Mathematical Analysis of Models of HIV Epidemiology

by

Oluwaseun Yusuf Sharomi

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Department of Mathematics

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Winnipeg

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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Abstract

The thesis is based on the design and analysis of suitable compartmental deterministic models for the transmission dynamics and control of HIV/AIDS in a population. A basic model, which incorporates the use of antiretroviral drugs for a single HIV strain, is designed first of all. In addition to incorporating treatment-related benefits (such as slow progression to AIDS and reduced transmissibility of treated individuals, in comparison to untreated people), the model includes the transmission of HIV by individuals in the AIDS stage of infection (the latter is often erroneously ignored in HIV transmission modelling). The model is used to evaluate various treatment strategies, such as the universal treatment of infected individuals (regardless of their stage of infection) and the targeted treatment of those with or without symptoms only. Using Lyapunov funtion theory, in conjunction with the LaSalle Invariance Principle, the model is shown to have a globally-asymptotically stable disease-free equilibrium whenever its associated reproduction number is less than unity, and has a unique locally-asymptotically stable endemic equilibrium whenever this number exceeds unity. The unique endemic equilibrium is shown to be globally-asymptotically stable for a special case. It is further shown that the treatment-free equivalent of the model exhibits similar qualitative dynamics. Numerous simulations of the model were carried out using a reasonable set of parameter values. The simulations show that the universal administration of the antiretroviral drugs is more beneficial, in terms of reducing the morbidity and HIV-related mortality, than its targeted use to either people with or without clinical symptoms of AIDS.

The treatment model is extended to include the dynamics of two HIV strains, namely a wild strain, which is susceptible to drug treatment, and a resistant strain. The global stability of the disease-free equilibrium, and the local stability of the associated boundary and co-existence equilibria are established. It is shown that the treatment-free equivalent of the model can have a continuum of co-existence equilibria, while the treatment model can exhibit two co-existence endemic equilibria, under certain conditions.

Finally, a model for assessing the potential impact of an imperfect HIV vaccine, which incorporates the differential infectivity and staged-progression properties of HIV disease as well as various vaccine characteristics, is designed and analyzed. In addition to showing the presence of backward bifurcation in the model, the study shows that the widespread use of an imperfect HIV vaccine can have detrimental impact in the community if the use of the vaccine makes a certain epidemiological quantity, known as "*vaccine impact*", negative.

Overall, this study shows that the prospect of effectively controlling the spread of HIV in a population using antiretroviral drugs and/or a vaccine is bright.

Acknowledgements

I would like to express my gratitude and appreciation to my supervisor, Professor Abba B. Gumel of the Department of Mathematics, University of Manitoba, for accepting me as a masters student and for his valuable guidance, comments and encouragement in the preparation of this thesis. He is like a father to me. I wish to thank my friend Chandra Nath Podder, a fellow graduate student in our group, for the many valuable discussions we have had over the course of this work. I also wish to express my profound gratitude to the Institute of Industrial Mathematical Sciences, together with the Department of Mathematics, of the University of Manitoba for the financial support during my M.Sc. program. I am grateful to my Thesis Committee members, namely Dr. J. Arino (Department of Mathematics), Dr. C. Bowman (Institute for Biodiagnostics) and Dr. S. Lui (Department of Mathematics) for their valuable comments and suggestions. I am grateful to the graduate students in the department for their friendship, particularly Julius Ehiemua (also a member of our research group). I am also grateful to the teaching and secretarial staff of the department, especially Professors Tom Berry and Joe Williams, for their support. I am thankful to Pastor (Dr.) Deborah and her husband, Dr. Sunday Olukoju, for their tireless support.

Finally, I am indebted to my mother, Adenike Sharomi, my brother Oluwakemi Sharomi and my other siblings for the sacrifices they have made in ensuring my success, and for always been there for me.

Dedication

To my lovely mother, Adenike Sharomi.

Contents

List of Tables

List of Figures

Glossary

Abbreviation	Meaning
LAS	Locally-asymptotically stable
GAS	Globally-asymptotically stable
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
AIDS	Acquired immune deficiency syndrome
HIV	Human immuno-deficiency virus
ARVs	Anti-retroviral drugs
HAART	Highly-active anti-retroviral therapy
SP	Staged-progression
DI	Differential infectivity
DISP	Differential infectivity and staged-progression

Chapter 1

Introduction/Background

1.1 Public health and socio-economic impact

Since its inception in the 1980s, the human immono-deficiency virus (HIV), the causative agent of the acquired immune deficiency syndrome (AIDS), continues to pose an unprecedented threat to global health and human development. An estimated 34−46 million people are currently living with HIV/AIDS. More than 20 million people have died from AIDS-related causes during the last 20 years, of which an estimated 3 million deaths occurred in 2003 alone [26]. AIDS is now the leading cause of death in sub-Saharan Africa and the fourth leading cause of death globally. The pandemic has cut life expectancy significantly in many countries in sub-Saharan Africa. For example, life expectancy in Botswana decreased from 65 years in 1985−1990 to 40 years in 2000−2005 [92].

In addition to being a serious public health problem, HIV has far reaching conse-

quences to all social and economic sectors of society. It exacerbates poverty, reduces educational opportunities, devastates the workforce, creates large numbers of orphans, and exerts tremendous pressure on already limited health and social services [86, 90]. For example, HIV/AIDS has cut annual growth rates in Africa by 2−4% per year [24]. The annual economic loss (slower economic growth) as a result of HIV-related death or disability in 50 countries (US, Russia, 5 in Asia, 8 in Latin America, and 35 in sub-Saharan Africa) during 1992−2000 is estimated at $25 billion [31].

HIV is transmitted in humans *via* a number of mechanisms including sexual, sharing contaminated needles by HIV drug users, mother-to-child, blood transfusion etc. Numerous anti-HIV preventive and therapeutic strategies have been embarked upon aimed at slowing the spread of the disease. These include condom use, voluntary HIV testing, education and counselling about safer sex practices, and the use of antiretroviral drugs (ARVs). Although the widespread use of ARVs, especially the highly-active antiretroviral therapy (HAART), in nations that can afford them has resulted in a significant decline in HIV cases, these drugs are still not generally accessible in resource poor nations. The World Health Organizations (WHO) reported that only 5% of people who need ARVs in developing nations actually have access to these drugs in 2003 [91]. Further, the widespread use of ARVs is associated with a number of side effects, and toxicity, in addition to the danger of the emergence of ARV-resistant strains. The use of an effective HIV prophylactic vaccine is widely considered to be the "best" way to slow or curtail the HIV/AIDS pandemic [19, 27]. However, it is unlikely that a highly-effective vaccine will be available soon. Instead, the current expectation is that

the most likely vaccine that will be developed in the foreseeable future may have lower efficacy in protecting against infection and/or result in a shorter duration of protection in successfully immunized people than most traditional vaccines. In other words, a future HIV vaccine is expected to be imperfect.

Owing to the huge HIV-related public health and socio-economic burden globally, coupled with the continuing spread of the disease (especially in resource-poor nations), the need for the development and implementation of effective and affordable preventive and therapeutic strategies for the worldwide control of HIV infection has become ever more pressing. The main aim of this thesis is to use mathematical modeling, based on the current knowledge of HIV biology and epidemiology, to gain insights into the transmission dynamics of HIV/AIDS in a population, and to evaluate control strategies. Although there are numerous anti-HIV preventive and therapeutic strategies, such as the ones enumerated above as well as other non-traditional methods (e.g., male circumcision [4, 5, 7, 67, 74, 76, 79, 85, 88] and the use of microbicides [6]), this study will focus on evaluating the impact of using ARVs and a putative HIV vaccine. A brief review of some of the key biological and epidemiological features of HIV disease, relevant to the modelling component of this thesis, is provided below.

1.2 Replication cycle (staged-progression)

HIV infects and replicates primarily in $CD4^+$ T cells. The virus enters the cells by fusion after binding to the CD4 glycoprotein in conjunction with a chemokine receptor. The virus also infects other CD4-bearing cells, such as monocytes, tissue macrophages

and dendritic cells, that replicate HIV inefficiently relative to $CD4^+$ T cells. HIV replication is essential for disease progression to AIDS. The typical course of HIV infection proceeds *via* the following three sequential stages:

1.2.1 Primary stage

Upon introduction into an individual, HIV infects both resting and activated $CD4^+$ T cells. However, it integrates and multiplies only in activated $CD4^+$ T cells. Initially, such replication proceeds virtually unopposed by the immune system. As a result, the rate of HIV replication is far greater than that of its clearance. This viral influx primes the immune system, eventually triggering the activation of HIV-specific B cells (antibody producing cells) and the clonal expansion and differentiation of CD8+ T cells into anti-HIV cytotoxic T lymphocytes (CTLs). This rise in HIV concentration (viremia) triggers the next round of activation of HIV-specific memory and residual naive $CD4^+$ T, $CD8^+$ T and B cell populations, resulting in the appearance of anti-HIV CTLs in the blood of the HIV-infected individual within 1 to 4 weeks, and anti-HIV antibodies within 8 to 12 weeks of initial infection. Although this anti-HIV immune response effectively suppresses HIV viremia, by reversing the rates of HIV replication and its clearance, it fails to completely eliminate HIV.

1.2.2 Asymptomatic (chronic) stage

A typical HIV infection is characterized by the appearance of a vigorous anti-HIV immune response usually capable of suppressing HIV replication leading to a dramatic

decline of HIV in circulation with a corresponding rise in the numbers of $CD4^+$ T cells. The anti-HIV CTLs play a crucial role in this process. The immune response, however, fails to block HIV replication completely. Such failure is characterized by the persistence of low levels of viral replication and a gradual, but steady, decline in $CD4^+$ T cells in the absence of clinical disease. This asymptomatic phase may last for many years or over a decade. In this phase, the rate of clearance of HIV is consistently greater than that of its replication.

1.2.3 AIDS stage

Although levels of HIV in circulation remain low during the asymptomatic phase, a gradual but steady decline in the numbers of $CD4^+$ T cells continues. Once the $CD4^+$ T cell numbers reach below a threshold, the HIV concentration in circulation begins to rise rapidly (reaching levels $> 10^6$ virions/ml blood) and the patient exhibits a precipitous loss of immunity to many other pathogens. This last phase of HIV disease is referred to as AIDS, during which the patient invariably acquires life-threatening opportunistic infections that lead to death. A notable feature of this phase of disease is the persistence of high concentrations of HIV in circulation with minimal $CD4^+$ T cell counts. Further information on modelling the immuno-pathogenesis of HIV can be found in [37, 41, 71, 72], and the references therein.

Figure 1.1 [71] depicts a schematic description of these stages. The early peak in viral load corresponds to primary infection. This is followed by a long asymptomatic period, during which the viral load changes slightly (lasting over 10 years on average).

Ultimately, the viral load increases and the symptoms of full-blown AIDS appear.

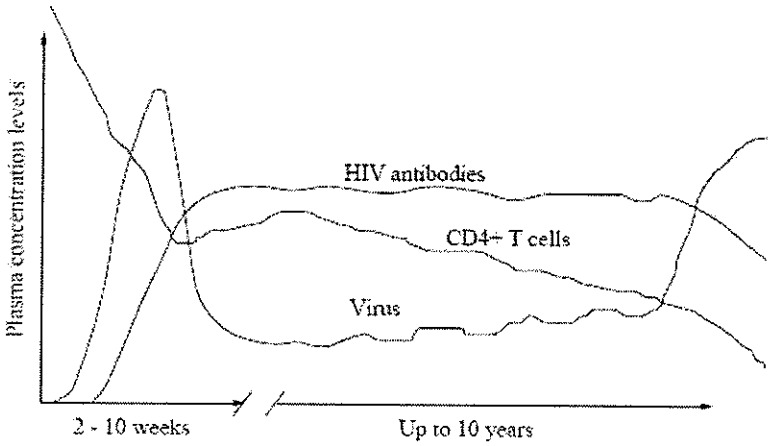


Figure 1.1: Time course of HIV infection in a typical adult.

1.3 Differential infectivity

In addition to the staged-progression property described in Section 1.2, another notable feature of HIV disease is differential infectivity [49]. Studies of HIV RNA in infected individuals show that viral levels vary widely between individuals, with individuals having higher viral loads during the chronic phase tending to develop AIDS more rapidly (because RNA levels are correlated with infectiousness [33]). The differential infectivity of HIV can then be defined as the variations in infectiousness, and the increase in the average progression time from infection to AIDS that goes along with a decreased viral load during the chronic phase of infection [49].

1.4 Incidence functions

Disease incidence in a community is defined in terms of the number of new infections generated per unit time in that community. Incidence, in disease models, is generally characterized by an incidence function (a function that describes the mixing pattern within the community). Various types of incidence functions have been used in disease modelling (see, for example, [47]), and the choice of such function can play an important role in the dynamics of the disease. Here, a general construction of incidence function required for modelling is given. Let $S(t)$, $Y(t)$ and $N(t)$ denote the number of susceptible individuals, infected individuals and the total population size at time t, respectively. Suppose $\beta(N)$ is the effective contact rate (i.e., the average number of contacts sufficient to transmit infection) per person per unit time. Then, $\beta(N)Y/N$ is the average number of contacts with infectious individuals a susceptible individual makes per unit time. Thus, the number of new cases coming from all susceptible individuals (S) is λS, where $\lambda = \beta(N)Y/N$ is the force of infection. If $\beta(N) = \beta$, a constant, then λS is referred to as a *standard incidence function.* When $\beta(N) = \beta N$ (that is, the contact rate depends on the total population), then λS is called *mass action incidence* [43, 46, 47]. It is worth stating that standard incidence models with constant total population ($N(t)$), such as the model in [54], are essentially mass action models. The aforementioned two incidence formulations (standard and mass) appear to be the most widely used in the mathematical epidemiology literature. Although some studies have suggested that the standard incidence formulation is more realistic for human diseases [2, 3], the choice of one over the other really depends on the disease being modeled

and, in some cases, the need for analytical tractability. Both standard incidence (see, for example, [8, 26, 49, 65]) and mass action incidence ([11, 36, 54, 71, 80]) have been used to model HIV epidemiology and immuno-pathogenesis. Standard incidence is used throughout this thesis, except in a single instance in Chapter 5, where a new mathematical fact (associated with mass action incidence) is illustrated.

1.5 Reproduction numbers

Compartmental mathematical models have been widely used to gain insights into the spread and control of emerging and re-emerging human diseases, dating back to the pioneering work of Bernoulli (on modelling the dynamics of smallpox) in 1760 and the likes of Ross, Kermack and McKendrick and others (see [2, 3, 47] and the references therein). The dynamics of these models tend to generally be completely determined by a threshold quantity, known as the *basic reproduction number* (denoted by $\mathcal{R}_0$), which measures the average number of new cases an index case can generate in a completely susceptible population [3, 22, 47]. Typically, when $\mathcal{R}_0$ is less than unity, a small influx of infected individuals will not generate large outbreaks, and the disease dies out in time (in this case, the corresponding disease-free equilibrium (DFE) is locally asymptotically stable (LAS)). On the other hand, the disease will persist if $\mathcal{R}_0$ exceeds unity, where a stable endemic equilibrium point (EEP) exists. This phenomenon, where the DFE and an EEP exchange their stability at $\mathcal{R}_0 = 1$, is known as *forward bifurcation* (or transcritical bifurcation). A schematic description is given in Figure 1.2.

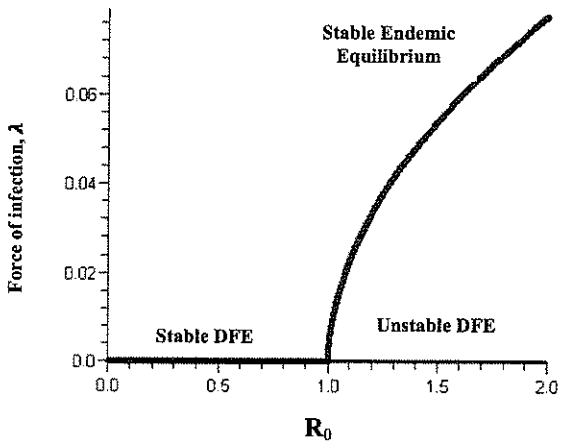


Figure 1.2: Forward bifurcation diagram

This phenomenon was first noted by Kermack and McKendrick [53], and has been observed in many disease transmission models ever since (see [14, 15, 16, 25, 44, 47, 55] and the references therein). In general, for models that exhibit forward bifurcation, the requirement $\mathcal{R}_0 < 1$ is necessary and sufficient for disease elimination (i.e., the number of infectives at steady state depends continuously on $\mathcal{R}_0$). In the presence of a control measure, such as the use of a vaccine in the community, the dynamics of the model is governed by another threshold quantity, known as the *effective reproduction number*, denoted by $\mathcal{R}_{eff}$. The threshold, $\mathcal{R}_{eff}$, represents the average number of secondary cases a typical infected individual will generate in a population where a fraction of the susceptible individuals are vaccinated. A number of studies have shown that whilst $\mathcal{R}_{eff} < 1$ is necessary for disease elimination, this requirement may not be sufficient. This is owing to the phenomenon of *backward bifurcation*, where a stable endemic equilibrium co-exists with a stable disease-free equilibrium for $\mathcal{R}_{eff} < 1$.

This phenomenon has been observed in numerous disease transmission models such as those for behavioural responses to perceived risks [40], multiple groups [14, 15, 80], vaccination [1, 26, 54], and transmission of *mycobacterium tuberculosis* with exogenous re-infection [16, 30]. In a backward bifurcation, disease control is only feasible if $\mathcal{R}_{eff}$ is reduced further to values below another sub-threshold less than unity. The phenomenon of backward bifurcation has important public health implication, since it renders the classical requirement of reproduction number being less than unity to be insufficient (in general) for disease elimination. A schematic description of the backward bifurcation phenomenon is given in Figure 1.3.

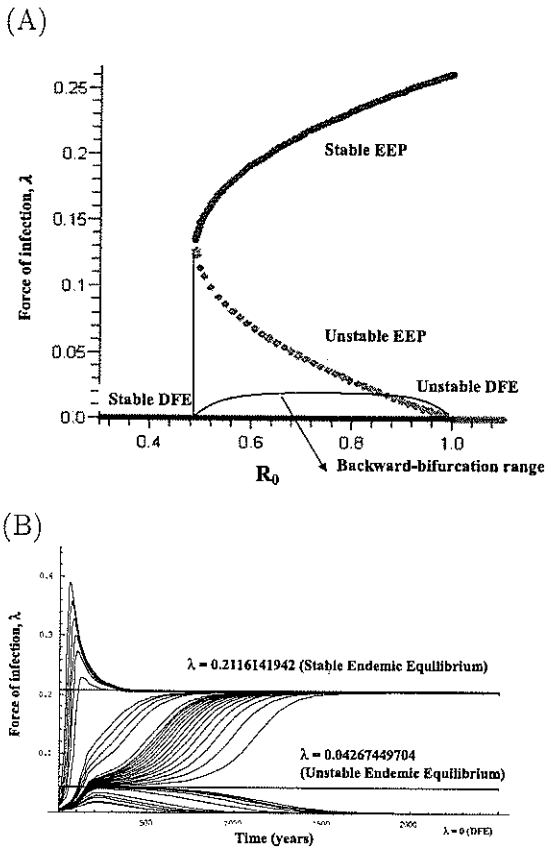


Figure 1.3: (A) Backward bifurcation diagram showing coexistence of a stable DFE and two branches of endemic equilibria (stable and unstable branch); (B) Time series plot with different initial conditions showing the two stable equilibria separated by an unstable (saddle) equilibrium point.

1.6 Thesis outline

The thesis is organized as follows. Some of the basic mathematical preliminaries needed to qualitatively analyze the models in this thesis are reviewed in Chapter 2. In Chapter 3, a basic HIV treatment model, which subdivides the total population into susceptible, untreated newly- and asymptomatically-infected, AIDS, and treated individuals, is

formulated and analyzed. Chapter 4 addresses the issue of resistance development as a result of using ARVs. In Chapter 5, a vaccination model, which incorporates the staged-progression and differential infectivity aspects of HIV disease, is studied. The main mathematical and epidemiological contributions of the thesis are summarized in Chapter 6. Areas for future work are also enumerated.

Chapter 2

Mathematical Preliminaries

This chapter summarizes some of the key mathematical theories and methodologies relevant to the thesis.

2.1 Equilibria of linear and non-linear autonomous systems

Consider the equation below

$$\dot{x} = f(x, t; \mu), \quad x \in U \subset \mathbb{R}^n, \quad t \in \mathbb{R}^1, \quad \text{and} \quad \mu \in V \subset \mathbb{R}^p, \tag{2.1}$$

where U and V are open sets in $\mathbb{R}^n$ and $\mathbb{R}^p$, respectively, and μ is a parameter. The overdot in (2.1) represents differentiation with respect to time ($\frac{d}{dt}$). The equation (2.1) is referred to as a *vector field* or an *ordinary differential equation.* Vector fields which explicitly depend on time are called *non-autonomous*, while vector fields which are

independent of time are called *autonomous*. This thesis considers only autonomous systems.

Consider the following general autonomous system

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.2}$$

Definition 2.1. *An equilibrium solution of* (2.2) *is a point* $\bar{x} \in \mathbb{R}$ *such that* $f(\bar{x}) = 0$.

2.2 Hartman-Grobman Theorem

Definition 2.2. *Let* $x = \bar{x}$ *be an equilibrium solution of* (2.2). *Then* $\bar{x}$ *is called hyperbolic if none of the eigenvalues of* $Df(\bar{x})$ *have zero real part. An equilibrium point that is not hyperbolic is called non-hyperbolic.*

Let

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.3}$$

be two C^r $(r \geq 1)$ vector fields on $\mathbb{R}^n$.

Definition 2.3. *The dynamics generated by the vector fields* f *and* g *of* (2.3) *are said to be locally* C^k *conjugate* $(k \leq r)$ *if there exist a* C^k *diffeomorphism* h *which takes the orbits of the flow generated by* f, $\phi(t, x)$, *to the orbits of the flow generated by* g, $\psi(t, y)$, *preserving orientation and parametrization by time* [89].

Theorem 2.1. (Hartman and Grobman [89]) *Consider a $C^r (r \geq 1)$ vector field*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.4}$$

with domain of f to be a large open subset of $\mathbb{R}^n$. Suppose also that (2.4) has a equilibrium solutions which are hyperbolic. Consider the associated linear vector field

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{2.5}$$

Then the flow generated by (2.4) is C^0 conjugate to the flow generated by the linearized system (2.5) in a neighborhood of the equilibrium point $x = \bar{x}$.

A direct application of the Hartman-Grobman Theorem is that orbit structure near equilibrium solution which are hyperbolic is qualitatively the same as the orbit structure given by the associated linearized dynamical system.

2.3 Stability theory

The following are standard definitions and theorems required to analyze the stability of an equilibrium of an autonomous system.

Let $\bar{x}(t)$ be any solution of (2.2). Then, $\bar{x}(t)$ is *stable* if solutions starting "close" to $\bar{x}(t)$ at a given time remain close to $\bar{x}(t)$ for all later times. It is *asymptotically stable* if nearby solutions actually converge to $\bar{x}(t)$ as $t \to \infty$. This is formally defined

below:

Definition 2.4. *The equilibrium $\bar{x}(t)$ is said to be stable if given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $y(t)$ of (2.2) satisfying $|\bar{x}(t_0) - y(t_0)| < \delta$, $|\bar{x}(t) - y(t)| < \epsilon$ for $t > t_0$, $t_0 \in \mathbb{R}$.*

Definition 2.5. *The equilibrium $\bar{x}(t)$ is said to be asymptotically stable if (i) it is stable and (ii) there exists a constant $c > 0$ such that if $|\bar{x}(t_0) - y(t_0)| < c$, then $\lim_{t\to\infty} |\bar{x}(t) - y(t)| = 0$.*

Definition 2.6. *A solution which is not stable is said to be unstable.*

Theorem 2.2. *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system (2.2) is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.*

2.4 Bifurcation theory

In general, systems of physical interest typically have parameters which appear in the defining systems of equations. As these parameters are varied, changes may occur in the qualitative structures of the solutions for certain parameter values. These changes are called *bifurcations.* The parameter values where bifurcation occurs are called *bifurcation values.* A standard definition for bifurcation at a point is given below.

Definition 2.7. *Let*

$$\dot{x} = f(x, \mu), \quad x \in \mathbb{R}, \ \mu \in \mathbb{R}, \tag{2.6}$$

be a one-parameter family of one-dimensional vector fields. An equilibrium solution of (2.6) *given by* $(x, \mu) = (0, 0)$ *is said to undergo bifurcation at* $\mu = 0$ *if the flow for* μ *near zero and* x *near zero is not qualitatively the same as the flow near* $x = 0$ *at* $\mu = 0$.

There are various types of bifurcations, including saddle-node, transcritical, pitchfork, backward, and hopf bifurcations [89]. Two of these, forward and backward bifurcations, are relevant to this thesis.

2.5 Non-existence of periodic solutions

Generally, models of disease transmission may have solutions that differ from the calculated equilibrium solutions. Such solutions affect the stability of the equilibria. These kinds of solutions are generally referred to as closed orbits (i.e., periodic orbits, homoclinic orbits, heteroclinic trajectories and polygons). In order to establish global properties of equilibria, it is sometimes necessary to show the non-existence of closed orbits in the feasible region of the model. Some methods for ruling out closed orbits in $\mathbb{R}^2$ are described below, after the following standard definitions.

Let $\dot{x} = f(x)$, $x \in \mathbb{R}^2$ be a vector field.

Definition 2.8. (Periodic solution). *A solution* $x(t)$ *is said to be periodic if* $x(t+T) = x(t)$ *for all* t, *for some* $T > 0$.

Example 1:

The system $\dot{x} = y, \dot{y} = -x - 5(x^2 - 1)y$ has a periodic orbit illustrated below.

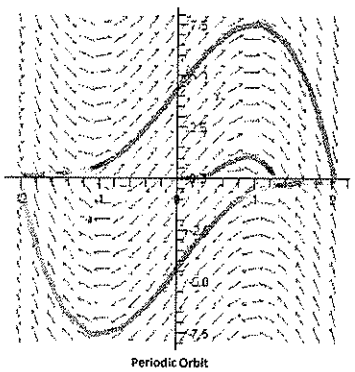


Figure 2.1: Periodic orbit

Definition 2.9. (Homoclinic orbits). *Homoclinic orbits are trajectories that start and end at the same saddle point. That is, they are trajectories connecting a single saddle node.*

Example 2:

The system $\dot{x} = y, \dot{y} = x + x^2$ has a homoclinic orbit as shown below.

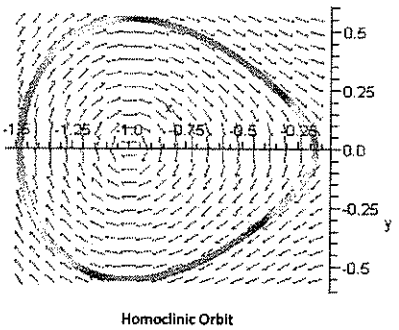


Figure 2.2: Homoclinic orbit

Definition 2.10. (Heteroclinic orbits). *Heteroclinic orbits are trajectories that start at*

one saddle node and end at the another saddle node. That is, they connect two saddle nodes.

Example 3:

The system $\dot{x} = y, \dot{y} = -\sin x$ has a heteroclinic orbit illustrated below.

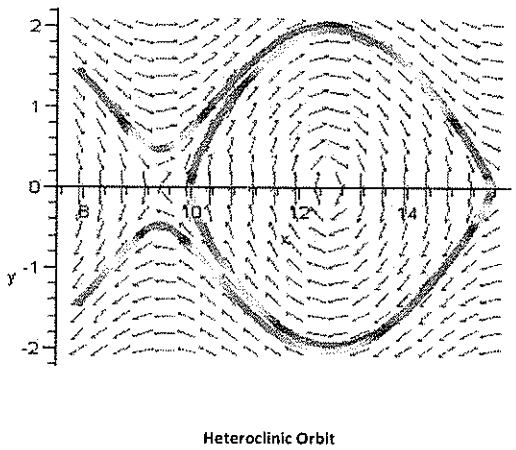


Figure 2.3: Heteroclinic orbit

Definition 2.11. (Polygons). *Polygons are trajectories connecting more than two saddle nodes.*

Example 4:

The system $\dot{x} = y + x^2 - y^2, \dot{y} = -x - 2xy$ has a polygon as shown below.

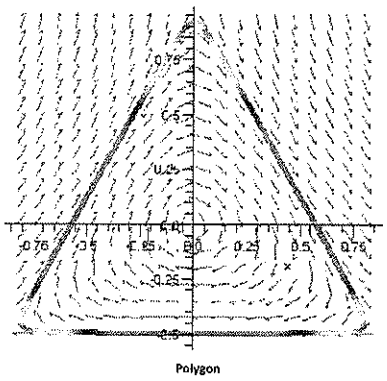


Figure 2.4: Polygon

2.5.1 Lyapunov functions and LaSalle's Invariance Principle

Lyapunov Functions

A powerful method for analyzing the stability of an equilibrium point is based on the use of Lyapunov functions. Lyapunov functions are energy-like functions that decrease along trajectories. If such a function exists, then closed orbits are forbidden [81].

