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Mathematical assessment of the role of pre-exposure prophylaxis on HIV transmission dynamics

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ABSTRACT

A new deterministic model for HIV/AIDS that incorporates pre-exposure prophylaxis (PrEP) is designed and used to assess the population-level impact of the use of PrEP on the transmission dynamics of the disease 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 parameters that have the most effect on the disease transmission dynamics. Numerical simulations show that, with the current rate of administration of antiretroviral treatment (to HIV-infected individuals), HIV burden decreases with increasing PrEP coverage. Furthermore, for this setting, this study suggests that HIV can be effectively controlled in the MSM population if, in addition to the current rate of administration of anti-retroviral therapy in the community, at least 61–77% (with mean of about 70%) of the susceptible members of the MSM community are on PrEP (adjusted by PrEP efficacy).

1. Introduction

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 [1,2]. The World Health Organization (WHO) estimates that 35.5 million people are currently living with HIV/AIDS, and that in the year 2013, about 1.5 million people have died of HIV-related illnesses worldwide [2]. 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) [3]. 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 [3,4].

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 mother to her child during pregnancy or child birth), through breast milk, by sharing contaminated needles (among injection drug users (IDUs) or within healthcare settings) and through blood transfusions [4,5]. In order for transmission to occur, these infected bodily fluids must come into contact with mucous membranes

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or damaged tissue or be directly injected into the bloodstream [4,5]. 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 [5]. It can also be spread less commonly by vertical transmission, occupational exposure, and rarely by organ transplants or blood transfusions [4]. The main risk groups in the U.S., by transmission category, are men who have sex with men (MSM), IDUs, heterosexual individuals, and men who have sex with men that are also intravenous drug users (MSM-IDU) [3]. MSM of all races and ethnicities currently have the largest number of new HIV infections and remain the group most severely affected by HIV in the United States [3].

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 counseling, access to sterile needles, and the use of antiretroviral treatment (ART) [6]. 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 [6]. These control strategies have proven to be effective in 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) [6]. However, although these strategies have slowed the spread of the disease, HIV remains a major public health concern in the United States [2,7]. Consequently, there is an urgent need to formulate effective strategies.

PrEP is a new anti-HIV preventive measure [8–10]. It involves administering an antiretroviral drug (such as Truvada®, which is a combination of two *nucleoside/nucleotide reverse transcriptase inhibitors* (NRTIs), *tenofovir* (TDF) and *emtricitabine* (FTC)) to HIV-negative individuals who are at a substantial risk of contracting the virus to help prevent infection [8–10]. It works by blocking pathways that the HIV virus uses to set up an infection in the body [8–10]. 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 [8–10]. It has been shown, in recent studies, that the effectiveness of PrEP depends upon the compliance in its usage [8,9,11–14]. 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) [8,9,11–14]. PrEP is not 100% effective, and should be used in conjunction with other preventive measures (e.g., condoms, reduction in risky sexual behaviors, using sterile syringes, getting tested for HIV, etc.…) [8–10].

The medication that is currently approved by the U.S. Food and Drug Administration (FDA) for PrEP is Truvada® [8–10]. Some clinical trials used *tenofovir* alone, but this has not been approved by the U.S. FDA for PrEP use [8–10]. For sexual transmission of HIV, the administration of PrEP entails giving drugs to anyone who [8–10]:

(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) has injected illicit drugs in the past six months using shared equipment or who has been in a treatment program for injection drug use.

A number of compartmental mathematical models have been developed and used to assess the impact of PrEP on HIV transmission in both homosexual [15] and heterosexual [16–19] populations. For instance, Pretorius et al. [17] used an age- and gender-structured model to study the impact and cost-effectiveness of PrEP, alongside ART and condom-use, on the generalized HIV epidemic in South Africa. This study shows that PrEP coverage has to be impractically high to lead to a significant reduction of HIV incidence (while ART coverage expands). Vissers et al. [18] studied the impact of PrEP and condom-use (or substitution) among targeted populations (general population and sex-workers population and their clients) in Bostwana, India and Kenya. This study emphasized the role of changes in risk behavior on the effectiveness of PrEP. Using a detailed mathematical model, Abbas et al. [16] showed that the combined use of PrEP and ART is likely to prevent more HIV infections in South Africa than the singular use of either strategy (but the former inducing higher prevalence of drug resistance). Supervie et al. [15] investigated the potential effects of PrEP intervention in reducing HIV infections in the MSM community in San Francisco, and whether or not PrEP intervention could significantly increase transmitted resistance. The impact of the wide-scale use of antiretroviral-based microbicides on the HIV epidemic was studied by Wilson et al. Most of these studies modeled HIV transmission dynamics in resource-limited and heterosexual populations, and conclude that the widespread use of PrEP has the potential to help prevent HIV infections and slow the HIV epidemic under certain conditions. These studies did not provide a detailed rigorous analysis of the mathematical models used.

The objective of the current study is to design, and rigorously analyse, a new stage-progression model for assessing the population-level impact of the use of PrEP in curtailing HIV spread within an MSM population. A novel feature of the model to be designed is that it stratifies the susceptible population on PrEP in terms of level (low or high) of PrEP adherence. The model is formulated in Section 2. Its PrEP-free equivalent is analyzed in Section 3. The PrEP model is analyzed is Section 4. Uncertainty and sensitivity analyses are carried out in Section 5.

2. Mathematical model

The model to be developed is based on the transmission dynamics of HIV/AIDS in a community of sexually-active adults MSM in the United States. One of the key assumptions to be made in the model formulation process is that all clinical standards of medical practice in the United States are in place (as defined by the CDC) [20]. The total population of the sexually-active MSM population at time t, denoted by $N(t)$, is divided into sub-populations of individuals who are wholly-susceptible to HIV infection (that is, individuals 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 who failed anitretroviral treatment ($F(t)$), and those 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 wholly-susceptible 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,

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

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 [21]. 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 [21]. Similarly, $\theta_F > 0$ represents the assumed variability of the infectiousness of failed treated HIV-infected individuals, in relation to acutely-infected individuals [21]. 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 [21]. 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 susceptible individuals with low adherence to PrEP (S_L) is increased by the administration of PrEP to wholly-susceptible individuals (at the rate ψ; a fraction, f, of these is assumed to adhere strictly to the prescribed PrEP regimen, and the remaining fraction, $1 - f$, are assumed to be low adherent to PrEP). 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 susceptible individuals who highly adhere to PrEP (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,

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

Thus, the model for the transmission of HIV/AIDS in a sexually-active community of MSM adults is given by the following deterministic system of non-linear differential equations:

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

A flow diagram of the model (2.2) is depicted in Fig. 1, and the associated state variables and parameters are tabulated in Table 1 (a glossary list of abbreviations is given in Table 2).

The model (2.2) is an extension of some of the aforementioned modeling studies. For instance,

(i) it extends the models in [15,17–19] by stratifying the susceptible population in terms of low- or high-adherence (S_L and S_H) to PrEP (a single susceptible class for PrEP is used in the models in [15,17–19]);
(ii) it extends the models in [16] by allowing for back-and-forth transitions between the low- and high-adherence PrEP-user susceptible populations at the rates ξ_L, from low- to high-adherent class, and ξ_H, from high- to low-adherent class (thereby accounting for change in risk behavior; this was not accounted in [16]). The model also allows for the possibility of PrEP users to give up PrEP altogether (and revert to a wholly susceptible class, at the rates ω_L, for low-, and ω_H, for high-adherent PrEP users);
(iii) it extends the models in [17–19] by including the stage-progression property of HIV disease (a single infected class is used in the models in [17–19]);
(iv) it extends the models in [15,17–19] by including the dynamics of infected individuals in whom ART has failed (by adding the compartment F).

Furthermore, this study extends those in [15–19] by carrying out a detailed rigorous analysis of the model (vis-à-vis the existence and asymptotic stability of the associated equilibria, as well as to characterize the bifurcation type the model may undergo). It is worth mentioning that the model considered in this study treats all parameters as constants (i.e., the model is autonomous). It is, however, plausible that some of the parameters (such as the treatment rates) may vary with time (thereby making the model non-autonomous) [22,23]. The authors plan to study the dynamics of the model (2.2) for the case when some of the parameters are time-dependent in the future.

