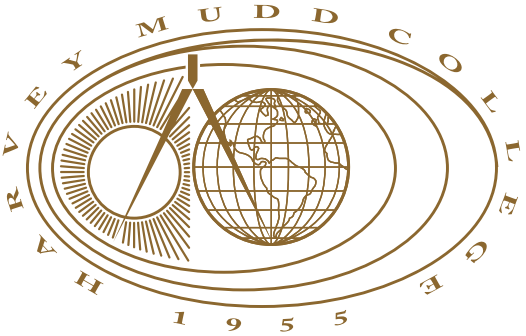
2009

Mathematical AIDS Epidemic Model: Preferential Anti-Retroviral Therapy Distribution in Resource Constrained Countries

Nadia Abuelezam
Harvey Mudd College



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Nadia Abuelezam

Lisette de Pillis, Advisor

Karl Haushalter, Reader

May, 2009

HARVEY MUDD COLLEGE
Department of Mathematics

Abstract

HIV/AIDS is one of the largest health problems the world is currently facing. Even with anti-retroviral therapies (ART), many resource-constrained countries are unable to meet the treatment needs of their infected populations. ART-distribution methods need to be created that prevent the largest number of future HIV infections. We have developed a compartment model that tracks the spread of HIV in multiple two-sex populations over time in the presence of limited treatment. The model has been fit to represent the HIV epidemic in rural and urban areas in Uganda. With the model we examine the spread of HIV among urban and rural regions and observe the effects of preferential treatment to rural areas on the spread of HIV in the country as a whole. We also investigate the effects of preferentially treating women on the spread of HIV. We find that preferentially treating urban women produces the most dramatic effect in reducing the number of infected male and females in rural and urban areas.

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Acknowledgments

I would like to thank Lisette de Pillis for her guidance and support throughout the year. I would also like to thank my second reader Karl Haushalter for his comments. Claire Connelly and Suzanne Frantz have provided me with invaluable help and support over the last year and I would like to thank them. I would additionally like to thank the Harvey Mudd College Mathematics Department, Darryl Yong and the Dean of Faculty Robert Cave for their support.

Chapter 1

Introduction

HIV/AIDS is currently the largest health problem the world faces and is going to continue facing throughout the next generation. We seek to mathematically explore rationing, an issue inherent in the treatment of this devastating disease, and the effects of various rationing strategies. This chapter outlines basic information on HIV/AIDS, ART, and our research.

1.1 HIV/AIDS

Every country and racial group has been affected by HIV and is dealing with the severe ramifications of this infection (Figure 1.1). HIV is a global problem that affects and is affected by many facets of sexuality, drug use, and health care. It is estimated that 33 million people were living with HIV in 2007, the majority of which were from sub-Saharan Africa (UNAIDS, 2007).

The human immunodeficiency virus (HIV) can be transmitted through contact with some bodily fluids. The three known modes of transmission are sexual contact, mother to child transmission, and sharing contaminated blood or blood products. Unprotected heterosexual contact is the main transmission route across the world, especially in developing nations (UNAIDS, 2005). Most new infections in developed countries occur in those sharing needles in injection drug use or in men having sex with men (UNAIDS, 2008).

The origins of HIV and the mode through which it was introduced to humans is largely accepted to have occurred through humans' interaction with chimpanzees, who suffered from an older form of the disease (Royce et al., 1997). Many researchers are getting closer to finding the date that the

transmission from chimpanzees to humans occurred (Worobey et al., 2008). HIV is a "retrovirus," a virus that is able to incorporate its own genome into the DNA of a cell it is infecting, thereby reversing the process of DNA replication (Okware et al., 2001). As a robust retrovirus, HIV is able to incorporate its RNA into cells even in stressful environments. HIV infection occurs over the course of a number of different stages. After the initial transfer of HIV through bodily fluids, the period that follows is called acute HIV infection (Powers et al., 2008). During this stage the virus rapidly replicates and the RNA viral levels rise. At this stage, an individual is most infectious and is most likely to pass the disease onto others. Also in this stage, the number of CD4+T cells in the body, an important component of the immune system, are dramatically reduced (Vernazza et al., 1999). The latency stage that follows is a result of the immune system's ability to reduce the number of viral particles in the blood stream. This period is marked by a reduced number of symptoms, although individuals are still infectious (Vernazza et al., 1999). Once the disease has progressed and the CD4+ count in the body falls below 200 cells, a person is diagnosed with AIDS, and immunity to infection is lost (Vernazza et al., 1999). Symptoms at this stage include moderate weight loss, respiratory-tract infections, skin rashes, and oral ulcerations (Powers et al., 2008). Untreated, AIDS ultimately leads to death.

HIV often affects the most biologically and socially productive members in society. Because the disease is transmitted sexually, young adults who are having unprotected sex are most at risk for contracting the disease just as they are beginning their careers or finishing their education (MOH, 2006). Because the disease can remain latent (without obvious symptoms) for up to 15 years, people who contract HIV at a young age are often affected during their working years and when their children need them most. Besides being a problem to children who lose their parents and become "AIDS orphans," the disease carries with it enormous public health implications.

About 39 million people will have been infected with HIV worldwide by the end of 2008 (UNAIDS, 2007). The United States currently has an HIV prevalence rate (the proportion of the population that is infected with HIV) of about 0.58 percent (Scott et al., 2008). The hardest hit communities within the United States are gay males, injection drug users, and black females. Haiti is the most devastated country in the western hemisphere, where HIV is currently the number one cause of death among young adults between the ages of 18-25 (UNAIDS, 2005). Haiti's pandemic is fast approaching the severity of the sub-Saharan Africa crisis. Currently sub-Saharan Africa contributes less then 10 percent of the world's population but more than 50

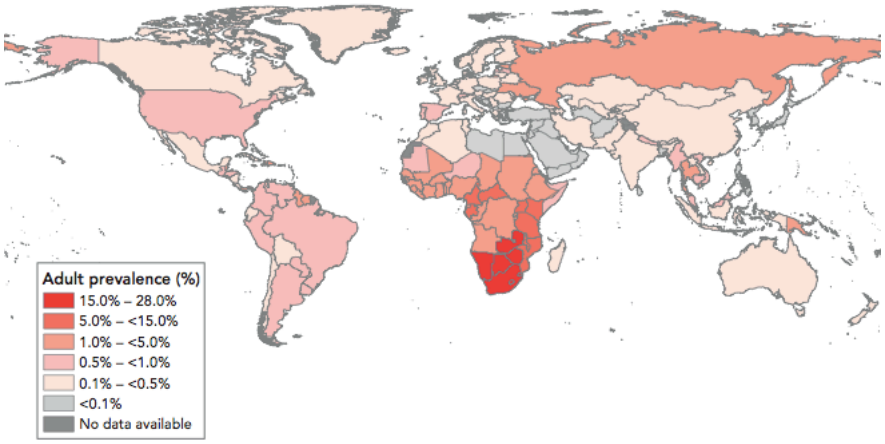


Figure 1.1: Number of HIV infected people living around the world in 2007, the majority of which are in sub-Saharan Africa (taken from UNAIDS (2008)).

percent of the world's HIV infected people, with an overall HIV prevalence rate of 8.57 percent (UNAIDS, 2005). In some countries, such as Rwanda and Botswana, nearly a quarter of the population (25 percent) is infected with HIV. HIV is difficult to tackle in developing nations, as societal factors and economic conditions often contribute to infection.

1.2 Uganda

For the majority of this project we will focus on a single sub-Saharan African country: Uganda. Uganda is of particular interest because of the country's success in reducing the prevalence of HIV over the course of 20 years by nearly 20 percent (UNAIDS, 2007). The country has gone through many changes in governance and attitudes about HIV. Currently, the reported prevalence is 6 percent, making Uganda the model for HIV prevention in sub-Saharan Africa (UNAIDS, 2007). During the past two decades Uganda has gained political stability with a new president who is proactive about decreasing the HIV prevalence rate. When President Museveni recognized that HIV was a problem, he decided to begin a program called "ABC," for which he went on national television and created advertisements encouraging citizens to "Abstain, Be Faithful and when those two fail, use Con-

doms" (UAC, 2003). In addition to the president's strong message, many organizations that worked to reduce stigma and increase social support for people living with HIV/AIDS were created. One such organization, The AIDS Support Organization (TASO), currently provides free counseling, free treatment, free medical care, and other social services to anyone who tests positive for HIV. This organization is working toward increasing its patient load, but relies heavily on major donors, including the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the World Health Organization (WHO), and the Bill and Melinda Gates Foundation (MOH, 2006).

1.3 Treatment: ART

Within the past decade significant progress has been made in finding ways to fight HIV within the body. The creation of anti-retroviral therapy (ART) has been a great stepping stone to allowing people living with HIV/AIDS to lead normal and healthy lives. The "triple cocktail" (three medications taken at the same time) is composed of chemicals that suppress a person's viral load to undetectable levels (Orrell et al., 2003). The medications are to be taken everyday for the rest of the patient's life and sometimes have debilitating side effects, including nausea, dizziness, pain, and inability to perform everyday functions (Powers et al., 2008). When these medications were first released, they were too expensive for developing nations to afford. As such, those most in need of treatment in developing nations were not receiving medication until fairly recently (Scott et al., 2008).

Issues of drug resistance with ART therapy frequently arise for patients who do not take their medication consistently. Because the virus multiplies in the body so rapidly, thousands of genetic variants are created every minute, and when drugs are taken inconsistently, there is a higher chance of drug resistance developing (Vernazza et al., 1999). Drug resistance needs to be taken into account when implementing a distribution strategy in developing nations, since distance to health centers has a strong influence on whether people can get their medications on time and thus be compliant (Abuelezam, 2008).

Currently only about 28 percent of individuals worldwide who need treatment are receiving it, even with the creation of generic drugs and the reduction in prices (UNAIDS, 2005). Many countries in sub-Saharan Africa have limited resources and depend on foreign aid and thus are unable to provide their citizens with the drugs they need to survive. Because gov-

ernments and health organizations do not have the budget or the infrastructure to provide medications to all citizens in need, rationing strategies must be undertaken to help the greatest number of people in need (Pence, 2007). There is a great deal of philosophical debate in the literature about the most ethical distribution strategy of ART in resource-constrained countries. The general consensus is that until universal access to treatment can be provided to all those in need, any rationing strategy will be deficient (Pence, 2007). It is hoped that increased contributions by the world's major powers to the HIV/AIDS crisis, as has been done with PEPFAR, will continue to contribute to global treatment of HIV.

The WHO recognizes that rationing is the only adequate strategy at the moment and has released a document describing its recommendations on the most appropriate distribution strategy (UNAIDS, 2005). In the WHO document, the organization outlines methods through which major health organizations should begin distributing HIV treatment. The WHO report clearly states that until universal access to treatment can be provided, disadvantaged populations should be given preference in the drug-distribution process (UNAIDS, 2005). Although preferential treatment seems highly controversial, the effect of preferential treatment on the spread of the virus has been relatively unexplored.

Currently, only about 25 percent of the people in need of treatment in Uganda are receiving treatment (UNAIDS, 2007). Because many clinics and centers are far away from rural villages, it is often impossible for individuals to get to clinics to receive their medication. There is a discrepancy between the ease of treatment in rural and urban areas simply due to distance to health centers (Abuelezam, 2008). In addition, more women seek medical attention than men, which suggests that more women will ultimately be treated (MOH, 2006). In Uganda, because the disease is primarily heterosexually transmitted, women are the most affected by the disease and so are at a sexual disadvantage because of their gender and role in society. Women who do not receive proper care and treatment often pass on the disease to their children, further motivating preferential treatment to women (Hogle et al., 2002).

1.4 Research Goals

The primary goal of this thesis project is to gain a greater understanding of the dynamics of treatment on the spread of HIV in Uganda. Further, we seek to explore the ramifications of the WHO proposed policy that recom-

mends preferential treatment to disadvantaged populations. We hope to accomplish these goals with the following concrete tasks:

- Produce a two-population and two-sex mathematical model that allows us to examine the dynamics of HIV in rural and urban Uganda. The compartmental epidemiological model should accurately reflect the dynamics of HIV transmission and prevention in Uganda and should allow us to make reasonable predictions regarding HIV prevalence and death associated with HIV/AIDS. The model should also be able to account for dynamics between populations that are in close proximity to one another as well as those that are distant from one another.
- Analyze the model and assess the effects of preferential treatment to women in rural areas on the future spread of HIV in the region. The model should be analyzed both analytically and numerically to better understand the properties and dynamics with and without treatment. A dynamical systems analysis should be performed on a simple model and expanded to a larger more complex model.
- Develop simulations of the spread of HIV across Uganda with different treatment regimes. These simulations should allow us to make conclusions that are in agreement or disagreement with the WHO guidelines for ART treatment distribution.

1.5 Literature

There are a number of mathematical models in the literature that aim to understand different aspects and end goals of HIV prevention and treatment strategies. Although our developed model is not a direct extension of specific models in the literature, many models are similar in structure, suggesting that we are progressing in the appropriate direction. A number of models that attempt to assess the spread of disease in Uganda consider interaction between sexes, whereas other models consider interactions between populations. It is our goal to combine these two approaches. Doyle et al. (1998) developed a two-sex, two-population model to better understand the spread of HIV in a heterosexual population and analyzed the model for existence and stability of solutions. Their model did not include treatment, and was concerned with a general AIDS class for both populations. Although this paper only provides a dynamical systems analysis and

not a numerical analysis, understanding the development and justification for this model was useful in developing our own model (Doyle et al., 1998). Sani et al. (2007) examine the dynamics of a two-population model while distinguishing between sexes. Although this model is stochastic, it has provided insight into the basic structure of the infection rate, as the infection rate is often the most difficult parameter to estimate and to represent mathematically.

Lloyd and May (1996) developed a generalized model for understanding the spread of HIV through multiple populations. The model they develop is analyzed very extensively through dynamical systems techniques and other techniques that assess the presence and stability of equilibria. This paper will be a useful beginning to a dynamical systems analysis of our own model and techniques applied in their analysis may also be of use (Lloyd and May, 1996).

Keeling and Rohani (2002) developed a model to examine spatial coupling and diffusion of individuals from geographically distant populations. In their model they considered the interactions of two populations of susceptible and infected individuals. Because they assume that the populations are far from each other, the length of stay and thus the interaction time between populations is extended when individuals interact with the other population. Their analysis will be useful to our overall goal of incorporating distance dynamics into our model. The majority of the models in the literature have both age structure and disease-stage structure, allowing for both the tracking of different age groups and the different infectiousness parameters of the different viral loads.

Preferential treatment has been looked at by a number of different authors. Wilson et al. (2006) developed a spatially explicit PDE model that distinguished between urban and rural populations and is the most extensive look at the problem in the literature currently. The model was parametrized to represent dynamics in South Africa, in the KwaZulu-Natal region (Wilson et al., 2006). The authors found that the distribution strategy that produced the fewest future infections was an urban-only approach where all the treatment was dedicated to the capital. This strategy also produced the highest levels of resistance (Wilson et al., 2006). A trade-off such as this one would be interesting to observe in our own studies.

1.6 Paper Outline

Chapter 2 discusses the development and motivation for our preliminary model and our model with treatment and AIDS. This chapter also presents information relevant to the analytical analysis discussed in Chapter 5. The basic reproductive number and its derivation is presented in Chapter 4 along with a discussion of some of the preliminary simulations run on the model. More extensive discussion of model simulations and the effect of various preferential treatment strategies follows in Chapter 6. A discussion of the various sensitivity analyses run on the preliminary and advanced model is presented in Chapter 3. Finally, future work and possible directions are outlined in Chapter 7.

Chapter 2

Models

This chapter outlines current progress in the development of an appropriate model. We have developed two separate models, one preliminary model that accounts only for new infections, and an advanced model that accounts for AIDS cases and incorporates treatment.

2.1 Preliminary Model

In order to understand better the dynamics we can expect from the model structure we have chosen, we decided to develop a preliminary model before expanding the model to include treatment and an AIDS class.

2.1.1 Assumptions

Our model has a number of underlying assumptions that will each be discussed in turn and evaluated for legitimacy. The first set of assumptions is based on biological and epidemiological justifications.

Risk of transmission is proportional to the number of sexual encounters.

Although this assumption has previously been assumed to be the standard indicator of risky behavior, many recent studies have shown that the risk of infection is not proportional to the number of sexual encounters someone has, but rather the number of concurrent partnerships an individual is in (Halperin and Epstein, 2004). We can imagine that in a society with monogamous relationships, if one person became infected with HIV, the disease

would not spread but would be contained within the monogamous relationship. In a society in which people maintain concurrent partnerships, if one person is infected with HIV, the rest of society is also at risk, because of the concurrent partnerships occurring (Halperin and Epstein, 2004). Although the assumption that risk is proportional to the number of sexual encounters is critical to determining the chosen infection rate, this assumption may be relaxed in future work.

This second set of assumptions are being made for mathematical expediency and will be loosened in future work.

Infection happens only through unprotected heterosexual contact.

