A Comparative Analysis of Mathematical Models for HIV Epidemiology

by

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Thesis presented in partial fulfilment of the requirements for the degree of Master of Science (Biochemistry) in the Faculty of Science at Stellenbosch University

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March 2015

Declaration

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Date: 23/02/2015

Abstract

HIV infection is one of the world's biggest health problems, with millions of people infected worldwide. HIV infects cells in the immune system, where it primarily targets $CD4^+$ T helper cells and without treatment, the disease leads to the collapse of the host immune system and ultimately death. Mathematical models have been used extensively to study the epidemiology of HIV/AIDS. They have proven to be effective tools in studying the transmission dynamics of HIV. These models provide predictions that can help better our understanding of the epidemiological patterns of HIV, especially the mechanism associated with the spread of the disease.

In this thesis we made a functional comparison between existing epidemiological models for HIV, with the focus of the comparison on the force of infection (FOI). The spread of infection is a crucial part of any infectious disease, as the dynamics of the disease depends greatly on the rate of transmission from an infectious individual to a susceptible individual.

First, a review was done to see what deterministic epidemiological models exist. We found that many manuscripts do not provide the necessary information to recreate the authors' results and only a small amount of the models could be simulated. The reason for this is mainly due to a lack of information or due to mistakes in the article.

The models were divided into four categories for the analysis. On the basis of the FOI, we distinguished between frequency- or density-dependent transmission, and as a second criterion we distinguished models on the sexual activity of the AIDS group. Subsequently, the models were compared in terms of their FOI, within and between these classes. We showed that for larger populations,

frequency-dependent transmission should be used. This is the case for HIV, where the disease is mainly spread through sexual contact.

Inclusion of AIDS patients in the group of infectious individuals is important for the accuracy of transmission dynamics. More than half of the studies that were selected in the review assumed that AIDS patients are too sick to engage in risky sexual behaviour. We see that including AIDS patients in the infectious individuals class has a significant effect on the FOI when the value for the probability of transmission for an individual with AIDS is bigger than that of the other classes.

The analysis shows that the FOI can vary depending on the parameter values and the assumptions made. Many models compress various parameter values into one, most often the transmission probability. Not showing the parameter values separately makes it difficult to understand how the FOI works, since there are unknown factors that have an influence. Improving the accuracy of the FOI can help us to better understand what factors influence it, and also produce more realistic results. Writing the probability of transmission as a function of the viral load can help to make the FOI more accurate and also help in the understanding of the effects that viral dynamics have on the population transmission dynamics.

Opsomming

MIV-infeksie is een van die wêreld se grootste gesondheidsprobleme, met miljoene mense wat wêreldwyd geïnfekteer is. MIV infekteer selle in die immuunstelsel, waar dit hoofsaaklik $CD4^+$ T-helperselle teiken. Sonder behandeling lei die siekte tot die ineenstorting van die gasheer se immuunstelsel en uiteindelik sy dood. Wiskundige modelle word breedvoerig gebruik om die epidemiologie van MIV/vigs te bestudeer. Die modelle is doeltreffende instrumente in die studie van die oordrag-dinamika van MIV. Hulle lewer voorspellings wat kan help om ons begrip van epidemiologiese patrone van MIV, veral die meganisme wat verband hou met die verspreiding van die siekte, te verbeter.

In hierdie tesis het ons ‘n funksionele vergelyking tussen bestaande epidemiologiese modelle vir MIV gedoen, met die fokus van die vergelyking op die tempo van infeksie (TVI). Die verspreiding van infeksie is ‘n belangrike deel van enige aansteeklike siekte, aangesien die dinamika van die siekte grootliks afhang van die tempo van oordrag van ‘n aansteeklike persoon na ‘n vatbare persoon.

‘n Oorsig is gedoen om te sien watter kompartementele epidemiologiese modelle alreeds bestaan. Ons het gevind dat baie van die manuskripte nie die nodige inligting voorsien wat nodig is om die resultate van die skrywers te repliseer nie, en slegs ‘n klein hoeveelheid van die modelle kon gesimuleer word. Die rede hiervoor is hoofsaaklik as gevolg van ‘n gebrek aan inligting of van foute in die artikel.

Die modelle is in vier kategorieë vir die analise verdeel. Op grond van die TVI het ons tussen frekwensie- of digtheidsafhanklike oordrag onderskei, en as ‘n tweede kriterium het ons die modelle op die seksuele aktiwiteit van die

vigs-groep onderskei. Daarna is die modelle binne en tussen die klasse vergelyk in terme van hul TVIs. Daar is gewys dat frekwensie-afhanklike oordrag gebruik moet word vir groter bevolkings. Dit is die geval van MIV, waar die siekte hoofsaaklik versprei word deur seksuele kontak.

Die insluiting van die vigs-pasiënte in die groep van aansteeklike individue is belangrik vir die akkuraatheid van die oordrag-dinamika van MIV. Meer as helfte van die uitgesoekte studies aanvaar dat vigs-pasiënte te siek is om betrokke te raak by riskante seksuele gedrag. Ons sien dat die insluiting van vigs-pasiënte in die groep van aansteeklike individue ‘n beduidende uitwerking op die TVI het wanneer die waarde van die waarskynlikheid van oordrag van ‘n individu met vigs groter is as dié van die ander klasse.

Die analise toon dat die TVI kan wissel afhangende van die parameter waardes en die aannames wat gemaak is. Baie modelle voeg verskeie parameter waardes bymekaar vir die waarskynlikheid van oordrag. Wanneer die parameter waardes nie apart gewys word nie, is dit moeilik om die werking van die TVI te verstaan, want daar is onbekende faktore wat ‘n invloed op die TVI het. Die verbetering van die akkuraatheid van die TVI kan ons help om die faktore wat dit beïnvloed beter te verstaan, en dit kan ook help om meer realistiese resultate te produseer. Om die waarskynlikheid van oordrag as ‘n funksie van die viruslading te skryf kan help om die TVI meer akkuraat te maak en dit kan ook help om die effek wat virale dinamika op die bevolkingsoordrag-dinamika het, beter te verstaan.

Acknowledgements

I would like to express my sincere gratitude to the following people and organisations:

- my supervisor, Prof Jacky Snoep, for his guidance and support,
- my friends and family for all the love and support they provided,
- SACEMA, the Biochemistry department and the Triple-J lab for assistance, and
- the National Research Foundation (NRF) for funding support.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
CTL	Cytotoxic T lymphocytes
FOI	Force of infection
HCT	HIV counselling and testing
HIV	Human immunodeficiency virus
MSM	Men who have sex with men
ODE	Ordinary differential equation
PrEP	Pre-Exposure prophylaxis
RT	Reverse transcriptase
STD	Sexually transmitted disease
TB	Tuberculosis

Chapter 1

Introduction

Since the discovery of the human immunodeficiency virus (HIV) more than 30 years ago, HIV infection has become one of the world's biggest health problems. Globally, an estimated 35.5 million people were HIV positive in 2012, of which 7.2 million lived in Southern Africa. According to UNAIDS estimates, the countries that are the worst affected by the epidemic are Botswana, Lesotho, South Africa, and Swaziland, with the numbers of infected individuals still increasing in these countries [1].

HIV infects cells in the immune system, where it primarily targets $CD4^+$ T helper cells and without treatment, the disease leads to the collapse of the host immune system and ultimately death. HIV infects and kills components of the immune system such as $CD4^+$ T helper cells, macrophages and dendritic cells [2]. The virus uses $CD4^+$ T cells to gain entry into host T cells and achieves this by binding to the viral envelope protein (gp120). Through this it decreases the number of $CD4^+$ cells, which are essential in fighting disease. $CD4^+$ T cells will continue to decrease as the viral load increases. Looking at the $CD4^+$ T cell count, HIV infection can be separated into four stages [3]. The stages include: primary HIV infection or acute stage, asymptomatic stage, symptomatic stage and the stage where individuals progress from HIV to acquired immunodeficiency syndrome (AIDS). The infectivity of an infected individual is the highest during the acute phase [4], when the viral load is the highest and the lowest during the asymptomatic stage. HIV infection is treated with antiretrovirals (ARVs). ARVs can only help to slow down the spread of the disease, but not cure it. The aim of antiretroviral therapy (ART) is to

keep the amount of virus in the body as low as possible. A lower viral load will result in an infected individuals being less infective. Individuals of whom treatment is successful, will stay in the asymptomatic stage of the disease.

HIV/AIDS has been the focus of many modelling studies since its discovery, starting with May and Anderson [5] who were concerned about the possible outcome of the AIDS epidemic. They designed models to understand the mathematical nature of HIV transmission. Mathematical models have proven to be effective tools for the epidemiology of HIV and have been used extensively to study the transmission dynamics of HIV. These models provide predictions that can help better our understanding of the epidemiological patterns of HIV, especially the mechanisms associated with the spread of the disease. New approaches to reduce the spread of HIV can be found by looking at the impact that treatment and interventions have on the population. Different prevention and treatment strategies have been used as an attempt to combat the HIV epidemic, including ART, condom use, HIV counselling and testing (HCT), male circumcision, and information campaigns. These are also the main focus of most epidemiological models.

There are two processes that are important in the study of the dynamics of HIV infection, i.e., the epidemiological process and the immunological process [6]. The epidemiological process occurs at population level and it takes the transmission between hosts into account. The immunological process occurs within the host and involves the virus-cell interaction. Both these processes develop on widely different time and spatial scales, which makes it difficult to incorporate both in a single model. Most existing models do not link these processes explicitly, but rather see them as a decoupled system. Epidemiological models consider only the interactions between susceptible and infected individuals without taking into account the viral dynamics within the host. Immunological models only take into account the viral dynamics within the host with no population dynamics. Some epidemiological models incorporate the infectivity of an individual in a certain class, but it still assumes that all individuals in that specific class have the same constant viral load.

There is a large amount of uncertainties in HIV modelling, especially with

regards to transmissibility and the effects of treatment. Due to these uncertainties, assumptions have to be made when estimating parameters and too many assumptions can cause a model's results to be inaccurate and unrealistic. Coupled models, that incorporate both the epidemiological and the immunological processes, can further the understanding of the interaction between the variables that determine the development and progress of the disease, and the variables that control the pattern of infection in a population. By studying these models we can see how within-host dynamics influence the disease dynamics at population level, and also the effect that the transmission dynamics at population level has on the within-host dynamics. Not many models exist that couple these processes, especially when focusing on HIV. A possible way to improve the accuracy of epidemiological HIV models could be through incorporating within-host dynamics in an epidemiological model, by expressing the probability of transmission as a function of the viral load. This will increase the reliability of the force of infection (FOI) of the model, which is important for the accuracy of the infection rate. The FOI is the rate at which individuals get infected.

1.1 Aims and outline

Our aim is to make a functional comparison between existing epidemiological models for HIV. The focus lies on the comparison of the different FOIs for the models. The FOI is important in understanding disease dynamics, as it is the driving force of disease transmission. The formulation of the force of infection differs between diseases and populations. What effect would the FOI have on the accuracy of a model? We specifically set out to:

- Review existing mathematical models for HIV epidemiology.
- Simulate the relevant models from the review for curation and the comparison.
- Compare and interpret the results by focusing on the force of infection for the different models.

The thesis is set out as follows: Chapter 2 provides background information on topics that are of importance to the study. Chapter 3 covers the review

of the existing models, along with a short discussion and Chapter 4 shows the simulation and comparison of the models. The general discussion and conclusion to the thesis are given in the last two chapters.

Chapter 2

Background information

The following chapter provides background information on the main research topics covered in this thesis. We start with mathematical modelling of infectious diseases, explaining how and why they are used. We then move onto HIV infection, where we look at both the whole body disease state as well as virus dynamics at cellular level. We also give an example of a basic HIV model, and then lastly focus on the force of infection, which is the main focus of this thesis.

2.1 Mathematical modelling of infectious diseases

Mathematical models provide detail that help us to understand the mechanisms associated with the spread and persistence of a disease. The impact of any intervention on the population can be determined through such models. The benefits of these models are that they can project how infectious diseases progress to help us understand what factors influence the dynamics of the disease, as well as show the likely outcome of an epidemic [7]. An epidemiological model combines the knowledge and data about an infectious disease by considering the pathogenesis of the disease, the transmission between individuals in a specific population, and the impact that interventions have on the population. All this can help inform public health interventions. Different diseases in a population, or the same disease in different populations can also be compared by using mathematical models.

Daniel Bernoulli constructed the earliest mathematical model for infectious diseases in 1760, where he looked at susceptible individuals exposed to smallpox [8]. This was followed by Ronald Ross's research into the spread of malaria, where he developed models to study the epidemiology of malaria. Building on this research done by Ross, Anderson McKendrick and William Kermack formulated a basic deterministic model that could successfully predict the behaviour of outbreaks, as these results were similar to trends in observed epidemics [9]. After this, Lowell Reed and Wade Frost developed a model that described the interactions between susceptible, infected and immune individuals in a population [10]. This model is called the Reed-Frost epidemic model.

Realistic models can be quite complex, and therefore simplified models are often used. These simplified models can still help to get a better understanding of population-level dynamics and the impact of interventions. The number of assumptions in a model can affect the accuracy of the results and a model should be able to represent the biological problem that is studied as accurately as possible [11]. Unnecessary detail can make it more difficult to estimate accurate parameters for the model, but if too many important details are excluded the conclusions can be inaccurate.

Infectious disease models are often used in the planning of prevention and treatment programmes which have a big impact on public health. For this reason, it is important that parameter values of such models are estimated using accurate and reliable methods. Mathematical models of any infectious disease should be based on the basic knowledge of the disease in question and the data collected to understand it. Mathematical models need validation, but challenges remain on the accuracy, availability and usefulness of the data that are used in epidemiological models. When analysing the results of these models, the following need to be taken into account: the sensitivity of the results to changes in the parameter values, the basic structure of the model and possible short-comings in data accuracy [12]. It is clear that no model can include all the processes that influence the spread of an epidemic, as this will make the model too complicated to work with.

Different types of models are used for modelling infectious diseases. The main types are deterministic and stochastic models [13]. For stochastic models, probability is used to determine the state of the system and the solution of such a system is a probability distribution for each of the variables. Deterministic models do not include elements of randomness, but rather rely on fixed parameter values and initial conditions. A deterministic model will always produce the same results for a given set of conditions. Stochastic models are suitable for modelling small populations and deterministic models are mainly used for larger populations.

2.2 HIV infection and transmission dynamics

HIV was fist discovered in 1981 in the United States, where patients showed symptoms of fungal infections such as *Pneumocystis carinii* pneumonia (PCP) and later a rare skin cancer known as Kaposi's sarcoma was also seen in patients. These diseases mainly occur in individuals with very compromised immune systems, and the previously mentioned patients had no know cause of weakened immune systems. HIV is mainly spread through sexual intercourse, infected blood, and from mother to child (vertical transmission).

There are two types of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2). Differences between the types are that HIV-2 is not as easily transmitted as HIV-1 and the development of the disease after initial infection is much slower in HIV-2 cases [14]. HIV is a retrovirus with RNA that is reverse transcribed by reverse transcriptase (RT) to DNA, after the virus has entered the host cell. The DNA is then integrated into the genome of the cell and replicated along with the cell. HIV-1 infection begins when the envelope glycoprotein, gp120, of HIV binds to CD4, the cellular receptor that is expressed on the host cell [15]. The cells that the virus attaches to include: T-helper cells, macrophages, and dendritic cells. A conformational change occurs in gp120 as a result of the binding to the CD4 receptor. This conformational change increases its affinity for a co-receptor and exposes gp41, an HIV protein that penetrates the cell membrane. The co-receptor that gp120 needs to bind to is either CCR5 or CXCR4, which are chemokine receptors.

After the binding of the HIV envelope and the host membrane, the nucleocapsid is released into the cell. Here, the viral RNA is transcribed into viral DNA which is then transported to the nucleus. In the nucleus the viral DNA integrates with the cell DNA, and the integrated viral DNA can remain latent (latent stage of HIV) until the cell is activated. When the cell is activated through the transcription of the viral DNA, virions are produced and bud out of the host cell membrane.

The clinical stages of HIV disease starts with the rapid replication of the virus. Infected individuals can develop a fever within two weeks after infection. The increase in the viral load in the blood in the first two months is significant. The viral load peaks around two months, after which there is a sudden decline. This is followed by an extended period of clinical latency, where the number of infected cells is very low. During this time, there is little viral activity in the blood, but the virus is still active in the lymphoid tissue [16]. Cytotoxic T lymphocytes (CTL) start to develop early on in the infection, and it kills the infected T-helper cells which leads to a decrease $CD4^+$ T cells. The number of $CD4^+$ T cells keeps decreasing, and AIDS develops when the number of $CD4^+$ T cells goes below 200 cells/mm^3.

2.2.1 Prevention strategies and treatment for HIV

Prevention of new HIV infections seems to be the key to managing the HIV/AIDS epidemic [17]. Prevention strategies for HIV require both behavioural and biological approaches. Behavioural approaches of HIV prevention include HIV counselling and testing (HCT), information campaigns, condom use and screening. Information campaigns largely focus on uninfected individuals, but it has been found that individuals who know their status, and are positive, may still engage in risky sexual behaviour. It also occurs among individuals who are receiving treatment, where their partners believe that they can no longer transmit HIV.

