EFFECTS OF TREATMENT, AWARENESS

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We develop a new a coinfection model for hepatitis C virus (HCV) and the human immunodeficiency virus (HIV). We consider treatment for both diseases, screening, unawareness and awareness of HIV infection, and the use of condoms. We study the local stability of the disease-free equilibria for the full model and for the two submod-els (HCV only and HIV only submodels). We sketch bifurcation diagrams for different parameters, such as the probabilities that a contact will result in a HIV or an HCV infection. We present numerical simulations of the full model where the HIV, HCV and double endemic equilibria can be observed. We also show numerically the qualitative changes of the dynamical behavior of the full model for variation of relevant param-eters. We extrapolate the results from the model for actual measures that could be implemented in order to reduce the number of infected individuals.

Keywords: Mathematical Models; HIV/AIDS; HCV; MSM; Screening Coinfection.

1. Introduction

Human immunodeficiency virus (HIV) affects 34 to 46 million people throughout the world. Of these, about 4 to 5 million people are coinfected with hepatitis C virus (HCV).[1] In Portugal, it is estimated that about 25% to 40% of the 41,086 people infected with HIV are coinfected with HCV.[2] Portugal is the third country, of the Western Europe, with higher prevalence and more new diagnosed cases of HIV/AIDS, per year.

The current international consensus, to control the HIV epidemic, 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. Mathematical models have been used extensively in the literature to model epidemiological and other biological phenomena.[3,4] In what concerns HIV/AIDS, new models incorporate a more detailed understanding of the mechanisms associated to HIV infection, such as dissemination, and distribution and impact of interventions on population.[5,6] Consequently, the impact of health policies, such as deficient access to health care, delayed treatment or the use of screening for asymptomatic cases can be evaluated with these models.[7] A model of HIV/AIDS with screening was introduced in Ref. 8 and recently extended in Ref. 9. Usually, the models of the dynamics of HIV/AIDS, incorporate progression, where an infected individual goes through various stages of infectiousness before developing clinical AIDS. In Ref. 8, a model in which infection leads to asymptomatic HIV infectives, who are later screened and then develop AIDS, without interventions, is considered. A similar approach was previously studied in Ref. 5 with differential infectivity and staged progression models. In Ref. 9, the model in Ref. 8, was modified to include highly active antiretroviral therapy (HAART) treatment.

Typically, the coinfection of HIV and other diseases is associated with more serious risks and severe consequences for patients. In the coinfection with HCV, HIV accelerates the progression of HCV, moreover, the risk of severe liver disease is higher if the CD4 count falls below 200 cells/mm^3.[2] In addition, there is a higher risk of cirrhosis, end-stage liver disease, hepatocellular carcinoma and liver-related death.[10] In Portugal, the end-stage liver disease is, after tuberculosis, the second leading cause of death among HIV-positive people.[2]

Recent studies show, however, some successful treatments for HCV using drug combination in individuals coinfected with HIV. Furthermore, most people with HCV can be treated successfully for HIV.[11] However, more studies are needed to show the efficacy of new antiviral drugs for HCV in people coinfected with HIV.

In this paper, we study a mathematical model for HIV and HCV coinfection in men who have sex with men (MSM). The model includes treatment for both diseases, screening, awareness and unawareness of HIV infection, and effective protection against HIV and HCV by condom use. We believe this is a relevant study, since HIV and HCV are common diseases worldwide and since 2000 outbreaks of acute HCV among HIV-positive MSM, who denied injecting drugs, have been reported in Europe,[12] United States[13] and Australia.[14] This fact added to the increased severity of the coexistence of the two diseases, makes it extremely important to unravel the dynamics of their coinfection.

HIV and HCV share the same transmission routes, namely by injection drug use (IDU), sexual contact, mother to child transmission during pregnancy or birth, blood and blood products transfusion, organs transplantation from infected donors and exposure to blood by health care professionals.[15] Here, we will only consider

the transmission of HIV and HCV by sexual activity. HCV transmission by sexual activity is believed to be inefficient and an accurate estimate for the value of the risk associated to different sexual activities is still to be found. Moreover, the HCV prevalence differs in what concerns the HIV transmission route, being the higher associated to IDU. Nevertheless, there is stronger proof of sexually transmitted HCV in HIV infected MSM.[16,17] There is also increased concern with the likely bridging of HCV transmission from the HIV-positive into the HIV-negative MSM.[17]

Bearing these ideas in mind, the paper is organized as follows. The model is described in Sec. 2. In Sec. 2.2, we compute the reproduction numbers and the local stability of the disease-free equilibria. In Sec. 3, we present several bifurcation diagrams that help to understand the dynamical behavior of the proposed model. We compute the sensitivity indices of the reproduction number to relevant parameters of the model in Sec. 4. Simulation results of the full model are presented in Sec. 5. Finally, in Sec. 6, we write the main conclusions of this work.

2. Model for HIV/AIDS and HCV Transmission

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

2.1. *Description of the model*

The total population, $N(t)$ is divided into the following 16 classes: the unscreened susceptible individuals, $S_{\tilde{s}}(t)$, the screened susceptible individuals, $S_s(t)$, the HIV unaware infected individuals, $I_{\tilde{a}}(t)$, the HIV aware infected individuals, $I_a(t)$, the unaware individuals showing symptoms of AIDS, $A_{\tilde{a}}(t)$, the aware individuals that developed AIDS, $A_a(t)$, the HCV infected individuals screened for HIV, $I_c(t)$, the HCV infected individuals unscreened for HIV, $I_{\tilde{c}}(t)$, the chronic HCV infected individuals unscreened for HIV, $C_{\tilde{s}}(t)$, the chronic HCV infected individuals screened for HIV, $C_s(t)$, the HCV and HIV unaware coinfected individuals, $I_c I_{\tilde{a}}(t)$, the HCV and HIV aware coinfected individuals, $I_c I_a(t)$, the chronic HCV and HIV unaware coinfected individuals, $CI_{\tilde{a}}(t)$, the chronic HCV and HIV aware coinfected individuals, $CI_a(t)$, the HCV and AIDS dually infected individuals, $I_c A(t)$, and the chronic HCV and AIDS coinfected individuals, $CA(t)$.

The schematic diagram of the model is given in Fig. 1.

The population of size $N(t)$, at time t, has constant inflow of susceptibles $S_{\tilde{s}}(t)$ and $S_s(t)$, $\Lambda = \Lambda_1 + \Lambda_2$. The natural mortality rate is μ in all classes. Susceptible
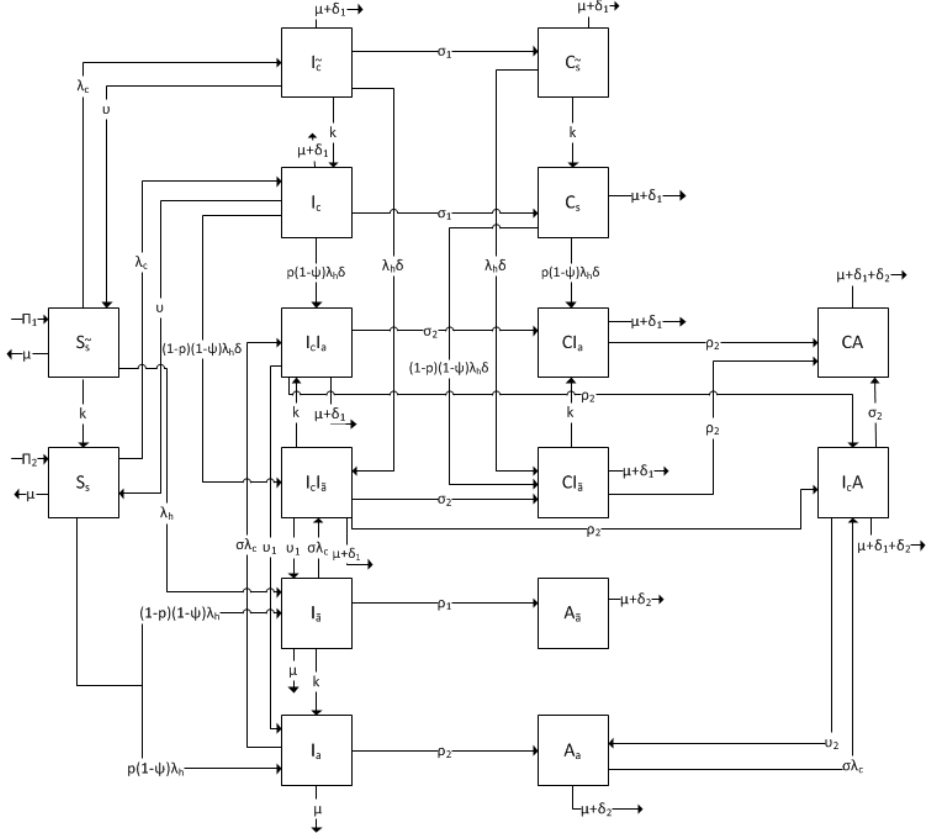
Fig. 1.   Flow chart of the model.

unscreened individuals, $S_{\tilde{s}}(t)$, get infected with HIV at a rate λ_h, where:

$$\lambda_h = c(1 - \theta)b_h \frac{I_a(t) + I_{\tilde{a}}(t) + \eta_1 (I_c I_{\tilde{a}}(t) + I_c I_a(t))}{N(t)}.$$

Parameter b_h is the probability that a contact will result in an HIV infection and c is the mean number of sexual partners that a susceptible individual acquires, annually. To model the impact of condom use as a primary prevention tool, we assume that the level of protection by condoms is given by $\theta \in [0, 1]$. If $\theta = 0$, then condoms do not offer any protection, whereas $\theta = 1$ implies perfect protection.[6] Parameter $\eta_1 > 1$ models the fact that dually infected individuals are more infectious than their corresponding counterparts.[18–20] Unscreened individuals are screened at a rate k and move to the class of screened susceptible individuals, $S_s(t)$.

