EFFECTS OF VACCINATION AND TREATMENT ON HIV TRANSMISSION

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Abstract

This paper is an investigation of the possible effects of vaccination and treatment on the dynamics of HIV-AIDS in a varying population. The devastating global impact of HIV has increased research efforts to find an effective vaccine, or drugs that would reduce the progression and transmission rate of the disease. Antiretroviral drugs used in treatment, such as AZT(zidovudine), ddc(didieosyinosine) are presently used as a chemotherapy treatment of HIV-AIDS.

The models discussed in this study are basically theoretical models since vaccination is not yet available, especially in the developing countries like Zimbabwe. First, an SIR model was used to define the general sense of modelling an infectious disease. We then discussed the general AIDS model to describe the dynamics of the disease in a situation without any intervention programs in place. Stability analysis was looked at using mathematical analysis. A model when vaccination policy is in effect was also discussed. Critical conditions for the eradication of the disease were derived. For the sake of arguments, numerical simulations on the effect of vaccination were carried out for the cases when the proportion vaccinated is below and when it is above the critical proportion.

Next we assumed a case when treatment alone is used as a control strategy for the control of the disease and when a combination of treatment and vaccination was used. Stability analysis was carried out for each model and critical conditions were derived. With these critical values we would be able to know the minimum portion of susceptible individuals to be vaccinated and the infectives to be treated so that we can effectively control the dynamics of the disease.

Declaration

No portion of the work in this thesis has been submitted for another degree or qualification of this or any other university or another institution of learning.

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have gone through a long way'; Ryan P., 'my achievements are your future challenges.'

Chapter 1

INTRODUCTION AND STATEMENT OF THE PROBLEM

AIDS is the fourth leading cause of death globally and the leading cause in Africa. As of the year 1996, approximately 23 million people were HIV positive worldwide. The latest number of HIV positive individuals worldwide stood at 42 million by end of 2003. Of the 42 million HIV positive individuals, 29 million were Africans. In 2003 alone, 3 million Africans died of AIDS [**?**]. The data given above shows that the situation is getting worse and requires serious intervention. The devastating global impact of HIV has increased research efforts to find an effective vaccine, or drugs that would reduce the progression and transmission rate of HIV. These efforts have been mildly successful since HIV evolves resistance to drugs and mutates extremely fast [**?**]. To date there is no vaccine even though there are candidate vaccines on trial. There are a number of antiretroviral drugs that have provided relief to sufferers but are not a cure. Antiretroviral drugs used in treatment, such as AZT(Zidovudine), ddc(didieosyinosine) also work temporarily, and required a combination of drugs to be effective to avoid drug resistance.

1.1 Research Overview

Mathematical models have been developed to describe the effects of vaccination and treatment on the dynamics of HIV-AIDS in a population. Models were formulated using systems of nonlinear ordinary differential equations and then analysed mathematically to provide, through certain threshold conditions, insights on the dynamics of the disease as influenced by the implementation of vaccination and treatment programs. A vaccination program could involve several components such as education as well as a clinical vaccination. Analysis of the mathematical models leads to the derivation of very important parameter, commonly known as the basic reproduction number, R_0, which is a dimensionless quantity measuring the average number of secondary infections caused by an infective individual introduced into a completely susceptible population. In epidemiology R_0 determines whether a disease will invade the host population or not. Such behaviour can be stated as follows in epidemiological terms: If the average number of secondary infections caused by an average infective is less than one, a disease will die out, but if it exceeds one then an epidemic will result [**?**]. Numerical simulations were also carried out on vaccination alone for the cases when $\phi < \phi^*$ and $\phi > \phi^*$.

1.2 Aims and Objectives

The main aims of this thesis are:

-To study the effect of vaccination on the spread of the disease,

-To study the effect of treatment on the spead of the disease,

-To study the combined effect of vaccination and treatment on the spread of the disease ,

-To contribute to policy formulation for implementation of intervention strategies

on the spread of HIV-AIDS.

1.3 Thesis Outline

Chapter 1 covers preliminary examples that will serve as an introduction to some terminology and results already known. I begin Chapter 2 by presenting a basic HIV model as an SIR type. A disease is classified as an SIR if it confer immunity to the recovered individuals. With HIV-AIDS, once infected you are infected forever and you are only removed by death. In this model the total population is divided into three groups-susceptibles, infectives and those with full blown AIDS. There is a constant replenishment from outside into the host population. Chapter 3 looked at vaccination as a control strategy. Threshold conditions for the control of the disease by vaccination were derived and numerical simulations were carried out. Chapter 4 looked at treatment and finally, Chapter 5 focused on an integrated intervention where vaccination and treatment strategies are carried out at the same time.

1.4 Work done by others

Ying-Hen Hsieh.Shin-Pyng Shen looked at the effects of density-dependent treatment and behaviour change on the dynamics of HIV transmission. In their work, they proposed a model for heterosexual transmission of HIV-AIDS in a varying population. They made an assumption that treatment induces behavioural change in treated individuals.They made this assumption because of its socio-economic implications which is important for public health considerations since density- dependent treatment-behaviour change may be more cost -saving than a program where treatment-behaviour change occurs linearly with respect to the

number of infecteds. In their model formulation, the active population in each sex is divided into three classes, susceptibles, untreated infecteds, and treated infecteds. The two -sex model is then reduced to one-sex model using the conservation law of total sexual contacts which simply assumes that each heterosexual contact involves only one male and one female. It is assumed that the detected infecteds are taken into treatment which leads to a change in either sexual behaviour, transmission probability, and -or incubation time. Denoting R_0 as the average number of individuals recruited during the period of infectiousness of an infected individual, Ying Hseh concluded that if $R_0 > 1$, the infected population increases and the susceptible population decreases going to extinction and if $R_0 < 1$, the infected population decreases and the susceptible population increases. It was then concluded that for the model with nonlinear treatment rate, the treatment program has no effect at all on the asymptotic behaviour of either the proportions or the population size. Their results showed that an intervention program with density-dependent treatment-behaviour change rate, while less costly than that of a linear treatment rate can not change the course of the epidemic if the disease was able to spread without treatment-behaviour change. The results for the reduction to one-sex model also show that, under the condition of conservation of total contacts given for their model, targeting strategy aiming prevention program at either sex is viable in the sense that we need only to consider the dynamics of one-sex model but the choice of either sex makes no difference on the outcome.

Shu-Fang Hsu Schimitz [**?**], looked at the effects of education,vaccination and treatment on HIV transmission in a population with genetic heterogeneity.This paper extended the idea from Shu-Fang Schmitz [**?**] by introducing a compartment of those suceptibles who receive education on HIV and study its effects on the disease dynamics. In their model, education means counselling to have fewer sex partners, abstain, and- or otherwise reduce risky behaviour. Their goal was to investigate effects of education, temporary vaccination and treatmenton

HIV transmission in a homosexually active population with genetic heterogeneity. Following Hsu Schmitz [**?**], they classified the homosexually active population into three classes of susceptible individuals: non-resistant, partially resistant and fully resistant to HIV infection. Infected individuals are classified as rapid, normal and slow progressors. All the other model assumptions are the same as those in Hsu Schmitz [**?**]. When modelling the effects of a public education campaign, it was assumed that a certain number of individuals from the susceptible class are educated at a given rate. Individuals in the educated class are those on whom education has had some effect in changing their behaviour to reduce potentially infective contacts. They derived the basic reproduction number for treatment, and derived conditions under which any (small) increase in treatment will reduce the basic reproduction number. Their results showed that treatment does not interfere with the effects of vaccination or education, in the sense that the presence of a treatment program does not prevent vaccination or education from reducing the basic reproduction number. Comparing the effects of treatment to those of vaccination or education proved difficult analytically and is only enlightening when they considered parameter analysis. They also looked at the effects of genetic resistance and results suggested that slower progressors do contribute less to infection than faster progressors, in which case both effects of partial genetic resistance are beneficial to the population as a whole. The variation of the model reproductive number as a function of the rate of getting educated and the overall effectiveness of the education campaign illustrated the impact of education on the spread of HIV. It was found that the basic reproduction number will be below one as long as the rate at which susceptibles go to the educated class is not close to 0 and the effectiveness of education is at least 60 percent effective. This means that educating even some small portion of susceptible individuals about the dangers of HIV will have a significant effect in reducing the generation of newly infective persons. To see the impact of vaccination on the reproductive number, [**?**] plotted the gragh of R_0 as a function of vaccine effectiveness and duration of protection against HIV. The results showed that $R_0 < 1$ only if the duration of protection is

close to zero and vaccine effectiveness is approaching one. That is, the program is effective only when the vaccine's protection is essentially complete, and either lasts indefinitely or is renewed regularly before it can wane. In their conclusions, it was noted that some integrated intervention strategies are far more superior to those based on a single approach, although treatment programs may have effects which counteract each other, and may cause genetic resistance.

1.5 Methodology and Techniques

Definition 1 *Consider the differential equation* $\frac{dx}{dt} = f(x)$ *where* $x = x(t)\varepsilon\Re^n$ *is a vector valued function of an independent variable (usually time) and* $\cup \longrightarrow \Re^n$ *is a smooth function defined on some subset* $\cup \subseteq \Re^n$. *System in which the vector field does not contain time explictly,are called autonomous.*

Definition 2 *The system* $\frac{dy}{dt} = f(t, y)$ *is said to be asymptotically autonomous on the set* Δ *if and only if :*
1)-$\lim_{t\longrightarrow\infty} f(t, y) = h(y)$ *for* $y\varepsilon\Delta$ *and*
2)-*For every* $\epsilon > 0$ *and every* $y\varepsilon\Delta$ *there exists a* $\delta(\epsilon, y) > 0$ *such that* $\mid f(t, x) - f(t, y) \mid < \epsilon_1$ *whenever* $\mid x - y \mid < \delta$ *for* $0 \leq t \leq \infty$.