The use of condoms as a prevention strategy is not always effective, due to inconsistent and incorrect use of condoms. This also makes it difficult to determine parameters that relate to condom use [11]. Recent surveys in various countries in sub-Saharan Africa have detected a decrease in condom use, even

though the supply of condoms are increasing [1]. There are several reasons for the low levels of condom use, including poverty, relationship with parents, lack of education on HIV, and beliefs and attitudes about HIV [18], but it is unclear why the use of condoms have decreased in these areas. Screening of infectives can have a positive impact on behaviour change, but studies have shown that individuals who tested negative will not necessarily change their behaviour [19, 20].

Biological approaches to HIV prevention include vaccines, microbicides, male circumcision, treatment of sexually transmitted diseases (STDs), ART, and the use of ART as pre-exposure prophylaxis (PrEP). The efficacy of PrEP as a preventive measure is highly effective if drug adherence is high. Unfortunately, the use of ART as prevention in the worst affected countries can not be sustained due to the high demand, and low adherence levels. PrEP administration can either increase the efficacy of the drug or it can cause drug resistance to develop [1]. In infected individuals, ART is used to suppress viral replication of HIV to such a level that it is below the level of detection [21]. This allows the immune system to function and help prevent opportunistic infections to develop, such as TB. It also delays the progression to AIDS [22].

ART is not able to clear the infection, and therefore cannot cure HIV infection completely. Using ART can decrease the infectivity of an infected individual, as a result of the decreased viral load [21, 23], but the complete prevention of transmission has not yet been proven. The use of treatment by infected individuals also increases their survival period, a result that can possibly have a negative effect on the epidemic as there are more infected individuals over a longer time, just with decreased infectivity. From this observation, several studies have come to the conclusion that treatment will only be effective in preventing new infections if the levels of risky sexual behaviour do not increase [24, 25]. Male circumcision has been shown to decrease the transmission of HIV, but it is more effective combined with treatment [26].

2.3 HIV models

Mathematical models of the transmission dynamics of HIV have been used extensively to determine the impact that prevention strategies have on the epidemic, since they provide short and long term prediction of HIV incidence. Starting with May and Anderson [5], who used models to understand the transmission dynamics of HIV, several modifications have been made to models to study how different components play a role in the prevalence of HIV. Among these modifications are the variability of the infection rates of the different subpopulations at risk, the incubation period before the onset of symptoms, and the evolution of the variability of infection in each individual. The within-host dynamics and infectious periods of infected individuals have to be considered when modelling HIV to take the persistence of the disease into consideration. The challenge remains to accurately express what impact the within-host processes have at population level. Changes in viral load, which correlate with different degrees of infectivity, are modelled by individuals moving between various infection stages [27]. Much focus has been put on developing realistic mathematical models for the transmission dynamics, within-host dynamics and control mechanisms of HIV. These models have made a considerable impact on the understanding of HIV infection and treatment [28, 29].

Coupled models take both the epidemiological and immunological dynamics into account. There are a few models incorporating both the systems by looking at a general infectious disease, but we see that it may be helpful to link the dynamics for HIV as well. Linking the prevalence of the disease to the viral load at the within-host level can help improve the accuracy of parameters. Combining these two components allows the viral load to vary as the epidemic changes [30].

HIV is a major driving-force of the tuberculosis (TB) epidemic, especially in poor regions. HIV is the biggest risk factor for latent TB to progress to active TB. TB is also the most widespread opportunistic infection among HIV infected individuals. It is the first sign of AIDS in more than 50% of HIV cases in developing countries [31]. HIV-positive individuals, co-infected with TB, have a shorter survival period, as TB increases the rate of progression

from HIV to AIDS. Therefore, it is essential to also study the transmission of HIV-TB co-infection in developing countries.

2.3.1 Basic HIV infection model formulation

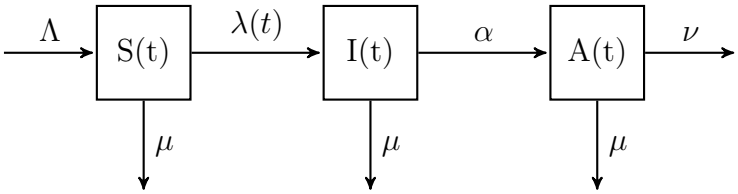


Figure 2.1: Diagram representing a basic HIV/AIDS model

Basic compartmental models consist of a set of ordinary differential equations (ODEs) which is formulated by observing the flow of individuals from one compartment to the other. The population under consideration is divided into separate classes, where the number of individuals per class change with time, as shown in Figure 2.1. The susceptible class (S) consists of those individuals who can be exposed to the disease but they are not yet infective. The infective class (I) consists of those individuals who are transmitting the disease to others and the AIDS class (A) consists of the individuals who have progressed to the AIDS stage of HIV infection. The susceptible class can interact with both the infective and AIDS classes, depending on the model assumptions. The total population (N) is given by

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

Individuals are recruited at a constant rate, Λ, and removed by death from each class at a rate, μ, which is called the natural death rate. This rate is proportional to the class size. Individuals are removed from the AIDS class by disease-related death at a rate, ν, called the disease-related death rate. The rate at which individuals get infected, that is the rate at which they move from the susceptible class to the infected class, is given by λ, this is also called the force of infection (FOI). The rate at which individuals progress to the AIDS stage of infection is given by α. Taking all of this into consideration, we get the following system of ODEs:

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - (\lambda + \mu)S \\ \frac{dI}{dt} &= \lambda S - (\alpha + \mu)I \\ \frac{dA}{dt} &= \alpha I - (\mu + \nu)A\end{aligned}$$

An example of an expression for the FOI is: $\lambda = \frac{\beta_1 I + \beta_2 A}{N}$. There are other possibilities for the form of the FOI, depending on the assumption made in the model. This is explained in detail in Section 2.4.

The differences in infectivity for individuals in each of the infectious compartments is represented by β_1 and β_2. β is either the probability of transmission from an infectious individual to a susceptible individual, given by β_1, or from an individual with AIDS to a susceptible individual, given by β_2. This parameter (β) is formed from two components, namely the likelihood of contact between two individuals for transmission to be possible, and the probability of successful transmission as a result of the contact. The probability of transmission is significant in measuring the FOI, but it is difficult to determine since it is associated with the attitude or behaviour of an individual. This then shows that the risk of acquiring HIV largely depends on an individuals behaviour. A few studies [17, 19, 32, 33] have stated that the future of the HIV/AIDS epidemic mostly depends on behaviour change of individuals.

It is possible to assume that the AIDS population is too sick to be sexually active, and therefore the AIDS class will not be infectious. If this is the case, then $\beta_2 = 0$. The transmission can also be either density-dependent or frequency-dependent. In the example given, frequency-dependent transmission is used. The types of transmission will be discussed in detail in the next section.

2.4 Force of infection

The spread of infection is a crucial part of any infectious disease. Understanding the transmission dynamics is an essential part of the planning of control and

prevention strategies for infectious diseases. The dynamics of any infectious disease depends greatly on the rate of transmission from infectious individuals to susceptible individuals. This rate, the FOI, is defined as the rate at which susceptible individuals become infected. Mechanistically, intervention strategies are usually aimed at decreasing the FOI. If these intervention strategies are successful, it will lead to a decrease in the prevalence of the disease. The FOI is a significant measure of efficacy when comparing intervention strategies, such as treatment or circumcision, as it has the biggest impact on determining the outcomes of the interventions, and ultimately the design of public health policy.

In many epidemic models the FOI is expressed by a single parameter, the probability of transmission, β. However, β can be divided into various biologically relevant components, such as the number of contacts between individuals and the probability that a contact leads to transmission of the disease. Behaviour change is also sometimes incorporated in β, or expressed separately in the FOI. Due to varying infectivity between different classes in a model, separate transmission terms could be applied to different classes. For example, an individual receiving treatment is assumed to be less infectious than individuals who are not on treatment, therefore the two classes will have different transmission rates.

There are two main types of transmission: density-dependent and frequency-dependent transmission. The main difference between the two is that with density-dependent transmission, the contact rate depends on the population density, and with frequency-dependent transmission, it does not. It is important to distinguish between the types of transmission in terms of the basic structure of contacts within the population. The transmission term depends on the mode of transmission for a specific disease, for example, airborne diseases, such as flu or TB, will often be modelled using density-dependent transmission, and sexually transmitted diseases, such as HIV, will often be modelled using frequency-dependent transmission. There are exceptions where these can be switched around.

Density-dependent transmission assumes that the contact rate increases as

the density of individuals increases [27]. This means that the FOI increases with the density of infected individuals. The reason is that if more people enter a given area, then the contact rate between the individuals will increase. Other terms that are used for density-dependent transmission is mass action or pseudo mass action transmission. An example of a FOI using density-dependent transmission would be: $\lambda = \beta I$, where the dimension of β is per individual per unit time. Density-dependent transmission is used for small populations, where the density of the population will have an effect on the transmission of the disease.

With frequency-dependent transmission, the FOI increases with the prevalence of infection, $\frac{I}{N}$, where I is the number of infectious individuals and N is the total population. Another term for frequency-dependent transmission is prevalence-dependent transmission [34], but this term is not generally used. Frequency-dependent transmission shows the case for which the number of contacts is independent of the population size. When using frequency-dependence for sexually transmitted diseases, it is assumed that the same patterns of transmission will occur in any large area, as the number of close contacts that can result in transmission is controlled by social behaviour. An example of a FOI using frequency-dependent transmission would be: $\lambda = \frac{\beta I}{N}$, where the dimension of β is time^{-1}.

There can be confusion about the correlation between homogeneous and heterogeneous mixing, and density-dependent and frequency-dependent transmission. There is no direct correlation between these, but they can appear interchangeable, which is not the case. Homogeneous mixing does not take the demography or spatial correlations between individuals into account, whereas with heterogeneous mixing these factors are considered. Frequency-dependent and density-dependent transmission can also lead to confusion and a lack of consistency if the terms are not used correctly.

The current chapter provided background information on HIV infection and the mathematical modelling of HIV epidemiology. We also looked at an example of a basic model for HIV epidemiology. FOI was discussed in detail and the different forms that it can take were explained. In the next chapter we will

do a review of existing mathematical models for HIV epidemiology, and from this determine which models can be used in Chapter 4 for our analysis.

Chapter 3

Review of existing mathematical models for HIV epidemiology

For our review of the models we focus on deterministic models for HIV epidemiology. The models must be HIV specific, but can focus on any interventions. Our goal is to make a comparative analysis of the FOI in existing mathematical models for HIV epidemiology. First we describe how the specific studies were chosen, then give a summary of them and lastly discuss the different studies.

3.1 Methods

A search of the Scopus database was conducted, using a specific search term: 'mathematical model AND (HIV OR AIDS) AND (prevent OR treat)'. We searched for papers published up to 2014. Reference lists of relevant articles were searched for more modelling studies. For the comparison of the models the papers must contain a deterministic model and be HIV specific, including co-infection models. We focus on deterministic models as we only look at studies that describe epidemiological factors. As mentioned in Section 2.1, deterministic models are mainly used for larger populations and when studying epidemiological factors, large populations are usually considered.

For each of the articles, the following information was recorded: the focus of the study, whether or not it contains a model, what type of model is used, the population modelled, and whether or not the authors supplied the system of ODEs, parameter values, initial conditions, and results from their numerical

simulations. The ODEs, parameter values and initial conditions are used in Chapter 4 for the simulations.

3.2 Results

The search generated 1215 results. 26 articles were excluded because they were either duplicates, commentaries or not available in English. The remaining 1189 abstracts were then examined and the following articles were excluded: 298 were not HIV specific, 96 described cost-effectiveness analyses of HIV interventions and treatment programmes, and 442 described within-host dynamics of HIV. The remaining 353 articles described epidemiological factors and were assessed in more detail. From the 353 articles that were left, only 100 studies contained deterministic models, of which 81 did not have enough information to simulate the models.

The 253 studies that were excluded due to not containing deterministic models, either did not contain a model, or described stochastic or statistical models. The 81 articles that contained deterministic model, but were excluded due to a lack of information, either did not provide all the parameter values or all the initial conditions. Most of the studies that were excluded did not give the initial conditions, and without the initial values we cannot replicate the models.

For the simulation of the models the ODEs, parameter values and initial conditions were needed. Five more studies that contained enough information to be simulated were found in reference lists of relevant articles. A detailed summary of the simulated studies is given in Table 3.1.

The epidemiological studies focused on a variety of different intervention strategies. The majority of the models focused on ART and what effect it has on the spread of HIV, as it is seen as an intervention that can both treat and prevent new infections. Not many studies included behaviour change in their models, which is another important parameter. The transmission probability of HIV is mainly determined by the behaviour of an individual and their viral load. This means that behaviour change and treatment are both important for model accuracy. There are some models that incorporate behaviour change in

other parameters, for example, condom use or testing and screening.

To make the analysis of a model more convenient, some studies assume a closed population. For example, Naresh and Tripathi [35] considered a closed population to show how the total amount of AIDS patients compare for a population that varies in size. If there is HIV infection present in a closed population, it will always result in eradication of the population, which makes a closed population model rarely realistic. Immigration and births have to be taken into account for a model to reflect real world scenarios.

Table 3.1: Summary of existing models that were simulated (listed according to date of publication).

Author(s)	**Focus of model**	**Assumptions**	**Main results**
Romieu *et al.*, 1991 [36]	Sex-structured model with decreased transmission using data from Mexico City, Mexico.	Adjusted transmission probability according to impact of prevention programmes. All infected individuals assumed to be infectious.	A small change in sexual behaviour can have a positive effect on the epidemic.
Gumel *et al.*, 2000 [22]	Treatment	Transmission only via sexual contact. AIDS class not sexually active.	Compared well with similar models and can be used to asses impact of therapy.
Moghadas and Gumel, 2003 [28]	Interaction between HIV and other pathogens.	HIV infected not susceptible to the pathogen. No ART available. AIDS class not sexually active.	Treatment of the competing pathogen, along with ART, can significantly reduce the number of HIV infections.
Bachar and Dorfmayr, 2004 [37]	Treatment (with time delay)	AIDS class not sexually active. No behaviour change.	Treatment without behaviour change is not as effective as treatment along with behaviour change.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Narash and Tripathi, 2005 [35]	HIV-TB co-infection	AIDS class not sexually active. HIV infected not susceptible to TB infection. No ART available.	If the treatment of TB is effective, then new HIV infections can be reduced.
Podder *et al.*, 2007 [26]	A sex-structured model focusing on male circumcision, condom use, and treatment using partial data from South Africa.	AIDS class sexually active.	Combining male circumcision and ART is more effective in reducing HIV infection than the use of male circumcision alone, or the combined use of male circumcision and condoms. This is the case for when the condom compliance rate is too low (below 60%).
Tripathi *et al.*, 2007 [20]	Screening of the Indian population.	Transmission only through sexual contact. AIDS class not sexually active.	Behaviour change due to screening can reduce the spread of the disease.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Bacaër *et al.*, 2008 [25]	HIV-TB co-infection with ART in a township near Cape Town, South Africa.	Model cannot distinguish between modes of transmission. AIDS class not considered.	Condom use, increased TB detection, and treatment as prevention has a positive impact on the HIV and TB epidemics, with ART decreasing the number of TB cases.
Nyabadza, 2008 [11]	Condom use, vertical transmission and treatment in Southern Africa.	Heterosexual transmission. AIDS class sexually active.	Condoms are not successful in completely preventing HIV transmission. Increased treatment programs may result in an increase in life expectancy over time, but this will increase the duration of infectiousness, which will in turn increase the number of infectious individuals.
Cai *et al.*, 2009 [38]	Treatment	AIDS class not sexually active.	ART can either result in the disease dying out, or persisting.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Hove-Musekwa and Nyabadza, 2009 [39]	Screening, treatment and partner acquisition.	Heterosexual transmission. No vertical transmission, blood transfusion or needle sharing. No HIV resistance. AIDS class sexually active.	Treatment, combined with screening, is more effective than treatment alone, in reducing the spread of HIV infection.
Lou *et al.*, 2009 [40]	Sex-role-preference model with treatment, a potential vaccine, condom use, behaviour change and other STDs (MSM population in China).	AIDS class not considered.	ART and a potential vaccine would have a positive impact on controlling the spread of HIV in an MSM population. Condom use has a limited effect on the control of the epidemic in an MSM population.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Nyabadza *et al.*, 2010 [17]	Public health information campaigns.	AIDS class sexually active. Heterosexual transmission.	An increase in information campaigns can result in a decrease in the prevalence of HIV. The combination of increased information campaigns and reduced sexual activity by individuals living with AIDS is the most effective intervention.
Al-Sheikh *et al.*, 2011 [41]	Screening	AIDS class not sexually active.	An increase in screening rates will reduce the spread of HIV.
Bhunu *et al.*, 2011 [42]	Educational programmes, HCT, and behaviour change.	AIDS class not sexually active.	Effective HCT can have a positive impact on the HIV/AIDS epidemic, along with educational programmes that encourage behaviour change.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Hove-Musekwa *et al.*, 2011 [43]	Transmission, hospitalisation, home-based care, and behaviour change in Zimbabwe.	AIDS class sexually active.	A combination of all the suggested interventions is the most effective in reducing the spread of the disease. Their projections show that the number of HIV infections will continue to decline but may start to increase again over time.
Naresh *et al.*, 2011 [44]	Contact tracing in India.	No treatment available. AIDS class not sexually active.	Awareness will lead to behaviour change, ultimately slowing down the rate of infection.
Nyabadza and Mukandavire, 2011 [19]	HIV counselling and testing programme, condom use, screening, and treatment in South Africa.	AIDS class sexually active.	Increased efficacy of HIV counselling and testing programmes can lead to a significant reduction in HIV prevalence.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Nyabadza *et al.*, 2011 [45]	Condom use, screening, behaviour change and treatment in South Africa.	AIDS class sexually active.	A multiple strategy approach will possibly have the most impact in reducing HIV prevalence.
Bhunu and Myshayabasa, 2012 [46]	Pre-exposure vaccines and treatment.	AIDS class sexually active.	In the presence of pre-exposure vaccines the number of HIV infections decreases, as compared to only treating infected individuals.
Raimundo *et al.*, 2012 [47]	Drug resistance (ART)	AIDS class not sexually active.	More effective ART will reduce prevalence of drug-sensitive individuals significantly, resulting in the total prevalence of HIV infected individuals decreasing. The prevalence of drug-resistant individuals will still increase, but will not affect the overall decrease in prevalence.