Definition 2.12. *A function $V : \mathbb{R}^n \to \mathbb{R}$ is said to be a positive definite function if*

- $V(x) > 0$ *for all* x,
- $V(x) = 0$ *if and only if* $x = 0$,
- $V(x) \to \infty$ *as* $x \to \infty$.

The general Lyapunov Function Theorem is given below.

Theorem 2.3. *Consider the following vector field*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.7}$$

Let $\bar{x}$ be an equilibrium solution of (2.7) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighborhood U of $\bar{x}$ such that

i) *V is positive definite*

ii) *$\dot{V}(x) \leq 0$ in $U \backslash \{\bar{x}\}$.*

Then $\bar{x}$ is stable. Moreover, if

iii) *$\dot{V}(x) < 0$ in $U \backslash \{\bar{x}\}$*

then $\bar{x}$ is globally asymptotically stable (GAS).

Any function V that satisfies the above is called a *Lyapunov function* [48, 89].

Example 5:

Consider the following vector field, with ϵ a real parameter,

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= -x - \epsilon x^2 y. \end{aligned}$$

The system has a non-hyperbolic equilibrium solution at $(x, y) = (0, 0)$. Let $V(x, y) =$

$(x^2+y^2)/2$. Clearly $V(0,0) = 0$ and $V(x,y) > 0$ in any neighborhood of $(0,0)$. Further,

$$\begin{aligned} \dot{V}(x,y) &= x\dot{x} + y\dot{y} \\ &= xy + y(-x - \epsilon x^2 y) \\ &= xy - xy - \epsilon x^2 y^2 \\ &= -\epsilon x^2 y^2 < 0 \quad \text{for } \epsilon > 0. \end{aligned}$$

Hence, $\dot{V} < 0$. Thus, by the Lyapunov Function Theorem (2.3), the equilibrium $(0,0)$ is stable for $\epsilon = 0$ and GAS for $\epsilon > 0$.

Limit Sets and Invariance Principle

Since general epidemiology models monitor human populations, it is necessary to consider that associated population sizes can never be negative. Thus, epidemiological models should be considered in (feasible) regions where such property (nonnegativity) is preserved.

Definition 2.13. *A point $x_0 \in \mathbb{R}^n$ is called an $\omega-$limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$, $t_i \to \infty$ such that*

$$\phi(t_i, x) \to x_0.$$

Definition 2.14. *A point $x_0 \in \mathbb{R}^n$ is called an $\alpha-$limit point of $x \in \mathbb{R}^n$, denoted by*

$\alpha(x)$, *if there exists a sequence* $\{t_i\}$, $t_i \to -\infty$ *such that*

$$\phi(t_i, x) \to x_0.$$

Definition 2.15. *The set of all* $\omega-$*limit points of a flow is called the* $\omega-$*limit set. Similarly, the set of all* $\alpha-$*limit points of a flow is called the* $\alpha-$*limit set* [89].

Definition 2.16. *Let* $S \subset \mathbb{R}^n$ *be a set. Then,* S *is said to be invariant under the vector field* $\dot{x} = f(x)$ *if for any* $x_0 \in S$ *we have* $x(t, 0, x_0) \in S$ *for all* $t \in \mathbb{R}$.

If we restrict the region to positive times (i.e., $t \geq 0$), then S is said to be a *positively-invariant set.* In other words, solutions in a positively-invariant set remain there for all time. The set is negatively-invariant if we go backward in time.

Theorem 2.4. *(LaSalle's Invariance Principle). Suppose there is a continuously differentiable, positive definite, and radially unbounded function* $V : \mathbb{R}^n \to \mathbb{R}$, *such that*

$$\frac{\partial V}{\partial x}(x - \bar{x})f(x) \leq W(x) \leq 0, \quad \forall\, x \in \mathbb{R}^n.$$

Then, $\bar{x}$ *is a globally stable equilibrium. The solution* $x(t)$ *converges to the largest invariant set* S *contained in* $E = \{x \in \mathbb{R}^n : W(x) = 0\}$ [38].

2.5.2 Dulac's criterion

Theorem 2.5. *(Dulac's Criterion). Let* $\dot{x} = f(x)$ *be a continuous differentiable vector field defined on a simply connected subset* $\mathbb{D}$ *of the plane. If there exists a continuously*

differentiable, real-valued function $g(x)$ such that $\nabla \cdot (g\dot{x})$ has one sign throughout $\mathbb{D}$, then there are no closed orbits lying entirely in $\mathbb{D}$ [81, 89].

Proof. Suppose there were closed orbit C lying entirely in the region $\mathbb{D}$. Let A denote a region inside C. Then, by Green's Theorem,

$$\iint_A \nabla \cdot (g\dot{\mathbf{x}}) dA = \oint_C g\dot{\mathbf{x}} \cdot \mathbf{n}\, d\ell,$$

where $\mathbf{n}$ is the outward normal and ℓ is the element of arc length along C. It is clear that the left hand-side of the integral is non-zero, since $\nabla \cdot (g\dot{\mathbf{x}})$ has one sign in $\mathbb{D}$. The right hand-side of the integral is zero since $\dot{\mathbf{x}} \cdot \mathbf{n} = \mathbf{0}$ everywhere by the assumption that C is a trajectory (the tangent vector $\dot{\mathbf{x}}$ is orthogonal to $\mathbf{n}$). This contradiction implies that no such C can exist [81].

□

Example 6

The system $\dot{x} = x(2 - x - y),\ \dot{y} = y(4x - x^2 - 3)$ has no closed orbits in the positive quadrant $x, y > 0$. To see this, let $g = 1/xy$, so that

$$\begin{aligned} \nabla \cdot (g\dot{\mathbf{x}}) &= \frac{\partial}{\partial x}(g\dot{x}) + \frac{\partial}{\partial y}(g\dot{y}) \\ &= \frac{\partial}{\partial x}\left(\frac{2 - x - y}{y}\right) + \frac{\partial}{\partial y}\left(\frac{4x - x^2 - 3}{x}\right) \\ &= -\frac{1}{y} < 0. \end{aligned}$$

Since the region $x, y > 0$ is simply connected, g and f satisfy the required smoothness

conditions. The Dulac's criterion implies that there are no closed orbits in the positive quadrant [81].

2.5.3 Busenberg - van den Driessche technique

Busenberg and van den Driessche [12] extended the Dulac's criterion to $\mathbb{R}^3$ as follows.

Theorem 2.6. *Let $S \subset \mathbb{R}^3$ be smooth, orientable, surface such that any piecewise smooth closed curve $\gamma(t) \in S$ is the boundary of surface $S' \subset S$. If $\gamma : \mathbb{R}^3 \to \mathbb{R}^3$ is smooth, $\boldsymbol{f} : \gamma(t) \to \mathbb{R}^3$ is Lipschitz, and $\boldsymbol{f}$ and $\boldsymbol{g}$ satisfy*

$$\boldsymbol{g}(\gamma(t)) \cdot \boldsymbol{f}(\gamma(t)) = 0,$$

$$(\text{curl } \boldsymbol{g}).\boldsymbol{n} > 0 \text{ on } S \ (< 0 \text{ on } S),$$

where $\boldsymbol{n}$ is the unit normal to S. Then $\gamma(t)$ is not a phase polygon (trajectories connecting more than one saddle nodes) of the differential equation $\dot{\boldsymbol{x}} = \boldsymbol{f}(x(t))$.

2.6 Methods for local stability of equilibria

Here, two standard methods for analyzing the local stability of the equilibria of disease transmission models are briefly described.

2.6.1 Linearization

Determining the stability of an equilibrium $\bar{x}(t)$ generally requires an understanding of the nature of solutions near $\bar{x}(t)$. Let

$$x = \bar{x}(t) + \epsilon \tag{2.8}$$

and suppose that (2.8) is substituted into the general autonomous vector field $\dot{x} = f(x)$, $x \in \mathbb{R}^n$ and f is twice differentiable. The Taylor series expansion about $\bar{x}(t)$ gives

$$\dot{x} = \dot{\bar{x}}(t) + \dot{\epsilon} = f(\bar{x}(t)) + Df(\bar{x}(t))\epsilon + O(|\epsilon|^2),$$

where Df is the derivative of f and $|\cdot|$ denotes norm on $\mathbb{R}^n$. Hence,

$$\dot{\epsilon} = Df(\bar{x}(t))\epsilon + O(|\epsilon|^2). \tag{2.9}$$

Equation (2.9) above describes the evolution of orbits near $\bar{x}(t)$. The behavior of solutions arbitrarily close to $\bar{x}(t)$ is obtained by studying the associated linear system

$$\dot{\epsilon} = Df(\bar{x}(t))\epsilon. \tag{2.10}$$

However, if $\bar{x}(t)$ is an equilibrium solution, i.e., $\bar{x}(t) = \bar{x}$, then $Df(\bar{x}(t)) = Df(\bar{x})$ is a matrix with constant entries, and the solution of (2.10) through the point $\epsilon_0 \in \mathcal{R}^n$ at

$t = 0$ is given by

$$\epsilon(t) = \exp(Df(\bar{x})t)\epsilon_0. \tag{2.11}$$

Theorem 2.7. *Suppose all of the eigenvalues of $Df(\bar{x})$ have negative real parts. Then, the equilibrium solution $x = \bar{x}$ of the nonlinear vector field $\dot{x} = f(x)$, $x \in \mathbb{R}^n$ is asymptotically stable.*

Example 7

Consider the vector field

$$\begin{aligned} \dot{x} &\equiv f_1(x, y) = y^2 - x, \\ \dot{y} &\equiv f_2(x, y) = x^2 - y. \end{aligned}$$

The system has a unique equilibrium point $\bar{x} = (0, 0)$. The Jacobian J of the vector field is given by

$$J(x, y) = Df(\bar{x}(t)) = \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix} = \begin{pmatrix} -1 & 2y \\ \\ 2x & -1 \end{pmatrix}.$$

Evaluating J at $\bar{x}$ gives

$$J(0, 0) = \begin{pmatrix} -1 & 0 \\ \\ 0 & -1 \end{pmatrix},$$

so that the eigenvalues of $J(0, 0)$, $\lambda_1 = \lambda_2 = -1$, have negative real parts. Hence, the equilibrium $\bar{x} = (0, 0)$ is asymptotically stable.

2.6.2 Next generation method

Whilst the linearization method above applies to analyzing the local stability of equilibria in general, the next generation method is used to establish the local asymptotic stability of the DFE (or a boundary equilibrium). The method was first introduced by Diekmann and Hesterbeek [23] and refined for epidemiological models by van den Driessche and Watmough [87]. Epidemiological models, of Kermack and Mckendrick type, typically subdivide the total population (N) into a number of mutually exclusive compartments depending on their disease status (see, for instance, Example 8). The formulation in [87] is now described. Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following system:

$$\dot{x}_i = f(x_i) = \mathrm{F}_i(x) - \mathrm{V}_i(x), \quad i = 1, \cdots, n, \tag{2.12}$$

where $\mathrm{V}_i = \mathrm{V}_i^- - \mathrm{V}_i^+$ and the function satisfy the following axioms below. First of all, $X_s = \{x \geq 0 | x_i = 0,\ i = 1, \cdots, m\}$ is defined as the disease-free states (non-infected state variables of the model) of the model, where $x = (x_1, \cdots, x_n)^t, x_i \geq 0$ represents the number of individuals in each compartment of the model.

(A1) if $x \geq 0$, then $\mathrm{F}_i, \mathrm{V}_i^+, \mathrm{V}_i^- \geq 0$ for $i = 1, \cdots, m$.

(A2) if $x_i = 0$, then $\mathrm{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathrm{V}_i^- = 0$ for $i = 1, \cdots, m$.

(A3) $\mathrm{F}_i = 0$ if $i > m$.

(A4) if $x \in X_s$, then $\mathrm{F}_i(x) = 0$ and $\mathrm{V}_i^+(x) = 0$ for $i = 1, \cdots, m$.

(A5) If $\mathrm{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

Here, $\mathrm{F}_i(x)$ represents the rate of appearance of new infections in compartment i; $\mathrm{V}_i^+(x)$ represents the rate of transfer of individuals into compartment i by all other means, and $\mathrm{V}_i^-(x)$ represents the rate of transfer of individuals out of compartment i. It is assumed that these functions are at least twice continuously differentiable in each variable [87].

Definition 2.17. ($M-$Matrix) *An $n \times n$ matrix A is an $M-$matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.*

Lemma 2.1. (van den Driessche and Watmough [87]) *If $\bar{x}$ is a DFE of (2.12) and $f_i(x)$ satisfy $(A1)-(A5)$, then the derivatives $D\mathrm{F}(\bar{x})$ and $D\mathrm{V}(\bar{x})$ are partitioned as*

$$D\mathrm{F}(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \; D\mathrm{V}(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

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

$$F = \left[\frac{\partial \mathrm{F}_i}{\partial x_j}(\bar{x})\right] \text{ and } V = \left[\frac{\partial \mathrm{V}_i}{\partial x_j}(\bar{x})\right] \text{ with } 1 \leq i, j \leq m.$$

Further, F is non-negative, V is a non-singular $M-$matrix and J_3, J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Theorem 2.8. (van den Driessche and Watmough [87]). *Consider the disease transmission model given by (2.12) with $f(x)$ satisfying axioms $(A1)-(A5)$. If $\bar{x}$ is a DFE*

of the model, then $\bar{x}$ is LAS if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is spectral radius), but unstable if $\mathcal{R}_0 > 1$.

Example 8

Consider the basic SIR model below (where the variables S, I, R represent the population of susceptible, infected and recovered individuals, respectively; and $N = S + I + R$ is the total population at time t)

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \frac{\beta SI}{N} - \mu S, \\
\frac{dI}{dt} &= \frac{\beta SI}{N} - (\mu + \sigma)I, \\
\frac{dR}{dt} &= \sigma I - \mu R.
\end{aligned}$$

The model has a DFE, given by $\mathcal{X}_0 = (\Pi/\mu, 0, 0)$. Here, the non-negative matrix, F, and the $M-$matrix, V, are given by

$$F = \left(\frac{\beta S^*}{N^*}\right) \text{ and } V = \left(\mu + \sigma\right), \text{ where } S^* = N^* = \frac{\Pi}{\mu}.$$

It is easy to verify that for this system, the conditions $A1$-$A5$ of Section 2.6.2 are satisfied (these conditions are also satisfied for all the subsequent models in this thesis). Thus, $\mathcal{R}_0 = \rho(FV^{-1}) = \dfrac{\beta}{\mu + \sigma}$. Hence, $\mathcal{X}_0$ is LAS whenever $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

Chapter 3

HIV Treatment Model

3.1 Introduction

Ever since their introduction in the early 1990s [71, 72], ARVs, particularly HAART, have had dramatic impact in curtailing the burden (morbidity and mortality) of the HIV pandemic in many countries where these drugs are accessible [70]. The use of such life-saving drugs, over long periods of time, reduces the viral loads in HIV-infected individuals to non-detectable levels (typically characterized by HIV RNA of less than 50 copies/ml) [52]. In addition to making these individuals less infectious (owing to the positive correlation between viral load and HIV transmission [33]), HAART extends the life, and the quality of life, of infected individuals [71].

The type of strategy for implementing a HIV control program based on using ARVs is influenced by a number of factors ranging from biological, availability of resources, and the efficiency of the public health care system to optimally administer the distribu-

tion of ARVs in the community. Although the cost of ARVs has reduced significantly over the years, these drugs are still not widely available in many resource-poor nations. The WHO [91] reported, in 2003, that only 5% of people who need ARVs in developing nations actually have access to these drugs. In nations where these drugs are readily available, some have opted for universal (mass) treatment of all diagnosed individuals regardless of their stage of infection (e.g., in Brazil [61]), while others have adopted a more targeted approach, where only individuals with low CD4 count (generally below 200 cells/ml) or displaying symptoms of AIDS are treated; individuals with such low CD4 count are essentially at the pre-AIDS or AIDS stage of HIV disease, and therefore have high viral loads. This late strategy is further justified by the results of the randomized clinical trials in [13, 32, 35, 39] which provide strong evidence of improved survival and reduced progression by treating symptomatic patients and patients with CD4 count of less than 200 cells/mm^3. Further, this strategy has the additional advantage of minimizing the possibility of the evolution and spread of ARV-resistant HIV strain in the community and also minimizing ARV-related side effects and toxicity. It is worth emphasizing that the latter strategy (treating those with CD4 < 200 cells/ml, or those with viral load above a certain threshold) forms part of the new HIV control guidelines in a number of countries such as the USA [21, 34] and Canada [86]. Some resource-poor nations, such as Botswana [64], also subscribe to the late (viral load-dependent) treatment strategy, perhaps due to reasons that may include economics. In summary, there are a number of ways ARV programs could be implemented including targeting (i) all infected individuals (universal treatment), (ii) newly-

and asymptomatically-infected individuals (i.e., infected individuals without the clinical symptoms of AIDS) and (iii) individuals with clinical symptoms of AIDS. From now on, Strategy (ii) is referred to as the "HIV-only" Strategy. The key modelling question here is which of these strategies is most effective in minimizing HIV-related burden (measured in terms of disease-related mortality and morbidity) in a community?

Several authors have, over the last two decades, used mathematical models, of the form of deterministic or stochastic systems of differential equations, to assess the impact of ARVs on HIV control [20, 33, 52, 58, 61, 62, 71, 72, 82]. However, many of these models do not incorporate the role of individuals with clinical AIDS symptoms in HIV transmission. That is, these studies assume that individuals in the AIDS stage of infection do not contribute in further spread of HIV. To the contrary, epidemiological evidence supports the hypothesis that AIDS patients are capable of, and do engage in, risky sexual behavior such as having multiple sexual partners or inconsistent condom use [59, 68, 69]. In this chapter, a HIV treatment model, which incorporates HIV transmission by AIDS individuals, is designed and used to evaluate the aforementioned treatment strategies.

3.2 Model formulation and basic properties

The total population, N, is subdivided into four mutually-exclusive compartments namely susceptible ($S(t)$), untreated newly- and asymptomatically-infected individuals ($I_u(t)$), infected individuals at the AIDS stage of infection ($A(t)$) and treated individuals ($I_T(t)$), so that $N(t) = S(t) + I_u(t) + A(t) + I_T(t)$.

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate Π. These individuals acquire infection, following contact with infected individuals in the I_u, A and I_T classes, at a rate λ, where

$$\lambda = \frac{\beta(I_u + \eta_A A + \eta_T I_T)}{N}$$

is the force of infection. The parameter β is the effective contact rate (contact capable of leading to infection), while $\eta_A \geq 1$ is the relative risk of infectiousness of individuals with AIDS (in comparison to those in the I_u class). The parameter $0 < \eta_T < 1$ accounts for the assumed reduced infectiousness of treated individuals relative to untreated individuals. Infected individuals in the I_u class progress to AIDS at a rate α. It is assumed that infected individuals in the I_u and A classes are treated with ARVs at a rate τ_u, (with efficacy ϵ_T). Treated individuals progress to AIDS at a reduced rate $\alpha\theta$, where $0 < \theta < 1$ is a modification parameter accounting for the slow progression of treated individuals (in comparison to untreated individuals). Further, natural mortality occurs in all classes at a rate μ, and AIDS individuals suffer an additional disease-induced mortality at a rate δ. The model is given by the following system of

differential equations (see Figure 3.1 for a flowchart diagram)

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda S - \mu S, \\
\frac{dI_u}{dt} &= \lambda S - \mu I_u - \alpha I_u - \epsilon_T \tau_u I_u, \\
\frac{dA}{dt} &= \alpha I_u - (\mu + \delta) A - \epsilon_T \tau_A A + \theta \alpha I_T, \\
\frac{dI_T}{dt} &= \epsilon_T \tau_u I_u + \epsilon_T \tau_A A - \mu I_T - \theta \alpha I_T.
\end{aligned} \tag{3.1}$$

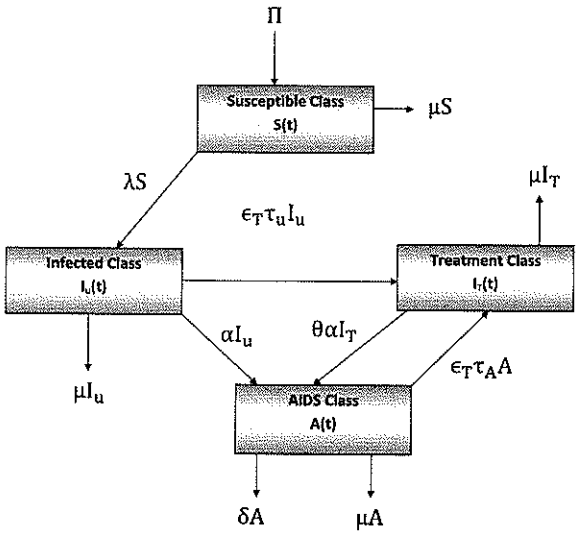


Figure 3.1: Flow diagram model (3.1)

It follows from the model (3.1) that setting $\tau_A = 0$ and $\tau_u \neq 0$ corresponds to the HIV-only strategy. Further, while the AIDS-only Strategy involves setting $\tau_u = 0$ and $\tau_A \neq 0$, the Universal Strategy entails having $\tau_u \neq 0$ and $\tau_A \neq 0$. That is, while Strategy (i) targets only individuals in the I_u class and Strategy (ii) targets those displaying clinical symptoms of AIDS only, the Universal Strategy (iii) entails treating infected individuals regardless of their stage of HIV infection.

Since the model (3.1) monitors human populations, it is assumed that all the state variables and parameters of the model are non-negative. Consider the biologically-feasible region

$$\mathcal{D} = \{(S, I_u, A, I_T) \in \mathbb{R}^4_+ : S + I_u + A + I_T \leq \Pi/\mu\}.$$

The following steps are followed to establish the positive invariance (i.e., solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all time) and attractivity property of $\mathcal{D}$. The rate of change of the total population, obtained by adding all the equations in model (3.1), is given by

$$\frac{dN}{dt} = \Pi - \mu N - \delta A. \tag{3.2}$$

Since the right hand side of (3.2) is bounded by $\Pi - \mu N$, a standard comparison theorem can be used to show that $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$. Thus, $\mathcal{D}$ is positively-invariant (that is, all solutions with initial conditions in $\mathcal{D}$ remain in $\mathcal{D}$ for $t \geq 0$). Further, whenever $N > \Pi/\mu$, then $dN/dt < 0$. Thus, it follows that every solution of the equations in model (3.1) with initial conditions in $\mathbb{R}^4_+$ tends toward $\mathcal{D}$ as $t \to \infty$. Therefore, the ω-limit sets of the system (3.1) are contained in $\mathcal{D}$. Hence, it is sufficient to consider the dynamics of the flow generated by (3.1) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed [47].

3.3 Treatment-free model

Before analyzing the full model (3.1), it is instructive to gain insights into the dynamics of the treatment-free version of the model ($\tau_u = \eta_T = \epsilon_T = I_T = 0$ in (3.1)) given by

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda S - \mu S, \\ \frac{dI_u}{dt} &= \lambda S - (\mu + \alpha) I_u, \\ \frac{dA}{dt} &= \alpha I_u - (\mu + \delta) A, \end{aligned} \tag{3.3}$$

where, now, $N = S + I_u + A$ and $\lambda = \dfrac{\beta(I_u + \eta A)}{N}$. For this model, it can be shown that the region

$$\mathcal{D}_1 = \{(S, I_u, A) \in \mathbb{R}^3_+ : S + I_u + A \leq \Pi/\mu\}$$

is positively-invariant and attracting. Thus, the dynamics of the treatment-free model will be considered in $\mathcal{D}_1$.

3.3.1 Local stability of DFE

The model (3.3) has a DFE, obtained by setting the right hand sides of the equations in the model to zero, given by

$$\mathcal{E}_0 = (S^*, I_u^*, A^*) = \left(\frac{\Pi}{\mu}, 0, 0\right). \tag{3.4}$$

The linear stability of $\mathcal{E}_0$ can be established using the next generation operator method on the system (3.3). Using the notation in [87], the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are, respectively, given by

$$F = \begin{pmatrix} \frac{\beta S^*}{N^*} & \frac{\beta \eta S^*}{N^*} \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \mu + \alpha & 0 \\ -\alpha & \mu + \delta \end{pmatrix}.$$

Thus,

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta}{\mu + \alpha} + \frac{\beta \eta \alpha}{(\mu + \alpha)(\mu + \delta)}. \tag{3.5}$$

The following results follows from Theorem 2 of [87].

Lemma 3.1. *The DFE of the model* (3.3), *given by* (3.4), *is LAS if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

The quantity $\mathcal{R}_0$ is the *basic reproduction number*. It measures the average number of new infections generated by a single infected individual in a completely susceptible population.

Biologically speaking, Lemma (3.1) implies that HIV can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of $\mathcal{E}_0$. To ensure that elimination of the virus is independent of the initial sizes of the sub-populations, it is necessary to show that the DFE is globally asymptotically stable. This is established below.

3.3.2 Global stability of DFE

Theorem 3.1. *The DFE of the model* (3.3)*, given by* (3.4)*, is GAS whenever* $\mathcal{R}_0 < 1$.

Proof. Consider the following Lyapunov function:

$$\mathcal{F} = \beta\{[(\mu+\delta)+\eta\alpha]I_u + \eta(\mu+\alpha)A\},$$

with Lyapunov derivative,

$$\begin{aligned}
\dot{\mathcal{F}} &= \beta\{[(\mu+\delta)+\eta\alpha]\dot{I}_u + \eta(\mu+\alpha)\dot{A}\} \\
&= \beta\{[(\mu+\delta)+\eta\alpha][\lambda S - (\mu+\alpha)I_u] + \eta(\mu+\alpha)[\alpha I_u - (\mu+\delta)A]\} \\
&= \beta[(\mu+\delta)+\eta\alpha]\lambda S - (\mu+\alpha)(\mu+\delta)\beta(I_u+\eta A) \\
&= \beta[(\mu+\delta)+\eta\alpha]\lambda S - (\mu+\alpha)(\mu+\delta)\lambda N \\
&= (\mu+\alpha)(\mu+\delta)\lambda N\left\{\frac{\beta S[(\mu+\delta)+\eta\alpha]}{N(\mu+\alpha)(\mu+\delta)} - 1\right\} \\
&\leq (\mu+\alpha)(\mu+\delta)\beta(I_u+\eta A)\left[\frac{\beta(\mu+\delta)+\beta\eta\alpha}{(\mu+\alpha)(\mu+\delta)} - 1\right] \text{ since } S \leq N \\
&= (\mu+\alpha)(\mu+\delta)\beta(I_u+\eta A)(\mathcal{R}_0 - 1) < 0 \text{ for } \mathcal{R}_0 < 1.
\end{aligned}$$

Since all the model parameters are nonnegative, it follows that $\dot{\mathcal{F}} < 0$ for $\mathcal{R}_0 < 1$ with $\dot{\mathcal{F}} = 0$ only if $(I_u = A = 0)$. Hence, $\mathcal{F}$ is a Lyapunov function on $\mathcal{D}_1$. Therefore, by the LaSalle's Invariance Principle [38], every solution to the equations in the model (3.3), with initial conditions in $\mathcal{D}_1$, approaches $\mathcal{E}_0$ as $t \to \infty$. □

The above result has important public health implications. It guarantees disease

elimination (in finite time) provided $\mathcal{R}_0$ can be made less than unity.

3.3.3 Existence and local stability of EEP

Existence

To find conditions for the existence of an equilibrium for which the disease is endemic in the population (i.e., at least one of I_u^{**} and A^{**} is non-zero), denoted by $\mathcal{E}_1 = (S^{**}, I_u^{**}, A^{**})$, the equations in (3.3) are solved in terms of the force of infection at steady-state given by

$$\lambda^{**} = \frac{\beta(I_u^{**} + \eta A^{**})}{N^{**}}. \tag{3.6}$$

Setting the right hand sides of the model to zero (and noting that $\lambda = \lambda^{**}$) gives

$$S^{**} = \frac{\Pi}{\mu + \lambda^{**}}, \quad I_u^{**} = \frac{\lambda^{**}\Pi}{(\mu+\alpha)(\mu+\lambda^{**})}, \quad A^{**} = \frac{\alpha\lambda^{**}\Pi}{(\mu+\delta)(\mu+\lambda^{**})(\mu+\alpha)}. \tag{3.7}$$

Using (3.7) in the expression for λ^{**} in (3.6) shows that the nonzero (endemic) equilibria of the model satisfy

$$b_1\lambda^{**} - c_1 = 0, \tag{3.8}$$

where $b_1 = \alpha + \mu + \delta$, and $c_1 = (\mu+\alpha)(\mu+\delta)(\mathcal{R}_0 - 1)$. It is clear that $b_1 > 0$, and $c_1 > 0$ for $\mathcal{R}_0 > 1$. Thus, the linear system (3.8) has a unique positive solution, given by $\lambda^{**} = c_1/b_1$, whenever $\mathcal{R}_0 > 1$. The components of the endemic equilibrium, $\mathcal{E}_1$, are

then determined by substituting $\lambda^{**} = c_1/b_1$ into (3.7). Noting that $\mathcal{R}_0 < 1$ implies that $c_1 < 0$. Thus, for $\mathcal{R}_0 < 1$, the force of infection at steady-state (λ^{**}) is negative. Hence the model has no positive equilibria in this case. These results are summarized below.

