To my husband, who through his support and encouragement, made this all possible
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<td>Neoplasm</td>
<td>An abnormal growth of tissue, a tumor.</td>
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<td>Immune deficiency</td>
<td>Inability of the immune system to function properly. Results in greater susceptibility to disease.</td>
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<td>Immunosuppression</td>
<td>Reduced immune system response to pathogens, such as virus, bacteria or fungi.</td>
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<td>Seropositive</td>
<td>Individual infected with HIV.</td>
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<tr>
<td>Retrovirus</td>
<td>RNA virus that synthesizes DNA through reverse transcriptase.</td>
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<tr>
<td>Lentivirus</td>
<td>Type of retrovirus characterized by presenting a long interval between infection and the onset of symptoms in hosts.</td>
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<tr>
<td>Reverse Transcriptase</td>
<td>Enzyme responsible for transcription of single-stranded RNA into double-stranded DNA.</td>
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<tr>
<td>Protease</td>
<td>HIV enzyme needed for assembly of an infectious virus particle.</td>
</tr>
<tr>
<td>Integrase</td>
<td>HIV enzyme used by the virus to incorporate its genetic material into that of the host cell.</td>
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<tr>
<td>CD4+ helper T cells</td>
<td>White blood cells that coordinate immune response.</td>
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<tr>
<td>Macrophages</td>
<td>Large immune system cells responsible for removing invading pathogens by enveloping them. These cells move freely throughout the body.</td>
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<tr>
<td>Dendritic cells</td>
<td>Immune system cells with long, tentacle branches. Function as specialized cells at the mucosa.</td>
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<tr>
<td>Receptor</td>
<td>A molecule on the surface of a cell that serves as a recognition or binding site for antigens, antibodies, or other cellular or immunological components.</td>
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<td>Fusin</td>
<td>A receptor present in all cells types that can be infected by HIV. Fusin is necessary for HIV invasion</td>
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<td>Opportunistic infection</td>
<td>Infection by an organism that does not ordinarily cause disease but which, under certain circumstances (impaired immune responses), becomes pathogenic.</td>
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<td>STD</td>
<td>Sexually transmitted disease.</td>
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<td>HAART</td>
<td>Highly active antiretroviral treatment: a combination of drugs aimed at fighting HIV in the body.</td>
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<td>Prevalence</td>
<td>Proportion of individuals in a population who are infected.</td>
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THE NEW FACE OF AIDS: A MATHEMATICAL MODELING APPROACH TO NEW TRENDS IN HIV TREATMENT AND PREVENTION

By

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August 2007

Chair: Maia Martcheva
Major: Mathematics

My study develops mathematical models to investigate prevention strategies aimed at a reduction of HIV prevalence in a population. It focuses primarily on the impact of coupling prevention effort with treatment delivery. It gives an overview of possible prevention strategies for the entire population as well as for the subgroup of individuals who are undergoing treatment and/or receiving HIV-related medical attention. My study focuses on exploring the effects of the most recent trend having a major impact in the HIV/AIDS epidemic: HAART treatment. Specifically, through simulation, it demonstrates the impact of integrating prevention efforts with the distribution of treatment and HIV-related medical support. It shows that educating HIV patients about risks of HIV transmission, reliability of condoms, and safer sexual behavior may effectively decrease the prevalence of HIV in the population as effectively as aiming these prevention programmes at the entire population, provided that availability of testing and HIV-related medical attention is adequate.
CHAPTER 1
INTRODUCTION

1.1 Motivation

Acquired immunodeficiency syndrome (AIDS) was first recognized in 1982 following a report published June 5, 1981 [1] of five cases of Pneumocystis carinii pneumonia (PCP) among previously healthy young men in Los Angeles, California. These incidents were latter attributed to a retrovirus that came to be known as human immunodeficiency virus (HIV). By August 1981, 70 new cases were recorded of PCP and Kaposi’s sarcoma (KS), a rare, malignant neoplasm (Table 1) previously seen before in elderly man [2]. Within a few months it was clear that the world was facing a dangerous new epidemic, but, no one could have imagined the extent of what became the AIDS pandemic.

Today, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS has killed more than 35 million people [3]. In 2006, there were 39.5 million people worldwide living with HIV, including 2.3 million children. An estimated 4.3 million people were newly infected that same year [4]. In these 25 years the disease has spread to pandemic proportions. HIV infection and AIDS remain leading causes of illness and death in many countries in the world, including the United States [5]. The disease that once was viewed as restricted to men who have sex with men has now become prevalent among men who are heterosexual, women and children [6].

With the advance of this dangerous disease, the world has become involved in a frenetic search for ways to treat or cure HIV infection. Over the last 25 years there has been enormous progress in the fight against AIDS that might suggest that there is hope for the future [3]. A cure or vaccine is not yet available, but there has been a significant advance in treatment, resulting in an increase in the life expectancy and quality of life of those diagnosed with HIV infection [7]. Today highly active antiretroviral therapy (HAART) is used to slow the progression of HIV infection and thus postpone death from
AIDS. HAART is credited as a major factor in significantly reducing annual deaths by AIDS in the U.S. [7].

However, even though treatment can increase life expectancy and health prospects in HIV infected individuals, treatment does not provide a cure for the infection. This and other factors influence the need for continued efforts to reduce further spread of the disease. With globalization and increased movement of people, the AIDS pandemic needs to be addressed as a global issue, especially given high cost of treatment both for individuals and for governments. Further, HIV is a highly mutable virus, so the risk of new multiresistant strains emerging is always present [3]. Therefore, efforts to prevent the spread of HIV are still very important.

There are, however, many issues that make it especially difficult to implement effective prevention programmes that reduce the prevalence of HIV infection in a population. Among these issues are difficulties in reaching a significant portion of the population with programmes for education about the disease and its transmission, the cost of prevention programmes, compliance of the population, and the fact that HIV infection is primarily a sexually transmitted disease and thus prevention strategies have to address many delicate issues of sexuality, intimacy and privacy [3, 6].

1.2 Goals of Research

I investigated the dynamics of HIV/AIDS in this new era of the epidemic marked by the introduction of HAART treatment. The clear need for improved, cost effective prevention and the difficulties in delivering prevention education to the entire population, or even to the group at higher risk of acquiring the disease, motivates me to seek a different focus for prevention. I suggest that, given sufficient availability of testing and medical support, aiming prevention programmes (education about condom use and reduction in number of sexual partners) towards persons receiving HIV treatment and medical attention can effectively reduce the prevalence of the disease in the overall population.
It is important to study the trends in the dynamics of the HIV epidemic. To effectively create and implement strategies of prevention it is necessary to focus on the driving forces of the epidemic and the impact of various epidemic parameters on the distribution of the pathogen in the population. Here I aim to explore the effects of a new and important dimension of HIV infection dynamics: treatment. Through analysis and simulation I illustrate and discuss some of the most relevant issues in today’s fight against HIV. I investigate the effects of different prevention strategies for HIV transmission in a population and possible counter-effects that these strategies may cause. I demonstrate the impact of effectively integrating prevention efforts with delivery of treatment to HIV patients, and I conclude that, in countries such as the United States, where testing and treatment are widely available, it is sufficient to focus prevention programmes on HIV patients rather than on the entire population. I also demonstrate the risk of unmodified sexual behavior in HIV patients and suggest prevention strategies that do not rely on reduced infectivity due to treatment.

1.3 The Disease

Human immunodeficiency virus (HIV) was first isolated in 1983 by Luc Montagnier at the Pasteur Institute in France. It has since been recognized as the pathogen responsible for the acquired immunodeficiency syndrome (AIDS) [6]. HIV is a lentivirus of the family Retroviridae (Table 1). It contains two copies of positive ribonucleic acid (RNA) that code for the virus’ nine genes. The RNA is bound to proteins and enzymes necessary for viral development, including reverse transcriptase, protease, and integrase, and is enveloped in two layers of phospholipids [8] (Table 1).

HIV primarily affects the human immune system by attacking helper T cells (more specifically, CD4\(^+\) cells), macrophages, and dendritic cells (Table 1) [9]. HIV attacks cells using protein receptors that are part of the normal immune response. The main receptor is the CD4 molecule on helper T cells. A secondary co-receptor is also necessary for the virus to invade a cell. The main co-receptor, present in all cell types that can be infected by
HIV, is called fusin [8]. As the infection develops, the virus causes depletion and increasing disruption of the immune system opening many doors for the onset of opportunistic (Table 1), life-threatening infections [8–10]. There is usually an asymptomatic period, during which no visible symptoms of the infection occur. Even during this time, however, the virus is actively multiplying, infecting and killing cells [7]. Viral particles are also, during this time, moving into secretions and body fluids, including blood, semen and vaginal secretions.

Treatment regiments today focuse on a combination of drugs that repress HIV reproduction and cell invasion, including: reverse transcriptase inhibitors and protease inhibitors (which impede viral reproduction), and fusion inhibitors (which block virus from entering cells)[11]. Other drugs aim to help prevent a number of opportunistic infections including PCP, toxoplasmosis, cryptococcus and cytomegalovirus infection [11].

1.4 The Epidemic: Origin, History and Treatment

It is believed that HIV originated in human populations in Africa, possibly from a spill-over from primate populations, which could have occurred as a result of human exposure to primate blood during hunting expeditions [12]. HIV was isolated and recognized as the pathogen responsible for AIDS in 1983. No cure, vaccine or treatment existed, and treatments to combat the opportunistic infections caused by the immune deficiency were very few [7]. In 1987 the first treatment emerged. The drug was called AZT, a reverse transcriptase inhibitor. By 1992 combinations of drugs were introduced to improve treatment.

