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Study of Infectious Diseases by Mathematical Models: Predictions and Controls

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Abstract

The aim of this thesis is to understand the spread, persistence and prevention mechanisms of infectious diseases by mathematical models. Microorganisms that rapidly evolve pose a constant threat to public health. Proper understanding of the transmission machinery of these existing and new pathogens may facilitate devising prevention tools. Prevention tools against transmissions, including vaccines and drugs, are evolving at a similar pace. Efficient implementation of these new tools is a fundamental issue of public health. We primarily focus on this issue and explore some theoretical frameworks.

Pre-exposure prophylaxis (PrEP) is considered one of the promising interventions against HIV infection as experiments on various groups and sites have reported its significant effectiveness. This study evaluates the effectiveness of Tenofovir gel, one of the widely used PrEPs for women, through a mathematical model. Our model has excellent agreement with the experimental data on the use of Tenofovir gel as a PrEP in South African women. Using our model, we estimate both male-to-female and female-to-male transmission rates with and without Tenofovir gel protection. Through these estimates, we demonstrate that the use of Tenofovir gel as a PrEP can significantly reduce the reproduction numbers, new infections, and HIV prevalence in South Africa. Our results further show that the effectiveness of Tenofovir gel largely depends on the level of adherence to the gel and the proportion of women under gel coverage. Even though Tenofovir gel alone may not be able to eradicate the disease, as indicated by our estimates of the reproduction numbers, together with other interventions, such as condom use, it can serve as a strong weapon to fight against HIV epidemics.

Another promising drug-oriented intervention against HIV infection is antiretroviral treatment (ART). We study some crucial aspects of this intervention on the HIV epidemic. ART has the potential to reduce mortality and disease progression among HIV infected individuals. It can reduce the viral load of the infected individual to an undetectable level and help prevent new infections. Whether the treatment should begin early or be delayed is still under debate. This study considers the impact of early versus delayed ART on the HIV epidemic and demonstrates the optimum timing of ART initiation. Our results highlight the long-term consequences of early treatment.

Finally, we investigate the consequences of vaccine implementation strategies for infectious diseases. Vaccines are said to be the intervention with the most potential against many infectious diseases. However, their success relies on proper and strategic management and distribution. In an infectious disease, the degree of infection may vary widely among those individuals. Reports show that individuals belonging to certain groups possess considerably

higher risk for infection. Integrating this phenomenon into vaccination strategies, the host is categorized into different groups to measure the outcome of the vaccination. A mathematical model is proposed and analyzed to evaluate this measure. Our results suggest that vaccinating a group with a certain priority may lead to effective elimination of the disease.

Keywords: Anitretroviral therapy (ART), HIV, Lyapunov functional, Pre-exposure prophylaxis (PrEP), Vaccine.

Co-Authorship Statement

This integrated-article thesis is based on three papers. Chapter 2 is based on the paper [1] for which Dr. Xingfu Zou and Dr. Naveen K. Vaidya provide assistance in formulating the model and in discussion. I was responsible for numerical calculations, analytical derivation of results, and the manuscript preparation. Chapter 3 is based on yet to be published paper [2] in which Dr. Xingfu Zou and Dr. Naveen K. Vaidya help in formulating the problem and I perform the calculations. Chapter 4 is based on the paper [3] for which Dr. Xingfu Zou provides significant assistance in various aspects.

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List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
DFE	Disease free equilibrium
EE	Endemic equilibrium
HIV	Human immunodeficiency virus
IDUs	Injection-drug users
MSM	Men-sex-with-men
ODE	Ordinary differential equation
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate

Chapter 1

Introduction

Infectious diseases pose a constant threat to human beings. Every individual on the earth can be affected by a disease. The emergence and re-emergence of infectious diseases have become a significant worldwide problem. Proper understanding of transmission mechanisms of diseases caused by existing and new pathogens may facilitate devising prevention tools. Prevention tools against transmissions, including vaccines and drugs, need to to be developed at a similar pace to that of the microbes. Implementation and proper use of these sophisticated tools against the microbes is another challenge. This thesis addresses this multi-faceted issue and explores some theoretical frameworks. The current chapter intends to provide some basic information about the infection mechanisms of microbes, their orientation, control mechanism and the role of mathematical models in the epidemiology.

1.1 Infectious diseases

An infectious disease is caused by various microbes or pathogen. Most of them are usually microorganisms. Few of them are visible by naked eyes. The most common pathogens are different types of viruses and bacteria. Fungi and Protozoa are also known as pathogens and are responsible for various diseases. Diseases caused by these pathogens are termed as 'infectious' as these pathogens can be easily transmitted from one infected person to another non-infected person. The most common and well-known example of such diseases could be influenza or flu that is caused by some kinds of viruses. HIV, mumps, measles, rubella, smallpox, malaria have also caused millions of infections and deaths [11, 38]. Many of these diseases are still prevalent at local or global scales and threaten public health [53].

1.1.1 Pathogens

As mentioned above, pathogens are solely responsible for causing an infectious disease. In this sub-section we briefly review some common pathogens that cause diseases. We highlight the life cycles and infection mechanisms of the pathogens that are useful and important information in modelling their spread.

Bacteria: Bacteria, single-celled organisms, are well known microbes that cause various diseases. However, most of the bacteria are harmless and some are even beneficial to human. Bacteria are useful in producing cheese, yogurt, and chemicals and medicines. They also play some critical role to synthesize food particles in our intestine to produce energy [50]. Insulin that saves millions of diabetic patients is also produced from genetically modified bacteria. Some bacteria, however, are harmful and life threatening. Gastritis, pneumonia, meningitis, gonorrhea are some examples caused by various bacteria [42, 46, 50]. Most of the bacterial diseases can be treated by antibiotics.

Viruses: Viruses are the most common and harmful microorganisms that cause severe diseases to human and other species. Influenza or flu which probably no one can avoid, is caused by viruses. Other examples of viral diseases include chickenpox, herpes, human papillomavirus (HPV), mumps, measles, rubella, viral hepatitis, viral meningitis, and viral pneumonia [49]. Human immunodeficiency virus (HIV) is another deadly virus that spreads mainly through sexual contacts and causes AIDS.

Viruses cannot live by themselves, and they need other living cells for their reproduction. Unlike bacterial diseases, viral diseases cannot be treated by antibiotics. Since viruses use host's cells for reproduction, an antiviral drug could be highly toxic and life-threatening for the host [40]. Thus, instead of killing the target cells, antiviral drugs are used to inhibit viral replication processes. Antiviral drugs act to limit the viral loads and helps keep the infected individual healthy until host's immune system controls the infection and eliminates the pathogen [40, 42]. In terms of the well-known characterization of HIV replication process, several antiretroviral drugs can be combined to hinder major steps of the viral replication such as fusion, reverse transcriptase, protease, and integrase. The positive side of viral infections, however, is that it develops immunity for the infected hosts which helps prevent them from a successive infection.

Fungi: Fungi are microorganisms that widely vary in sizes from uni-cellular, such as yeast, to multicellular, such as mushrooms and toadstools which can easily be seen with naked eyes. Fungi play a critical role in decomposing dead materials which in turn provide nutrients to the

land [40]. The life saving antibiotic penicillin is also produced from the fungus *Penicillium chrysogenum* [23, 25]. Some fungi are harmful by causing infections to plants and animals. Candidiasis, histoplasmosis, mucorycosis, ringworm are common examples of diseases caused by fungi. Vaginal yeast and thrush are fungal diseases that can cause infection to the immuno-compromised individuals relatively easily [40].

Protozoa: Protozoa are comparatively large single-celled organisms. Some protozoa are useful. For example, in the sewage treatment systems, protozoa are used for decomposing organic matters. Some others are human parasites that cause diseases, such as malaria, toxoplasmosis, cryptosporidiosis, trichomoniasis, leishmaniasis, amoebiasis, amoebic dysentery, and acanthamoeba keratitis [35]. Protozoa can be spread through contaminated food, water or through a vector or carrier like arthropod mosquito. The well-known protozoa species *Plasmodium vibax* that causes malaria spread through female anopheles mosquitoes. When a female mosquito bites an infected person it receives the parasite plasmodium. The parasite grows and reproduces inside the mosquito. When this mosquito bites another person the parasite can be transmitted through its saliva to that person. Malaria is one of the leading death causing diseases that is responsible for about 700,000 deaths each year worldwide [8].

There are some other pathogens that also cause infectious diseases, e.g parasitic helminths, ectoparasites and prions [8, 40], but the above four are most related to the topics of this thesis.

1.1.2 Modes of transmission

Infectious diseases can spread in various ways and pathogens cause infections by different modes of transmission. Some infections may take place through a direct contact while other may be caused through indirect contacts. Transmission can also be made through carriers or vectors. For examples, malaria, filariasis, west Nile, dengue, chikungunya, and many others spread through mosquitoes. However, two modes of transmission are particularly interesting: airborne diseases and sexually transmitted diseases, and they have been paid much attention. Many diseases, e.g. influenza, SARS, are airborne and can be transmitted through air. The airborne infection spreads from an infected person to an uninfected person through sneeze, cough and even through laugh. The microbes that are discharged from an infected person may remain on the dust particles or any other medium. An infection may take place when these microbes are inhaled or reach mucus membrane of an uninfected person through body contact [13]. Hand-shaking also could be a potential way for transmition of infections.

A significant number of diseases, on the other hand, are sexually transmitted diseases (STD) and they are also transmitted through contaminated blood and semen, breastfeeding, or during

childbirth. HIV is one of the most death causing STDs. Other STDs including herpes, syphilis, gonorrhea, chlamydia and trichomoniasis also cause significant infection and mortality [52]. Among the infectious diseases, STDs are the most troublesome to public health, as many of these diseases, such as AIDS and Herpes, cannot be cured and last for whole life. This poses severe social and economic consequences. Due to longer infectious life, infected individuals with STDs may contribute increased number of infections and hence remain a major problem in prevention of diseases. Another critical aspect of STDs is that they may not produce any symptoms to the infected person. As a consequence, infected individual may transmit infection unknowingly. Drug resistance is also a major threat to fighting STDs worldwide [51]. All these matters are reflected in HIV, which we witness about 37 million infections worldwide at the moment [53]. Since the beginning of the epidemic, nearly 34 million people have died from AIDS-related causes. HIV statistics shows that in 2014 alone about 1.2 million died of AIDS-related illnesses and at the same year around 2.0 million people became infected with HIV [53].

HIV and AIDS are now almost everywhere in the world. However, Sub-Saharan African countries are mostly affected. These countries have 25.8 million HIV-infected people and contribute about 70% of the total global HIV infection [53].

1.1.3 Host-defense and immune system

The human body is equipped with a strong defense system to protect against pathogenic infections. This defense system is designed to protect the host from very simple to sophisticated attacks by the pathogens. Our skin acts as a first defense by drawing a barrier for any harmful entities to get inside. Once this barrier is penetrated, some volunteers from the immune system come forward to act as a secondary defense. A pathogen has to face several stages of the immune defense before it can cause disease and harm to the host.

Our whole immune system is divided into two types innate immune system and adaptive immune system. The innate immune system is comprised of various immune cells, neutrophils, mast cells, natural killer cells, and monocytes, and can attack any suspected foreign intruders with no prior knowledge about the intruders. The innate immune system has a natural ability that can detect almost every invading microbes [1, 24]. This natural response is also referred to as to non-specific defense mechanism as it takes action almost immediately as soon as the pathogens enter into the body.

On the other hand, the adaptive immune system is antigen specific. It is also known as cell mediated immune system and is comprised of B cell and T cell. This immune system is much more complex than the innate immune system. It requires some information about

the pathogens in order to attack them efficiently. Such information can be provided by some components from the innate immune system or by somebody within the adaptive immune system. The adaptive immune mechanism also keeps memory of the previous infections or pathogens. This memory is used to prevent any successive infection at the first place before any signal is received from the innate system [1,24]. Therefore, a pathogen cannot infect a host successfully a second time unless it evolves significantly enough to evade the host's adaptive immune defense.

The combined efforts of innate and adaptive immune systems keep our body safe and healthy. However, in some pathogenic infections, host-pathogen battle may last longer (e.g. HIV infection) or immune defense may fail resulting in a tragic death of the host.

The infections that are cleared off by the innate immune system or by the drug supplement can be repeated. That means the host may be infected again by the same pathogen. Usually, bacterial infections fall into this category. On the other hand, viral infections cannot be cured by drug supplement. The adaptive immune system itself can clear the viral infections and also develop immunity. That is why most viral infections go away on their own in few days without any medication. Since a viral infection boosts immunity successive infection by the same virus seldom occur in the host. The host is now recovered permanently from that pathogenic infection. However, some viral infections such as herpes, Hepatitis B and C, and HIV can cause latent infection that lasts for a long time.

1.2 Disease prevention and control

One of the effective ways to control a disease is to reduce contacts. However, in the modern life with increased interactions among individuals, this way is not easy to achieve. In addition to maintaining social distance, alternate prevention measures need to be adopted. Vaccines and drugs are the two widely used prevention tools that can potentially reduce transmissions and control diseases.

1.2.1 Vaccines

A vaccine is used to boost immune system against some specific pathogen. The substance contained in a vaccine has similar physical properties to those of a pathogen. Typically a vaccine can be thought of a fake pathogen that has no ability to reproduce and to cause an infection. It can be made of a weak or killed pathogen. As vaccines are similar to pathogenic microorganism, they can stimulates the immune system of the host and builds up antibodies against

the pathogens to recognize them as foreigners. Thus, whenever such a true microorganism is encountered within a host, the immune system destroys it. This kind of phenomenon is known as immunity. Thus, as long as a vaccine for a disease is available, it is an ideal means of protecting a healthy population from the disease. After Edward Jenner's cowpox vaccine, known as the first vaccine ever in history, numerous successful campaigns have been launched against many infectious diseases [30]. In fact, vaccines have saved millions of lives. Before introducing the first measles vaccine in 1963, about 400,000 measles incidences used to be reported in the United States every year [37]. Polio, rubella, mumps and other child diseases also used to cause significant mortality and morbidity. With the implementation of the vaccines, these diseases are no longer epidemic [37].

Vaccines also have had a successful history against the transmission of influenza, the most common infectious disease around the world. Before the introduction of flu vaccines, controlling an influenza pandemic was an impossible task. It was estimated that about 20-50 million people worldwide died in the outbreak of Spanish flu in 1918-19. A century later, the global death toll for the 2009-10 pandemic was only around 300,000 [5]. It is the vaccine that has reduced the casualty rate to such an extent. Influenza vaccination now becomes a routine program. An individual is recommended to receive an updated flu-vaccine as a flu-season approaches with newer strains of flu viruses.

Though vaccines are very effective against transmission, typically, there are limits on the amounts, especially in developing countries. Thus, how to distribute the limited vaccines becomes crucial for optimal benefit. Social, economical and ethical issues could be major obstacles in implementation of vaccines [36]. Certain groups of individuals may have higher susceptibility to the infections than others. In influenza, for example, school-going children can be infected more easily and can spread the disease more rapidly than other individuals [17, 26, 32, 33]. Thus to control infections by using vaccines, a proper distribution and implementation strategy is very crucial. We address this issue in detail in Chapter 4.

1.2.2 Drugs

In addition to providing a cure, drugs can also play a significant role in reducing transmission. Taken either as a Pre-Exposure Prophylaxis (PrEP) or as a Post-Exposure Prophylaxis (PEP) they can prevent infection and reduce transmission. PrEP is prescribed for healthy individuals who are expected to expose themselves to an infection while PEP is prescribed for the infected individuals to stop or reduce transmission. In the case of malaria, for example, when individuals plan travel to a malaria infected area, they are advised to take malaria medication [10].

The medication could prevent travelers from malaria infection during their travel if bitten by an infected mosquito.

For many diseases, like HIV, effective vaccines have not been developed yet. Typically, vaccines take some time for development and production. During the interval when vaccines are not available, drug-oriented interventions can be an alternative strategy for reducing the infection burden. In HIV, remarkable progress has been reported on the use of Pre-exposure Prophylaxis (PrEP) and Post-exposure Prophylaxis (PEP) [7, 9, 12, 14]. Fairly extensive results have been published indicating significant reduction of viral loads of HIV infected person associated with antiretroviral therapy (ART). The reduction of viral load is linked to a less transmission probability. Thus a drug oriented intervention could be a potential approach to mitigate the current burden of HIV infection.

A large cohort study [27] on 889 heterosexual women with multiple partners has confirmed the profound impact of Tenofovir gel, one of the PrEPs, in reducing HIV infections, and its success has gained much attention around the world [3, 41]. Tenofovir gel is a coitally related vaginal gel that can be used by women. Since HIV acquisition among women is significantly high, this result is promising to subside the burden of HIV infections. Better understanding of the effectiveness of Tenofovir gel at the population level can be helpful for proper implementation of this gel to gain optimal benefits in preventing HIV infections. We investigate in detail the possible impact of Tenofovir gel on the HIV epidemic in Chapter 2.

Another successful episode of HIV prevention is the introduction of antiretroviral therapy (ART). Successful trials and tests of ART have demonstrated its significant effectiveness against HIV transmission and in suppress of viral loads [12]. Numerous results signifying the potential of ART can be found in [12, 14] and in the references therein. ART is expected to have a major impact on the dynamics of HIV and perhaps ART can highly contribute to marking the end of the HIV epidemic. However, trial results may not be translated to the population level and they are limited by numerous factors [45]. Trial results provide a short term scenario and are usually valid for ideal conditions or within a restricted environment. On the other hand, HIV patients need ART for a long term (life time) as ART cannot cure HIV infection. In addition, HIV patients usually progress through different disease stages characterized by CD4+ T cell counts. The disease progression is also attributed by viral loads of infected persons. Transmission rates of infected individuals at different stages are different. The role of transmission rates, detection of infections, proportion of treatment eligibility, period of treatment and many other uncertainties could substantially affect elimination effort [45]. A mathematical model can play an important role in discovering possible scenarios that help guide future directions.

We explore some possible scenarios for HIV epidemic under ART intervention in Chapter 3.

1.3 Mathematical models in infectious diseases

Mathematical models have been used to study the dynamics of infectious diseases for more than a century. In recent years, applications of mathematics in infectious disease have shown remarkably growing trends. As a result, separate branches like mathematical epidemiology have emerged. Rapid diagnostic test, available clinical data and electronic surveillance can facilitate the applications of mathematical models to testing scientific hypotheses and to design practical strategies [18, 22]. The emerging and reemerging diseases have stimulated the interest in mathematical modelling. Models can provide estimates of underlying parameters of a real world problem which are difficult or expensive to obtain through experiment or otherwise. By estimating transmission rate, reproduction number and other variables and parameters (see Chapter 3 and Chapter 4 for details), a model can predict whether the associated disease will spread through the population or die out. It can also estimate the impact of a control measure and provide useful guidelines to public health for further efforts required for disease elimination.

The earliest mathematical modelling can be traced back to the 18th century when Daniel Bernoulli formulated a model for smallpox to estimate the effectiveness of variolation of healthy population with smallpox [4, 22]. However, mathematical models have been growing since the middle of the 20th century after Kermack and McKendrick published their paper on epidemic models in 1927 which contains threshold results that determines whether an epidemic outbreak may occur or not [22,28]. Over the last two decades overwhelming increase in modelling practices has been exhibited in the biological sciences [2, 22, 43]. These models have addressed many aspects of biological phenomena such as stages of infection, vertical transmission, disease vectors, macro-parasitic loads, age structure, social and sexual mixing groups, spatial spread, chemotherapy, vaccination, quarantine, passive immunity, gradual loss of vaccine and disease-acquired immunity [2,18,22]. Some models specifically focus on diseases like measles, rubella, chickenpox, whooping cough, diphtheria, cancer, smallpox, malaria, filariasis, rabies, gonorrhea, herpes, syphilis, and HIV/AIDS [2, 22, 33, 48].

1.3.1 Epidemic models

An epidemic model describes the transmission process and traces the number of infected population. Such a model can identify the number or proportion of population that left uninfected

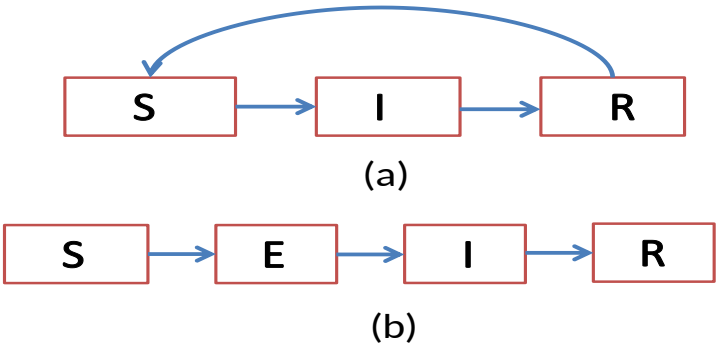

Figure 1.1: Two typical schematic diagrams for disease transmission. (a) SIRS infection, (b) SEIR infection.

at the end of an epidemic. In epidemic models, concept of population compartments is widely used [2, 15, 22, 39]. For mathematical convenience, these compartments are typically represented by letters such as S, E, I, and R denoting susceptible, exposed, infectious and recovered populations, respectively. Individuals who are vulnerable to infection are known as susceptible and belong to the S (susceptible) compartment. An individual who is already infected, but does not show symptoms or is unable to infect others belongs to the E (exposed) compartment. Once an infected individual starts infecting others, he/she is as an infectious and belongs to I compartment. Finally, when an individual is cured from the infection he/she belongs to the R (recovered) compartment. A recovered individual either remains there if he/she gets permanent recovery or may become susceptible again and move back into S compartment. Various models can be developed in terms of these compartments based on the nature of pathogens and diseases such as SIS, SIR, SIRS and so on. If an infected individual becomes susceptible again after cure, an SEIS or SIS type model would be appropriate for the disease dynamics. Bacterial infections could be such an example of SIS models. On the other hand, if recovery is permanent and the recovered individuals are no longer susceptible to that pathogen, as seen in viral infection, then an SIR type model would be appropriate. In these modelling exercises, population are assumed to be homogeneously mixed and individuals get infections or be cured at constant rates. Some schematic diagrams are shown in Figure 1.1.

