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Modeling the emergence of HIV-1 drug resistance resulting from antiretroviral therapy: Insights from theoretical and numerical studies

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ABSTRACT

The use of antiretroviral therapy has proven to be remarkably effective in controlling the progression of human immunodeficiency virus (HIV) infection and prolonging patient's survival. Therapy however may fail and therefore these benefits can be compromised by the emergence of HIV strains that are resistant to the therapy. In view of these facts, the question of finding the reason for which drug-resistant strains emerge during therapy has become a worldwide problem of great interest. This paper presents a deterministic HIV-1 model to examine the mechanisms underlying the emergence of drug-resistance during therapy. The aim of this study is to determine whether, and how fast, antiretroviral therapy may determine the emergence of drug resistance by calculating the basic reproductive numbers. The existence, feasibility and local stability of the equilibriums are also analyzed. By performing numerical simulations we show that Hopf bifurcation may occur. The model suggests that the individuals with drug-resistant infection may play an important role in the epidemic of HIV.

1. Introduction

The availability of new and more potent antiretroviral therapy (ART) has been successful in delaying the progression of AIDS disease and has dramatically improved the life expectancy of HIV infected patients. The initial goal of ART is to suppress HIV viral replication below the level of clinical detection. Thereby the immune function is maintained and the disease progression is prevented. However, there is a general agreement that ART is not effective in all patients and may fail to achieve complete viral suppression below the limit of viral detection. The suppression of viral replication by the use of ART is not in itself sufficient for clearing the infection, and ART cannot therefore cure the HIV infection completely. In view of these facts, in clinical practice, an ever increasing number of patients are reported to fail the therapy.

Although a clear definition does not exist (Gallant, 2000), treatment failure can be measured in three ways: clinically, by disease progression and WHO (World Health Organization) clinical staging; immunologically, using trends in CD4 counts over time, and virologically, by measuring HIV viral loads.

Viral load measurement is considered a more sensitive indicator of treatment failure compared to clinical or immunological indicators. However, because the definitions of clinical, immunological and virological failure currently used in different settings represent different biological end-points, it is still not clear which criteria are optimal (WHO, 2006). Thus, while no consensus on ART monitoring and the diagnosis of failure has been reached, there is a tendency to reduce reliance on clinical failure definitions, expand the use immunological criteria and use viral load testing for confirmation of clinical/immunological failure (WHO, 2010).

One of the critical decisions in ART management is when to switch from one regimen to another for treatment failure due to resistance. The emergence of HIV drug resistance is of increasing concern in countries where ART is widely used, and represents a potential impediment to the achievement of long-term success in treatment outcomes.

Epidemics of drug-sensitive and drug-resistant strains have different dynamics. Epidemics of drug-sensitive strains were generated only by transmission (Massad et al., 1994; Carvalho et al., 1996; Burattini et al., 2000; Moghadas et al., 2003; Moghadas and Gumel, 2003; Sharomi et al., 2007), while epidemics of drug-resistant strains are generated by both the transmission of drug-resistant strains and the treated individuals who were initially infected with drug-sensitive strains, but develop drug resistance during treatment. Insights into HIV drug resistance

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have been obtained from a large number of mathematical models (Bonhoeffer et al., 1977; MacLean and Nowak, 1992; Nowak et al., 1997; Kirschiner and Webb, 1997; Wein et al., 1998; Gumel et al., 2000; Blower et al., 2000, 2001; Smith and Wahl, 2005; Baggaley et al., 2005, 2006; Rong et al., 2007; Krakovska and Wahl, 2007a,b; Sharomi and Gumel, 2008; Qiu and Feng, 2010; Hoare et al., 2010; Supervie et al., 2010). Although clinical studies are essential in elucidating the complex effects of teraphy, these models have played an important role for understanding the pathogenesis of HIV-1 infection, the drug therapy strategies used against it, and the emergence of drug resistance.

The aim of this paper is to examine the mechanisms underlying the emergence of HIV-1 drug-resistance during therapy. We propose a mathematical model to understand and to predict the evolution of the epidemic of HIV-1. The model tracks two HIV-1 strains, one resistant to ART and one sensitive.

Due to the fact that drug-resistant strains are obviously less sensitive to ART, they are fitter than the drug-sensitive strains in the presence of drug. In practice, it still remains unclear which assay is most appropriate to measure the fitness of HIV. Fitness is a complex parameter aimed to describe the replicative and adaptability of an organism and it refers to the ability of an organism to adapt and reproduce in a defined environment (Quiñones-Matheu and Arts, 2001; Quiñones-Matheu, 2005). However, since the basic reproductive number is a commonly used measure of the absolute fitness of a virus within a host (Gilchrist et al., 2004), here we will examine the effect of ART on the HIV-1 fitness drug-resistant strains by analyzing the reproductive number in the presence of ART. Hence, by deriving the basic reproductive number important insights can also be gained through our theoretical and numerical studies.

This paper is organized as follows. The model is described in Section 2. In Section 3 we perform the steady-state analysis of the model. Section 4 is devoted to the numerical investigation of the system, which confirms our theoretical results and illustrate the possible existence of behaviors, including periodic solutions and Hopf bifurcation under certain parameter. We also assess what happens when therapy is switched to a less intensive maintenance regimen. The conclusion section closes the paper.

2. Model Formulation

To study the evolution of drug-resistant strains in the presence of drug therapy in an environment in which the drug-sensitive strains are already established, both drug-sensitive and drug-resistant HIV-1 infections are considered. Our model's assumption is that drug-resistance can evolve directly during the therapy for whatever reason, but it has only two outcomes. Either the drug-resistant strains already existed before the onset of therapy, or the drug-resistant strains evolved during therapy.

We distinguish patients who respond to a regimen (who typically experience reduction in viral load to undectable levels), and remain as a nonprogressor for a specified amount of time but may experience treatment failure, from those who do not respond and subsequently experience treatment failure. It is further considered that no effective treatment exists for individuals with the drug-resistant HIV-1 infection (Hoare et al., 2010; Sharomi and Gumel, 2008). This is in line with the fact that a drug-resistant strain is less responsive to therapy than a drug-sensitive strain (Blower et al., 2000), i.e., ART is more likely to fail in patients with drug-resistant HIV-1 infection because they have limited ability to achieve or maintain complete viral suppression.

In this context, we assumed that the patients with drug-sensitive HIV-1 infection may evolve to either compartments of "successfully treated" (i.e., satisfactory virus suppression) or "unsuccessfully treated" (treatment failure); however the drug-resistant HIV-1 patients may migrate only to a "state of failure".

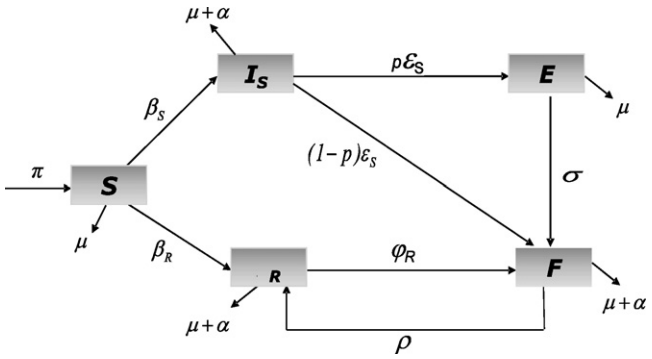

Fig. 1. Flow diagram of model (3).

The above assumptions lead to a model involving the total population, $\tilde{N}$ divided into five epidemiologic classes: $\tilde{S}$, susceptible individuals; $\tilde{I}_S$, treatment-naive patients with drug-sensitive HIV-1 infection; $\tilde{I}_R$, treatment-naive patients with drug-resistant HIV-1 infection; $\tilde{E}$, successfully treated patients with drug-sensitive HIV-1 infection; and $\tilde{F}$, HIV-1 infected individuals in therapeutic failure. The subscripts specify whether the infection is a drug-sensitive (S) or a drug-resistant (R) strain. Note that the model does not consider a class of individuals with clinical AIDS, composed of patients who progress to full-blown AIDS. We assumed this because of their illness, these patients do not play a role in the dynamic of the transmission of the drug-resistant HIV-1 infection.

A flow diagram of the model is given in Fig. 1. In this study, all the parameters of the model are positive. The vital dynamics includes a "birth and immigration process" given by a constant recruitment rate π and a "death process" given by natural mortality rate μ, as well as the progression rate to full-blown AIDS, described by the parameter α. For simplicity, the same value of α is considered for the individuals in therapeutic failure ($\tilde{F}$), drug-sensitive individuals ($\tilde{I}_S$) and drug-resistant individuals ($\tilde{I}_R$).

Our assumption is that HIV transmission is represented by pseudo mass-action incidence (Jong et al., 1994), i.e., the number of new infected individuals produced by random contacts is proportional to the size of susceptible and infected individuals. In our model the susceptible individuals $\tilde{S}$ can be infected with either a drug-sensitive or a drug-resistant HIV-1 strains, so the number of new sensitive and resistant cases are respectively $\tilde{\beta}_S\tilde{S}\tilde{I}_S$ and $\tilde{\beta}_R\tilde{S}\tilde{I}_R$. The transmission coefficients, $\tilde{\beta}_S$ and $\tilde{\beta}_R$, specify the transmissibility of drug-sensitive and drug-resistant HIV-1 strains, respectively. We take $\beta_R = k\beta_S$, where $0 < k < 1$ represents the transmission level of the drug-resistant HIV-1 strains, i.e., k indicates that drug-resistant strains are less transmissible (i.e., less fitness) than drug-sensitive strains (Velasco-Hernandez et al., 2002; Brown et al., 2003; Supervie et al., 2010; Hoare et al., 2010).

We let ε_S be the treatment rate for the drug-sensitive HIV-1 infected patients; p $(0 < p < 1)$ is the proportion of drug-sensitive patients who are successfully treated; and $(1-p)$ represents the proportion of the drug-sensitive patients who experience failure during therapy. We let σ and φ_R denote the treatment failure rates for the drug-sensitive and drug-resistant infected patients, respectively.

Finally, to estimate the time at which resistance dominates, we use the simplest possible assumption model, assuming that the rate at which resistance emerges per unit time, ρ, is constant

The associated variables and parameters of the model are described in Table 1.

Based on these assumptions, the dynamics of transmission is then formalized by the following nonhomogeneous

Table 1
Description of variables and parameters for model (3).