This assumption is valid when considering the model's application to sub-Saharan Africa. Heterosexual transmission accounts for nearly 40 percent of all HIV infections in sub-Saharan Africa, with vertical transmission accounting for a large percentage of the rest (UAC, 2003). HIV infections due solely to heterosexual transmission in sub-Saharan Africa are coming into question, and studies are showing that heterosexual transmission is declining in importance (Gisselquist et al., 2002). Because of these new epidemiological developments, it is necessary to keep this assumption in mind when validating the model and assessing the basic reproductive number. In attempting to represent dynamics occuring across the globe, we see that about 80 percent of the people infected with HIV are heterosexual (UAC, 2003), suggesting that unsafe heterosexual sex is a relevant mode of transmission. This assumption may be relaxed in the future in order to apply the model to locations where homosexual interactions and drug use are correlated with higher prevalences of disease.

Risk of transmission is intermediate for all sexual encounters.

There have been a number of studies aimed at determining the average probability of transmission per unsafe sexual encounter. Powers et al. (2008) performed a meta-analysis in which they claim that a single infection probability is impractical and misleading. Because some interactions produce a large probability of infection due to outside factors, such as the presence of sexually transmitted diseases (STI) (Powers et al., 2008), the authors suggest that when modeling, we should not use a single infection probability, but rather consider using a range of numbers. At the moment we are using a simple infection-force parameter and will consider using multiple parameters in future work.

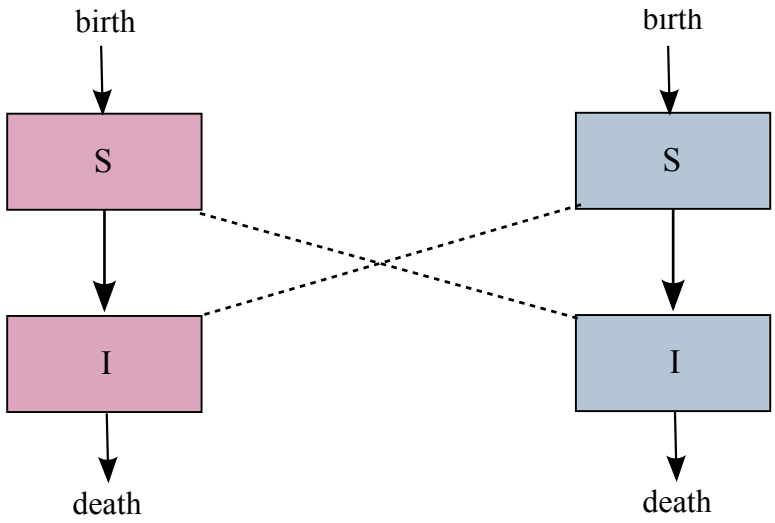


Figure 2.1: The interactions between the susceptible (S) and the infected (I) individuals of two populations are shown as modeled in the preliminary model. Dotted lines represent interactions leading to HIV infection.

2.1.2 Model Equations

In developing an appropriate mathematical model that would represent the dynamics of HIV transmission in Uganda, we wanted it to have a number of key components. Because we are interested in studying preferential distribution among different subgroups of the population, we seek to have different compartments for each of these groups. We ultimately decided to focus on women and those living in rural areas, and with this focus we found it necessary to distinguish between men and women, and also between rural and urban populations. Thus, a two-sex, two-population model suited our needs (Figure 2.1). After developing a basic model with two populations, each with two sexes, and two compartments (susceptibles and infecteds) it became apparent that we had to thoroughly understand the interaction term and its elements before proceeding.

The preliminary model is defined by the following eight differential equations:

$$
\begin{aligned}
\frac{dSW_1}{dt} &= bNW_1 - dSW_1 - \frac{\beta_{MW} SW_1 \left(c_1 IM_1 + c_2 IM_2\right)}{NM_1 + NM_2} \\
\frac{dIW_1}{dt} &= \frac{\beta_{MW} SW_1 \left(c_1 IM_1 + c_2 IM_2\right)}{NM_1 + NM_2} - dIW_1 \\
\frac{dSM_1}{dt} &= bNM_1 - dSM_1 - \frac{\beta_{WM} SM_1 \left(c_3 IW_1 + c_4 IW_2\right)}{NW_1 + NW_2} \\
\frac{dIM_1}{dt} &= \frac{\beta_{WM} SM_1 \left(c_3 IW_1 + c_4 IW_2\right)}{NW_1 + NW_2} - dIM_1 \\
\frac{dSW_2}{dt} &= bNW_2 - dSW_2 - \frac{\beta_{MW} SW_2 \left(c_5 IM_1 + c_6 IM_2\right)}{NM_1 + NM_2} \\
\frac{dIW_2}{dt} &= \frac{\beta_{MW} SW_2 \left(c_5 IM_1 + c_6 IM_2\right)}{NM_1 + NM_2} - dIW_2 \\
\frac{dSM_2}{dt} &= bNM_2 - dSM_2 - \frac{\beta_{WM} SM_2 \left(c_7 IW_1 + c_8 IW_2\right)}{NW_1 + NW_2} \\
\frac{dIM_2}{dt} &= \frac{\beta_{WM} SM_2 \left(c_7 IW_1 + c_8 IW_2\right)}{NW_1 + NW_2} - dIM_2.
\end{aligned}
$$

All parameter and state variables are described in Table 2.1 and Table 2.2.

In our creation of the model, we were concerned with the dynamics defined by the interaction term. Our first concern was accurately choosing the population to divide by in the interaction term $\frac{\beta_{MW} SW_1 (c_1 IM_1 + c_2 IM_2)}{NM_1 + NM_2}$. In the

Parameter	Definition
b	birth rate per year
d	death rate per year
β_{MW}	prob. of transmission from one sexual encounter (male is HIV+)
β_{WM}	prob. of transmission from one sexual encounter (female is HIV+)
c_{1-8}	average number of sexual encounters per year

Table 2.1: Definitions for parameters in preliminary model.

State Variable	Definition
SW_x	susceptible women in population x
SM_x	susceptible men in population x
IW_x	infected women in population x
IM_x	infected men in population x
NW_x	number of women in population x
NM_x	number of men in population x

Table 2.2: Definitions of state variables for preliminary model.

literature, there were models that divided by the size of the entire population (Doyle et al., 1998; van den Driessche and Watmough, 2002) and others that divided by only the population that was infecting (Scott et al., 2008; Sani et al., 2007; Baryarama et al., 2005), such as ours. We decided that since the entire term represents a person's chance of interacting with an infected individual and becoming infected, the denominator would have to be the total population size of the infected population. Although we considered making the interaction term a mass-action term to match some models in the literature (Sani et al., 2007), we have decided to stick with the current methodology.

We also referred to the literature to decide on an appropriate method for defining the units of the infection terms (Scott et al., 2008; Sani et al., 2007; Baryarama et al., 2005). The total infection parameter, βc, can be broken down to the following units: β is the probability of transmission upon a single encounter and c is the total number of sexual encounters in one year. These definitions of the infection force represent the dynamics we were hoping to see in a two-sex multipopulation model (see Section 4.2). Once

we attained appropriate and predicted behavior in this simple model, we decided to move on to a more complex model that incorporated disease stages, including an AIDS stage and a treated stage.

2.2 Model with AIDS Class and Treatment

Because the primary concern of our project is to understand better the dynamics of preferential treatment, it was necessary for us to incorporate both a treated class and an AIDS class into our model.

2.2.1 Assumptions

In addition to the assumptions outlined in Section 2.1.1, we have additional assumptions for the expanded model. As before, this first set of assumptions is based on biological and epidemiological justification.

Individuals with AIDS are too sick to have unprotected sexual encounters.

Our model assumes that members of the AIDS class are not being treated. AIDS significantly reduces stamina, health, and physical capacities of those who have developed it. To this extent, it is not unreasonable to assume that people at the AIDS stage are unable to have sexual intercourse (Royce et al., 1997).

Individuals who receive treatment have only protected sex.

We are assuming that individuals who receive treatment are educated about risky sexual practices at the health center they receive their medications from. To this extent, we would expect them to practice protected sex by using condoms and other methods described to them at health centers. This assumption is being studied extensively in the literature. In a recent study by Bunnell et al. (2008), the authors found that those people who knew their HIV status were three times more likely to use condoms in their last sexual encounter then those who had not been tested. Other studies and meta-analyses show that interventions, like treatment, reduce the risk of unprotected sex (Crepaz et al., 2006) and so the assumption holds in most instances. What is impractical about this assumption, however, is that it assumes that individuals have protected sex 100 percent of the time, which is not what studies have shown (Neumann et al., 2002).

Individuals with AIDS and with HIV are treated at the same rates.

From personal experiences working with The AIDS Support Organization (TASO) in Uganda, treatment levels are not positively correlated with AIDS diagnoses. Treatment in most health organizations is granted on the basis of interviews, as well as a patient's disease progression, and so patients do not often know whether or not they have AIDS before they are put on treatment.

The following additional assumption is added for mathematical expediency.

Individuals who are treated are compliant with their medication.

We are assuming that no resistant strains of HIV are being created in the population. One could imagine that a different model would take into account individuals who stop treatment, and therefore move to the infected class with a different strain of the disease (Wilson et al., 2006). The assumption of compliance is not completely unjustified, as many studies have shown that compliance rates in sub-Saharan Africa are high, and far surpass the rates predicted in developed countries (Crepaz et al., 2006). A study in South Africa of 289 HIV-infected individuals shows that the median adherence levels were 93.5 percent (Orrell 2003). This result along with many others, suggests that this assumption is not invalid, but maybe impractical in a world of HIV/AIDS.

2.2.2 Model Equations

Currently the model is composed of sixteen ordinary differential equations (ODEs), four for each subpopulation. We consider two geographically close populations, each with their own male and female subpopulations. We can imagine that there is a flow of individuals between the two populations and that infection can occur across population lines, as described by the interaction term (Figure 2.2). In this particular model, we were able to add additional death rates to account for increased death in AIDS and HIV subpopulations. The parameters and state variables are described in Table 2.3 and Table 2.4.

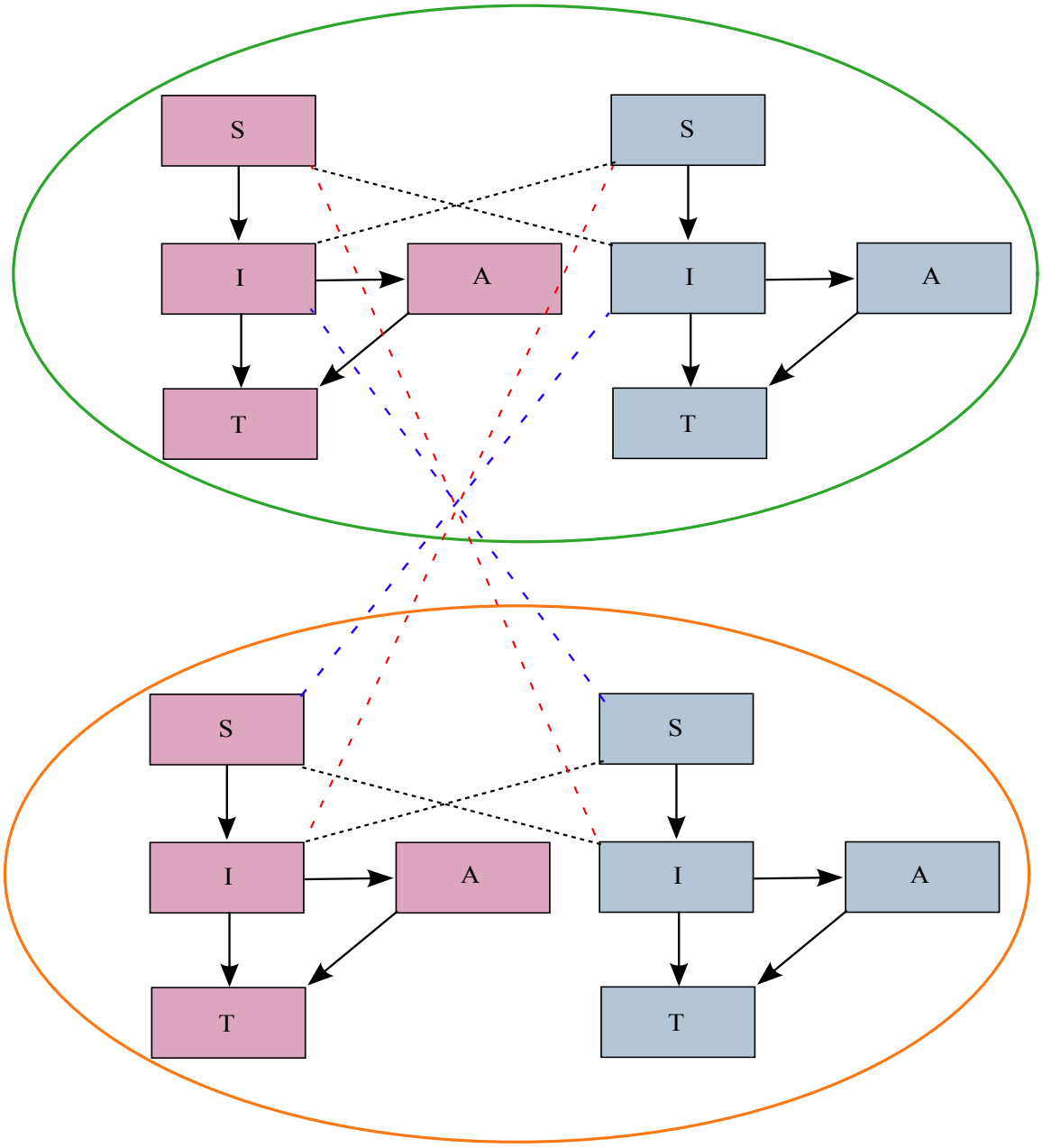


Figure 2.2: This figure describes the total dynamics in the expanded treatment and AIDS model. Each oval represents a distinct population. Within each population there are two sexes, each with susceptible individuals (S), infected individuals (I), treated individuals (T) and those with AIDS (A). The dotted lines account for interactions that lead to HIV infection.

Population 1: Women

$$\frac{dSW_1}{dt} = bNW_1 - dSW_1 - \frac{\beta_{MW} SW_1 \left(c_1 IM_1 + c_2 IM_2\right)}{NM_1 + NM_2}$$
$$\frac{dIW_1}{dt} = \frac{\beta_{MW} SW_1 \left(c_1 IM_1 + c_2 IM_2\right)}{NM_1 + NM_2} - (d+q)IW_1 - \tau_{W1} IW_1 - \alpha IW_1$$
$$\frac{dAW_1}{dt} = \alpha IW_1 - \tau_{W1} AW_1 - (l+d)AW_1$$
$$\frac{dTW_1}{dt} = \tau_{W1} IW_1 + \tau_{W1} AW_1 - dTW_1$$
$$\frac{dNW_1}{dt} = bNW_1 - dSW_1 - (d+q)IW_1 - (l+d)AW_1 - dTW_1$$

Population 1: Men

$$\frac{dSM_1}{dt} = bNM_1 - dSM_1 - \frac{\beta_{WM} SM_1 \left(c_3 IW_1 + c_4 IW_2\right)}{NW_1 + NW_2}$$
$$\frac{dIM_1}{dt} = \frac{\beta_{WM} SM_1 \left(c_3 IW_1 + c_4 IW_2\right)}{NW_1 + NW_2} - (d+q)IM_1 - \tau_{M1} IM_1 - \alpha IM_1$$
$$\frac{dAM_1}{dt} = \alpha IM_1 - \tau_{M1} AM_1 - (l+d)AM_1$$
$$\frac{dTM_1}{dt} = \tau_{M1} IM_1 + \tau_{M1} AM_1 - dTM_1$$
$$\frac{dNM_1}{dt} = bNM_1 - dSM_1 - (d+q)IM_1 - (l+d)AM_1 - dTM_1$$

Population 2: Women

$$\frac{dSW_2}{dt} = bNW_2 - dSW_2 - \frac{\beta_{MW} SW_2 (c_5 IM_1 + c_6 IM_2)}{NM_1 + NM_2}$$
$$\frac{dIW_2}{dt} = \frac{\beta_{MW} SW_2 (c_5 IM_1 + c_6 IM_2)}{NM_1 + NM_2} - (d+q)IW_2 - \tau_{W2} IW_2 - \alpha_{W2} IW_2$$
$$\frac{dAW_2}{dt} = \alpha IW_2 - \tau_{W2} AW_2 - (l+d)AW_2$$
$$\frac{dTW_2}{dt} = \tau_{W2} IW_2 + \tau_{W2} AW_2 - dTW_2$$
$$\frac{dNW_2}{dt} = bNW_2 - dSW_2 - (d+q)IW_2 - -(l+d)AW_2 - dTW_2$$

Population 2: Men

$$\frac{dSM_2}{dt} = bNM_2 - dSM_2 - \frac{\beta_{WM} SM_2 (c_7 IW_1 + c_8 IW_2)}{NW_1 + NW_2}$$
$$\frac{dIM_2}{dt} = \frac{\beta_{WM} SM_2 (c_7 IW_1 + c_8 IW_2)}{NW_1 + NW_2} - (d+q)IM_2 - \tau_{M2} IM_2 - \alpha_{M2} IM_2$$
$$\frac{dAM_2}{dt} = \alpha IM_2 - (l+d)AM_2 - \tau_{M2} AM_2$$
$$\frac{dTM_2}{dt} = \tau_{M2} IM_2 + \tau_{M2} AM_2 - dTM_2$$
$$\frac{dNM_2}{dt} = bNM_2 - dSM_2 - (d+q)IM_2 - (l+d)AM_2 - dTM_2$$

2.2.3 Parameters and State Variables

The system has a large number of parameters that must be estimated. An extensive literature search was undertaken to provide estimates for the parameters defined in Table 2.3. Because most of these parameters are estimated from studies and surveys, a range of parameter values is provided. These parameter ranges will be explored in the context of a sensitivity analysis, as described in Chapter 3. Many of the parameters that are specific to sexual behaviors in Uganda rely on data from the Sero-Behavioural Survey performed in 2005 by the Ugandan Ministry of Health (2006). This survey is often cited because the sample size was large and individuals

Parameter	Definition
b	birth rate per year
d	death rate per year
q	additional death rate for infected individuals per year
l	additional death rate for AIDS patients per year
β_{MW}	prob. of transmission from one sexual encounter (male is HIV+)
β_{WM}	prob. of transmission from one sexual encounter (female is HIV+)
c_{1-8}	average number of sexual encounters per year
τ_x	treatment rate for individual in pop. x per year
α	rate of progression to AIDS per year

Table 2.3: Definitions for parameters in expanded model.

were surveyed from a wide range of geographic locations and thus it gives an overview of HIV prevalence throughout Uganda. It should be noted, however, that there is controversy in the literature about the reliability of surveys in sub-Saharan Africa. Lagarde et al. (1995) have shown that oftentimes the agreement between partners' answers is limited, or answers are altered based on the sex of the interviewer (Lagarde et al., 1995). In some cases the researchers found that men were over reporting sexual activity. Although we will still use the information from this survey and other surveys, we will keep our literature searches in mind when analyzing our model.