A simple example of an SIR compartment model can be given by the following system of

ordinary differential equations (ODEs):

$$\begin{aligned} \frac{dS}{dt} &= -\beta S I, \\ \frac{dI}{dt} &= \beta S I - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1.1}$$

where β is the transmission rate and γ is the rate of recovery. Without considering the demography of the host population, this simple model describes how sub-populations of susceptible, infectious and recovered classes evolve. Model (1.1) has been modified by incorporating various factors to capture the main features of the problems that are concerned with, but such modification naturally increase the complexity of the model and make the analysis challenging and sometimes even impossible (see, e.g. [15, 19, 31, 39]). Therefore, balancing the rationality and mathematical tractibility of a model always remains an important issue when using mathematical modeling approach to study disease dynamics.

In model (1.1) the incidence term $\beta S I$ is referred to as bilinear or mass action infection which demonstrates that incidence increases with the numbers of susceptible and infectious. Various other nonlinear incidence rates such as standard and saturated, with their mathematical forms $\frac{\beta S I}{S+I}$, $\frac{\beta S I^a}{b+\alpha I^a}$, $\beta S^p I^q$, are also commonly used in the literature [19, 22, 29, 39]. For detailed explanations of these incidences, readers are referred to [15, 22].

A key threshold outcome of an epidemic model is typically determined by the basic reproduction number, often denoted by $\mathfrak{R}_0$ which is defined as the total number of secondary infections caused by a single infected individual during his/her entire infectious period in a completely susceptible population [15, 16]. Basic reproduction number is a fundamental determinant of the dynamics of disease infection in the population level. An epidemic will outbreak if and only if this number is larger than one. This threshold property provides important information about the potential of disease spread and impact of control mechanisms [15, 18, 39]. To eliminate epidemic by a control measure, one would be interested in reducing $\mathfrak{R}_0$ to below one. In the subsequent chapters of this thesis, one will see how to compute this threshold quantity for complex models and some potential applications of $\mathfrak{R}_0$.

1.3.2 Stability analysis

Mathematical models are becoming more and more complicated when higher degree of nonlinearity is adopted to address real-world problems. Finding an explicit solution of these mod-

els is almost impossible. Though numerical simulations can provide good approximating solutions with fixed parameters, general solution may remain unknown. When general solution is hard to achieve, stability analysis can be resorted to get a sense of solution's behavior. In fact, stability analysis can predict the long time behaviour of the model solutions very well.

In general, there are two types of stability analysis, local and global, widely used in the literature. Local stability is concerned with behaviour of the model solution near an equilibrium point, while global stability can describe solution behaviour in the whole domain. To define the notion of stability more precisely, we provide few definitions and related theorems [20, 21] below which will be used in the subsequent chapters.

Consider an autonomous system defined by

$$\dot{x} = f(x), \quad x \in U \subset \Re^n \tag{1.2}$$

where U is an open subset of $\Re^n$ and $f : U \to \Re^n$ satisfies those standard conditions that ensure existence and uniqueness of the solution to the initial value problem associated with (1.2). Then x_e is said to be an equilibrium of (1.2) if $f(x_e) = 0$.

Definition: An equilibrium x_e of (1.2) is said to be stable if for any given $\epsilon > 0$ there is a $\delta > 0$, (usually depending on ϵ), such that

$$\|x(t_0) - x_e\| < \delta \quad => \|x(t) - x_e\| < \epsilon \ \ \forall t > t_0. \tag{1.3}$$

If an equilibrium is not stable, then it is called an unstable equilibrium.

Definition: An equilibrium x_e is said to be asymptotically stable if it is stable and for initial values close to x_e, the corresponding solution $x(t)$ satisfies

$$\lim_{t\to\infty} x(t) = x_e. \tag{1.4}$$

An equilibrium x_e is said to be globally asymptotically stable if it is stable and (1.4) holds for any solutions of (1.2).

Definition: Let $V : U \subset \Re^n \to \Re$ be a continuous function. Then V is said to be positive definite on U if

$$(i) \ \ V(0) = 0;$$
$$(ii) \ \ V(x) > 0 \ \text{ for all } \ x \in U - \{0\}.$$

Theorem 1.3.1 *Let $x_e = 0$ be an equilibrium point of (1.2) and V be a positive definite function*

on a neighbourhood of x_e.

(i) *If* $\dot{V}(x) \leq 0$, *for all* $x \in U - \{0\}$ *then* 0 *is stable.*

(ii) *If* $\dot{V}(x) < 0$, *for all* $x \in U - \{0\}$ *then* 0 *is asymptotically stable.*

Definition: A function $V : U \subset \Re^n \to \Re$ is said to be Liapunov function for (1.2) if

(i) V is positive definite; *and*

(ii) $\dot{V}(x) < 0$, for all $x \in U - \{0\}$

Theorem 1.3.2 *Assume that* $f(0) = 0$ *and V is a Lyapunov function in U for (1.2). Let* $E = \{x \in U : \dot{V}(x) = 0\}$ *and M is the largest invariant subset in E with respect to (1.2). Then every bounded solution of (1.2) in U will approach M as* $t \to \infty$.

To determine local stability of an equilibrium, one can linearize the model at the equilibrium point and check the signs of the real parts of all the eigenvalues of the corresponding Jacobian matrix [15, 16]. Global stability can be determined by constructing a Lyapunov function [19, 29, 34]. For detailed procedures of these approaches, one can see [34, 39, 43, 44] and chapters 2, 3, and 4 of this thesis.

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Chapter 2

Impact of Tenofovir gel as a PrEP on HIV infection: A mathematical model

2.1 Introduction

During the last three decades, HIV/AIDS—with fifty-five million infections and sixteen million deaths [7]-has been one of the major threats to human beings. Despite remarkable progress on HIV treatments, elimination of HIV/AIDS is still out of reach, and approximately two-and-a-half million people get infected every year [5, 16]. Thus, the prevention of new infections remains a great challenge.

A vaccine is presumably the ideal means of protecting the general (healthy) population [31]. However, in the case of HIV, such vaccines have not been developed. In 1994, the placebo-controlled phase 3 trial of the rgp120 HIV vaccine showed only 6% effectiveness [11]. In 2007, the two HIV vaccine trials (HVTN 502 and Merck V520-023) were suspended due to issues of safety and efficacy [26]. The trial of the *RV 144 HIV* vaccine that induces humoral and cellular immune responses reported only 31% efficacy [30]. While more vaccine trials are currently underway [18], no successful HIV vaccine is available at present.

In the absence of a successful vaccine, drug-oriented interventions can be an alternate strategy for reducing infection burden. Recently, remarkable progress has been reported on the use of Pre-Exposure Prophylaxis (PrEP) [4, 6, 8, 14, 20, 33]. PrEP is the administration of low-level antiretrovirals, such as Tenofovir/TDF (Tenofovir disoproxil fumarate) and Truvada/TDF-FTC (TDF co-formulated with emtricitabine) to the susceptible population, usually, before their exposure to potential HIV sources. The oral TDF and TDF-FTC showed protection against HIV-1 infection in heterosexual couples by 67% and 75%, respectively [1]. The studies [5, 13]

also found TDF-FTC to reduce infection by 62% among uninfected heterosexually-active men and women, and 44% of infection among men and trans women who had sex with men. In addition to the use of Tenofovir (alone or in combination with other drugs) as an oral intake, Tenofovir has also been considered as a potential gel (a coitally-related vaginal gel to be used by women) for preventing new infections [19]. A large cohort study [19] on 889 heterosexual women with multiple partners has confirmed the profound impact of Tenofovir gel in reducing HIV infections, and its success has gained much attention around the world [23, 24, 35].

Tenofovir gel is safe, without any renal toxicity, which is one of the most important safety concerns of TDF [32]. The gel has the advantage of being less of a burden due to the method of its application as it is used only within ±12 hours of sexual acts, unlike the other forms of TDF, which require daily use [5, 13, 19]. According to Karim et al. [19], the gel is used by inserting it into vagina for two times in a 24-hour period; one dose within 12 hours before sex and another, as soon as possible, within 12 hours after sex [19]. In addition, the unique advantage of this formulation is that women at risk can use it without their partners' knowledge [35], avoiding any potential objections from the partner. Better understanding of the effectiveness of Tenofovir gel can be helpful for proper implementation of this gel to gain optimal benefits in preventing HIV burden.

In this chapter, we develop a mathematical model to quantitatively understand the effectiveness of Tenofovir gel for women in the control of HIV infection. Using our model and survey data from South Africa, we estimate the male-to-female and female-to-male transmission rates both with and without the use of Tenofovir gel. With these estimates we predict the role of Tenofovir gel in reducing reproduction numbers and new infections. We also evaluate the role of adherence and coverage in the success of Tenofovir gel when it is used as a PrEP against HIV epidemic.

2.2 Methods

2.2.1 Data

We obtained our data from the CAPRISA (Centre for the AIDS Programme of Research in South Africa) study [19]. In this study, 889 healthy women were selected and divided into two subgroups: 445 women were prescribed with Tenofovir gel and 444 women with Placebo gel. The number of new infections and the incidence rates were reported cumulatively during the study period of two-and-a-half years. From the given incidence rate [19] in the unit of percent women-year (i.e. the number of new infections, in one year, per one hundred susceptible

women), we calculate the cumulative new infections as follows: the cumulative total number of new infections is $W_0 T\alpha$, where W_0 is the number of susceptible women participants, T is the duration in the study (in year), and α is the incidence rate given in Karim et al. [19]. In the group using Tenofovir gel, for example, after 6 months ($\frac{1}{2}$ year) the incidence rate was 6.0 percent women-year. With the initial recruited (445) women, the total number of infections is calculated as $445 \times \frac{1}{2} \times 0.06$. In the same way the total number of infections after 24 months (2 years) is calculated as $445 \times 2 \times 0.056$, where the cumulative incidence rate is 5.6 percent women-year. The data obtained from our calculations are given in Table 2.1.

Table 2.1: Data obtained from our calculation based on CAPRISA study [19].

Months of follow-up :	6	12	18	24	30
Incidence rate : (in Tenofovir gel arm)	6	5.2	5.3	5.6	5.6
Cumulative HIV infections : (in Tenofovir gel arm)	13	23	35	50	62
Incidence rate : (in Placebo gel arm)	11.2	10.5	10.2	10.2	9.1
Cumulative HIV infections : (in Placebo gel arm)	25	47	68	83	101
Initial recruitment: Tenofovir gel arm = 445 women, Placebo gel arm = 444 women					

2.2.2 Mathematical model

We develop an HIV dynamic model in which we divide the total population into two groups: a general group and a study group. The general group consists of male and female subgroups. Consistent with the experimental study [19], all the individuals in the study group are female, and the study group is subdivided into the Tenofovir subgroup (individuals receiving Tenofovir gel) and the Placebo sub-group (individuals receiving Placebo gel). In our study, the individuals in the general group receive neither Tenofovir nor Placebo gels. Each subgroup is further divided into susceptible (S) and infected (I) subgroups. We assume, for simplicity, that the transmission occurs through heterosexual contact only. The susceptible women using Tenofovir gel (S_d) or Placebo gel (S_c) become infected (I_d or I_c, respectively) through effective contact with infected males (I_m) from the general population. Similarly, susceptible females (S_f) of the general population group become infected (I_f) through contact with infected males, I_m. Here, the study group constitutes only 1% of the total population, and the contribution by

the infected females in the study group (less than 0.2% of the whole population) to the new infection is negligible compared to that by the infected females in the general group. Therefore, we assume that the susceptible males get infected only by the infected females of the general group, and ignore the terms (in model) for the new infection due to females in the study groups. Note, however, that we also investigated our model by including the study population in the equations of the general population, and found no change in the results. The definition and symbols are summarized in Table 2.2-2.4. The schematic diagram showing the transmission in this dynamics is given in Figure 2.1.

Table 2.2: Description of variables with initial values of model (2.2).

Parameter	Description	Initial Value	Source
S_m	susceptible male in GP	33631	[19, 38]
I_m	infected male in GP	5248	[19, 38]
S_f	susceptible female in GP	31674	[19, 38]
I_f	infected female in GP	10446	[19, 38]
S_d	susceptible female under TG	445	[19]
I_d	infected female under TG	0	[19]
S_c	susceptible female under PG	444	[19]
I_c	infected female under PG	0	[19]
GP=General population, TG=Tenofovir gel group, PG=Placebo gel group			

Table 2.3: Fixed parameter values estimated from demographic data.

Parameter	Description	Value (per month)	Source
Λ_m	recruitment rate of S_m	173	[34]
Λ_f	recruitment rate of S_f	187	[34]
μ	natural death rate	6.67×10^{-4}	[9]
μ_l	rate of leaving from the network due to age	2.38×10^{-3}	estimated
ν	disease induced death rate	6.1×10^{-3}	[36]

The transmission rate from infected female to susceptible male is denoted by β_m. Similarly, the transmission rates from infected male to susceptible females in the general subgroup, the Tenofovir subgroup, and the Placebo subgroup are denoted by β_f, β_d, and β_c, respectively. These transmission rates are given by

$$\beta_i(t) = \beta_{i0}\zeta_{if}(t), \quad i = m, f, d, c,$$

Table 2.4: Estimated parameter values.

Parameter	Description	Value (per month)
β_f	transmission rate from I_m to S_f	0.0785
β_{d0}	per act transmission rate from I_m to S_d	0.0047
β_{c0}	per act transmission rate from I_m to S_c	0.0085
β_d	transmission rate from I_m to S_d	0.0219†
β_c	transmission rate from I_m to S_c	0.0396†
$\beta_m = \beta_f/2.3$	transmission rate from I_f to S_m	0.0341

†Calculated by using (2.3)

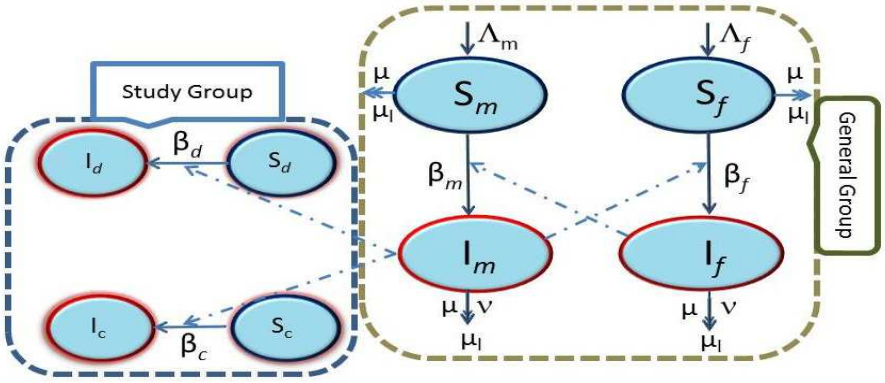

Figure 2.1: Schematic diagram. The solid arrows between the compartments indicate transfer of individuals while dashed-dotted arrows indicate cause of transfer of individuals.

where β_{i0} is the corresponding transmission rate per sexual act, and $\zeta_{if}(t)$ is the average number of sexual acts at time t. As seen in the data [19] the coital frequency for the study group decreases approximately linearly. Thus, we fit a linear curve to this coital frequency data [19] to obtain $\zeta_{if}(t) = \zeta_f(t) = 7.25 - 0.17t, i = d, c$, where t is in months. Thus, we have

$$\begin{aligned} \beta_d &= \beta_{d0}\zeta_f(t), \\ \beta_c &= \beta_{c0}\zeta_f(t). \end{aligned} \tag{2.1}$$

Since the coital frequency data for the general population groups are not available, the transmission rates β_m and β_f are assumed to be constant. We consider only the sexually active population group (age 15–49 years) in this network, and individuals crossing this age group leave our study at the rate of μ_l. We assume that there is no vertical transmission, and newly matured populations (turning 15 years old) are recruited to the susceptible male and female

subgroups of the general population at constant rates Λ_m and Λ_f, respectively. The natural death rate and disease death rate are denoted by μ and ν, respectively. Since no additional subjects were enrolled in the study group and only one individual died from this group, we do not include any birth/death term in the model for these sub-groups. With these assumptions, the dynamics of infection can be modeled by the following ODE system:

$$\begin{aligned}
\dot{S_m} &= \Lambda_m - \frac{\beta_m I_f S_m}{S_f + I_f} - (\mu + \mu_l) S_m, \\
\dot{I_m} &= \frac{\beta_m I_f S_m}{S_f + I_f} - (\mu + \mu_l + \nu) I_m, \\
\dot{S_f} &= \Lambda_f - \frac{\beta_f I_m S_f}{S_m + I_m} - (\mu + \mu_l) S_f, \\
\dot{I_f} &= \frac{\beta_f I_m S_f}{S_m + I_m} - (\mu + \mu_l + \nu) I_f, \\
\dot{S_d} &= -\frac{\beta_d I_m S_d}{S_m + I_m}, \\
\dot{I_d} &= \frac{\beta_d I_m S_d}{S_m + I_m}, \\
\dot{S_c} &= -\frac{\beta_c I_m S_c}{S_m + I_m}, \\
\dot{I_c} &= \frac{\beta_c I_m S_c}{S_m + I_m},
\end{aligned} \tag{2.2}$$

where dots represent the derivatives with respect to time t.

2.2.3 Parameter values and initial conditions

For the CAPRISA study [19], the women were selected from rural (Vulindlela) and urban (eThekwini) sites of South Africa. The total population in the rural site in 2007 was 90,000 [19]. Taking the similar proportion for the population in the network from the urban site, we use the total population in our study to be 180,000 [19]. According to Statistics South Africa (STATSSA) [34], 45% of the total population belongs to the age group 15–49 [34], among which 48% are male and 52% are female. Among the total population, 12% belong to the age group 10–14 [34], which helps us to estimate Λ_m = 173/month and Λ_f = 187/month. As mentioned above we assume that the recruitment only added to the susceptible subgroups of the general group. Using the male HIV prevalence (13.5 % [38]) and the female HIV prevalence (24.8% [19]) at the study site, we calculate the initial population in the general subgroups as

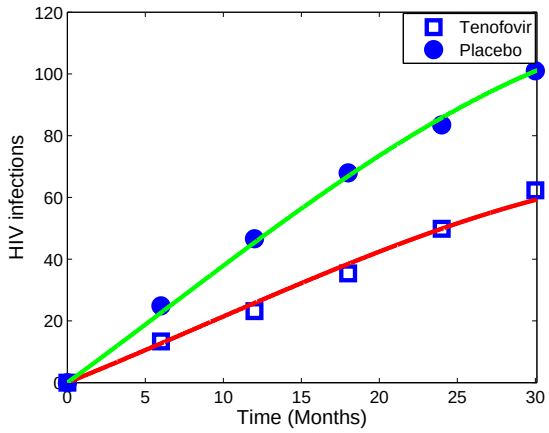

Figure 2.2: Data fitting with β_f, β_{d0}, and β_{c0} as variable parameters. The solid green curve shows the simulation of cumulative infection of Tenofovir gel user (I_d) while dots are the corresponding data. The red curve predicts the cumulative infection of Placebo gel user (I_c) while squares are the corresponding data. The predictions fit the data very well.

$S_m(0) = 33631$, $I_m(0) = 5248$, $S_f(0) = 31674$, and $I_f(0) = 10446$. The average life time of HIV infected individuals without any treatment is 13.5 years (8–19 years) [36], yielding $\nu = 0.074$ per year. The other (non-HIV) death rate of 15-49 age group in South Africa has been recorded as 8 per thousand per one year [9], giving $\mu = 0.008$ per year. Moreover, individuals leave the study after 35 years (15–49 years), which yields $\mu_l = 1/35$ per year. The female-to-male transmission rate is usually smaller than the male-to-female transmission rate [27, 28]. Nicolosi et al. [27] found that the ratio between male-to-female and female-to-male transmission rates is 2.3; we therefore take $\beta_m = \beta_f/2.3$. The three transmission rates β_f, β_{d0} and β_{c0}, are estimated from fitting our model to the data.

2.2.4 Data fitting

The HIV infection data corresponding to the Tenofovir and the Placebo groups are given in Table 2.1. We fix several parameters by estimating them from the demographic data (Table 2.3), and consider only β_f, β_{d0}, and β_{c0} as free parameters during the data fitting process. We solve the ODE system (2.2) using ode45, an ODE solver in MATLAB. We further use the MATLAB function 'fmincon' to estimate free parameters by minimizing the following error function.

$$J = \Sigma_{i=1}^{N} \left[(I_d(t_i) - \hat{I}_d(t_i))^2 + (I_c(t_i) - \hat{I}_c(t_i))^2 \right],$$

where $I_d(t_i)$ and $I_c(t_i)$ are the model solutions at time t_i; $\hat{I}_d(t_i)$, $\hat{I}_c(t_i)$ are data at time t_i; and N is the total number of data points for each group.