Table 3.1 (continued)

Author(s)	Focus of model	Assumptions	Main results
Abiodun *et al.*, 2013 [48]	Parental care when infected immigrant youths are present.	AIDS class is sexually active.	The most sensitive parameters are linked to the AIDS class. Infected immigrant youths do not have a big impact on HIV transmission if parental care over youths is effective.
Huo and Feng, 2013 [49]	Latent stages with treatment.	AIDS class not sexually active.	Treatment of individuals in slow and fast latent compartments can reduce the number of infectious individuals.
Zhao *et al.*, 2013 [50]	Pre-exposure prophylaxis use in South Africa.	AIDS class not sexually active. Fixed number of sexual acts per year. Perfect adherence to PrEP.	With perfect adherence, the use of PrEP will reduce the susceptibility and infectiousness of individuals.

3.3 Discussion

The review was done to see what type of epidemiological models exist. We only included deterministic models in our review. They are suitable for modelling the dynamics of the HIV epidemic, as mostly large populations are modelled. Many of the results generated through the search were theoretical models, which had to be excluded because they do not contain numerical results that can be simulated. We need to be able to simulate the results to see how the FOI compares between the models. The theoretical models mostly focus on stability analysis and basic reproduction numbers.

There is heterogeneity in the compartments of deterministic models which leads to splitting the compartments up. The splitting of the compartments then leads to parametrisation problems as we do not always have enough data for all the compartments. From this the problem arises of how to define the optimal number of compartments. This number largely depends on the available data, and how realistic the model should be.

Some models have combined several compartments while others have included more compartments to model specific interventions and stages of infection. As mentioned earlier, HIV infection has four stages, namely the acute stage, asymptomatic stage, symptomatic stage and the AIDS stage. Individuals in the different stages have varying viral loads, as a result they have different degrees of infectiousness. The models that incorporate this aspect of HIV infection could have more accurate estimations for the force of infection [17, 38, 49], as the infectivity of an individual has a direct effect on the FOI, and including the different stages of infection will depend on how accurate these stages, and the number of individuals in the different stages, can be determined. When modelling the different stages, modification parameters are used to scale the probability of transmission according to the infectiousness of that specific stage of infection.

There is still some dispute about the infectiousness between the classes when considering the different stages. The role of AIDS patients in the transmission of HIV is not always taken into account when determining the force of infec-

tion, despite the fact that epidemiological evidence were found that supports the assumption that AIDS patients are able to spread the disease through risky sexual behaviour [51]. More than half of the studies that were selected in the review assume that AIDS patients are too sick to engage in such behaviour. The viral load of an individual with AIDS is higher than that of an asymptomatic infected individual, which makes them more infectious [52]. When considering this, we can assume that the inclusion of AIDS patients in the group of infectious individuals is important for transmission dynamics, even though they are less sexually active than the other infectious classes.

The demographics of a population also has to be taken into account when constructing a model. In sub-Saharan Africa, HIV appears to be mainly spread through sexual contacts among heterosexual individuals, but in developed countries, homosexual and bisexual males account for most of the HIV cases. In reality a population consists of multiple sub-populations that have different dynamics, but they are influenced by the individuals who are in more than one sub-population. Most studies either model a heterosexual population or a bisexual and homosexual population. It is rare that homosexual and heterosexual population dynamics are considered in a single deterministic model. Podder *et al.* [26] and Romieu *et al.* [36] developed such models, which looked at the heterosexual population along with the homosexual and bisexual populations. The formulation of the FOI for models with multiple sub-populations is the same as when working with one population, except that with multiple sub-populations all susceptible individuals do not have contact with each other, therefore each sub-population will have their own FOI.

When looking at the assumptions made in the studies, it has to be taken into account during what period of time the models were constructed. The studies considered what was known about the disease at that point in time when they made their assumptions. For example, we know that HIV infection is one of the factors that drives the TB epidemic [53], but in the study by Naresh and Tripathi [35], they concluded that the spread of HIV can be slowed down if TB is effectively treated. However, as we now know, this assumption is wrong, though they might have thought it was a reasonable assumption at the time. This is a classical example of an erroneous causal interpretation based on the

observation of a correlation.

These remarks about existing mathematical HIV models and the assumptions that are made suggest that these models can not always be suitable for real-life populations, as they are much more complex than these models can allow for. It is important to note, however, that without limiting assumptions a manageable model and solution may not be possible. The limiting factor in making more precise models is the number of parameter values, the more parameter values there are, the more variability there is in the model, which can make it less accurate. Improving parameter estimations can make a model more accurate, but for this we need more data, which is not always available for epidemiological models.

Chapter 4

Simulation and comparison of models

In this chapter we show the simulation results from the models in Chapter 3. While working with the models, we noticed that they could be divided into four categories. On the basis of their FOI functions, we distinguished between frequency- or density-dependent transmission, and as a second criterion we distinguished models on the sexual activity of the AIDS group. We subsequently compared the models in terms of their FOI functions, first within these classes and then between the classes.

4.1 Methods

Studies that provide sufficient information to simulate the models were selected in Chapter 3. The models were simulated by using the ODEs, parameter values and initial values for the models provided by the authors. For a detailed description of the different models, refer to Appendix A. The information provided in Appendix A is given as used for the simulations, including changes that were verified by the authors. Mathematica [54] was used as a simulation tool, and the models were validated by comparing the resulting output to the graphs or steady state values that were provided in the articles. For our model analysis we chose to make a comparative study of the FOI dynamics. The method that we used was to plot the FOI of each model against time and the number of infectious individuals. The advantage of such a 3-D functional analysis is that it makes it possible to directly compare models, irrespective of

the types of equations used. The curated models will be uploaded to a public database, the JWS Online Model Database (http://jjj.biochem.sun.ac.za).

Here we give an example (Figure 4.1) of such a 3-D plot for one of the models. This is a typical example for the plots that were generated for our analysis and from this we can see how the FOI changes as the number of infectious individuals change over time. The FOI increases as the number of infectives increase with time, until the number of infectives reaches a limit and starts to decrease, while the FOI keeps increasing until both reach a steady state.

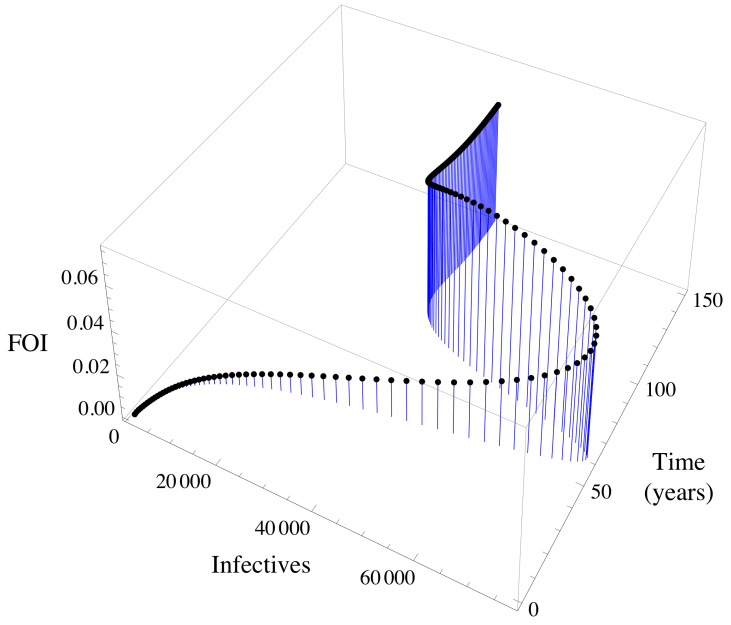


Figure 4.1: Example of a plot for the change of the force of infection as the number of infectious individuals change over time.

4.2 Results and Analysis

We have chosen to do a comparison on the basis of a functional analysis of the FOI. The problem with comparing these models is that they all include different parameters and variables. After studying the FOIs for the different models, it was seen that they had one of two forms, namely, density-dependent

transmission or frequency-dependent transmission. We divided the models into these two classes. The models were further divided into classes depending on whether they assumed the AIDS class to be sexually active or not. The reason for this was to see how the AIDS class affects the FOI.

4.2.1 Frequency-dependent transmission with sexually active AIDS class

This class contains nine models. We only show two of the models, as the other models show comparable behaviour. The FOI for the model in Figure 4.2a is given by:

$$\lambda(t) = \frac{\beta_1 I(t) + \beta_2 T(t) + \beta_3 A(t)}{N(t)},$$

where I is the infected individuals, T the infected individuals on treatment, and A those living with AIDS. $\beta_{1,2,3}$ represents the different transmission probabilities for the different classes. The values for the parameters are: $\beta_1 = 0.004$, $\beta_2 = 0.04$, and $\beta_3 = 0.3$. In this study they assumed that the AIDS class is sexually active and therefore also infectious. The graph shows that the FOI increases as the number of infectives increases until it reaches a limit. The FOI keeps increasing, even though the number of infectives are decreasing, until both reach a steady state.

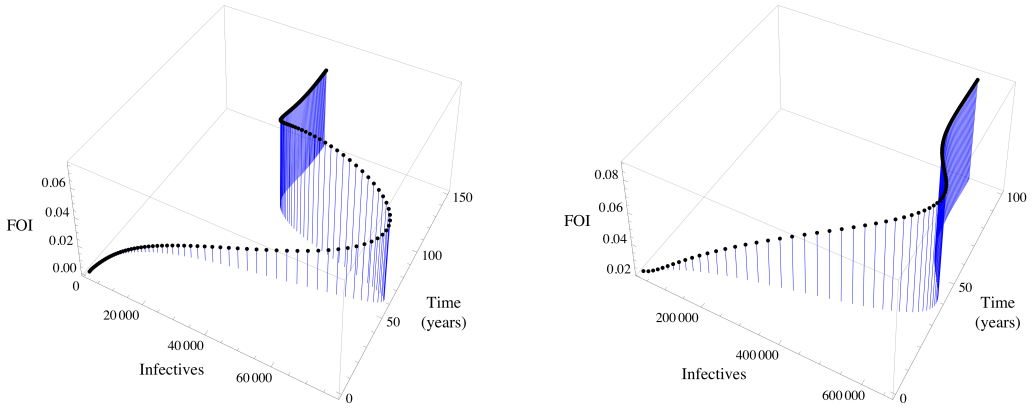
The FOI for the model in Figure 4.2b is given by:

$$\lambda(t) = \frac{k(\beta_1 I(t) + \beta_2 C(t) + \beta_3 T(t) + \beta_4 A(t))}{N(t)},$$

where I is the infected individuals, C the carriers (these are infected individuals unaware of their status), T the infected individuals on treatment, A the individuals living with AIDS, and N the total population. The values for the transmission probabilities are: $\beta_1 = 0.3$, $\beta_2 = 0.09$, $\beta_3 = 0.08$, $\beta_4 = 0.4$, and $k = 1.5$. Here k represents the behaviour change of the infected individuals, with a decrease in k indicating positive behaviour change. They also assumed that the AIDS class is sexually active. In Figure 4.2b we see the same trend as in Figure 4.2a, except that here the FOI does not increase as the number

of infectives decreases but rather stays constant.

To see how these models would compare to models that assume that the AIDS class is not sexually active, we set the probability of transmission for the AIDS class to zero for both the models in Figure 4.2. We saw that with the first model (Figure 4.3a) there is a big difference between having the AIDS class sexually active or not. The reason for this is that β_3 is so much bigger than β_1 and β_2, and removing β_3 decreases the overall infectivity significantly. With the second model (Figure 4.3b) there is not such a big difference than with the first, because the probability of transmission from an individual with AIDS is now similar to that of individuals in the infected class (I).



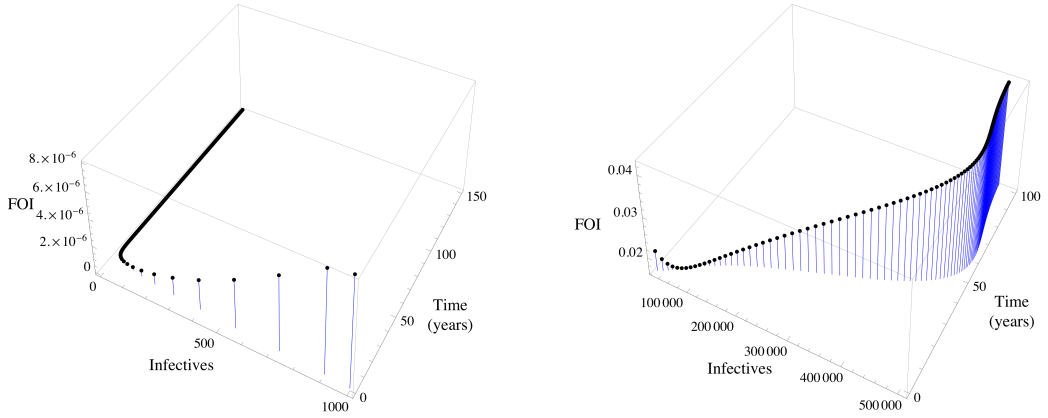
(a) Nyabadza [11] (b) Hove-Musekwa and Nyabadza [39]

Figure 4.2: Graphs showing models that use frequency-dependent transmission with the AIDS class sexually active.

4.2.2 Frequency-dependent transmission with AIDS class not sexually active

There are ten models in this class, and again we only show two as the other models are comparable with these. Here we have models that use frequency-dependent transmission but with the AIDS class not sexually active. The FOI for the model in Figure 4.4a is:

$$\lambda(t) = \frac{\beta_2 I_2(t) + \beta_3 I_2(t)}{N(t)},$$



(a) Nyabadza [11] (with AIDS class not sexually active)

(b) Hove-Musekwa and Nyabadza [39] (with AIDS class not sexually active)

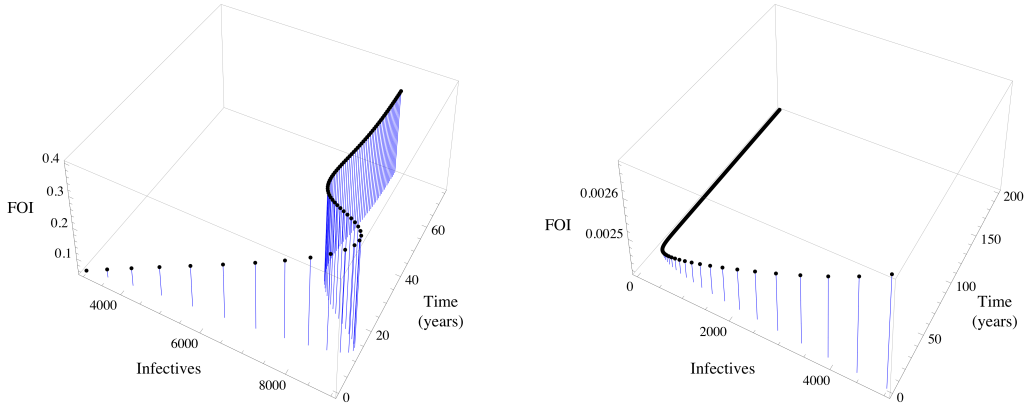
Figure 4.3: Graphs showing models that use frequency-dependent transmission with the AIDS class sexually active, but with a change in the probability of transmission from an individual with AIDS to 0.

where I_2 is HIV positive individuals. The two different transmission probabilities have to do with different contact rates and behaviour towards the other compartments, which includes individuals infected with TB. This graph looks similar to those in Figure 4.2 even though with this model they assumed that individuals living with AIDS are not sexually active.

The FOI for the model in Figure 4.4b is given by:

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

where I_1 is the infected individuals who are unaware of their status, I_2 is the infected individuals who are aware of their status and have decreased their risky sexual behaviour, and I_3 is the infected individuals who are aware of their status but have increased their risky sexual behaviour. β is the probability of transmission, c is the effective contact rate, and $\phi_{1,2}$ shows the behaviour change. In many models the authors include behaviour change in the transmission probability, and it is not always clear that it is included in this parameter, as they do not state how it is incorporated. Figure 4.4b shows how the FOI decreases as the number of infected individuals decrease until it reaches zero. This graph has the same trend as the one in Figure 4.3a, where we made the probability of transmission from the AIDS class 0.