Screened susceptible individuals, $S_s(t)$ are infected with HIV at a rate $(1-\psi)\lambda_h$, where $0 \le \psi \le 1$ measures the efficacy of screening in reducing disease transmission. If $\psi = 0$, then the screening has no effect on the behavior of individuals, on the

contrary, if $\psi = 1$ then screening is 100% effective in preventing HIV transmission. We consider that screened susceptible individuals can be infected. Routine testing serves only one individual knowing his or her HIV status and accessing care if he or she needs it. A proportion p of screened individuals enter the infected class of individuals who are aware of their condition, $I_a(t)$. A proportion $(1-p)$ of infected individuals that are not routinely screened go to the class $I_{\tilde{a}}(t)$ and are unaware of their infectious state. These unscreened individuals are screened after some time at a rate k and moved to class $I_a(t)$. Individuals at class $I_a(t)$ receive HAART treatment, nevertheless there are some that develop AIDS at a rate ρ_2. Individuals in class $I_{\tilde{a}}(t)$ may also develop AIDS at a rate ρ_1. We assume $\rho_1 \geq \rho_2$, since individuals at class $I_{\tilde{a}}(t)$ do not receive HAART treatment, due to their unawareness of the disease condition. The AIDS induced death rate is δ_2.

Considering now HCV infection, susceptible unscreened individuals, $S_{\tilde{s}}(t)$ are infected with HCV at a rate λ_c, and move to class $I_{\tilde{c}}$, where:

$$\lambda_{\tilde{c}} = c(1-\theta)b_c \frac{I_c(t) + I_{\tilde{c}}(t) + \eta_2(I_c I_{\tilde{a}}(t) + I_c I_a(t))}{N(t)}.$$

Parameter b_c is the probability that a contact will result in an HCV infection, $\eta_2 > 1$ models the fact that dually infected individuals are more infectious than their corresponding counterparts.[18–20] The HCV, unscreened for HIV, infected individuals, $I_{\tilde{c}}(t)$, recover spontaneously (or from treatment), at a rate υ, and return to class $S_{\tilde{s}}(t)$. They can also progress to a chronic stage, $C_{\tilde{s}}(t)$, at a rate σ_1. Or they can be screened at a rate k and move to class $I_c(t)$. These individuals are infected with HIV at a rate $\delta \lambda_h$, where δ accounts for the susceptibility to HIV infection for HCV infected people.[20,21]

The screened susceptible individuals, $S_s(t)$ are infected with HCV at a rate λ_c and moved to class $I_c(t)$. The screened HCV infected individuals are infected with HIV at a rate $(1-\psi)\lambda_h\delta$, recover at a rate υ and move back to class $S_s(t)$, or progress to a chronic phase at a rate σ_1 and move to class $C_s(t)$.

The chronic HCV infected individuals, unscreened for HIV, $C_{\tilde{s}(t)}$, are infected with HIV at a rate $\delta \lambda_h$ and move to the class $CI_{\tilde{a}}(t)$, and are screened at a rate k and move to class $C_s(t)$. The chronic HCV infected individuals, screened for HIV, $C_s(t)$, are infected with HIV at a rate $(1-\psi)\delta \lambda_h$.

The HIV unaware infected individuals, $I_{\tilde{a}}(t)$, are infected with HCV at a rate $\sigma \lambda_c$, and move to class $I_c I_{\tilde{a}}(t)$, where $\sigma > 1$ is the modification parameter modeling the increased risk of being infected with HCV when a person is already infected with HIV.[17,19,20] Reciprocally, the HCV infected individuals, screened for HIV, $I_c(t)$, are infected with HIV at a rate $(1-p)(1-\psi)\delta \lambda_h$ and also move to class $I_c I_{\tilde{a}}(t)$. Individuals in class $I_c I_{\tilde{a}}(t)$ spontaneously recover from HCV infection, at a rate υ_1, and move to class $I_{\tilde{a}}(t)$, or progress to AIDS at a rate ρ_2 and move to class $I_c A(t)$. They can also be screened for HIV and move to class $I_c I_a(t)$. Finally individuals in class $I_c I_{\tilde{a}}(t)$ can become chronic carriers at a rate σ_2 and move to class $CI_{\tilde{a}}(t)$.

The HIV aware infected individuals, $I_a(t)$, are infected with HCV at a rate $\sigma\lambda_c$, and move to class $I_c I_a(t)$. Reciprocally, the HCV infected individuals, $I_c(t)$, are infected with HIV at a rate $\delta(1-\psi)\lambda_h$. Individuals in class $I_c I_a(t)$ spontaneously recover from HCV infection at a rate υ_1 and move to the class $I_a(t)$. They progress to AIDS at a rate ρ_2, and move to class $I_c A(t)$. Or they may become HCV chronic carriers, at a rate σ_2, and move to class $CI_a(t)$.

The individuals with chronic HCV infection, and unscreened for HIV, $C_{\tilde{s}}(t)$, are infected with HIV at a rate $\delta\lambda_h$ and move to class $CI_{\tilde{a}}(t)$. Individuals in this class are screened at a rate k and move to class CI_a or progress to AIDS at a rate ρ_2. The HCV induced death is δ_1 in all HCV classes.

The HCV infected individuals at chronic phase, screened for HIV, $C_s(t)$, are infected with HIV at a rate $(1-\psi)\delta\lambda_h$. The chronic HCV carriers and HIV aware dually infected individuals, $CI_a(t)$ progress to AIDS at a rate ρ_2 and move to class $CA(t)$.

AIDS aware individuals, $A_s(t)$, are infected with HCV at a rate $\sigma\lambda_c$ and move to class $I_c A(t)$. The individuals in class $I_c A(t)$ are treated for HCV infection at a rate υ_2 and move to class A_s. The individuals in class $I_c A(t)$ become HCV chronic carriers at a rate σ_2 and move to class $CA(t)$.

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

The system of nonlinear ordinary differential equations for the proposed model is given by:

$$\frac{dS_{\tilde{s}}}{dt} = \Lambda_1 + \upsilon I_{\tilde{c}} - \lambda_h S_{\tilde{s}} - \lambda_c S_{\tilde{s}} - k S_{\tilde{s}} - \mu S_{\tilde{s}}$$

$$\frac{dS_s}{dt} = \Lambda_2 + k S_{\tilde{s}} - (1-\psi)\lambda_h S_s - \lambda_c S_s + \upsilon I_c - \mu S_s$$

$$\frac{dI_{\tilde{a}}}{dt} = (1-p)(1-\psi)\lambda_h S_s + \lambda_h S_{\tilde{s}} + \upsilon_1 I_c I_{\tilde{a}} - (k + \rho_1 + \sigma\lambda_c + \mu)I_{\tilde{a}}$$

$$\frac{dI_a}{dt} = p(1-\psi)\lambda_h S_s + k I_{\tilde{a}} + \upsilon_1 I_c I_a - (\sigma\lambda_c + \rho_2 + \mu)I_a$$

$$\frac{dA_{\tilde{a}}}{dt} = \rho_1 I_{\tilde{a}} - (\mu + \delta_2)A_{\tilde{a}}$$

$$\frac{dA_a}{dt} = \rho_2 I_a + \upsilon_2 I_c A - (\sigma\lambda_c + \mu + \delta_2)A_a$$

$$\frac{dI_{\tilde{c}}}{dt} = \lambda_c S_{\tilde{s}} - (k + \upsilon + \sigma_1 + \delta\lambda_h + \mu + \delta_1)I_{\tilde{c}}$$

$$\frac{dI_c}{dt} = \lambda_c S_s + k I_{\tilde{c}} - (\upsilon + \sigma_1 + (1-\psi)\delta\lambda_h + \mu + \delta_1)I_c$$

$$\frac{dC_{\tilde{s}}}{dt} = \sigma_1 I_{\tilde{c}} - (k + \delta\lambda_h + \mu + \delta_1)C_{\tilde{s}}$$

$$\frac{dC_s}{dt} = \sigma_1 I_c + k C_{\tilde{s}} - ((1-\psi)\delta\lambda_h + \mu + \delta_1)C_s$$

Table 1.   Definition of parameters and variable of model (2.1).

Variable/Parameter	Description
$S_s(t)$	susceptible screened individuals
$S_{\tilde{s}}(t)$	susceptible unscreened individuals
$I_a(t)$	HIV infected aware individuals
$I_{\tilde{a}}(t)$	HIV infected unaware individuals
$A_a(t)$	aware individuals showing symptoms of AIDS
$A_{\tilde{a}}(t)$	unaware individuals showing symptoms of AIDS
$I_c(t)$	screened for HIV, HCV infected individuals
$I_{\tilde{c}}(t)$	unscreened for HIV, HCV infected individuals
$C_s(t)$	screened for HIV, chronic HCV infected individuals
$C_{\tilde{s}}(t)$	unscreened for HIV, chronic HCV infected individuals
$I_c I_a(t)$	HCV and HIV aware coinfected individuals
$I_c I_{\tilde{a}}(t)$	HCV and HIV unaware coinfected individuals
$CI_a(t)$	HIV aware and chronic HCV dually infected individuals
$CI_{\tilde{a}}(t)$	HIV unaware and chronic HCV coinfected individuals
$I_c A(t)$	HCV and AIDS coinfected individuals
$CA(t)$	chronic HCV and AIDS coinfected individuals
Λ_1	recruitment rate of unscreened individuals
Λ_2	recruitment rate of screened individuals
μ	natural mortality rate
b_h	probability that a contact will result in an HIV infection
b_c	probability that a contact will result in an HCV infection
c	mean number sexual partners a susceptible individual acquires
θ	level of protection by condoms
p	proportion of screened individuals aware of their HIV status
ψ	efficacy of screening in reducing HIV transmission
$\upsilon, \upsilon_i,\ i = 1, 2$	recovery rate of treated for HCV
$\sigma_i,\ i = 1, 2$	rate of progression to chronic phase of HCV
δ_1	mortality due to HCV
$\rho_i,\ i = 1, 2$	rate of progression to AIDS
k	awareness of unscreened HIV infected individuals after being screened
δ_2	mortality due to HIV
$\eta_i,\ i =, 1, 2$	modification parameter
σ	modification parameter
δ	modification parameter

$$\frac{dI_c I_{\tilde{a}}}{dt} = (1-p)(1-\psi)\delta\lambda_h I_c + \delta\lambda_h I_{\tilde{c}} + \sigma\lambda_c I_{\tilde{a}} - (k + \sigma_2 + \rho_2 + \upsilon_1 + \mu + \delta_1)I_c I_{\tilde{a}}$$

$$\frac{dI_c I_a}{dt} = p(1-\psi)\delta\lambda_h I_c + \sigma\lambda_c I_a + kI_c I_{\tilde{a}} - (\upsilon_1 + \rho_2 + \sigma_2 + \mu + \delta_1)I_c I_a$$

$$\frac{dCI_{\tilde{a}}}{dt} = (1-p)(1-\psi)\lambda_h \delta C_s + \delta\lambda_h C_{\tilde{s}} + \sigma_2 I_c I_{\tilde{a}} - (k + \rho_2 + \mu + \delta_1)CI_{\tilde{a}}$$