2.3 Results

2.3.1 Effect of gel on transmission rates

In model-fitting we have three free parameters $\beta_f, \beta_{d0}, \beta_{c0}$. The estimated parameters are given in Table 2.4, and the fitted curves are shown in Figure 2.2. The model fits the data very well. To simplify the discussion, we approximate the average transmission rates β_d and β_c by

$$\begin{aligned} \beta_d &\approx \frac{\beta_{d0}}{D}\int_0^D \zeta_f(t)dt, \\ \beta_c &\approx \frac{\beta_{c0}}{D}\int_0^D \zeta_f(t)dt, \end{aligned} \tag{2.3}$$

where D is the duration of the study period (here $D = 30$ months). The values of the estimated parameters are $\beta_f = 0.0785$, $\beta_{d0} = 0.0047$, and $\beta_{c0} = 0.0085$ (Table 2.4). By using (2.3), we obtain $\beta_d = 0.0219$ and $\beta_c = 0.0396$.

The transmission rate from infected males to females under Tenofovir gel, β_d, is 45% smaller than that to females under Placebo gel, β_c, i.e., the relative effectiveness of Tenofovir gel over Placebo gel is 45%. This result is consistent with the findings of the CAPRISA study [19], in which 28% to 54% relative effectiveness of Tenofovir gel compared to Placebo gel were found.

We estimate the transmission rate β_d to be 72% smaller than β_f, indicating that the use of Tenofovir gel as a PrEP is 72% effective on reducing HIV transmission. It is worth noting that β_c is also 50% smaller than β_f. This indicates that Placebo gel itself provides protection against HIV infection. Though Placebo gel has no antiviral activity, a plausible explanation for this protection is that it forms a physical barrier for HIV to reach the target cell. This is consistent with the findings by Lai et al. [21] that the barrier at vaginal mucosa prevents the virus from reaching the target cells (CD4+ T cells) lying beneath the epithelial cell layer. The reduction of infection in the Placebo gel group may also be due to the fact that they received comprehensive counseling to minimize the risk of infection [19]. The results suggest that the net magnitude of the gel efficacy has to be interpreted carefully.

2.3.2 Reproduction numbers and effects of Tenofovir gel

We define the *male reproduction number*, $\mathfrak{R}_0^m$, by the total number of new male infections generated by an infected female individual in her entire life when she is introduced into an entirely susceptible male population; and the *female reproduction number*, $\mathfrak{R}_0^f$, is defined by the total number of new female infections generated by an infected male individual in his entire life when he is introduced into an entirely susceptible female population. Furthermore, we define *the basic reproduction number*, $\mathfrak{R}_0$, by the average number of secondary infections of the same-sex generated by a typical infected individual in his/her entire life when he/she is introduced into an entirely susceptible population. These numbers measuring the secondary same-sex individuals are important to study the sex-focused interventions such as the female-focused Tenofovir gel considered in this study.

From our model, the male and female reproduction numbers can be obtained as

$$\mathfrak{R}_0^m = \frac{\beta_m S_m(0)}{(\mu+\nu+\mu_l)S_f(0)}, \quad \mathfrak{R}_0^f = \frac{\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)}.$$

Similarly, the basic reproduction number in the absence of interventions is given by

$$\mathfrak{R}_0 = \mathfrak{R}_0^m \mathfrak{R}_0^f = \frac{\beta_m \beta_f}{(\mu+\nu+\mu_l)^2}. \tag{2.4}$$

Using our estimates, we obtain $\mathfrak{R}_0$ to be 31.53, with $\mathfrak{R}_0^m = 3.93$ and $\mathfrak{R}_0^f = 8.02$. This shows that women are much more vulnerable to the infection, consistent with many experimental findings [2, 15]. The basic reproduction numbers with and without interventions are summarized in Table 2.5. Note that the female-to-male transmission rate is not affected by the use of Tenofovir gel because only susceptible women, after having been tested for eligibility, use this gel as an intervention. Thus the gel has no effect on the male reproduction number ($\mathfrak{R}_0^m$), and it remains the same ($\mathfrak{R}_0^m = 3.93$), whether the women use the gel or not. Importantly, by the use of Tenofovir gel, $\mathfrak{R}_0^f$ is reduced from 8.02 to 2.23, and the resulting $\mathfrak{R}_0$ is reduced from 31.53 to 8.82.

Several studies [12, 25], in which the sexes were not distinguished, estimate that the basic reproduction number ($\mathfrak{R}_0$) of HIV infection in South Africa ranges from 4.5 to 7.0. In our model, we consider the male and female populations separately. For such a model, similar to vector-borne disease models, one faces a choice of either using $\mathfrak{R}_0 = \mathfrak{R}_0^m \mathfrak{R}_0^f$ (as in (2.4)), or $\mathfrak{R}_0 = \sqrt{\mathfrak{R}_0^m \mathfrak{R}_0^f}$ to define the basic reproduction number. The former is more biologically intuitive and tractable, while the latter is based on the next generation approach [37] and is

mathematically more rigorous. For our model, if we adopt the latter, meaning that we account for both male and female-borne "generations", we would obtain $\mathfrak{R}_0 = \sqrt{\mathfrak{R}_0^m \mathfrak{R}_0^f}$ by calculating the spectral radius of the next generation matrix. Using the values of $\mathfrak{R}_0^m$ and $\mathfrak{R}_0^f$ above, we then obtain $\mathfrak{R}_0 = \sqrt{31.5} \approx 5.61$, which is consistent with previous studies [12, 25].

While the use of Tenofovir gel is significantly effective on reducing the basic reproduction number, $\mathfrak{R}_0$ still remains quite large (> 1) even under the Tenofovir gel intervention. Therefore, additional interventions (e.g. condom use) are needed to achieve the desired result $\mathfrak{R}_0 < 1$, a sufficient condition for eradication of the disease from the community [10, 37]. Assuming other additional interventions can reduce the transmission rates β_m and β_f by fraction q, i.e. $\beta_m \to (1-q)\beta_m$ and $\beta_f \to (1-q)\beta_f$, we obtain that

$$\mathfrak{R}_0 = \frac{\beta_m \beta_f (1-q)^2}{(\mu + \nu + \mu_l)^2}$$

with other interventions only, while

$$\mathfrak{R}_0 = \frac{\beta_m \beta_d (1-q)^2}{(\mu + \nu + \mu_l)^2}$$

with a combination of other interventions and Tenofovir gel. This implies that to satisfy the condition $\mathfrak{R}_0 < 1$, we require

$$q > 1 - \frac{(\mu + \nu + \mu_l)}{\sqrt{\beta_m \beta_f}} = 0.82$$

with other interventions only, and

$$q > 1 - \frac{(\mu + \nu + \mu_l)}{\sqrt{\beta_m \beta_d}} = 0.66$$

if Tenofovir gel is added to other interventions. Thus, addition of Tenofovir gel to other interventions significantly reduces the level of other interventions required for successful eradication of the disease (requirement of at least 82% effectiveness vs. requirement of only 66% effectiveness).

2.3.3 Effect of Tenofovir gel on new infections

In this section, we consider the base-case, i.e. all susceptible women in the general population group use the gel with 72% adherence, and present the sensitivity of the coverage and adher-

Table 2.5: Effect of gel on HIV infection and reproduction numbers.

Transmission rates (βs)	New infections male (T_m) (in 1 year)	New infections female (T_f) (in 1 year)	Basic repr. number ($\mathfrak{R}_0$)	Male repr. number ($\mathfrak{R}_0^m$)	Female repr. number ($\mathfrak{R}_0^f$)
$\beta_f = 0.0785$	3786	4847	31.53	3.93	8.02
$\beta_d = 0.0219$	3311	1399	8.80	3.93	2.23

ence in a later section. We also assume that only susceptible women, after having been tested, are eligible [5] to use Tenofovir gel. We note that there might be some women on continued gel use from an unknown time of infection to the time of diagnosis. We ignore this time lag by assuming a frequent testing scenario, in which the proportion of unidentified infected women who are on continued gel is small.

Using the estimated transmission rates, we now calculate the total number of new infections. The total number of new infections of male and female, $T_m(t)$ and $T_f(t)$, respectively, can be obtained by integrating the infection terms of the model (2.2), and are given by

$$T_m(t) = \int_0^t \frac{\beta_m I_f(s) S_m(s)}{S_f(s) + I_f(s)} ds,$$
$$T_f(t) = \int_0^t \frac{\beta_f I_m(s) S_f(s)}{S_m(s) + I_m(s)} ds.$$

With the estimated parameters the total number of new male and female infections, in one year, are $T_m(12) = 3,786$ and $T_f(12) = 4,847$, respectively. By using Tenofovir gel the total male and female infections can be reduced to 3,311 and 1,399, respectively (Figure 2.3 and Table 2.5). This result showing 71% reduction in the women's infection due to Tenofovir gel is remarkable, and highlights the potential of Tenofovir gel to be used as a PrEP. Compared to Placebo gel [19], Tenofovir gel is 44% more effective on reducing new infections consistent with the trial study [19]. As mentioned earlier, Tenofovir gel is used by susceptible females only, and, as expected, male infection is reduced by 15% only.

We also calculate the probability of transmission per act from males to females [3] in the general population, the Tenofovir population, and the Placebo population as 0.24%, 0.08%, and 0.16%, respectively. These transmission probabilities are consistent with those found in previous studies [3, 17, 29].

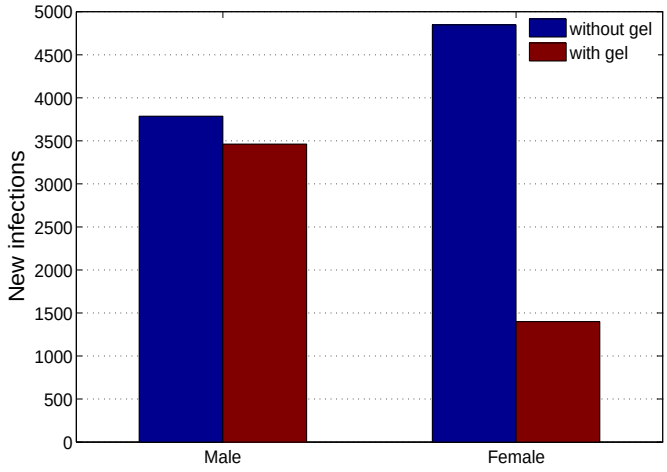

Figure 2.3: Comparison chart of new infection in one year with or without Tenofovir gel intervention.

2.3.4 Effect of Tenofovir gel on HIV prevalence

HIV prevalence is defined as the proportion of HIV infected individuals in the total population. More precisely, male, female and overall prevalence are defined by $\frac{\text{no. of HIV positive men}}{\text{total no. of men}} \times 100\%$, $\frac{\text{no. of HIV positive women}}{\text{total no. of women}} \times 100\%$, and $\frac{\text{no. of HIV positive individuals}}{\text{total population}} \times 100\%$, respectively. In the absence of interventions, both male and female prevalences increase over time as shown by the five year HIV dynamics (Figure 2.4). However, these HIV prevalence patterns can be altered by the use of Tenofovir gel as a PrEP. The overall HIV prevalence as well as the male and female prevalences can drastically be reduced by Tenofovir gel. In a five-year period, the use of Tenofovir gel as a PrEP reduces the overall, the male, and the female prevalences by 44%, 15% and 61%, respectively.

2.3.5 Adherence to Tenofovir gel application

As seen above, the use of Tenofovir gel significantly reduces the transmission rate. If r represents the reduction of transmission rate due to the gel, then

$$(1 - r)\beta_f = \beta_d. \tag{2.5}$$

Using our estimates of β_f and β_d, we obtain $r = 0.721$ ($\sim 72\%$). In this section, we further highlight that r primarily depends on two factors, the effectiveness (ϵ) of Tenofovir gel and

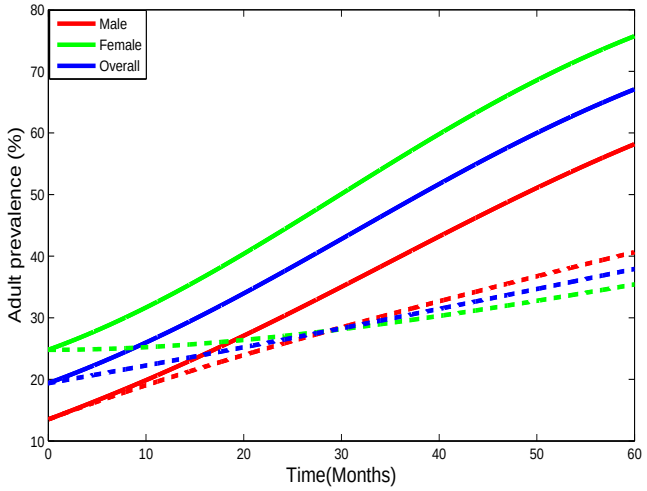

Figure 2.4: HIV prevalence (see Section 2.3.4 for definitions) of male, female and overall population with and without Tenofovir gel interventions over five years. The top three (solid line) curves represent prevalence with no gel while the bottom three (dashed line) curves represent prevalence with gel. The blue colour represents overall prevalence while red and green represent male and female prevalence respectively.

the adherence (a) to its application. The Tenofovir gel is prescribed as two doses within a 24-hour period of a sexual act; one dose of the gel within 12 hours before sex and another as soon as possible, within 12 hours after sex [19]. Since the average number of sexual acts for the study group is 5 per month (i.e. $\approx$1/week) [19], we may reasonably assume that the use of gel in the 24 hour-period of one sexual act does not affect the next sexual act. Assuming that the reduction rate r increases linearly with the adherence level, for a simple case we take $\epsilon a = r = 0.721$. Using the adherence level of 72.2%, reported in the trial study [19], we find that the gel efficacy is 99.86%, and use these values for the base-case computation.

We now evaluate the sensitivity of adherence on the reproduction numbers, new infections, and the prevalence. Note that in our simple model of $\epsilon a = r$, the sensitivity of the adherence level is equivalent to the sensitivity of the efficacy. When the adherence level is changed from 72.2% to 60% and to 80%, female infections are reduced by 59% and 79%, respectively, in one year under 100% coverage (Figure 2.5). Similarly, for 60% and 80% adherence levels, the basic reproduction number is changed to 12.61 and 6.31, respectively, and the female reproduction number is changed to 3.21 and 1.61, respectively. In these adherence levels (60% and 80%), the overall HIV prevalence reaches 44.37% and 33.46%, respectively, at the end of 5 years.

Note that this effect depends upon the gel coverage of susceptible female population. Thus, we further evaluate how changes in the coverage affect this outcome. Let us assume that a

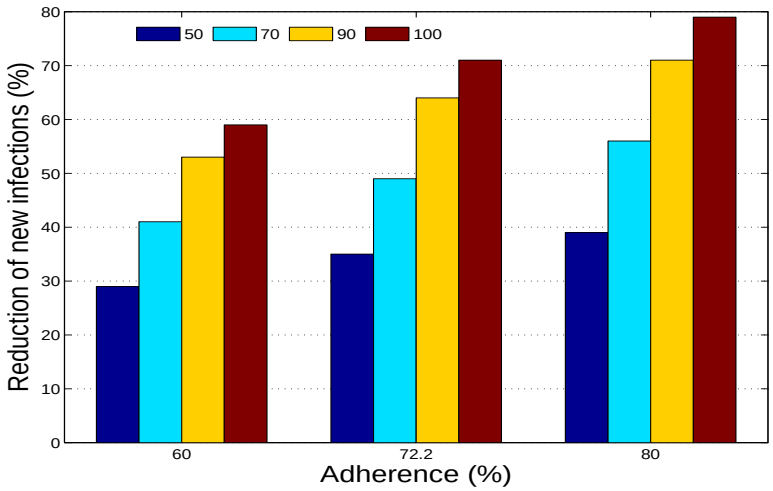

Figure 2.5: Reduction of female infections (in one year) with respect to adherence and coverage. The reduction rate increases with adherence and coverage. The adherence level 72.2% was observed in the study group [19]. Four different colour bars denote percentage of coverage.

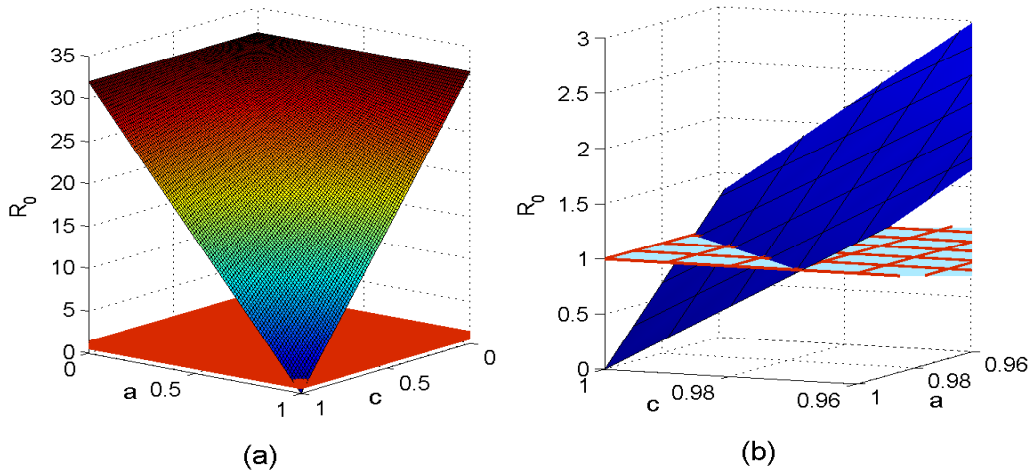

Figure 2.6: Impact of adherence and coverage on $\mathfrak{R}_0$. (a) Full image; (b) Highlighted area where $\mathfrak{R}_0$ passes through 1.

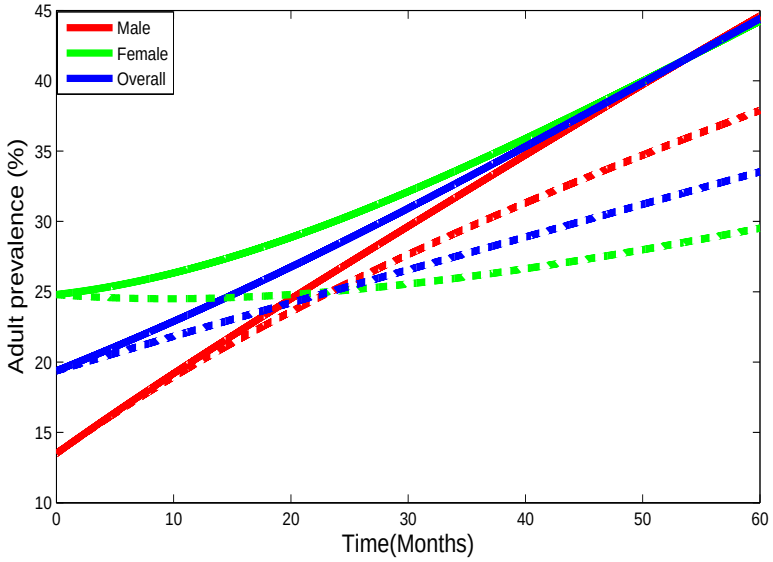

Figure 2.7: Impact of coverage on prevalence. The top three (solid line) curves represent prevalence with 60% gel coverage while the bottom three (dashed line) curves represent prevalence with 80% gel coverage. The blue colour represents overall prevalence while red and green represent male and female prevalence, respectively.

fraction c of the susceptible women are under the gel coverage, i.e. these women are infected at the rate of β_d, while the remaining fraction, 1-c, of the susceptible women are infected at the rate of β_f. As mentioned earlier, only susceptible women use Tenofovir gel; so it does not affect the infectivity of infected women to transmit the virus to susceptible men. Therefore, the gel does not affect the female-to-male transmission rate, β_m, or the male reproduction number, $\mathfrak{R}_0^m$. However, the gel affects $\mathfrak{R}_0^f$, which is given by

$$\mathfrak{R}_{0c}^f = \frac{(1-c)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)} + \frac{c\beta_d S_f(0)}{(\mu+\nu+\mu_l)S_m(0)},$$

for the coverage c. By using (2.5), the above formula becomes

$$\mathfrak{R}_{0c}^f = \frac{(1-c)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)} + \frac{c(1-\epsilon a)\beta_f S_f(0)}{(\mu+\nu+\mu_l)S_m(0)},$$

and the corresponding basic reproduction number, from (2.4), is given by

$$\mathfrak{R}_{0c} = \mathfrak{R}_0^m \mathfrak{R}_{0c}^f.$$

As seen in Figure 2.6, $\mathfrak{R}_{0c}$ decreases as the level of adherence and/or the coverage increases, and it becomes less than one if the product of the adherence and coverage levels is greater than 0.97 (Figure 2.6). The coverage also significantly affects the new infections (Figure 2.5) and the disease prevalence (Figure 2.7). For example, at 80% adherence level, if the coverage is increased from 70% to 90%, the reduction of yearly new infections increases from 56% to 71% of that of the case without the tenofovir gel (Figure 2.5). Similarly, at 100% adherence level, when the coverage is increased from 60% to 80%, the male prevalence, the female prevalence, and the overall prevalence are reduced by 6%, 15%, and 11%, respectively (Figure 2.7).