Parameter	Estimate	References
b	0.03–0.08	MOH (2006), Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2006)
d	0.01–0.05	MOH (2006), Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2006)
q	-	
l	-	
β_{MW}	0.0001–.01	Wawer et al. (2005),Gray et al. (2001), Royce et al. (1997)
β_{WM}	0.0004–0.008	Wawer et al. (2005), Gray et al. (2001), Royce et al. (1997)
c_{1-8}	36–120	Blanc and Rutenberg (1991), Wawer et al. (2005), Gray et al. (2001), Schopper et al. (1993)
τ_x	0.12–0.3	MOH (2006), UNAIDS (2007), UNAIDS (2005)
α	0.04–0.12	MOH (2006), Morgan et al. (2002)

Table 2.4: Estimates for parameters in expanded model

State Variable	Definition
SW_x	susceptible women in population x
SM_x	susceptible men in population x
IW_x	infected women in population x
IM_x	infected men in population x
AW_x	women with AIDS in population x
AM_x	men with AIDS in population x
TW_x	treated women in population x
TM_x	treated men in population x
NW_x	number of women in population x
NM_x	number of men in population x

Table 2.5: Definitions of state variables for expanded model.

Chapter 3

Sensitivity Analysis

A sensitivity analysis will help us better understand which of the twenty-two parameters in our model we should focus on estimating most precisely. This section describes both the preliminary and more advanced sensitivity analysis explored and how their results influence our future model simulations.

3.1 Preliminary Sensitivity Analysis

A sensitivity analysis allows us to determine which parameters affect the model results most and thus which will be most important to estimate precisely. We have performed a preliminary sensitivity analysis that determines the change of a specific end value when one parameter is changed by a specific percentage. For this sensitivity analysis, we observed the change in total prevalence with the increase and decrease of parameters by 25 percent. We also decided to observe how the total prevalence was affected at different time points, in order to understand whether an outbreak was more likely to occur with certain parameter values. The results of the sensitivity analysis for populations of equal sizes can be visualized in Figure 3.1. From this plot, we see that in the case that the two population sizes are relatively equal, the parameters that seem to have the largest positive effect on the total prevelance are the infection-rate parameters, β_{MW} and β_{WM}. The birth rate b has a negative effect on the total prevalence. From these results we can conclude that when population sizes are equal we would expect β and b to have the largest effect on the sensitivity of total prevalence. When the simulations were run with one large and one small population, we see that the parameters associated with the larger population have a larger ef-

fect on the outcome of the model (see Appendix A).

3.2 Latin Hypercube Sensitivity Analysis

In addition to running a basic sensitivity analysis on the model, we have also completed a preliminary Latin Hypercube Sensitivity analysis (LHS). This analysis allows us to examine a large portion of the parameter space quickly and effectively.

3.2.1 Theory

LHS was first introduced by McKay, Conover, and Beckman (1979). These authors proposed this method of sensitivity analysis because it was both fast and efficient at sampling parameters throughout the entire parameter space. The process has been performed on a number of different epidemiological models modeling HIV (Wilson et al., 2006; Blower and Dowlatabadi, 1994). In LHS, each parameter is treated as a random variable defined by a certain probability-distribution function (Blower and Dowlatabadi, 1994). Based on the number of samples, N, one wishes to perform, each parameter distribution is split into equal intervals. For each simulation and each parameter, a parameter value is chosen from a randomly selected interval. The intervals are sampled without replacement, ensuring that every part of the parameter space is tested (Blower and Dowlatabadi, 1994). The model is subsequently run N times. In this way, LHS is able to observe changes in parameter values efficiently, without potentially having redundant sample choices. The process can be visualized in Figure 3.2. The LHS design has been compared to simple random sampling and full-factorial sampling and has been found to be the most efficient method to accurately predict the model's sensitivity to parameter changes (Blower and Dowlatabadi, 1994).

The results from LHS can be analyzed using a statistical technique called partial-rank correlation coefficients (PRCC) analysis. PRCC is used to determine the statistical relationship between each input parameter and the output variables while keeping all other variables at a constant expected value. PRCC is especially useful because it illustrates the independent effects of each parameter. PRCC analysis can only be performed on parameters that cause a monotonic increase or decrease in the outcome variable, since the coefficient indicates the degree of monotonicity between the input and output parameters (Blower and Dowlatabadi, 1994). The partial-rank correlation coefficients can be compared qualitatively for positive or

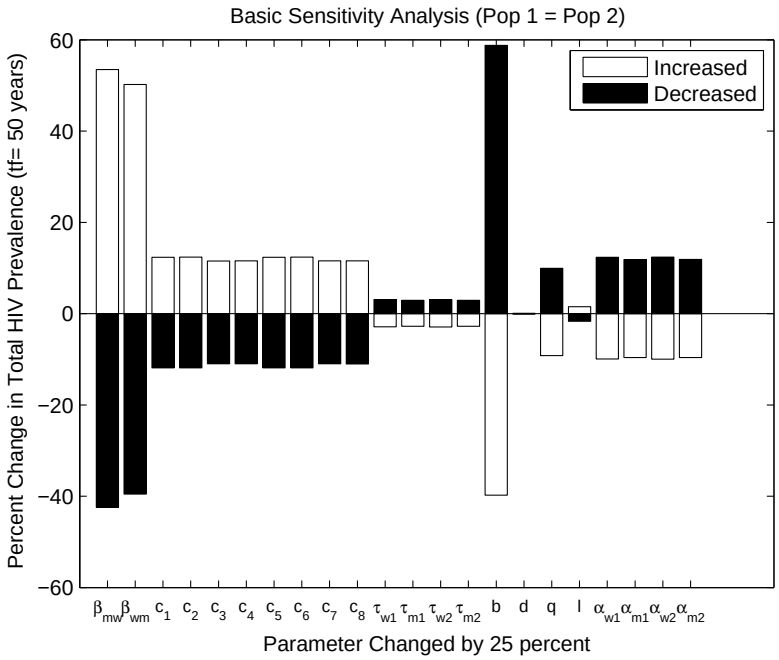


Figure 3.1: Basic sensitivity analysis for model with treatment and AIDS class. In this simulation, the size of population 1 was set equal to the size of population 2. The seed parameters needed to produce this plot are as follows: $\beta_{WM} = 0.001$, $\beta_{MW} = 0.003$, $\tau = 0.01$, $\alpha = 0.04$, $c_{1-8} = 60$, $b = 0.05$, $d = 0.02$, $q = 0.01$, and $l = 0.03$. The inital values were chosen as follows: 10 percent infected in all populations; 1 percent on treatment in all populations; 1 percent with AIDS in all populations; $N_{W1} = 500$, $N_{M1} = 500$, $N_{W2} = 500$, and $N_{M2} = 500$.

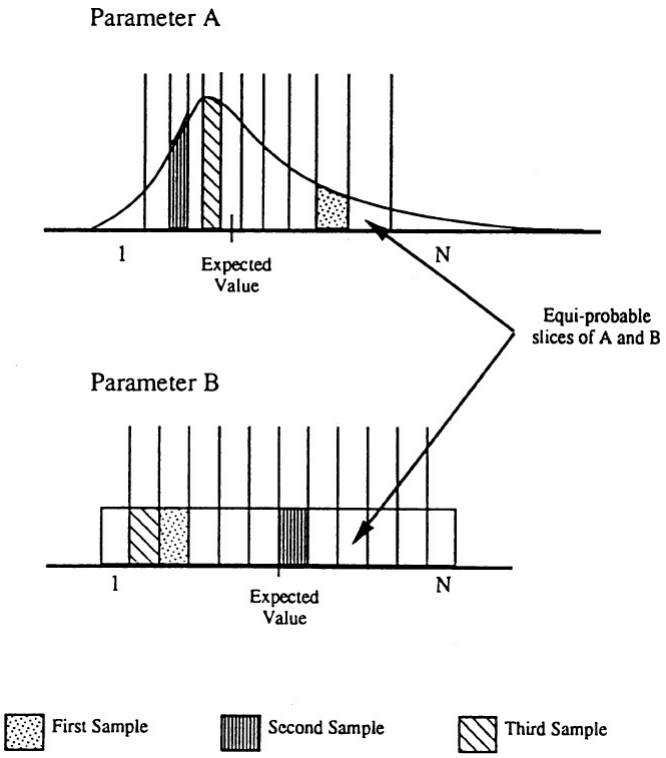


Figure 3.2: A pictorial description of the LHS method. Two parameters defined by particular probability-distribution functions are split into equal intervals and sampled without replacement. These parameter values are then run through the model, and the resulting output variables are analyzed using PRCC (taken from Blower and Dowlatabadi (1994)).

negative relationships and quantitatively with high PRCCs representing stronger monotonicity.

LHS and the subsequent PRCC analysis is a difficult process to implement, and it was therefore fortunate for us to find a program that both performed LHS and was able to analyze the results. The Sampling and Sensitivity Analyses Tools (SaSAT) were developed at the National Centre in HIV Epidemiology and Clinic Research at the University of New South Wales in Australia (Hoare et al., 2008). The program they developed produces a parameter table from randomly sampled values from probability distributions input by the user. These parameter values can then be passed through model simulations. Once simulation results have been attained, they can be run through the program for PRCC analysis and the creation of plots (Hoare et al., 2008). All plots presented as results from LHS have been produced using SaSAT.

3.2.2 Results

We have tried to assess the effects of all parameters on a variety of different end points including the prevalence within each population and within each sex, and the total HIV prevalence rate. This analysis was also run at a variety of different end points in order to determine whether or not sensitivity was time dependent. We have managed to run LHS on our model and observe the effects of changing parameter values on total prevalence (Figure 3.3). The basic sensitivity analysis predicted that the transmission parameters β_{MW} and β_{WM} should have the largest effect. LHS analysis confirms that effect, but also suggests that the rate at which individuals progress to AIDS has a large effect on the results.

One observation we have made regarding LHS is the importance of defining reasonable probability distribution functions for the parameters. Inputting too wide of a range of parameter values ultimately biases the results. It is therefore important to base our probability distributions on reliable surveys and literature. In addition, more work should be done to identify the patterns in sensitivity for other model outcomes.

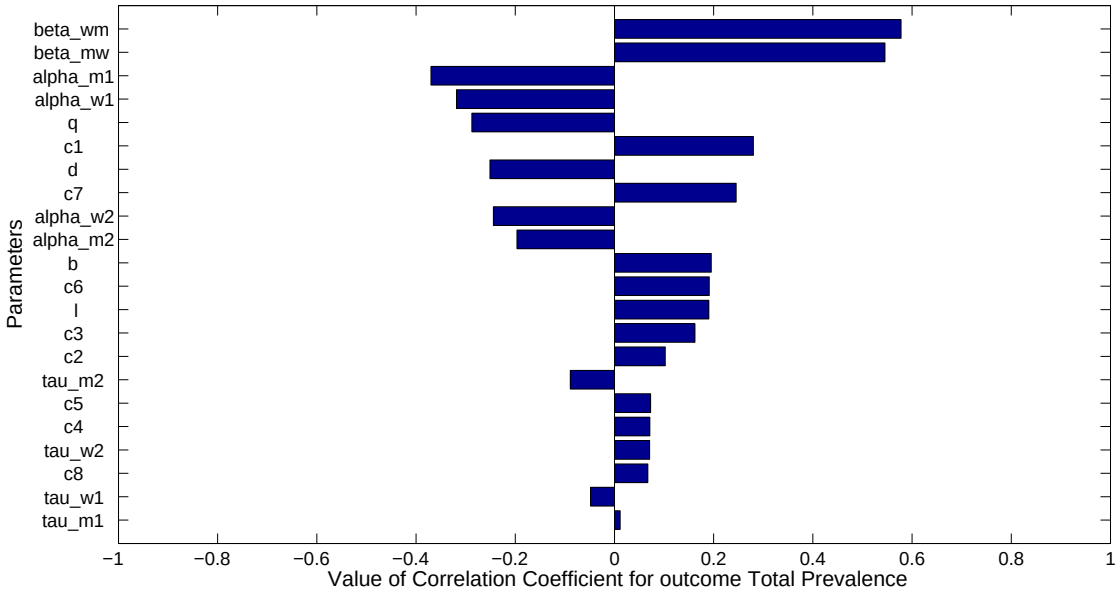


Figure 3.3: Preliminary LHS analysis results. This tornado plot shows the relative importance of each of the parameter choices compared to changes in the total prevalence. We see from this plot that the two infection forces β_{MW} and β_{WM} both have a large effect. We also see that parameters such as c_{1-8} or the α parameters do not have a clear pattern, which should be discussed in future work.

Chapter 4

Basic Reproductive Number

The basic reproductive number (R_0) of an epidemiological model is a parameter that helps determine whether a disease will become endemic in a population or die out based on the specific parameter combinations. Understanding the parameter values that yield endemic population values is essential to understanding the behavior of the model. This chapter describes how the basic reproductive number was characterized for our model.

4.1 Theory

The epidemiological definition of R_0 is the number of susceptible people an infected person could infect during one time period. We can imagine that if the infected person infects more than one person, and every subsequent infected person does the same, the disease will spread. We can also imagine that if the infected person does not infect any susceptible individuals the disease will die out. R_0 serves, therefore, as a threshold parameter that determines whether or not a disease will be endemic ($R_0 > 1$) or whether the disease will die out ($R_0 < 1$). In mathematical terms, the basic reproductive number is the spectral radius of the "next generation matrix" (Diekmann et al., 1990). The analysis of the basic reproductive number allows us to determine which parameters are most important in disease outbreak and, subsequently, which parameters we may be interested in altering to see the disease die out over time.

Calculating the basic reproductive number for simple epidemiological models is relatively straightforward, as it is often represented by the transmission rate divided by the death rate in the population (Lloyd and May, 1996). Because the dynamics of our model are dependent on both sex and

population characteristics, we have to resort to analytical techniques to determine the basic reproductive number. By reading the literature and observing the methods used to determine the basic reproductive number for other two-sex epidemic models (Doyle et al., 1998), we were led to a paper that explained how to calculate the basic reproductive number for a generic compartment model. van den Driessche and Watmough (2002) outline a precise definition for the basic reproduction number for compartment models producing systems of ordinary differential equations, which is summarized nicely by Heffernan et al. (2005).

Let us assume that a model has n compartments, m of which are compartments containing individuals that are infected. Let us also define x_i to be the number of individuals in the ith compartment. If we define $F_i(x_i)$ to be the rate of appearance of new infections in an infected compartment i and $V_i(x_i)$ to be the rate of transfer into and out of an infected compartment i by all other means, we can define the two matrices

$$F = \left[\frac{\delta F_i(x_0)}{\delta x_j}\right] \tag{4.1}$$

and

$$V = \left[\frac{\delta V_i(x_0)}{\delta x_j}\right], \tag{4.2}$$

where $i, j = 1, ..., m$ and x_0 represents the disease-free equilibrium. The next generation matrix is then defined by FV^{-1}, and the entries of this matrix give the rate at which infected individuals in x_j produce new infections in x_i, multiplied by the average time each individual spends in compartment j. The basic reproductive number is then defined as

$$R_0 = \sigma(F * V^{-1}), \tag{4.3}$$

where σ is the spectral radius of the matrix product (van den Driessche and Watmough, 2002).

