A coinfection model for HIV and HCV

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ABSTRACT

We study a mathematical model for the human immunodeficiency virus (HIV) and hepatites C virus (HCV) coinfection. The model predicts four distinct equilibria: the disease free, the HIV endemic, the HCV endemic, and the full endemic equilibria. The local and global stability of the disease free equilibrium was calculated for the full model and the HIV and HCV submodels. We present numerical simulations of the full model where the distinct equilibria can be observed. We show simulations of the qualitative changesof the dynamical behavior of the full model for variation of relevant parameters. From the results of the model, we infer possible measures that could be implemented in order to reduce the number of infectedindividuals.

Keywords: HIV/AIDS, HCV, Coinfection, Mathematical model

1. Introduction

HIV appears frequently associated with other diseases, such as tuberculosis (Naresh and Tripath, 2005) or hepatitis viruses (Maidana et al., 2005).

Throughout the world, 34–46 million people are infected with HIV, of which 4–5 millions are coinfected with HCV (Wolff et al., 2008). In the USA, 360,000 people are coinfected with HIV and HCV. Additionaly, 1.2 million are solely infected with HIV and more than 4 million are solely infected with HCV (Franciscus, 2012).

Worldwide, there are 150 million cases of chronic HCV carri- ers, and it is known that 85% of those with HCV exposure develop chronic infection (Hoofnagle, 1997; National, 1997). Chronic infec- tion results in a large number of deaths annualy due to cirrhosis and hepatocellular carcinoma. Moreover, liver transplants, for HCV induced liver disease patients, are a major part of health care costs (EASL, 1999).

HIV and HCV share the same transmission routes, namely by injection drug use, sexual contact, mother to child transmission during pregnancy or birth, blood and blood products transfusion, organs transplantation from infected donors, exposure to blood by health care professionals (Alter, 2006; Sulkowski, 2008).

Coinfection adds more severity for the two diseases involved. HIV accelerates the progression of HCV in dually infected patients. Having a count of CD4+ T cells below 200 cells/mm^3 increases the risk of severe liver disease (GAT, 2009). Moreover, there is a higher risk of cirrhosis, end-stage liver disease, hepatocarci- noma, and hepatic-related death (Thein et al., 2008; Departamento, 2011).

The current international consensus, to control the HIV epi- demic, focuses on the need for clear leadership on policies and programs for prevention, early diagnosis, treatment that respects human rights, and quality of health care, effective and accessible to everyone. In what concerns coinfection, some successful treat-ments for HCV using drug combination in individuals coinfected with HIV have been reported. Furthermore, most people with HCV can be treated successfully for HIV (Franciscus, 2012). However,more studies are needed to show the efficacy of new antiviral drugsfor HCV in people coinfected with HIV.

In the last few decades, mathematical models have been applied in the literature to the modeling of infectious diseases. HIV and known coinfections epidemiologies are the research topic of some of those models. In Vickerman et al. (2008), the authors proposed a transmission model for HCV/HIV coinfection, aimed at evaluating the cost-effectiveness of needle and syringe programs for injecting drug users (IDUs). They concluded that although the needle/syringe sharing events were defined as low risk in Rawalpindi, the preva- lence of HIV/HCV in IDUs would increase. They emphasized the importance of intervention measures in that low prevalence set- ting, in order to prevent the HIV/HCV prevalence. Recently, in Vickerman et al. (2012), the authors used a mathematical model to understand the trends in the prevalence of HIV and HCV. They determined the different epidemiological profiles and how these

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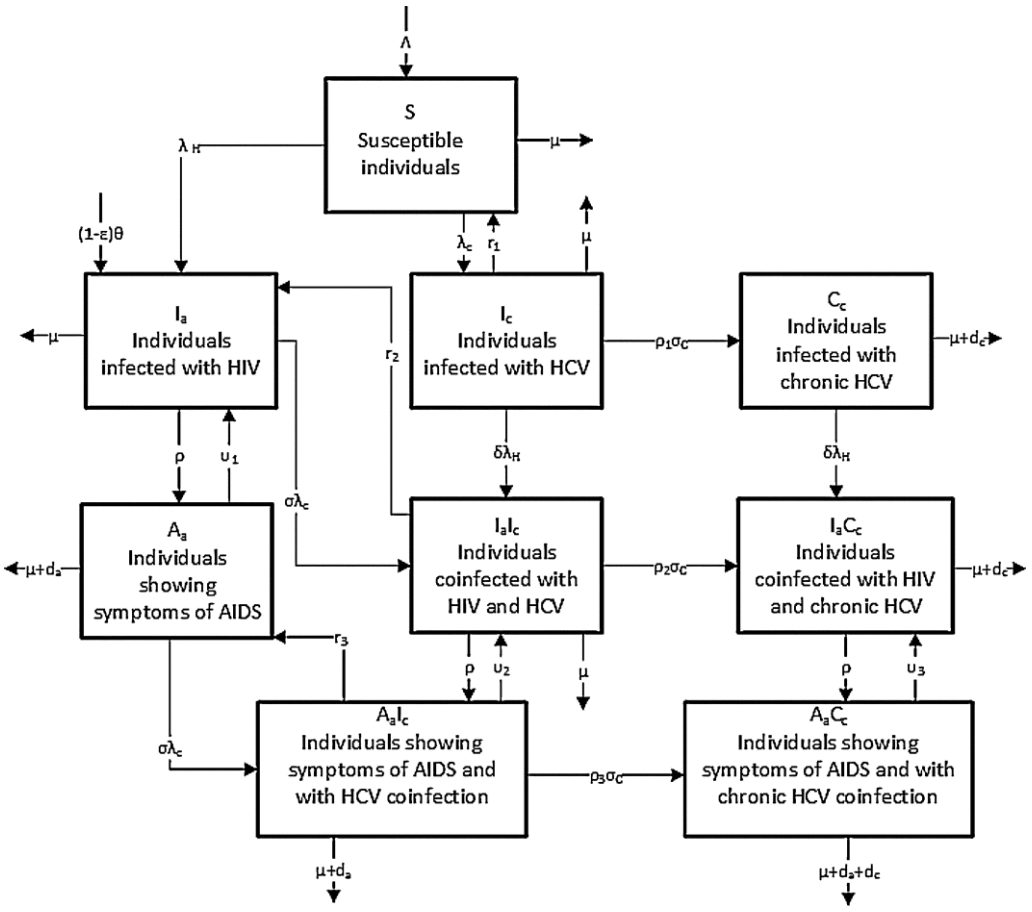


Fig. 1. Flow chart of the model.

profiles affect intervention impact. They concluded that there were threshold levels of HCV prevalence below which HIV risk was negli- gible. Nevetheless, these thresholds varied by setting. The authors infered that HIV and HCV prevalence settings could provide new insights into IDU risk behaviour and intervention impact. In de Vos et al. (2012), the authors proved that HCV prevalence could be used as an indicator of risk for successful HIV infection, in an IDU population. In Waziri et al. (2012), the authors formulated a mathe- matical model for HIV/AIDS treatment, where vertical transmission from mother to child was included. It is shown that highly active antiretroviral therapy (HAART) and control of vertical transmission rate were associated with a reduction of the HIV transmission. In Bhunu and Mushayabasa (2013), the authors studied a mathemat- ical model for HIV and HCV coinfection, that includes treatment for boh diseases. The model predicted that HCV had an ongoing prolonged negative effect on the population health, irrespective of their HIV status. The authors infered that specific measures to con- trol HCV should be taken/reinforced in resource limited settings. In 2013, Corson et al. (2013) proposed a mathematical model to explore the risk of HCV infection through the sharing of injecting paraphernalia (including filters, cookers and water). Namely, the sharing of injecting paraphernalia among IDUs is common, thus, HCV transmission through this route could contribute to the grow- ing burden in healthcare systems associated with it. The authors infered that more work was needed to detail the contribution of the paraphernalia sharing to the spread of HCV, and that health care providers should distribute sterile paraphernalia to prevent HCV infection.

In this paper, we study a mathematical model for HIV and HCV coinfection. The novelty of the model is in the inclusion of treat- ment for both diseases and of vertical transmission from mother to child, in the case of HIV, in one model. We are aware of HIV and HCV sharing several transmission routes, nevertheless, here we only consider sexual transmission for HIV and HCV and vertical transmission for HIV.

Bearing this in mind, the paper is organized as follows. The model is studied in Section 2. In Sections 2.2–2.3, we compute the reproduction numbers and the local and global stability of the dis- ease free equilibria. In Section 2.4, we present several bifurcation diagrams that reveal the dynamical behavior of the model for vari- ation of relevant parameters. Simulation results of the full model are presented in Section 3. Section 4 concludes this study and sheds some light on possible future research directions.

2. The HIV and HCV coinfection model

In this section, we describe the HIV and HCV coinfection model. We compute the reproduction numbers of the full model, and of the two submodels (HIV only and HCV only models). We study the local stability of the disease free equilibria for the full model and the global. We compute the sensitivity indices of the reproduction number to relevant parameters of the model. We present bifurca- tion diagrams, built with the help of XPPAUT, to better understand the dynamics of the proposed model.

2.1. Description of the model

The population of the model includes nine classes, namely, the susceptible individuals, S, the individuals infected with HIV, I_a, the individuals showing symptoms of AIDS, A_a, the individuals infected with HCV, I_c, the individuals infected with chronic HCV, C_c, the individuals coinfected with HIV and HCV, I_aI_c, the individuals coin- fected with HIV and with chronic HCV, I_aC_c, the individuals showing symptoms of AIDS and coinfected with HCV, A_aI_c, and the individ- uals showing symptoms of AIDS and with chronic HCV coinfection, A_aC_c.

In Fig. 1, it is presented the flow chart of the model. It repre- sents schematically the epidemiology of HIV and HCV coinfection. The different disease stages are reproduced by the different com- partments (rectangles) and the arrows indicate the way individuals progress from one stage to the other.