Variables	Description
S	Susceptible individuals
I_S	Treated-naive patients with drug-sensitive HIV-1 infection
I_R	Treated-naive patients with drug-resistant HIV-1 infection
E	Successfully treated patients with drug-sensitive HIV-1 infection
F	HIV-1 infected individuals in therapeutic failure
Parameters	Description
μ	Susceptibles recruitment rate (births and immigration) or natural mortality rate
β_S	Transmission coefficient of the drug-sensitive virus
β_R	Transmission coefficient of the drug-resistant virus
ε_S	Treatment rate for the drug-sensitive HIV-1 patients (reciprocal time for the patient to achieve complete viral suppression)
φ_R	Treatment rate for the drug-resistant patients (reciprocal time for the patient to experience incomplete viral suppression or viral rebound)
p	Proportion of the successfully treated drug-sensitive HIV-1 individuals
σ	Average time required for the drug-sensitive patients to develop drug resistance after achieving complete viral suppression
ρ	Rate per unit time at which resistance emerges
α	Progression rate to disease

linear system of ordinary differential equations with constant coefficients

$$\begin{cases} \dfrac{d\tilde{S}}{dt} = \pi - \tilde{\beta}_S\tilde{S}\tilde{I}_S - \tilde{\beta}_R\tilde{S}\tilde{I}_R - \mu\tilde{S} \\ \dfrac{d\tilde{I}_S}{dt} = \tilde{\beta}_S\tilde{S}\tilde{I}_S - (\varepsilon_S + \mu + \alpha)\tilde{I}_S \\ \dfrac{d\tilde{I}_R}{dt} = \tilde{\beta}_R\tilde{S}\tilde{I}_R + \rho\tilde{F} - (\varphi_R + \mu + \alpha)\tilde{I}_R \\ \dfrac{d\tilde{E}}{dt} = p\varepsilon_S\tilde{I}_S - (\sigma + \mu)\tilde{E} \\ \dfrac{d\tilde{F}}{dt} = (1-p)\varepsilon_S\tilde{I}_S + \varphi_R\tilde{I}_R + \sigma\tilde{E} - (\rho + \alpha + \mu)\tilde{F}. \end{cases} \quad (1)$$

By summing up the above equations, the total population size $\tilde{N}(t)$ is variable with

$$\frac{d\tilde{N}}{dt} = \pi - \mu\tilde{N} - \alpha(\tilde{I}_S + \tilde{I}_R + \tilde{F}). \quad (2)$$

When the treatment is effective in reducing disease progression, i.e., $\alpha = 0$, the population size $\tilde{N}$ evolves as an immigration model with natural mortality, i.e., according to $d\tilde{N}/dt = \pi - \mu\tilde{N}$. This equation has a single equilibrium $\overline{\tilde{N}} = N_0 = \pi/\mu$, for any initial value of N_0. Thus, in the long run the population size settles to this constant value. It follows from (2) that $\lim_{t\to\infty}\tilde{N}(t) \le \pi/\mu = N_0$.

The differential equation for $\tilde{N}$ implies that solutions of (1) starting in the positive orthant $\mathbb{R}^5_+$, either approach, enter, or remain in the subset $\mathbb{R}^5_+$ defined by

$$D = \{(\tilde{S}, \tilde{I}_S, \tilde{I}_R, \tilde{E}, \tilde{F}) \in \mathbb{R}^5_+ : \tilde{S} + \tilde{I}_S + \tilde{I}_R + \tilde{E} + \tilde{F} \le N_0\}.$$

Thus it suffices to consider solutions in region D. Solutions of the initial value problem starting in D and defined by (1) exist and are unique on a maximal interval (Hale, 1980). Since solutions remain bounded in the positively invariant region D, the initial value problem is then well posed both mathematically and epidemiologically (Hethcote, 2000). Consequently, we have the following lemma.

Lemma 2.1. *The biological feasible region D is positively invariant and attracts all solutions in $\mathbb{R}^5_+$.*

Hence, it is sufficient to consider the dynamics of the flow generated by model (1) in D.

Before analyzing the model (1) and to explore the stability behavior of its equilibria, we rescale the system by defining the new variables: $S = \tilde{S}/N_0$; $I_S = \tilde{I}_S/N_0$; $I_R = \tilde{I}_R/N_0$; $E = \tilde{E}/N_0$, $F = \tilde{F}/N_0$, $N = \tilde{N}/N_0$ and parameters $\beta_S = N_0\tilde{\beta}_S$ and $\beta_R = N_0\tilde{\beta}_R$. Using these changes of variables and parameters, the system (1) becomes:

$$\begin{cases} \dfrac{dS}{dt} = \mu - \beta_S S I_S - \beta_R S I_R - \mu S \\ \dfrac{dI_S}{dt} = \beta_S S I_S - (\varepsilon_S + \mu + \alpha) I_S \\ \dfrac{dI_R}{dt} = \beta_R S I_R + \rho F - (\varphi_R + \mu + \alpha) I_R \\ \dfrac{dE}{dt} = p\varepsilon_S I_S - (\sigma + \mu) E \\ \dfrac{dF}{dt} = (1-p)\varepsilon_S I_S + \varphi_R I_R + \sigma E - (\rho + \alpha + \mu) F, \end{cases} \quad (3)$$

and

$$\frac{dN}{dt} = \mu(1 - N) - \alpha(I_S + I_R + F),$$

so that the rescaled total population size is variable with $S + I_S + I_R + E + F = N \le 1$.

3. Existence and Stability of Equilibria

In order to make the mathematical formulation compatible with the real phenomenon it describes, we will study the evolution of trajectories in the neighborhood of the steady state solution $P = (S, I_S, I_R, E, F)$ of the system (3).

3.1. Disease-Free Equilibrium

In the absence of infection, i.e., for $I_S = I_R = 0$, the model has the disease-free equilibrium $P^{(0)} = (1, 0, 0, 0, 0)$ which is obtained by setting the right-hand sides of system (3) to zero. To establish the stability of this equilibrium, the Jacobian of the system is computed and evaluated at $P^{(0)}$. The equilibrium $P^{(0)}$ is locally asymptotically stable if the real part of the eigenvalues of the Jacobian matrix are all negative. Specifically, the Jacobian of system (3) at $P^{(0)}$ is given by

$$J_{P^{(0)}} = \begin{bmatrix} J_{11}^{P^{(0)}} & -\beta_S S & -\beta_R S & 0 & 0 \\ 0 & J_{22}^{P^{(0)}} & 0 & 0 & 0 \\ 0 & 0 & J_{33}^{P^{(0)}} & 0 & \rho \\ 0 & p\varepsilon_S & 0 & J_{44}^{P^{(0)}} & 0 \\ 0 & (1-p)\varepsilon_S & \phi_R & \sigma & J_{55}^{P^{(0)}} \end{bmatrix}, \quad (4)$$

where $J_{11}^{P^{(0)}} = -\mu$; $J_{22}^{P^{(0)}} = \beta_S S - (\varepsilon_S + \mu + \alpha)$; $J_{33}^{P^{(0)}} = \beta_R S - (\varphi_R + \mu + \alpha)$; $J_{44}^{P^{(0)}} = -(\mu + \sigma)$ and $J_{55}^{P^{(0)}} = -(\rho + \mu + \alpha)$.

The Jacobian (4) simplifies to give directly the three eigenvalues $\lambda_1 = -\mu$, $\lambda_2 = \beta_S - (\varepsilon_S + \mu + \alpha)$ and $\lambda_3 = -(\mu + \sigma)$, and the ones of the submatrix of order 2,

$$A_0 = \begin{bmatrix} J_{33}^{P^{(0)}} & \rho \\ \varphi_R & J_{55}^{P^{(0)}} \end{bmatrix}. \quad (5)$$

Note that $\lambda_2 = \beta_S - (\varepsilon_S + \mu + \alpha) < 0$ if $\beta_S < \beta_S^* = \varepsilon_S + \mu + \alpha$, or equivalently, if $\mathcal{R}_S < 1$, where

$$\mathcal{R}_S = \frac{\beta_S}{\beta_S^*}. \tag{6}$$

The characteristic equation of the submatrix (5) can be recasted as the quadratic polynomial

$$P(\lambda) = \lambda^2 + a_1\lambda + a_0,$$

where

$$a_1 = -\beta_R + (\varphi_R + \mu + \alpha) + (\mu + \alpha + \rho),$$
$$a_0 = -\beta_R(\mu + \alpha + \rho) + (\mu + \alpha)(\mu + \alpha + \rho + \varphi_R).$$

The Routh-Hurwitz conditions for the second order polynomial are $a_1 > 0$ and $a_0 > 0$, which imply in the following expressions

$$\beta_R < \beta_R^1 = [2(\mu + \alpha) + \rho + \varphi_R], \tag{7}$$

and

$$\beta_R < \beta_R^* = \frac{(\mu + \alpha)(\mu + \alpha + \rho + \varphi_R)}{(\mu + \alpha + \rho)}. \tag{8}$$

It is easy to verify that $\beta_R^* < \beta_R^1$. Therefore, the Routh-Hurwitz criteria is satisfied if the condition (8) holds, that is, if $\mathcal{R}_R < 1$, where

$$\mathcal{R}_R = \frac{\beta_R}{\beta_R^*}. \tag{9}$$

Hence, if $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$, then all eigenvalues of Jacobian matrix (4) have negative real part. Therefore, we have established the following result.

Proposition 3.1. *If the disease-free equilibrium* $P^{(0)} = (1, 0, 0, 0, 0)$ *exists, it is locally asymptotically stable if both* $\mathcal{R}_S < 1$ *and* $\mathcal{R}_R < 1$ *hold, otherwise it is unstable.*

For the case of a single infected population, a very general property of epidemic models states that a disease can be maintained in a population only if each infected individual produces, on average, more than one new infection, i.e., if the basic reproductive number satisfies $\mathcal{R}_0 > 1$. However, for our model this definition of $\mathcal{R}_0$ is insufficient. A more general basic reproductive number can be defined as the number of secondary cases or new infections generated by both drug-sensitive and drug-resistant infected individuals. Hence, here we have defined $\mathcal{R}_S$ and $\mathcal{R}_R$ as the basic reproductive number of the drug-sensitive and the drug-resistant strains, respectively. Thus, if both $\mathcal{R}_S$ and $\mathcal{R}_R$ are less than one, then the infection will be eradicated from the population. If, on the other hand, any one of or both the two reproductive numbers $\mathcal{R}_S$ and $\mathcal{R}_R$ are greater than one, then both sensitive and resistant HIV-1 infected individuals can establish an infection. Whether and how fast drug-resistant strains are likely to spread through a drug-sensitive population, it is determined by their relative reproductive numbers. Therefore, the basic reproductive number can provide a useful framework for the mathematical definition of drug resistance (Bonhoeffer and Nowak, 1997).

3.2. Endemic Equilibria

In the presence of infection, i.e., $I_S = I_R \neq 0$, the system (3) has two possible non-trivial equilibria. The boundary steady state $P_1 = (S^1, 0, I_R^1, 0, F^1)$ at which only the drug-resistant individuals are present has coordinates

$$\begin{cases} S^1 = \dfrac{1}{\mathcal{R}_R} \\ I_R^1 = \dfrac{\mu}{\beta_R}(\mathcal{R}_R - 1) \\ F^1 = \left[\dfrac{\varphi_R}{(\mu + \alpha + \rho)}\right] I_R^1. \end{cases} \tag{10}$$

The interior steady state where there is a coexistence of both the sensitive and the drug-resistant individuals $P_2 = (S^*, I_S^*, I_R^*, E^*, F^*)$ has coordinates

$$\begin{cases} S^* = \dfrac{1}{\mathcal{R}_S} \\ I_S^* = \dfrac{D_1(\mathcal{R}_S - \mathcal{R}_R)}{D_2} I_R^* \\ I_R^* = \dfrac{\mu D_2(\mathcal{R}_S - 1)}{\beta_S D_1(\mathcal{R}_S - \mathcal{R}_R) + \beta_R D_2} \\ E^* = \dfrac{D_1 p \varepsilon_S(\mathcal{R}_S - \mathcal{R}_R)}{D_2(\mu + \sigma)} I_R^* \\ F^* = \left[\dfrac{\varphi_R}{(\mu + \alpha + \rho)}\right] I_R^* + \dfrac{\varepsilon_S[\mu(1-p) + \sigma]}{(\mu + \alpha + \rho)(\mu + \sigma)} I_S^*, \end{cases} \tag{11}$$

where $D_1 > 0$ and $D_2 > 0$ are given by

$$D_1 = (\mu + \alpha)(\mu + \sigma)(\varepsilon_S + \mu + \alpha)(\mu + \alpha + \rho + \varphi_R),$$
$$D_2 = \rho \varepsilon_S \beta_S [\mu(1 - p) + \sigma].$$

Observe from the above expressions for the steady states (10) and (11) that the drug-resistant population will always be present. If $\mathcal{R}_R < 1$ and $\mathcal{R}_S < 1$, then the system (3) is inconsistent and there is no feasible endemic equilibria in this case: $S^1 > 1$, $I_R^1 < 0$ and $S^* > 1$. Thus, firstly we require $\mathcal{R}_R > 1$ and/or $\mathcal{R}_S > 1$ to ensure the existence and the feasibility of both endemic equilibria, P_1 and P_2.

