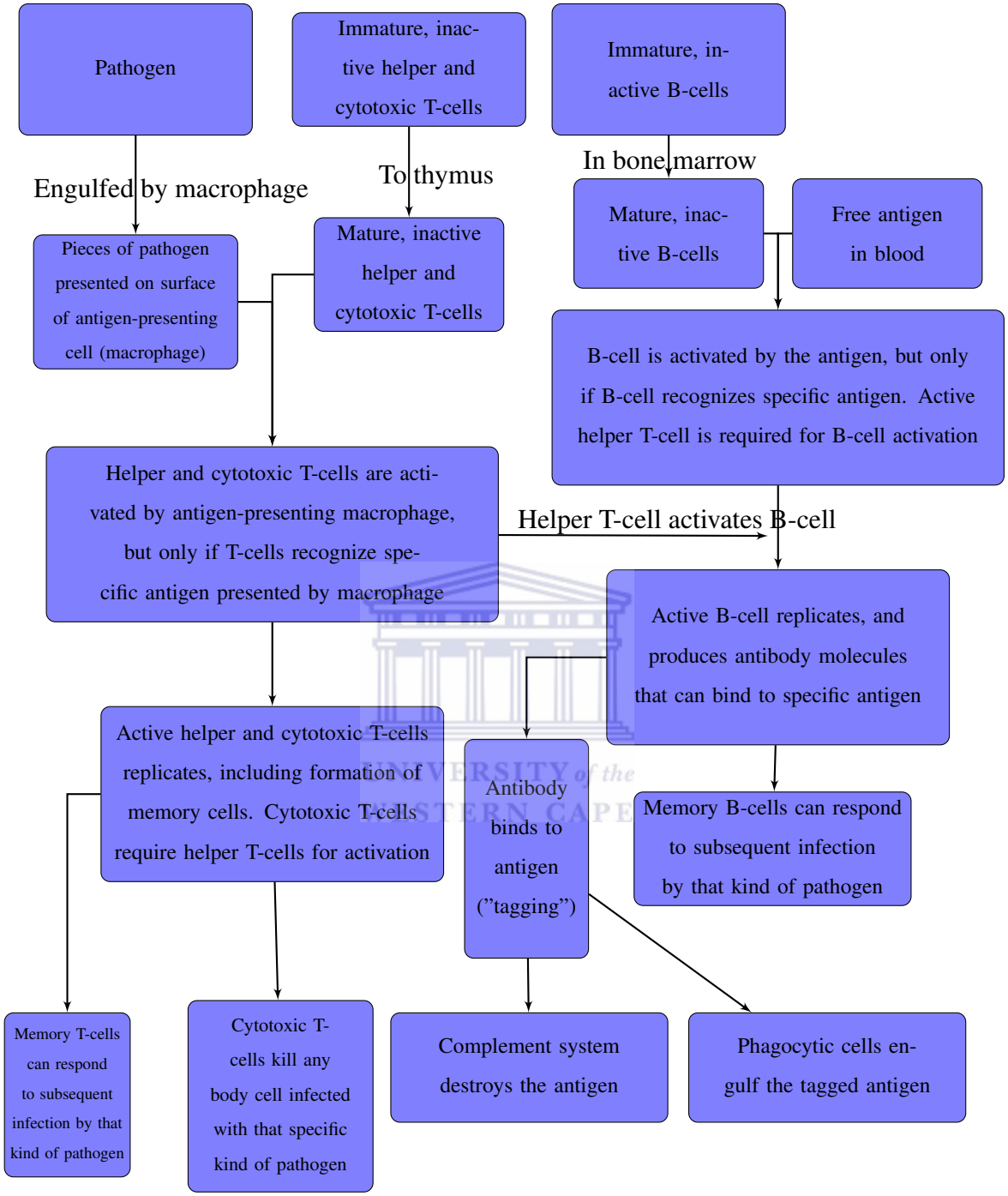

Figure 3.2: A flow chart of specific immune response [54].

3.2 Background to epidemiology

Giving a universally valid definition of epidemiology is difficult. Epidemiology is a scientific methodology which can be applied to a broad range of health and medical problems, from infectious diseases to health care. It is a constantly changing field of science, because new questions arise in population health and new statistical techniques are developed and adapted from other sciences. According to this definition, epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control or management of health problems [66]. Epidemiology is the fundamental science of public health and provides the evidence on which public health professionals should base their decisions and strategies [26, 66]. In this way, epidemiology provides the tools for the control of diseases and health promotion. More specifically, some important tasks of epidemiology for public health are:

- To elucidate the etiology of a disease
- To describe the spectrum of a disease, what kind of symptoms occur and how frequently they occur?
- To describe the natural history of a disease, what disease stages does a patient typically go through?
- To identify risk factors and protective factors, i.e., which factors enhance or prevent occurrence of a disease?
- To estimate disease burdens and health-care needs of a population
- To predict disease trends, to extrapolate from observations about time

trends in risk factors and the future occurrence of the disease

- To evaluate the effectiveness of interventions and public health programs.

It should first be emphasized that all epidemiological studies are or should be based on a particular source population also called the study population or base population followed over a particular risk period. Within this framework a fundamental distinction is between studies of disease incidence, i.e., the number of new cases of disease over time, and studies of disease prevalence, i.e., the number of people with the disease at a particular point in time.

3.2.1 Epidemiology of HIV/AIDS

Over the last few decades Acquired Immunodeficiency Syndrome (AIDS) has been one of the most devastating pandemic diseases humankind ever faced, causing more than 35 million people to die since its first discovery in 1981 and its etiologic agent Human Immunodeficiency Virus (HIV) in 1983. There are approximately 34 million people living with HIV worldwide and about 3 million become newly infected each year [27]. According to WHO [66], in the year 2008 an estimated 2 million people were killed by HIV/AIDS and more than 95 percent of HIV positive people are in the low and middle-income countries. Sub-Saharan Africa remains the most heavily affected region, accounting for 71 percent of all new HIV infections [27, 66].

UNAIDS estimates that approximately 2.7 million persons were newly infected with HIV at the end of 2010 and about 1.8 million deaths were attributed to AIDS worldwide [26]. Table 3.1 below, provides regional HIV and AIDS statistics in 2010. That is, regional estimates of adults and children newly infected with HIV, people living with HIV, and AIDS-related deaths.

Epidemiology of HIV/AIDS			
World region	Estimated prevalence of HIV infection (adults and children)	Estimated adult and child deaths during 2010	Adult prevalence
Worldwide	31.6 million - 35.2 million	1.6 to 1.9 million	0.8%
Sub-Saharan Africa	21.6 million - 24.1 million	1.2 million	5.0%
South and South-East Asia	3.6 million - 4.5 million	250,000	0.3%
East Europe and Central Asia	1.3million -1.7 million	90,000	0.9%
Latin America	1.2 million - 1.7million	67,000	0.4%
North America	1.0 million - 1.9 million	20,000	0.6%
East Asia	580,000 - 1.1 million	56,000	0.1%
Western and Central Europe	770,000 - 930,000	9,900	0.2%

Table 3.1: UNAIDS World Aids Day Report (2011) [26].

Many countries, particularly some in Africa, Asia and Eastern Europe are now experiencing rapid spread of HIV [27]. Because of the long incubation period from infection to end-stage disease, about 10 years in the absence of treatment, these countries are still in relatively early stages of the epidemic with the peak of HIV-related morbidity and mortality yet to come. As the world goes through a period of rapid HIV spread with a large gap between the number of new cases and the number of deaths of prevalent cases, HIV prevalence worldwide is expected to escalate for the foreseeable future.

The epidemic had spread rapidly worldwide by the late 1980*s*. In Africa, heterosexually-acquired HIV dominated the mode of transmission, as opposed to the homosexual and drug injecting associated epidemics in North America and Western Europe. In Asia, Latin America and the Caribbean, heterosexual and drug-use associated transmission led to rapid spread and recently, a drug-use associated epidemic has emerged in Eastern European nations [27].

Sub-Saharan Africa which is considered to be the epicenter of the global HIV/AIDS epidemic accounts for over 70% of prevalent cases of HIV worldwide. Countries like Lesotho, Botswana, South Africa, Swaziland and Zimbabwe have the highest HIV prevalence rates in the world. What the exact impact of the HIV/AIDS epidemic will be is still unknown, but the epidemic is likely to have an impact on nearly every aspect of life in Southern Africa. The region will be faced with great personal emotional suffering, a major decline in life expectancy, a great loss of both skilled and unskilled labour, rising costs of health care, social and economic disruption at the family and community level and a reduction of human and financial resources available for civil society organizations and the government. Some even consider HIV/AIDS a threat to social and political stability. Despite the warning signs of fertile ground for an infectious disease epidemic, HIV continues

to confound public health practitioners worldwide. As yet, there is no cure, and no vaccine. Furthermore, the ability to mount effective prevention and control efforts are complicated by social taboos, fear and prejudice associated with HIV/AIDS [27, 66].

3.2.2 South Africa and epidemiology of HIV/AIDS

Recent events show there are three major social factors that seem to place South Africa at a higher risk of HIV [14, 71]. Firstly, social inequalities in income and employment status are powerful predictors of HIV infection, although, interestingly, the correlation is neither linear nor clear. Several factors are involved in the association. For example, a low income or level of employment is associated with a greater exposure to risky sexual experience, diminished access to health information and to prevention, absent or delayed diagnosis and treatment, and less concern about one's health and the future, because of the harshness of the present and so forth [46]. Secondly, mobility is a well-known determinant of epidemics, but in South Africa the situation is particularly complex [39, 44, 64]. Mass resettlement of population under apartheid, seasonal labour migrations, and movements along major trade routes, e.g. truck drivers across borders, refugees fleeing political war in other parts of Africa, and, since 1990, return of political exiles and liberation soldiers have all contributed to the spread of infections [71]. Thirdly, sexual violence, whether by known or unknown perpetrators, in commercial or conjugal sex also facilitates viral transmission. Sexual violence is linked with common forms of social and political violence that have long been part of the everyday life in townships and inner city areas [64]. The combination of the three factors can be seen in the practice of survival sex, whereby young women in the townships, often migrants from impoverished rural areas, use their bodies as

an ordinary economic resource outside the context of prostitution but within the culture of male violence [64].

Inequality, mobility, and violence are partly the legacy of centuries of colonial exploitation and racial segregation, culminating in the institution of apartheid regime. In epidemiological terms, this segregation translates as differential HIV sero-prevalence between black and white groups and between social classes. A good example illustrating this legacy is the mining industry. The extraction of a black male labour force from the villages to work in the mines has been the motor of the South African economy since the end of the $19th$ century. These men are accommodated in hostels, far from their spouses, and commercial sex and access to alcohol are more or less institutionalized social activities in the hostel dwelling setting. In this instance, social context has a far greater bearing on risk of infection than individual sexual behavior [51].

The marks of apartheid are still deeply inscribed in the bodies and minds of the people who had to suffer under it, two decades after it ended, and the country's AIDS crisis manifests the legacy of the politics of the past [14]. For instance, within South Africa, some black people seems to believe that HIV/AIDS was developed by the apartheid government with an intention to eliminate the black population. But perhaps the key neglected factor in explaining the rapid spread of HIV over the last decade is population mobility. Researchers are still far from understanding in detail just how and to what extent migration and HIV/AIDS are interconnected. This dissertation seek to attempt filling in this gap by reviewing the current state of knowledge on the interconnections between mobility and HIV and argues for more research that will further our understanding of migrant vulnerability and the development of appropriate policies and models of intervention. The connections are difficult to unravel because HIV/AIDS arrived in the

country at a time when population mobility and systems of labour migration were undergoing rapid transformation.

3.2.3 Migration and HIV/AIDS

According to Lima *et al.*, [32], migration can be defined as the movement from one region to another and this movement can be either temporary or permanent and voluntary or involuntary. Recent literature review provides backing that migration induces important transfers of political, cultural, social and economic values between nations. While many studies have predominantly focused on transfers of positive norms, Docquier *et al.*,[13], in their paper assert that movements of people can also spread negative tremors across nations. History record have pointed out that migration was the source of propagation of pandemic diseases such as bubonic plague and Spanish flu within Europe and contributed to spread of many diseases during slave trade and colonialism from Europe to Africa and the rest of the world. It is therefore not surprising that again migration is also alleged as a reason for explaining the spreading of HIV/AIDS within and across nations, see [13].

According to UNAIDS [27] Africa is the most infected continent with average HIV prevalence rates approximately 25% or more in Sub-Saharan Africa. Many case studies have highlighted the mechanism through which workers' movement for instance has contributed to spread of HIV/AIDS all over the world. In Southern Africa, this is especially the case for male workers migrating or commuting to find jobs in South African mines, where there high activity of sex workers. This circular nature of migration and the maintenance of links with home through frequent end of year visits put people at risk at both ends of the migratory movement. While many migrants have regular sexual partners, some have relations with ca-

sual partners and face a higher risk to be infected by illness such as HIV/AIDS and to transmit it. This fact indicates that the truck drivers community is such a social group that is vulnerable to the dangers of HIV/AIDS and when infected, and in turn poses the risk of transmitting the disease. This is because the type of their work involves a lot of trans-countries traveling which means getting to meet casual partners along the way, often having unprotected sexual intercourse with these women who are not their regular partners so they are vulnerable to contracting HIV/AIDS and other sexual transmitted diseases Docquier *et al.* [13]. Although many cross-country studies have investigated the links between macroeconomic variables and HIV/AIDS of truck drivers, few have analyzed it using mathematical models to determine the HIV incidence.

Chapter 4

An overview of mathematical modelling of infectious diseases

4.1 Introduction

Mathematical modelling is of considerable importance in the study of infectious diseases because it may provide understanding on the underlying mechanisms which influence the disease spread and may help inform public health interventions. In particular, the first attempt to model and hence predict or explain patterns of infectious diseases dates back in the early nineteen hundreds by the work of Kermack and Mckendrick [8, 28]. These early models along with many subsequent revisions and improvements generally categorized individuals in a form of compartments such as susceptibles, infected and recovered (no longer infectious). In this review, we highlight briefly the use of the mathematical models for the study of infectious diseases with a special focus on the Acquired Immunodeficiency Syndrome (AIDS) and its etiologic agent Human Immunodeficiency Virus (HIV). Also, we provide the specific types of epidemic models being used.

4.2 Types of mathematical epidemic models

Mathematical models are usually developed based on assumptions. Which means that mathematical models are only as good or useful as the assumptions on which they are based. Mathematical models of epidemics of infectious diseases may be classified into two broad classes namely deterministic and stochastic. The term "stochastic" refers to being or having a random variable. A stochastic model is an important tool for estimating probability distributions of outcomes by allowing for random variation in one or more inputs over time. There are three different processes for formulating stochastic epidemic models. They include discrete time Markov chain (DTMC) models, continuous time Markov chain (CMTC) models and stochastic differential equation (SDE) models. These stochastic processes differ in the underlying assumptions regarding the time and the state variables. For instance, in a DTMC model, the time and the state variables are discrete. In a CTMC model, time is continuous, but the state variable is discrete. Finally, the SDE model is based on a diffusion process, where both the time and the state variables are continuous. Further expansion on the use and structure of these processes can be found in Allen [4].