Lemma 3.2. *The treatment-free model* (3.3) *has a unique positive endemic equilibrium whenever* $\mathcal{R}_0 > 1$ *and no positive endemic equilibrium whenever* $\mathcal{R}_0 < 1$.

Local stability

Lemma (3.2) above shows the existence of a unique positive endemic equilibrium if $\mathcal{R}_0 > 1$. The local stability property of this endemic equilibrium is now explored.

Theorem 3.2. *The unique endemic equilibrium of the model* (3.3) *is LAS if* $\mathcal{R}_0 > 1$.

Proof.

The proof is based on converting the problem (of the stability of an equilibrium point) to that of analyzing the stability of a fixed point. Substituting (3.7) into (3.6), and noting that

$$N^{**} = \frac{\Pi}{\mu + \lambda^{**}} + \frac{\lambda^{**}\Pi}{(\mu+\alpha)(\mu+\lambda^{**})} + \frac{\alpha\lambda^{**}\Pi}{(\mu+\delta)(\mu+\lambda^{**})(\mu+\alpha)},$$

gives a fixed point problem of the form $\lambda^{**} = f(\lambda^{**})$, where

$$f(\lambda^{**}) = \frac{\lambda^{**}C_1}{1+\lambda^{**}C_2},$$

with

$$C_1 = \frac{\beta}{\mu+\alpha} + \frac{\beta\alpha\eta}{(\mu+\alpha)(\mu+\delta)} \text{ and } C_2 = \frac{1}{\mu+\alpha} + \frac{\alpha}{(\mu+\alpha)(\mu+\delta)}.$$

It follows that

$$\frac{df}{d\lambda^{**}} = f'(\lambda^{**}) = \frac{C_1}{(1+\lambda^{**}C_2)^2}.$$

Evaluating $f'(\lambda^{**})$ at $\lambda^{**} = \frac{c_1}{b_1}$, and simplifying, gives

$$f'(\lambda^{**})\Big|_{\lambda^{**}=\frac{c_1}{b_1}} = \frac{1}{\mathcal{R}_0},$$

from which it is clear that $\left|\left\{f'(\lambda^{**})\Big|_{\lambda^{**}=\frac{c_1}{b_1}}\right\}\right| < 1$ whenever $\mathcal{R}_0 > 1$ [48, 89]. □

It should be mentioned that this result can also be obtained using standard linearization around the EEP; but this method (linearization) is more involved (requires more algebraic manipulations).

3.3.4 Global stability of EEP for $\delta = 0$.

The global stability analysis of the equilibria of disease transmission models (especially the endemic ones) is generally difficult to carry out. Consequently, the literature on global analysis of equilibria of disease transmission models (especially the endemic ones) is scant. Here, a global stability result of the unique endemic equilibrium of (3.3) is given for a special case ($\delta = 0$). It is based on the approach in [12]. First of all,

the model (3.3) with $\delta = 0$ is normalized by defining the following new variables and parameters:

$$X = \frac{\mu}{\Pi}S,\ \ Y_1 = \frac{\mu}{\Pi}I_u,\ \ Y_2 = \frac{\mu}{\Pi}A,\ \ \tilde{t} = t\mu,\ \ \tilde{\beta} = \frac{\beta}{\mu},\ \ \tilde{\alpha} = \frac{\alpha}{\mu}.$$

Using these change of variables and parameters, model (3.3) becomes:

$$\begin{aligned} \frac{dX}{d\tilde{t}} &= 1 - \tilde{\lambda}X - X, \\ \frac{dY_1}{d\tilde{t}} &= \tilde{\lambda}X - \tilde{\alpha}Y_1 - Y_1, \\ \frac{dY_2}{d\tilde{t}} &= \tilde{\alpha}Y_1 - Y_2, \end{aligned} \tag{3.9}$$

where,

$$\tilde{\lambda} = \frac{\tilde{\beta}(Y_1 + \eta Y_2)}{N_1} \text{ with } N_1(t) = X(t) + Y_1(t) + Y_2(t).$$

For the system (3.9), the DFE is $\tilde{\mathcal{E}}_0 = (1, 0, 0)$ and it can be shown that the corresponding basic reproduction number is $\tilde{\mathcal{R}}_0 = \dfrac{\tilde{\beta}(1 + \eta\tilde{\alpha})}{\tilde{\alpha} + 1}$. Let $\tilde{\mathcal{E}}_1 = (X^*, Y_1^*, Y_2^*)$ denote an EEP of system (3.9). The equation for the rate of change of the total population, N_1, is:

$$\frac{dN_1}{d\tilde{t}} = 1 - N_1. \tag{3.10}$$

Here, it is easy to show that $N_1 \in [0, 1]$, since at the DFE, $N_1 = X = 1$ and the natural expectation is that the spread of the disease in the population would reduce

N_1 ($N_1 < 1$). Therefore, the dynamics of the normalized model (3.9) will be studied in the region

$$\Omega = \{(X, Y_1, Y_2) \in \mathbb{R}^3_+ : X + Y_1 + Y_2 \leq 1\}.$$

Like the region $\mathcal{D}_1$, the region Ω is also positively-invariant. Further, it can be shown that the plane

$$\Omega^* = \{(X, Y_1, Y_2) \in \Omega : X + Y_1 + Y_2 = 1\}$$

is positively-invariant. We claim the following.

Lemma 3.3. *The model* (3.9) *has no periodic orbits, homoclinic orbits or polygons in* Ω^*.

Proof. The Bursenberg - van den Driessche technique (Theorem (2.6) of Chapter 2) will be used. Let $\mathbf{f}_1, \mathbf{f}_2, \mathbf{f}_3$ denote the right hand sides of the equations in model (3.9), respectively. The relation $X + Y_1 + Y_2 = 1$ is used to obtain $\mathbf{f}_j(Y_1, Y_2), \mathbf{f}_k(X, Y_2)$ and

$\mathbf{f}_l(X, Y_1)$, $j = 2, 3, k = 1, 3, l = 1, 2$, as follows:

$$\begin{aligned}
\mathbf{f}_1(X, Y_1) &= 1 - \tilde{\beta}\{Y_1 + \eta(1 - X - Y_1)\}X - X, \\
\mathbf{f}_1(X, Y_2) &= 1 - \tilde{\beta}(1 - X - Y_2 + \eta Y_2)X - X, \\
\mathbf{f}_2(X, Y_1) &= \tilde{\beta}\{Y_1 + \eta(1 - X - Y_1)\}X - (1 + \tilde{\alpha})Y_1, \\
\mathbf{f}_2(Y_1, Y_2) &= \tilde{\beta}(Y_1 + \eta Y_2)(1 - Y_2 - Y_1) - (1 + \tilde{\alpha})Y_1, \\
\mathbf{f}_3(X, Y_2) &= \tilde{\alpha}(1 - X - Y_2) - Y_2, \\
\mathbf{f}_3(Y_1, Y_2) &= \tilde{\alpha}Y_1 - Y_2.
\end{aligned}$$

Let $\mathbf{g} = \mathbf{g}_1 + \mathbf{g}_2 + \mathbf{g}_3$, where

$$\begin{aligned}
\mathbf{g}_1(Y_1, Y_2) &= \left[0, \frac{-f_3(Y_1, Y_2)}{Y_1 Y_2}, \frac{f_2(Y_1, Y_2)}{Y_1 Y_2}\right], \quad \mathbf{g}_2(X, Y_2) = \left[\frac{f_3(X, Y_2)}{XY_2}, 0, \frac{-f_1(X, Y_2)}{XY_2}\right], \\
\mathbf{g}_3(X, Y_1) &= \left[\frac{-f_2(X, Y_1)}{XY_1}, \frac{f_1(X, Y_1)}{XY_1}, 0\right].
\end{aligned}$$

Clearly, $\mathbf{g} \cdot \mathbf{f} = \mathbf{0}$ in the interior of Ω^*, where $\mathbf{f} = (\mathbf{f}_1, \mathbf{f}_2, \mathbf{f}_3)$. Using the normal vector $\mathbf{n} = (1, 1, 1)$ to Ω^*, it can be shown that (in $\Omega \backslash \{0\}$)

$$\text{Curl } \mathbf{g} \cdot (1, 1, 1) = -\left(\frac{\tilde{\beta}\eta}{Y_1^2} + \frac{Y_2 + \tilde{\alpha}X}{X^2 Y_2^2} + \frac{1}{X^2}\right) < 0.$$

Hence, by Lemma 3.1 in [12], the desired result is obtained. □

We claim the following.

Theorem 3.3. *The endemic equilibrium of the normalized model* (3.9) *is GAS in* $\Omega \setminus \Omega_0$, *where* $\Omega_0 = \{(X, Y_1, Y_2) \in \Omega : Y_1 = Y_2 = 0\}$, *whenever* $\tilde{\mathcal{R}}_0 > 1$.

Proof. Since Ω^* is positively-invariant, the $\omega-$limit set of each solution of the normalized model (3.9) is contained in Ω^*. Moreover, it is easy to see that the DFE, $\tilde{\mathcal{E}}_0 = (1, 0, 0)$ of (3.9), attracts Ω_0 (its stable manifold). Since from Lemma (3.2), a unique endemic equilibrium exists which is LAS (by Theorem (3.2)) whenever $\mathcal{R}_0 > 1$ $(\tilde{\mathcal{R}}_0) > 1)$ i.e., the DFE is unstable. By Lemma (3.3) above, there are no periodic solutions in Ω^*. It follows that every solution in a neighborhood of $\tilde{\mathcal{E}}_0$ in Ω^* will leave that neighborhood asymptotically, because there are no homoclinic orbits, containing $\tilde{\mathcal{E}}_0$ in Ω^*. Since Ω^* is positively-invariant, $\tilde{\mathcal{E}}_1$ is GAS in $\Omega^* \setminus \Omega_0$. □

It is worth noting that establishing the proof for the case $\delta \neq 0$ is not feasible using this approach. The reason is that, for $\delta \neq 0$, the dynamics of the model need to be considered in another region, Ω^{**}, given by $\Omega^{**} = \{(X, Y_1, (1+\tilde{\delta})Y_2) \in \Omega : X+Y_1+Y_2 = 1\}$. The problem is that Ω^{**} is not positively-invariant (since, for instance, solutions on the boundary of Ω^{**} do not necessarily remain there or enter Ω^{**}).

3.4 Analysis of the treatment model

3.4.1 Local stability of DFE

Consider, now, the full treatment model (3.1), with DFE given by

$$\mathcal{E}_0^T : (S^*, I_u^*, A^*, I_T^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right). \tag{3.11}$$

Here, the matrices F and V are given by

$$F = \begin{bmatrix} \frac{\beta S^*}{N^*} & \frac{\beta S^* \eta_A}{N^*} & \frac{\beta S^* \eta_T}{N^*} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} K_1 & 0 & 0 \\ -\alpha & K_2 & -\theta\alpha \\ -\epsilon_T\tau_u & -\epsilon_T\tau_A & K_3 \end{bmatrix},$$

with,

$$K_1 = \mu + \alpha + \epsilon_T\tau_u, \quad K_2 = \mu + \delta + \epsilon_T\tau_A, \quad K_3 = \mu + \theta\alpha,$$

with $N = S + I_u + A + I_T$. The *treatment reproduction number*, denoted by $\mathcal{R}_T = \rho(FV^{-1})$, is given by

$$\mathcal{R}_T = \frac{\beta}{K_1} + \frac{\beta Z_1}{K_1 Z_2} = \frac{\beta(Z_1 + Z_2)}{K_1 Z_2}, \tag{3.12}$$

with

$$\begin{aligned} Z_1 &= \eta_A\alpha(K_3 + \theta\epsilon_T\tau_u) + \eta_T(\alpha\epsilon_T\tau_A + K_2\epsilon_T\tau_u), \\ Z_2 &= \mu K_2 + \theta\alpha(\mu + \delta). \end{aligned}$$

Thus, the following result is established.

Lemma 3.4. *The DFE of the model* (3.1) *is LAS if* $\mathcal{R}_T < 1$ *and unstable if* $\mathcal{R}_T > 1$.

The global stability of the DFE is established as follows.

3.4.2 Global stability of DFE

Theorem 3.4. *The DFE of the model* (3.1) *is GAS if* $\mathcal{R}_T < 1$.

Proof. Consider the Lyapunov function,

$$\mathcal{F} = f_1 I_u + f_2 A + f_3 I_T,$$

where, $f_1 = Z_1 + Z_2,\ f_2 = K_1(\eta_A K_3 + \eta_T \epsilon_T \tau_A),\ f_3 = K_1(\eta_A \alpha\theta + \eta_T K_2)$. Thus,

$$
\begin{aligned}
\dot{\mathcal{F}} &= f_1\dot{I}_u + f_2\dot{A} + f_3\dot{I}_T \\
&= f_1[\lambda S - (\mu + \alpha + \epsilon_T\tau_u)I_u] + f_2[\alpha I_u - (\mu + \delta + \epsilon_T\tau_A)A + \theta\alpha I_T] \\
&\quad + f_3[\epsilon_T\tau_u I_u + \epsilon_T\tau_A A - (\mu + \theta\alpha)I_T] \\
&= f_1(\lambda S - K_1 I_u) + f_2(\alpha I_u - K_2 A + \theta\alpha I_T) + f_3(\epsilon_T\tau_u I_u + \epsilon_T\tau_A A - K_3 I_T) \\
&= f_1\lambda S - (f_1K_1 - f_2\alpha - f_3\epsilon_T\tau_u)I_u - (f_2K_2 - f_3\epsilon_T\tau_A)A + (f_2\theta\alpha - f_3K_3)I_T \\
&= f_1\lambda S - K_1(K_2K_3 - \epsilon_T\tau_A\alpha\theta)I_u - K_1(K_2K_3 - \epsilon_T\tau_A\alpha\theta)\eta_A A - K_1(K_2K_3 - \epsilon_T\tau_A\alpha\theta)\eta_T I_T, \\
&= f_1\lambda S - K_1(K_2K_3 - \theta\alpha\epsilon_T\tau_A)(I_u + \eta_A A + \eta_T I_T) \\
&= f_1\lambda S - K_1(K_2K_3 - \theta\alpha\epsilon_T\tau_A)\frac{\lambda N}{\beta} \\
&= K_1(K_2K_3 - \theta\alpha\epsilon_T\tau_A)\frac{\lambda N}{\beta}\left[\frac{f_1\beta S}{K_1(K_2K_3 - \theta\alpha\epsilon_T\tau_A)N} - 1\right] \\
&= K_1Z_2(I_u + \eta_A A + \eta_T I_T)\left[\frac{(Z_1 + Z_2)\beta S}{NK_1Z_2} - 1\right] \\
&\leq K_1Z_2(I_u + \eta_A A + \eta_T I_T)\left[\frac{\beta(Z_1 + Z_2)}{K_1Z_2} - 1\right] \text{ for } S \leq N \\
&= K_1Z_2(I_u + \eta_A A + \eta_T I_T)(\mathcal{R}_T - 1) < 0 \text{ for } \mathcal{R}_T < 1.
\end{aligned}
$$

The proof is completed using the same argument as in the proof of Theorem (3.1). □

3.4.3 Existence and local stability of EEP

Existence

Let $\mathcal{E}_1^T = (S^{**}, I_u^{**}, A^{**}, I_T^{**})$ be an endemic equilibrium of the full model (3.1). Further, let

$$\lambda^{**} = \frac{\beta(I_u^{**} + \eta_A A^{**} + \eta_T I_T^{**})}{N^{**}}. \tag{3.13}$$

Solving the equations in the model (3.1) at steady state, in terms of λ^{**}, gives

$$\begin{aligned} S^{**} &= \frac{\Pi}{\lambda^{**} + \mu}, \quad I_T^{**} = \frac{\lambda^{**}\Pi(\alpha\epsilon_T\tau_A + K_2\epsilon_T\tau_u)}{K_1(\lambda^{**} + \mu)Z_2}, \\ I_u^{**} &= \frac{\lambda^{**}\Pi}{K_1(\lambda^{**} + \mu)}, \quad A^{**} = \frac{\lambda^{**}\Pi\alpha(K_3 + \theta\epsilon_T\tau_u)}{K_1(\lambda^{**} + \mu)Z_2}. \end{aligned} \tag{3.14}$$

Using (3.14) in (3.13), and simplifying, gives

$$\lambda^{**} = \frac{\beta\lambda^{**}\left[\frac{1}{K_1} + \frac{\alpha\eta_A(K_3 + \theta\epsilon_T\tau_u)}{K_1Z_2} + \frac{r\eta_T(\alpha\epsilon_T\tau_A + K_2\epsilon_T\tau_u)}{K_1Z_2}\right]}{1 + \frac{\lambda^{**}}{K_1} + \frac{\alpha\lambda^{**}(K_3 + \theta\epsilon_T\tau_u)}{K_1Z_2} + \frac{\lambda^{**}(\alpha\epsilon_T\tau_A + K_2\epsilon_T\tau_u)}{K_1Z_2}}. \tag{3.15}$$

The positive endemic equilibrium of the model (3.1) can be obtained by solving for λ^{**} in (3.15) and substituting the result into (3.14). Clearly, $\lambda^{**} = 0$ is a fixed point of (3.15), which corresponds to the DFE, $\mathcal{E}_0^T$. For $\lambda^{**} \neq 0$, (3.15) can be simplified to:

$$b_2\lambda^{**} - c_2 = 0, \tag{3.16}$$

where,

$$b_2 = \frac{1}{K_1} + \frac{\alpha(K_3 + \theta\epsilon_T\tau_u)}{K_1 Z_2} + \frac{(\alpha\epsilon_T\tau_A + K_2\epsilon_T\tau_u)}{K_1 Z_2} \text{ and } c_2 = \mathcal{R}_T - 1.$$

Since all the model parameters are assumed to be non-negative, it follows that $b_2 > 0$ and $c_2 > 0$ for $\mathcal{R}_T > 1$. Thus, the linear equation (3.16) has a unique positive solution, given by $\lambda^{**} = \frac{c_2}{b_2}$, whenever $\mathcal{R}_T > 1$. Since $\mathcal{R}_T < 1$ implies $c_2 < 0$, it follows that for $\mathcal{R}_T < 1$, $\lambda^{**} < 0$. Hence, there is no positive solution when $\mathcal{R}_T < 1$. This result is summarized below.

Lemma 3.5. *The model* (3.1) *has a unique endemic equilibrium whenever* $\mathcal{R}_T > 1$.

The local asymptotic stability of this equilibrium is investigated below.

Local stability

Theorem 3.5. *The unique endemic equilibrium of the treatment model* (3.1) *is LAS whenever* $\mathcal{R}_T > 1$.

Proof. The proof is similar to that given in Section 3.3.3, but now after substituting (3.14) into (3.13), a fixed point problem of the form $\lambda^{**} = f(\lambda^{**})$ is obtained, where

$$f(\lambda^{**}) = \frac{\lambda^{**} C_{12}}{1 + \lambda^{**} C_{22}},$$

with,

$$\begin{aligned} C_{12} &= \frac{\beta}{K_1} + \frac{\beta\alpha\eta_A(K_3+\theta\epsilon_T\tau_u)}{K_1Z_2} + \frac{r\beta\eta_T(\alpha\epsilon_T\tau_A+K_2\epsilon_T\tau_u)}{K_1Z_2}, \\ C_{22} &= \frac{1}{K_1} + \frac{\alpha(K_3+\theta\epsilon_T\tau_u)}{K_1Z_2} + \frac{(\alpha\epsilon_T\tau_A+K_2\epsilon_T\tau_u)}{K_1Z_2}, \end{aligned}$$

and

$$f'(\lambda^{**}) = \frac{C_{12}}{(1+\lambda^{**}C_{22})^2}.$$

Evaluating $f'(\lambda^{**})$ at $\lambda^{**} = \dfrac{c_2}{b_2}$ shows that

$$f'(\lambda^{**})\Big|_{\lambda^{**}=\frac{c_2}{b_2}} = \frac{1}{\mathcal{R}_T} \text{ so that } \left|\left\{f'(\lambda^{**})\Big|_{\lambda^{**}=\frac{c_2}{b_2}}\right\}\right| < 1 \text{ whenever } \mathcal{R}_T > 1.$$

□

In summary, it is clear that the treatment model (3.1) has the same dynamical features as the treatment-free model (3.3) (both models have a globally-asymptotically stable DFE whenever the associated reproduction number is less than unity; and a unique locally-asymptotically stable endemic equilibrium whenever the reproduction number exceeds unity). Thus, adding treatment to the model (3.3) does not alter its dynamical features.

3.5 Numerical simulations and discussions

The treatment-free model (3.3) is a special case of model (3.1), and both models have been shown to exhibit similar qualitative dynamics. Consequently, numerical simulations will be carried out on the treatment model (3.1) using the parameter values in Table (3.2) (unless otherwise stated). Using this set of parameters, $\mathcal{R}_T = 2.3561$ (so that, by Theorem (3.5), the unique endemic equilibrium $\mathcal{E}_1^T$ is LAS). Figure 3.2 depicts time series plots of various variables of the model, using numerous initial conditions, illustrating the local stability property of the endemic equilibrium for this case.

The model is now simulated to assess the impact of the three different treatment strategies enumerated in section 3.2. Using a relatively low treatment rate of $\tau_u = \tau_A = 0.5$, Figure 3.3A shows that more new cases of HIV infection could be averted if the Universal Strategy is implemented. In this case, the HIV-only Strategy records the least number of cases averted. Figure 3.3B shows an increase in number of new cases averted with increasing treatment efficacy. Further simulations show that the Universal Strategy is most effective in reducing disease prevalence, followed by the AIDS-only, and then the HIV-only Strategy (Figure 3.3C). These simulations shows that for this value of τ, the Universal Strategy is always the best strategy. Low treatment rate can be thought of the case for which the supply of ARVs is limited.

The impact of the various treatment strategies on mortality is depicted in Figure 3.4. Here, the HIV-only Strategy records the most number of fatalities within a 10 year time. Figure 3.4A shows that the Universal Strategy prevents the most cumulative mortality, followed by the AIDS-only Strategy, and then the HIV-only Strategy.

Figures 3.4B-D depict mortality as a function of time with different treatment rates. The results obtained are consistent with those depicted in Figure 3.5A; except for the lower mortality in the Universal and AIDS-only Strategies when the treatment rate is increased.

Figure 3.5 depict the total number of infectives as a function of time, for different treatment rates. It is evident from this figure that the Universal Strategy gives the least number of total infectives. The highest number of infectives is recorded when no infected individual is treated. Here, too, a much lower number of total infectives is recorded when the treatment rate is increased.

In conclusion, these simulations show that the Universal Strategy is the best in terms of preventing new cases and mortality regardless of whether a low ($\tau_u = \tau_A = 0.5$) or high ($\tau_u = \tau_A = 5$) treatment rate is used. An extended version of the treatment model (3.1), incorporating the differential infectivity and staged-progression aspects of HIV disease, is studied in [77].

3.6 Summary

In summary, the analyses and simulations in this chapter show the following:

(i) Both the treatment-free and the treatment model have a globally-stable DFE whenever their associated reproduction number is less than unity; each of the models has a unique endemic equilibrium whenever its reproduction number exceeds unity;

(ii) The Universal Strategy gives the highest reduction in the total number of new cases and mortality;

(iii) The HIV-only Strategy results in more deaths than any of the other strategies;

(iv) In terms of reduction of new cases, the strategies are listed in descending order of significance as follows: Universal, AIDS-only and HIV-only strategies;

(v) For low treatment rates (associated with limited supply of ARVs), a targeted AIDS-only Strategy is quite competitive (but not as good as the Universal Strategy) in reducing new cases and HIV-related mortality.

Overall, the theoretical analyses in this chapter show that highest reductions in HIV burden can be achieved using the Universal Strategy rather than any of the other (two targeted) strategies. Further, the use of ARVs can lead to significant reductions of HIV burden, or even disease elimination, in the community.

Table 3.1: Description of variables and parameters for model (3.1)

Variable/Parameter	Description
$S(t)$	susceptible individuals
$I_u(t)$	newly- and asymptomatically-infected individuals
$A(t)$	individuals at AIDS stage of infection
$I_T(t)$	treated infected individuals
Π	recruitment rate into the sexually-active population
μ	natural death rate
δ	disease-induced mortality rate for individuals in AIDS stage
η_A	relative risk of infectiousness of AIDS individuals
η_T	relative risk of infectiousness of treated individuals
τ_u	treatment rate for individuals in the I_u class
τ_A	treatment rate for individuals in AIDS stage of infection
ϵ_T	efficacy of ARVs
α	progression rate to AIDS of individuals in the I_u class
θ	modification factor for progression to AIDS by treated individuals
β	contact rate

Table 3.2: Parameter values for model (3.1)

Parameters	**nominal values**
Π	1000
μ	1/32
δ	0.09
η_A	1.5
η_T	0.008
τ_u	variable
τ_A	variable
ϵ_T	0.5
α	0.8
θ	0.1
β	0.4

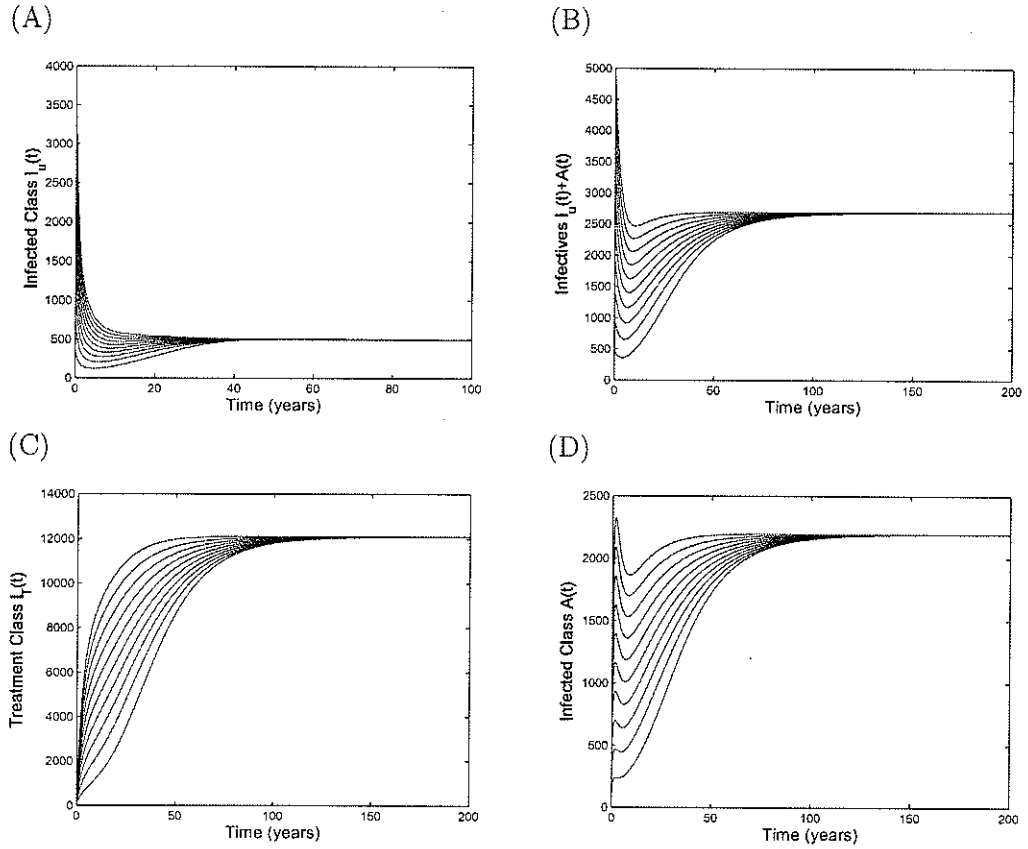
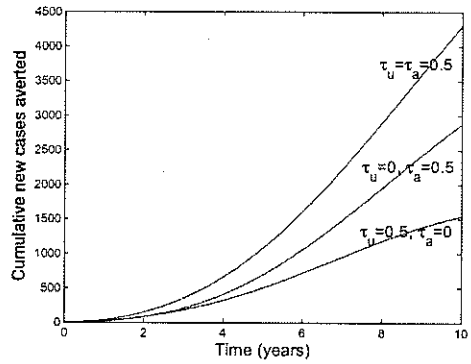
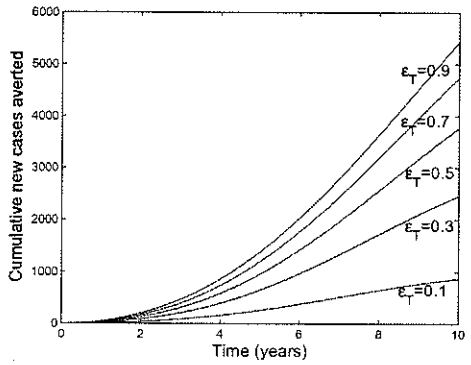


Figure 3.2: Time series plots for the treatment model (3.1) using different initial conditions. (A) $I_u(t)$; (B) $I_u(t) + A(t)$; (C) $I_T(t)$; (D) $A(t)$.