$$\frac{dCI_a}{dt} = p(1-\psi)\delta\lambda_h C_s + \sigma_2 I_c I_a + kCI_{\tilde{a}} - (\rho_2 + \mu + \delta_1)CI_a$$

$$\frac{dI_c A}{dt} = \sigma\lambda_c A_a + \rho_2 I_c I_{\tilde{a}} + \rho_2 I_c I_a - (\upsilon_2 + \sigma_2 + \mu + \delta_1 + \delta_2)I_c A$$

$$\frac{dCA}{dt} = \rho_2 CI_{\tilde{a}} + \rho_2 CI_a + \sigma_2 I_c A - (\mu + \delta_1 + \delta_2)CA$$

$$(2.1)$$

with non-negative initial conditions given by:

$$S_s(0) = S_{s0}, \quad S_{\tilde{s}} = S_{\tilde{s}0}, \quad I_{\tilde{a}}(0) = I_{\tilde{a}0}, \quad I_a = I_{a0}, \quad A_a(0) = A_{a0},$$

$$A_{\tilde{a}} = A_{\tilde{a}0}, \quad I_c(0) = I_{c0}, \quad I_{\tilde{c}} = I_{\tilde{c}0}, \quad C_s(0) = C_{s0},$$

$$C_{\tilde{s}} = C_{\tilde{s}0} I_c I_{\tilde{a}} = I_c I_{\tilde{a}0}, \quad I_c I_a(0) = I_c I_{a0}, \quad CI_{\tilde{a}}(0) = CI_{\tilde{a}0},$$ (2.2)

$$CI_a(0) = CI_{a0}, \quad I_c A(0) = I_c A_0, \quad CA(0) = CA_0$$

Model (2.1) will be analyzed in the domain $\Omega \subset \mathbb{R}^{16}_{+0}$, given by:

$$\Omega = \left\{ (S_s, S_{\tilde{s}}, I_a, I_{\tilde{a}}, A_a, A_{\tilde{a}}, I_c, I_{\tilde{c}}, C_s, C_{\tilde{s}}m, I_c I_a, CI_a, I_c I_{\tilde{a}}, CI_a, \right.$$

$$\left. CI_{\tilde{a}}, I_c A, CA) \in \mathbb{R}^{16}_+ : 0 \le N \le \frac{\Lambda_1 + \Lambda_2}{\mu} \right\}$$

Theorem 2.1. *The solutions of system* (2.1) *with initial conditions* (2.2) *satisfy* $S_{\tilde{s}}(t) \ge 0$, $S_s(t) \ge 0$, $I_{\tilde{a}}(t) \ge 0$, $I_a(t) \ge 0$, $A_{\tilde{a}}(t) \ge 0$, $A_a(t) \ge 0$, $I_{\tilde{c}}(t) \ge 0$, $I_c(t) \ge 0$, $C_{\tilde{s}}(t) \ge 0$, $C_s(t) \ge 0$, $I_c I_{\tilde{a}}(t) \ge 0$, $I_c I_a(t) \ge 0$, $CI_{\tilde{a}}(t) \ge 0$, $CI_a(t) \ge 0$, $I_c A(t) \ge 0$, $CA(t) \ge 0$ *for all* $t > 0$. *The region* $\Omega \in \mathbb{R}^{16}_{+0}$ *is positively invariant and attracting with respect to system* (2.1).

Proof. From the first equation of model (2.1) we have:

$$\dot{S}_{\tilde{s}} \ge -[\lambda_h + \lambda_c + k + \mu]S$$

thus:

$$S_{\tilde{s}}(t) \ge S_{\tilde{s}}(0) e^{[-\int_0^t [\lambda_h(s) + \lambda_c(s) + k + \mu] ds]} > 0.$$

Similarly for the second equation of system (2.1):

$$S_s \ge S_s(0) e^{[-\int_0^t ((1-\psi) + \lambda_c + \mu)]} > 0$$

In an analogous fashion, we can easily show that $I_a(t)$, $I_{\tilde{a}}$, $A_a(t)$, $A_{\tilde{a}}$, $I_c(t)$, $I_{\tilde{c}}$, $C_s(t)$, $C_{\tilde{s}}$, $I_c I_{\tilde{a}}(t)$, $I_c I_a(t)$, $CI_{\tilde{a}}(t)$, $CI_a(t)$, $I_c A(t)$ and $CA(t)$ are all positive for all $t > 0$. We now show that all feasible solutions are uniformly bounded in Ω. Adding all equations of system (2.1), we obtain:

$$\dot{N} = \Lambda_1 + \Lambda_2 - \mu N - \delta_2 (A_a + A_{\tilde{a}} + I_c A + CA)$$

$$- \delta_1 (I_c + I_{\tilde{c}} + C_s + C_{\tilde{s}} + I_c I_{\tilde{a}} + I_c I_a + CI_{\tilde{a}} + CI_a).$$

$$\dot{N} \le \Lambda_1 + \Lambda_2 - \mu N$$

Solving this differential equation, we note that:

$$0 \le N \le \frac{\Lambda}{\mu} + N(0) e^{-\mu t},$$

where $\Lambda = \Lambda_1 + \Lambda_2$, $N(0)$ represents the initial value of the model's variables. Then $0 \le N \le \frac{\Lambda}{\mu}$, as $t \to \infty$. Therefore, $\frac{\Lambda}{\mu}$ is an upper bound of N provided that

$N(0) \leq \frac{\Lambda}{\mu}$. If $N(0) > \frac{\Lambda}{\mu}$, then $N(t)$ will decrease to this level. Thus, all feasible solutions of the system enter or remain in the region Ω. Hence, the region of biological interest Ω is positively invariant under the flow induced by system (2.1). $\qquad \square$

2.2. *Reproduction numbers and stability of disease-free equilibria*

In this subsection, we compute the reproduction number, R_0, of model (2.1). The basic reproduction number is defined as the number of secondary infections due to a single infection in a completely susceptible population.

We begin by considering the following two sub-models of model (2.1). Model (2.3) is derived from model (2.1) by setting the variables concerning HIV dynamics ($I_{\tilde{a}}$, I_a, $A_{\tilde{s}}$, A_s, $I_c I_{\tilde{a}}$, $I_c I_a$, $CI_{\tilde{a}}$, CI_a, $I_c A$ and CA) to zero, and model (2.5) follows from model (2.1) by setting the variables concerning HCV dynamics ($I_{\tilde{c}}$, I_c, $C_{\tilde{s}}$, C_s, $I_c I_{\tilde{a}}$, $I_c I_a$, $CI_{\tilde{a}}$, CI_a, $I_c A$ and CA) to zero.

We now compute the reproduction number, R_{HCV}, of system (2.3). We use the next generation method.[22]

$$\frac{dS_{\tilde{s}}}{dt} = \Lambda_1 + \upsilon I_{\tilde{c}} - \lambda_c S_{\tilde{s}} - kS_{\tilde{s}} - \mu S_{\tilde{s}}, \quad \frac{dS}{dt} = \Lambda_2 + kS_{\tilde{s}} - \lambda_c S_s + \upsilon I_c - \mu S_s,$$

$$\frac{dI_{\tilde{c}}}{dt} = \lambda_c S_{\tilde{s}} - (k + \upsilon + \sigma_1 + \mu + \delta_1)I_{\tilde{c}}, \quad \frac{dI_c}{dt} = \lambda_c S_s - (\upsilon + \sigma_1 + \mu + \delta_1)I_c,$$

$$\frac{dC_{\tilde{s}}}{dt} = \sigma_1 I_{\tilde{c}} - (k + \mu + \delta_1)C_{\tilde{s}}, \quad \frac{dC_s}{dt} = \sigma_1 I_c + kC_{\tilde{s}} - (\mu + \delta_1)C_s,$$

$$(2.3)$$

where $\lambda_c = c(1-\theta)b_c \frac{I_c + I_{\tilde{c}}}{N}$.

The disease-free equilibrium of model (2.3) is given by:

$$P_0^1 = \left(\frac{\Lambda_1}{k+\mu}, \frac{\Lambda_2}{\mu} + \frac{k\Lambda_1}{\mu(k+\mu)}, 0, 0, 0, 0 \right).$$

Using the notation of Ref. 22, matrices for the new infection terms, F, and the other terms, V, are given by:

$$F = \begin{bmatrix} c(1-\theta)b_c \frac{\Lambda_1 \mu}{\Lambda_1(\mu+1)+\Lambda_2(k+\mu)} & c(1-\theta)b_c \frac{\Lambda_1 \mu}{\Lambda_1(\mu+1)+\Lambda_2(k+\mu)} & 0 & 0 \\ c(1-\theta)b_c \frac{\Lambda_1 \mu + \Lambda_2(k+\mu)}{\Lambda_1(\mu+1)+\Lambda_2(k+\mu)} & c(1-\theta)b_c \frac{\Lambda_1 \mu + \Lambda_2(k+\mu)}{\Lambda_1(\mu+1)+\Lambda_2(k+\mu)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} k+\upsilon+\sigma_1+\mu+\delta_1 & 0 & 0 & 0 \\ -k & \upsilon+\sigma_1+\mu+\delta_1 & 0 & 0 \\ -\sigma_1 & 0 & k+\mu+\delta_1 & 0 \\ 0 & -\sigma_1 & -k & \mu+\delta_1 \end{bmatrix}.$$

The associative basic reproduction number is thus:

$$R_{\text{HCV}} = \rho(FV^{-1}) = \frac{c(1-\theta)b_c}{\upsilon + \sigma_1 + \mu + \delta_1}, \tag{2.4}$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2,[22] we obtain the following lemma.

Lemma 2.1. *The disease-free equilibrium P_0^1 is locally asymptotically stable if $R_{\text{HCV}} < 1$ and unstable if $R_{\text{HCV}} > 1$.*

We proceed with the computation of the reproduction number, R_{HIV}, of model (2.5).

$$\frac{dS_{\tilde{s}}}{dt} = \Lambda_1 - \lambda_h S_{\tilde{s}} - k S_{\tilde{s}} - \mu S_{\tilde{s}}, \quad \frac{dS_s}{dt} = \Lambda_2 + k S_{\tilde{s}} - (1-\psi)\lambda_h S_s - \mu S_s,$$

$$\frac{dI_{\tilde{a}}}{dt} = (1-p)(1-\psi)\lambda_h S_s + \lambda_h S_{\tilde{s}} - (k + \rho_1 + \mu)I_{\tilde{a}},$$

$$\frac{dI_a}{dt} = p(1-\psi)\lambda_h S_s + k I_{\tilde{a}} - (\rho_2 + \mu)I_k,$$

$$\frac{dA_{\tilde{s}}}{dt} = \rho_1 I_{\tilde{a}} - (\mu + \delta_2)A_{\tilde{a}}, \quad \frac{dA}{dt} = \rho_2 I_a - (\mu + \delta_2)A, \tag{2.5}$$

where $\lambda_h = c(1-\theta)b_h \frac{I_{\tilde{a}} + I_a}{N}$.

