Basic properties of models for the spread of HIV/AIDS

by

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requirements for the degree of Master of Science
in Physical and Mathematical Analysis

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

Signature: ....

Date: ....

Summary

While research and population surveys in HIV/AIDS are well established in developed countries, Sub-Saharan Africa is still experiencing scarce HIV/AIDS information. Hence it depends on results obtained from models. Due to this dependence, it is important to understand the strengths and limitations of these models very well.

In this study, a simple mathematical model is formulated and then extended to incorporate various features such as stages of HIV development, time delay in AIDS death occurrence, and risk groups. The analysis is neither purely mathematical nor does it concentrate on data but it is rather an exploratory approach, in which both mathematical methods and numerical simulations are used.

It was found that the presence of stages leads to higher prevalence levels in a short term with an implication that the primary stage is the driver of the disease. Furthermore, it was found that time delay changed the mortality curves considerably, but it had less effect on the proportion of infectives. It was also shown that the characteristic behaviour of curves valid for most epidemics, namely that there is an initial increase, then a peak, and then

a decrease occurs as a function of time, is possible in HIV only if low risk groups are present.

It is concluded that reasonable or quality predictions from mathematical models are expected to require the inclusion of stages, risk groups, time delay, and other related properties with reasonable parameter values.
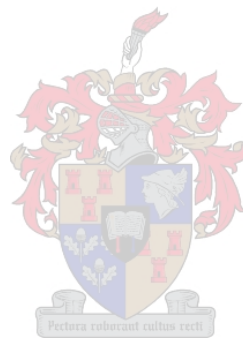
Opsomming

Terwyl navorsing en bevolkingsopnames oor MIV/VIGS in ontwikkelde lande goed gevestig is, is daar in Afrika suid van die Sahara slegs beperkte inligting oor MIV/VIGS beskikbaar. Derhalwe moet daar van modelle gebruik gemaak word. Dit is weens hierdie feit noodsaaklik om die moontlikhede en beperkings van modelle goed te verstaan.

In hierdie werk word ´n eenvoudige model voorgelê en dit word dan uitgebrei deur insluiting van aspekte soos stadiums van MIV outwikkeling, tydvertraging by VIGS-sterftes en risikogroepe in bevolkings. Die analise is beklemtoon nie die wiskundage vorme nie en ook nie die data nie. Dit is eerder ´n verkennende studie waarin beide wiskundige metodes en numeriese simulasie behandel word.

Daar is bevind dat insluiting van stadiums op korttermyn tot hoër voorkoms vlakke aanleiding gee. Die gevolgtrekking is dat die primêre stadium die siekte dryf. Verder is gevind dat die insluiting van tydvestraging wel die kurwe van sterfbegevalle sterk beïnvloed, maar dit het min invloed op die verhouding van aangestekte persone. Daar word getoon dat die kenmerkende gedrag van die meeste epidemië, naamlik `n aanvanklike styging, `n piek en

dan `n afname, in die geval van VIGS slegs voorkom as die bevolking dele bevat met lae risiko.

Die algehele gevolgtrekking word gemaak dat vir goeie vooruitskattings met sinvolle parameters, op grond van wiskundige modelle, die insluiting van stadiums, risikogroepe en vertragings benodig word.
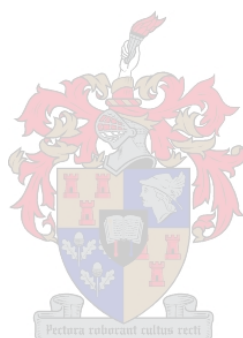
To my parents
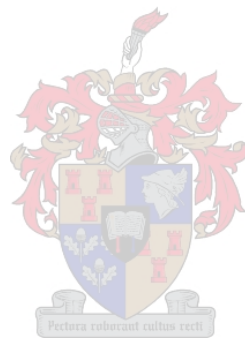
Acknowledgments

I would like to thank my supervisor, Professor Fritz Hahne not only for setting me to the task of epidemiological modelling, but also for having been of invaluable and patient assistance in my early confusions. I also thank him for inspiring me with my future research directions and I value his contribution to my life.
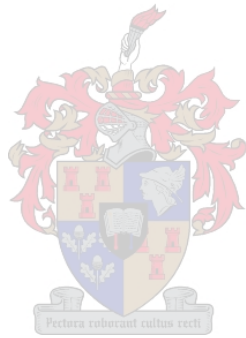
I acknowledge the African Institute for Mathematical Sciences (AIMS) for funding my studies. My gratitude to the AIMS staff, Jan, Mirjam, Igsaan and everybody else for their very best support throughout my stay. I would be in debt if I don't acknowledge the South African Centre for Epidemiological Modelling and Analysis (SACEMA) for their support and all people in the group who contributed in one way or another in my way to developing knowledge in this field.

Of course, I must say thanks to my family, and everybody else who loves me and gives me both spiritual and emotional support.
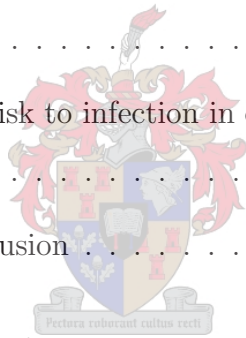
AM Lutambi, With God's grace

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Introduction

1.1 Motivation

HIV is the human immunodeficiency virus that causes the acquired immunodeficiency syndrome (AIDS). When a person is infected with HIV, the virus enters the body and lives and multiplies primarily in the white blood cells. These are the immune cells which normally protect us from diseases. The hallmark of HIV infection is the progressive loss of a specific type of immune cell called T-helper or CD4 cells. As the virus grows, it damages or kills these and other cells. Eventually, this leads to AIDS, a disease caused by the break - down of the body's immune system making it unable to fight off opportunistic infections and other illnesses that take advantage of a weakened immune system.

HIV emerged in 1980s. It is a sexually-transmitted disease which occurs

throughout the world. Its greatest impact is found in Sub-Saharan Africa. In 2005, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimated 40.3 million people to be living with HIV in the world, 4.9 million newly infected and 3.1 million AIDS deaths occurred in the year. Of these, 25.8 million lived in Sub-Saharan Africa with 3.2 million new infections and 2.4 million AIDS deaths occurring in the same year [1]. These estimates have increased from the numbers recorded in 2003 under which 37.5 million were living with HIV, with 4.6 million newly infected and 2.8 million AIDS deaths. With these estimates, the disease is seen to continue destroying the world's population especially the Sub-Saharan region.

The forementioned data on the spread of the HIV/AIDS epidemic are estimate values from models derived from scarce surveys. In African countries little research and few population or household surveys are done to get the real picture of the spread and effect of the HIV/AIDS epidemic in the population. These countries thus rely much on estimates produced by mathematical models. In South Africa, for example, data from models such as the ASSA model have been showing that by the start of the year 2004, about 4.9 million HIV infected individuals were estimated. On the other hand the UNAIDS came up with 5.6 millions HIV infected individuals [2]. The need for more population surveys and research is thus evident. More surveys also help in improving models and finding model parameters which lead to better estimates.

Since HIV research is still not well developed in Sub-Saharan Africa, mathematical models provide the best guide for various aspects of the spread of the disease. Apart from providing this alternative route, mathematical models

also provide researchers with almost instant results on studies that would have required several months or years to conduct in the populations. They thus help researchers and Governments to make complex choices on measures to control the transmission of the virus to the susceptible individuals. Mathematical models are constantly improving using the available data.

It is said that 95% of the world's HIV infected population [3] resides in developing countries. The accuracy of such statements depends clearly on how well the disease is modelled in less developed countries.

1.2 Thesis Objective

HIV prevalence estimates and projections based on fitting prevalence data are relatively insensitive to the specification of demographic rates such as birth and death rates, but absolute population size is more dependent on these rates. For risk groups where the demography is poorly specified, estimates of HIV cases or AIDS deaths must therefore be interpreted with caution. To generate a widely applicable model of the HIV epidemic much complexity has been ignored. The priority for improving estimates is to improve the coverage of sentinel sites, to understand the biases in sentinel data, clinical and biological information, socio-economic diversity, and to include behavioural data in surveillance. The question arises;

As the quality of data improves, can models that inform policy produce quality information on HIV/AIDS?

This study investigates aspects of the above question. To do that, we develop and study some simple HIV/AIDS spread models that may help us in understanding uncertainties that might occur in models and give a general idea on how one might get different results, or draw wrong conclusions, depending on the factors taken into account by the model.

The broader goal of this thesis is to make use of mathematical models to explore how different properties when incorporated in models may change estimates. If these properties exist among populations;

What contribution do they make in the spread of the disease?

This study also addresses this question.

1.3   Thesis outline

Having given the motivation of this work and its general objective, the rest of this thesis is structured as follows.

In chapter 2, a simple model is developed using ordinary differential equations to study the dynamic behaviour of HIV in the community. Since clinical studies have been showing the progression of HIV infected individuals from one stage to another, this model is extended to include stages of HIV progression. The results are compared to reveal the effect of introducing stages in HIV models.

In chapter 3, the staged model developed in chapter 2 is extended to include a time delay in AIDS death occurrence. The model is then used to investigate

the effects of the delay on estimates.

Chapter 4 extends the simple single stage model developed in chapter 2 to include risk groups, with different risks of contracting HIV. The very large effect this has on predictions is explained and disscussed.

In chapter 5, we summarize our findings and give some future directions which follow naturally from our work.
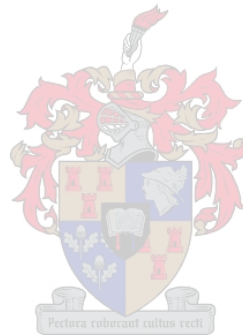
The effect of Stages of progression in HIV Models

In this chapter, two models for the spread of the HIV epidemic occurring via any transmission mechanism, except of mother-to-child transmission (MTCT), are formulated and studied. The two models have different characteristics. The first model is a simple model that describes the basic dynamic behaviour of the spread of HIV epidemic in the population and the second model is an extension of the first model to cater for the concept of HIV progression of an infected individual. The main idea of this chapter is based on the study done in Rakai - Uganda between $1994 - 1999$ [4, 5]. This study revealed the correlation between the stages of HIV infection and the transmission of the viruses to uninfected individuals. The study found individuals in the primary stage to be the leading group in the spread of HIV. This finding can not only be used to study how important stages of HIV infection are in the spread of the epidemic, but it is helpful in evaluating the

efficiency of HIV spread models that are used in projecting countries' HIV burden as well. Therefore, this chapter investigates the effects that occur if stages are included in HIV models.

2.1 Introduction

The study of an epidemic, such as HIV, and its spread process in any community, is different to an investigation in many other sciences. Data can not be obtained through experiments in the population, but can only be obtained from surveys and results of which are found in published or unpublished documents. These data are often not complete and not accurate and may vary with respect to methods used to collect them. Mathematical modelling and numerical simulation play an important role in analyzing the behaviour of the epidemic, measuring its past, present and future effect in a society.

It has been well established that HIV transmission is not uniform. It differs from one stage to another [4, 5, 6]. Hence epidemiologic modelling must use stages of HIV progression in order to capture the dynamics of transmission of the disease in the population.

As an infected person progress from one stage of HIV infection to another, the level of transmitting the viruses to others changes. Therefore, the transmission dynamics of the viruses can be categorized according to the stages of HIV progression of an infected individual. These stages of disease progression are divided into three phases [7, 8] as it is explained below:

Primary infection stage
This stage follows soon after the initial infection when infectiousness
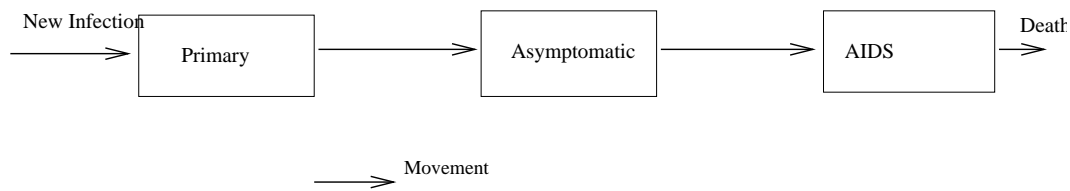
Figure 2.1: A schematic diagram for HIV progression of an infected individual

first rises and then drops. Seroconversion[1] typically occurs well before the end of the primary stage. During this phase the virus is distributed to many different organs of an infected individual.

Asymptomatic stage
During this period infectiousness is low, it produces few, if any, symptoms and the patient's blood contains a relatively small viral load, and antibodies to the virus. These antibodies are the basis of the most common test for HIV infection.

Symptomatic or AIDS stage
It is a period ($1 - 2$ years until death in cases without treatment) for which infectiousness rises again. The symptomatic stage begins while individuals are relatively healthy and active, although it also includes the more severe AIDS phase for which they develop AIDS and die.

Viral levels also vary greatly between these three stages. During the period

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[1]Seroconversion period is defined as a time during which a person who has an infection does not test positive for it. This period occurs before a person has produced a high enough number of antibodies for a test to detect the condition. The length of the seroconversion period depends on the type of infection. During the seroconversion period, an infected person can transmit the disease or condition even if he or she does not have signs of the infection.

of primary infection, viral levels are typically high. The viral levels drop as one enters the asymptomatic period, followed by a symptomatic/AIDS stage during which the viral loads are extremely high. This has been evident from a number of studies. For example, a community-based study for which consenting couples, whether discordant for HIV or not, were prospectively followed for 30 months to evaluate the risk of transmission in relation to viral load and other characteristics in Rakai - Uganda. This study discovered that the risk of infection increases as the HIV infected person's viral load increases [4]. In some other studies [9] it was postulated that the level of infecting for individuals carrying HIV is dependent on clinical status of the individual. Most of the infections an infected person causes occur shortly after infection, after which infections become low until the immune system begins to be seriously affected.

This variation in the levels of transmitting the disease over time can be explained using mathematical models in which infected individuals sequentially pass through a series of stages as described above [5, 4]. Thus, in this regard the present chapter tries to address the following questions: What effect does the transmission rate have on the spread of the epidemic and its predictive estimates? Does the survival period of infected individuals have any effect? In a situation where infected people progress from one stage to another, some of which have indicated to have more effect in terms of transmission, we desire to address the following question: What is the role of incorporating stages in models that give predictions of the HIV/AIDS burden given that all HIV infected persons pass through different stages in developing AIDS?

Currently we are faced with the need to predict the dynamics and transmission of transmitted diseases with a greater accuracy and over longer periods

of time, and more often with limited empirical data. In most epidemiological models, the assumption of constant total populations is often made. This assumption is only reasonable if the disease studied spreads for a short time only with limited effects on mortality and births. The relevance or validity of this assumption becomes not applicable when dealing with long time diseases such as HIV/AIDS. In such diseases, the effects of changes in population size and disease induced mortality are far from negligible and in fact can have a crucial influence on the dynamics of the disease.

Various mathematical models of diseases have dealt with a variable population size [10, 11, 12, 13, 14, 15]. The interactions between the epidemiological and demographic processes yield new features which are not found in epidemiological models with constant population size. For example, when the disease persists in the population, the disease related mortality and the reduced reproduction of infected individuals can reduce the growth rate or change a growing population into a population with a stable or even a decreasing size [16].
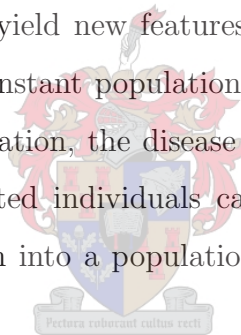
The HIV/AIDS epidemic has known to have a large impact in the population as a whole [1, 3] in some regions of the world. Considering a constant population might be not realistic as it is in some long time diseases. However, this assumption in the context of HIV/AIDS can be made in countries where the prevalence of HIV is low. Our study is therefore considering a variable size population.

2.2 The Simple HIV epidemic model

This section presents a simple model for the spread of HIV. It might not be realistic, but we present and analyze it so that other more complex models of HIV spread can be easily understood.

2.2.1 Model formulation

The HIV/AIDS model formulated in the present section considers the whole population in a single group. The assumption is made that the susceptible population, $Z(t)$ is homogeneous and the variations in risk behaviour, and many other factors associated with the dynamics of the HIV spread are not considered. The model does not contain assumptions about the mechanism of infection. It could be homosexual or heterosexual or any other means. However, the assumption that no fertility reduction for HIV infected individuals $(Y(t))$ is made and vertical transmission, (i.e. mother to child transmission) is ignored.

The demography of the model is described by the rates of entry and exit of individuals from the population. The larger population of susceptible individuals is assumed free of HIV initially and together with $Y(t)$ at time t provide a large source of uninfected individuals entering the population. The parameter b is the rate at which new individuals are recruited through births into the susceptible population. People exit from the population at a rate μ for which $1/\mu$ is the life expectancy of individuals when the population is free from the invasion of the disease. The parameter γ is the rate at which the infected individuals die of the HIV/AIDS disease. In this model,

an exponential decrease of the infected group due to disease mortality is assumed.

The dynamics of the model are governed by the following system of differential equations:

$$
\begin{aligned}
\frac{dZ(t)}{dt} &= bN(t) - r\frac{Z(t)Y(t)}{N(t)} - \mu Z(t) \\
\frac{dY(t)}{dt} &= r\frac{Z(t)Y(t)}{N(t)} - \mu Y(t) - \gamma Y(t)
\end{aligned}
\tag{2.1}
$$

where r is the disease transmission rate and $N(t)$ is the total population given by $N(t) = Z(t) + Y(t)$. Therefore the total population is given by

$$
\frac{dN(t)}{dt} = (b - \mu)N(t) - \gamma Y(t)
\tag{2.2}
$$

In a real situation, in most countries, the total populations varies. This is because the births are not equal to the deaths ($b \neq \mu$). However, even if $b = \mu$ the population does not remain constat because of increased mortality due to AIDS which is responsible for the term $-\gamma Y(t)$. Therefore we formulate this model for this requirement.

All parameters in the above model are positive and it is simple to show that the system is well posed in the sense that if the initial data $(Z(0), Y(0))$ are in the two dimension positive region, then the solutions will be defined for all $t \geq 0$ and remain in this region.

Due to the fact that the total population varies, it is convenient to work with the proportions of the subgroups in the population. With varying pop-

ulation, steady states are not expected in any parts of the population but they may occur for the proportions, therefore we formulate the model above (2.1) into equations for the proportions. We define $z(t) = Z(t)/N(t)$ and $y(t) = Y(t)/N(t)$ and obtain the following system that describes the dynamics of the proportion of individuals in each class

$$
\begin{aligned}
\frac{dz(t)}{dt} &= b - rz(t)y(t) - bz(t) + \gamma z(t)y(t) \\
\frac{dy(t)}{dt} &= rz(t)y(t) - by(t) - \gamma y(t) + \gamma y^2(t)
\end{aligned}
\tag{2.3}
$$

For which the system (2.3) is positively invariant in the region

$$
D = \{(z, y) : z(t) \geq 0, y(t) \geq 0, z(t) + y(t) = 1\}
$$

It is observed from system (2.3) that the system does not involve the total population $N(t)$ at all, and therefore the behaviour of the proportions can be analyzed without involving $N(t)$.

Note that the population sizes of each class can be obtained from the equation

$$
\frac{dN(t)}{dt} = \{b - \mu - \gamma y(t)\} N(t)
\tag{2.4}
$$

which integrates to

$$
N(t) = N_0 \exp\left\{ (b - \mu)t - \gamma \int_0^t y(t)dt \right\}.
\tag{2.5}
$$

Using the assumption we made above of constant demographical parameters of births and deaths, the variations and dynamics of the total population

are strongly governed by the proportions of those who are infected in the population (see equation (2.5)).

2.2.2 Model Analysis

The analysis of this model seeks to deriving stability conditions of the equilibrium points. Thus, we first define an equilibrium point as follows:

Definition 2.2.1 *Given a system of differential equations $(\dot{\boldsymbol{X}}(t))$, an equilibrium point of this system is a point in the state space for which $\boldsymbol{X}(t) = \boldsymbol{X}^*$ is a solution for all t.*

In the standard approach of calculating the equilibrium points, the derivatives simultaneously need to go to zero. In a variable population where all subpopulations are changing, this is not the case. This approach is not applicable in the system under consideration. However, for the proportions, the derivatives can be zero simultaneously. Thus, we calculate equilibrium points and perform the analysis using the system with proportions.

A threshold factor,

$$\chi = \frac{r}{(b + \gamma)} \tag{2.6}$$

is obtained using the system in equation (2.1) above. It is simply a product of the transmission rate r and $1/(b + \gamma)$. It is a dimensionless quantity that represents the average number of secondary infections caused by an infective individual introduced into a completely susceptible population. Note that χ is a measure of the potential of a disease to spread in a population but

it is not a measure of the rate at which the disease will spread. If $\chi < 1$, the disease cannot successfully invade the host population, and eventually dies out; if $\chi > 1$, however, the disease can invade, therefore producing an epidemic outbreak that in many cases ends up in the establishment of an endemic disease as a steady state in the population.

In the following theorem, we state and prove our result about the equilibrium points.

