

Dynamics of an HIV/AIDS Model that Incorporates
Pre-exposure Prophylaxis

by

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Abstract

This thesis is based on the use of mathematical theories, modelling, and simulations to study the transmission dynamics of HIV/AIDS in the presence of PrEP (pre-exposure prophylaxis) in the MSM (men who have sex with men) population in the United States. A new deterministic model for HIV/AIDS that incorporates PrEP is designed and used to assess the population-level impact of the use of PrEP on the transmission dynamics within an MSM population. Conditions for the effective control (or elimination) and persistence of HIV/AIDS in the MSM population are determined by rigorously analyzing this model. Uncertainty and sensitivity analysis is carried out, using data relevant to HIV transmission dynamics in the MSM community in the U.S. State of Minnesota, to determine the effect of the uncertainties in the parameter values on the outcome (response) variable (the associated reproduction number) and to identify the top-five parameters that have the most effect on the disease transmission dynamics. Numerical simulations show that HIV burden decreases with increasing PrEP coverage. HIV can be effectively controlled in the MSM population if at least [61% – 77%] of the susceptible MSM population can be on PrEP (adjusted by PrEP efficacy).

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Dedication

To my husband, Kevin Simpson, who has stood steadfast by my side and has provided never ending love and support through it all.

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Glossary

Abbreviation	Meaning
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
HIV	Human immunodeficiency virus
IDU	Intravenous drug user
LAS	Locally-asymptotically stable
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
PrEP	Pre-exposure prophylaxis

Chapter 1

Introduction

This chapter provides a brief overview of the HIV/AIDS epidemic in the United States.

1.1 HIV/AIDS

Since its inception in the 1980s, the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), remains one of the world's most serious public health and socio-economic challenges [22, 52]. The World Health Organization (WHO) estimates that 35.5 million people are currently living with HIV/AIDS, and that in 2013, 1.5 million people have died of HIV-related illnesses worldwide (Figure 1.1 depicts the global prevalence of adult HIV infection) [52]. The Centers for Disease Control and Prevention (CDC) estimates that up to 1.1 million people in the United States are living with HIV (and that nearly one in six of these people are unaware of their infection status) [9]. The annual number of new infections (incidence) is estimated to be about 50,000 in the U.S., and has remained relatively stable in recent years [9, 47].

HIV is transmitted sexually (*via* contact with infected bodily fluids such as blood, semen, pre-seminal fluid, rectal fluids, and vaginal fluids), vertically (from an infected

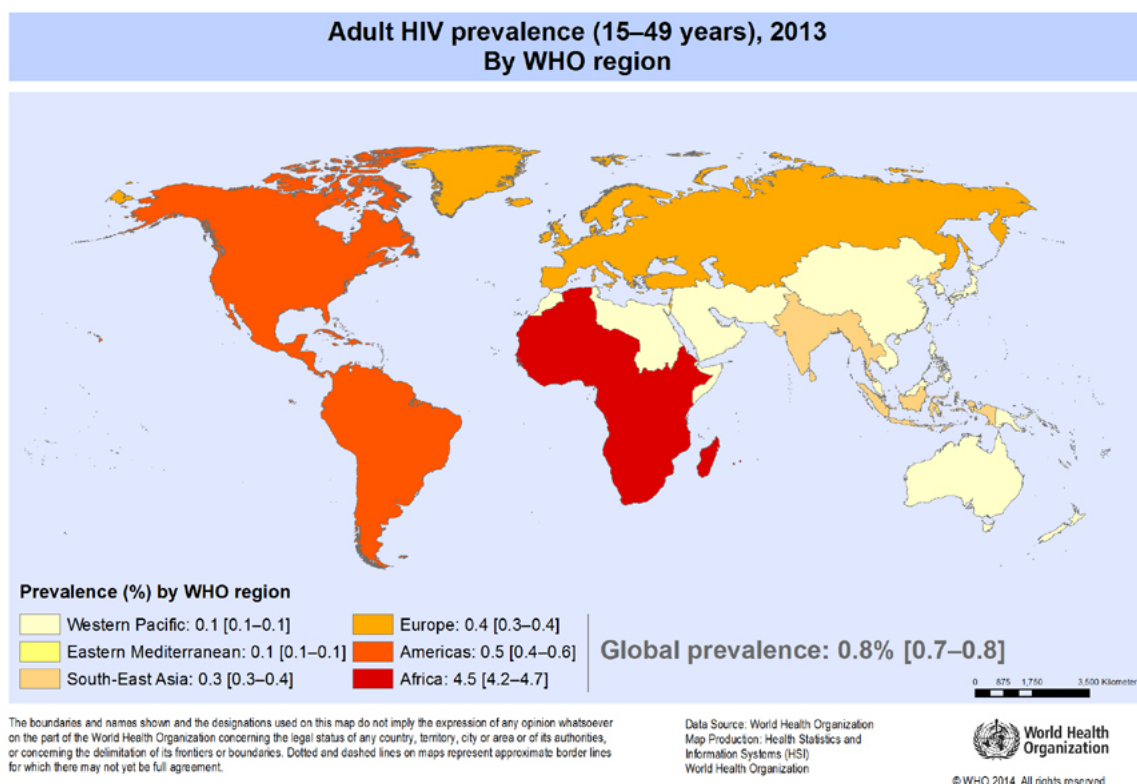


Figure 1.1: Worldwide Adult HIV Infection Prevalence [52].

mother to her child during pregnancy or child birth), through breastmilk, by sharing contaminated needles (among IDUs or within healthcare settings) and through blood transfusions [13, 47]. In order for transmission to occur, these infected bodily fluids must come into contact with mucous membranes or damaged tissue or be directly injected into the bloodstream [13, 47]. In the U.S., HIV is mainly spread sexually and by sharing needles, syringes, rinse water, or other equipment used to prepare injection drugs with someone infected with HIV [13]. It can also be spread less commonly by vertical transmission, occupational exposure, and rarely by organ transplants or blood transfusions [47]. The main risk groups in the U.S., by transmission category, are men who have sex with men (MSM), intravenous drug users (IDU), heterosexual individuals, and men who have sex with men that are also intravenous drug users (MSM-IDU) [9]. MSM of all races and ethnicities currently have the largest number

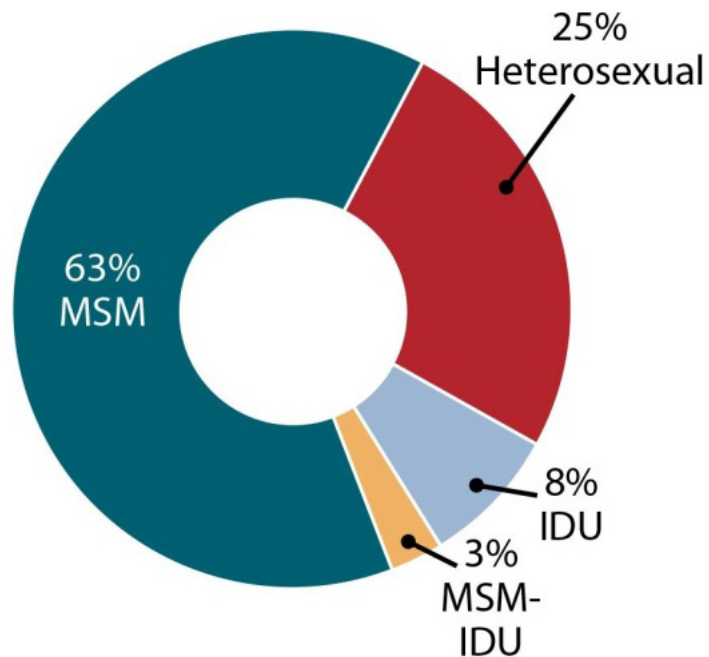


Figure 1.2: Estimated New HIV Infections by Route of Transmission, 2010 [9].

of new HIV infections and remain the group most severely affected by HIV in the United States [9]. Figure 1.2 depicts the percentage of estimated new HIV infections by route of transmission in the U.S. in 2010 [9].

1.2 Replication Cycle

The replication cycle of HIV disease (in the body of an infected host) starts when the virus infects a target $CD4^+$ T cell (also known as a helper T lymphocyte - a type of immune system cell) [3, 45, 37]. The virus binds to cell-surface CD4 receptors and co-receptors, and then fuses with the cell allowing the viral core to enter [3, 45, 37]. Once the viral core has entered the $CD4^+$ T cell, the virus is able to use the cell to replicate itself [3, 45, 37]. The virus also infects other CD4-bearing cells, such as monocytes, macrophages, and dendritic cells, but replicates most efficiently in $CD4^+$ T cells [3, 45, 33, 37]. The replication of HIV is essential for disease progression

to AIDS [3, 45, 33, 37]. This progression is observed *via* the following three main stages:

1.2.1 Acute stage

The acute stage (also known as the primary infection stage) is characterized by high viremia (high viral load; hence high probability of HIV transmission) [12, 24, 49]. The virus infects both quiescent and activated CD4⁺ T cells of the human host, although it primarily replicates in activated CD4⁺ T cells [54]. Initially, this replication at the site of infection is virtually unobstructed by the immune system [33]. The rate of viral replication is very high during this period, and is greater than the viral clearance rate [33].

This viral influx eventually triggers an immune system response, with the activation of B lymphocytes (antibody producing cells) and the production of virus-specific CD8⁺ cytotoxic T cells [3, 27, 33]. This process of developing antibodies is known as seroconversion, and takes place within the first 3-6 weeks of the viral replication process [2, 33]. The immune system response causes the virus to spread throughout the body by presenting the virus and viral infected cells to non-infected T cells in the lymph nodes [3, 27, 33]. Peak plasma viremia usually occurs within 21-28 days of infection [33]. During this peak, the CD4⁺ cell count drops, and many (but not all) infected individuals begin to feel flu-like symptoms, called “acute retroviral syndrome” (ARS) or “primary HIV infection” [12, 33, 49].

Symptoms, during this stage of infection, can include fever, sore throat, rash, muscle and joint pain, fatigue, and headache [33, 49]. Eventually the immune system response will suppress the virus and bring the viral load down to a viral set point allowing the CD4⁺ cell count to rebound, but typically not to pre-infection levels [12, 33, 49]. At this point the infected individual enters the chronic stage of the disease.

1.2.2 Chronic (asymptomatic) stage

The chronic (asymptomatic) stage of HIV infection is characterized by a decreased rate of viral replication (lower viral load) and a recovery of CD4⁺ cell counts (to near normal levels) [12, 33, 49]. Individuals tend to experience very mild symptoms or no symptoms [12, 33, 49]. Despite the fact that CD4⁺ cell counts increase during this stage, it has been well established that massive immune activation and an accelerated cell turnover takes place [33]. It is thought that this activation is a major driving force for immune exhaustion in HIV infection and helps lead to the progression to AIDS [33]. Towards the end of this stage, the viral load starts to increase, while the CD4⁺ cell count starts to decline (resulting in the weakening of the immune system) [12]. In the absence of antiretroviral therapy (ART) an infected individual will remain in this stage for a period of up to 10 years on average, before progressing to the AIDS stage [12, 49]. With antiretroviral treatment, individuals can remain in this stage for several decades, and may never progress to the AIDS stage [49].

1.2.3 AIDS stage

The AIDS stage is characterized by a high viral load and low CD4⁺ cell count (less than 200 *cells/mm*³) [12, 49]. This results in a greatly weakened immune system, and the infected individual succumbs to opportunistic infections (such as, *pneumocystis carinii pneumonia*, *Tuberculosis*, *mycobacterium avium complex*, Kaposi's sarcoma, etc...) [12, 49]. In the absence of anti-HIV treatment the AIDS patient typically succumbs to the disease within three years [12, 49]. A schematic description of the typical time course of HIV/AIDS infection in an untreated individual is given in Figure 1.3.

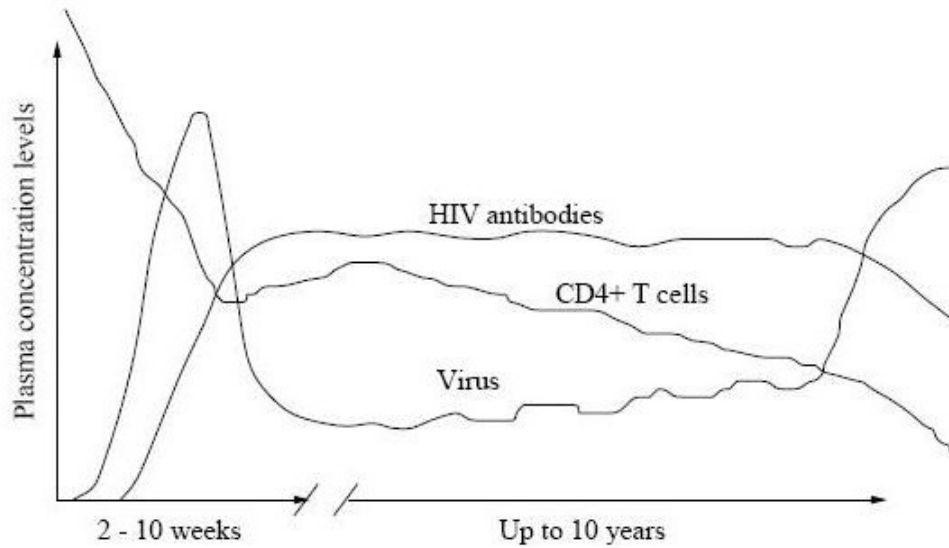


Figure 1.3: Time Course of HIV/AIDS in a Typical Infected Adult [36].

1.3 Control Strategies

Various preventive and therapeutic strategies are implemented to control the spread of HIV/AIDS in a population. These include condom use, voluntary HIV testing, public health education and counselling, access to sterile needles, and the use of ART [11]. In the U.S., for instance, the following are implemented; HIV testing and linkage to care, access to condoms and sterile syringes, prevention programs for people living with HIV and their partners, prevention programs for people at high-risk of HIV infection, substance abuse treatment, screening and treatment for other sexually transmitted diseases, and ART [11].

These control strategies have proven to be effective at reducing the risk of HIV infection in the U.S., especially when they are designed to address the social, economic, and structural factors that place specific groups at risk (resulting in a stable HIV incidence in recent years) [11]. However, although these strategies have slowed the spread of the disease, HIV remains a major public health concern in the United States (since it is yet to be eliminated). Consequently, there is an urgent need to formulate effective strategies.

1.3.1 Antiretroviral therapy

Antiretroviral therapy (ART) (also known as antiretrovirals (ARVs), highly-active antiretroviral therapy (HAART), or “The Cocktail”) has been widely used to treat and help prevent the spread of HIV since 1987, when the first drug, AZT, came on the market for use against HIV infection [46]. Since then, more than 30 drugs have been developed and approved to treat people living with HIV/AIDS [35, 46]. ART helps people living with HIV/AIDS live longer (delays progression to AIDS and HIV-related mortality) and lowers their risk of developing non-HIV related illnesses [46]. Furthermore, ART reduces transmissibility of treated individuals (by reducing their infectiousness) to susceptible individuals [10, 35, 46].

ARVs are classified into six different classes: *nucleoside/nucleotide reverse transcriptase inhibitors* (NRTIs), *non-nucleoside reverse transcriptase inhibitors* (NNRTIs), *protease inhibitors* (PIs), *entry/fusion inhibitors*, *integrase inhibitors*, and multi-class combination products [34, 46]. These classes are stratified based on how they inhibit HIV replication [34, 46]. For example, NRTIs act as faulty building blocks in HIV DNA and halts HIV DNA synthesis, and PIs prevent new HIV virus particles from assembling [34, 46]. Multi-class combination products combine two or more drugs from different classes into one pill at fixed doses [34, 46]. In general, a patient on ART will take three different drugs (from two different classes) [46]. ART is recommended for all HIV infected individuals to reduce the risk of disease progression [35]. Although ART is recommended for all people regardless of CD4⁺ cell count, its initiation still depends on the needs of the individual patient, in the United States, and the resources available in their local area [35].

1.3.2 Pre-exposure Prophylaxis (PrEP)

PrEP is a new anti-HIV preventive measure [14, 15, 48]. It involves administering an antiretroviral drug (such as Truvada[®], which is a combination of two NRTIs,

tenofovir (TDF) and *emtricitabine* (FTC)) to HIV-negative individuals who are at a substantial risk of contracting the virus to help prevent infection [14, 15, 48]. It works by blocking pathways that the HIV virus uses to set up an infection in the body [14, 15, 48]. Individuals on PrEP have to commit to taking it every day and see their health care provider every three months, for follow-up and HIV testing [14, 15, 48]. It has been shown, in recent studies, that the effectiveness of PrEP depends upon the compliance in its usage [4, 14, 15, 16, 19, 44]. The more compliant an individual is to PrEP, the more effective it will be in lowering the risk of contracting HIV (studies showed up to 92% reduction in risk of acquisition of infection for those who took the medications consistently compared to those who did not take them consistently) [4, 14, 15, 16, 19, 44]. PrEP is not 100% effective, and should be used in conjunction with other preventive measures (e.g., condoms, reduction in risky sexual behaviours, using sterile syringes, getting tested for HIV, etc...) [14, 15, 48].

The medication approved by the U.S. Food and Drug Administration (FDA) is Truvada[®] [14, 15, 48]. Some clinical trials used *tenofovir* alone but this has not been approved by the U.S. FDA for PrEP [14, 15, 48]. For sexual transmission of HIV, the administration of PrEP entails giving drugs to anyone who [14, 15, 48]:

- i) is in an ongoing sexual relationship with an HIV-positive person;
- ii) is in a non-mutually monogamous sexual relationship and is a gay or bisexual man that has had unprotected anal sex or have been diagnosed with a sexually transmitted disease (STD) in the last six months;
- iii) is in a non-mutually monogamous sexual relationship and is a heterosexual man or woman who does not regularly use condoms during sex with a partner of unknown HIV status;
- iv) have injected illicit drugs in the past six months using shared equipment or who have been in a treatment program for injection drug use.

A summary of CDC guidelines on PrEP is depicted in Figure 1.4 [15].

Summary of Guidance for PrEP Use			
	Men Who Have Sex With Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection:	<ul style="list-style-type: none"> Sexual partner with HIV Recent bacterial STD High number of sex partners History of inconsistent or no condom use Commercial sex work 	<ul style="list-style-type: none"> Sexual partner with HIV Recent bacterial STD High number of sex partners History of inconsistent or no condom use Commercial sex work Lives in high-prevalence area or network 	<ul style="list-style-type: none"> HIV-positive injecting partner Sharing injection equipment Recent drug treatment (but currently injecting)
Clinically eligible:	<ul style="list-style-type: none"> Documented negative HIV test before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function, no contraindicated medications Documented hepatitis B virus infection and vaccination status 		
Prescription	Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90 day supply		
Other services:	<ul style="list-style-type: none"> Follow-up visits at least every 3 months to provide: <ul style="list-style-type: none"> HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment At 3 months and every 6 months after, assess renal function Every 6 months test for bacterial STDs 		
	<ul style="list-style-type: none"> Do oral/rectal STD testing 	<ul style="list-style-type: none"> Assess pregnancy intent Pregnancy test every 3 months 	<ul style="list-style-type: none"> Access to clean needles/syringes and drug treatment services

Figure 1.4: Summary of Guidance for PrEP Use in the United States [15].

1.4 Thesis Objectives

The main purpose of this thesis is to gain qualitative and quantitative insight into the population-level impact of the administration of PrEP to susceptible MSM at high risk of contracting HIV infection in the United States. This is achieved by developing, rigorously analyzing, and simulating a new deterministic model for HIV/AIDS transmission that incorporates the effect of PrEP. Some of the main questions to be addressed in this thesis include:

1. What are the main qualitative features of the model with PrEP? The goal is to determine conditions for the existence and asymptotic stability of the associated equilibria of the model.
2. What is the population-level impact of the use of PrEP within an MSM population? In particular, what proportion of the susceptible MSM population need to be on PrEP to achieve significant population-level impact (measured

in terms of the effective control or elimination of the disease within the community)?