At time t, the population of size $N(t)$, has constant inflow of susceptible individuals, S, at a rate A. For all classes, the natural mortality rate is μ. Susceptible individuals, S, exposed to HIV, move to class I_a, at a rate A_H, given by:

$$\lambda_H = \frac{cb_h(I_a + A_a + \sigma_3(I_aI_c + I_aC_C))}{N}$$

Parameter b_h is the effective sexual contact rate for HIV infection to occur, and c is the average number of sexual partners per unit of time. On the other hand, when in contact with HCV patients, susceptible individuals, S, move to class I_c, at a rate:

$$\lambda_C = \frac{cb_c(I_c + C_c + \eta_1 I_aI_c + \eta_2 I_aC_c)}{N}$$

where parameter b_c is the effective contact rate for HCV infec- tion to occur. Parameters η_1, η_2, $a_3 > 1$ model the fact that dually infected individuals are more infectious than their corresponding counterparts.

A fraction of newborns are infected with HIV during birth and hence are directly recruited into the infectious class, I_a, at a rate $(1 - E)e$. Other children die at birth ($0 \le E \le 1$), where E is the frac- tion of newborns infected with HIV that die immediately after birth, and e is the rate of newborns infected with HIV. The individuals infected with HIV, I_a, move at a rate p to the AIDS class, A_a. Indi- viduals showing symptoms of AIDS are treated at a rate ν_1, and die because of AIDS at a rate d_a.

The individuals infected with HCV, I_c move to the susceptible class, S, after treatment at a rate r_1. They can progress to a chronic stage, C_c, at a rate p_1a_C, where p_1 is the proportion of infected indi- viduals who are chronic carriers and $1/a_C$ is the average time that an individual infected with HCV remains in a state of acute infec- tion. The individuals with chronic HCV infection, C_c, die because of HCV at a rate d_c.

We now define the dynamics of the coinfection. The individ- uals infected with HIV, I_a, are infected with HCV at a rate aA_C and move to class I_aI_c. Modification parameter $a > 1$ accounts for the fact that there is an increased risk of getting HCV for someone already infected with HIV, due to the vulnerability of the immune system. Reciprocally, the individuals infected with HCV, I_c are infected with HIV at a rate ιA_H and move to the class I_aI_c. Parameter $\iota > 1$ accounts for the increased susceptibility to HIV infection for HCV infected people, since HCV accelerates the decline of the immune function. Dually infected individuals, I_aI_c, recover from HCV infection at a rate r_2 and move to class I_a. On the other hand, they can progress to AIDS at a rate p and move to class A_aI_c. Moreover, I_aI_c individ- uals may become HCV chronic carriers, at a rate p_2a_C, and move to class I_aC_c. Parameter p_2 is the proportion of dually infected individ- uals who are chronic carriers. Dually HIV and chronic HCV infected individuals, I_aC_c, may progress to AIDS at a rate p and move to class A_aC_c.

Table 1
Description of the variables and the parameters of model (1).

Variable/Parameter	Description
S	Susceptible individuals
I_a	Individuals infected with HIV
A_a	Individuals showing symptoms of AIDS
I_c	Individuals infected with HCV
C_c	Individuals infected with chronic HCV
I_aI_c	Individuals coinfected with HIV and HCV
I_aC_c	Individuals coinfected with HIV and chronic HCV
A_aI_c	Individuals showing symptoms of AIDS and with HCV coinfection
A_aC_c	Individuals showing symptoms of AIDS and with chronic HCV coinfection
A	Recruitment rate
μ	Natural mortality rate
c	Average number of sexual partners
b_h	Effective sexual contact rate for HIV transmission to occur
b_c	Effective sexual contact rate for HCV transmission to occur
a_3	Modification parameter
η_i, = 1, 2	Modification parameter
r_i i = 1, 2, 3	HCV treatment rates
p_i, i = 1, 2, 3	Proportion of infected individuals who are chronic carries
d_c	Mortality due to HCV
E	Fraction of newborns infected with HIV that die immediately after birth
e	Rate of newborns infected with HIV
p	Rate of progression to AIDS
ν_i, i = 1, 2, 3	HIV treatment rate
d_a	Mortality due to HIV
a	Modification parameter
ι	Modification parameter
$\frac{1}{a_C}$	Average time that an individual infected with HCV remains in a state of acute infection

Individuals showing symptoms of AIDS, A_a, are infected with HCV at a rate aA_C and move to class A_aI_c. The individuals in class A_aI_c are treated and recover from HCV infection at a rate r_3 and move to class A_a or are treated and recover from AIDS stage at a rate ν_2 and move to class I_aI_c. The individuals in class A_aI_c become HCV chronic carriers at a rate p_3a_C and move to class A_aC_c. Parameter p_3 is the proportion of individuals in A_aI_c class who are chronic carriers. Individuals showing symptoms of AIDS and with chronic HCV coinfection, A_aC_c, are treated for HIV at a rate ν_3, and move to I_aC_c.

The following nonlinear system of ordinary differential equa- tions summarizes the description of the model:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda_H S - \lambda_C S + r_1 I_c - \mu S \\
\frac{dI_a}{dt} &= \lambda_H S - (\rho + \sigma\lambda_C + \mu)I_a + (1-\epsilon)\theta I_a + r_2 I_aI_c + \upsilon_1 A_a \\
\frac{dA_a}{dt} &= \rho I_a - (\upsilon_1 + d_a + \mu)A_a + r_3 A_aI_c - \sigma\lambda_C A_a \\
\frac{dI_c}{dt} &= \lambda_C S - (r_1 + \delta\lambda_H + \rho_1\sigma_C + \mu)I_c \\
\frac{dC_c}{dt} &= \rho_1\sigma_C I_c - (\delta\lambda_H + \mu + d_c)C_c \qquad (1) \\
\frac{dI_aI_c}{dt} &= \delta\lambda_H I_c + \sigma\lambda_C I_a + \upsilon_2 A_aI_c - (r_2 + \rho + \rho_2\sigma_C + \mu)I_aI_c \\
\frac{dI_aC_c}{dt} &= \rho_2\sigma_C I_aI_c + \delta\lambda_H C_c + \upsilon_3 A_aC_c - (\rho + \mu + d_c)I_aC_c \\
\frac{dA_aI_c}{dt} &= \sigma\lambda_C A_a + \rho I_aI_c - (r_3 + \upsilon_2 + \rho_3\sigma_C + \mu + d_a)A_aI_c \\
\frac{dA_aC_c}{dt} &= \rho_3\sigma_C A_aI_c + \rho I_aC_c - (\upsilon_3 + \mu + d_a + d_c)A_aC_c
\end{aligned}$$

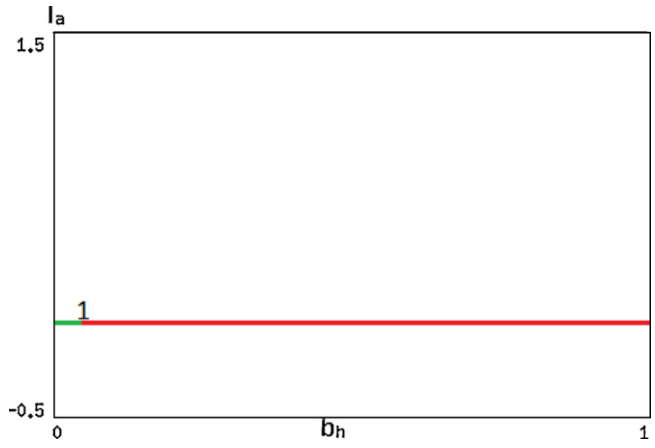


Fig. 2. Sketch of the bifurcation diagram of model (1), for different values of b_h , the effective sexual contact rate for a HIV infection to occur. Remaining parameter values are given in Table 2. Green: stable disease free equilibrium, red: stable HIV endemic equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

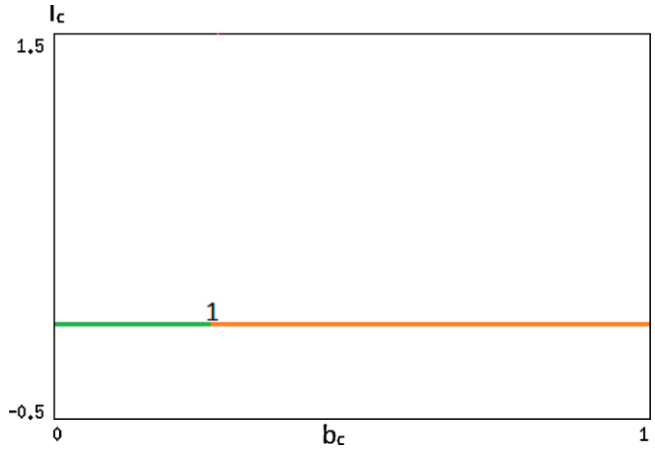


Fig. 3. Schematic bifurcation diagram of model (1), for different values of b_c , the effective contact rate for HCV infection to occur. Remaining parameter values are given in Table 2. Green: stable disease free equilibrium, orange: stable HCV endemic equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

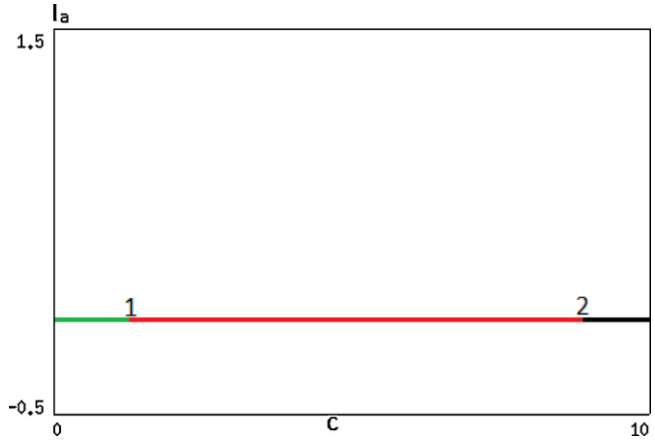


Fig. 4. Sketch of the bifurcation diagram of model (1), for different values of *c*, the average number of sexual partners. Remaining parameter values are given in Table 2. Green: stable disease free equilibrium, red: stable HIV endemic equilibrium, black: stable full endemic equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