Theorem 2.2.2 *For $r > \gamma$, the system in (2.3) always has a disease free equilibrium $DFE = (1,0)$ if $\chi < 1$ and a unique endemic equilibrium point $EEP = (z^*, y^*)$ with $z^* = b/(r - \gamma)$ and $y^* = r(\chi - 1)/\chi(r - \gamma)$ exist only if $\chi > 1$.*

Proof. From the second equation of (2.3) with the right hand side equal to zero at the large t, it can be seen that the equilibrium points must satisfy

$$y^* = 0 \tag{2.7}$$

or

$$y^* = \frac{r - (\gamma + b)}{(r - \gamma)} \tag{2.8}$$

if

$$z^* = 1 - y^*. \tag{2.9}$$

Substituting (2.7) and (2.8) in (2.9) or in the first equation in (2.3) with the right hand side equal to zero gives $z^* = 1$ or $z^* = b/(r - \gamma)$ respectively. But (2.6) can be rewritten as $b + \gamma = r/\chi$ and substituting it in (2.8) gives $y^* = r(\chi - 1)/\chi(r - \gamma)$. If $\chi < 1$, then the only equilibrium in the region
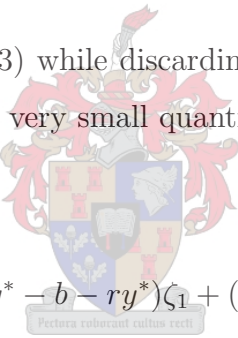
D is $DFE = (1, 0)$; if $\chi > 1$ then the only equilibrium in D is $EEP = (b/(r - \gamma), r(\chi - 1)/\chi(r - \gamma))$. Therefore, the model has only two equilibrium points. $\square$

The local stability of the equilibria of the system in (2.3) is analyzed by linearizing the system through the introduction of small perturbations (ζ_i, $i = 1, 2$) at the equilibrium points as

$$z = z^* + \zeta_1$$

$$y = y^* + \zeta_2$$

and Substituting them in (2.3) while discarding terms of higher order than one (first) since ζ_1 and ζ_2 are very small quantities gives

$$
\begin{aligned}
\frac{d\zeta_1}{dt} &= (\gamma y^* - b - r y^*)\zeta_1 + (\gamma z^* - r z^*)\zeta_2 \\
\frac{d\zeta_2}{dt} &= r y^* \zeta_1 + (r z^* - (b + \gamma) + 2\gamma y^*)\zeta_2
\end{aligned}
\tag{2.10}
$$

under which the coeffients of the perturbations gives the following Jacobian matrix which is then used to study the stability of the equilibria:

$$
J = \begin{bmatrix} \gamma y^* - b - r y^* & \gamma z^* - r z^* \\ r y^* & r z^* - (b + \gamma) + 2\gamma y^* \end{bmatrix}
\tag{2.11}
$$

At the disease free equilibrium, equation (2.11) will have the following characteristic equation:

$$\lambda^2 - (r - 2b - \gamma)\lambda + (b^2 + b\gamma - br) = 0 \tag{2.12}$$

with eigenvalues $\lambda_1 = -b$ and $\lambda_2 = r - (b+\gamma)$. By looking at the eigenvalues, one can easily see that the disease free equilibrium is *stable* if $r < b + \gamma$ for which the two eigenvalues are real and negative under which $\chi < 1$ and *unstable* if $r > b + \gamma$ ($\chi = r/(b+\gamma) > 1$) making the two eigenvalues to be of opposite signs with one solution (λ_1) approaching the equilibrium while the other (λ_2) moving away from the equilibrium point enabling the disease to spread in the population.

Turning to the endemic equilibrium and studying its stability; the Jacobian matrix ($J|_{EEP}$) evaluated at an endemic equilibrium point gives the following characteristic equation:

$$a_2\lambda^2 - a_1\lambda + a_0 = 0 \tag{2.13}$$

with

$$
\begin{aligned}
a_2 &= 1 \tag{2.14}\\
a_1 &= \left\{ \frac{r(\chi-1)}{\chi(r-\gamma)}(3\gamma - r) + \frac{rb}{r-\gamma} - 2b - \gamma \right\} \tag{2.15}\\
a_0 &= \frac{r^2(\chi-1)}{\chi(r-\gamma)} \left\{ \frac{2\gamma^2}{\chi(r-\gamma)} + \gamma + b + br \right\} + b\gamma + b^2 - B \tag{2.16}
\end{aligned}
$$

where

$$B = \left[\frac{r^3(\chi-1)}{\chi(r-\gamma)^2} \left\{ b + \frac{2\gamma(\chi-1)}{\chi} \right\} + \frac{\gamma r(\chi-1)}{\chi(r-\gamma)}(\gamma + 3b) + \frac{rb^2}{r-\gamma} \right]$$

If $\chi > 1$ this implies that $r > \gamma + b$ and therefore we can easily see that the trace, $tr(J|_{EEP}) = a_1 < 0$ since

$$\left\{ \frac{3\gamma r(\chi - 1)}{\chi(r - \gamma)} + \frac{rb}{(r - \gamma)} \right\} < \left\{ \frac{r^2(\chi - 1)}{\chi(r - \gamma)} + 2b + \gamma \right\}$$

and the determinant, $det(J|_{EEP}) = a_0 > 0$ since

$$\left\{ \frac{r^2(\chi - 1)}{\chi(r - \gamma)} \right\} \left\{ \frac{2\gamma^2}{\chi(r - \gamma)} + \gamma + b + br \right\} + b\gamma + b^2 > B,$$

thus by the Routh-Hurwitz criterion, all the eigenvalues have negative real parts and therefore the endemic equilibrium point is *stable*. On the other hand if $\chi < 1$, then $a_1 < 0$ and $a_0 < 0$ while $a_2 > 0$ thus, this makes one of the eigenvalue to have a positive real part. Therefore the endemic equilibrium point is *unstable*

2.3 The simple HIV staged model

The model studied in section (2.2) is extended to include stages of HIV progression of which an infected individual passes through. The infected persons are assumed to undergo a three stage progression of medical states that may be classied on the basis of CD4 cells counts per cubic milliliter as explained in section (2.1).

Lin et al [17] have studied a similar model that involved stages of HIV progression in a general way. This model was analyzed mathematically and some stability conditions under which the equilibrium points are stable were derived. In a similar manner, McCluskey [18] also studied a similar model

but with an extension to include the effect of antiretroviral therapies (ART). Under the use of treatment therapies, an infected individual returns to the previous stages of HIV progression.

Approaching such a problem or a model solely by mathematical analysis, one can face difficulties in understanding the practical part of the disease. It is not possible to know whether the conditions derived in a pure mathematical analysis have meaning or bring sense in respect to the disease in question when it comes to a practical application. For instance, under stability analysis; one can claim the disease to have approached its equilibrium (clearance or persistence). This might happen in some cases after a very long time has elapsed which might however not be relevant to the epidemic and meaningful to the society. With the numerical approach, one is able to observe whether the disease clearance or persistence occurs within a range of time that have meaning in relation to the kind of epidemic studied and be able to evaluate whether the model developed is good or not. We approach the problem from both the mathematical analysis and the numerical simulation of the model side. This makes it different from what has been done before.

2.3.1   The description of the model

In the present model, homogeneity of susceptible individuals $Z(t)$ is assumed again, and also the inflow of individuals from recruitment rate b and outflow due to natural death rate μ is maintained. The infected population is assumed to be subdivided into two subgroups $Y_1(t)$ and $Y_2(t)$ according to different infection stages of the HIV disease such that infected susceptible individuals enter the first subgroup $Y_1(t)$ and then fairly quickly progress from

subgroup $Y_1(t)$ to $Y_2(t)$. The rate of progression from $Y_1(t)$ to $Y_2(t)$ is ρ. This rate is assumed to be a constant that is derived from the time $(1/\rho)$ that an infected individual spends (waiting times) in the primary stage. Perelson et al [7, 8] described the waiting times in the first stage of HIV progression to be of about 2 to 10 weeks. The rate at which infected individuals in $Y_2(t)$ become removed or sexually inactive or uninfectious due to end-stage disease (becoming sick) is γ. Individuals in Subgroup $Y_2(t)$ are said to stay there for a period of 10 to 15 years [7, 8] which sets the value of $1/\gamma$.

The dynamics of the transmission of the HIV epidemic are governed by the following nonlinear system of ordinary differential equations:

$$
\begin{aligned}
\frac{dZ(t)}{dt} &= bN(t) - r_1 \frac{Z(t)Y_1(t)}{N(t)} - r_2 \frac{Z(t)Y_2(t)}{N(t)} - \mu Z(t) \\
\frac{dY_1(t)}{dt} &= r_1 \frac{Z(t)Y_1(t)}{N(t)} + r_2 \frac{Z(t)Y_2(t)}{N(t)} - \mu Y_1(t) - \rho Y_1(t) \quad (2.17) \\
\frac{dY_2(t)}{dt} &= \rho Y_1(t) - \mu Y_2(t) - \gamma Y_2(t)
\end{aligned}
$$

In the model above (2.17), the total active population alive at time t is given by:

$$
N(t) = Z(t) + Y_1(t) + Y_2(t). \quad (2.18)
$$

The parameters r_1 and r_2 determine transmission rates for interactions between the susceptible individuals and infected individuals in Subgroups $Y_1(t)$ and $Y_2(t)$ respectively. In a study done by Quinn et al [4] in Uganda showed that the transmission of the viruses from individuals in the primary stage to the individuals in the susceptible group is higher than those in the later stages, and therefore $r_1 > r_2$.

For convenience in the analysis and for reasons already given in section (2.2), we change the system of differential equations (2.17) above to fractions/proportions of the total population $z(t) = Z(t)/N(t)$, $y_1(t) = Y_1(t)/N(t)$ and $y_2(t) = Y_2(t)/N(t)$ in the susceptible and infectious classes respectively. We have a variable population size, and the relations are:

$$
\begin{aligned}
\frac{dz(t)}{dt} &= \frac{1}{N(t)} \left[\frac{dZ(t)}{dt} - z(t)\frac{dN(t)}{dt} \right] \\
\frac{dy_1(t)}{dt} &= \frac{1}{N(t)} \left[\frac{dY_1(t)}{dt} - y_1(t)\frac{dN(t)}{dt} \right] \\
\frac{dy_2(t)}{dt} &= \frac{1}{N(t)} \left[\frac{dY_2(t)}{dt} - y_2(t)\frac{dN(t)}{dt} \right]
\end{aligned}
\tag{2.19}
$$

where

$$
\frac{dN(t)}{dt} = \{b - \mu - \gamma y_2\} N(t)
\tag{2.20}
$$

integrating to

$$
N(t) = N_0 \exp \left\{ (b - \mu)t - \gamma \int_0^t y_2(t)dt \right\}.
\tag{2.21}
$$

The dynamic behaviour of the total population in this model is mainly governed by the group of people who are in the asymptomatic stage of HIV infection $(y_2(t))$. This is because it is only in this group that people die of AIDS which is signified by the higher death rate γ.

Having done some algebra the proportions of the Subpopulations are:

$$
\begin{aligned}
\frac{dz(t)}{dt} &= b - r_1 z(t) y_1(t) - r_2 z(t) y_2(t) - \mu z(t) - z(t)(b - \mu - \gamma y_2(t)) \\
\frac{dy_1(t)}{dt} &= r_1 z(t) y_1(t) + r_2 z(t) y_2(t) - (\rho + \mu) y_1(t) - y_1(t)(b - \mu - \gamma y_2(t)) \\
\frac{dy_2(t)}{dt} &= \rho y_1(t) - (\gamma + \mu) y_2(t) - y_2(t)(b - \mu - \gamma y_2(t))
\end{aligned}
\tag{2.22}
$$

with

$$
z(t) + y_1(t) + y_2(t) = 1 \tag{2.23}
$$

The above system of equations (2.22) have a feasible region which is positively invariant given by:

$$
U = \{(z(t), y_1(t), y_2(t)) : \ z(t) \geq 0, y_1(t) \geq 0, y_2(t) \geq 0, z(t) + y_1(t) + y_2(t) = 1\}
\tag{2.24}
$$

with all parameters being positive.

Using the model we study here, one can simply measure both the incidence and the prevalence of the disease. We define the incidence of the disease as the proportion of new cases occurring in a population during a defined time interval. We calculate it as follows:

$$
I = \frac{y_1(t)}{\langle t \rangle} \tag{2.25}
$$

with I being the incidence and $\langle t \rangle$ is the average time spent in the primary stage defined as

$$\langle t \rangle = \frac{\int_0^\infty t \exp\left(-(\rho + \mu)t\right)dt}{\int_0^\infty \exp\left(-(\rho + \mu)t\right)dt} \qquad (2.26)$$

We also define the prevalence as the proportion of infectives in a population. While the prevalence is given by $y_1 + y_2$, one can easily assume that the prevalence is y_2 because the time spent by newly infected individuals in the primary stage is so short.

2.3.2 Analysis of the model

This model has two infective groups. We determine the threshold quantity of this model using the Next-generation technique as presented by Van Den Driessche [19] for compartmental models especially those with several infected groups as shown in Appendix A.

The spectral radius of equation (A.6) is the maximum value of the eigenvalues which gives the effective threshold quantity of the model as:

$$\chi = \frac{r_1}{(\rho + b)} + \left\{\frac{\rho}{\rho + b}\right\}\frac{r_2}{(\gamma + b)} \qquad (2.27)$$

In this case, the threshold quantity of the model χ is a linear combination of the threshold quantity of the Subgroups of the infected individuals in the primary stage, $R_{y_1} = r_1/(\rho + b)$ and in the asymptomatic stage, $R_{y_2} = r_2/(\gamma + b)$ of the disease progression. A factor $\kappa = \rho/(\rho + b)$ can be defined as the probability that an infective individual will leave the primary stage of infection and enter the next stage of the asymptomatic infection.

Because of variable population size, system (2.22) is more complicated for calculating the equilibrium points especially the endemic equilibrium. Therefore a different approach from the standard method is used under which the dynamic behaviour of the population size (equation (2.21)) is considered. But, before we do this, our first result is a theorem concerned with the existence of this equilibrium. For this, we use our threshold obtained in equation (2.27). (Our proof to this theorem is similar to the one given by Lin et al [17]). Therefore, we start with the following definition:

Definition 2.3.1 *If as* $t \to \infty$ *an equilibrium is reached, we can define the equilibrium values as* $y_2(t) \to y_2^*$, $y_1(t) \to y_1^*$, *and* $z(t) \to z^*$.

Theorem 2.3.2 *The system in (2.22) has a unique endemic equilibrium point if the threshold quantity* $\chi > 1$ *and a disease free equilibrium otherwise.*
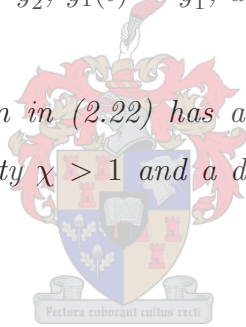
Proof. When the equilibrium is attained, the right hand side of system (2.22) become equal to zero. Using the third equation of equation (2.22) we obtain

$$y_1^* = \frac{(\gamma + b - \gamma y_2^*)y_2^*}{\rho}. \tag{2.28}$$

Substituting (2.28) in the second equation in (2.22) with (2.23) gives:

$$a_0 y_2^{*4} + a_1 y_2^{*3} + a_2 y_2^{*2} + a_3 y_2^* = 0 \tag{2.29}$$

where

$$a_0 = -\gamma^2 r_1$$

$$a_1 = -(2\gamma r_1(\gamma + b) - r_1\rho\gamma - r_2\rho\gamma + \gamma^2\rho)$$

$$a_2 = -(r_1\rho\gamma + r_1(\gamma + b)^2 + r_1\rho(\gamma + b) + r_2\rho(\gamma + b) + r_2\rho^2 - \gamma\rho(\rho + b) - \gamma\rho(\gamma + b))$$

$$a_3 = \rho(\rho + b)(\gamma + b)[\chi - 1] \tag{2.30}$$

Equation (2.29) gives $y_2^* = 0$ always.

If $y_2^* \neq 0$, then (2.29) becomes

$$F(y_2^*) = a_0 y_2^{*3} + a_1 y_2^{*2} + a_2 y_2^* + a_3 = 0 \tag{2.31}$$

But we know that $y_2^* \in (0,1)$, thus $F(0) = \rho(\rho + b)(\gamma + b)[\chi - 1]$ and $F(1) = r_2\rho\gamma - \gamma^2(r_1 + \rho) - (\gamma + b)^2(\rho + b)\left[\chi + \frac{\rho}{\gamma + b}\right]$. If $\chi < 1$ then $F(0) < 0$ & $F(1) < 0$; if $\chi > 1$ then $F(0) > 0$ & $F(1) < 0$. But also, $F'(y_2^*) < 0$ since $a_0 < 0$, $a_1 < 0$, and $a_2 < 0$ which makes the end points $F'(0) < 0$ and $F'(1) < 0$ for $0 \leq y_2^* \leq 1$. Thus, this shows that $F(y_2^*)$ is a decreasing function. Therefore, there is a unique root y_2^* which accounts for the endemic equilibrium when $\chi > 1$ and a disease free equilibrium otherwise. $\square$

If the system approaches a disease free equilibrium, then $\int_0^t y_2(t)dt \to c_0$ (constant) asymptotically and the total population in equation (2.21) change according to

$$N(t) = N_0 e^{(b-\mu)t} e^{-\gamma c_0} \tag{2.32}$$

But in this case, $c_0 = 0$. Therefore, if $b - \mu < 0$, then $N(t)$ decays asymptotically exponentially, $N(t)$ remains constant if $b - \mu = 0$, and grows asymp-

totically exponentially if $b - \mu > 0$. Thus, since $y_2(t) \to 0$ asymptotically, then from the third equation in (2.22), $y_1(t) \to 0$ asymptotically and also by (2.23) and (2.24), $z(t) \to 1$ asymptotically. Therefore, by 2.3.1, the disease free equilibrium $P_0 = (z^*, y_1^*, y_2^*) = (1, 0, 0)$.

If the system approaches the endemic equilibrium as it is proved in theorem 2.3.2, then $\int_0^t y_2(t) dt \to c_1 + y_2^* t$ asymptotically with $c_1 = \int_0^T y_2(t) dt - y_2^* T$ therefore from (2.21) we have

$$N(t) = N_0^* e^{ct} \tag{2.33}$$

where $N_0^* = N_0 e^{c_1}$ and

$$c = b - \mu - \gamma y_2^* \tag{2.34}$$

$N(t)$ decays asymptotically exponentially if $c < 0$, remains constant if $c = 0$ and grows asymptotically exponentially if $c > 0$. Since $0 < y_2^* < 1$, then c ranges from $b - \mu - \gamma$ when $y_2^* \to 1$ to $b - \mu$ when $y_2^* \to 0$ (i.e $c = (b - \mu - \gamma, b - \mu)$).

From (2.34), we obtain $y_2^* = (b - \mu - c)/\gamma$ and Substituting this in the third equation in (2.22) we have $y_1^* = (\mu + \gamma + c)(b - \mu - c)/\gamma\rho$. By (2.23), $z^* = \gamma\rho - (\mu + \gamma + c - \rho)(b - \mu - c)/\gamma\rho$ which gives the endemic equilibrium $P_e = (z^*, y_1^*, y_2^*)$.

To analyze the stability of the equilibria, we establish a Jacobian matrix J and employ the Routh-Hurwitz technique to study the local stability of the equilibria. The Jacobian matrix of the system (2.22) is as follows:

$$J = \begin{bmatrix} -b - r_1 y_1^* - r_2 y_2^* + \gamma y_2^* & -r_1 z^* & (\gamma - r_2) z^* \\ r_1 y_1^* + r_2 y_2^* & r_1 z^* - (\rho + b) + \gamma y_2^* & r_2 z^* + \gamma y_1^* \\ 0 & \rho & -(\gamma + b) + 2\gamma y_2^* \end{bmatrix} \quad (2.35)$$

At the disease free equilibrium P_0, (2.35) becomes

$$J|_{(P_0)} = \begin{bmatrix} -b & -r_1 & (\gamma - r_2) \\ 0 & r_1 - (\rho + b) & r_2 \\ 0 & \rho & -(\gamma + b) \end{bmatrix} \quad (2.36)$$

From the matrix in (2.36), we find that $\lambda_1 = -b$ and the rest of the eigenvalues λ_2 and λ_3 are obtained from

$$\begin{vmatrix} r_1 - (\rho + b) - \lambda & r_2 \\ \rho & -(\gamma + b) - \lambda \end{vmatrix} \quad (2.37)$$

which gives a characteristic equation

$$\lambda^2 - (r_1 - 2b - \rho - \gamma)\lambda + (\gamma + b)(\rho + b)\{1 - \chi\} = 0 \quad (2.38)$$

The roots of the characteristic equation above give the other two eigenvalues

$$\lambda_{2,3} = \frac{1}{2}\left\{(r_1 - 2b - \rho - \gamma) \pm \sqrt{(r_1 - 2b - \rho - \gamma)^2 - 4([(\gamma + b)(\rho + b)\{1 - \chi\}]}\right\}$$

of the Jacobian matrix obtained at the disease free equilibrium.