3. What are the parameters of the model that play a dominant role in driving the disease transmission process (or dynamics)?

1.5 Thesis Outline

The rest of the thesis is outlined as follows. The HIV/AIDS PrEP model is formulated in Chapter 2. The HIV/AIDS PrEP-free model is developed and rigorously analyzed in Chapter 3. In Chapter 4, the PrEP model is rigorously analyzed. Uncertainty and sensitivity analysis of the PrEP model are reported in Chapter 5. Numerical simulations of the PrEP model are also carried out.

Chapter 2

Formulation of PrEP Model for HIV/AIDS

2.1 Introduction

As stated in Chapter 1, HIV/AIDS has remained one of the leading public health burdens globally, since its inception in the early 1980s, with MSM being one of the leading risk-groups in the United States [9, 22, 52]. The widespread use of anti-HIV control strategies, such as access to condoms, HIV testing and counselling, and treatment with antiretrovirals, has resulted in a dramatic reduction in HIV incidence in the United States [11]. PrEP is a promising new control strategy and it is imperative that its population level impact is assessed. Consequently, it is worthwhile to study the transmission dynamics of HIV/AIDS among MSM in the presence of PrEP.

The main purpose of this chapter is to construct a new deterministic model for the transmission dynamics of HIV/AIDS in a community of MSM in the United States in the presence of PrEP.

2.2 Model Formulation

The model to be developed in this thesis is based on the transmission dynamics of HIV/AIDS in a community of sexually-active adult MSM in the United States. One of the key assumptions to be made in the formulation process is that all clinical standards of medical practice in the United States are in place (as defined by the CDC) [8]. The total population of sexually-active MSM in the United States at time t , denoted by $N(t)$, is divided into sub-populations of individuals who are susceptible to HIV infection but not on PrEP ($S(t)$), susceptible and on PrEP with low adherence ($S_L(t)$), susceptible and on PrEP with high adherence ($S_H(t)$), infected and in the acute stage of HIV infection ($I_1(t)$), infected and in the chronic stage of HIV infection ($I_2(t)$), infected and on antiretroviral treatment ($I_T(t)$), infected and failed antiretroviral treatment ($F(t)$), and individuals with clinical symptoms of AIDS ($A(t)$), so that

$$N(t) = S(t) + S_L(t) + S_H(t) + I_1(t) + I_2(t) + I_T(t) + F(t) + A(t).$$

The population of susceptible untreated individuals (that is, susceptible individuals not on PrEP) (S) is increased by the recruitment of newly sexually-active MSM who are HIV negative (at a rate of π). This population is also increased when individuals on PrEP abandon their PrEP treatment (at a rate of ω_L , for those with low PrEP adherence, and ω_H for those with high adherence). Members of this population acquire HIV infection, at a rate of λ , given by,

$$\lambda = \frac{\beta(I_1 + \theta_2 I_2 + \theta_T I_T + \theta_F F + \theta_A A)}{N}. \quad (2.1)$$

In (2.1), β is the effective contact rate. Furthermore, $0 < \theta_2 < 1$ is a modification parameter accounting for the assumption that individuals in the chronic stage of

HIV infection are less infectious than those in the acute stage [24]. The parameter $0 < \theta_T < 1$ accounts for the assumed reduction of infectiousness of treated HIV-infected individuals in comparison to those in the acute stage [24]. Similarly, $\theta_F > 0$ represents the assumed variability of the infectiousness of failed treated HIV-infected individuals, in relation to acutely-infected individuals [24]. Finally, $\theta_A \geq 1$ accounts for the assumption that individuals in the AIDS stage of infection are at least as infectious as those in the acute stage [24]. This population is further decreased by the administration of PrEP (at a rate of ψ) and natural death (at a rate of μ ; this rate is assumed to be the same for all epidemiological compartments). Thus,

$$\frac{dS}{dt} = \pi + \omega_L S_L + \omega_H S_H - \lambda S - \psi S - \mu S.$$

The population of individuals taking PrEP with low adherence (S_L) is increased by the administration of PrEP to a fraction, $1 - f$ (at the rate ψ ; a fraction, f , of these is assumed to adhere strictly to a PrEP regimen, and the remaining fraction, $1 - f$, do not). This population is further increased when highly-adherent PrEP users revert to low adherence status (at a rate of ξ_H). It is also decreased by infection (at a reduced rate of $\theta_L \lambda$, where the modification parameter, $0 < \theta_L < 1$, accounts for the assumption that low-adherent PrEP users acquire HIV infection at a lower rate than wholly-susceptible individuals, but at a higher rate than highly-adherent susceptible PrEP users). It is further decreased by individuals who either decide to take PrEP with high adherence (at a rate ξ_L) or who decide to stop taking PrEP altogether (at the rate ω_L) and natural death. Hence,

$$\frac{dS_L}{dt} = (1 - f)\psi S + \xi_H S_H - \theta_L \lambda S_L - (\xi_L + \omega_L + \mu) S_L.$$

The population of individuals taking PrEP with high adherence (S_H) is generated at the rates $f\psi$ and ξ_L . It is decreased by infection (at a reduced rate of $\theta_H \lambda$,

where the modification parameter, $0 < \theta_H < \theta_L < 1$, accounts for the assumption that highly-adherent PrEP users acquire HIV infection at a lower rate than both wholly-susceptible individuals and low-adherent susceptible PrEP users). It is further decreased by reversion to low adherence (at a rate ξ_H), cessation of PrEP (at the rate ω_H), and natural death. Thus,

$$\frac{dS_H}{dt} = f\psi S + \xi_L S_L - \theta_H \lambda S_H - (\xi_H + \omega_H + \mu)S_H.$$

The population of infected individuals in the acute stage of HIV infection (I_1) is generated at the rate of λ . It is decreased by progression to the chronic stage (at a rate σ_1), the administration of antiretroviral treatment (at a rate τ_1) and by natural death. Thus,

$$\frac{dI_1}{dt} = \lambda S - (\sigma_1 + \tau_1 + \mu)I_1.$$

The population of individuals in the chronic stage of HIV infection (I_2) is generated at the rate σ_1 . It is further increased by those who have failed treatment, and are still classified as having chronic HIV (at a rate γr , where $0 < r \leq 1$ is the fraction of individuals who have failed treatment and are classified as having chronic HIV). This population is decreased by treatment (at a rate τ_2), progression to AIDS (at a rate σ_2) and natural death. Thus,

$$\frac{dI_2}{dt} = \sigma_1 I_1 + \gamma r F - (\sigma_2 + \tau_2 + \mu)I_2.$$

The population of treated HIV-infected individuals (I_T) is generated following the treatment of individuals in the I_1 , I_2 and A classes (at the rates τ_1 , τ_2 and τ_A , respectively). It is decreased by treatment failure (at a rate κ) and by natural death. Hence,

$$\frac{dI_T}{dt} = \tau_1 I_1 + \tau_2 I_2 + \tau_A A - (\kappa + \mu)I_T.$$

The population of individuals who have failed antiretroviral treatment (F) is generated at the rate of κ . Transition out of this class occurs at a rate γ (a fraction, r , of which fail antiretroviral treatment, and the remaining fraction, $1 - r$, progress to AIDS). This population is also decreased by natural death. Thus,

$$\frac{dF}{dt} = \kappa I_T - (\gamma + \mu)F.$$

The population of individuals in the AIDS stage of HIV infection is generated following the progression of those in the chronic stage (at the rate σ_2) and those who failed antiretroviral treatment (at the rate $\gamma(1 - r)$). It is decreased by treatment (at the rate τ_A), natural death, and disease-induced death (at a rate δ). Hence,

$$\frac{dA}{dt} = \sigma_2 I_2 + \gamma(1 - r)F - (\tau_A + \mu + \delta)A.$$

Based on the above assumptions and formulations, the model for the transmission of HIV/AIDS in a community of MSM is given by the following deterministic system of non-linear differential equations:

$$\begin{aligned} \frac{dS}{dt} &= \pi + \omega_L S_L + \omega_H S_H - \lambda S - \psi S - \mu S, \\ \frac{dS_L}{dt} &= (1 - f)\psi S + \xi_H S_H - \theta_L \lambda S_L - (\xi_L + \omega_L + \mu)S_L, \\ \frac{dS_H}{dt} &= f\psi S + \xi_L S_L - \theta_H \lambda S_H - (\xi_H + \omega_H + \mu)S_H, \\ \frac{dI_1}{dt} &= \lambda(S + \theta_L S_L + \theta_H S_H) - (\sigma_1 + \tau_1 + \mu)I_1, \\ \frac{dI_2}{dt} &= \sigma_1 I_1 + \gamma r F - (\tau_2 + \sigma_2 + \mu)I_2, \\ \frac{dI_T}{dt} &= \tau_1 I_1 + \tau_2 I_2 + \tau_A A - (\kappa + \mu)I_T, \\ \frac{dF}{dt} &= \kappa I_T - (\gamma + \mu)F, \\ \frac{dA}{dt} &= \sigma_2 I_2 + \gamma(1 - r)F - (\tau_A + \mu + \delta)A, \end{aligned} \tag{2.2}$$

where,

$$\lambda = \frac{\beta(I_1 + \theta_2 I_2 + \theta_T I_T + \theta_F F + \theta_A A)}{N}.$$

A flow diagram of the model (2.2) is depicted in Figure 2.1, and the associated state variables and parameters are tabulated in Table 2.1.

2.2.1 Basic Properties

The basic properties of the PrEP model (2.2) will be explored. First, it is important to establish that all state-variables of model (2.2) are non-negative for all time $t > 0$ (i.e., the solutions of the PrEP model (2.2) with non-negative initial data remain non-negative for all $t > 0$).

Theorem 2.1. *Let the initial data for the model with PrEP (2.2) be $S(0) > 0$, $S_H(0) > 0$, $S_L(0) > 0$, $I_1(0) \geq 0$, $I_2(0) \geq 0$, $I_T(0) \geq 0$, $F(0) \geq 0$, $A(0) \geq 0$. Then the solutions $(S(t), S_H(t), S_L(t), I_1(t), I_2(t), I_T(t), F(t), A(t))$ of the model with positive initial data, will remain positive for all time $t > 0$.*

The proof of Theorem 2.1 is given in Appendix A.

Theorem 2.2. *The closed set*

$$\mathcal{D} = \left\{ (S, S_L, S_H, I_1, I_2, I_T, F, A) \in \mathbb{R}_+^8 : N \leq \frac{\pi}{\mu} \right\}$$

is positively-invariant and attracting with respect to the model (2.2).

Proof. Adding all eight equations of model (2.2) gives:

$$\frac{dN}{dt} = \pi - \mu N - \delta A \leq \pi - \mu N. \quad (2.3)$$

It follows from (2.3) that if $N \leq \frac{\pi}{\mu}$ then $\frac{dN}{dt} \leq 0$. Further, using a standard Comparison Theorem (see [25]),

$$N(t) \leq \left[N(0) - \frac{\pi}{\mu} \right] e^{-\mu t} + \frac{\pi}{\mu}.$$

Therefore, if $N(0) \leq \frac{\pi}{\mu}$, then $N(t) \leq \frac{\pi}{\mu}$. Thus, \mathcal{D} is positively-invariant. Furthermore, if $N(0) \geq \frac{\pi}{\mu}$, then either the solution enters \mathcal{D} in finite time or $N(t)$ approaches $\frac{\pi}{\mu}$ asymptotically. Therefore, \mathcal{D} attracts all solutions in \mathbb{R}_+^8 . \square

Thus, in the region \mathcal{D} , the model (2.2) can be considered as epidemiologically and mathematically well-posed [23].

Before analyzing the PrEP model (2.2), it is instructive to study the dynamics of the model in the absence of PrEP (to determine whether or not adding PrEP to the PrEP-free model for HIV/AIDS alters the qualitative dynamics of the PrEP-free model, with respect to the existence and asymptotic stability of its associated equilibria).

Table 2.1: Description of variables and parameters of model (2.2)

Variables	Description
$S(t)$	Population of susceptible individuals not on PrEP
$S_L(t)$	Population of susceptible individuals on PrEP with low adherence
$S_H(t)$	Population of susceptible individuals on PrEP with high adherence
$I_1(t)$	Population of acutely-infected individuals
$I_2(t)$	Population of chronically-infected individuals
$I_T(t)$	Population of treated individuals
$F(t)$	Population of individuals who failed treatment
$A(t)$	Population of infected individuals with clinical symptoms of AIDS
Parameter	Description
π	Recruitment rate
β	Effective contact rate
μ	Natural death rate
δ	Disease-induced death rate
f	Fraction of individuals on PrEP with high adherence rate
$1 - f$	Fraction of individuals on PrEP with low adherence rate
θ_2	Modification parameter for reduction in infectiousness of individuals in the chronic stage of HIV infection
θ_F	Modification parameter for reduction in infectiousness of individuals who fail treatment
θ_T	Modification parameter for reduction in infectiousness of treated individuals
θ_A	Modification parameter for reduction in infectiousness of individuals who have AIDS
ψ	Rate of administration of PrEP
ω_L	Rate of cessation of PrEP by low-adherent PrEP users
ω_H	Rate of cessation of PrEP by high-adherent PrEP users
ξ_L	Transition rate from low to high PrEP adherence
ξ_H	Transition rate from high to low PrEP adherence
θ_L	Modification parameter for reduction of transmission rate of those in the S_L class
θ_H	Modification parameter for reduction of transmission rate of those in the S_H class
σ_1	Progression rate from acute stage to chronic stage
σ_2	Progression rate from chronic stage to AIDS stage
κ	Transition rate out of the treatment class
γ	Transition rate out of failed treated class
r	Fraction of individuals who failed treatment and moved to chronic stage
$1 - r$	Fraction of individuals who failed treatment and moved to AIDS stage
τ_1, τ_2, τ_A	Treatment rate for HIV-infected individuals in I_1 , I_2 , and A classes

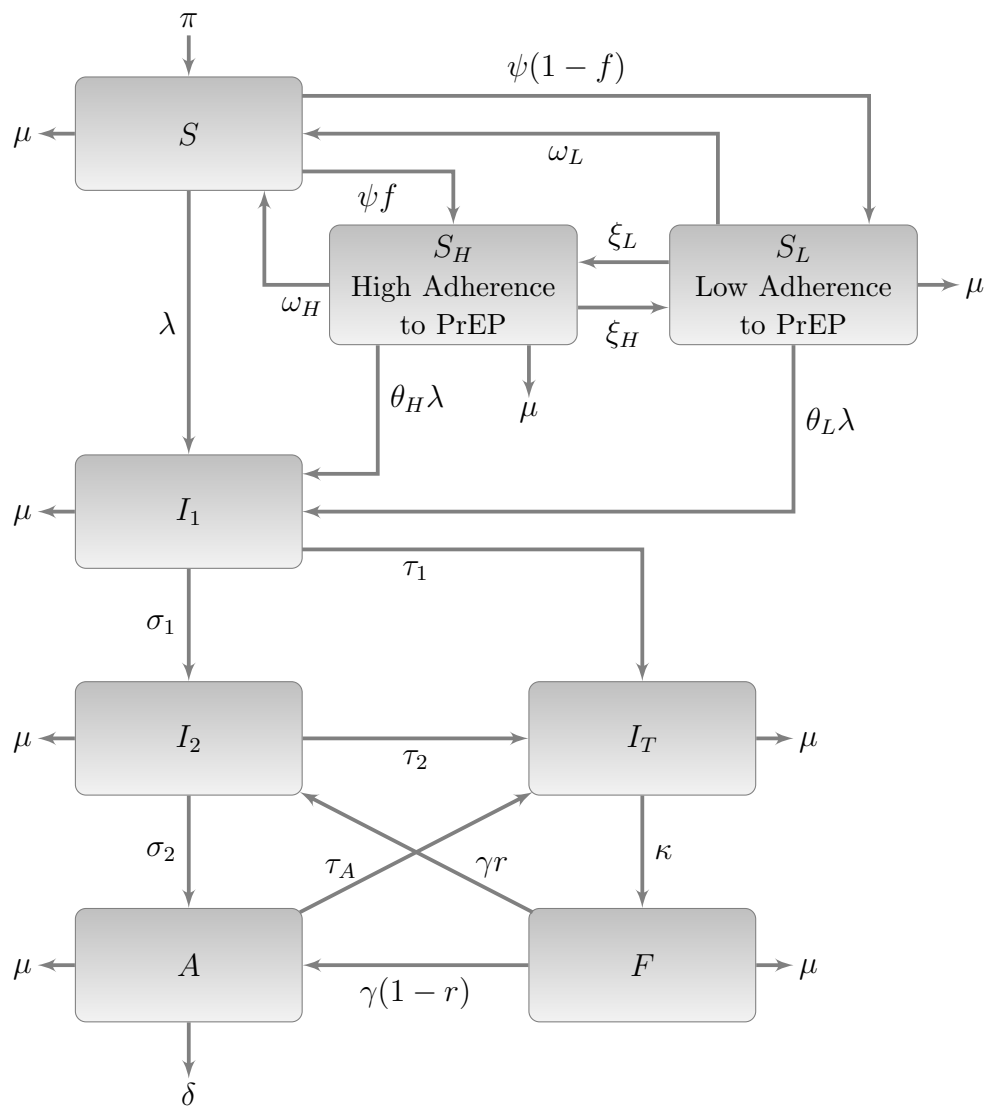


Figure 2.1: Flow Diagram for the PrEP Model (2.2).

Chapter 3

Analysis of PrEP-free HIV/AIDS

Model

In the absence of PrEP (i.e., $S_H = S_L = \omega_H = \omega_L = \psi = \xi_H = \xi_L = 0$), the PrEP model (2.2) reduces to the following (PrEP-free) model (where, now, $N(t) = S(t) + I_1(t) + I_2(t) + I_T(t) + F(t) + A(t)$):

$$\begin{aligned}\frac{dS}{dt} &= \pi - \lambda S - \mu S, \\ \frac{dI_1}{dt} &= \lambda S - (\sigma_1 + \tau_1 + \mu)I_1, \\ \frac{dI_2}{dt} &= \sigma_1 I_1 + \gamma r F - (\tau_2 + \sigma_2 + \mu)I_2, \\ \frac{dI_T}{dt} &= \tau_1 I_1 + \tau_2 I_2 + \tau_A A - (\kappa + \mu)I_T, \\ \frac{dF}{dt} &= \kappa I_T - (\gamma + \mu)F, \\ \frac{dA}{dt} &= \sigma_2 I_2 + \gamma(1-r)F - (\tau_A + \mu + \delta)A.\end{aligned}\tag{3.1}$$

As in Section 2.2.1, the following result can be established for the PrEP-free model (3.1).

Theorem 3.1. *The closed set*

$$\mathcal{D}_1 = \left\{ (S, I_1, I_2, I_T, F, A) \in \mathbb{R}_+^6 : N \leq \frac{\pi}{\mu} \right\}$$

is positively-invariant and attracting with respect to the PrEP-free model (3.1).