1.6 Kermac and McKendrick Models

We can consider one of the most simplest epidemiological models of SIR type to define terms and illustrate some of the techniques to be used in this research. In 1927, Kermac and McKendrick published a paper which involved the study of the transmission dynamics of a communicable disease that provide permanent immunity after recovery. Their model was used to study single epizootic outbreaks [**?**]. The assumptions of the model are that :

-An average infective individual make an adequate contact, that is, a contact sufficient to transmit infection.

-The probability of contact of an infective with a susceptible is $\frac{S}{N}$.

-A fraction γ of infectives recover per unit time.

-The demographic effects can be ignored since the epidemic time scale is very short.

The model equations are :

$$\begin{aligned} \frac{dS}{dt} &= \frac{-\beta SI}{N}, && (1.1)\\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I, && (1.2)\\ \frac{dR}{dt} &= \gamma I, && (1.3)\\ N(t) &= S(t) + I(t). && (1.4) \end{aligned}$$

S denotes the number of susceptibles, I is the number of infecteds (assumed infectious), and R is the number of recovered individuals (assumed to be permanently immune). β is the average number of susceptibles infected by one infectious individual per unit of time while γ is the per capita recovery rate (at which an infected individual leaves the I class). The disease free equilibrium point for this model is $P_0 = (N, 0, 0)$ and the basic reproduction number is given by $R_0 = \frac{\beta}{\gamma}$. The threshold theorem of Kermack and McKendrick says that if $R_0 > 1$ then an outbreak will take place while if $R_0 < 1$ there will be no outbreaks.

The addition of vital dynamics to the SIR model of Kermack and McKendrick, lead to the following system:

$$\begin{aligned}
\frac{dS}{dt} &= B - \frac{\beta SI}{N} - \mu S, && (1.5)\\
\frac{dI}{dt} &= \frac{\beta SI}{N} - (\mu+\gamma)I, && (1.6)\\
\frac{dR}{dt} &= \gamma I - \mu R, && (1.7)\\
\frac{dN}{dt} &= B - \mu N, && (1.8)\\
N &= S + I + R. && (1.9)
\end{aligned}$$

B is the birth rate and μ is the per capita natural death rate both assumed constant. The disease free equilibrium point of the model given above is given by $P_0 = (\frac{B}{\mu}, 0.0)$. The Jacobian matrix of the system is

$$\begin{pmatrix} \frac{-\beta I^*}{N} - \mu S^* & \frac{-\beta S^*}{N} \\ \frac{\beta I^*}{N} & \frac{\beta S^*}{N} - (\mu+\gamma) \end{pmatrix}$$

and at the disease free equilibrium point, we get

$$\begin{pmatrix} -B & -\beta \\ 0 & B-(\mu+\gamma) \end{pmatrix}.$$

Eigenvalues are $-B$ and $B-(\mu+\gamma)$. Therefore, the disease free equilibrium point is locally asymptotically stable if

$$B - (\mu+\gamma) < 0,$$

that is, if $R_0 < 1$ and unstable if $R_0 > 1$.

The threshold theorem of Kermack and McKendrick in this setting says that if $R_0 > 1$ then an outbreak will take place and the disease will persist while if $R_0 < 1$ the disease will die out.

Chapter 2

BASIC HIV MODEL

2.1 Introduction

The model for HIV follows the same pattern as the SIR model ([**?**]). The SIR model differs from the Aids model by the common assumption that in the SIR model, the recovered class consist of those individuals who after recovery, confer immunity (which include deaths: dead individuals are still counted) and do not become susceptible again. In the Aids model, all individuals will have full blown Aids and are removed by death only.

2.2 Model formulation

We now formulate this model, by dividing the total population into three classes-susceptibles (X_0), infectives (X_2) and the full blown AIDS (X_4) as illustrated by the compartmental model shown in fig 2.1. Let us consider an SIR type disease in the absence of vaccination and treatment but with a constant inflow of susceptibles. Let $X_0(t)$ be the number of individuals of the population who are

susceptible to an infection at time t and let $X_2(t)$ be the number of individuals of the population who are infective at time t. The total population size at time t is denoted by $N(t)$, with $N = X_0 + X_2$, since X_4 does not take part in the disease dynamics. When an infective makes contact, the probability of producing a new infection is $\frac{X_0}{N}$ since a new infection can be made only when a contact is made with a susceptible. Thus the rate of producing new infections is $\frac{c\beta_0 X_0 X_2}{N}$ where β_0 and c are constants. The population is replenished only through births. β_0 is the infectious constant rate per person in unit time and c is the mean number of sexual contacts per person.

We assume that all new recruitments enter the susceptible class at a constant rate and there is a disease induced death $\delta > \mu$ for the full blown class. In summary, the AIDS assumptions we have in this model are that X_0, X_2 and N are the number of susceptibles, infectives and the total population, respectively. There is a constant inflow of bN new members into the population in unit time who are susceptibles. There is a constant per capita natural death rate $\mu > 0$ in the X_0, X_1 classes. There is a constant death rate $\delta > \mu$ due to the disease in the full blown AIDS class. A fraction $\nu \geq 0$ of infectives progress to the AIDS class in unit time.

From fig 2.1, we have the following governing equations:

$$\frac{dX_0}{dt} = bN - \frac{c\beta_0 X_0 X_2}{N} - \mu X_0, \tag{2.1}$$

$$\frac{dX_2}{dt} = \frac{c\beta_0 X_0 X_2}{N} - (\mu + \nu) X_2, \tag{2.2}$$

$$\frac{dX_4}{dt} = \nu X_2 - (\mu + \delta) X_4. \tag{2.3}$$

Note that the first two equations do not depend on X_4 and this clearly shows that the X_4 class does not influence the dynamics of the HIV-AIDS disease. Hence, we can work with the first two equations. Therefore, the total population is the sum of two classes, susceptibles and infectives, thus :

$$N(t) = X_0(t) + X_2(t).$$

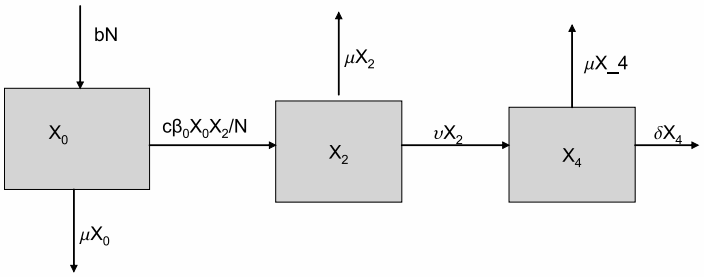

Figure 2.1: Compartmental model for the disease without intervention

It follows that $\frac{dN}{dt} = \frac{dX_0}{dt} + \frac{dX_2}{dt} = (b - \mu)N$. The system is now asymptotically autonomous, so we can define the limit value of N as follows:

$$\lim_{t \longrightarrow \infty} N(t) = \lim_{t \longrightarrow \infty} N_0 e^{(b-\mu)t} = \infty$$

only if $b > \mu$ but $N(t) \rightarrow 0$ if $b < \mu$. Introducing non-dimensional variables $x_0 = \frac{X_0}{N}$, $x_2 = \frac{X_2}{N}$, we have :

$$\frac{dx_0}{dt} = b - \beta_0 x_0 x_2 - b x_0, \tag{2.4}$$

$$\frac{dx_2}{dt} = c\beta_0 x_0 x_2 - b x_2. \tag{2.5}$$

2.3 Model Analysis

Setting the right hand of system (2.4)-(2.5) to zero, we get :

$$b - c\beta_0 x_0^\star x_2^\star - b x_0^\star = 0, \tag{2.6}$$

$$c\beta_0 x_0^\star x_2^\star - b x_2^\star = 0. \tag{2.7}$$

The system has two equilibrium points, namely disease free equilibrium point given by

$$(x_0^\star, x_2^\star) = (1, 0)$$

and the endemic equilibrium point given by :

$$(x_0^\star, x_2^\star) = (\frac{b}{c\beta_0}, \frac{c\beta_0 - b}{c\beta_0}),$$

where $c\beta_0 > b$.

Using R_0 , we can rewrite the equilibria.

$$(x_0^*, x_2^*) = (\frac{1}{R_0}, 1 - \frac{1}{R_0}) = (\frac{1}{R_0}, \frac{R_0 - 1}{R_0}).$$

Note that since $x_2^* \geq 0$, the endemic equilibrium point exists if and only if $R_0 \geq 1$.

Definition 3 *The Basic Reproduction number, R_0: The basic reproduction number, $R_0 = \frac{c\beta_0}{b}$, is the expected number of secondary cases produced, in a completely susceptible population during the period of infectiousness by a typical infective individual.*

To study the local stability of a fixed point we linearize our system first. Given the linearized matrix the, Jacobian matrix :

$$J_{|P_0} = \begin{pmatrix} -c\beta_0 x_2^* - b & -c\beta_0 x_0^* \\ c\beta_0 x_2^* & c\beta x_0^* - b \end{pmatrix}.$$

The Jacobian matrix at a disease-free equilibrium is given by:

$$\begin{pmatrix} -b & -c\beta_0 \\ 0 & c\beta_0 - b \end{pmatrix}.$$

From the eigenvalues $\lambda_1 = -b$ and $\lambda_2 = c\beta_0 - b$, one can easily see that the disease free equilibrium is stable if $c\beta_0 - b = b(R_0 - 1) < 0$, that is, if $R_0 < 1$. Now we can turn to an endemic equilibrium and study its stability closely. The Jacobian matrix evaluated at the endemic equilibrium is given by:

$$\begin{pmatrix} -c\beta_0 & -b \\ c\beta_0 - b & 0 \end{pmatrix}.$$

The trace of this matrix is always negative and the determinant is positive as long as $c\beta_0 - b = (R_0 - 1) > 0$, that is , the same condition as the one for existence of an endemic equilibrium.