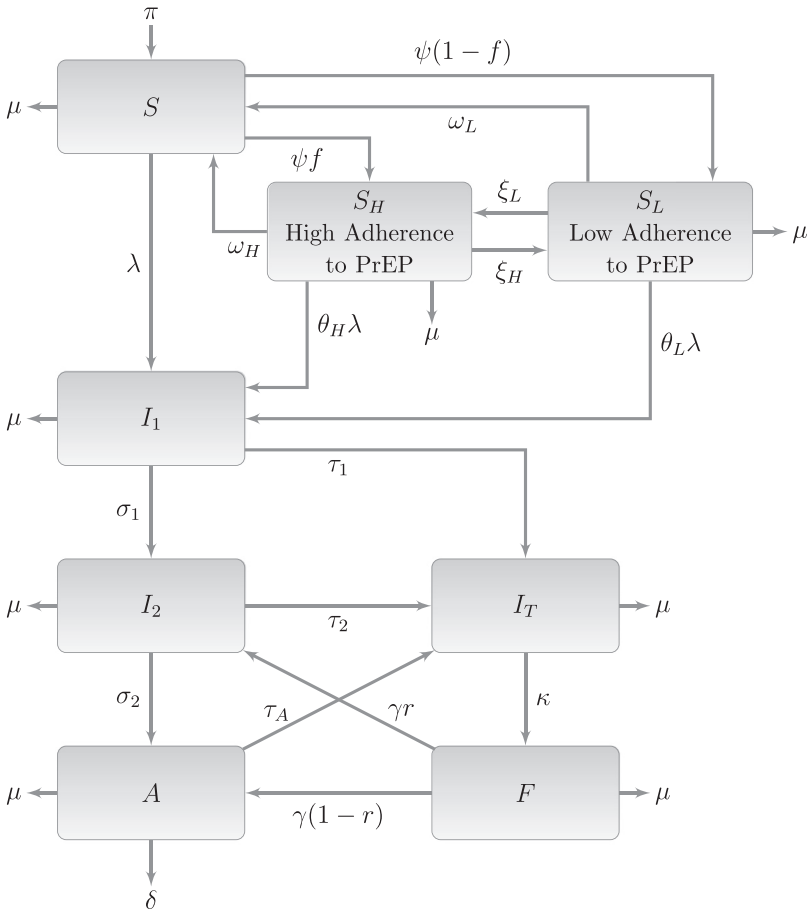

Fig. 1. Flow diagram for the PrEP model (2.2).

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 $t > 0$.*

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 equation of the PrEP model (2.2) that,

$$\frac{dS}{dt} = \pi + \omega_L S_L + \omega_H S_H - \lambda S - \psi S - \mu S \geq \pi - \lambda S - \psi S - \mu S, \tag{2.3}$$

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,

Table 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

Table 2
Glossary of abbreviations.

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

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

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. □

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:

$$\frac{dN}{dt} = \pi - \mu N - \delta A \leq \pi - \mu N. \tag{2.4}$$

It follows from (2.4) that if $N \leq \frac{\pi}{\mu}$, then $\frac{dN}{dt} \leq 0$. Further, using a standard Comparison Theorem (see [24]),

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

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 $\mathbb{R}^8_+$. □

Thus, in the region $\mathcal{D}$, the model (2.2) can be considered as epidemiologically and mathematically well-posed [25]. 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).

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 2.1, 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

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

The local stability of the DFE, $\mathcal{E}_0$, will be explored using the next generation operator method [26]. 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

$$\mathcal{H} = \begin{pmatrix} \beta & \theta_2\beta & \theta_T\beta & \theta_F\beta & \theta_A\beta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 \\ -\sigma_1 & K_2 & 0 & -\gamma r & 0 \\ -\tau_1 & -\tau_2 & K_3 & 0 & -\tau_A \\ 0 & 0 & -\kappa & K_4 & 0 \\ 0 & -\sigma_2 & 0 & -\gamma(1-r) & K_5 \end{pmatrix},$$

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* [25–27] (denoted by $\mathcal{R}_0$) of the model is given by (where ρ is the spectral radius):

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

with,

$$M_1 = \kappa\gamma K_2\tau_A r - \kappa\gamma K_2\tau_A - \kappa r\gamma K_5\tau_2 - \kappa r\gamma\sigma_2\tau_A + K_2K_3K_4K_5,$$
$$M_2 = \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r K_5\kappa\tau_1 + K_5K_4K_3\sigma_1,$$
$$M_3 = K_2K_5\tau_1 + K_5\sigma_1\tau_2 + \sigma_1\sigma_2\tau_A,$$
$$M_4 = \gamma r\kappa\sigma_2\tau_1 + K_3K_4\sigma_1\sigma_2 + \kappa\gamma(1-r)(K_2\tau_1 + \sigma_1\tau_2).$$

It can be shown (see Appendix A) that M_i $(i = 1, 2) > 0$, so that $\mathcal{R}_0 > 0$. The result below follows from Theorem 2 of [26].

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

Proof. The proof is based on a Comparison Theorem [24]. It should first be noted that the model (3.1) satisfies the Type K condition [28] (so that a Comparison Theorem [24] can be applied). The infected components of the PrEP-free model (3.1) can be re-written as

$$\frac{d}{dt}\begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} = (\mathcal{H} - \mathcal{V})\begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} - J\begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix}, \tag{3.3}$$

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,

$$\frac{d}{dt}\begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix} \leq (\mathcal{H} - \mathcal{V})\begin{pmatrix} I_1(t) \\ I_2(t) \\ I_T(t) \\ F(t) \\ A(t) \end{pmatrix}. \tag{3.4}$$

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 (3.4) is stable whenever $\mathcal{R}_0 < 1$. Hence, it follows by Comparison Theorem [24], that

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

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 $S(t) \to S^*$ as $t \to \infty$ for $(\mathcal{R}_0 < 1)$. Thus,

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

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

Theorem 3.3 shows that HIV can be eliminated from the MSM 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 the effective control (or elimination) of the disease within the MSM community.

3.2. Existence and stability of endemic equilibrium point (EEP)

3.2.1. Existence

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., $\delta = 0$). The assumption $\delta = 0$, although chosen for mathematical

convenience (to make the mathematical analysis more tractable), can be justified by considering the fact that AIDS-related mortality in the MSM population in Minnesota is negligible [29]. 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 $N(t) \to \frac{\pi}{\mu}$ as $t \to \infty$. Let,

$$\mathcal{E}_1 = (S^{**}, I_1^{**}, I_2^{**}, I_T^{**}, F^{**}, A^{**}), \tag{3.5}$$

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

$$\lambda^{**} = \frac{\beta\mu(I_1^{**} + \theta_2 I_2^{**} + \theta_T I_T^{**} + \theta_F F^{**} + \theta_A A^{**})}{\pi}. \tag{3.6}$$

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

$$\begin{aligned} S^{**} &= \frac{\pi}{\lambda^{**} + \mu}, \quad I_1^{**} = \frac{\lambda^{**} S^{**}}{K_1}, \\ I_2^{**} &= \frac{\sigma_1 I_1^{**} + \gamma r F^{**}}{K_2}, \quad I_T^{**} = \frac{\tau_1 I_1^{**} + \tau_2 I_2^{**} + \tau_A A^{**}}{K_3}, \\ F^{**} &= \frac{\kappa I_T^{**}}{K_4}, \quad A^{**} = \frac{\sigma_2 I_2^{**} + \gamma(1-r)F^{**}}{K_5}. \end{aligned} \tag{3.7}$$

Substituting the expressions (3.7) into (3.6) shows that non-zero (endemic) equilibria of the PrEP-free model (3.1) satisfy

$$\lambda^{**} = \mu(\mathcal{R}_1 - 1), \tag{3.8}$$

where $\mathcal{R}_1 = \mathcal{R}_0|_{\delta=0}$. Since all parameters of the model (3.1) are positive, it follows from (3.8) 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 (3.8) into the expressions in (3.7). 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.*

3.2.2. 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))

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

Theorem 3.5. *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 3.5, based on using Lyapunov function theory [30] and LaSalle's Invariance Principle [31], is given in Appendix B.

4. Analysis of PrEP model

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

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

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,

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

with,

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

As in Section 3.1.1, the local stability of the DFE will be explored using the next generation operator method [26]. It follows that the matrices $\mathcal{H}_P$ and $\mathcal{V}_P$, associated with the model (2.2), are given, respectively, by

$$\mathcal{H}_P = \begin{pmatrix} \frac{g\beta}{N^*} & \frac{g\theta_2\beta}{N^*} & \frac{g\theta_T\beta}{N^*} & \frac{g\theta_F\beta}{N^*} & \frac{g\theta_A\beta}{N^*} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{V}_P = \begin{pmatrix} C_1 & 0 & 0 & 0 & 0 \\ -\sigma_1 & C_2 & 0 & -\gamma r & 0 \\ -\tau_1 & -\tau_2 & C_3 & 0 & -\tau_A \\ 0 & 0 & -\kappa & C_4 & 0 \\ 0 & -\sigma_2 & 0 & -\gamma(1-r) & C_5 \end{pmatrix},$$

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

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

with,

$$\begin{aligned} Q_2 &= \kappa\gamma C_2\tau_A r - \kappa\gamma C_2\tau_A - \kappa r\gamma C_5\tau_2 - \kappa r\gamma\sigma_2\tau_A + C_2C_3C_4C_5, \\ Q_3 &= \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r C_5\kappa\tau_1 + C_5C_4C_3\sigma_1, \\ Q_4 &= C_2C_5\tau_1 + C_5\sigma_1\tau_2 + \sigma_1\sigma_2\tau_A, \\ Q_5 &= \gamma r\kappa\sigma_2\tau_1 + C_3C_4\sigma_1\sigma_2 + \kappa\gamma(1-r)(C_2\tau_1 + \sigma_1\tau_2). \end{aligned}$$

It can be shown (see Appendix A) that $\mathcal{R}_P > 0$. The result below follows from Theorem 2 of [26].