Clearly we see from the eigenvalues that $\lambda_1 < 0$ always, and if $\chi < 1$ then $\lambda_{2,3} < 0$, therefore the disease free equilibrium is *stable*. If $\chi > 1$, then either one or both $\lambda_{2,3} > 0$ and the disease free equilibrium is *unstable*. This is true because $\chi > 1$ allows the disease to spread in the population. If the disease free equilibrium could be stable, then the endemic equilibrium could not exist because the epidemic would die out before spreading in the entire population.

We study the stability of the endemic equilibrium point by linearizing our system around P_e to obtain the following characteristic equation:

$$a_0\lambda^3 - a_1\lambda^2 - a_2\lambda - a_3 = 0 \tag{2.39}$$

where

$$
\begin{aligned}
a_0 &= 1 \\
a_1 &= a + d + g \\
a_2 &= c_a b_1 + \rho f - g(d + a) - ad \\
a_3 &= g(ad - bc_a) + \rho(be - af)
\end{aligned}
$$

with $a = (\gamma - r_2)y_2^* - r_1 y_1^* - b$, $b_1 = r_1 y_1^* + r_2 y_2^*$, $c_a = -r_1 z^*$, $d = r_1 z^* + \gamma y_2^* - (\rho + b)$, $e = (\gamma - r_2)z^*$, $f = r_2 z^* + \gamma y_1^*$, and $g = 2\gamma y_2^* - (\gamma + b)$. Since all model parameters are positive, then it is clear that $c_a < 0$, $b_1 < 0$, $d < 0$, and $f > 0$. But also if $\gamma < r_2$ the condition that makes $\chi > 1$, then, $a < 0$, $g > 0$, and $e < 0$. Under these conditions, $a_1 < 0$, $a_2 < 0$, and $a_3 < 0$ with a_0 being always positive. By the Routh-Hurwitz criteria and the Descartes rule of signs, the characteristic equation in (2.39) has roots with only negative real parts and hence the endemic equilibrium point P_e is *stable*. If $\gamma > r_2$,

then $a > 0$, $g < 0$, and $e > 0$ and therefore, the endemic equilibrium point is *unstable*.

2.4 Numerical simulation

2.4.1 Parameter values

We split the exit rate from the population into two parts; the natural death rate, μ and the increased mortality due to AIDS, γ. We derive the values of μ from the life expectancy $1/\mu$ of people in a given country. In Sub-Saharan Africa for example, majority of the young adults are expected to live an average of 50 years [20]. Thus $\mu = 0.02$ years^{-1} with the birth rate being $b = 0.03$ on average for a general case might be suitable. Some cases where AIDS has already shown its impact, for example Swaziland for which $b = \mu = 0.02$; Botswana and Zambia where there are higher mortality rates than birth rates ($b = 0.02$ and $\mu = 0.03$) are ignored, as the rates are due to AIDS.

The survival times of a HIV/AIDS infected individual depends on factors like gender, vaccination and treatment, poverty and wealth, nutrition, biological make up and the region where the person lives. In Sub-Saharan Africa, a region where the large majority of HIV infections are spread heterosexually and the epidemic is more mature, there is a substantial difference in age of infection between men and women, with women becoming infected at an earlier age [21, 22, 23]. Furthermore, an approximate of 9.4 years survival time for women and 8.6 years for men [24] has been estimated by the UNAIDS. Vaccination and treatment of infected persons has also shown to cause a de-

lay in developing AIDS through reduction of the number of copies of viruses in the body [25]. This has led to an increase of survival rates of HIV positive individuals.

Perelson et al [7, 8] has shown that an infected individual stays in the asymptomatic stage of HIV progression before developing AIDS for about 10 to 15 years. In the AIDS stage an infected individual remains only for a period of about 1 to 2 years, as it has been revealed from the Rakai study [5]. So this confirms that the survival period of a HIV infected person can be less or more than 10 years.

Understanding how infectious a person can be when infected, and estimating the rate at which this person is able to transmit HIV to others, has been difficult in the scientific community since one can not perform experiments. Rapatski et al [6] using data from studies which were carried out in the Gay community in San Francisco City in the USA has shown using mathematical models (finding the best fit to data) that transmission rate of the viruses by stage differs when an infected individual progresses from one stage to another. The findings from the model showed that infected persons in the primary stage are 12 times more likely to infect the susceptible than those in the asymptomatic stage.

On the other hand, in communities such as Sub-Saharan Africa where heterosexual transmission is the main mode of HIV transmission, a Rakai study by Wawer et al [5] and Quinn et al [4] presented the analysis which provides the first empirical data on the substantial variation in transmission by stage of HIV infection after seroconversion. The study also showed that the rate of HIV transmission within the first two and a half months was almost 12 times higher than that observed in chronic couples. This presents observed

evidence that the HIV transmission rate for those individuals in the primary stage of HIV progression (r_1) is higher than that of individuals in the asymptomatic stage (r_2).

The transmission rate, r as used in the simple model is estimated using the second equation in (2.3) at the steady state as

$$r = \frac{b + \gamma - \gamma y^*}{1 - y^*} \tag{2.40}$$

where y^* is the endemic equilibrium state of infections which can take any value in the interval $(0, 1)$. The minimum value that r can take is $b + \gamma$ when $y^* \to 0$ and if $y^* \to 1$ then $r \to \infty$. Therefore, our model shows that r can take any value in $(b + \gamma, \infty)$.

According to our staged model, r_1 can be calculated as a function of y_2^*. Writing equation two in (2.22) at the steady state in terms of y_2^* with $r_2 = r_1/12$ gives

$$r_1 = \frac{(b + \rho - \gamma y_2^*)\Phi}{\{1 - (\Phi + 1)y_2^*\}\Phi + \{1 - (\Phi + 1)y_2^*\}/12} \tag{2.41}$$

with $\Phi = (\mu + \gamma + c)/\rho$ and c given by equation (2.34).

As the rate at which individuals become infected is increased, the prevalence level y^*, y_2^* at the steady state also increases (figure 2.2(a and b)). This tells us that a careful fitting of parameters r, r_1 and r_2 is required when using mathematical models to explain some biological systems such as population and the effect of HIV/AIDS. We also find that if the rates at which people become infected are at their minimum values, the models show a disease
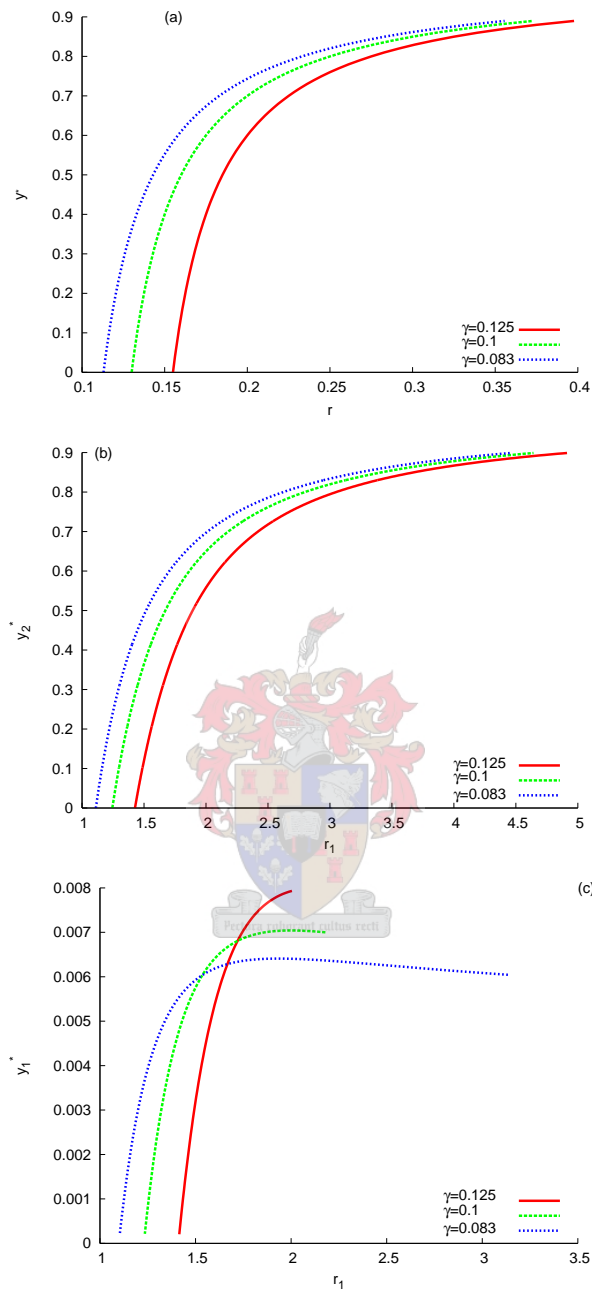
Figure 2.2: *A relationship between the transmission rate to the equilibrium value for (a) y^* (b) y_2^* in the interval $(0, 1)$ and (c) y_1^* with $c \in (-0.08, 0.01)$ with varying γyear^{-1}. Other parameters: $b = 0.03$, $\rho = 6.0$year^{-1} and $\mu = 0.02$*

clearance (i.e. $y^* = 0$, $y_2^* = 0$) and the quantity χ become equal to one. According to our models, a disease persists in the population if the transmission rates are above their minimum values. The rate at which infected individuals die due to AIDS is found to have an effect in the the equilibrium proportions. As γ is increased, more infected people die before the equilibrium is attained leading to low levels of y^* and y_2^*. It has also been found that y_1^* increases with r_1 to a peak value after which it decreases to b/ρ (figure 2.2(c)). For different values of the AIDS induced mortality, y_1^* is shown to increase as γ is decreased. This is due to the fact that the survival period of infected individuals is increased.

2.4.2   Effect of transmission rates in HIV estimation

When modelling, one has to be specific about the group of people in the society for which the HIV prevalence estimation is to be done. General models might lead to missunderstanding about the spread of the disease in a general population. The results shown in figure 2.3 give clear evidence on how difficult it can be to obtain quality information if one is to estimate the impact of HIV in a given community.

As the rate of transmitting HIV is increased, the proportion of the infected group rise more quickly. The increase in the transmission rates is also found to increase χ in both models. For example, in the simple model as r is increased from 0.167 to 0.5, χ increased from 1.28 to 3.85. In the staged model, as r_1 was increased from 2.0 to 6.0, r_2 from 0.167 to 0.5, χ also was found to increase from 1.61 to 4.82. Therefore, rates of transmitting the disease has an impact on the spread and estimations as the potential measure

of the disease growth (χ) has shown.

The proportions of infected individuals remain high over time after the initial rise (figure 2.3(b) and 2.3(c)) and a different behaviour of new infections is also shown (figure 2.3(a)). As shown, the peak occurs at high and low transmission rates, and the proportion then drops back to a non-zero value.

However, in the epidemiology of HIV, a disease that spreads quickly, we do not expect the peak incidence to occur after a very long period of time. Our results show that when r_1 is reduced to 2 and r_2 to 0.167, the curve for new infections peak can occur after a very long time has passed (2.3(a)). This kind of dynamic behaviour is possible in some groups of people with low risk behaviour under which the rate of disease acquisition is low.

Generally, the results obtained in this section have been representative of some section of a given population. In some populations, the disease has shown a very high impact with prevalence curves being high and incidence having a peak at short time, while in other cases the impact of the disease is low. In such a case, one has to avoid generalization of results to a general population, since they may lead to overestimation or underestimation.

2.4.3 Mortality effect in the spread of the epidemic

Since the number of infections depend on the number of susceptibles which an infected individual is able to infect, it is important to investigate the effect of survival time. Figure 2.4 show the effect caused by the change in AIDS mortality. As the death rate is increased, that is, as the survival period is lowered, the proportion of infected individuals increases slowly. The increase
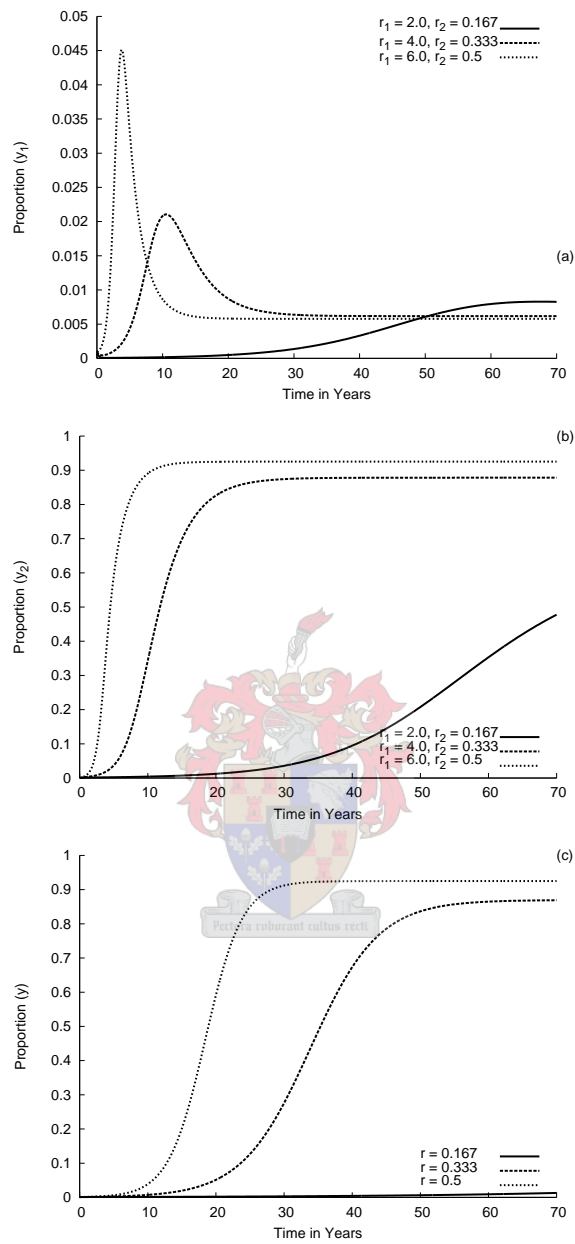
Figure 2.3: *Transmission effect for (a) proportion of new infections (b) Prevalence in the staged model and (c) Prevalence in the simple model. Parameters: $b = 0.03$, $\gamma = 0.1\text{year}^{-1}$, $\rho = 6.0\text{year}^{-1}$, $\mu = 0.02$ at $r_1 = 6.0$, 4.0 and 2.0, and $r_2 = r = 0.5$, 0.33 and 0.167.*

in HIV infection is low because more people are dying and therefore these have a small impact as compared to the case the AIDS mortality rates are low. AIDS mortality can be lowered by treating HIV infected individuals.

In the developed countries and in some developing countries, including those of Sub-Saharan Africa, the drug zidovudine (AZT) and other treatment combinations have suppressed the intensity of HIV development in the patients body and thus prolonged the incubation[2] period, for those who can afford the treatment. The prolonging patients incubation period is good in the sense that an individual lives longer and continues to serve the nation, but at the same time, it is expensive for both the individual as well as the nation. However, there is a danger that such patients can infect many individuals in a more destructive way as they can practice sexual activities, which can be a disadvantage for the society. The threshold quantity, χ proves in this regard that as the incubation period of an infected individual is increased by any means, the number of secondary infections also increases. For example, when the average infected person is to survive for 8 years ($\gamma = 0.125$ year^{-1}), 10 years ($\gamma = 0.1$year^{-1}) or 12 years ($\gamma = 0.08$year^{-1}); then χ have to be 2.13, 2.54 or 3.0 respectively.

Figure 2.4(a) shows a different kind of results. In the early stage of the epidemic, the proportion of new infection curves show very similar rise during this period. A switch between the curves occurs at the peak value and the difference between the curves becomes large and observable during the mature stage of the epidemic. At large t, lowering γ (increasing survival time of infected people) causes no more infections.

[2]An incubation period is defined as a period from HIV infection to AIDS development.
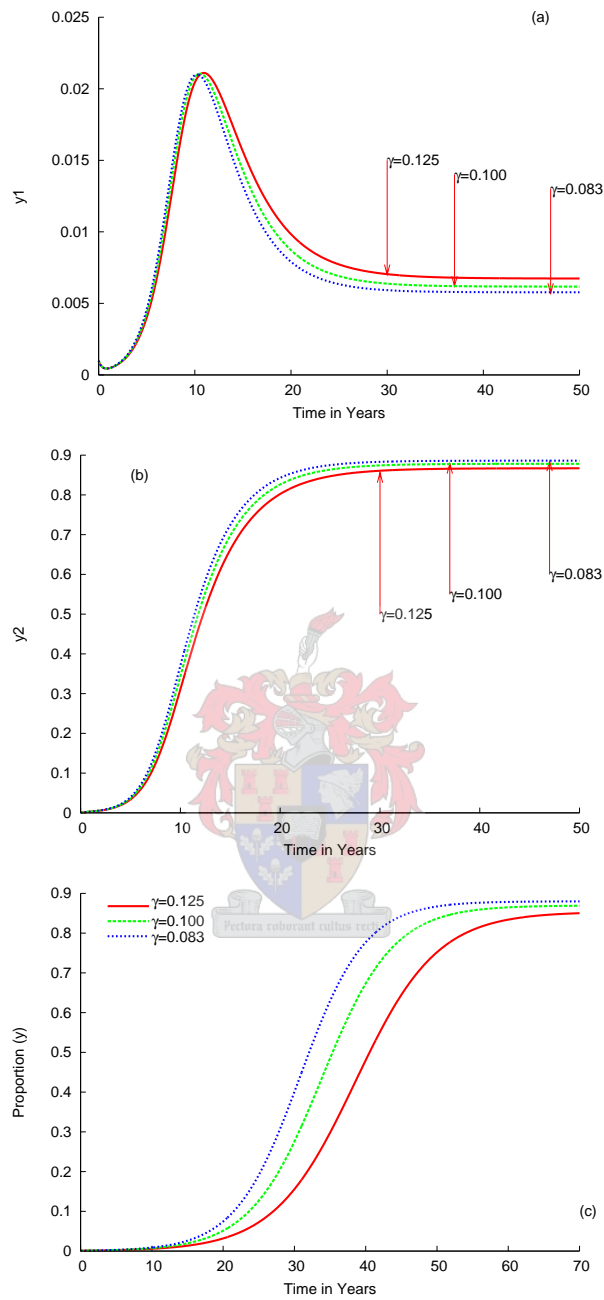
Figure 2.4: *Mortality effect for (a) proportion of new infections (b) Prevalence in the staged model and (c) Prevalence in the simple model. Parameters:* $b = 0.03$, $\rho = 6.0 \text{year}^{-1}$, $r_1 = 4.0$, $r_2 = r = 0.33$, $\mu = 0.02$ *at* $\gamma = 0.08$, 0.1 *and* 0.125 *year*$^{-1}$

2.4.4 The impact of stages in HIV predictions

To illustrate the effect of stages in this situation, we compare the results obtained from the two models. We address the question: is it necessary to incorporate stages of disease progression when modelling the spread of HIV/AIDS? Particularly, we are interested in understanding whether the inclusion of stages has or hasn't an effect on the overall infection and progression of the epidemic in the population as well as on estimation of future trend. If this does not have any effect, then extending the model to incorporate stages of progression is not an important factor and therefore modelling while considering a single group of infected individuals is a better and simpler way to understand the pattern of the epidemic and can produce quality information on the disease. If the effect exists, then a careful choice of the model is a good idea for modellers.

In comparing the two models, we run simulations by varying the transmission rates to find out whether there exist a value for r different from r_2 such that the results for the staged model are reproduced. We found no value for r that gives the above property. In all simulation trials performed, stages showed a large impact at low t while the single stage model had its impact at very large t. This made it difficult to fit the results from the two models. However, it was possible to fit the results from the two model for lower t than for large t.

As y_2 is as large as y because individuals in y_1 progress to y_2 within a very short period of time, we further considered the case where $r = r_2$ to find out more difference on the two models during a short term. The results for this case are shown in (figure 2.5). The results showed a clear difference in the prevalence, AIDS mortality rate curves and the total population (figure

2.5(a, c and d)). It was found that, the prevalence of infected individuals is high for the simple staged model and low for the model with a single group of infected individuals. y_2 rises highly just after the epidemic starts to exist in the population. For this example, we also found that the effective thresholds for the two models are different being high for the staged model ($\chi = 2.41$) and low for the model with a single group of infected people ($\chi = 1.92$). This difference may be due to the contribution by the primary stage shown in (figure 2.5(b)) because individuals in this stage are found to have a high amount of viruses in the bloodstream which makes the transmission of the HIV easier to others [4, 5, 8, 7].

Due to high prevalence of infected individuals, the AIDS mortality rates are also high (figure 2.5(c)). The difference in the AIDS mortality curves for the two models have a similar trend to that found in the prevalence curves. This has been due to the disease increased mortality being proportional to the prevalence levels of infected persons. As peoples' death affects the total population, the impact of the epidemic is found to be different for the populations of the two models. The population for the simple staged model experiences a mortality impact earlier than the total population for the simple model (figure 2.5(d)).