Theorem 1 *Consider system (2.4)-(2.5),*
i)-the disease free equilibrium is locally asymptotically stable if $R_0 < 1$ *and unstable if* $R_0 > 1$.
ii)-the endemic equilibrium point is locally asymptotically stable if $R_0 > 1$.

Heuristically, we can define R_0 as the product of infection rate $c\beta_0$ and mean duration of infection $\frac{1}{b}$. However, for more complicated models with several infected compartments this simple heuristic definition of R_0 is insufficient. A more general basic reproduction number can be defined as the number of new infections produced by a typical infective individual in a population at a disease

free equilibrium. Note that for this model the basic reproduction depends on the contact rate, β_0, the mean number of sexual contacts, c and the rate at which new susceptibles are introduced into the population, b.

Chapter 3

SVIR MODEL

3.1 Introduction

An SVIR model is a Susceptible-Vaccinated-Infected-Removal model. Mass vaccination as a control mechanism attempts to lower the degree of susceptibility of healthy individuals against a particular pathogenic agent, and in this case the HIV agent.This has the effect of reducing the number of infectives in a population, and maybe, the proportion of contacts with infected individuals giving rise to the concept of 'herd immunity'.
The model described below differs from the SIS model formulated by Kribs-Zaleta, [**?**], which assumes that the vaccine wears off at a constant rate θ.

3.2 Model Formulation

We now formulate this model, by dividing the population into four classes, namely susceptibles (X_0), vaccinated (X_1), infectives (X_2) and the full blown AIDS (X_4). Let us consider an SIR type disease when a vaccination program is in effect and

there is a constant inflow of susceptibles through births. Let X_0 be the number of susceptibles, X_1 the number of vaccinated, X_2 the number of infecteds , X_4 the number of full blown AIDS cases and N the total population. We model new infections using the simple mass-action law, so $\frac{c\beta_0 X_0 X_2}{N} + \frac{c(1-\gamma)\beta_0 X_1 X_2}{N}$ where β_0 is the rate of contact sufficient to transmit the disease . We also assume a constant progression rate ν_1.The vaccine has the effect of reducing the susceptibility to infection by a factor γ, $0 < \gamma < 1$ so that $\gamma = 0$ means that the vaccine is ineffective in preventing infection, while $\gamma = 1$ means that the vaccine is completely effective. The rate at which the susceptible population is vaccinated is ϕ.We assume that there is a disease related death and define δ to be the rate of disease-related death, while μ is the rate of natural death that is not related to the disease. The population is replenished at a rate bN where b is the birth rate (see fig 3.1).

The dynamics of the disease are described by a system of differential Equations given by:

$$\begin{aligned}
\frac{dX_0}{dt} &= bN - \frac{c\beta_0 X_0 X_2}{N} - (\phi + \mu)X_0, && (3.1)\\
\frac{dX_1}{dt} &= \phi X_0 - \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - \mu X_1, && (3.2)\\
\frac{dX_2}{dt} &= \frac{c\beta_0 X_0 X_2}{N} + \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - (\nu_1 + \mu)X_2, && (3.3)\\
\frac{dX_4}{dt} &= \nu_1 X_2 - (\mu + \delta)X_4, && (3.4)\\
\frac{dN}{dt} &= (b-\mu)N - \delta X_4, && (3.5)
\end{aligned}$$

with $X_0(t) + X_1(t) + X_2(t) = N(t)$. This system is a special case of the system studied by Kgosimore and Lungu [**?**].

Introducing non-dimensional variables $x_i = \frac{X_i}{N}$ for $i = 0, 1, 2$, we obtain

$$\frac{dx_i}{dt} = \frac{(\frac{dX_i}{dt} - x_i\frac{dN}{dt})}{N}.$$

Since the variable X_4 does not appear in the first three equations of the system above we shall consider the equations (3.1) - (3.3) only so that we can take

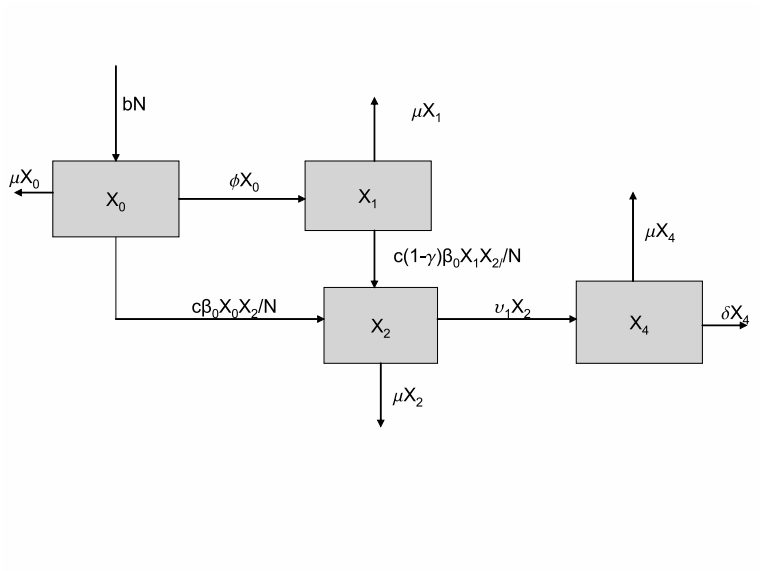

Figure 3.1: Compartmental model for the disease with vaccination

$\nu_1 = 0$. Clearly, the AIDS class does not influence the dynamics of this system. This assumption leads to the reduced system:

$$\begin{aligned}
\frac{dx_0}{dt} &= b - c\beta_0 x_0 x_2 - (\phi + b)x_0, \\
\frac{dx_1}{dt} &= \phi x_0 - c(1-\gamma)\beta_0 x_1 x_2 - b x_1, \\
\frac{dx_2}{dt} &= c\beta_0 x_0 x_2 + c(1-\gamma)\beta_0 x_1 x_2 - b x_2,
\end{aligned}$$

and

$$\sum_{i=0}^{2} x_i = 1.$$

Our resultant model is still a variable population model and our original objective of investigating the effects of vaccinating susceptible individuals on the spread of the disease can still be undertaken and is not affected by the simplifying assumption made. This is the system that we will analyse in order to illustrate the evolution of the disease. The equilibrium points for the model are obtained by setting the right hand side of the above system to zero. That is :

$$b - c\beta_0 x_0^* x_2^* - (\phi + b)x_0^* = 0, \tag{3.6}$$

$$\phi x_0^* - c(1-\gamma)\beta_0 x_1^* x_2^* - b x_1^* = 0, \tag{3.7}$$

$$c\beta_0 x_0^* x_2^* + c(1-\gamma)\beta_0 x_1^* x_2^* - b x_2^* = 0. \tag{3.8}$$

From (3.6)-(3.8)

$$x_2^*[c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - b] = 0,$$

which gives

$$x_2^* = 0$$

or

$$c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - b = 0.$$

The solution $x_2^* = 0$ leads to the disease free equilibrium point

$$(x_0^*, x_1^*, x_2^*) = (\frac{b}{\phi + b}, \frac{\phi}{\phi + b}, 0).$$

To compute the endemic equilibrium we make use of

$$c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - b = 0. \tag{3.9}$$

Now, from equation(3.9) we have

$$x_1^* = \frac{\phi x_0}{b + c(1-\gamma)\beta_0 x_2^*}$$
$$= \frac{b\phi}{(b+\phi+c\beta_0 x_2^*)(b+\beta_0 c(1-\gamma)x_2^*)}.$$

Substituting for x_0^* and x_1^* in (3.9) we obtain

$$B_1 x_2^{*2} + B_2 x_2^* + B_3 = 0, \tag{3.10}$$

where

$$B_1 = c^2\beta_0^2(1-\gamma),$$
$$B_2 = c\beta_0[(\phi+b)(1-\gamma)\beta_0 + b] - (1-\gamma)c\beta_0,$$
$$B_3 = (\phi+b)b(1 - \{\frac{c\beta_0}{b+\phi} + \frac{\phi c\beta_0(1-\gamma)}{b(b+\phi)}\})$$
$$= b[b+\phi][1-R]$$

where $R = \frac{c\beta_0}{b+\phi} + \frac{\phi(1-\gamma)c\beta_0}{b+\phi}$.
Defining $R_0 = \frac{c\beta_0}{b}$ and $R_{0v} = \frac{(1-\gamma)c\beta}{b}$, see [**?**], we have

$$R = \frac{b}{b+\phi}R_0 + \frac{\phi}{b+\phi}R_{0v}$$

and

$$x_2 = \frac{-B_2 + \sqrt{B_2^2 - 4B_1(\phi+b)[1-R]}}{2B_1}.$$

Theorem 2 *The endemic equilibrium point of (3.10) exists if* $R > 1$.

3.3 Stability analysis

We first construct the Jacobian matrix $J = Df(x_i)$ where $D = \frac{\partial}{\partial x_j}$ for $i, j = 0, 1, 2$.

$$J = \begin{pmatrix} -c\beta_0 x_2^\star - (\phi + b) & 0 & -c\beta_0 x_0^\star \\ \phi & -c(1-\gamma)\beta_0 x_2^\star - b & -c(1-\gamma)\beta_0 x_1^\star \\ c\beta_0 x_2^\star & c(1-\gamma)\beta_0 x_2^\star & c\beta_0 x_0^\star + c(1-\gamma)\beta_0 x_1^\star - b \end{pmatrix}.$$

At the disease free equilibrium point $P_0 = (\frac{b}{\phi+b}, \frac{\phi}{\phi+b}, 0)$, the Jacobian matrix becomes:

$$\begin{pmatrix} -(\phi + b) & 0 & \frac{c\beta_0 b}{\phi+b} \\ \phi & -b & \dfrac{-c(1-\gamma)\beta_0\phi}{\phi+b} \\ 0 & 0 & \dfrac{c(1-\gamma)\beta_0\phi}{\phi+b} + \dfrac{cb\beta_0}{\phi+b} - b \end{pmatrix}$$

and the eigenvalues of $J_| P_0$ are obtained from λ such that $\mid J_| P_0 - \lambda I \mid = 0$ The eigenvalues are $-(\phi + b), -b, \dfrac{c\beta_0 b}{\phi + b} + \dfrac{c(1-\gamma)\beta_0\phi}{\phi+b} - b$. For stability of the disease free equilibrium $\dfrac{c\beta_0 b}{\phi + b} + \dfrac{c(1-\gamma)\beta_0\phi}{\phi+b} - b < 0$ which leads to:

$$R(\phi) = \frac{c\beta_0}{\phi + b} + \frac{c(1-\gamma)\beta_0\phi}{b(\phi+b)},$$

$$= \frac{b}{b+\phi} R_0 + \frac{\phi}{b+\phi} R_{0v}$$

where $R_0 = \dfrac{c\beta_0}{b}$ and $R_{0v} = \dfrac{(1-\gamma)c\beta_0}{b}$. Here, R_0 is the basic reproduction number in the absence of intervention and R_{0v} is the basic reproduction number for the population where all individuals are vaccinated and $R(\phi)$ is the vaccination basic reproduction number.