2.3.6 Sensitivity analysis

To determine the robustness of our parameter estimates, we performed a sensitivity analysis by varying the fixed parameters by ±20%. We found that the estimations were insensitive to the change in most of the parameters. The most sensitive parameters are the initial values of the male and female prevalence. The sensitivity of the estimated parameters subject to the fixed parameters is provided in Table 2.6. When we vary the male and female initial prevalence randomly between 10% to 30%, the estimated transmission rate β_{d0} varies between 0.0032 and 0.0060. Similarly, β_f varies between 0.0652 and 0.0869, and β_{c0} varies between 0.0073 and 0.0110. The sensitivity analysis shows that our estimation is robust.

Table 2.6: Sensitivity of the estimated parameters on the fixed parameters.

Fixed parameters	Base-value	Changes (%)	Changes in β_f(%)	Changes in β_{d0}(%)	Changes in β_{c0}(%)
Λ_m	173m^{-1}	±20	0.01	0.37	0.47
Λ_f	187m^{-1}	±20	0.01	0.37	0.47
μ	$6.67\times10^{-4}\text{m}^{-1}$	±20	±0.03	0.37	0.47
μ_l	$2.38\times10^{-3}\text{m}^{-1}$	±20	-0.08	0.38	0.48
ν	$6.1\times10^{-3}\text{m}^{-1}$	±20	±2.48	0.45	0.54
initial male-prevalence	13.5%	±20	±13.97	±22.39	± 22.27
initial female-prevalence	24.8%	±20	±7.65	±2.26	± 2.35

2.4 Discussion

Tenofovir gel is one of the candidates with the highest potential for pre-exposure prophylaxis to provide protection to uninfected women who are at high risk of HIV infection. This is not a vaccine, but using it regularly or according to prescribed guidelines it may provide vaccine-like protection. The experimental data has revealed the significant effects of Tenofovir gel on protecting vulnerable women from HIV infection [19]. Thus Tenofovir gel has been thought to be an important potential PrEP in the absence of effective HIV vaccines as in the current situation. It is not yet well understood how much impact Tenofovir gel can have on population-level HIV dynamics when it is distributed as a PrEP to susceptible women in the community. Here, we developed a mathematical model to better understand the possible implications of Tenofovir gel as a PrEP against an HIV epidemic. Our model is consistent with the experimental data on the use of Tenofovir gel as a PrEP in South Africa (Figure 2.2).

This study provides the HIV transmission rates from male-to-female and from female-to-male with and without the use of Tenofovir gel. We found that Tenofovir gel can reduce the male-to-female transmission rate by 72%. As a result, yearly women infections can be reduced by almost 80% (Figure 2.5) when Tenofovir gel is used as a PrEP. Given the nature of the gel application, i.e. only susceptible women use it, it is expected that the gel does not have direct impact on the female-to-male transmission rate. However, the male population also receives a benefit of 15% annual infection reduction due to indirect female protection. These annual reductions of male and female infections also reflect on the long-term prevalence (Figure 2.4). By implementing the gel as a PrEP over the five-year period, the male and female prevalence can be reduced by 15% and 61%, respectively, with 44% reduction in the overall prevalence. As demonstrated by our results, these remarkable effects of Tenofovir gel on reducing infection rates, new infections, and prevalence further highlight the potential of Tenofovir gel for its broader use as a PrEP.

We defined and calculated the male (female) reproduction number, $\mathfrak{R}_0^m$ ($\mathfrak{R}_0^f$), as well as the basic reproduction number ($\mathfrak{R}_0$). Without intervention, our estimates provide $\mathfrak{R}_0 = 31.53$ for the Vulindlela and eThekwini regions of South Africa. This high value of $\mathfrak{R}_0$ reflects the devastating impact of the HIV/AIDS epidemic in South Africa. Our estimation shows that the female reproduction number ($\mathfrak{R}_0^f$) is twice that of the male reproduction number ($\mathfrak{R}_0^m$), indicating that women are particularly vulnerable to HIV infection as mentioned previously [2, 15]. With the use of Tenofovir gel as a PrEP by susceptible women, both $\mathfrak{R}_0$ and $\mathfrak{R}_0^f$ can be brought down significantly to 8.80 and 2.23, respectively. However, despite the use of Tenofovir gel, $\mathfrak{R}_0$ still remains greater than 1, implying that the use of Tenofovir gel alone will

not be able to eliminate the disease. A partial explanation for the lack of strength of Tenofovir gel to eradicate disease could be that Tenofovir gel does not reduce the male transmission rate (or male reproduction number), and the infection of women is governed by the infected male population. Thus our results suggest that a combination program incorporating Tenofovir gel as a PrEP into other additional interventions, such as condom protection, may result in the successful eradication of HIV/AIDS.

Our results support the hypothesis that adherence and coverage are key for the success of Tenofovir gel as a PrEP. The individual protection depends on the adherence level while overall impact depends on the coverage of susceptible women by Tenofovir gel. Both adherence and coverage have a positive effect on the reduction of infections, reproduction numbers, and prevalence (Figures 2.5, 2.6, 2.7). These observations suggest that the adherence and coverage must be taken into account while evaluating the outcomes of Tenofovir gel as a PrEP. Moreover, HIV prevention programs with Tenofovir gel as a PrEP need to be designed aiming at a higher level of adherence and coverage. For example, to increase the adherence level, an alternate form of Tenofovir gel, such as an intravaginal ring (IRV) [22], can be suggested. Similarly, an optimal coverage can be achieved by identifying women at high risk and bringing them under gel coverage.

One of the interesting findings of our study is that Placebo gel also shows some effectiveness against HIV infection, as opposed to the general expectation that Placebo gel has negligible effect. To understand this in detail, we also considered the model with $\beta_f = \beta_c$ assuming that Placebo gel has no effect. Interestingly, we found that the model with $\beta_f = \beta_c$ provides significantly worse fit ($p = 0.0025$, F-test) to the data compared to our original model. This surprising effect could be due to the fact that though Placebo gel does not contain any anti-viral agent, it may form a physical barrier against HIV reaching the target cell [21]. It may also be due to the fact that the study group under Placebo gel received comprehensive counseling to minimize the risk of infection. The results suggest that the net effectiveness of Tenofovir gel has to be interpreted carefully.

While this study offers some valuable insights into the implication of Tenofovir gel as a PrEP on HIV dynamics, we identify several limitations of our study. Our estimates are based on limited data sets from South Africa. We assumed that the adherence of gel increases the protection linearly, which may not be the case for each individual. The drug concentration and its efficacy might also play a role in determining the overall effects on transmission. Our model further assumes that only susceptible women use Tenofovir gel [5]. However, there might be some infected women on continued gel from the time of infection to the time of

diagnosis. To the best of our knowledge, there is no clear evidence about the effects of gel on the transmission from women to men. If these unknowingly-infected women continue gel use, which may provide additional protection not accounted for in our study, then the benefits of Tenofovir gel can be expected to be more than those found in this study. In this case, we have underestimated the benefit from Tenofovir gel. While these infected women on the continued gel use can be ignored in some regions with frequent testing facilities as in our computation, the model needs to be improved to include this group in the regions with poor resources. Finally, we acknowledge that the women in the experimental study [19] benefited from supplementary care, including education, counseling, and motivation; our estimates of the benefits from Tenofovir gel might have been affected by these. Further studies with more data sets may help achieve a deeper understanding of the actual benefit of Tenofovir gel as a PrEP.

In summary, Tenofovir gel as a PrEP for women can be an effective tool to fight against HIV infection. In the absence of a successful vaccine, Tenofovir gel can be used as a PrEP to provide significant direct protection to women, and indirectly to men, from HIV infection. In combination with other interventions, Tenofovir gel as a PrEP has the potential to eradicate HIV/AIDS, the most devastating current human epidemic. A strategic and prudent use of this gel is required to obtain the optimal impact.

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Chapter 3

Impact of early antiretroviral treatment on HIV epidemics: A mathematical model study

3.1 Introduction

Prevention of HIV transmission has been one of the prime concerns and challenges in the past three decades. Repeated failure of vaccine development aggravates this challenge [22, 34, 38]. In the absence of vaccines, the use of antiretroviral agents such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) has shown promising results [9, 11, 13, 16]. In particular, trials on early antiretroviral therapy (ART) as prevention have demonstrated significant effectiveness in reducing HIV transmission [13, 16, 21].

A study with 1763 serodiscordant couples from nine countries found 89% reduction of HIV transmission with early initiation of ART [13]. Similarly, a community based cross-sectional study in South Africa estimated up to 71.8% reduction of annual risk of HIV transmission with early ART [5]. This is mainly because of the significantly lower viral load in successfully treated individuals [16].

In addition, ART can help recover the CD4+ T cell population in infected individuals. It is well established that the CD4+ T cell count is a crucial marker that plays an important role in immunity and treatment decisions during HIV infection [28, 46]. CD4+ T cells, the main target for HIV infection, are rapidly depleted during the disease progression towards AIDS. CD4+ T cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy [20,

28, 32, 46]. The measurement of CD4+ T cell counts also has an important role in decisions for screening and prophylaxis for major opportunistic infections, including malaria, severe bacterial infections, P. jiroveci pneumonia, and toxoplasmosis [42]. Thus, it is important for public health to know the proportion or number of HIV infected individuals that belong to certain CD4+ T cell count thresholds under a treatment program.

Several studies and modelling efforts outlined the possible impact of initiation timing of ART and found a reduction of HIV incidence associated with early initiation of ART [8, 23, 31, 33, 41]. A comprehensive test-and-treat model among MSM in New York City showed that the cumulative number of new infections can be reduced by 69.1% over a 20-year period [41]. Another study showed a reduction of disease progression and serious non-AIDS events when ART was initiated before the CD4+ T cell count was reached 350 cells compared with delaying until the CD4+ T cell count had dropped to less than 250 [46]. A dynamical model developed by the World Health Organzation (WHO) predicted that annual HIV testing and immediate treatment could reduce HIV incidence and mortality in South Africa to less than 1 case per thousand people per year in five years and HIV prevalence to less than 1% in fifty years [23]. However, none of these studies considered the fact that ART improves the immunity level of the infected individuals (i.e. increases their CD4+ T cell counts) [4]. Improved immunity tends to reduce the death of infected individuals and slows the disease progression. Moreover, improved immunity collectively benefits community health which is important for controlling other opportunistic diseases. The actual contribution of treated individuals to the total number of new infections, the immunity level of the community, and HIV prevalence is not well understood. Thus, the quantification of these measurements is important for better formulating treatment strategies.

Moreover, the timing of ART initiation is important for increased levels of immunity and decreased disease mortality and morbidity. Depending on the time of ART initiation, an HIV patient may even have a normal life expetancy. A longitudinal cohort study found increased AIDS-related mortality and morbidity associated with delay in initiation of ART [6]. In the French cohort [4, 20], ART patients who maintained CD4+ T cell count > 500 had mortality similar to those in the general population. Since ART reduces the transmission rate, but prolongs the life span of the HIV infected individual, the initiation time of ART is critical to the outcomes of ART programs. In this study, we develop a model to explore the consequences of various ART programs and their initiation timing on the population-level HIV transmission dynamics.

The remainder of this chapter is organized as follows: in Section 3.2 we develop a mathe-

matical model. Basic properties of the model and stability analysis are presented in Section 3.3. In Section 3.4, we estimate parameters and perform data fitting. In Section 3.5, the results from various treatment programs are shown. Finally, we summarize our findings with discussions in Section 3.6.

3.2 Mathematical Model

In HIV infection, an individual's disease condition is associated primarily with their CD4+ T cell count. In fact, HIV primarily weakens an infected individual's immune system by destroying their CD4+ T cells. Therefore, CD4+ T cell count is a crucial marker to measure the strength of the immune system in HIV infected individuals [6, 28]. Moreover, a decision as to whether the treatment should begin or not is usually made based on a patient's CD4+ T cell level. Here we develop a model based on an individual's CD4+ T cell count level. In ART programs, HIV infected individuals are generally divided into three groups or stages based on their CD4 T+ cell counts (below 350, 350-500 and above 500) and receive mild to strong recommendation for initiating ART [2, 46]. Based on these guidelines, we divide the total HIV infected population into three stages according to their corresponding CD4+ T cell levels. Stage I consists of the individuals with CD4+ T cell counts more than 500, stage II with CD4+ T cell count between 350 and 500, and stage III with CD4+ T cell count less than 350. Once infected, an individual generally progresses through these stages if they remain untreated. The individual usually regains their CD4+ T cell count through treatment [29]. The amount of CD4+ T cell count recovery depends on the level of CD4+ T cell count at the time the person begins treatment. In addition to the regain of CD4+ T cell count, the treatment can also suppress the viral load down to an undetectable level. Thus, an infected individual becomes significantly less infectious under treatment [40]. In our model, the treatment can have two consequences: increase in CD4+ T cell count in treated individuals and decrease in HIV transmission by treated individuals.

We consider a homogeneous sexually active (age 15-49 years) population and divide them into seven groups: a susceptible group, S, three infected groups (categorised based on CD4+ T cell count) without treatment, I_1, I_2, I_3 and three infected groups (categorised based on CD4+ T cell count) with treatment, T_1, T_2, T_3. The transmission dynamics are as follows: a susceptible individual moves to the compartment I_1 when he/she comes in successful contact with an individual from any of the infected compartments. The individuals of I_1 either get treatment and move to T_1 at the rate of τ_1 or they move to I_2 compartment (due to their CD4+ T cell count

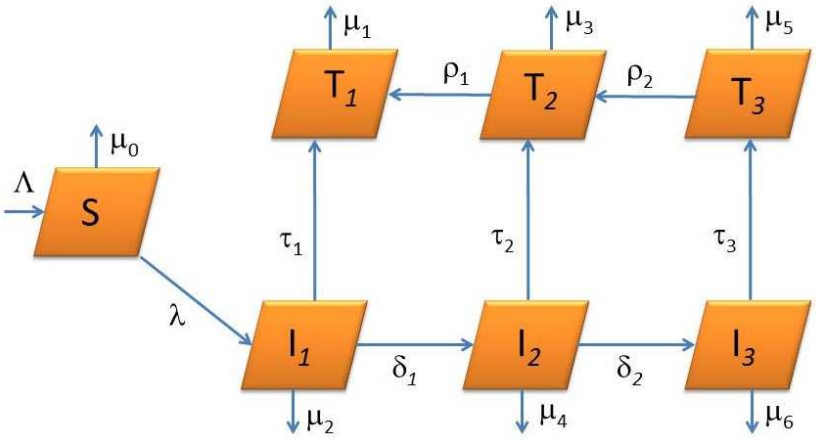


Figure 3.1: Schematic diagram of infection.

decline) at the rate of δ_1. Similarly, individuals move from compartment I_2 to T_2 at the rate of τ_2 (treatment) or to I_3 at the rate of δ_2 (CD4+ T cell decline). The individuals of compartment I_3 get treatment and move to T_3 at the rate of τ_3. Treated individuals gain CD4+ T cell count and move from T_3 to T_2 and from T_2 to T_1 at rates ρ_2 and ρ_1, respectively.

The infectivity of individuals at different stages are different [15]. The rate of transmission by HIV infected individuals without treatment is high during acute infection (few months), decreases to a low level that continues for a long period (usually 6-7 years), and then increases slightly during the last 2-3 years [27]. Therefore, we take different transmission rates, β_1, β_2, and β_3 for I_1, I_2, and I_3 compartments, respectively. Since the viral load of individuals in all treated compartments usually remains low with a low transmission probability [13, 40], we do not distinguish infectivity of different compartments of treated groups, and take the same transmission rate β for all T_1, T_2, and T_3. The definition and symbols of the model variables are summarized in Table 3.1-3.2. The flow of the population in these transmission dynamics is shown in Figure 3.1.

Following the assumptions discussed above, the infection dynamics can be modeled by the following system of ODEs :

Table 3.1: Description of variables of model (3.1).

Variable	Description
S	number of susceptibles
I_1	number of infected individuals with CD4+ T cell count > 500
I_2	number of infected individuals with CD4+ T cell count 350-500
I_3	number of infected individuals with CD4+ T cell count < 350
T_1	number of treated individuals with CD4+ T cell count > 500
T_2	number of treated individuals with CD4+ T cell count 350-500
T_3	number of treated individuals with CD4+ T cell count < 350
N	total number of individuals

$$\begin{aligned}
\dot{S} &= \Lambda - (\lambda + \mu_0)S \\
\dot{I}_1 &= \lambda S - (\tau_1 + \delta_1 + \mu_2)I_1 \\
\dot{I}_2 &= \delta_1 I_1 - (\tau_2 + \delta_2 + \mu_4)I_2 \\
\dot{I}_3 &= \delta_2 I_2 - (\tau_3 + \mu_6)I_3 \\
\dot{T}_1 &= \tau_1 I_1 + \rho_1 T_2 - \mu_1 T_1 \\
\dot{T}_2 &= \tau_2 I_2 + \rho_2 T_3 - (\rho_1 + \mu_3)T_2 \\
\dot{T}_3 &= \tau_3 I_3 - (\rho_2 + \mu_5)T_3
\end{aligned} \tag{3.1}$$

where the force of infection, λ, is given by

$$\lambda = \frac{\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)}{N} e^{-a(I_1+I_2+I_3+T_1+T_2+T_3)},$$

and

$$N = S + I_1 + I_2 + I_3 + T_1 + T_2 + T_3.$$

The exponential term in λ represents 'behavioural changes' due to media or social awareness [35]. When the number of infected individuals is small, this term has negligible effect and the effect increases as the number of infected individual increases.

Table 3.2: Description of parameters of (3.1).

Parameter	Description
Λ	recruitment rate
λ	force of infection
β_1	transmission rate for I_1
β_2	transmission rate for I_2
β_3	transmission rate for I_3
β	transmission rate for treated groups
τ_1	rate of treatment for I_1
τ_2	rate of treatment for I_2
τ_3	rate of treatment for I_3
δ_i	rate of transfer due to CD4+ T cell decline (i=1,2)
ρ_i	rate of transfer due to CD4+ T cell increase (i=1,2)
μ_i	rate of death (i=0,1,...,6)
a	rate associated with reduction of incidence due to behavioral changes

3.3 Model analysis

3.3.1 Well-posedness

The model (3.1) has seven coupled equations. Following [37] it can be shown that $S(t) \geq 0$. Similarly, we can show that all the other state variables are also non-negative as long as the initial values are non-negative.