A key theoretical distinction between models is that a deterministic model is based on population averages and a stochastic model is based on individual-based simulations. In individual-based simulations, each individual in the population is modeled as a discrete entity and characteristics are determined separately. For models based on population averages, it is assumed that all individuals in the population have identical characteristics [25]. These two approaches have common characteristics, i.e., they divide the population into cohorts of individuals. The individuals in the same cohort are assumed to share the same characteristics. For instance,

the characteristics used to define cohorts in HIV/AIDS models are usually factors such as age, sex, level of sexual risk behaviour. Also, cohorts are usually defined according to disease status, i.e., susceptibles, infected (possibly further split according to the stage of the disease), removed (either by natural death or disease induced death).

In mathematical epidemiology, stochastic models are often used with individual-based simulations, as these kinds of models will allow events such as HIV infection and death to be simulated by random process. Deterministic models on the other hand, calculate expected numbers of events in cohorts of individuals and are therefore used with models based on population averages. Deterministic models generate unique solutions, because they are based only on average values of random process. A stochastic model, however, generates different trajectories each time it is run because the answers depend on the actual simulation of the random process [20, 25] .

A widely recognized need to accommodate this variation and uncertainty has given rise to a rather large literature on stochastic models of epidemics, which takes into account variability in the development of epidemics and quantifies the uncertainties as to what course an epidemic may take in terms of probabilities. Because, for the most part, the mathematics underlying stochastic formulations is more difficult to penetrate than that used in deterministic formulations, this difficulty has in the past proven to be a barrier to applying stochastic models in practical situations. However, with the help of computer intensive methods designed to compute sample realizations of an epidemic, practical illustrations of the variability inherent in the evolution of a stochastic process are provided, and the barriers to practical application may, in part, be removed [31].

One of the most important differences between the deterministic and stochastic epidemic models is their asymptotic dynamics. It may happen that eventually stochastic solutions (sample paths) converge to the disease-free state even though the corresponding deterministic solution converges to an endemic equilibrium. For stochastic differential equations in general, this phenomenon is discussed in Mao's book [36] for instance. Other properties that are unique to the stochastic epidemic models include the probability of an outbreak, the quasi-stationary probability distribution, the final size distribution of an epidemic and the expected duration of an epidemic.

4.3 Mathematical models and infectious diseases

On a year to year basis, a large number of people worldwide suffer and die from infectious diseases such as measles, malaria, tuberculosis, Human Immunodeficiency Virus (HIV). Taking a closer look into historical deaths of infectious diseases, classic examples of these deaths include the Black Death and smallpox and influenza disasters. In the fourteenth century, 25 million deaths in Europe from the Black Death is estimated to have killed 30%-60% of Europe's population, reducing the world's population from an estimated 450 million to between 350 and 375 million [69]. The pre-Columbian Mesoamerican people of central Mexico, also known as Aztecs, lost half their population of 3.5 million from smallpox. Approximately 20 million people worldwide died from influenza pandemic in the year 1919 [69].

There are other diseases like Influenza, Cholera, Tuberculosis (TB), Human Immunodeficiency Virus (HIV) which continue to kill millions of people presently. According to World health Organization (WHO), over one million people die from

malaria each year, mostly children under five years of age, with 90% of malaria cases occurring in Sub-Saharan Africa. An estimated 300-600 million people suffer from malaria each year. More than 40 percent of the world's population lives in malaria-risk areas. Measles is a highly contagious virus, spread by contact with an infected person through coughing and sneezing. Approximately 4000 mostly children less than five years of age die from measles-related complications each day, or 17 deaths every hour. About 1.5 million people die from tuberculosis each year, and it is thought that as many as one third of the current seven billion human population may be infected with Mycobacterium tuberculosis. Cholera is an acute, diarrhea illness caused by infection of the intestine with the bacterium Vibrio cholerae. An estimated 3-5 million cases and over $100,000$ deaths occur each year around the world. According to estimates by WHO and UNAIDS, 35 million people were living with HIV globally at the end of 2013. That same year some 2.1 million people became newly infected, and 1.5 million died of AIDS-related causes. A particularly interesting case is that of Ebola virus disease (EVD) which erupted in the year 2014 in West Africa. According to Centers for Disease Control and Prevention (CDC) on Ebola outbreak in West Africa [70], there are at least $25,178$ suspected cases, $14,764$ laboratory confirmed cases and over $10,445$ total deaths and counting.

The total burden of discomfort and suffering that result from these diseases is clearly immense, and an understanding of mathematical modelling techniques can be useful towards informing how to alleviate this terrible state of affairs. While there may be many complicating factors behind these deaths, simple mathematical models can provide much insight into the dynamics of disease epidemics and help global health officials make informed decisions about public health policies. We highlight briefly some examples on the use of mathematical models of infectious diseases. Okuonghae [48] studied some qualitative properties of a

delayed differential equation model that explored some qualitative properties of Tuberculosis (TB). Elsje Pienaar and Maria Lerm [49] proposed a mathematical model of the initial interaction between Mycobacterium Tuberculosis (M-TB) and macrophages, where their model considered the interplay between bacterial killing and the pathogen's interference with macrophage function. Zhenguo Bai and Dan Liu [5] modelled seasonal measles transmission in China where they studied and formulated a discrete-time deterministic measles model with periodic transmission rate. Okosun and Makinde [47], proposed and examined a deterministic model for the co-infection of malaria and cholera diseases with optimal control. Concerning HIV disease, Abiodun *et al.*, [1], studied a model for control of HIV/AIDS with parental care. Immonen et al. [21] proposed a new hybrid stochastic-deterministic, spatially distributed computational model to simulate growth competition assays on a relatively immobile monolayer of peripheral blood mono-nuclear cells (PBMCs), commonly used for determining ex vivo fitness of human immunodeficiency virus type-1 (HIV-1). Witbooi [63] proposed and analyzed the stability of an SEIR epidemic model with independent stochastic perturbations. Many sources on the study of infectious disease modelling can be found in the infectious diseases literature.

Chapter 5

The compartmental model for HIV/AIDS

5.1 Model formulation

With the model of Bhunu *et al.* [6], as a basis, we form a new model of the HIV epidemic. The new model allows for an inflow of infecteds into the population. We first describe the variables and parameters as from [6]. The model we present has six compartments which are the susceptibles (S); the individuals who are HIV positive and do not know their status (I_1); the individuals who are HIV positive and know their status and have reduced their risky sexual behavior as a result of knowing their status (I_2); the individuals who are HIV positive and know their status and have increased their risky sexual behavior as a result of knowing their status (I_3); HIV positive individuals who have become sexually inactive (I_4); AIDS patients (A). The total population is $N(t)$ and we have

$$N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t) + A(t). \tag{5.1}$$

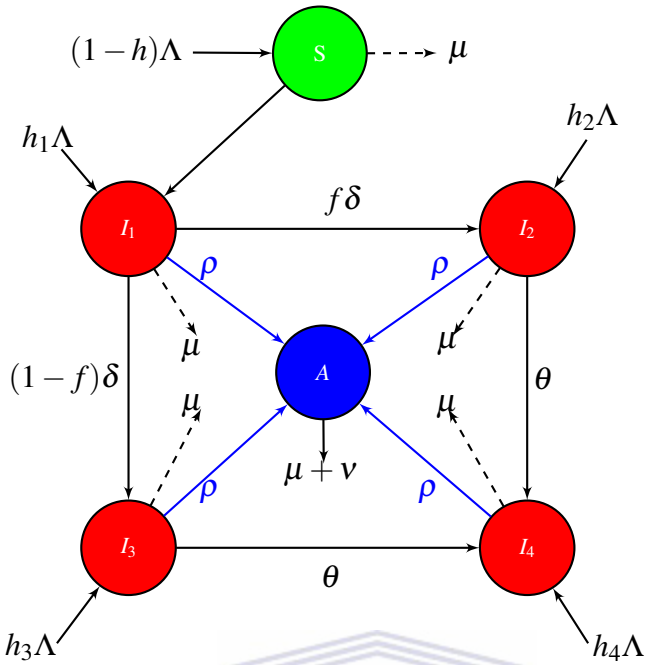

Figure 5.1: The transfer diagram for the HIV model.

Let h, h_1, h_2, h_3 and h_4 be non-negative constants with $h = h_1 + h_2 + h_3 + h_4 \leq 1$. Now we assume that for each $j = 1,2,3,4$, there is an inflow of magnitude $h_j\Lambda$ into the compartment I_j, together with a recruitment $(1-h)\Lambda$ into the $S(t)$ compartment, as shown in Figure 5.1.

The per capita natural death rate is denoted by $\mu > 0$ in all classes. The disease-induced mortality rate is denoted by ν.

The force of infection is:

$$\lambda(t) = \frac{\beta c(I_1(t) + \phi_1 I_2(t) + \phi_2 I_3(t))}{N(t)} \tag{5.2}$$

where β represents the transmission rate probability per sexual contact, c is the effective contact rate, $\phi_1 \in (0,1)$ models the effect of a positive behavioral change as a result of knowing one's HIV positive status while $\phi_2 > 1$ accounts for increase in risky behaviour from knowing one's HIV positive status. Susceptible individuals who become infected with HIV will move into the class of HIV infected people not knowing their status (I_1). Individuals in the class (I_1) will know know their HIV status at a rate δ through testing and counseling. HIV positive individuals who know their status will move into the sexually inactive class I_4 at a rate θ. A proportion f of HIV positive people knowing their status will move into the class I_2 and the complementary fraction $(1-f)$ will move into the class I_3, respectively. HIV positive people in classes I_1, I_2, I_3 and I_4 progress to the AIDS class (A) at a rate ρ.

The above transfer diagram with recruitment of infecteds gives rise to six ordinary differential equations as follows:

$$\begin{cases} \frac{dS}{dt} = (1-h)\Lambda - (\lambda + \mu)S \\ \frac{dI_1}{dt} = h_1\Lambda + \lambda S - (\mu + \rho + \delta)I_1 \\ \frac{dI_2}{dt} = h_2\Lambda + f\delta I_1 - (\mu + \theta + \rho)I_2 \\ \frac{dI_3}{dt} = h_3\Lambda + (1-f)\delta I_1 - (\mu + \theta + \rho)I_3 \\ \frac{dI_4}{dt} = h_4\Lambda + \theta(I_2 + I_3) - (\mu + \rho)I_4 \\ \frac{dA}{dt} = \rho(I_1 + I_2 + I_3 + I_4) - (\mu + \nu)A \end{cases} \tag{5.3}$$

5.2 Positivity and boundedness

In this section, we study the existence and other basic properties of the solutions of the model system (5.3). Using an approach described in papers [45, 15], we establish the positivity and the boundedness of solutions of model system (5.3) in a subset Γ of $\mathbb{R}^6$ defined as:

$$\Gamma = \{z \in \mathbb{R}^6 : \sum_{i=1}^{6} z_i \leqslant \frac{\Lambda}{\mu}\}. \tag{5.4}$$

Like in Bhunu et al., [6], we require some auxiliary results from [58], which we quote below.

Lemma 5.1 *[58]. Let F:* $\mathbb{R}^n_+ \to \mathbb{R}^n, F(x) = (F_1(x), F_2(x), \ldots, F_n(x)), x = (x_1, x_2, \ldots, x_n)$ *be continuous and have partial derivatives* $\frac{\partial F_j}{\partial x_k}$ *which exist and are continuous in* $\mathbb{R}^n_+$ *for* $j,k = 1,2,\ldots,n$. *Then F is locally Lipschitz continuous in* $\mathbb{R}^n_+$.

Theorem 5.2 *[58]. Let F:* $\mathbb{R}^n_+ \to \mathbb{R}^n$ *be locally Lipschitz continuous and for each* $j = 1,2,\ldots,n$ *satisfy* $F_j(x) \geq 0$ *whenever* $x \in \mathbb{R}^n_+, x_j = 0$. *Then for every* $x_0 \in \mathbb{R}^n_+$, *there exists a unique solution of* $\bar{x} = F(x)$, $\bar{x}(0) = x_0$ *with values in* $\mathbb{R}^n_+$ *which is defined in some interval* $(0,b]$ *with* $b \in (0,\infty]$. *If* $b < \infty$, *then* $\sup_{0 \leq t \leq b} \sum_{j=1}^{n} x_j(t) = \infty$.

We note: $F_j(x) \geq 0$ whenever $x \in \mathbb{R}^n_+, x_j = 0$.

Now we can prove the following theorem, similar to that in [6].

Theorem 5.3 *Given any* $y \in \Gamma$, *there exists a unique solution of model* (5.3) *with* $x(0) = y$ *and* $x(t) \in \Gamma$ *for all* $t > 0$.

Proof. By Lemma 5.1 and Theorem 5.2, it follows that there exists $b > 0$ such that over the interval $t \in [0, b)$ we have a unique positive solution,

$$x(t), \text{ with } x(0) = y \in \Gamma.$$

Given such a solution $x(t)$, we now proceed to prove that $\sum_{i=1}^{6} \leq \frac{\Lambda}{\mu}$.

Adding up the equations of model system (5.3), we obtain:

$$\begin{aligned}
\frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI_1}{dt} + \frac{dI_2}{dt} + \frac{dI_3}{dt} + \frac{dI_4}{dt} + \frac{dA}{dt} \\
&= (1-h)\Lambda - (\lambda+\mu)S + \Lambda + \lambda S - (\mu+\rho+\delta)I_1 \\
&+ h_2\Lambda + f\delta I_1 - (\mu+\theta+\rho)I_2 + h_3\Lambda + (1-f)\delta I_1 - (\mu+\theta+\rho)I_3 \\
&+ h_4\Lambda + \theta(I_2+I_3) - (\mu+\rho)I_4 + \rho(I_1+I_2+I_3+I_4) - (\mu+\nu)A \\
&= \Lambda - \mu N - \nu A
\end{aligned} \tag{5.5}$$

Now we note the following inequality:

$$\frac{dN}{dt} = \Lambda - \mu N - \nu A \leq \Lambda - \mu N(t).$$

Let

$$Q(t) = \frac{\Lambda}{\mu} - N(t).$$

Then

$$-\frac{dQ(t)}{dt} \leq \Lambda - \mu N(t) = \mu Q(t),$$

$$\frac{dQ(t)}{dt} \geq -\mu Q(t).$$

Therefore

$$\frac{dQ(t)}{dt} = -\mu Q(t) + K(t) \tag{5.6}$$

where $K(t) > 0$ is some positive function. The derivative $\frac{dQ}{dt}$ constitutes a first order linear differential equation [2].