3.4 Model Analysis

Now we can study the stability of the endemic equilibrium.The Jacobian matrix evaluated at the endemic equilibrium is given by:

$$\begin{pmatrix} -c\beta_0 x_2^* - (\phi + b) & 0 & -c\beta_0 x_0^* \\ \phi & -c(1-\gamma)\beta_0 x_2^* - b & -c\beta_0 x_1^* \\ c\beta_0 x_2^* & c(1-\gamma)\beta_0 x_2^* & c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - b \end{pmatrix}.$$

The trace of this matrix is always negative and the determinant is positive as long as $c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - b < 0$, that is, the same condition as the one for existance of an endemic equilibrium. In summary there is change in stability as $R(\phi)$ increases across $R(\phi) = 1$.

Theorem 3 *If $R(\phi) < 1$, the disease free equilibrium is locally asympotically stable,and the endemic equilibrium unstable. If $R(\phi) > 1$, the disease free equilibrium does not exist and the endemic equilibrium exists, and is locally asymptotically stable where $R(\phi) = \frac{c\beta_0}{\phi + b} + \frac{c\beta_0(1-\gamma)\phi}{b(\phi + b)}$ is the vaccination reproduction number.*

3.5 Analysis of the Vaccination Reproduction number

In this section, we determine the necessary and sufficient conditions that slow down the development of the disease and that reduce the reproduction number below the threshold of one. For vaccination, this is done by looking at Δ_ϕ which shows the differences between the basic reproduction number and the reproduction numbers due to vaccination . A positive difference in this case mean that vaccination is effective in lowering infectivity[**?**]. We also look at the derivative

and critical value of the reproductive numbers of vaccination .

To investigate long term expected effect of vaccination as a control strategy for the spread of HIV-AIDS, we address the problem in which vaccination is available to a proportion of the population.
We seek to derive conditions under which vaccination alone can slow down or eradicate the disease.The reproduction number in the presence of a vaccination strategy ϕ is

$$R(\phi) = R_0\{\frac{b + (1-\gamma)\phi}{\phi + b}\}.$$

We can see that $R(\phi)$ is a decreasing function of ϕ with $R(0) = R_0$.
Let us assume that all susceptibles are vaccinated immediately, that is , $\phi \to \infty$.
We see that

$$R(\phi) = R_0\{\frac{b + (1-\gamma)\phi}{\phi + b}\}$$

$$= R_0\{1 - \frac{\gamma\phi}{\phi + b}\} < R_0.$$

$$\lim_{\phi\to\infty} R(\phi) = \lim_{\phi\to\infty} R_0\{1 - \frac{\gamma\phi}{\phi + b}\}$$

$$= R_0 \lim_{\phi\to\infty}\{1 - \frac{\gamma\phi}{\phi + b}\}$$

$$= (1-\gamma)R_0 < R_0.$$

When $R_0 < 1$, the disease cannot develop into an epidemic, and vaccination will not be necessary in this case. If $R_0 > 1$, we want to consider the vaccination strategy that reduces the reproduction number $R(\phi)$ to below the threshold of one.

We consider this as a problem of finding the critical value ϕ^* for which a vaccination program succeeds in slowing down or in eradicating the disease.
We first look at the difference between the reproduction number R_0 and $R(\phi)$ which satisfies the Hsu-Schmitz [**?**] condition that

$$\Delta_\phi = R_0 - R(\phi) = R_0 - R_0(\frac{b + (1-\gamma)\phi}{\phi + b}),$$

$$= \frac{\gamma\phi}{\phi + b} R_0 > 1$$

and then, on differentiating the vaccination reproduction number $R(\phi)$ with respect to ϕ gives

$$\frac{dR(\phi)}{d\phi} = R_0\{\frac{(\phi + b)(1-\gamma) - [b + (1-\gamma)\phi]}{(\phi + b)^2},$$

which simplifies to :

$$\frac{dR(\phi)}{d\phi} = \frac{-\gamma b R_0}{(\phi + b)^2} < 0.$$

Clearly, this condition is necessary for slowing down the development of the disease. This result is true from the fact that $R(\phi)$ is a decreasing function of ϕ.
We can determine the critical fraction ϕ^* for which the vaccination program succeeds in reducing $R(\phi)$ below the threshold of one.
Setting the vaccination reproduction number equal to one, that is,

$$R(\phi) = 1,$$

we get

$$\phi^* = \frac{b(R_0 - 1)}{1 - (1-\gamma)R_0} > 0$$

and that it exists for $R_0 > 1 > (1-\gamma)R_0$. Note that for $R_0 > (1-\gamma)R_0 > 1$, there is no ϕ for which $R(\phi) < 1$. Therefore, for $R_0 > (1-\gamma)R_0 > 1$ the disease will remain endemic in the population.

3.6 Numerical Simulations on the effect of Vaccination on HIV Transmission

As shown in the previous sections, the dynamics of the HIV transmission may be controlled by vaccinating the susceptible individuals.
In order to obtain numerical hints about the discussed conditions we analyse simulations of the model with vaccination for a given set of parameters [**?**].

Table 3.1: approximate values/year for the parameters and variables used in the numerical simulations.

c	mean number of sexual contacts per person	5
γ	mean reduction factor in susceptibility due to vaccination	0.6
β_0	the infectious constant rate	0.05
μ	natural death rate	0.02
b	mean birth rate	0.03
ν_1	progression rate to the full blown AIDS class	0.23
δ	disease-induced death rate	0.88
S	susceptible population	5000
V	vaccinated population	4950
I	infected population	50
A	full blown AIDS population	0
N	total population	10000
ϕ^*	critical value of the proportion of susceptibles vaccinated	0.264

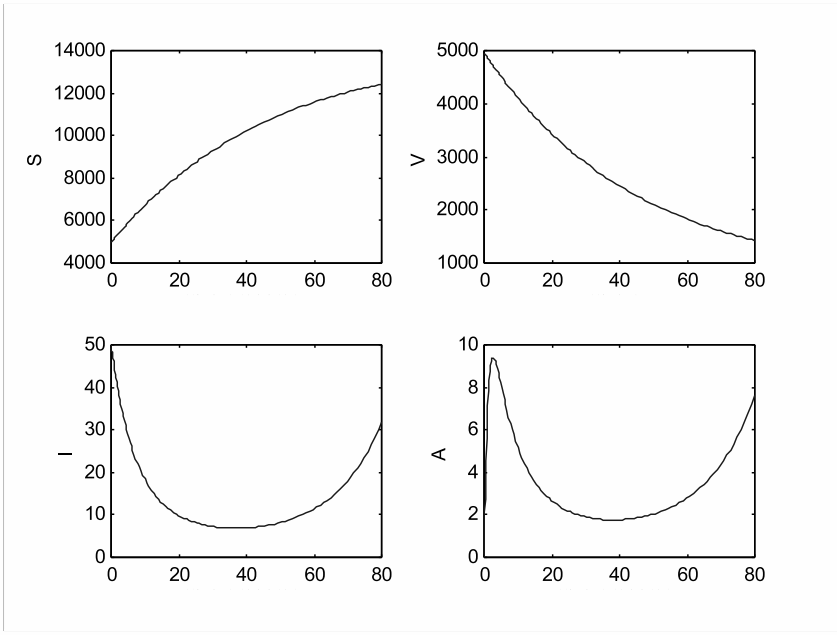

Figure 3.2: Model simulation (3.1)-(3.4) on the effects of vaccinating a proportion $\phi = 0.001 < \phi^*$

3.7 Numerical results on the effect of vaccinating a proportion $\phi < \phi^*$

By vaccinating a proportion $\phi < \phi^*$ of susceptibles, it can be seen from figure 3.2 below that the number of susceptible individuals (X_0 *or* S) will increase with time and the number of vaccinated individuals (X_1 *or* V) will decrease.

There will be a 'fake' decline in the number of infected individuals (X_2 *or* I) due to vaccination for the first 20 years but in the long run the HIV infected individuals will increase.

Also the number of individuals with full blown AIDS (X_4 *or* A) will rise to

a peak during the first 20 years and then start to decline before they start to increase again after 60 years.
Looking at the vaccination reproduction numbers which settle at $R(\phi) = 8.0699$, we can see that the number of new cases of infections produced by an infected individual in a population that is vaccinated below the critical proportion ϕ^* will increase.