In 1996 evidence of the efficacy of a new treatment, called highly active antiretroviral therapy (HAART), was presented for the first time at the 11th International AIDS Conference in Vancouver [6]. Since 2000 UNAIDS and WHO have been trying to increase access to HIV treatment in developing countries. By the end of 2005 1.3 million people in low- and middle-income countries have received access to antiretroviral therapy [6]. Today,
successful treatment has changed the face of AIDS from a disease that killed in just a few years into a sustainable, chronic condition.

By 2001, however, there was growing concern with both medication toxicity and effectiveness [11]. Although HAART has clear benefits, it also has its shortcomings and risks. HAART is not a cure: the drugs only control HIV, they cannot eliminate the virus from the body [7, 13]. This means that HIV can still be transmitted. The drugs have a strict schedule and adherence is difficult [6]. Understanding the ultimate impact of HAART upon HIV prevalence requires a quantitative approach.

1.5 Highly Active Antiretroviral Therapy

A complicated dynamic exists between HIV prevention and treatment. As treatment access expands in resource-limited countries, the health, longevity and quality of life for people with HIV will improve [6, 14], potentially increasing opportunities for sexual transmission. At the same time, optimism about the treatment or misperceptions about the effects of antiretroviral drugs may also cause some people to increase their risk behavior [15–17]. On the other hand, and a goal of this thesis, the introduction of treatment in the population provides a clear target group for prevention efforts and a clear path through which to deliver such prevention programmes by integrating prevention efforts with delivery of treatment to HIV positive individuals.

Since the introduction of HAART, increases in the quality of life and life expectancy for HIV-positive individuals under treatment has reshaped the face of the epidemic. HAART has been able to increase life expectancy and significantly reduce virus load in HIV positive patients, sometimes to levels below those that can be detected by HIV tests [7]. In women, low blood plasma virus load has been correlated with lower vaginal virus load, indicating the possibility of a lower risk of perinatal and female-to-male heterosexual transmission from women under treatment [18]. Perinatal transmission rates have been reduced with screening of pregnant women, combined with prophylactic administration of HAART drugs [5].
However, since 2005 long term side effects of HIV medication use have become evident. Drugs for HAART require a strict schedule and requirements. Adherence to the treatment is difficult, and today many patients fail to follow through with treatment because of difficulties with drug schedules, cost of drugs, and side effects [3, 9]. Another major issue with HAART is the possibility of new resistant strains of HIV arising and increasing in frequency. For these reasons, some health experts recommend delaying drug treatment, while maintaining regular medical checkups [19].

1.6 Transmission and Prevention

HIV can be transmitted either through sexual contact where one partner is infected or through needles or syringes containing infected blood. Before blood was screened for HIV, the virus was also transmitted through contaminated blood transfusions [7]; however, after the introduction of screening of plasma for HIV in 1985 [6], the risk of transmission of HIV through such a path has become extremely small. HIV can also be transmitted from mother to child during pregnancy, birth or through nursing [7]. Prenatal HIV testing and HAART have reduced this transmission significantly [5]. There is no evidence that HIV can be transmitted by casual household or social contact or by insects [7, 20]. HIV is not transmitted through sweat, tears, kissing, or sharing common household items, such as eating utensils [20].

Today, the majority of HIV infections are acquired through sexual relations between partners, one of whom has HIV [4, 7]. This makes understanding the dynamics regulating sexual transmission of HIV very important. Parameters that affect the sexual transmission of HIV include the correct use of barrier prevention methods such as male or female condoms, the number of different sexual partners that an individual acquires, and the presence of other sexually transmitted diseases (STDs) that can enhance transmission [20].

Goals of behavior change for HIV prevention include abstinence and delayed sexual debuts for young people, monogamy within relationships, reduction in the number of partners, and correct and consistent use of condoms [3, 4]. Various studies suggest that
these strategies can reduce the prevalence of the disease and the risk of transmission [7, 20, 21].

It has been shown that even though HAART may reduce viral load in infected individuals significantly, eradication of the virus within a patient cannot yet be achieved. Levels of plasma virus load below detection do not necessarily reflect low levels of virus in other secretions such as semen [13]. Still, some studies have suggested that there might be a correlation between low viral load in the blood and reduced infectivity [5, 22]. It so, treatment can be a facet of a prevention strategy.

However, many issues arise when treatment is used as a prevention strategy. The first is the high cost of treatment, both for individuals and for governments. Another issue is that, even if there is a correlation between low viral load and reduced infectivity, lower viral loads can only be achieved with adherence to the treatment, which is difficult to maintain [3] and may not even be the best immediate course of action for the patient early in infection [19]. But, delayed start of drug treatment means delayed reduction in infectivity. Finally, widespread use of treatment increases the risk of producing multiresistant strains of HIV. However, delayed start of drug treatment means delayed reduction in infectivity.

It has also been confirmed that there have been increases in bacterial STDs and risk behaviors correlated with the introduction of HAART [15]. The population as a whole perceives a reduced danger in HIV/AIDS, but the most significant issue might be the false overconfidence that treatment prevents transmission. Individuals who believe that treatment effectively reduces infectivity might increase risky behaviors, for instance, reducing compliance with the use of condoms and increasing the number of new sexual partners.

Based on a study using self-reported surveys, the Centers for Disease Control and Prevention (CDC) found that infected individuals who know of their HIV-positive status have a significant reduction in high-risk behavior from before they learn about their
status [5]. However, other studies [16, 17] have shown that HIV-positive patients are getting infected with bacterial STDs at rates comparable to or higher than those of HIV-negative patients. In a study in Brazil, the incidence of new gonorrhea infections (an acute bacterial STD) in women with known HIV infection was 12.9%, while the incidence among women who are HIV-negative was 8.33% in promiscuous women and 2% in non-promiscuous women for the same cohort [16]. A study in Nigeria found that 14% of HIV-positive individuals, but only 2.0% of HIV-negative individuals, tested positive for syphilis [17].

The Brazilian and Nigerian results raise the question of the effectiveness of changes in behavior due to the knowledge that one is seropositive (see Table 1). Even if persons that become aware of their HIV infection believe that they are substantially increasing precautions to prevent the spread of HIV [5], the fact that they are acquiring bacterial STDs suggest that the prevention measures they are taking have not been sufficient.

It is clear then that assuming that treatment will prevent the spread of HIV through reduced infectivity or through change in behavior without counseling is not ideal. Here I will argue that, if enough testing and medical counseling are available, it is possible to achieve comparable prevention results by focusing traditional, cost-effective prevention programmes of education and support directly on the sub-population receiving HIV-related medical care. These programmes prevent new infections due to increased compliance with correct and consistent condom use and reduced number of sexual partners. I also illustrate that incorporating education programmes into HIV-related medical attention can be substantially more effective than relying in reduced infectivity alone. Thus it is desirable to incorporate preventive changes in behavior for individuals who become aware of their seropositive status and receive treatment.

1.7 Mathematical Models of STDs and the Basic Reproduction Number

In the early 1900's, Sir Ronald Ross, who received a Nobel Prize in 1902 for his work on malaria, laid the foundation of the field of mathematical epidemiology. In his efforts
to establish that it is not necessary to eradicate the vector (mosquito) population in order to eliminate the disease in humans, he introduced the first concepts and models of mathematical epidemiology. In a mathematical model of malaria from 1911, he showed that bringing the mosquito population below a certain threshold was sufficient to eliminate malaria [23].

Such threshold phenomena have been central in mathematical epidemiology ever since [23, 25]. Traditionally, the threshold that determines the ability of an infectious disease to invade a stable susceptible population has been called the basic reproductive number, and denoted $R_0$. The basic reproductive number should reflect the reproductive success of a pathogen in a host population [25]. In classical mathematical epidemiology the reproductive number of the disease has been defined as the number of secondary cases of the disease that one typical infective individual will produce over his or her infective lifetime in an entirely susceptible stable population [23, 25]. A value greater than one is needed for disease persistence.

In models that are homogeneous with respect to infectivity of individuals within a population, it is possible to construct the basic reproductive number in a straightforward and intuitive manner from this definition. With the appearance and spread of AIDS worldwide, more attention has been drawn to the dynamics of sexually transmitted diseases (STDs)[23, 24]. One of the most important and distinguishing aspects of modeling STD transmission versus classical modeling of infectious disease dynamics lies in the substantial heterogeneity of transmission within the population. Number of contacts ranks high in defining this heterogeneity, together with issues of social and interpersonal relationships [23]. It is known that sexual partner acquisition rates vary enormously among communities and among individuals, possibly ranging from less than 1 to 100 partners per year [24]. A consideration of contact processes is central to the understanding of threshold phenomena such as the basic reproduction number [23].
Mathematical models of STDs, and specifically of HIV/AIDS, that aim to incorporate heterogeneity of susceptibility and infectivity (see [24], [25], [26], [27]), or non-homogenous mixing of individuals (see [28]) face a major problem in the computation of $R_o$ because the mathematical description of what is a typical infectious individual is difficult to achieve in populations with high degrees of heterogeneity [23]. Many researches have sought to resolve this issue either by assuming that the population in question is homogeneous in its infectivity and susceptibility using an average value for each individual or, probably more appropriately, by incorporating the heterogeneity of the population in the model and then letting $R_o$ be the appropriate weighted average of the heterogeneous trait (such as number of sexual partners) in the population (see [23], [24], [29]).