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

It is convenient to define $\mathcal{R}_P^* = \mathcal{R}_P|_{\delta=0}$.

4.2. Backward bifurcation analysis

The analysis in this section will be carried out for the special case of the model (2.2) with $\delta = 0$ (for mathematical convenience). Let,

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

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

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

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

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

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

$$\lambda^{**} = \frac{\mu\beta B_5\lambda^{**}\left[\theta_H\theta_L(\lambda^{**})^2 + B_1\lambda^{**} + B_2\right]}{C_1Q_2\left[\theta_H\theta_L(\lambda^{**})^3 + B_3(\lambda^{**})^2 + B_4\lambda^{**} + Q_1\right]},$$

where,

Table 3
Number of possible real positive roots of Eq. (4.6) for $\mathcal{R}_P^* > 1$ and $\mathcal{R}_P^* < 1$.

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

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

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^{**}),

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

where,

$$
\begin{aligned}
a_3 &= C_1Q_2\theta_H\theta_L,\\
a_2 &= C_1Q_2[\theta_L(\xi_H + \omega_H + \mu) + \theta_H(\xi_L + \omega_L + \mu) + \theta_H\theta_L(\psi + \mu)] - \mu\beta B_5\theta_H\theta_L,\\
a_1 &= C_1Q_2[\psi[\theta_L(\xi_H + \omega_H(1-f) + \mu) + \theta_H(\xi_L + \omega_L f + \mu)] + \mu[\theta_L(\xi_H + \omega_H + \mu) + \theta_H(\xi_L + \omega_L + \mu)]\\
&\quad + \xi_L(\omega_H + \mu) + (\omega_L + \mu)(\xi_H + \omega_H + \mu)]\\
&\quad - \mu\beta B_5[\theta_L[\xi_H + \omega_H + \mu + \psi\theta_H(1-f)] + \theta_H(\xi_L + \omega_L + \mu + \psi f\theta_L)],\\
a_0 &= C_1Q_2Q_1(1 - \mathcal{R}_P^*),
\end{aligned} \tag{4.7}
$$

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 A 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 coefficients 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 3.

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 1–3 of Table 3 hold;*
(ii) *could have more than one endemic equilibrium if $\mathcal{R}_P^* > 1$ and whenever Case 4 of Table 3 holds;*
(iii) *could have two endemic equilibria if $\mathcal{R}_P^* < 1$ and whenever Cases 2–4 of Table 3 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 [25,32–35], 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 [35]). 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 (C.5), given in Appendix C, holds.*

The proof of Theorem 4.3, based on using center manifold theory, is given in Appendix C. It is worth mentioning that none of the aforementioned HIV modeling studies that incorporate the use of PrEP [15–19] established the presence of this phenomenon. In other words, this study may be the first to show that the widespread use of PrEP could induce the phenomenon of backward bifurcation in HIV transmission dynamics in a population. A possible cause of this phenomenon is explored below.

Table 4
Baseline values and ranges of the parameters of the PrEP model (2.2).

Parameter	Baseline value (*per* year)	Range (*per* year)	Reference
π	1160	[1044, 1276]	[29]
β	0.25	[0.225, 0.275]	[38]
μ	1/80	[0.01125, 0.01375]	[37,38]
δ	0.07	[0.063, 0.077]	[29]
θ_2	0.43	[0.387, 0.473]	[38]
θ_T	0.008	[0.0072, 0.0088]	[39]
θ_F	0.70	[0.63, 0.77]	Assumed
θ_A	1.5	[1.35, 1.65]	[39]
σ_1	8.67	[7.80, 9.54]	[37,38]
σ_2	0.05	[0.045, 0.055]	[37,38]
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]	[15]
τ_2	0.7	[0.6, 0.8]	[15]
τ_A	0.7	[0.6, 0.8]	[15]
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]	[15,16]
θ_H	0.11	[0.099, 0.121]	[15,16]

4.2.1. 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 (C.2) in Appendix C), reduces to (since β^*, ν_4, x_1 and $Y_4 > 0$, as given in Appendix C)

$$a = \frac{-2\beta^*\nu_4 x_1 \mu^2 Y_4}{C_2^2 C_4^2 \pi^2} < 0.$$

Since the bifurcation coefficient $a < 0$, it follows from Theorem 4.1 of [36] 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, [25,32–34]). 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).

The analyses in Sections 3 and 4 show that adding PrEP to the PrEP-free model (3.1) could induce the phenomenon of backward bifurcation in HIV transmission dynamics in an MSM population (it should be recalled that the PrEP-free model (3.1) does not exhibit backward bifurcation).

5. Uncertainty and sensitivity analysis

The PrEP-free model (3.1) and the PrEP model (2.2) are simulated using the parameter values given in Table 4, unless otherwise stated. Some of the parameter values are taken from the literature (such as in [15,16,29,37–39]). Any assumed parameter value was estimated based on parameter values in [15,16], data from MDH [29,40] and the following studies [8,9,11–14]. In particular, the recruitment rate (π) is estimated based on the HIV transmission surveillance data of the MSM community in Minnesota [29,40]. The approximate size of the MSM community in Minnesota is 92,800 [40]. The natural death rate (μ) is estimated to be $\frac{1}{80}$ *per* year [41]. 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) [42,43]. 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 [29]. 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 [29].

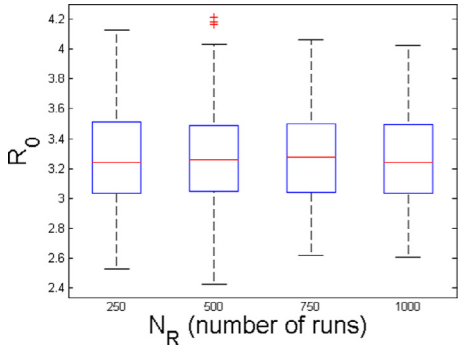

Fig. 2. Box plots of the reproduction number ($\mathcal{R}_0$), as a function of the number of LHS runs (N_R) carried out, for the PrEP-free model (3.1).

Table 5
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

5.1. PrEP-free model (3.1)

The PrEP-free model (3.1) contains 16 parameters. Hence, uncertainties in the parameter values are expected to occur. Uncertainty analysis is carried out by using latin hypercube sampling (LHS). The LHS method entails defining a baseline value and range for each parameter of the PrEP-free model (3.1) (as in Table 4) 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, $\mathcal{R}_0$) [44,45]. Each parameter is assumed to abide by a uniform distribution [44,45]. Box plots of the reproduction number, $\mathcal{R}_0$, as a function of the number of LHS runs carried out, are depicted in Fig. 2. The lower and upper horizontal lines on each box denotes the 25th and 75th percentiles of $\mathcal{R}_0$, respectively [46]. The middle horizontal line within each box denotes the 50th percentile (median value) of $\mathcal{R}_0$ [46]. 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 [46]. Values of $\mathcal{R}_0$ lie within the range [2.43, 4.13].

Moreover, partial rank correlation coefficients (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 and Fig. 3 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 4, is decreased by 10% all at once;
(ii) the baseline value of each top-five PRCC-ranked parameter, given in Table 4, is increased by 10% all at once.

The results of these simulations, depicted in Figs. 4 and 5, 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, $\mathcal{R}_0$.

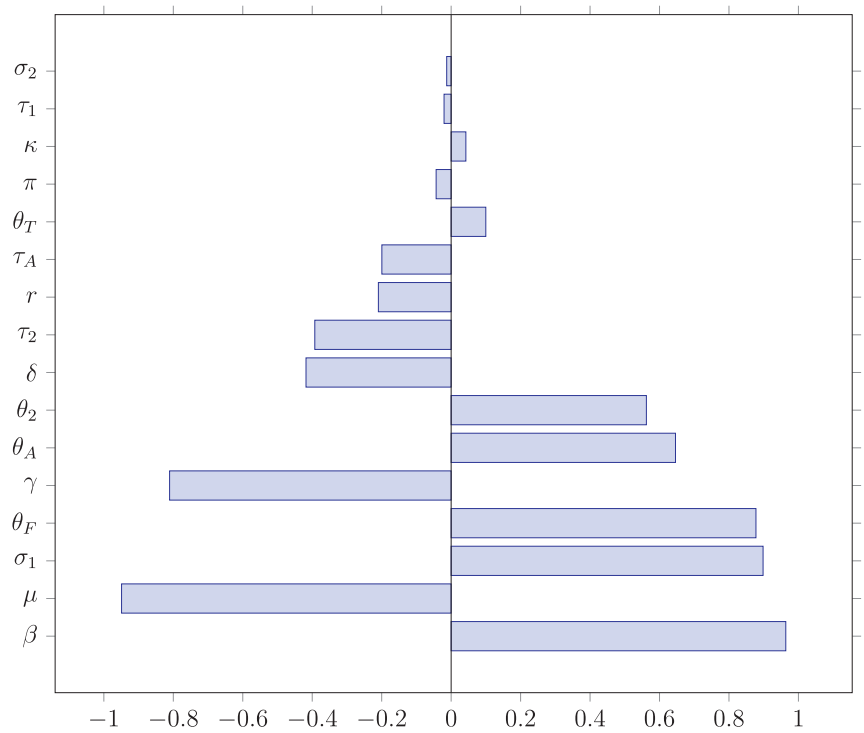

Fig. 3. PRCC values of the parameters of the PrEP-free model (3.1) with $\mathcal{R}_0$ as the outcome (response) variable. Parameter values and ranges used are as given in Table 4.