3.8 Numerical results on the effect of vaccinating a proportion $\phi > \phi^*$

Vaccinating a proportion $\phi > \phi^*$ of susceptibles will result in a decrease in the number of susceptibles to below 1000 and then levels off in the long run (see figure 3.3 below). The vaccinated individual population (X_1 *or* V) will rise during the first $10 - 15$ years and level off in the long run above 8000 because a greater proportion $\phi = 0.5$ has been vaccinated. The infected individual population (X_2 *or* I) decreases to zero during the first 20 years and there will not be any new cases of infection. Full blown AIDS cases (X_4 *or* A) will rise slightly for the first $5 - 12$ years before it come to zero cases.
Clearly, vaccination is effective in eradicating the HIV virus provided a proportion greater than the critical proportion ϕ^* of susceptibles is vaccinated. The value of the vaccination reproduction numbers which settles at $R(\phi) = 0.6289$ clearly support this fact since new cases of infection produced by an infected individual in a population which is vaccinated at a proportion $\phi > \phi^*$ is below one.

Note 1 *Note that some of the parameter values used in the simulation are quoted in [?] and some are there for the sake of arguments.*

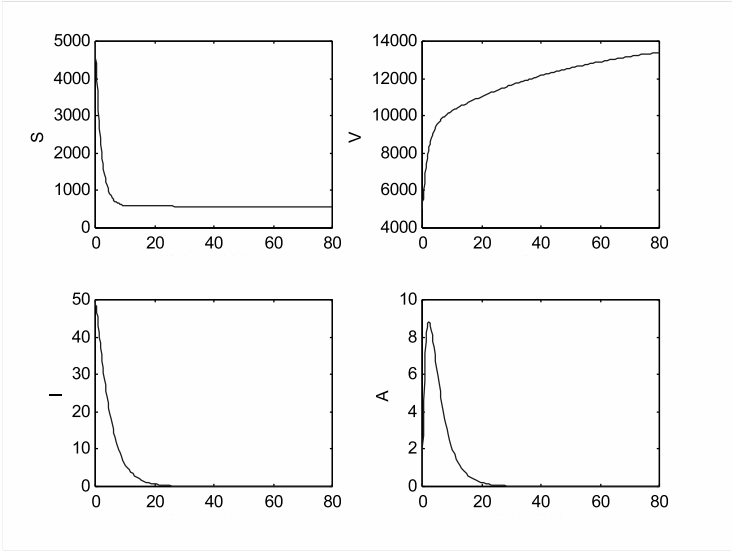

Figure 3.3: Model simulation (3.1)-(3.4) on the effects of vaccinating a proportion $\phi = 0.5 > \phi^*$

Chapter 4

TREATMENT MODEL

4.1 Introduction

Treatment also reduces the viral load of infected individuals thereby decreasing the level of infectiousness and hopefully the rate of transmission[**?**].

4.2 Model Formulation

Assuming that all infected individuals are identified immediately after infection we can consider treatment where ρ is the proportion of the treated infected individuals. ν is the rate of progression of the untreated infected individuals into the AIDS class and ν_1 is the rate of progression of the treated infected individuals into the AIDS class where $\nu > \nu_1$. δ is the death rate due to the disease.We illustrate the disease dynamics by means of a compartmental model given below.

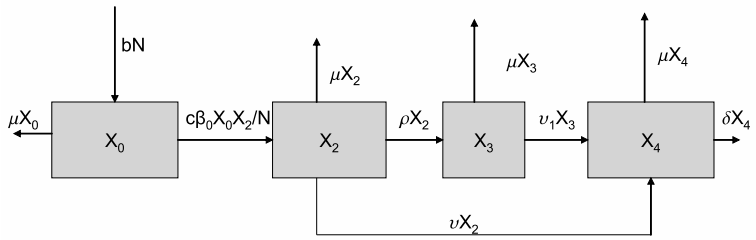

Figure 4.1: Compartmental model for the disease with treatment

The differential equations for the compartment presented above are:

$$\frac{dX_0}{dt} = bN - \frac{c\beta_0 X_0 X_2}{N} - \mu X_0, \tag{4.1}$$

$$\frac{dX_2}{dt} = \frac{c\beta_0 X_0 X_2}{N} - (\rho + \mu + \nu)X_2, \tag{4.2}$$

$$\frac{dX_3}{dt} = \rho X_2 - (\mu + \nu_1)X_3, \tag{4.3}$$

$$\frac{dX_4}{dt} = \nu_1 X_3 + \nu X_2 - (\mu + \delta)X_4, \tag{4.4}$$

and $\frac{dN}{dt} = (b - \mu)N$ where $N = X_0 + X_2 + X_3$.

Introducing non-dimensional variables $x_i = \frac{X_i}{N}$ for $i = 0, 2, 3$, we obtain

$$\frac{dx_i}{dt} = \frac{(\frac{dX_i}{dt} - x_i \frac{dN}{dt})}{N}.$$

As in the previous model, we consider the first three equations and assume that $\nu = 0$ and $\nu_1 = 0$. This eliminates the AIDS class and leads to the reduced system:

$$\begin{aligned}
\frac{dx_0}{dt} &= b - c\beta_0 x_0 x_2 - b x_0, && (4.5)\\
\frac{dx_2}{dt} &= c\beta_0 x_0 x_2 - (\rho + b) x_2, && (4.6)\\
\frac{dx_3}{dt} &= \rho x_2 - b x_3, && (4.7)\\
\frac{dN}{dt} &= (b - \mu) N, && (4.8)
\end{aligned}$$

where $x_0 + x_2 + x_3 = 1$.

The model is still a variable population model and our objective to investigate effects of treating infected individuals on the disease can still be done and is not affected by the simplifying assumption made.

4.3 Model Analysis

By setting the right hand side of the above system to zero we get:

$$b - c\beta_0 x_0^* x_2^* - b x_0^* = 0,$$

$$c\beta_0 x_0^* x_2^* - (\rho + b) x_2^* = 0,$$

$$\rho x_2^* - b x_3^* = 0.$$

For the disease free equilibrium point, we consider a case when $x_2^* = 0$. From the first condition of the system above, we get $x_0^* = 1$ and therefore the disease free equilibrium point becomes

$$P_0 = (1, 0, 0).$$

The endemic equilibrium point of system is obtained when $c\beta_0 x_0^* = \rho + b$, which gives:

$$x_0^* = \frac{\rho + b}{c\beta_0}.$$

After come calculations, we get the endemic equilibrium point as:

$$P_e = (\frac{\rho + b}{c\beta_0}, \frac{b[c\beta_0 - (\rho + b)]}{c\beta_0(\rho + b)}, \frac{[\rho(c\beta_0 - (\rho + b)]}{c\beta_0(\rho + b)}), c\beta_0 - (\rho + b) > 0.$$

To study the local stability of the fixed points we linearize our system first. The Jacobian matrix is given by:

$$J = \begin{pmatrix} -c\beta_0 x_2^* - b & -c\beta_0 x_0^* \\ c\beta_0 x_2^* & c\beta_0 x_0^* - (\rho + b) \end{pmatrix}.$$

The Jacobian matrix at the disease free equilibrium is given by :

$$\begin{pmatrix} -b & -c\beta_0 \\ 0 & c\beta_0 - (\rho + b) \end{pmatrix}.$$

and its eigenvalues are $-b$ and $c\beta_0 - (\rho + b)$. Therefore, the disease free equilibrium point is stable if $c\beta_0 - (\rho + b) < 0$.

Now, we can turn to the endemic equilibrium and study its stability. The Jacobian matrix evaluated at the endemic equilibrium is given by:

$$\begin{pmatrix} -b\{c\beta_0 - (\rho + b)\} - b & -(\rho + b) \\ \frac{b\{c\beta_0 - (\rho + b)\}}{\rho + b} & 0 \end{pmatrix}.$$

The trace of this matrix is always negative and the determinant is positive as long as $R(\rho) > 1$, that is, the same condition as the one for existence of an endemic equilibrium. We can summerise these results as follows:

Theorem 4 *If $R(\rho) < 1$ the disease free equilibrium is locally asymptotically and unstable if $R(\rho) > 1$.*

If $R(\rho) > 1$ the endemic equilibrium point is locally stable.

4.4 Analysis of the treatment reproduction number $R(\rho)$

At present, in most developing countries there are no vaccination programs due to high costs when purchasing these drugs. However, some of the HIV-AIDS infected individuals can afford the cost of antiretroviral drugs as treatment, and in Zimbabwe, the government introduced an AIDS levy to all its workers, both private and civil servants and they are channeling a portion of this money to the purchasing of antiretroviral drugs that they administer to some of the needy infected individuals.

For this reason, the analysis of the treatment reproduction number $R(\rho)$ is very important under the prevailing conditions and the results could help planners or policy makers make informed decisions when designing treatment control strategies. The treatment reproduction number in this case is given by $R(\rho) = \frac{c\beta_0}{\rho + b}$. We now consider the extent and the conditions treatment alone can slow down or eradicate the disease. It can be clearly seen that $R(\rho)$ is a decreasing function of ρ and $R(0) = R_0, R(\infty) = 0$. Therefore, $R_0 > R(\rho)$. If $R_0 < 1$, the disease cannot establish itself in the population and treatment will not be necessary. The condition $R_0 > 1$ will be of interest. One can ask 'for what critical value of ρ can the reproduction number $R(\rho)$ be kept below the threshold of one?'. Such a problem is solved as follows:

First, the Hsu Schmitz [**?**] difference between R_0 and $R(\rho)$ gives:

$$\Delta_\rho = R_0 - R(\rho) = c\beta_0(\frac{1}{b} - \frac{1}{\rho + b}) = \frac{c\beta_0\rho}{\rho + b} > 0. \tag{4.9}$$

If we differentiate $R(\rho)$ with respect to ρ we get :

$$\frac{dR(\rho)}{d\rho} = \frac{-c\beta_0}{(\rho + b)^2} < 0. \tag{4.10}$$

From (4.9) and (4.10) , we can see that a necessary condition for slowing down the growth of the disease is $R_0 > R(\rho)$.
Now we want to determine a critical value ρ^* that will reduce $R(\rho)$ below the threshold of one. Equating $R(\rho)$ one, we get

$$\frac{c\beta_0}{\rho + b} = 1$$

which gives

$$\rho^* = b(R_0 - 1)$$

as the critical choice of ρ for which treatment succeeds in bringing $R(\rho)$ to below the threshold one and that ρ^* exists for $R_0 > 1 > R(\rho)$.