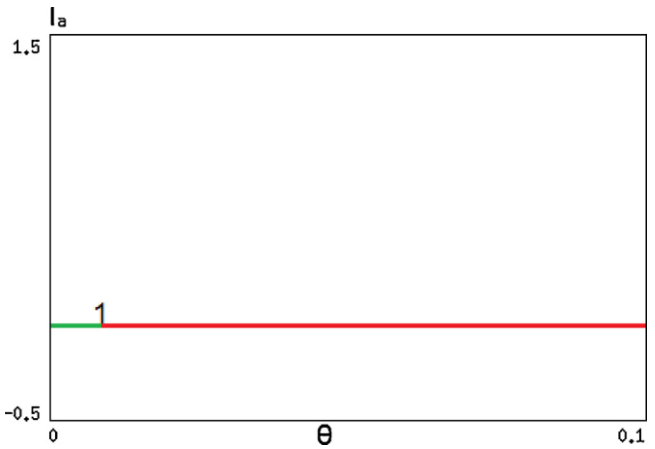


Fig. 5. Sketch of the bifurcation diagram of model (1), for different values of *e*, the fraction of newborns infected with HIV during birth. Remaining parameter values are given in Table 2. Red: stable HIV endemic equilibrium, green: stable disease free equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

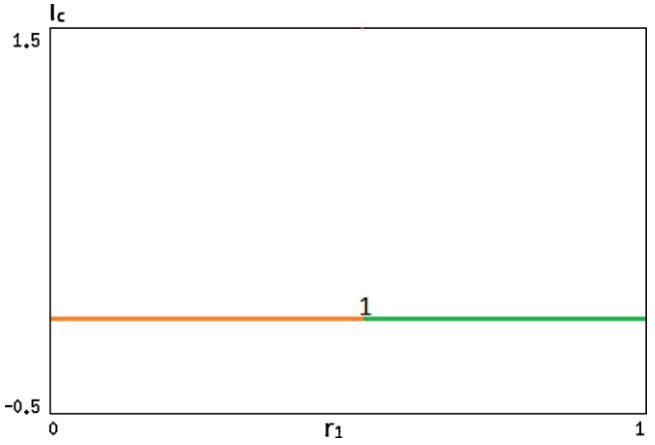


Fig. 6. Bifurcation diagram of model (1), for different values of r_1 , the treatment rate for individuals solely infected with HCV. Remaining parameter values are given in Table 2, except for $b_c = 0.5$. Orange: stable HCV endemic equilibrium, green: stable disease free equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

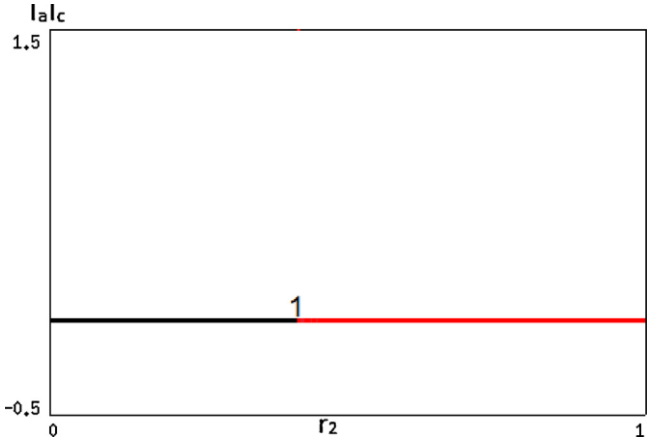


Fig. 7. Sketch of the bifurcation diagram of model (1), for different values of r_2 , the treatment rate for HCV of individuals dually infected with HIV and HCV. Remaining parameter values are given in Table 2, except for $b_h = 0.15$, $b_c = 0.5$ and $a_C = 0.43$. Black: stable two disease endemic equilibrium, red: stable HIV endemic equilibrium. For more information, see text. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

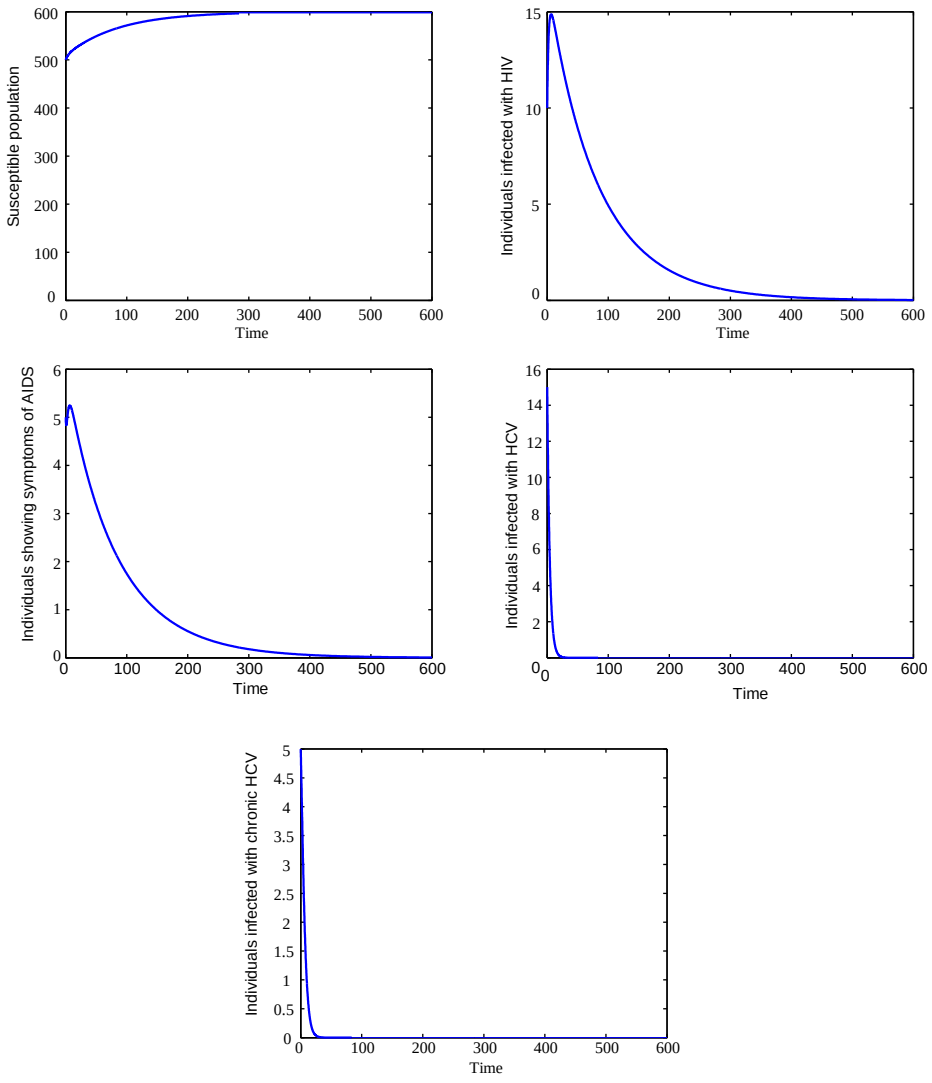


Fig. 8. Disease free equilibrium of system (1) for parameter values given in Table 2 and initial conditions ($R_{HIV} = 0.1813$, $R_{HCV} = 0.7895$, $R_0 = 0.7895$). Remaining variables tend asymptotically to zero.

The dynamics of the total population $N(t) = S(t) + I_a(t) + A_a(t) + I_c(t) + C_c(t) + I_aI_c(t) + I_aC_c(t) + A_aI_c(t) + A_aC_c(t)$ is given by:

$$\frac{dN}{dt} = \Lambda + (1-\epsilon)\theta I_a - \mu N - d_a(A_a + A_aI_c + A_aC_c) - d_c(C_c + I_aC_c + A_aC_c)$$

In Table 1, we summarize the parameters and the variables of model (1).

2.2. Reproduction numbers and stability of disease free equilibria

In this subsection, we compute the reproduction number of model (1), R_0. The basic reproduction number is defined as the num- ber of secondary infections due to a single infection in a completely susceptible population (Driessche and Watmough, 2002).

We begin by considering two sub-models of model (1). Model (2) is obtained from model (1) by setting the variables concerning HCV dynamics (I_c, C_c, I_aI_c, I_aC_c, A_aI_c and A_aC_c) to zero, and model (4) follows from model (1) by setting the variables concerning HIV dynamics (I_a, A_a, I_aI_c, I_aC_c, A_aI_c and A_aC_c) to zero.

We start by computing the reproduction number of the sys- tem (2), R_{HIV}. We use the next generation method (Driessche and Watmough, 2002).