(a) Naresh and Tripathi [35] (b) Bhunu *et al.* [42]

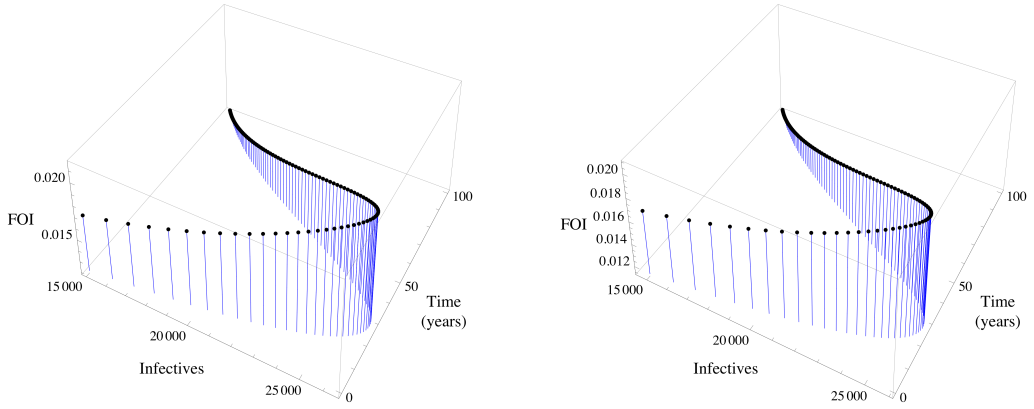
Figure 4.4: Graphs showing models that use frequency-dependent transmission with AIDS class not sexually active.

4.2.3 Density-dependent transmission with AIDS class sexually active

This class only has one model and it is shown here. The FOI for the model by Abiodun *et al.* [48] is given by:

$$\lambda(t) = \beta_1 c_1 I_1(t) + \beta_2 c_2 H(t) + \beta_3 c_3 A(t),$$

where I_1 is the newly infected individuals, H the infected individuals who have not yet developed AIDS, and A the individuals with AIDS. $\beta_{1,2,3}$ represents the probability of transmission and the number of sexual partners are given by c_1, c_2, and c_3 respectively. The values for these parameters are: $\beta_1 = 3.4 \times 10^{-7}$, $\beta_2 = 2.3 \times 10^{-7}$, $\beta_3 = 1.5 \times 10^{-7}$, $c_1 = 4$, $c_2 = 3$, and $c_3 = 1$. Abiodun *et al.* [48] uses density-dependent transmission for a big population, but to compensate for that, they use small values for the probability of infection. In effect, using density-dependent transmission in this way, is the same as using frequency-dependent transmission, except that now the probability of transmission will not change as the total population changes, since the total population is not a variable in density-dependent transmission. In Figure 4.5b we changed the probability of transmission from an individual with AIDS to 0. We see no noticeable change between the two graphs, because β_3 is much smaller than β_1 and β_2.



(a) Abiodun *et al.* [48]

(b) Abiodun *et al.* [48] (with AIDS class not sexually active)

Figure 4.5: Graphs showing density-dependent transmission with AIDS class sexually active and with the probability of transmission from the AIDS class changed to 0.

4.2.4 Density-dependent transmission with AIDS class not sexually active

There are four models in this class. We only show two of the models here. The FOI for the model by Al-Sheikh *et al.* [41] is given by:

$$\lambda(t) = \beta_1 I_1(t) + \beta_2 I_2(t),$$

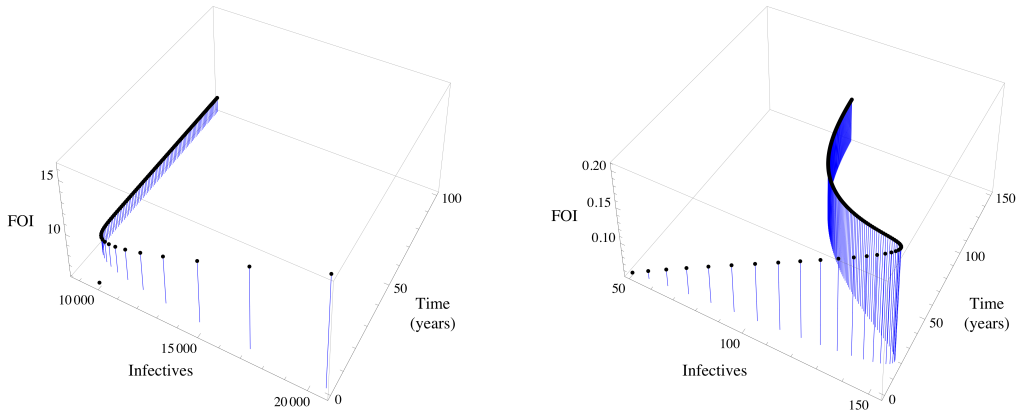
where I_1 is infected individuals who are unaware of their status and I_2 is infected individuals who know their status. The values for the transmission probabilities are: $\beta_1 = 0.0009$ and $\beta_2 = 0.00027$. The initial value for the FOI in this model is very high, causing a spike in the infectious individuals in the first time step, as seen in Figure 4.6a. They used density-dependent transmission for a big population, which is the reason for the big values of the FOI.

The FOI for the model in 4.6b is given by:

$$\lambda(t) = \beta I(t) + \beta b J(t),$$

where I is the infected individuals in the asymptomatic phase and J is the infected individuals in the symptomatic phase. The parameter values are:

$\beta = 0.0005$ and $\beta b = 0.00015$. Cai *et al.* [38] used a small population in their simulations. This makes it possible to use density-dependent transmission for the disease.



(a) Al-Sheikh *et al.* [41] (b) Cai *et al.* [38]

Figure 4.6: Graphs showing models that use density-dependent transmission with AIDS class not sexually active.

The simulations for all the models can be seen in Appendix B, where they are sorted into the different categories.

4.2.5 Models not showing similar behaviour

A few of the models are different from the others. These models include sex-structured models, models with different ways of formulating the FOI and models that result in oscillations. There are a few sex-structured models that were simulated. The model by Romieu *et al.* [36] has a very small FOI, as they start with only one infected individual. This causes the FOI to grow slowly, in the case of the female population, and to decrease slowly in the case of the homosexual male population. The total population becomes very big after a period of time. This is caused by the number of infections that grows slowly. The FOI is zero for the homosexual male population after a period of time, but the number of infected individuals still grows. With sex-structured models each sub-population has its own FOI, and some of the sub-populations overlap, which makes it possible for the number of infected individuals to keep increasing even though the FOI of one of the sub-populations is zero.

The FOI for the model of Nyabadza *et al.* [17] has a different equation than the rest of the models in the review. Here they do not divide by the total population, but rather the mass-action rate for infection plus 1. Which essentially cancels out the two terms for large values, and we are left with $c\beta$. The FOI approaches the probability of infection for very large values of I_1, I_2 and A. The probability of infection is set really low, so the initial value for the FOI is also really low.

The oscillations seen in the model by Raimundo *et al.* [47] (Figure B.4c) is due to the value for the treatment rate of drug-sensitive individuals. For a certain value of this parameter the drug-sensitive and the drug-resistant populations are at the same level, and beyond this value the drug-resistant individuals will have control. With the increase of the treatment rate for drug-sensitive individuals, the proportion of drug-sensitive individuals decreases fast, while the proportion of drug-resistant individuals increases very slowly. The resistant strain will become more fit as both the virus strains compete for the same resources. The authors suggested that the reason we only see oscillations for certain values of the treatment rate is due to resonance. This model used density-dependent transmission, and did not include the AIDS class in the FOI.

4.3 Discussion

Using the four different classes made the comparison of the models easier, and showed that the models are comparable within and between the different classes. The models mostly have the same behaviour within the classes, but it also depends on the parameter values used in the model. The parameters that are used for the FOI within the classes cannot always be compared, especially in the density-dependent classes. Sometimes the transmission parameter consists only of one term (β), and in other models it consists of products of parameters. If only one term is used, then the other parameters are most likely incorporated in this parameter.

When comparing the frequency-dependent transmission graphs that assumed the AIDS class to be sexually active with those that assume that the AIDS

class is not sexually active, we see that they have the same trend, even though the one group did not include the AIDS class and the other group did. This has to do with the parameter values that were chosen for the probability of transmission for the different classes. Movement of individuals between the classes can also have a big impact on the behaviour of the FOI. We see that including AIDS patients in the infectious individuals does not have a significant effect on the FOI when the value for the probability of transmission for an individual with AIDS is much smaller than that of the other classes, as we see no apparent difference between the simulations. If it is assumed that the AIDS class is much more infective than the infected class, then including the AIDS class will make a bigger difference. An example of this can be seen in the model by Nyabadza [11] (Figure 4.2a), where the probability of infection for the infected class is 0.004, and for the AIDS class it is 0.3.

As explained in Chapter 2, density-dependent transmission is usually used for smaller populations and frequency-dependent transmission for larger populations. In Figure 4.6a, it can be seen that a large population was modelled, but density-dependent transmission was used. As a result of this, the FOI for this model is very high, causing a spike after the first time step. The model by Abiodun *et al.* [48], seen in Figure 4.5a, also used density-dependent transmission for a large population, but they adjusted the probability of infection for the different classes such that the values for the FOI are realistic. They used very small values for the transmission probabilities, which can make it seem like frequency-dependent transmission is used, but the problem with this is that the total population is no longer included as a variable in the FOI. Both Cai *et al.* [38] and Huo and Feng [49] used density-dependent transmission in the appropriate way, as they modelled small populations. For smaller populations, the transmission rate will be dependent on the density of the population.

It is possible to change the transmission of the model from density-dependent to frequency-dependent, and from frequency-dependent to density-dependent. It mainly depends on the parameter values that are used. When working with a large population and using density-dependent transmission, the value for the probability of transmission has to be small, otherwise the FOI is going to be too big in relation with the rest of the parameter values. Using the probability

of transmission divided by the total population ($\frac{\beta}{N}$) can be the same as using frequency-dependent transmission in some cases, except that here the transmission rate, $\frac{\beta}{N}$, will not change with time, since the total population is no longer a variable.

Some of the simulations differ a lot, even though the FOIs look the same, for example, the model by Raimundo *et al.* [47]. For this model, the proportion of infected individuals oscillate as a result of parameters specifically chosen to see under which conditions the drug-resistant strain will emerge. The fitness of the strain will determine which population has control. The FOI of sex-structured models looks slightly different. When looking at sex-structured models, the infectious individuals that affect the FOI is specific to that FOI. Say for example a sex-structured model with men who have sex with men (MSM) is considered, then the FOI for the homosexual male population will only be influenced by the homosexual and bisexual male populations, and not the total population. It is only the proportion of individuals that has contact with that specific class that will influence the FOI.

We saw that the simulations of the models are comparable within the classes as they use the same basic structure for the FOI. From the results it can be seen that many assumptions are made regarding the FOI, which makes it difficult to determine exactly why the FOI behaves in a certain way.

Chapter 5

General Discussion

The focus of our study was on the comparison of the different FOIs for the different models. This thesis had three main objectives. The first objective was to do a review of existing mathematical models for HIV epidemiology. Secondly, we simulated the relevant models for curation and comparison. The last ojective was to compare and interpret the results by focusing on the FOI for the different models. This chapter is a general discussion of some of the topics considered throughout the thesis.

We found through the review that many manuscripts in which mathematical models for HIV epidemiology are described do not provide the necessary information for simulating the models. Without the parameter and initial values it is not possible to recreate the authors' results. There is also a great amount of theoretical models that mainly focus on stability and theoretical analysis. To help inform public health policy, models using accurate data is needed, but data is not always available or accurate. When there is not enough data available, authors have to use parameter values from other studies or make assumptions. Inaccurate results can be generated from making wrong assumptions, or by ignoring the assumptions made in other studies. This has a big influence on the FOI when deciding on whether to use density-dependent transmission or frequency-dependent transmission.

Frequency-dependent transmission and density-dependent transmission makes a difference when it is used in the wrong situation. It was seen that for large populations using density-dependent transmission would not be realistic. The

reason for this is that with large populations, the transmission is not dependent on the density of the population. It is possible to use density-dependent transmission with larger populations by decreasing the value for the probability of infection, but this is still not the same as frequency-dependent transmission, since the total population is no longer a variable.

Most of the models compare well when looking at the predictions they make. The analysis of the models shows that the force of infection can vary depending on the parameter values and the classes that are included in the infectious individuals. For example, when the model assumes that individuals living with AIDS are also infectious it can differ from when it is assumed that the AIDS class is not infectious. Some models assume that these individuals refrain from having sex, and therefore do not see them as infectious. Individuals with AIDS are assumed to be too sick to participate in sexual acts, but as mentioned earlier there is evidence that proves otherwise.

The difference between the models that include the AIDS class and the ones that do not is the values of the transmission rates for the different classes. There are models that assume that the AIDS class is infectious, but that they are less infectious than say for example the symptomatic class. This then compared with the models that do not include the AIDS class, has the same effect. The major difference comes in when the AIDS class is much more infectious than the other classes, as this is the last class where all the infected individuals progress to, as such, it will increase the FOI significantly as more individuals get infected.

The FOI depends on various parameter values and assumptions. Many models compress various parameter values into one, most often the transmission probability. Not showing the parameter values separately makes it hard to analyse the contribution of the individual components since these are all implicit in a single parameter value. Writing the probability of transmission as a function of the viral load can help to make the FOI more accurate and also help in the understanding of the effects that viral dynamics have on the population transmission dynamics.

Chapter 6

Conclusion and Future work

There are a number of mathematical models for the epidemiology of HIV/AIDS. The review showed that there is a problem with reporting, and that it is not always possible to reproduce the models. It is recommended that journals should have a policy to check mathematical models, such as provided by JWS Online. The reason we could not simulate most of the models were either due to a lack of information or due to mistakes in the article.

There is an inherent difficulty when using compartmentalised models. As soon as there is heterogeneity in such compartments, it is hard to use a single parameter set. From this the problem arises of deciding whether to use average parameter values for a compartment or using a large number of compartments, that would then not be heterogeneous but it would be very hard to determine the parameters for each of the classes. As an example we can look at the viral load between the different classes. The viral load is important for the FOI, as it affects the probability of transmission, but the viral load varies significantly within the different classes that are used. Now we can ask the question: how to define a FOI for a class that has very different viral loads? A possible solution could be to express the probability of transmission as a function of the viral load, but it still does not take the variability of the viral load into account.

We focused on comparing the force of infection for different models, as dynamics of any infectious disease is heavily dependent on the rate of transmission from infectious to susceptible individuals. It was found that inclusion of individuals with AIDS in the FOI does not necessarily have a big impact on

the FOI. Comparing the models that do not include the AIDS class with the models that do, showed only a small difference. If the value for the probability of infection for the AIDS class is much bigger than that of the other infectious classes, then it will have a more significant effect on the FOI.

The use of density-dependent and frequency-dependent transmission were analysed in the models, and it was seen that it is not always used in the correct way. When modelling a small population, it is recommended that density-dependent transmission is used. The smaller the population, the more the transmission will depend on the density of the population. For larger populations, frequency-dependent transmission should be used. This is the case for HIV, where the disease is mainly spread through sexual contact.

We saw that the FOI is heavily dependent on the assumptions made in the model. A model could assume that the number of infected individuals is going down due to effective treatment, but there could be various other reasons for the amount of infected individuals going down. Improving the accuracy of the FOI can help us to better understand what factors influence it, and also produce more realistic results. Possible factors to take into account can include the effect of behavioural change on the FOI and the use of the transmission probability as a function of the viral load. Further analysis of the FOI for different infectious diseases and also for stochastic models can show us how the FOI compares between different diseases and how the types of transmission differ.

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Appendices

Appendix A

Model descriptions

A.1 Modelling the AIDS epidemic in Mexico City (Romieu *et al.* [36])

Romieu *et al.* [36] designed a model to predict the number of people who will be diagnosed with AIDS in Mexico City for a certain period and to determine how prevention strategies will impact the epidemic. The population is divided into 12 classes. These classes include susceptible (u_h), infected (l_h) and AIDS (s_h) homosexual men, susceptible (u_b), infected (l_b) and AIDS (s_b) bisexual men, susceptible (u_w), infected (l_w), and AIDS (s_w) heterosexual women, and susceptible (u_m), infected (l_m), and AIDS (s_m) heterosexual men. The initial conditions used are: $u_h(0) = 100000, u_b(0) = 75000, u_w(0) = 700000$, $u_m(0) = 700000$, $l_h(0) = 1, l_b(0) = 0, l_w(0) = 0$, $l_m(0) = 0$, $s_h(0) = 0, s_b(0) = 0, s_w(0) = 0$, and $s_m(0) = 0$ The values for the parameters are given in Table A.1.