4.2 Results

We can define F and V for our models as follows:

$$F = \begin{bmatrix} 0 & \frac{\beta_{MW}c_1}{2} & 0 & \frac{\beta_{MW}c_2}{2} \\ \frac{\beta_{WM}c_3}{2} & 0 & \frac{\beta_{WM}c_4}{2} & 0 \\ 0 & \frac{\beta_{MW}c_5}{2} & 0 & \frac{\beta_{MW}c_6}{2} \\ \frac{\beta_{WM}c_7}{2} & 0 & \frac{\beta_{WM}c_8}{2} & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} q+d+\tau_{W1}+\alpha & 0 & 0 & 0 \\ 0 & q+d+\tau_{M1}+\alpha & 0 & 0 \\ 0 & 0 & q+d+\tau_{W2}+\alpha & 0 \\ 0 & 0 & 0 & q+d+\tau_{M2}+\alpha \end{bmatrix}.$$

The basic reproductive number for the preliminary model, without the AIDS class and without treatment, can be found explicitly:

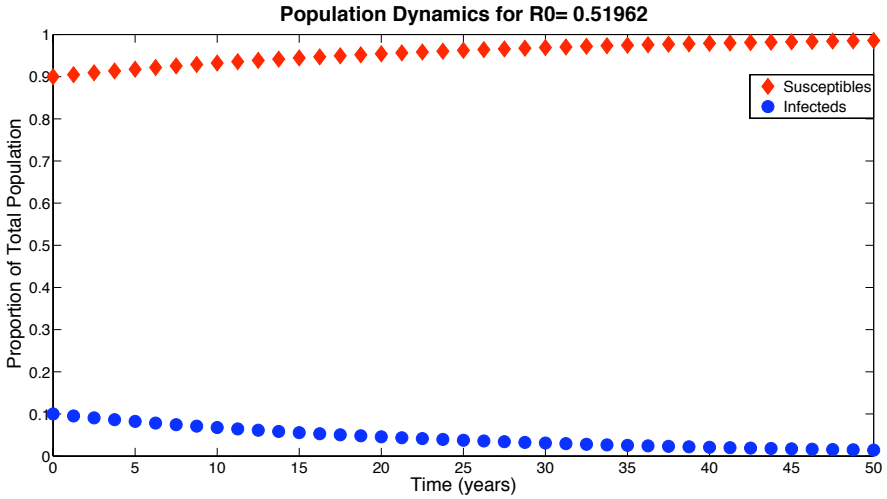
$$\begin{aligned} R_0 =& \frac{1}{4d}(2\beta_{MW}\beta_{WM}c_3c_1 + 2\beta_{MW}\beta_{WM}c_4c_5 + 2\beta_{MW}\beta_{WM}c_8c_6 + 2\beta_{MW}\beta_{WM}c_2c_7 \\ &+ 2\beta_{MW}\beta_{WM}(c_3^2c_1^2 + 2c_3c_1c_4c_5 - 2c_8c_6c_3c_1 + 2c_3c_1c_2c_7 + c_4^2c_5^2 + 2c_4c_5c_8c_6 \\ &- 2c_4c_5c_2c_7 + c_8^2c_6^2 + 2c_8c_6c_2c_7 + c_2^2c_7^2 + 4c_3c_5c_8c_2 + 4c_7c_6c_4c_1)^{\frac{1}{2}})^{\frac{1}{2}}. \end{aligned}$$

The basic reproductive number for the preliminary model has been found to be an accurate predictor of model behavior (Figure 4.1).

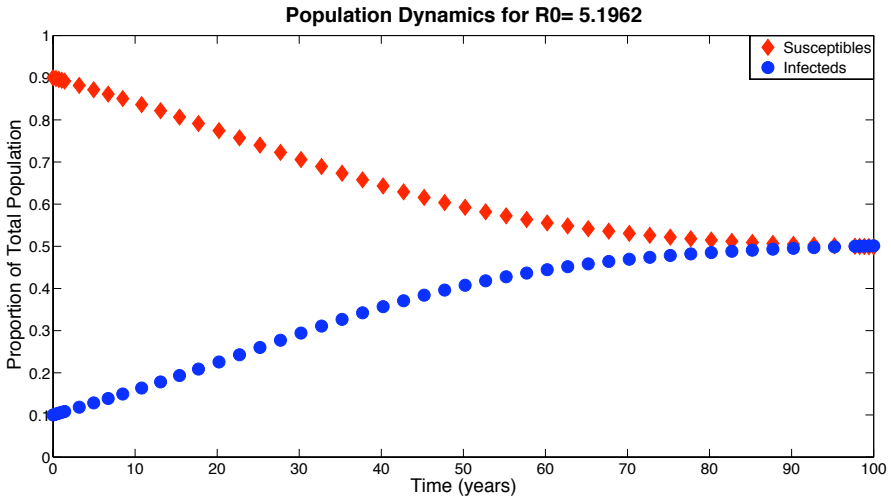
When deriving the basic reproductive number for the model with both treatment and the AIDS class it was found to contain over 10^6 lines of Maple code and would therefore be unreasonable to print here. We can estimate the value of the R_0 for the advanced model by solving for the dominant eigenvalue of the product of FV^{-1} in each simulation. From a number of simulations, we have observed that this basic reproductive number predicts the dynamics of the model on the long term (Figure 4.2) and is therefore a robust measure to consider in making predictions.

4.3 Simulations

The basic reproductive number allows us to understand the parameter values at which we would expect to observe the presence of an endemic equilibrium. After running a number of simulations focusing on varying the probability of transmission, β (see Chapter 3), we have observed that low transmission probabilities do not favor the presence of endemic equilibria (Figure 4.3). The basic reproductive number could therefore be used to predict stability of equilibria from certain parameter spaces.

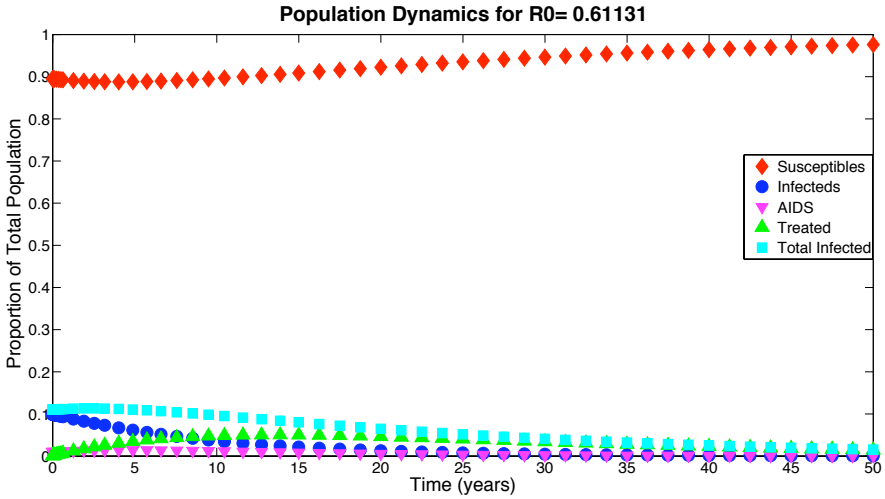


(a) $R_0 < 1$.

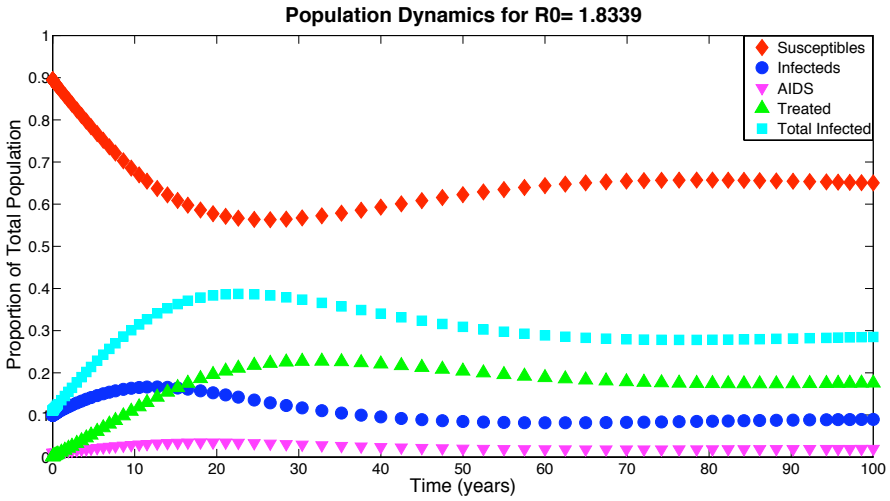


(b) $R_0 > 1$.

Figure 4.1: R_0 and preliminary model simulation agreement. Parameters were defined as follows for both plots: $c_{1-8} = 60$, $b = 0.02$, and $d = 0.05$. The first plot was produced with $\beta_{MW} = 0.0003$ and $\beta_{WM} = 0.0001$. The second plot was produced with $\beta_{MW} = 0.003$ and $\beta_{WM} = 0.001$. Initial conditions for both plots were 10 percent with HIV in both populations, $N_{W1} = 500$, $N_{M1} = 500$, $N_{W2} = 500$, and $N_{M2} = 500$.



(a) $R_0 < 1$.



(b) $R_0 > 1$.

Figure 4.2: R_0 and advanced model simulation agreement. Parameters were defined as follows for both plots: $b = 0.05$, $d = 0.02$, $q = 0.01$, $l = 0.03$, $c_{1-8} = 60$, $\tau = 0.1$, and $\alpha = 0.04$. Parameters used for plot 1 were $\beta_{MW} = 0.003$ and $\beta_{WM} = 0.001$. Parameters used for plot 2 were $\beta_{MW} = 0.009$ and $\beta_{WM} = 0.003$. Initial conditions for both plots were 10 percent with HIV in both populations; 1 percent with HIV in both populations; 1 percent on treatment in both populations; $N_{W1} = 500$, $N_{M1} = 500$, $N_{W2} = 500$, and $N_{M2} = 500$.

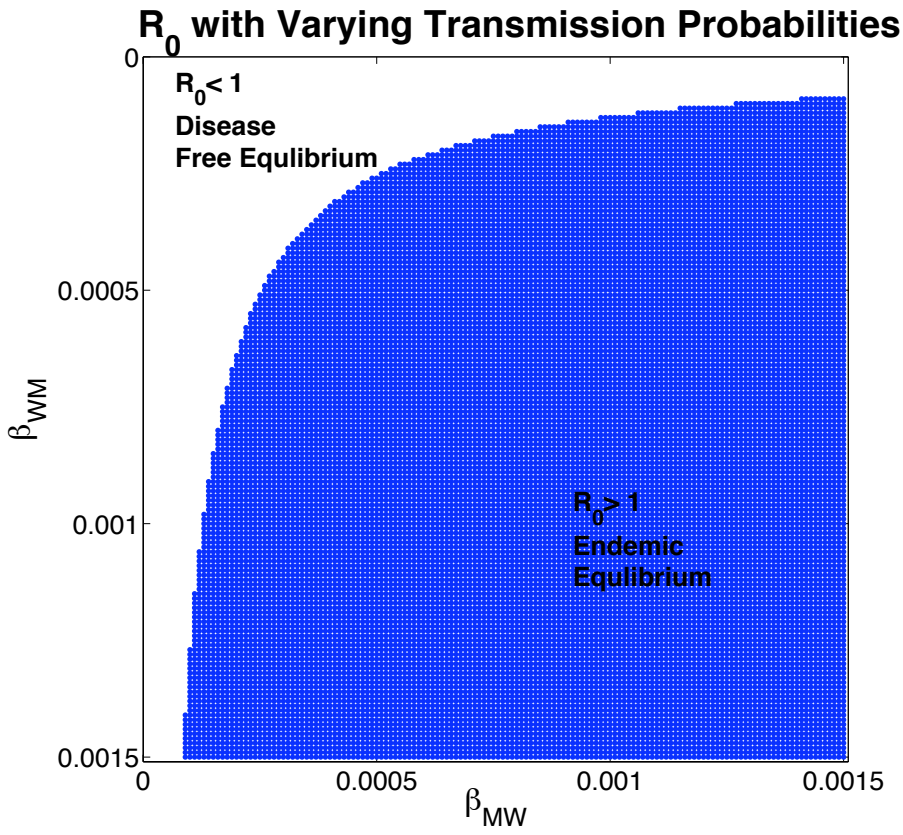


Figure 4.3: Stability of endemic equilibria over varying probability of transmission values.

Chapter 5

Equilibria and Stability Analysis

In order to understand the dynamics of the model in full, we seek to define as thoroughly and precisely as possible the endemic equilibria. We also would like to have conditions under which we would expect these endemic equilibria to exist. Because our model with treatment and AIDS is complex and contains a great number of parameters, we often need to refer to our simpler model for analysis and then extend these results to the larger model.

5.1 Definition of Endemic Equilibria

We are interested in observing the effects of treatment on the future spread of HIV in all populations. We are therefore interested in instances where infected individuals are present. This motivates the understanding of the conditions under which endemic equilibria occur.

5.1.1 Theory

As described in detail in Lloyd and May (1996), the equilibria of the model can be solved for analytically by setting each of the differential equations in our model to zero and solving for the respective state variables. This process is more complicated in models with internal structure and coupling. Often large sets of nonlinear algebraic equations need to be solved in order to analytically determine the values of the equilibria. We began our analysis with the preliminary model without treatment and AIDS classes

and proceeded to complete the analysis for the model with treatment and AIDS classes. In the following discussion, all state variables with a star ($*$) superscript will be assumed to be equilibrium values.

5.1.2 Preliminary Model

Due to our desire to define endemic equilibria as explicitly as possible, it was often necessary to begin the analysis on small pieces of the model. With this requirement, the model was broken down by both sex and population. In each case we define a quantity λ^* that acts as the main transmission term and a recovering term in all equilibrium states.

Population 1: Women

Following the analysis presented by Lajmanovich and Yorke (1976), let us define

$$\lambda_1^* = \frac{\beta_{MW}(c_1 IM_1^* + c_2 IM_2^*)}{NM_1 + NM_2}.$$

Then the explicit equilibria equations for women in the first population are as follows:

$$SW_1^* = \frac{bNW_1}{(d+\lambda_1^*)},$$
$$IW_1^* = \frac{bNW_1}{(d+\lambda_1^*)}\frac{\lambda_1^*}{d}.$$

Population 1: Men

Similarly, let us define the quantity

$$\lambda_2^* = \frac{\beta_{WM}(c_3 IW_1^* + c_4 IW_2^*)}{NW_1 + NW_2}.$$

Then the explicit equilibria equations for men in the first population are

$$SM_1^* = \frac{bNM_1}{(d+\lambda_2^*)},$$
$$IM_1^* = \frac{bNM_1}{(d+\lambda_2^*)}\frac{\lambda_2^*}{d}.$$

Population 2: Women

Additionally, let us define the quantity

$$\lambda_3^* = \frac{\beta_{MW}(c_5 IM_1^* + c_6 IM_2^*)}{NM_1 + NM_2}.$$

Then the explicit equilibria equations for women in the second population are

$$SW_2^* = \frac{bNW_2}{(d + \lambda_3^*)},$$
$$IW_2^* = \frac{bNW_2}{(d + \lambda_3^*)} \frac{\lambda_3^*}{d}.$$

Population 2: Men

Finally, let us define the quantity

$$\lambda_4^* = \frac{\beta_{WM}(c_7 IW_1^* + c_8 IW_2^*)}{NW_1 + NW_2}.$$

Then the explicit equilibria equations for men in the second population are

$$SM_2^* = \frac{bNM_2}{(d + \lambda_4^*)},$$
$$IM_2^* = \frac{bNM_2}{(d + \lambda_4^*)} \frac{\lambda_4^*}{d)}.$$

The equilibria equations would then form a nonlinear system of equations from which the λ^* can be solved and explicit equations for the equilibria states can be found.

5.1.3 Model with AIDS and Treatment

Following the same strategy elicited above, the endemic equilibria for the larger model with AIDS and treatment can be found. We will be adding two additional equilibrium states to each subpopulation here by expanding the complexity of the system.