The number of new sexual partners constitutes an important aspect of heterogeneity within a population when we consider epidemics of STDs. The distribution of this number has been used for heterogeneous model formulations of HIV/AIDS [23, 29]. Here I plan to incorporate a similar approach to the issues of heterogeneity in number of sexual partners in a population with a more explicit rendering of $R_o$ where the effects of heterogeneity in acquisition of new sexual partners can be explicitly treated, but still maintaining a general fidelity to the definition of $R_o$. A similar approach was used in [24], but there the heterogeneity in question was in the intrinsic viral infectivity variability between individuals, based on the assumption that there was a correlation between plasma viral load and infectivity.
CHAPTER 2
FORMULATION OF THREE MODELS

I consider a compartmental model of a population that consists of susceptible individuals \( S \), HIV-infected individuals who have not developed AIDS and are not receiving treatment or HIV-related medical support \( U \), HIV-infected individuals under treatment and/or other HIV-related medical support who have not developed AIDS \( T \) and infected individuals who have developed AIDS \( A \). The term *AIDS* will apply here only to the more advanced stage of HIV infection categorized by a CD4+ T cell count below 200 cells per cubic millimeter of blood, coupled with severe clinical conditions, most of which are opportunistic infections [7]. For this reason, I assume here that individuals in class \( A \) are removed from the sexually active population, given that they have developed severe opportunistic infections and/or cancers and are assumed to be severely debilitated or hospitalized [7]. I only consider the transmission of HIV via sexual intercourse and therefore the population under consideration is sexually active. I take into account that susceptible individuals and infected individuals (both with and without medical support) may differ in the number of sexual partners per unit of time. Thus, I subdivide the susceptible and infected classes into several subclasses \( S_i, U_i, T_i, i = 1, ..., m \) with \( i \) corresponding to the number of sexual partners that individuals in each subclass will have per unit of time. It is assumed that formation of sexual pairs is random (does not depend on subclass).

Let \( \Lambda_i, i = 1, ..., m \), be the recruitment rates of individuals to the sexually active susceptible classes \( S_i \), \( \mu \) be the natural death rate and removal rate and \( d \) be the disease induced death rate. Upon a sexual encounter, without protection, with an infected individual from subclasses \( U_i \) or \( T_i \), a susceptible individual will become infected with probability \( \eta_i \) and \( \eta_i^\ast \), respectively. To account for the effects of condom use, we assume condoms have an efficacy \( \varepsilon \) and compliance \( u_i \). So the product \( \rho_i = \varepsilon u_i \) represents the condom protection.
To account for the fact that often individuals who are infected and not under treatment are not aware of their status and thus cannot seek treatment, I introduce the parameter $\nu_i$, $i = 1, \ldots, m$, where $\nu_i$ is the proportion of infected individuals in class $U_i$ who undergo testing and subsequently know their status. I assume tested individuals begin receiving medical support at a rate $\delta$ and thereafter develop AIDS at a rate $\gamma_i$. I assume untreated individuals develop AIDS at a rate $\alpha_i$. Variable and parameter descriptions are summarized in Table 2-1.

The total population size is given by $N = \sum_{i=1}^{m} S_i + \sum_{i=1}^{m} U_i + \sum_{i=1}^{m} T_i + A$, and it satisfies the equation

$$\frac{dN}{dt} = \sum_{i=1}^{m} \lambda_i - \mu N - dA. \quad (2-1)$$

We also define the total population within each class as $N_i$ where $N_i = S_i + U_i + T_i$.

Standard incidence is appropriate for large populations [? ] and is used here with the result that interactions are made independent of total population size. The idea behind this being that an increased population size does not necessarily make individuals more promiscuous.

Thus we get the following system of nonlinear differential equations for $i = 1, 2, \ldots, m$,

$$\frac{dS_i}{dt} = \lambda_i - \mu S_i - \left( \sum_{j=1}^{m} j(1 - \rho_j)\eta_j U_j + \sum_{j=1}^{m} j(1 - \rho_j)\eta_j^* T_j \right) \frac{iS_i}{\sum_{j=1}^{m} jN_j} \quad (2-2)$$

$$\frac{dU_i}{dt} = \left( \sum_{j=1}^{m} j(1 - \rho_j)\eta_j U_j + \sum_{j=1}^{m} j(1 - \rho_j)\eta_j^* T_j \right) \frac{iS_i}{\sum_{j=1}^{m} jN_j} - (\mu + \nu_i \delta + \alpha_i)U_i \quad (2-3)$$

$$\frac{dT_i}{dt} = \nu_i \delta U_i - (\gamma_i + \mu)T_i \quad (2-4)$$

$$\frac{dA}{dt} = \sum_{j=1}^{m} \alpha_j U_j + \sum_{j=1}^{m} \gamma_j T_j - (\mu + d)A \quad (2-5)$$
| Variable | Description | | Variable | Description |
|----------|-------------| |----------|-------------|
| $S_i$    | Susceptible individuals with $i$ average number of new sexual partners per unit of time | | $n, s$   | Average number of new sexual partners that an individual acquires per unit of time |
| $U_i$    | HIV-infected individuals, with $i$ average number of new sexual partners per unit of time, who have not developed AIDS and are not under treatment or HIV-related medical support | | $\Lambda_i$ | Recruitment rate for individuals entering the sexually active population in the subclass $S_i$ |
| $T_i$    | HIV-infected individuals, with $i$ average number of new sexual partners per unit of time, who have not developed AIDS but are receiving treatment and/or HIV-related medical support | | $\mu$ | Natural death rate |
| $A$      | HIV-infected individuals who have developed AIDS | | $d$ | AIDS induced death rate |
| $N$      | Total population size | | $\eta_i$ | Infectivity from individuals in the subclass $U_i$ |
| $N_i$    | $N_i = S_i + U_i + T_i$ | | $\eta^*_i$ | Infectivity from individuals in the subclass $T_i$ |
| $\varepsilon$ | Condom efficacy (intrinsic) | | $u_i$ | Compliance with the use of condom for individuals with $i$ average number of new sexual partners per unit of time |
| $\rho_i$ | Condom induced protection ($p_i = \varepsilon u_i$) | | $\nu_i$ | proportion of HIV-infected individuals with $i$ average number of new sexual partners per unit of time who have undergone testing and know their status |
| $\delta$ | rate at which HIV-infected individuals who know their status receive treatment and/or HIV-related medical support | | $\alpha_i$ | rate at which HIV-infected individuals with $i$ average number of new sexual partners per unit of time develop AIDS without treatment |
| $\gamma_i$ | rate at which HIV-infected individuals with $i$ average number of new sexual partners per unit of time develop AIDS with the treatment | | | |
2.1 The Model Without Treatment

I will consider the above model (\((2-2)-(2-5)\)) for two discrete subclasses of susceptible individuals, infected individuals not on treatment or HIV-related medical support, and infected individuals undergoing treatment and/or receiving HIV-related medical support. I let \(S_n, U_n\) and \(T_n\) be the subclasses of individuals in the susceptible, infected but not under treatment or medical support, and infected under treatment and/or medical support classes, respectively, who have relatively small number of new sexual partners per unit of time. These will henceforth be collectively referred to as the moderately sexually active class. Similarly I let \((S_s), (U_s)\) and \((T_s)\) be the subclasses of individuals in the susceptible, infected not under treatment or medical support, and infected under treatment and/or medical support classes, respectively, who have relatively large number of new sexual partners per unit of time. These will be henceforth collectively referred to as the highly sexually active class. I let \(n\) be the average number of new sexual partners that individuals in \(S_n, U_n\) and \(T_n\) acquire per unit of time and \(s\) be the average number of sexual partners that individuals in \(S_s, U_s\) and \(T_s\) acquire per unit of time. I then consider the general model above for \(i = n, s\).

I will focus first on a special case of this model assuming no individuals get treatment \(\left(\nu_i = 0\right)\). I will, in this case, let \(I_i\) be the total number of infective individuals with \(i\) number of new sexual partners per unit of time.

Then the model (\((2-2)-(2-5)\)) simplifies to the following:

\[
\frac{dS_n}{dt} = \Lambda_n - \mu S_n - \left(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s\right) \frac{nS_n}{nN_n + sN_s} \quad (2-6)
\]

\[
\frac{dS_s}{dt} = \Lambda_s - \mu S_s - \left(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s\right) \frac{sS_s}{nN_n + sN_s} \quad (2-7)
\]

\[
\frac{dI_n}{dt} = \left(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s\right) \frac{nS_n}{nN_n + sN_s} - \left(\mu + \alpha_n\right)I_n \quad (2-8)
\]

\[
\frac{dI_s}{dt} = \left(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s\right) \frac{sS_s}{nN_n + sN_s} - \left(\mu + \alpha_s\right)I_s \quad (2-9)
\]

\[
\frac{dA}{dt} = \alpha_n I_n + \alpha_s I_s - (\mu + d)A \quad (2-10)
\]
\[ \frac{dN}{dt} = \Lambda_n + \Lambda_s - \mu N - dA \] (2-11)

### 2.2 The Model With Treatment but Without Change in Behavior

I will also consider the above model ((2-2)-(2-5)) including medical intervention and treatment. The model is described by the flow chart diagram in Figure 2-1.