(A)



(B)



(C)

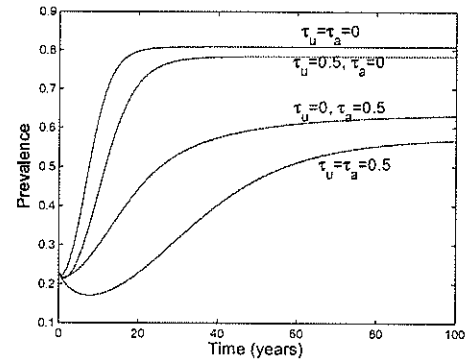


Figure 3.3: (A) Cumulative new cases averted using model (3.1) for different treatment strategies; (B) Cumulative new cases averted using model (3.1) with different treatment efficacies ($\epsilon_T = 0.1, 0.3, 0.5, 0.7, 0.9$) and $\tau_i = 0.5$; (C) Prevalence as a function of time for model (3.1) with different treatment strategies.

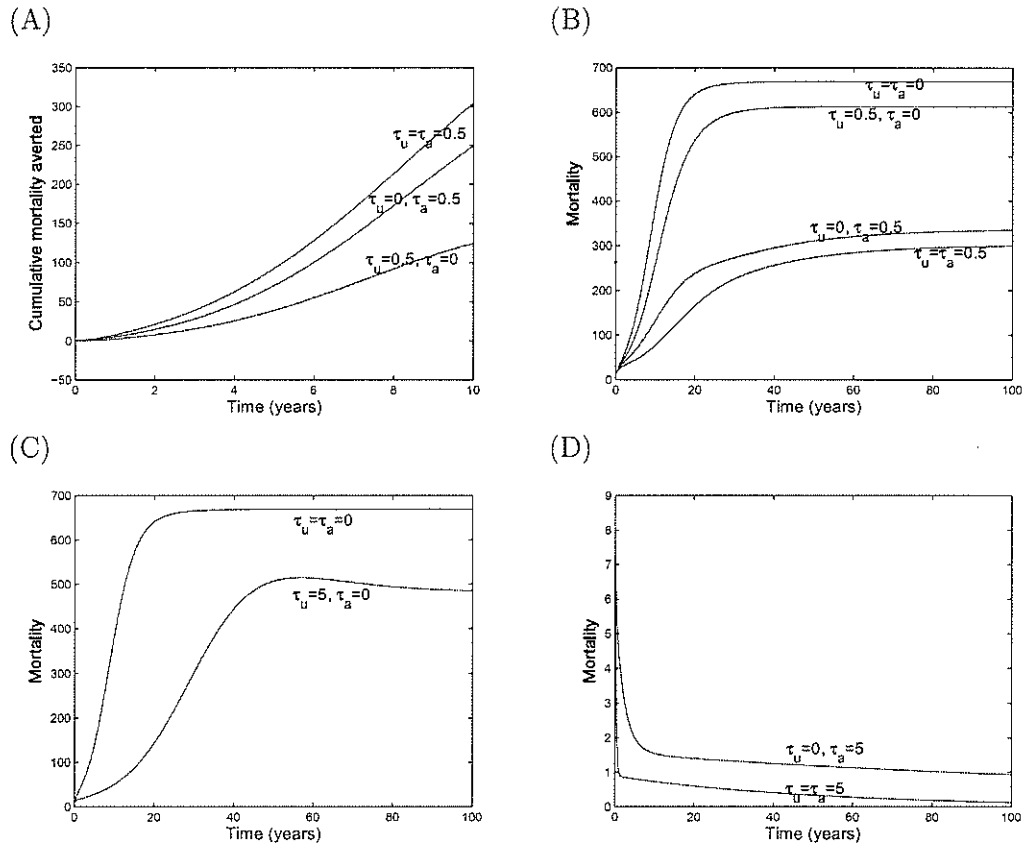


Figure 3.4: (A) Cumulative mortality averted for model (3.1) with different treatment strategies using $\tau_i = 0.5$; (B) Mortality as a function of time for model (3.1) with different treatment strategies using $\tau_i = 0.5$; (C&D) Mortality as a function of time for model (3.1) with different treatment strategies using $\tau_i = 5$.

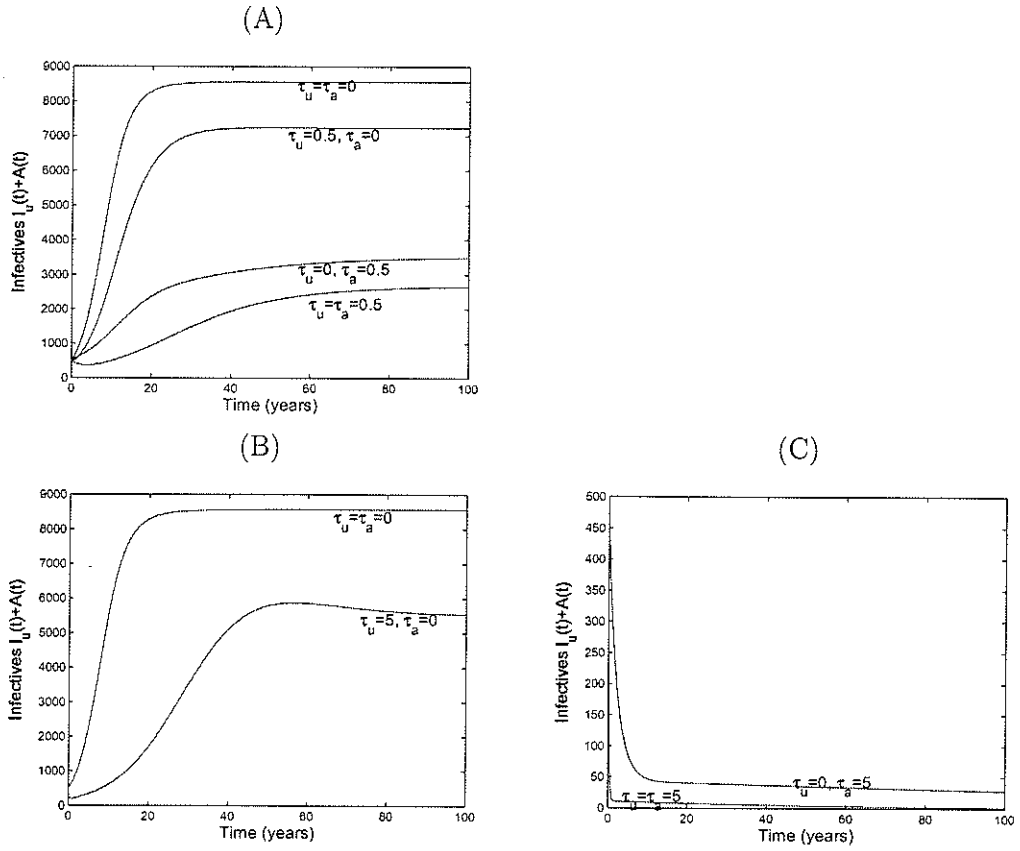


Figure 3.5: (A) Total infectives as a function of time for model (3.1) with different treatment strategies using $\tau_i = 0.5$; (B&C) Total infectives as a function of time for model (3.1) with different treatment strategies using $\tau_i = 5$.

Chapter 4

HIV Treatment Model with Wild and Resistant Strains

4.1 Introduction

One of the main epidemiological problems associated with the use of ARVs in a population is the emergence and transmission of ARV-resistant strains in the population. These new mutants arise due to numerous factors ranging from incomplete compliance to the specified ARV regimen to biological factors as well as to the primary infection of susceptible individuals with the resistant strain. In this chapter, the treatment model discussed in Chapter 3 is extended to account for two HIV strains, a wild (susceptible to ARV treatment) and an ARV-resistant strain. In this model, it is assumed that no treatment for the resistant strain exists. The objective is to quantify the epidemiological impact of the drug resistant strain, as well as to gain insights into the dynamics

of the two strains. Although models for multiple HIV subtypes or strains have been presented in the literature (see, for instance, [9, 10, 75]), this chapter complements and extends these studies by, first of all, including the transmission of HIV by AIDS individuals (which is not explicitly included in these models) and carrying out a detailed qualitative analysis of the resulting model.

4.2 Model formulation and basic properties

The total population, N, is subdivided into susceptible ($S(t)$), newly- and asymptomatically -infected individuals with the wild strain ($I_w(t)$), newly- and asymptomatically -infected individuals with resistant strain ($I_r(t)$), AIDS individual infected with the wild ($A_w(t)$), and resistant ($A_r(t)$) strain and treated individuals ($I_T(t)$), so that $N(t) = S(t) + I_w(t) + I_r(t) + A_w(t) + A_r(t) + I_T(t)$.

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate Π. These individuals acquire infection, following contact with infected individuals (in the I_w, I_r, A_w, A_r and I_T classes) at a rate λ_w and λ_r, where

$$\lambda_w = \frac{\beta(I_w + \eta_w A_w + \eta_T I_T)}{N} \text{ and } \lambda_r = \frac{\beta(I_r + \eta_r A_r)}{N}.$$

The parameter β is the effective contact rate, while $\eta_w \geq 1$ is the relative risk of infectiousness of individuals with AIDS (with wild strain) in comparison to individuals in the I_w class. The modification parameters $\eta_r > 1$ is similarly defined. Treated individ-

uals are assumed to be less infectious, where $0 < \eta_T < 1$ is a modification parameter. This model assumes that the wild and resistant strains are equally transmissible (albeit some studies, e.g. [75], suggest that the resistant strain is less transmissible than the wild strain).

Individuals in the I_w and I_r classes progress to AIDS at a rate σ_w and σ_r, respectively. Individuals infected with the wild strain (I_w or A_w) are treated at a rate τ_w. Treated individuals progress to AIDS at a slower rate $\theta\sigma_w$, where $0 < \theta < 1$ is a modification parameter. It is assumed that treated individuals become resistant to ARV treatment at a rate γ_{wr}. Further, natural mortality occurs in all classes, at a rate μ; and AIDS individuals suffer a disease-induced death at rates δ_w and δ_r for the wild strain-infected and the resistant strain-infected individuals, respectively. The model is given by (a flow diagram is given in Figure 4.1)

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_w S - \lambda_r S - \mu S, \\
\frac{dI_w}{dt} &= \lambda_w S - (\mu + \sigma_w + \tau_w) I_w, \\
\frac{dI_r}{dt} &= \lambda_r S - (\mu + \sigma_r) I_r + \gamma_{wr} I_T, \\
\frac{dA_w}{dt} &= \sigma_w I_w - (\tau_w + \mu + \delta_w) A_w + \theta\sigma_w I_T, \\
\frac{dA_r}{dt} &= \sigma_r I_r - (\mu + \delta_r) A_r, \\
\frac{dI_T}{dt} &= \tau_w I_w + \tau_w A_w - (\mu + \gamma_{wr} + \theta\sigma_w) I_T.
\end{aligned} \tag{4.1}$$

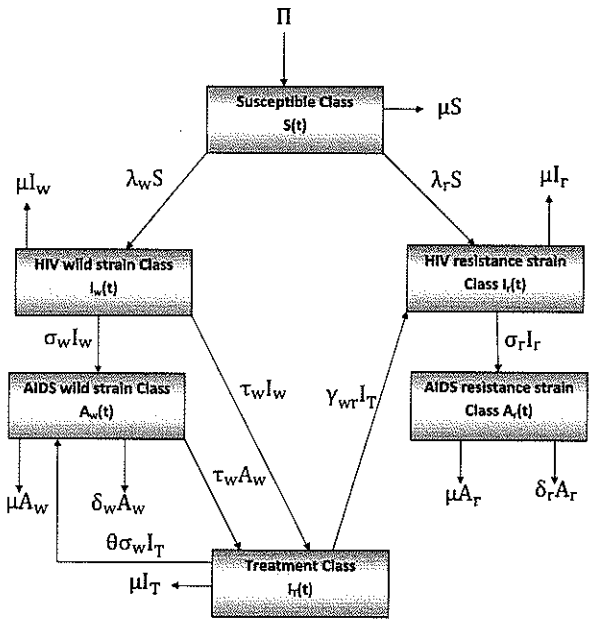


Figure 4.1: Flow diagram for model (4.1)

As in model (3.1), it is assumed that all the state variables and parameters of the model (4.1) are non-negative. Consider the biologically-feasible region

$$\mathcal{D} = \{(S, I_w, I_r, A_w, A_r, I_T) \in \mathbb{R}^6_+ : S + I_w + I_r + A_w + A_r + I_T \leq \Pi/\mu\}.$$

Using the method described in Section 3.2.1, it can be shown that $\mathcal{D}$ is positively-invariant and attracting, so that it is sufficient to consider the dynamics of the model there.

4.3 Treatment-free model

Consider the treatment-free version of the model (4.1) (obtained by setting $\tau_w = \eta_T = \gamma_{wr} = \theta = I_T = 0$ in (4.1)) given by

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_w S - \lambda_r S - \mu S, \\
\frac{dI_w}{dt} &= \lambda_w S - (\mu + \sigma_w) I_w, \\
\frac{dI_r}{dt} &= \lambda_r S - (\mu + \sigma_r) I_r, \\
\frac{dA_w}{dt} &= \sigma_w I_w - (\mu + \delta_w) A_w, \\
\frac{dA_r}{dt} &= \sigma_r I_r - (\mu + \delta_r) A_r,
\end{aligned} \tag{4.2}$$

with, $\lambda_w = \dfrac{\beta(I_w + \eta_w A_w)}{N}$ and $\lambda_r = \dfrac{\beta(I_r + \eta_r A_r)}{N}$. For the model (4.2), it can be shown that the following region is positively-invariant and attracting

$$\mathcal{D}_1 = \{(S, I_w, I_r, A_w, A_r) \in \mathbb{R}^5_+ : S + I_w + I_r + A_w + A_r \leq \Pi/\mu\},$$

so that it is sufficient to consider the dynamics of the model (4.2) in $\mathcal{D}_1$.

4.3.1 Local stability of DFE

The model (4.2) has a DFE given by

$$\mathcal{E}_0 = (S^*, I_w^*, I_r^*, A_w^*, A_r^*) = (\Pi/\mu, 0, 0, 0, 0). \tag{4.3}$$

For this model,

$$F = \begin{bmatrix} \frac{\beta S^*}{N^*} & 0 & \frac{\beta \eta_w S^*}{N^*} & 0 \\ 0 & \frac{\beta S^*}{N^*} & 0 & \frac{\beta \eta_r S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, V = \begin{bmatrix} P_1 & 0 & 0 & 0 \\ 0 & P_2 & 0 & 0 \\ -\sigma_w & 0 & P_3 & 0 \\ 0 & -\sigma_r & 0 & P_4 \end{bmatrix},$$

where,

$$P_1 = \mu + \sigma_w \text{ and } P_2 = \mu + \sigma_r, \quad P_3 = \mu + \delta_w \text{ and } P_4 = \mu + \delta_r.$$

It follows that the *basic reproduction number*, denoted by $\mathcal{R}_0 = \rho(FV^{-1})$, is given by

$$\mathcal{R}_0 = max\{\mathcal{R}_r, \mathcal{R}_w\},$$

with,

$$\mathcal{R}_r = \frac{\beta(P_4 + \eta_r \sigma_r)}{P_2 P_4} \text{ and } \mathcal{R}_w = \frac{\beta(P_3 + \eta_w \sigma_w)}{P_1 P_3}.$$

Using Theorem 2 in [87], the following result is established.

Lemma 4.1. *The DFE of the model* (4.2), *given by* (4.3), *is LAS if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

It is worth stating that $\mathcal{R}_r$ is the reproduction number of the resistant strain, while $\mathcal{R}_w$ is the reproduction number of the wild strain.

4.3.2 Global stability of DFE

Theorem 4.1. *The DFE of the model* (4.2)*, given by* (4.3)*, is GAS whenever* $\mathcal{R}_0 < 1$.

Proof. Consider the following Lyapunov function:

$$\mathcal{F} = (P_3 + \eta_w\sigma_w)I_w + P_1\eta_w A_w + (P_4 + \eta_r\sigma_r)I_r + P_2\eta_r A_r,$$

with Lyapunov derivative,

$$\begin{aligned}
\dot{\mathcal{F}} &= (P_3 + \eta_w\sigma_w)\dot{I}_w + P_1\eta_w\dot{A}_w + (P_4 + \eta_r\sigma_r)\dot{I}_r + P_2\eta_r\dot{A}_r \\
&= (P_3 + \eta_w\sigma_w)(\lambda_w S - P_1 I_w) + P_1\eta_w(\sigma_w I_w - P_3 A_w) + (P_4 + \eta_r\sigma_r)(\lambda_r S - P_2 I_r) \\
&\quad + P_2\eta_r(\sigma_r I_r - P_4 A_r) \\
&= (P_3 + \eta_w\sigma_w)\lambda_w S - P_1P_3(I_w + \eta_w A_w) + (P_4 + \eta_r\sigma_r)\lambda_r S - P_2P_4(I_r + \eta_r A_r) \\
&= (P_3 + \eta_w\sigma_w)\lambda_w S - P_1P_3N\lambda_w + (P_4 + \eta_r\sigma_r)\lambda_r S - P_2P_4N\lambda_r \\
&= P_1P_3N\lambda_w\left[\frac{(P_3 + \eta_w\sigma_w)S}{P_1P_3N} - 1\right] + P_2P_4N\lambda_r\left[\frac{(P_4 + \eta_r\sigma_r)S}{P_2P_4N} - 1\right] \\
&\leq P_1P_3(I_w + \eta_w A_w)\left[\frac{\beta(P_3 + \eta_w\sigma_w)}{P_1P_3} - 1\right] + P_2P_4(I_r + \eta_r A_r)\left[\frac{\beta(P_4 + \eta_r\sigma_r)}{P_2P_4} - 1\right] \text{ for } S \leq N \\
&= P_1P_3(I_w + \eta_w A_w)(\mathcal{R}_w - 1) + P_2P_4(I_r + \eta_r A_r)(\mathcal{R}_r - 1) < 0 \text{ for } \mathcal{R}_0 < 1.
\end{aligned}$$

The proof is completed using similar arguments as in the proof of Theorem (3.1). □

4.3.3 Existence and local stability of boundary equilibria

The non-trivial equilibria of the model (4.2), where at least one of the infected variables is non-zero, cannot be cleanly expressed in closed form. The approach in [51] will be used to explore the possibility of the existence and stability of non-trivial equilibria. The possible equilibria of the model (by inspection) are:

(i) Wild strain-only boundary equilibrium, $\mathcal{E}_w = (S^*, I_w^*, 0, A_w^*, 0)$; (no resistant strain)

(ii) Resistant strain-only boundary equilibrium, $\mathcal{E}_r = (S^*, 0, I_r^*, 0, A_r^*)$; (no wild strain)

(iii) Co-existence equilibria, $\mathcal{E}_{wr} = (S^{**}, I_w^{**}, I_r^{**}, A_w^{**}, A_r^{**})$; (both strains exist).

Solving the model at steady state gives

$$S^{**} = \frac{\Pi}{\lambda_w^{**} + \lambda_r^{**} + \mu}, \quad A_r^{**} = \frac{\sigma_r \lambda_r^{**} \Pi}{P_2 P_4 (\lambda_w^{**} + \lambda_r^{**} + \mu)}, \quad A_w^{**} = \frac{\sigma_w \lambda_w^{**} \Pi}{P_1 P_3 (\lambda_w^{**} + \lambda_r^{**} + \mu)}$$

$$I_r^{**} = \frac{\lambda_r^{**} \Pi}{P_2 (\lambda_w^{**} + \lambda_r^{**} + \mu)}, \quad I_w^{**} = \frac{\lambda_w^{**} \Pi}{P_1 (\lambda_w^{**} + \lambda_r^{**} + \mu)}. \tag{4.4}$$

Substituting the expressions in (4.4) into $\lambda_w^{**} = \dfrac{\beta(I_w^{**} + \eta_w A_w^{**})}{N^{**}}$ and $\lambda_r^{**} = \dfrac{\beta(I_r^{**} + \eta_r A_r^{**})}{N^{**}}$ gives

$$\begin{aligned} \lambda_w^{**} &= \phi_1(\lambda_w^{**}, \lambda_r^{**}) = \frac{\dfrac{\beta \Pi \lambda_w^{**}}{\lambda_w^{**} + \lambda_r^{**} + \mu}\left(\dfrac{1}{P_1} + \dfrac{\eta_w \sigma_w}{P_1 P_3}\right)}{N^{**}}, \\ \lambda_r^{**} &= \phi_2(\lambda_w^{**}, \lambda_r^{**}) = \frac{\dfrac{\beta \Pi \lambda_r^{**}}{\lambda_w^{**} + \lambda_r^{**} + \mu}\left(\dfrac{1}{P_2} + \dfrac{\eta_r \sigma_r}{P_2 P_4}\right)}{N^{**}}, \end{aligned} \tag{4.5}$$

where,

$$N^{**} = \frac{\Pi}{\lambda_w^{**} + \lambda_r^{**} + \mu}\left[1 + \lambda_w^{**}\left(\frac{1}{P_1} + \frac{\sigma_w}{P_1 P_3}\right) + \lambda_r^{**}\left(\frac{1}{P_2} + \frac{\sigma_r}{P_2 P_4}\right)\right].$$

The equilibria of the model can be obtained by finding the fixed points of the equation

$$x = \Phi(x) = \begin{pmatrix} \phi_1(\lambda_w^{**}, \lambda_r^{**}) \\ \\ \phi_2(\lambda_w^{**}, \lambda_r^{**}) \end{pmatrix}, \quad \text{where } x = \begin{pmatrix} \lambda_w^{**} \\ \\ \lambda_r^{**} \end{pmatrix}.$$

Existence and stability of wild strain-only boundary equilibrium ($\mathcal{E}_w$)

Theorem 4.2. *The model* (4.2) *has a unique positive wild strain-only boundary equilibrium, $\mathcal{E}_w$, which is LAS whenever $\mathcal{R}_r < 1 < \mathcal{R}_w$.*

Proof. It is clear from (4.5) that $\phi_2(\lambda_w^{**}, 0) = 0$. Thus, a fixed point of $\phi_1(\lambda_w^{**}, \lambda_r^{**})$ is obtained by solving the equation $\phi_1(\lambda_w^{**}, 0) = \lambda_w^{**}$. It follows that λ_w^{**} is the root of the equation

$$\lambda_w^{**}(a_{11}\lambda_w^{**} + c_{11}) = 0, \tag{4.6}$$

where,

$$a_{11} = P_3 + \sigma_w \text{ and } c_{11} = P_1 P_3(1 - \mathcal{R}_w).$$

It is clear that $\lambda_w^{**} = 0$ and $\lambda_w^{**} = -c_{11}/a_{11}$ are the roots of the equation (4.6), and it is worth noting here that $\lambda_w^{**} = 0$ corresponds to the DFE. It is easy to see that $a_{11} > 0$ and $c_{11} > 0$ ($c_{11} < 0$) whenever $\mathcal{R}_w < 1$ ($\mathcal{R}_w > 1$). Hence, $\lambda_w^{**} > 0$ whenever $c_{11} < 0$ ($\mathcal{R}_w > 1$). For $\mathcal{E}_w$ to exist, it is necessary that the resistant strain does not exist (i.e., $\mathcal{R}_r < 1$). Thus, a unique wild strain-only boundary equilibrium exists whenever $\mathcal{R}_r < 1 < \mathcal{R}_w$.

The local stability property of $\mathcal{E}_w$ is now shown. The Jacobian of Φ is given by

$$J = \begin{pmatrix} \dfrac{\partial \phi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}} & \dfrac{\partial \phi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}} \\ \\ \dfrac{\partial \phi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}} & \dfrac{\partial \phi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}} \end{pmatrix}.$$

Evaluating J at $(\lambda_w^{**}, 0)$ gives

$$J(\lambda_w^{**}, 0) = \begin{pmatrix} \dfrac{1}{\mathcal{R}_w} & \left.\dfrac{\partial \phi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}}\right|_{(\lambda_w^{**}, 0)} \\ \\ 0 & \mathcal{R}_{wr}^b \end{pmatrix},$$

where,

$$\mathcal{R}_{wr}^b = \frac{P_1 P_3 (P_4 + \eta_r \sigma_r)}{P_4 P_2 (P_3 + \eta_w \sigma_w)}.$$

For stability, we require $\frac{1}{\mathcal{R}_w} < 1$ (i.e., $\mathcal{R}_w > 1$) and $\mathcal{R}_{wr}^b < 1$ (i.e., $\mathcal{R}_r < \mathcal{R}_w$); note that $\mathcal{R}_r < 1$ in this case. Combining all these shows that the boundary equilibrium $\mathcal{E}_w$ is

LAS provided $\mathcal{R}_r < 1 < \mathcal{R}_w$. □

Existence and stability of resistant strain-only boundary equilibrium ($\mathcal{E}_r$)

We claim the following result.

Theorem 4.3. *The model* (4.2) *has a unique resistant strain-only boundary equilibrium, $\mathcal{E}_r$, which is LAS whenever $\mathcal{R}_w < 1 < \mathcal{R}_r$.*

Proof. Here, too, it is easy to see that $\phi_1(0, \lambda_r^{**}) = 0$. Thus, a fixed point of $\phi_2(\lambda_w^{**}, \lambda_r^{**})$ is obtained by solving the equation $\phi_2(0, \lambda_r^{**}) = \lambda_r^{**}$, from which it follows that λ_r^{**} is the root of the equation

$$\lambda_r^{**}(a_{22}\lambda_r^{**} + c_{22}) = 0, \tag{4.7}$$

where,

$$a_{22} = P_4 + \sigma_r \text{ and } c_{22} = P_2P_4(1 - \mathcal{R}_r).$$

It is clear that $\lambda_r^{**} = 0$ (corresponding to the DFE) and $\lambda_r^{**} = -c_{22}/a_{22}$ are roots of the equation (4.7). It is easy to see that $a_{22} > 0$, while $c_{22} > 0$ ($c_{22} < 0$) whenever $\mathcal{R}_r < 1$ ($\mathcal{R}_r > 1$). Hence, $\lambda_r^{**} > 0$ whenever $c_{22} < 0$ ($\mathcal{R}_r > 1$). Here, since there is no wild strain, $\mathcal{R}_w < 1$. Thus, a unique resistant strain-only equilibrium, $\mathcal{E}_r$, exists whenever $\mathcal{R}_w < 1 < \mathcal{R}_r$.

Evaluating J at $(0, \lambda_r^{**})$ gives

$$J(0,\lambda_r^{**}) = \begin{pmatrix} \dfrac{1}{\mathcal{R}_{wr}^b} & 0 \\ \dfrac{\partial \phi_1(\lambda_w^{**},\lambda_r^{**})}{\partial \lambda_r^{**}}\Big|_{(0,\lambda_r^{**})} & \dfrac{1}{\mathcal{R}_r} \end{pmatrix}.$$

For local stability of $\mathcal{E}_r$, we require $\frac{1}{\mathcal{R}_r} < 1$ ($\mathcal{R}_r > 1$) and $\frac{1}{\mathcal{R}_{wr}^b} < 1$ ($\mathcal{R}_w < \mathcal{R}_r$). Thus, $\mathcal{E}_r$ is LAS provided $\mathcal{R}_w < 1 < \mathcal{R}_r$. □

4.3.4 Existence and local stability of co-existence equilibria

First of all, the expressions in (4.5) can be re-written as

$$\begin{aligned} \lambda_w^{**} &= \frac{\beta(I_w^{**} + \eta_w A_w^{**})}{N^{**}} \equiv \frac{\lambda_w^{**}\mathcal{R}_w}{1 + \lambda_w^{**}L_1 + \lambda_r^{**}L_2}, \\ \lambda_r^{**} &= \frac{\beta(I_r^{**} + \eta_r A_r^{**})}{N^{**}} \equiv \frac{\lambda_r^{**}\mathcal{R}_r}{1 + \lambda_w^{**}L_1 + \lambda_r^{**}L_2}, \end{aligned} \tag{4.8}$$

where,

$$L_1 = \frac{1}{P_1} + \frac{\sigma_w}{P_1 P_3} \text{ and } L_2 = \frac{1}{P_2} + \frac{\sigma_r}{P_2 P_4}.$$

It follows from (4.8) that

$$\begin{aligned} \lambda_w^{**}L_1 + \lambda_r^{**}L_2 &= \mathcal{R}_w - 1, \\ \lambda_w^{**}L_1 + \lambda_r^{**}L_2 &= \mathcal{R}_r - 1. \end{aligned} \tag{4.9}$$

Since the left hand sides of the equations in (4.9) are always positive, it is necessary that $\mathcal{R}_w > 1$ and $\mathcal{R}_r > 1$. If $\mathcal{R}_w \neq \mathcal{R}_r$, then system (4.9) is inconsistent; and there is no positive co-existence equilibria in this case. Hence, for the two equations in (4.9) to be consistent, it is necessary that $\mathcal{R}_w = \mathcal{R}_r > 1$. It is worth mentioning that, in this case, a continuum (infinitely many) of endemic equilibria will arise (this phenomenon was also observed in a study of TB dynamics [18]). That is, setting $\mathcal{R}_w = \mathcal{R}_r = \mathcal{R}_i > 1$ implies that

$$\lambda_w^{**} L_1 + \lambda_r^{**} L_2 = \mathcal{R}_i - 1, \tag{4.10}$$

so that $0 < \lambda_w^{**} < \dfrac{\mathcal{R}_i - 1}{L_1}$, and $0 < \lambda_r^{**} < \dfrac{\mathcal{R}_i - 1}{L_2}$. This result is summarized below.