Suppose now that $I_R^* > 0$. Here also, it is easy to see that whenever $\mathcal{R}_R > max(\mathcal{R}_S, 1)$, then the system (3) has no feasible coexistence endemic equilibrium P_2, because $I_S^* < 0$ and $E^* < 0$.

If $\mathcal{R}_R > \max(\mathcal{R}_S, 1)$, then the average number of new infections generated by a single drug-resistant infected individual exceeds those generated by a single drug-sensitive infected individual. Indeed, the two viral strains compete for the same resources, the drug treatment. However, due to the reduced viral fitness (i.e., smaller transmissibility) of the drug-sensitive strain compared with the drug-resistant strain, the drug-resistant population will out-compete the sensitive one due to the competitive exclusion principle. Therefore, the unique endemic equilibrium feasible is P_1 at which only the drug-resistant individuals are present.

In contrast, the drug-resistant population cannot exist alone if its viral fitness is reduced compared with the drug-sensitive individuals. Despite of the fact that drug-resistant strains are less responsive to the therapy, both drug-sensitive and drug-resistant individuals will coexist whenever $\mathcal{R}_S > \mathcal{R}_R$.

Hence, which population will dominate depends on the fitness of each population. It is clear that the model (3) has a coexistence equilibrium P_2 only when the reproductive number of the drug-sensitive is greater than unity ($R_S > 1$) and exceeds the reproductive number of the drug-resistant ($R_S > R_R$). In such case, if $\mathcal{R}_R > 1$, then both equilibria P_1 and P_2 are feasible. If $\mathcal{R}_R < 1$, then only P_2 is feasible.

Therefore, we establish the following results:

Proposition 3.2. *In the system (3),*

(i) *if* $\mathcal{R}_S > 1$ *and* $\mathcal{R}_R > 1$ *then both endemic equilibria exist;*
(ii) *if* $\mathcal{R}_R > 1$ *then the single endemic equilibrium* P_1 *exists;*
(iii) *if* $\mathcal{R}_S > 1$ *and* $\mathcal{R}_S > \mathcal{R}_R$ *then the single endemic equilibrium* P_2 *exists;*
(iv) *if neither (i), (ii) nor (iii) occur then there are no endemic equilibria.*

Next, we will show that these existence conditions also provide conditions for the stability of the steady states.

3.3. Stability Results

We now study the stability of the endemic equilibrium points. We begin with the Jacobian of system (3) at $P_1 = (S^1, 0, I_R^1, 0, F^1)$ namely

$$J_{P_1} = \begin{bmatrix} J_{11}^{P_1} & -\beta_S S^1 & -\beta_R S^1 & 0 & 0 \\ 0 & J_{22}^{P_1} & 0 & 0 & 0 \\ \beta_R I_R^1 & 0 & J_{33}^{P_1} & 0 & \rho \\ 0 & p\varepsilon_S & 0 & J_{44}^{P_1} & 0 \\ 0 & (1-p)\varepsilon_S & \phi_R & \sigma & J_{55}^{P_1} \end{bmatrix}, \tag{12}$$

where $J_{11}^{P_1} = -(\beta_R I_R^1 + \mu)$; $J_{22}^{P_1} = -\beta_S S^1 - (\varepsilon_S + \mu + \alpha)$; $J_{33}^{P_1} = -\beta_R S^1 - (\mu + \alpha + \varphi_R)$; $J_{44}^{P_1} = -(\mu + \sigma)$ and $J_{55}^{P_1} = -(\rho + \mu + \alpha)$.

The Jacobian matrix (12) gives explicitly two eigenvalues, namely $\lambda_1 = -(\mu + \sigma) < 0$, and $\lambda_2 = \beta_S S^1 - (\varepsilon_S + \mu + \alpha)$. Substituting the value of S^1 (see (10)), we have $\lambda_2 = \beta_S(1/\mathcal{R}_R - 1/\mathcal{R}_S) < 0$ if and only if

$$\mathcal{R}_R > \mathcal{R}_S. \tag{13}$$

The remaining eigenvalues are found by the corresponding third degree characteristic equation

$$\begin{aligned} F_3(\lambda) = {} & (\beta_R I_R^1 + \mu + \lambda)(\mu + \alpha + \lambda)(\varphi_R + \mu + \alpha + \rho + \lambda) \\ & - (\mu + \lambda)\beta_R S^1(\mu + \rho + \alpha + \lambda). \end{aligned} \tag{14}$$

We now consider the characteristic polynomial (14) in terms of the basic reproductive numbers. We rewrite (14) as a third degree polynomial, in its following closed-form $F_3(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$, where

$$a_2 = \beta_R S^1 + \beta_R I_R^1 + [\varphi_R + 2(\mu + \alpha) + \rho + \mu]$$

$$a_1 = \mu\rho(\varphi_R + \mu + \alpha + \rho) + [\varphi_R + 2(\mu + \alpha) + \rho]\mu(\mathcal{R}_R - 1)$$

$$a_0 = \mu(\mu + \alpha)(\varphi_R + \mu + \alpha + \rho)(\mathcal{R}_R - 1).$$

By using the Routh-Hurwitz criteria it follows that $a_0 > 0$, $a_1 > 0$, $a_3 > 0$ and $a_1 a_2 - a_0 > 0$ if and only if $\mathcal{R}_R > 1$. Therefore, we establish the following stability result:

Proposition 3.3. *The endemic equilibrium point* $P_1 = (S^1, 0, I_R^1, 0, F^1)$ *exists and it is locally asymptotically stable if both* $\mathcal{R}_R > 1$ *and* $\mathcal{R}_R > \mathcal{R}_S$ *hold.*

Similarly, we have the corresponding Jacobian matrix of (3) at the steady state $P_2 = (S^*, I_S^*, I_R^*, E^*, F^*)$ given by

$$J_{P_2} = \begin{bmatrix} J_{11}^{P_2} & -\beta_S S^* & -\beta_R S^* & 0 & 0 \\ \beta_S S^* & J_{22}^{P_2} & 0 & 0 & 0 \\ \beta_R I_R^* & 0 & J_{33}^{P_2} & 0 & \rho \\ 0 & p\varepsilon_S & 0 & J_{44}^{P_2} & 0 \\ 0 & (1-p)\varepsilon_S & \phi_R & \sigma & J_{55}^{P_2} \end{bmatrix}, \tag{15}$$

where $J_{11}^{P_2} = -(\beta_S I_S^* + \beta_R I_R^* + \mu)$; $J_{22}^{P_2} = -[\beta_S S^* + (\mu + \alpha + \varepsilon_S)]$; $J_{33}^{P_2} = \beta_R S^* - (\mu + \alpha + \varphi_R)$; $J_{44}^{P_2} = -(\mu + \sigma)$ and $J_{55}^{P_2} = -(\rho + \mu + \alpha)$.

The corresponding fifth degree characteristic polynomial for the steady state P_2 is

$$\begin{aligned} F_5(\lambda) = {} & (J_{44}^{P_2} - \lambda)(\beta_S)^2 S^* I_S^*[(J_{33}^{P_2} - \lambda)(J_{55}^{P_2} - \lambda) - \varphi_R\rho] \\ & + (J_{44}^{P_2} - \lambda)\beta_S\beta_R I_R^* S^*\rho(1-p)\varepsilon_S - \beta_S\beta_R I_S^* S^*\sigma\rho p\varepsilon_S \\ & + \lambda\rho\varphi_R(J_{44}^{P_2} - \lambda)(J_{11}^{P_2} - \lambda) - \lambda[(J_{44}^{P_2} - \lambda)(J_{55}^{P_2} - \lambda)]\det A = 0, \end{aligned} \tag{16}$$

where

$$A = \begin{bmatrix} J_{11}^{P_2} - \lambda & -\beta_R S^* \\ \beta_R I_R^* & J_{33}^{P_2} - \lambda \end{bmatrix}.$$

To verify the stability of the equilibrium point P_2 we look at the Routh-Hurwitz stability criterion. We know that the stability conditions for a fifth degree polynomial $P(\lambda) = \lambda^5 + b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5$ hold if and only if (i) $b_i > 0$ ($i = 1, \ldots, 5$), (ii) $b_1 b_2 b_3 > b_3^2 + b_1^2 b_4$ and (iii) $(b_1 b_4 - b_5)(b_1 b_2 b_3 - b_3^2 - b_1^2 b_4) > b_5(b_1 b_2 - b_3)^2 + b_1 b_5^2$ (May, 1973).

Here, we need some clarifications. Theoretically, the closed-form expression of the characteristic polynomial (16) can be found after some manipulations. However, the coefficients b_i are very complex, thereby making impossible to verify these conditions analytically. Therefore, the stability analysis will be explored only by numerical methods in the next section. However, before proceeding with the numerical analysis of our model, a useful explicity condition for the stability of P_2 can be obtained from the independent term of (16),

$$b_5 = \left\{ \frac{[\mu(1-p)\varepsilon_S + \sigma\varepsilon_S](\varepsilon_S + \mu + \alpha)\rho\beta_R D_1}{D_2} I_R^* + k_1 \right\}(\mathcal{R}_S - \mathcal{R}_R),$$

where

$$k_1 = (\mu + \sigma)(\mu + \alpha)(\varphi_R + \mu + \alpha + \rho)(\varepsilon_S + \mu + \alpha) > 0.$$

Recall that the drug-resistant steady state P_1 exists and it is locally asymptotically stable if only if $\mathcal{R}_R > 1$ and $\mathcal{R}_R > \mathcal{R}_S$ hold. Further, the coexistence steady state P_2 exists if and only if $\mathcal{R}_S > 1$ and $\mathcal{R}_S > \mathcal{R}_R$, from which it follows that $b_5 > 0$. On the other hand, it is also known that a sufficient condition for instability amounts to $b_5 < 0$. However, notice that $b_5 < 0$ implies $\mathcal{R}_S < \mathcal{R}_R$, and in such case the only endemic equilibrium locally asymptotically stable is P_1 (see Eq. (13)).

We conjecture therefore that in such case when $b_5 > 0$, P_1 is unstable, then $\mathcal{R}_S > \mathcal{R}_R$, and the only endemic equilibrium that exists and can be locally asymptotically stable is the coexistence equilibrium point P_2.