The disease-free equilibrium state P_0^2 of model (2.5) is given by:

$$P_0^2 = \left(\frac{\Lambda_1}{k+\mu}, \frac{\Lambda_2}{\mu} + \frac{k\Lambda_1}{\mu(k+\mu)}, 0, 0, 0, 0 \right)$$

Using the notation of Ref. 22, matrices for the new infection terms, F, and the other terms, V, are the following:

$$F = \begin{bmatrix} \frac{c(1-\theta)b_h}{(\Lambda_1+\Lambda_2)(\mu+k)}[(1-p)(1-\psi)(k\Lambda_1 + \Lambda_2(k+\mu)) + \Lambda_1\mu] \\ p(1-\psi)c(1-\theta)b_h \frac{k\Lambda_1 + \Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} \\ 0 \\ 0 \end{bmatrix}$$

$$\begin{matrix} \frac{c(1-\theta)b_h}{(\Lambda_1+\Lambda_2)(\mu+k)}[(1-p)(1-\psi)(k\Lambda_1 + \Lambda_2(k+\mu)) + \Lambda_1\mu] & 0 & 0 \\ p(1-\psi)c(1-\theta)b_h \frac{k\Lambda_1 + \Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{matrix} \Bigg],$$

$$V = \begin{bmatrix} k + \rho_1 + \mu & 0 & 0 & 0 \\ -k & \rho_2 + \mu & 0 & 0 \\ -\rho_1 & 0 & \mu + \delta_2 & 0 \\ 0 & -\rho_2 & 0 & \mu + \delta_2 \end{bmatrix}.$$

The associative basic reproduction number is given by:

$$R_{\mathrm{HIV}} = \rho(FV^{-1})$$

$$= \frac{c(1-\theta)b_h}{(k+\mu+\rho_1)(\rho_2+\mu)(\Lambda_1+\Lambda_2)(\mu+k)}[(1-\psi)(k\Lambda_1+\Lambda_2(k+\mu))$$

$$\times (k+\mu+\rho_2+p(\rho_1-\rho_2))+\Lambda_1\mu(k+\mu+\rho_2)], \qquad (2.6)$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2,[22] we obtain the following lemma.

Lemma 2.2. *The disease-free equilibrium P_0^2 is locally asymptotically stable if $R_{\mathrm{HIV}} < 1$ and unstable if $R_{\mathrm{HIV}} > 1$.*

We now proceed with the calculation of the reproduction number, R_0, of the full model (2.1). The disease-free equilibrium state P_0 of model (2.1) is given by:

$$P_0 = \left(\frac{\Lambda_1}{k+\mu}, \frac{\Lambda_2}{\mu} + \frac{k\Lambda_1}{\mu(k+\mu)}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 \right).$$

Using the notation in Ref. 22 on system (2.1), we compute the matrices for the new infection terms, F, and the other terms, V, and the marix FV^{-1}. Then, the reproduction number is the spectral radius of FV^{-1}. After some algebra manipulation R_0 is given by (please check the Appendix for a detailed proof):

$$R_0 = \rho(FV^{-1}) = \max\{R_{\mathrm{HIV}}, R_{\mathrm{HCV}}\} \qquad (2.7)$$

By Theorem 2,[22] we obtain the following lemma.

Lemma 2.3. *The disease-free equilibrium P_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

3. Bifurcation Analysis

In this section, we use XPPAUT[23] to build bifurcation diagrams for distinct parameters of model (2.1).

Figure 2 shows the sketch of the bifurcation diagram for different values of β_c, the probability that a contact will result in an HCV infection. We start from a disease-free equilibrium and increase β_c. At $\beta_c = 0.2031$, there is a bifurcation point (1), at which the model bifurcates to the stable HCV endemic equilibrium. This means that increasing the probability that a contact will result in an HCV infection originates new cases of HCV infections. This is a realistic prediction.

Figure 3 depicts the bifurcation diagram for different values of β_h, the probability that a contact will result in an HIV infection. We start from a disease-free equilibrium and increase β_h. At $\beta_h = 0.034$, there is a bifurcation point (1), at which the model bifurcates to the stable HIV endemic equilibrium. This means that increasing the probability that a contact will result in an HIV infection promotes the appearance of new cases of HIV infections, as biologically expected.
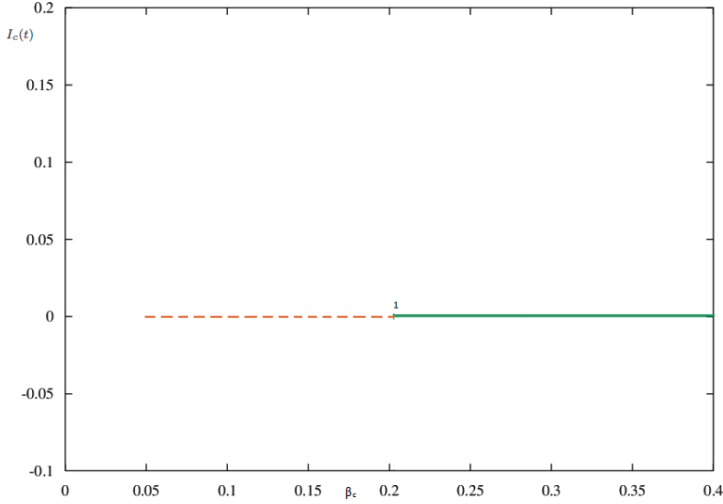
Fig. 2. Sketch of the bifurcation diagram for different values of β_c, the probability that a contact will result in HCV transmission. Remaining parameter values are given in Table 3, except for $\beta_h = 0.032$. At the bifurcation point (1) $\beta_c \simeq 0.2031$. Orange dashed line — stable disease-free equilibrium, green filled line — stable HCV endemic equilibrium. For more information, see text.

Fig. 3. Drawing of the bifurcation diagram for different values of β_h, the probability that a contact will result in HIV transmission. Remaining parameter values are given in Table 3. At the bifurcation point (1) $\beta_h \simeq 0.034$. Orange dashed line — stable disease-free equilibrium, red filled line — stable HIV endemic equilibrium. For more information, see text.

Figure 4 depicts the bifurcation diagram for different values of β_c, the probability that a contact will result in an HCV infection. We start from an HIV endemic equilibrium and increase β_c. At $\beta_c = 0.2503$, there is a bifurcation point (1), at which the model bifurcates to the stable two endemic equilibrium. This means
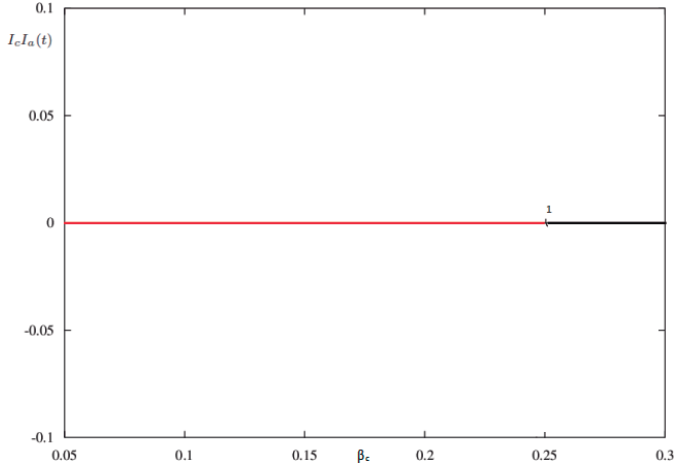
Fig. 4. Sketch of the bifurcation diagram for different values of β_c, the probability that a contact will result in an HCV infection. Remaining parameter values are given in Table 3. At the bifurcation point (1) $\beta_c = 0.2503$. Red filled line — stable HIV endemic equilibrium, black filled line — stable two-endemic equilibrium. For more information, see text.
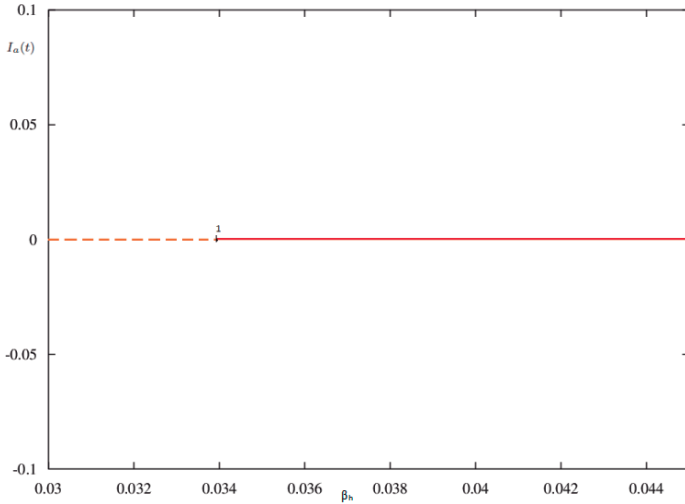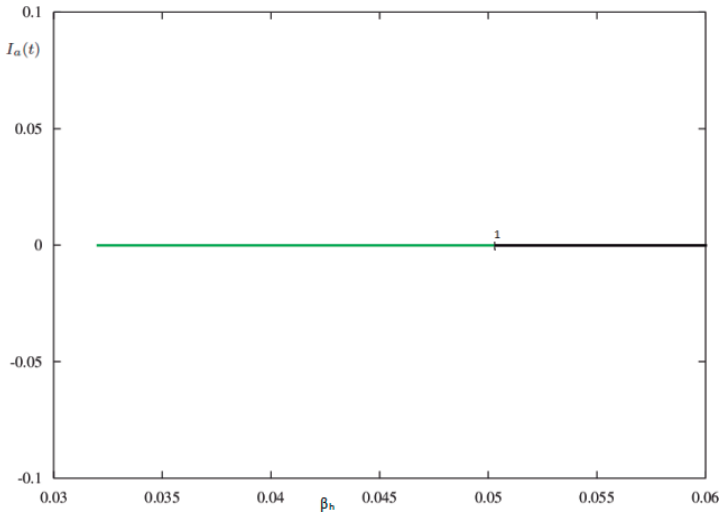

Fig. 5. Sketch of the bifurcation diagram for different values of β_h, the probability that a contact will result in an HIV infection. Remaining parameter values are given in Table 3. At the bifurcation point (1) $\beta_h = 0.0503$. Green filled line — stable HCV endemic equilibrium, black filled line — stable two-endemic equilibrium. For more information, see text.

that in a population already infected with HIV, with lowered defense mechanisms, increasing the probability of a contact resulting in HCV infection will set off new coinfection cases.