Rearranging (5.6), we obtain

$$\frac{dQ}{dt} + \mu Q(t) = K(t),$$

and an integrating factor denoted by $e^{\int P(t)\mathrm{d}t} = e^{\mu t}$.

Multiplying both sides of the equation (5.6) by the integrating factor $e^{\mu t}$, we obtain

$$\frac{d(Q(t)e^{\mu t})}{dt} = K(t)e^{\mu t}.$$

Now for any $\tau \in (0, b]$, we have $Q(\tau)e^{\mu\tau} - Q(0) = \int_0^\tau K(t)e^{\mu t}dt \geq 0$.

Thus:

$$Q(\tau)e^{\mu\tau} \geq Q(0).$$

Since $N(0) < \frac{\Lambda}{\mu}$, it follows that $Q(0) > 0$.

Therefore also

$$Q(\tau) > 0, \text{i.e, } N(\tau) < \frac{\Lambda}{\mu}.$$

We have proved that the solution is bounded. Therefore by Theorem 5.2 it follows that $b = \infty$. This completes the proof. ■

5.3 Global stability analysis of the disease-free equilibrium

The disease-free equilibrium (DFE) exists only if $h_i = 0$ for all $i = 1, 2, 3, 4$. The DFE of the model (5.3) is the point $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0)$. Of course then, from the work of Bhunu *et al.* [6] we have the following basic reproduction number:

$$\mathcal{R}_A = \frac{\beta c(\mu+\rho+\theta+(f\phi_1+(1-f)\phi_2)\delta)}{(\mu+\rho+\theta)(\mu+\delta+\rho)} \tag{5.7}$$

Theorem 5.4 *The disease-free equilibrium E_0, exist, and is locally asymptotically stable for $\mathcal{R}_A < 1$ and unstable otherwise.*

Regarding global stability, in the paper [6], global stability of the DFE was proved subject to another property, but was not proved absolutely.

We now prove global stability, using a Lyapunov function and we state the following Theorem 5.5.

Theorem 5.5 *Consider the condition $h_i = 0$, $i = 1,2,3,4$. If $\mathcal{R}_A < 1$, then the disease-free equilibrium of the model is globally asymptotically stable.*

Proof. We seek to construct a Lyapunov function. To this end let us introduce a number of constants.

We first define m_1, m_2 and m_3 as follows:

$$m_1 = \mu+\rho+\delta,$$
$$m_2 = \mu+\rho+\theta,$$
$$m_3 = \frac{2\theta}{\mu+\rho}+1.$$

In particular then we note that R_A can be written as

$$\mathcal{R}_A = (m_1 m_2)^{-1}\beta c(m_2+\delta(f\phi_1+(1-f)\phi_2)).$$

Now we define $V : \mathbb{R}^5 \to \mathbb{R}$ by the formula,

$$V = bI_5 + \sum_{r=1}^{4} a_r I_r,$$

where $I_5 = A$ and constants $b, a_1,\ a_2,\ a_3,\ a_4$ are chosen as below, and they are all positive. In particular $b > 0$ because we assume that $\mathcal{R}_A < 1$.

$$
\begin{aligned}
a_1 &= 1 \\
a_2 &= \frac{1}{m_2}(\beta c\phi_1 + \rho b(1 + \frac{2\theta}{\mu+\rho}) \\
a_3 &= \frac{1}{m_2}(\beta c\phi_2 + \rho b(1 + \frac{2\theta}{\mu+\rho}) \\
a_4 &= \frac{2b\rho}{\mu+\rho} \\
b &= \frac{1}{2}\rho^{-1}m_1(1-R_A)[1 + \frac{\delta}{m_2}(1 + \frac{2\theta}{\mu+\rho})]^{-1},
\end{aligned}
$$

After calculating the time derivative $\dot{V}$, we present it in the form

$$
\begin{aligned}
\dot{V} &= b\dot{I_5} + \Sigma_{r=1}^{4} a_r \dot{I_r} \\
&= b[\rho(I_1 + I_2 + I_3 + I_4) - (\mu+\nu)A] + a_1(h_1\Lambda + \lambda S - (\mu+\rho+\delta)I_1) \\
&+ a_2(h_2\Lambda + f\delta I_1 - (\mu+\theta+\rho)I_2) + a_3(h_3\Lambda + (1-f)\delta I_1 - (\mu+\theta+\rho)I_3) \\
&+ a_4(h_4\Lambda + \theta(I_2 + I_3) - (\mu+\rho)I_4) \\
&= b\rho I_1 - a_1(\mu+\rho+\delta)I_1 - a_2 f\delta I_1 - a_3(1-f)\delta I_1 \\
&+ b\rho I_2 - a_2(\mu+\theta+\rho)I_2 - a_4\theta I_2 + b\rho I_3 - a_3(\mu+\theta+\rho)I_3 - a_4\theta I_3 \\
&+ b\rho I_4 - a_4(\mu+\nu)I_4 - b(\mu+\nu)I_5 \\
&= K_5\dot{I_5} + \Sigma_{r=1}^{4} K_r \dot{I_r}.
\end{aligned}
\tag{5.8}
$$

where the coefficients K_i are being expressed in terms of $S(t)$, $N(t)$ and the parameters. The idea is to show that $\dot{V}$ is a negative-definite function, by showing that each of these K_r are strictly negative. In fact after some routine calculations, we obtain the coefficients K_i to be as follows.

$$
\begin{aligned}
K_1 &= c\beta\tfrac{S(t)}{N(t)} - m_1 + \delta f a_2 - \delta(1-f)a_3 + \rho b \\
K_2 &= \phi_1 c\beta\tfrac{S(t)}{N(t)} - m_2 a_2 - \theta a_4 + \rho b \\
K_3 &= \phi_2 c\beta\tfrac{S(t}{N(t)} - m_2 a_3 - a_4\theta + \rho b \\
K_4 &= -(\mu+\rho)a_4 + \rho b \\
K_5 &= -(\mu+\nu)b
\end{aligned}
$$

It immediately follows that $K_5 < 0$ (since $b > 0$).

Also,

$$K_4 = -(\mu+\rho)\frac{2\rho b}{\mu+\rho} + \rho b = -\rho b < 0.$$

Now we note that $\frac{S(t)}{N(t)} \leq 1$ for all $t > 0$.

We also observe that

$$\theta a_4 + \rho b = \rho b(1 + \tfrac{2\theta}{\mu+\rho}).$$

We continue to check the negativity of the coefficients K_3, K_2 and K_1

$$\begin{aligned} K_3 &< \phi_1 c\beta - m_2 a_3 + \theta a_4 + \rho b \\ &= \phi_1 c\beta - [\beta c\phi_1 + \rho b(1 + \tfrac{2\theta}{\mu+\rho})] + \theta a_4 + \rho b\rho b - \tfrac{2\rho b}{\mu+\rho} - \theta\tfrac{2b\rho}{\mu+\rho} + b\rho \\ &= 0. \end{aligned}$$

Therefore $K_3 < 0$. Likewise $K_2 < 0$. Finally, for K_1 we have the following

$$\begin{aligned} K_1 &< c\beta - m_1 + \delta f a_2 + \delta(1-f)a_3 + \rho b \\ &= c\beta - m_1 + \tfrac{\delta f}{m_2}(\beta c\phi_1 + \rho b(1 + \tfrac{2\theta}{\mu+\rho}) + \tfrac{\delta(1-f)}{m_2}(\beta c\phi_2 + \rho b(1 + \tfrac{2\theta}{\mu+\rho}) + \rho b \\ &= c\beta - m_1 + \tfrac{c\beta\delta}{m_2}(f\phi_1 + (1-f)\phi_2) + \tfrac{\delta}{m_2}\rho b(1 + \tfrac{2\theta}{\mu+\rho}) + \rho b \\ &= -m_1 + c\beta[1 + \tfrac{\delta}{m_2}(f\phi_1 + (1-f)\phi_2)] + \rho b[1 + \tfrac{\delta}{m_2}(1 + \tfrac{2\theta}{\mu+\rho})] \\ &= m_1[-1 + (m-1m_2)^{-1}c\beta[m_2 + \delta(f\phi_1 + (1-f)\phi_2)]] + \rho b[1 + \tfrac{\delta}{m_2}(1 + \\ &\tfrac{2\theta}{\mu+\rho})] \\ &= m_1[R_A - 1] + \tfrac{1}{2}m_1[1 - R_A] \\ &= \tfrac{1}{2}m_1[R_A - 1] < 0. \end{aligned}$$

This completes the proof. ■

5.4 Endemic equilibrium solution and numerical example

Using Mathematica program to compute, the model system (5.3) admits a unique endemic equilibrium solution, which is given by

$$E^* = (S^*, I_1^*, I_2^*, I_3^*, I_4^*, A)$$

where,

$$S^* = \frac{\Lambda(1-h)}{(\lambda+\mu)}$$

$$I_1{}^* = \frac{\Lambda(\lambda+(\lambda+\mu)h_1-\lambda h)}{(\lambda+\mu)(\delta+\mu+\rho)}$$

$$I_2{}^* = \frac{\Lambda(f\delta(\lambda+\mu)h_1+(\lambda+\mu)(\delta+\mu+\rho)h_2-f\delta\lambda(-1+h))}{(\lambda+\mu)(\delta+\mu+\rho)(\theta+\mu+\rho)}$$

$$I_3{}^* = \frac{\Lambda(-(-1+f)(\lambda+\mu)h_1+(\lambda+\mu)(\lambda+\mu+\rho)h_3+(-1+f)\lambda(-1+h))}{(\lambda+\mu)(\delta+\mu+\rho+)(\theta+\mu+\rho)}$$

$$I_4{}^* = \frac{\Lambda}{\mu+\rho}[-h_4 - \frac{1}{(\lambda+\mu)(\delta+\mu+\rho)(\theta+\mu+\rho)}[\theta(-1(-1+f)(\lambda+$$
$$\mu)h_1+(\lambda+\mu)(\delta+\mu+\rho)h_3+(-1+f)\lambda(-1+h)$$
$$+\theta(f\delta(\lambda+\mu)h_1+(\lambda+\mu)(\delta+\mu+\rho)h_2-f\delta\lambda(-1+h))]]$$

$$A^* = \frac{1}{(\lambda+\mu)(\mu+\rho)(\delta+\mu+\rho)}(\Lambda\rho(-\lambda(-1+h)(1-f+f\delta+\mu+\rho)$$
$$+(\lambda+\mu)(1+f(-1+\delta)+\mu+\rho)h_1+(\lambda+\mu)(\delta+\mu+\rho)h_2+\delta\lambda h_3+$$
$$\delta\mu h_3+\mu^2 h_3+\lambda\rho h_3+\mu\rho h_3+\delta\lambda h_4+\delta\mu h_4+\lambda\mu h_4+\mu^2 h_4+\lambda\rho h_4+$$
$$\mu\rho h_4))$$

Since the disease-free equilibrium is globally asymptotically stable, as illustrated in Theorem 5.5, it is evident that E^* is unique.

Numerical solutions to the coordinates of an endemic equilibrium above are executed using MAPLE program with realistic hypothetical parameter values and initial conditions as follows.

Model parameters similar to Bhunu *et al.* [6]:

$\Lambda = 0.26,\ \beta c = 0.275,\ \phi_1 = 0.01,\ \phi_2 = 1.01,\ \delta = 0.1,\ \ f = 0.85,$
$h = 0.015,\ \ h_1 = 0.21,\ \ h_2 = 0.03,\ \ h_3 = 0.045,\ \ h_4 = 0.04,\ \ \mu = 0.02,$
$\nu = 0.4,\ \ \rho = 0.1,\ \ \theta = 0.2.$

Initial conditions (in units of millions):

$S(0) = 7,\ \ I_1(0) = 1,\ \ I_2(0) = 1.4,\ \ \ I_3(0) = 2.6,\ \ I_4(0) = 0.7,\ \ \ A(0) = 0.3.$

The numerical solutions are:

$S^* = 11.1471,\ \ I_1{}^* = 0.0975,\ \ I_2{}^* = 0.0503,\ \ I_3{}^* = 0.0411,$
$I_4{}^* = 0.2390,\ \ \ A^* = 0.1019.$

It is important to note that the parameter values above were chosen such that the total population never goes into extinction and threshold parameter yields $\mathcal{R}_A = 1.3198 > 1$ in the absence of vaccination and treatment. Therefore, it means that the HIV/AIDS disease will prevail and persist in a population.

5.5 Numerical simulations

In this section, we numerically analyze the effect of the rate of knowing one's HIV status through counseling and testing (δ) for model system (5.3), using model parameters in Table 5.1 with model equations coded in MATLAB.

Using the Euler scheme to determine stability analysis of disease-free equilibrium,

when there are no recruitment of infecteds, i.e., $h_1 = h_2 = h_3 = h_4 = 0$, Figures 5.2, 5.3, and 5.4, gives the graphical representation of the effects of knowing one's HIV status through counselling and testing (δ) as well as in conjunction with effective contact rate c for HIV infection and probability of HIV transmission per contact (β).

The parameter values used in this section are similar as in the paper presented in Bhunu *et al.*, [6], as follows $S(0) = 2000$; $I_1(0) = 1500$; $I_2(0) = 1000$; $I_3(0) = 1000$; $I_4(0) = 2000$; $A(0) = 1000$; $\Lambda = 32$; $\mu = 0.02$; $\delta = 0.02$; $\rho = 0.01$; $\phi_1 = 0.25$; $\phi_2 = 1.01$; $f = 0.85$; $\nu = 0.4$; $\beta c = 0.2$; $\theta = 0.2$.

It is worth noting here that disease free equilibrium, in Figures 5.3 and 5.4, etc., is shown to be globally asymptotically stable when the corresponding basic reproduction number is less than unity as stated by the aforementioned theorem.

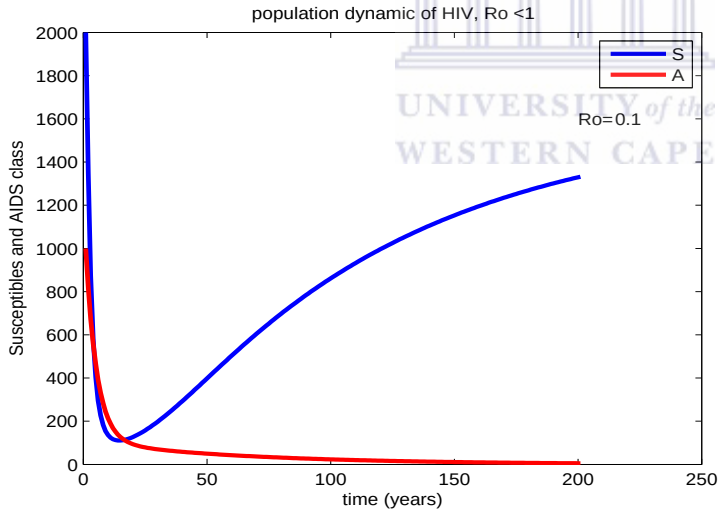

Figure 5.2: Deterministic trajectories of epidemic model (5.3) $\beta = 0.5; c = 4;\ \delta = 0.02$.