Population 1: Women

For women in the first population, let us define the quantity

$$\lambda_1^* = \frac{\beta_{MW}(c_1 IM_1^* + c_2 IM_2^*)}{NM_1 + NM_2}.$$

Then the equations describing the equilibrium values for women in the first population are

$$\begin{aligned}
SW_1^* &= \frac{bNW_1}{(d+\lambda_1^*)}, \\
IW_1^* &= \frac{bNW_1}{(d+\lambda_1^*)} \frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)}, \\
AW_1^* &= \frac{bNW_1}{(d+\lambda_1^*)} \frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)} \frac{\alpha}{(\tau_{W1}+l+d)}, \\
TW_1^* &= \frac{\tau_{W1}}{d}\left(\frac{bNW_1}{(d+\lambda_1^*)} \frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)} + \frac{bNW_1}{(d+\lambda_1^*)} \frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)} \frac{\alpha}{(\tau_{W1}+l+d)}\right).
\end{aligned}$$

Population 1: Men

Let us define the quantity

$$\lambda_2^* = \frac{\beta_{WM}(c_3 IW_1^* + c_4 IW_2^*)}{NW_1 + NW_2}.$$

Then the equations describing the equilibrium values for men in the first population are

$$\begin{aligned}
SM_1^* &= \frac{bNM_1}{(d+\lambda_2^*)}, \\
IM_1^* &= \frac{bNM_1}{(d+\lambda_2^*)} \frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)}, \\
AM_1^* &= \frac{bNM_1}{(d+\lambda_2^*)} \frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)} \frac{\alpha}{(\tau_{M1}+l+d)}, \\
TM_1^* &= \frac{\tau_{M1}}{d}\left(\frac{bNM_1}{(d+\lambda_2^*)} \frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)} + \frac{bNM_1}{(d+\lambda_2^*)} \frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)} \frac{\alpha}{(\tau_{M1}+l+d)}\right).
\end{aligned}$$

Population 2: Women

For women in the second population, let us define the quantity

$$\lambda_3^* = \frac{\beta_{MW}(c_5 IM_1^* + c_6 IM_2^*)}{NM_1 + NM_2}.$$

Then the equations describing the equilibrium values for women in the second population are

$$\begin{aligned}
SW_2^* &= \frac{bNW_2}{(d+\lambda_3^*)}, \\
IW_2^* &= \frac{bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)}, \\
AW_2^* &= \frac{bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)}\frac{\alpha}{(\tau_{W2}+l+d)}, \\
TW_2^* &= \frac{\tau_{W2}}{d}\left(\frac{bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)} + \frac{bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)}\frac{\alpha}{(\tau_{W2}+l+d)}\right).
\end{aligned}$$

Population 2: Men

Finally, let us define the quantity

$$\lambda_4^* = \frac{\beta_{WM}(c_7 IW_1^* + c_8 IW_2^*)}{NW_1 + NW_2}.$$

Then the equations describing the equilibrium values for men in the second population are

$$\begin{aligned}
SM_2^* &= \frac{bNM_2}{(d+\lambda_4^*)}, \\
IM_2^* &= \frac{bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)}, \\
AM_2^* &= \frac{bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)}\frac{\alpha}{(\tau_{M2}+l+d)}, \\
TM_2^* &= \frac{\tau_{M2}}{d}\left(\frac{bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)} + \frac{bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)}\frac{\alpha}{(\tau_{M2}+l+d)}\right).
\end{aligned}$$

It will be possible to solve for each of these equilibrium values once we solve the following nonlinear set of equations for each of the λ^* values:

$$\lambda_1^* = \frac{\beta_{MW}}{(NM1+NM2)}\left(\frac{c_1 bNM_1}{(d+\lambda_2^*)}\frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)} + \frac{c_2 bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)}\right),$$
$$\lambda_2^* = \frac{\beta_{WM}}{(NW1+NW2)}\left(\frac{c_3 bNW_1}{(d+\lambda_1^*)}\frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)} + \frac{c_4 bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)}\right),$$
$$\lambda_3^* = \frac{\beta_{MW}}{(NM1+NM2)}\left(\frac{c_5 bNM_1}{(d+\lambda_2^*)}\frac{\lambda_2^*}{(d+q+\tau_{M1}+\alpha)} + \frac{c_6 bNM_2}{(d+\lambda_4^*)}\frac{\lambda_4^*}{(d+q+\tau_{M2}+\alpha)}\right),$$
$$\lambda_4^* = \frac{\beta_{WM}}{(NW1+NW2)}\left(\frac{c_7 bNW_1}{(d+\lambda_1^*)}\frac{\lambda_1^*}{(d+q+\tau_{W1}+\alpha)} + \frac{c_8 bNW_2}{(d+\lambda_3^*)}\frac{\lambda_3^*}{(d+q+\tau_{W2}+\alpha)}\right).$$

After exhausting analytical solving strategies, we have determined that these equations are practically impossible to solve analytically. We are therefore left with no analytical expression of the equilibrium values for the model with treatment and AIDS. We will be working harder to determine numerically the possibility and existence of endemic equilibria as described in Section 5.2.

5.2 Stability of Endemic Equilibria

Besides attempting to describe the endemic equilibria in analytical terms, we would also like to better understand the conditions under which we would expect to observe endemic equilibria. To do so, we made a thorough search of the literature to better understand the methods through which we could predict the presence of endemic equilibria. We also sought to compare these conditions to the results from our definition of the basic reproduction number. If we could get agreement on both conditions under which we would expect endemic equilibria and also where the basic reproduction number is greater then one, we could be confident that our analyses on both fronts is accurate and thorough.

Throughout the literature there are papers that describe conditions and analyses through which one can better understand the presence of endemic equilibria in various models. The paper that has been most useful was Lajmanovich and Yorke (1976). In this paper, the authors prove a theorem that we have used to produce a condition on our preliminary model for which we would expect endemic equilibria to occur. The analysis presented in Lajmanovich and Yorke (1976) does not allow us to include treatment and

AIDS classes. After doing a thorough search of the literature we were able to find a number of papers that dealt with models with additional classes in addition to infected and susceptible classes.

Hethcote (1978) describes his analysis of a model with additional removal classes like our own. We have yet to do a thorough analysis such as that presented in the paper, in part because of our unfamiliarity with the methods used. Lloyd and Jansen (2004) also provide an analysis of a metapopulation model with removal rates, and their analysis focuses on the simplification of more complex models to those that represent basic susceptible-infected-recovered (SIR) models. Future work should be taken to understand the analyses being presented in these papers and potentially apply them to our own models. The rest of this chapter will focus on our own analysis that follows the analysis provided in Lajmanovich and Yorke (1976).

5.2.1 Theory

Lajmanovich and Yorke (1976) assume for their analysis that the model in question has a constant disease-free solution characterized by only susceptible individuals. Their analysis and proof seek to show that either the disease-free equilibrium is globally asymptotically stable or that there is another constant solution (i.e., an endemic equilibria) that is asymptotically stable. In order to prove this assertion, the authors proceed to partition the equations of the model into smaller parts. They define the matrix A, which constitutes the bulk of their analysis, as follows: Let us assume that $A = (a_{ij})$, where i, j are indices distinguishing populations or sexes. They define the elements of A based on the values of i and j. If $i \neq j$ then $a_{ij} = \beta_{ij} c_{ij} N_i$ where β_{ij} is the probability of transmission from i to j; c_{ij} is the number of encounters per year between i and j; and N_i is the population size. The quantity a_{ij} basically represents the infection rate in the population. If, however, $i = j$, then the elements $a_{ij} = -r$ or simply the recovery rate (the rate at which infected individuals are reintroduced as susceptibles) in the model. The authors proceed to prove that if none of the eigenvalues of the matrix A is greater than zero, than the disease-free equilibrium is globally asymptotically stable. If, on the other hand at least one of the eigenvalues of A is greater than zero, then there exists an endemic equilibrium that is globally asymptotically stable. (Refer to Lajmanovich and Yorke (1976) for greater detail on the analysis taking place and for proofs of the concepts stated above.)

5.2.2 Preliminary Model

After attempting the analysis described in Lajmanovich and Yorke (1976) on our own preliminary model, we were able to obtain the matrix A, which is represented as follows:

$$A = \begin{bmatrix} 0 & \frac{\beta_{MW} c_1 NW_1}{NM1+NM2} & 0 & \frac{\beta_{MW} c_2 NW_1}{NM1+NM2} \\ \frac{\beta_{WM} c_3 NM_1}{NW_1+NW_2} & 0 & \frac{\beta_{WM} c_4 NM_1}{NW_1+NW_2} & 0 \\ 0 & \frac{\beta_{MW} c_5 NW_2}{NM_1+NM_2} & 0 & \frac{\beta_{MW} c_6 NW_2}{NM_1+NM_2} \\ \frac{\beta_{WM} c_7 NM_2}{NW_1+NW_2} & 0 & \frac{\beta_{WM} c_8 NM_2}{NW_1+NW_2} & 0 \end{bmatrix}.$$

Using Mathematica, we are able to find the eigenvalues explicitly for this matrix; because of their length and their complexity, they will not be replicated. The sign and relative magnitude of these eigenvalues depend on the values of the parameters chosen for each simulation of the model. We see, therefore, that in order to make any conclusions about the stability or existence of endemic equilibria, it is necessary to do a numerical simulation, evaluate the values of the eigenvalues of A, and determine whether those eigenvalues are greater than, less than, or equal to zero to determine the stability of the system with regard to that specific parameter set (as described in Section 5.2.1).

5.3 Agreement Between R_0 and Stability Analysis

We have found that there is general agreement in the predictions of the basic reproductive number (described in Chapter 4) and the stability analysis. Unfortunately, the agreement is only true for β values greater than 0.0001. We have observed that the predictions of the analytical analysis do not match those of the basic reproductive number for small β. We see that in these cases, R_0 is the better predictor of the existence of endemic equilibria according to simulation. We are confident in the predictive power of our stability analysis otherwise and seek to find the basis for the contradiction in future work.

Chapter 6

Treatment Simulations

In order to determine whether or not preferential treatment strategies will be effective at combatting the future spread of HIV/AIDS in rural and urban communities, it will be important to test the effect of varying treatment strategies on this spread. In this chapter we will describe the progress we have made in determining which treatment strategy will deter the largest number of future HIV/AIDS-related deaths and also the largest number of future infections.

6.1 Exploratory Simulations

In order to begin our analysis, we chose to run a number of basic simulations with varying treatment strategies to see what would happen to the infected proportions of both male and female populations and rural and urban populations over time. We did so by changing the treatment rate while keeping all other variables constant in our simulations. The parameter values chosen for each simulation are those found to be the most robust and in closest agreement with the literature (see Table 6.1). In the following simulations, population one is assumed to be urban (i.e., large population sizes and higher frequency of interactions) and population two is assumed to be rural (i.e., small population sizes and smaller frequencies of interactions).

6.1.1 Treating Only Women

There have been many studies in the literature that have pointed towards the use of preferential treatment for women as a way to prevent the future spread of HIV/AIDS in both rural and urban communities. This strategy is

Parameter	Value	Parameter	Value
t_0	0	NW_1	2,742,879
t_f	100	NM_1	2,732,463
b	0.046	NW_2	605,376
q	0.01	NM_2	603,168
d	0.0134	$tw_1 = tw_2$	0.166
l	0.03	$tm_1 = tm_2$	0.1
pw_1	0.408	$c_1 = c_6$	60
pm_1	0.198	c_2	36
pw_2	0.472	c_3	108
pm_2	0.180	c_4	84
$a_{W1} = a_{W2}$	0.04	c_5	36
$a_{M1} = a_{M2}$	0.04	c_7	48
$\alpha_{W1} = \alpha_{W2}$	0.04	c_8	72
$\alpha_{M1} = \alpha_{M2}$	0.04		

Table 6.1: Parameter values for all simulations in Section 6.1

also advertised and suggested by the WHO, because it considers women to be a disadvantaged group in many developing countries (UNAIDS, 2005). Based on this theory, we performed simulations in which we only treated women and did not treat men, to see the effects this approach would have on the infected populations over an extended period of time (100 years).

The results can be visualized in Figure 6.1. We observe that if we treat both urban and rural women at the same rate, which in this case means treating 10 percent of the infected women over an extended period of time (100 years), we can control the potential spread of HIV/AIDS in these populations. We are assuming (as described by the model assumptions in Section 2.2.1) that the AIDS class and infected classes are not interacting, and thus if these interactions were taken into account we might expect to observe very different dynamics.

6.1.2 Treating Only Urban Women

Accessibility to drugs and health centers is often an issue for individuals living in rural areas, and so many health organizations and nonprofit organizations have focused their prevention efforts on individuals within urban areas that are within reach (UNAIDS, 2005). It is also often the case that

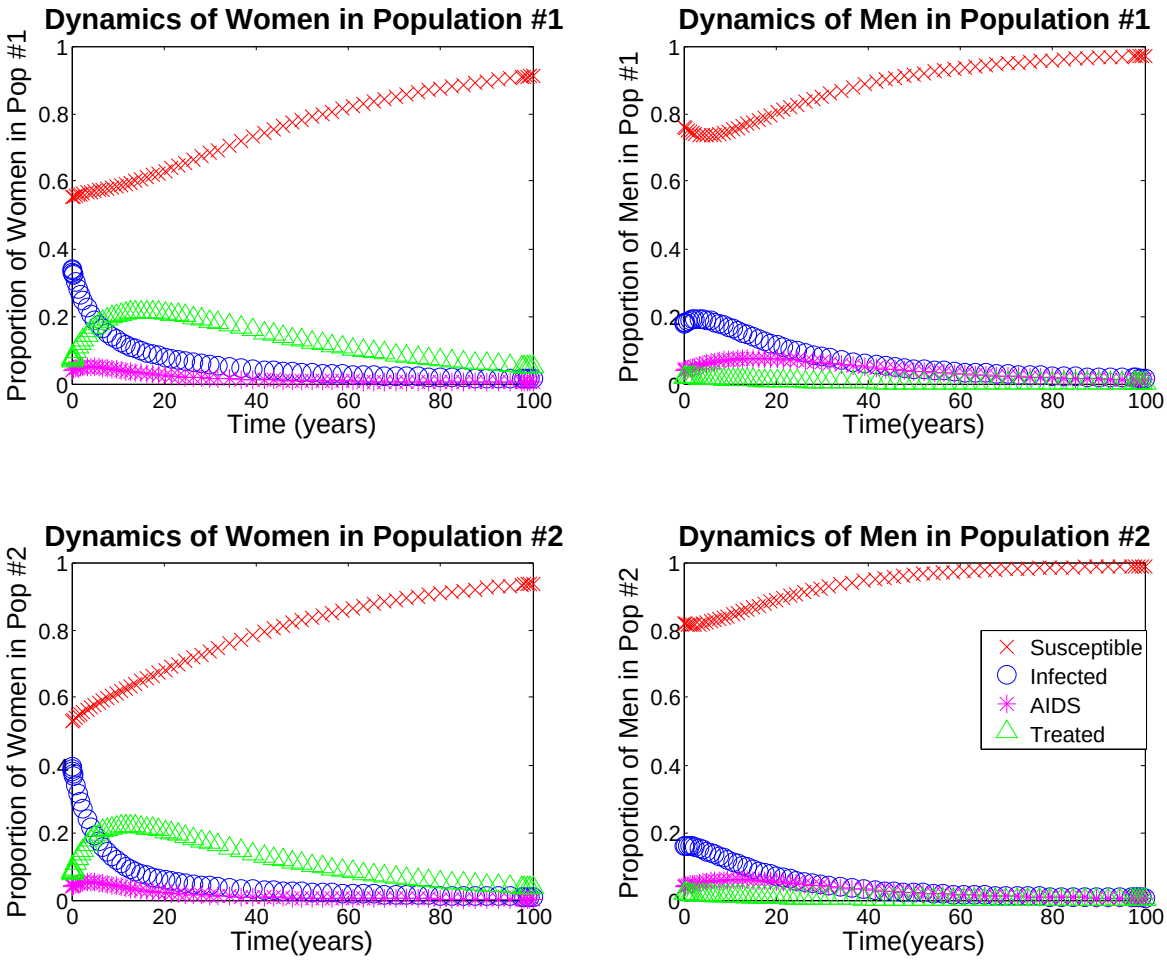


Figure 6.1: Simulation results for preferential treatment of rural and urban women. These plots show that focusing treatment efforts on women may have a positive effect on the future spread of HIV in both urban and rural communities. The parameter values unique to this plot are: $\beta_{MW} = 0.0032$; $\beta_{WM} = 0.001$; $\tau_{W1} = \tau_{W2} = 0.1$; and $\tau_{M1} = \tau_{M2} = 0$.

those individuals living in urban areas are better educated than those who live in rural areas. There may, therefore, be advantages to focusing treatment and prevention programs on women living in urban areas. Putting large amounts of resources and effort into treating women living in urban areas is thus a relevant and interesting treatment scheme to explore.

When we explored treating women living in urban areas exclusively in our simulations (Figure 6.2), we see that we are successful at controlling the future spread of HIV/AIDS in both rural and urban communities. This result is not surprising for two main reasons. First, the number of women and people in the urban areas is very large and therefore treating 30 percent of the infected female population is treating a large number of women. Second, one of our implicit assumptions in the model structure is that women in urban areas will have more encounters with men then women living in rural areas, simply because of the density of people and the difference in the amount of social interaction expected for these two groups.

6.1.3 Treating Only Rural Women

In addition to the large number of programs and health organizations that focus their efforts on urban populations, there are a large number of private organizations and local organizations that attempt to provide medication to those individuals living in rural areas (UNAIDS, 2005). These organizations focus the majority of their energy and resources in treating people that are far away from city centers and major health facilities. The effects of dedicating a large number of resources to treating individuals with lower amounts of promiscuous sexual encounters and dealings with urban areas is an interesting simulation to consider.