By adding all the equations of (3.1), the total population N satisfies

$$\dot{N} \leq \Lambda - \mu N,$$

where

$$\mu = \min\{\mu_0, \mu_1, \mu_2, \mu_3, \mu_4, \mu_5, \mu_6\}.$$

By comparison, it implies that $\lim_{t\to\infty} \sup N \leq \Lambda/\mu$. Therefore, the total population is bounded. This suggests that the biologically feasible region of the model is given by

$$\Gamma = \{(S, I_1, I_2, I_3, T_1, T_2, T_3) : S, I_1, I_2, I_3, T_1, T_2, T_3 \geq 0, N \leq \Lambda/\mu\}.$$

3.3.2 Basic reproduction number

The basic reproduction number, denoted by $\mathfrak{R}_0$, of a model is a threshold value that determines whether the disease persists or dies out. It is defined as the total number of secondary infections caused by a typical infected individual in a completely susceptible population [18]. Using the next generation matrix approach [44], the new infection and the transfer matrices of our model are given by

$$F = \begin{pmatrix} \beta_1 & \beta_2 & \beta_3 & \beta & \beta & \beta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \alpha_1 & 0 & 0 & 0 & 0 & 0 \\ -\delta_1 & \alpha_2 & 0 & 0 & 0 & 0 \\ 0 & -\delta_2 & \alpha_3 & 0 & 0 & 0 \\ -\tau_1 & 0 & 0 & \alpha_4 & -\rho_1 & 0 \\ 0 & -\tau_2 & 0 & 0 & \alpha_5 & -\rho_2 \\ 0 & 0 & -\tau_3 & 0 & 0 & \alpha_6 \end{pmatrix},$$

where

$$\alpha_1 = \tau_1 + \delta_1 + \mu_2,\ \alpha_2 = \tau_2 + \delta_2 + \mu_4,\ \alpha_3 = \tau_3 + \mu_6,\ \alpha_4 = \mu_1,\ \alpha_5 = \rho_1 + \mu_3,\ \alpha_6 = \rho_2 + \mu_5.$$

It follows that

$$\begin{aligned} \mathfrak{R}_0 = \rho\left(FV^{-1}\right) = \frac{\beta_1}{\alpha_1} + \frac{\beta_2\delta_1}{\alpha_2\alpha_1} + \frac{\beta_3\delta_2\delta_1}{\alpha_3\alpha_2\alpha_1} + \frac{\beta}{\alpha_5}\left(\frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\right) \\ + \frac{\beta}{\alpha_6}\left(\frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\right) + \frac{\beta}{\alpha_1}\left(\frac{\tau_1}{\alpha_1} + \frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2}\frac{\rho_1}{\alpha_5} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\frac{\rho_1}{\alpha_5}\right). \end{aligned} \tag{3.2}$$

3.3.3 Stability analysis

The model (3.1) has a unique disease free equilibrium (DFE), $E_0 = (\Lambda/\mu_0, 0, 0, 0, 0, 0, 0)$, and possibly an endemic equilibrium (EE) E^*. The existence of endemic equilibria is given in the following sub-section. The stability analysis of these equilibria can reveal whether the disease can survive or not. According to [44], we have the local stability result of E_0, given in the following theorem:

Theorem 3.3.1 *If $\mathfrak{R}_0 < 1$, the DFE, E_0, is locally asymptotic stable, and if $\mathfrak{R}_0 > 1$, E_0 is unstable.*

We can further prove that E_0 is globally asymptotically stable:

Theorem 3.3.2 *If $\mathfrak{R}_0 < 1$, the DFE, E_0, is globally asymptotically stable.*

Proof. Let us consider the auxiliary function

$$L = c_1 I_1 + c_2 I_2 + c_3 I_3 + c_4 T_1 + c_5 T_2 + c_6 T_3, \tag{3.3}$$

where $c_i, i = 1...6$ are positive constants to be determined. Taking the derivative of L, with respect to t, along the trajectories of (3.1), we have

$$\begin{aligned}
\dot{L} =& c_1\dot{I}_1 + c_2\dot{I}_2 + c_3\dot{I}_3 + c_4\dot{T}_1 + c_5\dot{T}_2 + c_6\dot{T}_3 \\
=& c_1(\lambda S - \alpha_1 I_1) + c_2(\delta_1 I_1 - \alpha_2 I_2) + c_3(\delta_2 I_2 - \alpha_3 I_3) + c_4(\tau_1 I_1 + \rho_1 T_2 - \alpha_4 T_1) \\
&+ c_5(\tau_2 I_2 + \rho_2 T_3 - \alpha_5 T_2) + c_6(\tau_3 I_3 - \alpha_6 T_3) \\
\leq& c_1 \frac{\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)}{N} S - c_1\alpha_1 I_1 + c_2\delta_1 I_1 - c_2\delta_2 I_2 \\
&+ c_3\delta_2 I_2 - c_3\alpha_3 I_3 + c_4\tau_1 I_1 + c_4\rho_1 T_2 - c_4\alpha_4 T_1 \\
&+ c_5\tau_2 I_2 + c_5\rho_2 T_3 - c_5\alpha_5 T_2 + c_6\tau_3 I_3 - c_6\alpha_6 T_3 \\
\leq& c_1(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)) + (c_2\delta_1 - c_1\alpha_1 + c_4\tau_1) I_1 \\
&+ (c_3\delta_2 - c_2\alpha_2 + c_5\tau_2) I_2 + (-c_3\alpha_3 + c_6\tau_3) I_3 - c_4\alpha_4 T_1 \\
&+ (-c_5\alpha_5 + c_4\rho_1) T_2 + (c_5\rho_2 - c_6\alpha_6) T_3 \\
=& (\mathfrak{R}_0 - 1)[\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3 + \beta(T_1 + T_2 + T_3)],
\end{aligned} \tag{3.4}$$

where

$$\begin{aligned}
c_1 &= \frac{\beta_1}{\alpha_1} + \frac{\beta_2\delta_1}{\alpha_2\alpha_1} + \frac{\beta_3\delta_2\delta_1}{\alpha_3\alpha_2\alpha_1} + \frac{\beta}{\alpha_4}\left(\frac{\tau_1}{\alpha_1} + \frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2}\frac{\rho_1}{\alpha_5} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\frac{\rho_1}{\alpha_5}\right) \\
&+ \frac{\beta}{\alpha_5}\left(\frac{\delta_1}{\alpha_1}\frac{\tau_2}{\alpha_2} + \frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\frac{\rho_2}{\alpha_6}\right) + \frac{\beta}{\alpha_6}\left(\frac{\delta_1}{\alpha_1}\frac{\delta_2}{\alpha_2}\frac{\tau_3}{\alpha_3}\right), \\
c_2 &= \frac{\beta_2}{\alpha_2} + \frac{\beta_3\delta_2}{\alpha_3\alpha_2} + \frac{\beta\tau_3\delta_2}{\alpha_2\alpha_3\alpha_6} + \frac{\beta\rho_1(\tau_2\alpha_3\alpha_6 + \rho_2\tau_3\delta_2)}{\alpha_2\alpha_3\alpha_4\alpha_5\alpha_6} + \frac{\beta(\tau_2\alpha_3\alpha_6 + \rho_2\tau_3\delta_2)}{\alpha_2\alpha_3\alpha_5\alpha_6}, \\
c_3 &= \frac{\beta_3}{\alpha_3} + \frac{\beta\tau_3}{\alpha_3\alpha_6} + \frac{\beta\rho_1\rho_2\tau_3}{\alpha_3\alpha_4\alpha_5\alpha_6} + \frac{\beta\rho_2\tau_3}{\alpha_3\alpha_5\alpha_6},\ c_4 = \frac{\beta}{\alpha_4},\ c_5 = \frac{\beta}{\alpha_5} + \frac{\beta\rho_1}{\alpha_4\alpha_5}, \\
c_6 &= \frac{\beta}{\alpha_6} + \frac{\beta\rho_1\rho_2}{\alpha_4\alpha_5\alpha_6} + \frac{\beta\rho_2}{\alpha_5\alpha_6}.
\end{aligned}$$

Therefore, $\dot{L} \leq 0$ when $\mathfrak{R}_0 < 1$ with the equality holding only when state variables regarding infection are zero. By Theorem 3.1 (page no. 143 in [25]), all positive solutions approach $\mathcal{M}$, the largest invariant subset of the set $\{\frac{dL}{dt} = 0\}$. Since $\frac{dL}{dt}$ is zero only at disease free state, $\mathcal{M} = \{E_0\}$ is a singleton set. Thus, the equilibrium E_0 is globally attractive. By virtue of the Theorem 3.3.1, E_0 is globally asymptotically stable.

3.3.4 Persistence of the disease

In the previous section, we proved that if $\mathfrak{R}_0 < 1$ then the disease dies out regardless of the initial size of the outbreak. On the other hand, when $\mathfrak{R}_0 > 1$ the DFE becomes unstable. In this sub-section, we show that the infectious populations $I_1,\ I_2,\ I_3, T_1,\ T_2$ and T_3 will remain persistent in this case.

Theorem 3.3.3 *Assume that* $\Re_0 > 1$. *Then the disease is uniformly persistent in the sense that there exists an* $\eta > 0$ *such that for every positive solution of* (3.1)*, there holds*

$$\liminf_{t\to\infty} I_i(t) > \eta, \ \ \liminf_{t\to\infty} T_i(t) > \eta, \ \ i = 1, 2, 3.$$

Moreover, there exists an endemic equilibrium E^* *in this case.*

Proof. We apply a theorem in [43] to prove the uniform persistence. To this end, let

$$\begin{aligned}
U &= (S, I_1, I_2, I_3, T_1, T_2, T_3), \ \ \bar{U} = (I_1, I_2, I_3, T_1, T_2, T_3),\\
X &= \Big\{U \in \mathcal{R}^7_+ | U_i \geq 0, i = 1...7, \text{where } U_i \text{ is the i'th component of } U\Big\},\\
X_0 &= \Big\{U \in X | U_i > 0, i = 2...7\Big\},\\
Y &= X/X_0 = \Big\{U \in X | U_i = 0, \text{for some } \ i = 2...7\Big\}.
\end{aligned}$$

Now we show that the system (3.1) is uniformly persistent with respect to (X_0, Y). Since Y contains a single equilibrium E_0, it is sufficient to show that $W^s(E_0) \cap X_0 = \phi$, where $W^s(E_0)$ denotes the stable manifold of E_0. Suppose this is not true. Then there is a solution $(S, I_1, I_2, I_3, T_1, T_2, T_3) \in X_0$ of (3.1) such that

$$\lim_{t\to\infty}(S(t), I_1(t), I_2(t), I_3(t), T_1(t), T_2(t), T_3(t)) \to (\Lambda/\mu, 0, 0, 0, 0, 0, 0).$$

Then for any $\xi > 0$, we have

$$\begin{aligned}
&\frac{\Lambda}{\mu} - \xi \leq S \leq \frac{\Lambda}{\mu} + \xi,\\
&0 \leq U_i \leq \xi, i = 2...7
\end{aligned}$$

for large t. It follows from the system (3.1) that

$$\begin{aligned}
\begin{pmatrix} \dot{I}_1 \\ \dot{I}_2 \\ \dot{I}_3 \\ \dot{T}_1 \\ \dot{T}_2 \\ \dot{T}_3 \end{pmatrix} &= \begin{pmatrix} \lambda S \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} -\alpha_1 & 0 & 0 & 0 & 0 & 0 \\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0 \\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0 \\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0 \\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2 \\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6 \end{pmatrix} \begin{pmatrix} I_1 \\ I_2 \\ I_3 \\ T_1 \\ T_2 \\ T_3 \end{pmatrix}, \\
&\geq \begin{pmatrix} \beta_1\tilde{S}(\xi) - \alpha_1 & \beta_2\tilde{S}(\xi) & \beta_3\tilde{S}(\xi) & \beta\tilde{S}(\xi) & \beta\tilde{S}(\xi) & \beta\tilde{S}(\xi) \\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0 \\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0 \\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0 \\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2 \\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6 \end{pmatrix} \begin{pmatrix} I_1 \\ I_2 \\ I_3 \\ T_1 \\ T_2 \\ T_3 \end{pmatrix}, \\
&\equiv \tilde{J}(\xi)\bar{U},
\end{aligned}$$

where,

$$\tilde{S}(\xi) = \frac{\Lambda/\mu_0 - \xi}{\Lambda/\mu_0 + 7\xi},$$

and

$$\tilde{J}(0) = \begin{pmatrix} \beta_1 - \alpha_1 & \beta_2 & \beta_3 & \beta & \beta & \beta \\ \delta_1 & -\alpha_2 & 0 & 0 & 0 & 0 \\ 0 & \delta_2 & -\alpha_3 & 0 & 0 & 0 \\ \tau_1 & 0 & 0 & -\alpha_4 & \rho_1 & 0 \\ 0 & \tau_2 & 0 & 0 & -\alpha_5 & \rho_2 \\ 0 & 0 & \tau_3 & 0 & 0 & -\alpha_6 \end{pmatrix}. \tag{3.5}$$

Note that $\tilde{J}(0)$ is equal to $(F - V)$, has at least one eigenvalue with positive real part when $\mathfrak{R}_0 > 1$ [44]. Since $\xi > 0$ is arbitrary, one can make ξ small enough so that $s(\tilde{J}(\xi))$ is positive, where $s(A)$ is the largest real part of the eigenvalues of A. Then there exist solutions of the linear system

$$\dot{\bar{U}} = \tilde{J}(\xi)\ \bar{U}\ ,$$

that grow exponentially near $\bar{U} = 0$. By comparison, the solutions $\bar{U}$ become unbounded as $t \to \infty$. This is a contradiction to the fact that the solutions of the system (3.1) are ultimately

Table 3.3: HIV prevalence data from South Africa [48].

Year :	1990	1991	1992	1993	194	1995	1996	1997	1998	1999	2000	2001
Prev.:	0.3	0.6	1.1	2.0	3.3	5.0	7.0	9.2	11.3	13.2	14.9	16.2
Year :	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Prev. :	17.1	17.8	18.3	18.5	18.7	18.8	18.9	18.9	18.9	18.8	18.9	

bounded. Therefore, $W^s(E_0) \cap X_0 = \phi$. Following Theorem 4.6 [43], it can be concluded that system (3.1) is uniformly persistent with respect to (X_0, Y).

Furthermore, system (3.1) is dissipative, therefore, by Theorems 3.3 in [24], it implies that system (3.1) has an endemic equilibrium E^* (i.e. all components are positive). The proof of the theorem is complete. ∎

Due to the presence of nonlinear incidence with an exponential term in the model (3.1), the stability analysis of E^* becomes a challenging task. We leave this analysis and move to applications of the model with data fitting. In the following sections, we fit the model (3.1) to HIV prevalence data and obtain some results of ART programs.

3.4 Data fitting and parameter estimation

3.4.1 Data

We used the World Bank data for HIV infection in South Africa [48]. The yearly adult HIV prevalence data from 1990 to 2012 were considered. The 'adult prevalence' is defined as the percentage of adult infected individuals among the 15-49 years old population. The data are given in Table 3.3.

3.4.2 Parameter values and initial conditions

HIV mortality is primarily attributed to CD4+ T cell counts and disease stage; the mortality is higher in patients with low CD4+ T cell counts. Mortality is also highly affected by treatment. An individual with successful treatment can have almost a normal life [4]. Following the previous studies [6, 8, 30], we estimated the mortality rates of the individuals in different compartments as $\mu_0 = 0.0288$, $\mu_2 = 0.0888, \mu_4 = 0.1368, \mu_6 = 0.3108$, $\mu_1 = 0.0408, \mu_3 = 0.0528$ and $\mu_5 = 0.1752$.

HIV infected individuals, if they remain untreated, are highly infectious during the first few months (stage I) [15]. Then the infectivity declines and remains low during the asymptotic period for about 6-7 years (stage II), followed by an increase to a higher level during stage III. To represent these different infectivities for I_1, I_2, and I_3, we set $\beta_1 = m_1\beta_2$, $\beta_3 = m_2\beta_2$, and estimate the constants m_1, m_2. On the other hand, the trated individuals have little contribution in transmission. The reduction of trasnmission due to treatment could reach as high as 96% [13]. Folowing this result, we considered $\beta = 0.04 \times \beta_2$. Since no treatment was available for the individuals with higher CD4+ T cell counts, we take $\tau_1 = 0$, and $\tau_2 = 0$ for data fitting.

The population [19, 48] corresponding to the year 1990 is taken as the initial value as the data begins at the year 1990. According to Day et al. [17] and Dorrington et al. [19], 37.08 million people lived in South Africa in 1990, among which 45% were adult (15-49 years). Using HIV prevalence data [48] and CD4+ T cell count distribution among HIV positive individuals [5] we calculated the initial population for our model to be $S(0) = 17.94$ million, $I_1(0) = 0.0163$ million, $I_2(0) = 0.009$ million, and $I_3(0) = 0.011$ million. Since there were no treatments available for HIV infected individuals in South Africa in 1990, the initial populations in treatment compartments are taken to be zero.

3.4.3 Data fitting

We fit the model (3.1) to the data (Table 3.3) to estimate nine parameters δ_1, δ_2, ρ_1, ρ_2, τ_3, m_1, m_2, a, and β_2. The parameters are estimated using MATLAB built-in functions 'ode45' and 'fmincon' to minimize the following error function

$$E = \sum_{i=1}^{i=23} \left(\frac{I_1(t_i) + I_2(t_i) + I_3(t_i) + T_1(t_i) + T_2(t_i) + T_3(t_i)}{N(t_i)} \times 100 - P(t_i) \right)^2,$$

where $I_1(t_i), I_2(t_i), I_3(t_i), T_1(t_i), T_2(t_i), T_3(t_i), N(t_i)$ are numerically computed model solutions at time t_i and $P(t_i)$ is the HIV prevalence data at time t_i.

3.5 Results

3.5.1 Model fit to the data

We obtained some of the model parameters from the primary literature [4, 6, 8, 29, 30], and estimated the remaining nine parameters by fitting the model to the World Bank data (Table 3.3) [48]. The model solution using the best parameter estimates along with the data are shown

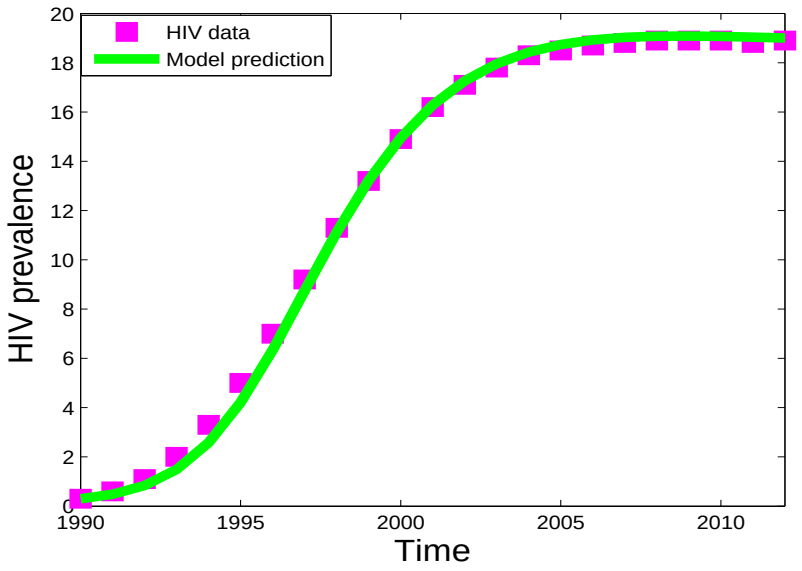


Figure 3.2: Data fitting result. The solid green curve shows the yearly adult prevalence of HIV infections predicted by the model and squares are the data (Table 3.3).

in Figure 3.2. The model fits the data very well. The set of parameter values that generates the best fit is given in Table 3.4.

3.5.2 Community immunity level

The immunity of individual is divided into three levels: high, intermediate, and low. The immunity level is high if CD4+ T cells count of the individual is above 500, intermediate if the count falls between 350 and 500, and low if the count is below 350. According to our model setting, individuals belonging to stage I (I_1 & T_1) have the high immunity level whereas individuals at stage II and stage III have intermediate and low immunity levels, respectively. The fraction of individuals in the community at each immunity level can be used as health indicators of the community and are important for public health management to control other opportunistic diseases. We define these fractions as community levels of immunity which we investigate under various HIV treatment programs. Our model predicts that in the presence of CD4+ T cell recovery, the high, intermediate and low immunity levels can reach to 90%, 8%, and 2%, respectively in 5 years. However, when recovery rates are considered to be absent ($\rho_1 = \rho_2 = 0$), those immunity levels become 51%, 32%, and 17%, respectively (Figure 3.3). These estimates thus show the effect of recovery of CD4+ T cells on immunity levels.

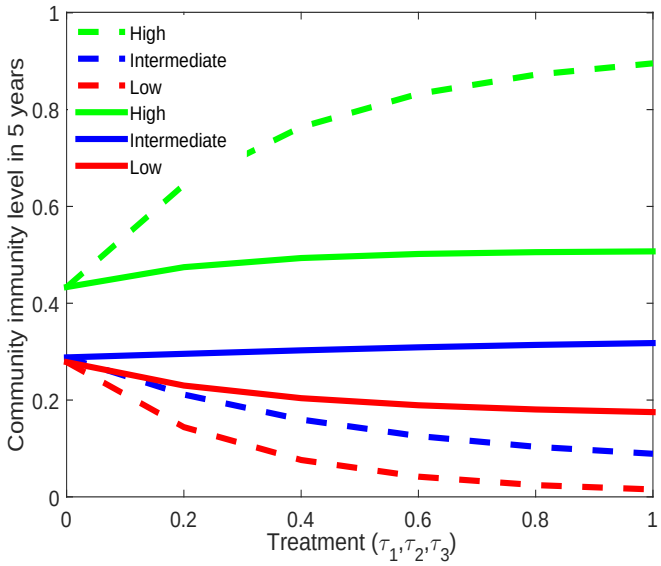


Figure 3.3: Community immunity level in 5 years under universal treatment with antiretroviral therapy. Solid curves show the immunity levels in absence of recovery of CD4+ T cells and dashed curves show the immunity levels in the presence of CD4+ T cells recovery.

3.5.3 HIV transmission

Our estimates show that the value of m_1 and m_2 are 12.57 and 4.54 indicating β_1 is about 13 times higher and β_3 is about 5 times higher than β_2. These estimates are consistent with the experimental results which found m_1 between 7 and 26 and m_2 between 2 and 6 [27, 40, 45]. These results show that HIV-infected individuals in stages I and III have more contribution than stage II to the transmission of HIV, thus implying that individuals in these groups (I & III) can be potential targets for treatment as prevention of HIV transmission. With these transmission rates, our model predicts that the total new infections generated in 5 years by the individuals in the stages I, II, III are 1.89 million, 0.11 million, and 0.47 million, respectively, without treatment, while they reduce to 0.58 million, 0.029 million, and 0.11 million, respectively, with treatment.

3.5.4 CD4+ T cell count loss and recovery

The disease progression rates estimated by our model are $\delta_1 = 0.33$ and $\delta_2 = 0.34$. That is, an HIV infected individual, if untreated, takes about 3 years, on average, to progress from stage I to stage II, and also 3 years from stage II to stage III. These progression rates are in agreement with the experimental results [26, 28, 32]. Our estimates of CD4+ T cell count recovery rates,

Table 3.4: Values of the estimated parameters .

Parameters	Estimated value (per year*)
β_2	0.082
m_1	12.57
m_2	4.54
ρ_1	0.57
ρ_2	0.82
δ_1	0.33
δ_2	0.34
τ_3	0.11
a	2.4744e-7 (*per number)
$\beta_1 = m_1\beta_2, \beta_3 = m_2\beta_2$	

$\rho_1 = 0.57, \rho_2 = 0.82$, show that with treatment HIV patients can recover CD4+ T cell count to the level of above 350 within 1 year on average and to the level of above 500 within the next 2 years on average. This finding of CD4+ T cell recovery rates is in agreement with the experimental results [29] in which the median of CD4+ T cell count is found to be increased from 180 to 350 in about 15 months and from 350 to 500 in about 21 months after initiation of ART.