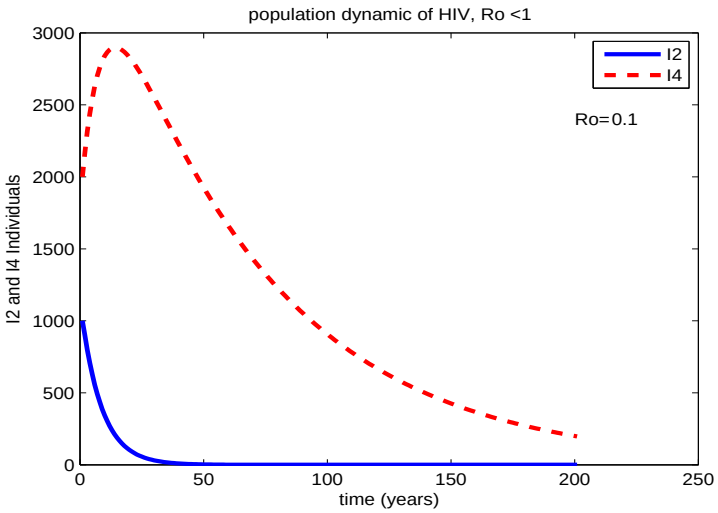

Figure 5.3: Deterministic trajectories of epidemic model (5.3) $\beta = 0.5; c = 4;\ \delta = 0.02$.

5.6 Sensitivity analysis

In this section we carry out the sensitivity analysis to determine the robustness of the basic reproduction number, $\mathcal{R}_A$, to the model parameter values. That is, to help us identify the parameters that have high impact on $\mathcal{R}_A$. We employ Mathematica software to derive the normalized forward index of $\mathcal{R}_A$ with respect to each model parameters as follows:

$$\frac{\partial \mathcal{R}_A}{\partial \beta} \times \frac{\beta}{\partial \mathcal{R}_A} = 1$$

$$\frac{\partial \mathcal{R}_A}{\partial c} \times \frac{c}{\partial \mathcal{R}_A} = 1$$

$$\frac{\partial \mathcal{R}_A}{\partial \mu} \times \frac{\mu}{\partial \mathcal{R}_A} = -\mu\Delta$$

$$\frac{\partial \mathcal{R}_A}{\partial \rho} \times \frac{\rho}{\partial \mathcal{R}_A} = -\rho\Delta$$

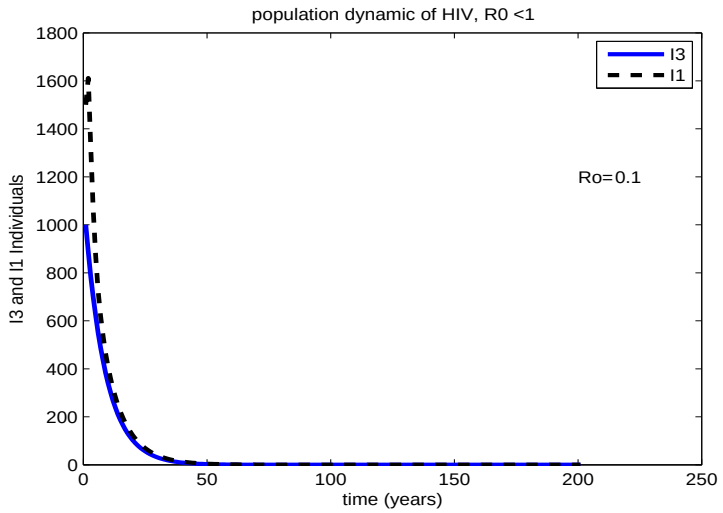

Figure 5.4: Deterministic trajectories of epidemic model (5.3) $\beta = 0.5; c = 4;\ \delta = 0.02$.

$$\frac{\partial \mathcal{R}_A}{\partial \theta} \times \frac{\theta}{\partial \mathcal{R}_A} = -\frac{\delta\theta(f\phi_1 - (-1+f)\phi_2)}{(\delta+\mu+\rho)(\theta+\mu+\rho+f\delta\phi_1+(\delta-f\delta)\phi_2)}$$

$$\frac{\partial \mathcal{R}_A}{\partial \phi_1} \times \frac{\phi_1}{\partial \mathcal{R}_A} = \frac{f\delta\phi_1}{(\theta+\mu+\rho+f\delta\phi_1+(\delta-f\delta)\phi_2)}$$

$$\frac{\partial \mathcal{R}_A}{\partial \phi_2} \times \frac{\phi_2}{\partial \mathcal{R}_A} = \frac{(1-f)\delta\phi_2}{(\theta+\mu+\rho+f\delta\phi_1+(\delta-f\delta)\phi_2)}$$

$$\frac{\partial \mathcal{R}_A}{\partial \delta} \times \frac{\delta}{\partial \mathcal{R}_A} = -\frac{\delta(\theta+\mu+\rho-f(\mu+\rho)\phi_1+(-1+f)(\mu+\rho)\phi_2)}{(\delta+\mu+\rho)(\theta+\mu+\rho+f\delta\phi_1+(\delta-f\delta)\phi_2)}$$

$$\frac{\partial \mathcal{R}_A}{\partial \phi_2} \times \frac{\phi_2}{\partial \mathcal{R}_A} = \frac{f\delta(\phi_1-\phi_2)}{(\theta+\mu+\rho+f\delta\phi_1+(\delta-f\delta)\phi_2)}$$

where $\Delta = \dfrac{((\theta+\mu+\rho)^2+f\delta(\delta+\theta+2(\mu+\rho))\phi_1-(-1+f)\delta(\delta+\theta+2(\mu+\rho))\phi_2)}{(\delta+\mu+\rho)(\theta+\mu+\rho)(\theta+\mu+f\delta\phi_1+(\delta-f\delta)\phi_2)}$.

The following Table 5.1 illustrates the sensitivity indices of $\mathcal{R}_A$ with respect to model parameter. Parameters are arranged from most sensitive to the least. The most sensitive parameters are the recruitment rate probability of HIV transmission

per contact (βc) and abstinence rate (θ). The least is the proportion reducing risky sexual behaviour as a result of knowing ones status. The sensitivity index of $\mathcal{R}_A$ with respect to the transmission probability of getting HIV infection (β) is $+1$, implying that, increasing or decreasing β by 10%, increases $\mathcal{R}_A$ by approximately 10%. Similarly, increasing or decreasing abstinence rate by 10% increases $\mathcal{R}_A$ by 5.612%.

Parameter values and sensitivity index of $\mathcal{R}_A$				
Parameter description	**Parameter**	**Value**	**Source**	**Sensitivity**
Probability of HIV transmission per contact	βc	0.95	Bhunu et al.[6]	+1
Abstinence rate	θ	0.2	Bhunu et al.[6]	+0.5612
Natural rate of progression to AIDS	ρ	0.1	Bhunu et al.[6]	+0.2806
Rate of knowing ones HIV status through counseling and testing	δ	0.1	Bhunu et al.[6]	+0.1021
Modification parameter	ϕ_1	0.25	Bhunu et al.[6]	+0.0596
Percapita natural death rate	μ	0.02	Bhunu et al.[6]	+0.0561
Modification parameter	ϕ_2	1.01	Bhunu et al.[6]	+0.0425
Proportion reducing risky sexual behaviour as a result of knowing ones status	f	0.85	Bhunu et al.[6]	-0.1813

Table 5.1: Sensitivity index of $\mathcal{R}_A$

Chapter 6

Public health education for HIV/AIDS control

6.1 Model formulation

In this section we determine efficient roll-out of public health education for the control of HIV/AIDS in a population. We investigate the effect of education as a function of time, on the transmission of HIV infection. We assume that as a result of education on HIV, behavioral patterns will change for the better and HIV transmission will decrease. In particular, with respect to infected individuals from elsewhere moving into a given population, it it expected that through education, there will be much more caution. It is fair to expect that due to HIV information, people will avoid sexual intercourse with complete strangers or even partners that they do not know well.

Let us use the symbol $u(t)$ to denote the magnitude of the effort of education that is being rolled-out.

The set $\mathcal{U}$ of admissible controls: $[0,T] \to \mathbb{R}$ is defined as follows.

$$\mathcal{U} = \{u(t) |\ u(t) \text{ is measurable}, ||u||_\infty < a < 1, t \in [0,T]\}. \tag{6.1}$$

We assume that there are constants η_1 and η_2 such that in the model (5.3), we can replace the θ related to the I_2 class by $\theta(1+\eta_1 u(t))$ and θ of I_3 class by $\theta(1+\eta_2 u(t))$. Thus our system takes the form:

$$\begin{cases} \frac{dS}{dt} = (1-h)\Lambda - (\lambda+\mu)S \\ \frac{dI_1}{dt} = h_1\Lambda + \lambda S - (\mu+\rho+\delta)I_1 \\ \frac{dI_2}{dt} = h_2\Lambda + f\delta I_1 - (\mu+\theta(1+\eta_1 u(t))+\rho)I_2 \\ \frac{dI_3}{dt} = h_3\Lambda + (1-f)\delta I_1 - (\mu+\theta(1+\eta_2 u(t))+\rho)I_3 \\ \frac{dI_4}{dt} = h_4\Lambda + \theta(I_2+I_3) + \theta(\eta_1 I_2 + \eta_2 I_3)u(t) - (\mu+\rho)I_4 \\ \frac{dI_5}{dt} = \rho(I_1+I_2+I_3+I_4) - (\mu+\nu)I_5 \end{cases} \tag{6.2}$$

Where $I_5 = A$. Our goal is to minimize the total number of infective individuals with the use of educational campaign on $[0,T]$. Towards investigating the optimal level of public health education effort needed to control the disease in question, we formulate the control problem.

6.2 Optimal control problem

We intend to find $||u||_\infty < a < 1$, to maximize the following objective functional:

$$J(u) = \int_0^T S(t) - cu^2(t)dt \tag{6.3}$$

subject to the system of equations (6.2)

and

$$S(0) \geq 0, I_1(0) \geq 0, I_2(0) \geq 0, I_3(0) \geq 0, I_4(0) \geq 0, A(0) \geq 0.$$

Our aim is to maximize the total number of susceptible individuals while also optimizing the use of educational campaign at the minimum cost possible given the initial population sizes of all compartments $S(0)$, $I_1(0)$, $I_2(0)$, $I_3(0)$, $I_4(0)$, $A(0)$. The symbol c is a weight parameter which describes the importance of the educational campaign while the term $u^2(t)$ represent the educational campaign itself. The quadratic term is particularly chosen to describe the nonlinear behaviour of implementing the educational campaign.

We need to find an optimal control $u^*(t)$ such that

$$J(u^*) = \max\{J(u(t))|\ u \in \mathcal{U}\}. \tag{6.4}$$

6.3 Optimality

We use the Pontryagin's Maximum principle since it is a constrained control problem, see for instance Lenhart and Workman [31]. The necessary conditions that an optimal system must satisfy come from Pontryagin's Maximum principle. What this principle does, is to convert system (6.2) and equation of objective functional (6.3) into the problem of maximizing a Hamiltonian $\mathcal{H}$ with respect to $u(t)$.

The Hamiltonian function $\mathcal{H}$ is obtained as follows, with $\xi_S, \xi_{I_1}, \xi_{I_2}, \xi_{I_3}, \xi_{I_4}, \xi_{I_5}$ being Lagrange multipliers, also called co-state variables, associated with respective classes.

The Hamiltonian function takes the following form:

$$\mathcal{H} = S(t) - cu^2(t) + \xi_S \frac{dS}{dt} + \sum_{i=1}^{5} \xi_{I_i} \frac{dI_i}{dt} \tag{6.5}$$

which can be expanded as,

$$\begin{aligned}
\mathcal{H} &= S(t) - cu^2(t) + \xi_S[(1-h)\Lambda - (\lambda+\mu)S] \\
&+ \xi_{I_1}[h_1\Lambda + \lambda S - (\mu+\rho+\delta)I_1] \\
&+ \xi_{I_2}[h_2\Lambda + f\delta I_1 - (\mu+\theta(1+\eta_1 u)+\rho)I_2] \\
&+ \xi_{I_3}[h_3\Lambda + (1-f)\delta I_1 - (\mu+\theta(1+\eta_2 u)+\rho)I_3] \\
&+ \xi_{I_4}[h_4\Lambda + \theta(I_2+I_3) + \theta(\eta_1 I_2 + \eta_2 I_3)u - (\mu+\rho)I_4] \\
&+ \xi_{I_5}[\rho(I_1+I_2+I_3+I_4) - (\mu+\nu)I_5]
\end{aligned} \tag{6.6}$$

Necessary conditions for our optimal solution are as follows:

$$-\dot{\xi}_S = (\xi_S - \xi_{I_1})\beta c(I_1 + \phi_1 I_2 + \phi_2 I_3)\left(\frac{N-S}{N^2}\right) - 1$$

$$\begin{aligned}
-\dot{\xi}_{I_1} &= (\xi_S - \xi_{I_1})\frac{\beta c(N-(I_1+\phi_1 I_2+\phi_2 I_3))}{N^2} + \xi_{I_1}(\mu+\rho+\delta) - \xi_{I_2} f\delta \\
&\quad - \xi_{I_3}(1-f)\delta - \xi_{I_5}\rho
\end{aligned}$$

$$\begin{aligned}
-\dot{\xi}_{I_2} &= (\xi_S - \xi_{I_1})\frac{\beta c(\phi_1 N-(I_1+\phi_1 I_2+\phi_2 I_3))}{N^2} + \xi_{I_2}(\mu+\theta(1+u\eta_1)+\rho) \\
&\quad - \xi_{I_4}(\theta + u\eta_1\theta) - \xi_{I_5}\rho
\end{aligned}$$

$$\begin{aligned}
-\dot{\xi}_{I_3} &= (\xi_S - \xi_{I_1})\frac{\beta c(\phi_2 N-(I_1+\phi_1 I_2+\phi_2 I_3))}{N^2} + \xi_{I_3}(\mu+\theta(1+u\eta_2)+\rho) \\
&\quad - \xi_{I_4}(\theta + u\eta_2\theta) - \xi_{I_5}\rho
\end{aligned}$$

$$-\dot{\xi}_{I_4} = (\xi_{I_1} - \xi_S)\frac{\beta cS(I_1+\phi_1 I_2+\phi_2 I_3)}{N^2} + \xi_{I_4}(\mu+\rho) - \xi_{I_5}\rho$$

$$-\dot{\xi}_{I_5} = (\xi_{I_1} - \xi_S)\frac{\beta cS(I_1+\phi_1 I_2+\phi_2 I_3)}{N^2} + \xi_{I_5}(\mu+\nu)$$

The six equations above represented by $-\dot{\xi}_i(t) = \frac{\partial \mathcal{H}}{\partial i}$, $i = S, I_1, I_2, I_3, I_4, I_5$ are called the adjoint equations.