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_H S - \mu S \\ \frac{dI_a}{dt} &= \lambda_H S - (\rho + \mu) I_a + (1-\epsilon)\theta I_a + \upsilon_1 A_a \\ \frac{dA_a}{dt} &= \rho I_a - (\upsilon_1 + d_a + \mu) A_a \end{aligned} \qquad (2)$$

where $\lambda_H = cb_h(I_a + A_a)/N$

The disease free equilibrium of model (2) is given by:

$$P_0^1 = (S_0^1, I_{a0}^1, A_{a0}^1,) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$$

Using the notation in Driessche and Watmough (2002) on sys- tem (2), matrices for the new infection terms, F, and the other terms,

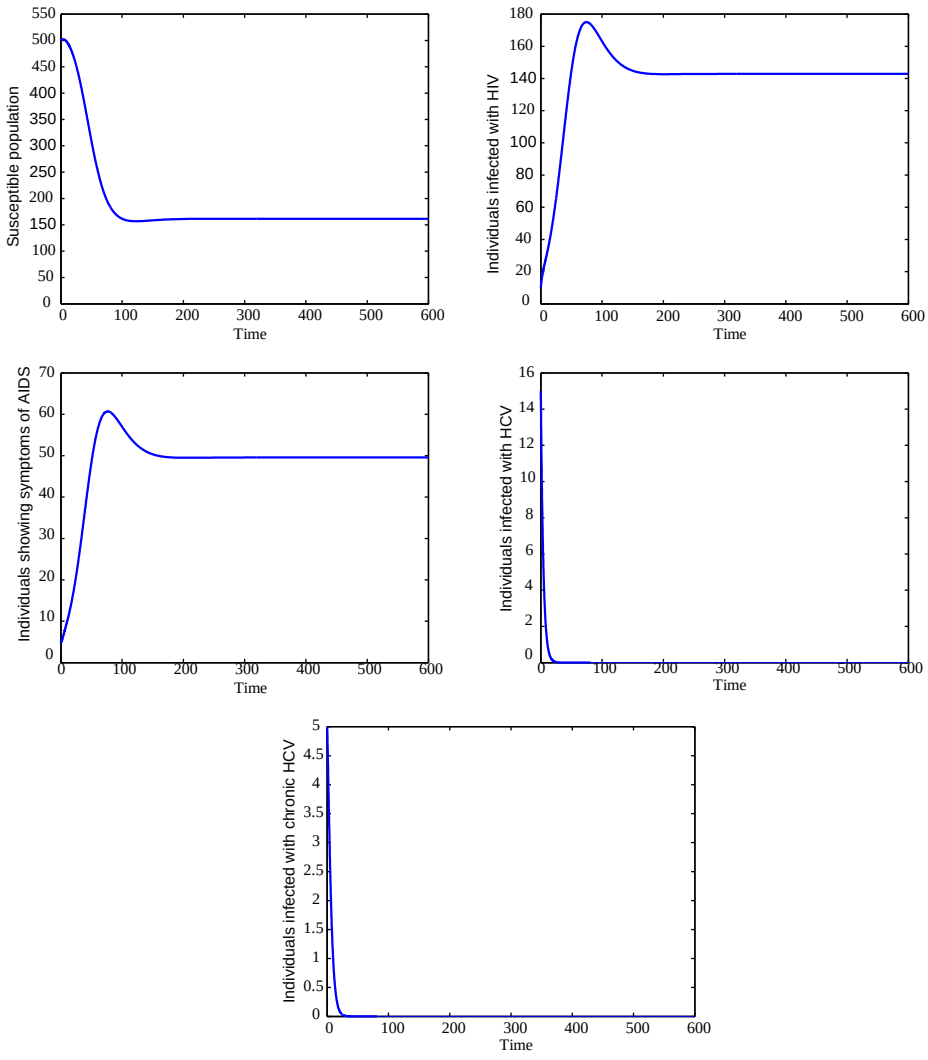


Fig. 9. Stable endemic HIV equilibrium of system (1) for given parameter values in Table 2, except $b_h = 0.1$, and initial conditions ($R_{HIV} = 2.1930$, $R_{HCV} = 0.1813$, $R_0 = 2.1930$). Remaining variables go asymptotically to zero.

V, are given by:

$$F = \begin{bmatrix} cb_h & cb_h \\ 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \rho + \mu - (1-\epsilon)\theta & -\upsilon_1 \\ -\rho & \upsilon_1 + d_a + \mu \end{bmatrix}$$

The associative basic reproduction number is given by:

$$R_{HIV} = \rho(FV^{-1}) = \frac{b_h c(\upsilon_1 + d_a + \mu + \rho)}{\rho(d_a + \mu) + (\mu - (1-\epsilon)\theta)(\upsilon_1 + d_a + \mu)} \qquad (3)$$

where p indicates the spectral radius of FV^{-1}. By Theorem 2 in Driessche and Watmough (2002), we obtain the following lemma.

Lemma 1. *The disease free equilibrium* P^1_0 *is locally asymptotically stable if* $R_{HIV} < 1$ *and unstable if* $R_{HIV} > 1$.

We proceed with the computation of the reproduction number of submodel (4) below, R_{HCV}.

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_C S + r_1 I_c - \mu S \\ \frac{dI_c}{dt} &= \lambda_C S - (r_1 + \rho_1 \sigma_C + \mu) I_c \\ \frac{dC_c}{dt} &= \rho_1 \sigma_C I_c - (\mu + d_c) C_c \end{aligned} \qquad (4)$$

where $\lambda_C = cb_c(I_c + C_c)/N$.

The disease free equilibrium state P^2 of model (4) is given by:

$$P^2_0 = (S^2_0, I_{c0}^2, C_{c0}^2) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$$

Using the notation in Driessche and Watmough (2002) on sys- tem (4), matrices for the new infection terms, F, and the other terms, V, are given by:

$$F = \begin{bmatrix} cb_c & cb_c \\ 0 & 0 \end{bmatrix}$$

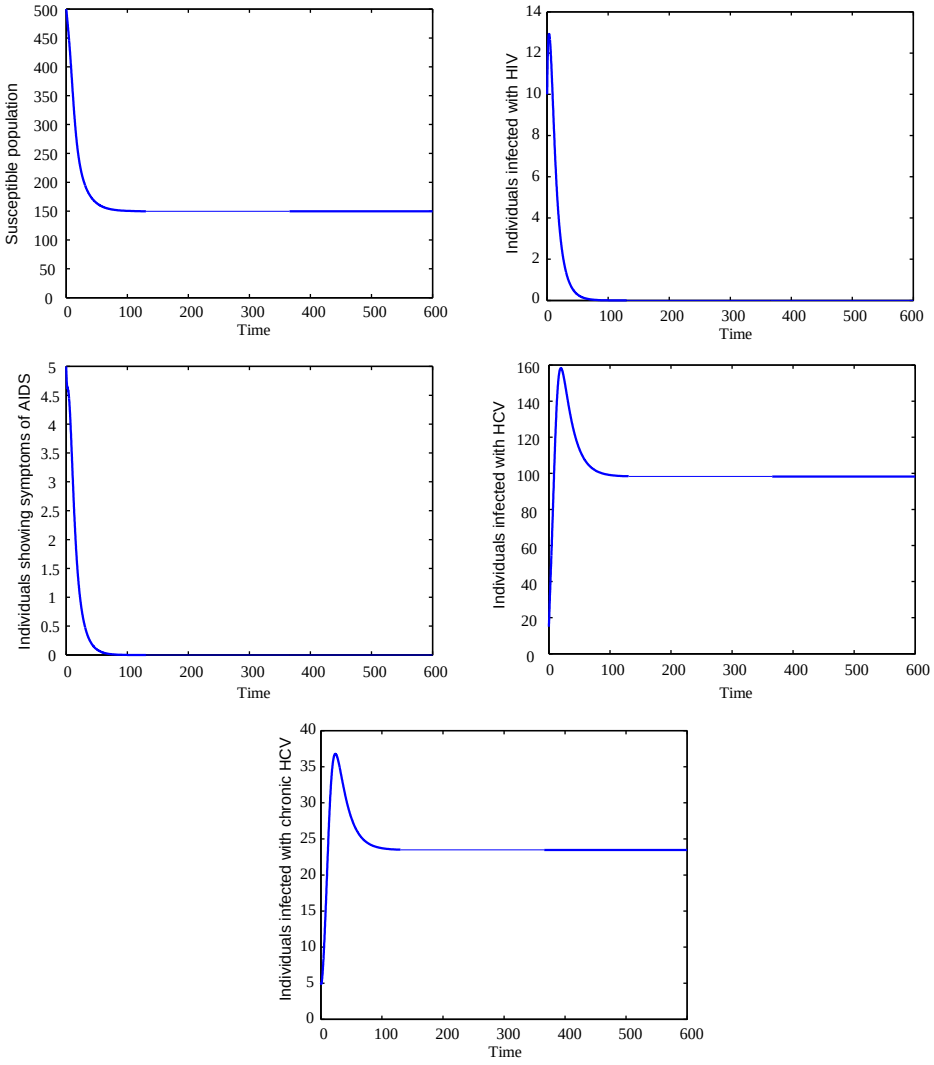


Fig. 10. Stable HCV endemic equilibrium of system (1) for parameter values given in Table 2, except $b_c = 0.5$, and initial conditions ($R_{HIV} = 0.7895$, $R_{HCV} = 1.8129$, $R_0 = 1.8129$). Remaining variables tend asymptotically to zero.

$$V = \begin{bmatrix} r_1 + \rho_1\sigma_C + \mu & 0 \\ -\rho_1\sigma_C & d_c + \mu \end{bmatrix}$$

The associative basic reproduction number is given by:

$$R_{HCV} = \rho(FV^{-1}) = \frac{cb_c(d_c + \mu + \rho_1\sigma_C)}{(d_c + \mu)(r_1 + \rho_1\sigma_C + \mu)} \qquad (5)$$

where p indicates the spectral radius of FV^{-1}. By Theorem 2 in Driessche and Watmough (2002), we obtain the following result.