The system of ODEs is given by:

$$\begin{aligned}
\frac{du_h}{dt} &= \frac{-p_h u_h(l_h+l_b)}{(u_h+l_h+u_b+l_b)} + H(t)b - mu_h \\
\frac{du_b}{dt} &= \frac{-p_b u_b(l_h+l_b)}{(u_h+l_h+u_b+l_b)} + \frac{(-p_m u_b l_w)}{(u_w+l_w)} + B(t)b - mu_b \\
\frac{du_w}{dt} &= \frac{-p_w u_w(l_b+l_m)}{(u_b+l_b+u_m+l_m)} + W(t)b - mu_w \\
\frac{du_m}{dt} &= \frac{-p_m u_m l_w}{(u_w+l_w)} + M(t)b - mu_m \\
\frac{dl_h}{dt} &= \frac{p_h u_h(l_h+l_b)}{(u_h+l_h+u_b+l_b)} - p_2 l_h - ml_h \\
\frac{dl_b}{dt} &= \frac{p_b u_b(l_h+l_b)}{u_h+u_b+l_h+l_b} + \frac{p_m u_b l_w}{(u_w+l_w)} - p_2 l_b - ml_b \\
\frac{dl_w}{dt} &= \frac{p_w u_w(l_b+l_m)}{(u_m+l_m+u_b+l_b)} - p_2 l_w - ml_w \\
\frac{dl_m}{dt} &= \frac{p_m u_m l_w}{(u_w+l_w)} - p_2 l_m - ml_m \\
\frac{ds_h}{dt} &= p_2 l_h \\
\frac{ds_b}{dt} &= p_2 l_b \\
\frac{ds_w}{dt} &= p_2 l_w \\
\frac{ds_m}{dt} &= p_2 l_m,
\end{aligned}$$

where $H(t) = u_h + l_h + s_h$, $B(t) = u_b + l_b + s_b$, $W(t) = u_w + l_w + s_w$, and $M(t) = u_m + l_m + s_m$.

Table A.1: Parameter values for the system of ODEs for the model by Romieu *et al.* [36].

Parameter	Value	Description
p_h	0.0671	Transmission probability for homosexual men
p_b	0.0421	Transmission probability for bisexual men
p_w	0.00651	Transmission probability for heterosexual women
p_m	0.0021	Transmission probability for heterosexual men
p_2	0.0082	Rate at which individuals move to the AIDS class
b	0.033	Birth rate
m	0.0043	Death rate

A.2 Numerical and bifurcation analyses for a population model of HIV chemotherapy (Gumel *et al.* [22])

Gumel *et al.* [22] focused on new methods for numerical and bifurcation analyses. They assumed that treatment slows the rate of progression to AIDS. The population is divided into three classes, namely, the susceptible class, S_u, the untreated infected class, Y_u, and the treated infected class, Y_v. The total population is: $N = S_u + Y_u + Y_v$. The initial conditions for the system are $S_u(0) = 500, Y_u(0) = 300$, and $Y_v(0) = 200$. The parameter values are given in Table A.2.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_u}{dt} &= \mu N - \mu S_u - c\left(\frac{\beta_1 Y_u}{N} + \frac{\beta_2 Y_v}{N}\right) S_u \\
\frac{dY_u}{dt} &= c\left(\frac{\beta_1 Y_u}{N} + \frac{\beta_2 Y_v}{N}\right) S_u - (\mu + \gamma + \tau) Y_u \\
\frac{dY_v}{dt} &= \tau Y_u - (d + \mu) Y_v.
\end{aligned}$$

Table A.2: Parameter values for the system of ODEs for the model by Gumel *et al.* [22].

Parameter	Value	Description
μ	0.03125	Rate at which sexual activity stops
β_1	0.6	Probability of transmission
β_2	0.3	Probability of transmission
γ	0.4	Rate at which AIDS develops
d	0.01	Rate at which AIDS develops when on treatment
c	4	Number of sexual partners
τ	0.2	Treatment rate

A.3 An epidemic model for the transmission dynamics of HIV and another pathogen (Moghadas *et al.* [28])

Moghadas *et al.* [28] designed and analysed a model for the transmission dynamics of HIV and a competing pathogen that is assumed to be curable for a given population. They did not include a compartment for co-infected individuals and they also assumed that individuals that were effectively treated for the pathogen cannot return to the infected class again. The population is divided into five classes. These classes are: susceptible individuals (X), individuals infected with the pathogen (Y_1), individuals infected with HIV (Y_2), individuals with AIDS (A), and non-infectious individuals (Z). The initial values used are: $X(0) = 120000$, $Y_1(0) = 10$, $Y_2(0) = 70100$, $A(0) = 80000$, and $Z(0) = 30$. The parameter values for the system is given in Table A.3.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dX}{dt} &= \Pi - \mu X - \left(\frac{c\beta_1 Y_1 + c\beta_2 Y_2}{N}\right) X \\
\frac{dY_1}{dt} &= \frac{(1-\tau)c\beta_1 Y_1 X}{N} - \frac{c\beta_2 Y_1 Y_2}{N} - \mu Y_1 \\
\frac{dY_2}{dt} &= \frac{c\beta_2 Y_2 X}{N} + \frac{c\beta_2 Y_1 Y_2}{N} - (\mu + \nu) Y_2 \\
\frac{dA}{dt} &= \nu Y_2 - (\mu + d) A \\
\frac{dZ}{dt} &= \frac{\tau c\beta_1 Y_1 X}{N} - \mu Z.
\end{aligned}$$

Table A.3: Parameter values for the system of ODEs for the model by Moghadas *et al.* [28].

Parameter	Value	Description
Π	2000	Recruitment rate
μ	0.031	Natural death rate
β_1	0.05	Rate of infection with the pathogen
β_2	0.005	Rate of HIV infection
ν	0.02	Rate of progression to AIDS
d	0.06	Disease-related death rate
τ	0.85	Treatment of Y_1

A.4 HIV treatment models with time delay (Bachar and Dorfmayr [37])

Bachar and Dorfmayr [37] looked at how ART affects the spread of HIV infection. The population is divided into the following three classes: susceptible individuals (S), and two infectious stages before AIDS (I_1 and I_2). The total population is N. The initial conditions are given as $S(0) = 4999950$, $I_1(0) = 50$, and $I_2(0) = 0$. The parameter values for the system of ODEs are given in Table A.4.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= bN - c\beta\frac{S}{N}(I_1 + aI_2) - dS \\
\frac{dI_1}{dt} &= c\beta\frac{S}{N}(I_1 + aI_2) - (d + k_1 I_1 + \alpha I_2) \\
\frac{dI_2}{dt} &= k_1 I_1 - (d + k_2 + \alpha)I_2.
\end{aligned}$$

Table A.4: Parameter values for the system of ODEs for the model by Bachar and Dorfmayr [37].

Parameter	Value	Description
b	0.001	Birth rate
d	0.0006	Natural death rate
c	0.3	Average number of contacts
β	0.5	Transmission probability for individuals in first infectious stage
$a\beta$	0.3	Transmission probability for individuals in second infectious stage
k_1	0.019	Disease progression rate
k_2	0.0159	Disease progression rate
α	0.2	Successful treatment rate

A.5 Modelling and analysis of HIV-TB co-infection in a variable size population (Naresh and Tripathi [35])

Naresh and Tripathi [35] designed and analysed a co-infection model for the transmission dynamics of HIV and TB. The population is divided into four classes: Susceptible individuals (S), TB infected individuals (I_1), HIV infected individuals (I_2), and individuals with AIDS (A). The total population is given by N. The initial values used for the simulations are: $S(0) = 14500$, $I_1(0) = 2000$, $I_2(0) = 3000$, and $A(0) = 500$. The parameter values are given in Table A.5.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= Q_0 - \left(\frac{\beta_1 S I_1 + \beta_2 S I_2}{N}\right) - dS + \lambda I_1 \\
\frac{dI_1}{dt} &= \frac{\beta_1 S I_1}{N} - \frac{\beta_3 I_1 I_2}{N} - (\lambda + d) I_1 \\
\frac{dI_2}{dt} &= \frac{\beta_2 S I_2}{N} + \frac{\beta_3 I_1 I_2}{N} - (\delta + d) I_2 \\
\frac{dA}{dt} &= \delta I_2 - (\alpha + d) A.
\end{aligned}$$

Table A.5: Parameter values for the system of ODEs for the model by Naresh and Tripathi [35].

Parameter	Value	Description
Q_0	2000	Recruitment rate
d	0.02	Natural death rate
β_1	0.925	Transmission probability of TB
β_2	0.365	Transmission probability of HIV
β_3	1.15	Transmission probability of HIV
λ	0.3	Recovery rate of I_1
α	1	Disease-related death rate
δ	0.2	Rate of progression to AIDS class

A.6 To Cut or Not to Cut: A modelling approach for assessing the role of male circumcision in HIV control (Podder *et al.* [26])

Podder *et al.* [26] looked at the impact of male circumcision by using a sex-structured model. They also included the use of condoms and ART in the model. The population was divided into ten classes. These classes are: Susceptible women, S_f, susceptible men who are not circumcised, S_{mu}, susceptible men who are circumcised, S_{mc}, infected women, I_f, infected men who are not circumcised, I_{mu}, infected men who are circumcised, I_{mc}, women with AIDS, A_f, men with AIDS, A_m, treated infected women, T_f, and treated infected men, T_m. The initial values are given by: $S_f(0) = 9972000$, $S_{mu}(0) = 7000000$, $S_{mc}(0) = 2200000$, $I_f(0) = 1400000$, $I_{mu}(0) = 1400000$, $I_{mc}(0) = 1018000$, $A_f(0) = 1005000$, $A_m(0) = 1005000$, $T_f(0) = 0$, and $T_m(0) = 0$. The parameter values for the system is given in Table A.6.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_f}{dt} &= \Pi_1 - \lambda_m(1-\nu c)S_f - \mu S_f \\
\frac{dS_{mu}}{dt} &= \Pi_2 - \lambda_f(1-\nu c)S_{mu} - \xi q\epsilon S_{mu} - \mu S_{mu} \\
\frac{dS_{mc}}{dt} &= \Pi_3 + \xi q\epsilon S_{mu} - \lambda_f(1-\nu c)(1-\epsilon)S_{mc} - \mu S_{mc} \\
\frac{dI_f}{dt} &= \lambda_m(1-\nu c)S_f - \sigma I_f - \tau_1 I_f - \mu_f \\
\frac{dI_{mu}}{dt} &= \lambda_f(1-\nu c)S_{mu} - \sigma I_{mu} - \tau_1 I_{mu} - \mu I_{mu} \\
\frac{dI_{mc}}{dt} &= \lambda_f(1-\nu c)(1-\epsilon)S_{mc} - \sigma I_{mc} - \tau_1 I_m c - \mu I_{mc} \\
\frac{dA_f}{dt} &= \sigma I_f + \theta_t \sigma T_f - \delta A_f - \tau_2 A_f - \mu A_m \\
\frac{dA_m}{dt} &= \sigma I_{mu} + \sigma I_{mc} + \theta_t \sigma T_m - \tau_2 A_m - \delta A_m - \mu A_m \\
\frac{dT_f}{dt} &= \tau_1 I_f + \tau_2 A_f - \theta_t \sigma T_f - \mu T_f \\
\frac{dT_m}{dt} &= \tau_1(I_{mu} + I_{mc}) + \tau_2 A_m - \theta_t \sigma T_m - \mu T_m,
\end{aligned}$$

where $\lambda_f = \frac{\beta_f(I_f+\eta A_f+\eta_f T_f)}{N_f}$ and $\lambda_m = \frac{\beta_m(I_{mu}+Imc+\eta A_m+\eta_m T_m)}{N_m}$, with $N_f = S_f + I_f + A_f + T_f$ and $N_m = S_{mu} + Smc + Imu + Imc + A_m + T_m$

Table A.6: Parameter values for the system of ODEs for the model by Podder *et al.* [26].

Parameter	Value	Description
Π_1	1000	Recruitment rate of female population
Π_2	1000	Recruitment rate of uncircumcised male population
Π_3	1000	Recruitment rate of circumcised male population
β_f	0.45	Probability of transmission for females
β_m	0.4	Probability of transmission for males
q	0.6	Fraction of circumcised men
η	1.1	Modifying parameter
η_f	0.02	Modifying parameter
η_m	0.02	Modifying parameter
θ_t	0.1	Progression rate to AIDS of treated individuals
ϵ	0.6	Efficacy of circumcision
ξ	1	Circumcision rate
ν	0.87	Condom efficacy
c	0.6	Condom compliance
τ_1	5	Treatment rate
τ_2	5	Treatment rate
μ	0.037	Natural death rate
δ	0.102	Disease-related death rate

A.7 Modelling the effect of screening of unaware infectives on the spread of HIV infection (Tripathi *et al.* [20])

Tripathi *et al.* [20] modelled screening of HIV infected individuals. The population used is divided into 4 classes. These classes are susceptible individuals (S), HIV positive individuals that do not know they are infected (I_1), HIV positive individuals that know they are infected (I_2), and those with AIDS (A). The initial values used are $S(0) = 2500$, $I_1(0) = 10000$, $I_2(0) = 2000$, $A(0) = 500$. The total population is given by: $N(t) = S(t)+I_1(t)+I_2(t)+A(t)$.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dN}{dt} &= Q_0 - \left(\frac{\beta_1 SI_1 + \beta_2 SI_2}{N}\right) - dS \\
\frac{dI_1}{dt} &= \frac{\beta_1 SI_1}{N} + \frac{\beta_2 SI_2}{N} - (\theta + \delta + d)I_1 \\
\frac{dI_2}{dt} &= \theta I_1 - (\delta + d)I_2 \\
\frac{dA}{dt} &= \delta I_1 + \delta I_2 - (\alpha + d)A.
\end{aligned}$$

The parameter values for the system is shown in Table A.7

Table A.7: Parameter values for the system of ODEs for the model by Tripathi *et al.* [20].

Parameter	Value	Description
β_1	1.344	Contact rate for susceptible individuals
β_2	0.15	Contact rate for susceptible individuals
θ	0.015	Rate of screening
δ	0.1	Natural death rate
α	1	Disease related death rate
Q_0	2000	Constant recruitment rate

A.8 Modelling the joint epidemics of TB and HIV in a South African Township (Bacaër *et al.* [25])

Bacaër *et al.* [25] developed a co-infection model for HIV and TB infection. The population is divided into six classes: HIV negative individuals not infected with TB, S_1, HIV positive individuals not infected with TB, S_2, HIV negative individuals with latent TB, E_1, HIV positive individuals with latent TB, E_2, HIV negative individuals with active TB, I_1, and HIV positive individuals with active TB, I_2. The total population is given by $P = S_1 + E_1 + I_1 + S_2 + E_2 + I_2$ and HIV prevalence is $H = (S_2 + E_2 + I_2)/P$. The initial conditions for the system are: $S_1(0) = 3904$, $E_1(0) = 5764$, $I_1(0) = 27$, $S_2(0) = 1$, $E_2(0) = 0$, and $I_2(0) = 0$. The parameter values are given in Table A.8.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_1}{dt} &= B - S_1\frac{(k_1I_1 + k_2I_2)}{P} - \mu_1 S_1 - f(H)HS_1 \\
\frac{dE_1}{dt} &= (p_1'S_1 - q_1E_1)\frac{(k_1I_1 + k_2I_2)}{P} - (a_1 + \mu_1)E_1 + b_1I_1 - f(H)HE_1 \\
\frac{dI_1}{dt} &= (p_1S_1 - q_{1E_1})\frac{(k_1I_1 + k_2I_2)}{P} - (b_1 + m_1)I_1 + a_1E_1 - f(H)HI_1 \\
\frac{dS_2}{dt} &= -S_2\frac{(k_1I_1 + k_2I_2)}{P} - \mu_2 S_2 + f(H)HS_1 \\
\frac{dE_2}{dt} &= (p_2'S_2 - q_2E_2)\frac{(k_1I_1 + k_2I_2)}{P} - (a_2 + \mu_2)E_2 + b_2I_2 + f(H)HE_1 \\
\frac{dI_2}{dt} &= (p_2S_2 - q_2E_2)\frac{(k_1I_1 + k_2I_2)}{P} - (b_2 + m_2)I_2 + a_2E_2 + f(H)HI_1,
\end{aligned}$$

where $f(H) = de^{-\lambda H}$, $p_1' = 1 - p_1$, $p_2' = 1 - p_2$, $b_1 = \beta_1 + \gamma_1\epsilon_1$, and $b_2 = \beta_2 + \gamma_2\epsilon_2$.

Table A.8: Parameter values for the system of ODEs for the model by Bacaër *et al.* [25].