Hence, we now establish the following result. The coexistence equilibrium point $P_2 = (S^*, I_S^*, I_R^*, E^*, F^*)$ exists and it can be locally asymptotically stable whenever $\mathcal{R}_S > 1$ and $\mathcal{R}_S > \mathcal{R}_R$.

Fig. 2 shows that if a probability of drug resistance emerging during treatment exists, only four epidemiological outcomes are possible. This in fact depends on both drug-sensitive and drug-resistant fitness, specified by the effective reproductive numbers, $\mathcal{R}_S$ and $\mathcal{R}_R$, respectively.

All the existence and stability results for the model (3) are summarized in Table 2.

4. Numerical Investigations

In this section we illustrate some of the theoretical results obtained in this paper. We will integrate the system (3) by fourth

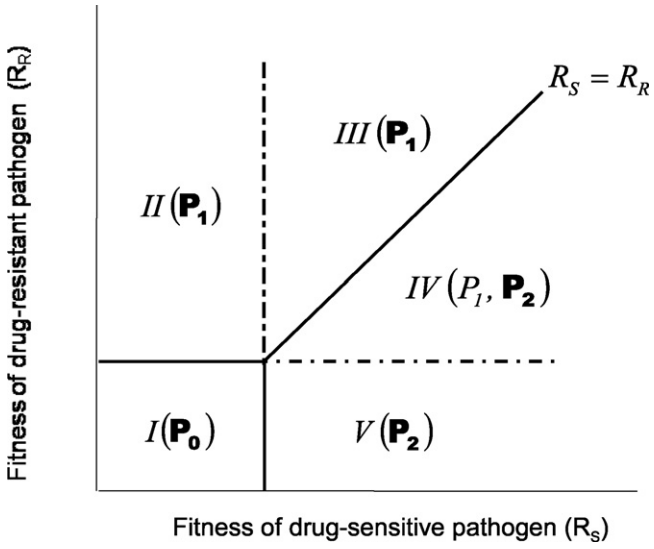

Fig. 2. Steady states of model (3) and stability regions (the steady states in bold type is stable in that region).

Table 2
Stability of trivial and endemic equilibria (see Fig. 2).

Fitness conditions	Eventual epidemiological outcomes
$\mathcal{R}_S < 1, \mathcal{R}_R < 1$	Disease eradication: $P^{(0)}$ stable
$\mathcal{R}_S < 1, \mathcal{R}_R > 1, \mathcal{R}_S < \mathcal{R}_R$	Persistence of HIV-1 drug-resistant population: P_1 stable
$\mathcal{R}_S > 1, \mathcal{R}_R > 1, \mathcal{R}_S < \mathcal{R}_R$	Persistence of HIV-1 drug-resistant population: P_1 stable
$\mathcal{R}_S > 1, \mathcal{R}_R > 1, \mathcal{R}_S > \mathcal{R}_R$	Persistence of both HIV-1 drug-sensitive and drug-resistant populations: P_2 stable
$\mathcal{R}_S > 1, \mathcal{R}_R < 1, \mathcal{R}_S > \mathcal{R}_R$	Persistence of both HIV-1 drug-sensitive and drug-resistant populations: P_2 stable

order Runge–Kutta method, and the results of the simulations will be displayed graphically.

The objective of these simulations is to provide useful insights about the emergence of drug-resistance by considering both the "optimistic" and the "pessimistic" scenarios. For this purpose, we will explore the variation of both treatment rates and transmission coefficients, which also vary over the interval where the system (3) undergoes a Hopf bifurcation. Baseline parameters were selected after a review of literature and are presented as follows.

Because of several studies (Fatkenheuer et al., 1997; Snedecor, 2005) have reported treatment failure within the first year of therapy in a substantial portion of treated patients, we consider $1 \leq \varphi_R \leq 2$ and $1 \leq \sigma \leq 2$ (6 months to 1 year). Moreover, drug resistance would develop (on average) in 3–5 years (Vardavas and Blower, 2007), so we consider $0.2 < \rho < 0.33$. The average progression time to AIDS for HIV infected patients is 14 years (Vardavas and Blower, 2007), we take then $\alpha = 1/14$ years. The inflow of at-risk susceptible adults is chosen to be $\mu = 0.0147$ per year (WHO, 2011). Finally, we take $p = 0.6$ (Gumel et al., 2001). It is important to stress that such limited efficacy of therapy (60%) may be due to many reasons including sub-optimal usage of the regimen, poor compliance, poor absorption of certain drugs, etc.

Unless otherwise stated, the baseline parameters set and the initial conditions values are summarized in Table 3.

Next, in Figs. 3–10 both "optimistic" and "pessimistic" scenarios are shown. It should be mentioned that only the dynamic of infected subpopulations (I_S^* and I_R^*) are shown because the other subpopulations have a similar pattern.

4.1. "Optimistic" Scenario

The "optimistic" scenario assumes that the drug treatment will be sufficiently potent to eradicate the disease.

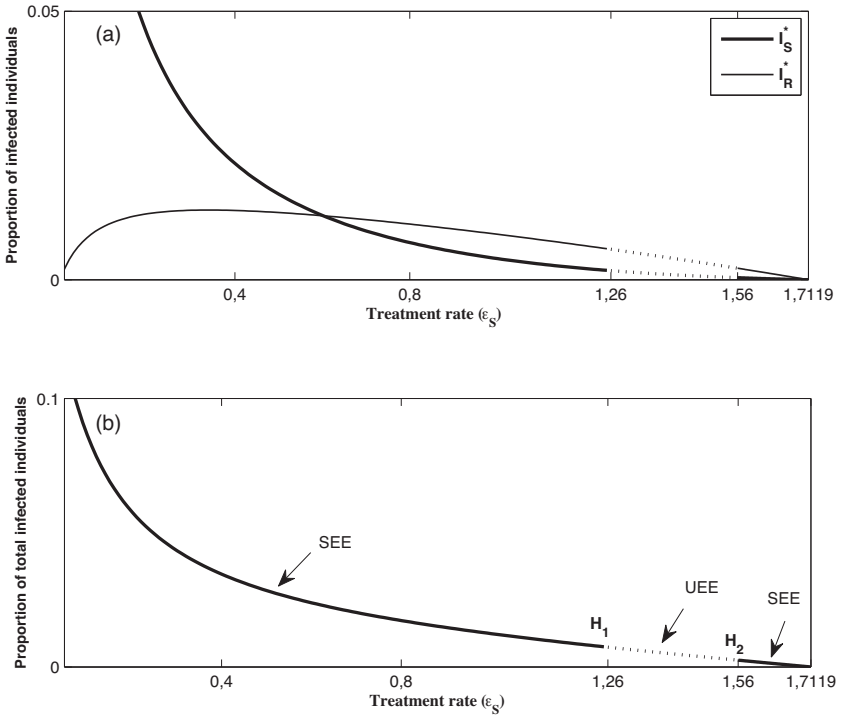

Fig. 3. Profile of populations of the endemic equilibrium P_2 as a function of drug treatment rate (ε_S) with $\beta_S = 1.8$, $\beta_R = 0.45$. All other parameter values are listed in Table 3. In (a) the proportion of drug-sensitive (I_S^*) and the drug-resistant infected (I_R^*) individuals; in (b) the total proportion of infected individuals ($I_S^* + I_R^*$). SEE stands for the stable endemic equilibrium (solid curve) and UEE stands for the unstable endemic equilibrium (dotted curve). H denotes Hopf bifurcation, and it shows that two Hopf bifurcations occur at $\varepsilon_S^1 = 1.26$ (H_1) and $\varepsilon_S^2 = 1.56$ (H_2). For $0 < \varepsilon_S < \varepsilon_S^1$ and $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres} = 1.7119$ the endemic equilibrium P_2 exists and it is asymptotically stable. For $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$, the endemic equilibrium P_2 is unstable and the solution converges to a stable limit cycle.

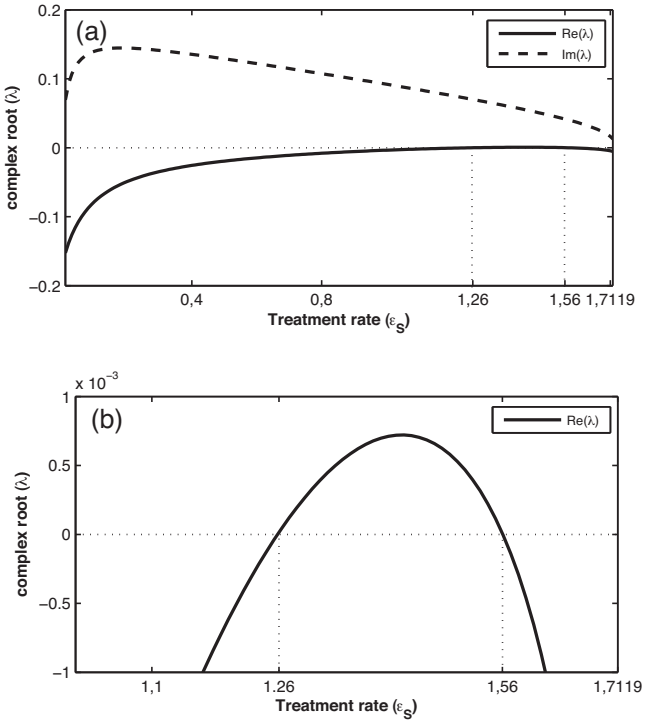

Fig. 4. The critical values of $\varepsilon_S^i (i = 1, 2)$ at which equation (16) has a pair of purely imaginary roots $\pm i\lambda_0$ and system (1) undergoes a Hopf bifurcation. In (a) the graph of polynomial $F_5(\lambda)$, given as the complex roots of equation 16, is plotted versus the parameter ε_S. In (b), a zoom of (a) with the real part of complex roots shows the values of the two Hopf bifurcations.

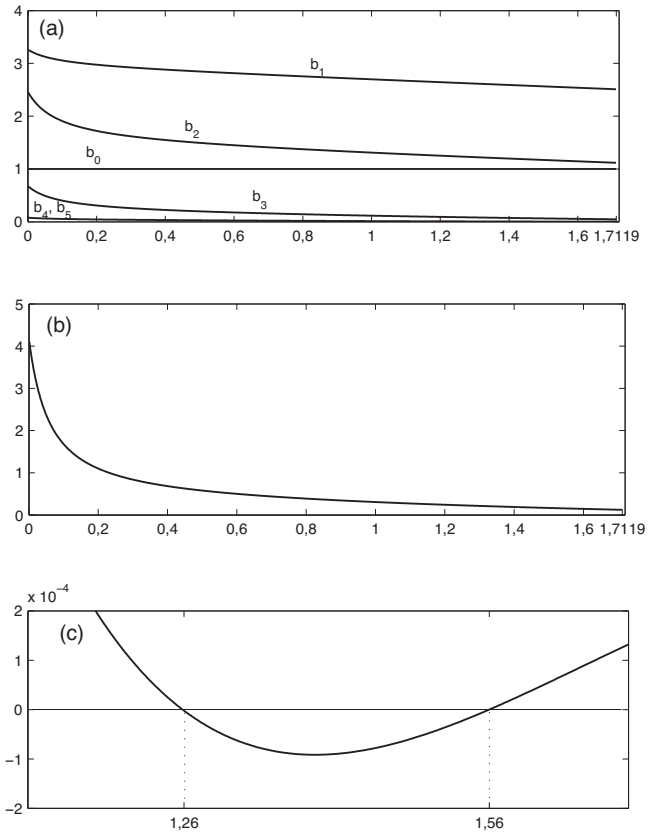

Fig. 5. Plot of the Routh-Hurwitz stability conditions for the 5th degree polynomial (16).