As can be seen from the simulation results (Figure 6.3), treating rural women has a large effect on reducing the number of infected women in the rural population, but does little to reduce the amount of infection in the urban populations. We do see a steady decrease in infection in all populations, but nothing significant enough to be able to conclude that solely treating rural women would be a sufficient and adequate strategy to fight future HIV infection in rural and urban communities.

6.1.4 Treating Only Men

In contrast to the studies cited above, some studies support focusing prevention and treatment programs on men's reproductive health (Crepaz et al., 2006). It is often seen, and assumed in our simulations, that men have

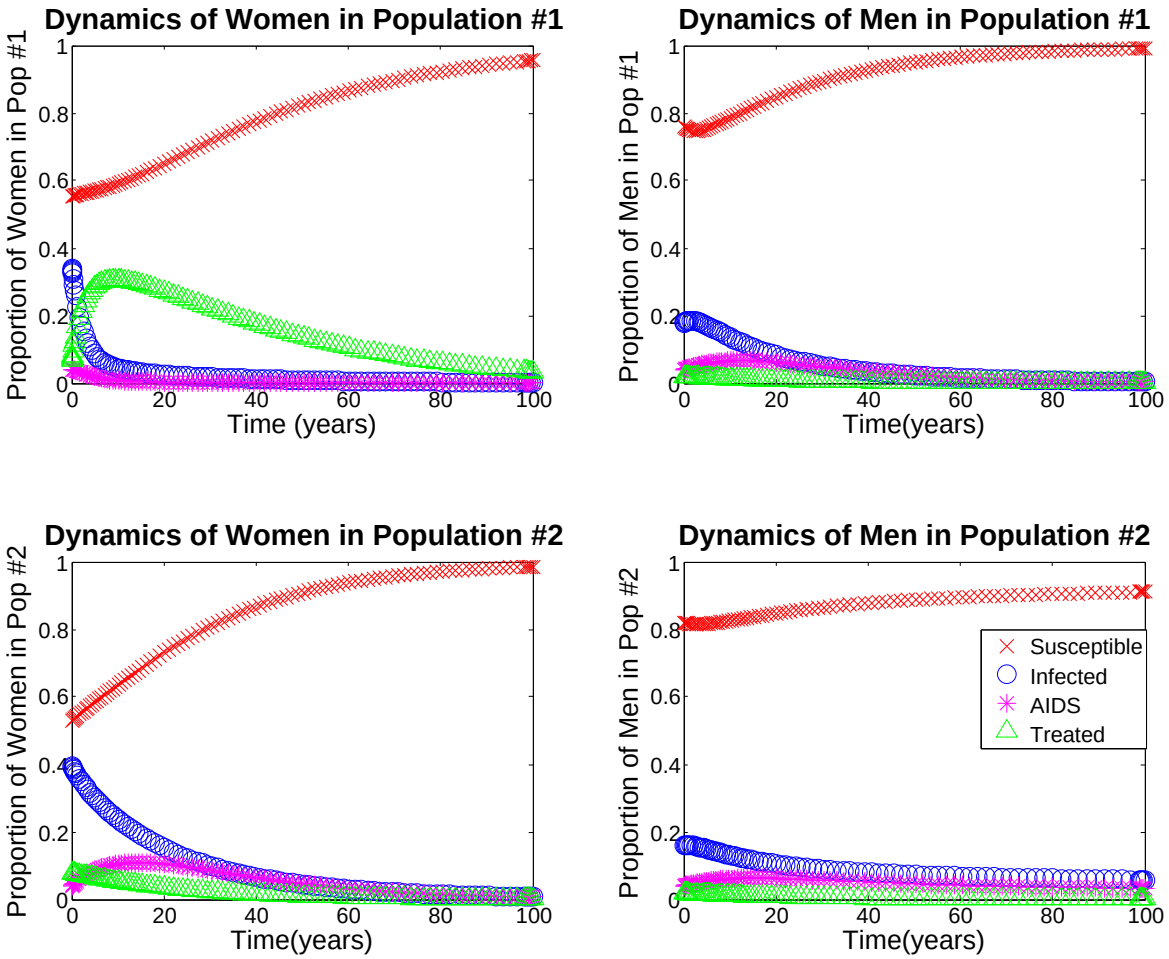


Figure 6.2: Simulation results for preferential treatment of urban women. These plots show that treating urban women thoroughly has a positive effect on the future spread of HIV in all population subgroups. The parameter values unique to this plot are: $\beta_{MW} = 0.0032$; $\beta_{WM} = 0.001$; $\tau_{W1} = 0.3$; and $\tau_{W2} = \tau_{M1} = \tau_{M2} = 0$.

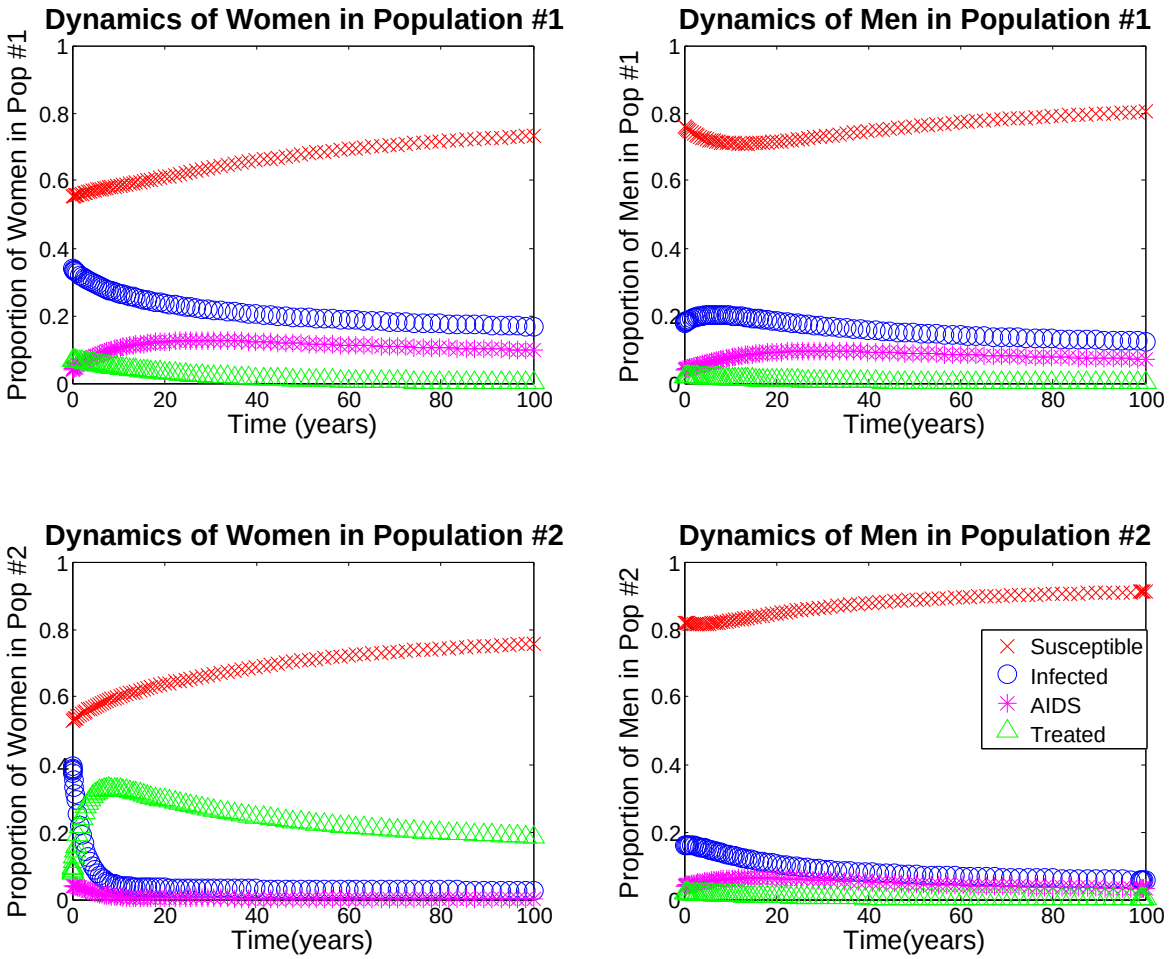


Figure 6.3: Simulation results for preferential treatment of rural women. This plot shows that treating rural women is not an effective strategy for reducing the spread of HIV in both urban and rural populations. The parameter values unique to this plot are: $\beta_{MW} = 0.0032$; $\beta_{WM} = 0.001$; $\tau_{W2} = 0.3$; and $\tau_{W1} = \tau_{M1} = \tau_{M2} = 0$.

many more sexual encounters then women per year, and a large proportion of these sexual encounters is promiscuous. It is also the case that the probability of transmission from males to females is much higher then the transmission rate of females to males. Thus, it may be the case that focusing prevention and treatment strategies on males may actually be a decent strategy to prevent the future spread of HIV infection in both female and male populations in both rural and urban areas.

When we run simulations in which treatment is limited to men (Figure 6.4), we see a similar result to that observed for solely treating women. The prevalence rates in all populations slowly decreases, until after 100 years we actually observe very little infection present in any of the populations studied. We see that there is symmetry present in the model that allows this to happen, but based on studies and other published material, we wouldn't expect this symmetry to be present. That is, we might expect there to be an advantage to treating men over women or women over men but not both. Thus Section 6.1.7 is dedicated to exploring how changes to our infection parameters affect the prevention of infection in these populations, as we are assuming that changing parameter values may disrupt this symmetry.

6.1.5 Treating Urban Areas

The proximity of urban populations to health centers and ART distribution centers puts urban residents at a distinct advantage over those living in rural areas. Resource-constrained countries would have to put little to no energy into treating those living in urban areas and this makes the strategy very appealing. In addition, most resource-constrained countries, like Uganda, would not have to improve infrastructure in order to treat a significant portion of the population. When we run simulations in which treatment is limited to men and women in urban areas (Figure 6.5) we see that this strategy has an extremely positive effect on the future spread of HIV in all populations. These results confirm and agree with those described in Section 1.5 by Wilson et al. (2006).

6.1.6 Treating Rural Areas

In contrast to the supply of drugs in urban areas, the distribution of drugs in rural areas is stunted by distance from health-care centers and the lack of infrastructure in rural areas of resource-constrained countries. We examine the distribution of drugs to rural areas in order to explore the WHO

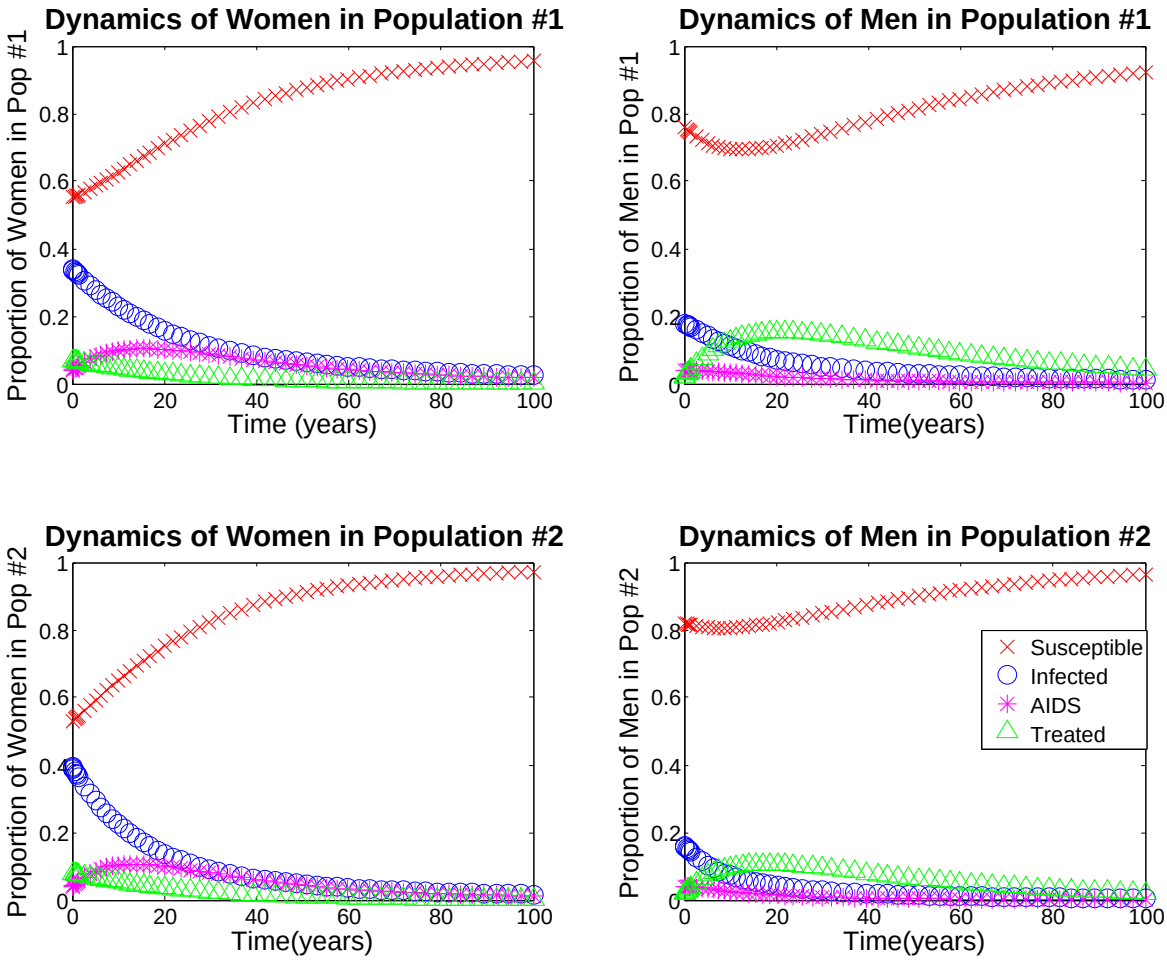


Figure 6.4: Simulation results for preferential treatment of rural and urban men. This plot shows that the treatment of men has very similar repercussions to the treatment of women, and motivates investigation into this symmetry. The parameter values unique to this plot are: $\beta_{MW} = 0.0032$; $\beta_{WM} = 0.001$; $\tau_{M1} = \tau_{M2} = 0.1$; and $\tau_{W1} = \tau_{W2} = 0$.

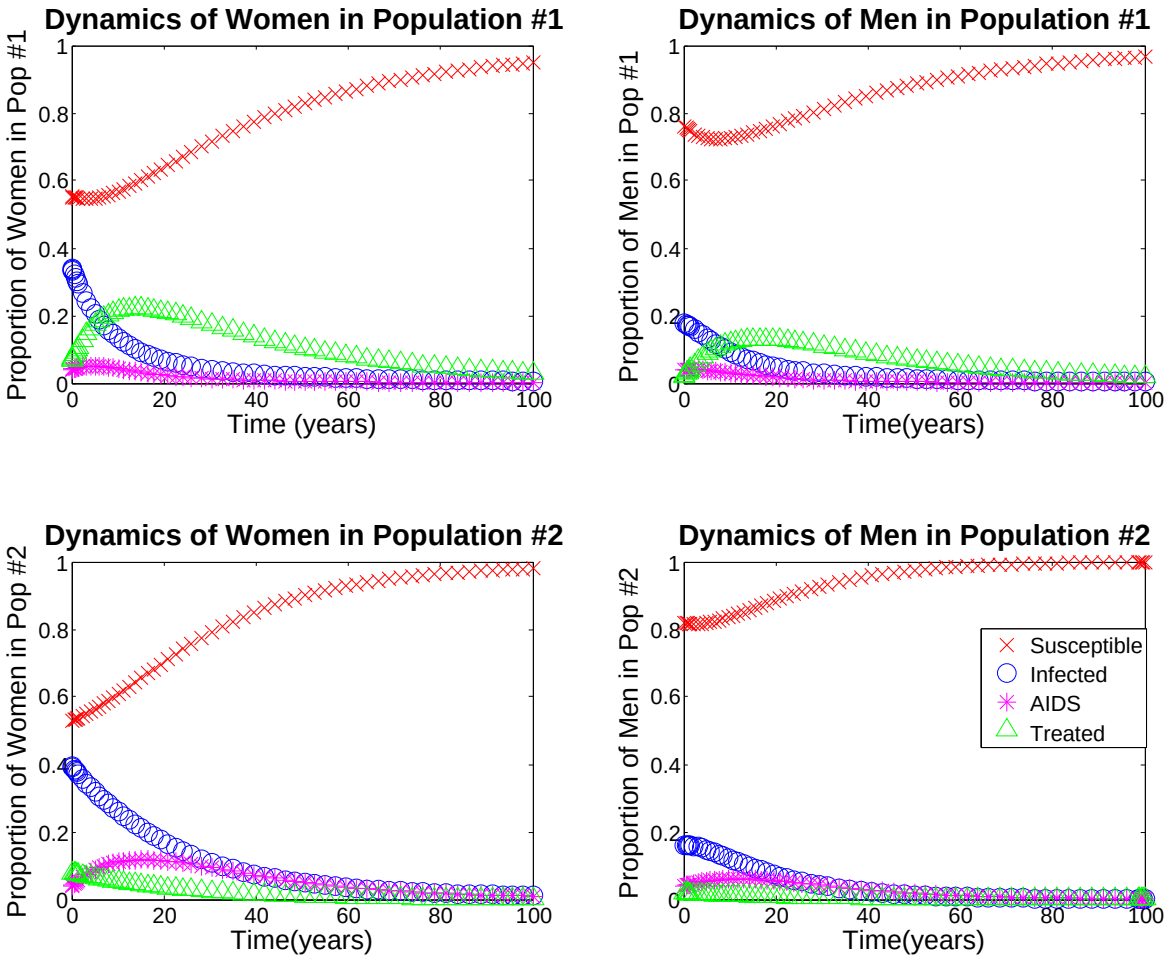


Figure 6.5: Simulation results for preferential treatment of urban areas. We see that treating urban populations has a large positive effect on both urban and rural areas, suggesting this is the best preferential treatment strategy. The parameter values unique to this plot are $\beta_{MW} = 0.003$; $\beta_{WM} = 0.001$; $\tau_{M1} = \tau_{W1} = 0.1$; and $\tau_{M2} = \tau_{W2} = 0$.

document's recommendation of focusing treatment to disadvantaged populations. We see that in the simulations (Figure 6.6) preferential treatment to rural areas alone does not have a positive effect on the future spread of HIV. In fact, this strategy does not reduce the infected population load nearly as much as any other treatment rationing strategy.