Figure 5 depicts the bifurcation diagram for different values of β_h, the probability that a contact will result in an HIV infection. We start from a HCV endemic

equilibrium and increase β_h. At $\beta_h = 0.0503$, there is a bifurcation point (1), at which the model bifurcates to the stable two-endemic equilibrium. This means that in a population with impaired immune system due to infection with HCV, increasing the probability of a contact resulting in HIV infection will trigger new coinfection cases.

4. Sensitivity Analysis

In this section, we perform the sensitivity indexes of the reproduction number, R_0, to relevant parameters of model (2.1). We follow the procedure developed in Ref. 24. The sensitivity analysis is used to measure the relative change in a state variable when a given parameter is varied. Measuring the R_0 sensitivity indices is extremely important since the value of R_0 determines the spread or the eradication of the disease.

The sensitivity index of $R_0 = \max\{R_{\text{HIV}}, R_{\text{HCV}}\}$ with respect to parameter $\beta_c = c(1 - \theta)b_c$ is given by:

$$\frac{\partial R_0}{\partial \beta_c} \times \frac{\beta_c}{R_0} = 1.$$

The sensitivity index of R_0 with respect to parameter $\beta_h = c(1-\theta)b_h$ is given by:

$$\frac{\partial R_0}{\partial \beta_h} \times \frac{\beta_h}{R_0} = 1.$$

These values for this sensitivity index mean that the probability of HCV or HIV transmission has strong influence in HCV and HIV control and management. Similar expressions may be obtained for the other parameters of R_0. Nevertheless, most of the expressions for the sensitivity indices are complex with little obvious structure. Therefore, we compute the corresponding values for the parameter values given in Table 3. The signs of the sensitivity indices may be found in Table 2. A positive sign implies that increases in the corresponding parameter values translate in an increase in the value of R_0. Inversely for a negative sign, a negative index

Table 2. Parameters used in the numerical simulations of model (2.1).

Parameter	Sensitivity index sign
β_c	+
β_h	+
θ	−
ν	−
σ_1	−
σ_2	−
p	+
k	+
ρ_2	−
ρ_1	−

Table 3. Parameters used in the numerical simulations of model (2.1), where the appropriate units are yr^{-1}.

Parameter	Value	Reference
Λ_1	8	Assume
Λ_2	4	Assume
c	8	Assume
θ	0.20	[25]
b_h	0.036	[26]
b_c	0.05	[17]
η_1	1.0002	[20]
η_2	1.0002	[20]
υ	0.25	[17]
υ_1	0.27	Assume
υ_2	0.25	Assume
μ	0.020	[20]
p	0.0367	[27]
ψ	0.0288	[27]
k	0.00388	[27]
ρ_1	0.1908	[27]
ρ_2	0.1511	[27]
δ_1	0.2801	Assume
δ_2	0.2801	[27]
δ	1.0001	[20]
σ	1.001	[20]
σ_1	0.75	[28]
σ_2	0.75	[28]

means than an increase in the parameter value implies a decrease in the value of R_0. For example, an increase of 5% in the values of β_h or β_c augments 5% the value of R_0. Similar inferences may be performed for the other indices.

5. Numerical Results

In this section, we present the numerical simulations of model (2.1). The parameter values used in the simulations can be found in Table 3 and the following initial conditions: $S_{\tilde{s}}(0) = 500$, $S_s(t) = 0$ (we assume that no individuals were screened initially), $I_{\tilde{a}}(0) = 80$, $I_a(0) = 0$, $A_a(t) = 0$, $A_{\tilde{a}} = 15$, $I_c(t) = 0$, $I_{\tilde{c}} = 20$, $C_s(0) = 0$, $C_{\tilde{s}} = 5$, $I_c I_a(0) = I_c I_{\tilde{a}} = C I_a = C I_{\tilde{a}} = I_c A = C A = 0$ are used.

In Fig. 6, we observe that the model approaches asymptotically the stable HIV endemic equilibrium.

Figure 7 shows the stable HCV endemic equilibrium for system (2.1).

In Fig. 8, we plot the dynamics of the variables of system (2.1). We observe that, for the given parameters values and initial conditions, the model approaches asymptotically the stable two-disease endemic equilibrium.

In Fig. 9, we plot the dynamics of the relevant variables of system (2.1) for different values of θ, the level of protection against HIV and HCV by the use of condoms. We observe that as θ decreases, the system (2.1) bifurcates from the stable
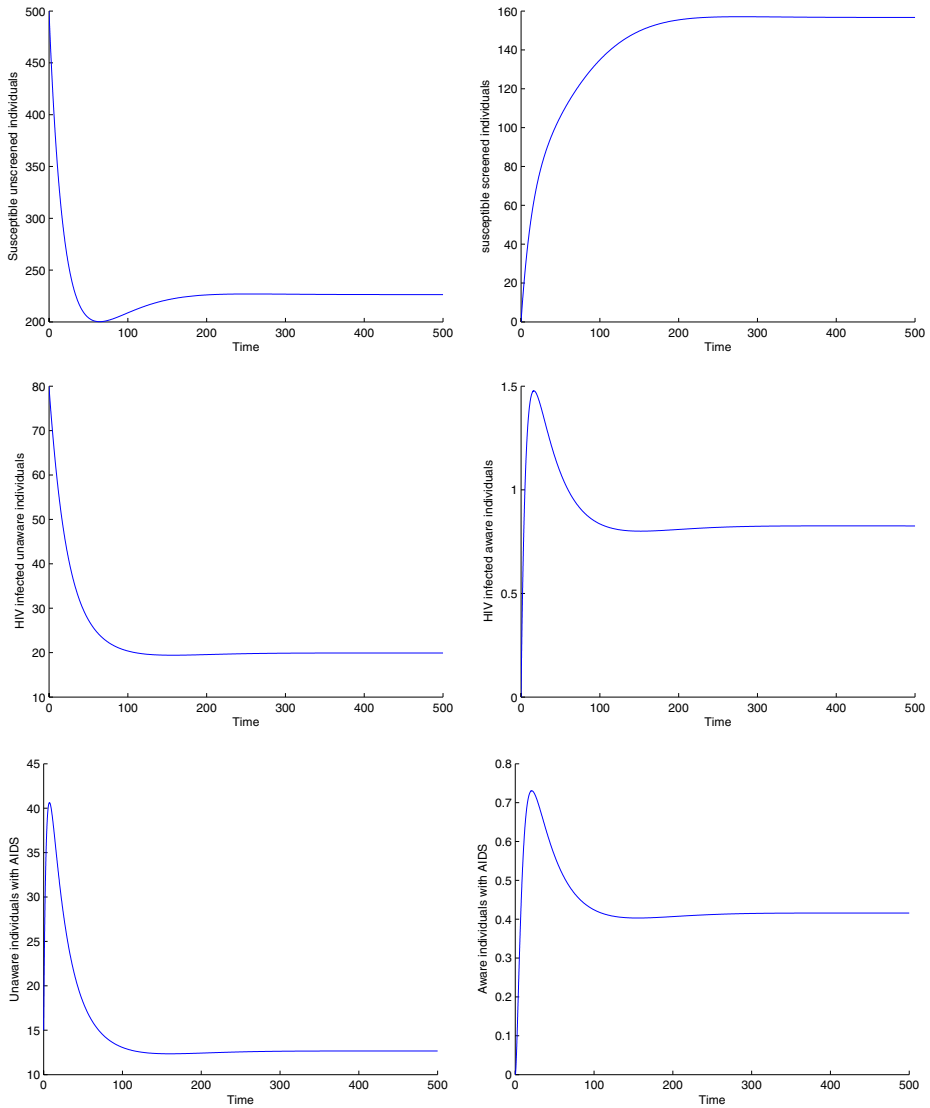
Fig. 6. Stable HIV endemic equilibrium of system (2.1) for given parameter values in Table 3, and given initial conditions ($R_{\mathrm{HIV}} = 1.0875$, $R_{\mathrm{HCV}} = 0.2461$, $R_0 = 1.0875$). The remaining variables go asymptotically to 0. For more information, see text.

disease-free equilibrium to the stable HIV endemic equilibrium. This suggests that individuals should, as expected, use condom, to prevent being infected with HIV.