Lemma 2. *The disease free equilibrium P^2 is locally asymptotically stable if $R_{HCV} < 1$ and unstable if $R_{HCV} > 1$.*

We now continue with the calculation of the reproduction number of the full model (1), R_0. The disease free equilibrium state, P_0, of model (1) is given by:

$$P_0 = (S^0, I_a^0, A_a^0, I_c^0, C_c^0, I_aI_c^0, I_aC_c^0, A_aI_c^0, A_aC_c^0)$$
$$= \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0\right) \qquad (6)$$

Using the notation in Driessche and Watmough (2002) on sys- tem (1), matrices for the new infection terms, F, and thee other terms, V, are given by:

$$F = \begin{pmatrix} cb_h & cb_h & 0 & 0 & cb_h\sigma_3 & cb_h\sigma_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & cb_c & cb_c & cb_c\eta_1 & cb_c\eta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

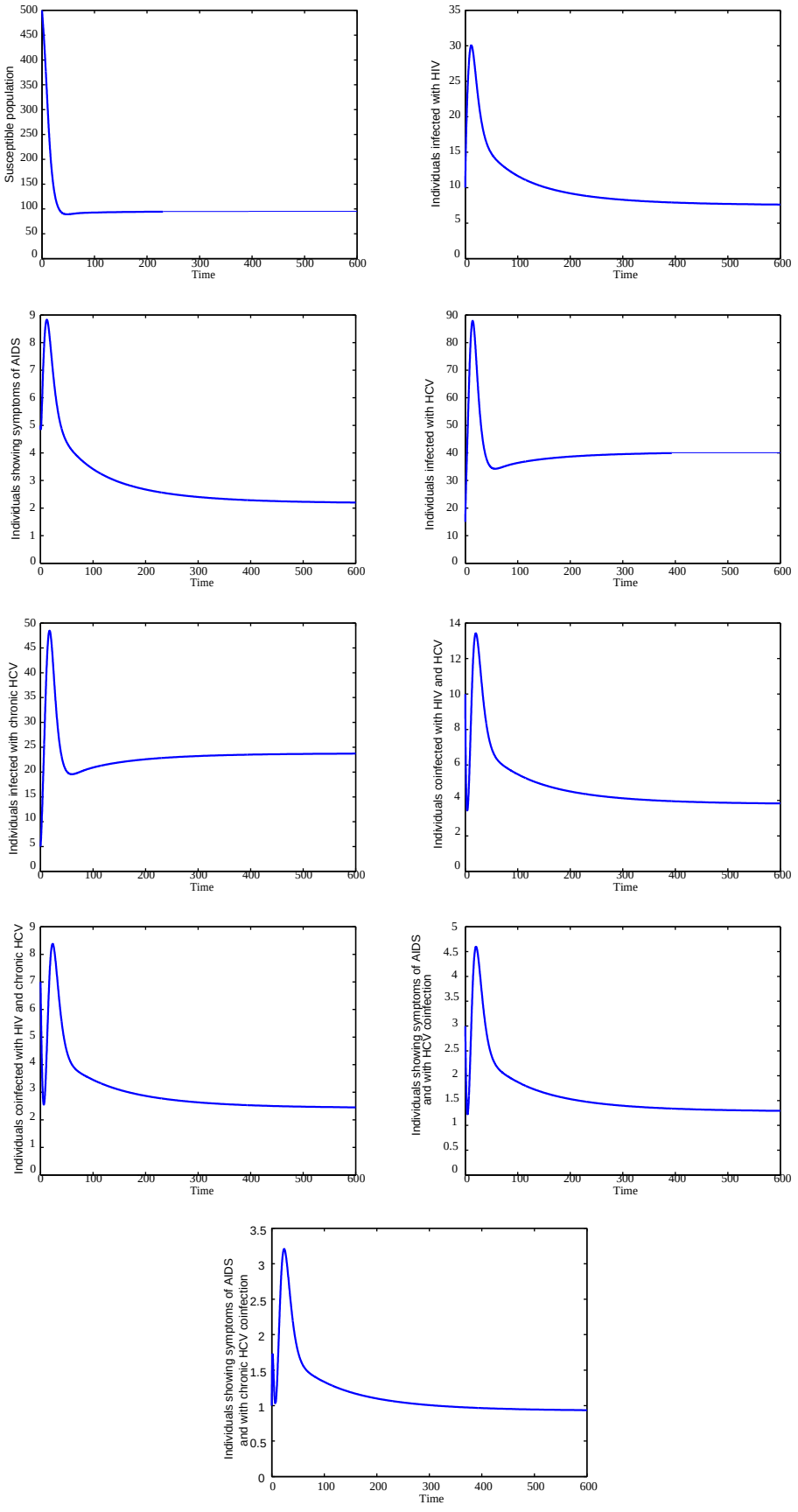


Fig. 11. Stable two disease endemic equilibrium of system (1) for given parameter values in Table 2, except for $b_h = 0.15$, $a_C = 0.43$ and $b_c = 0.5$, and initial conditions ($R_{HIV} = 3.2895$, $R_{HCV} = 1.7764$, $R_0 = 3.2895$).

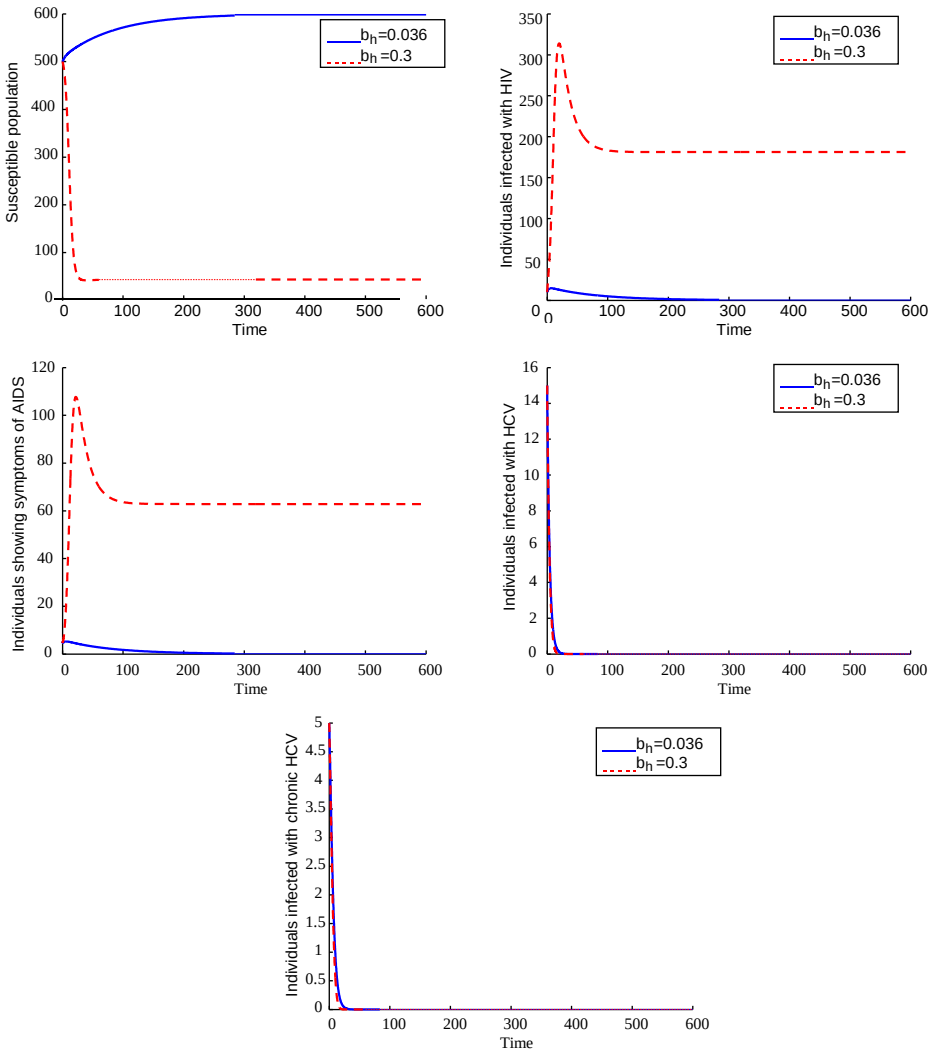


Fig. 12. Dynamics of the relevant variables of system (1) for different values of b_h, the effective sexual contact rate for HIV transmission to occur, for given parameter values in Table 2 and initial conditions. For more information, see text.

$$V = \begin{pmatrix} \rho+\mu-(1-\epsilon)\theta & -\upsilon_1 & 0 & 0 & -r_2 & 0 & 0 & 0 \\ -\rho & \upsilon_1+d_a+\mu & 0 & 0 & 0 & 0 & -r_3 & 0 \\ 0 & 0 & r_1+\rho_1\sigma_c+\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\rho_1\sigma_c & d_c+\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & r_2+\rho+\rho_2\sigma_c+\mu & 0 & -\upsilon_2 & 0 \\ 0 & 0 & 0 & 0 & -\rho_2\sigma_c & \rho+d_c+\mu & 0 & -\upsilon_3 \\ 0 & 0 & 0 & 0 & -\rho & 0 & r_3+\upsilon_2+\rho_3\sigma_c+d_a+\mu & 0 \\ 0 & 0 & 0 & 0 & 0 & -\rho & -\rho_3\sigma_c & \upsilon_3+\mu+d_a+d_c \end{pmatrix}$$

The associative basic reproduction number is computed to be:

$$R_0 = \rho(FV^{-1}) = \max\{R_{HIV}, R_{HCV}\} \tag{7}$$

whe
re p indicates the spectral radius of FV^{-1}. By Theorem 2 Driessche and Watmough (2002), we derive the following lemma.

Lemma 3. *The disease free equilibrium P_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

2.3. Global stability of the disease free equilibria

In this section, we compute the global stability of the disease free equilibrium of the full model (1). We begin by calculating the stability of the disease free equilibria of the two submodels (2) and (4).