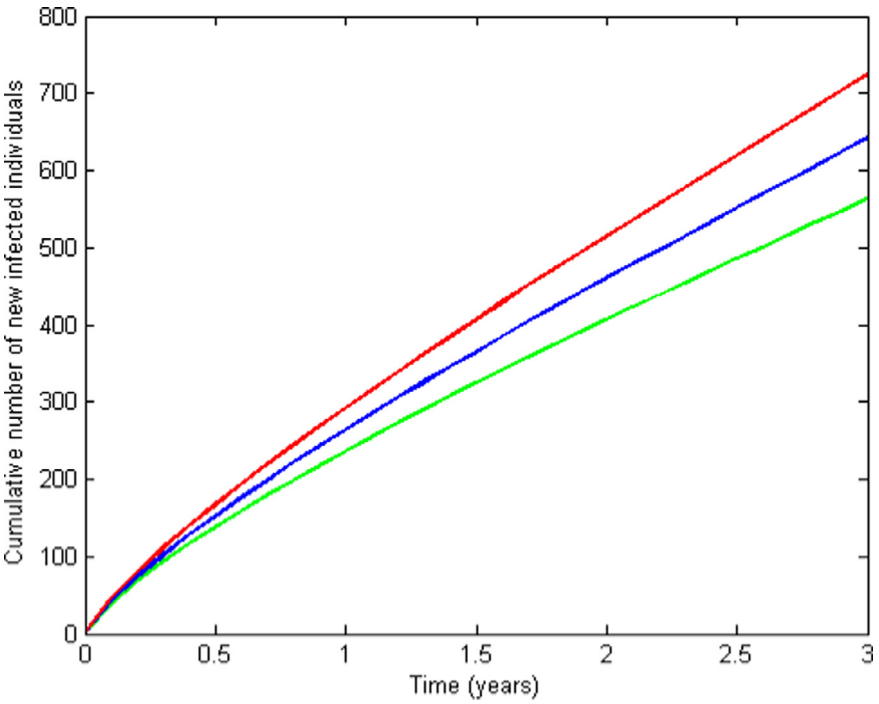

Fig. 4. Simulations of the PrEP-free model (3.1), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 4 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 4 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

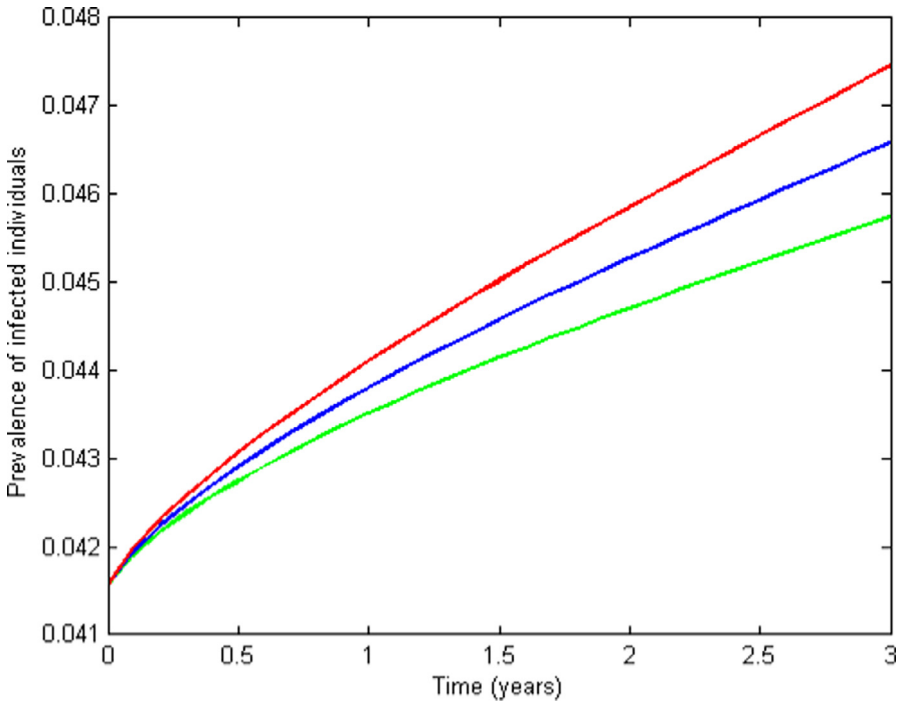

Fig. 5. Simulations of the PrEP-free model (3.1), showing the prevalence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 4 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 4 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

5.2. PrEP model (2.2)

Like for the PrEP-free model (3.1), 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 5.1 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 [44,45]. 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 Fig. 7, 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 5.1 (this is a measure of the utility of PrEP in reducing new cases of HIV infection, since the same baseline and ranges for ART administration are used in both the PrEP-free and the PrEP model, it should be noted that, in this case, the rate of administration of PrEP is 1% (i.e., $\psi = 0.01$)). Furthermore, 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 (Fig. 8). 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, in this case, 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 6 and depicted in Fig. 6. 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 5.1, 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 4, are all decreased by 10% at once;
(ii) the baseline value of each top-five PRCC-ranked parameter, given in Table 4, are increased by 10% at once.

Figs. 9 and 10 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

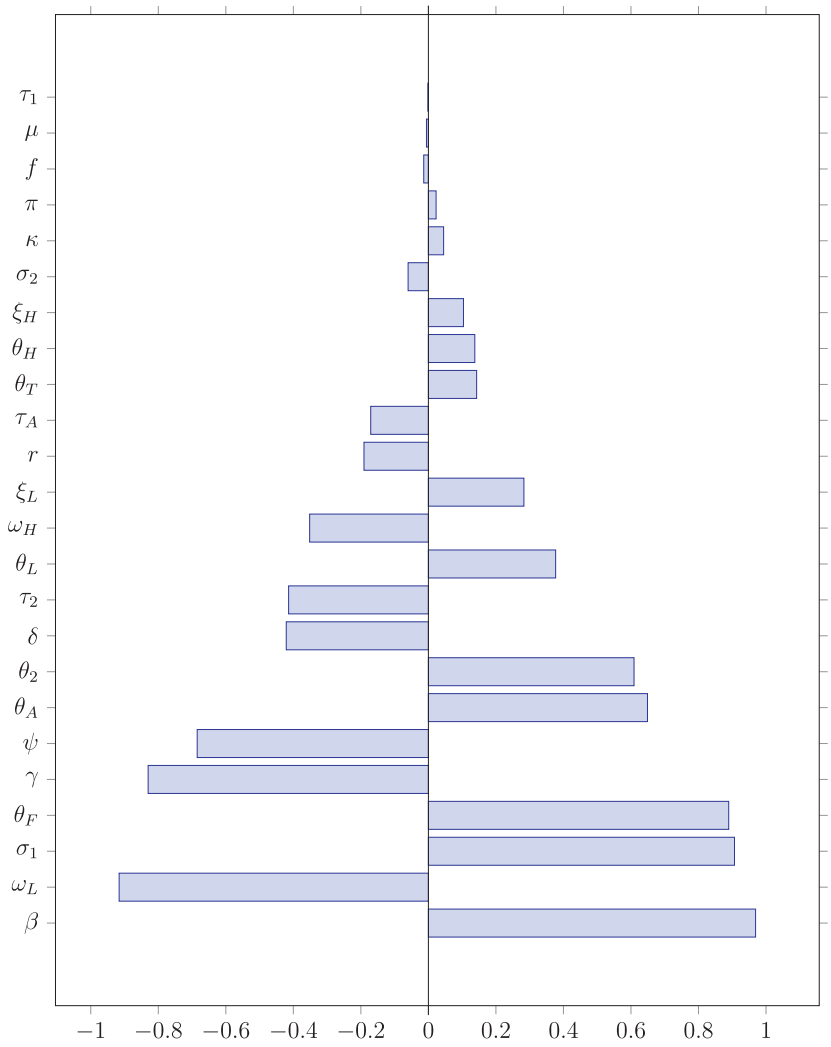

Fig. 6. PRCC values of the parameters of the PrEP model (2.2) with $\mathcal{R}_P$ as the outcome (response) variable. Parameter values and ranges used are as given in Table 4.