In Fig. 10, we show the dynamics of the relevant variables of system (2.1) for different values of β_h, the probability that a contact will result in an HIV infection. We observe that increasing the system (2.1) has a bifurcation point as β_h increases from 0.030 till 0.1. The system bifurcates from a stable disease-free equilibrium to
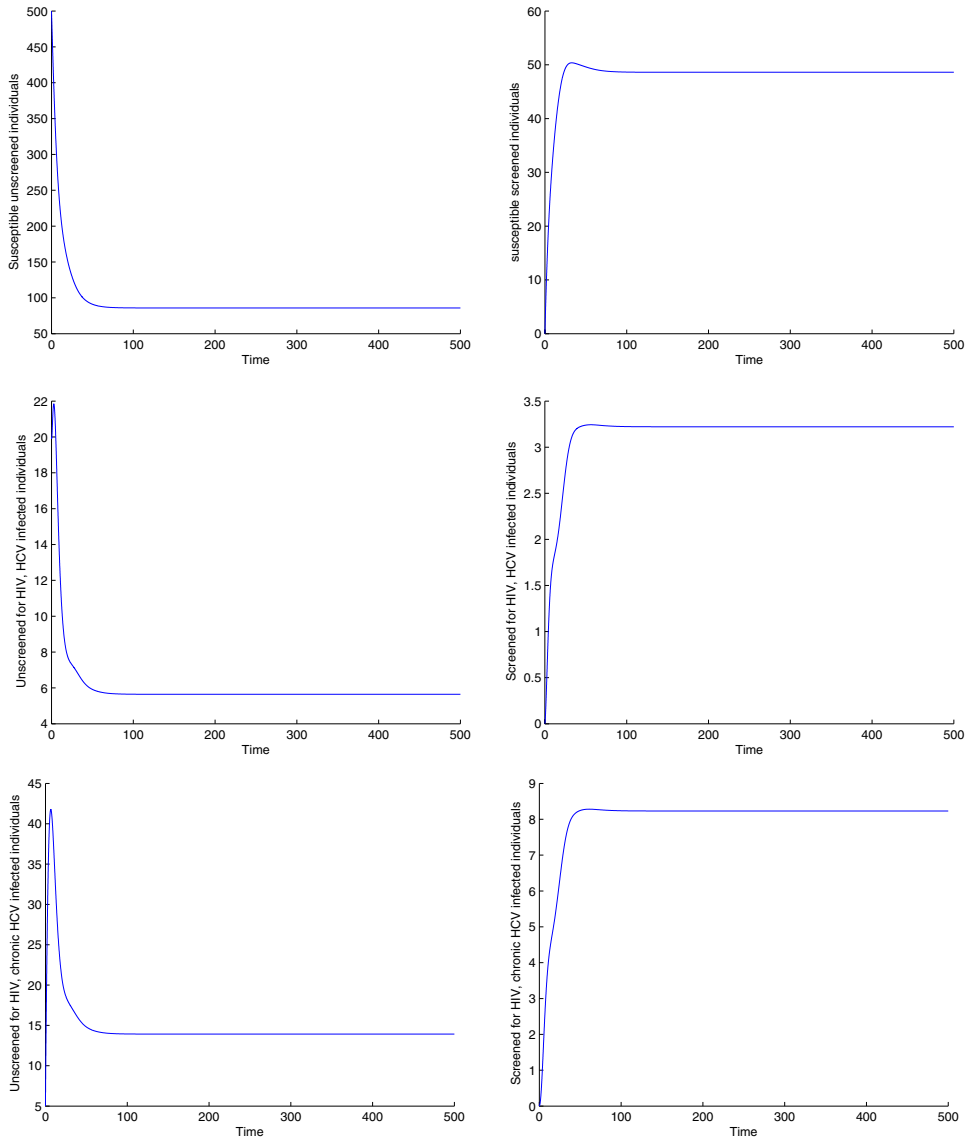
Fig. 7. Stable HCV endemic equilibrium of system (2.1) for parameter values given in Table 3, except $\beta_c = 0.25$ and $\beta_h = 0.032$, and given initial conditions ($R_{\text{HIV}} = 0.9667$, $R_{\text{HCV}} = 1.2307$, $R_0 = 1.2307$). The remaining variables go asymptotically to 0. For more information, see text.

a stable HIV endemic equilibrium. This was a predictable outcome and suggests the measures that reduce this probability β_h should be taken under consideration in order to reduce HIV transmission.

In Fig. 11, we plot the dynamics of the relevant variables of system (2.1) for different values of β_c, the probability that a contact will result in an HCV infection.

Fig. 8. Stable two-disease endemic equilibrium of system (2.1) for given parameter values in Table 3, except for $b_h = 0.054$, $b_c = 0.25$, and given initial conditions ($R_{\text{HIV}} = 1.6313$, $R_{\text{HCV}} = 1.2307$, $R_0 = 1.6313$) (relevant variables). For more information, see text.
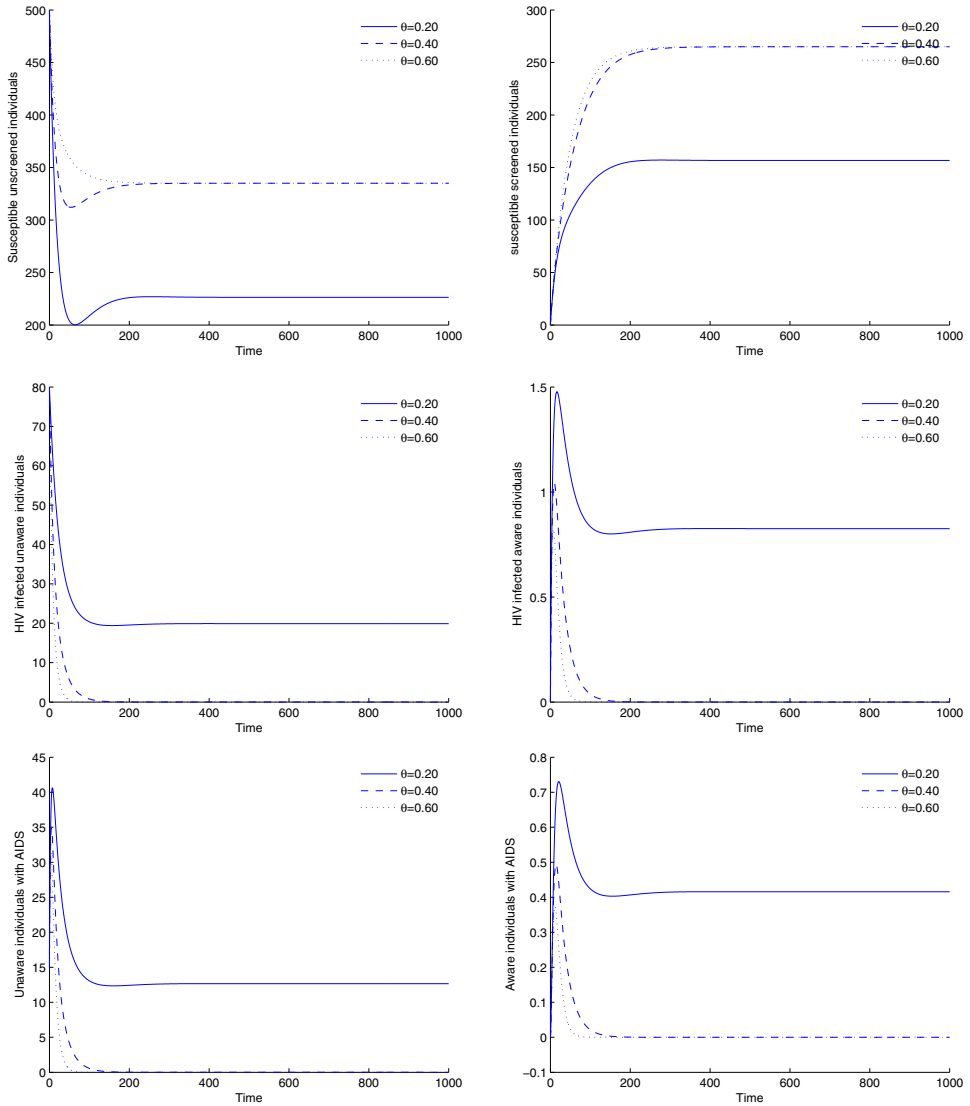
Fig. 9. Dynamics of the relevant variables of the system (2.1) for different values of θ, the level of protection against HIV and HCV by condom use. Parameter values are given in Table 3 and initial conditions are in the text. The remaining variables go asymptotically to zero. For more information, see text.

We observe that as β_c increases from 0.05 to 0.25 there is a bifurcation from a state without disease to a state with HCV infection that persists with the continuous increase of β_c. The number of chronic carriers also increases. Biologically this is a reasonable outcome, one would expect an augment in the number of new disease cases as the probability of transmission increases.
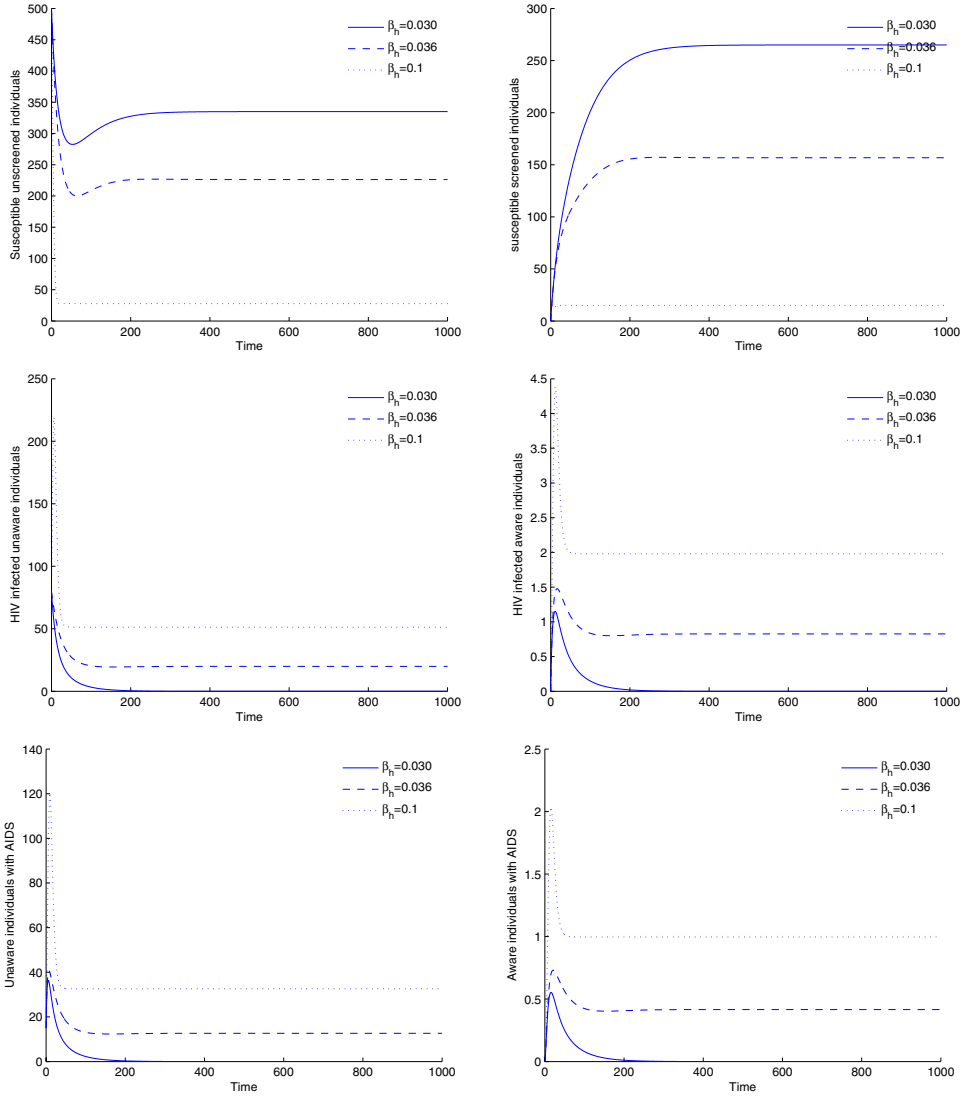
Fig. 10. Dynamics of the relevant variables of the system (2.1) for different values β_h, the probability that a contact will result in an HIV infection. Parameter values are given in Table 3 and initial conditions are in the text. The remaining variables go asymptotically to zero. For more information see text.