3.1 Asymptotic Stability of the Disease Free Equilibrium (DFE)

3.1.1 Local

The DFE of the PrEP-free model (3.1) is given by

$$\mathcal{E}_0 = (S^*, I_1^*, I_2^*, I_T^*, F^*, A^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0 \right). \quad (3.2)$$

The local stability of the DFE, \mathcal{E}_0 , will be explored using the next generation operator method [50]. The matrices, \mathcal{H} , of the new infection terms of the model (3.1), and \mathcal{V} , of the transition terms of model (3.1), are given, respectively, by

$$\mathcal{H} = \begin{pmatrix} \beta & \theta_2\beta & \theta_T\beta & \theta_F\beta & \theta_A\beta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 \\ -\sigma_1 & K_2 & 0 & -\gamma r & 0 \\ -\tau_1 & -\tau_2 & K_3 & 0 & -\tau_A \\ 0 & 0 & -\kappa & K_4 & 0 \\ 0 & -\sigma_2 & 0 & -\gamma(1-r) & K_5 \end{pmatrix},$$

where,

$$K_1 = \sigma_1 + \tau_1 + \mu, \quad K_2 = \tau_2 + \sigma_2 + \mu, \quad K_3 = \kappa + \mu, \quad K_4 = \gamma + \mu, \quad K_5 = \tau_A + \mu + \delta.$$

It follows that the *basic reproduction number* [17, 23, 50] (denoted by \mathcal{R}_0) of the model is given by (where ρ is the spectral radius):

$$\mathcal{R}_0 = \rho(\mathcal{H}\mathcal{V}^{-1}) = \frac{\beta(M_1 + \theta_2 M_2 + \theta_T K_4 M_3 + \kappa \theta_F M_3 + \theta_A M_4)}{M_1 K_1},$$

with,

$$M_1 = \kappa \gamma K_2 \tau_A r - \kappa \gamma K_2 \tau_A - \kappa r \gamma K_5 \tau_2 - \kappa r \gamma \sigma_2 \tau_A + K_2 K_3 K_4 K_5,$$

$$M_2 = \gamma \kappa \sigma_1 \tau_A r - \gamma \kappa \sigma_1 \tau_A + \gamma r K_5 \kappa \tau_1 + K_5 K_4 K_3 \sigma_1,$$

$$M_3 = K_2 K_5 \tau_1 + K_5 \sigma_1 \tau_2 + \sigma_1 \sigma_2 \tau_A,$$

$$M_4 = \gamma r \kappa \sigma_2 \tau_1 + K_3 K_4 \sigma_1 \sigma_2 + \kappa \gamma (1-r)(K_2 \tau_1 + \sigma_1 \tau_2).$$

It can be shown that M_i ($i = 1, 2$) > 0 , so $\mathcal{R}_0 > 0$ (see Appendix B). The result below follows from Theorem 2 of [50].

Theorem 3.2. *The DFE, \mathcal{E}_0 , of the PrEP-free model (3.1) is locally-asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The epidemiological implication of Theorem 3.2 is that HIV/AIDS can be effectively-controlled (or eliminated) from the community when $\mathcal{R}_0 < 1$ if the initial sizes of the sub-populations of the PrEP-free model (3.1) are in the basin of attraction of the DFE (\mathcal{E}_0). For the effective control (or elimination) of HIV/AIDS to be independent

of the initial sizes of the sub-populations, the DFE of the PrEP-free model (3.1) will need to be shown to be globally-asymptotically stable (GAS) if $\mathcal{R}_0 < 1$. The global asymptotic stability property of the DFE of the model (3.1) is explored below.

3.1.2 Global

Theorem 3.3. *The DFE, \mathcal{E}_0 , of the PrEP-free model (3.1), is GAS in \mathcal{D}_1 whenever $\mathcal{R}_0 < 1$.*

The proof of Theorem 3.3 is based on using a Comparison Theorem [25], and is given in Appendix C.

The epidemiological implication of Theorem 3.3 is that HIV will be eliminated from the community whenever the threshold quantity, \mathcal{R}_0 , can be brought to (and maintained at) a value less than unity. In other words, for the PrEP-free model (3.1), the classical epidemiological requirement of having the reproduction threshold (\mathcal{R}_0) less than unity is necessary and sufficient for effective control (or elimination) of the disease within the MSM population.

3.2 Existence and Asymptotic Stability of the Endemic Equilibrium Point (EEP)

In this section, the number of positive (endemic) equilibrium points of the PrEP-free model (3.1) will be determined for the special case where the associated disease-induced mortality is zero (i.e., $\delta = 0$). This assumption $\delta = 0$, although chosen for mathematical convenience (to make the mathematical analysis more tractable), it can be justified considering the fact that AIDS-related mortality in the MSM population in Minnesota is negligible [32]. Setting $\delta = 0$ in the model (3.1), and adding the equations of the model, gives $\frac{dN(t)}{dt} = \pi - \mu N(t)$, so that $N(t) \rightarrow \frac{\pi}{\mu}$ as $t \rightarrow \infty$.

Let,

$$\mathcal{E}_1 = (S^{**}, I_1^{**}, I_2^{**}, I_T^{**}, F^{**}, A^{**}), \quad (3.3)$$

represent any endemic equilibrium of the PrEP-free model (3.1) (i.e., an equilibrium where the infected components of the PrEP-free model (3.1) are non-zero with $\delta = 0$).

Moreover, let the *force of infection* at steady-state of the PrEP-free model (3.1) be defined as (where the total population $N(t)$ is now replaced by its limiting value

$$N^* = \frac{\pi}{\mu})$$

$$\lambda^{**} = \frac{\beta\mu(I_1^{**} + \theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**})}{\pi}. \quad (3.4)$$

Solving the equations of model (3.1) at the endemic steady-state gives (it should be recalled that $0 < r < 1$, so that $A^{**} > 0$)

$$\begin{aligned} S^{**} &= \frac{\pi}{\lambda^{**} + \mu}, & I_1^{**} &= \frac{\lambda^{**} S^{**}}{K_1}, \\ I_2^{**} &= \frac{\sigma_1 I_1^{**} + \gamma r F^{**}}{K_2}, & I_T^{**} &= \frac{\tau_1 I_1^{**} + \tau_2 I_2^{**} + \tau_A A^{**}}{K_3}, \\ F^{**} &= \frac{\kappa I_T^{**}}{K_4}, & A^{**} &= \frac{\sigma_2 I_2^{**} + \gamma(1-r)F^{**}}{K_5}. \end{aligned} \quad (3.5)$$

Substituting the expressions from (3.5) into (3.4) shows that non-zero (endemic) equilibria of the PrEP-free model (3.1) satisfy

$$\lambda^{**} = \mu(\mathcal{R}_1 - 1), \quad (3.6)$$

where $\mathcal{R}_1 = \mathcal{R}_0|_{\delta=0}$. Since all parameters of the model (3.1) are positive, it follows from (3.6) that $\lambda^{**} > 0$ whenever $\mathcal{R}_1 > 1$ (i.e., the PrEP-free model (3.1), with $\delta = 0$, has a unique EEP whenever $\mathcal{R}_1 > 1$). Furthermore, when $\mathcal{R}_1 = 1$, then $\lambda^{**} = 0$. Hence, the EEP collapses into the DFE in this case. Each component of the unique EEP can be obtained in terms of \mathcal{R}_1 by substituting (3.6) into the expressions in (3.5). These results are summarized below.

Theorem 3.4. *The PrEP-free model (3.1), with $\delta = 0$, has a unique positive endemic equilibrium point whenever $\mathcal{R}_1 > 1$, and no positive endemic equilibrium point otherwise.*

3.2.1 Stability

The global asymptotic stability of the unique EEP, \mathcal{E}_1 , of the model (3.1) will now be explored for the special case with $\delta = 0$. Further, let $\mathcal{R}_1 > 1$ (so that the unique EEP, \mathcal{E}_1 , exists in line with Theorem 3.4). It is convenient to define the invariant region (the stable manifold of the DFE, \mathcal{E}_0 , of the PrEP-free model (3.1))

$$\mathcal{D}_0 = \{(S, I_1, I_2, I_T, F, A) \in \mathcal{D}_1 : I_1 = I_2 = I_T = F = A = 0\}.$$

The following definitions and theorems will be used in proving Theorem 3.7 below.

Definition 3.1. [51]. *Consider the autonomous system (where a dot represents differentiation with respect to time)*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{3.7}$$

A point $\bar{x} \in \mathbb{R}^n$ is called an equilibrium point of the autonomous system (3.7) if $f(\bar{x}) = 0$.

Definition 3.2. [51]. *Let $S \subset \mathbb{R}^n$ be a set, then S is said to be invariant under the flow generated by $\dot{x} = f(x)$ if for any $x_0 \in S$, $\phi(t, x_0) \in S$ for all $t \in \mathbb{R}$.*

Definition 3.3. [51]. *A function $V : \mathbb{R}^n \rightarrow \mathbb{R}$ is said to be positive definite at \bar{x} if*

(i) $V(x) > 0$ for all $x \neq \bar{x}$,

(ii) $V(x) = 0$ if and only if $x = \bar{x}$.

Theorem 3.5. [51]. Consider the system (3.7). Let \bar{x} be an equilibrium solution of system (3.7) and, let $V : U \rightarrow \mathbb{R}$ be a C^1 function defined on some neighborhood U of \bar{x} such that

(i) V is positive definite,

(ii) $\dot{V}(x) \leq 0$ in $U \setminus \{\bar{x}\}$.

Then any function, V , that satisfies conditions (i) and (ii) is called a Lyapunov function.

Theorem 3.6. (LaSalle's Invariance Principle [28]). Suppose that there exists a positive definite C^1 function $V : \mathbb{R}^n \rightarrow \mathbb{R}$ whose derivative along the solutions of the system (3.7) satisfies the inequality $\dot{V} \leq 0$. Let M be the largest invariant set contained in the set $\{x : \dot{V}(x) = 0\}$. Then the system (3.7) is stable and every solution that remains bounded for $t \geq 0$ approaches M as $t \rightarrow \infty$. Furthermore, if all solutions remain bounded and $M = \{\bar{x}\}$ for $t \geq 0$, then the solution is globally-asymptotically stable.

Theorem 3.7. The unique EEP (\mathcal{E}_1), of the PrEP-free model (3.1) with $\delta = 0$, is GAS in $\mathcal{D}_1 \setminus \mathcal{D}_0$ whenever $\mathcal{R}_1 = \mathcal{R}_0|_{\delta=0} > 1$.

The proof of Theorem 3.7, based on using Lyapunov function theory (Theorem 3.5) and LaSalle's Invariance Principle (Theorem 3.6), is given in Appendix D.

3.3 Chapter Summary

This chapter is based on the design and rigorous qualitative analysis of a PrEP-free model for HIV/AIDS. The main theoretical results obtained are summarized below.

- i) The disease-free equilibrium of the PrEP-free model (3.1) is locally- and globally-asymptotically stable whenever $\mathcal{R}_0 < 1$.

- ii) The special case of the PrEP-free model (3.1) in the absence of disease-induced mortality ($\delta = 0$) has a unique and globally-asymptotically stable endemic equilibrium point whenever the associated reproduction number (\mathcal{R}_1) exceeds unity.

Chapter 4

Analysis of PrEP Model

In this chapter, the PrEP model (2.2) will be rigorously analyzed (with the goal of determining whether or not it has certain dynamical features that are not present in the PrEP-free model (3.1)).

4.1 Asymptotic Stability Analysis

The DFE of the PrEP model (2.2) is given by

$$\mathcal{E}_0^P = (S^*, S_L^*, S_H^*, I_1^*, I_2^*, I_T^*, F^*, A^*) = (S^*, S_L^*, S_H^*, 0, 0, 0, 0, 0), \quad (4.1)$$

where,

$$\begin{aligned} S^* &= \frac{\pi[\xi_L(\omega_H + \mu) + (\omega_L + \mu)(\xi_H + \omega_H + \mu)]}{Q_1}, \\ S_L^* &= \frac{\pi\psi[\xi_H + (1 - f)(\omega_H + \mu)]}{Q_1}, \\ S_H^* &= \frac{\pi\psi[f(\omega_L + \mu) + \xi_L]}{Q_1}, \end{aligned}$$

and,

$$Q_1 = \mu \left[\xi_L(\omega_H + \mu) + (\omega_L + \mu)(\xi_H + \omega_H + \mu) + \psi(\xi_H + (1 - f)\omega_H + \mu + f\omega_L + \xi_L) \right],$$

(now)

$$N^* = S^* + S_L^* + S_H^* = \frac{\pi}{\mu}.$$

As in Section 3.1.1, the local stability of the DFE will be explored using the next generation operator method [50]. It follows that the matrices \mathcal{H}_P and \mathcal{V}_P , associated with the model (2.2), are given, respectively, by

$$\mathcal{H}_P = \begin{pmatrix} \frac{g\beta}{N^*} & \frac{g\theta_2\beta}{N^*} & \frac{g\theta_T\beta}{N^*} & \frac{g\theta_F\beta}{N^*} & \frac{g\theta_A\beta}{N^*} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{V}_P = \begin{pmatrix} C_1 & 0 & 0 & 0 & 0 \\ -\sigma_1 & C_2 & 0 & -\gamma r & 0 \\ -\tau_1 & -\tau_2 & C_3 & 0 & -\tau_A \\ 0 & 0 & -\kappa & C_4 & 0 \\ 0 & -\sigma_2 & 0 & -\gamma(1 - r) & C_5 \end{pmatrix},$$

where,

$$g = S^* + \theta_L S_L^* + \theta_H S_H^*,$$

and,

$$C_1 = \sigma_1 + \tau_1 + \mu, \quad C_2 = \tau_2 + \sigma_2 + \mu, \quad C_3 = \kappa + \mu, \quad C_4 = \gamma + \mu, \quad C_5 = \tau_A + \mu + \delta.$$

It follows that the *effective reproduction number* of the PrEP model (2.2), denoted by \mathcal{R}_P , is given by

$$\mathcal{R}_P = \rho(\mathcal{H}_P \mathcal{V}_P^{-1}) = \frac{\beta g(Q_2 + \theta_2 Q_3 + \theta_T C_4 Q_4 + \theta_F \kappa Q_4 + \theta_A Q_5)}{Q_2 C_1 N^*},$$

with,

$$Q_2 = \kappa \gamma C_2 \tau_A r - \kappa \gamma C_2 \tau_A - \kappa r \gamma C_5 \tau_2 - \kappa r \gamma \sigma_2 \tau_A + C_2 C_3 C_4 C_5,$$

$$Q_3 = \gamma \kappa \sigma_1 \tau_A r - \gamma \kappa \sigma_1 \tau_A + \gamma r C_5 \kappa \tau_1 + C_5 C_4 C_3 \sigma_1,$$

$$Q_4 = C_2 C_5 \tau_1 + C_5 \sigma_1 \tau_2 + \sigma_1 \sigma_2 \tau_A,$$

$$Q_5 = \gamma r \kappa \sigma_2 \tau_1 + C_3 C_4 \sigma_1 \sigma_2 + \kappa \gamma (1 - r)(C_2 \tau_1 + \sigma_1 \tau_2).$$

It can be shown that $\mathcal{R}_P > 0$ (see Appendix B). The result below follows from Theorem 2 of [50].

Theorem 4.1. *The DFE, \mathcal{E}_0^P , of the PrEP model (2.2) is locally-asymptotically stable if $\mathcal{R}_P < 1$, and unstable if $\mathcal{R}_P > 1$.*

The threshold quantity, \mathcal{R}_P , can be epidemiologically interpreted as in Section 3.1.1. It is convenient to define $\mathcal{R}_P^* = \mathcal{R}_P|_{\delta=0}$.

4.1.1 Backward Bifurcation Analysis

As in Section 3.2, the analysis in this section will be carried out for the special case $\delta = 0$ (for mathematical convenience). Let,

$$\mathcal{E}_1^P = (S^{**}, S_H^{**}, S_L^{**}, I_1^{**}, I_2^{**}, I_T^{**}, F^{**}, A^{**}), \quad (4.2)$$

represent any endemic equilibrium of a special case of the PrEP model (2.2) with no disease-induced mortality (i.e., $\delta = 0$). It is convenient to define (where the total

population at time t , $N(t)$, is replaced by its limiting value $N^* = \frac{\pi}{\mu}$

$$\lambda^{**} = \frac{\beta\mu(I_1^{**} + \theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**})}{\pi}. \quad (4.3)$$

Solving the equations of the PrEP model (2.2) at the endemic steady-state gives

$$\begin{aligned} S^{**} &= \frac{\pi + \omega_L S_L^{**} + \omega_H S_H^{**}}{\lambda^{**} + \psi + \mu}, & S_H^{**} &= \frac{\psi f S^{**} + \xi_L S_L^{**}}{\theta_H \lambda^{**} + \xi_H + \omega_H + \mu}, \\ S_L^{**} &= \frac{\psi(1-f)S^{**} + \xi_H S_H^{**}}{\theta_L \lambda^{**} + \xi_L + \omega_L + \mu}, & I_1^{**} &= \frac{\lambda^{**}(S^{**} + \theta_H S_H^{**} + \theta_L S_L^{**})}{C_1}, \\ I_2^{**} &= \frac{\sigma_1 I_1^{**} + \gamma r F^{**}}{C_2}, & I_T^{**} &= \frac{\tau_1 I_1^{**} + \tau_2 I_2^{**} + \tau_A A^{**}}{C_3}, \\ F^{**} &= \frac{\kappa I_T^{**}}{C_4}, & A^{**} &= \frac{\sigma_2 I_2^{**} + \gamma(1-r)F^{**}}{C_5}, \end{aligned} \quad (4.4)$$

where, now, $C_5 = \tau_A + \mu$. Substituting the equations in (4.4) into (4.3) gives:

$$\lambda^{**} = \frac{\mu\beta B_5 \lambda^{**} [\theta_H \theta_L (\lambda^{**})^2 + B_1 \lambda^{**} + B_2]}{C_1 Q_2 [\theta_H \theta_L (\lambda^{**})^3 + B_3 (\lambda^{**})^2 + B_4 \lambda^{**} + Q_1]},$$

where,

$$\begin{aligned} B_1 &= \theta_L [\xi_H + \omega_H + \mu + \psi \theta_H (1-f)] + \theta_H [\xi_L + \omega_L + \mu + \psi f \theta_L], \\ B_2 &= \xi_L (\omega_H + \mu) + (\omega_L + \mu) (\xi_H \omega_H + \mu) + \theta_L \psi [\xi_H + (\omega_H + \mu) (1-f)] \\ &\quad + \theta_H \psi [f (\omega_L + \mu) \xi_L], \\ B_3 &= \theta_L (\xi_L + \omega_L + \mu) + \theta_H (\xi_L + \omega_L + \mu) + \theta_H \theta_L (\psi + \mu), \\ B_4 &= \psi [\xi_H + \omega_H + \mu + \psi \theta_H (1-f) + \theta_H (\xi_L + \omega_L f + \mu)] \\ &\quad + \mu [\theta_L (\xi_H + \omega_H + \mu) + \theta_H (\xi_L + \omega_L + \mu)] \\ &\quad + \xi_L (\omega_H + \mu) + (\omega_L + \mu) (\xi_H + \omega_H + \mu), \\ B_5 &= Q_2 + \theta_2 Q_3 + \theta_T C_4 Q_4 + \theta_F \kappa Q_4 + \theta_A Q_5. \end{aligned} \quad (4.5)$$

It follows then that the non-zero (endemic) equilibria of the PrEP model (2.2), with $\delta = 0$, satisfy the following polynomial (in terms of λ^{**}),

$$a_3(\lambda^{**})^3 + a_2(\lambda^{**})^2 + a_1\lambda^{**} + a_0 = 0 \quad (4.6)$$

where,

$$\begin{aligned} a_3 &= C_1 Q_2 \theta_H \theta_L, \\ a_2 &= C_1 Q_2 [\theta_L(\xi_H + \omega_H + \mu) + \theta_H(\xi_L + \omega_L + \mu) + \theta_H \theta_L(\psi + \mu)] \\ &\quad - \mu \beta B_5 \theta_H \theta_L, \\ a_1 &= C_1 Q_2 \left[\psi [\theta_L(\xi_H + \omega_H(1 - f) + \mu) + \theta_H(\xi_L + \omega_L f + \mu)] \right. \\ &\quad \left. + \mu [\theta_L(\xi_H + \omega_H + \mu) + \theta_H(\xi_L + \omega_L + \mu)] \right. \\ &\quad \left. + \xi_L(\omega_H + \mu) + (\omega_L + \mu)(\xi_H + \omega_H + \mu) \right] - \mu \beta B_5 \left[\theta_L [\xi_H + \omega_H \right. \\ &\quad \left. + \mu + \psi \theta_H(1 - f)] + \theta_H(\xi_L + \omega_L + \mu + \psi f \theta_L) \right], \\ a_0 &= C_1 Q_2 Q_1 (1 - \mathcal{R}_P^*), \end{aligned} \quad (4.7)$$

where $\mathcal{R}_P^* = \mathcal{R}_P|_{\delta=0}$. It follows from (4.7) that the coefficient a_3 , of the cubic (4.6), is always positive (it should be recalled from Appendix B that $Q_2 > 0$) and a_0 is positive (negative) if \mathcal{R}_P^* is less (greater) than unity. Thus, the number of possible positive real roots the polynomial (4.6) can have depends on the signs of the coefficient a_2 and a_1 of the cubic (4.6). The possible number of real positive roots of the cubic (4.6) are given in Table 4.1.