3.5.5 Outcomes of treatment program

In this section, we evaluate the outcomes of various treatment programs on HIV epidemic. We particularly focus on the single group and the multiple group treatment programs. For the purpose of demonstration, we presented our simulation for the treatment rate from 0 to 1 per year. However, our simulation can be easily extended beyond to higher treatment rates. For longer term, our qualitative results do not change.

Single group treatment program

We estimated the total new infections generated during the five year period from 2015 to 2020 as a function of treatment rates τ_1, τ_2, τ_3 (Figure 3.4), implemented one at a time (single group). As expected, te results show that treatment can reduce infections significantly. However, it is important to note that treatment at stage I can reduce the total number of new infections by 50% and 45% more than those at stage II and stage III, respectively. More importantly, treatment at

stage I alone is more effective at reducing new infections than the treatments at stages II and III combined (Figure 3.4 a,b).

The effect of treatment on disease death is also remarkable. However, in contrast to the effect seen in preventing new infections, treatments at the different stages are not significantly different in preventing disease death during this 5 year period (Figure 3.5 a). Almost 30% of disease death can be reduced by implementing any of the single group treatment programs (i.e. τ_1 or τ_2 or $\tau_3 = 1$). This result is important as it predicts that the early treatment strategy might not be significantly beneficial in preventing deaths.

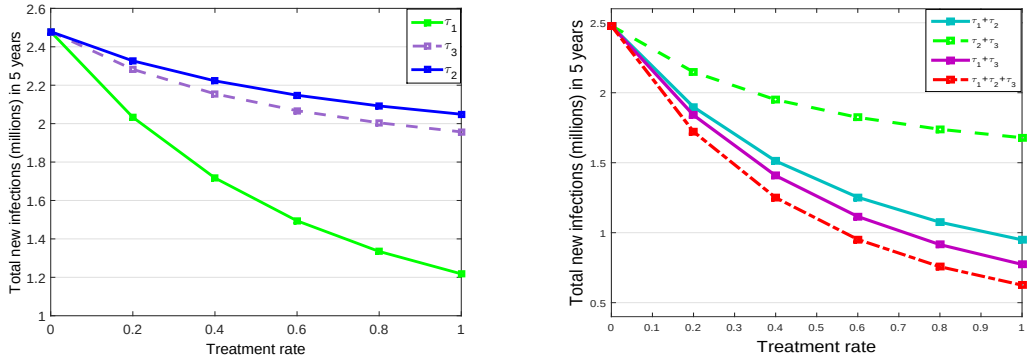
The yearly death avoidance (YDA) (number of individuals' lives saved per year) increases as the treatment rates increase (Figure 3.6 a-d). The YDA is also increased over time. In the first year, treatment at stage III has the highest YDA followed by treatment at stage II and stage I. After 3 years, however, a reverse order is observed, showing that the early treatment is beneficial in saving lives in a long run (or in the later part of the epidemic). On increasing treatment rates from 0.20 to 0.40 in any stage, the YDA can be increased by 1.5 fold in the 5th year (Figure 3.6 a, b). Similarly, an increase in treatment from 0.20 to 0.80 results in YDA twice as large in the 5th year (Figure 3.6 a, d).

We predict 10-year HIV prevalence under the single group treatment program. The prevalence can be reduced from 19% to 11%, 17% and 18% by treating individuals at stages I, II and III, respectively. These results show that treatment programs at stage I and II are less effective compared to stage I, to reduce the prevalence. We also observe a similar effect on the basic reproduction number, $\mathfrak{R}_0$. Treatment at stage I can reduce R_0 as much as 66% (from 3.3 to 1.1) while there is negligible effect of treatments at stages II and III on $\mathfrak{R}_0$. Unfortunately, single group treatment programs (at $\tau_i = 1,\ i = 1, 2, 3$) do not reduce $\mathfrak{R}_0$ below 1 indicating that the single group treatment program alone at this rate is not enough to eliminate the disease (Theorem 3.3.1).

Multi-group treatment program

We found that almost 80% of new infections can be reduced by universal treatment (at $\tau_i = 1,\ i = 1, 2, 3$), i.e. by treating individuals in all stages (Figure 3.4 b), which is almost twice as much as that achieved from any single group treatment. Only 30% reduction of new infections can be achieved by treatment at both stages II and III combined. With treatment programs combining stages I and II, or stages I and III, the total new infections can be reduced by 60% and 68%, respectively.

With treatment program focused on any two stages combined, the disease death can be



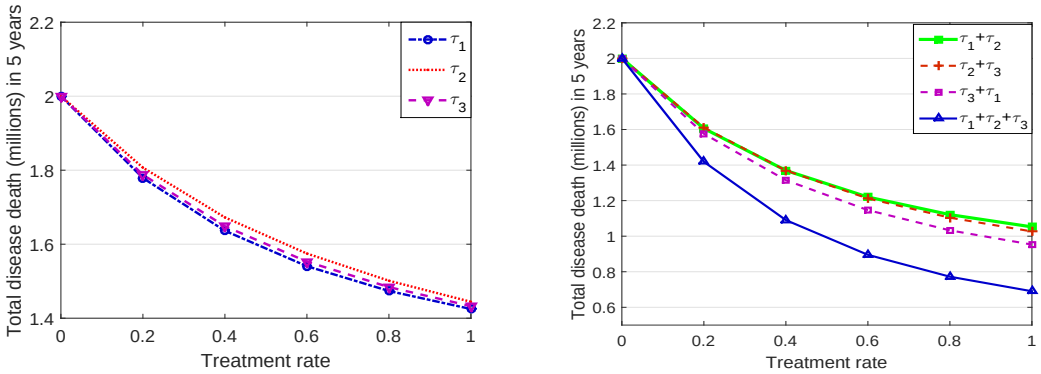
(a) (b)

Figure 3.4: Total new infections in five year period with (a) single group treatment program, (b) multi-group treatment program.

reduced by almost 50% in 5 years. In this case, the YDA can be achieved up to about 35% at 20% treatment level. When all three stages are included in the treatment program (universal treatment) the disease death can be reduced by 65% in 5 years (Figure 3.5 b). This reduction is twice as much as that achieved from any single group treatment program (Figure 3.5 a,b). By increasing the universal treatment rate to 0.80 the YDA can be achieved up to 85% (Figure 3.7 d).

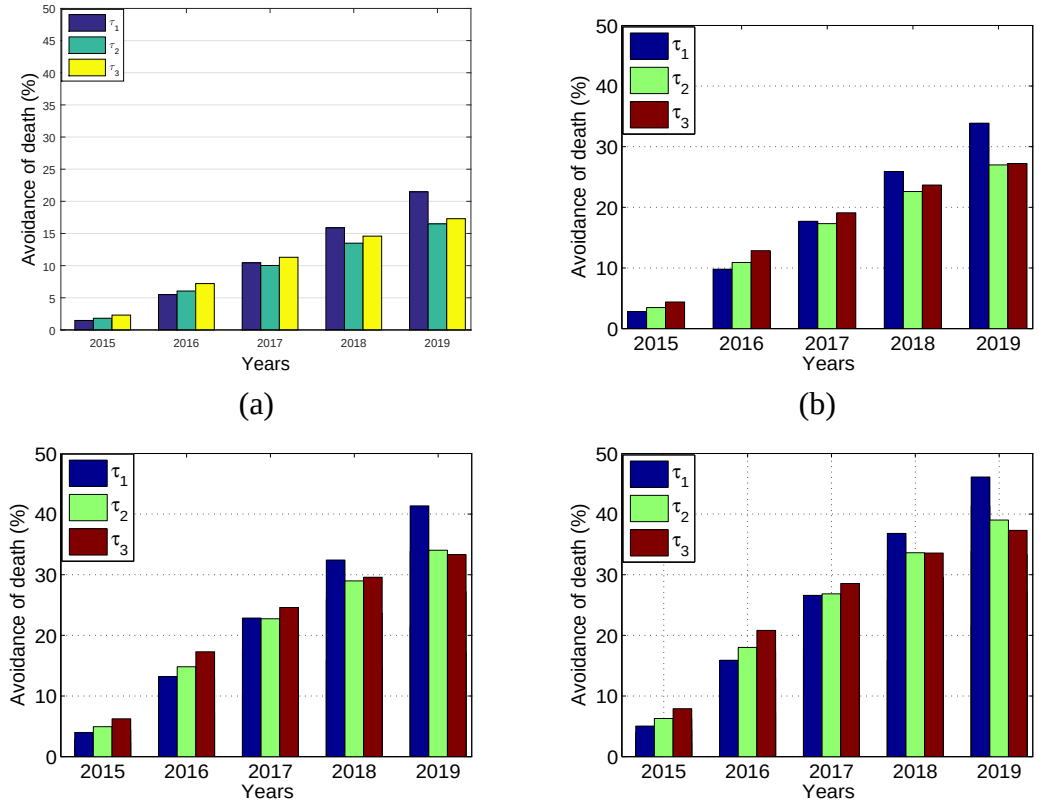
With universal treatment, HIV prevalence can be reduced from 19% to 11% in 10 years (Figure 3.8 b). The longterm prevalence under the universal treatment program predicted by our model shows that at least 50 years are required to reduce the prevalence to below 5% (Figure 3.8 c), indicating that treatment alone might not be an efficient way for reducing the current HIV prevalence in a relatively short time period.

We also computed $\mathfrak{R}_0$ under various treatment combinations. With treatment at stage II and stage III combined (i.e. $\tau_2 = \tau_3 = 1$), $\mathfrak{R}_0$ reduces from 3.30 to 2.67. The other treatment combinations (stage I and stage II or stage II and stage III, or stages I, II, and III) show significant effective in reduction of $\mathfrak{R}_0$. All of these remaining treatment combinations can reduce $\mathfrak{R}_0$ from 3.30 to 0.85 (Figure 3.9 b). Importantly, the universal treatment program can reduce $\mathfrak{R}_0$ to below 1. However, to reduce R_0 to below 1, a high treatment rate is required (Figure 3.9 b). The region in treatment-parameter space where $\mathfrak{R}_0 < 1$ is shown in Figure 3.10. Since treatment at stage II and stage III combined does not reduce $\mathfrak{R}_0$ to less than 1, we did not include this graph.



(a) (b)

Figure 3.5: Total AIDS death in five year period with (a) single group treatment program, (b) multi-group treatment program.



(a) (b)

(c) (d)

Figure 3.6: Yearly death avoidance (YDA) by single group treatment program, (a) treatment rate 0.20, (b) treatment rate 0.40, (c) treatment rate 0.60, (d) treatment rate 0.80.

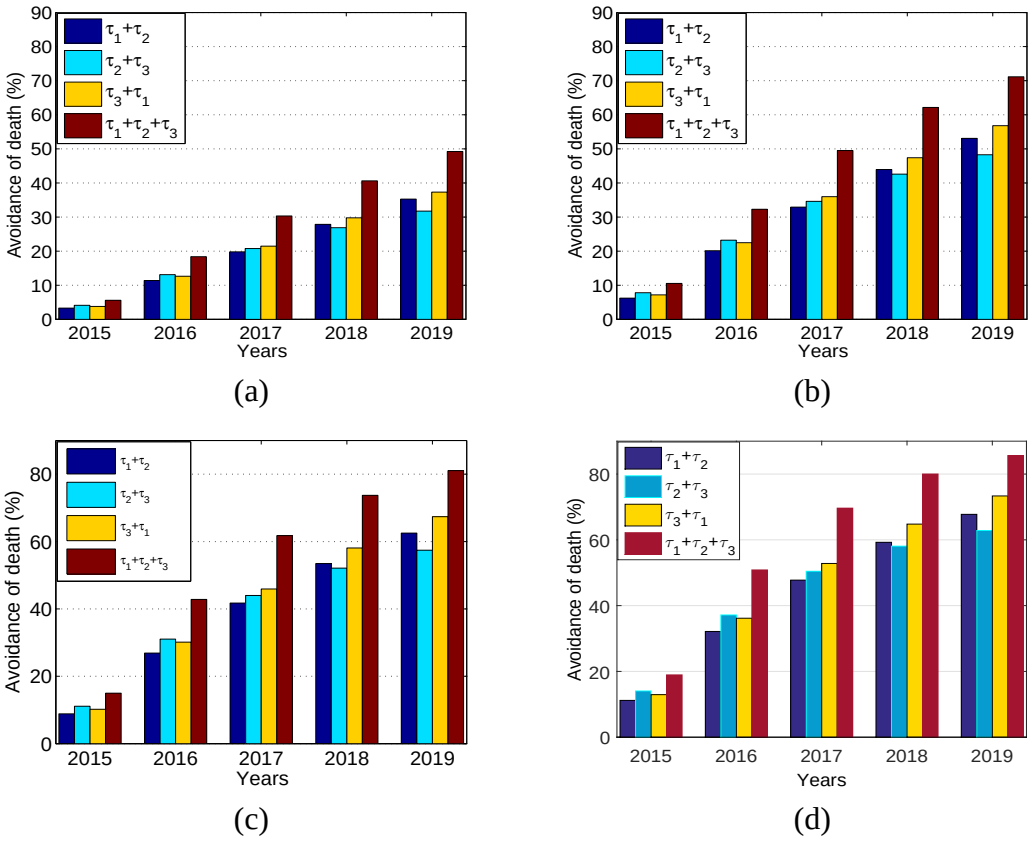
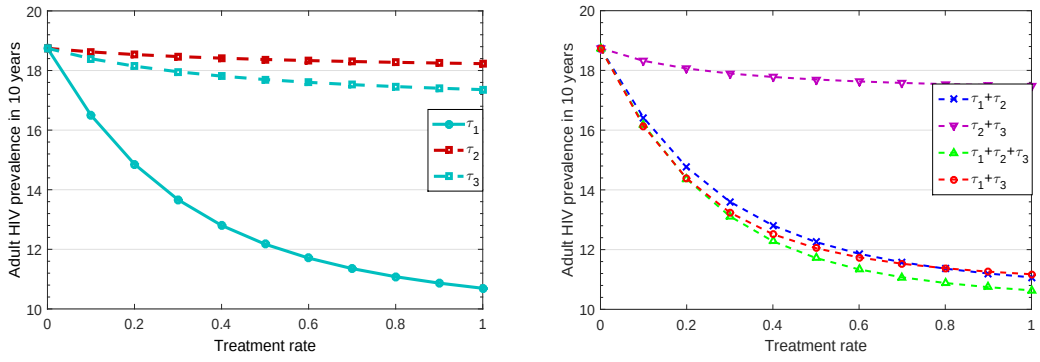
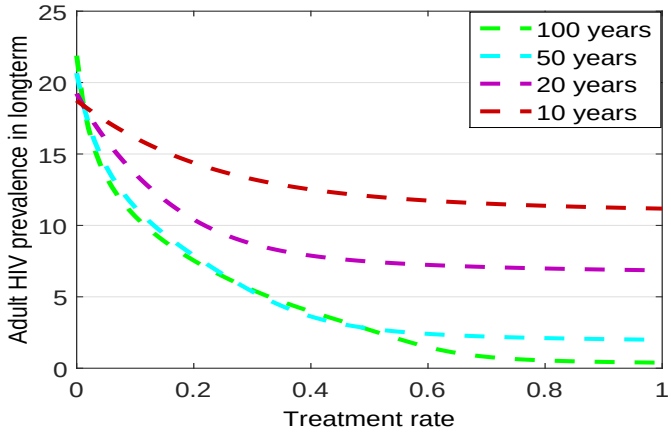


Figure 3.7: Yearly death avoidance (YDA) by multi group treatment program, (a) treatment rate 0.20, (b) treatment rate 0.40, (c) treatment rate 0.60, (d) treatment rate 0.80.

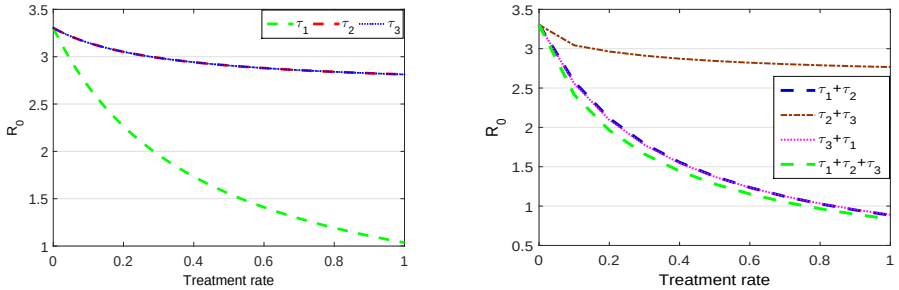


(a) (b)



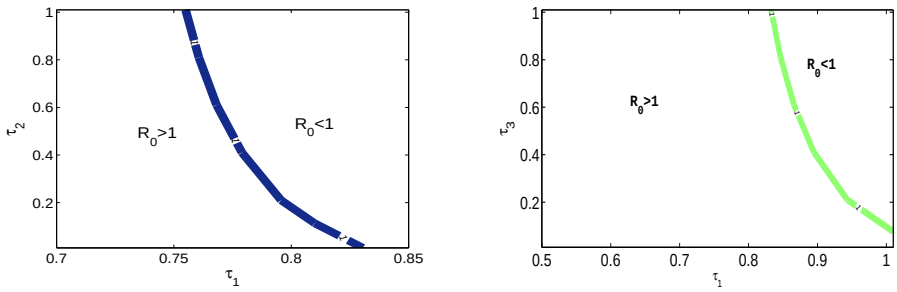
(c)

Figure 3.8: Model prediction of HIV prevalence under treatment program; (a) prevalence after 10 years with single group treatment program, (b) prevalence after 10 years with multi-group treatment program, (c) long term projections with universal treatment program.



(a) (b)

Figure 3.9: $\mathfrak{R}_0$ vs. treatment coverage level, (a) single group treatment program, (b) multi-group treatment program.



(a) (b)

Figure 3.10: Region where $\mathfrak{R}_0 < 1$ and $\mathfrak{R}_0 > 1$ (a) in τ_1-τ_2 parameter space, (b) in τ_1-τ_3 parameter space.

3.6 Discussion

Studies show that early ART can be a successful intervention for HIV infection. However, appropriate initiation timing of ART still remains unclear. This study takes the modeling approach to highlight the population dynamics of HIV infection under treatment programs with various initiation timing of ART. The model developed here is unique in the sense that it is based on individual's CD4+ T cell count, which is important in disease progression, HIV transmission and treatment decisions.

CD4+ T cells are key components of our immune system and the main target of HIV infection. The T cell count can reflect the overall strength of the immune system in an individual. As ART can aid recovery of CD4+ T cells in HIV infected individuals, inclusion of this recovery rate in modeling can predict the true effect of ART on the immune levels of treated individuals. Our model considers this recovery rate and predicts the immune levels of the HIV infected community with treatment programs. It also estimates the immune levels without this recovery rate and shows the effect of recovery on the immunity of the treated population (Figure 3.3). Thus, our model is suitable for evaluating the strength and timing of treatment programs. Moreover, our model has excellent agreement with HIV prevalence data for a long period (Figure 3.2).

Using our model, we evaluate the benefits of initiating ART at different CD4+ T cell count stages. We evaluate the effects of ART programs designed to target a single group or multiple groups in the population. Using a case study in South Africa, we found that early treatment (treatment at stage I) can reduce new infections by 2.5 fold more than treatment at stage II and treatment at stage III. It also shows that early treatment can reduce the total number of new infections by 25% more than treatment at stage II and stage III combined (Figure 3.4

a,b). Treatment at stage I also has a greater effect on adult prevalence and $\mathfrak{R}_0$ as compared to treatments at stage II and stage III. An early ART program prevents transmission of infections much earlier while late treatment allows HIV positive individual to spread infections for a longer period; as a result early treatment works better to reduce $\mathfrak{R}_0$ and adult prevalence in the long run. A study of universal testing with immediate ART [23] suggests that prevalence can be reduced to below 1% in 50 years; consistent with this, our study also finds that universal treatment at the 50% level can reduce the prevalence to less than 3% in 50 years (Figure 3.8, c).

In contrast, the timing of initiation of ART does not have a significant effect on the total disease death (Figure 3.5). However, treatment at stage III is more effective to avoid death at the beginning of the treatment program, while treatment at stage I is more beneficial in avoiding death in the long run or later part of the treatment program (Figure 3.6).

The universal treatment program shows a better outcome than single group treatment programs. In each of the cases of new infections, disease death, prevalence, and $\mathfrak{R}_0$, a universal treatment program can provide significantly more benefit than a single group treatment programs (Figure 3.4).

Treatment has significant effects on HIV transmission and prevalence, but it may not be able to eliminate the disease unless an extremely high proportion of HIV infected individuals is brought into the treatment program. Since this high coverage of ART is highly unlikely, elimination of disease is unlikely by ART alone and alternate interventions (such as condom promotion, pre-exposure prophylaxis etc.) should be implemented in combination.