Characterization of the optimal control u^* is derived by computing $\dfrac{\mathcal{H}}{\partial u}$ as follows,

$$0 = \frac{\partial H}{\partial u} = -2cu - \xi_{I_2}\theta\eta_1 I_2 - \xi_{I_3}\theta\eta_2 I_3 + \xi_{I_4}\theta(\eta_1 I_2 + \eta_2 I_3).$$

Therefore u^* takes the form:

$$u^* = \begin{cases} 0 & if \quad m^* \leq 0, \\ m^* & if \quad 0 < m^* < 1, \\ 1 & if \quad m^* \geq 1 \end{cases} \tag{6.7}$$

where $m^* = \dfrac{\xi_{I_4}\theta(\eta_1 I_2 + \eta_2 I_3) - \theta(\xi_{I_2}\eta_1 I_2 + \xi_{I_3}\eta_2 I_3)}{2c}$.

6.4 Numerical simulations

We used Pontryagin's maximum principle to characterize the optimal level of the control denoted by u^* and derived the optimality system (6.6). This system consists of six ordinary differential equations arriving from the state equations together with six adjoint equations. We use the forward-backward sweep method (FBSM) to solve the differential optimality system generated by the Maximum Principle that characterizes the solution. The numerical computations of the FBSM algorithm were implemented using MATLAB.

The differential equation solver of MATLAB used, is an iterative fourth order Runge-Kutta scheme. The idea exploited by the FBSM is that the initial value

problem of the state equation is solved forward in time with an estimate for the control and costate variables. Consequently, the costate final value problem is solved backwards in time. The iterations run until the convergence is obtained. The FBSM algorithm was discussed in the paper by McAsey *et al.* [38], obtained from the textbook by Lenhart and Workman [31].

The simulation results view in fig 6.1 (a-d) and fig 6.2 (e-g) shows information about HIV/AIDS population dynamics over time (in months) without optimal control strategies and with optimal control, respectively. The simulation is executed using initial conditions (in units of millions) for each state variables and parameters values similar as in the paper of Bhunu *et al.* [6] as follows,

$S(0) = 20.0$, $I_1(0) = 10.0$, $I_2(0) = 35.0$, $I_3(0) = 15.0$, $I_4(0) = 25.0$, $N(0) = 105$, $\Lambda = 0.029$, $\mu = 0.02$, $\delta = 0.1$, $\rho = 0.1$, $\phi_1 = 0.95$, $\phi_2 = 4.01$, $f = 0.85$, $\beta c = 0.015$, $\theta = 0.4$, $h = 0.095$, $h_1 = 0.006$, $h_2 = 0.005$, $h_3 = 0.08$, $h_4 = 0.954$, $\eta_1 = 2$, $\eta_2 = 3$.

Lets take a closer look at the population of infected individuals without optimal control strategy, that is fig 6.1(b) and also at fig 6.2(e), representing the population of infected individuals with optimal control strategy of state variable I_2. We observe that in fig 6.1(b) the population decreases significantly from the $50th$ month than the individuals without control strategy which only start decreasing from $150th$ month in time. This shows that public health educational campaign intervention plays a vital role as the disease decreases much faster. Similarly this can be observed for state variable I_3. In fig 6.2(g), that is, the number of HIV positive people who are sexually inactive (I4), the numerical simulation shows that the number of infected people rises significantly from 25 million to about 105 million when optimal control education is implemented. Thus we can easily conclude that education control strategy gives optimal results.

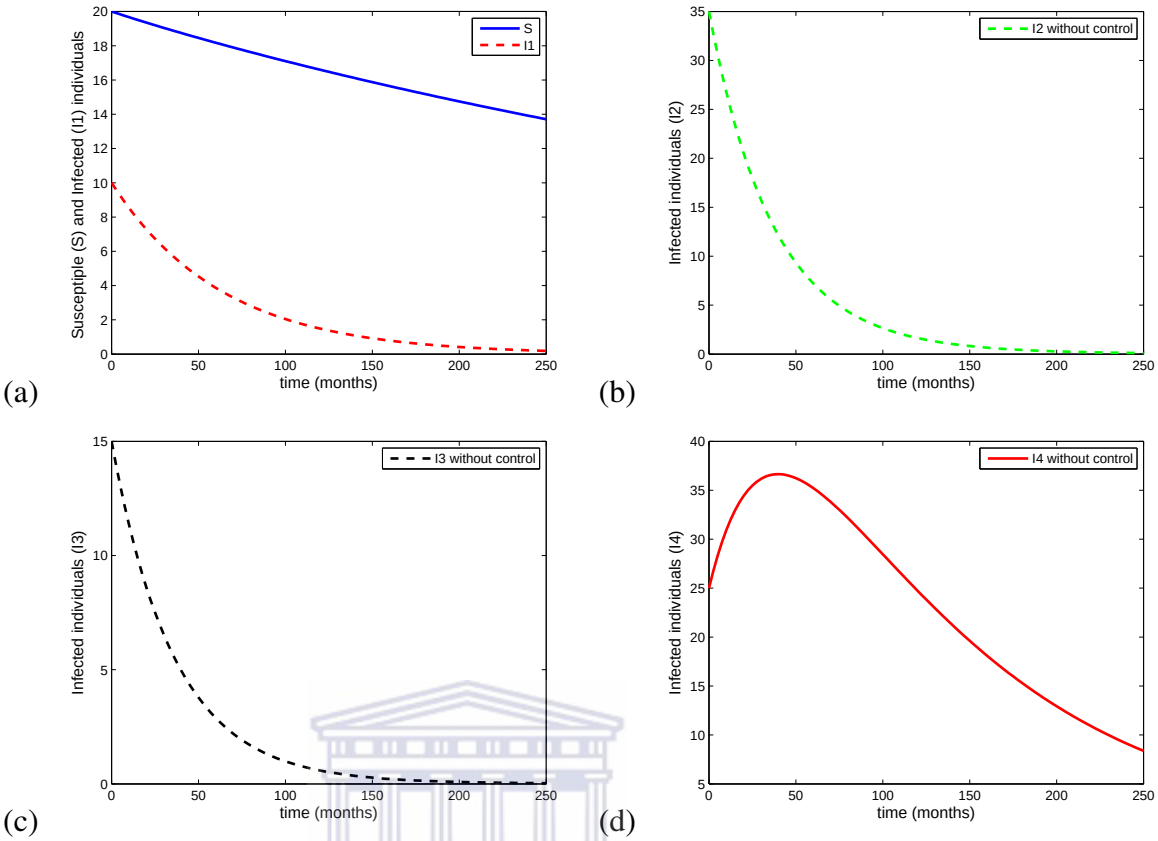

Figure 6.1: Simulation showing HIV/AIDS population dynamics without optimal control strategies.

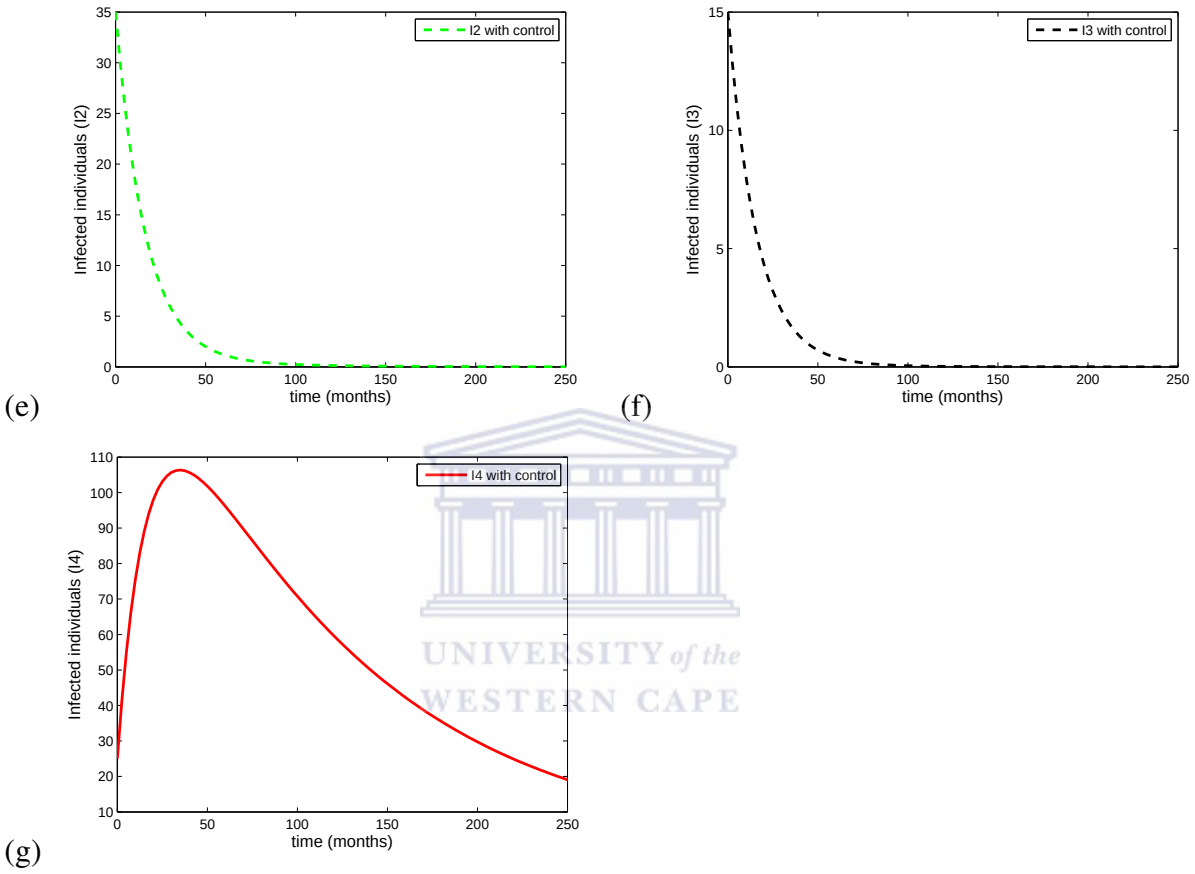

Figure 6.2: Simulation showing HIV/AIDS population dynamics with optimal control strategies.

Chapter 7

Basics on stochastic differential equations

7.1 Introduction

Stochastic differential equations (usually abreviated to SDE's), are used to model diverse phenomena such as fluctuating stock prices or physical systems subject to randomness or noise. Typically, SDEs incorporate random white noise which can be thought of as the "derivative" of Brownian motion. Also, other types of random fluctuations include jump processes. In this dissertation, and on this chapter, our focus is mainly on the Brownian motion which is also known as the Wiener process. We briefly introduce some phenomenon of stochastic differential equations with a focus on epidemiological modelling. This includes, filtered probability space, Brownian motion, Itô's formula, Stochastic stability, etc. A brief background of Brownian motion is provided. Readers are referred to the indicated references for the proofs of the results.

7.2 Filtered probability space

Let $(\Omega, \mathcal{F}, \mathcal{P})$ be a probability space. A *filtration* is a nested family $\{\mathcal{F}_t\}_{t \geq t_0}$ of sub-σ-algebras of $\mathcal{F}$ with $\mathcal{F}_t \subset \mathcal{F}_s \subset \mathcal{F}$ for all $t_0 \leq t < s < \infty$.

The filtration is said to be *right continuous* if $\mathcal{F}_t = \bigcap_{s>t} \mathcal{F}_s$ for all $t \geq 0$.

When the probability space is complete, the filtration is said to satisfy the usual conditions if it is right continuous and $\mathcal{F}_0$ contains all $\mathcal{P}$-null sets.

7.3 Brownian motion

We live in a day and age where human lives are full of uncertainties, as with many natural phenomena. No one can easily foresee what will happen in the near future not even in the next second. Rather than accepting the fact that the future is always uncertain, many models and algorithms have been continually formulated to bring about the prediction of matters involving uncertain elements. One of them is the Brownian model.

Brownian motion is the random movement of particles that are suspended in a fluid medium (a liquid or gas) resulting from their collision with the molecules in the gas or liquid. The phenomenon was discovered by the botanist Robert Brown in 1827, while he was looking through a microscope at particles found in pollen grains in water. He noted that the particles moved to and fro through the water in a random manner but was not able to determine the mechanisms that caused this movement.

It was in 1905 that a quantitative analysis was brought about, when Albert Einstein

in his investigation explained in precise detail how the movement that Brown had observed was a result of the pollen being moved by individual water molecules. This irregular motion of suspended particles subsequently became known as Brownian motion. An amazing number of scientists like Louis Bachelier, Albert Einstein, Norbert Wiener, and Paul Levy, to mention just a few, contributed to the theory of Brownian motion.

The Wiener process describes a random, but continuous movement of a particle, subject to the influence of a large number of chaotically moving molecules of the liquid. Any displacement of the particle over an interval of time as a sum of many almost independent small influences is normally distributed with expectation zero and variance proportional to the length of the time interval.

Brownian motion is a formal concept, which is defined in Definition 7.1 below. The mathematical model of Brownian motion has several real-world applications such as in physics, population dynamics, epidemiology, finance and so on. For instance, in the stock market, Brownian motion is a limiting phenomenon in the random walk theory. Brownian motion and the random walk hypothesis offer a way to understand how markets and economies function, and provides a basis for a speculative view of stock market fluctuations. In basic terms, a "random walk" is essentially a Brownian motion, where the previous change in the value of a variable is unrelated to future or past changes. Other amazing applications of Brownian motion involves its usage in epidemiology, see for example, Mao [36]. Herewith we refer to the book of Mao [36] for a mathematical definition of Brownian motion.

Definition 7.1 Let $(\Omega, \mathcal{F}, \mathcal{P})$ be a probability space with a filtration $\{\mathcal{F}_t\}_{t \geq t_0}$. A (standard) one-dimensional Brownian motion is a real-valued continuous $\mathcal{F}_t$

adapted process $\{\mathcal{B}_t\}_{t\geq t_0}$ with the following properties:

(i) $B_0 = 0$ almost surely;

(ii) for $0 \leq s < t < \infty$, the increment $B_t - B_s$ is normally distributed with mean zero and variance $t - s$;

(iii) for $0 \leq s < t < \infty$, the increment $B_t - B_s$ is independent of $\mathcal{F}_s$;

(iv) B_t is continuous in $t \geq 0$.

For further reading, see the text by Mao [36]. In particular there are obvious higher dimensional analogues of the concept of Brownian motion.

7.4 Itô's formula

Itô's formula is an identity used to find the differential of a time-dependent function of a stochastic process. The basic definition is to evaluate the integral and it plays a key role in stochastic analysis. We hereby establish the one-dimensional Itô formula.