Theorem 4.4. *The model* (4.2) *has a continuum (family) of positive co-existence endemic equilibria,* $\mathcal{E}_{wr}^n$ *(*$n \in \mathbb{Z}_+$*), whenever all of the following hold*

(a) $\mathcal{R}_w = \mathcal{R}_r > 1$,

(b) $0 < \lambda_r^{**} < \dfrac{\mathcal{R}_r - 1}{L_2}$,

(c) $0 < \lambda_w^{**} < \dfrac{\mathcal{R}_w - 1}{L_1}$,

(d) $\lambda_w^{**} = \dfrac{\mathcal{R}_w - 1 - \lambda_r^{**} L_2}{L_1}$,

and no co-existence endemic equilibria otherwise.

Theorem 4.5. *Let* $\mathcal{R}_{wr}^n = \dfrac{T_0 + \sqrt{T_0^2 - 4T_1}}{2}$, $(n \in \mathbb{Z}_+)$, *with*

$$T_0 = \left(\frac{\partial \phi_1}{\partial \lambda_w^{**}} + \frac{\partial \phi_2}{\partial \lambda_r^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})} \text{ and } T_1 = \left(\frac{\partial \phi_1}{\partial \lambda_w^{**}}\frac{\partial \phi_2}{\partial \lambda_r^{**}} - \frac{\partial \phi_1}{\partial \lambda_r^{**}}\frac{\partial \phi_2}{\partial \lambda_w^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})}.$$

Then, $\mathcal{E}^n_{wr}$ is LAS whenever $|\mathcal{R}^n_{wr}| < 1$, for each $n \in \mathbb{Z}_+$.

Proof. Evaluating the Jacobian of Φ at each $(\lambda_w^{**}, \lambda_r^{**})$ in the regions **(b)** to **(d)**, gives

$$J(\lambda_w^{**}, \lambda_r^{**}) = \begin{pmatrix} \left.\dfrac{\partial \phi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} & \left.\dfrac{\partial \phi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} \\ \\ \left.\dfrac{\partial \phi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} & \left.\dfrac{\partial \phi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} \end{pmatrix},$$

with eigenvalues given by the roots of the equation

$$\chi^2 - \chi\left(\frac{\partial \phi_1}{\partial \lambda_w^{**}} + \frac{\partial \phi_2}{\partial \lambda_r^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})} + \left(\frac{\partial \phi_1}{\partial \lambda_w^{**}}\frac{\partial \phi_2}{\partial \lambda_r^{**}} - \frac{\partial \phi_1}{\partial \lambda_r^{**}}\frac{\partial \phi_2}{\partial \lambda_w^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})} = 0.$$

It is easy to show that the dominant eigenvalue of $J(\lambda_w^{**}, \lambda_r^{**})$ is $\mathcal{R}^n_{wr}$. Thus, the family of co-existence endemic equilibrium, $\mathcal{E}^n_{wr}$, is LAS whenever $|\mathcal{R}^n_{wr}| < 1$ for each n. □

It is worth noting that for the case $\mathcal{R}_w = \mathcal{R}_r = 1$, the solution of system (4.9) is the trivial solution $(0, 0)$ (corresponding to the DFE). Finally, we offer the following conjectures (competitive exclusion):

Conjecture 4.1. *The model (4.2) has a unique and LAS positive resistant strain-only boundary equilibrium, $\mathcal{E}_r$, whenever $\mathcal{R}_w < \mathcal{R}_r$ and $\mathcal{R}_r > 1$.*

Conjecture 4.2. *The model (4.2) has a unique and LAS positive wild strain-only boundary equilibrium, $\mathcal{E}_w$, whenever $\mathcal{R}_r < \mathcal{R}_w$ and $\mathcal{R}_w > 1$.*

4.4 Analysis of the treatment model

4.4.1 Local stability of DFE

Consider, now, the full model (4.1). Its DFE is

$$\mathcal{E}_0^t = (S^*, I_w^*, I_r^*, A_w^*, A_r^*, I_T^*) = (\Pi/\mu, 0, 0, 0, 0, 0). \tag{4.11}$$

Further, the next generation matrices are given by:

$$F = \begin{bmatrix} \frac{\beta S^*}{N^*} & 0 & \frac{\beta\eta_w S^*}{N^*} & 0 & \frac{\beta\eta_T S^*}{N^*} \\ 0 & \frac{\beta S^*}{N^*} & 0 & \frac{\beta\eta_r S^*}{N^*} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, V = \begin{bmatrix} P_{11} & 0 & 0 & 0 & 0 \\ 0 & P_{12} & 0 & 0 & -\gamma_{wr} \\ -\sigma_w & 0 & P_{13} & 0 & -\theta\sigma_w \\ 0 & -\sigma_r & 0 & P_{14} & 0 \\ -\tau_w & 0 & -\tau_w & 0 & P_{15} \end{bmatrix},$$

where,

$$P_{11} = \mu + \sigma_w + \tau_w,\ P_{12} = \mu + \sigma_r,\ P_{13} = \mu + \delta_w + \tau_w,\ P_{14} = \mu + \delta_r,\ P_{15} = \mu + \gamma_{wr} + \theta\sigma_w.$$

It follows that the *treatment reproduction number*, denoted by $\mathcal{R}_0^t = \rho(FV^{-1})$, is

$$\mathcal{R}_0^t = max\{\mathcal{R}_r^t, \mathcal{R}_w^t\},$$

with,

$$\mathcal{R}_r^t = \frac{\beta(P_{14}+\eta_r\sigma_r)}{P_{12}P_{14}} \text{ and } \mathcal{R}_w^t = \frac{\beta}{P_{11}}\left\{1+\frac{\eta_w\sigma_w(P_{15}+\theta\tau_w)+\eta_T\tau_w(P_{13}+\sigma_w)}{P_{13}(\mu+\gamma_{wr})+\theta\sigma_w(\mu+\delta_w)}\right\}.$$

The following result holds by Theorem 2 of [87].

Lemma 4.2. *The DFE of the model* (4.1), *given by* (4.11), *is LAS if* $\mathcal{R}_0^t < 1$ *and unstable if* $\mathcal{R}_0^t > 1$.

Further, we claim the following:

4.4.2 Global stability of DFE

Theorem 4.6. *The DFE of the model* (4.1), *given by* (4.11), *is GAS whenever* $\mathcal{R}_0^t < 1$.

Proof. The proof is based on using a comparison theorem. Notice, first of all, that the

equations for the infected components in (4.1) can be written in terms of

$$\begin{pmatrix} \frac{dI_w(t)}{dt} \\ \frac{dI_r(t)}{dt} \\ \frac{dA_w(t)}{dt} \\ \frac{dA_r(t)}{dt} \\ \frac{dI_T(t)}{dt} \end{pmatrix} = (F - V) \begin{pmatrix} I_w(t) \\ I_r(t) \\ A_w(t) \\ A_r(t) \\ I_T(t) \end{pmatrix} - \left(1 - \frac{S}{N}\right) \begin{pmatrix} \beta & 0 & \beta\eta_w & 0 & \beta\eta_T \\ 0 & \beta & 0 & \beta\eta_r & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} I_w(t) \\ I_r(t) \\ A_w(t) \\ A_r(t) \\ I_T(t) \end{pmatrix},$$

where the matrices F and V are as defined above. Since $S \leq N$ (for all $t \geq 0$) in $\mathcal{D}$, it follows that

$$\begin{pmatrix} \frac{dI_w(t)}{dt} \\ \\ \frac{dI_r(t)}{dt} \\ \\ \frac{dA_w(t)}{dt} \\ \\ \frac{dA_r(t)}{dt} \\ \\ \frac{dI_T(t)}{dt} \end{pmatrix} \leq (F-V) \begin{pmatrix} I_w(t) \\ \\ I_r(t) \\ \\ A_w(t) \\ \\ A_r(t) \\ \\ I_T(t) \end{pmatrix}. \tag{4.12}$$

Using the fact that the eigenvalues of the matrix $F - V$ all have negative real parts (see local stability result in Lemma (4.2), where $\rho(FV^{-1}) < 1$ if $\mathcal{R}_0^t < 1$, which is equivalent to $F - V$ having eigenvalues with negative real parts when $\mathcal{R}_0^t < 1$), it follows that the linearized differential inequality system (4.12) is stable whenever $\mathcal{R}_0^t < 1$. Consequently, $(I_w(t), I_r(t), A_w(t), A_r(t), I_T(t)) \to (0, 0, 0, 0, 0)$ as $t \to \infty$. It follows by comparison theorem (see, for instance, [56], p. 31 and [83], Theorem B.1; Appendix B) that $(I_w(t), I_r(t), A_w(t), A_r(t), I_T(t)) \to (0, 0, 0, 0, 0)$. Substituting $I_w = I_r = A_w = A_r = I_T = 0$ in the first equation of (4.1) gives $S(t) \to S^*$ as $t \to \infty$. Thus, $(S(t), I_w(t), I_r(t), A_w(t), A_r(t), I_T(t)) \to (S^*, 0, 0, 0, 0, 0)$ as $t \to \infty$ for $\mathcal{R}_0^t < 1$, so that $\mathcal{E}_0^t$ is GAS if $\mathcal{R}_0^t < 1$. □

4.4.3 Existence and local stability of boundary equilibria

The existence and stability of the equilibria associated with the model (4.1) is investigated here. The possible equilibria of the model are:

(i) Resistant strain-only boundary equilibrium $\mathcal{E}_r^t = (S^*, 0, I_r^*, 0, A_r^*, 0)$; (no wild strain);

(ii) *Low endemicity* co-existence equilibrium, corresponding to $I_r = 0, A_r = 0$ in (4.1), denoted by $\mathcal{E}_{wr1}^t = (S^*, I_w^*, I_r^*, A_w^*, A_r^*, I_T^*)$; (both strains co-exist);

(iii) *High endemicity* co-existence equilibrium, denoted by $\mathcal{E}_{wr2}^t = (S^{**}, I_w^{**}, I_r^{**}, A_w^{**}, A_r^{**}, I_T^{**})$, (both strains co-exist).

It should be noted that the model (4.1) cannot have a wild strain-only boundary equilibrium, except if $\lim_{t\to\infty} I_T = 0$.

As before, the model (4.1) is solved at steady state, in terms of

$$\lambda_w^{**} = \frac{\beta(I_w^{**} + \eta_w A_w^{**} + \eta_T I_T^{**})}{N^{**}} \text{ and } \lambda_r^{**} = \frac{\beta(I_r^{**} + \eta_r A_r^{**})}{N^{**}}, \tag{4.13}$$

giving,

$$S^{**} = \frac{\Pi}{\lambda_w^{**} + \lambda_r^{**} + \mu}, \qquad A_w^{**} = \frac{\sigma_w \lambda_w^{**} \Pi (P_{15} + \theta \tau_w)}{P_{11}(\lambda_w^{**} + \lambda_r^{**} + \mu)[P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)]},$$

$$I_w^{**} = \frac{\lambda_w^{**} \Pi}{P_{11}(\lambda_w^{**} + \lambda_r^{**} + \mu)}, \quad I_T^{**} = \frac{(\sigma_w + P_{13}) \tau_w \lambda_w^{**} \Pi}{P_{11}(\lambda_w^{**} + \lambda_r^{**} + \mu)[P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)]}, \tag{4.14}$$

$$I_r^{**} = \frac{[\lambda_r^{**} P_{11}\{P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)\} + \gamma_{wr} \lambda_w^{**} \tau_w (\sigma_w + P_{13})]\Pi}{(\lambda_w^{**} + \lambda_r^{**} + \mu)[P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)] P_{11} P_{12}},$$

$$A_r^{**} = \frac{\sigma_r [\lambda_r^{**} P_{11}\{P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)\} + \gamma_{wr} \lambda_w^{**} \tau_w (\sigma_w + P_{13})]\Pi}{(\lambda_w^{**} + \lambda_r^{**} + \mu)[P_{13}(\mu + \gamma_{wr}) + \theta \sigma_w (\mu + \delta_w)] P_{11} P_{12} P_{14}}.$$

Substituting the components of the equilibrium at steady state into the expressions in (4.13), gives (noting that $N^{**} = S^{**} + I_w^{**} + I_r^{**} + A_w^{**} + A_r^{**} + I_T^{**}$) a fixed-point problem of the form

$$x = \Psi(x) = \begin{pmatrix} \psi_1(\lambda_w^{**}, \lambda_r^{**}) \\ \\ \psi_2(\lambda_w^{**}, \lambda_r^{**}) \end{pmatrix}, \quad \text{with } x = \begin{pmatrix} \lambda_w^{**} \\ \\ \lambda_r^{**} \end{pmatrix},$$

where ψ_1 and ψ_2 are defined as the right-hand side of the resulting two equations, respectively.

Existence and stability of resistant strain-only boundary equilibrium ($\mathcal{E}_r^t$)

Theorem 4.7. *The model* (4.1) *has a unique and LAS resistant strain-only boundary equilibrium,* $\mathcal{E}_r^t$*, whenever* $\mathcal{R}_w^t < 1 < \mathcal{R}_r^t$*, and no boundary equilibrium otherwise.*

Proof. The proof is as in Section 4.5. Here, $\psi_1(0, \lambda_r^{**}) = 0$ so that the fixed point of $\psi_2(\lambda_w^{**}, \lambda_r^{**})$ is obtained by solving the equation $\psi_2(0, \lambda_r^{**}) = \lambda_r^{**}$. It follows that λ_r^{**} satisfies the equation

$$a_{33}\lambda_r^{**} + b_{33} = 0,$$

where,

$$a_{33} = P_{13} + \sigma_r \text{ and } b_{33} = P_{12}P_{14}(1 - \mathcal{R}_r^t).$$

Here, $\lambda_r^{**} = -b_{33}/a_{33}$. Clearly, a_{33} is positive, and whenever $\mathcal{R}_r^t > 1$, then $b_{33} < 0$ ($\lambda_r^{**} > 0$). Hence, a unique resistant strain-only equilibrium exists whenever $\mathcal{R}_r^t > 1$ (note that $\mathcal{R}_w^t < 1$ here). For the local stability of this equilibrium, the Jacobian of Ψ, given by

$$J = \begin{pmatrix} \dfrac{\partial \psi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}} & \dfrac{\partial \psi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}} \\ \\ \dfrac{\partial \psi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}} & \dfrac{\partial \psi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}} \end{pmatrix},$$

is evaluated at $(0, \lambda_r^{**})$. This gives

$$J(0,\lambda_r^{**}) = \begin{pmatrix} \dfrac{1}{\mathcal{R}_{wr}^{bb}} & 0 \\ \dfrac{\partial \psi_1(\lambda_w^{**},\lambda_r^{**})}{\partial \lambda_r^{**}}\Big|_{(0,\lambda_r^{**})} & \dfrac{1}{\mathcal{R}_r^t} \end{pmatrix},$$

where,

$$\mathcal{R}_{wr}^{bb} = \frac{\mathcal{R}_r^t}{\mathcal{R}_w^t}.$$

Further, for stability, we require $\frac{1}{\mathcal{R}_r^t} < 1$ ($\mathcal{R}_r^t > 1$) and $\frac{1}{\mathcal{R}_{wr}^{bb}} < 1$ ($\mathcal{R}_w^t < \mathcal{R}_r^t$). Combining all these shows that $\mathcal{E}_r^t$ is LAS provided $\mathcal{R}_w^t < 1 < \mathcal{R}_r^t$. □

4.4.4 Existence and local stability of co-existence equilibria

Existence and stability of the low endemicity co-existence equilibrium ($\mathcal{E}_{wr1}^t$)

It is worth emphasizing here that, in the absence of transmission of the resistant strain in the community ($\lambda_r = 0$), individuals infected with the wild strain will still develop resistance, due to treatment (thereby moving into the ARV-resistant class, (I_r)). Thus, the I_r and A_r compartments will always be non-empty (even when $\lambda_r = 0$), except if $\lim_{t\to\infty} I_T = 0$. In other words, $\lim_{t\to\infty} I_r \neq 0$ and $\lim_{t\to\infty} A_r \neq 0$ even if $\lambda_r = 0$. Since the equilibrium is obtained by setting $\lambda_r = 0$ (so that $I_r = A_r = 0$) in (4.1), it is termed the low endemicity coexistence equilibrium (to distinguish it from the other co-existence equilibrium for which λ_r was not set to zero). We claim the following.

Theorem 4.8. *Let* $\mathcal{R}_w^{tt} = \dfrac{T_{10} + \sqrt{T_{10}^2 - 4T_{20}}}{2}$ *with*

$$T_{10} = \left(\frac{\partial \psi_1}{\partial \lambda_w^{**}} + \frac{\partial \psi_2}{\partial \lambda_r^{**}}\right)\Bigg|_{(\lambda_w^{**},0)} \text{ and } T_{20} = \left(\frac{\partial \psi_1}{\partial \lambda_w^{**}}\frac{\partial \psi_2}{\partial \lambda_r^{**}} - \frac{\partial \psi_1}{\partial \lambda_r^{**}}\frac{\partial \psi_2}{\partial \lambda_w^{**}}\right)\Bigg|_{(\lambda_w^{**},0)}.$$

In the absence of infection by resistant strain ($\lambda_r = 0$)*, the model* (4.1) *has a unique and LAS low endemicity co-existence equilibrium, denoted by* $\mathcal{E}_{wr1}^t$*, whenever* $\mathcal{R}_w^t > 1$ *and* $|\mathcal{R}_w^{tt}| < 1$.

Proof. Letting $\lambda_r^{**} = 0$ in (4.14), accounting for the absence of transmission of the resistant strain, gives

$$S^{**} = \frac{\Pi}{\lambda_w^{**} + \mu}, \qquad A_w^{**} = \frac{\sigma_w \lambda_w^{**} \Pi (\lambda_w^{**} + \mu)^{-1}(P_{15} + \theta\tau_w)}{P_{11}[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]},$$

$$I_w^{**} = \frac{\lambda_w^{**}\Pi}{P_{11}(\lambda_w^{**} + \mu)}, \qquad I_T^{**} = \frac{(\lambda_w^{**} + \mu)^{-1}(\sigma_w + P_{13})\tau_w \lambda_w^{**}\Pi}{P_{11}[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]}, \tag{4.15}$$

$$I_r^{**} = \frac{\Pi\gamma_{wr}\lambda_w^{**}\tau_w(\lambda_w^{**} + \mu)^{-1}(\sigma_w + P_{13})}{[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]P_{11}P_{12}}, \qquad A_r^{**} = \frac{\Pi\sigma_r\gamma_{wr}\lambda_w^{**}\tau_w(\lambda_w^{**} + \mu)^{-1}(\sigma_w + P_{13})}{[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]P_{11}P_{12}P_{14}}.$$

Substituting the expressions in (4.15) into the expression for λ_w^{**} in (4.13) shows that the non-zero equilibria of the model satisfy

$$a_{44}\lambda_w^{**} + b_{44} = 0, \tag{4.16}$$

where,

$$
\begin{aligned}
a_{44} &= (P_{13}+\sigma_w)[\gamma_{wr}\tau_w(P_{14}+\sigma_r)+P_{14}P_{12}(\tau_w+P_{15})], \\
b_{44} &= P_{11}P_{12}P_{14}[P_{13}(\mu+\gamma_{wr})+\theta\sigma_w(\mu+\delta_w)](1-\mathcal{R}_w^t).
\end{aligned}
$$

Here, now, $\lambda_w^{**} = -b_{44}/a_{44}$; and it is easy to see that a_{44} is positive, while $\mathcal{R}_w^t > 1$ is required for b_{44} to be negative so that $\lambda_w > 0$. This proves the existence of the low endemicity co-existence equilibrium. Its local stability is investigated by evaluating the Jacobian J at $(\lambda_w^{**}, 0)$, giving

$$
J(\lambda_w^{**},0) = \begin{pmatrix}
\left.\dfrac{\partial\psi_1(\lambda_w^{**},\lambda_r^{**})}{\partial\lambda_w^{**}}\right|_{(\lambda_w^{**},0)} & \left.\dfrac{\partial\psi_1(\lambda_w^{**},\lambda_r^{**})}{\partial\lambda_r^{**}}\right|_{(\lambda_w^{**},0)} \\
\left.\dfrac{\partial\psi_2(\lambda_w^{**},\lambda_r^{**})}{\partial\lambda_w^{**}}\right|_{(\lambda_w^{**},0)} & \left.\dfrac{\partial\psi_2(\lambda_w^{**},\lambda_r^{**})}{\partial\lambda_r^{**}}\right|_{(\lambda_w^{**},0)}
\end{pmatrix},
$$

with eigenvalues satisfying

$$
\chi^2 - \chi\left(\frac{\partial\psi_1}{\partial\lambda_w^{**}}+\frac{\partial\psi_2}{\partial\lambda_r^{**}}\right)\Bigg|_{(\lambda_w^{**},0)} + \left(\frac{\partial\psi_1}{\partial\lambda_w^{**}}\frac{\partial\psi_2}{\partial\lambda_r^{**}} - \frac{\partial\psi_1}{\partial\lambda_r^{**}}\frac{\partial\psi_2}{\partial\lambda_w^{**}}\right)\Bigg|_{(\lambda_w^{**},0)} = 0.
$$

It is easy to show that the dominant eigenvalue of $J(\lambda_w^*, 0)$ is $\mathcal{R}_w^{tt}$. Hence, the low endemicity equilibrium is LAS whenever $|\mathcal{R}_w^{tt}| < 1$. □

Existence and stability of the high endemicity co-existence equilibrium ($\mathcal{E}^t_{wr2}$)

First of all, it should be noted from (4.13) that, at steady state,

$$\begin{aligned}\lambda^{**}_w &= \frac{\beta(I^{**}_w + \eta_w A^{**}_w + \eta_T I^{**}_T)}{N^{**}} \equiv \frac{\lambda^{**}_w \mathcal{R}^t_w}{1 + \lambda^{**}_w H_1 + \lambda^{**}_r H_2},\\ \lambda^{**}_r &= \frac{\beta(I^{**}_r + \eta_r A^{**}_r)}{N^{**}} \equiv \frac{\lambda^{**}_r \mathcal{R}^t_r + \lambda^{**}_w H}{1 + \lambda^{**}_w H_1 + \lambda^{**}_r H_2},\end{aligned} \tag{4.17}$$

where,

$$\begin{aligned}H &= \frac{\gamma_{wr}\tau_w(\sigma_w + P_{13})\mathcal{R}^t_r}{[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]P_{12}}, \quad H_2 = \frac{1}{P_{12}} + \frac{\sigma_r}{P_{12}P_{14}},\\ H_1 &= \frac{\sigma_w(P_{15} + \theta\tau_w) + \tau_w(\sigma_w + P_{13})}{P_{11}[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]} + \frac{1}{P_{11}} + \frac{\gamma_{wr}\tau_w(\sigma_w + P_{13})}{[P_{13}(\mu + \gamma_{wr}) + \theta\sigma_w(\mu + \delta_w)]P_{11}P_{12}}\left[1 + \frac{\sigma_r}{P_{14}}\right].\end{aligned}$$

Thus, (4.17) is equivalent to

$$\begin{aligned}\lambda^{**}_w H_1 + \lambda^{**}_r H_2 &= \mathcal{R}^t_w - 1,\\ \lambda^{**}_w H_1 + \lambda^{**}_r H_2 - \frac{\lambda^{**}_w H}{\lambda^{**}_r} &= \mathcal{R}^t_r - 1,\end{aligned} \tag{4.18}$$

so that,

$$\lambda^{**}_w = \frac{(\mathcal{R}^t_w - \mathcal{R}^t_r)\lambda^{**}_r}{H}. \tag{4.19}$$

Since the left hand side of the first equation in (4.18) is positive, it follows that $\mathcal{R}^t_w > 1$ for consistency. Note also that for co-existence of the two strains, the forces of infection

λ_w^{**}, and λ_r^{**}, at steady-state, must be nonzero. Hence, from (4.19), $\mathcal{R}_w^t > \mathcal{R}_r^t$ (i.e., $\lambda_w > \lambda_r$) is required for the co-existence of the two strains. Thus, we have established the following result.

Theorem 4.9. *The model* (4.1) *has a unique positive high endemicity co-existence endemic equilibrium,* $\mathcal{E}_{wr2}^t$, *whenever* $\mathcal{R}_w^t > \mathcal{R}_r^t$ *and* $\mathcal{R}_w^t > 1, \mathcal{R}_r^t > 1$.

Theorem 4.10. *The unique positive co-existence endemic equilibrium of the model* (4.1) *is LAS whenever* $|\mathcal{R}_{wr}^t| < 1$.

Proof. Evaluating the Jacobian of Ψ at $(\lambda_w^{**}, \lambda_r^{**})$, gives

$$J(\lambda_w^{**}, \lambda_r^{**}) = \begin{pmatrix} \left.\frac{\partial \psi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} & \left.\frac{\partial \psi_1(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} \\ \\ \left.\frac{\partial \psi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_w^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} & \left.\frac{\partial \psi_2(\lambda_w^{**}, \lambda_r^{**})}{\partial \lambda_r^{**}}\right|_{(\lambda_w^{**}, \lambda_r^{**})} \end{pmatrix},$$

with eigenvalues given by the roots of the equation,

$$\chi^2 - \chi\left(\frac{\partial \psi_1}{\partial \lambda_w^{**}} + \frac{\partial \psi_2}{\partial \lambda_r^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})} + \left(\frac{\partial \psi_1}{\partial \lambda_w^{**}}\frac{\partial \psi_2}{\partial \lambda_r^{**}} - \frac{\partial \psi_1}{\partial \lambda_r^{**}}\frac{\partial \psi_2}{\partial \lambda_w^{**}}\right)\Bigg|_{(\lambda_w^{**}, \lambda_r^{**})} = 0.$$

The dominant eigenvalue of $J(\lambda_w^{**}, \lambda_r^{**})$ is given by

$$\mathcal{R}_{wr}^t = \frac{T_{11} + \sqrt{T_{11}^2 - 4T_{21}}}{2},$$

where,

$$T_{11} = \left(\frac{\partial \psi_1}{\partial \lambda_w^{**}} + \frac{\partial \psi_2}{\partial \lambda_r^{**}}\right)\Big|_{(\lambda_w^{**}, \lambda_r^{**})} \text{ and } T_{21} = \left(\frac{\partial \psi_1}{\partial \lambda_w^{**}}\frac{\partial \psi_2}{\partial \lambda_r^{**}} - \frac{\partial \psi_1}{\partial \lambda_r^{**}}\frac{\partial \psi_2}{\partial \lambda_w^{**}}\right)\Big|_{(\lambda_w^{**}, \lambda_r^{**})}.$$

Thus, the co-existence equilibria is LAS whenever $|\mathcal{R}_{wr}^t| < 1$.

□

It is clear that the treatment model (4.1) exhibits some dynamical features which are different from the treatment-free model (4.2). For example, while the treatment-free model can have an infinite number (continuum) of coexistence equilibria when the reproduction numbers of the wild and resistant strains are greater than unity, the treatment model shows coexistence only when the reproduction number of the wild strain is greater than unity and exceeds that of the resistant strain.

It is worth to emphasizing that whenever $\mathcal{R}_w^t = \mathcal{R}_r^t = 1$, then $\lambda_w^{**} = 0$ and equation (4.18) reduces to

$$\lambda_r^{**} H_2 = 0 \quad \Rightarrow \quad \lambda_r^{**} = 0.$$

Hence, if both reproduction numbers are the same and equal to unity, then $\lambda_r^{**} = 0$ and $\lambda_w^{**} = 0$; corresponding to the DFE. Finally, the case when $\mathcal{R}_r^t > \mathcal{R}_w^t > 1$ results in $\lambda_w^{**} < 0$ in (4.19). In this case, the equation for $\frac{dI_w}{dt}$ in (4.1) becomes

$$\begin{aligned} \frac{dI_w}{dt} &= -\lambda_w S - (\mu + \sigma_w + \tau_w) I_w, \\ &\leq -(\mu + \sigma_w + \tau_w) I_w, \end{aligned}$$

so that $\lim_{t\to\infty} I_w = 0$. Thus, the system of equations in (4.1) becomes decoupled in A_w and I_T, giving

$$\begin{aligned} \frac{dA_w}{dt} &= -(\tau_w + \mu + \delta_w)A_w + \theta\sigma_w I_T, \\ \frac{dI_T}{dt} &= \tau_w A_w - (\mu + \gamma_{wr} + \theta\sigma_w)I_T. \end{aligned} \tag{4.20}$$

It easy to show that the system of linear differential equation (4.20) has a unique equilibrium $(A_w^*, I_T^*) = (0, 0)$, so that eventually all the components of the wild strain goes to 0 whenever $\mathcal{R}_w^t < \mathcal{R}_r^t$. Thus, Theorem (4.7) is not only valid for $\mathcal{R}_w^t < 1 < \mathcal{R}_r^t$, it is also valid for $\mathcal{R}_w^t < \mathcal{R}_r^t$. In summary, whilst the treatment-free model has a continuum of co-existence endemic equilibria, the treatment-free model has a low and high endemicity co-existence equilibria.