2.5 Summary and Conclusion

In this chapter, we formulated and explored two simple models for the spread of the HIV epidemic one of which incorporated stages of HIV progression of an infected individual. The local analysis of these models are performed and numerical simulation examples are also performed to understand some
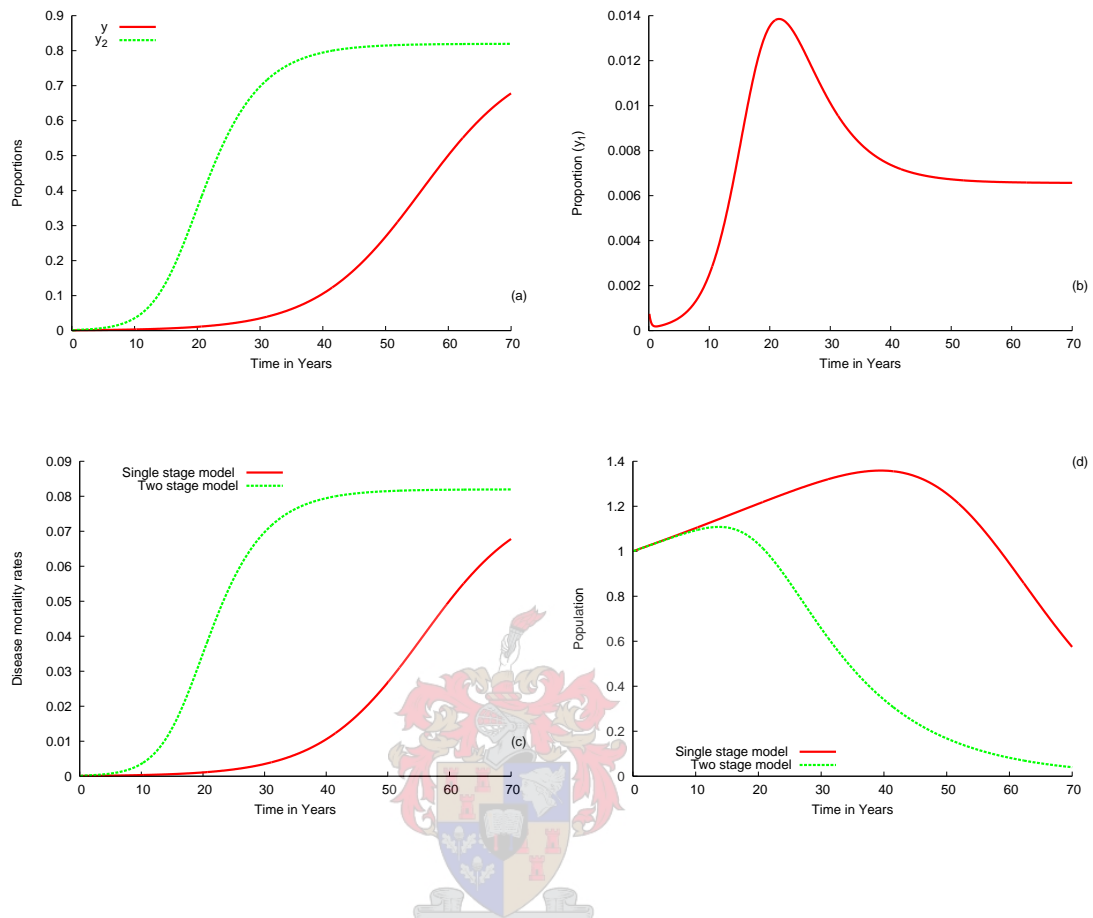
Figure 2.5: *A comparison between the simple HIV model and the staged model for (a) Prevalence, (b) proportion of new infections, (c) AIDS mortality rates, and (d) Total population at $r_1 = 3.0$, $r_2 = r = 0.25$, $\rho = 6.0$, $\gamma = 0.1$, $\mu = 0.02$ and $b = 0.03$*

demographical and epidemiological dynamical behaviour. A comparison for these models is also carried out to reveal the effect of introducing stages of HIV progression.

We analyzed the effect of varying the two main parameters, the rates of transmitting the disease r, r_1, r_2 and the disease caused death rate (γ). The findings show that the rate of transmitting the viruses is the driving force

in the spread of the disease while the disease death rate has little impact in general.

Apart from the results found to be general for both models, there are some specific findings shown by the staged model. When r_1 and r_2 are varied, a switch between the new infection curves is found to occur at large t. This is an interesting result which needs careful attention when dealing with disease incidence and transmission rate. One can easily draw different conclusions on the relation between the transmission rate and the persistence of new infections.

From the explorations, it was found that the majority of the infectives do not spread the disease during its early stage (figure 2.5(a)). Instead, individuals in the primary stage play a major role in transmitting the viruses. If this group could somehow be identified and convinced to refrain from risky behaviours, at least while they are highly infectious, the impact of the epidemic could perhaps be reduced.
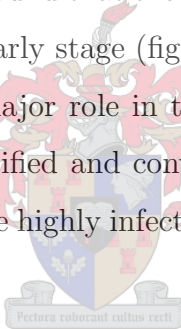
The results from the models gave the expected trend or behaviour of HIV/AIDS. Since the models were formulated without considering all important factors for the spread of HIV and simulated not by fitting parameters to any existing data, we could not expect to obtain results which are consistent with reality. But in general, stages showed a large impact in the overall results. It is therefore important to use this approach (incorporating stages) when modelling the spread of the HIV.

Delayed death in HIV spread models

HIV infected patients survive for some years after they have acquired the disease. The disease does not kill immediately, it takes some time before weakening the immune system although the viruses replicate[1] quickly in the human body. An infected person has a long time to transmit the viruses to other people. In such a case, a disease is to spread within the human population and therefore cause some other unexpected dynamical behaviour. Due to the emergence of several efforts in preventing and treating HIV patients, treatment - drugs have been developed and they played an important role in reducing HIV/AIDS - related mortality in industrialized countries as well as for those who have access to them in resource poor settings. The increase in the life expectancy of an infected individual has been due to the sustained

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[1]reproduction and generation of new viruses

reduction of viral reproduction by these drugs, which improves immune function and prolongs AIDS - free survival. With this motivation, this chapter investigates the effects that may arise in estimating the impact of HIV using mathematical models. We do this by studying a model that takes into account a constant time delay in the occurrence of AIDS death by assuming an equal survival period in all infected individuals in any setting.
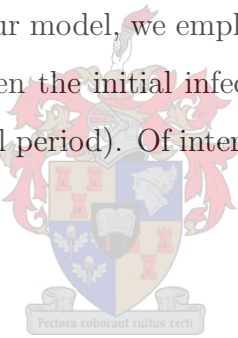
3.1 Introduction

Mathematical models of the spread of HIV/AIDS used for predictions are constrained by the differences in survival times that exist between HIV infected individuals. These differences are due to genetic heterogeneity, socio-economic aspects of life and geographical locations. The development of treatment interventions has also increased the differences in HIV survival among people in developed countries and in developing nations. As there has been no common survival time for all HIV infected individuals, the modelling approach on AIDS death has become more difficult to carry out.

The Weibull distribution has been commonly used as an incubation distribution [26, 27]. A similar distribution is used to explain the survival probabilities of HIV infected individuals [28, 24] under which this probability decreases as one progresses from HIV infection to death. This distribution is found to have a good fit to data in a short term. Due to the introduction of an effective antiretroviral therapy (ART), the incubation period defined with approximately parameterized Weibull distribution could form a different shape in a long term.

Although it has been difficult to estimate the HIV survival period, HIV/AIDS models have been studied by several authors [29, 30, 11]. Most of which have assumed an exponential distribution of the infectious period. This assumption is equivalent to assuming that the chance of dying of AIDS within a given time interval is constant, regardless of time since infection. In the present chapter we consider the opposite case. The case where all infected individuals have the same survival period, and after this time has lapsed an individual must die. Doing this, a step functional behaviour of HIV survival is considered through the introduction of a single and constant time delay in the occurrence of AIDS death.

In the course of developing our model, we employ a delay to mathematically represent the time lag between the initial infection and the death of an infected individual (i.e. survival period). Of interest are delay equations of the form:

$$\frac{du(t)}{dt} = F(u(t), u(t - \tau))$$ (3.1)

where $\tau > 0$ is the time delay with an initial condition being a function defined in the interval $[-\tau, 0]$.

The application of delay equations has been carried out by many other authors especially in population studies and epidemiology [31, 14], with application to HIV spread models [10, 15, 32]. Among the deficiencies of the models we studied in the second chapter is that we considered the entire population. In models which consider only the sexually active population, the recruitment rate into the adult population can not be considered to act instantaneously as there is a time delay to take into account the time to

adulthood. In such cases, some authors have considered this time delay that determine the maturation of individuals moving from childhood to adulthood and or age structure in populations [33, 24, 34]. This time delay in HIV/AIDS spread models is mostly considered to be 14 or 15 years that represent the number of years for an individual to be considered an adult in a sexually active population.

In this chapter, we further extend the deterministic model with stages of HIV progression studied in chapter 2 to include a time delay in the occurrence of AIDS death of HIV infected individuals. As it has been known that HIV infected individuals do not die immediately after they are infected, they survive for a given period of time. We devote this chapter to the investigation of the question: Does it matter to have a delay in AIDS mortality; what effect does this have?

3.2 Model derivation

Since the infected class is divided into two subclasses; those in the primary stage $Y_1(t)$ and those in the asymptomatic stage $Y_2(t)$ as it has been described in chapter 2, the mortality increase due to the disease occurs in $Y_2(t)$. Assuming τ to be the expected period for an infected individual to survive which in the present study is assumed to be constant for all infected individuals, then $Y_2(t)$ can be redefined as an integral as follows:

$$Y_2(t) = \rho \int_0^t Y_1(s)e^{-\mu(t-s)}\theta(s - (t - \tau))ds \tag{3.2}$$

The integral is the summation of all individuals who got infected and en-

tered Y_1 at time $s \geq 0$ and have remained infective through to time t. The term $e^{-\mu(t-s)}$ is the survivor probability of infected individuals from causes other than HIV/AIDS. These individuals became infected at time s and have survived to time t. Our step function $\theta(x)$ is defined as follows:

$$\theta(x) = \begin{cases} 1 & \text{if } x \geq 0 \\ 0 & \text{if } x < 0 \end{cases} \tag{3.3}$$

The integral in equation (3.2) when differentiated under (3.3) is equivalent to the delay differential equation (DDE)

$$\frac{dY_2(t)}{dt} = \rho Y_1(t) - \mu Y_2(t) - \rho Y_1(t - \tau)e^{-\tau\mu} \tag{3.4}$$

which describes the dynamics of the group of individuals in the asymptomatic stage.
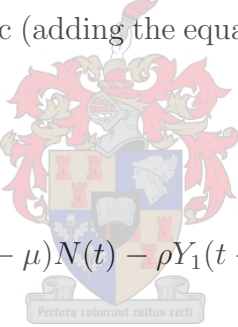
The term $\rho Y_1(t - \tau)e^{-\tau\mu}$ represents the number of individuals who were infected τ years ago and have survived from natural death and are currently dying of AIDS. Note that these individuals are in the asymptomatic stage of HIV progression.

Therefore, the dynamics of the disease in the population with a time delay in the AIDS death changes according to the system of nonlinear differential equations below:

$$\frac{dZ(t)}{dt} = bN(t) - r_1\frac{Z(t)Y_1(t)}{N(t)} - r_2\frac{Z(t)Y_2(t)}{N(t)} - \mu Z(t)$$

$$\frac{dY_1(t)}{dt} = r_1\frac{Z(t)Y_1(t)}{N(t)} + r_2\frac{Z(t)Y_2(t)}{N(t)} - \mu Y_1(t) - \rho Y_1(t) \qquad (3.5)$$

$$\frac{dY_2(t)}{dt} = \rho Y_1(t) - \mu Y_2(t) - \rho Y_1(t-\tau)e^{-\tau\mu}$$

where $N(t)$ is the population size at time t given by $Z(t) + Y_1(t) + Y_2(t)$. Note that all parameter and variable definitions in this model stay similar to those in the previous chapters.

The total population changes exponentially in the absence of the disease, and in the presence of the epidemic (adding the equations in (3.5)) the population changes according to

$$\frac{dN(t)}{dt} = (b - \mu)N(t) - \rho Y_1(t-\tau)e^{-\tau\mu} \qquad (3.6)$$

In terms of proportions; $z(t) = Z(t)/N(t)$, $y_1(t) = Y_1(t)/N(t)$, and $y_2(t) = Y_2(t)/N(t)$, the system in (3.5) gives

$$\frac{dz(t)}{dt} = b - bz(t) - r_1z(t)y_1(t) - r_2z(t)y_2(t) + \rho e^{-\tau\mu}z(t)y_1(t-\tau)\alpha(t) \quad (3.7)$$

$$\frac{dy_1(t)}{dt} = r_1z(t)y_1(t) + r_2z(t)y_2(t) - (\rho + b)y_1(t) + \rho e^{-\tau\mu}y_1(t)y_1(t-\tau)\alpha(t)$$

$$\frac{dy_2(t)}{dt} = \rho y_1(t) - by_2(t) - \rho e^{-\tau\mu}y_1(t-\tau)\alpha(t) + \rho e^{-\tau\mu}y_1(t-\tau)y_2(t)\alpha(t)$$

with

$$y_1(t-\tau) = \frac{Y_1(t-\tau)}{N(t-\tau)} \qquad (3.8)$$

and

$$\alpha(t) = \frac{N(t-\tau)}{N(t)}. \tag{3.9}$$

Equation (3.6) also becomes

$$\frac{dN(t)}{dt} = \left\{b - \mu - \rho e^{-\tau\mu} y_1(t-\tau)\alpha(t)\right\} N(t) \tag{3.10}$$

integrating to

$$N(t) = N_0 \exp\left(\int_0^t \left\{b - \mu - \rho e^{-\tau\mu} y_1(s-\tau)\alpha(s)\right\} ds\right) \tag{3.11}$$

3.3 Model Outcomes

In this section, the equilibrium points are found. A question is raised, 'How do different parameter values affect the equilibrium points?' To answer this question, a full analysis in a numerical approach is applied.

3.3.1 Equilibria

Definition 3.3.1 *If as $t \to \infty$ the system in equation (3.7) attain an equilibrium state, then we can define $y_1(t-\tau) \to y_1^*$, $y_1(t) \to y_1^*$, $y_2(t) \to y_2^*$ and $\alpha(t) \to \alpha^*$.*

Setting the system in equation (3.7) to zero at the equilibrium and applying the definition (3.3.1), the disease free equilibrium $(1, 0, 0)$ is found.

But also from the third equation we can obtain y_2^* as

$$y_2^* = \frac{\rho y_1^*(e^{-\tau\mu}\alpha^* - 1)}{\rho e^{-\tau\mu}\alpha^* y_1^* - b} \tag{3.12}$$

To calculate y_1^* from the system above is more difficult, therefore, we use a similar approach to that used in the staged model. Using equation (3.9) and (3.11) we can obtain

$$\begin{aligned}
\alpha(t) &= \exp\left[-\tau(b-\mu) + \rho\exp(-\tau\mu)\left\{\int_0^t y_1(s-\tau)\alpha(s)ds + \int_0^{t-\tau} y_1(s-\tau)\alpha(s)ds\right\}\right] \\
&= \exp\left[-\tau(b-\mu) + \rho\exp(-\tau\mu)\left\{\int_{t-\tau}^t y_1(s-\tau)\alpha(s)ds\right\}\right] \tag{3.13}
\end{aligned}$$

Choosing t large in such a way that within the interval $(t-\tau, t)$ both $\alpha(t)$ and $y_1(t-\tau)$ are constant, (3.13) gives

$$\alpha^* = \exp\left[-\tau(b-\mu) + \tau\rho e^{-\tau\mu}y_1^*\alpha^*\right] \tag{3.14}$$

from which we find

$$y_1^* = \frac{\ln\alpha^* + \tau(b-\mu)}{\tau\rho\alpha^* e^{-\tau\mu}} \tag{3.15}$$

and substituting equation (3.15) in (3.12) gives y_2^* in terms of α^* as

$$y_2^* = \frac{\rho(e^{-\tau\mu}\alpha^* - 1)(\ln\alpha^* + \tau(b-\mu))}{\alpha^*\rho e^{-\tau\mu}(\ln\alpha^* - \tau\mu)} \tag{3.16}$$

and $z^* = 1 - y_1^* - y_2^*$ which approximates the endemic equilibrium point.

3.3.2 Relationship between transmission rate and the equilibrium values

Since the transmission rate of HIV to uninfected individuals has been the most important factor in the spread of the disease, we analyze its relation to the endemic equilibrium derived in the above section. This provides us with an understanding of the disease persistence in the population at large t. This is in contrast to most of our discussions which are limited to a small interval of time under which the model has physical meaning for the disease studied.

Considering the system in equation (3.7) at the steady state, we can obtain r_1 from the second equation. Applying the definition given in (3.3.1) and the relation $r_2 = r_1/12$, then

$$r_1 = \frac{(\rho + b)y_1^* - \rho e^{-\tau\mu}\alpha^* y_1^{2*}}{(1 - y_1^* - y_2^*)(y_1^* + \frac{y_2^*}{12})}. \tag{3.17}$$

Knowing that $y_1^* \in (0,1)$, and $y_2^* \in (0,1)$, one can find the space in which r_1 lies. But since both y_1^* and y_2^* depend on α^*, the ranges of steady state variables can be different and hence change the range of r_1. Thus, it is better to find the range of α^*. To do this, we consider the condition that $y_1^* + y_2^* \leq 1$. Therefore, from this we find $\alpha^* \in (e^{\tau\mu}, \infty)$.

Figure 3.1(a) shows the relation that exists between the transmission rate and the equilibrium value for the proportion of infected individuals in the primary stage (y_1^*). The proportion of new infections increases rapidly as r_1 is increased to a critical value of $r_{1\tau}$ dependent on τ at which y_1^* peaks.
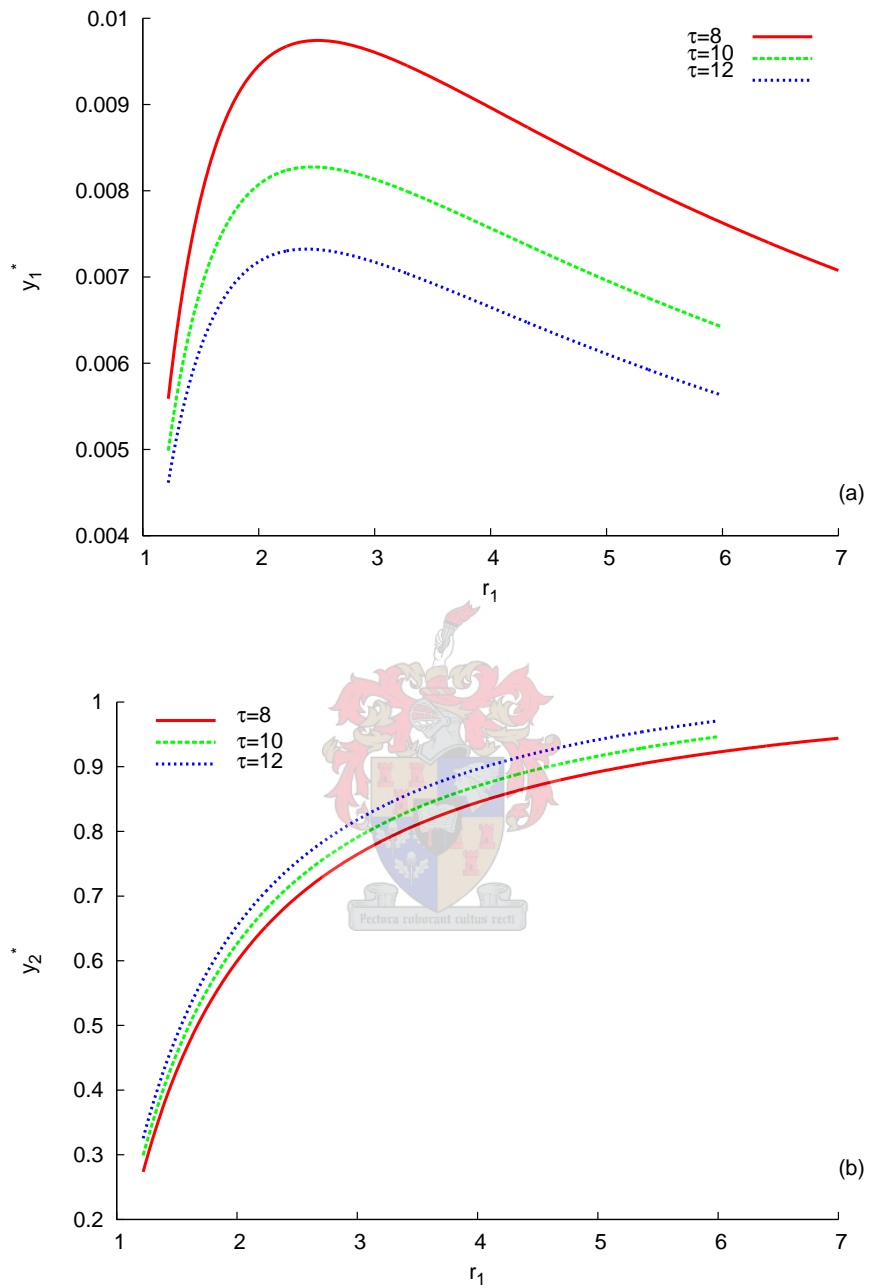
Figure 3.1: *Relationship between the transmission rate (r_1) and the equilibrium values. (a) y_1^* and (b) y_2^* with $\alpha^* \in (e^{\tau\mu}, 8)$ at $b = 0.03$, $\mu = 0.02$, $\rho = 6.0$year^{-1}, and $\tau = 8$, 10 and 12 years*

Above the critical value, y_1^* decreases to a non zero value. This has to do with the fact that as the transmission rate is increased, more new infections occur earlier (i.e. when t is small) which results in a reduction of susceptible persons during the early stage of the epidemic. This phenomenon suppresses y_1 at large t causing it to stabilize at a lower proportion. It has been also found that if r_1 is below 1, the endemic equilibrium does not appear and only the disease free equilibrium holds.