Let $\{\mathcal{B}_t\}_{t\geq t_0}$ be a one dimensional Brownian motion defined on the complete probability space $(\Omega, \mathcal{F}, \mathcal{P})$ adapted to the filtration $\{\mathcal{F}_t\}_{t\geq t_0}$.

Let $\mathcal{L}^1(\mathbb{R}_+; \mathbb{R}^d)$ denote the family of $\mathbb{R}^d$-valued measurable $\{\mathcal{F}_t\}$-adapted process $f = \{f(t)\}_{t\geq t_0}$ such that

$$\int_0^T |f(t)|dt < \infty \qquad \text{almost surely (or a.s.)} \qquad \text{for every } T > 0.$$

Definition 7.2 A one-dimensional Itô process is a continuous adapted process $x(t)$ on $t \geq 0$ of the form

$$x(t) = x(0) + \int_0^t f(s,x(s))ds + \int_0^t g(s,x(s))dB_s,$$

where $f \in \mathcal{L}^1(\mathbb{R}_+;\mathbb{R}^d)$ and $g \in \mathcal{L}^2(\mathbb{R}_+;\mathbb{R}^d)$. We shall say that $x(t)$ has stochastic differential $dx(t)$ on $t \geq 0$ given by

$$dx(t) = f(t,x(t))dt + g(t,x(t))dB_t.$$

Let $V \in C^{2,1}(\mathbb{R} \times \mathbb{R}_+;\mathbb{R})$. Then $V(x(t),t)$ is an Itô process with the stochastic differential given by

$$dV(x(t),t) = \left[V_t(x(t),t) + V_x(x(t),t)f(t) + \frac{1}{2}V_x x(x(t),t)g^2(t)\right]dt + V_x(x(t),t)g(t)dB_t \quad \text{a.s.}$$

Note: $dtdt = 0, dB_i dt = 0, dB_i dB_i = dt, dB_i dB_j = 0$ if $i \neq j$.

For further reading, refer Mao, [36].

7.5 Stochastic stability

There are at least three different types of stochastic stability: stability in probability, moment stability and almost sure exponential stability. We highlight only stability in probability and almost sure exponential stability.

Consider the general n-dimensional stochastic system

$$dX(t) = f(t,X(t))dt + g(t,X(t))dB(t) \tag{7.1}$$

and assume that $f(t,0) = g(t,0) = 0$ for all $t \geq 0$.

7.5.1 Stable in probability

Definition 7.3 The trivial solution of the system (7.1) is said to be stochastically stable or stable in probability if for every pair of numbers $\varepsilon \in (0,1)$ and $r > 0$, there exists a $\delta = \delta(\varepsilon, r, t_0) > 0$ such that

$$P\{|\, x(t;t_0,x_0)\,| < r \; for\; all\; t \geq t_0\} \geq 1-\varepsilon$$

whenever $|\, x_0\,| < \delta$. Otherwise, it is said to be stochastically unstable.

7.5.2 Almost sure exponential stability

Definition 7.4 The trivial solution of the system (7.1) is said to be almost surely exponentially stable if

$$\lim_{t\to\infty} \sup \frac{1}{t} \log |\, x(t;t_0,x_0)\,| < 0$$

for all $x_0 \in \mathbb{R}^d$.

For further reading, see the text by Mao [36].

7.6 Differential operator

Define the differential operator L associated with the system (7.1) by

$$L = \frac{\partial}{\partial t} + \sum_{i=1}^{d} f_i(x,t)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{d}\left[g(x,t)g^T(x,t)\right]_{i,j}\frac{\partial^2}{\partial x_i \partial x_j}.$$

If L acts on a function $V \in C^{2,1}(S_h \times \mathbb{R}_+; \mathbb{R}_+)$, then

$$LV(x,t) = V_t(x,t) + V_x(x,t)f(x,t) + \frac{1}{2}\text{trace}\left[g^T(x,t)V_{xx}(x,t)g(x,t)\right].$$

where

$$V_t = \frac{\partial V}{\partial t},$$
$$V_x = \left(\frac{\partial V}{\partial x_1}, \ldots, \frac{\partial V}{\partial x_d} \right)$$
$$V_{xx} = \left(\frac{\partial^2 V}{\partial x_i \partial x_j} \right)_{d \times d} = \begin{pmatrix} \frac{\partial^2 V}{\partial x_1 \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_1 \partial x_d} \\ \vdots & & \vdots \\ \frac{\partial^2 V}{\partial x_d \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_d \partial x_d} \end{pmatrix}.$$

For further reading, refer to Mao [36].

Chapter 8

An HIV model with stochastic perturbations

8.1 Introduction

The HIV/AIDS pandemic remains extremely dynamic, persistent, and volatile. Travel and migration patterns, particularly when they involve mobility to higher risk environments with higher levels of STD's, have been related to increases in risky sexual behaviours and increase in the transmission of HIV infection [39, 51, 62]. Within this context, HIV infection is subject to some random environmental effects. These random effects have an influence on the spread of diseases on a significant level and in particular the case of HIV transmission [63]. An enormous amount of mathematical research has been carried out on modelling the HIV transmission using ordinary differential equations (ODE's). Usually ode models do not take into account the inherent randomness that influences the HIV transmission. ODE models like other deterministic models, work on averages of effects. One can obtain more realistic results by including stochastic effects in a more explicit way in the model. Thus, in this chapter we propose a system of

stochastic differential equations (sde's) to help us model the randomness that influences the HIV transmission. The concept of Brownian motion is helpful for simulating this inherent randomness.

We proceed to introduce the stochastic perturbations into our proposed model system (5.3). There is no unique way to introduce stochastic perturbation into a compartmental model. It depends heavily on the particular item or parameter which carries the randomness. This means that it is possible to either perturb a specific variable or parameter of a model. This is seen, for example, in a model of Witbooi [63] with only three of the four variables carrying stochastic perturbations while the model of Dalal *et al.* [11] has only two of the four variables perturbed. In our model, stochastic perturbation is introduced on all variables but the susceptibles. We suppose that the susceptibles could be kept safe by their positive behavioral change stemming from direct impact of HIV/AIDS educational awareness campaigns taking place in a community.

8.2 Model formulation

Let us assume having a filtered complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq t_0}, P)$. We consider a *5-dimensional* Wiener process *W(t)* denoted by

$$W(t) = (W_1(t), W_2(t), W_3(t), W_4(t), W_5(t))$$

defined on the filtered probability space.

With the model of Bhunu et al. [6] as a basis, we introduce stochastic perturbations to form a perturbed model as follows.

Let σ_1, σ_2, σ_3, σ_4, and σ_5 denote positive constants serving as the intensities of

the stochastic perturbations in the following sde model system:

$$\begin{cases} dS = ((1-h)\Lambda - (\lambda+\mu)S)dt \\ dI_1 = [h_1\Lambda + \lambda S - (\mu+\theta+\delta)I_1]dt + \sigma_1 I_1 dW_1 \\ dI_2 = [h_2\Lambda + f\delta I_1 - (\mu+\theta+\rho)I_2]dt + \sigma_2 I_2 dW_2 \\ dI_3 = [h_3\Lambda + (1-f)\delta I_1 - (\mu+\theta+\rho)I_3]dt + \sigma_3 I_3 dW_3 \\ dI_4 = [h_4\Lambda + \theta(I_2+I_3) - (\mu+\rho)I_4]dt + \sigma_4 I_4 dW_4 \\ dI_5 = [\rho(I_2+I_3+I_3+I_4) - (\mu+\nu)I_5]dt + \sigma_{I_5} I_5 dW_5 \end{cases} \tag{8.1}$$

8.3 Positivity of solutions

In order for our model to be realistic, its solutions will have to be positive. Let us denote a solution $(S(t), I_1(t), I_2(t), I_3(t), I_4(t), I_5(t))$ of the system (8.1) by $X(t)$. Then system (8.1) can be written in the form:

$$dX(t) = F(X(t))dt + G(X(t))dW \tag{8.2}$$

$F(X(t))$ and $G(X(t))$ being 6×6 matrices. In our quest for feasible solutions we shall let Ω_1 be the subset of paths in Ω for which the system (8.1) has a nonnegative solution over the interval $(0, \infty)$. Therefore,

$$\Omega_1 = \left\{ w \in \Omega | X(t, w(t)), \in \mathbb{R}_+^6 \right\}. \tag{8.3}$$

We illustrate that when we restrict to Ω_1, then the disease free equilibrium point is almost surely exponentially stable. Towards the proof we note the following

remark.

Remark 8.1 We observe that the coefficients of the matrices F and G are all locally Lipschitz. Therefore by [30, 36], equation (8.1) has a solution $X(t,w(t))$ over an interval on $t \in [0,\tau_e]$, where τ_e is the explosion time. The explosion time refers to the maximum stopping time up to which a solution of the equation can be defined. A stopping time is a random variable that describes a rule that is used to decide to stop. The idea is now to prove that $\tau_e = \infty$, a.s., which means that the solution is global *a.s.* A crucial ingredient of towards proving that $\tau_e = \infty$, is to show that there is a certain boundedness.

For the purpose of the following result, Proposition 8.1, we define the following stochastic process:

$$R = -\ln\left(SI_1I_2I_3I_4I_5\right).$$

Proposition 8.1 *For any stopping time τ, the expectation $\mathbb{E}[R(X(\tau,w(\tau))]$ is bounded above.*

Proof. Let us write R in the form:

$$R = -\ln S - \sum_{j=1}^{5} \ln I_j.$$

Then

$$dR = -\frac{1}{S}dS - \sum_{j=1}^{5}\frac{1}{I_j}dI_j + \frac{1}{2}\sum_{j=1}^{5}\frac{1}{{I_j}^2}\left(\sigma_j I_j\right)^2 dt.$$

The latter sde can be expressed as

$$dR = Qdt + \sum_{j=1}^{5}\frac{\sigma_j I_j}{I_j}dW_j,$$

with

$$
\begin{aligned}
Q = &-\frac{1}{S}\big[\,((1-h)\Lambda-(\lambda+\mu)S)\,\big]-\frac{1}{I_1}\big[\,(h_1\Lambda+\lambda S-(\mu+\theta+\delta)I_1)\,\big]\\
&-\frac{1}{I_2}\big[\,(h_2\Lambda+f\delta I_1-(\mu+\theta+\rho)I_2)\,\big]-\frac{1}{I_3}\big[\,(h_3\Lambda+(1-f)\delta I_1-(\mu+\theta+\rho)I_3)\,\big]\\
&-\frac{1}{I_4}\big[\,(h_4\Lambda+\theta(I_2+I_3)-(\mu+\rho)I_4)\,\big]-\frac{1}{I_5}\big[\,(\rho(I_2+I_3+I_3+I_4)-(\mu+\nu)I_5)\,\big]\\
&+\frac{1}{2}\sum_{j=1}^{5}\sigma_j^2.
\end{aligned}
$$

Now we find an upper bound for Q. Among other things, we remove the negative terms towards finding an upper bound.

We proceed as follows:

$$
\begin{aligned}
Q &\leq \frac{1}{S}(\lambda+\mu)S+\frac{1}{I_1}(\mu+\theta+\delta)I_1+\frac{1}{I_2}(\mu+\theta+\rho)I_2\\
&+\frac{1}{I_3}(\mu+\theta+\rho)I_3+\frac{1}{I_4}(\mu+\rho)I_4+\frac{1}{I_5}(\mu+\nu)I_5+\frac{1}{2}\sum_{j=1}^{5}\sigma_j^2\\
&=(\lambda+\mu)+(\mu+\theta+\delta)+(\mu+\theta+\rho)+(\mu+\theta+\rho)\\
&+(\mu+\rho)+(\mu+\nu)+\frac{1}{2}\sum_{j=1}^{5}\sigma_j^2\\
&=Q_0
\end{aligned}
$$

Next we observe that for each j, by the martingale property,

$$\mathbb{E}\big[\int_0^{\tau}\sigma_j I_j dW_j\big]=0.$$

Therefore,

$$\mathbb{E}\big[R(\tau)-R(0)\big]=\mathbb{E}\big[\int_0^{\tau}Q dt+\int_0^{\tau}\sigma_j I_j dW_j\big]\leq Q_0.$$

This completes the proof. ■

Remark 8.2 Using $R(X(\tau, w(\tau)))$ above, by means of Lyapunov method that was also used in [36, 30], one can check whether the solution of (8.1) is global. We assume that the set Ω_1, of all paths for which there are global unique positive solutions, is of measure 1.

8.4 Almost sure stability

Theorem 8.3 *Assume that $h_1 = h_2 = h_3 = h_4 = 0$, and only consider paths $w \in \Omega_1$. If $\mathcal{R}_A < 1$, then the point $(I_1(t), I_2(t), I_3(t), I_4(t), I_5(t))$ almost surely converges to 0.*

Proof. Similarly as in the proof of Proposition 5.5, let a_1, a_2, a_3, a_4, and a_5 be positive constants as below:

$$
\begin{aligned}
a_1 &= 1 \\
a_2 &= \tfrac{1}{m_2}(\beta c \phi_1 + \rho b(1 + \tfrac{2\theta}{\mu+\rho}) \\
a_3 &= \tfrac{1}{m_2}(\beta c \phi_2 + \rho b(1 + \tfrac{2\theta}{\mu+\rho}) \\
a_4 &= \tfrac{2b\rho}{\mu+\rho} \\
a_5 &= \tfrac{1}{2}\rho^{-1} m_1(1 - R_A)[1 + \tfrac{\delta}{m_2}(1 + \tfrac{2\theta}{\mu+\rho})]^{-1}.
\end{aligned}
$$

We consider the stochastic process,

$$z = a_1 I_1(t) + a_2 I_2(t) + a_3 I_3(t) + a_4 I_4(t) + a_5 I_5(t), \tag{8.4}$$

and we note that it suffices to prove that $z(t) \to 0$, almost surely exponential stability, as $t \to 0$.