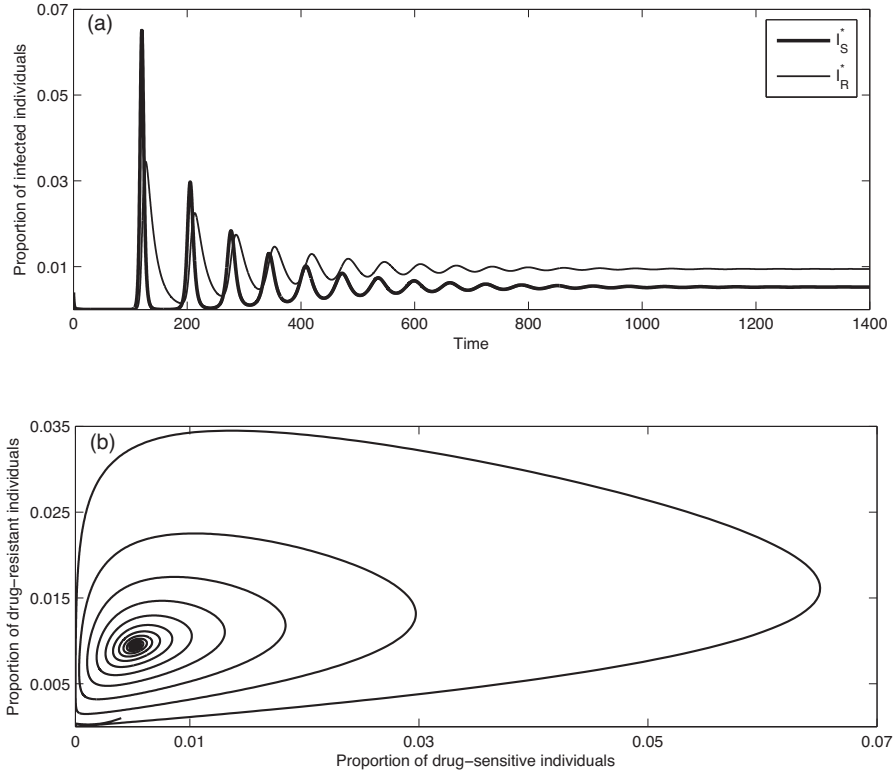

Fig. 6. Time plot (a) and phase portrait (b) of system (3) using the same parameter values as in Fig. 3, except that $\varepsilon_S = 0.9$. It shows that solutions will converge to the endemic equilibrium P_2, regardless of initial conditions.

Table 3
Baseline values of some key model parameters for model (3), with sources (see Section 4.1).

Parameters	Values
φ_R	2 years^{-1}
σ	1/2 years^{-1}
ρ	1/4 years^{-1}
α	1/14 years^{-1}
μ	1/68 years^{-1}
p	0.60
Variables	Values
$S(0)$	0.004
$I_S(0)$	0.004
$I_R(0)$	0.001
$E(0)$	0
$F(0)$	0

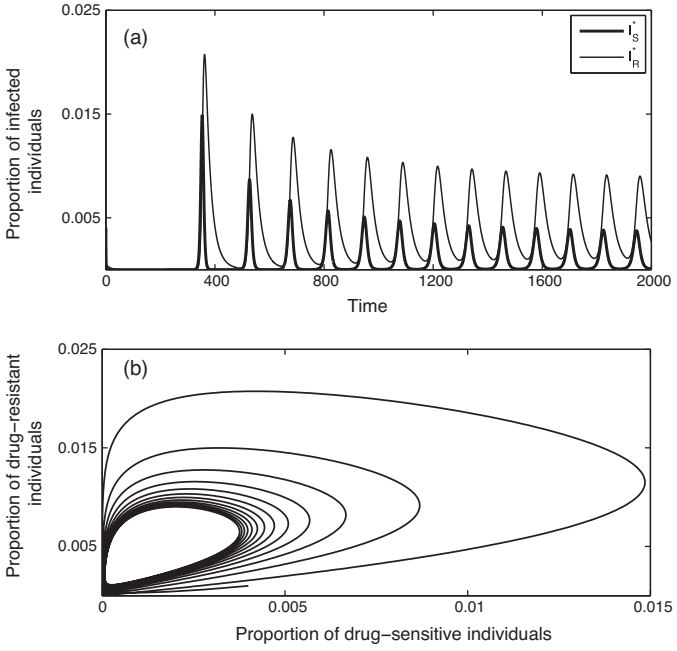

Fig. 7. Time plot (a) and phase portrait (b) of system (3) using the same parameter values as in Fig. 3, except that $\varepsilon_S = 1.4$. It shows that a stable periodic solution exists and the unique biologically viable equilibrium P_2 is unstable, regardless of initial conditions.

Figs. 3–8 illustrate this scenario with $\beta_S = 1.8$ and $\beta_R = 0.45$ (i.e., $k = 0.25$) as ε_S increases. Under this "optimistic" scenario, the solution of the system (3) is originally in region V, at which only P_2 exists and can be locally and asymptotically stable (see Table 2). In such case, since the endemic equilibrium P_1 is not feasible, as ε_S increases, the solution will converge to the disease-free equilibrium $P^{(0)}$, corresponding to the region I (see Fig. 2). It is also important to underline that in such case a Hopf bifurcation may occur, so a stable limit cycle can bifurcate from the unstable endemic equilibrium P_2.

Fig. 3 shows that as the therapy becomes more effective (i.e., as the time for the patient to achieve complete viral suppression is smaller), the prevalence of drug-sensitive individuals (I_S^*) is reduced dramatically, and in spite of the increase in the prevalence of drug-resistant individuals (I_R^*) (Fig. 3a), the total prevalence of HIV-1 infected individuals ($I_S^* + I_R^*$) still decreases (Fig. 3b).

Fig. 3 also shows a bifurcation diagram for the system (3), where ε_S is choosen as a bifurcation parameter. Although the critical values of the bifurcation could not be found analytically due to the high dimension of the system (3), this task can be performed numerically. The simulations show that there exist two critical values (ε_S^i, $i = 1, 2$) where the model (3) undergoes a Hopf bifurcation. At the

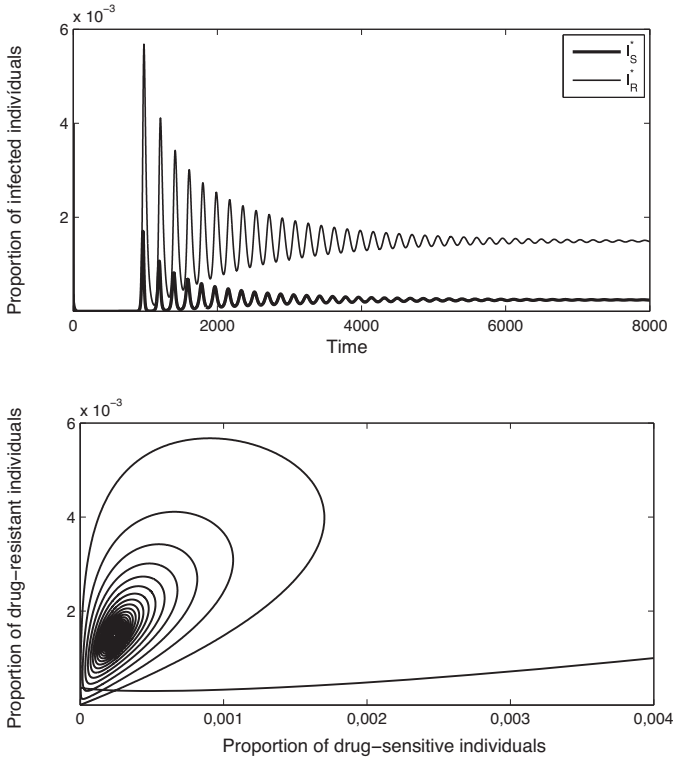

Fig. 8. Time plot (a) and phase portrait (b) of system (3) using the same parameter values as in Fig. 3, except that $\varepsilon_S = 1.6$. It shows disappearance of the stable limit cycle and convergence of the solution to the stable endemic equilibrium P_2, regardless of initial conditions.

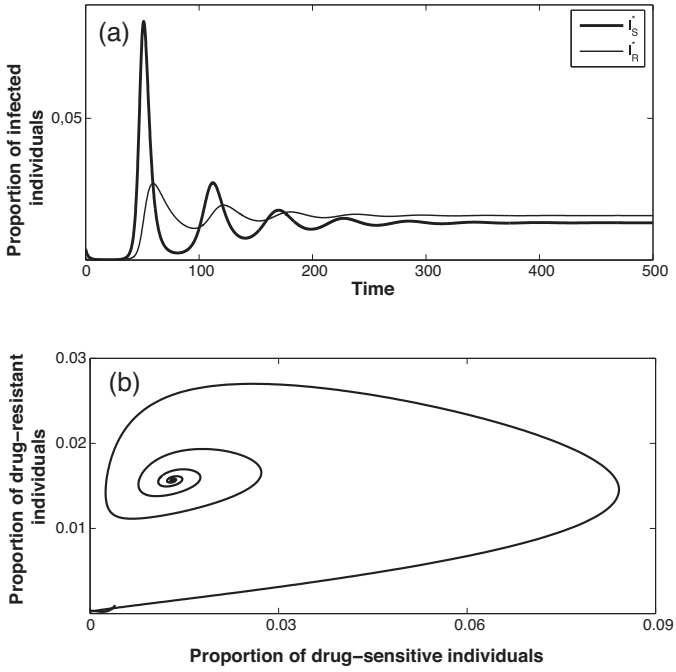

Fig. 9. Time plot (a) and phase portrait (b) of system (3) using the same parameter values as in Table 3. It illustrates one of the "pessimistic-case" scenario with $\beta_S = 1.8$, $\beta_R = 1.35$, $\varepsilon_S < \varepsilon_S^{thres^*}$ which shows damped oscillations of infected individuals followed by convergence to the endemic equilibrium P_2, regardless of the initial conditions.