What we find in figure 3.1(b) is different from what we have seen in figure 3.1(a). The equilibrium level for the prevalence, y_2^* has a different kind of relationship with the transmission rate. As r_1 is increased, y_2^* also increases approaching a constant value.

A reduction in the equilibrium value for the prevalence levels can be achieved by reducing the rate at which individuals become infected. We also learn that, focusing on the stabilization of the proportion of new infections of the epidemic in the population can give false information on the burden and spread of the epidemic. One might think that the rate of transmission is low by just looking at the new infection proportion stabilization. This may also give false information on the prevalence. In fact, even if the new infections stabilizes at a low level, still the prevalence might stabilize at a higher level. This also might give incorrect impression if one is to use new infections to estimate the infection rate. This imbalance between the new infections and prevalence stabilization cause confusion as it can give different information on the spread of the disease in the society. Therefore, one has to be careful when using these two different epidemiological and demographical pieces of information to address the epidemic problem in any society since any change in the infection rate results in a shift in equilibrium values.

3.3.3 Transmission effect and the emergence of Oscillations

Further analysis of the model (equation 3.7) shows the variation that may occur in the proportion of new infection and prevalence curves as the transmission rates are changed. The incidence curves in figure 3.2(a) shows a quick rise when the rates are increased. Increasing the rates of transmission enables more people who are in the risk group to acquire the disease and therefore increase the new infections in the population. This continues until a peak is attained, after which the curve drops very quickly in a similar manner to its initial rise. But, the new infections continue while decreasing, and eventually they stabilize at low proportions if the rates are at large values.

It has also been found that if the transmission rate is increased, a quick rise and stabilization in the prevalence (figure 3.2(b)) occurs at very high levels which seem to be unrealistic to have such a large fraction of the population infected. A different behaviour for the stabilization of the prevalence when compared to that of the proportion of new infections is also observed. Prevalence curves tend to stabilize at high values as r_1 and r_2 are increased. This is because most of the infections occur at low t, and the fact that mortality is delayed.

In addition we found the occurrence of small oscillations which then die out immediately before the endemic equilibrium is achieved(figure 3.2). However, the parameter values for which these periodic solutions occur may be unrealistic. In the special cases when $b = \mu = 0$, $b = \mu \neq 0$, and $b \neq 0$ but $\mu = 0$, oscillations still arise in the solutions. This leads us to a conclusion that oscillations occurring are due to the delayed death of infected individ-
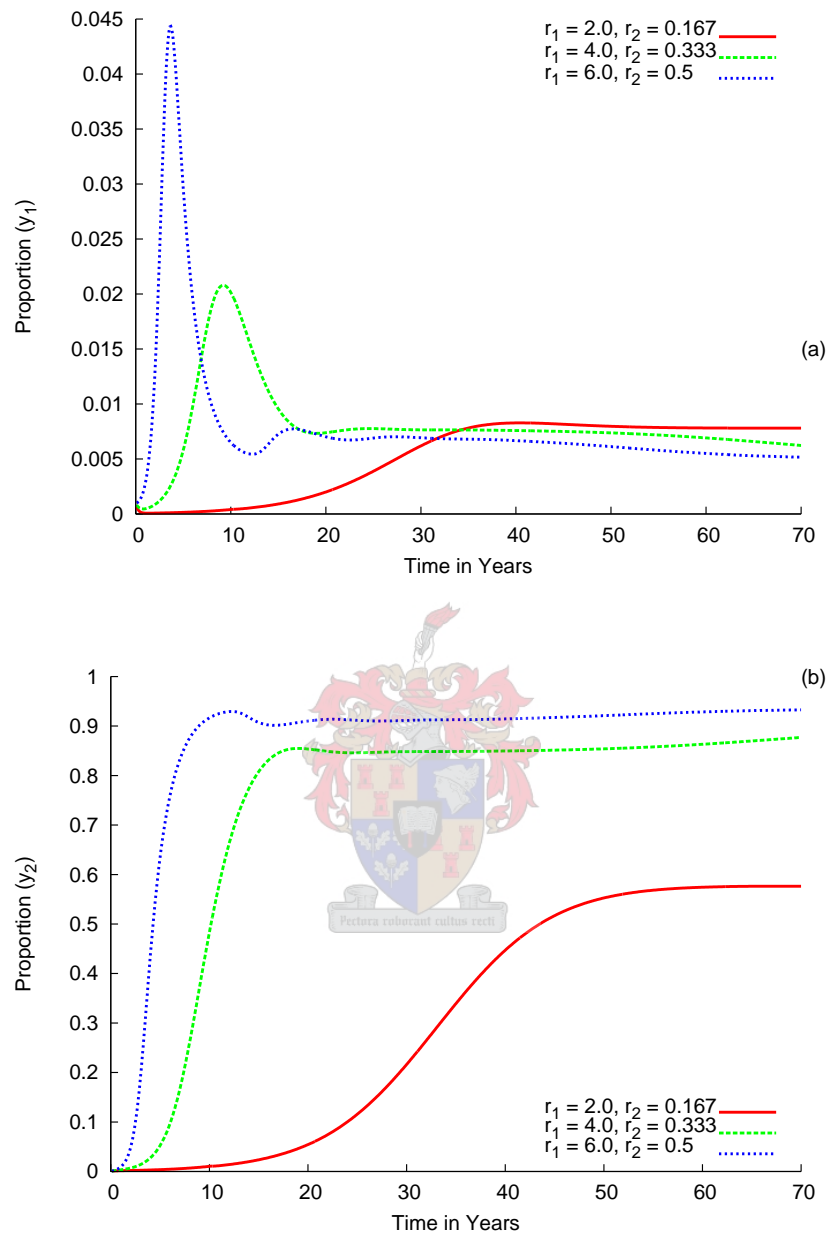
Figure 3.2: *Development of periodic solutions in the (a) new infection curves and (b) prevalence curves for the system in (3.7) when r_1 and r_2 are increased from 2.0 to 6.0 and 0.167 to 0.5 respectively with $b = 0.03$, $\mu = 0.02$, $\rho = 6.0\text{year}^{-1}$, and $\tau = 10\text{years}$.*

uals. Hethcote and Van de Driessche [10] in their model that consisted of both a variable population and a delay, found that a constant delay for the infectious period can lead to periodic solutions. These oscillations do not occur for the analogous ordinary differential equations SIS models for example, in which recovery is proportional to the number of infectives. It is therefore important to understand the correlation that exist between rates of infection, and the incidence and prevalence levels in models with delay.

3.4 The influence of a delay

This section investigates the effect that may occur as a result of introducing a delay in the model. We do this through changing some parameter values while leaving others unchanged and a comparison between the simple staged model discussed in chapter 2 together with the model with delay is made to reveal the delay effect.
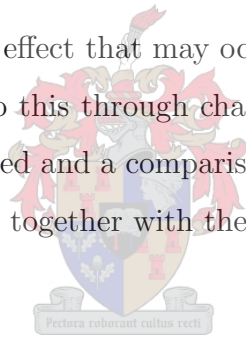
3.4.1 Effect of survival time of HIV positive persons

The main difficulty with forecasting is that many different empirical curves fit the available data; in some cases well. Although these curves give reasonably consistent predictions in a short term, the predictions can be quite divergent in a long term. (This model ignores the possibility of changes that occur through medical break-through. For example, to date, the effectiveness of combination anti-retroviral therapy, have been demonstrating a large reduction in both progressions to AIDS and AIDS-related deaths. But there have been no data on the exact size of treatment-induced delay on AIDS

caused mortality [35]). Therefore, simulation results for different values of τ (figure 3.3) are generated to investigate effects caused by the life expectancy of infected individuals.
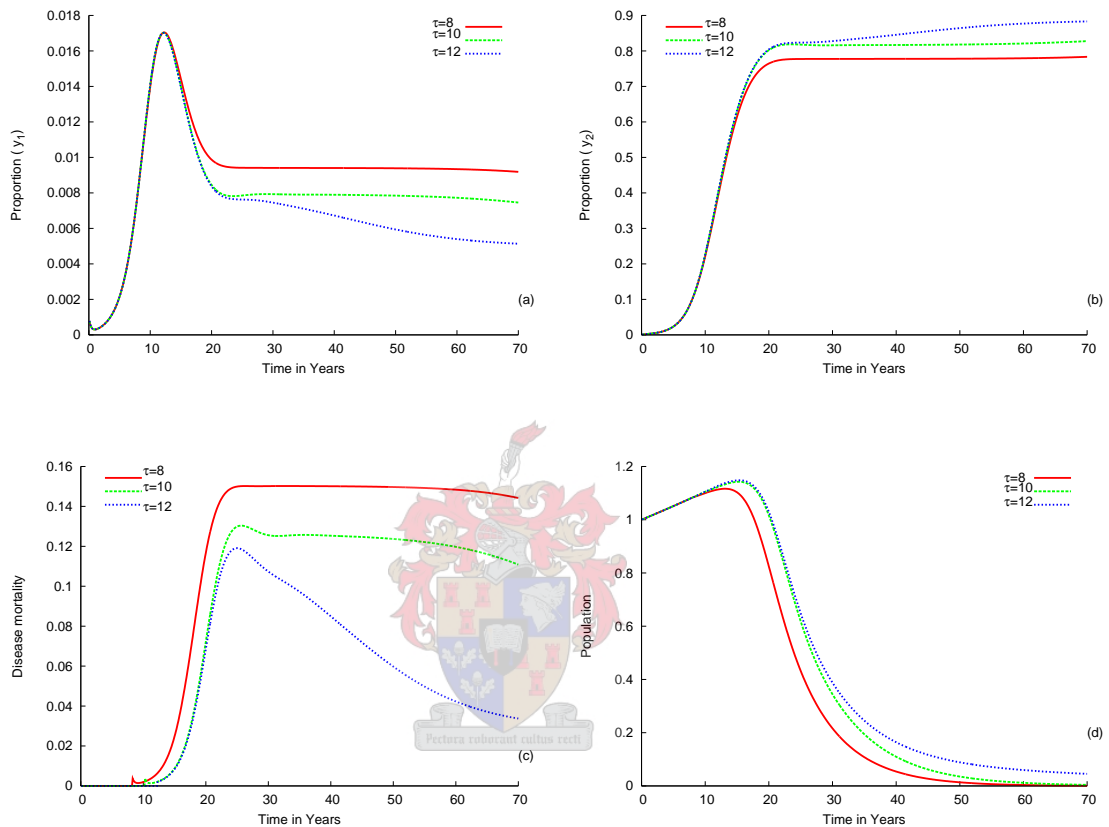
Figure 3.3: *Effect of the survival periods, τ years for the (a) Proportion of new infections, y_1 (b) Prevalence, y_2 (c) AIDS mortality rates and (d) Total population. Parameters: $r_1 = 3.50$, $r_2 = 0.292$, $\mu = 0.020$, $b = 0.030$ and $\rho = 6.0 year^{-1}$.*

It has been found from the results that as τ is increased, predictions show roughly similar results in a short period of about 10 years measured from the start of the epidemic for the incidence, prevalence and the total population. However, differences arise at large t. During low t, mortality due to the epidemic are not occurring and people are still surviving although they are

infected. Another related finding is that, as τ is increased, the proportion of infected individuals in the primary stage is lowered while that in the asymptomatic stage is increased. For the disease like HIV/AIDS, treatment as a means to life extension reduces the amount of virus copies which then allows these individuals to move back to their previous stages, the asymptomatic stage of HIV development [18]. As the transmission rates is proportional to the viral load [4, 5], then these individuals have a low chance to transmit the disease.

3.4.2 A comparison with the staged model

The effect of a delay in AIDS mortality is assessed by considering the changes in the demographics. The results of the model developed in this chapter which takes into account the effect of delay, are compared to the results obtained from the simple staged model (No-delay) developed in chapter 2. The comparison is made by considering two scenarios.

Scenario one: A similar rise in the prevalence.
In this scenario, a similar rise in the prevalence curves in both models is considered. We assume that the asymptomatic group in both models is similar at the early stage of the disease noting that AIDS mortality in both models have not shown their impact yet. With a similar rise in prevalence level in this case, the prevalence level in both models is set at 40% when t is at 20 years (figure 3.4(b)). To obtain this, the rates of transmission in the No-delay model were set higher values ($r_1 = 3.065$ and $r_2 = 0.255$) than in the model with delay ($r_1 = 2.689$ and $r_2 = 0.224$). This is due to the fact that before $t = 10$ years, the asymptomatic group in the model without

delay experiences disease caused mortality immediately after it starts to exist. This is not the case for the model with delay. During this period, there is no disease related mortality at all since the survival period of all infected individuals is not reached at 10 years (i.e. $y_1(t-10) = 0$). So, the prevalence of infected individuals in this model is expected to rise more quickly than in the model without delay. We investigated the difference that occur in the prevalence itself at $t > 20$ years and study the effect that happens in the proportions of infected individuals in the primary stage (figure 3.4(a)), disease caused mortality rates (figure 3.4(c)) and the population size (figure 3.4(d)) for all t.

Since r_1 and r_2 are higher in the model without delay, most of the infections occurs earlier and the proportion of new infections become higher during this period (figure 3.4(a)). This results in high prevalence level (figure 3.4(b)) at large t. The saturation of uninfected people at a low level leads to low occurrence of new infections later. Despite the fact that the new infections curves have a difference in their rise, still we find that they both peak at the same time (i.e. $t = 20$ years) although at different levels. It is also found the mortality rates for the model with delay to be higher than those in the model without delay at large t. This is simply because when infected people start dying, they do so at a very high rate in the model with delay.

The rising rates of deaths due to the disease are expected to result in a reduction of population growth and hence a decrease of population size in both models. The population size is affected in two ways: the first way is due to the increase in disease "mortality rates" and the second way is due to a reduction in "births" as a result of deaths occurring. Generally, it is found that the population size in the model without delay begins to show
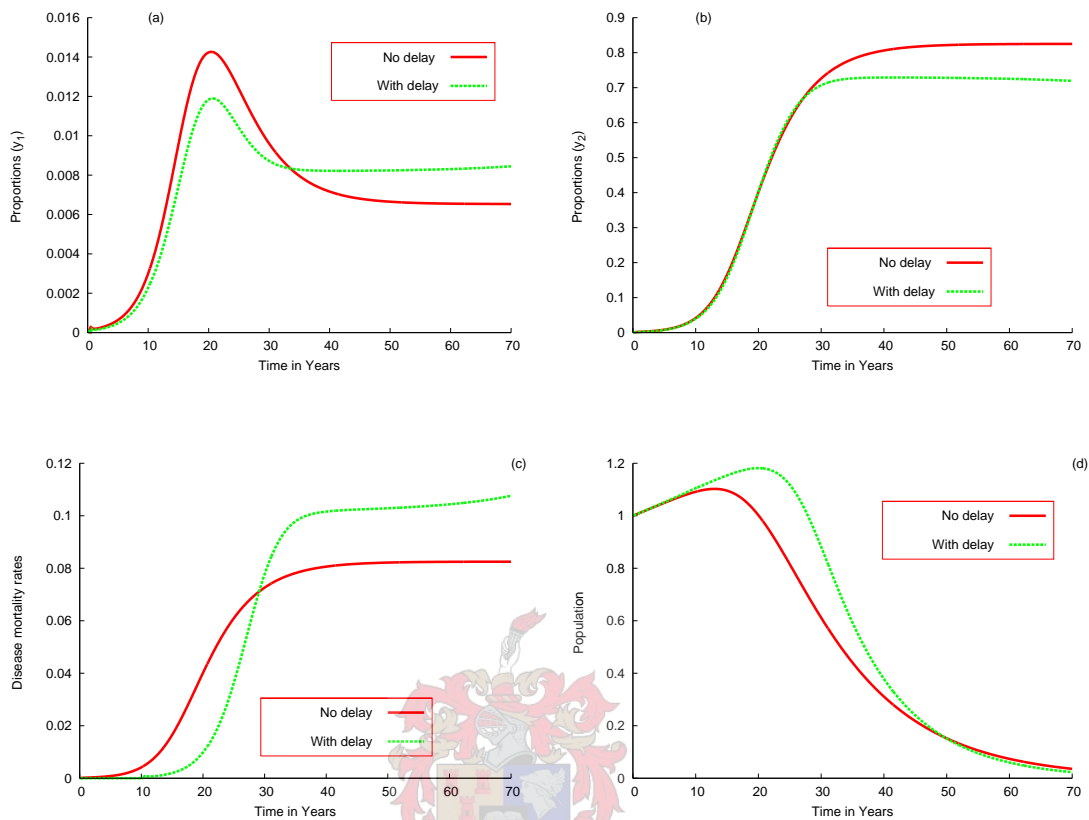
Figure 3.4: *A comparison between the simple staged model (No delay case) and the model with delay while considering same initial rise in the prevalence curve (y_2). (a) Proportion of new infections, y_1 (b) Prevalence, y_2 (c) AIDS mortality rates and (d) Total population. Parameters: $r_1 = 3.065$ and $r_2 = 0.255$ for the No delay case and $r_1 = 2.689$ and $r_2 = 0.224$ for the model with delay. Other parameters: $\rho = 6.0\text{year}^{-1}$, $\mu = 0.02$ and $b = 0.03$.*

a decrease as the disease mortality starts to occur earlier. The population size in the model with delay continues to grow for almost 10 years longer measured from the time at which the population in the No-delay model start showing a decrease. This is due to $\tau = 10$ years as it has been used in the numerical simulation. By the time when the mortality rises to the high plateau values, the total population is decreased at a very high rate causing

it to switch over with the population size for the model without delay.

Scenario two: Same transmission rates.

Having studied the scenario where the rates of transmitting the disease are low and different, we now consider the second scenario in which large and same values for the transmission rates are assigned in the two models. For $t < 10$ years, this produces a quick and similar rise in the incidence level for both models (figure 3.5(a)). However, at very small scale, a small difference is observed which is not significant. Although during this period disease caused mortality exist in the model without delay, they are not high enough to cause a large impact. This causes the rise of the prevalence curves (figure 3.5(b)) for both models to be similar too.