![Diagram of the model with treatment](image)

**Figure 2-1.** Diagram of the model with treatment

For \( \lambda(t) = (n(1 - \rho_n)\eta_n U_n + s(1 - \rho_s)\eta_s U_s + n(1 - \rho_n)\eta_n^* T_n + s(1 - \rho_s)\eta_s^* T_s) \), the resulting model is given by the following system of nonlinear differential equations:

\[ \frac{dS_n}{dt} = \Lambda_n - \mu S_n - \lambda(t) \frac{nS_n}{nN_n + sN_s} \] (2-12)

\[ \frac{dS_s}{dt} = \Lambda_s - \mu S_s - \lambda(t) \frac{sS_s}{nN_n + sN_s} \] (2-13)
\[
\frac{dU_n}{dt} = \lambda(t) \frac{nS_n}{nN_n + sN_s} - (\mu + \nu_n\delta + \alpha_n)U_n \tag{2-14}
\]
\[
\frac{dU_s}{dt} = \lambda(t) \frac{sS_s}{nN_n + sN_s} - (\mu + \nu_s\delta + \alpha_s)U_s \tag{2-15}
\]
\[
\frac{dT_n}{dt} = \nu_n\delta U_n - (\mu + \gamma_n)T_n \tag{2-16}
\]
\[
\frac{dT_s}{dt} = \nu_s\delta U_s - (\mu + \gamma_s)T_s \tag{2-17}
\]
\[
\frac{dA}{dt} = \alpha_n U_n + \alpha_s U_s + \gamma_n T_n + \gamma_s T_s - (\mu + d)A \tag{2-18}
\]
\[
\frac{dN}{dt} = \Lambda_n + \Lambda_s - \mu N - dA \tag{2-19}
\]

2.3 The Model With Treatment and Change in Behavior

Now I introduce behavior change in the population under treatment. We will allow for individuals who are under treatment, and thus assumed to know their serological status, to undergo a behavioral change. I introduce the parameters \(n_o\) and \(s_o\) defined as the average number of new partners that individuals in \(T_n\) and \(T_s\) acquire per unit of time, respectively. Similarly, I also introduce the parameter \(\rho_{n_o}\) and \(\rho_{s_o}\) for the condom related protection of individuals in subclass \(T_n\) and \(T_s\), respectively. The generalized model becomes the following. For \(\lambda(t) = n(1 - \rho_n)\eta_n U_n + s(1 - \rho_s)\eta_s U_s + n_o(1 - \rho_{n_o})\eta_{n_o}T_n + s_o(1 - \rho_{s_o})\eta_{s_o}T_s\),

\[
\frac{dS_n}{dt} = \Lambda_n - \mu S_n - \lambda(t) \frac{nS_n}{nN_n + (n_o - n)T_n + sN_s + (s_o - s)T_s} \tag{2-20}
\]
\[
\frac{dS_s}{dt} = \Lambda_s - \mu S_s - \lambda(t) \frac{sS_s}{nN_n + (n_o - n)T_n + sN_s + (s_o - s)T_s} \tag{2-21}
\]
\[
\frac{dU_n}{dt} = \lambda(t) \frac{nS_n}{nN_n + (n_o - n)T_n + sN_s + (s_o - s)T_s} - (\mu + \nu_n\delta + \alpha_n)U_n \tag{2-22}
\]
\[
\frac{dU_s}{dt} = \lambda(t) \frac{sS_s}{nN_n + (n_o - n)T_n + sN_s + (s_o - s)T_s} - (\mu + \nu_s\delta + \alpha_s)U_s \tag{2-23}
\]
\[
\frac{dT_n}{dt} = \nu_n\delta U_n - (\mu + \gamma_n)T_n \tag{2-24}
\]
\[
\frac{dT_s}{dt} = \nu_s\delta U_s - (\mu + \gamma_s)T_s \tag{2-25}
\]
\[
\frac{dA}{dt} = \alpha_n U_n + \alpha_s U_s + \gamma_n T_n + \gamma_s T_s - (\mu + d)A \quad (2-26)
\]
\[
\frac{dN}{dt} = \Lambda_n + \Lambda_s - \mu N - dA \quad (2-27)
\]
CHAPTER 3  
ANALYSIS OF THE MODEL WITHOUT TREATMENT  

3.1 Existence and Local Stability of the DFE  

The following result concerns the existence of a unique disease-free equilibrium (DFE).

**Theorem 1.** The system (2-6) - (2-11) has a unique disease-free equilibrium which is given by \( \varepsilon_o = (\frac{\Lambda_n}{\mu}, \frac{\Lambda_s}{\mu}, 0, 0, 0) \).

**Proof** Consider the model in the absence of infection. That is, let \( I_n = I_s = A = 0 \). At equilibrium, setting the right hand side of (2-6) - (2-11) equal to zero, we get \( S_n = \frac{\Lambda_n}{\mu} \) and \( S_s = \frac{\Lambda_s}{\mu} \). So there exists a unique disease-free equilibrium given by \( \varepsilon_o = (\frac{\Lambda_n}{\mu}, \frac{\Lambda_s}{\mu}, 0, 0, 0) \). ■

The following results concern with the local stability of the disease-free equilibrium (DFE).

I now linearize the system (2-6) - (2-11) around the DFE. The Jacobian matrix for this system, which I will call \( J \) from here on, at the DFE is given as follows:

![Figure 3-1. The model without treatment: diagram](image-url)
\[
J(\frac{\Lambda_n}{\mu}, \frac{\Lambda_s}{\mu}, 0, 0, 0) = \\
\begin{pmatrix}
-\mu & 0 & -n(1 - \rho_n)\eta_n \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} & -s(1 - \rho_s)\eta_s \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} & 0 \\
0 & -\mu & -n(1 - \rho_n)\eta_n \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} & -s(1 - \rho_s)\eta_s \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} & 0 \\
0 & 0 & n(1 - \rho_n)\eta_n \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} - (\mu + \alpha_n) & s(1 - \rho_s)\eta_s \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} & 0 \\
0 & 0 & n(1 - \rho_n)\eta_n \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} & s(1 - \rho_s)\eta_s \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} - (\mu + \alpha_s) & 0 \\
0 & 0 & \alpha_n & \alpha_s & -\mu - d
\end{pmatrix}
\]
Let $J(DFE)$ be the Jacobian matrix for this system at the disease free equilibrium given above. It is clear that three of the eigenvalues of $J(DFE)$ are given by $\lambda_{1,2} = -\mu$ and $\lambda_3 = -(\mu + d)$. The remaining eigenvalues are eigenvalues of the 2x2 matrix

$$J_o = \begin{pmatrix} n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} - (\mu + \alpha_n) & s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} \\ n(1 - \rho_n) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} & s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} - (\mu + \alpha_s) \end{pmatrix}$$

I now compute the determinant of $J_o$.

$$|J_o| = -n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_s) - s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_n) + (\mu + \alpha_n)(\mu + \alpha_s).$$

It is clear that when

$$n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_s) + s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_n) < (\mu + \alpha_n)(\mu + \alpha_s) \quad (3-1)$$

then the determinant of $J_o$ is positive.

If

$$-n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_s) - s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_n) + (\mu + \alpha_n)(\mu + \alpha_s) > 0$$

then we have

$$-(\mu + \alpha_s) [n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} - (\mu + \alpha_n)] - s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_n) > 0.$$

But since

$$-s(1 - \rho_s) \frac{s \Lambda_s}{n \Lambda_n + s \Lambda_s} (\mu + \alpha_n)$$

is clearly negative, we must have that

$$-(\mu + \alpha_s) [n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} - (\mu + \alpha_n)]$$

is positive. Thus,

$$n(1 - \rho_n) \frac{n \Lambda_n}{n \Lambda_n + s \Lambda_s} - (\mu + \alpha_n)$$

is negative.
Analogous considerations lead to the fact that

\[ s(1 - \rho_s)\eta_s \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} - (\mu + \alpha_s) \]

is also negative. Therefore all diagonal entries of \( J_o \) are negative. That is, assuming that the determinant of \( J_o \) is positive, the trace of \( J_o \) is negative.

Therefore I reach the condition that determines the local stability of our system at the DFE. If \( \text{det}(J_o) > 0 \), then I showed that the trace of \( J_o < 0 \) and Theorem 5.4 [30] implies that the eigenvalues of \( J_o \) have negative real part. Then all eigenvalues of \( J(DFE) \) have negative real part. Therefore the DFE is locally asymptotically stable. If condition 3–1 is not satisfied, \( \text{det}(J_o) < 0 \), then \( J_o \) has an eigenvalue with a positive real part. Thus the DFE is unstable.

I can now write the above threshold condition as \( R_c > 1 \) for

\[ R_c = \frac{n(1 - \rho_n)\eta_n}{n\Lambda_n + s\Lambda_s} \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} + \frac{s(1 - \rho_s)\eta_s}{(\mu + \alpha_s)} \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} \]

This leads to the following result:

**Theorem 2.** The DFE for the system (2–6) - (2–11) is locally asymptotically stable if \( R_c < 1 \) and unstable if \( R_c > 1 \), for

\[ R_c = \frac{n(1 - \rho_n)\eta_n}{(\mu + \alpha_n)} \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} + \frac{s(1 - \rho_s)\eta_s}{(\mu + \alpha_s)} \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} \]

In section 3.2 I show that the value \( R_c \) can actually be understood in terms of basic reproduction number, \( R_o \), which epidemiologically describes the reproductive success of the pathogen in a susceptible host population. Biologically, stability of the DFE means that the infection, if initially rare, will fade away.

### 3.2 The Basic Reproduction Number and Its Interpretation

The quantity \( R_o \) reflects the reproductive success of a pathogen in a host population. In classical epidemiology the reproductive number of the disease can be constructed from the number of secondary cases of the disease that one infective individual will produce over its infective lifetime in an entirely susceptible stable population. This number then determines if an initial surge of an epidemic will be possible [23, 31].
However, because the models studied here deal with a heterogeneous host population where individuals in the host population differ in the number of contacts they make, this simple definition poses a particular problem for these models. Namely, the number of secondary cases that one infective individual in $I_n$ will produce will be different than the number of secondary cases that one infective individual in $I_s$ will produce, and, more importantly, the long-term behavior of the disease is dependent on the original structure of the susceptible population in terms of subclasses $S_n$ and $S_s$. Therefore I propose that this definition needs to be further specified for this model. Such specifications have been studied in more complex epidemiological models for which heterogeneity was introduced [29, 31].

Here I make a distinction between the basic reproductive number of the disease in the population, the usual $R_o$, or population $R_o$, and the intrinsic $R_o$ of an individual in the population. The population $R_o$ is the measurement of reproductive success of the pathogen in the host population. The intrinsic $R_o$ is the number of secondary cases of the disease that one infective individual will produce over its infective lifetime in an entirely susceptible stable population. The latter is commonly used in the construction of the population $R_o$ in homogeneous populations [31].