Let

$$Y(t) = \ln z(t). \tag{8.5}$$

Then for $w \in \Omega_1$, $z(t,w(t)) > 0$ and therefore $Y(t,w(t))$ is well-defined. We prove that $z(t)$ converges exponentially to 0 as $t \to \infty$. We start by calculating the differential dY, using the Itô formula.

$$\begin{aligned}
dY = &\frac{a_1}{z}\big[\lambda S - (\mu+\theta+\delta)I_1\big]dt + \frac{a_1}{z}\sigma_1 I_1 dW_1 - \frac{{a_1}^2}{2z^2}{\sigma_1}^2{I_1}^2 dt \\
&+ \frac{a_2}{z}\big[f\delta I_1 - (\mu+\theta+\rho)I_2\big]dt + \frac{a_2}{z}\sigma_2 I_2 dW_2 - \frac{{a_2}^2}{2z^2}{\sigma_2}^2{I_2}^2 dt \\
&+ \frac{a_3}{z}\big[(1-f)\delta I_1 - (\mu+\theta+\rho)I_3\big]dt + \frac{a_3}{z}\sigma_3 I_3 dW_3 - \frac{{a_3}^2}{2z^2}{\sigma_3}^2{I_3}^2 dt \\
&+ \frac{a_4}{z}\big[\theta(I_2+I_3) - (\mu+\rho)I_4\big]dt + \frac{a_4}{z}\sigma_4 I_4 dW_4 - \frac{{a_4}^2}{2z^2}{\sigma_4}^2{I_4}^2 dt \\
&+ \frac{a_5}{z}\big[\rho(I_2+I_3+I_3+I_4) - (\mu+\nu)A\big]dt + \frac{a_5}{z}\sigma_5 I_5 dW_5 - \frac{{a_5}^2}{2z^2}{\sigma_5}^2{I_5}^2 dt
\end{aligned} \tag{8.6}$$

Using simplifications similarly as in the proof of 5.5 we arrive at :

$$dY = \sum_{i=1}^{5}\frac{1}{z}K_i I_i dt - \sum_{i=1}^{5}\frac{{a_i}^2\sigma_i^2 I_i^2}{2z^2}dt + \sum_{i=1}^{n}\frac{a_i\sigma_i I_i}{z}dW_i \tag{8.7}$$

with

$$\begin{aligned}
K_1 &= c\beta\frac{S(t)}{N(t)} - m_1 + \delta f a_2 - \delta(1-f)a_3 + \rho b \\
K_2 &= \phi_1 c\beta\frac{S(t)}{N(t)} - m_2 a_2 - \theta a_4 + \rho b \\
K_3 &= \phi_2 c\beta\frac{S(t}{N(t)} - m_2 a_3 - a_4\theta + \rho b \\
K_4 &= -(\mu+\rho)a_4 + \rho b \\
K_5 &= -(\mu+\nu)b
\end{aligned}$$

We note that the term

$$-\sum_{i=1}^{5}\frac{{a_i}^2\sigma_i^2 I_i^2}{2z^2}dt$$

is negative. Thus we can write

$$dY \leq \frac{1}{z}(\sum_{i=1}^{5} K_i I_i)dt + \sum_{i=1}^{5} \frac{a_i \sigma_i I_i}{z} dW_i \tag{8.8}$$

We further observe that for each i, $\frac{a_i I_i}{z} \leq 1$. Now we note that very much as in Remark 3.6 of [63], we find that for each i,

$$\limsup_{t\to\infty} \frac{1}{t} \int_{t_0}^{t} \frac{a_i \sigma_i I_i}{z} dW_i = 0. \tag{8.9}$$

Also $Y(t_0)$ is a constant, and so

$$\limsup_{t\to\infty} \frac{Y(t_0)}{t} = 0. \tag{8.10}$$

Therefore

$$\limsup_{t\to\infty} \frac{1}{t} Y(t) \leq \limsup_{t\to\infty} \frac{1}{t} \int_{t_0}^{t} \sum_{i=1}^{5} \frac{1}{z(s)} K_i I_i(s) ds. \tag{8.11}$$

We can deduce that when $\mathcal{R}_A < 1$, then

$$\int_{t_0}^{t} [\sum_{i=1}^{5} K_i \frac{a_i I_i(s)}{z(s)}] ds < 0.$$

Therefore

$$\limsup_{t\to\infty} \frac{1}{t} Y(t) < 0$$

This completes the proof. ■

8.5 Numerical simulations

In order to illustrate Theorem 8.3, the system (8.1) are simulated for various sets of parameters similar as in the paper by Bhunu et al. [6].

$\mu = 0.02$, $\delta = 0.1$, $\phi_1 = 0.2$, $\phi_2 = 2.01$, $f = 0.8$, $\nu = 0.35$, $\theta = 0.00419$, $\rho = 0.1$

The infective individuals (I_1, I_2, I_3, I_4) is plotted against the susceptible individuals (S).

We assume the proportion of influx of infecteds to be $h_1 = 0.0030$, $h_2 = 0.0073$, $h_3 = 0.0061$ and $h_4 = 0.0081$, and initial conditions (in units of millions) are taken as follows:

$S(0) = 80.0$, $I_1(0) = 20.0$, $I_2(0) = 25.0$, $I_3(0) = 18.0$, $I_4(0) = 30.0$, $I_5(0) = 40.0$, $N(0) = 213$.

The simulations of $S(t)$, $I_1(t)$, $I_2(t)$, $I_3(t)$, $I_4(t)$, $I_5(t)$, run over different time horizons as indicated on the graphs. Fig. 8.1 illustrates that the dynamical behaviour described by the deterministic system (5.3), stabilizes at the disease free equilibrium, whenever $\mathcal{R}_A = 0.891 < 1$ (i.e., with $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = \sigma_5 = 0$). Fig. 8.2 also described by the deterministic system (5.3), stabilizes at the endemic level, whenever $\mathcal{R}_A = 1.05 > 1$ (i.e., with $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = \sigma_5 = 0$).

The Fig's. 8.3 - 8.5, illustrate the cases, where the intensity of the white noise $(\sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5)$ verified the conditions of the Theorem (8.3) in cases where $\mathcal{R}_A < 1$ and $\mathcal{R}_A > 1$. Fig. 8.3 supports Theorem (8.3) which asserts that the system (8.1) converges to E_0 only with the condition $\mathcal{R}_A = 0.865 < 1$. In this case, we consider the situation when all the immigrants are susceptible without direct inflow of HIV infectives (i.e. $h_1 = h_2 = h_3 = h_4 = 0$) and the individuals

in pre-AIDS (I_4) class do not take part in sexual interaction as they may either be aware of their infection or sexually inactive. As a result of absence of infective immigrants into the community, the susceptible individuals ultimately increases. Furthermore, the variation of HIV infected individuals (I_1, I_2, I_3, I_4) and that of AIDS patients (I_5) individuals is shown for different rates of inflow of infectives and contact rates of pre-AIDS patients. It is clear that when the pre-AIDS patients do not take part in sexual interaction and the direct inflow of infectives is also restricted (i.e. $h_1 = h_2 = h_3 = h_4 = 0$), the number of infectives decreases, leading to decline in AIDS population. We can see that when the noise $(\sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5)$ is kept sufficiently small, the disease-free equilibrium state E_0 is stochastically stable. Whenever the intensity gets larger, the endemic equilibrium becomes unstable and the solution of the system (8.1) rapidly converges to E_0, as shown in Fig. 8.5.

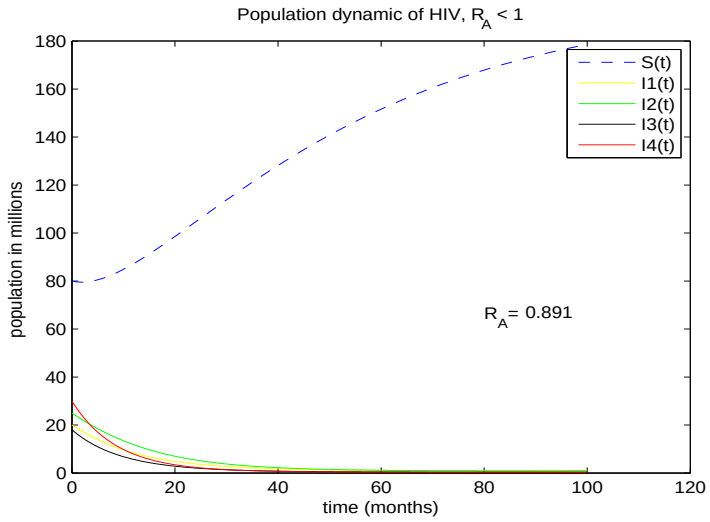

Figure 8.1: Deterministic trajectories of epidemic model (8.1) with parameter values: $\beta = 0.135$, $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = \sigma_5 = 0$.

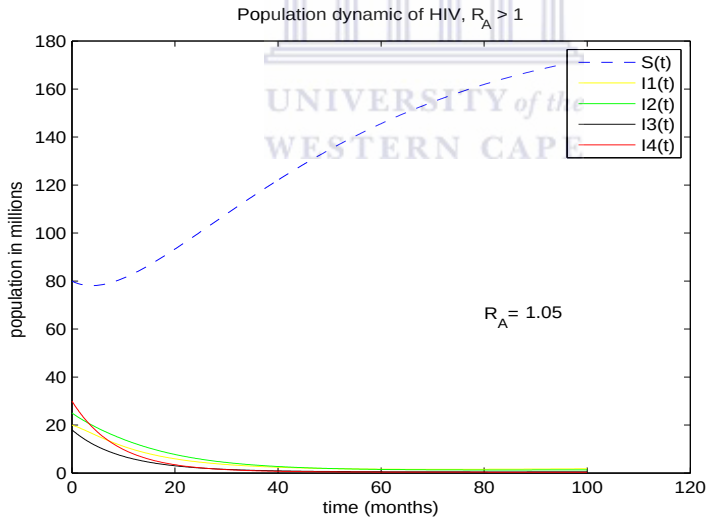

Figure 8.2: Deterministic trajectories of epidemic model (8.1) with parameter values: $\beta = 0.1595$, $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = \sigma_5 = 0$.

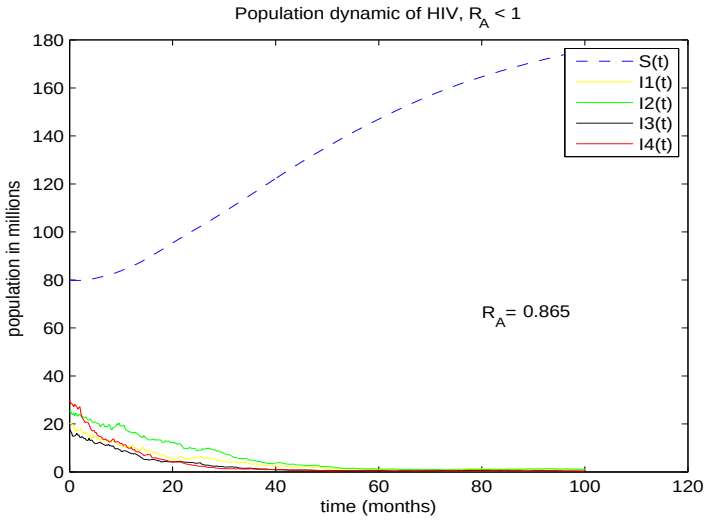

Figure 8.3: Stochastic trajectories of epidemic model (8.1) with parameter values: $\beta = 0.131$, $h_1 = h_2 = h_3 = h_4 = 0$,$\sigma_1 = 0.1637$, $\sigma_2 = 0.1286$, $\sigma_3 = 0.1525$, $\sigma_4 = 0.1587$, $\sigma_5 = 0.1922$.

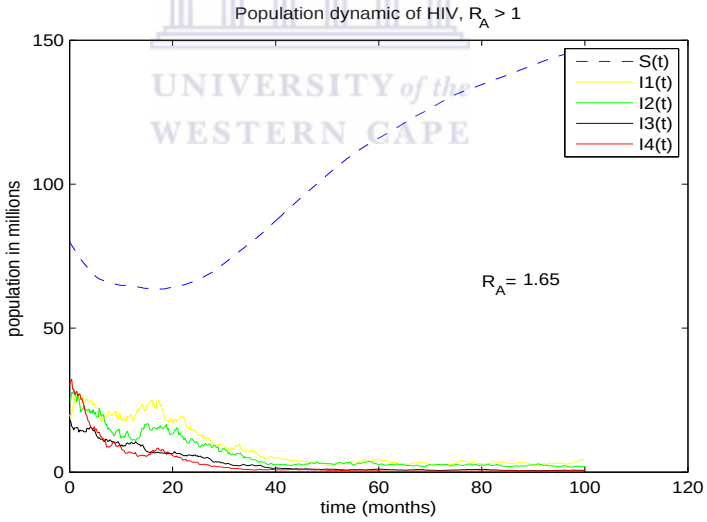

Figure 8.4: Stochastic trajectories of epidemic model (8.1) with parameter values: $\beta = 0.25$, $\sigma_1 = 0.2327$, $\sigma_2 = 0.2864$, $\sigma_3 = 0.2256$, $\sigma_4 = 0.2487$, $\sigma_5 = 0.2185$.

Chapter 9

Conclusion

In this dissertation, a mathematical model to study the escalation of HIV/AIDS with recruitment of infecteds in a population is proposed and analyzed. We assumed that susceptible individuals become infected through sexual engagement with those infected by HIV virus. We studied the impact of public health education awareness campaigns on HIV/AIDS epidemic.

In Chapter 5, we studied the existence and other basic properties of the solutions of the model system (5.3). Using an approach described in papers [15, 45], we establish the positivity and the boundedness of solutions of model system (5.3). We proved the global stability of the disease free equilibrium (E_0) using Lyapunov method. Furthermore, we carried out a numerical study of the model (5.3) to see the effects of certain key parameters on the spread of the disease. We performed the sensitivity analysis of basic reproduction number, $\mathcal{R}_A$, using Mathematica software tool to determine the robustness of $\mathcal{R}_A$ to the model parameter values. That is, to help us identify the parameters that have high impact on $\mathcal{R}_A$.

In Chapter 6, we used the optimal control theory to identify the effort of public health education, that is being rolled-out to control the HIV/AIDS. The aim was to maximize the use of public health education campaigns on the infecteds and

susceptible individuals. In this regard, we used Pontryagin's maximum principle to characterize the control and derive the optimal system. A comparison between optimal control and no control is presented. We can see that the optimal education campaign is much more effective for reducing the number of infected individuals. Observations from numerical simulations on the resulting optimality system, showed that educational programs regarding HIV/AIDS may have a positive impact on the HIV/AIDS epidemic. Educating those infected with HIV/AIDS to increase the awareness about the disease and the protection techniques may cause behavioural changes that can, in turn, reduce HIV/AIDS infections. In order to show the picture of the epidemic, the numbers of susceptible and infected individuals under the optimal control and no control are shown in simulations.

In Chapter 8, we explored a stochastic differential model describing the population dynamics of an HIV/AIDS epidemic. We perturbed the deterministic compartmental model (5.3) by introducing a mutually independent white noise terms into the model. We established the positivity of solutions of the perturbed model (8.1). We proved the almost sure exponential stability of the system (8.1) under suitable conditions of Theorem 8.3. Numerical simulations of the perturbed model (8.1) supported the Theorem 8.3 which asserts that the system (8.1) converges to E_0 only with the condition $\mathcal{R}_A < 1$. Whenever the intensity gets larger, the solution of the system (8.1) converges to E_0 even more rapidly.

To determine the role of recruitment of infecteds in the HIV/AIDS epidemic, we started with a qualitative investigation of the long-term transmission dynamic behaviour of HIV/AIDS in host areas with large influx of infecteds into a population. Our primary finding is that migration does contribute drastically on the overall epidemiology of HIV/AIDS, which has also been confirmed by the simulations with the model.