Chapter 5

VACCINATION AND TREATMENT MODEL

5.1 Introduction

In this section we investigate the effect of a combined intervention strategy and consider a case when both vaccination and treatment programs are carried out at the same time. The model formulated below differs from that in Lungu and Kgosimore [**?**] in that it does not distinguish between infectives as to whether they were vaccinated or not vaccinated as susceptibles . We assume that the untreated infecteds progress to the AIDS class at a rate ν_1 and the treated infecteds progress to the AIDS class at a rate ν_2, where $\nu_1 > \nu_2$. Also the treated infectives are not infectious due to behaviour change.

5.2 Model Formulation

In this case we consider the compartmental model given below.

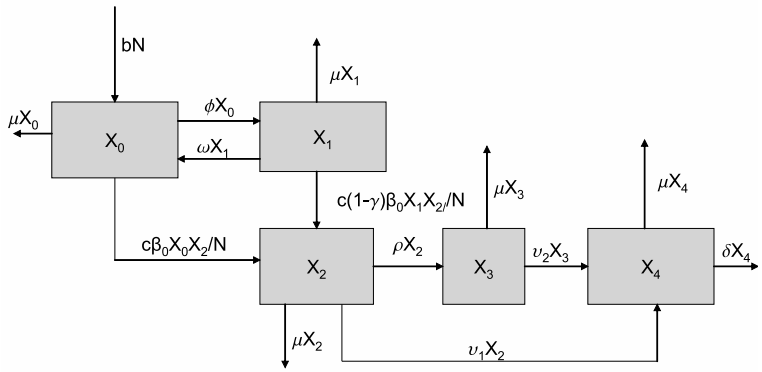

Figure 5.1: Compartmental model for the disease with vaccination and treatment

The compartmental differential eqations are:

$$\frac{dX_0}{dt} = bN - \frac{c\beta_0 X_0 X_2}{N} - (\phi + \mu)X_0 + \omega X_1, \tag{5.1}$$

$$\frac{dX_1}{dt} = \phi X_0 - \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - (\mu + \omega)X_1, \tag{5.2}$$

$$\frac{dX_2}{dt} = \frac{c\beta_0 X_0 X_2}{N} + \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - (\rho + \mu + \nu_1)X_2, \tag{5.3}$$

$$\frac{dX_3}{dt} = \rho X_2 - (\nu_2 + \mu)X_3, \tag{5.4}$$

$$\frac{dX_4}{dt} = \nu_2 X_3 + \nu_1 X_2 - \delta X_4, \tag{5.5}$$

and $N = \sum_{i=0}^{3} X_i$ since X_4 does not take part in disease dynamics.

Introducing non-dimensional variables $x_i = \frac{X_i}{N}$ for $i = 0, 1, 2, 3$ and setting $\nu_1 = \nu_2 = 0$, we obtain:

$$\frac{dx_i}{dt} = \frac{(\frac{dx_i}{dt} - x_i \frac{dN}{dt})}{N}.$$

We get the reduced system:

$$\begin{aligned}
\frac{dx_0}{dt} &= b - c\beta_0 x_0 x_2 - (\phi + b)x_0 + \omega x_1, && (5.6)\\
\frac{dx_1}{dt} &= \phi x_0 - c(1-\gamma)\beta_0 x_1 x_2 - (\omega + b)x_1, && (5.7)\\
\frac{dx_2}{dt} &= c\beta_0 x_0 x_2 + c(1-\gamma)\beta_0 x_1 x_2 - (\rho + b)x_2, && (5.8)\\
\frac{dx_3}{dt} &= \rho x_2 - b x_3, && (5.9)\\
\frac{dN}{dt} &= (b - \mu)N, && (5.10)
\end{aligned}$$

and $\sum_{i=0}^{3} x_i = 1$. This model is still a variable population model and our objective of investigating the effects of treating and vaccinating infected individuals on the disease can still be undertaken.

5.3 Model Analysis

Setting the right hand side of the above system to zero, we get:

$$b - c\beta_0 x_0^* x_2^* - (\phi + b)x_0^* + \omega x_1^* = 0,$$

$$\phi x_0^* - c(1-\gamma)\beta_0 x_1^* x_2^* - (\omega + b)x_1^* = 0,$$

$$c\beta_0 x_0^* x_2^* + c(1-\gamma)\beta_0 x_1^* x_2^* - (\rho + b)x_2^* = 0.$$

For the disease free equilibrium point, we consider a case when $x_2^* = 0$. We get the disease free equilibrium point:

$$P_0 = (\frac{(\omega + b)}{(\phi + \omega + b)}, \frac{\phi}{(\phi + \omega + b)}, 0, 0).$$

For the endemic equilibrium point of the system we consider a case when

$$x_1^* = \frac{(\rho + b) - c\beta_0 x_0^*}{c(1-\gamma)\beta_0}.$$

We obtain:

$$x_0^* = \frac{(\omega + b)(\rho + b) + c(1-\gamma)\beta_0(\rho + b)x_2^*}{\phi c(1-\gamma)\beta_0 + (\omega + b)c\beta_0 + c^2\beta_0^2(1-\gamma)x_2^*},$$

$$x_1^* = \frac{(\rho + b)\phi c(1-\gamma)\beta_0 + [(\rho + b)c^2\beta_0^2(1-\gamma) + c(1-\gamma)\beta_0(\rho + b)]x_2^*}{c(1-\gamma)\beta_0[\phi c(1-\gamma)\beta_0 + (\omega + b)c\beta_0 + c^2\beta_0^2(1-\gamma)]x_2^*}$$

and

$$E{x_2}^{*2} + Dx_2^* + F = 0 \tag{5.11}$$

where

$$E = c^2\beta_0^2(1-\gamma)^2(\rho + b),$$

$$D = (\phi+b)c(1-\gamma)^2\beta_0(\rho+b) - 2\omega c(\rho+b)\beta_0(1-\gamma) + c\beta_0(1-\gamma)(\omega+b)(\rho+b) - c^2(1-\gamma)^2\beta_0^2 b,$$

$$F = (\phi+b)(1-\gamma)(\omega+b)(\rho+b) - [\omega(\rho+b)\phi(1-\gamma) + c(1-\gamma)\beta_0 b(\omega+b) + c(1-\gamma)^2 b\phi\beta_0]$$

$$= (1-\gamma)(\rho + b)(\omega + \phi + b)(1 - R(\phi, \rho))$$

where $R(\phi, \rho) = \dfrac{c\beta_0 b[(\omega + b) + (1-\gamma)\phi]}{(\rho + b)[(\phi + b)(\omega + b) - \omega\phi)]}$.

Theorem 5 *The endemic equilibrium point of system (5.1)-(5.5) exists if and only if* $R(\phi, \rho) > 1$

Therefore, the endemic equilibrium point is $P_e = (x_0^*, x_1^*, x_2^*, x_3^*)$ where
$x_2^* = \dfrac{-D + \sqrt{D^2 - 4EF}}{2E} > 0$ since $E > 0$ and $F < 0$.

5.4 Computation of $R(\phi, \rho)$

$R(\phi, \rho)$ is the basic reproduction number due to vaccination and treatment. We can compute this threshold parameter using Diekmann's method, [**?**]. We sort the compartments so that the first two compartments correspond to infected individuals, that is,

$$\begin{aligned}
\frac{dX_2}{dt} &= \frac{c\beta_0 X_0 X_2}{N} + \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - (\rho + \mu + \nu_1)X_2, && (5.12)\\
\frac{dX_3}{dt} &= \rho X_2 - (\nu_2 + \mu)X_3, && (5.13)\\
\frac{dX_0}{dt} &= bN - \frac{c\beta_0 X_0 X_2}{N} - (\phi + \mu)X_0 + \omega X_1, && (5.14)\\
\frac{dX_1}{dt} &= \phi X_0 - \frac{c(1-\gamma)\beta_0 X_1 X_2}{N} - (\mu + \omega)X_1. && (5.15)
\end{aligned}$$

Redefining the state variables as follows:
$\mathbf{y} = (y_0, y_1, y_2, y_3)' = (x_2, x_3, x_0, x_1)'$, and defining $\mathbf{x}_s$ as the set of two infective groups as follows:
$\mathbf{x_s} = (x_2, x_3) = (y_0, y_1)$, we can apply the technique by van den Driesche and Watmough to obtain

$$\frac{d\mathbf{y}}{dt} = \mathbf{f} = \mathcal{F} - \mathcal{V}, \tag{5.16}$$

where $\mathbf{f} = (f_0, f_1, f_2, f_3)'$.
The system (5.6)-(5.9) becomes

$$\begin{aligned}
\frac{dy_0}{dt} &= c\beta y_2 y_0 + c(1-\gamma)\beta y_3 y_0 - (\rho + b)y_0, && (5.17)\\
\frac{dy_1}{dt} &= \rho y_0 - b y_1, && (5.18)\\
\frac{dy_2}{dt} &= b - c\beta_0 y_2 y_0 - (\phi + b)y_2 + \omega y_3, && (5.19)\\
\frac{dy_3}{dt} &= \phi y_2 - c(1-\gamma)\beta_0 y_3 y_0 - (b + \omega)y_3. && (5.20)
\end{aligned}$$

Let $\mathcal{F}_i(y), i = 0, 1, 2, 3$ be the rate of appearance of new infections in the compartment i. That is,

$$\mathcal{F}(y) = \begin{pmatrix} \frac{c\beta_0 y_2 y_0}{N} + \frac{c(1-\gamma)\beta_0 y_3 y_0}{N} \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$\mathcal{V}_i^+(y), i = 0, 1, 2, 3$ be the rate of transfer of individuals into compartment i by all other means, and is given by

$$\mathcal{V} = \begin{pmatrix} 0 \\ \rho y_0 \\ bN + \omega y_3 \\ \phi X_0 \end{pmatrix},$$

$\mathcal{V}_i^-$ be the rate of transfer of individuals out of compartment i by all other means, and

$$\mathcal{V}^- = \begin{pmatrix} (\mu+\rho)y_0 \\ \mu y_1 \\ \frac{c\beta_0 y_2 y_0}{N} + (\phi+\mu)y_2 \\ \frac{c(1-\gamma)\beta_0 y_3 y_0}{N} + (\mu+\omega)y_3 \end{pmatrix}.$$

Therefore

$$\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+ = \begin{pmatrix} (\mu+\rho)y_0 \\ \mu y_1 - \rho y_0 \\ (\phi+\mu)y_2 - (bN + \omega y_3) \\ \frac{c(1-\gamma)\beta_0 y_3 y_0}{N} + (\mu+\omega)y_3 \end{pmatrix}.$$

The disease transmission model becomes $\frac{dy_i}{dt} = f_i(y) = \mathcal{F}_i(x) - \mathcal{V}_i(y), i = 2, 3, 0, 1.$

Assumptions as in van den Driesche and Watmough [?]