During $t \geq 10$ years, differences are found to occur under which the delay results in the occurrence of oscillatory behaviour for the proportions of new infections, prevalence, and mortality rates as $y_1(t - 10) \neq 0$. Since $y_1(t - 10)$ takes a rise similar to $y_1(t)$ in the last 10 years, therefore, within the time interval $10 < t < 20$, the curve for mortality rates for the model with delay (figure 3.5(c)) rises quickly. Therefore, this has a large impact in the proportions of new infections (figure 3.5(a)), prevalence level (figure 3.5(b)), and the population size (figure 3.5(d)). Infections in this case are allowed to take place fast in the risk population and therefore disease mortality are found to be lower. Hence the population size in the delay model experience a large impact and decreases faster than in the model without delay.
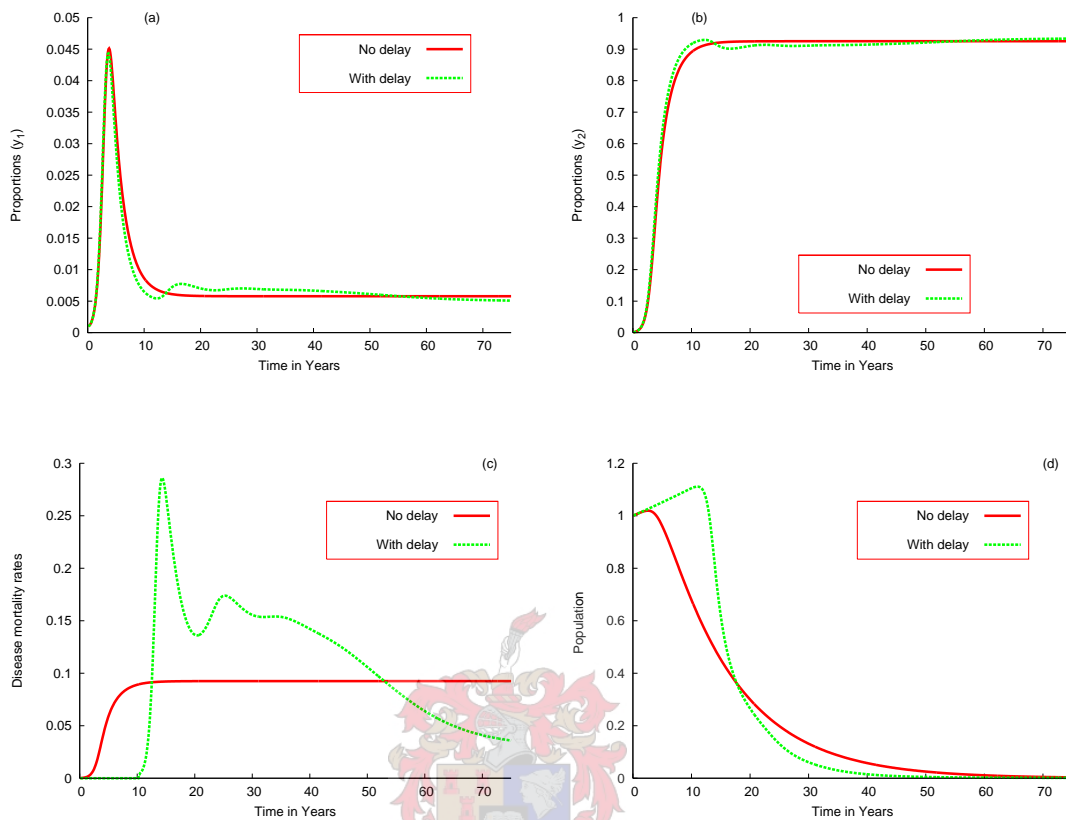
Figure 3.5: *A comparison between the simple staged model (No delay case) and the models with delay at the same transmission rates. (a) Proportion of new infections, y_1 (b) Prevalence, y_2 (c) AIDS mortality rates and (d) Total population. Parameters: $r_1 = 4.0$, $r_2 = 0.33$, $\rho = 6.0 \text{year}^{-1}$, $\mu = 0.02$ and $b = 0.03$*

3.5 Summary and Conclusion

Deficiencies of national statistics in countries most severely affected by HIV/AIDS make it difficult to assess the impact of the epidemic on mortality. When working with limited and defective data it is important to utilize all available sources of information. This chapter discussed a model describing the dynamics of the population affected by HIV and the role played by introducing

a time delay in the occurrence of AIDS deaths for infected individuals.

It was shown that the proportion of new infections and the prevalence of the disease are mainly determined by transmission rates not by HIV survival period extension. The model showed these results as it was compared with the simple staged model discussed in chapter 2. The two models did not show a large difference in the prevalence and the proportion of infected individuals in the primary stage of HIV progression. However, some oscillatory behaviour in the solutions were shown though they seemed to occur at transmission rate values which are higher than those required in most populations.

The effect of increasing HIV survival period was also investigated. The hypothesis was that increasing HIV infected individuals' survival time through treatment increases the proportion of infected individuals in the population or facilitate the spread of HIV as the time to continue infecting is increased. From the model simulations, it was shown that HIV survival has a low impact in the spread of the disease. Survival time was found not a facilitator of the spread of the disease in its early stage but a low impact was found to occur during the maturity stage.

The main finding in this chapter has been the effect of the delay in the model. Our simulations have indicated that models of death strongly determine disease mortality rates. AIDS mortality rates for the model with delay were found to be far higher than those in the model without delay. From this, the results suggest that if one is to project AIDS mortality using mathematical models, then a delay in the mortality must be included as more treatment efforts are now in action.

Prolonged incubation periods of HIV/AIDS was found to enlarge the epi-

demic in a model that included a time delay by Mukandavire et al [32]. Our results have shown that increasing the survival time of HIV positive individuals may increase the prevalence of the HIV disease but decrease the new infections in a long term. This happens due to the accumulation of infected individuals in the asymptomatic group which measures the disease prevalence.
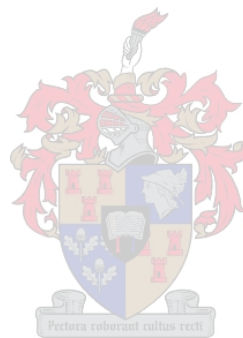
The role of risk groups in HIV predictive estimates

An individual's belief in his or her personal risk level to illness or disease is an important element in nearly all models, both general and HIV/AIDS specific, as it influences the adoption of risk reducing behaviour and/or preventive strategies. Survey results for the year 2005 [21] in South Africa have shown the presence of people (66%) who believed that they would NOT contract HIV. However, there are differences in HIV risk levels among different groups [23]. Some HIV models, whose projections are widely used, have included the group of individuals NOT at risk to HIV infection in addition to groups of various levels of risk. For instance this was done in the Epidemic Projection Package (EPP) developed by the UNAIDS [28] and the ASSA model for South Africa [33]. This chapter extends the models discussed in chapter 2 to include risk groups. We do this by investigating the effect of different aspects such as initialization, levels of risk, and the division of new recruits into the

groups of the model

4.1 Introduction

The spread of HIV in any population varies from one group of individuals to another due to differences in exposure. In different regions marked variations occur in both HIV incidence and prevalence [23, 21]. The possible explanations for these variations lies in the differences of risk factors. These can be categorized into three main groups as follows:

- Behavioural factors
  These include commercial and transactional sex, sex and alcohol consumption, violence in sexual relationships, non-disclosure of HIV status, and partner concurrency [1]

- Socio-economic and demographic factors
  These include income, education and employment, economic migration, urban-rural differentials, age and risk factors for transmission among intravenus drug users (IDUs)

- Biomedical factors
  These include sexually transmitted infections (STIs) such as syphilis, herpes, gonorrhoea, and bacteria vaginosis, the use of hormonal contraceptive especially injectable contraceptives, and younger age especially in women.

---

[1]Having more than one partner

On the basis of data from Carletonville in South Africa, MacPhail et al [36] found that among biological risk factors, susceptibility to HIV infection was 30% higher in females than in men. In a similar way, in a national population-based survey conducted in the year 2002 in South Africa, females were found to have a higher prevalence (about 12.8%) than males (about 9.5%) [37].

While biological factors are clearly important, a number of survey studies have suggested that social and behavioural factors are equally important [21, 23]. Rehle et al [37] showed that major differences in HIV prevalence exist within locality, province, race, and age. The study found the highest prevalence in the African community (12.9%) followed by the white community (6.2%), coloured (6.1%) and Indians (1.6%).

Despite these obvious differences in HIV prevalence and differences in risk factors among individuals, most of the mathematical models of the spread of the HIV epidemic have not captured this fully. In most models a uniform risk group of people is considered. In some cases the infected group is divided according to infectiousness. We ask the question: are these models representative? In some models the population is divided into core groups [13, 12] and in some risk behaviour in sexually transmitted disease have been considered [38].

When modeling while including risk groups, one need to consider how new individuals are recruited into the groups. Hyman and Li [39] studied a model that considered susceptibility of individuals. In their model, new individuals were distributed into the subgroups of susceptible, based on their inherent susceptibility. According to this, we ask the question: does the manner new individuals are recruited into the risk groups matter?

In any modeling approach, it is important to know how many individuals are in a given risk group. However, this has been not possible for surveys as individuals may not give correct information about their behaviour or disease related information. With this, different assumptions are being made regarding the initial population groups. Therefore, initialization is also an important aspect in producing predictive estimates of the HIV impact in the population since the more people are assumed not to be at risk, the smaller the impact of the disease. In that case, we ask a question: how does the initial size of the risk groups change model results?

Since it has not been easy to identify or obtain information about individuals' risk levels, modellers are required to assume values and we ask another question: How do assumptions about risk groups affect predictive estimates of the spread of the disease?

In this chapter, we focus, investigating in a numerical approach the above questions by extending the simple model for the spread of HIV developed in chapter 2 to include risk groups.

4.2 Including the NOT group

4.2.1 With recruitment proportional to the size of the group

This section investigates the effect of introducing the non risk group of individuals (NOT group). We assume a community that has two groups of people with no interaction between them. One of them is exposed to HIV

infection and the other is not. New individuals are recruited into their respective groups at a rate proportional to the size of the group. That is, those born by the NOT group $X(t)$ are also assumed to be NOT at risk and those born by the risk group $(Z(t)+Y(t))$ are assumed to be at risk. Thus, with all parameter definitions and conditions remaining similar to the models studied in the previous chapters, we can write our system of equations as follows:

$$\begin{aligned}
\frac{dX(t)}{dt} &= bX(t) - \mu X(t) \\
\frac{dZ(t)}{dt} &= b(Z(t) + Y(t)) - r\frac{Z(t)Y(t)}{N(t)} - \mu Z(t) \\
\frac{dY(t)}{dt} &= r\frac{Z(t)Y(t)}{N(t)} - \mu Y(t) - \gamma Y(t)
\end{aligned} \tag{4.1}$$

With $N(t) = X(t) + Z(t) + Y(t)$ and $\frac{dN(t)}{dt} = (b - \mu)N(t) - \gamma Y(t)$

Writing the system of equations above in terms of proportions, we have:

$$\begin{aligned}
\frac{dx(t)}{dt} &= \gamma x(t)y(t) \\
\frac{dz(t)}{dt} &= by(t) - rz(t)y(t) + \gamma z(t)y(t) \\
\frac{dy(t)}{dt} &= rz(t)y(t) - by(t) - \gamma y(t) + \gamma y^2(t)
\end{aligned} \tag{4.2}$$

where $x(t) + z(t) + y(t) = 1$

Model outcomes

Since the NOT fraction $x(t)$ satisfies $x(t) = 1 - z(t) - y(t)$, we can work with the last two equations in (4.2). At the equilibrium state, $\frac{dz(t)}{dt} = \frac{dy(t)}{dt} = 0$

and therefore,

$$by^* - rz^*y^* + \gamma z^*y^* = 0 \qquad (4.3)$$

$$rz^*y^* - by^* - \gamma y^* + \gamma y^{*2} = 0 \qquad (4.4)$$

We see that, equation (4.3) is satisfied when $y^* = 0$ or $z^* = \frac{b}{r-\gamma}$.

Substituting $y^* = 0$ into equation (4.4) we see that both equations (4.3) and (4.4) are satisfied for any value of z^*. If we substitute $z^* = \frac{b}{r-\gamma}$ into equation (4.4) we obtain $y^* = 1 - \frac{b}{r-\gamma}$. Therefore, we have two equilibria of which one is a disease free equilibrium $DFE = (z^*, 0)$ with $0 < z^* \leq 1$ and the other is an endemic equilibrium given by $EEP = (z^*, y^*) = (\frac{b}{r-\gamma}, 1 - \frac{b}{r-\gamma})$.

But from equation (4.2), one can see that the solution $x(t)$ can only be zero if and only if $x(0) = 0$. Otherwise $x(t) > 0$ for all t. But from the equilibria obtained, the endemic equilibrium point has shown that the equilibrium value for x^* is zero. For a population that has a non risk group, $x(0)$ is never zero. Therefore, we can discard the endemic equilibrium point as it is not applicable according to the demand of the model. Thus, only the disease free equilibrium holds. However, this disease free equilibrium depends on the initial conditions as we see from the phase portrait diagram shown below (figure 4.1).

The long-term behaviour of the solutions
From the phase portrait above (figure 4.1), $\lim_{t \to \infty} z(t) > 0$ if $z(0) > 0$ and $\lim_{t \to \infty} y(t) = 0$ for all initial values $(z(0), y(0))$. This means that every orbit in the plane tends to an equilibrium point on the line $y = 0$, that is, eventually all infectives die, and the disease dies out.
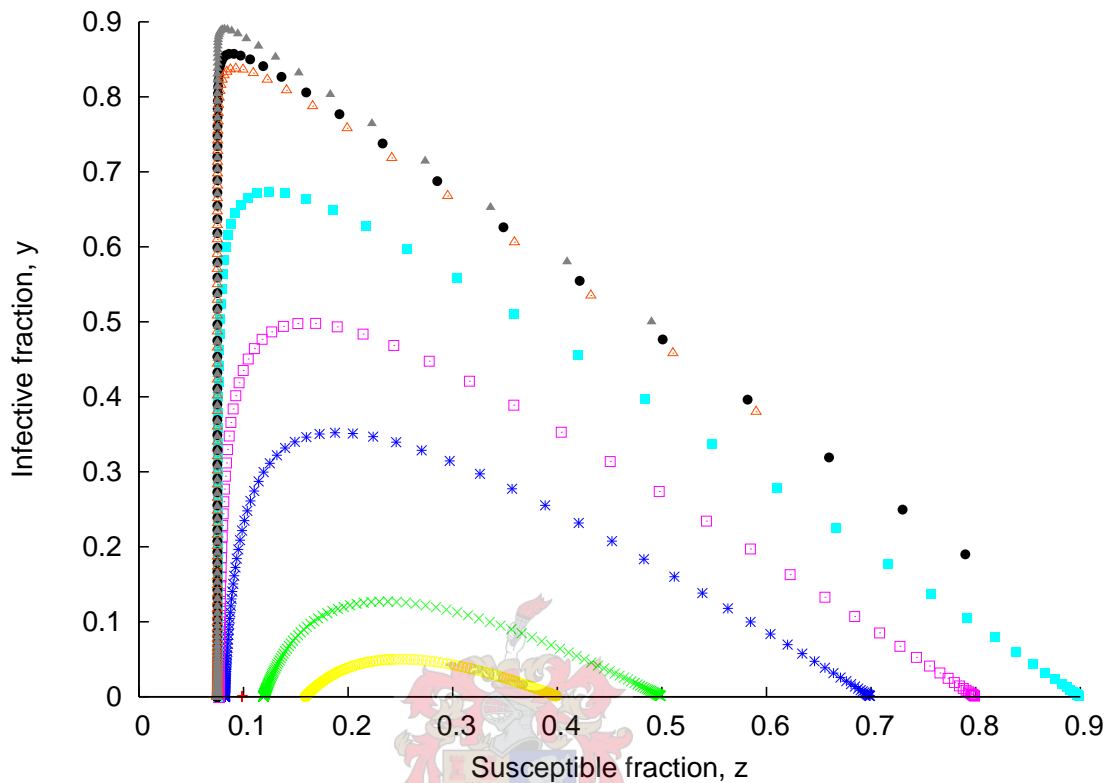
Figure 4.1: *A phase portrait showing the dependence of the disease free equilibrium on initial conditions. Parameters: $b = 0.03$, $\mu = 0.02$, $\gamma = 0.1$, and $r = 0.5$*

Our model has shown a distinctive characteristic behaviour of a typical epidemic outbreak; that an infective fraction curve must first increase from an initial value near zero, reach peak, and then decrease towards zero as a function of time (figure 4.1 and 4.2). The susceptible fraction $z(t)$ is also shown to decrease, but the final susceptible fraction is not zero (i.e. $z(\infty) > 0$), in fact it is easy to see that $z^* > b/(r - \gamma)$.
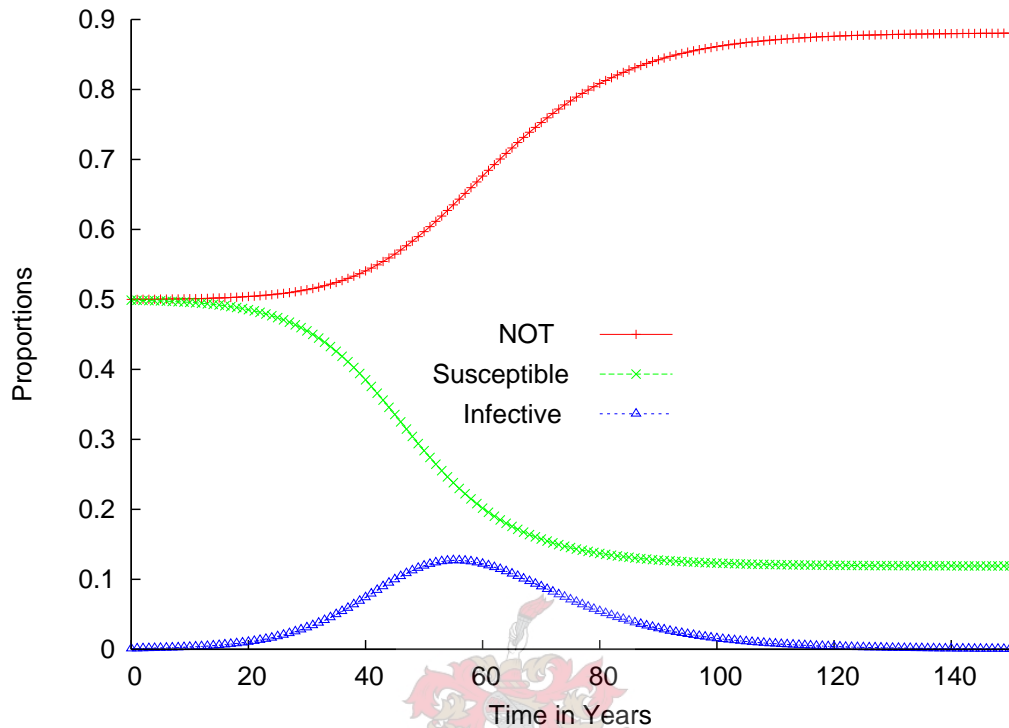
Figure 4.2: *A Time series diagram for the proportions. Parameters:* $b = 0.03$, $\mu = 0.02$, $\gamma = 0.1$, *and* $r = 0.5$ *at* $x(0) = 0.5$, $z(0) = 0.499$ *and* $y(0) = 0.001$.

4.2.2 With recruitment proportional to the total population

In this model, one new parameter is introduced: p, the recruitment fraction. The equation for the infective class (Y) remains as in the basic model. This follows the assumption we made in chapter 2 that vertical transmission is not taken into account. Due to this assumption, our extended model describes the dynamics of the disease with new individuals recruited only into the NOT group (X) and the susceptible class (Z). The model assumes that even though some of the new individuals might have been born by individuals

who are exposed to infection, they may not inherit their parents behaviour. And therefore they are recruited into the NOT group. Some of those born by individuals who are completely not exposed to infection may also develop risk behaviour and therefore they are recruited into the susceptible class. That is, of the total number of offspring of the total population, $bN(t)$, a fraction p are recruited into X, while fraction $1-p$ are recruited into Z. Our model is thus given by:

$$
\begin{aligned}
\frac{dX(t)}{dt} &= pbN(t) - \mu X(t) \\
\frac{dZ(t)}{dt} &= (1-p)bN(t) - r\frac{Z(t)Y(t)}{N(t)} - \mu Z(t) \\
\frac{dY(t)}{dt} &= r\frac{Z(t)Y(t)}{N(t)} - \mu Y(t) - \gamma Y(t)
\end{aligned}
\tag{4.5}
$$

With population size $N(t)$ being $X(t) + Z(t) + Y(t)$ which changes dynamically as

$$
\frac{dN(t)}{dt} = (b - \mu)N(t) - \gamma Y(t)
\tag{4.6}
$$

All other parameters have similar definitions as in previous models.

Following a similar calculation, we can now write the above equations in proportions as:

$$
\begin{aligned}
\frac{dx(t)}{dt} &= pb - bx(t) + \gamma x(t)y(t) \\
\frac{dz(t)}{dt} &= (1-p)b - bz(t) - rz(t)y(t) + \gamma z(t)y(t) \\
\frac{dy(t)}{dt} &= rz(t)y(t) - by(t) - \gamma y(t) + \gamma y^2(t)
\end{aligned}
\tag{4.7}
$$

where $x(t) + z(t) + y(t) = 1$ and

$$\frac{dN(t)}{dt} = (b - \mu - \gamma y(t))N(t) \tag{4.8}$$

Model outcomes

We define a threshold quantity

$$R = rz(t)/(\gamma + b) \tag{4.9}$$

as a replacement number of our model. This quantity depends on the susceptible proportion $z(t)$ at any point in time. We also found two equilibrium points,

- Equilibrium 1: No disease is found to establish itself. This is a trivial outcome of the model and it is given by $(x^*, z^*, y^*) = (p, 1 - p, 0)$. At this point, we can write the model replacement number in equation (4.9) as $R_{DFE} = r(1 - p)/(b + \gamma)$. Using the normal method of local stability, the eigenvalues obtained from the Jacobian matrix at this equilibrium are as follows: $\lambda_1 = \lambda_2 = -b$ and $\lambda_3 = (b + \gamma)[R_{DFE} - 1]$. If $R_{DFE} < 1$, we find that $\lambda_{1,2,3} < 0$ and therefore, the equilibrium is *stable*. Otherwise, $\lambda_{1,2} < 0$ while $\lambda_3 > 0$. For this case, this point is *unstable*.