$R_o$ of the model with two distinct subclasses without treatment. First, notice that, as mentioned above, the total host population is assumed to be subdivided into two classes: a moderately sexually active subpopulation and a highly sexually active subpopulation, namely individuals who respectively have $n$ or $s$ number of sexual partners per unit of time. If there are only susceptible individuals, the total population becomes $\Lambda_n + \Lambda_s \mu$.

I consider the number of secondary cases that one individual in the moderately active subclass ($I_n$) will produce over its entire infective lifetime. The average rate at which an infective individual in $I_n$ leaves the infective class is $\alpha_n + \mu$, and therefore the average time that he or she remains infective is given by $\frac{1}{\alpha_n + \mu}$. The number of new contacts that such
an individual has per unit of time is \( n \). The probability that each of these contacts will be with a susceptible is \( \frac{nS_n + sS_s}{nN_n + sN_s} \). The probability of transmission per partner is \((1 - \rho_n)\eta_n\). Therefore, the average number of transmissions by one infective individual in \( I_n \) per unit of time is given by \( n(1 - \rho_n)\eta_n \frac{nS_n + sS_s}{nN_n + sN_s} \). In an entirely susceptible population, the expected number of secondary cases that one infective individual in \( I_n \) will produce over its infective lifetime is \( \frac{n(1 - \rho_n)\eta_n}{\alpha_n + \mu} \). This can be thought of as an intrinsic reproductive number for an individual in \( I_n \). I will refer to this as \( R^n_o \).

Thus I have \( R^n_o = \frac{n(1 - \rho_n)\eta_n}{\alpha_n + \mu} \), and similarly by the same construction as above for one infective individual in \( I_s \) I obtain \( R^s_o = \frac{s(1 - \rho_s)\eta_s}{\alpha_s + \mu} \).

One can see now that the overall population \( R_o \) (the measurement of reproductive success of the pathogen in the entire population) that was derived by the analysis of the local stability of the DFE is given by a weighted sum of the intrinsic reproductive number of hosts in each of the two host classes. More specifically, \( R_o = R^n_o \left( \frac{nS_n}{nN_n + sN_s} \right) + R^s_o \left( \frac{sS_s}{nN_n + sN_s} \right) \) at the disease free equilibrium. Since the entirely susceptible population has \( S_n = \frac{\Lambda_n}{\mu} \) and \( S_s = \frac{\Lambda_s}{\mu} \), it follows that \( R_o = R^n_o \left( \frac{n\Lambda_n}{n\Lambda_n + s\Lambda_s} \right) + R^s_o \left( \frac{s\Lambda_s}{n\Lambda_n + s\Lambda_s} \right) \) for \( R^n_o = \frac{n(1 - \rho_n)\eta_n}{\alpha_n + \mu} \) and \( R^s_o = \frac{s(1 - \rho_s)\eta_s}{\alpha_s + \mu} \). A similar result can be found in \([23]\).

This can be understood the following way. I consider a typical infective individual to be an individual chosen at random from the original susceptible population and then made infective. An individual is chosen through a sexual contact. The probability of a random sexual contact being with an individual of type \( S_i \) is \( \frac{i\Lambda_i}{n\Lambda_n + s\Lambda_s} \) for \( i = n, s \). This accounts for the structure of the susceptible population in which the pathogen is being introduced. Thus, I arrive at the value of \( R_o \): the sum of the products of the intrinsic reproductive number of hosts in each of the two host classes and the probability that an individual chosen at random (through a sexual contact) to become infected is from each of the classes. Thus, \( R_o \) is an appropriately weighted sum of the \( R_o \)s that would result if the population was made up of just one (or the other) of the two classes.
It is interesting to notice that this construction of $R_o$ could be generalized to any number of host population classes defined by average number of sexual partners. If the total population were subdivided into $m$ classes, I could construct $R_o$ as above and get

$$R_o = \sum_{i=1}^{m} R_o^i \left( \sum_{j=1}^{m} A_j \right)$$ for $R_o^i = \frac{i(1-\rho_i)\eta_i}{\alpha_i + \mu}$.

It is possible to rewrite the basic reproduction number in a more intuitive way as the product of the mean duration of infection, mean probability of transmission per partner, and an appropriately weighted average number of partners per unit time. This allows $R_o$ to be interpreted as the average number of individuals that an individual infected at random will infect in a completely susceptible population.

### 3.3 Existence of an Endemic Equilibrium

First, let $R_o^n = \frac{n(1-\rho_n)\eta_n}{\alpha_n + \mu}$ and $R_o^s = \frac{s(1-\rho_s)\eta_s}{\alpha_s + \mu}$. Now, I proceed to prove the existence of an endemic equilibrium.

**Theorem 3.** If $R_o > 1$ then the system (2-6) - (2-11) has at least one endemic equilibrium which is given by $\varepsilon^* = (S_n^*, S_s^*, I_n^*, I_s^*, A^*)$.

**Proof** We again consider the system (2–6) - (2–11) at equilibria and we get the following equations:

$$0 = \Lambda_n - \mu S_n - (n(1-\rho_n)\eta_n I_n + s(1-\rho_s)\eta_s I_s) - \frac{n S_n}{n N_n + s N_s} \quad (3–2)$$
$$0 = \Lambda_s - \mu S_s - (n(1-\rho_n)\eta_n I_n + s(1-\rho_s)\eta_s I_s) - \frac{s S_s}{n N_n + s N_s} \quad (3–3)$$
$$0 = (n(1-\rho_n)\eta_n I_n + s(1-\rho_s)\eta_s I_s) - \frac{n S_n}{n N_n + s N_s} - (\mu + \alpha_n) I_n \quad (3–4)$$
$$0 = (n(1-\rho_n)\eta_n I_n + s(1-\rho_s)\eta_s I_s) - \frac{s S_s}{n N_n + s N_s} - (\mu + \alpha_s) I_s \quad (3–5)$$
$$0 = \alpha_n I_n + \alpha_s I_s - (\mu + d) A \quad (3–6)$$
$$0 = \Lambda_n + \Lambda_s - \mu N - d A \quad (3–7)$$

Now I proceed to find an endemic equilibrium and therefore assume $I_n \neq 0$ or $I_s \neq 0$. 

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Notice that if either \( I_n = 0 \) or \( I_s = 0 \), then both \( I_n = I_s = 0 \) and \( A = 0 \).

Therefore, system (2–6)-(2–11) can only have two kinds of equilibria: the disease-free equilibrium given by \( \varepsilon_o = (\frac{\Lambda_n}{\mu}, \frac{\Lambda_s}{\mu}, 0, 0, 0) \) and possible endemic equilibria given as \( \varepsilon^* = (S_n^* > 0, S_s^* > 0, I_n^* > 0, I_s^* > 0, A > 0) \).

From equations (3–4) and (3–5) I get the following

\[
(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s) nS_n nN_n + sN_s = (\mu + \alpha_n) I_n \tag{3–8}
\]

\[
(n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s) sS_s sN_s + nN_n = (\mu + \alpha_s) I_s \tag{3–9}
\]

Let \( \lambda = n(1 - \rho_n)\eta_n I_n + s(1 - \rho_s)\eta_s I_s \). Multiplying both sides of equation (3–8) by \( \frac{n(1 - \rho_n)\eta_n}{\mu + \alpha_n} \) and both sides of equations (3–9) by \( \frac{s(1 - \rho_s)\eta_s}{\mu + \alpha_s} \) and then adding (3–8) and (3–9) I get

\[
\frac{n(1 - \rho_n)\eta_n}{\mu + \alpha_n} \lambda nS_n nN_n + sN_s + \frac{s(1 - \rho_s)\eta_s}{\mu + \alpha_s} \lambda sS_s sN_s + nN_n + sN_s = \lambda \tag{3–10}
\]

Then I can write equation (3–10) as

\[
\mathcal{R}_n^0 \lambda nS_n nN_n + \mathcal{R}_s^0 \lambda sS_s sN_s = \lambda \tag{3–11}
\]

Thus I get the following relation (assuming \( \lambda \neq 0 \))

\[
\mathcal{R}_n^0 nS_n + \mathcal{R}_s^0 sS_s = nN_n + sN_s \tag{3–12}
\]

Now I rewrite equations (3–2) and (3–3) using (3–12):

\[
0 = \mathcal{R}_n^0 \Lambda_n - \mathcal{R}_n^0 \mu S_n - \lambda \frac{\mathcal{R}_n^0 nS_n}{\mathcal{R}_n^0 nS_n + \mathcal{R}_s^0 sS_s} \tag{3–13}
\]

\[
0 = \mathcal{R}_s^0 \Lambda_s - \mathcal{R}_s^0 \mu S_s - \lambda \frac{\mathcal{R}_s^0 sS_s}{\mathcal{R}_n^0 nS_n + \mathcal{R}_s^0 sS_s} \tag{3–14}
\]

Now adding equations (3–13) and (3–14) I get the following

\[
0 = \mathcal{R}_n^0 \Lambda_n + \mathcal{R}_s^0 \Lambda_s - \mathcal{R}_n^0 \mu S_n - \mathcal{R}_s^0 \mu S_s - \lambda \tag{3–15}
\]
which can be written in the form

\[ \mu(\mathcal{R}_o^n S_n + \mathcal{R}_o^s S_s) = \mathcal{R}_o^n \Lambda_n + \mathcal{R}_o^s \Lambda_s - \lambda \]  

(3–16)

Equation (3–14) can be rewritten as

\[ 0 = \Lambda_s - \mu S_s - \lambda \frac{s S_s}{\mathcal{R}_o^n n S_n + \mathcal{R}_o^s s S_s} \]  

(3–17)

Now I multiply equation (3–17) by \( \mathcal{R}_o^n n S_n + \mathcal{R}_o^s s S_s \) to get the following

\[ 0 = (\Lambda_s - \mu S_s)(\mathcal{R}_o^n n S_n + \mathcal{R}_o^s s S_s) - \lambda s S_s \]  