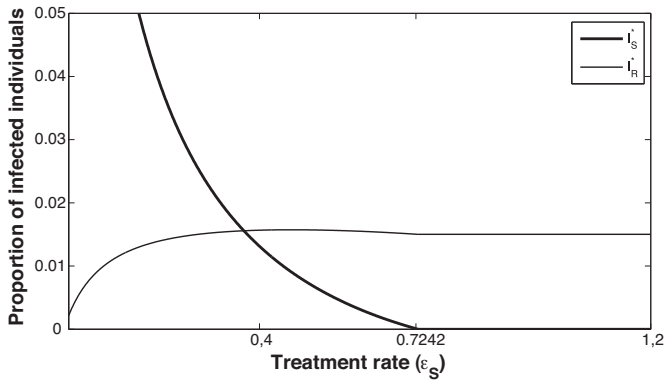

Fig. 10. Profile of the proportion of sensitive (I_S^*) and the drug-resistant infected (I_R^*) individuals as a function of drug treatment rate (ε_S). It illustrates one of the "pessimistic-case" scenario with $\beta_S = 1.8$, $\beta_R = 1.35$ as in Fig. 9. For $\varepsilon_S > \varepsilon_S^{thres^*} = 0.7242$, $I_S^* = 0$, P_2 becomes unstable and the only endemic equilibrium that exists and is locally asymptotically stable is P_1.

point H_1, where $\varepsilon_S^1 = 1.26$, and at the point H_2, where $\varepsilon_S^2 = 1.56$. Moreover, for $\varepsilon_S = \varepsilon_S^1$, we have $\mathcal{R}_S = 1.331$ and $\mathcal{R}_R = 0.739$; for $\varepsilon_S = \varepsilon_S^2$, $\mathcal{R}_S = 1.092$ and $\mathcal{R}_R = 0.739$. Therefore, as ε_S increases, $\mathcal{R}_S > 1$ is decreasing, $\mathcal{R}_R < 1$ is constant (note that $\mathcal{R}_R$ does not depend on ε_S) and $\mathcal{R}_S > \mathcal{R}_R$.

It is also noted from Fig. 3 that whenever $0 < \varepsilon_S < \varepsilon_S^1$, the equilibrium P_2 exists and is locally asymptotically stable (solid curve), and the Hopf bifurcation takes place when ε_S crosses ε_S^1 to the left ($\varepsilon_S < \varepsilon_S^1$). It then folows that the equilibrium solution P_2 loses stability (dotted curve). From Lemma 1, it follows that every solution of the equations in model (1) with initial conditions in $\mathbb{R}_+^5$ tends towards D as $t \to \infty$. Hence, if both equilibrium points P_1 and P_2 of the system (1) are unstable whenever $\varepsilon_S \in [\varepsilon_S^1, \varepsilon_S^2] = D_1 \subset D$, and D attracts all solutions in $\mathbb{R}_+^5$, then a stable periodic solution bifurcates from P_2, as ε_S crosses ε_S^1 to the left. In the same way, when ε_S crosses ε_S^2 to the left ($\varepsilon_S < \varepsilon_S^2$), P_2 becomes locally asymptotically stable (solid curve) once again. Moreover, we also define ε_S^{thres} as the threshold value for which P_2 is locally asymptotically stable.

Thus, for $0 < \varepsilon_S < \varepsilon_S^1$ and $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$ P_2 is locally asymptotically stable, i.e., the characteristic polynomial (16) has one pair of complex eigenvalues with negative real parts. For $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$ the endemic equilibrium P_2 is unstable, i.e., the characteristic polynomial (16) has one pair of complex eigenvalues with positive real parts. In these three cases the others three eigenvalues are real, negative and distincts. Moreover, at $\varepsilon_S = \varepsilon_S^1$ and at $\varepsilon_S = \varepsilon_S^2$, the characteristic polynomial (16) has one pair of pure-imaginary eigenvalues, $\lambda = \pm 0.0702i$ and $\lambda = \pm 0.0405i$, respectively. Hence, the system (3) undergoes a supercritical Hopf bifurcation with the appearance of a stable limit cycle when ε_S passes through ε_S^1; and a subcritical Hopf bifurcation with the disappearance of the stable limit cycle and the convergence of the solution to the equilibrium P_2, when ε_S passes through ε_S^2.

For $\varepsilon_S = \varepsilon_S^{thres} = 1.7119$, we have $\mathcal{R}_S = 1.0$ and $\mathcal{R}_R = 0.739$. The characteristic polynomial (16) has one eigenvalue $\lambda = 0$, while the others have real parts of the same sign (negative) and hence, the endemic equilibrium P_2 cannot be a saddle point. In such case, $P_2 = P^{(0)}$, and the only point that exists is the trivial equilibrium, $P^{(0)}$.

Hence, for values of $\varepsilon_S > \varepsilon_S^{thres}$, the endemic equilibrium P_2 is no longer feasible. So, the only equilibrium that exists and is locally asymptotically stable is the trivial equilibrium, $P^{(0)}$. It then follows that $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$, corresponding to region I (see Fig. 2).

The bifurcation values (ε_S^1 and ε_S^2) are showed in Fig. 4a and b. The complex root ($\lambda = a + bi$, with a and b real numbers) of characteristic polynomial (16) for the steady state P_2 is plotted versus ε_S.

Fig. 5 shows the plotting of the Routh-Hurwitz conditions for the characteristic polynomial (16) using the baseline values in Table 3, $\beta_S = 1.8$, $\beta_R = 0.45$ and $0 < \varepsilon_S < \varepsilon_S^{thres}$. Panel (a) shows the plot of the coefficients b_i; panel (b) gives the curve of the second stability condition, $b_1 b_2 b_3 - b_3^2 + b_1^2 b_4$; and panel (c) gives the plot of the third condition $(b_1 b_4 - b_5)(b_1 b_2 b_3 - b_3^2 - b_1^2 b_4) - b_5(b_1 b_2 - b_3)^2 + b_1 b_5^2$. The first two conditions are satisfied for all values of ε_S, while the third one does not hold for $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$.

It follows that whenever $0 < \varepsilon_S < \varepsilon_S^1$ and $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$, the Routh-Hurwitz stability criterion holds, i.e., all eigenvalues of equation (16) have negative real part, and so the equilibrium point P_2 is locally asymptotically stable. Otherwise, i.e., for $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$, Routh-Hurwitz stability criterion does not hold, and P_2 is unstable. Hence, changes in the parameter ε_S may cause a Hopf bifurcation in our model (Moghadas and Alexander, 2006; Zhou et al., 2007). In practical terms this means that while the disease remains endemic in the population it will fluctuate periodically over time rather than remaining at a fixed level.

Figs. 6–8 show some "optimistic" scenarios. The top panel gives the profiles of prevalence of infected individuals (I_S^* and I_R^*), while the bottom panel displays the phase portraits for them. The values of the treatment rate (ε_S) were chosen according to bifurcation diagram in Fig. 3, and the other parameter values are the baselines values depicted in Table 3. The results show that there is a unique feasible and locally asymptotically stable endemic equilibrium given by P_2 whenever $0 < \varepsilon_S < \varepsilon_S^1$ and $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$.

In Fig. 6, $P_2 = (0.5489, 0.0052, 0.0095, 0.0055, 0.0696)$ is shown to be locally asymptotically stable for $\varepsilon_S = 0.9 < \varepsilon_S^1$. Fig. 6b displays the phase portraits by showing the convergence of the solution to P_2.

Fig. 7, for $\varepsilon_S = 1.4$, which is larger than ε_S^1 but less than ε_S^2, the trajectory shown is a stable periodic solution, as in this case the unique biologically viable equilibrium P_2 is unstable. The bottom panel illustrates the appearance of a stable limit cycle.

In Fig. 8, for $\varepsilon_S = 1.6$, which is slightly larger than ε_S^2 but less than ε_S^{thres} the feasible equilibrium $P_2 = (0.9378, 0.0002, 0.0015, 0.0004, 0.0099)$ is shown to be locally asymptotically stable. The bottom panel illustrates a disappearance of the stable limit cycle and the covergence of the solution to the stable endemic equilibrium, P_2.

It is worth mentioning that a Hopf bifurcation is only possible from the non-trivial equilibrium P_2 and the parameter values were chosen for this purpose. It is clear from the "optimistic case" scenario that as the efficiency level of the treatment increases ($\varepsilon_S \to \varepsilon_S^{thres}$), the prevalence of total infected individuals decreases, even if the resistant population has a higher prevalence. In this scenario, at the "optimal" treatment regimen (i.e., the "shortest" time for the patient to achieve viral suppression, ε_S^{thres}), both P_2 and $P^{(0)}$ are feasible. For $\varepsilon_S > \varepsilon_S^{thres}$, $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$ and the prevalence of infected individuals converges to zero. Therefore, the smaller the fitness of both drug-sensitive and drug-resistant virus and the shortest the time for the drug-sensitive patient to achieve viral suppression, the faster the eradication of disease. In such case the proportion of drug-sensitive individuals is smaller than the proportion of drug-resistant individuals. Epidemiologically, the "optimistic-case" scenario implies that if infectiousness of drug-resistant strains was reduced (either by increasing condom usage in treated patients or by developing more effective drugs for successful treatment – viral suppresion), then HIV-1 could be eliminated from the population.

4.2. "Pessimistic" Scenario

In contrast, under the "pessimistic" scenario, the drug resistance will dominate initially because the drug treatment is efficient to eliminate only the drug-sensitive population. In such scenario,

it is still necessary a more effective treatment for drug-resistant patients to eliminate the disease.

Figs. 9 and 10 illustrate the "pessimistic-case" scenario, with $\beta_S = 1.8$, $\beta_R = 1.35$ (i.e., $k = 0.75$). These parameters values were appropriately chosen such that the solution of the system (3) is originally in the region *IV*, at which both P_1 and P_2 exist, but where only P_2 can be locally and asymptotically stable (see Table 2). It should be noted that in this "pessimistic-case" scenario the Hopf bifurcation cannot occur and both P_1 and P_2 are feasible, such that the solution of the system jumps from one to the other point. That is, the solution of the system is originally in region *IV*, then goes to the region *III* and after to region *II*, as ε_S increases (see Fig. 2).

In Fig. 9a, $P_2 = (0.2712, 0.0131, 0.0157, 0.0061, 0.1079, 0.0288)$ is shown to be locally asymptotically stable $\varepsilon_S = 0.4$. Fig. 9b displays the phase portraits of them by showing the convergence of the solution to P_2.

In Fig. 10, when ε_S increases from zero to $\varepsilon_S^{thres^*} = 0.7242$, we have $\mathcal{R}_R > 1$ constant, $\mathcal{R}_S > 1$ is decreasing, with $\mathcal{R}_S > \mathcal{R}_R$, such that P_2 is the only endemic equilibrium locally asymptotically stable, corresponding to the region *IV*. For $\varepsilon_S = \varepsilon_S^{thres^*}$, $\mathcal{R}_S = \mathcal{R}_R > 1$ and $P_2 = P_1$. In such case, the characteristic polynomial (16) has one eigenvalue $\lambda = 0$, while the others have real parts of the same sign (negative) and hence, the endemic equilibrium P_2 cannot be a saddle point. Moreover, P_2 becomes unstable for $\varepsilon_S > \varepsilon_S^{thres^*} = 0.7242$, so the only endemic equilibrium that exists and is locally asymptotically stable is P_1. In such case, $\mathcal{R}_R > 1$ is constant, $\mathcal{R}_S > 1$ is decreasing, but $\mathcal{R}_S < \mathcal{R}_R$, which correspond to the region *III*. Moreover, as ε_S is increasing, $\mathcal{R}_S < 1$ is decreasing and $\mathcal{R}_S < \mathcal{R}_R$ which corresponds to the region *II* (see Fig. 2).

In other words, since the use of treatment can reduce $\mathcal{R}_S$ below $\mathcal{R}_R$, the sensitive strain would be eliminated from the community via competitive exclusion, as ε_S increases.

Thus, in the "pessimist" scenario, the widespread use of treatment can increase the drug-sensitive strain (competitive exclusion), so that the proportion of drug-sensitive individuals will exceed a drug-resistant one, but in the long run, the drug-resistant population will dominate (the competitive exclusion wins). That is, the greater the fitness of the drug-resistant virus and the shortest the time for the drug-sensitive patient to achieve viral suppression, the faster the emergence of drug resistance. In such case the proportion of drug-resistant individuals is greater than the proportion of drug-sensitive individuals.