Lemma 4. *For model* (2), *the disease free equilibrium P_0^1 is globally asymptotically stable if $R_{HIV} < 1$.*

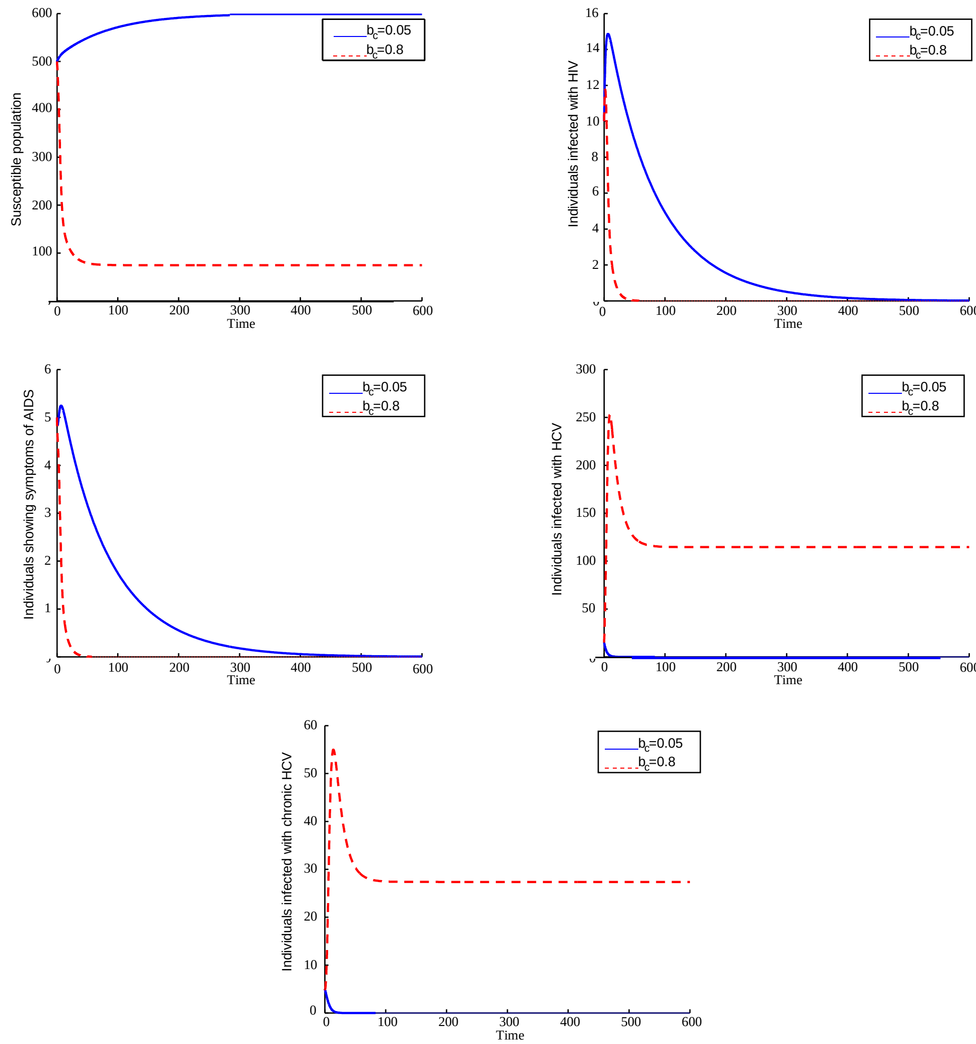


Fig. 13. Dynamics of the relevant variables of system (1) for different values of b_c, the effective contact rate for HCV infection to occur. Parameter values are in Table 2 and initial conditions in the text. For more information, see text.

Proof. We use the comparison theorem to prove the global stability of the disease free equilibrium of submodel (2). The rate of change of the variables (I_a, A_a) of system (2) can be rewritten as follows.

$$\begin{pmatrix} \dot{I}_a \\ \dot{A}_a \end{pmatrix} = (F-V)\begin{pmatrix} I_a \\ A_a \end{pmatrix} - \left(1-\frac{S}{N}\right)F\begin{pmatrix} I_a \\ A_a \end{pmatrix} \quad (8)$$

a

where F and V are as defined above for system (2). Since $S \le N$ for all $t \ge 0$, then:

$$\begin{pmatrix} \dot{I}_a \\ \dot{A}_a \end{pmatrix} \le (F-V)\begin{pmatrix} I_a \\ A_a \end{pmatrix} \quad (9)$$

If $R_{HIV} < 1$, then $p(FV^{-1}) < 1$, which is equivalent to say that the matrix $F-V$ has all eigenvalues in the left-half plane (Driessche and Watmough, 2002). It follows that the linear system given by equality (9) is stable whenever $R_{HIV} < 1$, and hence $(I_a(t), A_a(t)) \to (0, 0)$ as $t \to \infty$ for this linear ordinary differential equation (ODE) system. Consequently, after using a standard comparison theorem (Lakshmikantham et al., 1989; Smith and Waltman, 1995), we obtain $(I_a(t), A_a(t)) \to (0, 0)$, for the nonlinear system given by the last two equations of system (2). Returning now to the first equation 0) as $t \to \infty$ for $R_{HIV} < 1$, so that P^1_0 is globally asymptotically stable if $R_{HIV} < 1$. D

We now repeat the same procedure for the computation of the global stability of the disease free equilibrium of submodel (4).

Lemma 5. *For the submodel* (4), *the disease free equilibrium* P^2_0 *is globally asymptotically stable if* $R_{HCV} < 1$.

Proof. We use a comparison theorem to prove the global stability of the disease free equilibrium of submodel (4). The rate of change of the variables (I_c, C_c) of system (4) can be rewritten as:

$$\begin{pmatrix} \dot{I}_c \\ \dot{C}_c \end{pmatrix} = (F-V)\begin{pmatrix} I_c \\ C_c \end{pmatrix} - \left(1-\frac{S}{N}\right)F\begin{pmatrix} I_c \\ C_c \end{pmatrix} \quad (10)$$

where F and V are as defined above for system (4). Since $S \le N$ for all $t \ge 0$, then:

$$\begin{pmatrix} \dot{I}_c \\ \dot{C}_c \end{pmatrix} \le (F-V)\begin{pmatrix} I_c \\ C_c \end{pmatrix} \quad (11)$$

of model (2) and substituting $I_a = A_a = 0$ in this equation, we obtain a linear

system with $S(t) \rightarrow A/\mu$. Thus, $(S(t), I_a(t), A_a(t)) \rightarrow (A/\mu, 0,$

If $R_{HCV} < 1$, then $p(FV^{-1}) < 1$, which is equivalent to say that the matrix $F - V$ has all eigenvalues in the left-half plane (Driesscheand Watmough, 2002). It follows that the linear system given

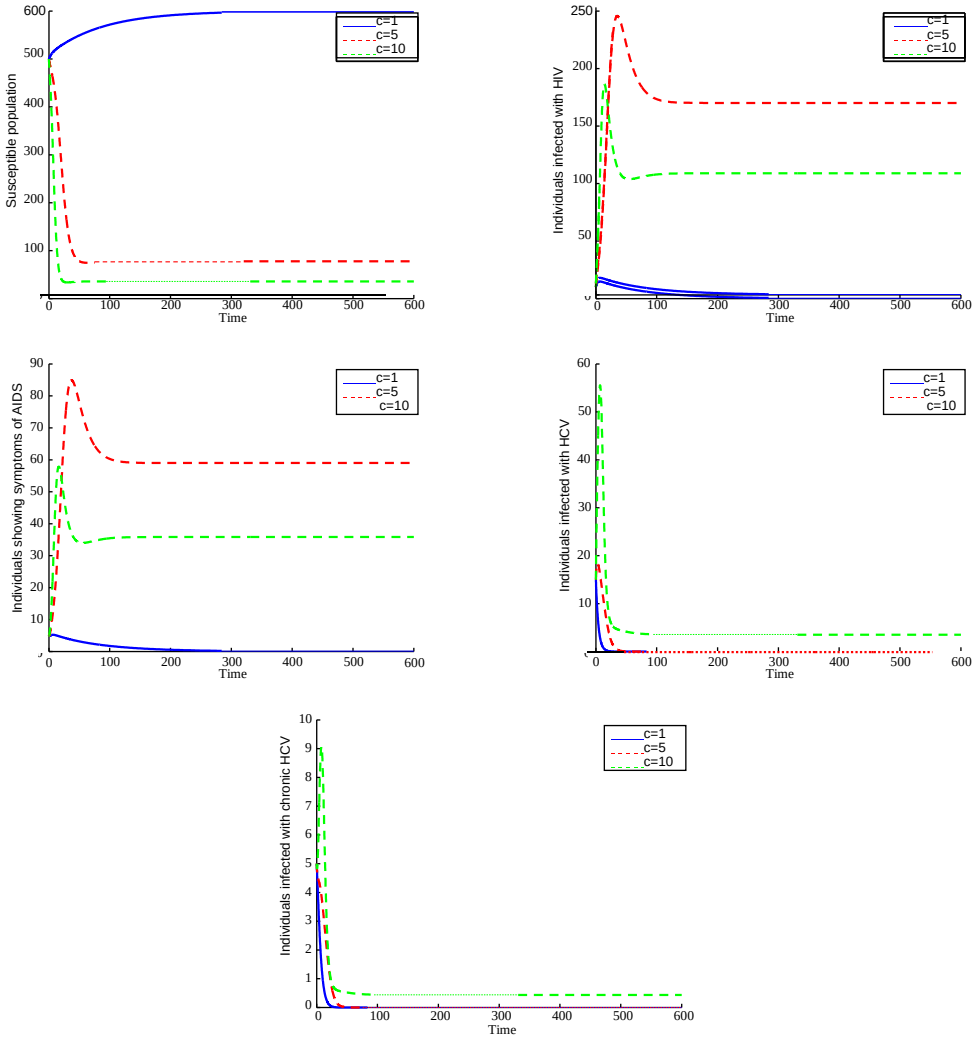


Fig. 14. Dynamics of the relevant variables of system (1) for different values of c, the average number of sexual partners per unit of time, for given parameter values in Table 2 and initial conditions. For more information, see text.

by the equality (11) is stable whenever $R_{HCV} < 1$, and hence $(I_c(t), C_c(t)) \to (0, 0)$ as $t \to \infty$ for this linear ODE system. Consequently, after using a standard comparison theorem (Lakshmikantham et al., 1989; Smith and Waltman, 1995), we obtain $(I_c(t), C_c(t)) \to (0, 0)$ for the nonlinear system, given by the last two equations of (4). Returning now to the first equation of submodel (4) and substitut- ing $I_c = C_c = 0$ in this equation gives a linear system with $S(t) \to A/\mu$. Thus, $(S(t), I_c(t), C_c(t)) \to (A/\mu, 0, 0)$ as $t \to \infty$ for $R_{HCV} < 1$, so that P^2 is globally asymptotically stable if $R_{HCV} < 1$. D

The global stability of the disease free equilibrium of model (1), can only be achieved in very specific conditions, namely, when new coinfection cases are prevented from occurring. Patients infected with HIV or HCV could not become coinfected in such conditions. We feel that this condition is somewhat unrealistic and do not include it here. New techniques will be applied in future work in order to try to prove the global stability of the disease free equilib-rium.