4.5 Numerical simulations and discussions

Treatment-free model: The treatment-free model (4.2) is simulated using the parameters in Table (4.2). With this set of parameters, and $\beta = 0.05, \sigma_w = 1.9$, the reproduction numbers $\mathcal{R}_w = 0.3003, \mathcal{R}_r = 0.7234$, so that $\mathcal{R}_0 = 0.7234 < 1$. Thus, by Theorem (4.1), the DFE is GAS. Figure 4.3C depicts simulations of this model, under this scenario, with various initial conditions, confirming the global asymptotic stability property of the DFE. Additional simulations, shown in Figures 4.3A,B,D,E, illustrate the fact that, for $(\mathcal{R}_i > \mathcal{R}_j)$ with $\mathcal{R}_i > 1$ $(i, j = w, r)$ and $(i \neq j)$, the strain with the higher reproduction number always drives out the other (competitive exclusion).

This is in line with Theorems (4.2) and (4.3) and Conjectures (4.1) and (4.2). It is also shown that whenever the two reproduction numbers ($\mathcal{R}_w$ and $\mathcal{R}_r$) are equal and greater than unity, the two strains co-exist -*via* a continuum of co-existing equilibria (Figure 4.3F).

Treatment model: The treatment model (4.1) is simulated using the parameters in Table (4.2), unless otherwise stated. These simulations show that the wild strain dies out whenever $\mathcal{R}_w^t < 1$ (Figure 4.5A) or $\mathcal{R}_w^t > \mathcal{R}_r^t > 1$ (Figure 4.5C). In both of these cases, the resistant strain dominates (wins the competition). For the case where $\mathcal{R}_w^t$ exceeds $\mathcal{R}_r^t$, it is shown that both strains co-exist (Figures 4.5B, D). Here, it is worth noting that the resistant strain has a higher steady-state prevalence.

Simulations for the case where $\mathcal{R}_w^t$ and $\mathcal{R}_r^t$ are equal and greater than unity shows the dominance of the resistant strain, while the wild strain dies out (Figure 4.7A). When $\mathcal{R}_w^t$ and $\mathcal{R}_r^t$ are equal and less than unity, the two strains die out (Figure 4.7B). This (latter) result also holds for $\mathcal{R}_w^t = \mathcal{R}_r^t = 1$.

4.6 Summary

In summary, the main findings in this chapter are as follows:

(i) Both the treatment-free and the treatment model have a globally-stable DFE whenever the maximum of the two reproduction numbers for each model is less than unity. Thus, effective disease control, or elimination, is feasible using ARVs;

(ii) For the treatment-free model, the strain with the higher reproduction number always dominates, and the other strain goes extinct;

(iii) The treatment-free model can have a continuum of coexistence endemic equilibria when the two reproduction numbers are equal and greater unity. This feature is not present in the treatment model;

(iv) For the treatment model, competitive exclusion occurs only when $\mathcal{R}_r^t > 1$ and $\mathcal{R}_r^t > \mathcal{R}_w^t$;

(v) Unlike in the case of the treatment-free model, the treatment model exhibits a low and high endemicity co-existence equilibrium under certain conditions.

Table 4.1: Description of variables and parameters for model (4.1)

Parameters	nominal values
$S(t)$	susceptible individuals
$I_w(t)$	newly- and asymptomatically-infected individuals infected with wild strain
$I_r(t)$	newly- and asymptomatically-infected individuals infected with resistant strain
$A_w(t)$	AIDS individuals infected with wild strain
$A_r(t)$	AIDS individuals infected with resistant strain
$I_T(t)$	treated infected individuals
Π	recruitment rate into the sexually-active population
μ	natural death rate
δ_w	disease-induced mortality for individuals in AIDS stage infected with wild strain
δ_r	disease-induced mortality for individuals in AIDS stage infected with resistant strain
η_w	relative risk of infectiousness of AIDS individuals infected with wild strain
η_r	relative risk of infectiousness of AIDS individuals infected with resistant strain
η_T	relative risk of infectiousness of treated individuals
σ_w	progression rate to AIDS for individuals infected with wild strain
σ_r	progression rate to AIDS for individuals infected with resistant strain
τ_w	treatment rate for individuals infected with wild strain
γ_{wr}	rate of resistance development of treated individuals
θ	modification factor for progression to AIDS by treated individuals
β	contact rate

Table 4.2: Parameter values for model (4.1)

Variable/Parameter	**Value**
Π	1000
μ	1/32
δ_w	0.09
δ_r	0.08
η_w	1.5
η_r	1
η_T	0.008
σ_w	0.2
σ_r	0.1
τ_w	0.5
γ_{wr}	0.5
θ	0.8
β	0.4

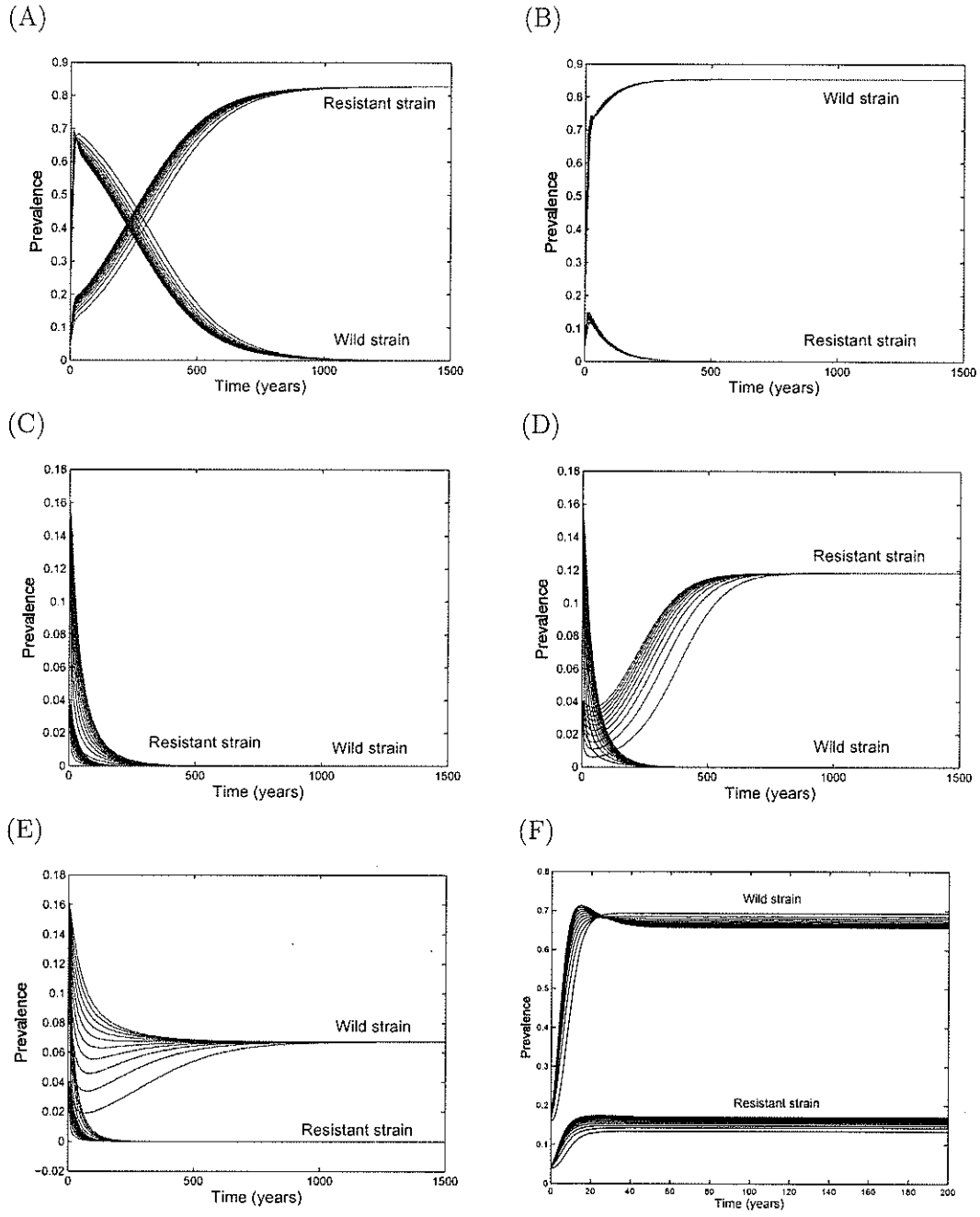


Figure 4.2: Prevalence (total number of infected individuals divided by the total population) as a function of time for model (4.2). (A) $\mathcal{R}_r > \mathcal{R}_w > 1$ ($\sigma_w = 0.5$); (B) $\mathcal{R}_w > \mathcal{R}_r > 1$ ($\sigma_w = 0.1$); (C) $\mathcal{R}_r < \mathcal{R}_w < 1$ ($\sigma_w = 0.1, \beta = 0.05$); (D) $\mathcal{R}_w < 1 < \mathcal{R}_r$ ($\sigma_w = 0.1, \beta = 0.05, \eta_r = 2.2$); (E) $\mathcal{R}_r < 1 < \mathcal{R}_w$ ($\sigma_w = 0.1, \eta_w = 2.2, \beta = 0.05$); (F) $\mathcal{R}_w = \mathcal{R}_r > 1$ ($\eta_w = 1.42205$). Other parameters as in Table (4.2).

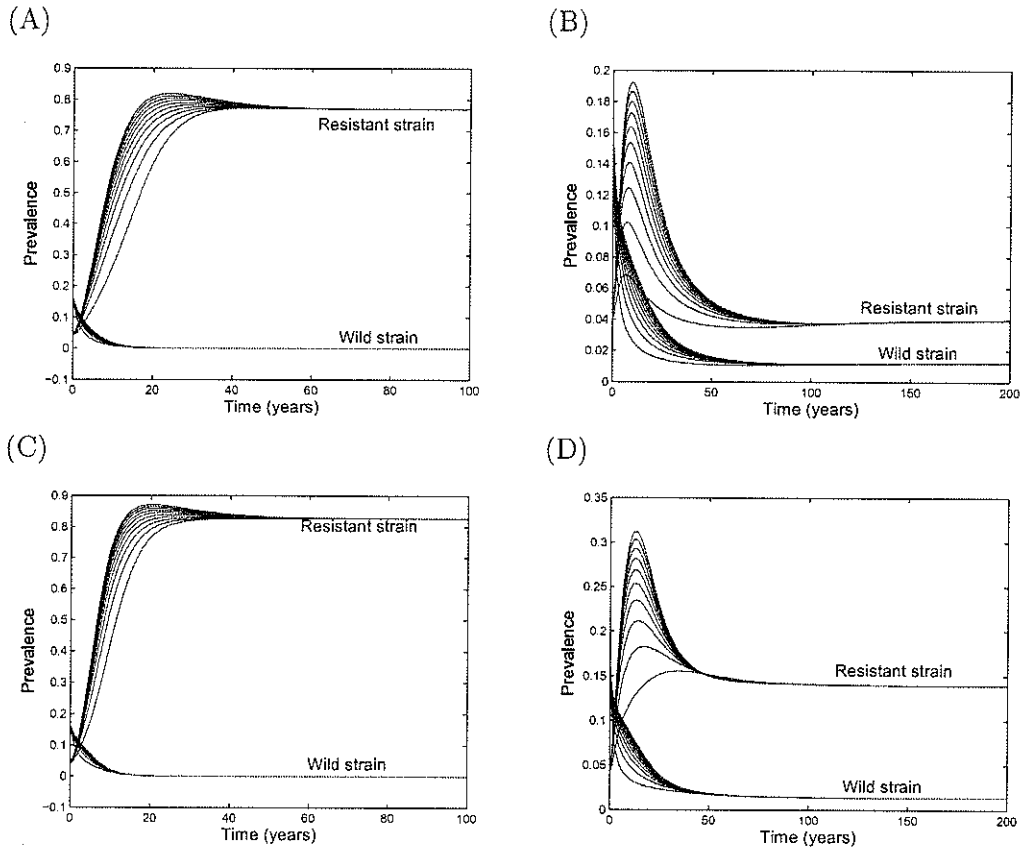
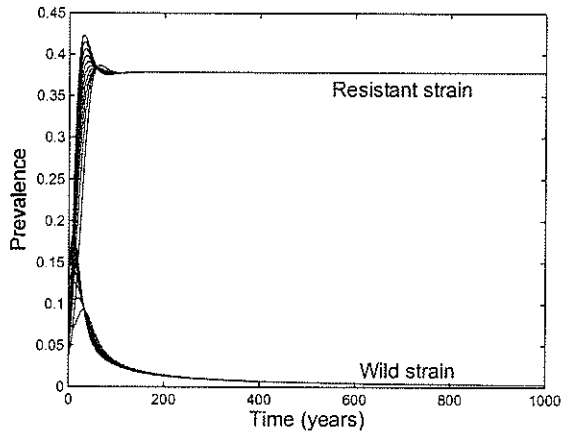


Figure 4.3: Prevalence as a function of time for the model (4.1) when: (A) $\mathcal{R}_w^t < 1 < \mathcal{R}_r^t$ ($\beta = 0.3$); (B) $\mathcal{R}_r^t < 1 < \mathcal{R}_w^t$ ($\sigma_r = 1.1, \delta_r = 0.8$); (C) $\mathcal{R}_r^t > \mathcal{R}_w^t > 1$; (D) $\mathcal{R}_w^t > \mathcal{R}_r^t > 1$ ($\sigma_w = 0.3, \sigma_r = 0.6, \delta_r = 0.8$). Other parameters as in Table (4.2).

(A)



(B)

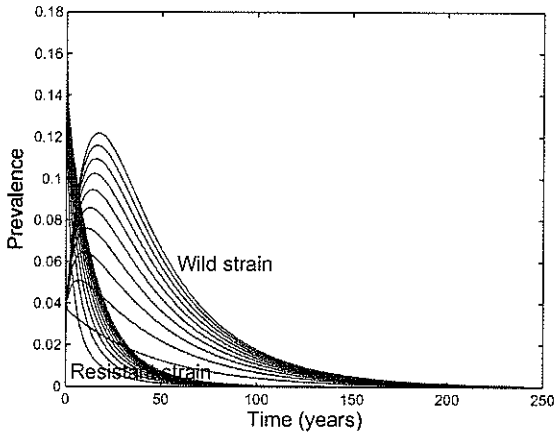


Figure 4.4: Prevalence as a function of time for model (4.1) when: (A) $\mathcal{R}_w^t = \mathcal{R}_r^t > 1$ ($\beta = 0.2, \eta_w = 1.79505, \sigma_w = 2.6, \delta_r = 1.8$); (B) $\mathcal{R}_w^t = \mathcal{R}_r^t < 1$ ($\beta = 0.1, \eta_w = 1.79505, \sigma_w = 2.6, \delta_r = 1.8$). Other parameters as in Table (4.2).

Chapter 5

HIV Vaccine Model with Differential Infectivity and Staged-Progression (DISP)

5.1 Introduction

The models discussed so far in this thesis are based on the use of ARVs. Further, none of the models in these chapters incorporate the differential infectivity and staged-progression properties of HIV disease. In this chapter, a HIV vaccine model which accounts for the above properties will be designed and analyzed.

The key motivation for modelling HIV vaccine is the fact that whilst the use of ARVs has resulted in significant decline in HIV burden in rich nations, HIV prevalence and AIDS-related mortality continue to rise in most parts of the developing world

(largely due to the lack of widespread availability of ARVs in these nations). This, together with the dangers associated with the evolution and transmission of ARV-resistant strains, raises a major dilemma in the quest for effectively controlling HIV globally. It is now believed by many that using a vaccine is necessary for combatting HIV spread globally [19, 27]. Although a number of anti-HIV vaccines are undergoing various phases of clinical trials, it is generally believed that any future HIV vaccine will be imperfect. That is, it may have lower efficacy in protecting against infection and/or result in a shorter duration of protection in successfully immunized people than most traditional vaccines. In addition, by eliciting broad cellular immune responses, such a vaccine may reduce viral RNA concentrations and reduce infectiousness in infected vaccinated individuals. The vaccine may also offer some therapeutic benefits by altering the clinical course of the disease (see [26] and references therein).

This chapter focusses on analyzing the potential impact of an imperfect HIV vaccine. The vaccine is assumed to have numerous characteristics, such as having effect in some, but not all, people; reducing, but not fully eliminating, susceptibility in those immunized; waning protective immunity with time; reducing the transmissibility of virus and/or reducing the mean duration of infectiousness of breakthrough infections. In this chapter, a HIV model, incorporating the above vaccine characteristics as well as the aforementioned differential infectivity and staged-progression nature of HIV disease will be designed. While the differential infectivity component accounts for the variations in viral RNA amongst infected individuals (those with high viral RNA upon primary infection are more infectious and progress to AIDS faster than those

with low viral RNA), the staged-progression component accounts for the fact that an HIV-infected individual typically passes through several infection stages, being highly infectious during the pre-antibody phase (primary infection stage), maintaining low infectivity during the asymptomatic phase (secondary infection stage), and becoming highly infectious as s/he progresses toward AIDS (AIDS stage) [29, 45, 49, 60, 66, 71]. These properties (differential infectivity and staged-progression) are essential aspects of HIV transmission dynamics, and incorporating these in our model adds to its realism (albeit significantly adds to the difficulty in the mathematical analysis).

5.2 Model formulation and basic properties

The total population, N, is subdivided into mutually-exclusive compartments namely susceptible ($S(t)$), vaccinated susceptible ($V(t)$), infected individuals in the differential infectivity group i stage j ($Y_{i,j}(t)$), for $(i,j = 1,2)$, vaccinated infected individuals in the differential infectivity group i stage j ($W_{i,j}(t)$), for $(i,j = 1,2)$, HIV infected individuals at the AIDS stage of infection ($A(t)$), so that

$$N = S + V + \sum_{i=1}^{2}\sum_{j=1}^{2}(Y_{i,j} + W_{i,j}).$$

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate Λ. These individuals acquire infection, following

contact with infected individuals in the $Y_{i,j}$, $W_{i,j}$ $(i,j=1,2)$ classes, at a rate λ, where

$$\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}\left(\beta_{i,j}\frac{Y_{i,j}}{N} + s_{i,j}\beta_{i,j}\frac{W_{i,j}}{N}\right).$$

It is assumed, for mathematical convenience, that AIDS individuals do not partake in further HIV transmission. The parameter $\beta_{i,j}$ is the effective contact rate of infected individuals in subgroups ($Y_{i,j}$ and $W_{i,j}$), while $s_{i,j}$ is the relative risk of infectiousness of vaccinated individuals. A fraction, ρ_1, of the newly-infected unvaccinated susceptible individuals move to the differential infectivity group 1 stage 1 ($Y_{1,1}$), while the remaining fraction, $\rho_2 = 1-\rho_1$, move to the differential infectivity group 2 stage 1 ($Y_{2,1}$). Infected individuals in the unvaccinated differential infectivity group 1 stage 1 ($Y_{1,1}$) progress to unvaccinated differential infectivity group 1 stage 2 ($Y_{1,2}$), at a rate $\sigma_{1,1}$; while infected individuals in the unvaccinated differential infectivity group 2 stage 1 ($Y_{2,1}$) progress to the unvaccinated differential infectivity group 2 stage 2 ($Y_{2,2}$), at a rate $\sigma_{2,1}$. Infected individuals in differential infectivity groups 1 and 2 and stage 2 of infection progress to the AID stage at a rate $\sigma_{1,2}$ and $\sigma_{2,2}$ with $\sigma_{1,2} < \sigma_{2,2}$ respectively. It is assumed that a fraction, p, of susceptible individuals are vaccinated. It is further assumed that the vaccine induced protection acquired by vaccinated individuals wanes, at a rate γ (so that these vaccinated individuals move to the susceptible class at the rate γ). Since vaccinated individuals are not fully-protected against infection (owing to the vaccine imperfection), it is assumed that vaccinated individuals acquire infection at a rate that is q times lower than that of unvaccinated susceptible individuals. A fraction, π_1, of the newly-infected vaccinated individuals move to the vaccinated differential in-

fectivity group 1 stage 1 ($W_{1,1}$), while the remaining fraction, $\pi_2 = 1 - \pi_1$, move to the vaccinated differential infectivity group 2 stage 1 ($W_{2,1}$). Infected individuals in the vaccinated differential infectivity group 1 stage 1 ($W_{1,1}$) progress to vaccinated differential infectivity group 1 stage 2 ($W_{1,2}$) at a rate $\theta_{1,1}\sigma_{1,1}$, while infected individuals in the vaccinated differential infectivity group 2 stage 1 ($W_{2,1}$) progress to the vaccinated differential infectivity group 2 stage 2 ($W_{2,2}$) at a rate $\theta_{2,1}\sigma_{2,1}$. Infected individuals in both final stages progress to the AIDS stage at a rate $\theta_{1,2}\sigma_{1,2}$ and $\theta_{2,2}\sigma_{2,2}$ respectively (where $\theta_{i,j} < 1$ $(i, j = 1, 2)$, account for the reduced vaccine-induced progression to AIDS). Further, natural mortality occurs in all classes, at a rate μ, and AIDS individuals suffer a disease-induced death, at a rate α. In summary, the differential infectivity and staged-progression (DISP) HIV vaccine model is given by [78] (see Figure 5.1 for a flow diagram).

$$
\begin{aligned}
\frac{dS}{dt} &= (1-p)\Lambda - \mu S - \lambda S + \gamma V, \\
\frac{dV}{dt} &= p\Lambda - \mu V - q\lambda V - \gamma V, \\
\frac{dY_{1,1}}{dt} &= \rho_1 \lambda S - (\mu + \sigma_{1,1}) Y_{1,1}, \\
\frac{dY_{1,2}}{dt} &= \sigma_{1,1} Y_{1,1} - (\mu + \sigma_{1,2}) Y_{1,2}, \\
\frac{dY_{2,1}}{dt} &= \rho_2 \lambda S - (\mu + \sigma_{2,1}) Y_{2,1}, \\
\frac{dY_{2,2}}{dt} &= \sigma_{2,1} Y_{2,1} - (\mu + \sigma_{2,2}) Y_{2,2}, \\
\frac{dW_{1,1}}{dt} &= \pi_1 q \lambda V - (\mu + \theta_{1,1}\sigma_{1,1}) W_{1,1}, \\
\frac{dW_{1,2}}{dt} &= \sigma_{1,1}\theta_{1,1} W_{1,1} - (\mu + \theta_{1,2}\sigma_{1,2}) W_{1,2}, \\
\frac{dW_{2,1}}{dt} &= \pi_2 q \lambda V - (\mu + \theta_{2,1}\sigma_{2,1}) W_{2,1}, \\
\frac{dW_{2,2}}{dt} &= \sigma_{2,1}\theta_{2,1} W_{2,1} - (\mu + \theta_{2,2}\sigma_{2,2}) W_{2,2}, \\
\frac{dA}{dt} &= \sigma_{1,2} Y_{1,2} + \sigma_{2,2} Y_{2,2} + \theta_{1,2}\sigma_{1,2} W_{1,2} + \theta_{2,2}\sigma_{2,2} W_{2,2} - (\alpha + \mu) A.
\end{aligned}
\tag{5.1}
$$

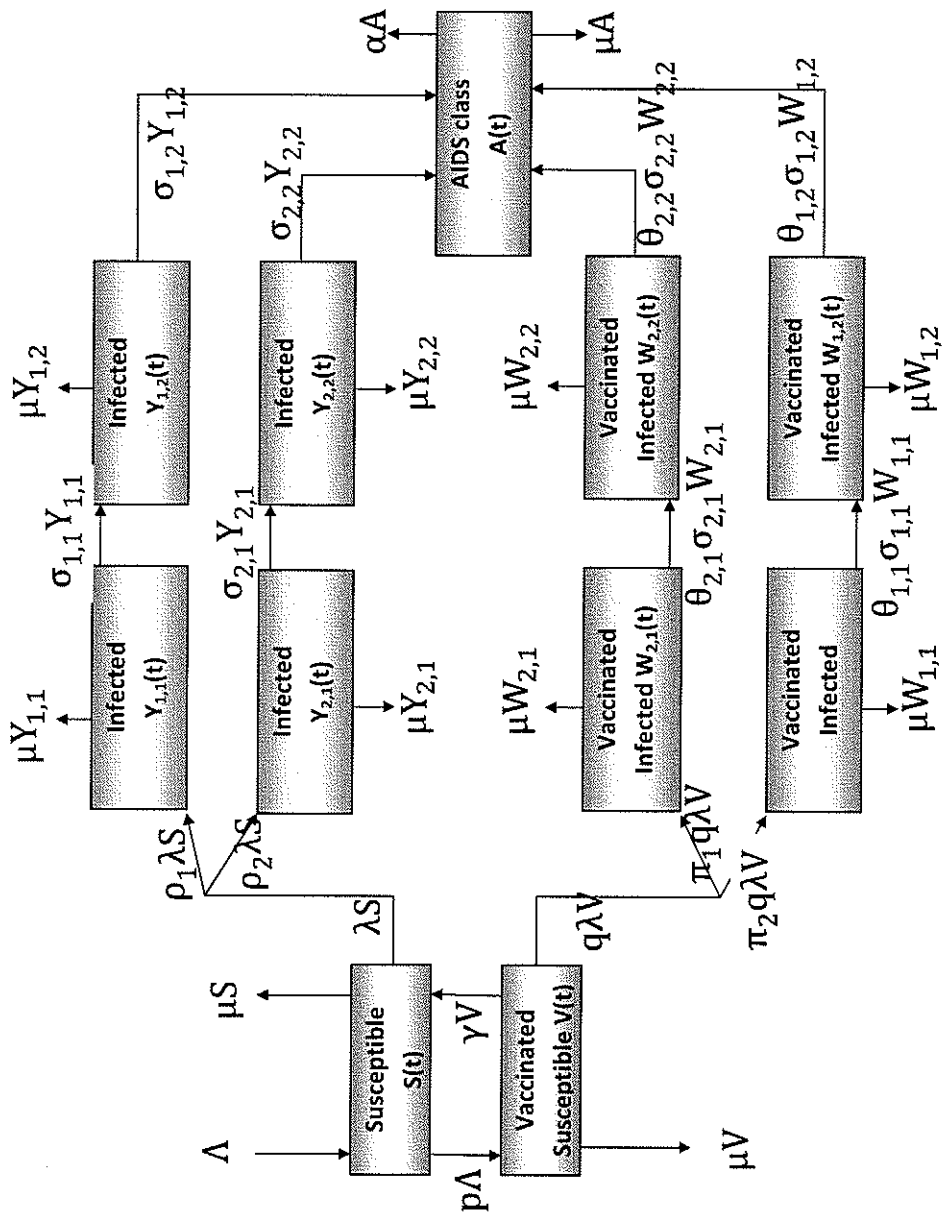


Figure 5.1: Flow diagram for the DISP vaccination model (5.1).

$Y_{i,j}$: unvaccinated infected individuals in differential infectivity group i stage j,

$W_{i,j}$: vaccinated infected individuals in differential infectivity group i stage j.

All the parameters of the model (5.1) are assumed to be non-negative. Using the method described in Section 3.2.1, it can be shown that the following region is positively-invariant and attracting

$$\begin{aligned}\mathcal{D} &= \{(S, V, Y_{1,1}, Y_{1,2}, Y_{2,1}, Y_{2,2}, W_{1,1}, W_{1,2}, W_{2,1}, W_{2,2}) \in \mathbb{R}^{10}_{+} : \\ &\quad S + V + Y_{1,1} + Y_{1,2} + Y_{2,1} + Y_{2,2} + W_{1,1} + W_{1,2} + W_{2,1} + W_{2,2} \leq \Lambda/\mu\}.\end{aligned}$$

5.3 Vaccination-free model

5.3.1 Local and global stability of DFE

We consider, first of all, the model (5.1) in the absence of vaccination. In this case, $p = \gamma = V = W_{1,1} = W_{1,2} = W_{2,1} = W_{2,2} = 0$, so that the model (5.1) reduces to

$$\begin{aligned}\frac{dX}{dt} &= \Lambda - \mu S - \lambda S, \\ \frac{dY_{1,1}}{dt} &= \rho_1 S\lambda - (\mu + \sigma_{1,1})Y_{1,1}, \\ \frac{dY_{1,2}}{dt} &= \sigma_{1,1}Y_{1,1} - (\mu + \sigma_{1,2})Y_{1,2}, \\ \frac{dY_{2,1}}{dt} &= \rho_2 S\lambda - (\mu + \sigma_{2,1})Y_{2,1}, \\ \frac{dY_{2,2}}{dt} &= \sigma_{2,1}Y_{2,1} - (\mu + \sigma_{2,2})Y_{2,2}, \\ \frac{dA}{dt} &= \sigma_{1,2}Y_{1,2} + \sigma_{2,2}Y_{2,2} - (\alpha + \mu)A,\end{aligned} \tag{5.2}$$

with,

$$\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}\frac{\beta_{i,j}Y_{i,j}}{N} \text{ and } N = S + Y_{1,1} + Y_{1,2} + Y_{2,1} + Y_{2,2} + A. \tag{5.3}$$

The model has a DFE given by,

$$\mathcal{E}_0 = (S^*, Y^*_{1,1}, Y^*_{1,2}, Y^*_{2,1}, Y^*_{2,2}, A^*) = (\Lambda/\mu, 0, 0, 0, 0, 0).$$

Here, the next generation matrices are given by

$$F = \begin{bmatrix} \frac{\rho_1\beta_{1,1}S^*}{N^*} & \frac{\rho_1\beta_{1,2}S^*}{N^*} & \frac{\rho_1\beta_{2,1}S^*}{N^*} & \frac{\rho_1\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\rho_2\beta_{1,1}S^*}{N^*} & \frac{\rho_2\beta_{1,2}S^*}{N^*} & \frac{\rho_2\beta_{2,1}S^*}{N^*} & \frac{\rho_2\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} K_{32} & 0 & 0 & 0 \\ -\sigma_{1,1} & K_{33} & 0 & 0 \\ 0 & 0 & K_{34} & 0 \\ 0 & 0 & -\sigma_{2,1} & K_{35} \end{bmatrix},$$

where,

$$K_{32} = \mu + \sigma_{1,1}, \quad K_{33} = \mu + \sigma_{1,2}, \quad K_{34} = \mu + \sigma_{2,1}, \quad K_{35} = \mu + \sigma_{2,2}.$$

The *basic reproduction number*, $\mathcal{R}_0$, is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\rho_1 K_{34}K_{35}(\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}) + \rho_2 K_{32}K_{33}(\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1})}{K_{32}K_{33}K_{34}K_{35}} \tag{5.4}$$

Thus, the following result is established.