Moreover, the "pessimistic" scenario also implies that if infectiousness of drug-resistant strains cannot be reduced, HIV drug-resistant individuals will not be eliminated from the population even for the case when the treatment for the drug-sensitive patients is highly effective and, consequently, the drug resistance will dominate.

However, the prevalence of the drug resistance could decreases if the treatment for drug-resistant patients (φ_R) becomes more and more effective. This scenario is illustrated in Fig. 11 where the values of the transmission coefficients (β_S and β_R) were chosen such that the solution of the system (3) is originally in region *II* (see Fig. 2).

Remembering that P_2 is not feasible in region *II*, the solution of the system will converge either to P_1 or to $P^{(0)}$, as φ_R increases. Hence, P_1 and $P^{(0)}$ jump from one to the other, and P_1 loses its stability at the critical stability boundary $\varphi_R^{thres} = 1.389$. Thus, the endemic equilibrium P_1 is locally asymptotically stable whenever $0 < \varphi_R < \varphi_R^{thres}$. For $\varphi_R = \varphi_R^{thres}$, $\mathcal{R}_S < 1$ and $\mathcal{R}_R = 1$ and $P_1 = P^{(0)}$ (see 10). There is no Hopf bifurcation from the equilibrium solution P_1, the characteristic polynomial (16) has one eigenvalue $\lambda = 0$, while the others have real parts of the same sign (negative) and hence, the endemic equilibrium P_1 cannot be a saddle point. For $\varphi_R > \varphi_R^{thres}$, P_1 is no longer feasible because some of its coordinate assumes negative values (see Fig. 11, $I_R^* < 0$). Hence, the only equilibrium that exists and is locally asymptotically stable is the trivial equilibrium, $P^{(0)}$, which correspond to the region *I* (see Fig. 2).

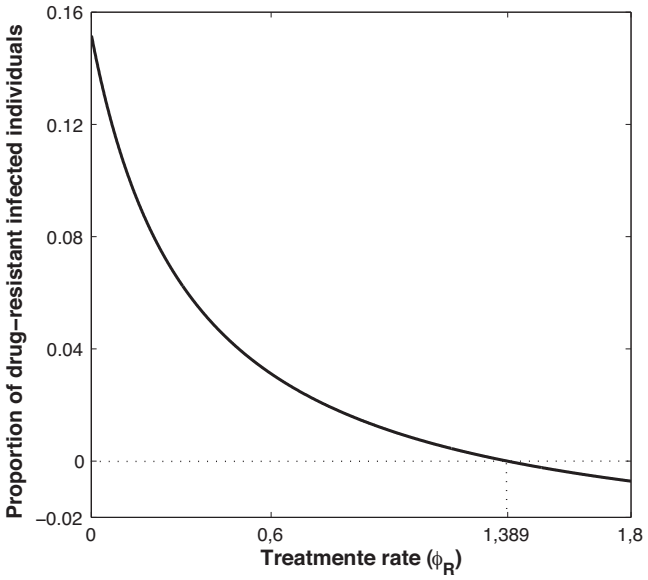

Fig. 11. Time plot of the proportion of drug-resistant infected individuals with $\beta_S = 0.045$, $\beta_R = 0.45$, $\varepsilon_S = 2$ and φ_R increasing. The other parameters and the initial conditions are the same as those in Table 3. The endemic equilibrium P_1 is locally asymptotically stable if $0 < \varphi_R < \varphi_R^{thres} = 1.389$, while for $\varphi_R > \varphi_R^{thres}$, the only endemic equilibrium that exists and is locally asymptotically stable is the trivial equilibrium, $P^{(0)}$.

Fig. 11 shows the plot of proportion of drug-resistant infected individuals, with $\beta_S = 0.045$ and $\beta_R = 0.45$, $\varepsilon_S = 2$ constant, but φ_R is increasing. In such case, $\mathcal{R}_S < \mathcal{R}_R$, $\mathcal{R}_R > 1$ is decreasing and $\mathcal{R}_S < 1$ is a constant ($\mathcal{R}_S$ does not depend on φ_R). Observe that the smaller the time, such that the patient experiences incomplete viral suppression (i.e., the larger the drug efficacy, φ_R), the lower the prevalence of drug-resistant individuals.

4.3. Discussion

The stability results and the conditions for Hopf bifurcation to occur for the model (3) are as follows: (i) If $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$, then the infection-free steady state $P^{(0)}$ is locally asymptotically stable. Otherwise, it is unstable. (ii) If $\mathcal{R}_R > 1$, then the steady state, P_1, exists. It is locally asymptotically stable if $\mathcal{R}_R > \mathcal{R}_S$ for $0 < \varepsilon_S < \varepsilon_S^{thres^*}$. Otherwise, it is unstable. (iii) If $\mathcal{R}_S > 1$ and $\mathcal{R}_S > \mathcal{R}_R$ then P_2 exists and it is locally asymptotically stable for $0 < \varepsilon_S < \varepsilon_S^1$ or $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$, and it is unstable for $\varepsilon_S \in (\varepsilon_S^1, \varepsilon_S^2)$. Furthermore, the system (1) exhibits Hopf bifurcations at $\varepsilon_S = \varepsilon_S^1$ and $\varepsilon_S = \varepsilon_S^2$ and for $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$ exists a stable limit cycle; (iv) if neither (ii) nor (iii) occur then there is no endemic equilibria.

Hence, having numerically established (a) the existence and stability of the model equilibria and (b) that a Hopf bifurcation is only possible from the equilibrium P_2, we can now discuss some important biological implications.

It is worth remembering that in both the "pessimistic" and the "optimistic" scenarios, the proportion of drug-sensitive individuals initially exceeds the proportion of drug-resistant individuals. However, as ε_S increases from zero to its threshold value, the proportion of drug-sensitive individuals undergoes a fast decrease whereas the proportion drug-resistant individuals increases very slowly. There is a value of ε_S for which the two populations are at the same level, and past this value, the proportion of drug-resistant individuals will dominate.

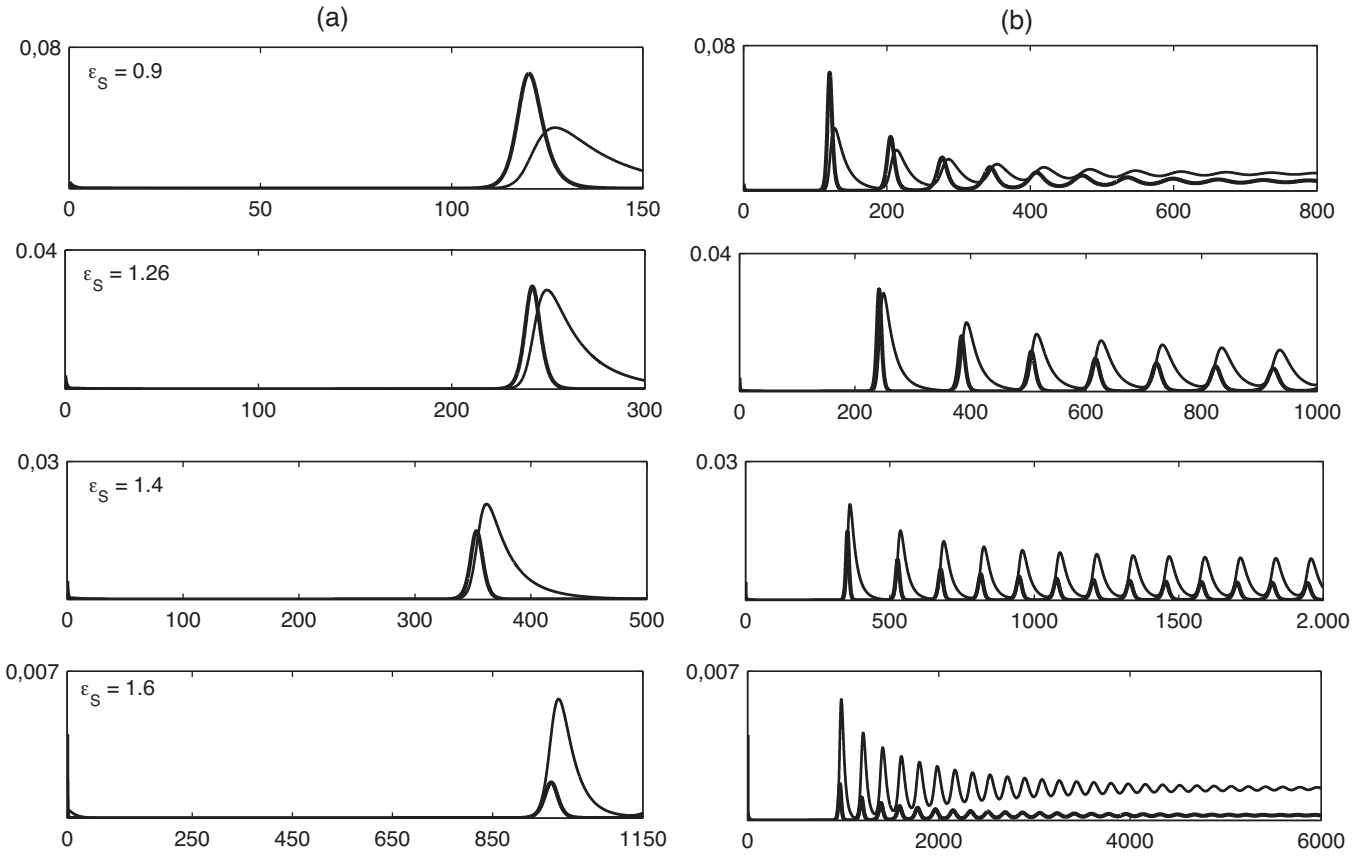

Fig. 12. Profiles of proportion of HIV infected individuals with $\beta_S = 1.8$, $\beta_R = 0.45$, as ε_S increases. The left column (a): the time plot of the first peak of both drug-sensitive infected population (I_S^*, thick line) and drug-resistant infected population (I_R^*, thin line). The right column (b): the time plot of both drug-sensitive infected population (I_S^*, thick line) and the drug-resistant infected population (I_R^*, thin line).

Firstly, in the "pessimistic-case" scenario we observed that, as ε_S increases, the drug-resistant individuals cannot be completely suppressed, but their level can be kept at a low level when $0 < \varepsilon_S < \varepsilon_S^{thres^*}$. Past the value $\varepsilon_S^{thres^*}$, the number of drug-resistant individuals becomes dominant and the value $\varepsilon_S^{thres^*}$ represents the lowest drug treatment level where the ART allows two strains to coexist. For $\varepsilon > \varepsilon_S^{thres^*}$ the drug-sensitive virus would probably be replaced by the resistant virus. As a result, the drug-resistant individuals dominate and the drug-resistance epidemic starts to propagate among the population. It is important to note that under therapy when $\varepsilon_S > \varepsilon_S^{thres^*}$ the drug-sensitive virus can be suppressed even when the basic reproductive number R_S is greater than one. This is not surprising because the two virus strains compete for exactly the same resources, hence the resistant strain becomes more fit ($\mathcal{R}_R > \mathcal{R}_S$) and will outcompete the sensitive one due to the competitive exclusion principle.