Theorem 4.2. *The special case of the PrEP model (2.2) with $\delta = 0$:*

- (i) *has a unique endemic equilibrium if $\mathcal{R}_P^* > 1$ and whenever Cases 1, 2 and 3 of Table 4.1 hold;*

(ii) could have more than one endemic equilibrium if $\mathcal{R}_P^* > 1$ and whenever Case 4 of Table 4.1 holds;

(iii) could have two endemic equilibria if $\mathcal{R}_P^* < 1$ and whenever Cases 2-4 of Table 4.1 holds.

Item (iii) of Theorem 4.2 suggests the possibility of backward bifurcation. The phenomenon of backward bifurcation, which has been observed in numerous epidemiological settings [6, 18, 20, 23, 41], is characterized by the co-existence of multiple stable equilibria when the threshold quantity, \mathcal{R}_P^* , is less than unity. The epidemiological effect of this phenomenon is that disease control (when $\mathcal{R}_P^* < 1$) is dependent upon the initial sizes of the sub-populations of the model (see, for example [41]). Accordingly, the existence of backward bifurcation in the transmission dynamics of a disease makes it difficult to achieve effective control (or elimination) of that disease in the community. The existence of such phenomenon in the PrEP model (2.2) is now explored.

Theorem 4.3. *The PrEP model (2.2) with $\delta = 0$ undergoes backward bifurcation at $\mathcal{R}_P^* = 1$ whenever the inequality (E.5), given in Appendix E, holds.*

The proof of Theorem 4.3, based on using center manifold theory, is given in Appendix E. It should be recalled that the phenomenon of backward bifurcation does not occur in the PrEP-free model (3.1). In other words, the PrEP model (2.2) with $\delta = 0$ has one dynamical feature (backward bifurcation) that is not present in the PrEP-free model (3.1). A possible cause of this phenomenon is explored below.

4.1.2 Non-existence of Backward Bifurcation

Consider the special case of the PrEP model (2.2) in the absence of disease-induced mortality ($\delta = 0$) and PrEP is assumed to be 100% effective in preventing HIV infection (i.e., $\theta_L = \theta_H = 0$). In this case, it can be shown that the backward

bifurcation coefficient, a (given by (E.2) in Appendix E), reduces to (since β^*, v_4, x_1 and $Y_4 > 0$, as given in Appendix E)

$$a = \frac{-2\beta^* v_4 x_1 \mu^2 Y_4}{C_2^2 C_4^2 \pi^2} < 0.$$

Since $a < 0$, it follows from Theorem 4.1 of [7] that the special case of the PrEP model (2.2) with $\theta_L = \theta_H = \delta = 0$ does not undergo backward bifurcation. Thus, this study shows that the imperfect nature of PrEP use in preventing HIV infection (i.e., $0 < \theta_L, \theta_H < 1$) can cause the phenomenon of backward bifurcation in HIV transmission dynamics (even in the absence of disease-induced mortality). The presence of such PrEP-induced backward bifurcation makes efforts to effectively control the spread of HIV in the MSM community difficult (because, in such a backward bifurcation scenario, bringing the associated reproduction threshold, \mathcal{R}_P^* , to a value less than unity, while necessary, is no longer sufficient for effective control of the disease). Much greater reduction in the value of $\mathcal{R}_P^* < 1$ is needed for such effective control to be feasible (see, for instance, [6, 18, 20, 23]). This is, to the author's knowledge, the first time PrEP use is shown to cause the phenomenon of backward bifurcation of HIV (or any other disease).

4.2 Chapter Summary

The aim of this chapter was to rigorously analyze the PrEP model (2.2) to observe if it has certain dynamical features that are not present in the PrEP-free model (3.1). The main results are summarized below.

- i) The DFE \mathcal{E}_0^P is LAS whenever $\mathcal{R}_P < 1$.
- ii) A special case of the PrEP model (2.2) without disease-induced mortality undergoes the phenomenon of backward bifurcation when the associated re-

production number \mathcal{R}_P^* is less than unity. This is a dynamical feature not present in the PrEP-free model (3.1).

- iii) It is shown that backward bifurcation is caused by the imperfect nature of PrEP in preventing new HIV infections.

The results in this chapter addressed Question 1 in Section 1.4.

Cases	a_3	a_2	a_1	a_0	\mathcal{R}_P^*	Number of Sign Changes	Number of Possible Positive Roots
1	+	+	+	+	$\mathcal{R}_P^* < 1$	0	0
	+	+	+	-	$\mathcal{R}_P^* > 1$	1	1
2	+	-	-	+	$\mathcal{R}_P^* < 1$	2	0,2
	+	-	-	-	$\mathcal{R}_P^* > 1$	1	1
3	+	+	-	+	$\mathcal{R}_P^* < 1$	2	0,2
	+	+	-	-	$\mathcal{R}_P^* > 1$	1	1
4	+	-	+	+	$\mathcal{R}_P^* < 1$	2	0,2
	+	-	+	-	$\mathcal{R}_P^* > 1$	3	1,3

Table 4.1: Number of possible real positive roots of Equation (4.6) for $\mathcal{R}_P^* > 1$ and $\mathcal{R}_P^* < 1$.

Chapter 5

Uncertainty and Sensitivity Analysis

5.1 Introduction

Mathematical models of disease transmission are formulated based on epidemiological assumptions and often include a large number of different types of input parameters (biological, demographic, etc. . .) [5, 39]. The input parameter values are usually assumed or estimated from empirical data, so there is uncertainty in their precise value. Thus, the effect of these uncertainties on the outcome variable(s) (the reproduction number in the case of disease transmission models) needs to be explored through uncertainty and sensitivity analysis. Uncertainty analysis is used to determine the variability in the outcome variable(s) that is due to the uncertainties of the input parameters [5, 39]. Sensitivity analysis extends uncertainty analysis by identifying which input parameters have the biggest impact on the variability of the value of the outcome variable(s) [5, 39].

Latin Hypercube Sampling (LHS) is a reliable method that can be used to help analyze the uncertainties of parameter values in disease transmission models [5, 29,

39]. LHS is a stratified sampling method and can be viewed as an extension of Latin Square sampling [5, 29]. In LHS, each input parameter, $X_i \dots X_k$, is treated as a random variable, then probability distribution functions (pdfs) are defined for each parameter (based on the biology and/or epidemiology of the modelled disease) [5, 29]. The range of each X_k is divided into N strata of equal marginal probability, $\frac{1}{N}$, and one sample is randomly chosen from each stratum [5, 29]. The advantage of this method is that each parameter is used only once in this analysis, making this method very efficient for sampling design [5, 29].

Partial rank correlation coefficients (PRCC) can be used for sensitivity analysis. Calculation of PRCCs allows the statistical relationships between each input parameter and each outcome variable to be determined while holding all of the other input parameters constant at their expected value [5]. The sign of the PRCC indicates the qualitative relationship between each input parameter and each outcome variable [5]. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the specific input parameter and its contribution to prediction inaccuracies of the outcome variable [5]. The relative importance of the input parameters can be assessed by comparing the PRCC values [5, 39]. The value of a PRCC can range from -1 to $+1$, where a perfect linear relationship between the input parameter and outcome variable is indicated by a PRCC of $+1$ (or -1 for a negative linear relationship) and 0 for no linear relationship [30]. LHS and PRCCs will be used to assess the uncertainties and sensitivity of the parameter values of both the PrEP-free and PrEP models in the following two sections.

The PrEP-free model (3.1) and the PrEP model (2.2) are simulated using the parameter values given in Table 5.1, unless otherwise stated. Some of the parameter values are taken from the literature (such as in [1, 21, 32, 38, 40, 43]). In particular, the recruitment rate (π) is estimated based on the HIV transmission surveillance data of the MSM community in Minnesota [31, 32]. The approximate size of the MSM

community in Minnesota is 92,800 [31]. The natural death rate (μ) is estimated to be $\frac{1}{80}$ per year [53]. Thus, $\pi \approx 1,160$ per year. It is assumed that the duration of the acute infection stage is 6 weeks (that is, $\sigma_1 = 8.67$ per year) [2, 33]. The mean duration of the chronic (asymptomatic) stage is assumed to be 20 years (that is, $\sigma_2 = 0.05$ per year). The disease-induced death rate (δ) is estimated from the Minnesota Department of Health HIV/AIDS mortality surveillance data to be 0.07 per year [32]. Further, data from the Minnesota Department of Health shows that there are currently 3,857 MSM living with HIV/AIDS in the state of Minnesota [32].

5.2 PrEP-free Model (3.1)

The PrEP-free model (3.1) contains 16 parameters. Uncertainties in the parameter values are expected to occur. Uncertainty analysis is carried out by using the method of LHS. The LHS method entails defining a baseline value and range for each parameter of the PrEP-free model (3.1) (as in Table 5.1) and generating multiple runs ($N_R = 1000$) for a given outcome variable or response function (which, in this case, is chosen to be the basic reproduction number, \mathcal{R}_0) [5, 39]. Each parameter is assumed to abide by a uniform distribution [5, 39]. Box plots of the reproduction number, \mathcal{R}_0 , as a function of the number of LHS runs carried out, are depicted in Figure 5.1. The lower and upper horizontal lines on each box denotes the 25th and 75th percentiles of \mathcal{R}_0 , respectively [30]. The middle horizontal line within each box denotes the 50th percentile (median value) of \mathcal{R}_0 [30]. The upper and lower whiskers on each box represents the most extreme values of \mathcal{R}_0 and anything lying beyond the whiskers are classified as outliers [30]. Values of \mathcal{R}_0 lie within the range [2.43, 4.13].

Moreover, PRCCs are used to determine the parameter(s) that most affect the outcome variable \mathcal{R}_0 (hence, the parameter(s) that most affect the disease transmission dynamics of the PrEP-free model (3.1)). It follows from Table 5.2 that the

parameters that most affect the value of \mathcal{R}_0 are the effective contact rate (β), the natural death rate (μ), the progression rate from the acute stage to the chronic stage (σ_1), the modification parameter for reduction in infectiousness of individuals who fail treatment (θ_F), and the transition rate out of the failed treatment class (γ). Thus, this analysis identifies the primary parameters that play a dominant role in the dynamics of HIV/AIDS within the community of MSM. The effect of these top-five PRCC-ranked parameters on the cumulative incidence and prevalence of HIV/AIDS is further assessed by simulating the PrEP-free model (3.1) for the following two cases:

- i) the baseline value of each top-five PRCC-ranked parameter, given in Table 5.1, is decreased by 10% all at once;
- ii) the baseline value of each top-five PRCC-ranked parameter, given in Table 5.1, is increased by 10% all at once.

The results of these simulations, depicted in Figures 5.3 and 5.4, show that a 10% increase (decrease) in all of the top-five PRCC-ranked baseline parameter values at once leads to a corresponding increase (decrease) in the cumulative incidence and prevalence of HIV/AIDS over a 3-year period, respectively. These simulations further confirm the sensitivities of the input parameters, and their effect, on the uncertainty of the outcome variable, \mathcal{R}_0 .

5.3 PrEP Model (2.2)

Like for the PrEP-free model (3.1) discussed in Section 5.2, the impact of the uncertainty in the estimates and sensitivity of the parameter values for the PrEP model (2.2), which contains 24 parameters, needs to be assessed. The same approach in Section 5.2 is used and the associated reproduction number (\mathcal{R}_P) is chosen as the

response function. Again, each parameter is assumed to follow a uniform distribution [5, 39]. Furthermore, PRCCs are found between each parameter value and the outcome variable, \mathcal{R}_P , in order to measure the sensitivity of the parameter values.

Box plots of the reproduction number \mathcal{R}_P , as a function of the number of LHS runs ($N_R = 1000$) carried out, depicted in Figure 5.5, show a range of \mathcal{R}_P from 1.80 to 2.85. It is worth noting that the range of \mathcal{R}_P is a little lower than that of \mathcal{R}_0 given in Section 5.2 (this is a measure of the utility of PrEP in reducing new cases of HIV infection, it should be noted that, in this case, the rate of administration of PrEP is 1% ($\psi = 0.01$)). When the rate of administration of PrEP is increased to 50% (i.e., $\psi = 0.5$), the range of \mathcal{R}_P significantly decreases to $\mathcal{R}_P \in [0.73, 1.25]$, further underlying the effect of PrEP on HIV incidence (Figure 5.6). Further, and perhaps more importantly, the mean value of \mathcal{R}_P is decreased to a value below unity (mean value of $\mathcal{R}_P = 0.98 < 1$), which implies that community-wide effective control (or elimination) of the disease is feasible (taking into consideration the effect of the phenomenon of backward bifurcation in the PrEP model (2.2)).

The PRCC values for each parameter are given in Table 5.3. It follows from those values that the most dominant parameters (that is, those parameters that drive the dynamics of the PrEP model (2.2)) are the effective contact rate (β), the rate of cessation of PrEP by low-adherent PrEP users (ω_L), the progression rate from the acute stage to the chronic stage of infection (σ_1), the modification parameter for a reduction in infectiousness of individuals who fail treatment (θ_F), and the transition rate out of the failed treatment class (γ).

As in Section 5.2, the effect of these top-five PRCC-ranked parameters on the cumulative incidence and prevalence of HIV/AIDS is further assessed by simulating the PrEP model (2.2) for the following two cases:

- i) the baseline value of each top-five PRCC-ranked parameter, given in Table 5.1, are all decreased by 10% at once;

- ii) the baseline value of each top-five PRCC-ranked parameter, given in Table 5.1, are increased by 10% at once.

Figures 5.8 and 5.9 show that a 10% increase (decrease) in all of the top-five PRCC-ranked baseline values at once leads to a corresponding increase (decrease) in the cumulative incidence and prevalence of HIV/AIDS in a 3-year period, respectively. These simulations further confirm the sensitivities of the input parameters and their effect on the uncertainty of the outcome variable, \mathcal{R}_P . The effect of the rate of administration of PrEP (ψ) on the incidence of HIV infection is depicted in Figure 5.10. It follows from this figure, as expected, that a higher rate of administration of PrEP corresponds to a decrease in the incidence of HIV infection.

5.3.1 Threshold Analysis

It is instructive to determine conditions for the effective control of the disease in terms of p . It is convenient to define the fraction of susceptible individuals on PrEP (adjusted by PrEP efficacy) at the disease-free equilibrium, given by,

$$p = \frac{(1 - \theta_L)S_L^* + (1 - \theta_H)S_H^*}{N^*},$$

where $0 < \theta_L \leq 1$ and $0 < \theta_H \leq 1$ are the modification parameters for reduction of the transmission rate of those in the S_L class and S_H class, respectively. This allows for the determination of the critical fraction of individuals needed to be on PrEP in order to achieve effective control of the disease within the MSM community. Some sort of “*herd immunity*” [23] in this context can occur if enough susceptible individuals have PrEP-acquired immunity, so that the introduction of one infective into the MSM community does not cause a major outbreak of the disease [23]. The associated reproduction number for the PrEP model (2.2), \mathcal{R}_P , can be defined in

terms of the fraction, p , as follows:

$$\mathcal{R}_P = (1 - p)\mathcal{R}_0,$$

where, \mathcal{R}_0 is the basic reproduction number of the PrEP-free model (3.1). It follows from the above equation that the reproduction threshold (\mathcal{R}_P) is a decreasing function of the fraction (p) of susceptible individuals on PrEP adjusted by PrEP efficacy (that is, as expected, PrEP use, adjusted by the efficacy $(1 - \theta_L)$ and $(1 - \theta_H)$, induces a positive population-level impact, by minimizing HIV burden in the community (since it decreases \mathcal{R}_P). Furthermore, setting $\mathcal{R}_P = 1$, and solving for the critical fraction, $p = p_c$, gives

$$p_c = 1 - \frac{1}{\mathcal{R}_0}. \quad (5.1)$$

From (5.1), p_c is positive if $\mathcal{R}_0 > 1$ (that is, in the case where HIV is endemic in the community). For the PrEP model (2.2) with $\mathcal{R}_0 > 1$, if the fraction of untreated susceptible individuals administered PrEP, adjusted by PrEP efficacy at steady-state, exceeds the threshold p_c (that is, $p > p_c$), then $\mathcal{R}_P < 1$ and the DFE (\mathcal{E}_0^P) of the PrEP model (2.2) is LAS. This means that HIV/AIDS can be effectively-controlled (or eliminated) from the community when $\mathcal{R}_P < 1$ if the initial sizes of the sub-populations of the PrEP model (2.2) are in the basin of attraction of the DFE (\mathcal{E}_0^P).

The quantity $1 - \frac{1}{\mathcal{R}_0}$ in (5.1) is the minimum PrEP coverage level needed to effectively control (or eliminate) HIV/AIDS in the MSM community [23]. Using the data in Table 5.1, simulations of the PrEP model (2.2), depicted in Figure 5.11, show the distribution of the threshold p_c values in the range $p_c \in [0.61, 0.77]$ (with a mean of $p_c \approx 0.69$). Thus, this study shows that HIV can be effectively controlled in the MSM community in the State of Minnesota if 61% to 77% of the susceptible population are on PrEP.

The population-level effect of the efficacy-adjusted fraction of susceptible individuals on PrEP (p) is assessed by simulating the PrEP model (2.2) with various values of p . The results obtained, depicted in Figure 5.12, show that the cumulative number of new HIV cases decreases with increasing values of p . For instance, while treating 25% of susceptible individuals with PrEP (efficacy-adjusted at steady state, so that $p = 0.25$) resulted in about 392 cumulative new cases of HIV infection, increasing the treatment coverage to 75% resulted in about 360 new infections. It follows from this figure, as expected, that a higher efficacy-adjusted fraction of susceptible individuals on PrEP corresponds to a decrease in the incidence of HIV infection.

5.4 Chapter Summary

This chapter focuses on uncertainty and sensitivity analysis, numerical simulations of the PrEP-free model (3.1) and PrEP model (2.2), and determining the elimination conditions in terms of the threshold fraction p . The main results are summarized below.

- i) The top-five parameters that most affect the disease transmission dynamics of the PrEP-free model (3.1) (with respect to the basic reproduction number \mathcal{R}_0 , as the response variable) are:
 - (a) the effective contact rate (β);
 - (b) the natural death rate (μ);
 - (c) the progression rate from the acute stage to the chronic stage (σ_1);
 - (d) the modification parameter for reduction in infectiousness of individuals who failed antiretroviral treatment (θ_F);
 - (e) the transition rate out of the failed treatment class (γ).