Fig. 11. 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. 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*" [25] 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 [25]. 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

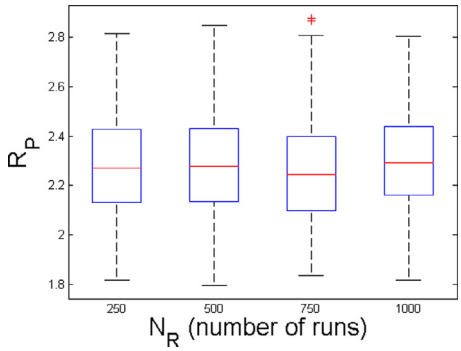

Fig. 7. Box plots of the reproduction number ($\mathcal{R}_P$), as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2). Parameter values and ranges used are as given in Table 4.

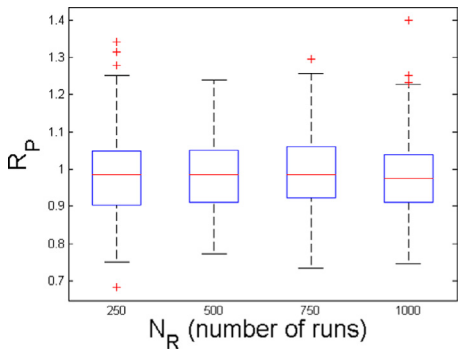

Fig. 8. Box plots of the reproduction number ($\mathcal{R}_P$), as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2) with an increased proportion of the susceptible population on PrEP ($\psi = 50\%$). Parameter values and ranges used are as given in Table 4.

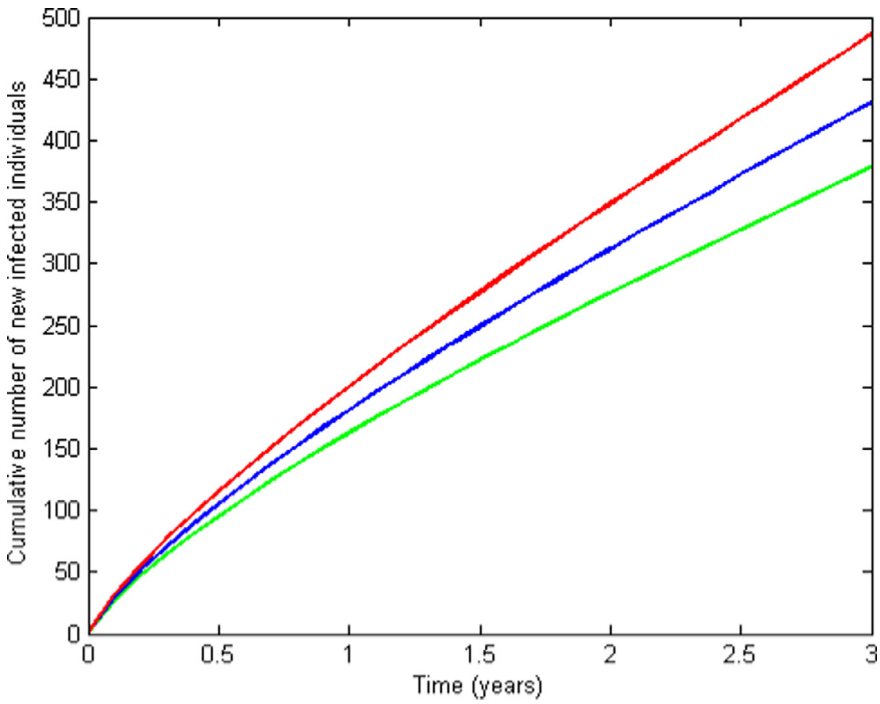

Fig. 9. Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 4 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 4 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

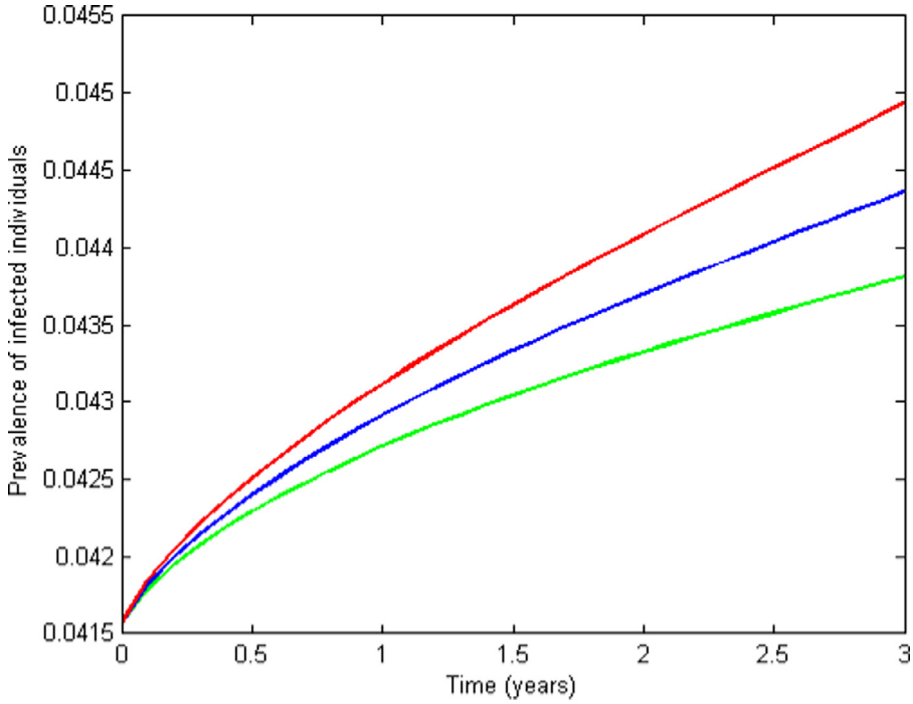

Fig. 10. Simulations of the PrEP model (2.2), showing the prevalence of HIV/AIDS, as a function of time, for various values of the top-five PRCC ranked parameters. Parameter values used are as given in Table 4 (unless otherwise stated). Green curve: the top-five PRCC ranked parameters are all decreased at once by 10%. Blue curve: baseline values given in Table 4 used. Red curve: the top-five PRCC ranked parameters are all increased at once by 10%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

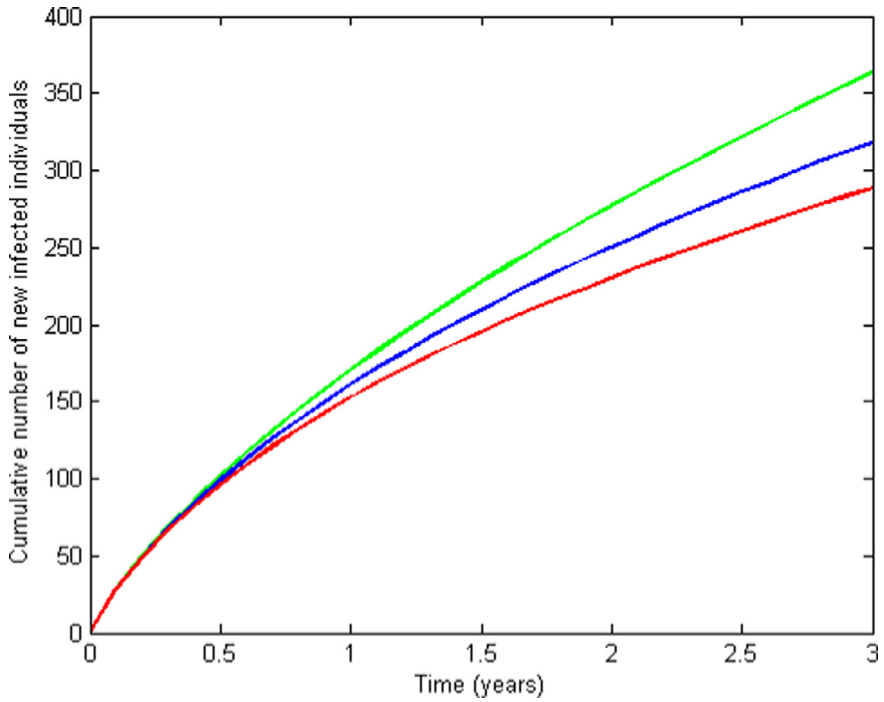

Fig. 11. Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the rate of administration of PrEP (ψ). Parameter values used are as given in Table 4 (unless otherwise stated). Green curve: $\psi = 0.25$ ($\mathcal{R}_P = 1.04$). Blue curve: $\psi = 0.5$ ($\mathcal{R}_P = .98$). Red curve: $\psi = 0.75$ ($\mathcal{R}_P = .96$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

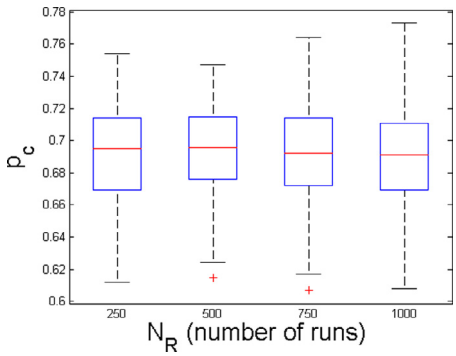

Fig. 12. Box plots of the critical fraction of susceptible individuals on PrEP (adjusted by PrEP efficacy), p_c, as a function of the number of LHS runs (N_R) carried out, for the PrEP model (2.2). Parameter values and ranges used are as given in Table 4.