In contrast, in the "optimistic" scenario, as ε_S increases, the drug-resistant individuals can be completely suppressed, due to the occurrence of Hopf bifurcation from the non-trivial equilibrium point P_2. To investigate the stability of the periodic solutions associated with the Hopf bifurcation occurring in this scenario, we could invoke the criterion for super or subcritical Hopf bifurcations given by (Guckenheimer and Holmes, 1983). This leads however to intractable calculations. We thus examined the stability of this Hopf bifurcation numerically and will try to explain it epidemiologically now. From Figs. 3–8 we observed that the proportion of the infected individuals is kept at low level as ε_S crosses into the region defined by $[H_1, H_2]$. At $\varepsilon_S = \varepsilon_S^1$ the endemic equilibrium P_2 loses its stability, but around it limit cycles arise via a Hopf bifurcation. In this situation, when a stable limit cycle surrounds the unstable endemic equilibrium, the proportion of the infected individuals tends to a periodic function and the infection will therefore exhibit regular oscillations. Hence, the infection has periodic outbreaks as time evolves and furthermore it will persist as time flows.

For $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$, the number of drug-resistant infected individuals dominates, but at much lower level compared with $0 < \varepsilon_S < \varepsilon_S^1$. As ε_S approaches ε_S^{thres}, the number of HIV-1 infected individuals keeps decreasing, so that the steady state P_2 decreases to zero. Thus, at $\varepsilon_S = \varepsilon_S^{thres}$, P_2 loses its stability, and as a result, the HIV-1 infected individuals are completely wiped out, i.e., the only existing equilibrium which is locally asymptotically stable is then the trivial equilibrium, $P^{(0)}$. It is important to note that under drug therapy the two viral strains compete for exactly the same resources, but the steady state level undergoes a substantial decrease and remains at a very low level when ε_S approaches ε_S^{thres}. The two strains coexist but neither the drug-sensitive nor the drug-resistant can persist because of their reduced fitness ($\mathcal{R}_S < 1, \mathcal{R}_R < 1$). Consequently, for $\varepsilon_S \geq \varepsilon_S^{thres}$, both strains are completely suppressed and the infection will be eradicated.

The Hopf bifurcation shows the existence of a region of instability in the neighborhood of an endemic equilibrium where the population survives undergoing regular fluctuations. Throughout our numerical analysis, we have made it clear that this limit cycle is just one of the stable limit cycles bifurcating from the endemic equilibrium P_2. However, another insight from our numerical study could also explain the emergence of the epidemic cycles: treatment can interact with both sensitive and resistant strains and cause resonance. Although resonance is known to occur in physics and engineering, in biology and medicine its presence is less recognized. Some application cases of treatment of HIV infection have revealed

this phenomenon when the antiretroviral drugs cannot reduce the viral load (Breban and Blower, 2006).

Here we also suggest that the phenomenon of resonance could help us to explain why certain oscillations appear only for certain values of treatment rate. In this way, Fig. 12 shows the occurrence of infection outbreaks for constant treatment rates with $\beta_S = 1.8$ and $\beta_R = 0.45$ for $0 < \varepsilon_S < \varepsilon_S^{thres}$. With these parameter values of the transmission coefficients, as ε_S increases, $\mathcal{R}_S > 1$ decreases and $\mathcal{R}_R$ is constant and smaller than unity.

In Fig. 12a the profiles of population of HIV-1 infected individuals (I_S^* and I_R^*) against time show that, as the treatment rate (ε_S) increases, the smaller and slower the amplitude of the first peak of drug-sensitive infected population (I_S^*) is, the higher and slower the amplitude of the first peak of drug-resistant infected population (I_R^*) becomes. As ε_S approaches $\varepsilon_S^1 = 1.26$, where the system (3) undergoes a Hopf bifurcation, the two populations coexist, and the amplitudes of the first peak of both population are about the same. However, as ε_S increases, the drug-resistant population gains a competitive advantage (competitive exclusion) and the amplitude of the first peak of drug-resistant population is higher than the one shown by the drug-sensitive population. These dynamics of both populations could indicate a resonance phenomenon.

In Fig. 12b we also notice that the drug-resistant population always decays more slowly than the drug-sensitive population, even at resonance ($\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$). At resonance, the system (3) responds strongly to perturbation and therefore the populations fluctuate widely, whereas when the system is far from resonance fluctuation ($0 < \varepsilon_S < \varepsilon_S^1$ and $\varepsilon_S^2 < \varepsilon_S < \varepsilon_S^{thres}$) the oscillations are damped and decrease in amplitude when the system approaches the equilibrium point. Fig. 12b also shows that for smaller ε_S (i.e., a larger time is needed for the patient to achieve complete viral suppression), the drug-sensitive population dominates, i.e., the larger time to the drug-sensitive patient to achieve complete viral suppression, the smaller the possibility of the emergence of a drug-resistant population. Therefore, with smaller ε_S, we have $\mathcal{R}_S > \mathcal{R}_R$, and the drug-sensitive outbreak substantially dominates the one of the drug-resistant population. Although the use of antiretroviral appears to be essential to fight the drug-sensitive strain, it can potentially lead to the spread of drug-resistance. Unfortunately, the treatment does not completely block the emergence of the drug-resistant population. Therefore, increasing ε_S (i.e., allowing a smaller the time for the patient to achieve complete viral suppression), leads to a reduction of drug-sensitive strains, followed by a reduction in the drug-sensitive population. Furthermore, increase in the treatment rate ε_S enhances the spread of the drug-resistant population and leads to the coexistence of outbreaks, followed by a sharp increase in the drug-resistant infected population. Therefore, with higher ε_S, R_S is reduced to about unity, and the drug-resistant outbreak substantially dominates the one of the drug-sensitive population.

Summarizing, for lower values of ε_S the drug-sensitive strain ($\mathcal{R}_S > 1$) dominates and feeds the drug-resistant strain ($\mathcal{R}_R < 1$), which alone is incapable of self-maintenance. On the other hand, for higher values of ε_S the drug-resistant strain dominates, due to high feeding from drug-sensitive strain, which declines in incidence ($\mathcal{R}_S$ approaches one). As a consequence, the non-trivial equilibrium point is stable. The change of dominance from drug-sensitive strain to drug-resistant strain does not occur at exactly one value of ε_S, but occurs gradually. At intermediated values of ε_S, i.e., $\varepsilon_S^1 < \varepsilon_S < \varepsilon_S^2$, where neither the drug-sensitive strain nor the drug-resistant strain dominates, the non-trivial equilibrium point loses its stability, and regular oscillations arise, i.e., the system has a limit cycle. Hence, the stable equilibrium point can be related to dominance of one of the strains, while the limit cycle can be understood as a gradual change of dominance from one strain to another.

5. Conclusion

In this work we have studied the global behavior of an HIV-1 epidemic model in the presence of antiretroviral drugs by combining qualitative and numerical analyses. We developed a simple mathematical model to explore the following questions: if the drug treatment is effective against the drug-sensitive strain, then under what conditions will the drug-resistant strain emerge? Which is the less intensive drug-regimen (optimal treatment) that will be successful in maintaining the drug-resistant strain at low levels? What is the prevalence of both drug-sensitive and drug-resistant populations in the case where eradication does not occur?

In this way, the model allowed different scenarios, including the most pessimistic and optimistic situations, to evaluate the performance of "optimal" treatment that minimizes the risk of resistance emergence. As the reproduction numbers ($\mathcal{R}_R$, $\mathcal{R}_S$) vary, we have shown that there are two possibilities for the outcome of the disease transmission. First, the disease will disappear as time evolves. Second, there is a region such that if the initial conditions lies in it, drug-resistance can emerge and persist even though the treatment rate (ε_S) becomes more and more effective. We have shown that the system (3) undergoes a Hopf bifurcation, and there exist some values of the treatment rate such that system (3) has a stable limit cycle.

Thus, optimistically, even though drug-resistance evolves during therapy, the treatment should be administered so that the patient achieves complete virological suppression. However, our simulations show that the treatment fails to contain the infection and large outbreaks of resistant cases can emerge (Figs. 6–8). Moreover, since the transmission fitness of resistant strains is generally lower than the one of the sensitive strains, the spread of the infection could still be reduced by decreasing the time to the patient to achieve complete viral suppression. In such case, as ε_S approaches its threshold value (ε_S^{thres}), the total population of HIV-1 infected individuals ($I_S^* + I_R^*$) begins to decrease. According to our "optimist case" scenario the infection could be eradicated. Hence, for eradication to occur, the drug regimen must roughly be as powerful against drug-resistant as it is against drug-sensitive strains.

From the expressions of the infected steady states we also observed that the drug-resistant populations will always be present. Because of the reduced viral fitness of the drug-resistant strain compared with the drug-sensitive strain, $\mathcal{R}_R < \mathcal{R}_S$, both the drug-sensitive and the drug-resistant strains will coexist, and the treatment fails primarily due to the drug-sensitive virus. If $\mathcal{R}_R > \max(\mathcal{R}_S, 1)$ then the drug-resistant populations outcompete the drug-sensitive populations. If highly transmissible resistant strains emerge (even though they are less transmissible than the drug-sensitive strains) they will significantly reduce the beneficial overall impact of antiretroviral therapies on the HIV-1 epidemic.

Great efforts should be made to prevent cases of acquired resistance developing during treatment, because these cases can lead to cases of transmitted resistance. Although it has not been possible to distinguish the mechanisms experimentally, our model suggests that under therapy the drug-sensitive strain can be suppressed even when $\mathcal{R}_S > 1$. We conclude that if drug-resistant HIV-1 is transmitted less frequently than drug-sensitive HIV-1 then there is coexistence of both resistant and sensitive strains. However, if drug-resistant HIV-1 is transmitted substantially more frequently than drug-sensitive HIV-1 then there is competition between both resistant and sensitive strains, and the drug-resistant population emerges while the drug-sensitive population will go to extinction.

Another important question raised by human infectious diseases is what determines which oscillations dominate in a given situation. Some diseases, particularly childhood diseases such as measles, whooping cough and rubella, as well influenza and respiratory syncytial virus (RSV), also show seasonal variation in

incidence, although the underlying causes remain uncertain. The standard method to address this problem is based on the bifurcation diagram. Although such diagrams provide a geometric map of the bifurcations there is little insight provided into why the diagram has the shape and structure it has. In this paper we have presented an alternative insight that could be based on the resonance rather than on bifurcation structure. The oscillations which are not damped, or damp very weakly, can also be produced in deterministic epidemic models in several ways, which amount essentially to make the model complex. So what we have not attempted in this paper is an algebraic analysis of this phenomenon and the finding of an expression for resonance peaks. Our objective was to understand only the structure of these sustained oscillations, in particular the epidemiological conditions under which they appear and disappear. We have used two visualization techniques to investigate the behavior of an epidemiological model under external forcing, namely the treatment: the bifurcation diagram and the resonance diagram. However, it seems that the precise mechanism underlying the existence of the cycles has not so far been elucidated because it involves the analysis of stochastic systems, and also because it involves concepts such as resonance, which are more familiar to physicists than biologists. Thus, in a future paper we intend to apply these approaches to much simpler model than the HIV model presented in this paper, modeling the evolution of drug resistance with an evolutionary stochastic process.

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