Literature on public health indicates that migration is increasingly becoming a major factor in the dissemination of HIV. Lack of knowledge and current myths on the disease in both developed and developing countries is a big challenge. These factors exacerbate the HIV/AIDS stigma. Historically, visitors living with HIV infection are usually regarded or treated as a threat to hosting countries. For instance, since 1993, people living with HIV/AIDS were prohibited from visiting or immigrating to the United States. Under the ban which was based on fear rather than fact, visitors or immigrants who were seeking a new residency visa or the renewal of the existing one were forcefully subjected to mandatory HIV/AIDS testing. Those applicants found to be HIV positive were denied the residency visa and were immediately deported. In all these years, only five years ago, Barack Obama, the current president of the U.S.A. instituted a new policy rule to eliminate this travel ban, quote, *"Now, we talk about reducing the stigma of this disease, yet we've treated a visitor living with it as a threat"* [73]. The consequences of stigma and discrimination are everywhere. To mention just a few, some people are rejected by family, peers and the wider community, while others face poor treatment in healthcare and education settings and so forth. These all limit access to HIV testing, treatment and other available HIV preventive services. In order to combat HIV/AIDS pandemic, we need to reduce its stigma. More research on collaborative evidence-based interventions in terms of public health awareness campaigns aimed at reducing the stigma to prevent the infection is needed. This will encourage everyone, immigrant or not to get tested and receive a treatment and preventive services. It is likely that this may also improve the overall rate of HIV diagnosis especially among minority populations.

Our proposed model serves as an important tool that can help quantify these aforementioned factors which influence the spread of HIV infection. In this regard, this model provides an appropriate optimal control strategy aimed at optimizing HIV

testing, prevention, and public health education roll-out intervention programs, at a least cost possible for the nations experiencing high volumes of infecteds. Numerical results are provided. Considering the subjectivity of HIV infection to some other random environmental factors, our proposed model have also included the stochastic perturbations to provide a better understanding of the disease and predictions about the disease behaviour. Numerical simulations illustrating these predictions are also presented. As a follow-up on this work, it will also be helpful to bring about a good parameter estimate that can be used to characterize an HIV stigma to help to curb the further spread of the disease on a population as a whole.

Bibliography

[1] G.J. Abiodun, N. Marcus, K. Okosun, P.J. Witbooi. *A Model for control of HIV/AIDS with parental care*. Vol. **06** (2013), [15 pages]. DOI: 10.1142/S179352451350006X.

[2] R.P. Agarwal, D. O'Regan. *Ordinary and partial differential equations: with special functions, fourier series, and boundary value problems*. Springer Science and Business Media, LLC 2009.

[3] L.J.S. Allen. *An Introduction to mathematical biology*. Prentice Hall, USA (2007).

[4] L.J.S. Allen. *An Introduction to stochastic epidemic models*. Department of Mathematics and Statistics Texas Tech University 79409-1042, USA (2008).

[5] Z. Bai, D. Liu. Modeling seasonal measles transmission in China. *Commun Nonlinear Sci Numer Simulat*. Vol. **25** (215), 19-26.

[6] C.P. Bhunu, S. Mushayabasa, H. Kojouharov, J.M. Tchuenche. Mathematical analysis of an HIV/AIDS model: impact of educational programs and abstinence in sub-Saharan Africa. *J. Math. Model. Algorithms*. Vol. **10**, 31-55.

[7] F. Brauer, P. van den Driessche. Models for Transmission of Disease with Immigration of Infectives. *Mathematical Biosciences*. Volume **171** (1995), 143-154.

[8] F. Brauer, P. van den Driessche. *Mathematical epidemiology: mathemtical biosciences subseries, lecture notes in mathematics*. Springer-Verlag, Berlin, Heidelberg, 2008.

[9] F. Brauer, P. van den Driessche. Models for transmission of disease with immigration of infectives. *Mathematical Biosciences*. Volume **171** (1995), 143-154.

[10] J.C. Butcher. *Numerical methods for ordinary differential equations*. John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England.

[11] N. Dalal, D. Greenhalgh, X. Mao. Stochastic model of AIDS and condom use. *Journal of Mathematical Analysis and Applications*. Vol. **325** (2007), 36-53.

[12] D.J. Dalley, J. Gani. *Epidemic modelling: an introduction*. Cambridge University Press (1997).

[13] F. Docquier, C. Vasilakis, D. Tamfutu Munsi. International migration and the propagation of HIV in Sub-Saharan Africa. *Journal of Health Economics*. Vol. **35** (2014), 20-33.

[14] D. Fassin. Embodied History: Uniqueness and exemplary of South African AIDS. *African Journal of AIDS Research*. Vol. **1** (2002), 65-70.

[15] K. Hattaf, N. Yousfi. Mathematical model of the influenza A (H1N1) infection. *Advanced Studies in Biology*, Vol. **1** (2009), no. 8, 383-390.

[16] J.M. Heffernan, R.J. Smith and L.M. Wahl. Perspectives on the basic reproductive ratio. *J. R. Soc. Interface*. Vol. **2** (2005), 281-293.

[17] Y.H. Hsieh, C. H. Chen. Modelling the social dynamics of a sex industry: its implications for spread of HIV/AIDS. *Bull. Math. Biol*. Vol. **66** (2004), 143-166.

[18] N. Hussaini, M. Winter. Qualitative assessment of the role of public health education program on HIV transmission dynamics. *Mathematical Medicine and Biology*. Vol. **28** (2011), 245-270.

[19] A.B. Haider. AIDS epidemic worldwide and the millennium development strategies: A light for lives. *HIV AIDS Review*. Vol. **11** (2012), 87- 94.

[20] M. Iannelli, F.A. Milner, A. Pugliese, M. Gonzo. The HIV/AIDS epidemics among drug injectors: A study of contact structure through a mathematical model. *Mathematical Biosciences*. Vol. **139** (01 January 1997), no. 1, 25-58.

[21] T. Immonen, R. Gibson, T. Leitner, M.A. Miller, E.J. Arts, E. Somersalo, D. Calvetti. A hybrid stochasticdeterministic computational model accurately describes spatial dynamics and virus diffusion in HIV-1 growth competition assay. *Journal of Theoretical Biology*. Vol. **312** (2012), 120-132.

[22] International Organization for Migration (IOM)/ World migration Report 2011. International organization for migration, 17 route des Morillons, 1211 Geneva 19, Switzerland. http://www.iom.int.

[23] Z. Jia, G. Tang, Z. Jin, C. Dye, S.J. Vlas, X. Li, D. Feng, L. Fang, W. Zhao, W. Cao. Modeling the impact of immigration on the epidemiology of tuberculosis. *Theoretical Population Biology*. Vol. **73** (2008), 437-448.

[24] L. Johnson, D. Budlender. HIV risk factors: a review of the demographic socio-economic, biomedical and behavioural determinants of HIV prevalencein South Africa, Cape Town. Center for Actuarial Research. University of Cape Town. 2002.

[25] L. Johnson. An Introduction to Mathematics of HIV/AIDS modelling. Center for Actuarial Research. 2004.

[26] Joint United Nations Programme on AIDS(UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2011.

[27] Joint United Nations Programme on AIDS(UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2013.

[28] M.J. Keeling, L. Danon. Mathematical modelling of infectious diseases. *British Medical Bulletin*. Vol. **92** (2009), 33-42.

[29] C.M. Kribs-Zaleta, M. Lee, C. Roman, S. Wiley, C.M. Hernandez-Suarez. The Effect of the HIV/AIDS Epidemic on Africa's Truck Drivers. *Math. Bios. Engg*. Vol. **2** (2005), 771-788.

[30] A. Lahrouz, L. Omari, D. Kiouach. Global analysis of a deterministic and stochastic nonlinear SIRS epidemic model. *Nonlinear Analysis: Modelling and Control*. Vol. **16** (2011), No. 1, 59-76.

[31] S. Lenhart, J. Workman. *Optimal control applied to biological models*. Mathematical and Computational Biology Series, Chapman and Hall/CRC, London, UK, 2007.

[32] V. Lima, K. Fernandes, B. Rachlis, E. Druyts, J. Montaner, R. Hogg. Migration adversely affects antiretroviral adherence in a population-based cohort of HIV/AIDS patients. *Social Science Medicine*. Vol. **68** (2009), 1044-1049.

[33] M. Lurie, A. Harrison, D. Wilkinson, S.A. Karim. Circular migration and sexual networking in rural KwaZulu-Natal: Implications for the spread of HIV and other sexually transmitted diseases. *Health Transition Review*, Supplement 3 to Volume **7** (1997), 17-27.

[34] M. Lurie. Migration and AIDS in South Africa: a review. *South African Journal of Science*. Vol. **96** (2000), 343-347.

[35] M. Liu, C. Bai, K. Wang. Asymptotic stability of a two-group stochastic SEIR model with infinite delays. *Commun. Nonlinear. Sci Numer. Simulat.*. Vol. **19** (2014), 3444-3453.

[36] X. Mao. *Stochastic differential equations and applications*, Horwood Chichester, 1997.

[37] R.M. May, R.M. Anderson. Transmission dynamics of HIV infection. *Nature*. Vol. **3426** (1987), 137 - 142.

[38] M. McAsey, L. Mou, W. Han. Convergence of the forward-backward sweep method in optimal control. *Comput Optim Appl*. Vol. **53** (2012), 207226.

[39] Z.A. Memish, A.O. Osoba. International Travel and Sexually Transmitted Diseases. *Travel Medicine and Infectious Disease*. Vol. **4** (2006), 86-93.

[40] S.J. Merrill. The stochastic dance of early HIV infection. *Journal of Computational and Applied Mathematics*. Vol. **184** (2005), 242-257.

[41] C.J. Mode, C.K. Sleeman. A new design of stochastic partnership models for epidemics of sexually transmitted diseases with stages. *Mathematical Biosciences* Vol. **156** (1999), 95-122.

[42] C.J. Mode, C.K. Sleeman. An algorithmic synthesis of the deterministic and stochastic paradigms via computer intensive methods. *Mathematical Biosciences*. Vol. **180** (2002), 115-126.

[43] Z. Mukandavire, W. Garira and J. Tchuenche. Modeling effects of public health educational campaigns on HIV/AIDS transmission dynamics. *Applied Mathematical Modelling*. Vol. **33** (2009), 2084 - 2095.

[44] R. Naresh, A. Tripathi, D. Sharma. Modelling and analysis of the spread of AIDS epidemic with immigration of HIV Infectives. *Mathematical and Computer Modelling*. Vol. **49** (2009), 880-892.

[45] F. Nyabadza. Analysis of an HIV/AIDS Model with public-health information campaigns and individual withdrawal. *Journal of Biological Systems*, Vol. 18, No. **2** (2010), 357-375.

[46] K.O. Okosun, O. D. Makinde, I. Takaidza. Analysis of recruitment and industrial human resources management for optimal productivity in the presence of the HIV/AIDS epidemic. *Journal of Biological Physics*. Volume **39** (January, 2012), Issue 1, 99-121.

[47] K.O. Okosun, O. D. Makinde. A co-infection model of malaria and cholera diseases with optimal control. *Mathematical Biosciences*. Vol. **258** (2014), 19-32.

[48] D. Okuonghae. A note on some qualitative properties of a Tuberculosis differential equation model with a time delay. *Differ. Equ. Dyn. Syst*. Vol. **23 (2)** (April 2015), 181194.

[49] E. Pienaar, M. Lerm. A mathematical model of the initial interaction between Mycobacterium tuberculosis and macrophages. *Journal of Theoretical Biology*. Vol. **342** (2014), 23-32.

[50] G. Ramjee, E. Gouws. Prevalence of HIV among truck drivers visiting sex workers in KwaZulu-Natal, South Africa. *Journal of the American Sexually Transmitted Disease Association*. Volume **29** (2002), Issue 1, 44-49.

[51] M.G. Shedlin, E. Drucker, C.U. Decena, S. Hoffman, G. Bhattacharya, S. Beckford, R. Barreras. Immigration and HIV/AIDS in the New York metropolitan area. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*. Vol. **83** (2006), No. 1.

[52] A.K. Shetty, G. Powell. Children orphaned by AIDS: a global perspective. Immigration and HIV/AIDS in the New York Metropolitan Area. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*. Vol. **83** (2006), No. 1.

[53] E. Shim. A Note on epidemic models with infective immigrants and vaccination. *Math. Bio. Engg*. Vol. **3** (2006), 557-566.

[54] R.W. Shonkwiler, J. Herod. *Mathematical Biology: An Introduction with Maple and Matlab*. Springer (2009).

[55] C.K. Sleeman, C.J. Mode. A methodology study on fitting a nonlinear stochastic model on the Aids epidemic in Philadelphia. *Math. Comput. Modelling* Vol. **26** (1997), No. 2, 33-51.

[56] C.K. Sleeman, C.J. Mode. A computer exploration of some properties of non-linear stochastic partnership models for sexually transmitted diseases with stages. *Mathematical Biosciences*. Vol. **156** (1999), 123-145.

[57] Statistics South Africa. Mid-year population estimates. Statistical Release P0302. 2013.

[58] H.R. Thieme. *Mathematics in population biology*. Princeton University Press, Princeton and Oxford (2003)

[59] J. Tumwiine, J.Y.T. Mugisha, L.S. Luboobi. A Host-vector model for malaria with infective immigrants. *J. Math. Anal. Appl*. Vol. **361** (2010), 139149.

[60] United Nations Development Report. 2013.

[61] P. van den Driessche and J. Watmough. Reproduction numbers and sub threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*. Vol. **180** (2002), 29-48.

[62] B.J. Ward, P. Plourde. Travel and sexually transmitted infections. *Journal of Travel Medicine*. Volume **13** (2006), Issue 5, 300-317.

[63] P. Witbooi. Stability of an SEIR epidemic model with independent stochastic perturbations. *Physica A*. Vol. **392** (2013) 4928 - 4936.

[64] K. Wood. F. Maforah. R. Jewkess. He forced me to love him: Putting violence on adolescent sexual agendas. *Soc Sci Med*. Vol. **47(2)** (July 1998), 233-42.

[65] 2012 International Bank for Reconstruction and Development / The World Bank 1818 H Street NW, Washington DC 20433. Internet: www.worldbank.org.

[66] The World Health Organization Report 2012.

[67] World economic forum on travel and tourism competitiveness index report, 2013.

[68] Y. Zhou, K. Khan, Z. Feng, J. Wu. Projection of Tuberulosis Incidence with Increasing Immigration Trends. *Journal of Theoretical Biology*. Vol. **254** (2008), 215-228.

[69] http://www.saylor.org/site/wp-content/uploads/2011/06/Black-Death.pdf

[70] http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html

[71] http://www.iom.int/jahia/webdav/site/myjahiasite/shared/shared/mainsite /events/docs/2005_AIDS_Population_Mobility.pdf

[72] http://www.collectionscanada.gc.ca/eppp-archive/100/201/300/cdn_medical_association/cmaj/vol-152/1826e.htm.

[73] http://cis.org/feere/hivban