A1)-each function of (5.16) is continously differentiable at least twice in each

variable,

A2) since each function represents a direct transfer of individuals, they are all non-negative, that is if $\mathbf{y} = (y_0, y_1, y_2, y_3) \geq 0$ then $\mathcal{F}_i(y), \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0, i = 0, 1, 2, 3,$

A3)-if a compartment is empty,then there can be no transfer of individuals out of the compartment by death,infection, nor any other means, that is, if $y_i = 0$ then $\mathcal{V}_i^- = 0$ for $i = 2, 3,$

A4)-$\mathcal{F}_i(x) = 0$ if $i = 2, 3,$

A5)-if $y_0 = y_1 = 0$,then $\mathcal{F}_i(y) = 0$ and $\mathcal{V}_i{}^+(y) = 0$ for $i = 0, 1,$

A6)-if $\mathcal{F}(y)$ is set to zero, then all eigenvalues of $D\mathcal{F}(y) \mid P_0$ negative real parts.

Lemma 1 *If $P_0 = (x_0^*, x_1^*, 0, 0)$ is a disease free equilibrium of (5.16) and $f_i(x)$ satisfying assumptions (A1)-(A6), then the derivatives $D\mathcal{F}(x)$ evaluated at P_0 and $D\mathcal{V}(x) \mid P_0$ are partitioned as:*

$$D\mathcal{F}(x) \mid P_0 = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix},$$

$$D\mathcal{V}(x) \mid P_0 = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

where F and V are the 2×2 matrices defined by :

$$F = [\frac{\partial \mathcal{F}_i}{\partial x_j} \mid P_0]$$

and

$$V = [\frac{\partial V_i(x)}{\partial x_j} \mid P_0], i, j = 2, 3.$$

$F \geq 0$, V is non-singular and all eigenvalues of J_3 and J_4 have positive real parts.

proof 1 *For details of the proof, see [?].*

Theorem 6 *Consider the disease transmission model given by (5.16) with $f(x)$ satisfying (A1)-(A6). If P_0 is a disease free equilibrium of the model, then P_0 is locally asymptotically stable if $R(\phi, \rho) < 1$, but unstable if $R(\phi, \rho) > 1$, where $R(\phi, \rho) = \rho(FV^{-1})$ and $\rho(FV^{-1})$ is the spectral radius of FV^{-1}.*

proof 2 *Let $J_1 = F - V$. Since V is a non-singular M-matrix and F is non-singular, $-J_1 = V - F$ has the Z sign pattern[?]. $\Rightarrow$ $s(J_1) < 0 \Leftrightarrow -J_1$ is a non-singular M matrix where $s(J_1)$ denotes the maximum real part of all the eigenvalues of the matrix J_1 (spectral abscissa of J_1). Since FV^{-1} is non-negative*

$$-J_1V^{-1} = (V - F)V^{-1}$$

$$= I - FV^{-1}$$

also has the Z sign pattern. Applying Lemma 5 of [?],with $H = V$ and $B = -J_1 = V - F \Rightarrow -J_1$ is a non-singular matrix $\Leftrightarrow I - FV^{-1}$ is a non-singular M-matrix. Since FV^{-1} is non-negative, all eigenvalues of FV^{-1} have magnitude less than or equal to $\rho(FV^{-1})$. Thus $I - FV^{-1}$ is a non-singular M-matrix $\Leftrightarrow \rho(FV^{-1}) < 1$. $\Rightarrow s(J_1) < 0 \Leftrightarrow R(\phi, \rho) < 1$. Similarly

$$s(J_1) = 0 \Leftrightarrow -J_1$$

is a singular matrix

$$\Leftrightarrow I - FV^{-1}$$

is a singular M matrix

$$\Leftrightarrow \rho(FV^{-1}) = 1.$$

Using *Lemma* 1 and the above theorem, to the model (5.17)-(5.20), we get

$$F = \begin{pmatrix} \frac{c\beta_0 y_2^*}{N} + \frac{c(1-\gamma)\beta_0 y_3^*}{N} & 0 \\ 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu + \rho & 0 \\ -\rho & \mu \end{pmatrix}.$$

The inverse of matrix V is given by

$$V^{-1} = \begin{pmatrix} \dfrac{1}{\mu+\rho} & 0 \\ \dfrac{\rho}{\mu(\rho+\mu)} & \dfrac{1}{\mu} \end{pmatrix}$$

and

$$FV^{-1} = \begin{pmatrix} \dfrac{c\beta_0 y_2^* + c(1-\gamma)\beta_0 y_3^*}{N(\mu+\rho)} & 0 \\ 0 & 0 \end{pmatrix}.$$

The spectral radius of FV^{-1} is

$$\rho(FV^{-1}) = \frac{c\beta_0 y_2^* + c(1-\gamma)\beta_0 y_3^*}{N(\mu+\rho)} < 0$$

if the disease free equilibrium point is stable. On substituting

$$y_2^* = \frac{bN[(\phi+\mu)(\mu+\omega)-\phi\omega)] + \omega\phi bN}{(\phi+\mu)[(\phi+\mu)(\mu+\omega)-\phi\omega]},$$

$$y_3^* = \frac{\phi bN}{(\phi+\mu)(\mu+\omega)-\phi\omega};$$

into $\rho(FV^{-1})$ we get

$$R(\phi,\rho) = \frac{c\beta_0 b[(\omega+b)+(1-\gamma)\phi]}{(\rho+b)[(\phi+b)(\omega+b)-\omega\phi)]}$$

5.5 Stability analysis

To study the local stability of a fixed point one can linearize the system first. The Jacobian matrix is

$$J = \begin{pmatrix} -c\beta_0 x_2^\star - (\phi+b) & \omega & -c\beta_0 x_0^\star \\ \phi & -c(1-\gamma)\beta_0 x_2^\star - (b+\omega) & -c(1-\gamma)\beta_0 x_1^* \\ c\beta_0 x_2^\star & c(1-\gamma)\beta_0 x_2^\star & c\beta_0 x_0^\star + c(1-\gamma)\beta_0 x_1^\star - (\rho+b) \end{pmatrix}.$$

The Jacobian matrix at the disease free equilibrium is :

$$\begin{pmatrix} -(\phi+b) & \omega & \dfrac{-c\beta_0 b(\omega+b)}{(\phi+b)(\omega+b)-\omega\phi} \\ \phi & -(\omega+b) & \dfrac{-c(1-\gamma)\beta_0\phi b}{(\phi+b)(\omega+b)-\omega\phi} \\ 0 & 0 & \dfrac{c\beta_0 b(\omega+b)+c(1-\gamma)\beta_0\phi b}{(\phi+b)(\omega+b)-\omega\phi}-(\rho+b) \end{pmatrix}.$$

By looking at eigenvalues, one can see that the disease free equilibrium is stable if

$$\frac{c\beta_0 b(\omega+b)+c(1-\gamma)\beta_0\phi b}{(\phi+b)(\omega+b)-\omega\phi}-(\rho+b)<0.$$

This condition can be written as

$$(\rho+b)(R(\phi,\rho)-1)<0$$

where

$$R(\phi,\rho)=\frac{c\beta_0 b[(\omega+b)+(1-\gamma)\phi]}{(\rho+b)[(\phi+b)(\omega+b)-\omega\phi)]}.$$

Now we can turn to an endemic equilibrium and study its stability.The Jacobian matrix evaluated at the endemic equilibrium is :

$$\begin{pmatrix} -c\beta_0 x_2^*-(\phi+b) & \omega & -c\beta_0 x_0^* \\ \phi & -c(1-\gamma)\beta_0 x_2^*-(\omega+b) & -c(1-\gamma)\beta_0 x_1^* \\ c\beta_0 x_2^* & c(1-\gamma)\beta_0 x_2^* & c\beta_0 x_0^*+c(1-\gamma)\beta_0 x_1^*-(\rho+b) \end{pmatrix},$$

where

$$x_0^*=\frac{(\omega+b)(\rho+b)+c(1-\gamma)\beta_0(\rho+b)x_2^*}{\phi c(1-\gamma)\beta_0+c^2\beta_0^2(1-\gamma)x_2^*+(\omega+b)c\beta_0},$$

$$x_1^*=\frac{(\rho+b)\phi c(1-\gamma)\beta_0+[(\rho+b)c^2\beta_0^2(1-\gamma)+c(1-\gamma)\beta_0(\rho+b)]x_2^*}{c(1-\gamma)\beta_0[\phi c(1-\gamma)\beta_0+c^2\beta_0^2(1-\gamma)]x_2^*]+(\omega+b)c\beta_0},$$

and
$x_2^* = \dfrac{-D + \sqrt{D^2 - 4(1-\gamma)(\rho+b)(\omega+\phi+b)(1-R(\phi,\rho))E}}{2E}$. The trace of this matrix is always negative and the determinant is positive as long as
$c\beta_0 x_0^* + c(1-\gamma)\beta_0 x_1^* - (\rho+b) < 0$.