(3–18)

Now rewriting (3–18) using (3–16) as follows

\[ 0 = (\Lambda_s - \mu S_s)(\mathcal{R}_o^s (s - n) S_s + n(\frac{\mathcal{R}_o^n \Lambda_n + \mathcal{R}_o^s \Lambda_s - \lambda}{\mu} - \mathcal{R}_o^s S_s)) - \lambda s S_s \]  

(3–19)

\[ 0 = (\Lambda_s - \mu S_s)(\mathcal{R}_o^s (s - n) S_s + n(\frac{\mathcal{R}_o^n \Lambda_n + \mathcal{R}_o^s \Lambda_s - \lambda}{\mu}) - \lambda S_s \]  

(3–20)

Multiplying everything out in (3–20) I get the following quadratic equation in \( S_s \)

\[ 0 = (s - n) \mathcal{R}_o^s \mu S_s^2 + (n \mathcal{R}_o^n \Lambda_n + n \mathcal{R}_o^s \Lambda_s - (s - n) \mathcal{R}_o^s \Lambda_s + (s - n) \lambda) S_s \]

\[ - \frac{n \Lambda_s}{\mu}(\Lambda_n \mathcal{R}_o^n + \Lambda_s \mathcal{R}_o^s - \lambda) \]

(3–21)

Since \( s > n \) there is a unique positive solution to equation (3–21) for all \( 0 \leq \lambda < \Lambda_n \mathcal{R}_o^n + \Lambda_s \mathcal{R}_o^s \).

I can write \( S_s \) and \( S_n \) as functions of \( \lambda \). Thus let \( S_s = f_s(\lambda) \) and \( S_n = f_n(\lambda) \) for

\[ 0 \leq \lambda \leq \mathcal{R}_o^n \Lambda_n + \mathcal{R}_o^s \Lambda_s \text{ and } S_n(0) = f_n(0) = \frac{\Delta_n}{\mu} \text{ and } S_s(0) = f_s(0) = \frac{\Delta_s}{\mu}. \]

Let \( \lambda^* = \mathcal{R}_o^n \Lambda_n + \mathcal{R}_o^s \Lambda_s \). I also have \( S_n(\lambda^*) = f_n(\lambda^*) = 0 \) and \( S_s(\lambda^*) = f_s(\lambda^*) = 0 \).

Now I go back to equations (3–4) and (3–5) where the denominator has been replaced with the left hand side of equation (3–12).

\[ \frac{n S_n}{n \mathcal{R}_o^n S_n + s \mathcal{R}_o^s S_s} = (\mu + \alpha_n) I_n \]  

(3–22)
Therefore, provided this limit exists.

So the quotient To see that this limit exists, consider equations (3–12) I have

Recalling (3–12) I have

Let

The functions $F(\lambda)$ and $G(\lambda)$ are continuous functions of $\lambda$ for $0 \leq \lambda < \lambda^*$. 

At $\lambda = 0$, $G(0) = 0$ and $F(0) = (R^n - 1)n\frac{A_n}{\mu} + (R^s - 1)s\frac{A_s}{\mu} > 0$ since $R_o > 1$.

Therefore, $F(0) > G(0)$. At $\lambda = \lambda^*$, $G(\lambda)$ is not defined. I define $G(\lambda^*) = \lim_{\lambda \to \lambda^*} G(\lambda)$, provided this limit exists.

To see that this limit exists, consider equations (3–2) and (3–3).

So the quotient $\frac{S_n}{S_s} = \frac{s(A_n - \mu S_n)}{n(A_s - \mu S_s)}$. Thus $\frac{f_n(\lambda)}{f_s(\lambda)} = \frac{s(A_n - \mu f_n(\lambda))}{n(A_s - \mu f_s(\lambda))}$. 

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Now let $\lambda \to \lambda^*$.  

$$\lim_{\lambda \to \lambda^*} \frac{f_n(\lambda)}{f_s(\lambda)} = n \frac{s \Lambda_n}{n \Lambda_s} \quad (3-33)$$

That is, the limit $\lim_{\lambda \to \lambda^*} \frac{f_n(\lambda)}{f_s(\lambda)}$ is finite and nonzero. Therefore $\lim_{\lambda \to \lambda^*} G(\lambda)$ exists and is positive.

In addition, $\lim_{\lambda \to \lambda^*} F(\lambda) = 0$. Consequently, $G(\lambda^*) > F(\lambda^*)$.

The Intermediate Value Theorem implies that there exists at least one endemic equilibrium for the system $(2-6)$-$(2-11)$.

There is at least one $\lambda$ with $0 \leq \lambda < \lambda^*$ for which equation $(3-21)$ is satisfied which gives a positive value for $S_s$.

If $S_s = f_s(\lambda) > 0$ for $0 \leq \lambda < \lambda^*$ and $f_s(\lambda^*) = 0$, then I want to show $S_n = f_n(\lambda) > 0$ in the interval $0 \leq \lambda < \lambda^*$.

$$f_n(0) = \frac{\Delta_n}{\mu} > 0.$$ Assume there exists a $\lambda^{**}$ in $0 < \lambda^{**} < \lambda^*$ such that $S_n = f_n(\lambda^{**}) = 0$ and $S_s > 0 f_s(\lambda^{**}) > 0$.

At $\lambda^{**}$ from equation $(3-16)$ I have $\mu R_o S_s = \frac{\Delta_n}{\mu} \Lambda_n + R_o \Lambda_s - \lambda^{**}$.

At $\lambda^{**}$ from $(3-18)$ we have $0 = (\Lambda_s - \mu S_s) R_o S_s - \lambda^{**} s S_s$ and thus $0 = \Lambda_s R_o - \mu R_o S_s - \lambda^{**}$. So I have $\mu R_o S_s = \Lambda_s \frac{\Delta_n}{\mu} - \lambda^{**}$.

So I get a contradiction: $R_o \Lambda_n + \Lambda_s R_o - \lambda^{**} = \Lambda_s \frac{\Delta_n}{\mu} - \lambda^{**}$ since $R_o \Lambda_n \neq 0$.

So $S_n = f_n(\lambda) \neq 0$ for all $\lambda$ with $0 < \lambda < \lambda^*$, and the proof is completed. ■
CHAPTER 4
SIMULATIONS ON THE THREE MODELS

4.1 The Model Without Treatment

To understand the possible outcomes of different prevention strategies in the absence of medical intervention or treatment, I first simulate the baseline model without treatment given by system (2–6)-(2–11).

Parameters of the models were estimated from the literature and are summarized in Table 4-1. Values for the simulations where chosen within these ranges. Below, I discuss briefly these estimates.

Partner acquisition rates vary greatly within populations of non-monogamous sexually active individuals, ranging from 1 per year to 100 partners per year [24]. The removal rate $\mu$, that tracks natural death rate and removal from the sexually active population by changes in sexual behavior was taken from [24]. The individuals in question are assumed to be sexually active young adults who are expected to live an average of 50 years and engage in non-monogamous sexual relations for 20 years [24]. The parameters $\alpha_n$ and $\alpha_s$, that track the duration of infectivity, or the time it takes for an infected individual to develop the terminal symptoms of AIDS and be thus removed to the class of AIDS patients (who are not sexually active), are taken close to values found in [32], with variations introduced here correlating with level of sexual activity. The study in [32] was chosen for these parameters because this study was performed before the introduction of HAART therapy and many other anti-retroviral treatments and therefore does not incorporate the impact of treatments in the average time to the development of AIDS. The values for $\eta_n$, $\eta_n^*$, $\eta_s$, $\eta_s^*$, the probability of transmission per partner, depend on the number of contacts per partner and the probability of transmission per contact [24], as well as infectivity of seropositive individuals. Estimates on the transmission probability per sexual contact range from 0.0003, for transmission from female to male, to 0.08, for transmission from male to male [24]. The number of contacts per partner is taken from [24] to be 2

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Table 4-1: Simulation parameters and their value ranges

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n, s$</td>
<td>$0.08 - 10$ partner month$^{-1}$</td>
<td>Average number of new sexual partners acquired per unit of time</td>
<td>[24]</td>
</tr>
<tr>
<td>$\Lambda_n$</td>
<td>$0.90\Lambda_T^*$</td>
<td>Proportion of individuals entering the moderately sexually active population</td>
<td>[33]</td>
</tr>
<tr>
<td>$\Lambda_s$</td>
<td>$0.10\Lambda_T^*$</td>
<td>Proportion of individuals entering the highly sexually active population</td>
<td>[33]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$0.01$ month$^{-1}$</td>
<td>Natural death rate and removal from sexually active class</td>
<td>[24]</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$0.125$ month$^{-1}$</td>
<td>AIDS induced death rate</td>
<td>[24]</td>
</tr>
<tr>
<td>$\eta_i, \eta_i^*, \eta_i^o$</td>
<td>$0.0003 - 0.64$</td>
<td>Infectivity (Probability of transmission per susceptible partner without preventive strategies)</td>
<td>[24, 34]</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>$80%-95%$</td>
<td>Condom efficacy (intrinsic)</td>
<td>[11]</td>
</tr>
<tr>
<td>$u_n$</td>
<td>$35%-50%$</td>
<td>Compliance with the use of condom for individuals in steady relationships</td>
<td>[35]</td>
</tr>
<tr>
<td>$u_s$</td>
<td>$59%-63%$</td>
<td>Compliance with the use of condom for individuals engaging in casual sexual relationships</td>
<td>[35]</td>
</tr>
<tr>
<td>$\rho_i$</td>
<td>$0.008 - 0.0667$ month$^{-1}$</td>
<td>Condom induced protection ($\rho_i = \varepsilon u_i$)</td>
<td>[3, 7]</td>
</tr>
<tr>
<td>$\nu_i$</td>
<td>$0.008 - 0.0667$ month$^{-1}$</td>
<td>Rate at which HIV-infected individuals undergo testing and know their status</td>
<td>[3, 7]</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$1%-100%$ (mean $80%$)</td>
<td>Proportion of HIV-infected individuals who know their status and receive treatment and/or other medical support</td>
<td>[3]</td>
</tr>
<tr>
<td>$\alpha_i$</td>
<td>$0.01$ month$^{-1}$</td>
<td>Rate at which HIV-infected individuals develop AIDS without treatment or HIV-related medical support</td>
<td>[32]</td>
</tr>
<tr>
<td>$\gamma_i$</td>
<td>$0.005 - 0.006$ month$^{-1}$</td>
<td>Rate at which HIV-infected individuals develop AIDS with the treatment and/or HIV-related medical support</td>
<td>[19]</td>
</tr>
</tbody>
</table>

* $\Lambda_T$: Total recruitment into sexually active population
per week for individuals with few sexual partners, and 1 per partner for individuals with many partners. The probability of transmission per partner are given by the probability of transmission per contact multiplied by the number of contacts.