In Fig. 12, we plot the dynamics of the relevant variables of system (2.1) for different values of ψ, the parameter that measures the efficacy of screening in reducing HIV transmission. We observe that as ψ increases, the number of individuals infected with HIV and suffering from AIDS decreases, in fact, the system (2.1) is initially at a stable HIV endemic equilibrium and changes its qualitative behavior

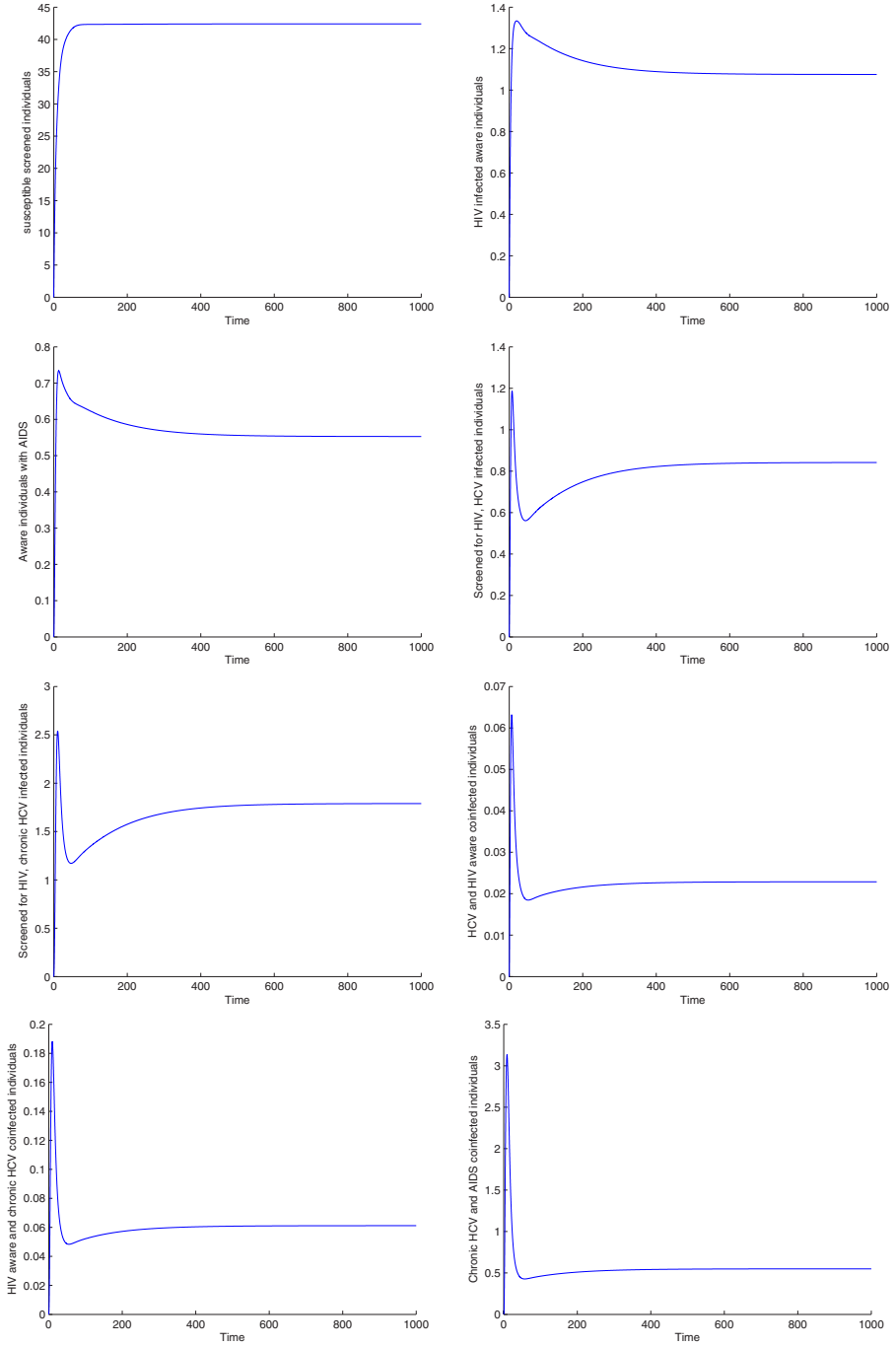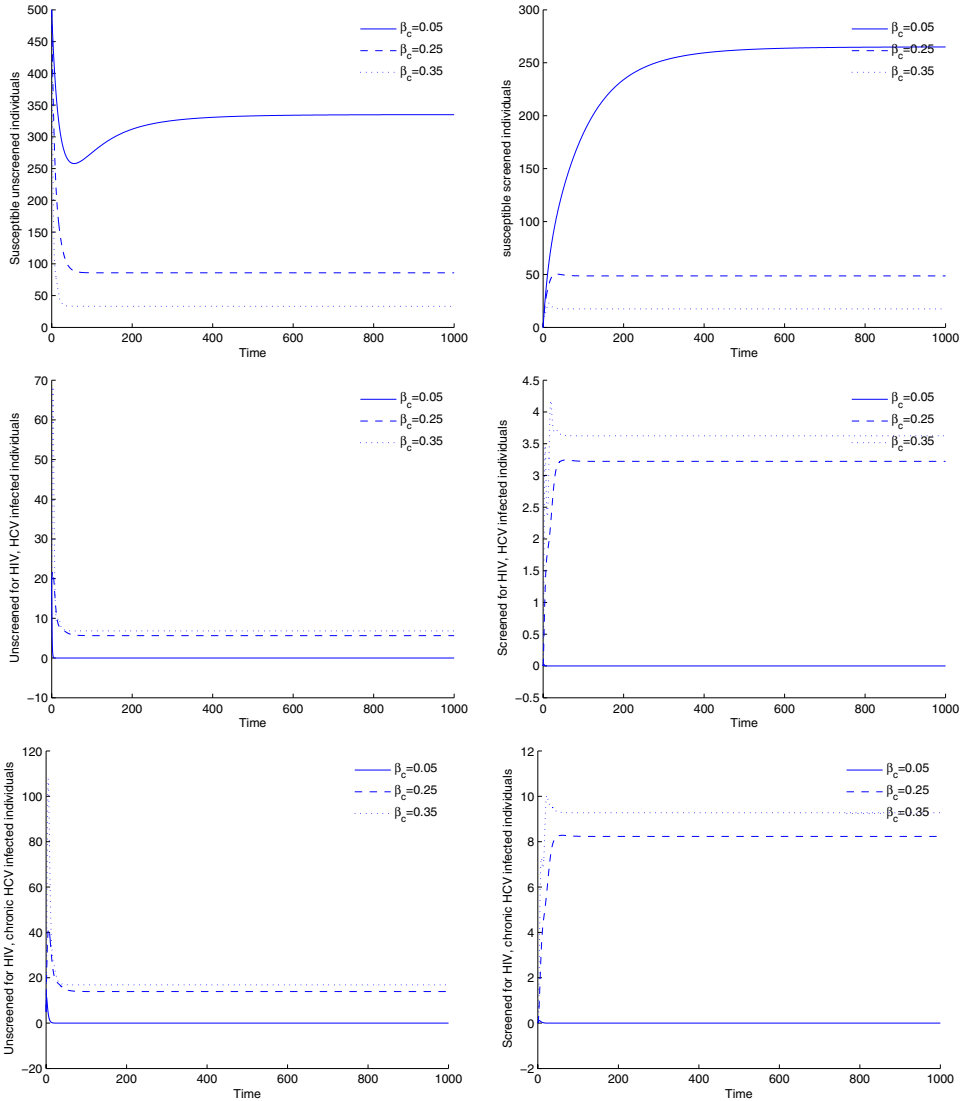Fig. 11. Dynamics of the relevant variables of the system (2.1) for different values of β_c, the probability that a contact will result in an HCV infection. Parameter values are given in Table 3, except $b_h = 0.032$ and initial conditions are in the text. For more information, see text.

to a stable disease-free equilibrium. In real life, this means that individuals that are screened should change their behavior in order to prevent transmission of the disease. In fact, there are some studies that show that screened HIV infectives tend to change their behavior and those whose test is negative do not.[29] Nevertheless, the tests are meant to promote behavior change and to access to health care for all screened individuals.
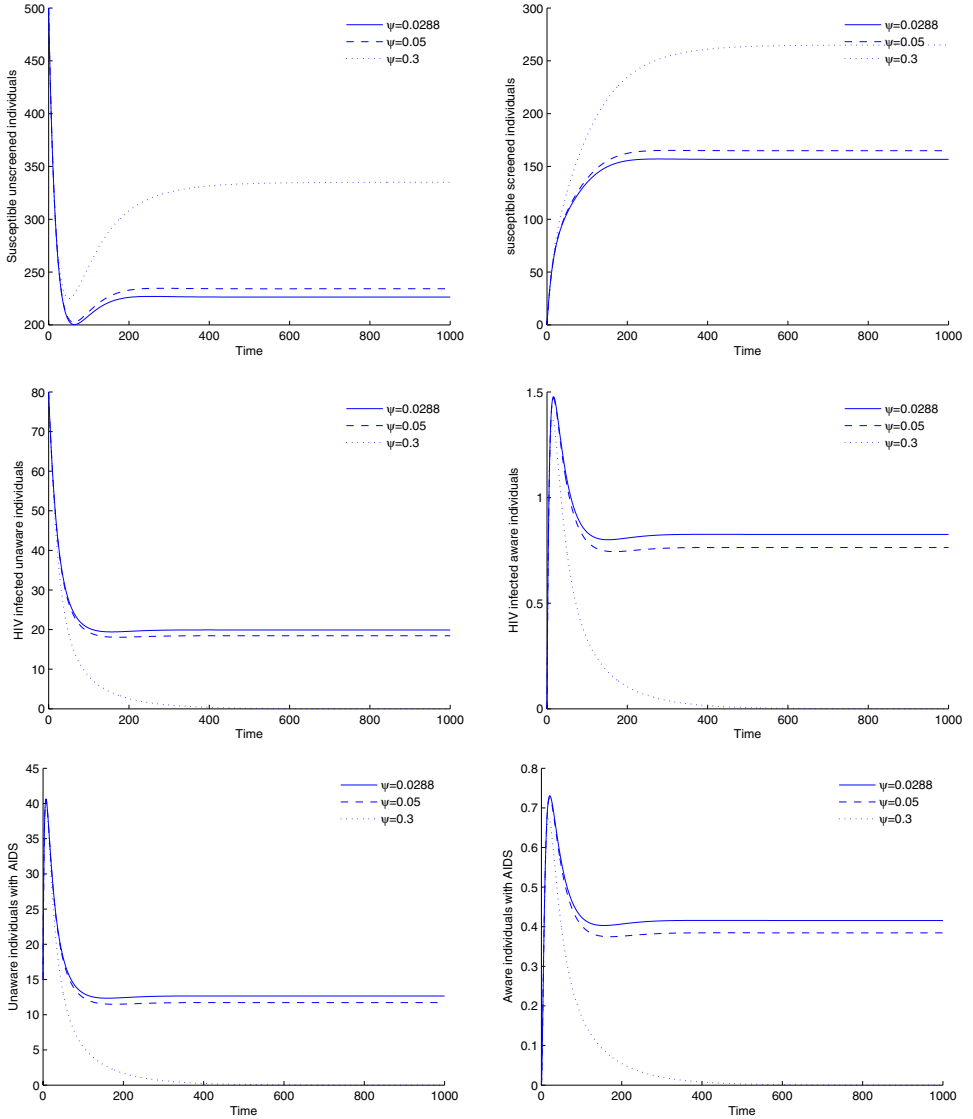
Fig. 12. Dynamics of the relevant variables of the system (2.1) for different values of ψ, the parameter that measures the efficacy of screening in reducing HIV transmission. Parameter values are given in Table 3 and initial conditions are in the text. Remaining variables go asymptotically to zero. For more information, see text.