- ii) The top-five parameters that most affect the disease transmission dynamics of the PrEP model (2.2) (with respect to the associated reproduction number \mathcal{R}_P) are:
- (a) the effective contact rate (β);
 - (b) the rate of cessation of PrEP by low-adherent PrEP users (ω_L);
 - (c) the progression rate from the acute stage to the chronic stage (σ_1);
 - (d) the modification parameter for reduction in infectiousness of individuals who failed antiretroviral treatment (θ_F);
 - (e) the transition rate out of the failed treatment class (γ).
- iii) Numerical simulations show that disease burden decreases with increasing PrEP coverage. For instance, effective disease control can be achieved in the MSM community of Minnesota if [61% – 77%] of susceptible members of the community are on PrEP (adjusted by PrEP efficacy). It should be cautioned that owing to the presence of the phenomenon of PrEP-induced backward bifurcation in HIV transmission dynamics (shown in this thesis), this result is dependent on the initial number of HIV-infected people in the MSM community.

The results in this chapter addressed Questions 2 and 3 in Section 1.4.

Table 5.1: Baseline values and ranges of the parameters of the PrEP model (2.2).

Parameter	Baseline Value (<i>per year</i>)	Range (<i>per year</i>)	Reference
π	1160	[1044, 1276]	[32]
β	0.25	[0.225, 0.275]	[38]
μ	1/80	[0.01125, 0.01375]	[21, 38]
δ	0.07	[0.063, 0.077]	[32]
θ_2	0.43	[0.387, 0.473]	[38]
θ_T	0.008	[0.0072, 0.0088]	[40]
θ_F	0.70	[0.63, 0.77]	Assumed
θ_A	1.5	[1.35, 1.65]	[40]
σ_1	8.67	[7.80, 9.54]	[21, 38]
σ_2	0.05	[0.045, 0.055]	[21, 38]
κ	0.10	[0.09, 0.11]	Assumed
γ	0.5	[0.45, 0.55]	Assumed
r	0.75	[0.675, 0.825]	Assumed
τ_1	0.7	[0.6, 0.8]	[43]
τ_2	0.7	[0.6, 0.8]	[43]
τ_A	0.7	[0.6, 0.8]	[43]
f	0.75	[0.675, 0.825]	Assumed
ψ	0.01	[0.009, 0.011]	Assumed
ω_L	0.005	[0.0045, 0.0055]	Assumed
ω_H	0.0001	[0.00009, 0.00011]	Assumed
ξ_L	0.75	[0.675, 0.825]	Assumed
ξ_H	0.25	[0.225, 0.275]	Assumed
θ_L	0.8	[0.72, 0.88]	[1, 43]
θ_H	0.11	[0.099, 0.121]	[1, 43]

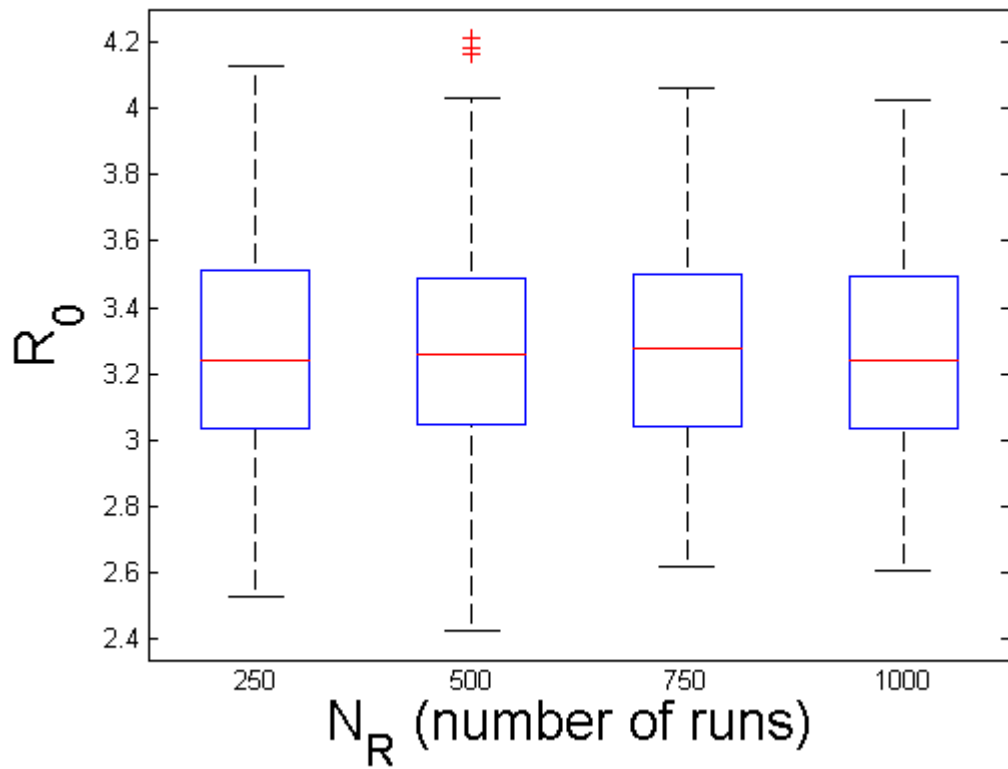


Figure 5.1: Box plots of the reproduction number (\mathcal{R}_0), as a function of the number of LHS runs (N_R) carried out, for the PrEP-free model (3.1).

Table 5.2: PRCC values of the parameters of the PrEP-free model (3.1).

Parameter	PRCC Value
β	0.9636
μ	-0.9490
σ_1	0.8982
θ_F	0.8777
γ	-0.8107
θ_A	0.6460
θ_2	0.5622
δ	-0.4179
τ_2	-0.3926
r	-0.2095
τ_A	-0.1995
θ_T	0.0998
π	-0.0432
κ	0.0424
τ_1	-0.0204
σ_2	0.0128

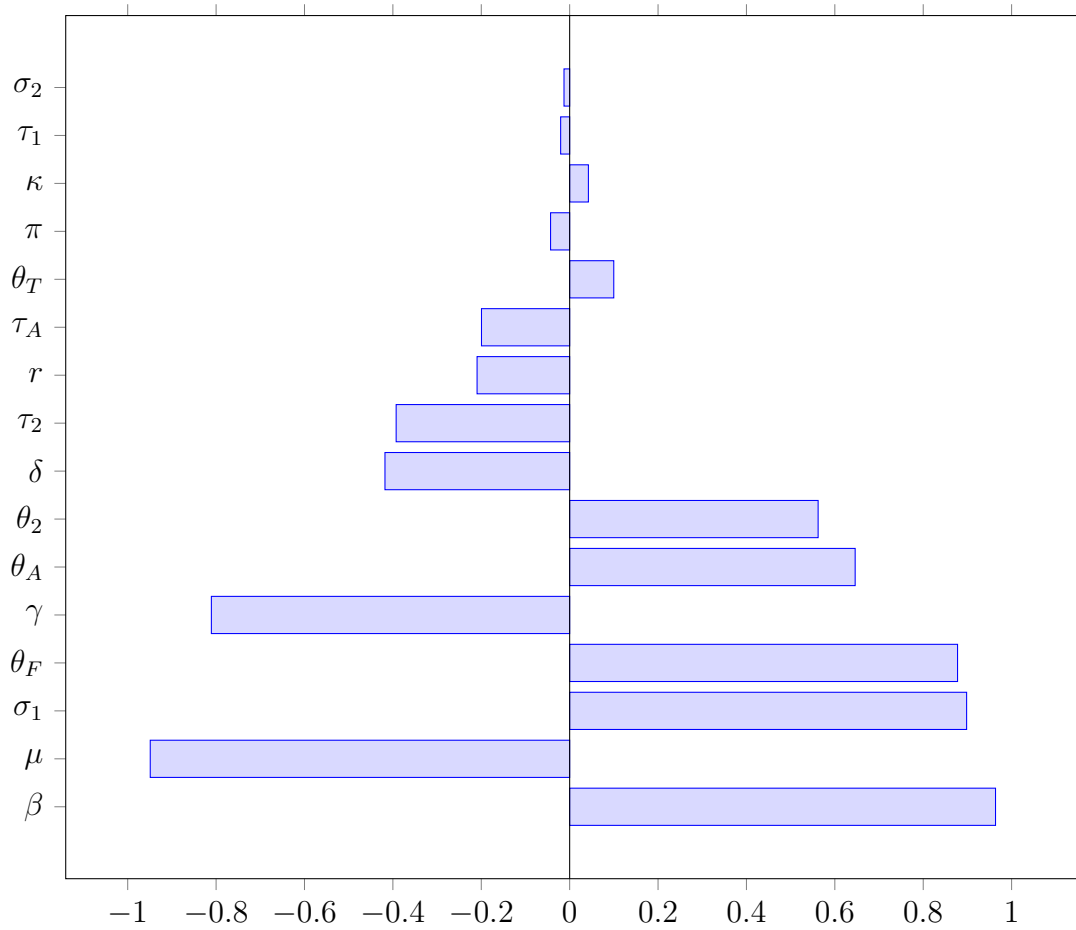


Figure 5.2: PRCC values of the parameters of the PrEP-free model (3.1) with \mathcal{R}_0 as the outcome (response) variable. Parameter values and ranges used are as given in Table 5.1.

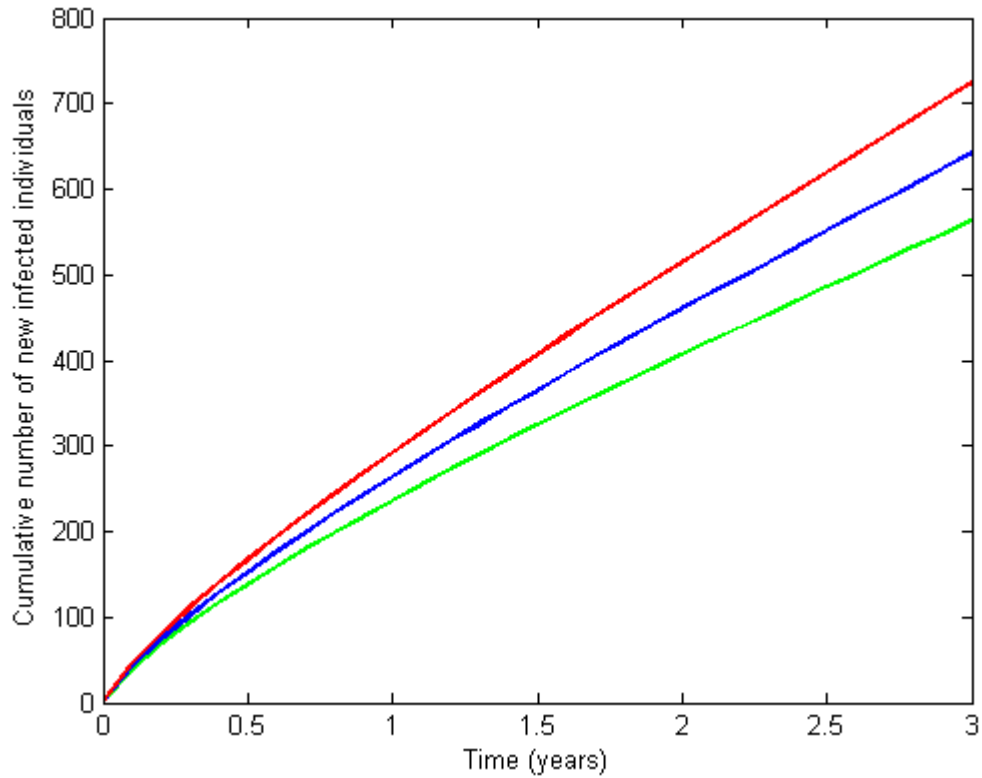


Figure 5.3: Simulations of the PrEP-free model (3.1), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 5.1 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 5.1 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%.

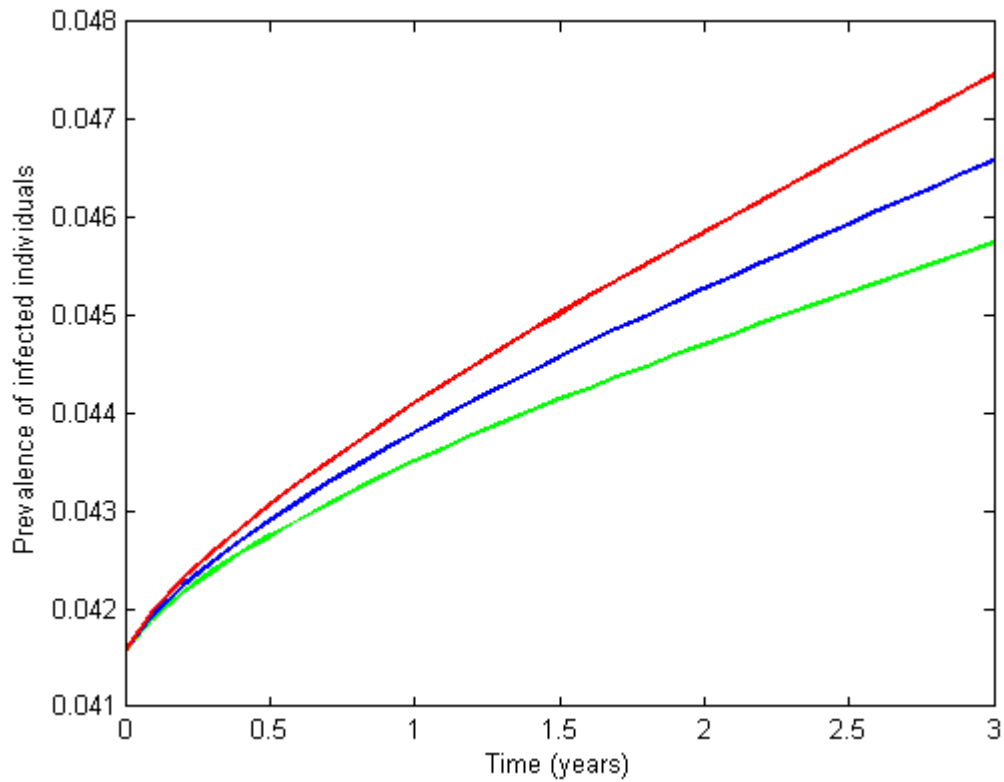


Figure 5.4: Simulations of the PrEP-free model (3.1), showing the prevalence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 5.1 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 5.1 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%.

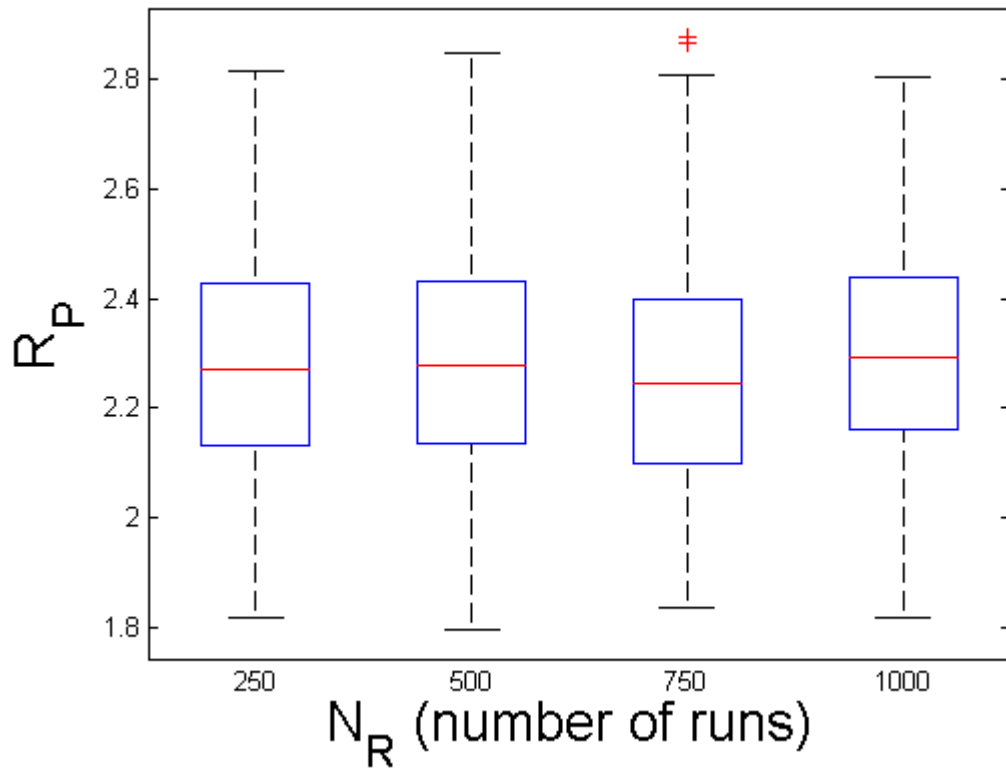


Figure 5.5: Box plots of the reproduction number (\mathcal{R}_P), as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2). Parameter values and ranges used are as given in Table 5.1.

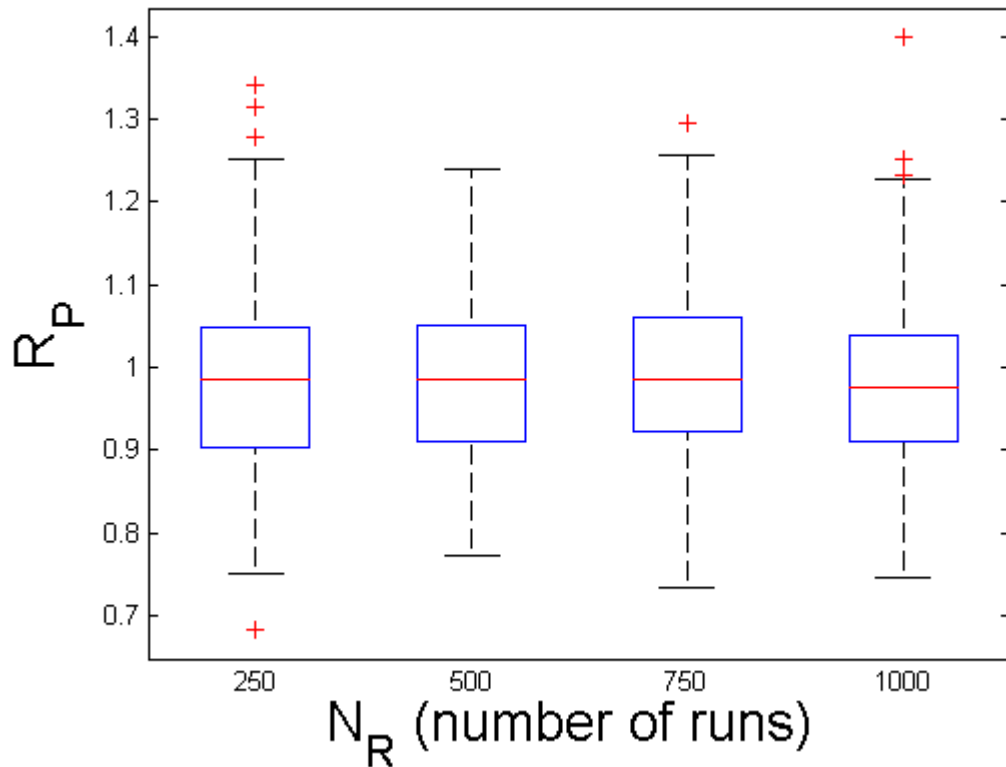


Figure 5.6: Box plots of the reproduction number (\mathcal{R}_P), as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2) with an increased proportion of the susceptible population on PrEP ($\psi = 50\%$). Parameter values and ranges used are as given in Table 5.1.

Table 5.3: PRCC values of the parameters of the PrEP model (2.2).