Table 6
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

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

$$p_c = 1 - \frac{1}{\mathcal{R}_0}. \tag{5.1}$$

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 [25]. Using the data in Table 4, simulations of the PrEP model (2.2), depicted in Fig. 12, 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 61–77% 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 Fig. 13, show that the cumulative number of new HIV cases decreases with increasing values of p. For instance, while treating 25% of susceptible individuals

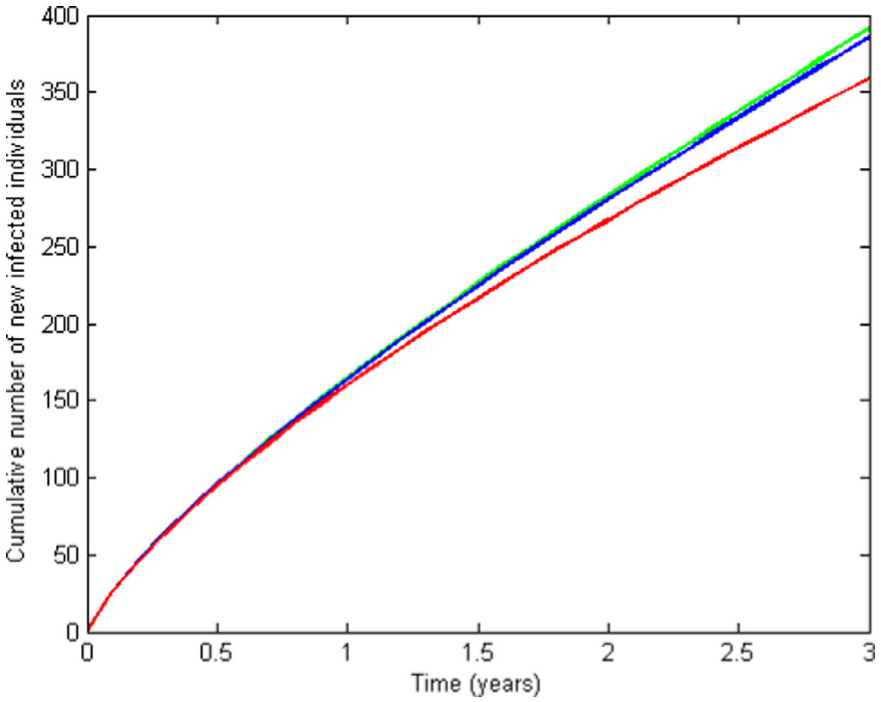

Fig. 13. Simulations of the PrEP model (2.2), showing the cumulative incidence of HIV/AIDS, as a function of time, for various values of the efficacy-adjusted fraction of susceptible individuals on PrEP (p): green curve ($p = 0.25$), blue curve ($p = 0.5$), red curve ($p = 0.75$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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.

Conclusions

The aim of this study was to assess the population-level impact of the use of pre-exposure prophylaxis (PREP) on the control of the spread of HIV/AIDS in a sexually-active MSM community. To achieve this objective, a new model, which extends numerous other HIV transmission models in the literature (that incorporate PrEP), is designed, analysed and simulated numerically. The main results obtained, including the determination of a minimum threshold level of PrEP coverage needed for the effective control (or elimination) of HIV, are summarized below.

(i) The DFE of the PrEP model (2.2) $\mathcal{E}_0^P$ 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 reproduction 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.
(iv) The 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: 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 failed antiretroviral treatment (θ_F), and the transition rate out of the failed treatment class (γ).
(v) The 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: 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 (σ_1), the modification parameter for reduction in infectiousness of individuals who failed antiretroviral treatment (θ_F), and the transition rate out of the failed treatment class (γ).
(vi) Numerical simulations of the PrEP model (2.2) show that (using the current coverage rate for ART administration to infected individuals in the U.S. State of Minnesota) 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; and noting the aforementioned ART administration). It should be cautioned that owing to the presence of the phenomenon of PrEP-induced backward bifurcation in HIV transmission dynamics (shown in this paper), this result is dependent on the initial number of HIV-infected people in the MSM community. Nonetheless, this study suggests that the combined use of ART (for infected individuals) and a reasonably attainable PrEP coverage (61–77%, with a mean of 69%) provides a realistic scenario for the effective control (or elimination) of HIV in an MSM population.

Appendix A. Positivity of $\mathcal{R}_0$ and $\mathcal{R}_P$

A1. Positivity of $\mathcal{R}_0$

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

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

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

$$\begin{aligned}
M_1 &= \kappa\gamma K_2\tau_A r - \kappa\gamma K_2\tau_A - \kappa r\gamma K_5\tau_2 - \kappa r\gamma\sigma_2\tau_A + K_2K_3K_4K_5\\
&= \kappa\gamma K_2\tau_A r + \delta\mu^3 + \delta\mu^2\gamma + \delta\mu^2\sigma_2 + \delta\mu^2\tau_2 + \delta\mu\gamma\kappa + \delta\mu\gamma\sigma_2 + \delta\mu\kappa\sigma_2 + \delta\mu\kappa\tau_2\\
&\quad + \delta\gamma\kappa\sigma_2 + \delta\gamma\kappa\tau_2(1-r) + \mu^4 + \mu^3\gamma + \mu\kappa + \mu^2\sigma_2 + \mu^3\tau_A + \mu^2\gamma\kappa + \mu^2\gamma\sigma_2 + \mu^2\gamma\tau_2\\
&\quad + \mu^2\gamma\tau_A + \mu^2\kappa\sigma_2 + \mu^2\kappa\tau_2 + \mu^2\kappa\tau_A + \mu^2\sigma_2\tau_A + \mu^2\tau_2\tau_A + \mu\gamma\kappa\sigma_2 + \mu\gamma\kappa\tau_2(1-r)\\
&\quad + \mu\kappa\sigma_2\tau_A + \mu\kappa\tau_2\tau_A + \gamma\kappa\sigma_2\tau_A(1-r) + \gamma\kappa\tau_2\tau_A(1-r) > 0,\\
M_2 &= \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r K_5\kappa\tau_1 + K_5K_4K_3\sigma_1\\
&= \gamma\kappa\sigma_1\tau_A r + \gamma r K_5\kappa\tau_1 + \delta\kappa\mu\sigma_1 + \delta\kappa\gamma\sigma_1 + \delta\mu^2\sigma_1 + \delta\mu\gamma\sigma_1 + \kappa\mu^2\sigma_1 + \kappa\mu\gamma\sigma_1\\
&\quad + \kappa\mu\sigma_1\tau_A + \mu^3\sigma_1 + \mu^2\gamma\sigma_1 + \mu^2\sigma_1\tau_A + \mu\gamma\sigma_1\tau_A > 0,\\
M_3 &= K_2K_5\tau_1 + K_5\sigma_1\tau_2 + \sigma_1\sigma_2\tau_A > 0,\\
M_4 &= \gamma r\kappa\sigma_2\tau_1 + K_3K_4\sigma_1\sigma_2 + \kappa\gamma(1-r)(K_2\tau_1 + \sigma_1\tau_2) > 0\\
&\quad (\text{since } \ 0 < r < 1).
\end{aligned}$$

A2. Positivity of $\mathcal{R}_P$

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

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

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

$$\begin{aligned}
g &= S^* + \theta_H S_H^* + \theta_L S_L^* > 0,\\
Q_2 &= \kappa\gamma C_2\tau_A r - \kappa\gamma C_2\tau_A - \kappa r\gamma C_5\tau_2 - \kappa r\gamma\sigma_2\tau_A + C_2C_3C_4C_5\\
&= \kappa\gamma C_2\tau_A r + \delta\mu^3 + \delta\mu^2\gamma + \delta\mu^2\sigma_2 + \delta\mu^2\tau_2 + \delta\mu\gamma\kappa + \delta\mu\gamma\sigma_2 + \delta\mu\kappa\sigma_2 + \delta\mu\kappa\tau_2\\
&\quad + \delta\gamma\kappa\sigma_2 + \delta\gamma\kappa\tau_2(1-r) + \mu^4 + \mu^3\gamma + \mu\kappa + \mu^2\sigma_2 + \mu^3\tau_A + \mu^2\gamma\kappa + \mu^2\gamma\sigma_2 + \mu^2\gamma\tau_2\\
&\quad + \mu^2\gamma\tau_A + \mu^2\kappa\sigma_2 + \mu^2\kappa\tau_2 + \mu^2\kappa\tau_A + \mu^2\sigma_2\tau_A + \mu^2\tau_2\tau_A + \mu\gamma\kappa\sigma_2 + \mu\gamma\kappa\tau_2(1-r)\\
&\quad + \mu\kappa\sigma_2\tau_A + \mu\kappa\tau_2\tau_A + \gamma\kappa\sigma_2\tau_A(1-r) + \gamma\kappa\tau_2\tau_A(1-r) > 0,\\
Q_3 &= \gamma\kappa\sigma_1\tau_A r - \gamma\kappa\sigma_1\tau_A + \gamma r C_5\kappa\tau_1 + C_5C_4C_3\sigma_1\\
&= \gamma\kappa\sigma_1\tau_A r + \gamma r C_5\kappa\tau_1 + \delta\kappa\mu\sigma_1 + \delta\kappa\gamma\sigma_1 + \delta\mu^2\sigma_1 + \delta\mu\gamma\sigma_1 + \kappa\mu^2\sigma_1 + \kappa\mu\gamma\sigma_1\\
&\quad + \kappa\mu\sigma_1\tau_A + \mu^3\sigma_1 + \mu^2\gamma\sigma_1 + \mu^2\sigma_1\tau_A + \mu\gamma\sigma_1\tau_A > 0,\\
Q_4 &= C_2C_5\tau_1 + C_5\sigma_1\tau_2 + \sigma_1\sigma_2\tau_A > 0,\\
Q_5 &= \gamma r\kappa\sigma_2\tau_1 + C_3C_4\sigma_1\sigma_2 + \kappa\gamma(1-r)(C_2\tau_1 + \sigma_1\tau_2) > 0,\\
&\quad (\text{since } \ 0 < r < 1 \ \text{ and } \ 0 < f < 1).
\end{aligned}$$