6.1.7 Simulations with Increasing Transmission Probabilities

Following the results of our sensitivity analysis (Chapter 3), in which we concluded that the parameter that would have the largest effect on our simulation and model analysis was the probability of transmission (β), we decided to run simulations to determine whether changing these parameters had an effect on the future spread of infection. In the following simulations, we wanted to observe the effect of increasing the probability of transmission from male to female (β_{MW}) while keeping the female to male probability of transmission (β_{WM}) constant to see what effect variation in β would have on the differences in outcomes of treating men and women. We would expect that as we increase the probability of transmission from males to females we would see a larger positive effect from the treatment of males then from treating females.

What we see in the simulation results for both treatment of only women and treatment of only men (Figures 6.7 and 6.8, respectively), is that when the probability of transmission is high, it is harder to prevent the future spread of HIV, even with treatment. We see that when we treat only women, we are able to reduce the amount of HIV prevalence in both rural and urban women and men, respectively, but we are unable to get the larger population's prevalence rates as low as we can by lowering transmission rates. We see that in the case of treating only men that although there is an initial decrease in the prevalence of HIV among women, we do not see a drastic reduction in prevalence over time as we see in the case with a lower probability of transmission.

These simulations confirm the results of the sensitivity analysis; changes in the probability of transmission have an effect on the future spread of HIV/AIDS.

6.2 Conclusions

Of all the treatment strategies explored in the simulations, we can conclude that the preferential treatment of urban populations may be the most ef-

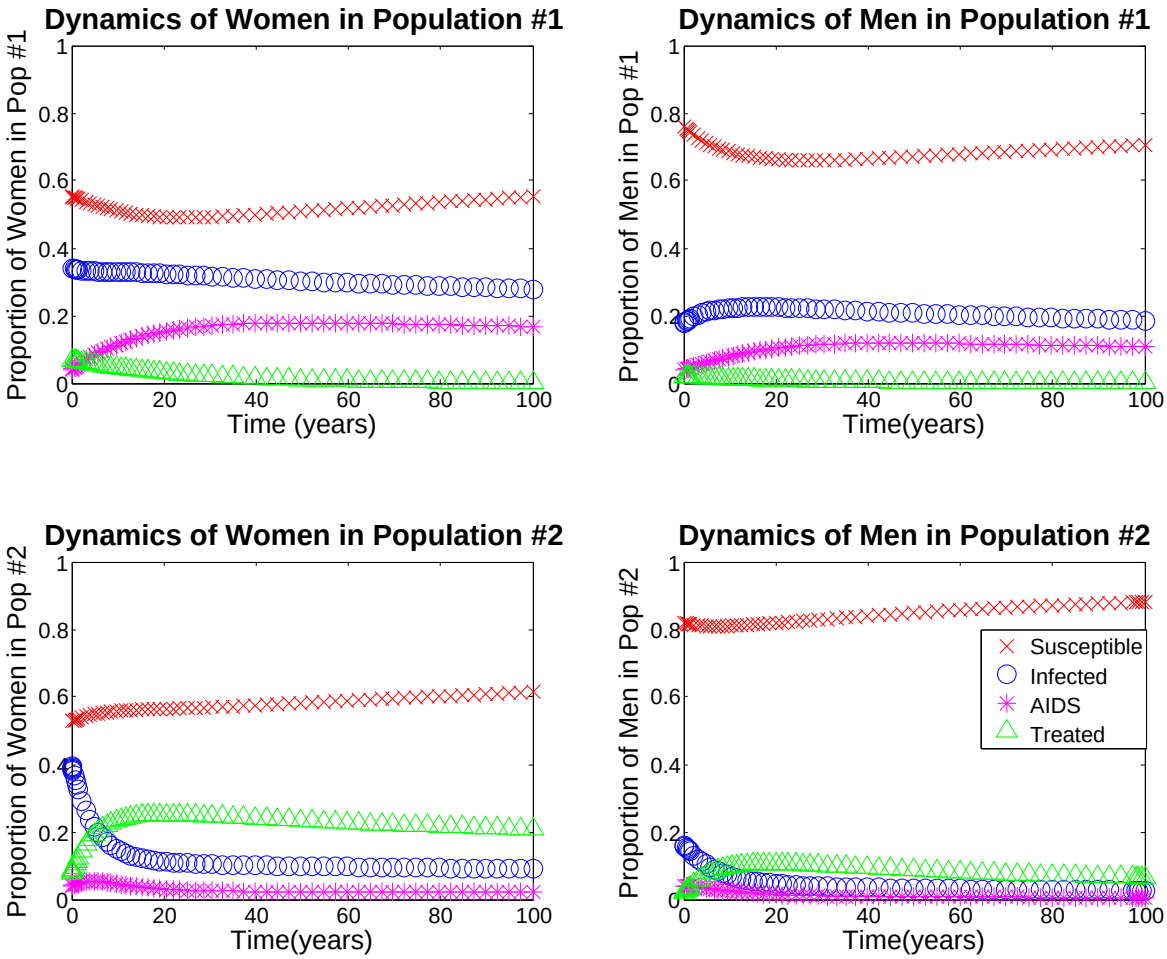


Figure 6.6: Simulation results for preferential treatment of rural areas. These simulation results suggest that preferential treatment in rural areas is not a reasonable strategy to fight future HIV infections. The parameter values unique to this plot are $\beta_{MW} = 0.003$; $\beta_{WM} = 0.001$; $\tau_{W1} = \tau_{M1} = 0$; and $\tau_{W2} = \tau_{M2} = 0.1$.

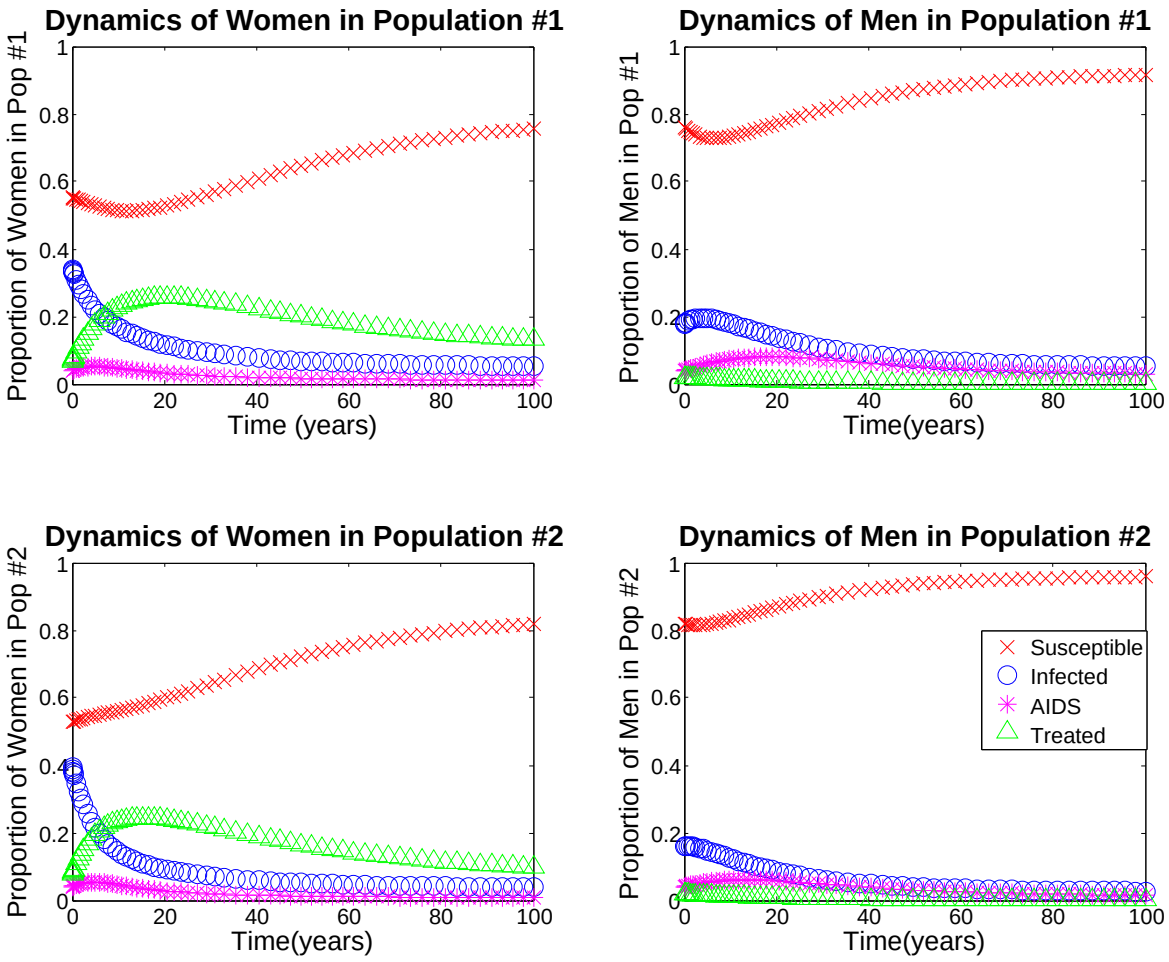


Figure 6.7: Simulation results for preferential treatment of women with increased β_{MW}. This plot shows that with stronger male-to-female transmission probabilities, treating women does not have as strong an effect on the future spread of HIV as seen in the scenario depicted in Figure 6.1. The parameter values unique to this plot are $\beta_{MW} = 0.005$; $\beta_{WM} = 0.001$; $\tau_{W1} = \tau_{W2} = 0.1$; and $\tau_{M1} = \tau_{M2} = 0$.

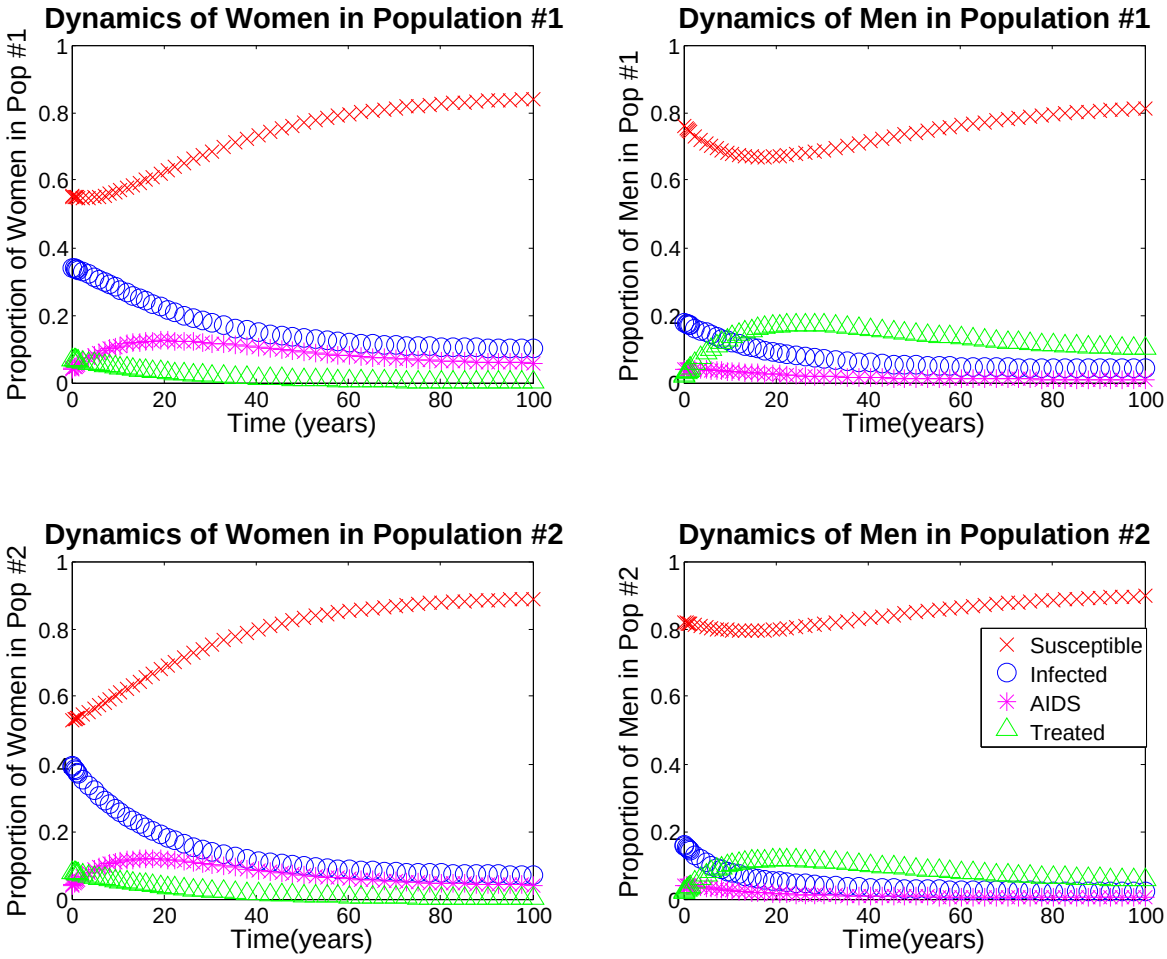


Figure 6.8: Simulation results for preferential treatment of men with increased β_{MW}. This plot shows that when the probability of transmission from men to women is increased, the effect of treating only men is not as strong in preventing infection in women as in the scenario are depicted in Figure 6.4. The parameter values unique to this plot are $\beta_{MW} = 0.005$; $\beta_{WM} = 0.001$; $\tau_{M1} = \tau_{M2} = 0.1$; and $\tau_{W1} = \tau_{W2} = 0$.

fective at reducing the number of future infections in all populations. We see that by focusing prevention and treatment strategies on women in urban areas, resource-constrained countries may be able to reduce the disease characteristics of urban and rural areas as a whole. Because we assume that urban women have more sexual encounters then rural women, and further that urban men have more interactions then rural men, we see that the treatment of women has a drastic effect on the spread of the disease in all populations. Treating both urban women and rural women has a similar effect on the reduction of future HIV infection, but does not reduce infection in all populations as quickly has the sole treatment of urban women or the treatment of men and women in urban populations.

Our results differ slightly, therefore, then the recommendations by the WHO. Focusing treatment distribution in rural areas, we have found, reduces the infection prevalence in those ares but does very little to affect the prevalence rates in urban areas. On the other hand, focusing attention to the more populated urban areas has a positive effect on both the urban and rural areas. Our results do confirm though that the preferential treatment of women, considered here a disadvantaged population, in urban areas is a legitimate and positive step towards decreasing the rate of infection in all regions.

Chapter 7

Future Work

We hope that further research into dynamical systems analysis methods for the determination of the existence and stability of an endemic equilibria will make clear the reasons for the discrepancy in the predictions of the basic reproductive number and the analysis presented in Lajmanovich and Yorke (1976). In addition, looking more closely into the analysis presented by Hethcote (1978) and attempting to apply it to our own model may be a fruitful endeavor. We hope that by finding agreement between these two predictors of stability we will further understand the stability of the model and the presence of endemic equilibria.

Future work should also seek to relax the assumptions described in the previous section. Relaxation needs to begin with a better understanding of the consensus in the literature on many of the issues. Two assumptions that need to be addressed, in particular, are those regarding treated individuals having only protected sex and the estimate of intermediate probability for the infection parameter. Two assumptions that we seek to eliminate from the model to make it more realistic are those that assume heterosexual transmission is the only form of infection and that of individuals being completely compliant with medication. In many cases, the assumptions may not be relaxed, but all attempts should be made to make the model as realistic as possible in order to understand the true dynamics of HIV prevalence in Uganda. The relaxation of assumptions should be approached cautiously, attempting to minimize the number of new parameters introduced in the process. At a certain point, the relaxation of assumptions must be limited in order to limit the number of parameters that need to be estimated and analyzed.