Our model (3.1) captures some vital aspects of HIV dynamics and is in excellent agreement with the data [48]. The model however has several limitations. First, the model does not distinguish the population by sexes. Second, the model does not address the issues of adherence to ART and drug resistance. If a patient misses doses of ART and/or resistance arises, our results may be altered. Third, we did not distinguish individuals with known and unknown status and assumed that once an individual is HIV positive, he/she is able to start receiving ART if he/she belongs to the target group. Moreover, we ignore the possible behaviour changes of individuals after he/she becomes infected.

We explored a mathematical model to estimate the potential benefits of ART at the population level and to assess the impact on its time of initiation. Our results based on a South African population suggest that early ART has the potential to alter the epidemic greatly. The impact of ART on this South African population can be extrapoated to other countries or regions world wide. However, these results are subject to change with updates to ART efficacy and newly

available interventions.

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Chapter 4

Modelling the impact of vaccination on infectious disease dynamics

4.1 Introduction

Vaccine has a successful history since Edward Jenner's discovery of smallpox vaccine in the eighteenth century [17]. His innovation is widely regarded as the foundation of immunology. With the rapid pace of vaccine development medical science has saved millions of lives from dreadful diseases during the last two centuries. Small pox eradication can be worth mentioning as a successful example in this regard [1, 29]. Vaccines also contribute significantly to reducing infections of influenza, polio and many other life threatening diseases [20, 28]. In today's life it is unusual and rare for a child not to receive any vaccines.

A vaccine has similar physical properties to those of a pathogen. Similar to pathogens vaccines can stimulate the immune system of hosts and builds up antibody against the pathogen. Thus, whenever such a microorganism is encountered within a host, the immune system destroys it. This kind of phenomenon is known as immunity. Thus, as long as a vaccine for a disease is available, it is an ideal means of protecting healthy population from the disease.

An individual may receive vaccines available for a disease that is prevalent in his region. Vaccines of some diseases are already developed and one can take the vaccine if the particular disease is threaten for him. For example, an individual can take a polio vaccine or a seasonal flu vaccine which are already available. However, when a new infectious disease emerges but no vaccine is available for it, the disease may cause significant infections and deaths. It takes some time to devise an effective vaccine if successful.

Once a vaccine is available, a natural and immediate question arises: how to allocate and

implement this vaccine [30, 33]. Certainly we can not vaccinate all the individuals to eradicate the disease overnight. In addition to social and ethical issues, high cost may prevent universal distribution of vaccines [24]. Certain group of individuals may pose higher risk to the infections than the others. In influenza, for example, school-going children can be infected more easily and can spread the disease more rapidly than other individuals [9, 15, 19, 20]. Thus to control infections by using vaccines, a proper distribution and implementation strategy is very important. Priority may need to be given to certain group(s) or individuals by the health professionals. Current practice of vaccine allocation highlights the importance of identifying the groups which are at highest risk for adverse health [23]. Effectiveness of such a vaccine allocation strategy can be determined through analysis of a mathematical model. In this chapter, we aim to shed some light on this critical issue and hope to provide a useful guideline to the policymaker.

To properly implement the vaccination campaign, a plausible and intellectual idea may be to immunize individuals belonging to certain groups or locations that are most vulnerable to infections. The transmission rates in these groups are much higher than those in the other groups in which individuals are less susceptible or they are located in a comparatively safe area. The individuals in the target groups may need more protections so that the overall infections can be controlled effectively. In this chapter, we formulate and analyze a mathematical model that incorporates prioritized group-vaccination strategy.

The rest of this chapter is organized as follows. In Section 4.2, we formulate a two-group model based on the individual's risk status. The basic reproduction number of the model, the equilibria of the model and their stability, as well as the disease persistence are discussed in Section 4.3. Finally, in Section 4.4, we discuss the policy of vaccine allocation and distribution based on the model outcomes and offer some concluding remarks.

4.2 Mathematical Model

As indicated in the previous section, we divide the total population into two groups: the risky (r) group in which the transmission rates are much higher within the group; and the critical (c) group in which the individuals are conscious in their social behavior, or the individuals that remain isolated and are less likely to have contact with the infected group, and subsequently their transmission rate is much lower within the group.

Let the number of population in each group be divided into susceptible (S) and infected (I) sub-classes. Having infection from either infected sub-class, a susceptible individual becomes

infected and remains in that sub-class in his/her entire life. The susceptible individuals from each group are vaccinated at a constant rate and transferred into a common vaccinated (V) sub-class. We do not consider the vertical infection and assume that susceptibles are recruited at constant rates. The flow diagram of population is shown in Figure 4.1.

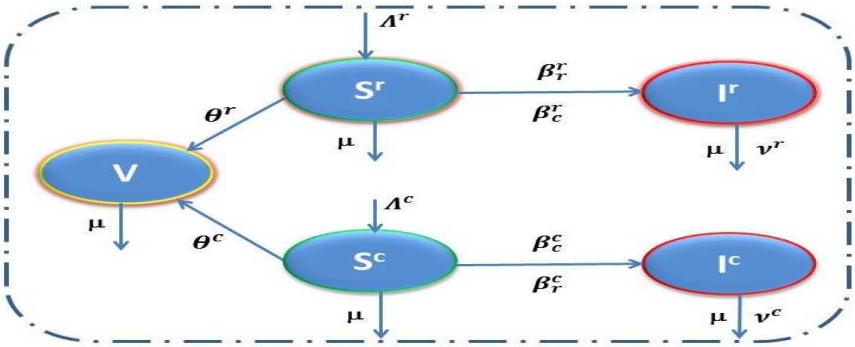

Figure 4.1: Schematic diagram.

As mentioned earlier, we consider two different groups in the population according to their risk level. The symbols and notations are explained in Table 4.1. The infection mechanism is considered to be followed by saturating incidence [2, 3, 14] defined by

$$h(I) = \frac{I}{1 + \alpha I}, \tag{4.1}$$

where $\alpha \geq 0$ determines the saturation level when the infectious population is large. When $\alpha = 0$, this reduces to the mass action incidence rate. The infection rate increases with the number of infected individuals when this number is small. As the infected number increases the infection rate becomes plateaued. This phenomenon reflects the saturation of infected numbers also known as 'crowding effect'. With this assumption the dynamics of the population is governed by the following equations.

$$\begin{cases} \dot{S^r} = \Lambda^r - \left(\beta_r^r \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^r \dfrac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \theta^r) S^r, \\ \dot{S^c} = \Lambda^c - \left(\beta_r^c \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^c \dfrac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \theta^c) S^c, \\ \dot{I^r} = \left(\beta_r^r \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^r \dfrac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\ \dot{I^c} = \left(\beta_r^c \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^c \dfrac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c, \\ \dot{V} = \theta^r S^r + \theta^c S^c - \mu V. \end{cases} \tag{4.2}$$

Table 4.1: Description of variables and parameters of model (4.3).

Parameter	Description
S^r	number of susceptible in group r
S^c	number of susceptible in group c
I^r	number of infected in group r
I^P	number of infected in group c
V	number of vaccinated individuals
N	total number of individuals
β_i^j	contact rate of susceptible and infective ($i, j = r, c$)
ν^i	disease induced death rate ($i = r, c$)
μ	natural death rate
θ^r	vaccination rate to the group r
θ^c	vaccination rate to the group c

We distinguish the groups according to contact rates and our assumption is

$$\beta_r^r \gg \beta_r^c \geq \beta_c^r \gg \beta_c^c.$$

4.3 Analysis of the model

4.3.1 Well-posedness of the model

The model (4.2) consists of five equations, but the last equation is decoupled. To analyze the model, it suffices to consider the dynamics of the following system

$$\begin{cases} \dot{S^r} = \Lambda^r - \left(\beta_r^r \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^r \dfrac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \theta^r) S^r, \\ \dot{S^c} = \Lambda^c - \left(\beta_r^c \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^c \dfrac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \theta^c) S^c, \\ \dot{I^r} = \left(\beta_r^r \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^r \dfrac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\ \dot{I^c} = \left(\beta_r^c \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^c \dfrac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c. \end{cases} \tag{4.3}$$

For biological reason, we need to investigate the boundedness and positivity of the solutions of our model. To this end, the first equation can be written as

$$\dot{S^r} = \Lambda^r - \phi(t) S^r,$$

where

$$\phi(t) = \beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c} + \mu + \theta^r.$$

It follows that

$$S^r = S_0^r e^{-\int_0^t \phi(s)ds} + \Lambda^r e^{-\int_0^t \phi(s)ds} \int_0^t e^{\int_0^\tau \phi(s)ds} d\tau,$$

which is non-negative as long as $S_0^r \geq 0$. Similarly, it can be shown that $S^c \geq 0$. To show that I^r and I^c are non-negative, consider the sub-system of (4.3)

$$\begin{cases} \dot{I}^r = \left(\beta_r^r \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^r \dfrac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\ \dot{I}^c = \left(\beta_r^c \dfrac{I^r}{1+\alpha_r I^r} + \beta_c^c \dfrac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c. \end{cases} \tag{4.4}$$

Since S^r and S^c are non-negative, this sub-system is cooperative. By monotone property [31] we conclude that I^r and I^c are non-negative provided that $I^r(0) \geq 0$ & $I^c(0) \geq 0$.

Now we consider the boundedness of the model. By adding all the equations in (4.3) it can be shown that the total number of individuals satisfies

$$\limsup_{t\to\infty} (S^r + S^c + I^r + I^c) \leq (\Lambda^r + \Lambda^c)/(\mu + \theta),$$

where $\theta = \min\{\theta^r, \theta^c\}$. Therefore, the biologically feasible region of the model (4.3) is

$$\Omega = \left\{(S^r, S^c, I^r, I^c) : S^r, S^c, I^r, I^c \geq 0, S^r + S^c + I^r + I^c \leq (\Lambda^r + \Lambda^c)/(\mu + \theta)\right\}.$$

4.3.2 Basic reproduction number

The model (4.3) has a disease-free equilibrium (DFE) $E_0 = (\Lambda^r/(\mu + \theta^r), \Lambda^c/(\mu + \theta^c), 0, 0)$, but there are no boundary endemic equilibria (i.e. one infected class is present while other is absent). The stability of E_0 is closely related to the notion of the basic reproduction number for the model, denoted by $\Re_0$, which plays an important role in determining the disease persistence. The number $\Re_0$ is defined as "the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual" (see, e.g., [7]). This threshold parameter determines whether the disease persists or dies out from the population. We use next-generation matrix [34] to compute $\Re_0$. The non-negative matrix F and the non-singular M-matrix T, known as new-infection and transition matrices respectively, for the system (4.3),

are given by

$$F = \begin{pmatrix} \beta_r^r \frac{\Lambda^r}{(\mu+\theta^r)} & \beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)} \\ \\ \beta_r^c \frac{\Lambda^c}{(\mu+\theta^c)} & \beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)} \end{pmatrix}, \quad T = \begin{pmatrix} \mu+\nu^r & 0 \\ 0 & \mu+\nu^c \end{pmatrix}.$$

It follows that

$$FT^{-1} = \begin{pmatrix} \beta_r^r \frac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} & \beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^c)} \\ \\ \beta_r^c \frac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^r)} & \beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)} \end{pmatrix}.$$

The basic reproduction number is then defined by

$$\Re_0 = \rho\left(FT^{-1}\right),$$

where $\rho(A)$ is the spectral radious of A. The explicit formula for $\Re_0$ is given in Section 4.4. By Theorem 2 in [34], we obtain the following result on the stability/instability of E_0.

Theorem 4.3.1 *If $\Re_0 < 1$, the DFE E_0 is locally asymptotically stable; E_0 is unstable if $\Re_0 > 1$.*

4.3.3 Global stability of E_0

In this section, we study the global stability of the DFE E_0 for the model (4.3). The *local* stability of E_0 is already established by Theorem 4.3.1; however we use this theorem to further obtain the *global* stability of E_0.

The Jacobian matrix of (4.3) at E_0 is given by

$$J(E_0) = \begin{pmatrix} -(\mu+\theta^r) & 0 & -\beta_r^r \frac{\Lambda^r}{(\mu+\theta^r)} & -\beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)} \\ 0 & -(\mu+\theta^c) & -\beta_r^c \frac{\Lambda^c}{(\mu+\theta^c)} & -\beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)} \\ \\ 0 & 0 & \beta_r^r \frac{\Lambda^r}{(\mu+\theta^r)} - (\mu+\nu^r) & \beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)} \\ 0 & 0 & \beta_r^c \frac{\Lambda^c}{(\mu+\theta^c)} & \beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)} - (\mu+\nu^c) \end{pmatrix}.$$

Clearly, $-(\mu+\theta^r)$ and $-(\mu+\theta^c)$ are two eigenvalues of $J(E_0)$ which are negative, and the other two eigenvalues are determined by the lower right block of $J(E_0)$, that is,

$$J_{22} = \begin{pmatrix} \beta_r^r \frac{\Lambda^r}{(\mu+\theta^r)} - (\mu+\nu^r) & \beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)} \\ \\ \beta_r^c \frac{\Lambda^c}{(\mu+\theta^c)} & \beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)} - (\mu+\nu^c) \end{pmatrix}.$$

Hence, the stability of E_0 fully depends on the matrix J_{22}.

For any given square matrix A, let $s(A)$ denote the stability modulu of A (i.e., the largest real part of all eigenvalues of A). Combining the above observation with Theorem 4.3.1, we immediately have following corollary.

Corollary 4.3.2 *If $\Re_0 < 1$, then $s(J_{22}) < 0$; if $\Re_0 > 1$, then $s(J_{22}) > 0$.*

We are now able to prove the following *global* result.

Theorem 4.3.3 *When $\Re_0 < 1$, E_0 is globally asymptotically stable.*

Proof: From the $\dot{S}^r$ equation in (4.3), we have $\dot{S^r} \leq \Lambda^r - (\mu + \theta^r)S^r$, which implies that

$$\limsup_{t\to\infty} S^r(t) \leq \frac{\Lambda^r}{\mu + \theta^r}.$$

Similarly,

$$\limsup_{t\to\infty} S^c(t) \leq \frac{\Lambda^c}{\mu + \theta^c}.$$

Thus, for any $\varepsilon > 0$, there exists $T_1 > 0$ such that

$$S^r(t) \leq \frac{\Lambda^r + \varepsilon}{(\mu + \theta^r)}, \;\; S^c(t) \leq \frac{\Lambda^c + \varepsilon}{(\mu + \theta^c)} \;\text{ for }\; t \geq T_1. \tag{4.5}$$

Applying the estimates in (4.5) to (4.4), we obtain

$$\begin{pmatrix} \dot{I}^r \\ \\ \dot{I}^c \end{pmatrix} = \begin{pmatrix} (\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c})S^r - (\mu + \nu^r)I^r \\ \\ (\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c})S^c - (\mu + \nu^c)I^c \end{pmatrix}$$

$$\leq \begin{pmatrix} (\beta_r^r I^r + \beta_c^r I^c)S^r - (\mu + \nu^r)I^r \\ \\ (\beta_r^c I^r + \beta_c^c I^c)S^c - (\mu + \nu^c)I^c \end{pmatrix}$$

$$\leq \begin{pmatrix} \beta_r^r \frac{\Lambda^r+\varepsilon}{(\mu+\theta^r)} - (\mu + \nu^r) & \beta_c^r \frac{\Lambda^r}{(\mu+\theta^r)} \\ \\ \beta_r^c \frac{\Lambda^c+\varepsilon}{(\mu+\theta^c)} & \beta_c^c \frac{\Lambda^c}{(\mu+\theta^c)} - (\mu + \nu^c) \end{pmatrix} \begin{pmatrix} I^r \\ I^c \end{pmatrix} \;\text{ for }\; t \geq T_1.$$

Thus, the sub-system (4.4) has an upper comparison system which is linear and cooperative with following coefficient matrix

$$A(\varepsilon) = \begin{pmatrix} \beta_r^r \frac{\Lambda^r+\varepsilon}{(\mu+\theta^r)} - (\mu+\nu^r) & \beta_c^r \frac{\Lambda^r+\varepsilon}{(\mu+\theta^r)} \\ \\ \beta_r^c \frac{\Lambda^c+\varepsilon}{(\mu+\theta^c)} & \beta_c^c \frac{\Lambda^c+\varepsilon}{(\mu+\theta^c)} - (\mu+\nu^c) \end{pmatrix}.$$

Obviously, $A(\varepsilon)$ depends on ε continuously and $A(0) = J_{22}$. Since $s(J_{22}) < 0$, by continuity, we can choose ε sufficiently small so that $s(A(\varepsilon)) < 0$. Thus, all solutions of this comparing linear system tend to $(0,0)^T$ as $t \to \infty$. By the standard comparison argument [31], we conclude that for every non-negative solution of (4.3), its I^r and I^c components also approach to 0 as $t \to \infty$.

The above established limits $I^r(t) \to 0$ and $I^c(t) \to 0$ as $t \to \infty$ indicate that the subsystem of (4.3) consisting of $\dot{S}^r$ and $\dot{S}^c$ equations has the following limit system:

$$\begin{cases} \dot{S^r} = \Lambda^r - (\mu+\theta^r)S^r, \\ \dot{S^c} = \Lambda^c - (\mu+\theta^c)S^c. \end{cases} \tag{4.6}$$

Since every solution of (4.6) tends to $(\Lambda^r/(\mu+\theta^r), \Lambda^c/(\mu+\theta^c))^T$, by the theory of asymptotically autonomous systems (see,e.g., Castillo-Chaves and Thieme [6]), the $(S^r(t), S^c(t))$ portion of any non-negative solution of (4.3) also approaches $(\Lambda^r/(\mu+\theta^r), \Lambda^c/(\mu+\theta^c))^T$. Therefore, every non-negative solution of (4.3) converges to the disease free equilibrium E_0. The global attractiveness of E_0 and the local stability established in Theorem 4.3.1 lead to the global asymptotical stability of E_0, completing the proof of the theorem. ∎

4.3.4 Persistence of the disease

When $\Re_0 > 1$, the DFE becomes unstable and it is natural to expect that the infectious populations I^r and I^c will remain persistent in this case. In this sub-section, we confirm this expectation. Indeed, we will prove the following theorem.

Theorem 4.3.4 *Assume that* $\Re_0 > 1$. *Then the disease is uniformly persistent in the sense that there exists an* $\eta > 0$ *such that for every positive solution of* (4.3), *there holds*

$$\liminf_{t\to\infty} I^r(t) > \eta, \quad \liminf_{t\to\infty} I^c(t) > \eta.$$

Moreover, there exists an endemic equilibrium E_* *in this case.*

Proof. We shall apply a theorem in [32] to prove the uniform persistence. To this end, we set

$$\begin{aligned} X &= \Big\{(S^r, S^c, I^r, I^c) \in \mathbb{R}^4_+\Big\}, \\ X_0 &= \Big\{(S^r, S^c, I^r, I^c) \in X : I^r, I^c > 0\Big\}, \\ Y &= X/X_0 = \Big\{(S^r, S^c, I^r, I^c) \in X : \textit{and } I^r = 0 \textit{ or } I^c = 0\Big\}. \end{aligned}$$

Now we show that the system (4.3) is uniformly persistent with respect to (X_0, Y). Since Y contains only a single equilibrium E_0, we need to show that $W^s(E_0) \cap X_0 = \phi$, where $W^s(E_0)$ denotes the stable manifold of E_0. Suppose this is not true. Then there is a $(S^r_0, S^c_0, I^r_0, I^c_0) \in X_0$ and the corresponding solution of (4.3) with this initial point satisfies

$$\lim_{t\to\infty}(S^r(t), S^c(t), I^r(t), I^c(t)) \to (\Lambda^r/(\mu+\theta^r), \Lambda^c/(\mu+\theta^c), 0, 0).$$

Thus, for any $\xi > 0$, there is $T_2 > 0$ such that

$$\begin{aligned} &(\Lambda^r - \xi)/(\mu+\theta^r) \le S^r \le (\Lambda^r + \xi)/(\mu+\theta^r), \\ &(\Lambda^c - \xi)/(\mu+\theta^c) \le S^c \le (\Lambda^c + \xi)/(\mu+\theta^c), \quad \text{for } t \ge T_2. \\ &0 \le I^r \le \xi,\ 0 \le I^c \le \xi, \end{aligned} \tag{4.7}$$

It follows from (4.3) and (4.7) that

$$\begin{pmatrix} \dot{I}^r \\ \\ \dot{I}^c \end{pmatrix} \ge \begin{pmatrix} \beta^r_r \frac{\Lambda^r-\xi}{\mu+\theta^r}\frac{1}{1+\alpha_r\xi} - (\mu+\nu^r) & \beta^r_c \frac{\Lambda^r-\xi}{\mu+\theta^r}\frac{1}{1+\alpha_c\xi} \\ \\ \beta^c_r \frac{\Lambda^c-\xi}{\mu+\theta^c}\frac{1}{1+\alpha_r\xi} & \beta^c_c \frac{\Lambda^c-\xi}{\mu+\theta^c}\frac{1}{1+\alpha_c\xi} - (\mu+\nu^c) \end{pmatrix} \begin{pmatrix} I^r \\ \\ I^c \end{pmatrix},$$

$$=: \tilde{J}(\xi) \begin{pmatrix} I^r \\ \\ I^c \end{pmatrix}, \quad \text{for } t \ge T_2.$$

This means that the subsystem (4.4) has a lower comparison system which is linear and coop-

erative with the coefficient matrix

$$\tilde{J}(\xi) = \begin{pmatrix} \beta_r^r \frac{\Lambda^r - \xi}{\mu + \theta^r} \frac{1}{1+\alpha_r \xi} - (\mu + \nu^r) & \beta_c^r \frac{\Lambda^r - \xi}{\mu + \theta^r} \frac{1}{1+\alpha_c \xi} \\ \\ \beta_r^c \frac{\Lambda^c - \xi}{\mu + \theta^c} \frac{1}{1+\alpha_r \xi} & \beta_c^c \frac{\Lambda^c - \xi}{\mu + \theta^c} \frac{1}{1+\alpha_c \xi} - (\mu + \nu^c) \end{pmatrix}.$$

Note that $s(\tilde{J}(\xi))$ is continuous in ξ and $s(\tilde{J}(0)) > 0$ (since $\Re_0 > 1$), we can choose $\xi > 0$ sufficiently small such that $s(\tilde{J}(\xi)) > 0$, implying that positive solutions of the lower comparing system grow exponentially. By the standard comparison argument, $I^r(t)$ or/and $I^c(t)$ components of the solution of (4.3) grow unbounded as $t \to \infty$. This is a contradiction to the fact that the solutions of the system (4.3) are ultimately bounded. Therefore, $W^s(E_0) \cap X_0 = \phi$. Now the persistence of the system (4.3) follows from the Theorem 4.6 in [32]. Further more, by Theorems 3.3 in [13], we know that uniform persistence and the dissipativity established in previous sub-section implies that system (4.3) has an endemic equilibrium (i.e. all components are positive) E_*. The proof of the theorem is completed. ∎

The stability of E_* will be discussed in the next sub-section.