Appendix B. Proof of Theorem 3.5

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:

$$\mathcal{L} = \left(S - S^{**} - S^{**} ln\frac{S}{S^{**}}\right) + \left(I_1 - I_1^{**} - I_1^{**} ln\frac{I_1}{I_1^{**}}\right) + b_1\left(I_2 - I_2^{**} - I_2^{**} ln\frac{I_2}{I_2^{**}}\right) + b_2\left(I_T - I_T^{**} - I_T^{**} ln\frac{I_T}{I_T^{**}}\right)$$

$$+ b_3\left(F - F^{**} - F^{**} ln \frac{F}{F^{**}}\right) + b_4\left(A - A^{**} - A^{**} ln \frac{A}{A^{**}}\right) \tag{B.1}$$

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

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

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

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

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

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

$$\begin{aligned}
\dot{\mathcal{L}} &= \left(\mu S^{**} + \frac{\beta\mu S^{**} I_1^{**}}{\pi}\right)\left(2 - \frac{S}{S^{**}} - \frac{S^{**}}{S}\right) + \frac{\beta\mu S^{**}\theta_2 I_2^{**} G_6}{\pi G_1}\left(3 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_2}{S^{**} I_1 I_2^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2}\right) \\
&\quad + \frac{\beta\mu S^{**} G_7}{I_1^{**}\pi G_1}\left(3 - \frac{I_2 I_T^{**}}{I_2^{**} I_T} - \frac{I_2^{**} F}{I_2 F^{**}} - \frac{I_T F^{**}}{I_T^{**} F}\right) + \frac{\beta\mu S^{**} G_8}{\pi G_1}\left(3 - \frac{I_T F^{**}}{I_T^{**} F} - \frac{I_T^{**} A}{I_T A^{**}} - \frac{F A^{**}}{F^{**} A}\right) \\
&\quad + \frac{\beta\mu S^{**}\theta_T I_T^{**} G_9}{\pi G_1}\left(3 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_T}{S^{**} I_1 I_T^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T}\right) + \frac{\beta\mu S^{**} G_{10}}{I_1^{**}\pi G_1}\left(4 - \frac{I_2 F^{**}}{I_T^{**} F} - \frac{I_2 A^{**}}{I_2^{**} A} - \frac{I_T F^{**}}{I_T^{**} F} - \frac{I_T^{**} A}{I_T A^{**}}\right) \\
&\quad + \frac{\beta\mu S^{**}\theta_T I_T^{**} G_{11}}{\pi G_1}\left(4 - \frac{S^{**}}{S} - \frac{S I_1^{**} I_T}{S^{**} I_1 I_T^{**}} - \frac{I_1 I_2^{**}}{I_1^{**} I_2} - \frac{I_2 I_T^{**}}{I_2^{**} I_T}\right) \\
&\quad + \frac{\beta\mu S^{**}\theta_F F^{**} G_{12}}{\pi G_1}\left(4 - \frac{S^{**}}{S} - \frac{S I_1^{**} F}{S^{**} I_1 F^{**}} - \frac{I_1 I_T^{**}}{I_1^{**} I_T} - \frac{I_T F^{**}}{I_T^{**} F}\right)
\end{aligned}$$

$$
\begin{aligned}
&+\frac{\beta\mu S^{**}\theta_A A^{**}G_{13}}{\pi G_1}\left(4-\frac{S^{**}}{S}-\frac{SI_1^{**}A}{S^{**}I_1A^{**}}-\frac{I_1I_2^{**}}{I_1^{**}I_2}-\frac{I_2A^{**}}{I_2^{**}A}\right)\\
&+\frac{\beta\mu S^{**}\theta_2 I_2^{**}G_{14}}{\pi G_1}\left(5-\frac{S^{**}}{S}-\frac{SI_1^{**}I_2}{S^{**}I_1I_2^{**}}-\frac{I_1I_T^{**}}{I_1^{**}I_T}-\frac{I_2^{**}F}{I_2F^{**}}-\frac{I_TF^{**}}{I_T^{**}F}\right)\\
&+\frac{\beta\mu S^{**}\theta_T I_T^{**}I_2^{**}A^{**}\sigma_1\sigma_2\tau_A}{\pi G_1}\left(5-\frac{S^{**}}{S}-\frac{SI_1^{**}I_T}{S^{**}I_1I_T^{**}}-\frac{I_1I_2^{**}}{I_1^{**}I_2}-\frac{I_2A^{**}}{I_2^{**}A}-\frac{I_T^{**}A}{I_TA^{**}}\right)\\
&+\frac{\beta\mu S^{**}\theta_F F^{**}G_{15}}{\pi G_1}\left(5-\frac{S^{**}}{S}-\frac{SI_1^{**}F}{S^{**}I_1F^{**}}-\frac{I_1I_2^{**}}{I_1^{**}I_2}-\frac{I_2I_T^{**}}{I_2^{**}I_T}-\frac{I_TF^{**}}{I_T^{**}F}\right)\\
&+\frac{\beta\mu S^{**}\theta_A A^{**}G_{16}}{\pi G_1}\left(5-\frac{S^{**}}{S}-\frac{SI_1^{**}A}{S^{**}I_1A^{**}}-\frac{I_1I_T^{**}}{I_1^{**}I_T}-\frac{I_TF^{**}}{I_T^{**}F}-\frac{FA^{**}}{F^{**}A}\right)\\
&+\frac{\beta\mu S^{**}\theta_F F^{**}I_2^{**}A^{**}\sigma_1\sigma_2\tau_A}{\pi G_1}\left(6-\frac{S^{**}}{S}-\frac{SI_1^{**}F}{S^{**}I_1F^{**}}-\frac{I_1I_2^{**}}{I_1^{**}I_2}-\frac{I_2A^{**}}{I_2^{**}A}-\frac{I_T^{**}A}{I_TA^{**}}-\frac{I_TF^{**}}{I_T^{**}F}\right)\\
&+\frac{\beta\mu S^{**}\theta_A A^{**}I_2^{**}F^{**}(1-r)\gamma\sigma_1\tau_2}{\pi G_1}\left(6-\frac{S^{**}}{S}-\frac{SI_1^{**}A}{S^{**}I_1A^{**}}-\frac{I_1I_2^{**}}{I_1^{**}I_2}-\frac{I_2^{**}I_T}{I_2I_T^{**}}-\frac{I_TF^{**}}{I_TF}-\frac{FA^{**}}{F^{**}A}\right)\\
&+\frac{\beta\mu S^{**}\theta_A A^{**}I_2^{**}F^{**}r\gamma\sigma_2\tau_1}{\pi G_1}\left(6-\frac{S^{**}}{S}-\frac{SI_1^{**}A}{S^{**}I_1A^{**}}-\frac{I_1I_T^{**}}{I_1^{**}I_T}-\frac{I_2^{**}F}{I_2F^{**}}-\frac{I_TF^{**}}{I_TF}-\frac{I_2A^{**}}{I_2^{**}A}\right),
\end{aligned}
$$