I chose parameters for the simulations within the ranges in Table 4-1 and summarize them in Table 4-2. I investigate two major prevention focal points: reducing number of partners and condom use. I further investigate possible counter effects of these focused prevention efforts. For the case of an effort to reduce the number of new sexual partners per unit of time, I explore the changes in the value of $R_o$ when there is no other change in behavior, and when individuals have a reduced compliance with the correct and consistent use of condoms because they feel more secure with fewer partners. Similarly, I consider the strategy of prevention that focuses on increasing the correct and consistent use of condoms. I simulate the scenario where there is no other change in behavior and the possible effects of increased risk behavior in increased number of new partners per unit of time that can result from overconfidence in condom protection.

Results of the simulation are given in Figures 4-1 and 4-2. It can be noted that given enough compliance with either of the focused prevention strategies, $R_o$ decreases even given some counter effect to the programme. However, it is also clear that when there are secondary changes in behavior, for example an increase in number of sexual partners due to overconfidence in condom protection, the prevention strategy becomes less efficient. The results seem to suggest that there should be some concern with preventing secondary counter effective changes in behavior when implementing any prevention program that focuses mostly in one area of prevention, but also that as long as such counter effective changes are kept at manageable levels, the focused prevention program is still better than no prevention at all.

The explicit division of the population into two discrete classes based on the number of sexual partners that individuals acquire, allows for the investigation of the effect of reducing the proportion of the population that becomes highly sexually active. Efforts
Table 4-2: Specific parameter values used in simulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>0.08 partner month$^{-1}$</td>
<td>Average number of new sexual partners per month for individuals who are moderately sexually active</td>
</tr>
<tr>
<td>$s$</td>
<td>10 partner month$^{-1}$</td>
<td>Average number of new sexual partners per month for individuals who are highly sexually active</td>
</tr>
<tr>
<td>$\eta_n$</td>
<td>0.08</td>
<td>Probability of transmission from moderately sexually active infective individual per susceptible partner without preventive strategies</td>
</tr>
<tr>
<td>$\eta_s$</td>
<td>0.02</td>
<td>Probability of transmission from highly sexually active infective individual per susceptible partner without preventive strategies</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>90%</td>
<td>Condom efficacy (intrinsic)</td>
</tr>
<tr>
<td>$u_n$</td>
<td>40%</td>
<td>Compliance with the use of condom for individuals in steady relationships</td>
</tr>
<tr>
<td>$u_s$</td>
<td>60%</td>
<td>Compliance with the use of condom for individuals engaging in casual sexual relationships</td>
</tr>
<tr>
<td>$\rho_n$</td>
<td>36%</td>
<td>Condom induced protection ($\rho_i = \epsilon u_i$)</td>
</tr>
<tr>
<td>$\rho_s$</td>
<td>54%</td>
<td>Condom induced protection ($\rho_i = \epsilon u_i$)</td>
</tr>
<tr>
<td>$\nu_n$</td>
<td>0.036 month$^{-1}$</td>
<td>Rate at which HIV-infected individuals undergo testing and know their status</td>
</tr>
<tr>
<td>$\nu_s$</td>
<td>0.03675 month$^{-1}$</td>
<td>Rate at which of HIV-infected highly active individuals undergo testing and know their status</td>
</tr>
<tr>
<td>$\delta$</td>
<td>100%</td>
<td>Proportion of HIV-infected individuals who know their status and receive treatment and/or other medical support</td>
</tr>
<tr>
<td>$\alpha_n$</td>
<td>0.09 month$^{-1}$</td>
<td>Rate at which moderately sexually active HIV-infected individuals develop AIDS without intervention of treatment or HIV-related medical support</td>
</tr>
<tr>
<td>$\alpha_s$</td>
<td>0.012 month$^{-1}$</td>
<td>Rate at which highly sexually active HIV-infected individuals develop AIDS without intervention of treatment or HIV-related medical support</td>
</tr>
<tr>
<td>$\gamma_n$</td>
<td>0.005 month$^{-1}$</td>
<td>Rate at which moderately sexually active HIV-infected individuals develop AIDS with the intervention of treatment and/or HIV-related medical support</td>
</tr>
<tr>
<td>$\gamma_s$</td>
<td>0.006 month$^{-1}$</td>
<td>Rate at which highly sexually active HIV-infected individuals develop AIDS with the intervention of treatment and/or HIV-related medical support</td>
</tr>
</tbody>
</table>
Figure 4-1. Prevention focused on decreasing number of partners only. Let $p$ be the percentage decrease in average number of new sexual partners per unit of time. Thus, average number of new sexual partners per unit of time of moderately sexually active class here is given by $n(1 - p)$ and average number of new sexual partners per unit of time of highly sexually active class is given by $s(1 - p)$. Graph shows $R_0$ versus $p$. Let $q$ be the percentage decrease in correct and consistent condom use. Then condom use protection is given by $1 - (u_n(1 - q)e)$ for moderately active group and $1 - (u_s(1 - q)e)$ for highly active group. I show curves for $q = p$, $q = 0.5p$ and $q = 2p$. The line S1 is the baseline case where there is a reduction in number of partners and no other change in behavior. Curves S2 - S4 illustrate a reduction in number of partners coupled with an increasing reduction in the correct and consistent use of condoms.
Let $p$ be the percentage increase in correct and consistent condom use. Thus, condom use protection is given by $1 - (u_n(1 + p)\epsilon)$ for moderately sexually active individuals and $1 - (u_s(1 + p)\epsilon)$ for highly sexually active individuals. Graph shows $R_0$ versus $p$. Let $q$ be the percentage increase in average number of new sexual partners per unit of time. Then average number of new sexual partners per unit of time of moderately sexually active class here is given by $n(1 + q)$ and average number of new sexual partners per unit of time of highly sexually active class is given by $s(1 + q)$. I show curves for $q = p$, $q = 0.5p$ and $q = 2p$. The line S1 is the base line case where there is increase in correct and consistent condom use and no other change in behavior. Curves S2 - S4 illustrate an increase in condom use coupled with an increase in number of new sexual partners per unit of time as a result of possible overconfidence that the use of condoms will protect against the transmission of HIV.
Figure 4-3. Prevention focused on changing recruitment only. Changes in recruitment proportions can be used as a prevention strategy with low possible counter effects.

to educate young people who are about to become sexually active about safer sexual practices involving a low number of different sexual partners has a clear impact in disease prevention as illustrated in Figure 4-3.

4.2 The Model With Treatment but Without Change in Behavior: Treatment as a Prevention Strategy

Now I focus on examining the model which incorporates the new trends in treatment.

The parameters $\nu_n$ and $\nu_s$ refer to the rate at which sexually active individuals get tested. According to the U.S. Department of Health and Human Services [7] and the UNAIDS Report on the Global AIDS Epidemic [4], in the U.S. one-quarter of those
individuals who are infected with HIV do not get tested and are unaware of their status. The parameter $\delta$ reflects the proportion of the population made up of seropositive individuals who know their status that actually receive treatment and medical support. Also according to UNAIDS, in the world today, 80% of seropositive individuals requiring treatment and medical support do not get it. In some countries less than 1% of known HIV-positive individuals have access to treatment and medical support, while there are countries that have achieved 100% coverage, the mean world value being 80% [3]. I focus on the current scenario in U.S. and let treatment availability be at 100%. According to the CDC, HAART treatment can just about double life expectancy of seropositive individuals[19].

First, I explore the effects of treatment in the absence of any further prevention strategy. Some literature suggests that even though treatment lowers the plasma virus load of seropositive patients, this reduction does not correlate with a reduction in virus load in other body fluids, such as semen [13]. However, some studies of couples with discordant serostatus, individuals with lower virus load have a lower probability of transmitting HIV [5], while it is not clear by how much. I show the effects of reduced infectivity of individuals undergoing treatment (Table 4-3). The incidence without treatment was of 146 individuals in 100,000. Without reduction of infectivity or change in risk behavior the introduction of treatment increases incidence of HIV infections. With a decrease in infectivity, introducing treatment reduces the incidence of HIV infection. It is important to recall that not all individuals who receive HIV related medical attention are actually taking HAART drugs. Some health professionals delay the start of HAART but still provide medical attention in the form of viral load screening, bacterial STDs treatment, and treatment of opportunistic infections. For this simulation, however, I assume individuals receiving medical intervention are actually receiving HAART drugs.
Table 4-3: Reduced infectivity in individuals receiving HAART treatment

<table>
<thead>
<tr>
<th>Infectivity reduction</th>
<th>Incidence in 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>151</td>
</tr>
<tr>
<td>10%</td>
<td>140</td>
</tr>
<tr>
<td>20%</td>
<td>135</td>
</tr>
<tr>
<td>30%</td>
<td>129</td>
</tr>
<tr>
<td>40%</td>
<td>120</td>
</tr>
<tr>
<td>50%</td>
<td>112</td>
</tr>
<tr>
<td>60%</td>
<td>103</td>
</tr>
<tr>
<td>70%</td>
<td>92</td>
</tr>
<tr>
<td>80%</td>
<td>78</td>
</tr>
<tr>
<td>90%</td>
<td>60</td>
</tr>
</tbody>
</table>

I recall that to effectively reduce viral load there needs to be adherence to treatment at all times (which has proved difficult), that delayed start of HAART drugs might be appropriate, and that treatment always carries the risk of producing multiresistant strains.