Lemma 5.1. *The DFE of the vaccination-free model* (5.2)*, given by* $\mathcal{E}_0$*, is LAS if*

$\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Further, we claim the following result.

Theorem 5.1. *The DFE of the vaccination-free model* (5.2)*, given by* $\mathcal{E}_0$*, is GAS if* $\mathcal{R}_0 < 1$.

Proof. Consider the Lyapunov function given by,

$$\mathcal{F} = \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}Y_{1,1} + \frac{\beta_{1,2}}{K_{33}}Y_{1,2} + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}Y_{2,1} + \frac{\beta_{2,2}}{K_{35}}Y_{2,2}$$

with Lyapunov derivative given by,

$$\begin{aligned}
\dot{\mathcal{F}} &= \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}\dot{Y}_{1,1} + \frac{\beta_{1,2}}{K_{33}}\dot{Y}_{1,2} + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}\dot{Y}_{2,1} + \frac{\beta_{2,2}}{K_{35}}\dot{Y}_{2,2}, \\
&= \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}(\rho_1 S\lambda - K_{32}Y_{1,1}) + \frac{\beta_{1,2}}{K_{33}}(\sigma_{1,1}Y_{1,1} - K_{33}Y_{1,2}), \\
&\quad + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}(\rho_2 S\lambda - K_{34}Y_{2,1}) + \frac{\beta_{2,2}}{K_{35}}(\sigma_{2,1}Y_{2,1} - K_{35}Y_{2,2}), \\
&= N\lambda\left[\frac{S\rho_1 K_{34}K_{35}(\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}) + \rho_2 K_{32}K_{33}(\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1})}{NK_{32}K_{33}K_{34}K_{35}} - 1\right], \\
&\leq \lambda_1\left[\frac{\rho_1 K_{34}K_{35}(\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}) + \rho_2 K_{32}K_{33}(\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1})}{K_{32}K_{33}K_{34}K_{35}} - 1\right], \\
&= \lambda_1(\mathcal{R}_0 - 1) < 0 \text{ for } \mathrm{S} \leq \mathrm{N} \text{ and } \mathcal{R}_0 < 1.
\end{aligned}$$

where,

$$\lambda_1 = \sum_{i=1}^{2}\sum_{j=1}^{2}\beta_{i,j}Y_{i,j}.$$

The proof is completed using similar argument as in the proof of Theorem (3.1). □

5.3.2 Existence and local stability of EEP

Setting the right hand side of (5.2) to zero and solving at steady state (i.e., when $Y_{1,1} \neq Y_{1,2} \neq Y_{2,1} \neq Y_{2,2} \neq 0$) gives $\mathcal{E}_1 = (S^{**}, Y_{1,1}^{**}, Y_{1,2}^{**}, Y_{2,1}^{**}, Y_{2,2}^{**})$, where

$$\begin{aligned} S^{**} &= \frac{\Lambda}{\mu + \lambda^{**}}, \quad Y_{1,1}^{**} = \frac{\rho_1 \lambda^{**} \Lambda}{K_{32}(\mu + \lambda^{**})}, \quad Y_{1,2}^{**} = \frac{\sigma_{1,1}\rho_1 \lambda^{**} \Lambda}{K_{33}K_{32}(\mu + \lambda^{**})}, \\ Y_{2,1}^{**} &= \frac{\rho_2 \lambda^{**} \Lambda}{K_{34}(\mu + \lambda^{**})}, \quad Y_{2,2}^{**} = \frac{\sigma_{2,1}\rho_2 \lambda^{**} \Lambda}{K_{35}K_{34}(\mu + \lambda^{**})}. \end{aligned} \tag{5.5}$$

Using (5.5) in (5.3), it follows that the endemic equilibria of (5.2) satisfy

$$\lambda^{**}\Lambda(b_3\lambda^{**} + c_3) = 0, \tag{5.6}$$

where,

$$b_3 = \rho_2 K_{32}K_{33}(K_{35} + \sigma_{2,1}) + \rho_1 K_{34}K_{35}(K_{33} + \sigma_{1,1}), \quad c_3 = K_{32}K_{33}K_{34}K_{35}(1 - \mathcal{R}_0).$$

Clearly, $\lambda^{**} = 0$ is one solution, which corresponds to the DFE. The other solution is

$$\lambda^{**} = -\frac{c_3}{b_3}. \tag{5.7}$$

It is easy to see that $b_3 > 0$ and that for $\lambda > 0$, it is necessary that $c_3 < 0$ (i.e., $\mathcal{R}_0 > 1$). Thus, the model (5.2) has a unique positive endemic equilibrium whenever $\mathcal{R}_0 > 1$. This result is summarized below.

Theorem 5.2. *The vaccination-free model* (5.2) *has a unique positive endemic equi-*

librium if and only if $\mathcal{R}_0 > 1$.

Further, the following result can be established.

Theorem 5.3. *The unique positive endemic equilibrium of the model* (5.2) *is LAS whenever* $\mathcal{R}_0 > 1$.

Proof. Let

$$\lambda^{**} = \sum_{i=1}^{2}\sum_{j=1}^{2}\frac{\beta_{i,j}Y_{i,j}^{**}}{N^{**}}. \tag{5.8}$$

Substituting (5.5) into (5.8) and simplifying gives a fixed point problem of the form $\lambda^{**} = f(\lambda^{**})$, where

$$f(\lambda^{**}) = \frac{\lambda^{**}C_3}{1+\lambda^{**}C_4},$$

with,

$$\begin{aligned} C_3 &= \frac{\rho_1}{K_{32}}\left(\beta_{1,1} + \frac{\beta_{2,1}\sigma_{1,1}}{K_{33}}\right) + \frac{\rho_2}{K_{34}}\left(\beta_{2,1} + \frac{\beta_{2,2}\sigma_{2,1}}{K_{35}}\right), \\ C_4 &= \frac{\rho_1}{K_{32}}\left(1 + \frac{\sigma_{1,1}}{K_{33}}\right) + \frac{\rho_2}{K_{34}}\left(1 + \frac{\sigma_{2,1}}{K_{35}}\right), \end{aligned}$$

and,

$$f'(\lambda^{**}) = \frac{C_3}{(1+\lambda^{**}C_4)^2}.$$

Evaluating $f'(\lambda^{**})$ at (5.7) shows that

$$f'(\lambda^{**})\Big|_{\lambda^{**}} = \frac{1}{\mathcal{R}_0} \text{ so that } \left|\left\{f'(\lambda^{**})\Big|_{\lambda^{**}}\right\}\right| < 1 \text{ whenever } \mathcal{R}_0 > 1.$$

□

5.4 DISP model with wholly-vaccinated population

Consider model (5.1) in which every member of the population is vaccinated (obtained by setting $Y_{1,1} = Y_{1,2} = Y_{2,1} = Y_{2,2} = p = 0$ in (5.1)), given by

$$\begin{aligned}
\frac{dV}{dt} &= \Lambda - q\lambda V - \mu V, \\
\frac{dW_{1,1}}{dt} &= \pi_1 q\lambda V - (\mu + \theta_{1,1}\sigma_{1,1})W_{1,1}, \\
\frac{dW_{1,2}}{dt} &= \sigma_{1,1}\theta_{1,1}W_{1,1} - (\mu + \theta_{1,2}\sigma_{1,2})W_{1,2}, \\
\frac{dW_{2,1}}{dt} &= \pi_2 q\lambda V - (\mu + \theta_{2,1}\sigma_{2,1})W_{2,1}, \\
\frac{dW_{2,2}}{dt} &= \sigma_{2,1}\theta_{2,1}W_{2,1} - (\mu + \theta_{2,2}\sigma_{2,2})W_{2,2}, \\
\frac{dA}{dt} &= \theta_{1,2}\sigma_{1,2}W_{1,2} + \theta_{2,2}\sigma_{2,2}W_{2,2} - (\alpha + \mu)A,
\end{aligned} \tag{5.9}$$

with $N = V + \sum_{i=1}^{2}\sum_{j=1}^{2} W_{i,j}$ and $\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2} s_{i,j}\beta_{i,j}\frac{W_{i,j}}{N}$.

5.4.1 Local and global stability of DFE

The model (5.9) has a DFE given by

$$\mathcal{E}_{0v} = (V^*, W^*_{1,1}, W^*_{1,2}, W^*_{2,1}, W^*_{2,2}) = (\Lambda/\mu, 0, 0, 0, 0), \tag{5.10}$$

with the associated next generation matrices,

$$F = \begin{bmatrix} \frac{\pi_1 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_1 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_1 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_1 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_2 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_2 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_2 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_2 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} K_{36} & 0 & 0 & 0 \\ -\theta_{1,1}\sigma_{1,1} & K_{37} & 0 & 0 \\ 0 & 0 & K_{38} & 0 \\ 0 & 0 & -\theta_{2,1}\sigma_{2,1} & K_{39} \end{bmatrix},$$

where,

$$K_{36} = \mu + \theta_{1,1}\sigma_{1,1}, \quad K_{37} = \mu + \theta_{1,2}\sigma_{1,2}, \quad K_{38} = \mu + \theta_{2,1}\sigma_{2,1}, \quad K_{39} = \mu + \theta_{2,2}\sigma_{2,2}.$$

Thus, the *basic vaccination reproduction number*, denoted by $\mathcal{R}_{0v} = \rho(FV^{-1})$, is

$$\mathcal{R}_{0v} = \frac{q[\pi_1 K_{38}K_{39}(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}) + \pi_2 K_{36}K_{37}(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1})]}{K_{36}K_{37}K_{38}K_{39}}. \tag{5.11}$$

The following result is established.

Lemma 5.2. *The DFE of the model* (5.9)*, given by* $\mathcal{E}_{0v}$*, is LAS if* $\mathcal{R}_{0v} < 1$*, and unstable if* $\mathcal{R}_{0v} > 1$.

Further, we claim the following.

Theorem 5.4. *The DFE of the model* (5.9)*, given by* $\mathcal{E}_{0v}$*, is GAS if* $\mathcal{R}_{0v} < 1$.

Proof. Consider the Lyapunov function given by,

$$\begin{aligned}\mathcal{F} &= \frac{s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}}{K_{36}K_{37}}W_{1,1} + \frac{s_{1,2}\beta_{1,2}}{K_{37}}W_{1,2} \\ &\quad + \frac{s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}}{K_{38}K_{39}}W_{2,1} + \frac{s_{2,2}\beta_{2,2}}{K_{39}}W_{2,2},\end{aligned}$$

with Lyapunov derivative given by,

$$\begin{aligned}\dot{\mathcal{F}} &= \frac{s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}}{K_{36}K_{37}}\dot{W}_{1,1} + \frac{s_{1,2}\beta_{1,2}}{K_{37}}\dot{W}_{1,2} \\ &\quad + \frac{s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}}{K_{38}K_{39}}\dot{W}_{2,1} + \frac{s_{2,2}\beta_{2,2}}{K_{39}}\dot{W}_{2,2} \\ &= \frac{s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}}{K_{36}K_{37}}(\pi_1 q\lambda V - K_{36}W_{1,1}) + \frac{s_{1,2}\beta_{1,2}}{K_{37}}(\sigma_{1,1}\theta_{1,1}W_{1,1} - K_{37}W_{1,2}) \\ &\quad + \frac{s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}}{K_{38}K_{39}}(\pi_2 q\lambda V - K_{38}W_{2,1}) + \frac{s_{2,2}\beta_{2,2}}{K_{39}}(\sigma_{2,1}\theta_{2,1}W_{2,1} - K_{39}W_{2,2}) \\ &= N\lambda\left[\frac{Vq[\pi_1 K_{38}K_{39}(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}) + \pi_2 K_{36}K_{37}(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1})]}{NK_{36}K_{37}K_{38}K_{39}} - 1\right] \\ &< \lambda_2\left[\frac{q[\pi_1 K_{38}K_{39}(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}) + \pi_2 K_{36}K_{37}(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1})]}{K_{36}K_{37}K_{38}K_{39}} - 1\right] \\ &= \lambda_2(\mathcal{R}_{0v} - 1) \leq 0, \text{ for } V \leq N \text{ and } \mathcal{R}_{0v} < 1,\end{aligned}$$

where,

$$\lambda_2 = \sum_{i=1}^{2}\sum_{j=1}^{2} s_{i,j}\beta_{i,j}W_{i,j}.$$

The proof is completed using similar argument as in the proof of Theorem (3.1). □

5.4.2 Existence and local stability of EEP

Solving the system (5.9) at steady state, in terms of λ^{**}, gives

$$\begin{aligned} V^{**} &= \frac{\Lambda}{\mu + q\lambda^{**}}, \quad W_{1,1}^{**} = \frac{\pi_1 q\lambda^{**}\Lambda}{K_{36}(\mu + q\lambda^{**})}, \quad W_{2,2}^{**} = \frac{\theta_{2,1}\sigma_{2,1}\pi_2 q\lambda^{**}\Lambda}{K_{38}K_{39}(\mu + q\lambda^{**})}, \\ W_{1,2}^{**} &= \frac{\theta_{1,1}\sigma_{1,1}\pi_1 q\lambda^{**}\Lambda}{K_{36}K_{37}(\mu + q\lambda^{**})}, \quad W_{2,1}^{**} = \frac{\pi_2 q\lambda^{**}\Lambda}{K_{38}(\mu + q\lambda^{**})}, \end{aligned} \tag{5.12}$$

with,

$$\lambda^{**} = \sum_{i=1}^{2}\sum_{j=1}^{2} s_{i,j}\beta_{i,j}\frac{W_{i,j}^{**}}{N^{**}}. \tag{5.13}$$

Substituting (5.12) into (5.13) shows that the non-zero equilibria of the model (5.9) satisfy

$$b_{11}\lambda^{**} + c_{11} = 0,$$

with,

$$\begin{aligned} b_{11} &= [\pi_1 q K_{38} K_{39}(\theta_{1,1}\sigma_{1,1} + K_{37}) + \pi_2 q K_{36} K_{37}(\theta_{2,1}\sigma_{2,1} + K_{39})], \\ c_{11} &= K_{36} K_{37} K_{38} K_{39}(1 - \mathcal{R}_{0v}), \end{aligned}$$

so that,

$$\lambda^{**} = -\frac{c_{11}}{b_{11}}. \tag{5.14}$$

It is worth noting that $\lambda^{**} = 0$ corresponds to the DFE of the model (5.9). Further, $b_{11} > 0$ and $c_{11} < 0$ whenever $\mathcal{R}_{0v} > 1$. Thus, the model (5.9) has a unique positive endemic equilibrium whenever $\mathcal{R}_{0v} > 1$. Hence, we have the following result.

Theorem 5.5. *The model* (5.9) *has a unique endemic equilibrium whenever* $\mathcal{R}_{0v} > 1$.

Theorem 5.6. *The unique positive endemic equilibrium of the model* (5.9) *is LAS whenever* $\mathcal{R}_{0v} > 1$.

Proof. Substituting (5.12) into (5.13) gives the fixed point problem of the form $\lambda^{**} = f(\lambda^{**})$, where

$$f(\lambda^{**}) = \frac{\lambda^{**} C_5}{1 + \lambda^{**} C_6},$$

with,

$$\begin{aligned} C_5 &= \frac{\pi_1 q}{K_{36}}\left(\beta_{1,1}s_{1,1} + \frac{\beta_{2,1}s_{1,2}\theta_{1,1}\sigma_{1,1}}{K_{37}}\right) + \frac{\pi_2 q}{K_{38}}\left(\beta_{2,1}s_{2,1} + \frac{\beta_{2,2}s_{2,2}\theta_{2,1}\sigma_{2,1}}{K_{39}}\right), \\ C_6 &= \frac{\pi_1 q}{K_{36}}\left(1 + \frac{\theta_{1,1}\sigma_{1,1}}{K_{37}}\right) + \frac{\pi_2 q}{K_{38}}\left(1 + \frac{\theta_{2,1}\sigma_{2,1}}{K_{39}}\right), \end{aligned}$$

and,

$$f'(\lambda^{**}) = \frac{C_5}{(1+\lambda^{**}C_6)^2}.$$

Evaluating $f'(\lambda^{**})$ at (5.14) shows that

$$f'(\lambda^{**})\Big|_{\lambda^{**}} = \frac{1}{\mathcal{R}_{0v}} \text{ so that } \left|\left\{f'(\lambda^{**})\Big|_{\lambda^{**}}\right\}\right| < 1 \text{ whenever } \mathcal{R}_{0v} > 1.$$

□

Thus, in summary, both the vaccination-free DISP model (5.2) and the wholly-vaccinated DISP model (5.9) exhibit similar qualitative dynamics (where the DFE is GAS whenever the associated reproduction number is less than unity, and a unique and LAS endemic equilibrium exists when the number exceeds unity).

5.5 Analysis of the full DISP vaccination model

5.5.1 Existence and local stability of DFE

The model (5.1) has a disease-free equilibrium (DFE) given by

$$\begin{aligned}\mathcal{E}_0 &= (S^*, V^*, Y^*_{1,1}, Y^*_{1,2}, Y^*_{2,1}, Y^*_{2,2}, W^*_{1,1}, W^*_{1,2}, W^*_{2,1}, W^*_{2,2}) \\ &= \left(\frac{[\gamma + (1-p)\mu]\Lambda}{\mu(\mu+\gamma)}, \frac{p\Lambda}{\mu+\gamma}, 0, 0, 0, 0, 0, 0, 0, 0\right). \end{aligned} \tag{5.15}$$

Using the next generation method, we have that $F = \left(G_1 | G_2\right)$, where,

$$G_1 = \begin{pmatrix} \frac{\rho_1\beta_{1,1}S^*}{N^*} & \frac{\rho_1\beta_{1,2}S^*}{N^*} & \frac{\rho_1\beta_{2,1}S^*}{N^*} & \frac{\rho_1\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\rho_2\beta_{1,1}S^*}{N^*} & \frac{\rho_2\beta_{1,2}S^*}{N^*} & \frac{\rho_2\beta_{2,1}S^*}{N^*} & \frac{\rho_2\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_1 q\beta_{1,1}V^*}{N^*} & \frac{\pi_1 q\beta_{1,2}V^*}{N^*} & \frac{\pi_1 q\beta_{2,1}V^*}{N^*} & \frac{\pi_1 q\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_2 q\beta_{1,1}V^*}{N^*} & \frac{\pi_2 q\beta_{1,2}V^*}{N^*} & \frac{\pi_2 q\beta_{2,1}V^*}{N^*} & \frac{\pi_2 q\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$G_2 = \begin{pmatrix} \frac{\rho_1 s_{1,1}\beta_{1,1}S^*}{N^*} & \frac{\rho_1 s_{1,2}\beta_{1,2}S^*}{N^*} & \frac{\rho_1 s_{2,1}\beta_{2,1}S^*}{N^*} & \frac{\rho_1 s_{2,2}\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\rho_2 s_{1,1}\beta_{1,1}S^*}{N^*} & \frac{\rho_2 s_{1,2}\beta_{1,2}S^*}{N^*} & \frac{\rho_2 s_{2,1}\beta_{2,1}S^*}{N^*} & \frac{\rho_2 s_{2,2}\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_1 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_1 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_1 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_1 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_2 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_2 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_2 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_2 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} K_{32} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{1,1} & K_{33} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & K_{34} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_{2,1} & K_{35} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_{36} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\theta_{1,1}\sigma_{1,1} & K_{37} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & K_{38} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{2,1}\sigma_{2,1} & K_{39} \end{pmatrix},$$

with,

$$K_{31} = \mu + \gamma, \quad K_{32} = \mu + \sigma_{1,1}, \quad K_{33} = \mu + \sigma_{1,2}, \quad K_{34} = \mu + \sigma_{2,1}, \quad K_{35} = \mu + \sigma_{2,2},$$

$$K_{36} = \mu + \theta_{1,1}\sigma_{1,1}, \quad K_{37} = \mu + \theta_{1,2}\sigma_{1,2}, \quad K_{38} = \mu + \theta_{2,1}\sigma_{2,1}, \quad K_{39} = \mu + \theta_{2,2}\sigma_{2,2}.$$

The *vaccination reproduction number*, $\mathcal{R}_{vac}$, is given by

$$\mathcal{R}_{vac} = \frac{1}{N^*}\left[\frac{AS^*}{K_{32}K_{33}K_{34}K_{35}} + \frac{BV^*}{K_{36}K_{37}K_{38}K_{39}}\right], \tag{5.16}$$

with,

$$\begin{aligned} A &= \rho_1 K_{34}K_{35}(\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}) + \rho_2 K_{32}K_{33}(\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}), \\ B &= q[\pi_2 K_{36}K_{37}(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}) + K_{38}K_{39}\pi_1(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1})]. \end{aligned}$$

The following result is established by Theorem 2 of [87].

Lemma 5.3. *The DFE of the model* (5.1), *given by* (5.15), *is LAS if* $\mathcal{R}_{vac} < 1$ *and unstable if* $\mathcal{R}_{vac} > 1$.

5.5.2 Existence of backward bifurcation

Setting the right-hand side of the equations in model (5.1) to zero and solving at steady state, in terms of λ, shows that the non-zero equilibria of the model (5.1) satisfy

$$a_4\lambda^2 + b_4\lambda + c_4 = 0, \tag{5.17}$$

where,

$$
\begin{aligned}
a_4 &= q[pK_{32}K_{34}K_{35}K_{33}\{\pi_2 K_{37}K_{36}(\sigma_{1,2}\theta_{1,2}+K_{39})+\pi_1 K_{38}K_{39}(K_{37}+\sigma_{1,1}\theta_{1,1})\}] \\
&\quad +q[K_{37}K_{36}K_{39}K_{38}\{\rho_2 K_{32}K_{33}(K_{35}+\sigma_{2,1})+\rho_1 K_{34}K_{35}(K_{33}+\sigma_{1,1})\}(1-p)], \\
b_4 &= K_{37}K_{36}K_{39}K_{38}K_1[\rho_2 K_{32}K_{33}(K_{35}+\sigma_{2,1})+\rho_1 K_{34}K_{35}(K_{33}+\sigma_{1,1})](1-p) \\
&\quad +\pi_2 K_{32}K_{33}K_{34}K_{35}K_{36}K_{37}pq\mu(K_{39}+\sigma_{1,2}\theta_{1,2})+pq\mu K_{32}K_{33}K_{34}K_{35}K_{38}K_{39}\pi_1(K_{37}+\sigma_{1,1}\theta_{1,1}) \\
&\quad +p\gamma K_{32}K_{33}K_{36}K_{37}K_{38}K_{39}\rho_2(K_{35}+\sigma_{2,1})+p\gamma K_{34}K_{35}K_{36}K_{37}K_{38}K_{39}\rho_1(K_{33}+\sigma_{1,1}) \\
&\quad +pK_{32}K_{37}K_{36}K_{34}K_{35}K_{33}K_{39}K_{38}+K_{32}K_{37}K_{36}K_{34}K_{35}K_{33}K_{39}K_{38}q(1-p)(1-\mathcal{R}_0) \\
&\quad -pK_{32}qK_{34}K_{35}K_{33}[\pi_1 K_{38}K_{39}(s_{1,1}\beta_{1,1}K_{37}+s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}) \\
&\quad +\pi_2 K_{36}K_{37}(s_{2,1}\beta_{2,1}K_{39}+s_{2,2}\beta_{2,2}\sigma_{1,2}\theta_{1,2})] \\
c_4 &= K_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39}(\mu+\gamma)(1-\mathcal{R}_{vac}).
\end{aligned}
$$

It is worth noting that the coefficient a_4 is always positive, and c_4 is positive (negative) if $\mathcal{R}_{vac}$ is less than (greater than) unity, respectively. Hence, the following result is established:

Theorem 5.7. *The DISP model* (5.1) *has*

(i) *a unique endemic equilibrium if* $c_4 < 0 \Leftrightarrow \mathcal{R}_{vac} > 1$;

(ii) *a unique endemic equilibrium if* $b_4 < 0$, *and* $c_4 = 0$ *or* $b_4^2 - 4a_4c_4 = 0$;

(iii) *two endemic equilibria if* $c_4 > 0$, $b_4 < 0$ *and* $b_4^2 - 4a_4c_4 > 0$;

(iv) *no endemic equilibrium otherwise.*

Case (*iii*) indicates the possibility of backward bifurcation in the model (5.1) when $\mathcal{R}_{vac} < 1$. To check for this, the discriminant $b_4^2 - 4a_4c_4$ is set to zero and solved for the critical value of $\mathcal{R}_{vac}$, giving

$$\mathcal{R}_{vac}^c = 1 - \frac{b_4^2}{4a_4K_{31}K_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39}},$$

from which it can be shown that backward bifurcation occurs for values of $\mathcal{R}_{vac}$ such that $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$. This is illustrated by simulating the model (5.1) with the following set of parameter values: $\rho_1 = 0.02, \rho_2 = 0.98, \sigma_{1,1} = 0.72, \sigma_{1,2} = 0.01, \sigma_{2,1} = 15, \sigma_{2,2} = 15, \beta_{1,1} = 0.55, \beta_{1,2} = 0.82, \beta_{2,1} = 0.05, \beta_{2,2} = 0.02, s_{1,1} = 1, s_{1,2} = 1, s_{2,1} = 1, s_{2,2} = 1, \pi_1 = 0.1, \pi_2 = 0.9, \theta_{1,1} = 0.5, \theta_{1,2} = 0.5, \theta_{2,1} = 0.5, \theta_{2,2} = 0.5, q = 0.5, \mu = 0.02, \gamma = 0.07, \Lambda = 1, p = 0.999$ so that $\mathcal{R}_0 = 0.5513222627 < 1, \mathcal{R}_{vac} = 0.7908416180 < 1$, and $\mathcal{R}_{vac}^c = 0.6255824745$ (i.e., $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$). Figure (5.2A), shows the DFE (corresponding to $\lambda = 0$) and two endemic equilibria (corresponding to $\lambda = 0.2116141942$ and $\lambda = 0.04267449704$, respectively). This figure shows that one of the endemic equilibria ($\lambda = 0.2116141942$) is LAS, and the other ($\lambda = 0.04267449704$) is unstable (a saddle), and the DFE is LAS. This clearly shows the co-existence of two stable equilibria when $\mathcal{R}_{vac} < 1$, confirming that the model (5.1) undergoes the phenomenon of backward bifurcation (see Figure (5.2B) for a time series plot). Thus, the following result is established.

Theorem 5.8. *The DISP model* (5.1) *undergoes backward bifurcation when Case* (*iii*)

of Theorem (5.7) *holds and* $0 < \mathcal{R}_{vac}^{c} < \mathcal{R}_{vac} < 1$.

It should be noted that for the case of a perfect vaccine ($q = 0$), the coefficients $a_4 = 0$ and $b_4 > 0$. Thus, the quadratic in (5.17) becomes linear in λ (with $\lambda = -c_4/b_4$). In this case, the DISP vaccination model (5.1) has a unique endemic equilibrium if and only if $c_4 < 0$ (i.e., $\mathcal{R}_{vac} > 1$), ruling out backward bifurcation in this case.

In summary, unlike the vaccination-free DISP model (5.2) and the wholly-vaccinated DISP model (5.9), the full DISP vaccination model (5.1) undergoes the phenomenon of backward bifurcation. The reason for such backward bifurcation is the imperfect nature of the HIV vaccine ($q \neq 0$).