Parameter	Value	Description
B	200	Birth rate
μ_1	0.2	Death rate of individuals without active TB
μ_2	0.1	Death rate of individuals without active TB
k_1	11.4	Transmission rate of TB
k_2	7.6	Transmission rate of TB
p_1	0.11	Proportion of individuals with fast progression to TB
p_2	0.3	Proportion of individuals with fast progression to TB
q_1	0.077	Proportion of reinfections
q_2	0.225	Proportion of reinfections
a_1	0.0003	Progression rate from latent to active TB
a_2	0.08	Progression rate from latent to active TB
β_1	0.25	Recovery from active TB without treatment
β_2	0.4	Recovery from active TB without treatment
γ_1	0.74	Detection rate of active TB
γ_2	3	Detection rate of active TB
ϵ_1	0.8	Probability of successful treatment
ϵ_2	0.8	Probability of successful treatment
m_1	0.25	Death rate for individuals with active TB
m_2	1.6	Death rate for individuals with active TB
d	0.7	Transmission rate of HIV
λ	5.9	Behaviour change

A.9 On the complexities of modelling HIV/AIDS in Southern Africa (Nyabadza [11])

Nyabadza [11] designed a model to look at how condom use, treatment and varying numbers of sexual partners can influence the HIV epidemic. The population is divided into four classes. These classes are the susceptible individuals (S), infected individuals (I), individuals under treatment (T), and those with AIDS (A). The total population is: $N = S + I + T + A$. The initial conditions used are $S(0) = 500000$, $I(0) = 1000$, $T(0) = 0$, and $A(0) = 0$.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \pi + b(1-\epsilon)e^{-\mu_0\tau}I_A - c(1-p_1)\lambda S - \mu S \\
\frac{dI}{dt} &= c(1-p_1)\lambda S - (\mu + \sigma + \nu_1)I \\
\frac{dT}{dt} &= m_1 I + m_4 A - (\mu + \nu_n)(1-R_R)T \\
\frac{dA}{dt} &= m_2 T + m_3 I - (\mu + d + \rho)(1-R_A)A,
\end{aligned}$$

where $I_A = I + T + A$,

$$m_1 = \sigma + bq\epsilon e^{-\mu_0\tau},\ m_2 = \nu_2 + b(1-q)\epsilon e^{-\mu_0\tau},\ m_3 = \nu_1 + b(1-q)\epsilon e^{-\mu_0\tau},$$
$$m_4 = \rho + bq\epsilon e^{-\mu_0\tau},\ R_T = \frac{bq\epsilon e^{-\mu_0\tau}}{\mu + \nu_2}, \text{and } R_A = \frac{b(1-q)\epsilon e^{-\mu_0\tau}}{\mu + d}.$$

The force of infection is given by

$$\lambda = \frac{\beta_1 I + \beta_2 T + \beta_3 A}{N}$$

The parameter values for the system is given in Table A.9

Table A.9: Parameter values for the system of ODEs for the model by Nyabadza [11].

Parameter	Value	Description
μ	0.02	Natural death rate
ν_1	0.6	Rate of progression from infected class to AIDS class
ν_2	0.7	Treatment adjusted rate of progression to AIDS class
ϵ	0.06	Fraction of children born with the virus
b	0.03	Birth rate
σ	0.09	Rate at which individuals seek treatment
π	10000	Recruitment rate
d	0.4	Disease related death rate
β_1	0.004	Probability of susceptible individuals getting infected through contact with the infected class
β_2	0.04	Probability of susceptible individuals getting infected through contact with the treated class
β_3	0.3	Probability of susceptible individuals getting infected through contact with the AIDS class
μ_0	0.002	Natural death rate of children
c	4	Rate of acquisition of new partners
q	0.01	Proportion of children, born with the virus, under treatment that move to the treated class when they survive the maturation age
ρ	0	Rate at which individuals with AIDS seek treatment
p_1	0.5	Condom induced preventability
τ	15	Maturation age

A.10 Stability analysis of an HIV/AIDS epidemic model with treatment (Cai *et al.* [38])

Cai *et al.* [38] designed a model with stages to analyse the effect of treatment on the disease. The population is divided into the susceptible individuals, S, asymptomatic infected individuals, I, symptomatic infected individuals, J, and individuals with AIDS, A. The initial conditions are: $S(0) = 150$, $I(0) = 30$, $J(0) = 20$, and $A(0) = 0$. The parameter values for the system are shown in Table A.10.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \mu K - c\beta(I + bJ)S - \mu S \\
\frac{dI}{dt} &= c\beta(I + bJ)S - (\mu + k_1)I + \alpha J \\
\frac{dJ}{dt} &= k_1 I - (\mu + k_2 + \alpha)J \\
\frac{dA}{dt} &= k_2 J - (\mu + d)A.
\end{aligned}$$

Table A.10: Parameter values for the system of ODEs for the model by Cai *et al.* [38].

Parameter	Value	Description
K	120	Recruitment constant
β	0.0005	Probability of transmission
b	0.3	Modifying parameter
μ	0.02	Natural death rate
k_1	0.01	Rate of progression to symptomatic phase
k_2	0.02	Rate of progression to AIDS phase
α	0.01	Treatment rate
d	0.333	Disease-related death rate

A.11 The dynamics of an HIV/AIDS model with screened disease carriers (Hove-Musekwa and Nyabadza [39])

Hove-Musekwa and Nyabadza [39] focused on screening of carriers. The population is divided into seven classes: susceptible individuals (S), infected individuals (I), carriers (C), screened carriers (Cs), treated infected individuals (T), individuals with AIDS (A), and treated individuals with AIDS (A_t). The initial conditions for the system is as follows: $S(0) = 465000$, $I(0) = 20000$, $C(0) = 10000$, $C_s(0) = 5000$, $T(0) = 500$, $A(0) = 200$, and $A_t(0) = 0$. The parameter values are given in Table A.11.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda(I, C, T, A)S - \mu S \\
\frac{dI}{dt} &= \lambda(I, C, T, A)S - (\mu + \sigma + \rho_1 + \gamma_1)I \\
\frac{dC}{dt} &= \sigma I - (\mu + \rho_2 + \psi)C \\
\frac{dC_s}{dt} &= \phi C - (\mu + \rho 3 + \gamma_2)C_s \\
\frac{dT}{dt} &= \gamma_1 I + \gamma_2 C_s - (\mu + \rho_4)T \\
\frac{dA}{dt} &= \rho_1 I + \rho_2 C + \rho_3 C_s + \rho_4 T - (\mu + \gamma_3 + \delta_1)A \\
\frac{dA_t}{dt} &= \gamma_3 A - (\mu + \delta)A_t,
\end{aligned}$$

where $\lambda(I, C, T, A) = k(\frac{\beta_1 I + \beta_2 C + \beta_3 T + \beta_4 A}{N})$.

Table A.11: Parameter values for the system of ODEs for the model by Hove-Musekwa and Nyabadza [39].

Parameter	Value	Description
k	1.5	Average number of sexual partners
β_1	0.3	Probability of infection
β_2	0.09	Probability of infection
β_3	0.08	Probability of infection
β_4	0.2	Probability of infection
μ	0.022	Natural death rate
Π	100000	Recruitment constant
σ	0.2	Rate of progression form I to C
ρ_1	0.001	Rate of progression to AIDS class
ρ_2	0.09	Rate of progression to AIDS class
ρ_3	0.45	Rate of progression to AIDS class
ρ_4	0.2	Rate of progression to AIDS class
ψ	0.2	Rate at which carriers are screened
γ_1	0.3	Rate at which infected seek treatment
γ_2	0.15	Rate at which infected seek treatment
γ_3	0.3	Rate at which infected seek treatment
δ_1	0.33	Disease-related death rate
δ_2	0.33	Disease-related death rate

A.12 A sex-role-preference model for HIV transmission among men who have sex with men in China (Lou *et al.* [40])

Lou *et al.* [40] constructed a sex-role-preference model for a MSM population to analyse intervention strategies. The population is divided into six classes: S_T, S_B, and S_V which represents the susceptible males in the Only Top, Only Bottom and Versatile categories, and I_T, I_B, and I_V which represents the infected males in the different categories. The initial conditions for the system are: $S_T(0) = 2425100$, $S_B(0) = 2590800$, $S_V(0) = 15418000$, $I_T(0) = 36931$, $I_B(0) = 39455$, and $I_V(0) = 234800$. The parameter values are given in Table A.12.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_T}{dt} &= r_T - S_T\left(\frac{\beta_{BT}I_B + \beta_{VT}I_V}{N_B + N_V}\right) - d_M S_T \\
\frac{dI_T}{dt} &= S_T\left(\frac{\beta_{BT}I_B + \beta_{VT}I_V}{N_B + N_V}\right) - d_I I_T \\
\frac{dS_V}{dt} &= r_V - S_V\left(\frac{\beta_{TV}I_T + \beta_{BV}I_B + \beta_{VV}I_V}{N_T + N_V + N_B}\right) - d_M S_V \\
\frac{dI_V}{dt} &= S_V\left(\frac{\beta_{TV}I_T + \beta_{BV}I_B + \beta_{VV}I_V}{N_T + N_V + N_B}\right) - d_I I_V \\
\frac{dS_B}{dt} &= r_B - S_B\left(\frac{\beta_{TB}I_T + \beta_{VB}I_V}{N_T + N_V}\right) - d_M S_B \\
\frac{dI_B}{dt} &= S_B\left(\frac{\beta_{TB}I_T + \beta_{VB}I_V}{N_T + N_V}\right) - d_I I_B,
\end{aligned}$$

where $N_T = S_T + I_t$,$N_V = S_V + I_V$, and $N_B = S_B + I_B$.

Table A.12: Parameter values for the system of ODEs for the model by Lou *et al.* [40].

Parameter	Value	Description
r_T	96667	Recruitment rate of Only-Top MSM
r_V	603950	Recruitment rate of Versatile MSM
r_B	70817	Recruitment rate of Only-Bottom MSM
d_M	0.022	Natural death rate
d_I	0.105	Disease-related death rate
β_{TB}	0.5786	Rate of infection
β_{TV}	0.5653	Rate of infection
β_{BT}	0.2563	Rate of infection
β_{VB}	0.5786	Rate of infection
β_{VT}	0.2563	Rate of infection
β_{BV}	0.2826	Rate of infection
β_{VV}	0.4239	Rate of infection

A.13 Analysis of an HIV/AIDS model with public-health information campaigns and individual withdrawal (Nyabadza *et al.* [17])

Nyabadza *et al.* [17] constructed a model looks at media campaigns and behaviour change for HIV/AIDS. The model is divided into four classes: the susceptible individuals (S), asymptomatic infected individuals (I_1), symptomatic infected individuals (I_2), and individuals with AIDS (A). The initial conditions are given as: $S(0) = 730000$, $I_1(0) = 20000$, $I_2(0) = 10000$, and $A(0) = 1000$. The parameter values are given in Table A.13.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \mu b - \mu S - \lambda(I, A)S \\
\frac{dI_1}{dt} &= \lambda(I, A)S - (\mu + \sigma)I_1 \\
\frac{dI_2}{dt} &= \sigma I_1 - (\mu + \rho)I_2 \\
\frac{dA}{dt} &= \rho I_2 - (\mu + \delta)A,
\end{aligned}$$

where $\lambda(I, A)S = \frac{c\beta(I_1+\eta_1 I_2+\eta_2(1-q)A)}{1+\alpha(I_1+\eta_1 I_2+\eta_2(1-q)A)}$.

Table A.13: Parameter values for the system of ODEs for the model by Nyabadza *et al.* [17].

Parameter	Value	Description
μb	40000	Recruitment rate
μ	0.02	Natural death rate
α	1	Effectiveness of information campaigns
ρ	0.06	Rate of progression to AIDS class
β	0.00000002	Probability of infection
σ	0.18	Rate of progression from I_1 to I_2
η_1	1.6	Relative infectivity of I_2
η_2	1.8	Relative infectivity of A
q	0.1	Proportion of individuals who withdraw from sexual activity
δ	0.33	Disease-related death rate
c	1	Number of sexual partners

A.14 Stability analysis of an HIV/AIDS epidemic model with screening (Al-Sheikh *et al.* [41])

Al-Sheikh *et al.* [41] designed a mathematical model for the screening of HIV infected individuals. The population is divided into the susceptible individuals, S, infected individuals who are not aware of their status, I_1, infected individuals who are aware of their status, I_2, and individuals with AIDS, A. The initial conditions is given by: $S(0) = 15300$, $I_1(0) = 5400$, $I_2(0) = 4500$, and $A(0) = 1800$. The parameter values are shown in Table A.14.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= Q_0 - (\beta_1 I_1 + \beta_2 I_2)S - \mu S \\
\frac{dI_1}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S - (\theta + \mu + \delta)I_1 \\
\frac{dI_2}{dt} &= \theta I_1 - (\mu + \delta)I_2 \\
\frac{dA}{dt} &= \delta(I_1 + I_2) - (\mu + d)A.
\end{aligned}$$

Table A.14: Parameter values for the system of ODEs for the model by Al-Sheikh *et al.* [41].

Parameter	Value	Description
Q_0	3000	Recruitment rate
β_1	0.0009	Probability of transmission
β_2	0.00027	Probability of transmission
μ	0.04	Natural death rate
θ	0.02	Rate of screening
δ	0.3	Rate of progression to the AIDS class
d	1	Disease-related death rate

A.15 Mathematical Analysis of an HIV/AIDS Model: Impact of educational programs and abstinence in Sub-Saharan Africa (Bhunu *et al.* [42])

Bhunu *et al.* [42] designed a model to analyse how testing and counselling along with decreased sexual activity will influence the HIV epidemic. The population divided into six classes. These classes are: susceptible individuals, S, individuals who are HIV positive and unaware of their status, I_2, individuals who are HIV positive and know their status and reduced their risky sexual behaviour, I_2, individuals who are HIV positive and know their status and increased their risky sexual behaviour, I_3, individuals who are HIV positive and sexually inactive, I_4, and individuals with AIDS, A. The total population is $N = S + I_1 + I_2 + I_3 + I_4 + A$. The initial conditions for the system are: $S(0) = 200000$, $I_1(0) = 5000$, $I_2(0) = 0$, $I_3(0) = 0$, $I_4(0) = 0$, and $A(0) = 0$. The parameter values for the model are shown in Table A.15.

The system of ODEs is given by:

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

where $\lambda = \frac{\beta c(I_1 + \phi_1 I_2 + \phi_2 I_3)}{N}$.

Table A.15: Parameter values for the system of ODEs for the model by Bhunu *et al.* [42].

Parameter	Value	Description
Λ	0.029	Recruitment rate
μ	0.02	Natural death rate
δ	0.1	Rate of counselling and testing
ρ	0.1	Rate of progression to AIDS
ϕ_1	0.25	Modifying parameter
ϕ_2	1.01	Modifying parameter
f	0.85	Behaviour change
ν	0.333	Disease-related death rate
βc	0.011	Probability of transmission
θ	0.2	Abstinence rate

A.16 Modelling hospitalisation, home-based care and individual withdrawal for people living with HIV/AIDS in high prevalence settings (Hove-Musekwa *et al.* [43])

Hove-Musekwa *et al.* [43] looked at how voluntary counselling and screening, hospitalisation, screening and home-based care will influence the HIV/AIDS epidemic. The population is divided into six classes. These classes are the susceptible individuals (S), unscreened infected individuals (I), screened infected individuals (I_s), individuals who have AIDS (A), individuals who are hospitalised (H), and individuals who are under home-based care (H_b). The total population is given by: $N = S + I + I_s + A + H + H_b$. The initial conditions for the system are: $S(0) = 4519960$, $I(0) = 550000$, $I_s(0) = 50000$, $A(0) = 100000$, $H(0) = 3640$, and $H_b(0) = 36400$. The parameter values are given in Table A.16.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S \\
\frac{dI}{dt} &= \lambda S - (\mu + \sigma + \gamma_1) I \\
\frac{dI_s}{dt} &= \sigma I - (\mu + \gamma_2 + \rho_1) I_s \\
\frac{dA}{dt} &= \gamma_1 I + \gamma_2 I_s - (\mu + \theta + \delta_1) A \\
\frac{dH}{dt} &= \theta A - (\mu + \rho_2 + \delta_2) H \\
\frac{dH_b}{dt} &= \rho_1 I_s + \rho_2 H - (\mu + \delta_3) H_b,
\end{aligned}$$

where $lambda = \beta e^{-m(\delta_1 A + \delta_2 H + \delta_3 H_b)} \left(\frac{I + \eta_1 I_s + (1-p)(\eta_2 A + \eta_3 (1-\phi) H_b)}{N} \right)$.

Table A.16: Parameter values for the system of ODEs for the model by Hove-Musekwa *et al.* [43].

Parameter	Value	Description
μ	0.029	Natural death rate
p	0.4	Fraction of AIDS individuals who withdraw from sexual activity
η_1	0.3	Modifying parameter
η_2	1.1	Modifying parameter
η_3	0.7	Modifying parameter
ϕ	0.05	Efficacy of home-based care
ρ_1	0.053	Treatment rate
ρ_2	0.06	Rate of home-based care
σ	0.143	Screening rate
γ_1	0.1	Rate of progression to AIDS
γ_2	0.084	Rate of progression to AIDS
θ	0.425	Rate of hospitalisation
δ_1	0.2	Disease-related death rate
δ_2	0.1	Disease-related death rate
δ_3	0.2	Disease-related death rate
Λ	52600	Recruitment rate
m	105	Response parameter
β	0.8297	Effective contact rate

A.17 A nonlinear HIV/AIDS model with contact tracing (Naresh *et al.* [44])

Naresh *et al.* [44] constructed a model that incorporates contact tracing. The population is divided into the susceptible individuals, S, unaware infected individuals, I_1, aware infected individuals, I_2, and individuals with AIDS, A. The total population is given by: $N = S + I_1 + I_2 + A$. The initial conditions for the model are: $S(0) = 3800$, $I_1(0) = 5000$, $I_2(0) = 1000$, and $A(0) = 200$. The parameter values are given in Table A.17.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= Q_0 - \left(\frac{\beta_1 S I_1 + \beta_2 S I_2}{N}\right) - \mu S \\
\frac{dI_1}{dt} &= \frac{\beta_1 S I_1}{N} + \frac{(1-\epsilon)\beta_2 S I_2}{N} - (\theta + \delta_1 + \mu) I_1 - h(I1, I2) \\
\frac{dI_2}{dt} &= \frac{\epsilon \beta_2 S I_2}{N} + \theta I_1 - (\delta_2 + \mu) I_2 + h(I1, I2) \\
\frac{dA}{dt} &= \delta_1 I_1 + \delta_2 I_2 - (\alpha + \mu) A,
\end{aligned}$$

where $h(I_1, I_2) = k I_1 I_2$.