Parameter	PRCC Value
β	0.9671
ω_L	-0.9160
σ_1	0.9066
θ_F	0.8895
γ	-0.8301
ψ	-0.6848
θ_A	0.6489
θ_2	0.6091
δ	-0.4210
τ_2	-0.4140
θ_L	0.3769
ω_H	-0.3517
ξ_L	0.2892
r	-0.1908
τ_A	-0.1708
θ_T	0.1429
θ_H	0.1375
ξ_H	0.1039
σ_2	-0.0601
κ	0.0451
π	0.0228
f	-0.0138
μ	-0.0057
τ_1	-0.0013

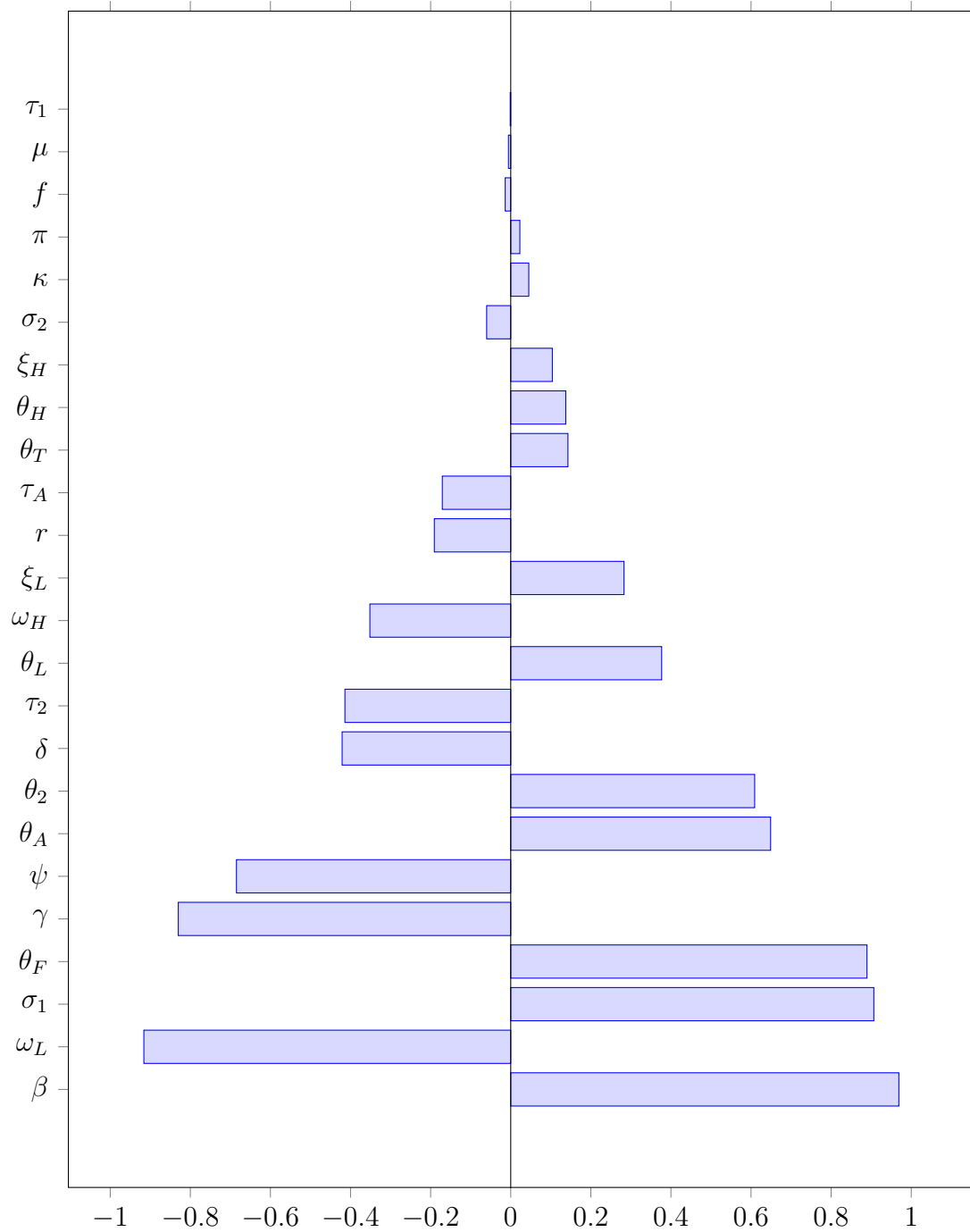


Figure 5.7: PRCC values of the parameters of the PrEP model (2.2) with \mathcal{R}_P as the outcome (response) variable. Parameter values and ranges used are as given in Table 5.1.

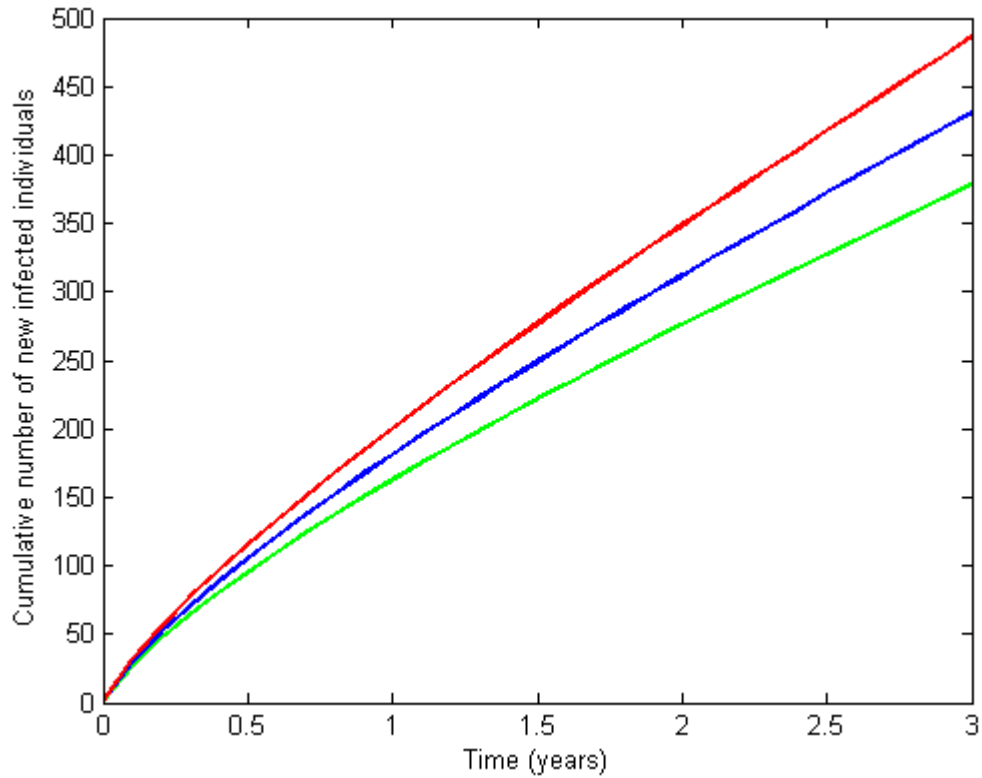


Figure 5.8: Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 5.1 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 5.1 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%.

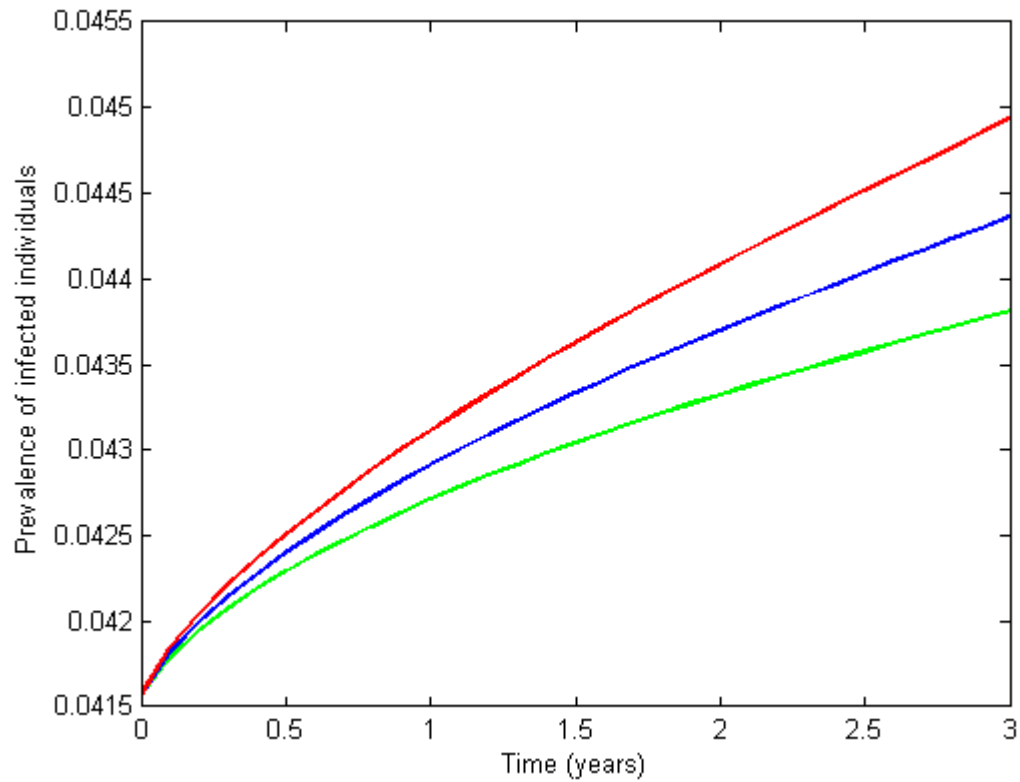


Figure 5.9: Simulations of the PrEP model (2.2), showing the prevalence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 5.1 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 5.1 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%.

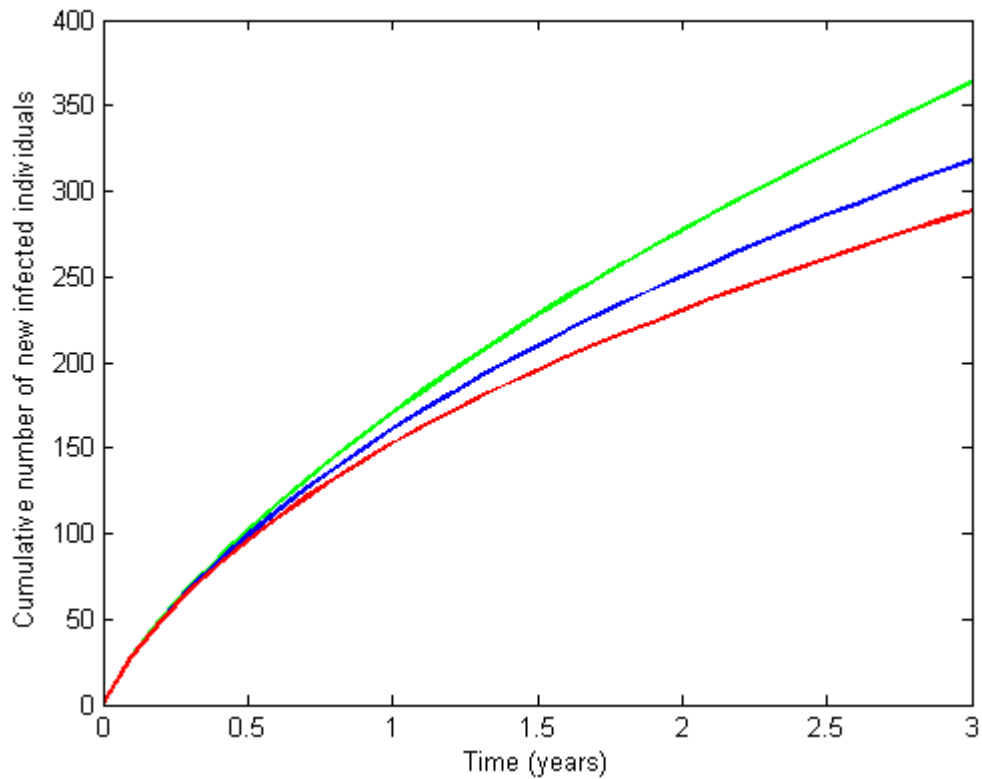


Figure 5.10: Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the rate of administration of PrEP (ψ). Parameter values used are as given in Table 5.1 (unless otherwise stated). Green curve: $\psi = 0.25$ ($\mathcal{R}_P = 1.04$). Blue curve: $\psi = 0.5$ ($\mathcal{R}_P = .98$). Red curve: $\psi = 0.75$ ($\mathcal{R}_P = .96$).

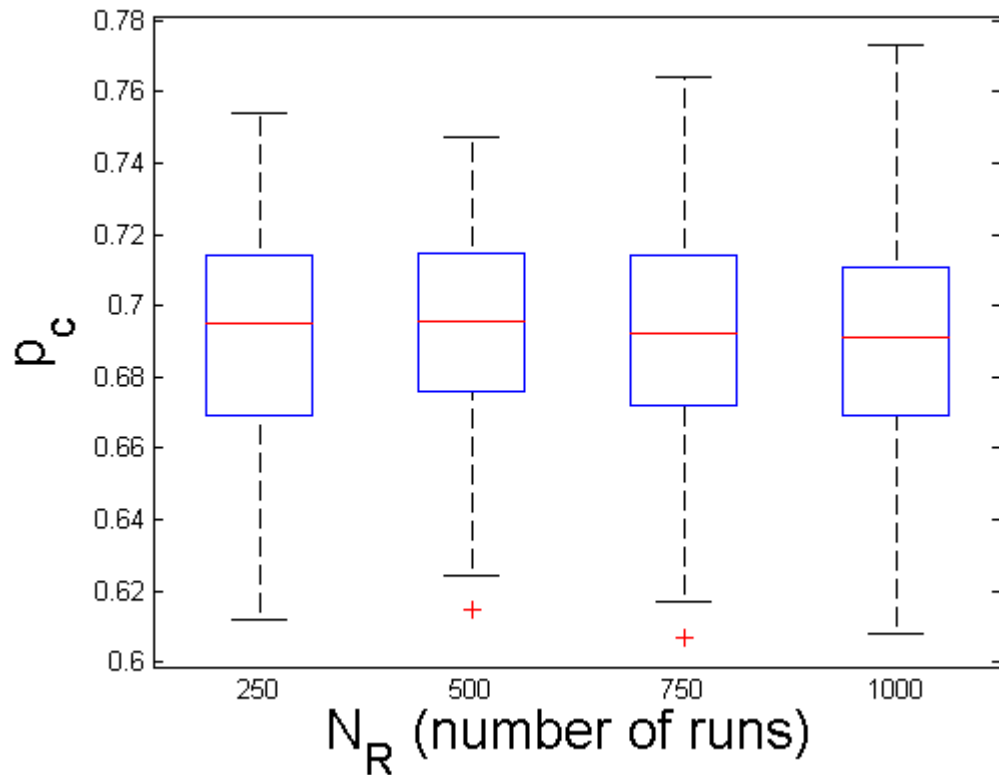


Figure 5.11: Box plots of the critical fraction of susceptible individuals on PrEP (adjusted by PrEP efficacy), p_c , as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2). Parameter values and ranges used are as given in Table 5.1.

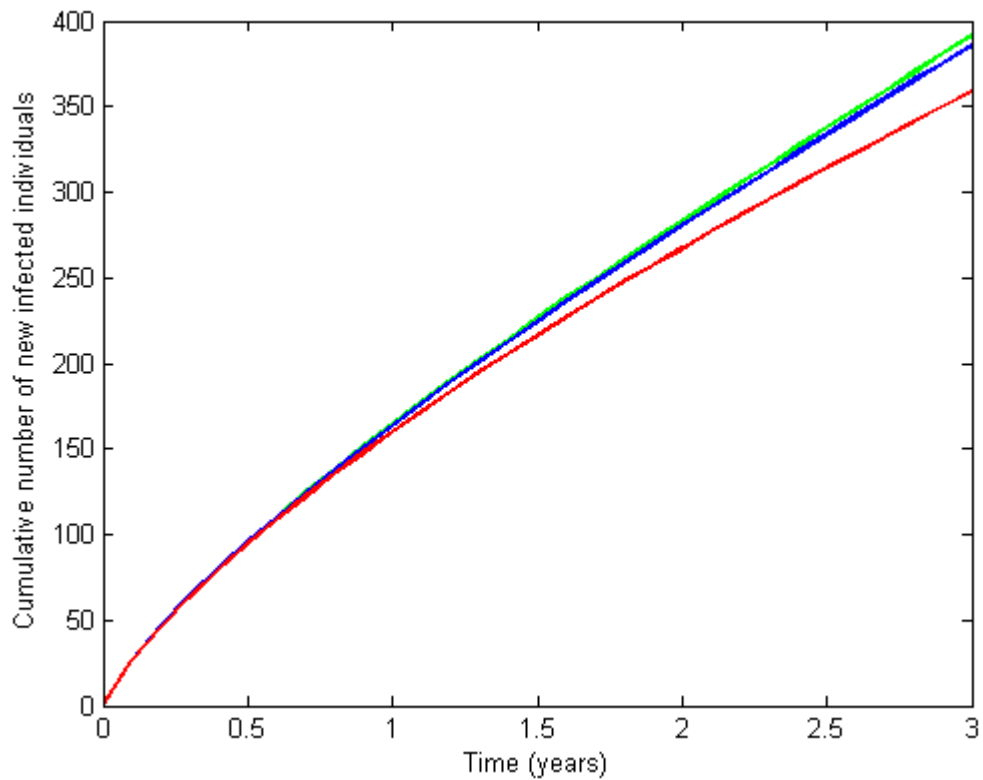


Figure 5.12: Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the efficacy-adjusted fraction of susceptible individuals on PrEP (p): green curve ($p = 0.25$), blue curve ($p = 0.5$), red curve ($p = 0.75$).

Appendix A

Proof of Theorem 2.1

Proof. Let $t_1 = \sup\{t > 0 : S(t) > 0, S_H(t) > 0, S_L(t) > 0, I_1(t) > 0, I_2(t) > 0, I_T(t) > 0, F(t) > 0, A(t) > 0\} > 0$. It follows from the first of the PrEP model (2.2) that,

$$\frac{dS}{dt} = \pi + \omega_L S_L + \omega_H S_H - \lambda S - \psi S - \mu S \geq \pi - \lambda S - \psi S - \mu S \quad (\text{A.1})$$

which can be re-written as:

$$\frac{d}{dt} \left(S(t) \exp \left[(\mu + \psi)t + \int_0^t \lambda(u) du \right] \right) \geq \pi \exp \left[(\mu + \psi)t + \int_0^t \lambda(u) du \right].$$

Hence,

$$S(t_1) \exp \left[(\mu + \psi)t_1 + \int_0^{t_1} \lambda(u) du \right] - S(0) \geq \int_0^{t_1} \pi \left(\exp \left[(\mu + \psi)y + \int_0^y \lambda(u) du \right] \right) dy,$$

so that,

$$\begin{aligned}
S(t_1) \geq & S(0) \exp \left[-(\mu + \psi)t_1 - \int_0^{t_1} \lambda(u) du \right] \\
& + \exp \left[-(\mu + \psi)t_1 - \int_0^{t_1} \lambda(u) du \right] \int_0^{t_1} \pi \left(\exp \left[(\mu + \psi)y + \int_0^y \lambda(u) du \right] \right) dy > 0.
\end{aligned}$$

Similarly, it can be shown that $S_H(t) > 0$, $S_L(t) > 0$, $I_1(t) \geq 0$, $I_2(t) \geq 0$, $I_T(t) \geq 0$, $F(t) \geq 0$, and $A(t) \geq 0$ for all time $t > 0$. Therefore, all solutions of the model (2.2) remain positive for all non-negative initial conditions. \square

Appendix B

Positivity of \mathcal{R}_0 and \mathcal{R}_P

B.1 Positivity of \mathcal{R}_0

Recall from Section 3.1.1 that (with all associated variables as defined in section 3.1.1)

$$\mathcal{R}_0 = \frac{\beta(M_1 + \theta_2 M_2 + \theta_T K_4 M_3 + \theta_F \kappa M_3 + \theta_A M_5)}{M_1 K_1}.$$

It follows that \mathcal{R}_0 is positive since,

$$\begin{aligned}
M_1 &= \kappa\gamma K_2\tau_A r - \kappa\gamma K_2\tau_A - \kappa r\gamma K_5\tau_2 - \kappa r\gamma\sigma_2\tau_A + K_2K_3K_4K_5 \\
&= \kappa\gamma K_2\tau_A r + \delta\mu^3 + \delta\mu^2\gamma + \delta\mu^2\sigma_2 + \delta\mu^2\tau_2 + \delta\mu\gamma\kappa + \delta\mu\gamma\sigma_2 + \delta\mu\kappa\sigma_2 + \delta\mu\kappa\tau_2 \\
&\quad + \delta\gamma\kappa\sigma_2 + \delta\gamma\kappa\tau_2(1-r) + \mu^4 + \mu^3\gamma + \mu\kappa + \mu^2\sigma_2 + \mu^3\tau_A + \mu^2\gamma\kappa + \mu^2\gamma\sigma_2 + \mu^2\gamma\tau_2 \\
&\quad + \mu^2\gamma\tau_A + \mu^2\kappa\sigma_2 + \mu^2\kappa\tau_2 + \mu^2\kappa\tau_A + \mu^2\sigma_2\tau_A + \mu^2\tau_2\tau_A + \mu\gamma\kappa\sigma_2 + \mu\gamma\kappa\tau_2(1-r) \\
&\quad + \mu\kappa\sigma_2\tau_A + \mu\kappa\tau_2\tau_A + \gamma\kappa\sigma_2\tau_A(1-r) + \gamma\kappa\tau_2\tau_A(1-r) > 0,
\end{aligned}$$

$$\begin{aligned}
M_2 &= \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r K_5\kappa\tau_1 + K_5K_4K_3\sigma_1 \\
&= \gamma\kappa\sigma_1\tau_A r + \gamma r K_5\kappa\tau_1 + \delta\kappa\mu\sigma_1 + \delta\kappa\gamma\sigma_1 + \delta\mu^2\sigma_1 + \delta\mu\gamma\sigma_1 + \kappa\mu^2\sigma_1 + \kappa\mu\gamma\sigma_1 \\
&\quad + \kappa\mu\sigma_1\tau_A + \mu^3\sigma_1 + \mu^2\gamma\sigma_1 + \mu^2\sigma_1\tau_A + \mu\gamma\sigma_1\tau_A > 0,
\end{aligned}$$

$$M_3 = K_2K_5\tau_1 + K_5\sigma_1\tau_2 + \sigma_1\sigma_2\tau_A > 0,$$

$$M_4 = \gamma r \kappa \sigma_2 \tau_1 + K_3 K_4 \sigma_1 \sigma_2 + \kappa \gamma (1-r)(K_2 \tau_1 + \sigma_1 \tau_2) > 0$$

(since $0 < r < 1$).