4.3.5 Global stability of E_*

In this sub-section, we investigate the global stability of the endemic equilibrium E_* under the condition $\Re_0 > 1$. To this end, we apply a Lyapunov function similar to those recently used by [11, 16, 21]. Such Lyapunov functions take advantage of the properties of the function

$$g(x) = x - 1 - \ln(x), \tag{4.8}$$

which is positive in $(0, \infty)$ except at $x = 1$ where it vanishes. For convenience of notations in constructing Lyapunov functions, we also make use of the following two functions:

$$f_i(x) = \frac{x}{1 + \alpha_i x}, \quad i = c, r.$$

Now we establish following result.

Theorem 4.3.5 *The endemic equilibrium $E_* = (S_*^r, S_*^c, I_*^r, I_*^c, V_*$ is globally attractive whenever it exists.*

Proof: Consider the Lyapunov function

$$L = S_*^r g\left(\frac{S^r}{S_*^r}\right) + S_*^c g\left(\frac{S^c}{S_*^c}\right) + I_*^r g\left(\frac{I^r}{I_*^r}\right) + I_*^c g\left(\frac{I^c}{I_*^c}\right) + V_* g\left(\frac{V}{V_*}\right).$$

Obviously, V is non-negative in the positive cone Ω and attains zero at E_*. We need to show that $\dot{L}$ is negative definite. Differentiating V along the trajectories of (4.2), we obtain

$$\begin{aligned}
\dot{L} &= \left(1-\frac{S^r_*}{S^r}\right)\dot{S}^r + \left(1-\frac{S^c_*}{S^c}\right)\dot{S}^c + \left(1-\frac{I^r_*}{I^r}\right)\dot{I}^r + \left(1-\frac{I^c_*}{I^c}\right)\dot{I}^c + \left(1-\frac{V_*}{V}\right)\dot{V} \\
&= \left(1-\frac{S^r_*}{S^r}\right)\left(\Lambda^r - \beta^r_r\frac{I^rS^r}{1+\alpha_rI^r} - \beta^r_c\frac{I^cS^r}{1+\alpha_cI^c} - (\mu+\theta^r)S^r\right) \\
&+ \left(1-\frac{S^c_*}{S^c}\right)\left(\Lambda^c - \beta^c_r\frac{I^rS^c}{1+\alpha_rI^r} + \beta^c_c\frac{I^cS^c}{1+\alpha_cI^c} - (\mu+\theta^c)S^c\right) \\
&+ \left(1-\frac{I^r_*}{I^r}\right)\left(\beta^r_r\frac{I^rS^r}{1+\alpha_rI^r} + \beta^r_c\frac{I^cS^r}{1+\alpha_cI^c} - (\mu+\nu^r)I^r\right) \\
&+ \left(1-\frac{I^c_*}{I^c}\right)\left(\beta^c_r\frac{I^rS^c}{1+\alpha_rI^r} + \beta^c_c\frac{I^cS^c}{1+\alpha_cI^c} - (\mu+\nu^c)I^c\right) \\
&+ \left(1-\frac{V_*}{V}\right)(\theta^rS^r + \theta^cS^c - \mu V)\,.
\end{aligned}$$

Now using the equilibrium equation at E_* and simplifying, we have

$$\begin{aligned}
\dot{L} &= \beta^r_rS^r_*f_r(I^r_*)\left[2 + \frac{f_r(I^r)}{f_r(I^r_*)} - \frac{I^r_*S^rf_r(I^r)}{I^rS^r_*f_r(I^r_*)} - \frac{S^r_*}{S^r} - \frac{I^r}{I^r_*}\right] \\
&+ \beta^r_cS^r_*f_c(I^c_*)\left[2 + \frac{f_c(I^c)}{f_c(I^c_*)} - \frac{I^r_*S^rf_c(I^c)}{I^rS^r_*f_c(I^c_*)} - \frac{S^r_*}{S^r} - \frac{I^r}{I^r_*}\right] \\
&+ \beta^c_rS^c_*f_r(I^r_*)\left[2 + \frac{f_r(I^r)}{f_r(I^r_*)} - \frac{I^c_*S^cf_r(I^r)}{I^cS^c_*f_r(I^r_*)} - \frac{S^c_*}{S^c} - \frac{I^c}{I^c_*}\right] \\
&+ \beta^c_cS^c_*f_c(I^c_*)\left[2 + \frac{f_c(I^c)}{f_c(I^c_*)} - \frac{I^c_*S^cf_c(I^c)}{I^cS^c_*f_c(I^c_*)} - \frac{S^c_*}{S^c} - \frac{I^c}{I^c_*}\right] \\
&+ \mu S^r_*\left(2 - \frac{S^r_*}{S^r} - \frac{S^r}{S^r_*}\right) + \mu S^c_*\left(2 - \frac{S^c_*}{S^c} - \frac{S^c}{S^c_*}\right) \\
&+ \theta^rS^r_*\left(3 - \frac{S^r_*}{S^r} - \frac{V}{V_*} - \frac{S^rV_*}{S^r_*V}\right) + \theta^cS^c_*\left(3 - \frac{S^c_*}{S^c} - \frac{V}{V_*} - \frac{S^cV_*}{S^c_*V}\right).
\end{aligned}$$

In the above expression the last four terms are obviously non-positive. We only need to show that the terms in the square brackets are non-positive. Due to similarity we only deal with one group of square brackets and show that it is non-positive. By using g function defined in (4.8),

we proceed with the expression of first square bracket of the last equation as

$$\begin{aligned}
&2 + \frac{f_r(I^r)}{f_r(I^r_*)} - \frac{I^r_* S^r f_r(I^r)}{I^r S^r_* f_r(I^r_*)} - \frac{S^r_*}{S^r} - \frac{I^r}{I^r_*} \\
&= -g\left(\frac{S^r}{S^r_*}\right) - \ln\left(\frac{S^r_*}{S^r}\right) - g\left(\frac{I^r_* S^r f_r(I^r)}{I^r S^r_* f_r(I^r_*)}\right) - \ln\left(\frac{I^r_* S^r f_r(I^r)}{I^r S^r_* f_r(I^r_*)}\right) + \frac{f_r(I^r)}{f_r(I^r_*)} - \frac{I^r}{I^r_*} \\
&\leq -\ln\left(\frac{I^r_* f_r(I^r)}{I^r f_r(I^r_*)}\right) + \frac{f_r(I^r)}{f_r(I^r_*)} - \frac{I^r}{I^r_*} \\
&= -\ln\left(\frac{1+\alpha_r I^r_*}{1+\alpha_r I^r}\right) + \frac{I^r}{I^r_*}\left(\frac{1+\alpha_r I^r_*}{1+\alpha_r I^r}\right) - \frac{I^r}{I^r_*}.
\end{aligned}$$

Now we show that the above quantity is non-positive. Let

$$H(x) = -ln\left(\frac{1+ax_0}{1+ax}\right) + \frac{x}{x_0}\frac{1+ax_0}{1+ax} - \frac{x}{x_0}.$$

Taking the derivative, we have

$$H'(x) = \frac{1}{(1+ax)^2 x_0}\left[ax_0(1+ax) + 1 + ax_0 - (1+ax)^2\right].$$

Note that $H'(x)$ only has a positive zero x_0. It is easy to see that $H(x)$ attains the maximum $H(x_0) = 0$ only at x_0. Consequently, $\dot{L} \leq 0$ with equality holding only at the equilibrium E_*. By [12], all positive solutions approach $\mathcal{M}$, the largest invariant subset of the set $\{\frac{dL}{dt} = 0\}$. Since $\frac{dL}{dt}$ is zero only at E_*, $\mathcal{M} = \{E_*\}$ is a singleton set. Thus, the equilibrium E_* is globally attractive. ∎

4.4 Discussion

In this chapter we aim to investigate the vaccine implementation policy of an infectious disease in a resource constrained environment. Transmission of a disease largely depends on the nature of infected individuals, locations, modes of transmission, infection-causing organisms. Certain group(s) of people may have high risk of receiving and transmitting infections whereas other individuals exhibit less susceptibility and infectivity. Therefore, the infection of disease significantly depends on individual's risk level. Considering this fact, we have proposed a simple two-group model incorporating vaccination rates. In our analysis, the model demonstrate a global threshold dynamics in terms of the combined parameter $\Re_0$ — the secondary infection rate referred to as the basic reproduction number, as described in Theorem 4.3.1, Theorem 4.3.3, Theorem 4.3.4 and Theorem 4.3.5. More precisely, if $\Re_0 < 1$, then the disease will be

eliminated over time; and $\Re_0 > 1$ the disease will remain endemic and infectious populations will approach to positive constant levels.

Obviously, from the viewpoint of controlling the disease, one would naturally like to reduce the basic reproduction number. Thus, it is worthwhile to investigate how we can reduce $\Re_0$ effectively by a proper implementation of vaccines. Calculating the spectral radius of the next generation matrix FV^{-1} gives the following explicit formula for $\Re_0$:

$$\Re_0 = \frac{1}{2}\left[\frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} + \frac{\beta_c^c\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}\right.$$

$$\left. + \sqrt{\left(\frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} - \frac{\beta_c^c\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}\right)^2 + \frac{4\beta_c^r\beta_r^c\Lambda^r\Lambda^c}{(\mu+\theta^r)(\mu+\nu^r)(\mu+\theta^c)(\mu+\nu^c)}}\right]$$

$$= \frac{1}{2}\left[\beta_r^rG_r^r + \beta_c^cG_c^c + \sqrt{(\beta_r^rG_r^r - \beta_c^cG_c^c)^2 + 4\beta_c^r\beta_r^cG_c^rG_r^c}\right],$$

where

$$G_r^r = \frac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)}, \quad G_c^r = \frac{\Lambda^c}{(\mu+\theta^r)(\mu+\nu^c)},$$
$$G_r^c = \frac{\Lambda^r}{(\mu+\theta^c)(\mu+\nu^r)}, \quad G_c^c = \frac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}.$$

Based on the above formula, we have following observations on $\Re_0$.

Observation I: The two groups are weakly connected

In this case, the contact matrix is nearly reducible, that is, at least one of the cross contact rates β_c^r or β_r^c is near 0. Then, the threshold parameter $\Re_0$ has the following approximation:

$$\Re_0 \approx \frac{1}{2}\left[\beta_r^rG_r^r + \beta_c^cG_c^c + |(\beta_r^rG_r^r - \beta_c^cG_c^c)|\right] = max\{\beta_r^rG_r^r, \beta_c^cG_c^c\}.$$

Due to higher contact rate of risky group, we may assume that $\beta_r^rG_r^r > \beta_c^cG_c^c$. Then we have

$$\Re_0 \approx \beta_r^rG_r^r = \frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)}.$$

That is, $\Re_0$ does not depend on vaccination of critical group anymore. Moreover, $\Re_0$ is decreasing with θ^r (the vaccination rate of risky group). The vaccination rate has positive effect on the reduction of disease. The condition $\beta_r^rG_r^r > \beta_c^cG_c^c$ will hold in a region where the disease is

highly infectious (just like Ebola outbreak in West African countries [8, 18]). In this situation, when question arises on vaccine implementation, "vaccine to risky group only" strategy would be better policy. This policy seems to be more crucial when vaccines are economically costly and insufficient, and more doses are required to provide full-immunity. Providing enough doses to the risky individuals rather than single shot to randomly chosen individuals from both groups should be more effective to control disease.

Now we consider the case $\beta_r^r G_r^r < \beta_c^c G_c^c$ which may occur when the recruitment to risky group is significantly smaller than that in the critical group. This scenario prevails in a region where comparatively greater portion of the population are less susceptive (small β_c^c) and incoming susceptibles with lower susceptibility are also considerably larger (big Λ^c) in the respective group. By symmetry, the basic reproduction number becomes

$$\mathfrak{R}_0 \approx \beta_c^c G_c^c = \frac{\beta_c^c \Lambda^c}{(\mu + \theta^c)(\mu + \nu^c)}.$$

It is surprising that vaccine to the risky individuals do not bring any benefit to reduce $\mathfrak{R}_0$. Because of weak connections ($\beta_c^r \approx 0$ or $\beta_r^c \approx 0$) between the groups, the risky group could not deteriorate the disease situation in the whole population. However, the susceptible individuals in risky group are more vulnerable to infection. So, if vaccines are available they also need to be immunized to protect them even though this vaccination may not have a major effect on global disease control.

Observation II: Both groups are strongly connected

Now we investigate the scenario when both groups are strongly connected (i.e. contacts matrix is irreducible). Assume that both cross-contact rates β_c^r and β_r^c are positive. We need to look into the threshold parameter $\mathfrak{R}_0$ more deeply. Observe that $\mathfrak{R}_0$ depends on four compound parameters $\beta_r^r G_r^r$, $\beta_c^r G_c^r$, $\beta_r^c G_r^c$ and $\beta_c^c G_c^c$. So we need to determine the key parameter among the following four components

$$\beta_r^r G_r^r = \frac{\beta_r^r \Lambda^r}{(\mu + \theta^r)(\mu + \nu^r)}, \quad \beta_c^r G_c^r = \frac{\beta_c^r \Lambda^r}{(\mu + \theta^r)(\mu + \nu^c)},$$

$$\beta_r^c G_r^c = \frac{\beta_r^c \Lambda^c}{(\mu + \theta^c)(\mu + \nu^r)}, \quad \beta_c^c G_c^c = \frac{\beta_c^c \Lambda^c}{(\mu + \theta^c)(\mu + \nu^c)},$$

that contribute more to increase $\mathfrak{R}_0$ in the absence of vaccination. Notice that the quantities differ significantly on $\beta_i^j G_i^j$ $(i, j = r, c)$. By the nature of grouping, it is assumed $\beta_i^r \gg \beta_i^c$ $(i = r, c)$ so that $\beta_i^r \Lambda^r > \beta_i^c \Lambda^c$ $(i = r, c)$. Therefore, increasing θ^r (vaccination rate in risky group)

would be more effective than uniform vaccination policy.

In this work, we divide the host into two groups for implementing vaccines effectively. However, in reality there may be no clearly well-defined line between the groups. Moreover, there may be more than two groups, differed by contact rates or risk factors etc. The immunization campaign may be administered by giving priorities to the groups having higher risk factor. The population may be grouped in different ways, but we would emphasize the importance of some grouping before initiating vaccine campaign.

Our model or the group-strategic method can be applied to implement vaccines or control measures in various infectious diseases, for example, influenza, measles or ebola. In fact, the grouping strategy can be found in the current practice of vaccine distributions [5, 20] and proven to be effective against a possible outbreak [33]. In influenza, school-going children are considered to be the most target group followed by elderly individuals [9, 25]. Vaccinating healthy children against influenza has the potential to reduce the epidemic [9, 15, 19, 20]. It is found that by vaccinating 70% school-going children the over-all influenza infection can be reduced to below the epidemic level [20]. The children posses less pre-immunity while encounter highest exposures- become easy target for transmission disease. The age-specific population with increased risk, pregnant women, individuals with critically illness and health workers could be other potential target groups. The group-strategic method can also be applied to HIV or STDs (sexually transmitted diseases). However, an appropriate model is required for STDs as our model (4.2) is, in general, not suitable to the STDs. STD can be spread more rapidly in some particular groups such as sexual workers, men-sex-with-men (MSM) group, injection-drug users (IDUs) and so on [4, 10]. These core groups should be given highest priority for allocating and implementing vaccines.

Another grouping of the host can be made through regional basis. A disease may outbreak in a certain region with facile transmissibility and high case fatality where as individuals in the other regions are comparatively safe due to geographical distance. The recent outbreak of Evola virus, for example, in West Africa threats with striking case fatality (50-90%) and transmissibility [8, 18, 22, 26]. The individuals surrounding the region are highly risky than those are in the outer world. In this scenario, the individuals in that region should be vaccinated with utmost priority. Next preference may be given to the health workers of outer region. Since they are among the first line of exposures. As reported, some nurses in USA got infected while caring of Ebola infected patients [27].

While this study offers some guideline on vaccine implementations, our model has some limitations. We do not consider the behavior change or the movement between the two groups.

For simplicity, the model do not distinguish the infected population according to their disease progression (certain disease like HIV progress over the time) and uses a single transmission rate from all infected individuals. In our model (4.3), we do not distinguish the mode of transmission and population are not divided into sexes. In case of sexually transmitted disease (STD), an individual can be infected through sexual contact or by sharing needles; other diseases, like flu or dengue, can be spread through airborne or vector-borne transmissions. We also ignore vertical transmission (mother to new born) and passive immunity to keep the model simple.

Finally, our goal is to find out an optimal vaccination strategy, not to demonstrate a rigorous analysis of a mathematical model. The formulation of the model (4.3) may underestimate or overestimate the real $\mathfrak{R}_0$. However, this estimate does not influence the consequences of the outcome of our analysis. That is, the proper estimation of $\mathfrak{R}_0$ does not violate the grouping idea; rather it helps group management. The model can be improved by incorporating several realistic aspects. For example, to assert on immunization we may further investigate into the delay and waning of vaccine immunity, lack of vaccine efficacy and impact of vaccine complicacy. We leave these as possible future research projects.

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Chapter 5

Conclusions and future directions

In this thesis, we studied transmission and prevention mechanisms of some infectious diseases through mathematical models. Persistence of current infections and their possible dynamics under existing and new interventions are investigated. We also addressed global stability of some epidemic models.

In Chapter 1, we reviewed some basic features of infectious diseases, their orientation, historical background, and intervention efforts. This chapter also highlights the role of modelling and its challenges.

In Chapter 2, we considered an HIV model to project the effectiveness of tenofovir gel against HIV transmission and prevalence on the adult population of South Africa. This particular pre-exposure prophylaxis gel was experimented in a small scale near the Durban city of South Africa and showed 39%-54% effectiveness against women infection. Our model predicts that the tenofovir gel can reduce the population level transmission by up to 72% along with existing interventions. This study demonstrates that coverage and retention of gel are key factors that determine the optimum benefits from the gel and suggested that resistance can also affect the outcomes.

In Chapter 3, we developed an HIV model to demonstrate the consequences of antiretroviral treatment on the new infections, community immunity level, and long term prevalence. The model is based on CD4+ T cell counts that signify individual's immunity level. This study addressed the impact of various ART programs on the HIV epidemic and demonstrated the effect of ART on the community immunity levels. The study also demonstrated that early treatment is significantly effective as compared to delayed treatment program on HIV epidemic. Our results found that ART alone is unlikely to eliminate HIV, but it can significantly contribute to reduce the overall HIV transmission and prevalence, and to alter the current trend of HIV

dynamics.

In Chapter 4, we investigated the aspect of hierarchies of susceptible population in terms of their risk of susceptibility and how these hierarchies can determine the distribution policy of vaccines and others intervention tools. A mathematical model was developed to investigate the optimum strategy of vaccine distribution. This study suggest that susceptible populations should be divided into groups by risk status to secure optimum benefit from a vaccine campaign. Our results support the ongoing vaccine distribution strategy and its results for influenza.

We addressed certain aspects of the underlying problems and ignored several other aspects of those problems to keep the models simple. As further studies and future directions, one may include additional realistic features in our models. Some additional aspects include age-structure, latency delay, spatial heterogeneity and networking. These are all important aspects for some diseases and should be considered when modelling these diseases' dynamics.

In many infectious diseases such as Ebola, measures of control change continuously based on surveillance, intensity of infection, resource availability, and invention of new tools. One may investigate time dependency on transmission rate and other parameters of a model under a continuous changes of control measures. Drug resistance is a critical issue in HIV infection. By including drug resistance in HIV models (Chapters 2 & 3), we may improve modelling outcomes significantly .

Curriculum Vitae

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