2.4. Bifurcation analysis of the model

In this section, we use XPPAUT (Ermentrout, 2006) to draw schematic bifurcation diagrams for six relevant parameters of the model (1). Changing colors indicates a change in the stability of the equilibria.

Fig. 2 is a sketch of the bifurcation diagram of model (1) for the variation of parameter b_h, the effective sexual contact rate for a HIV infection to occur. We start from a disease free equilibriumand increase b_h. At $b_h = 0.0456$, there is a bifurcation point (1), atwhich the model bifurcates to the stable HIV endemic equilibrium.The color green means that the disease free equilibrium is stableand the color red means that it has lost stability, and now is the HIVendemic equilibrium that it is stable. Thus, increasing the effective sexual contact rate for HIV infection to occur will translate in newcases of HIV infections.

Fig. 3 depicts the sketch of the bifurcation diagram of model (1), for different values of b_c, the effective contact rate for HCV infec- tion to occur. We start from a stable disease free equilibrium and increase b_c. At $b_c = 0.2758$, there is a bifurcation point (1), where the model bifurcates to the stable HCV endemic equilibrium. This means that increasing the effective contact rate for HCV infection to occur will promote the appearance of new cases of HCV.

In Fig. 4 we plot a sketch of the bifurcation diagram of model (1), for variation of parameter c, the average number of sexual partners. We start from a disease free equilibrium and increase c. At $c = 1.267$, there is a bifurcation point (1), at which the model bifurcates to the

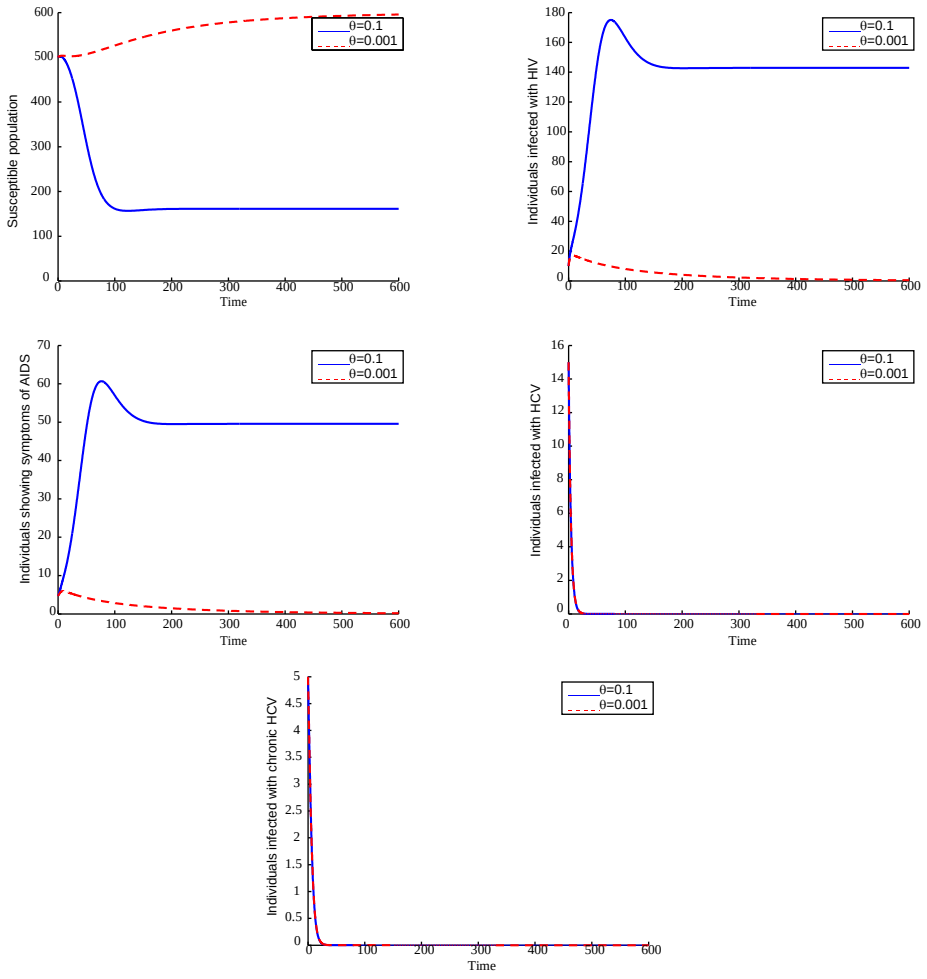


Fig. 15. Dynamics of the relevant variables of system (1) for different values of e, the fraction of newborns infected with HIV during birth, for given parameter values in Table 2, except for b_h = 0.1, and initial conditions. For more information, see text.

stable HIV endemic equilibrium. This means that increasing the average number of sexual partners of susceptible individuals will, as expected, translate in new cases of HIV infections. Increasing further c, a secondary bifurcation occurs at c = 8.651 (2), at which the model changes the dynamical behavior to a stable full endemic equilibrium. Biologically this implies that increasing the average number of sexual partners will burst coinfection cases. Note that as both diseases, HIV and HCV share the same transmission route, in this case, by sexual contact, increasing the average number of sexual partners affects both diseases. Moreover, as HCV is more difficult to be transmitted through sexual intercourse, it is reason- able that for HCV to occur a larger number of sexual partners is needed.

In Fig. 5 we depict a schematic bifurcation diagram of model (1), for different values of e, the fraction of newborns infected with HIV during birth. We start from a stable HIV endemic equilibrium and decrease e. At e = 0.0084 there is a bifurcation point (1), at which the model bifurcates to the stable disease free equilibrium. The model predicts, in this case, that decreasing the number of infectednewborns will decrease the number of HIV infected individuals.

Fig. 6 shows the sketch of the bifurcation diagram for differ- ent values of r_1, the treatment rate for individuals solely infected with HCV. We start from a a stable HCV endemic equilibrium and increase r_1. At r_1 = 0.5277, there is a bifurcation point (1), at which the model bifurcates to the disease free equilibrium. This means that increasing the treatment rate for individuals solely infected with HCV is a successful strategy, since patients recover from HCV infection.

In Fig. 7 we draw a schematic bifurcation diagram of model (1), for different values of r_2, the treatment rate for HCV, of individ- uals dually infected with HIV and HCV. We start from a stable two disease endemic equilibrium. At r_2 = 0.4203 there is a bifurcationpoint (1), at which the model bifurcates to the stable HIV endemic equilibrium. Biologically, this means that increasing the treatment rate for HCV of individuals dually infected with HIV and HCV leads to a recovery from the HCV infection. The individual returns to thestage of HIV solely infection.

In the next section we will present numerical simulations where bifurcation between distinct equilibria can be observed, for varia- tion of the parameters considered above.

3. Numerical results

We present the numerical simulations of model (1). The param- eter values used in the simulations can be found in Table 2 and the following initial conditions $S(0)$ = 500, $I_a(0)$= 10= $I_aI_c(0)$, $A_a(0)$= 5, $C_c(0)$= 5, $I_c(0)$ = 15, $I_aC_c(0)$ = 10, $A_aI_c(0)$= 3, $A_aC_c(0)$ = 1 are used.

In Fig. 8, we plot the dynamics of the relevant variables of system (1). We observe that, for the given parameter values and initial conditions, the model approaches asymptotically the stable disease free equilibrium.

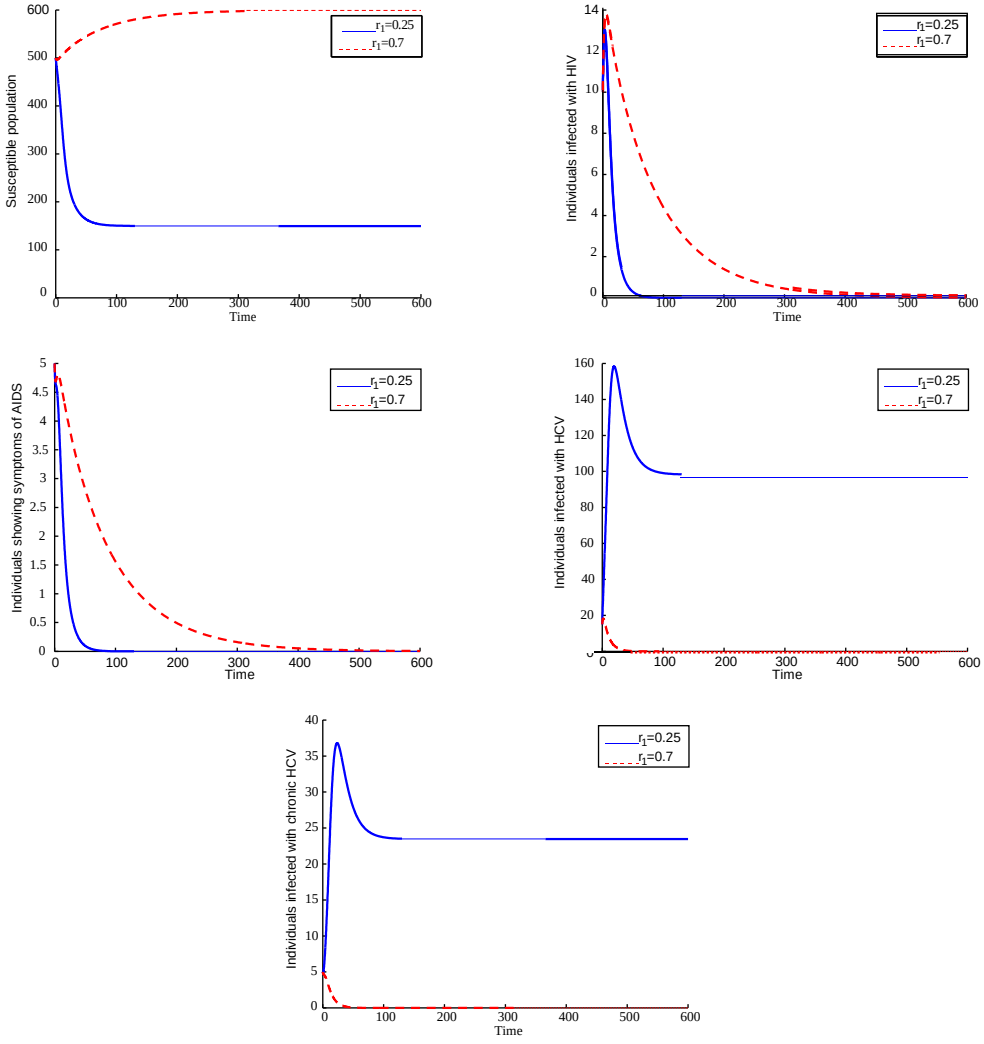


Fig. 16. Dynamics of the relevant variables of system (1) for different values of r_1, the treatment rate for individuals solely infected with HCV, for given parameter values in Table 2, except for $b_c = 0.5$, and initial conditions. For more information, see text.