B.2 Positivity of \mathcal{R}_P

Recall from Section 4.1 that (with all associated variables as defined in section 4.1)

$$\mathcal{R}_P = \frac{\beta g(Q_2 + \theta_2 Q_3 + \theta_T C_4 Q_4 + \theta_F \kappa Q_4 + \theta_A Q_5)}{Q_2 C_1 N^*}$$

It follows that \mathcal{R}_P is positive since,

$$g = S^* + \theta_H S_H^* + \theta_L S_L^* > 0,$$

$$\begin{aligned} Q_2 &= \kappa\gamma C_2 \tau_A r - \kappa\gamma C_2 \tau_A - \kappa r \gamma C_5 \tau_2 - \kappa r \gamma \sigma_2 \tau_A + C_2 C_3 C_4 C_5 \\ &= \kappa\gamma C_2 \tau_A r + \delta\mu^3 + \delta\mu^2\gamma + \delta\mu^2\sigma_2 + \delta\mu^2\tau_2 + \delta\mu\gamma\kappa + \delta\mu\gamma\sigma_2 + \delta\mu\kappa\sigma_2 + \delta\mu\kappa\tau_2 \\ &\quad + \delta\gamma\kappa\sigma_2 + \delta\gamma\kappa\tau_2(1-r) + \mu^4 + \mu^3\gamma + \mu\kappa + \mu^2\sigma_2 + \mu^3\tau_A + \mu^2\gamma\kappa + \mu^2\gamma\sigma_2 + \mu^2\gamma\tau_2 \\ &\quad + \mu^2\gamma\tau_A + \mu^2\kappa\sigma_2 + \mu^2\kappa\tau_2 + \mu^2\kappa\tau_A + \mu^2\sigma_2\tau_A + \mu^2\tau_2\tau_A + \mu\gamma\kappa\sigma_2 + \mu\gamma\kappa\tau_2(1-r) \\ &\quad + \mu\kappa\sigma_2\tau_A + \mu\kappa\tau_2\tau_A + \gamma\kappa\sigma_2\tau_A(1-r) + \gamma\kappa\tau_2\tau_A(1-r) > 0, \end{aligned}$$

$$\begin{aligned} Q_3 &= \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r C_5 \kappa\tau_1 + C_5 C_4 C_3 \sigma_1 \\ &= \gamma\kappa\sigma_1\tau_A r + \gamma r C_5 \kappa\tau_1 + \delta\kappa\mu\sigma_1 + \delta\kappa\gamma\sigma_1 + \delta\mu^2\sigma_1 + \delta\mu\gamma\sigma_1 + \kappa\mu^2\sigma_1 + \kappa\mu\gamma\sigma_1 \\ &\quad + \kappa\mu\sigma_1\tau_A + \mu^3\sigma_1 + \mu^2\gamma\sigma_1 + \mu^2\sigma_1\tau_A + \mu\gamma\sigma_1\tau_A > 0, \end{aligned}$$

$$Q_4 = C_2 C_5 \tau_1 + C_5 \sigma_1 \tau_2 + \sigma_1 \sigma_2 \tau_A > 0,$$

$$Q_5 = \gamma r \kappa \sigma_2 \tau_1 + C_3 C_4 \sigma_1 \sigma_2 + \kappa \gamma (1-r)(C_2 \tau_1 + \sigma_1 \tau_2) > 0,$$

(since $0 < r < 1$ and $0 < f < 1$).

Appendix C

Proof of Theorem 3.3

Proof. The proof is based on a Comparison Theorem [25]. It should first be noted that the model (3.1) satisfies the Type K condition [42] (so that a Comparison Theorem [25] can be applied). The infected components of the PrEP-free model (3.1) can be re-written as

$$\frac{d}{dt} \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} = (\mathcal{H} - \mathcal{V}) \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} - J \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix}, \quad (\text{C.1})$$

where the matrices \mathcal{H} and \mathcal{V} are as defined in Section 3.1.1 and

$$J = \left(1 - \frac{S}{N}\right) \mathcal{H}.$$

It should be noted that J is a non-negative matrix since, $S(t) \leq N(t) \leq \frac{\pi}{\mu}$ in \mathcal{D}_1 .

Thus,

$$\frac{d}{dt} \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} \leq (\mathcal{H} - \mathcal{V}) \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} \quad (\text{C.2})$$

Using the fact that the eigenvalues of the matrix $\mathcal{H} - \mathcal{V}$ all have negative real parts (see Theorem 3.2 for the LAS result if $\mathcal{R}_0 < 1$), it follows that the linearized differential equation inequality system (C.2) is stable whenever $\mathcal{R}_0 < 1$. Hence, it follows by Comparison Theorem [25], that

$$\lim_{t \rightarrow \infty} (I_1(t), I_2(t), I_T(t), F(t), A(t)) \rightarrow (0, 0, 0, 0, 0).$$

Substituting $I_1(t) = I_2(t) = I_T(t) = F(t) = A(t) = 0$ into the first equation of the PrEP-free model (3.1) gives $S(t) \rightarrow S^*$ as $t \rightarrow \infty$ for ($\mathcal{R}_0 < 1$). Thus,

$$\lim_{t \rightarrow \infty} (S(t), I_1(t), I_2(t), I_T(t), F(t), A(t)) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0 \right) = \mathcal{E}_0.$$

Therefore, the DFE (\mathcal{E}_0) of the model (3.1) is GAS in \mathcal{D}_1 whenever $\mathcal{R}_0 < 1$. □

Appendix D

Proof of Theorem 3.7

Proof. Consider the PrEP-free model (3.1) with $\delta = 0$ and $\mathcal{R}_1 = \mathcal{R}_0|_{\delta=0} > 1$ (so that the unique EEP, \mathcal{E}_1 , exists in line with Theorem 3.4). Consider the following non-linear Lyapunov function:

$$\begin{aligned} \mathcal{L} = & \left(S - S^{**} - S^{**} \ln \frac{S}{S^{**}} \right) + \left(I_1 - I_1^{**} - I_1^{**} \ln \frac{I_1}{I_1^{**}} \right) \\ & + b_1 \left(I_2 - I_2^{**} - I_2^{**} \ln \frac{I_2}{I_2^{**}} \right) + b_2 \left(I_T - I_T^{**} - I_T^{**} \ln \frac{I_T}{I_T^{**}} \right) \\ & + b_3 \left(F - F^{**} - F^{**} \ln \frac{F}{F^{**}} \right) + b_4 \left(A - A^{**} - A^{**} \ln \frac{A}{A^{**}} \right) \end{aligned} \quad (\text{D.1})$$

where,

$$b_1 = \frac{\beta \mu S^{**} I_2^{**} G_2}{\pi I_1^{**} G_1}, \quad b_2 = \frac{\beta \mu S^{**} G_3}{\pi I_1^{**} G_1},$$

$$b_3 = \frac{\beta \mu S^{**} F^{**} G_4}{\pi I_1^{**} \kappa I_T^{**} G_1}, \quad b_4 = \frac{\beta \mu S^{**} A^{**} G_5}{\pi I_1^{**} G_1},$$

and (note that $0 < r < 1$, so that the coefficients of the Lyapunov function (D.1) are all positive),

$$\begin{aligned}
G_1 &= (F^{**})^2 \gamma^2 (1-r)r\tau_1 + I_1^{**} F^{**} \gamma (1-r)\sigma_1\tau_1 + I_2^{**} F^{**} (1-r)\gamma\sigma_1\tau_2 \\
&\quad + I_2^{**} F^{**} \gamma r\sigma_2\tau_1 + I_1^{**} I_2^{**} \sigma_1\sigma_2\tau_1 + (I_2^{**})^2 \sigma_1\sigma_2\tau_2 + I_2^{**} A^{**} \sigma_1\sigma_2\tau_A, \\
G_2 &= I_1^{**} F^{**} (1-r)\gamma\tau_1\theta_2 + (\theta_2 I_2^{**} + \theta_A A^{**}) (I_1^{**} \sigma_2\tau_1) \\
&\quad + (\theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) (F^{**} (1-r)\gamma\tau_2 + A^{**} \sigma_2\tau_A + I_2^{**} \sigma_2\tau_2), \\
G_3 &= (\theta_T I_T^{**} + \theta_F F^{**}) (I_1^{**} I_2^{**} \sigma_1\sigma_2) \\
&\quad + (\theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) (I_1^{**} F^{**} \gamma (1-r)\sigma_1) \\
&\quad + (\theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) (I_2^{**} F^{**} r\gamma\sigma_2 + (F^{**})^2 (1-r)r\gamma^2), \\
G_4 &= (\sigma_1 I_1^{**} \sigma_2 I_2^{**} \theta_F) [\tau_1 I_1^{**} + \tau_2 I_2^{**} + \tau_A A^{**}] \\
&\quad + (\theta_F F^{**} + \theta_A A^{**}) [I_1^{**} I_2^{**} \gamma (1-r)\sigma_1\tau_2 + (I_1^{**})^2 \gamma (1-r)\sigma_1\tau_1] \\
&\quad + (\theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) [I_1^{**} A^{**} \gamma (1-r)\sigma_1\tau_A] \\
&\quad + (\theta_2 I_2^{**} + \theta_F F^{**} + \theta_A A^{**}) [I_1^{**} F^{**} \gamma^2 (1-r)r\tau_1 + I_1^{**} I_2^{**} \gamma r\sigma_2\tau_1] \\
&\quad + (\theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) [(I_2^{**})^2 \gamma r\sigma_2\tau_2 + F^{**} A^{**} \gamma^2 (1-r)r\tau_A \\
&\quad + I_2^{**} F^{**} \gamma (1-r)r\tau_2 + I_2^{**} A^2 \gamma r\sigma_2\tau_A], \\
G_5 &= I_2^{**} F^{**} \gamma r\tau_A \theta_2 + (I_T^{**} \theta_T + F^{**} \theta_F + \theta_A A) (I_1^{**} \sigma_1\tau_A + F^{**} \gamma r\tau_A) \\
&\quad + [I_1^{**} F^{**} \gamma r\tau_1 + (I_1^{**})^2 \sigma_1\tau_1 + I_1^{**} I_2^{**} \sigma_1\tau_2] \theta_A.
\end{aligned}$$

The Lyapunov derivative of (D.1) is given by

$$\begin{aligned}
\dot{\mathcal{L}} = & \left(1 - \frac{S^{**}}{S}\right) \left[\pi + \lambda S - \mu S\right] + \left(1 - \frac{I_1^{**}}{I}\right) \left[\lambda S - (\sigma_1 + \tau_1 + \mu)I_1\right] \\
& + b_1 \left(1 - \frac{I_2^{**}}{I_2}\right) \left[\sigma_1 I_1 + \gamma r F - (\sigma_2 + \tau_2 + \mu)I_2\right] \\
& + b_2 \left(1 - \frac{I_T^{**}}{I_T}\right) \left[\tau_1 I_1 + \tau_2 I_2 + \tau_A A - (\kappa + \mu)I_T\right] \\
& + b_3 \left(1 - \frac{F^{**}}{F}\right) \left[\kappa I_T - (\gamma + \mu)F\right] \\
& + b_4 \left(1 - \frac{A^{**}}{A}\right) \left[\sigma_2 I_2 + \gamma(1-r)F - (\tau_A + \mu)A\right].
\end{aligned} \tag{D.2}$$

The following relations at the endemic steady-state will be used to simplify (D.2),

$$\begin{aligned}
\pi = \lambda S^{**} + \mu S^{**}, \quad (\sigma_1 + \tau_1 + \mu) &= \frac{\lambda^{**} S^{**}}{I_1^{**}}, \quad (\sigma_2 + \tau_2 + \mu) = \frac{\sigma_1 I_1^{**} + \gamma r F^{**}}{I_2^{**}}, \\
(\kappa + \mu) &= \frac{\tau_A A^{**}}{I_T^{**}}, \quad (\gamma + \mu) = \frac{\kappa I_T^{**}}{F^{**}}, \quad (\tau_A + \mu) = \frac{\sigma_2 I_2^{**} + \gamma(1-r)F^{**}}{A^{**}}.
\end{aligned} \tag{D.3}$$

Substituting (D.3) into (D.2), and simplifying, gives:

$$\begin{aligned}
\dot{\mathcal{L}} = & \left(\mu S^{**} + \frac{\beta \mu S^{**} I_1^{**}}{\pi} \right) \left(2 - \frac{S}{S^{**}} - \frac{S^{**}}{S} \right) \\
& + \frac{\beta \mu S^{**} \theta_2 I_2^{**} G_6}{\pi G_1} \left(3 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_2}{S^{**} I_1 I_2^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} \right) \\
& + \frac{\beta \mu S^{**} G_7}{I_1^{**} \pi G_1} \left(3 - \frac{I_2 I_T^{**}}{I_2^{**} I_T} - \frac{I_2^{**} F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**} F} \right) \\
& + \frac{\beta \mu S^{**} G_8}{\pi G_1} \left(3 - \frac{I_T F^{**}}{I_T^{**} F} - \frac{I_T^{**} A}{I_T A^{**}} - \frac{F A^{**}}{F^{**} A} \right) \\
& + \frac{\beta \mu S^{**} \theta_T I_T^{**} G_9}{\pi G_1} \left(3 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_T}{S^{**} I_1 I_T^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} \right) \\
& + \frac{\beta \mu S^{**} G_{10}}{I_1^{**} \pi G_1} \left(4 - \frac{I_2 F^{**}}{I_2^{**} F} - \frac{I_2 A^{**}}{I_2^{**} A} - \frac{I_T F^{**}}{I_T^{**} F} - \frac{I_T^{**} A}{I_T A^{**}} \right) \\
& + \frac{\beta \mu S^{**} \theta_T I_T^{**} G_{11}}{\pi G_1} \left(4 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_T}{S^{**} I_1 I_T^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 I_T^{**}}{I_2^{**} I_T} \right) \\
& + \frac{\beta \mu S^{**} \theta_F F^{**} G_{12}}{\pi G_1} \left(4 - \frac{S^{**}}{S} - \frac{S I_1^{**} F}{S^{**} I_1 F^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} - \frac{I_T F^{**}}{I_T^{**} F} \right) \\
& + \frac{\beta \mu S^{**} \theta_A A^{**} G_{13}}{\pi G_1} \left(4 - \frac{S^{**}}{S} - \frac{S I_1^{**} A}{S^{**} I_1 A^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 A^{**}}{I_2^{**} A} \right) \\
& + \frac{\beta \mu S^{**} \theta_2 I_2^{**} G_{14}}{\pi G_1} \left(5 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_2}{S^{**} I_1 I_2^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} - \frac{I_2^{**} F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**} F} \right) \\
& + \frac{\beta \mu S^{**} \theta_T I_T^{**} I_2^{**} A^{**} \sigma_1 \sigma_2 \tau_A}{\pi G_1} \left(5 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_T}{S^{**} I_1 I_T^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 A^{**}}{I_2^{**} A} - \frac{I_T^{**} A}{I_T A^{**}} \right) \\
& + \frac{\beta \mu S^{**} \theta_F F^{**} G_{15}}{\pi G_1} \left(5 - \frac{S^{**}}{S} - \frac{S I_1^{**} F}{S^{**} I_1 F^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 I_T^{**}}{I_2^{**} I_T} - \frac{I_T F^{**}}{I_T^{**} F} \right) \\
& + \frac{\beta \mu S^{**} \theta_A A^{**} G_{16}}{\pi G_1} \left(5 - \frac{S^{**}}{S} - \frac{S I_1^{**} A}{S^{**} I_1 A^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} - \frac{I_T F^{**}}{I_T^{**} F} - \frac{F A^{**}}{F^{**} A} \right) \\
& + \frac{\beta \mu S^{**} \theta_F F^{**} I_2^{**} A^{**} \sigma_1 \sigma_2 \tau_A}{\pi G_1} \times \\
& \left(6 - \frac{S^{**}}{S} - \frac{S I_1^{**} F}{S^{**} I_1 F^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 A^{**}}{I_2^{**} A} - \frac{I_T^{**} A}{I_T A^{**}} - \frac{I_T F^{**}}{I_T^{**} F} \right) \\
& + \frac{\beta \mu S^{**} \theta_A A^{**} I_2^{**} F^{**} (1-r) \gamma \sigma_1 \tau_2}{\pi G_1} \times \\
& \left(6 - \frac{S^{**}}{S} - \frac{S I_1^{**} A}{S^{**} I_1 A^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2^{**} I_T}{I_2 I_T^{**}} - \frac{I_T F^{**}}{I_T F} - \frac{F A^{**}}{F^{**} A} \right) \\
& + \frac{\beta \mu S^{**} \theta_A A^{**} I_2^{**} F^{**} r \gamma \sigma_2 \tau_1}{\pi G_1} \times \\
& \left(6 - \frac{S^{**}}{S} - \frac{S I_1^{**} A}{S^{**} I_1 A^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} - \frac{I_2^{**} F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T F} - \frac{I_2 A^{**}}{I_2^{**} A} \right)
\end{aligned}$$

where,

$$\begin{aligned}
G_6 &= I_2^{**} A^{**} \sigma_1 \sigma_2 \tau_A + I_1^{**} I_2^{**} \sigma_1 \sigma_2 \tau_1 + (I_2^{**})^2 \sigma_1 \sigma_2 \tau_2 + I_2^{**} F^{**} (1-r) \gamma \sigma_1 \tau_2 \\
&\quad + I_1^{**} F^{**} (1-r) \gamma \sigma_1 \tau_1, \\
G_7 &= (\theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) [(I_2^{**})^2 F^{**} \gamma r \sigma_2 \tau_2 + (F^{**})^2 (1-r) r \gamma^2 \tau_2], \\
G_8 &= \left[\frac{\theta_2 I_2^{**} (F^{**})^2 A^{**} (1-r) r \gamma^2 \tau_2}{I_1^{**}} \right] + \left(\theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**} \right) \times \\
&\quad \left[\left(\frac{(F^{**})^2 A^{**} (1-r) r \gamma^2 \tau_2}{I_1^{**}} \right) + F^{**} A^{**} (1-r) \gamma \sigma_1 \tau_A \right], \\
G_9 &= I_1^{**} I_2^{**} \sigma_1 \sigma_2 \tau_1 + I_2^{**} F^{**} r \gamma \sigma_2 \tau_1 + (F^{**})^2 (1-r) r \gamma^2 \tau_1 + I_1^{**} F^{**} (1-r) \gamma \sigma_1 \tau_1, \\
G_{10} &= (\theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**}) (I_2^{**} F^{**} A^{**} r \gamma \sigma_2 \tau_A), \\
G_{11} &= (I_2^{**})^2 \sigma_1 \sigma_2 \tau_2 + I_2^{**} F^{**} (1-r) \gamma \sigma_1 \tau_2, \\
G_{12} &= (F^{**})^2 (1-r) r \gamma^2 \tau_1 + I_1^{**} F^{**} (1-r) \gamma \sigma_1 \tau_1 + I_2^{**} F^{**} r \gamma \sigma_2 \tau_1 + I_1^{**} I_2^{**} \sigma_1 \sigma_2 \tau_1, \\
G_{13} &= I_1^{**} I_2^{**} \sigma_1 \sigma_2 \tau_1 + (I_2^{**})^2 \sigma_1 \sigma_2 \tau_2 + I_2^{**} A^{**} \sigma_1 \sigma_2 \tau_A, \\
G_{14} &= I_2^{**} F^{**} r \gamma \sigma_2 \tau_1 + (F^{**})^2 (1-r) r \gamma^2 \tau_1, \\
G_{15} &= I_2^{**} F^{**} (1-r) \gamma \sigma_1 \tau_2 + (I_2^{**})^2 \sigma_1 \sigma_2 \tau_2, \\
G_{16} &= (F^{**})^2 (1-r) r \gamma^2 \tau_1 + I_1^{**} F^{**} (1-r) \gamma \sigma_1 \tau_1,
\end{aligned}$$