where,

$$
\begin{aligned}
G_6 &= I_2^{**}A^{**}\sigma_1\sigma_2\tau_A+I_1^{**}I_2^{**}\sigma_1\sigma_2\tau_1+(I_2^{**})^2\sigma_1\sigma_2\tau_2+I_2^{**}F^{**}(1-r)\gamma\sigma_1\tau_2\\
&\quad+I_1^{**}F^{**}(1-r)\gamma\sigma_1\tau_1,\\
G_7 &= \left(\theta_2I_2^{**}+\theta_TI_T^{**}+\theta_FF^{**}+\theta_AA^{**}\right)\left[(I_2^{**})^2F^{**}\gamma r\sigma_2\tau_2+(F^{**})^2(1-r)r\gamma^2\tau_2\right],\\
G_8 &= \left[\frac{\theta_2I_2^{**}(F^{**})^2A^{**}(1-r)r\gamma^2\tau_2}{I_1^{**}}\right]+\left(\theta_TI_T^{**}+\theta_FF^{**}+\theta_AA^{**}\right)\\
&\quad\times\left[\left(\frac{(F^{**})^2A^{**}(1-r)r\gamma^2\tau_2}{I_1^{**}}\right)+F^{**}A^{**}(1-r)\gamma\sigma_1\tau_A\right],\\
G_9 &= I_1^{**}I_2^{**}\sigma_1\sigma_2\tau_1+I_2^{**}F^{**}r\gamma\sigma_2\tau_1+(F^{**})^2(1-r)r\gamma^2\tau_1+I_1^{**}F^{**}(1-r)\gamma\sigma_1\tau_1,\\
G_{10} &= \left(\theta_2I_2^{**}+\theta_TI_T^{**}+\theta_FF^{**}+\theta_AA^{**}\right)\left(I_2^{**}F^{**}A^{**}r\gamma\sigma_2\tau_A\right),\\
G_{11} &= (I_2^{**})^2\sigma_1\sigma_2\tau_2+I_2^{**}F^{**}(1-r)\gamma\sigma_1\tau_2,\\
G_{12} &= (F^{**})^2(1-r)r\gamma^2\tau_1+I_1^{**}F^{**}(1-r)\gamma\sigma_1\tau_1+I_2^{**}F^{**}r\gamma\sigma_2\tau_1+I_1^{**}I_2^{**}\sigma_1\sigma_2\tau_1,\\
G_{13} &= I_1^{**}I_2^{**}\sigma_1\sigma_2\tau_1+(I_2^{**})^2\sigma_1\sigma_2\tau_2+I_2^{**}A^{**}\sigma_1\sigma_2\tau_A,\\
G_{14} &= I_2^{**}F^{**}r\gamma\sigma_2\tau_1+(F^{**})^2(1-r)r\gamma^2\tau_1,\\
G_{15} &= I_2^{**}F^{**}(1-r)\gamma\sigma_1\tau_2+(I_2^{**})^2\sigma_1\sigma_2\tau_2,\\
G_{16} &= (F^{**})^2(1-r)r\gamma^2\tau_1+I_1^{**}F^{**}(1-r)\gamma\sigma_1\tau_1,
\end{aligned}
$$

Since the arithmetic mean exceeds the geometric mean, it follows that $\dot{\mathcal{L}}\leq 0$. Hence,

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

Furthermore, it follows from the LaSalle's Invariance Principle [47] that the unique endemic equilibrium, $\mathcal{E}_1$, of the PrEP-free model (3.1) with $\delta=0$, is GAS in $\mathcal{D}_1\backslash\mathcal{D}_0$ whenever $\mathcal{R}_1>1$. □

Appendix C. 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

$$
\begin{aligned}
\frac{dS}{dt} &= f_1=\pi+\omega_Lx_2+\omega_Hx_3-\lambda x_1-\psi x_1-\mu x_1,\\
\frac{dS_L}{dt} &= f_2=(1-f)\psi x_1+\xi_Hx_3-\theta_L\lambda x_2-(\xi_L+\omega_L+\mu)x_2,
\end{aligned}
$$

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

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 $\mathbf{f} = [f_1, \ldots, f_8]^T$ represents the vector field of the model (2.2). Evaluating the Jacobian of the system (C.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,

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

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

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

The transformed system (C.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 [36]) can be applied to analyze the dynamics of (C.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,

$$w_1 = \frac{-\mu\beta^*[(U_2U_4 - \xi_L\xi_H)x_1 + (U_4\omega_L + \xi_L\omega_H)\theta_L x_2 + (U_2\omega_H + \xi_H\omega_L)\theta_H x_3]Y_1}{\pi Q_1 C_2 C_4},$$
$$w_2 = \frac{-\mu\beta^* Y_1 Y_2}{\pi Q_1 C_2 C_4}, \quad w_3 = \frac{-\mu\beta^* Y_1 Y_3}{\pi Q_1 C_2 C_4}, \quad w_4 = w_4 > 0, \quad w_5 = \frac{C_4\sigma_1 w_4 + \gamma\kappa r w_6}{C_2 C_4},$$
$$w_6 = w_6 > 0, \quad w_7 = \frac{\kappa w_6}{C_4}, \quad w_8 = w_8 > 0.$$

and,

$$Y_1 = C_2C_4(w_4 + \theta_T w_6 + \theta_A w_8) + C_2\kappa\theta_F w_6 + \theta_2(C_4\sigma_1 w_4 + \gamma\kappa r w_6),$$
$$Y_2 = [f\xi_H + (1-f)U_4]\psi x_1 + [U_4(\mu+\psi) - f\psi\omega_H]\theta_L x_2 + [(1-f)\psi\omega_H + \xi_H(\mu+\psi)]\theta_H x_3,$$
$$Y_3 = [fU_2 + (1-f)\xi_L]\psi x_1 + [f\psi\omega_L + \xi_L(\mu+\psi)]\theta_L x_2 + [U_2(\mu+\psi) - (1-f)\psi\omega_L]\theta_H x_3.$$

Computation of bifurcation coefficients, a and b:

It can be shown (by computing the associated non-zero partial derivatives of the system (C.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 [36])

$$a = \sum_{k,i,j=1}^{8} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}_0^P, \beta^*)$$
$$= \frac{2v_4\mu^3\beta^* Y_1}{\pi^3 Q_1 C_2^2 C_4^2}[Y_5Y_4 + \beta^* Y_6 Y_1 - (Y_7Y_4 + \beta^* Y_8 Y_1)], \tag{C.2}$$

and

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

where,

$$Y_4 = C_2C_4(w_4 + w_6 + w_8) + C_2\kappa w_6 + C_4\sigma_1 w_4 + \gamma\kappa r w_6,$$
$$Y_5 = [(U_2\omega_H + \omega_L\xi_H)f\psi + (U_4\omega_L + \omega_H\xi_L)(1-f)\psi + \xi_H\xi_L(\mu+\psi)](x_1+x_2+x_3)(x_1 + \theta_L x_2 + \theta_H x_3),$$
$$Y_6 = (U_2U_4x_1 + U_2\omega_H\theta_H x_3 + U_4\omega_L\theta_L x_2 + \omega_H\xi_L\theta_L x_2 + \omega_L\xi_H\theta_H x_3)(\theta_L x_2 + \theta_H x_3) + U_2(x_1 + \theta_L x_2)[f\psi x_1 + (\mu+\psi)\theta_H x_3]$$
$$+ U_4(x_1 + \theta_H x_3)[(1-f)\psi x_1 + (\mu+\psi)\theta_L x_2] + \xi_H\xi_L(x_2+x_3)x_1$$
$$+ f\psi(\xi_H(x_1 + \theta_H x_3)x_1 + [\omega_H\theta_L(x_1+x_3) + \omega_L(x_1 + \theta_L x_2)]\theta_L x_2) + (1-f)\psi(\xi_L(x_1 + \theta_L x_2)x_1$$
$$+ [\omega_L\theta_H(x_1+x_2) + \omega_H(x_1 + \theta_H x_3)]\theta_H x_3) + (\mu+\psi)[\xi_L(x_1+x_2)\theta_L x_2 + \xi_H(x_1+x_3)\theta_H x_3],$$
$$Y_7 = U_2U_4(\mu+\psi)(x_1+x_2+x_3)(x_1 + \theta_L x_2 + \theta_H x_3),$$
$$Y_8 = (U_2U_4x_1 + U_4\omega_L\theta_L x_2 + U_2\omega_H\theta_H x_3)(x_2+x_3) + U_2\theta_H[f\psi x_1 + (\mu+\psi)\theta_H x_3](x_1+x_2)$$
$$+ U_4\theta_L[(1-f)\psi x_1 + (\mu+\psi)\theta_L x_2](x_1+x_3)$$
$$+ (\xi_H\xi_L(\theta_L x_2 + \theta_H x_3) + \psi[f\xi_H\theta_L(x_1+x_3) + (1-f)\xi_L\theta_H(x_1+x_2)])x_1$$
$$+ (\omega_H\theta_L[\xi_L(x_2+x_3) + f\psi x_1] + \theta_H\theta_L([\xi_L(\mu+\psi)$$
$$+ \omega_L f\psi](x_1+x_2) + \omega_H f\psi x_3))x_2 + (\omega_L\theta_H[\xi_H(x_2+x_3) + (1-f)\psi x_1]$$
$$+ \theta_H\theta_L([\xi_H(\mu+\psi) + \omega_H(1-f)\psi](x_1+x_3) + \omega_L(1-f)\psi x_2))x_3. \tag{C.4}$$

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

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

where, $J_1 = Y_5Y_4 + \beta^* Y_6 Y_1$ and $J_2 = Y_7Y_4 + \beta^* Y_8 Y_1$. Hence, it follows from Theorem 4.1 of [36], that the PrEP model (2.2) (or, equivalently (C.1)) undergoes backward bifurcation at $\mathcal{R}_P^* = 1$ whenever Inequality (C.5) holds. □

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