Table A.17: Parameter values for the system of ODEs for the model by Naresh *et al.* [44].

Parameter	Value	Description
Q_0	2000	Recruitment rate
μ	0.02	Natural death rate
β_1	1.5	Contact rate
β_2	0.5	Contact rate
α	1	Disease-related death rate
δ_1	0.2	Rate of progression to AIDS
δ_2	0.1	Rate of progression to AIDS
ϵ	0.01	Fraction of aware infected individuals
θ	0.015	Rate of screening
k	0.00001	Detection rate through contact tracing

A.18 Modelling HIV/AIDS in the presence of an HIV testing and screening campaign (Nyabadza and Mukandavire [19])

Nyabadza and Mukandavire [19] constructed a model that incorporates condom use and HIV counselling and testing (HCT). The population is divided into 7 classes. These classes are susceptible and not screened individuals (S_n), susceptible and screened individuals (S_s), infected and unscreened individuals (I_n), infected and screened individuals(S_s), infected individuals under treatment (I_T), those who have developed AIDS and not screened (A_n), and individuals who have developed AIDS and screened (A_s). The total population is given by: $N(t) = S_n(t)+S_s(t)+I_n(t)+I_s(t)+I_T(t)+A_n(t)+A_s(t)$. The initial conditions for the system are: $S_n(0) = 18373000$, $S_s(0) = 0$, $I_n(0) = 145000$, $I_s(0) = 0$, $I_T(0) = 0$, $A_n(0) = 20000$, $A_s(0) = 0$. The parameter values are shown in Table A.18.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_n}{dt} &= \Pi_n - \lambda S_n - (\mu + k)S_n \\
\frac{dS_s}{dt} &= \Pi_s + kS_n - (1-\psi)\lambda S_s - \mu S_s \\
\frac{dI_n}{dt} &= q(1-\psi)\lambda S_s + \lambda S_n - (\mu + k + \rho_1)I_n \\
\frac{dI_s}{dt} &= p(1-\psi)\lambda S_s + kI_n - (\mu + \sigma + \rho_2)I_s \\
\frac{dI_T}{dt} &= \sigma I_s - (\mu + \rho_3)I_T \\
\frac{dA_n}{dt} &= \rho_1 I_n - (\mu + \delta_1)A_n \\
\frac{dA_s}{dt} &= \rho_2 I_s + \rho_3 I_T - (\mu + \delta_2)A_s,
\end{aligned}$$

where the force of infection is given by

$$\lambda(t) = f(A)\left(\frac{I_n(t) + \eta_1(I_s(t) + \phi_1 I_T(t)) + \eta_2(A_n(t) + \phi_2 A_s(t))}{N(t)}\right),$$

$$f(A) = c(1-\theta)\beta e^{-\varphi(\delta_n A_n + \delta_s A_s)}$$

Table A.18: Parameter values for the system of ODEs for the model by Nyabadza and Mukandavire [19].

Parameter	Value	Description
Π_n	920540	Constant recruitment rate of unscreened
Π_s	750000	Constant recruitment rate of screened individuals
δ_1	0.2930	Disease related death rate
σ	0.0655	Rate at which infected individuals seek
c	1.5892	Mean number of annual sexual partners of susceptible individuals
ψ	0.2915	Efficacy of screening
β	0.4584	Probability of infection through contact with infected individuals
φ	45.1202	Measure of behaviour change
η_1	0.7203	Transmission probability of screened
η_2	1.3785	Transmission probability of those with AIDS
θ	0.1605	Level of protection by condoms
ϕ_1	0.1000	Treatment-induced reduction in infectivity
p	0.1000	Proportion of screened individuals that enter I_s
q	0.9000	Proportion of susceptible individuals that the class of infected individuals without being screened
ρ_1	0.2371	Rate of progression from I_n to A_n
ρ_2	0.1828	Rate of progression from I_s to A_s
ρ_3	0.1300	Rate of progression from I_T to A_s
k	0.0388	Rate of screening
δ_2	0.3379	Disease related death rate
ϕ_2	0.000073471	Screening-induced reduction in infectivity
μ	0.0320	Natural death rate

A.19 Modelling the HIV/AIDS epidemic trends in South Africa: Insights from a simple mathematical model (Nyabadza *et al.* [45])

Nyabadza *et al.* [45] look at how the epidemic will be affected if HIV prevention efforts were scaled up. The population is divided into 6 classes. These classes are susceptible individuals (S), asymptomatic infectives (I_1), screened infectives (I_2), symptomatic infectives (pre-AIDS stage) (I_3), treated infectives (I_4), and those with AIDS (A) The total population is given by: $N(t) = S(t) + I_1(t) + I_2(t) + I_3 + I_4 + A(t)$. The initial values used are: $S(0) = 20000000$, $I_1(0) = 140000$, $I_2(0) = 0$, $I_3(0) = 20000$, $I_4(0) = 0$, and $A(0) = 10000$. The parameter values for the system are shown in Table A.19.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - k(1-\theta)\lambda S - \mu S \\
\frac{dI_1}{dt} &= k(1-\theta)\lambda S - (\mu + k_1 + k_2)I_1 \\
\frac{dI_2}{dt} &= k_1 I_1 - (\mu + \gamma_1 + \sigma)I_2 \\
\frac{dI_3}{dt} &= k_2 I_1 + \sigma I_2 - (\mu + \gamma_2 + \rho_1)I_3 \\
\frac{dI_4}{dt} &= \gamma_1 I_2 + \gamma_2 I_3 - (\mu + \rho_2)I_4 \\
\frac{dA}{dt} &= \rho_1 I_3 + \rho_2 I_4 - (\mu + \delta)A,
\end{aligned}$$

where $\lambda = \beta e^{-m\delta A}(\frac{I_1 + \eta_1 I_2 + \eta_2 I_3 + \eta_3 I_4 + A}{N})$

Table A.19: Parameter values for the system of ODEs for the model by Nyabadza *et al.* [45].

Parameter	Value	Description
Π	527200	Recruitment rate
μ	0.029	Natural death rate
k_1	0.2628	Screening rate
k_2	0.2994	Rate of progression for unscreened
γ_1	0.003	Treatment rate
γ_2	0.0005	Treatment rate
ρ_1	0.6999	Rate of progression to AIDS
ρ_2	0.08	Rate of progression to AIDS
δ	0.2	Disease-related death rate
m	80	Measure of behaviour change
η_1	0.45	Relative infectiousness
η_2	1.6	Relative infectiousness
η_3	0.4	Relative infectiousness
η_4	1.5	Relative infectiousness
σ	0.295	Rate of progression to symptomatic stage
k	2.6	Number of sexual partners
θ	0.65	Condom protection level
β	0.499	Contact rate

A.20 Assessing the impact of using antiretroviral drugs as pre-exposure vaccines (Bhunu and Mushayabasa [46])

Bhunu and Mushayabasa [46] designed and analysed a model to determine the impact of ART as pre-exposure vaccines on the spread of HIV infection. The population is divided into six classes, namely: the susceptible individuals not receiving ART (S_u), susceptible individuals receiving ART (S_v), HIV infected individuals (I_u), HIV infected individuals receiving ART (I_v), individuals with AIDS (A_u), and individuals with AIDS receiving ART (A_v). The total population is given by: $N = S_u + S_v + I_u + I_v + A_u + A_v$. The initial conditions for the model are: $S_u(0) = 1000000$, $S_v(0) = 10000$, $I_u(0) = 1000$, $I_v(0) = 0$, $A_u(0) = 0$, and $A_v(0) = 0$. The parameter values are given in Table A.20.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS_u}{dt} &= \Lambda - (\lambda + \mu + \alpha_s)S_u \\
\frac{dS_v}{dt} &= \alpha_s S_u - (\sigma\lambda + \mu)S_v \\
\frac{dI_u}{dt} &= \lambda S_u - (\mu + \rho_u + \alpha_i)I_u \\
\frac{dI_v}{dt} &= \sigma\lambda S_v + \alpha_i I_u - (\mu + \rho_v)I_v \\
\frac{dA_u}{dt} &= \rho_u I_u - (\mu + \nu + \alpha_a)A_u \\
\frac{dA_v}{dt} &= \alpha_a A_u + \rho_v I_v - (\mu + \nu)A_v,
\end{aligned}$$

where $\lambda = \frac{\beta(A_u + \theta_v A_v + \theta_i(I_u + \theta_v I_v))}{N}$.

Table A.20: Parameter values for the system of ODEs for the model by Bhunu and Mushayabasa [46].

Parameter	Value	Description
Λ	5800	Recruitment rate
μ	0.02	Natural death rate
β	0.125	Probability of transmission
ρ_u	0.1	Rate of progression to AIDS
ρ_v	0.1	Rate of progression to AIDS
α_s	0.15	Vaccination rate
α_i	0.33	Treatment rate
α_a	0.33	Treatment rate
θ_i	0.125	Modifying parameter
θ_v	0.125	Modifying parameter
σ	0.25	Modifying parameter
ν	0.333	Disease-related death rate

A.21 Modelling the emergence of HIV-1 drug resistance resulting from antiretroviral therapy: Insights from theoretical and numerical studies (Raimundo *et al.* [47])

Raimundo *et al.* [47] looked at HIV drug-resistance during treatment. The population is divided into: susceptible individuals, S, drug-sensitive HIV infected individuals, I_S, drug-resistant HIV infected individuals, I_R, successfully treated drug-sensitive patients, E, and individuals in therapeutic failure, F. The initial values used for the system are: $S(0) = 0.004$, $I_S(0) = 0.004$, $I_R(0) = 0.001$, $E(0) = 0$, and $F(0) = 0$. The parameter values are given in Table A.21.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \beta_S S I_S - \beta_R S I_R - \mu S \\
\frac{dI_S}{dt} &= \beta_S S I_S - (\epsilon_S + \mu + \alpha) I_S \\
\frac{dI_R}{dt} &= \beta_R S I_R + \rho_F - (\phi_R + \mu + \alpha) I_R \\
\frac{dE}{dt} &= p\epsilon_S I_S - (\sigma + \mu) E \\
\frac{dF}{dt} &= (1-p)\epsilon_S I_S + \phi_R I_R + \sigma E - (\rho + \alpha + \mu) F.
\end{aligned}$$

Table A.21: Parameter values for the system of ODEs for the model by Raimundo *et al.* [47].

Parameter	Value	Description
μ	0.01470588	Recruitment rate or natural death rate
p	0.6	Proportion of successfully treated drug-sensitive individuals
β_S	1.8	Probability of transmission
β_R	0.45	Probability of transmission
ϵ_S	0.9	Treatment rate
ϕ_R	2	Treatment rate
σ	0.5	Average time from drug-sensitive to drug-resistant
α	0.07142857	Rate of progression to AIDS

A.22 A model for control of HIV/AIDS with parental care (Abiodun *et al.* [48])

Abiodun *et al.* [48] constructed a model that describes the dynamics of HIV infection among immigrants. The population is divided into susceptible individuals (S), newly HIV infected individuals (I), individuals in the pre-AIDS stage (H), and individuals with AIDS (A). The initial conditions are given by: $S(0) = 85000$, $I(0) = 10000$, $H(0) = 5000$, and $A(0) = 0$. The parameter values are shown in Table A.22.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho u_1)\mu K - S(1-u_2)(Ic_1\beta_1 + Hc_2\beta_2 + Ac_3\beta_3) - \mu S \\
\frac{dI}{dt} &= \rho u_1 \mu K + S(1-u_2)(Ic_1\beta_1 + Hc_2\beta_2 + Ac_3\beta_3) - (\gamma+\mu)I \\
\frac{dH}{dt} &= \gamma I - (\mu+\sigma)H \\
\frac{dA}{dt} &= \sigma H - (\alpha+\mu)A
\end{aligned}$$

Table A.22: Parameter values for the system of ODEs for the model by Abiodun *et al.* [48].

Parameter	Value	Description
K	100000	Recruitment constant
β_1	$3.4 \times 10^{-}7$	Probability of transmission
β_2	$2.3 \times 10^{-}7$	Probability of transmission
β_3	$1.5 \times 10^{-}7$	Probability of transmission
c_1	4	Number of sexual partners
c_2	3	Number of sexual partners
c_3	1	Number of sexual partners
μ	0.02	Natural death rate
α	0.33	Disease-related death rate
γ	0.18	Rate of progression to H
σ	0.05	Rate of progression to A
u_1	0	Screening control
u_2	0	Parental care
ρ	0	Proportion of infectious youths

A.23 Global stability for an HIV/AIDS epidemic model with different latent stages and treatment (Huo and Feng [49])

Huo and Feng [49] designed a model for different latent stages of HIV infection. The population is divided into five classes. These classes are: the susceptible individuals, S, individuals in the slow latent class, I_1, individuals in the fast latent class, I_2, infected individuals in the symptomatic stage, J, and individuals with AIDS, A. The initial condition are: $S(0) = 50$, $I_1(0) = 30$, $I_2(0) = 40$, $J(0) = 20$, and $A(0) = 10$. The parameter values for the system are given in Table A.23.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 I_2 S - \beta_2 J S - \mu S \\
\frac{dI_1}{dt} &= p\beta_1 I_2 S + q\beta_2 J S - (\epsilon + \mu) I_1 + \xi_1 J \\
\frac{dI_2}{dt} &= (1-p)\beta_1 I_2 S + (1-q)\beta_2 J S + \epsilon I_1 - (p_1 + \mu) I_2 + \xi_2 J \\
\frac{dJ}{dt} &= p_1 I_2 - (\xi_1 + \xi_2 + p_2 + \mu) J \\
\frac{dA}{dt} &= p_2 J - (\mu + \alpha) A.
\end{aligned}$$

Table A.23: Parameter values for the system of ODEs for the model by Huo and Feng [49].

Parameter	Value	Description
Λ	0.55	Recruitment rate
β_1	0.0001	Probability of transmission
β_2	0.0006	Probability of transmission
p	0.9	Fraction of S being infected by I_2
q	0.8	Fraction of S being infected by J
ϵ	0.002	Rate of progression to I_2
p_1	0.01	Rate of progression to J
p_2	0.03	Rate of progression to A
ξ_1	0.8	Treatment rate
ξ_2	0.9	Treatment rate
μ	0.01	Natural death rate
α	0.01	Disease-related death rate

A.24 Mathematical insights in evaluating state dependent effectiveness of HIV prevention interventions (Zhao *et al.* [50])

Zhao *et al.* [50] designed a model for HIV transmission to analyse the effect of PrEP on the HIV epidemic. The population is divided into 4 classes. The classes include susceptible individuals (S), susceptible individuals using PrEP (S^p), infected individuals (I), and infected individuals using PrEP (I^p). The initial values for the system are: $S(0) = 667200$, $S^p(0) = 166800$, $I(0) = 149400$, and $I^p(0) = 16600$. The parameter values are given in Table A.24.

The system of ODEs is given by:

$$\begin{aligned}
\frac{dS}{dt} &= (1-k)\Lambda - \beta\frac{IS}{N} - (1-\alpha_i)\beta\frac{I^pS}{N} - \mu S \\
\frac{dS^p}{dt} &= k\Lambda - (1-\alpha_s)\beta\frac{S^pI}{N} - (1-\alpha_s)(1-\alpha_i)\beta\frac{I^pS^p}{N} - \mu S^p \\
\frac{dI}{dt} &= \beta\frac{IS}{N} + (1-\alpha_i)\beta\frac{I^pS}{N} - (\mu+d)I \\
\frac{dI^p}{dt} &= 1-\alpha_s)\beta\frac{S^pI}{N} - (1-\alpha_s)(1-\alpha_i)\beta\frac{I^pS^p}{N} - (\mu+d)I,
\end{aligned}$$

where $\beta = 1-(1-b_a)^n$.

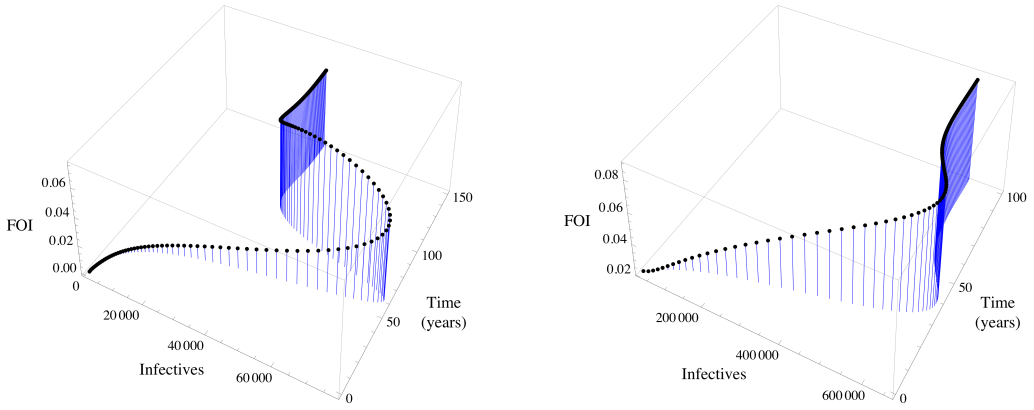
Table A.24: Parameter values for the system of ODEs for the model by Zhao *et al.* [50].