Since the arithmetic mean exceeds the geometric mean, it follows that

$$\begin{aligned}
& \left(2 - \frac{S}{S^{**}} - \frac{S^{**}}{S} \right) \leq 0 \\
& \left(3 - \frac{S^{**}}{S} - \frac{SI_1^{**}I_2}{S^{**}I_1I_2^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} \right) \leq 0 \\
& \left(3 - \frac{I_T F^{**}}{I_T^{**}F} - \frac{I_T^{**}A}{I_T A^{**}} - \frac{FA^{**}}{F^{**}A} \right) \leq 0 \\
& \left(3 - \frac{I_2 I_T^{**}}{I_2^{**}I_T} - \frac{I_2^{**}F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**}F} \right) \leq 0 \\
& \left(3 - \frac{S^{**}}{S} - \frac{SI_1^{**}I_T}{S^{**}I_1I_T^{**}} - \frac{I_1I_T^{**}}{I_1^{**}I_T} \right) \leq 0 \\
& \left(4 - \frac{I_2 F^{**}}{I_T^{**}F} - \frac{I_2 A^{**}}{I_2^{**}A} - \frac{I_T F^{**}}{I_T^{**}F} - \frac{I_T^{**}A}{I_T A^{**}} \right) \leq 0 \\
& \left(4 - \frac{S^{**}}{S} - \frac{SI_1^{**}I_T}{S^{**}I_1I_T^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2I_T^{**}}{I_2^{**}I_T} \right) \leq 0 \\
& \left(4 - \frac{S^{**}}{S} - \frac{SI_1^{**}F}{S^{**}I_1F^{**}} - \frac{I_1I_T^{**}}{I_1^{**}I_T} - \frac{I_T F^{**}}{I_T^{**}F} \right) \leq 0 \\
& \left(4 - \frac{S^{**}}{S} - \frac{SI_1^{**}A}{S^{**}I_1A^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2A^{**}}{I_2^{**}A} \right) \leq 0 \\
& \left(5 - \frac{S^{**}}{S} - \frac{SI_1^{**}I_2}{S^{**}I_1I_2^{**}} - \frac{I_1I_T^{**}}{I_1^{**}I_T} - \frac{I_2^{**}F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**}F} \right) \leq 0 \\
& \left(5 - \frac{S^{**}}{S} - \frac{SI_1^{**}I_T}{S^{**}I_1I_T^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2A^{**}}{I_2^{**}A} - \frac{I_T^{**}A}{I_T A^{**}} \right) \leq 0 \\
& \left(5 - \frac{S^{**}}{S} - \frac{SI_1^{**}F}{S^{**}I_1F^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2I_T^{**}}{I_2^{**}I_T} - \frac{I_T F^{**}}{I_T^{**}F} \right) \leq 0 \\
& \left(5 - \frac{S^{**}}{S} - \frac{SI_1^{**}A}{S^{**}I_1A^{**}} - \frac{I_1I_T^{**}}{I_1^{**}I_T} - \frac{I_T F^{**}}{I_T^{**}F} - \frac{FA^{**}}{F^{**}A} \right) \leq 0 \\
& \left(6 - \frac{S^{**}}{S} - \frac{SI_1^{**}F}{S^{**}I_1F^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2A^{**}}{I_2^{**}A} - \frac{I_T^{**}A}{I_T A^{**}} - \frac{I_T F^{**}}{I_T^{**}F} \right) \leq 0 \\
& \left(6 - \frac{S^{**}}{S} - \frac{SI_1^{**}A}{S^{**}I_1A^{**}} - \frac{I_1I_2^{**}}{I_1^{**}I_2} - \frac{I_2^{**}I_T}{I_2 I_T^{**}} - \frac{I_T F^{**}}{I_T^{**}F} - \frac{FA^{**}}{F^{**}A} \right) \leq 0 \\
& \left(6 - \frac{S^{**}}{S} - \frac{SI_1^{**}A}{S^{**}I_1A^{**}} - \frac{I_1I_T^{**}}{I_1^{**}I_T} - \frac{I_2^{**}F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**}F} - \frac{I_2A^{**}}{I_2^{**}A} \right) \leq 0
\end{aligned}$$

hence, $\dot{\mathcal{L}} \leq 0$. It follows that then,

$$\lim_{t \rightarrow \infty} (S(t), I_1(t), I_2(t), I_T(t), F(t), A(t)) \rightarrow (S^{**}, I_1^{**}, I_2^{**}, I_T^{**}, F^{**}, A^{**}).$$

Furthermore, it follows from the LaSalle's Invariance Principle [26] (Theorem 3.6 in this thesis) that the unique endemic equilibrium, \mathcal{E}_1 , of the PrEP-free model (3.1) with $\delta = 0$ is GAS in $\mathcal{D}_1 \setminus \mathcal{D}_0$ whenever $\mathcal{R}_1 > 1$. □

Appendix E

Proof of Theorem 4.3

Proof. Consider the special case of the PrEP model (2.2) with $\delta = 0$. The proof is based on using center manifold theory. It is convenient, first of all, to let

$$S = x_1, \quad S_L = x_2, \quad S_H = x_3, \quad I_1 = x_4, \quad I_2 = x_5, \quad I_T = x_6, \quad F = x_7, \quad A = x_8,$$

so that the special case of the PrEP model (2.2) with $\delta = 0$ can be re-written as

$$\begin{aligned} \frac{dS}{dt} &= f_1 = \pi + \omega_L x_2 + \omega_H x_3 - \lambda x_1 - \psi x_1 - \mu x_1, \\ \frac{dS_L}{dt} &= f_2 = (1 - f)\psi x_1 + \xi_H x_3 - \theta_L \lambda x_2 - (\xi_L + \omega_L + \mu)x_2, \\ \frac{dS_H}{dt} &= f_3 = f\psi x_1 + \xi_L x_2 - \theta_H \lambda x_3 - (\xi_H + \omega_H + \mu)x_3, \\ \frac{dI_1}{dt} &= f_4 = \lambda(x_1 + \theta_L x_2 + \theta_H x_3) - (\sigma_1 + \tau_1 + \mu)x_4, \\ \frac{dI_2}{dt} &= f_5 = \sigma_1 x_4 + \gamma r x_7 - (\tau_2 + \sigma_2 + \mu)x_5, \\ \frac{dI_T}{dt} &= f_6 = \tau_1 x_4 + \tau_2 x_5 + \tau_A x_8 - (\kappa + \mu)x_6, \\ \frac{dF}{dt} &= f_7 = \kappa x_6 - (\gamma + \mu)x_7, \\ \frac{dA}{dt} &= f_8 = \sigma_2 x_5 + \gamma(1 - r)x_7 - (\tau_A + \mu)x_8, \end{aligned} \tag{E.1}$$

where,

$$\lambda = \frac{\beta(x_4 + \theta_2 x_5 + \theta_T x_6 + \theta_F x_7 + \theta_A x_8)}{\sum_{i=1}^8 x_i},$$

and $\mathbf{f} = [f_1, \dots, f_8]^T$ represents the vector field of the model (2.2). Evaluating the Jacobian of the system (E.1) at the DFE (\mathcal{E}_0^P) gives

$$J(\mathcal{E}_0^P) = \begin{pmatrix} -\mu - \psi & \omega_L & \omega_H & -U_1 & -U_1\theta_2 & -U_1\theta_T & -U_1\theta_F & -U_1\theta_A \\ (1-f)\psi & -U_2 & \xi_H & -U_3 & -U_3\theta_2 & -U_3\theta_T & -U_3\theta_F & -U_3\theta_A \\ f\psi & \xi_L & -U_4 & -U_5 & -U_5\theta_2 & -U_5\theta_T & -U_5\theta_F & -U_5\theta_A \\ 0 & 0 & 0 & U_6 - C_1 & U_6\theta_2 & U_6\theta_T & U_6\theta_F & U_6\theta_A \\ 0 & 0 & 0 & \sigma_1 & -C_2 & 0 & \gamma r & 0 \\ 0 & 0 & 0 & \tau_1 & \tau_2 & -C_3 & 0 & \tau_A \\ 0 & 0 & 0 & 0 & 0 & \kappa & -C_4 & 0 \\ 0 & 0 & 0 & 0 & \sigma_2 & 0 & (1-r)\gamma & -C_5 \end{pmatrix},$$

where,

$$U_1 = \frac{\beta\mu x_1}{\pi}, \quad U_2 = (\xi_L + \omega_L + \mu), \quad U_3 = \frac{\beta\mu\theta_L x_2}{\pi}, \\ U_4 = (\xi_H + \omega_H + \mu), \quad U_5 = \frac{\beta\mu\theta_H x_3}{\pi}, \quad U_6 = \frac{\beta\mu(x_1 + \theta_L x_2 + \theta_H x_3)}{\pi}.$$

Consider the case when $\mathcal{R}_P^* = 1$. Also, suppose that β is chosen as the bifurcation parameter. Solving for β when $\mathcal{R}_P^* = 1$ gives

$$\beta = \beta^* = \frac{Q_2 C_1 N^*}{g(Q_2 + \theta_2 Q_3 + \theta_T C_4 Q_4 + \theta_F \kappa Q_4 + \theta_A Q_5)}.$$

The transformed system (E.1), with $\beta = \beta^*$, has a simple eigenvalue with zero real part (and all other eigenvalues have negative real parts). Thus, center manifold

theory (particularly the approach in [7]) can be applied to analyze the dynamics of (E.1) near β^* . The application of the center manifold theory entail the following computations.

Eigenvectors of $J(\mathcal{E}_0^P)|_{\beta=\beta^*}$:

Let $J(\mathcal{E}_0^P)|_{\beta=\beta^*} = J_{\beta^*}$. The matrix has a left eigenvector (associated with the zero eigenvector) given by,

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8],$$

where,

$$\begin{aligned} v_1 &= 0, \quad v_2 = 0, \quad v_3 = 0, \quad v_4 = v_4 > 0, \\ v_5 &= \frac{\beta^* \mu \theta_2 v_4 (x_1 + \theta_L x_2 + \theta_H x_3) + \pi (\tau_2 v_6 + \sigma_2 v_8)}{\pi C_2}, \quad v_6 = v_6 > 0, \\ v_7 &= \frac{\beta^* \mu v_4 (\gamma r \theta_2 + C_2 \theta_F) (x_1 + \theta_L x_2 + \theta_H x_3) + \pi (\gamma r \tau_2 v_6 + [\gamma r \sigma_2 + (1-r) \gamma C_2] v_8)}{\pi C_2 C_4}, \\ v_8 &= v_8 > 0. \end{aligned}$$

Furthermore, the matrix J_{β^*} has a right eigenvector (associated with the zero eigenvector) given by,

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8]^T,$$

where,

$$\begin{aligned} w_1 &= \frac{-\mu \beta^* [(U_2 U_4 - \xi_L \xi_H) x_1 + (U_4 \omega_L + \xi_L \omega_H) \theta_L x_2 + (U_2 \omega_H + \xi_H \omega_L) \theta_H x_3] Y_1}{\pi Q_1 C_2 C_4}, \\ w_2 &= \frac{-\mu \beta^* Y_1 Y_2}{\pi Q_1 C_2 C_4}, \quad w_3 = \frac{-\mu \beta^* Y_1 Y_3}{\pi Q_1 C_2 C_4}, \quad w_4 = w_4 > 0, \quad w_5 = \frac{C_4 \sigma_1 w_4 + \gamma \kappa r w_6}{C_2 C_4}, \\ w_6 &= w_6 > 0, \quad w_7 = \frac{\kappa w_6}{C_4}, \quad w_8 = w_8 > 0. \end{aligned}$$

and,

$$Y_1 = C_2 C_4 (w_4 + \theta_T w_6 + \theta_A w_8) + C_2 \kappa \theta_F w_6 + \theta_2 (C_4 \sigma_1 w_4 + \gamma \kappa r w_6),$$

$$Y_2 = [f \xi_H + (1 - f) U_4] \psi x_1 + [U_4 (\mu + \psi) - f \psi \omega_H] \theta_L x_2 + [(1 - f) \psi \omega_H + \xi_H (\mu + \psi)] \theta_H x_3,$$

$$Y_3 = [f U_2 + (1 - f) \xi_L] \psi x_1 + [f \psi \omega_L + \xi_L (\mu + \psi)] \theta_L x_2 + [U_2 (\mu + \psi) - (1 - f) \psi \omega_L] \theta_H x_3.$$

Computation of bifurcation coefficients, a and b :

It can be shown (by computing the associated non-zero partial derivatives of the system (E.1) at the DFE (\mathcal{E}_0^P) and simplifying) that the associated backward bifurcation coefficients a and b are given, respectively, by (see Theorem 4.1 of [7])

$$\begin{aligned} a &= \sum_{k,i,j=1}^8 v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} (\mathcal{E}_0^P, \beta^*) \\ &= \frac{2v_4 \mu^3 \beta^* Y_1}{\pi^3 Q_1 C_2^2 C_4^2} \left[Y_5 Y_4 + \beta^* Y_6 Y_1 - (Y_7 Y_4 + \beta^* Y_8 Y_1) \right], \end{aligned} \quad (\text{E.2})$$

and

$$b = \sum_{k,i=1}^8 v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta} (\mathcal{E}_0^P, \beta^*) = \frac{v_4 \mu Y_1 (x_1 + \theta_L x_2 + \theta_H x_3)}{\pi C_2 C_4} > 0, \quad (\text{E.3})$$

where,

$$\begin{aligned}
Y_4 &= C_2 C_4 (w_4 + w_6 + w_8) + C_2 \kappa w_6 + C_4 \sigma_1 w_4 + \gamma \kappa r w_6, \\
Y_5 &= [(U_2 \omega_H + \omega_L \xi_H) f \psi + (U_4 \omega_L + \omega_H \xi_L) (1 - f) \psi + \xi_H \xi_L (\mu + \psi)] \times \\
&\quad (x_1 + x_2 + x_3) (x_1 + \theta_L x_2 + \theta_H x_3), \\
Y_6 &= (U_2 U_4 x_1 + U_2 \omega_H \theta_H x_3 + U_4 \omega_L \theta_L x_2 + \omega_H \xi_L \theta_L x_2 \\
&\quad + \omega_L \xi_H \theta_H x_3) (\theta_L x_2 + \theta_H x_3) + U_2 (x_1 + \theta_L x_2) [f \psi x_1 + (\mu + \psi) \theta_H x_3] \\
&\quad + U_4 (x_1 + \theta_H x_3) [(1 - f) \psi x_1 + (\mu + \psi) \theta_L x_2] + \xi_H \xi_L (x_2 + x_3) x_1 \\
&\quad + f \psi \left(\xi_H (x_1 + \theta_H x_3) x_1 + [\omega_H \theta_L (x_1 + x_3) + \omega_L (x_1 + \theta_L x_2)] \theta_L x_2 \right) \\
&\quad + (1 - f) \psi \left(\xi_L (x_1 + \theta_L x_2) x_1 + [\omega_L \theta_H (x_1 + x_2) + \omega_H (x_1 + \theta_H x_3)] \theta_H x_3 \right) \\
&\quad + (\mu + \psi) [\xi_L (x_1 + x_2) \theta_L x_2 + \xi_H (x_1 + x_3) \theta_H x_3], \\
Y_7 &= U_2 U_4 (\mu + \psi) (x_1 + x_2 + x_3) (x_1 + \theta_L x_2 + \theta_H x_3), \\
Y_8 &= (U_2 U_4 x_1 + U_4 \omega_L \theta_L x_2 + U_2 \omega_H \theta_H x_3) (x_2 + x_3) \\
&\quad + U_2 \theta_H [f \psi x_1 + (\mu + \psi) \theta_H x_3] (x_1 + x_2) \\
&\quad + U_4 \theta_L [(1 - f) \psi x_1 + (\mu + \psi) \theta_L x_2] (x_1 + x_3) \\
&\quad + \left(\xi_H \xi_L (\theta_L x_2 + \theta_H x_3) + \psi [f \xi_H \theta_L (x_1 + x_3) + (1 - f) \xi_L \theta_H (x_1 + x_2)] \right) x_1 \\
&\quad + \left(\omega_H \theta_L [\xi_L (x_2 + x_3) + f \psi x_1] + \theta_H \theta_L ([\xi_L (\mu + \psi) \right. \\
&\quad \left. + \omega_L f \psi] (x_1 + x_2) + \omega_H f \psi x_3) \right) x_2 \\
&\quad + \left(\omega_L \theta_H [\xi_H (x_2 + x_3) + (1 - f) \psi x_1] \right. \\
&\quad \left. + \theta_H \theta_L ([\xi_H (\mu + \psi) + \omega_H (1 - f) \psi] (x_1 + x_3) + \omega_L (1 - f) \psi x_2) \right) x_3.
\end{aligned} \tag{E.4}$$

It follows from (E.2), with (E.4), that the bifurcation coefficient, a , is positive whenever

$$J_1 > J_2, \tag{E.5}$$

where, $J_1 = Y_5 Y_4 + \beta^* Y_6 Y_1$ and $J_2 = Y_7 Y_4 + \beta^* Y_8 Y_1$. Hence, it follows from Theorem 4.1 of [7], that the PrEP model (2.2) (or, equivalently (E.1)) undergoes backward bifurcation at $\mathcal{R}_P^* = 1$ whenever Inequality (E.5) holds. \square

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