4.3 The Model With Treatment and Change in Behavior: Incorporating Prevention Programmes in HIV-Related Medical Intervention

Now I allow for a behavior change in individuals who come to know of their HIV-positive status and receive treatment. Consider the model (2–20) - (2–26). As a result of expanded treatment access, millions of people living with HIV are periodically visiting health-care delivery sites to monitor their disease and treatment progress [3]. I believe this provides an important path through which to incorporate prevention programmes that focus on behavior change. In countries like the United States, where only about 25% of HIV infections are unknown, many individuals who know of their seropositive status have the opportunity to receive medical support and treatment to improve their lifestyle and increase their longevity. I explore the outcome of integrating change of behavior prevention programmes focused on these individuals with the delivery of treatment and HIV medical support.

Assuming effective prevention efforts implemented through integration of prevention and medical support, in general, assume that \( n_o < n \) and \( s_o < s \) as well as \( \rho_{n_o} > \rho_n \) and \( \rho_{s_o} > \rho_s \). Infectivity is assumed do be reduced by 50% for treated individuals.
The values for parameters are taken as before but now I introduce behavior change in persons who know of their seropositive status and are undergoing treatment and/or medical counseling. Results of this simulation are given in Table 4-4 and Table 4-5.

**Table 4-4: Prevalence of HIV infection with increase in condom use and decrease in number of sexual partners per unit of time**

<table>
<thead>
<tr>
<th>Increased prevention</th>
<th>For the entire population</th>
<th>For the group under treatment (5% of total population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>7.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>5%</td>
<td>6.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>10%</td>
<td>6.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>15%</td>
<td>5.4%</td>
<td>6.0%</td>
</tr>
<tr>
<td>20%</td>
<td>4.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>25%</td>
<td>3.9%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

**Table 4-5: Incidence (per 100 000) of HIV infections with increase in condom use and decrease in number of sexual partners per unit of time**

<table>
<thead>
<tr>
<th>Increased prevention</th>
<th>For the entire population</th>
<th>For the group under treatment (5% of total population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>5%</td>
<td>104</td>
<td>109</td>
</tr>
<tr>
<td>10%</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>15%</td>
<td>85</td>
<td>98</td>
</tr>
<tr>
<td>20%</td>
<td>76</td>
<td>90</td>
</tr>
</tbody>
</table>

Observe that with increased effective prevention aimed only at the subgroup of the population consisting of seropositive individuals receiving medical support the values for the resulting prevalence of HIV infection in the population are very close to the values reached by increasing effective prevention on the entire population. The group under treatment corresponds to 5.25% of the entire population.

To reach an incidence level of 90 new cases in 100 000 per unit of time, there needs to be an increase of 20% in prevention in the group under treatment, while for the same level of incidence there needs to be around 12% increase in prevention in the entire population. Notice reaching 20% of the individuals in the treated group corresponds to effectively reaching 1000 individuals, while changing 12.5% of the entire population corresponds
to effectively reaching 12500 individuals. In both cases, the resulting incidence is 90 individuals per 100 000.

Here I reach my main result: given that testing and treatment availability are comparable to the United States, it is not necessary to effectively reach the entire population with increased prevention programmes to reduce the prevalence and incidence of HIV. It is sufficient to effectively change the behavior of the subgroup of the population composed of individuals of known seropositive status who are receiving HIV related medical support and counseling. But more than that, these results show that coupling prevention efforts with treatment delivery could be as effective as targeting prevention to the entire population.

This conclusion demonstrates how large an impact individuals of known seropositive status who receive medical intervention can have in the prevention of HIV. By actively incorporating and improving prevention strategies, individuals who are aware of their seropositive status can effectively help reduce the prevalence of HIV in the population and slow the epidemic. It is very important then not to neglect HIV prevention related education for these individuals. It is clear from reports of the CDC [5] that individuals who become aware of their seropositive status do actively try to prevent further transmission of the disease. Therefore, it is necessary for society to provide appropriate tools for these individuals to effectively help in the fight against HIV/AIDS. It is necessary to provide clear information, resources, and support to those individuals who are infective and who are receiving HIV related medical attention.
CHAPTER 5
CONCLUSION

The model with treatment and differentiated rate of partner acquisition, which to my knowledge has not been previously studied, accounts for heterogeneities among individuals in their behavior towards acquisition of new partners and use of condoms while exploring the effects of treatment and medical support, with and without prevention counseling, on the overall disease dynamics. The model without treatment accounts for heterogeneities among individuals in their behavior towards acquisition of new partners and use of condoms, but emphasizes these mechanisms explicitly, especially in the explicit rendering of $R_o$, and gives further insight on prevention strategies.

For the model without treatment I derived the explicit formula for the basic reproduction number and proved existence of at least one endemic equilibrium when $R_o > 1$. I discuss the value of the basic reproduction number in view of other more traditional epidemiological papers and the meaning of this value of $R_o$.

Using simulations, I examined the transmission dynamics of the disease in a population where HAART is introduced, with and without focal prevention efforts. The main result I reach is that prevention programmes do not need to reach the entire population, but only need to focus on the group receiving HIV-related medical attention. This approach to prevention is cost-effective, since the target population is significantly smaller than the total population, since there is a clear channel for the delivery of treatment, and since this channel does not rely on the costly antiretroviral drugs for reduced infectivity. Coupling prevention programmes, such as counseling and education programmes, with the delivery of HIV-related medical attention can liberate HAART from being used as a prevention strategy, so that the start of HAART drugs can be delayed if necessary and the risk of producing multiresistant HIV strains can be reduced. This approach prevents seropositive patients from increasing risky behavior due to overconfidence in treatment and reduced infectivity. There also exists a clear
path for delivery of prevention programmes to HIV patients, since contrary to the target population of individuals under high risk of acquiring the disease, HIV patients are a known, well-defined subgroup of the total population.

With this model I advocate that health policies for prevention of HIV infection in a population should not rely solely on reduced infectivity due to treatment for the prevention of the transmission of HIV from seropositive patients, but rather it should take an active approach to prevention focusing on change of behavior of these individuals. Further, I advocate that it is more effective to focus change of behavior prevention on the subgroup of the population receiving treatment to achieve a significant reduction in the prevalence of the disease, given rates of testing comparable to the United States, than are indiscriminate measures.

In the absence of a cure or vaccine, the world must rely on effective implementation of prevention strategies all of which involve behavior change of the population as a whole or, and maybe especially, of the individuals of known seropositive status. Ideally, all infected individuals should be tested and provided with treatment [24], as well as information and support to incorporate changes in risk behavior and prevention techniques in everyday life. Also, ideally all individuals who are aware of having seropositive status would have the will, the resources and the support to actively engage in prevention. However, changes in behavior, especially sexual behavior, are always a challenge.

Relatively few studies have been undertaken to measure the effectiveness of behavioral interventions for prevention for people living with HIV, but emerging evidence indicates that such programmes are effective in reducing the likelihood that people with HIV will engage in sexual activity that might expose others to the virus [36]. Thus, it is very useful to focus prevention on this group.

Although the possibility that there exists variation in susceptibility of individuals was not explored in these models, it is increasingly important to acknowledge that possibility as supported by [24] and [37]. I intend to further explore this in future research.
Although my study sought to improve the accuracy of contact patterns in the population by creating discrete subclasses of individuals with varying number of new sexual partners, future research is desirable that further improves the accuracy with which patterns of contact in STD dynamics models are formulated. I intend to explore a network approach to formation of sexual partnerships to better describe contact patterns in STD models.
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BIOGRAPHICAL SKETCH

Fernanda Oliveira Melo was born on April 29, 1981 in Brasília, Brazil. The daughter of two medical doctors, she developed a passion for the sciences early on. Her early school years were spent mostly in a small bilingual school, Escola das Nações, in her hometown. In high school she enrolled in the American School of Brasília.

In 1998, she moved to the United States with her parents. She lived in Orlando, Florida for 3 years. She completed high school at Dr. Phillips High School and received an associate in arts degree from Valencia Community College. Upon receiving her A.A. she moved to Gainesville, Florida to begin her undergraduate studies in mathematics at the University of Florida. In August 2003, at the end of her junior year, she married Edgar Melo.

Fernanda was awarded a bachelor of science degree in mathematics with a minor in education in August 2004. She graduated with magna cum laude. She specialized in applied mathematics and produced, under the sponsorship of Dr. Serguei Pilyugin, an undergraduate thesis entitled An SIR model with discrete immunity subclasses. In April 2005, her first son, Lucas, was born in Kissimmee, Florida.

She started graduate school at the Mathematics Department in the University of Florida in 2005. During her two years as a graduate student there, she had the opportunity to take individual research courses under biomathematicians such as Dr. Maia Martcheva, Dr. Serguei Pilyugin and Dr. Patrick DeLenher.

Upon graduating with her M.S. in applied mathematics, Fernanda will be moving to the Zoology Department at the University of Florida to complete a doctorate degree under the mentorship of theoretical biologists Dr. Benjamin M. Bolker and Dr. Robert Holt. There she hopes to further her research in the area of infectious disease dynamics, combining theoretical biology with her knowledge of biomathematics.