Theorem 7 *1)-The disease free equilibrium point of system (5.1)-(5.5) is locally asymptotically stable if* $R(\phi,\rho) < 1$ *and unstable if* $R(\phi,\rho) > 1$.
2)-The endemic equilibrium point of (5.6)-(5.9) is locally asymptotically stable if $R(\phi,\rho) > 1$.

5.6 Effects of a combination of Treatment and Vaccination as a control strategy

We finally consider an intervention program in which a proportion ϕ of susceptibles is vaccinated, and a proportion ρ of infected individuals is treated(provided with Antiretroviral drugs). The reproduction number $R(\phi,\rho)$ which is defined as :

$$R(\phi,\rho) = R(\rho)\frac{b[(\omega+b)+(1-\gamma)\phi]}{[(\phi+b)(\omega+b)-\omega\phi]}$$

$$= R(\rho)[1 - \frac{\gamma\phi}{\omega+b+\phi}] < R(\rho)$$

is a decreasing function of ϕ and ρ . Setting off vaccination and treatment, we get $R(0,0) = R_0$. Also $R(0,\rho) = R(\rho), R(\phi,0) = R(\phi)$ when $\omega = 0$.
Let us consider a situation when $R(\phi,\rho) > 1$ and look at the critical values of ϕ and ρ such that a vaccination and treatment program can slow down or eradicate the disease.
Like we did before, we calculate the Hsu Schmitz difference between R_0 and

$R(\phi, \rho)$ which is given by:

$$\Delta_{\phi,\rho} = \frac{c\beta_0}{b}\{1 - \frac{b^2[(\omega + b) + (1 - \gamma)\phi]}{(\rho + b)(\phi b + \omega^2 + \omega b)}\} > 0$$

and on differentiating $R(\phi, \rho)$ partially with respect to ϕ and ρ, we obtain

$$\frac{\partial R(\phi, \rho)}{\partial \phi} = \frac{c\beta_0 b}{(\rho + b)}\{\frac{[(\phi + b)(\omega + b) - \omega\phi](1 - \gamma) - b[(\omega + b) + (1 - \gamma)\phi]}{[(\phi + b)(\omega + b) - \omega\phi]^2}\},$$

$$\frac{\partial R(\phi, \rho)}{\partial \rho} = \frac{-c\beta_0 b[(\omega + b) + (1 - \gamma)\phi][(\phi + b)(\omega + b) - \omega\phi]}{(\rho + b)^2[(\phi + b)(\omega + b) - \omega\phi]^2},$$

$$\frac{\partial^2 R(\phi, \rho)}{\partial \phi \partial \rho} = \frac{-c\beta_0 b\{[(\phi + b)(\omega + b) - \omega\phi](1 - \gamma) - b\{(\omega + b) + (1 - \gamma)\phi\}][[(\phi + b)(\omega + b) - \omega\phi]^2]}{(\rho + b)^2[(\phi + b)(\omega + b) - \omega\phi]^4}.$$

The conditions $\Delta_{\phi,\rho} > 0$,$\frac{\partial R(\phi,\rho)}{\partial \phi} < 0$, $\frac{\partial R(\phi,\rho)}{\partial \rho} < 0$ and $\frac{\partial^2 R(\phi,\rho)}{\partial \phi \partial \rho} < 0$ yield the following sufficient conditions:

$$(\rho + b)[(\phi + \omega)(\omega + b) - \omega\phi] > b^2\phi(\omega + b)(1 - \gamma)$$

and

$$b[(\omega + b) + (1 - \gamma)\phi] > [(\phi + b)(\omega + b) - \omega\phi](1 - \gamma).$$

For the critical values ϕ^* and ρ^* for the success of vaccination and treatment respectively, we find the values of ϕ and ρ such that $R(\phi, \rho) = 1$.
This gives:

$$\phi^* = \frac{c\beta_0 b(\omega + b) - b(\rho + b)(\omega + b)}{(\rho + b)(\omega + b) - [c\beta_0 b(1 - \gamma) + \omega(\rho + b)]}$$

and

$$\rho^* = \frac{b\{c\beta_0[(\omega + b) + (1 - \gamma)\phi] - [(\phi + b)(\omega + b) - \omega\phi]\}}{(\phi + b)(\omega + b) - \omega\phi}.$$

Therefore, the combination of vaccination and treatment program would succeed in lowering the reproduction number $R(\phi, \rho)$ below the threshold one only if the proportion $\phi > \phi^*$ of susceptibles is vaccinated, the proportion $\rho > \rho^*$ of normal infectives is treated.

The results show that the success of a vaccination and treatment program is certain when the conditions

$$(\rho + b)[(\phi + \omega)(\omega + b) - \omega\phi] > b^2\phi(\omega + b)(1 - \gamma)$$

and

$$b[(\omega + b) + (1 - \gamma)\phi] > [(\phi + b)(\omega + b) - \omega\phi](1 - \gamma)$$

are satisfied.

Chapter 6

CONCLUSIONS

The purpose of this study is to take a close look at the effects of vaccination and treatment on HIV-AIDS dynamics. To a simple AIDS model we studied the effects of vaccination first. The result of our mathematical analysis indicates that a vaccination campaign can succeed if a proportion $\phi > \phi^*$ is vaccinated as this has the effect of lowering R_0 below 1. That is, we can manage to control the disease if we vaccinate a proportion ϕ of susceptible individuals. If all the susceptibles are vaccinated immediately, the basic reproduction number will be reduced by a factor $(1 - \gamma)$. If the quality of the vaccine is also improved and education campaigns on behaviour change are effective so that $\gamma = 1$, we see that $R(\phi) = (1 - \gamma)R_0$ will be reduced to zero, meaning that there will not be any new cases of infection.

We have seen in our analysis that $R(\phi)$ is a decreasing function of the vaccination parameter ϕ. Clearly, there are benefits associated with this strategy.

For a model with treatment, it was seen that a proportion $\rho > \rho^*$ must be treated in order for a treatment policy to be effective. The reproduction number $R(\rho)$ is a decreasing function of the treatment parameter ρ. Again we can clearly see the benefits of treatment.

In the case of a combined effect of vaccination and treatment, the result tells us

that the combined intervention strategy is more effective than a single strategy. Vaccinating a proportion $\phi > \phi^*$ and treating a proportion $\rho > \rho^*$ can effectively control the dynamics of the disease provided the sufficient conditions derived in the combined strategy are met.

These theoretical and numerical results obtained are in agreement with those found by Lungu and Kgosimore, ([**?**]) and Shu-Fang ([**?**],[**?**]).

References

[1] C. Castillo-Chavez et al, On the computation of R_0 and its role on global stability, pp 4-6.

[2] C. M. Kribs-Zaleta and Jorge X.Velasco-Hern*a*ndez: A simple model with multiple endemic states, Math. Biosci. 164 (2000) 183-201 pp 187.

[3] E. M. Lungu and M. Kgosimore, Effects of vaccination and treatment on the transmission of HIV-AIDS, 2004.

[4] J. D. Murray, Mathematical Biology, 2nd edition, pp 611-612.

[5] J. M. Hyman et al, An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations, Math. Biosci. 167 (2000) 65-86.

[6] J. Roberto et al, Modeling the spread of HIV in homosexual populations with heterogeneous preventive attitude, J. of Bio. systems,vol 12, 4 (2004) 439-456 pp. 449-454.

[7] M.S Moghadas et al, Could condoms stop the AIDS epidemic, Journal of Theoretical Medicine, J. Theoretical Medicine,(2004).

[8] P. V. Driessche et al, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 167 (2000) 65-86, pp30-34, pp47.

[9] S. F. Hsu Schmitz, Effects of treatment or and vaccination on HIV transmission in homosexuals with genetic heterogeneity, Math. Biosci. 167 (2000) 1-18.

[10] S. F. Hsu Schmitz et al, Effects of education, vaccination and treatment on HIV transmission in homosexuals with genetic heterogeneity, Math. Biosci. 187(2004) 111-133.

[11] V. Hernandez et al, Effects of treatment and behaviour changes on the dynamics of HIV and AIDS in a highly sexually active population. Technical report,1994.

Appendix A

Appendix

Programs used for the numerical simulations on the model with vaccination:
function dydt = vaccination(t,y) global b c beta0 phi mu gamma nu1 delta N mu=0.02; c=5; nu1=0.23; b=0.03; gamma=0.98; delta=0.88; beta0=0.05; N=10000; phi=0.5; dydt = [b*N - (mu + phi)*y(1) - c*beta0*y(3)*y(1)/N; phi*y(1) - mu*y(2) - c*(1 - gamma)*beta0*y(2)*y(3)/N; c*(1-gamma)*beta0*y(2)*y(3)/N + c*beta0*y(3)*y(1)/N - (mu + nu1)*y(3); nu1*y(3) - (mu + delta)*y(4)];

R = c*beta0/(phi + b) + c*(1 - gamma)*beta0*phi/(b*(phi+b))

2):

[t,y] = ode45('vaccination',[0 80],[5000;4950;50;0]); figure plot(t,y(:,1),'-','t,y(:,2),'+',t,y(:,3),'o',t,y(:,4),'.') title('Solution of the Immunology Model'); xlabel('time t'); ylabel('Solution y'); legend ($'y_1', 'y_2', 'y_3', 'y_4', 'y_5$) figure subplot(2,2,1) plot(t,y(:,1)); xlabel('time t (years)'); ylabel('S');

subplot(2,2,2) plot(t,y(:,2)); xlabel('time t'); ylabel('V');

subplot(2,2,3) plot(t,y(:,3)); xlabel('time t (years)'); ylabel('I');

subplot(2,2,4) plot(t,y(:,4)); xlabel('time t (years)'); ylabel('A');