- Equilibrium 2: A disease establishes itself and persists. This point is given by:

$$x^* = \frac{\sqrt{A_x r^2 + \left(-4\,b\,\gamma^2\,p - 2\,\gamma^3 + 2\,b\,\gamma^2\right)\,r + \gamma^4} + B_x}{2\,\gamma\,r}$$

$$z^* = \frac{\sqrt{4\,b\,\gamma\,p\,r^2 + \gamma^2\,r^2 - 2\,b\,\gamma\,r^2 + B_z} + A_z}{2\,r^2 - 2\,\gamma\,r}$$

$$y^* = \frac{-\sqrt{4\,b\,\gamma\,p\,r^2 + \gamma^2\,r^2 - 2\,b\,\gamma\,r^2 + B_y} + A_y}{2\,\gamma\,r - 2\,\gamma^2} \tag{4.10}$$

where

$$A_x = 4\,b\,\gamma\,p + \gamma^2 - 2\,b\,\gamma + b^2$$

$$B_x = (\gamma - b)\,r - \gamma^2$$

$$A_z = (\gamma + b)\,r - \gamma^2$$

$$B_z = b^2\,r^2 - 4\,b\,\gamma^2\,p\,r - 2\,\gamma^3\,r + 2\,b\,\gamma^2\,r + \gamma^4$$

$$A_y = (\gamma + b)\,r - \gamma^2 - 2\,b\,\gamma$$

$$B_y = b^2\,r^2 - 4\,b\,\gamma^2\,p\,r - 2\,\gamma^3\,r + 2\,b\,\gamma^2\,r + \gamma^4$$

To perform the stability analysis of this point is fairly complicated, therefore, we use a numerical approach, to study how results change as a function of our new parameter.

Long term effect of the recruitment fraction

On the equilibrium

Our endemic equilibrium above (equation 4.10) has a dependence on our new parameter, the recruitment fraction, p. While keeping all other parameters unchanged, we study its effect on the equilibrium by the use of phase diagrams (figure 4.3). The findings from this investigation show that the endemic equilibrium is stable (figure 4.3). But the equilibrium shifts when the

recruitment fraction is varied. When this parameter is increased, more new individuals are recruited into the NOT group which then makes a susceptible group small. This leads to few infections and as infections continue, deaths occurs and hence a low level in the stability points is attained.
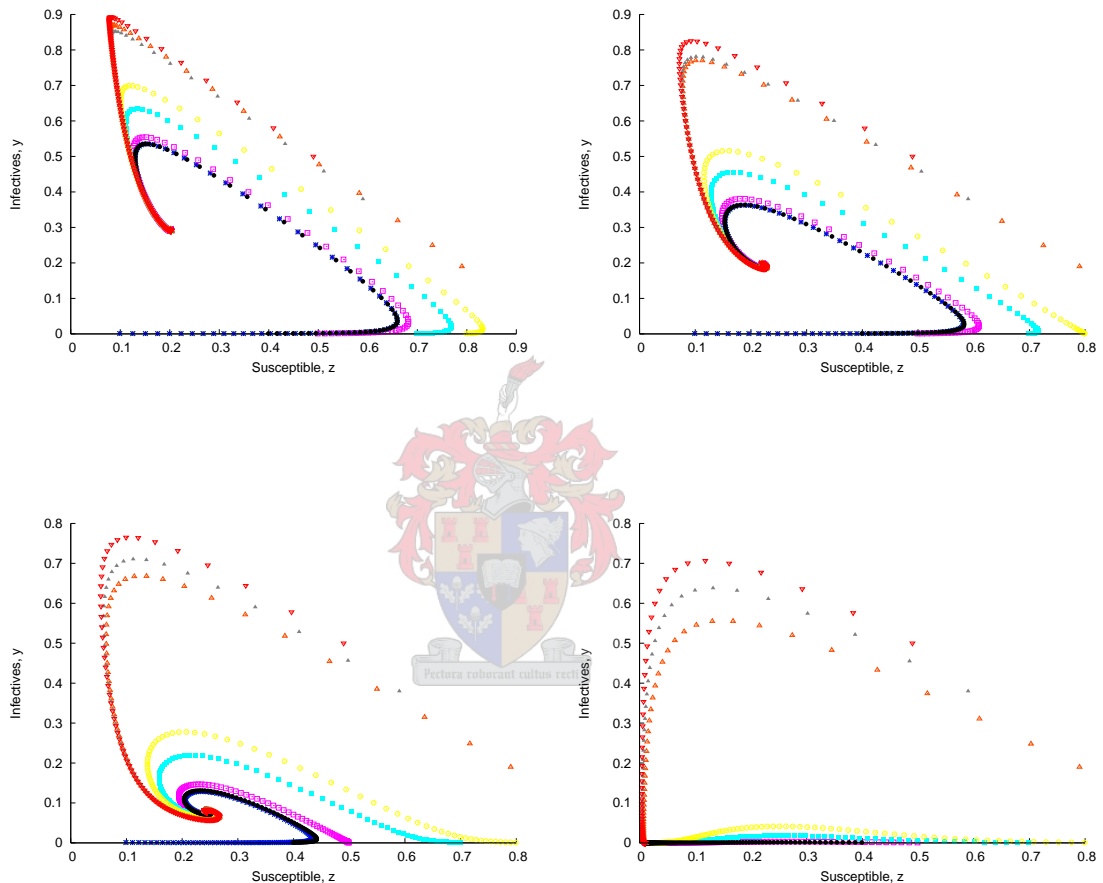
Figure 4.3: *Phase portraits showing the shifting pattern of the endemic equilibrium due to change in the recruitment fraction p at different initial conditions. p increases from top left to bottom right with p = 0.01, 0.2, 0.5 to 0.99 respectively. Parameters: b = 0.03, μ = 0.02, γ = 0.1, r = 0.5*

Although the equilibrium point is dependent on the new parameter, it is not influenced by initial conditions. This implies that, in any community, the

development of the disease in a long term does not depend on how many individuals were initially subject to infection. Although, the initial division is important in the early stage of the epidemic.

On the proportions

Dividing a population into risk and non-risk groups of uninfected individuals means a careful recruitment of new individuals into the groups is required. Results from our model have shown that, when the recruitment fraction is increased, fewer new individuals are recruited into the susceptible group and more of the them into the non-risk group (figure 4.4). As expected, this is found to decrease the proportion of the infected group as the majority of individuals in the population are not subjected to infection. As infections take place in the small risk group, this group decreases leading to low infections in the long term.

Although the rise in the curves for the proportions of infected individuals might be quite similar at low t for a small change in the recruitment fraction, the long term results still show a difference (figure 4.4). This is due to the fact that, when p is increased, the risk group is increased by a smaller value and hence it gets saturated at lower levels at large t. This then reduces the number of individuals getting infected or entering the infected group.

Another result found from our simulation is that, the recruitment fraction does not affect the peaking property of an epidemic curve. Even if the epidemic does not show a significant impact, the peak in the prevalence does not disappear. Instead its occurrence continues to exist at all values of $p \in [0, 1]$.
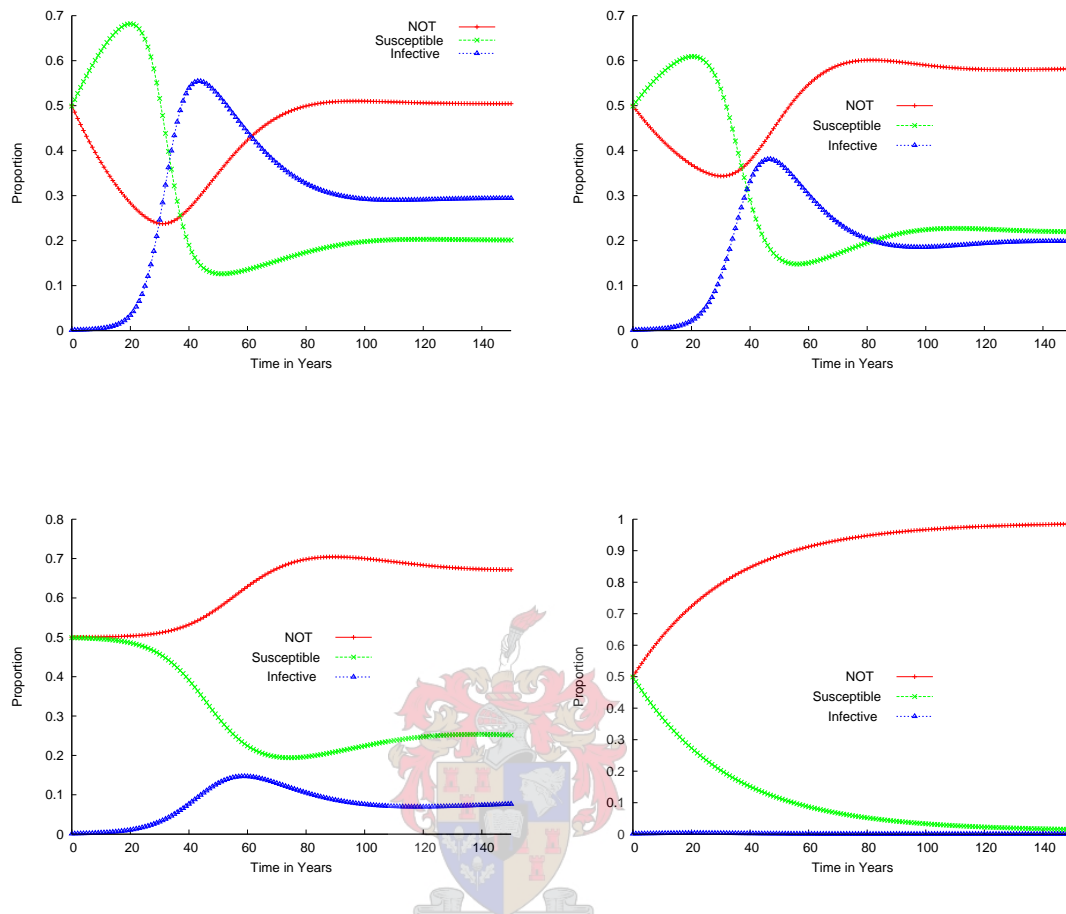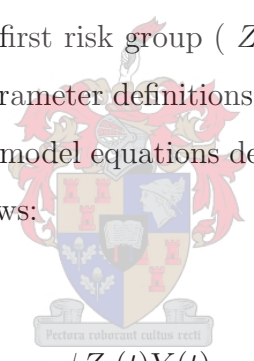
Figure 4.4: *Time series diagrams at different values of the recruitment fraction parameter p. p increases from top left to bottom right with $p = 0.01$, 0.2, 0.5 to 0.99 respectively. Parameters: $b = 0.03$, $\mu = 0.02$, $\gamma = 0.1$, $r = 0.5$*

4.3 Risk variations

In this section, we further extend the simple model studied in chapter 2. The extension is made through the introduction of an equation describing levels of risk to infection. This equation represents a susceptible population (Z_1) in which the risk level varies between high and low values. We assume that the risk level for the second group $(Z = Z_2)$ does not change. The model

does not include direct or individual parameters which are responsible for the change of a risk behavior of individuals (e.g. concelling, education, STI or STDs, etc). We assume a parameter ϕ to describe only the relative risk level of the subgroup, Z_1 (i.e. individuals are assumed to have homogeneous risk). A reduction of ϕ represents a decrease in risk factors of individuals in group Z_1.

Since we have divided our susceptible group into two subgroups, then the next task is to decide how we are to recruit new individuals into these groups. We assume a similar manner of new individuals entrance into these two groups as in the model discussed in section 4.2.2. A fraction p of new individuals $bN(t)$ are recruited into the first risk group (Z_1) and $1 - p$ into the second risk group (Z_2). All other parameter definitions remain similar to those used in the previous models. The model equations describing the dynamics of our population are given as follows:

$$
\begin{aligned}
\frac{dZ_1(t)}{dt} &= pbN(t) - \frac{r\phi Z_1(t)Y(t)}{N(t)} - \mu Z_1(t) \\
\frac{dZ_2(t)}{dt} &= (1-p)bN(t) - \frac{rZ_2(t)Y(t)}{N(t)} - \mu Z_2(t) \\
\frac{dY(t)}{dt} &= \frac{r\phi Z_1(t)Y(t)}{N(t)} + \frac{rZ_2(t)Y(t)}{N(t)} - \mu Y(t) - \gamma Y(t)
\end{aligned}
\tag{4.11}
$$

With $N(t) = Z_1 t) + Z_2(t) + Y(t)$ and $\frac{dN(t)}{dt} = (b - \mu)N(t) - \gamma Y(t)$ and the corresponding proprotions are

$$
\begin{aligned}
\frac{dz_1(t)}{dt} &= pb - r\phi z_1(t)y(t) - bz_1(t) + \gamma z_1(t)y(t) \\
\frac{dz_2(t)}{dt} &= (1-p)b - rz_2(t)y(t) - bz_2(t) + \gamma z_2(t)y(t) \qquad (4.12) \\
\frac{dy(t)}{dt} &= r\phi z_1(t)y(t) + rz_2(t)y(t) - by(t) - \gamma y(t) + \gamma y^2(t)
\end{aligned}
$$

where $z_1(t) + z_2(t) + y(t) = 1$

4.3.1 The role of risk to infection in determining model outcomes

To illustrate the effect of changing the risk levels, we run simulations using the system with proportions (equation 4.12). Since our main concern is to study the behaviour that may be due to the risk levels, we compare different scenarios of changing ϕ with equal division in recruitment of new individuals into the two risk groups.
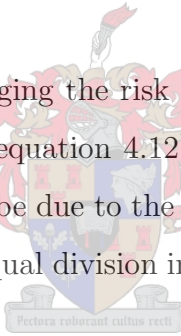
If the risk parameter (ϕ) is decreased to lower values, a low rise in the prevalence curve occurs (figure 4.5). It has also been found that the prevalence curve of the disease peaks and remains endemic at a relatively low level when group (Z_1) is at low risk. We also note that in the absence of any risk factor (when $\phi = 0$), the model in (equation 4.11) becomes the same to the model in equation (4.5).

When ϕ is increased to higher values, the prevalence curve (figure 4.5(b)), does not peak. The curve shows that the disease remains endemic at a very high level. For $\phi = 1$, Z_1 becomes like to Z_2 and therefore forming a single group with a uniform risk level as in the original form (see equation (2.1)).
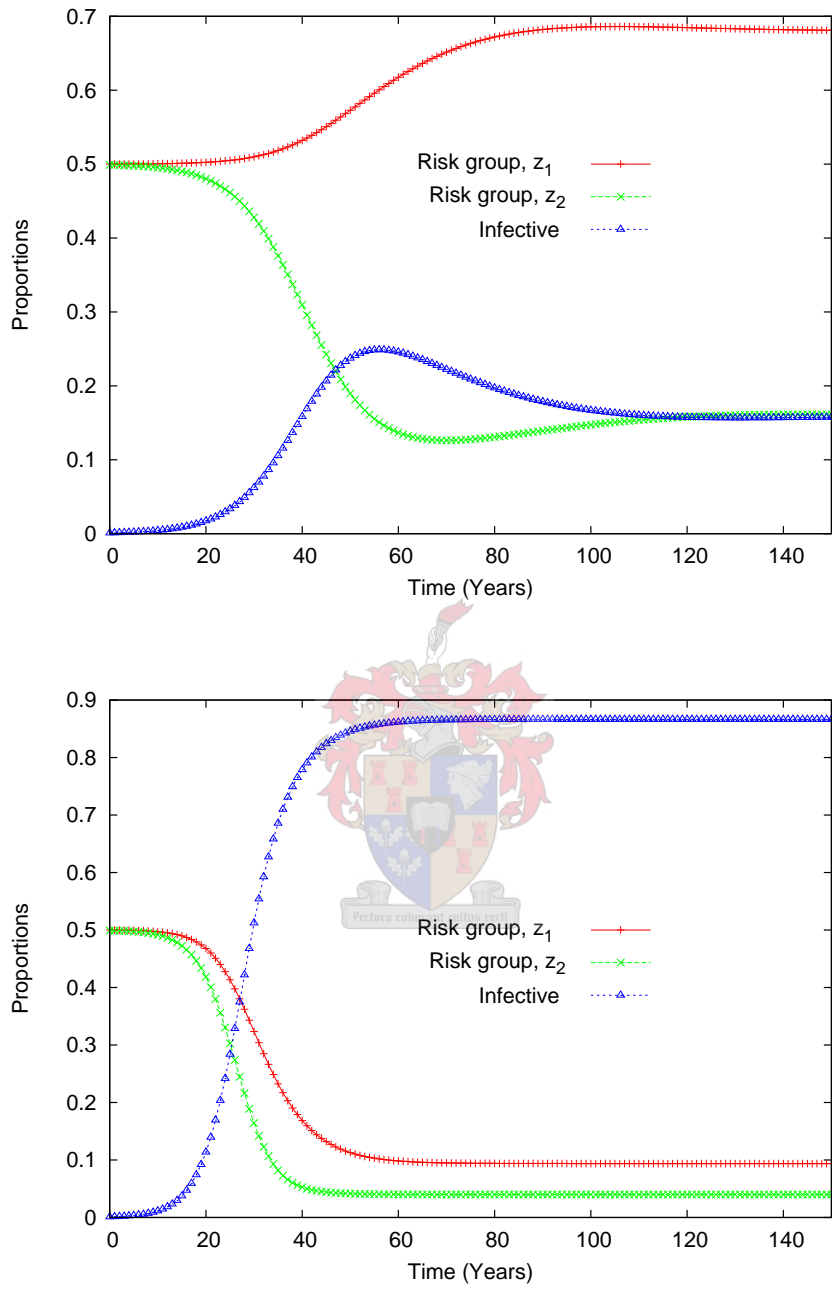
Figure 4.5: *Effect of the risk parameter ϕ (a)Top: $\phi = 0.1$ and (b)Bottom: $\phi = 0.5$ Parameters: $p = 0.5$, $b = 0.03$, $\mu = 0.02$, $\gamma = 0.1$, $r = 0.5$*

4.4 Summary and conclusion

In this chapter we have investigated some of the key properties of epidemic models. The aspect of dividing new individuals into the risk groups was shown to have a critical impact on results. Our study on this aspect has shown that new individuals born by individuals who have no risk behaviour, should retain or inherit their parents behaviour. This would enable the disease to die out in the long term.

Furthermore, our investigation explored some initialization aspects of the uninfected groups. Our results show, that in the case of recruitment staying within its group, a small change in the initial conditions may result in a large change in the equilibrium point. However, from some initial division onwards, the equilibrium may continue to be fairly stable.

The effect of different risk levels was also investigated. It was found that a group risk level is the determinant of the occurrence of a peak in the epidemic curve. As most epidemic curves have been showing peaks, with our results we can conclude that these peaks are due to the presence of groups which have low risk of disease infection. Therefore, it should not be generalized that a peak in prevalence occurs in any population.

Discussion and Conclusion

5.1 Summary and conclusions
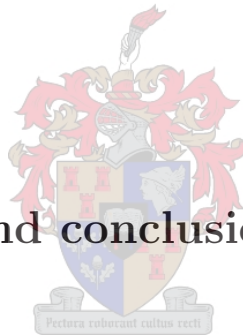
This study has been concerned with developing a very simple HIV/AIDS spread model which is then extended to explain different properties that arise in any population where HIV exists. We were specifically interested in understanding how these properties influence the spread of HIV/AIDS and their effects on predictions. Specifically, we wanted to determine the contribution of these properties in making HIV/AIDS predictive estimates close to reality, as HIV surveillance systems and methods are improving, and the dynamic behaviour of the disease is becoming clearly understood. In studying these properties, we raised some other issues such as the rate of HIV transmission, the survival period of HIV infected individuals, the degree of risk behaviour in acquiring HIV, the manner new individuals are

recruited into different risk groups and the decision on how many individuals are initially present in a given risk group.

To explore these properties and describe the contribution of stages of HIV progression in the spread of HIV and in changing predictive estimates, we used the simple HIV model as a starting point. After studying the model for our quantitative study, and incorporating the stages explicitly, we showed that this inclusion of the stages qualitatively captured the dynamics we believe to be important in the early stages of HIV progression. A search in the literature resulted in reasonable estimates for many of the parameters in the models, and analysis of the model equations provided conditions that were used to estimate the remaining parameters, the transmission rates. We discovered that, there are differences in results between the two models, with predictions being higher in a short term when stages are considered and low when they are not. It appears that the main driver is the presence of the primary stage. These findings are confirmed by the results obtained from clinical studies [4, 5].
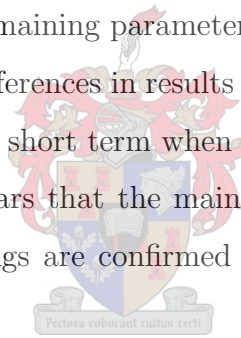
In an attempt to understand what key details were left out of the staged model, we extended our model to include other reasonable details. In the extended model, we assumed that AIDS deaths have a profound effect on both the spread of the disease and predictions. We altered the mechanism of AIDS deaths occurrence and consider an explicit constant time delay for all infected individuals from their initial infection to death. The main difference occurs in the mortality rates curves as they depend much on how long infected individuals live.

For further understanding of the key properties, our simple single staged model in chapter (2) was then extended to include risk groups. It is shown

that for the disease not to have a large impact on the population, the majority of individuals must refrain from risk behaviour. This can lead to disease clearance especially when new individuals do not develop risk behaviors (e.g. NOT group), instead they inherit their parent's behaviour.