Parameter	Value	Description
d	0.1302	Rate of progression to AIDS
Λ	38094	Rate at which individuals become sexually active
μ	0.25	Rate at which individuals are no longer sexually active
b_a	0.003	HIV transmission risk
n	65.8494	Number of sexual acts
k	0.2	Proportion of individuals that start using PrEP
α_s	0.5	Efficacy of PrEP
α_i	0.5	Efficacy of PrEP

Appendix B

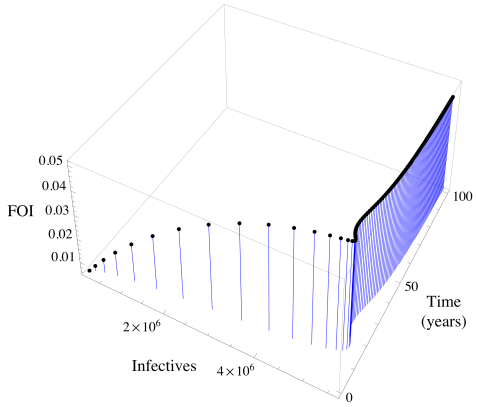
Simulations of FOI for all the models

B.1 Frequency-dependent with AIDS

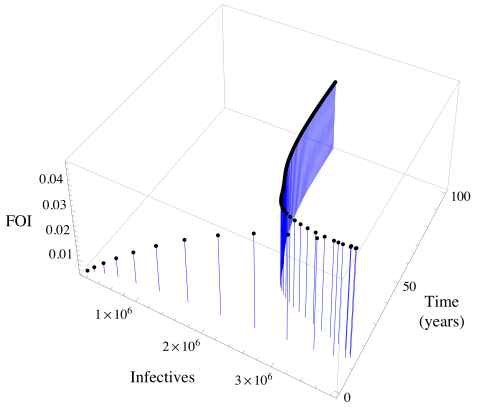


(a) Nyabadza [11] (b) Hove-Musekwa and Nyabadza [39]

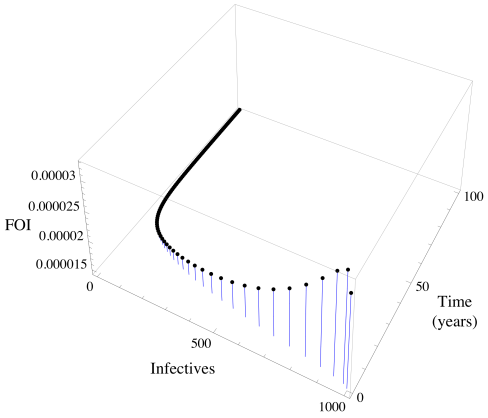
Figure B.1: Graphs show models that use frequency-dependent transmission with AIDS.



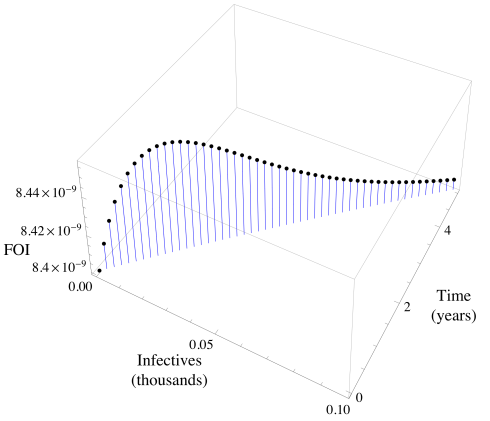
(c) Nyabadza and Mukandavire [19]



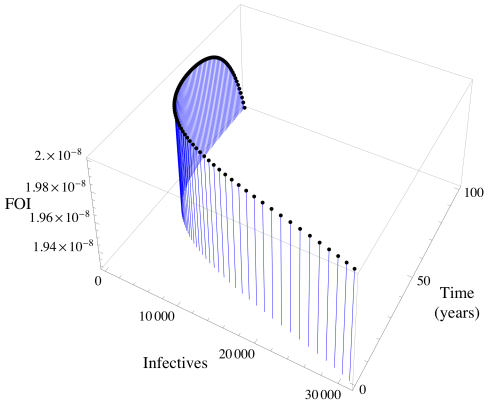
(d) Nyabadza *et al.* [45]



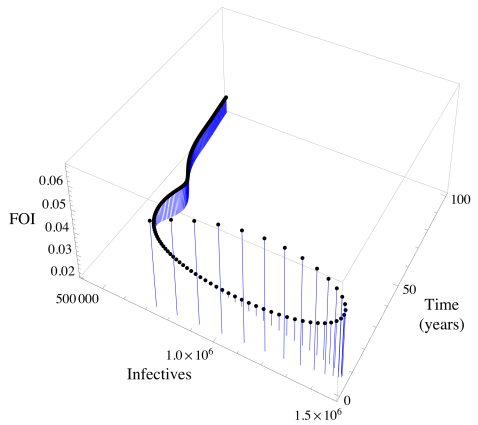
(e) Bhunu and Mushayabasa [46]



(f) Romieu *et al.* [36]

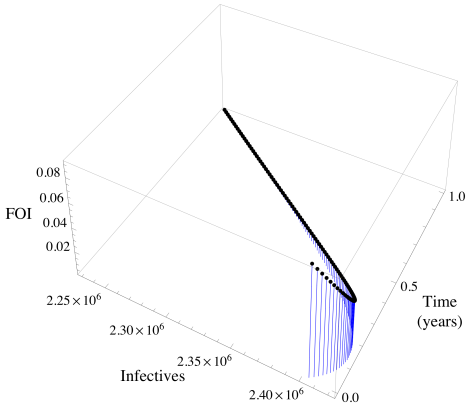


(g) Nyabadza *et al.* [17]



(h) Hove-Musekwa *et al.* [43]

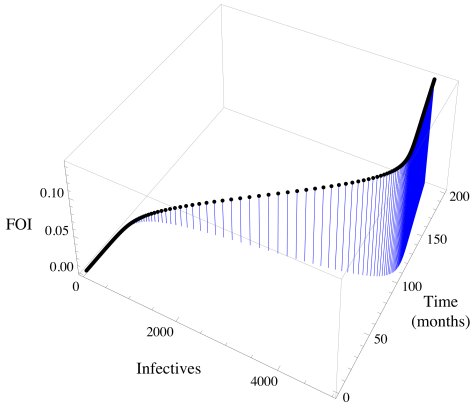
Figure B.1: (Continued) Graphs show models that use frequency-dependent transmission with AIDS.



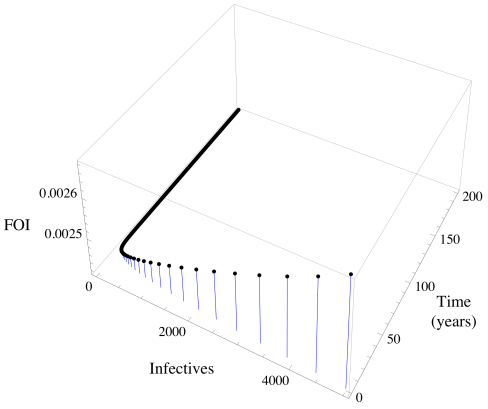
(i) Podder *et al.* [26]

Figure B.1: (Continued) Graphs show models that use frequency-dependent transmission with AIDS.

B.2 Frequency-dependent without AIDS

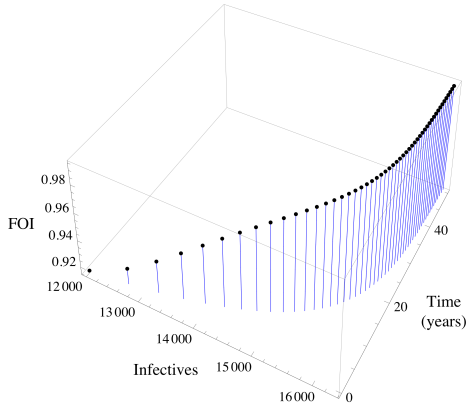


(a) Bachar and Dorfmayr [37]

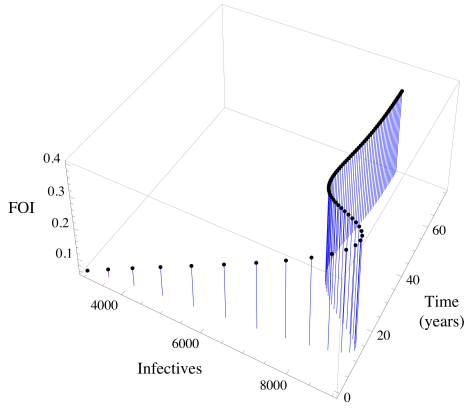


(b) Bhunu *et al.* [42]

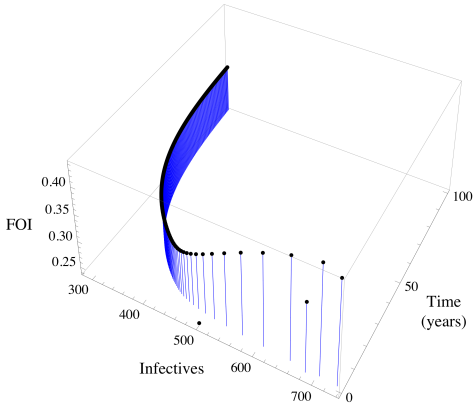
Figure B.2: Graphs show models that use frequency-dependent transmission without AIDS.



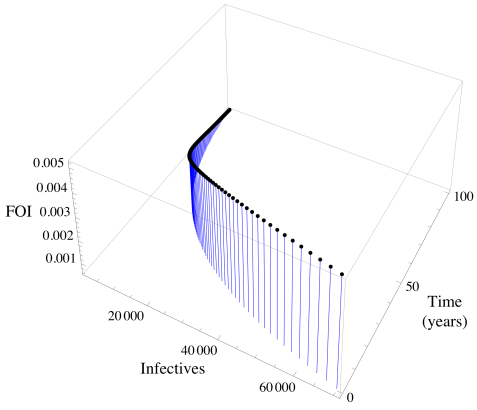
(c) Tripathi *et al.* [20]



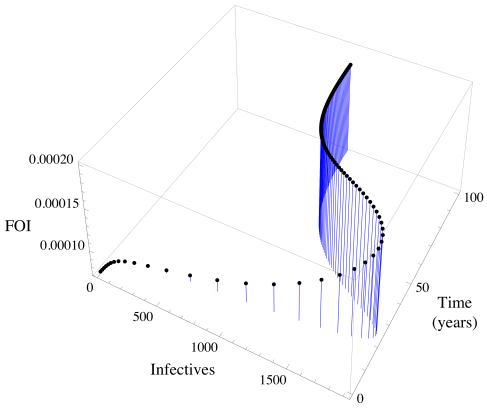
(d) Naresh and Tripathi [35]



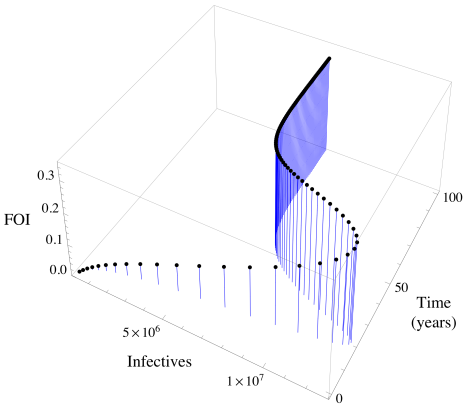
(e) Gumel *et al.* [22]



(f) Moghadas *et al.* [28]

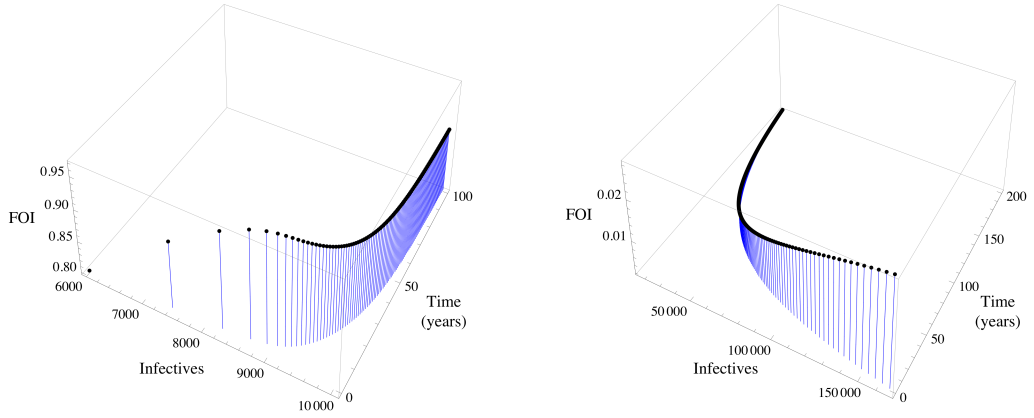


(g) Bacaër *et al.* [25]



(h) Lou *et al.* [40]

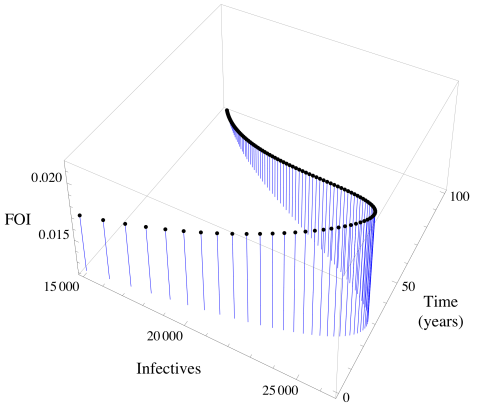
Figure B.2: (Continued) Graphs show models that use frequency-dependent transmission without AIDS.



(i) Naresh *et al.* [44] (j) Zhao *et al.* [50]

Figure B.2: (Continued) Graphs show models that use frequency-dependent transmission without AIDS.

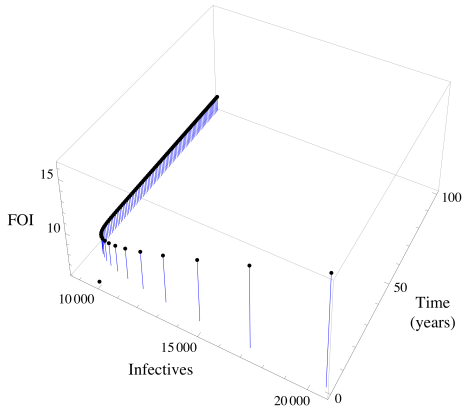
B.3 Density-dependent with AIDS



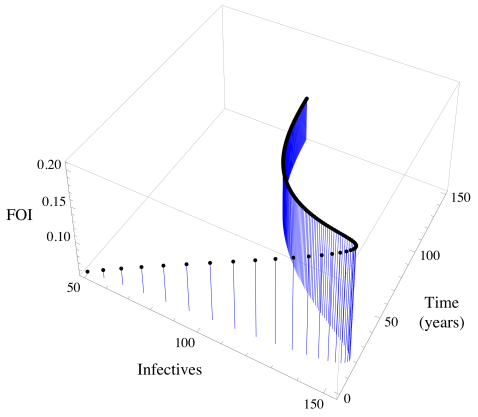
(a) Abiodun *et al.* [48]

Figure B.3: (Continued) Graphs show models that use density-dependent transmission with AIDS.

B.4 Density-dependent without AIDS

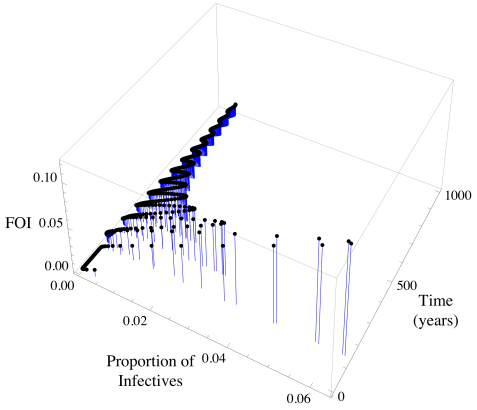


(a) Al-Sheikh *et al.* [41]

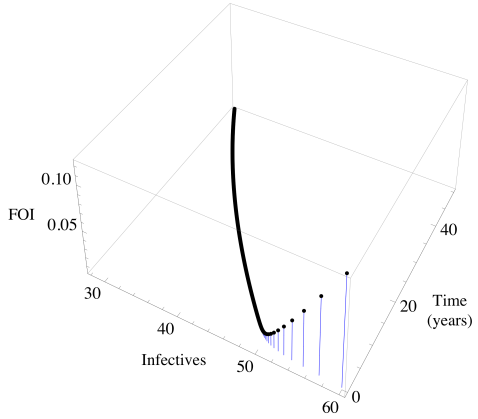


(b) Cai *et al.* [38]

Figure B.4: Graphs show models that use density-dependent transmission without AIDS.



(c) Raimundo *et al.* [47]



(d) Huo and Feng [49]

Figure B.4: (Continued) Graphs show models that use density-dependent transmission without AIDS.

Appendix C

Deterministic models

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