In Fig. 9, we observe that the model approaches asymptotically the stable endemic HIV equilibrium.

Fig. 10 shows the stable endemic HCV equilibrium for system (1).

In Fig. 11, we depict the dynamics of the variables of system (1). We observe that, for the given parameter values and initial conditions, the model approaches asymptotically the stable two disease endemic equilibrium.

Fig. 12 shows the dynamics of the variables of system (1) for different values of b_h, the effective contact rate for HIV infection to occur. We observe that as b_h increases the system (1) bifur-cates from the stable disease free equilibrium to the stable HIV endemic equilibrium. Realistically, augmenting the sexual contact rate between individuals is followed by a burst of HIV infection.

In Fig. 13, it is shown the dynamics of the variables of system (1) for different values of b_c, the effective contact rate for HCV infectionto occur. We observe that as b_c increases the system (1) bifurcates from the stable disease free equilibrium to the stable HCV endemic equilibrium. This behavior translates, biologically, in new cases of HCV for higher values of b_c.

Fig. 14 depicts the behavior of system (1) for different values of c, the average number of sexual partners per unit of time. We observe that as c increases the system (1) bifurcates from the stable disease free equilibrium to the stable HIV endemic equilibrium and then, increasing further the value of c, there is another bifurcation to the full endemic equilibrium. Biologically, this means that augmenting the average number of sexual partners fuels the appearance of new cases of HIV infection, and, after some value, it even promotes the appearance of coinfection cases.

In Fig. 15 are depicted the dynamics of the variables of system (1) for different values of of e, the fraction of newborns infected with HIV during birth. We observe that as e increases the system (1) bifurcates from the stable disease free equilibrium to the stable HIV endemic equilibrium.

In Fig. 16 we plot the behavior of system (1) for different val- ues of r_1, the treatment rate for individuals solely infected withHCV. We observe that as r_1 increases the stable HCV endemic stategives rise to the stable disease free equilibrium. This means that the treatment was successful and patients recovered from HCV.

In Fig. 17 we can observe the effects on the dynamics of model (1), for variation of r_2, the treatment rate for individuals dually infected with HIV and HCV. As r_2 increases the system (1) bifur- cates from the stable full endemic equilibrium to the stable HIV endemic equilibrium. Thus, patients recover from HCV infection.

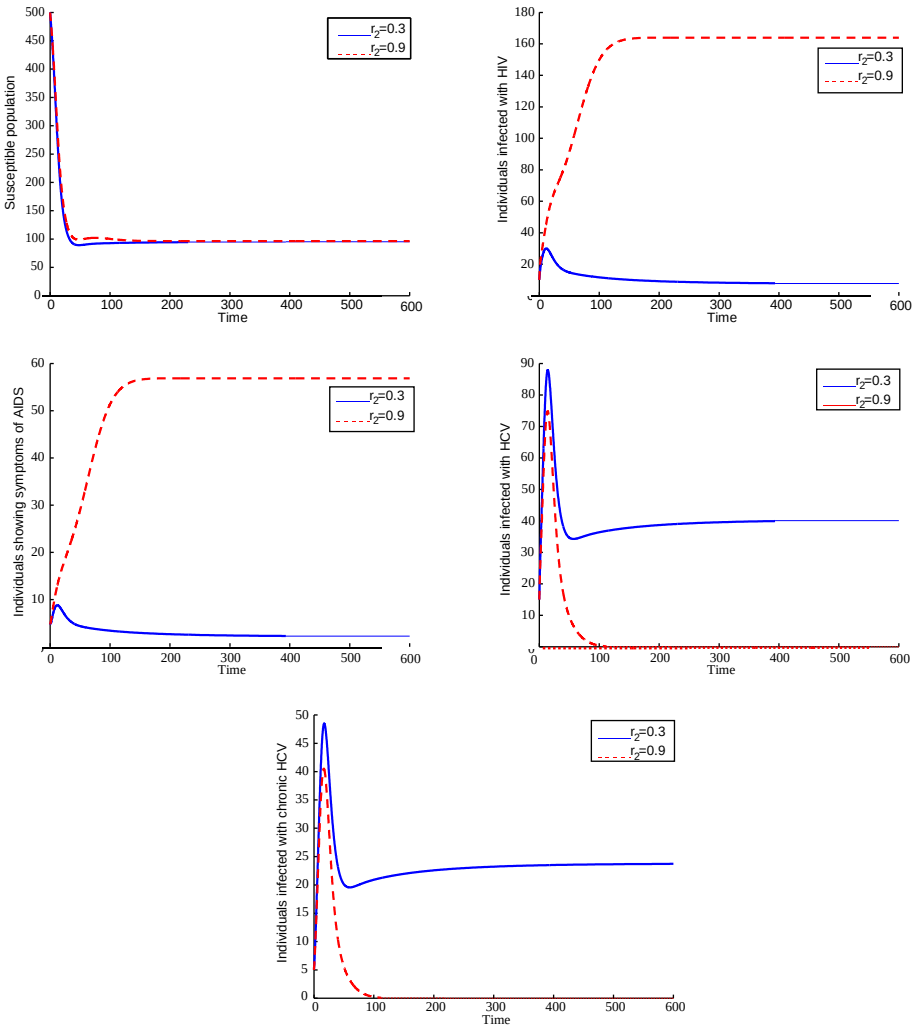


Fig. 17. Dynamics of the relevant variables of system (1) for different values of r_2, the treatment rate for HCV in individuals dually infected with HIV and HCV, for given parameter values in Table 2, except for $b_h = 0.15$, $b_c = 0.5$, and $a_C = 0.43$, and initial conditions. For more information, see text.

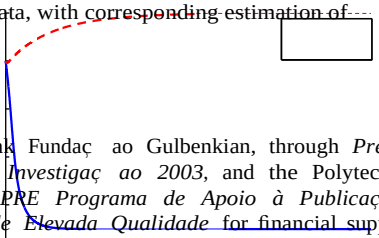
Table 2
Parameters used in the numerical simulations of model (1). Where appropriate the units are year^{-1}.

Parameter	Value	Reference
c	1	Estimated
b_h	0.036	Hollingsworth et al. (2008)
a_3	1.0002	Estimated
b_c	0.05	van de Laar et al. (2010)
π_1	1.0002	Bhunu and Mushayabasa (2013)
π_2	1.002	Estimated
A	12	Estimated
μ	0.02	Bhunu and Mushayabasa (2013)
r_1	0.25	Bhunu and Mushayabasa (2013)
r_2	0.2	Estimated
r_3	0.15	Estimated
p	0.1908	Nyabadza and Mukandavire(2011)
a	1.001	Bhunu and Mushayabasa (2013)
E	0.2	Waziri et al. (2012)
e	0.1	Estimated
v_1	0.2	Bhunu and Mushayabasa (2013)
v_2	0.2	Estimated
v_3	0.15	Estimated
d_a	0.33	Bhunu and Mushayabasa (2013)
d_c	0.2801	Bhunu and Mushayabasa (2013)
ι	1.001	Bhunu and Mushayabasa (2013)
p_1	0.43	Sanchez et al. (2013)
p_2	0.45	Estimated
p_3	0.47	Estimated
a_C	0.1667	Sanchez et al. (2013)

4. Conclusion

In this paper, we analyzed a mathematical model for the coinfec- tion of HIV and HCV, that includes treatment for both diseases, and vertical transmission in the case of HIV. We studied the local sta-bility of the disease free equilibria for the full model and the global stability of the disease free equilibria for the two submodels (HCV only and HIV only submodels). XPPAUT was used to sketch bifur- cation diagrams, for relevant parameters, e.g., the mean number ofsexual partners, the sexual contact rates, and the treatment rates. Numerical results illustrate the change on the dynamical behaviorof the model for these parameters. The outcomes suggest that spe- cific measures should be considered, by the policy makers, in orderto reduce HIV infection, such as: distributing more condoms to indi-viduals; develop campaigns in order to warn individuals about the consequences of having many sexual partners; continuing treat-ment for AIDS and pursuing the investigation of new and better drugs to combat HIV, treat newborns infected with HIV and advise pregnant women for the benefits of HIV treatment. Considering HCV infection, treatment is highly recommended as well as other measures (e.g., more informational campaigns about the disease, its transmission routes, amongst others) in order to decrease the num-ber of infectious and of chronic carriers. Future work will focus on the study of regular screening for HIV and of condom use, of the effects of needle sharing, as well as an application/validation of the

model to real portuguese data, with corresponding estimation of parameter values.



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