In all models considered in this study, stages have shown an important role. Their inclusion increases the prevalence level of the disease in the population especially during its early development. The difference between the model that considers a single group of infected individuals and the model with stages (that divides infected individuals according to stages), is that with a single group of infected people, all individuals in this group transmit the viruses at an equal rate. In the staged model, individuals transfer the viruses to uninfected individuals at different rates. It is this factor that is important. The study has shown that even if the model with a single group of infected individuals include all other factors, it still can not reproduce results of the model with stages.

In addition, our study discovered an important feature in epidemiological modelling and the spread of diseases. HIV/AIDS like other diseases, its epidemic curves are claimed to rise to a peak and then decrease to a constant value if the disease is assumed to persist in the population. This feature has been occurring in survey data as well as in results predicted by mathematical models of disease dynamics in populations. Our study revealed that, if the population does not have risk groups, then this feature in epidemic curves can not occur. As shown by our model results in chapter (2) and chapter (3), in a long-term, the epidemic curves are not affected either by introducing stages or time delay in AIDS mortality. The prevalence curves can only grow to form a plateau but not a peak. This is true for prevalence curves, while

curves for incidence or proportion of new infections can indeed have a peak. The introduction of risk groups has lead to an occurrence of peaks in the prevalence curves.

5.2 Limitations and future directions

In this study, we developed, expanded and improved on the simple HIV spread model to address some specific questions on spread and predictions of HIV/AIDS. Our results have been based on estimated parameter values which may however not apply in some cases. All of the models in this study dealt with an idealized situation. By creating a model using differential equations, we have assumed that all individuals in a given stage or risk group in acquiring the disease, modeled with same parameter values. A more realistic model would allow for the possibility that parameter values are not constant over time, and are different in different regions.

The assumption that the total population is not constant has lead to increased non linearity of the terms in the proportion forms of the models. We have assumed that the total population decreases asymptotically due to the disease persistence. This has lead us to approximate the endemic equilibrium points in some models. However, this assumption is not applicable to the models which incorporated risk groups. The total population might not decrease asymptotically due to the presence of groups which are at less risk or no risk at all to infection.

Our study is also limited by having few parameters in the models. For example, we have studied the effect of changing survival periods of infected

individuals in a general case. It could be interesting if one would include parameters that describe the effects due to treatment programmes directly. The time delay introduced in the model studied in chapter (3) assumed that people die following a step function distribution which is an extreme case. It would be interesting to have a distribution which is between the step function and an exponential distribution to explain the occurrence of AIDS deaths.

Another limitation of this work is that the models studied considered a single sex group of people. It does not divide individuals according to gender. Both males and females are treated equally and the HIV transmission rate is equally considered. In reality, females are at more risk than males [23, 21, 22, 40, 36]. Although the models in chapter (4) divides the population into subgroups like the NOT group and other groups with different risk levels, still the models do not allow movement of individuals from one risk group to another. It would be helpful to allow these movements as some individuals refrain from risk behaviour while others are increasing risk.

In general, our work has provided an understanding of how difficult it can be to produce quality HIV/AIDS information using mathematical models. However, a model that combines all the features studied in this thesis would be an added advantage. As HIV/AIDS data has been improving through improvements in collection methods, clear understanding of the disease and its characteristics etc, more complexity in models will be needed.

Determination of the reproduction number for the staged model
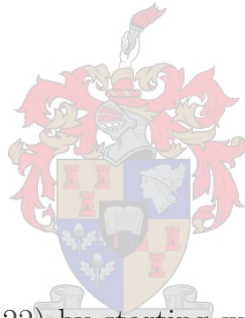
We rearrange the system (2.22) by starting with the infectious groups and ending with the susceptible group as

$$(\frac{dy_1(t)}{dt}, \frac{dy_2(t)}{dt}, \frac{dz(t)}{dt})^T. \tag{A.1}$$

From our new system (A.1), we define a matrix F with new infections and a matrix V by negating the inflow and outflow of individuals in the system. Thus

$$F = \begin{pmatrix} r_1 z y_1 + r_2 z y_2 \\ 0 \\ 0 \end{pmatrix} \qquad (\text{A.2})$$

$$V = \begin{pmatrix} (\rho + b) y_1 - \gamma y_1 y_2 \\ -\rho y_1 + (\gamma + b) y_2 - \gamma y_2^2 \\ b(1 - z) + r_1 z y_1 + r_2 z y_2 - \gamma z y_2 \end{pmatrix} \qquad (\text{A.3})$$

Differentiating F and V with respect to the infected subgroups y_1 and y_2 at the disease free equilibrium, the following matrices are obtained:

$$F = \begin{pmatrix} r_1 & r_2 \\ 0 & 0 \end{pmatrix} \qquad (\text{A.4})$$

$$V = \begin{pmatrix} (\rho + b) & 0 \\ -\rho & (\gamma + b) \end{pmatrix} \qquad (\text{A.5})$$

Next we find the a Jaconbian matrix using F and the inverse of a matrix V

$$FV^{-1} = \begin{pmatrix} \frac{r_1}{\rho+b} + \frac{r_2\rho}{(\rho+b)(\gamma+b)} & \frac{r_2}{\gamma+b} \\ 0 & 0 \end{pmatrix} \qquad (\text{A.6})$$

The eigenvalues of equation (A.6) are $\lambda_1 = \frac{r_1}{\rho+b} + \frac{r_2\rho}{(\rho+b)(\gamma+b)}$ and $\lambda_2 = 0$.

Computer programs

The python programs presented here are used for the simulation of the systems with proportions.

B.1   Simple HIV model program

```
#Importing the modules
from scipy import *
from scipy.integrate import odeint

#Parameter assignment
b = 0.03
rho = 0.12
mu = 0.02
r = 0.4 #This parameter can vary

# Function definitions for f0 = dz/dt, y[0] = z, y[1]=y, y[2] = dN/dt
def f0(y,t):
    return b - r*y[1]*y[0] - b*y[0] + rho*y[0]*y[1]
```

```
def f1(y,t):
    return  r*y[1]*y[0] -b*y[1] - rho*y[1] + rho*y[1]*y[1]

def fN(y,t):
    return (b - mu - rho*y[1])*y[2]

y_dot = [0,0,0]
def f(y,t):
    y_dot[0] = f0(y,t)
    y_dot[1] = f1(y,t)
    y_dot[2] = fN(y,t)
    return y_dot

#Initialization of z0 and y0
y_initial = [0.999,0.001,1.0] # Can be changed

t = arange(0.,500.,0.01)      # Times at which y is calculated
y = odeint(f,y_initial,t)     # calling odeint solver

fout = open('simple_model.data','w')

data=[]
for i in range(len(t)):
    data.append([t[i], y[i][0], y[i][1], y[i][2]])

print >> fout, array(data) #writing data to a file for plotting
fout.close()

#computing data for y* and ra=r
data1 = []
for y_star in arange(0.,0.9,0.01):
    ra =((b + gamma) - gamma*y_star)/(1-y_star)
    data1 = data1 + [[y_star,ra]]
equilibData = take(data1,[0,1],axis = 1)
```

B.2   Simple staged model program

```python
from scipy import *
from scipy.linalg import *
import math

#parameter assignment: b,mu and rho are assumed constant
b = 0.03
mu = 0.02
r1 =  4.0
r2 = r1/12
rho = 6.0
gamma = 0.1


fout = open('staged_model.data','w')

#Function definition for the model equations
def fy1(t,y1,y2): #for dy1/dt
    equationy1=r1*(1-y1-y2)*y1+r2*(1-y1-y2)*y2-(rho + b)*y1+gamma*y1*y2
    return  equationy1

def fy2(t,y1,y2): #for dy2/dt
    equationy2 = rho*y1 - (gamma + b)*y2 + gamma*y2*y2
    return  equationy2

def fN(t,y2,N): #for dN/dt
    equationN = (b - mu - gamma*y2)*N
    return equationN

#Defining the rungekutta order four function
def rk4(fy1,fy2,fN,t,y1,y2,N,h,tmax):
    table = [[t,y1,y2,N]]
    while t < tmax:
            d1 = h*fy1(t,y1,y2)
            p1 = h*fy2(t,y1,y2)
            g1 = h*fN(t,y2,N)

            d2 = h*fy1(t+0.5*h,y1+0.5*d1,y2+0.5*p1)
            p2 = h*fy2(t+0.5*h,y1+0.5*d1,y2+0.5*p1)
            g2 = h*fN(t+0.5*h,y2+0.5*p1,N+0.5*g1)
```

```
                    d3 = h*fy1(t+0.5*h,y1+0.5*d2,y2+0.5*p2)
                    p3 = h*fy2(t+0.5*h,y1+0.5*d2,y2+0.5*p2)
                    g3 = h*fN(t+0.5*h,y2+0.5*p2,N+0.5*g2)

                    d4 = h*fy1(t+h,y1+d3,y2+p3)
                    p4 = h*fy2(t+h,y1+d3,y2+p3)
                    g4 = h*fN(t+h,y2+p3,N+g3)

                    t += h

                    y1 += (d1+2.*d2+2.*d3+d4)/6.
                    y2 += (p1+2.*p2+2.*p3+p4)/6.
                    N += (g1+2.*g2+2.*g3+g4)/6.

                    mortalityRate = gamma*y2
                    table.append([t,y1,y2,N])
                    print >> fout,' %f %f %f %f %f' %(t,y1,y2,N,mortalityRate)
        return table

#Function call
mytable = rk4(fy1,fy2,fN,0,0.001,0.0,1.0,0.1,500)

# Computation of the reproduction nummber,Xi
Ry1 =  r1/(rho+b)
Ry2 =  r1/((gamma+b)*12)
Xi = Ry1 + rho*Ry2/(rho+b)

print >> fout,'# Ry1=%f Ry2=%f Xi=%f r1=%f r2=%f' %(Ry1,Ry2,Xi,r1,r2)
fout.close()

#computing r1a=r1  for y2_st=y2* in range(0,1)
data1 = []
for  y2_st in arange(0.,0.95,0.01):
    c_a = b - mu - gamma*y2_st #c_a = c
    y1_st = ( (mu+gamma+c_a)/rho )*y2_st
    kappa = (mu + gamma + c_a)/rho
    numerator = (b + rho - gamma*y2_st)*kappa
    denominator = ((1-(kappa+1)*y2_st)*kappa)+((1 - (kappa+1)*y2_st)/12)
    r1a =  numerator/denominator
    r2a = r1a/12
```

```
    data1 = data1 + [[y2_st,y1_st,r1a]]
equlibriumData = take(data1,[0,1,2],axis = 1)
```

B.3   Delay model program

```
from scipy import *
from scipy.linalg import *
from math import *

b = 0.03
mu = 0.02
r1 = 4.0
r2 = r1/12
rho = 6.0
delay = 10 #delay = tau


fout = open('delaymodel.data','w')

# Function definitions
def fz(t,z,y1,y2,y1delay,Ndelay,N):
    equationz=b-b*z-r1*z*y1 -
r2*z*y2+rho*exp(-delay*mu)*y1delay*z*(Ndelay/N)
    return equationz

def fy1(t,z,y1,y2,y1delay,Ndelay,N):
    equationy1 =   r1*z*y1 + r2*z*y2 - (b + rho)*y1 +
 rho*exp(-delay*mu)*y1*y1delay*(Ndelay/N)
    return   equationy1

def fy2(t,y1,y2,y1delay,Ndelay,N):
    equationy2=rho*y1-b*y2-rho*exp(-delay*mu)*y1delay*(1-y2)*(Ndelay/N)
    return   equationy2

def fN(t,y1delay,Ndelay,N):
    equationN = (b - mu)*N - rho*exp(-delay*mu)*y1delay*Ndelay
    return equationN
```

```
#defining a runge kutta function
def RK4(fz,fy1,fy2,fN,t,z,y1,y2,N,h,tmax):

    table = [[t,z,y1,y2,N]]
    i = 0

    while t < tmax:
        if t-h <=delay  :
            y1delay = 0
            Ndelay = 0
            i+=1

        else:
            y1delay = table[i-101][2]
            Ndelay = table[i-101][4]
            i+=1

        k1 = h*fz(t,z,y1,y2,y1delay,Ndelay,N)
        d1 = h*fy1(t,z,y1,y2,y1delay,Ndelay,N)
        p1 = h*fy2(t,y1,y2,y1delay,Ndelay,N)
        g1 = h*fN(t,y1delay,Ndelay,N)

        k2=h*fz(t+0.5*h,z+0.5*k1,y1+0.5*d1,y2+0.5*p1,y1delay+0.5*d1,
 Ndelay+0.5*g1,N+0.5*g1)
        d2=h*fy1(t+0.5*h,z+0.5*k1,y1+0.5*d1,y2+0.5*p1,y1delay+0.5*d1,
 Ndelay+0.5*g1,N+0.5*g1)
        p2 = h*fy2(t+0.5*h,y1+0.5*d1,y2+0.5*p1,y1delay+0.5*d1,
 Ndelay+0.5*g1,N+0.5*g1)
        g2 = h*fN(t+0.5*h,y1delay+0.5*d1,Ndelay+0.5*g1,N+0.5*g1)

        k3=h*fz(t+0.5*h,z+0.5*k2,y1+0.5*d2,y2+0.5*p2,y1delay+0.5*d2,
Ndelay+0.5*g2,N+0.5*g2)
        d3=h*fy1(t+0.5*h,z+0.5*k2,y1+0.5*d2,y2+0.5*p2,y1delay+0.5*d2,
Ndelay+0.5*g2,N+0.5*g2)
        p3 = h*fy2(t+0.5*h,y1+0.5*d2,y2+0.5*p2,y1delay+0.5*d2,
   Ndelay+0.5*g2,N+0.5*g2)
        g3 = h*fN(t+0.5*h,y1delay+0.5*d2,Ndelay+0.5*g2,N+0.5*g2)

        k4 = h*fz(t+h,z+k3,y1+d3,y2+p3,y1delay+d3,Ndelay+g3,N+g3)
        d4 = h*fy1(t+h,z+k3,y1+d3,y2+p3,y1delay+d3,Ndelay+g3,N+g3)
        p4 = h*fy2(t+h,y1+d3,y2+p3,y1delay+d3,Ndelay+g3,N+g3)
```

```
        g4 = h*fN(t+h,y1delay+d3,Ndelay+g3,N+g3)

        t += h

        z += (k1+2.*k2+2.*k3+k4)/6.
        y1 += (d1+2.*d2+2.*d3+d4)/6.
        y2 += (p1+2.*p2+2.*p3+p4)/6.
        N += (g1+2.*g2+2.*g3+g4)/6.

        mortalityRate=rho*exp(-delay*mu)*y1delay*Ndelay/N

        table.append([t,z,y1,y2,N,M])

        print >> fout,'%f %f %f %f  %f  %f %f %f %f
 %f'%(t,z,y1,y2,N,mortalityRate,M,y1delay,Ndelay)
    return table

print >> fout,' #r1 = %f  r2 = %f mu = %f b = %f rho = %f  delay = %f'
 %(r1,r2,mu,b,rho,delay)

results = RK4(fz,fy1,fy2,fN,fdeath,0,0.999,0.001,0,1,0,0.1,400)
fout.close()

# Calculating data for r1,y1* and y2* in a given range of
#alpha* for delay = 10years
datar1=[]
for alpha in arange(1.22,8.,0.01):
    y1a = (log(alpha) + delay*(b - mu))/(delay*rho*exp(-delay*mu)*alpha)
    y2a = (rho*y1a*(exp(-delay*mu)*alpha - 1))/
(rho* exp(-delay*mu)*alpha*y1a - b )
    za = 1-y1a-y2a
    numerator = (rho + b)*y1a - rho*exp(-delay*mu)*alpha*y1a*y1a
    denomenator  =  (1-y1a-y2a)*(y1a + (y2a/12))
    r1a = (numerator/denomenator)
    r2a=r1a/12
    datar1 = datar1 + [[alpha,r1a,y1a,y2a,za]]
```

B.4 Model with NOT group program: part one

```
from scipy import *
from scipy.integrate import odeint


b = 0.03
gamma = 0.1
r1 = 6.0 # for comparison, r2 = r=r1/12
r =  r1/12
mu = 0.02

# Functions definitions with  y[0] = x, y[1]=z, y[2]=y, y[3] = N
#f0 = dx/dt
def f0(y,t):
    return gamma*y[0]*y[2]

#f1 = dz/dt
def f1(y,t):
    return  b*y[2] - r*y[1]*y[2] + gamma*y[1]*y[2]

#f1 = dy/dt
def f2(y,t):
    return  r*y[1]*y[2] - (b + gamma)*y[2] + gamma*y[2]*y[2]

#fN = dN/dt
def f3(y,t):
    return (b - mu - gamma*y[2])*y[3]

y_dot = [0,0,0,0]
def f(y,t):
    y_dot[0] = f0(y,t)
    y_dot[1] = f1(y,t)
    y_dot[2] = f2(y,t)
    y_dot[3] = f3(y,t)
    return y_dot

#Initialization of x0, z0, y0 and N0, can be changed
y_initial = [0.5,0.499,0.001, 1.0] #N0 can be any
```

```
t = arange(0.,500.,1.)
y = odeint(f,y_initial,t)

fout = open('modelNorecruit.data','w')

data=[]
for i in range(len(t)):
    data.append([t[i], y[i][0], y[i][1], y[i][2], y[i][3] ])

all = take(data, [0, 1, 2, 3, 4], axis = 1)

print >> fout, " b = %f r = %f  mu = %f  gamma = %f" %(b,r,mu,gamma)
print >> fout, All
fout.close()
```

B.5 Model with NOT group program: part two

```
from scipy import *
from scipy.integrate import odeint

b = 0.03
p = 0.01
gamma = 0.1
r1 = 6.0
r = r1/12
mu = 0.02

# Functions definitions with  y[0] = x, y[1]=z, y[2]=y, y[3] = N
#f0 = dz/dt
def f0(y,t):
    return p*b - b*y[0] + gamma*y[0]*y[2]


#f1 = dz/dt
def f1(y,t):
    return  (1-p)*b -b*y[1] - r*y[1]*y[2] + gamma*y[1]*y[2]
```

```
#f2 = dy/dt
def f2(y,t):
    return  r*y[1]*y[2] - (b + gamma)*y[2] + gamma*y[2]*y[2]


#fN = dN/dt
def f3(y,t):
    return (b - mu - gamma*y[2])*y[3]


y_dot = [0,0,0,0]
def f(y,t):
    y_dot[0] = f0(y,t)
    y_dot[1] = f1(y,t)
    y_dot[2] = f2(y,t)
    y_dot[3] = f3(y,t)
    return y_dot


#Initialization of x0, z0, y0 and N0
#y_initial = [0.5,0.499,0.001, 1.0]


t = arange(0.,500.,1.)
y = odeint(f,y_initial,t)


fout = open('modelRecruit.data','w')


data=[]
for i in range(len(t)):
    data.append([t[i], y[i][0], y[i][1], y[i][2], y[i][3] ])


Alldata = take(data, [0, 1, 2, 3, 4], axis = 1)


print >> fout, " b = %f p = %f r = %f  mu = %f  gamma = %f" %(b,p,r,mu,gamma)
print >> fout, Alldata
fout.close()
```

B.6   Risk variation model program

```
#Importing modules
from scipy import *
```

```
from scipy.integrate import odeint

#Parameter asignment
b = 0.03
p = 0.5 #Can  be changed
gamma = 0.1
r1 = 6.0
r = r1/12
mu = 0.02
phi = 0.5 #Can be changed

# Functions definitions for f0 = dz1/dt, y[0] = z1, y[1]=z2,
# y[2]=y, y[3] = N
def f0(y,t):
    return p*b - r*phi*y[0]*y[2] - b*y[0] + gamma*y[0]*y[2]

def f1(y,t):
    return  (1-p)*b - r*(1-phi)*y[1]*y[2] - b*y[1] + gamma*y[1]*y[2]

def f2(y,t):
    return  r*phi*y[0]*y[2] + r*(1-phi)*y[1]*y[2] -
(b + gamma)*y[2] + gamma*y[2]*y[2]

def f3(y,t):
    return (b - mu - gamma*y[2])*y[3]

y_dot = [0,0,0,0]
def f(y,t):
    y_dot[0] = f0(y,t)
    y_dot[1] = f1(y,t)
    y_dot[2] = f2(y,t)
    y_dot[3] = f3(y,t)
    return y_dot

#Initialization of x0, z0, y0 and N0
y_initial = [0.2,0.799,0.001, 1.0]

t = arange(0.,500.,1.)
y = odeint(f,y_initial,t)

fout = open('riskVariation_model.data','w')
```
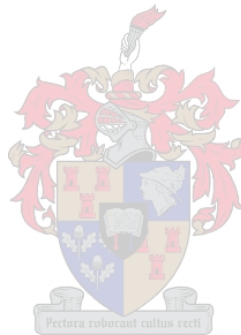
```
#data collection
data=[]
for i in range(len(t)):
    data.append([t[i], y[i][0], y[i][1], y[i][2], y[i][3] ])

All = take(data, [0, 1, 2, 3, 4], axis = 1)

print >> fout, "# b = %f  p = %f  gamma = %f r = %f phi = %f mu = %f"
       %(b,p,gamma,r,phi,mu)
print >> fout, All
fout.close()
```

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