6. Conclusions

We proposed a coinfection model for HCV and HIV infections, that includes treatment for both diseases, unawareness and awareness if HIV infection, and the use of condom. We studied the local stability of the disease-free equilibria for the full

model and for the two submodels (HCV only and HIV only submodels). Bifurcation diagrams were sketched for relevant parameters, such as the probabilities that a contact will result in a HIV or an HCV infection. Numerical examples are used to illustrate the change of the dynamical behavior of certain relevant parameters. The results obtained suggest that specific measures should be considered in order to reduce HIV infection, such as: distributing more condoms to individuals and try to forward the message that condoms should be used during anal intercourse (though this might not be well accepted in MSM population due to unprotected sex negotiation); develop campaign in order to warn individuals about the consequences of having many sexual partners; continuing treatment for AIDS and pursuing the investigation of new and better drugs to combat the virus and regular screening. Considering HCV infection, treatment is also highly recommended as well as other measures (e.g., more informational campaign about the disease) in order to decrease the number of infectious and of chronic carriers. MSM population is at risk of HCV reinfection following successful treatment and documented clearance of HCV, they should be warned about this important risk. Future work will consider the effect of needle sharing in the case of HIV and HCV transmission rates, and an application of the model to real Portuguese data, with corresponding estimation of parameter values.

Acknowledgments

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Appendix

In this appendix, we present the detailed calculations of the reproduction number R_0 (see Sec. 2.2).

$$F = \begin{pmatrix}
\frac{c(1-\theta)b_h}{(\Lambda_1+\Lambda_2)(\mu+k)}\big[(1-p)(1-\psi)(k\Lambda_1+\Lambda_2(k+\mu))+\Lambda_1\mu\big] & \frac{c(1-\theta)b_h}{(\Lambda_1+\Lambda_2)(\mu+k)}\big[(1-p)(1-\psi)(k\Lambda_1+\Lambda_2(k+\mu))+\Lambda_1\mu\big] & 0 & 0 & 0 & \cdots \\
p(1-\psi)c(1-\theta)b_h\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} & p(1-\psi)c(1-\theta)b_h\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & c(1-\theta)b_c\frac{\Lambda_1\mu}{(\Lambda_1+\Lambda_2)(\mu+k)} & c(1-\theta)b_c\frac{\Lambda_1\mu}{(\Lambda_1+\Lambda_2)(\mu+k)} & 0 & \cdots \\
0 & 0 & c(1-\theta)b_c\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} & c(1-\theta)b_c\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)} & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots
\end{pmatrix}$$

$$
V =
\begin{pmatrix}
k+\rho_1+\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -v_1 & 0 & 0 & 0 & 0 & 0 \\
-k & \rho_2+\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -v_1 & 0 & 0 & 0 & 0 \\
-\rho_1 & 0 & \mu+\delta_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\rho_2 & 0 & \mu+\delta_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k+v+\sigma_1\mu+\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -k & v+\sigma_1+\mu+\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\sigma_1 & -\sigma_1 & k+\mu+\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -k & \mu+\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k+\sigma_2+\rho_2+v_1+\mu+\delta_1 & -\sigma_2 & 0 & 0 & -v_2 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k & v_1+\rho_2+\mu+\delta_1 & -k & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\sigma_2 & -\sigma_2 & k+\rho_2+\mu+\delta_1 & \rho_2+\mu+\delta_1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\rho_2 & 0 & 0 & v_2+\sigma_2+\mu+\delta_1+\delta_2 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\rho_2 & -\rho_2 & -\rho_2 & -\rho_2 & -\sigma_2 & \mu+\delta_1+\delta_2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
$$

$$FV^{-1} = \begin{pmatrix}
\dfrac{A}{k+\mu+\rho_1}+\dfrac{Ak}{(k+\mu+\rho_1)(\mu+\rho_2)} & \dfrac{A}{\mu+\rho_2} & 0 & 0 & 0 & 0 & 0 & \star & \star & 0 & 0 & 0 & 0 \\[2ex]
\dfrac{B}{k+\mu+\rho_1}+\dfrac{Bk}{(k+\mu+\rho_1)(\mu+\rho_2)} & \dfrac{B}{\mu+\rho_2} & 0 & 0 & 0 & 0 & 0 & \star & \star & 0 & 0 & 0 & 0 \\[2ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & \dfrac{C}{\delta_1+k+\mu+\sigma_1+v}+\dfrac{Ck}{(\delta_1+\mu+\sigma_1+v)(\delta_1+k+\mu+\sigma_1+v)} & \dfrac{C}{\delta_1+\mu+\sigma_1+v} & 0 & \star & \star & 0 & 0 & 0 & 0 \\[2ex]
0 & 0 & 0 & 0 & \dfrac{D}{\delta_1+k+\mu+\sigma_1+v}+\dfrac{Dk}{(\delta_1+\mu+\sigma_1+v)(\delta_1+k+\mu+\sigma_1+v)} & \dfrac{D}{\delta_1+\mu+\sigma_1+v} & 0 & \star & \star & 0 & 0 & 0 & 0 \\[2ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\[1ex]
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}$$

where $A = \frac{c(1-\theta)b_h}{(\Lambda_1+\Lambda_2)(\mu+k)}[(1-p)(1-\psi)(k\Lambda_1 + \Lambda_2(k+\mu)) + \Lambda_1\mu]$, $B = p(1-\psi)c(1-\theta)b_h\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)}$, $C = c(1-\theta)b_c\frac{\Lambda_1\mu}{(\Lambda_1+\Lambda_2)(\mu+k)}$, and $D = c(1-\theta)b_c\frac{k\Lambda_1+\Lambda_2(k+\mu)}{(\Lambda_1+\Lambda_2)(\mu+k)}$. The formulas represented by $\star$ are irrelevant to compute the eigenvalues, so, for the sake of simplicity, we decided not to include those here.

In order to compute R_0, the basic reproduction number for the whole model (2.1), we need to compute the eigenvalues of the matrix FV^{-1}, since R_0 is the spectral radius of FV^{-1}, i.e., it is the dominant eigenvalue of this matrix.

Let us now proceed with the computation of the eigenvalues by calculating the determinant below:

$$FV^{-1} = \begin{pmatrix} \frac{A}{k+\mu+\rho_1} + \frac{Ak}{(k+\mu+\rho_1)(\mu+\rho_2)} - \lambda & \frac{A}{\mu+\rho_2} \\ \frac{B}{k+\mu+\rho_1} + \frac{Bk}{(k+\mu+\rho_1)(\mu+\rho_2)} & \frac{B}{\mu+\rho_2} - \lambda \\ 0 & 0 \\ 0 & 0 \end{pmatrix}$$

$$\begin{pmatrix} 0 & 0 \\ 0 & 0 \\ \frac{C}{\delta_1+k+\mu+\sigma_1+\upsilon} + \frac{Ck}{(\delta_1+\mu+\sigma_1+\upsilon)(\delta_1+k+\mu+\sigma_1+\upsilon)} - \lambda & \frac{C}{(\delta_1+\mu+\sigma_1+\upsilon)} \\ \frac{D}{\delta_1+k+\mu+\sigma_1+\upsilon} + \frac{Dk}{(\delta_1+\mu+\sigma_1+\upsilon)(\delta_1+k+\mu+\sigma_1+\upsilon)} & \frac{D}{(\delta_1+\mu+\sigma_1+\upsilon)} - \lambda \end{pmatrix}.$$

As FV^{-1} is a matrix of the form: $\begin{bmatrix} U_1 & 0 \\ 0 & U_2 \end{bmatrix}$, then its eigenvalues are the ones of matrices U and V, where:

$$U_1 = \begin{pmatrix} \frac{A}{k+\mu+\rho_1} + \frac{Ak}{(k+\mu+\rho_1)(\mu+\rho_2)} - \lambda & \frac{A}{\mu+\rho_2} \\ \frac{B}{k+\mu+\rho_1} + \frac{Bk}{(k+\mu+\rho_1)(\mu+\rho_2)} & \frac{B}{\mu+\rho_2} - \lambda \end{pmatrix};$$

$$U_2 = \begin{pmatrix} \frac{C}{\delta_1+k+\mu+\sigma_1+\upsilon} + \frac{Ck}{(\delta_1+\mu+\sigma_1+\upsilon)(\delta_1+k+\mu+\sigma_1+\upsilon)} - \lambda & \frac{C}{(\delta_1+\mu+\sigma_1+\upsilon)} \\ \frac{D}{\delta_1+k+\mu+\sigma_1+\upsilon} + \frac{Dk}{(\delta_1+\mu+\sigma_1+\upsilon)(\delta_1+k+\mu+\sigma_1+\upsilon)} & \frac{D}{(\delta_1+\mu+\sigma_1+\upsilon)} - \lambda \end{pmatrix}.$$