Further, we seek to incorporate long distance population dynamics, us-

ing the method described by Keeling and Rohani (2002). Incorporating these dynamics will allow us to make conclusions about the dynamics between faraway villages in Uganda and thus understand HIV transmission in rural areas. Incorporating these long distance dynamics will also allow us to develop, potentially, a spatial map that tracks HIV prevalence over time according to certain population levels and transmission rates across the country.

Appendix A

Additional Equations and Tables

This appendix provides additional tables, equations, and figures. The first figures presented are those representing the results from the basic sensitivity analysis when population sizes were not equal (Figures A.1 and A.2). Note that when the intial size of population 1 is twice that of population 2, the parameters associated with population 1 also take on greater importance in the sensitivity analysis. This result is consistent with intuition, because changes to the dynamics of the larger population should be expected to dominate the overall population dynamics. We see a similar pattern when population 2 is twice the size of population 1 (Figure A.2). What is interesting here is that the magnitudes of these changes in total prevalence are not the same for both changes, suggesting that our model is placing more emphasis on population 1 then on population 2. This imbalance is something that needs to be addressed in future work.

Results from PRCC are presented in Table A.1. There are a number of parameters that have significant correlations with changes in total prevalence. The two parameters with the lowest p-values are those of the infection rates β_{MW} and β_{WM}, as expected. The fact that c_7 is significant while the other c constants are not indicates weight being placed on c_7 and the populations it connects in the model. This abnormality should be looked at more closely in future work as well.

Parameter	PRCC	P-value	Significant?
β_{MW}	0.545	$2.02x10^{-7}$	**
β_{WM}	0.578	$2.45x10^{-8}$	**
c_1	0.280	0.012	**
c_2	0.102	0.369	
c_3	0.162	0.153	
c_4	0.071	0.531	
c_5	0.073	0.523	
c_6	0.191	0.091	
c_7	0.245	0.029	**
c_8	0.067	0.555	
τ_{W1}	-0.048	0.672	
τ_{M1}	0.011	0.920	
τ_{W2}	0.071	0.534	
τ_{M2}	-0.089	0.435	
b	0.195	0.085	
d	-0.250	0.026	**
q	-0.288	0.010	**
l	0.190	0.093	
α_{W1}	-0.312	0.004	**
α_{M1}	-0.37	0.001	**
α_{W2}	-0.244	0.030	**
α_{M2}	-0.196	0.083	

Table A.1: LHS partial rank correlation coefficients. Parameters with significant correlations at the $\alpha = 0.5$ level are demarcated by two stars. The infection force β seems to have the largest effect on total prevalence.

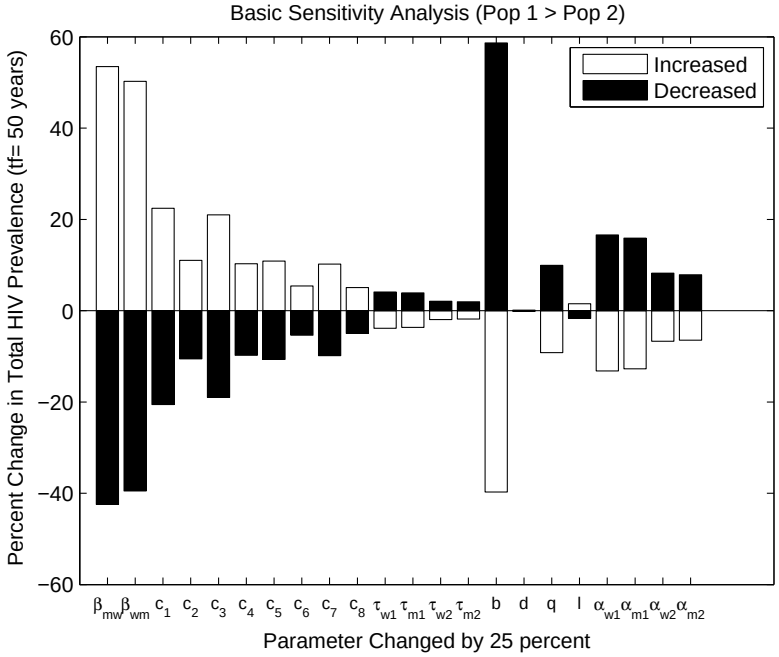


Figure A.1: Basic sensitivity analysis for model with treatment and AIDS class. In this simulation, the size of population 1 was set to be twice the size of population 2. The seed parameters needed to produce this plot are: $\beta_{WM} = 0.001$; $\beta_{MW} = 0.003$; $\tau = 0.01$; $\alpha = 0.04$; $c_{1-8} = 60$; $b = 0.05$; $d = 0.02$; $q = 0.01$; and $l = 0.03$. The inital values were chosen as follows: 10 percent infected in all populations; 1 percent on treatment in all populations; 1 percent with AIDS in all populations; $N_{W1} = 1000$, $N_{M1} = 1000$, $N_{W2} = 500$, and $N_{M2} = 500$.

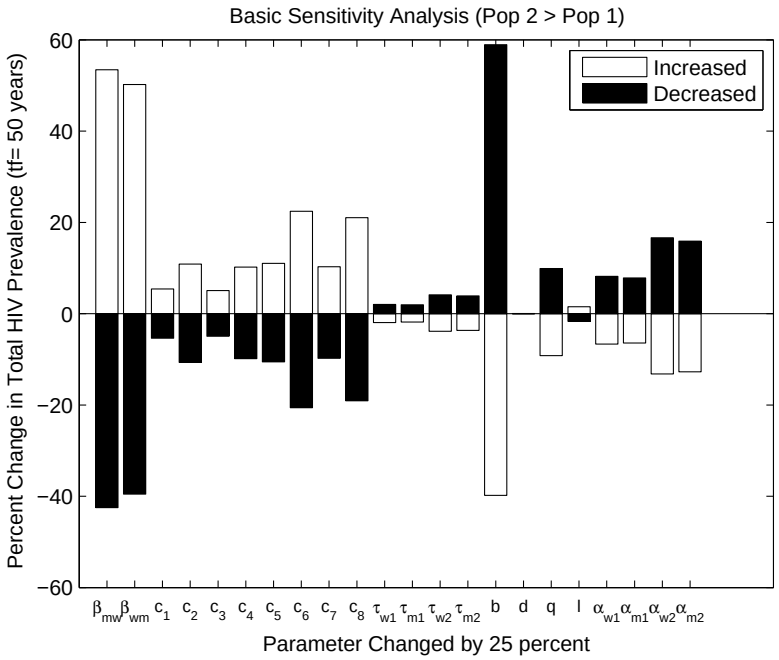


Figure A.2: Basic sensitivity analysis for model with treatment and AIDS class. In this simulation, the size of population 2 was set to be twice the size of population 1. The seed parameters needed to produce this plot are: $\beta_{WM} = 0.001$; $\beta_{MW} = 0.003$; $\tau = 0.01$; $\alpha = 0.04$; $c_{1-8} = 60$; $b = 0.05$; $d = 0.02$; $q = 0.01$; and $l = 0.03$. The inital values were chosen as follows: 10 percent infected in all populations; 1 percent on treatment in all populations; 1 percent with AIDS in all populations; $N_{W1} = 500$, $N_{M1} = 500$, $N_{W2} = 1000$, and $N_{M2} = 1000$.

Bibliography

Abuelezam, Nadia. 2008. Personal Experiences Working at TASO. 1.3

Ahmed, S., T. Lutalo, M. Wawer, D. Serwadda, N. K. Sewankambo, F. Nalugoda, F. Makumbi, F. Wabwire-Mangen, N. Kiwanuka, and G. Kigozi. 2001. HIV incidence and sexually transmitted disease prevalence associated with condom use: A population study in Rakai, Uganda. *AIDS* 15(16):2171.

Baryarama, F., J. Y. T. Mugisha, L. S. Luboobi, M. De la Sen, B.B.K. Huat, F.H. Ali, S. Hashim, A.A. Al-Abduljabbar, R.J.A. Richard, and N. Sriraam. 2005. An HIV/AIDS model with variable force of infection and its application to the epidemic in Uganda. *American Journal of Applied Sciences* 2(9):1274–1278. 2.1.2, 2.1.2

Blanc, A.K., and N. Rutenberg. 1991. Coitus and contraception: the utility of data on sexual intercourse for family planning programs. *Studies in Family Planning* 22(3):162–176. 2.2.3

Blower, S.M., and H. Dowlatabadi. 1994. Sensitivity and uncertainty analysis of complex models of disease transmission: An HIV model, as an example. *International Statistical Review* 62(2):229–243. 3.2.1, 3.2.1, 3.2

Bunnell, R., A. Opio, J. Musinguzi, W. Kirungi, P. Ekwaru, V. Mishra, W. Hladik, J. Kafuko, E. Madraa, and J. Mermin. 2008. HIV transmission risk behavior among HIV infected adults in Uganda: Results of a nationally representative survey. *AIDS* 22(5):617. 2.2.1

Crepaz, N., C.M. Lyles, R.J. Wolitski, W.F. Passin, S.M. Rama, J.H. Herbst, D.W. Purcell, R.M. Malow, and R. Stall. 2006. Do prevention interventions reduce HIV risk behaviours among people living with HIV? A meta-analytic review of controlled trials. *AIDS* 20(2):143. 2.2.1, 2.2.1, 6.1.4

Diekmann, O., J.A.P. Heesterbeek, and J.A.J. Metz. 1990. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* 28(4):365–382. 4.1

Doyle, M., D. Greenhalgh, and S. Blythe. 1998. Equilibrium analysis of a mathematical model for the spread of AIDS in a two sex population with mixing constraints. *Journal of Biological Systems* 6(2):159–185. 1.5, 2.1.2, 4.1

Foss, A.M., M. Hossain, P.T. Vickerman, and C.H. Watts. 2007. A systematic review of published evidence on intervention impact on condom use in sub-Saharan Africa and Asia. *British Medical Journal* 83(7):510–516.

Gisselquist, D., R. Rothenberg, J. Potterat, and E. Drucker. 2002. HIV infections in sub-Saharan Africa not explained by sexual or vertical transmission. *International Journal of STD and AIDS* 13(10):657. 2.1.1

Goodrich, J., K. Wellings, and D. McVey. 1998. Using condom data to assess the impact of HIV/AIDS preventive interventions. *Health Education Research* 13(2):267–274.

Gray, R.H., M.J. Wawer, R. Brookmeyer, N.K. Sewankambo, D. Serwadda, F. Wabwire-Mangen, T. Lutalo, X. Li, T. vanCott, and T.C. Quinn. 2001. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *The Lancet* 357(9263):1149–1153. 2.2.3

Halperin, D.T., and H. Epstein. 2004. Concurrent sexual partnerships help to explain Africa's high HIV prevalence: Implications for prevention. *The Lancet* 364(9428):4–6. 2.1.1

Heffernan, J.M., R.J. Smith, and L.M. Wahl. 2005. Perspectives on the basic reproductive ratio. *Journal of The Royal Society Interface* 2(4):281–293. 4.1

Hethcote, H.W. 1978. An immunization model for a heterogeneous population. *Theoretical Population Biology* 14(3):338–349. 5.2, 7

Hoare, A., D.G. Regan, and D.P. Wilson. 2008. Sampling and Sensitivity Analyses Tools (SaSAT) for Computational Modeling. *Theoretical Biology and Medical Modelling* 5(1):4. 3.2.1

Hogle, J.A., Agency for International Development, Synergy Project, United States, and Office of HIV/AIDS. 2002. *What Happened in Uganda:*

Declining HIV Prevalence, Behavior Change, and the National Response. Synergy Project. 1.3

Keeling, M.J., and P. Rohani. 2002. Estimating spatial coupling in epidemiological systems: A mechanistic approach. *Ecology Letters* 5(1):20–29. 7

Lagarde, E., C. Enel, and G. Pison. 1995. Reliability of reports of sexual behavior: A study of married couples in rural West Africa. *American Journal of Epidemiology* 141(12):1194–1200. 2.2.3

Lajmanovich, A., and J.A. Yorke. 1976. A deterministic model for gonorrhea in a nonhomogeneous population. *Mathematical Biosciences* 28:221–236. 5.1.2, 5.2, 5.2.1, 5.2.2, 7

Lloyd, A.L., and V.A.A. Jansen. 2004. Spatiotemporal dynamics of epidemics: Synchrony in metapopulation models. *Mathematical Biosciences* 188:1–16. 5.2

Lloyd, A.L., and R.M. May. 1996. Spatial heterogeneity in epidemic models. *Journal of Theoretical Biology* 179:1–11. 1.5, 4.1, 5.1.1

MOH, Uganda. 2006. CDC: Uganda HIV/AIDS sero-behavioural survey 2004–2005 report. 1.1, 1.2, 1.3, 2.2.3

Morgan, D., C. Mahe, B. Mayanja, J.M. Okongo, R. Lubega, and J. A.G. Whitworth. 2002. HIV-1 infection in rural Africa: Is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 16(4):597. 2.2.3

Neumann, M.S., W.D. Johnson, S. Semaan, S.A. Flores, G. Peersman, L.V. Hedges, and E. Sogolow. 2002. Review and meta-analysis of HIV prevention intervention research for heterosexual adult populations in the United States. *Journal of Acquired Immune Deficiency Syndromes* 30:S106. 2.2.1

Okware, S., A. Opio, J. Musinguzi, and P. Waibale. 2001. Fighting HIV/AIDS: Is success possible? *Bulletin of the World Health Organization* 79:1113–1120. 1.1

Orrell, C., D.R. Bangsberg, M. Badri, and R. Wood. 2003. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 17(9):1369. 1.3

Pence, G.E. 2007. *The Elements of Bioethics*. McGraw-Hill. 1.3

Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. 2006. World population prospects: The 2006 revision and world urbanization prospects. Tech. rep., United Nations. URL `http://esa.un.org/unpp`. 2.2.3

Powers, K.A., C. Poole, A.E. Pettifor, and M.S. Cohen. 2008. Rethinking the heterosexual infectivity of HIV-1: A systematic review and meta-analysis. *The Lancet Infectious Diseases* 8(9):553–563. 1.1, 1.3, 2.1.1

Royce, R.A., A. Sena, W. Cates, and M.S. Cohen. 1997. Sexual transmission of HIV. *New England Journal of Medicine* 336(15):1072–1078. 1.1, 2.2.1, 2.2.3

Sani, A., D.P. Kroese, and P.K. Pollett. 2007. Stochastic models for the spread of HIV in a mobile heterosexual population. *Mathematical biosciences* 208(1):98–124. 1.5, 2.1.2, 2.1.2

Schopper, D., S. Doussantousse, and J. Orav. 1993. Sexual behaviors relevant to HIV transmission in a rural African population. how much can a KAP survey tell us? *Social Science and Medicine (1982)* 37(3):401–412. LR: 20041117; PUBM: Print; JID: 8303205; ppublish. 2.2.3

Scott, S., J. Mossong, W.J. Moss, F.T. Cutts, and S. Cousens. 2008. Predicted impact of the HIV-1 epidemic on measles in developing countries: Results from a dynamic age-structured model. *International Journal of Epidemiology* 37(2):356. 1.1, 1.3, 2.1.2, 2.1.2

UAC, Ugandan AIDS Commission. 2003. HIV/AIDS surveillance report. 1.2, 2.1.1

UNAIDS, WHO. 2005. Guidance on ethics and equitable access to HIV treatment and care. Tech. rep., WHO/UNAIDS. 1.1, 1.3, 2.2.3, 6.1.1, 6.1.2, 6.1.3

———. 2007. UNAIDS/WHO epidemiological fact sheets on HIV/AIDS and sexually transmitted infections, Uganda 2004 update. 1.1, 1.2, 1.3, 2.2.3

———. 2008. Report on the global AIDS epidemic. Tech. rep., Joint Programme on HIV/AIDS, UNAIDS. 1.1, 1.1

van den Driessche, P., and J. Watmough. 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences* 180(1-2):29–48. 2.1.2, 4.1, 4.1

Vernazza, P.L., J.J. Eron, S.A. Fiscus, and M.S. Cohen. 1999. Sexual transmission of HIV: Infectiousness and prevention. *AIDS* 13(2):155. 1.1, 1.3

Wawer, M.J., R.H. Gray, N.K. Sewankambo, D. Serwadda, X. Li, O. Laeyendecker, N. Kiwanuka, G. Kigozi, M. Kiddugavu, and T. Lutalo. 2005. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *Journal of Infectious Diseases* 191(9):1403–1409. 2.2.3

Wilson, D.P., J. Kahn, and S.M. Blower. 2006. Predicting the epidemiological impact of antiretroviral allocation strategies in KwaZulu–Natal: The effect of the urban-rural divide. *Proceedings of the National Academy of Sciences* 103(38):14,228–14,233. 1.5, 2.2.1, 3.2.1, 6.1.5

Worobey, M., M. Gemmel, D.E. Teuwen, T. Haselkorn, K. Kunstman, M. Bunce, J.J. Muyembe, J.M.M. Kabongo, R.M. Kalengayi, E. Van Marck, et al. 2008. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. *Nature* 455(7213):661–664. 1.1