5.6 DISP model with mass action incidence

The presence of backward bifurcation phenomenon in some models has been attributed to many factors, such as the incomplete degree protection for vaccination models [1, 26, 54], exogenous re-infection for TB models [16, 30], and behavioural responses in core group models [40]. In this chapter, the role of the choice of incidence function in bifurcation direction for models of HIV epidemiology that employ an imperfect vaccine will be explored. Since the DISP vaccination model with standard incidence, given by (5.1), undergoes backward bifurcation, it is instructive to determine whether or not its mass action equivalent (where the total population, N, is removed from the force of infection) also exhibits such dynamics. To do so, we consider the model (5.1) with

mass action incidence, given by,

$$
\begin{aligned}
\frac{dS}{dt} &= (1-p)\Lambda - \mu S - \lambda S + \gamma V, \\
\frac{dV}{dt} &= p\Lambda - \mu V - q\lambda V - \gamma V, \\
\frac{dY_{1,1}}{dt} &= \rho_1 \lambda S - (\mu + \sigma_{1,1}) Y_{1,1}, \\
\frac{dY_{1,2}}{dt} &= \sigma_{1,1} Y_{1,1} - (\mu + \sigma_{1,2}) Y_{1,2}, \\
\frac{dY_{2,1}}{dt} &= \rho_2 \lambda S - (\mu + \sigma_{2,1}) Y_{2,1}, \\
\frac{dY_{2,2}}{dt} &= \sigma_{2,1} Y_{2,1} - (\mu + \sigma_{2,2}) Y_{2,2}, \\
\frac{dW_{1,1}}{dt} &= \pi_1 q \lambda V - (\mu + \theta_{1,1}\sigma_{1,1}) W_{1,1}, \\
\frac{dW_{1,2}}{dt} &= \sigma_{1,1}\theta_{1,1} W_{1,1} - (\mu + \theta_{1,2}\sigma_{1,2}) W_{1,2}, \\
\frac{dW_{2,1}}{dt} &= \pi_2 q \lambda V - (\mu + \theta_{2,1}\sigma_{2,1}) W_{2,1}, \\
\frac{dW_{2,2}}{dt} &= \sigma_{2,1}\theta_{2,1} W_{2,1} - (\mu + \theta_{2,2}\sigma_{2,2}) W_{2,2}, \\
\frac{dA}{dt} &= \sigma_{1,2} Y_{1,2} + \sigma_{2,2} Y_{2,2} + \theta_{1,2}\sigma_{1,2} W_{1,2} + \theta_{2,2}\sigma_{2,2} W_{2,2} - (\alpha + \mu) A,
\end{aligned}
\tag{5.18}
$$

where, now, $\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}(\beta_{i,j} Y_{i,j} + s_{i,j}\beta_{i,j} W_{i,j})$. The model has the same DFE given by (5.15). Here, the next generation matrices are $F = \left(H_1 | H_2\right)$, where

$$H_1 = \begin{pmatrix} \rho_1\beta_{1,1}S^* & \rho_1\beta_{1,2}S^* & \rho_1\beta_{2,1}S^* & \rho_1\beta_{2,2}S^* \\ 0 & 0 & 0 & 0 \\ \rho_2\beta_{1,1}S^* & \rho_2\beta_{1,2}X^* & \rho_2\beta_{2,1}S^* & \rho_2\beta_{2,2}S^* \\ 0 & 0 & 0 & 0 \\ \pi_1 q\beta_{1,1}V^* & \pi_1 q\beta_{1,2}V^* & \pi_1 q\beta_{2,1}V^* & \pi_1 q\beta_{2,2}V^* \\ 0 & 0 & 0 & 0 \\ \pi_2 q\beta_{1,1}V^* & \pi_2 q\beta_{1,2}V^* & \pi_2 q\beta_{2,1}V^* & \pi_2 q\beta_{2,2}V^* \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$H_2 = \begin{pmatrix} \rho_1 s_{1,1}\beta_{1,1}S^* & \rho_1 s_{1,2}\beta_{1,2}S^* & \rho_1 s_{2,1}\beta_{2,1}S^* & \rho_1 s_{2,2}\beta_{2,2}S^* \\ 0 & 0 & 0 & 0 \\ \rho_2 s_{1,1}\beta_{1,1}S^* & \rho_2 s_{1,2}\beta_{1,2}S^* & \rho_2 s_{2,1}\beta_{2,1}S^* & \rho_2 s_{2,2}\beta_{2,2}S^* \\ 0 & 0 & 0 & 0 \\ \pi_1 q s_{1,1}\beta_{1,1}V^* & \pi_1 q s_{1,2}\beta_{1,2}V^* & \pi_1 q s_{2,1}\beta_{2,1}V^* & \pi_1 q s_{2,2}\beta_{2,2}V^* \\ 0 & 0 & 0 & 0 \\ \pi_2 q s_{1,1}\beta_{1,1}V^* & \pi_2 q s_{1,2}\beta_{1,2}V^* & \pi_2 q s_{2,1}\beta_{2,1}V^* & \pi_2 q s_{2,2}\beta_{2,2}V^* \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} K_{32} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{1,1} & K_{33} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & K_{34} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_{2,1} & K_{35} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_{36} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\theta_{1,1}\sigma_{1,1} & K_{37} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & K_{38} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{2,1}\sigma_{2,1} & K_{39} \end{pmatrix}.$$

The *vaccination reproduction number* of (5.18), denoted by $\mathcal{R}^m_{vac} = \rho(FV^{-1})$, is

$$\mathcal{R}^m_{vac} = \frac{AS^*}{K_{32}K_{33}K_{34}K_{35}} + \frac{BV^*}{K_{36}K_{37}K_{38}K_{39}}, \tag{5.19}$$

so that the following result is established

Lemma 5.4. *The DFE of the mass action model* (5.18)*, given by* (5.15)*, is LAS if* $\mathcal{R}^m_{vac} < 1$ *and unstable if* $\mathcal{R}^m_{vac} > 1$.

5.6.1 Non-existence of endemic equilibria for $\mathcal{R}^m_{vac} \leq 1$

Theorem 5.9. *The mass action model* (5.18) *has no endemic equilibrium when* $\mathcal{R}^s_{vac} \leq 1$*, and has a unique endemic equilibrium otherwise.*

Proof. Solving the equations in model (5.18) in terms of λ gives

$$\begin{aligned}
S^{**} &= \frac{\Lambda[(K_{31}+q\lambda)(1-p)+\gamma p]}{(\mu+\lambda)(q\lambda+K_{31})}, & V^{**} &= \frac{p\Lambda}{q\lambda+K_{31}},\\
Y_{1,1}^{**} &= \frac{\rho_1\lambda\Lambda[(K_{31}+q\lambda)(1-p)+\gamma p]}{K_{32}(\mu+\lambda)(q\lambda+K_{31})}, & W_{1,1}^{**} &= \frac{\pi_1 q\lambda p\Lambda}{K_{36}(q\lambda+K_{31})},\\
Y_{2,1}^{**} &= \frac{\rho_2\lambda\Lambda[(K_{31}+q\lambda)(1-p)+\gamma p]}{K_{34}(\mu+\lambda)(q\lambda+K_{31})}, & W_{2,1}^{**} &= \frac{\pi_2 q\lambda p\Lambda}{K_{38}(q\lambda+K_{31})},\\
Y_{1,2}^{**} &= \frac{\sigma_{1,1}\rho_1\lambda\Lambda[(K_{31}+q\lambda)(1-p)+\gamma p]}{K_3K_{32}(\mu+\lambda)(q\lambda+K_{31})}, & W_{1,2}^{**} &= \frac{\sigma_{1,1}\theta_{1,1}\pi_1 q\lambda p\Lambda}{K_{37}K_{36}(q\lambda+K_{31})},\\
Y_{2,2}^{**} &= \frac{\sigma_{2,1}\rho_2\lambda\Lambda[(K_{31}+q\lambda)(1-p)+\gamma p]}{K_{35}K_{34}(\mu+\lambda)(q\lambda+K_{31})}, & W_{2,2}^{**} &= \frac{\sigma_{1,2}\theta_{1,2}\pi_2 q\lambda p\Lambda}{K_{39}K_{38}(q\lambda+K_{31})}.
\end{aligned} \tag{5.20}$$

Substituting (5.20) into $\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}(\beta_{i,j}Y_{i,j} + s_{i,j}\beta_{i,j}W_{i,j})$, and simplifying, shows that the non-zero equilibria of the mass action model (5.18) satisfy,

$$a_5\lambda^2 + b_5\lambda + c_5 = 0, \tag{5.21}$$

where,

$$\begin{aligned}
a_5 &= qK_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39},\\
b_5 &= \mu qK_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39} + F_1\Lambda K_{36}K_{37}K_{38}K_{39}\left[\frac{\gamma}{\mu} + (1-p)(1-q)\right]\\
&\quad + K_{31}K_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39}(1-\mathcal{R}_{vac}^m),\\
c_5 &= \mu K_{31}K_{32}K_{33}K_{34}K_{35}K_{36}K_{37}K_{38}K_{39}(1-\mathcal{R}_{vac}^m).
\end{aligned}$$

Clearly, $a_5 > 0$; and whenever $\mathcal{R}_{vac}^m < 1$, then $b_5 > 0$ and $c_5 > 0$. Thus, by the Routh Hurwitz criterion, the quadratic in (5.21) has no positive root. Hence, no endemic

equilibrium exists when $\mathcal{R}_{vac}^m < 1$. The case $\mathcal{R}_{vac}^m = 1$ makes $c_5 = 0$ and $b_5 > 0$. Thus, the quadratic in (5.21) reduces to the linear equation $a_5\lambda + b_5 = 0$, so that $\lambda = \dfrac{-b_5}{a_5} < 0$. Therefore, no endemic equilibrium exists whenever $\mathcal{R}_{vac}^m \leq 1$. For $\mathcal{R}_{vac}^m > 1$, $c_5 < 0$. In this case, the quadratic has two roots with opposite signs. Thus, the proof is completed.

□

The above result indicates the impossibility of backward bifurcation in the mass action model (5.18), since it has no endemic equilibria when $\mathcal{R}_{vac}^m \leq 1$ (a necessary requirement for the existence of backward bifurcation). A global stability result for the DFE of the mass action model (5.18) is given below.

5.6.2 Global stability of the DFE

The following feasible region:

$$\begin{aligned}\mathcal{D} \;=\; & \{(S, V, Y_{1,1}, Y_{1,2}, Y_{2,1}, Y_{2,2}, W_{1,1}, W_{1,2}, W_{2,1}, W_{2,2}) \in \mathbb{R}_+^{10} : \\ & S + V + Y_{1,1} + Y_{1,2} + Y_{2,1} + Y_{2,2} + W_{1,1} + W_{1,2} + W_{2,1} + W_{2,2} \leq \Lambda/\mu\}\end{aligned}$$

is also positively-invariant. Further, it can be shown that $\mathcal{D}$ attracts solutions outside $\mathcal{D}$ but in $\mathbb{R}_+^{10}$. Next, we show that the set

$$\mathcal{D}_* = \{(S, V, Y_{1,1}, Y_{1,2}, Y_{2,1}, Y_{2,2}, W_{1,1}, W_{1,2}, W_{2,1}, W_{2,2}) \in \mathcal{D} : S \leq S^*, V \leq V^*\} \quad (5.22)$$

is positively-invariant and then find a Lyapunov function for (5.18) on $\mathcal{D}_*$.

From the first equation in (5.18),

$$\begin{aligned}\frac{dS}{dt} &\leq (1-p)\Lambda + \gamma V - \mu S,\\ &\leq (1-p)\Lambda + \gamma(\Lambda/\mu - S - Y - W) - \mu S,\\ &\leq \frac{((1-p)\mu+\gamma)\Lambda}{\mu} - (\mu+\gamma)S = (\mu+\gamma)(S^* - S).\end{aligned}$$

Hence, $S(t) \leq S(0)e^{-\mu t} + \frac{\Lambda[\gamma+\mu(1-p)](1-e^{-\mu t})}{\mu(\mu+\gamma)}$. Further, if $N(0) \leq \Lambda/\mu$ and $S(0) \leq S^*$, then $S(t) \leq S^*$ for all $t \geq 0$. Finally, from the second equation of (5.18),

$$\frac{dV}{dt} \leq p\Lambda - (\mu+\gamma)V = (\mu+\gamma)(V^* - V).$$

Hence, $V(t) \leq \frac{p\Lambda}{\mu+\gamma} + \left[V(0) - \frac{p\Lambda}{\mu+\gamma}\right]e^{-(\mu+\gamma)t}$ and, in particular, $V(t) \leq V^*$ if $V(0) \leq V^*$. Thus, the set $\mathcal{D}_*$ is positively-invariant.

Theorem 5.10. *The DFE, $\mathcal{E}_0^m$, of the mass action model* (5.18) *is GAS if $\mathcal{R}_{vac}^m \leq 1$.*

Proof. Consider the Lyapunov function

$$\begin{aligned}\mathcal{F} &= \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}Y_{1,1} + \frac{\beta_{1,2}}{K_{33}}Y_{1,2} + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}Y_{2,1}\\ &+ \frac{\beta_{2,2}}{K_{35}}Y_{2,2} + \frac{(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1})}{K_{36}K_{37}}W_{1,1} + \frac{s_{1,2}\beta_{1,2}}{K_{37}}W_{1,2}\\ &+ \frac{(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1})}{K_{38}K_{39}}W_{2,1} + \frac{s_{2,2}\beta_{2,2}}{K_{39}}W_{2,2},\end{aligned}$$

so that,

$$
\begin{aligned}
\dot{\mathcal{F}} &= \frac{\beta_{1,1}K_{33}+\beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}\dot{Y}_{1,1}+\frac{\beta_{1,2}}{K_{33}}\dot{Y}_{1,2}+\frac{\beta_{2,1}K_{35}+\beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}\dot{Y}_{2,1} \\
&\quad +\frac{\beta_{2,2}}{K_{35}}\dot{Y}_{2,2}+\frac{(s_{1,1}\beta_{1,1}K_{37}+s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1})}{K_{36}K_{37}}\dot{W}_{1,1}+\frac{s_{1,2}\beta_{1,2}}{K_{37}}\dot{W}_{1,2} \\
&\quad +\frac{(s_{2,1}\beta_{2,1}K_{39}+s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1})}{K_{38}K_{39}}\dot{W}_{2,1}+\frac{s_{2,2}\beta_{2,2}}{K_{39}}\dot{W}_{2,2} \\
&= \lambda\left[\frac{AS}{K_{32}K_{33}K_{34}K_{35}}+\frac{BV}{K_{36}K_{37}K_{38}K_{39}}-1\right] \\
&\leq \lambda\left[\frac{AS^*}{K_{32}K_{33}K_{34}K_{35}}+\frac{BV^*}{K_{36}K_{37}K_{38}K_{39}}-1\right] \text{ since } X\leq X^*,\ V\leq V^* \\
&= \lambda(\mathcal{R}^m_{vac}-1)<0 \quad \text{for } \mathcal{R}^m_{vac}<1.
\end{aligned}
$$

Since all the model parameters are assumed to be non-negative, it follows that $\dot{\mathcal{F}}<0$ if $\mathcal{R}^m_{vac}<1$ with equality if and only if $\lambda=0$. It follows from the LaSalle's Invariance Principle [38], that $\lambda\to 0$ as $t\to\infty$. That is, the disease dies out. Since the DFE $\mathcal{E}^m_0$ is GAS for the reduced system with $\lambda=0$, it follows that the DFE is GAS on $\mathcal{D}_*$. Since the above comparisons imply that $\mathcal{D}_*$ is absorbing as well as positively-invariant, the DFE is GAS for all non-negative initial conditions if $\mathcal{R}^m_{vac}<1$. □

If the initial conditions are not in $\mathcal{D}_*$, then although the Lyapunov function is decreasing asymptotically, it is initially increasing and there is a disease outbreak. This is not of interest in practice, since the population would be initially above the assumed carrying capacity Λ/μ.

The consequence of the above theorem, *vis-a-vis* backward bifurcation, is summarized below.

Theorem 5.11. *The mass action model* (5.18) *does not undergo backward bifurcation.*

Proof.

It follows from Theorem (5.9), where no endemic equilibrium exist whenever $\mathcal{R}_{vac}^{m} \leq 1$, and Theorem (5.10) where $\mathcal{E}_0^m$ is GAS whenever $\mathcal{R}_{vac}^{m} \leq 1$. □

These results show that the substitution of standard incidence in the basic model (5.18) with mass action incidence, whilst retaining everything else, removes its backward bifurcation property. It is worth mentioning that this result also holds if continuous vaccination, where a fraction of the susceptible individuals is continuously vaccinated, is added to the cohort vaccination in model (5.1) (details given in [78]).

5.7 Measure of vaccine impact

Since a future HIV vaccine is expected to be imperfect, it is instructive to determine whether or not its widespread use will always be beneficial (or not) to the community. To investigate this, the vaccinated reproduction number, $\mathcal{R}_{vac}$, is re-written as

$$\mathcal{R}_{vac} = \mathcal{R}_0\left[1 - \frac{p\mu}{K_{31}}\left(1 - \frac{\mathcal{R}_{0v}}{\mathcal{R}_0}\right)\right], \tag{5.23}$$

where $\mathcal{R}_0$, $\mathcal{R}_{0v}$ and K_{31} are as defined in Sections 5.3 and 5.4. Using the notation in [8, 65], a measure of the vaccine impact for the model (5.1) is defined as

$$\phi = \frac{p\mu}{K_{31}}\left(1 - \frac{\mathcal{R}_{0v}}{\mathcal{R}_0}\right). \tag{5.24}$$

We claim the following result.

Theorem 5.12. *For the DISP vaccine model* (5.1), *the use of mass vaccination will have*

(i) *positive impact on the community if* $\phi > 0$ $(\mathcal{R}_{vac} < \mathcal{R}_0)$,

(ii) *no impact if* $\phi = 0$, $(\mathcal{R}_{vac} = \mathcal{R}_0)$ *and*

(iii) *negative impact if* $\phi < 0$ $(\mathcal{R}_{vac} > \mathcal{R}_0)$.

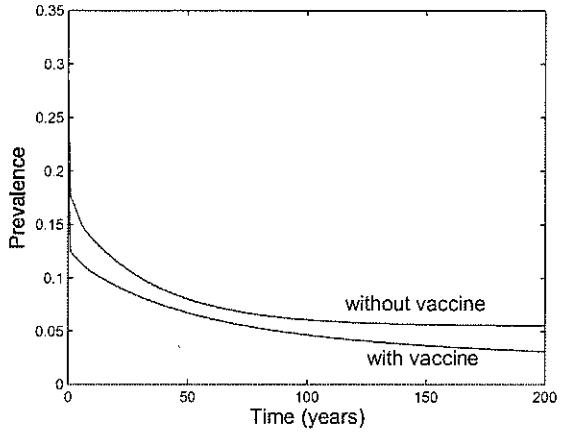
Proof. Starting from (5.23) with (5.24), $\mathcal{R}_{vac} = \mathcal{R}_0(1-\phi)$, it follows that

$$\frac{\mathcal{R}_{vac}}{\mathcal{R}_0} = 1 - \phi.$$

Thus, whenever $\mathcal{R}_{vac} < \mathcal{R}_0$ (positive impact), $1 - \phi < 1$ so that $\phi > 0$. Similarly, whenever $\mathcal{R}_{vac} > \mathcal{R}_0$ (negative impact), $1 - \phi > 1$ so that $\phi < 0$. Finally, if $\mathcal{R}_{vac} = \mathcal{R}_0$ (no impact), $1 - \phi = 1$, so that $\phi = 0$. □

Figure 5.2 illustrates the cases where the vaccine has positive (Figure 5.2A) or detrimental (Figure 5.2B) impact.

(A)



(B)

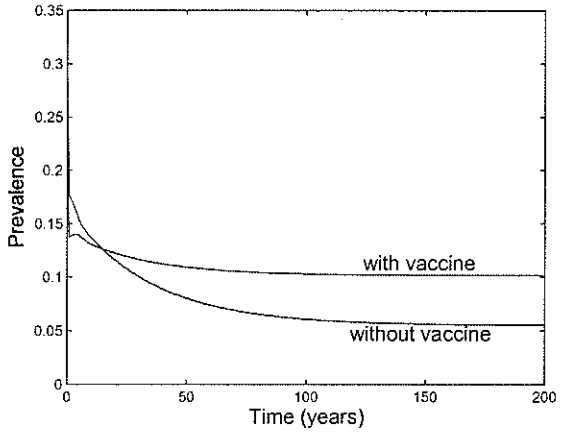


Figure 5.2: (A) Prevalence as a function of time for (5.1) depicting positive impact of the vaccine ($\mathcal{R}_0 = 1.4236, \mathcal{R}_{0v} = 0.7887, \phi = 0.0990, \mathcal{R}_{vac} = 1.287$); (B) Prevalence as a function of time for (5.1) depicting negative impact of the vaccine ($q = 0.1, \mathcal{R}_0 = 1.4236, \mathcal{R}_{0v} = 3.9436, \phi = -0.3930, \mathcal{R}_{vac} = 1.9380$). Other parameters as in Table (5.2)

5.8 Summary

This chapter shows the following:

(i) The phenomenon of backward bifurcation in HIV models with standard incidence

can be removed by substituting such an incidence function with mass action incidence. In other words, this study suggests that the presence or absence of standard incidence may be crucial to the presence or absence of backward bifurcation in vaccination models;

(ii) The reason for the backward bifurcation phenomenon in the vaccination model (5.1) is the imperfect nature of the HIV vaccine;

(iii) The mass action model has a globally-stable DFE, and no endemic equilibrium, whenever $\mathcal{R}_{vac}^{m} \leq 1$;

(iii) A HIV vaccine will have positive impact if $\mathcal{R}_{vac} < \mathcal{R}_0$, negative impact if $\mathcal{R}_{vac} > \mathcal{R}_0$, and no impact if $\mathcal{R}_{vac} = \mathcal{R}_0$.

Table 5.1: Description of variables and parameters for the vaccination model (5.1)

Variables/ Parameters	Description
$S(t)$	unvaccinated susceptible individuals
$V(t)$	vaccinated susceptible individuals
$Y_{1,1}(t)$	unvaccinated infected individuals with high viral load, stage 1
$Y_{1,2}(t)$	unvaccinated infected individuals with high viral load, stage 2
$Y_{2,1}(t)$	unvaccinated infected individuals with low viral load, stage 1
$Y_{2,2}(t)$	unvaccinated infected individuals with low viral load, stage 2
$W_{1,1}(t)$	vaccinated infected individuals with high viral load, stage 1
$W_{1,2}(t)$	vaccinated infected individuals with high viral load, stage 2
$W_{2,1}(t)$	vaccinated infected individuals with low viral load, stage 1
$W_{2,2}(t)$	vaccinated infected individuals with low viral load, stage 2
$A(t)$	individuals in AIDS stage of infection
Λ	rate of recruitment into the population
$\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}$	transmission coefficients (contact rates)
p	fraction of individuals vaccinated
$1-q$	vaccine efficacy
$s_{1,1}, s_{1,2}, s_{2,1}, s_{2,2}$	rate of infectiousness
$\theta_{1,1}, \theta_{1,2}, \theta_{2,1}, \theta_{2,2}$	modification parameters
μ	natural death rate
γ	waning rate of vaccine
$\sigma_{1,1}, \sigma_{1,2}, \sigma_{2,1}, \sigma_{2,2}$	progression rates
α	disease-induced mortality rate
$\rho_1, \rho_2, \pi_1, \pi_2$	probabilities

Table 5.2: Parameter values for model (5.1)

Parameters	**nominal values**
Λ	100
$\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}$	2.55,1.82,1.85,0.82
p	0.999
q	0.5
$s_{1,1}, s_{1,2}, s_{2,1}, s_{2,2}$	1
$\theta_{1,1}, \theta_{1,2}, \theta_{2,1}, \theta_{2,2}$	0.5
μ	0.02
γ	0.07
$\sigma_{1,1}, \sigma_{1,2}, \sigma_{2,1}, \sigma_{2,2}$	0.72,0.01,15,15
$\rho_1, \rho_2, \pi_1, \pi_2$	0.02,0.08,0.1,0.9

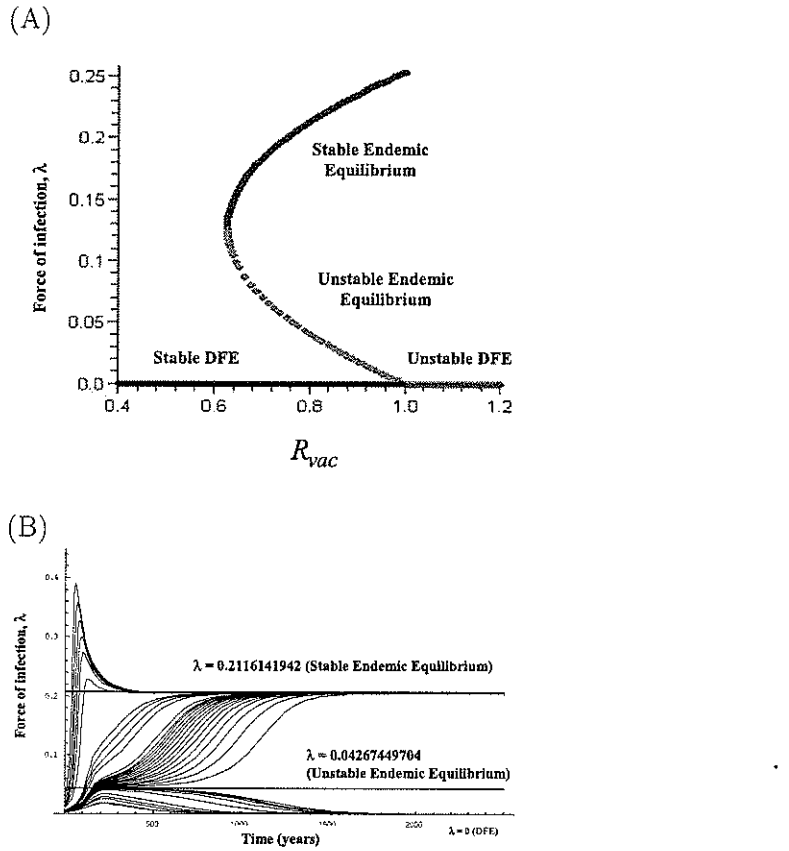


Figure 5.3: (A) Bifurcation diagram and (B) time series plot using different initial conditions for the force of infection λ for the model (5.1). Parameters: $\rho_1 = 0.02, \rho_2 = 0.98, \sigma_{1,1} = 0.72, \sigma_{1,2} = 0.01, \sigma_{2,1} = 15, \sigma_{2,2} = 15, \beta_{1,1} = 0.55, \beta_{1,2} = 0.82, \beta_{2,1} = 0.05, \beta_{2,2} = 0.02, s_{1,1} = 1, s_{1,2} = 1, s_{2,1} = 1, s_{2,2} = 1, \pi_1 = 0.1, \pi_2 = 0.9, \theta_{1,1} = 0.5, \theta_{1,2} = 0.5, \theta_{2,1} = 0.5, \theta_{2,2} = 0.5, q = 0.5, \mu = 0.02, \gamma = 0.07, \Lambda = 1, p = 0.999$.

Chapter 6

Contributions of the Thesis and Future Work

6.1 Contributions

This thesis contributes in three main categories. The first is in the design of appropriate mathematical models for the transmission dynamics and control of HIV/AIDS in a community. The second is in the rigorous analyses of the resulting deterministic systems of nonlinear differential equations. The third category entails the use of these models (and analytical results) to evaluate the potential impact of some anti-HIV public health control strategies (notably the use of ARVs and an imperfect HIV vaccine). The main specific contributions are itemized below:

(i) The design of realistic models for assessing the impact of ARVs and an imperfect putative HIV vaccine to control the spread of HIV in a population;

(ii) Establishing the global asymptotic stability property of the disease-free equilibrium of the treatment models, as well as those of their treatment-free equivalents. This is based on using Lyapunov function theory, in conjunction with the LaSalle Invariance Principle, and Comparison theorem;

(iii) Establishing the existence and local stability of the endemic (and/or boundary) equilibria of the models. A global stability result of the endemic equilibrium of the treatment model (3.1) is given for a special case;

(iv) Showing that, in the case of a single strain HIV model, the qualitative dynamics of the treatment model and its treatment-free equivalent are similar;

(v) Establishing that the Universal treatment strategy, using ARVs, is more beneficial to the community (in terms of reducing new HIV cases and HIV-related mortality) than the targeted use of ARVs (to people with or without clinical symptoms of AIDS). This is followed by the AIDS-only and the HIV-only strategies. It is further shown that when ARV supply is limited, prioritizing such scarce resources to those with clinical symptoms of AIDS can effectively reduce disease burden (albeit the universal strategy is still the best option);

(vi) Showing that a multi-strain HIV model can have a continuum of co-existence endemic equilibria in the absence of treatment, and can have two co-existing endemic equilibria in the presence of treatment;

(vii) Establishing the presence of vaccine-induced backward bifurcation in a vaccination model which incorporates differential infectivity and staged-progression

properties of HIV disease;

(viii) Determining a threshold quantity for assessing the impact of a future HIV vaccine. The vaccine will have positive (negative) impact if the threshold is positive (negative).

It is worth emphasizing that the relatively large nature and nonlinearity of some of the models considered in this thesis makes their mathematical analyses daunting and challenging. Thus, my contributions should be viewed in this light.

6.2 Future Work

Although this study shows that the prospects of the effective control of HIV using ARVs and a putative HIV vaccine are bright, it can be extended in a number of areas, such as:

(1) **Model refinement**: the models can be further refined to include, for instance,

(a) other anti-HIV intervention strategies such as condom use, male circumcision, voluntary testing and screening, e.t.c.;

(b) low fitness (transmissibility) of the resistant strain as well as the use of treatment against such strain;

(c) studying a comprehensive DISP model that incorporates the suggestions in (a) and (b) above.

(2) **Mathematical analysis**: An important future work is the design of technique(s) for establishing the global asymptotic stability of the endemic and/or boundary equilibria of relatively large disease transmission models, such as some of the ones considered in this thesis.

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