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DYNAMIC ANALYSIS FOR DELAYED HCV INFECTION IN *VIVO* WITH ANTI-RETRO VIRAL TREATMENT

P. Krishnapriya[1] and Ho Geun Hyun[2]

Department of Mathematics, Mary Matha College of Arts and Science
Periyakulam-625 604, India
e-mail: priyaprithu1205@gmail.com

Department of Mathematics Education, Kyungnam University
Changwon, Gyeongnam, 51767, Korea
e-mail: hyunhg8285@kyungnam.ac.kr

Abstract. In this paper, we study a within-host mathematical model of HCV infection and carry out mathematical analysis of the global dynamics and bifurcations of the model in different parameter regimes. We explore the effect of reverse transcriptase inhibitors (RTI) on spontaneous HCV clearance. The model can produce all clinically observed patient profiles for realistic parameter values; it can also be used to estimate the efficacy and/or duration of treatment that will ensure permanent cure for a particular patient. From the results of the model, we infer possible measures that could be implemented in order to reduce the number of infected individuals.

1. Introduction

In recent years, great attention has been paid to the dynamics properties of the epidemic models which have a significant biological background. Many excellent and interesting results have been obtained [1, 2, 3, 4, 5, 6, 7, 8, 9]. It is well known that epidemic models are investigated on the transmission dynamics of infectious diseases in the host population. Nowadays, mathematical theories for the dynamics of viral infections have been around for several

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[0]Corresponding author: P. Krishnapriya (priyaprithu1205@gmail.com),
H.G. Hyun (hyunhg8285@kyungnam.ac.kr).

decades now. These theories have proved to be valuable in understanding the dynamics of viral infections and in evaluating the effectiveness of various forms of antiviral therapy.

A model of HIV infection [10, 11] was adapted by Neumann et al., [12] to study the kinetics of chronic HCV infection during [12] treatment. Since then, viral kinetics modeling has played an important role in the analysis of HCV-RNA decay during antiviral therapy (see review [13]).

In this paper, we extend the original model of HCV infection under therapy [12] to account for the proliferation of hepatocytes (herein termed the extended model), as was recently used to model HCV-RNA kinetics in primary infection in chimpanzees [14]. To establish our results, we carry out mathematical analysis on the existence and number of steady states, local stability of infection-free, and chronic-infection steady states. To completely describe the global dynamics, we have also established the global stability of the infection-free steady state when it is the only steady, and that of the chronic steady state when it is unique. Our proof of the infection-free steady state is new and is developed to handle the logistic terms. Our proof of global stability of the unique chronic-infection steady state uses the approach of Lyapunov function. To relate our mathematical results to the biological context, we have derived the basic reproduction number R_0 interpreted our mathematical results in terms of R_0.

The original HCV infection model [12] contains three differential equations (herein deemed the original model). Specifically, it models the populations of target cells, productively infected cells, and the virus. We simplified the model (herein deemed the four-equation model) by assuming that a constant the population of target cells was used to estimate the rates of viral clearance and infected cell loss by fitting the observed biphasic the decline of HCV RNA in patients during therapy. Later on, Dahari and co-workers [15, 16], specifically for hepatitis C viral, extended the basic model [12, 17, 18] to include mitotic proliferation terms for both uninfected and infected hepatocytes. Their model describes four populations. These populations include: uninfected target cells (hepatocytes) $T(t)$, productively infected hepatocytes cells $I(t)$, free HCV virus $V(t)$, and immune system of $CD4^+$ cells of HCV, $H(t)$. Here, we assume that the proliferation of cells due to mitotic division obey a logistic growth law. The mitotic proliferation of uninfected cells is described by $aT\left(1-\dfrac{T+I}{T_{max}}\right)$. New infectious transmission occurs at a rate βTV, while new mitotic transmission occurs at a rate $aI\left(1-\dfrac{T+I}{T_{max}}\right)$. As long as the total number of cells, $T(t)+I(t)$, is less than T_{max}. Dependence of the HCV

clearance rate on $CD4^+$ count α and dependence of the HCV clearance rate of $CD4^+$ cells on HCV infected cell count γ. The DDE model is as follows:

In this paper, we investigate a class of HCV infection models with full logistic proliferation and incorporating RTI-based ART. The model takes the following form:

$$\begin{aligned}
\frac{dT}{dt} &= s + aT\left(1 - \frac{T+I}{T_{max}}\right) - dT - (1-\epsilon)\beta TV, \\
\frac{dI}{dt} &= (1-\epsilon)\beta T(t-\tau_1)V(t-\tau_1) + aI\left(1 - \frac{T+I}{T_{max}}\right) - \delta I - \delta\alpha HI, \\
\frac{dV}{dt} &= pI - cV, \\
\frac{dH}{dt} &= \gamma I(t-\tau_2) - d_H H, \qquad (1.1)
\end{aligned}$$

where τ_1 represents the time from entry to production of new virus [2, 3], τ_2 is the immune cells at time t that were activated by infected cells at time $t-\tau_2$, where $0 \leq 1-\epsilon \leq 1$ is the rate of reduction in numbers of productively-infected target cells due to interruption of reverse transcription by the RTI-based drugs. Parameter $1-\epsilon$ is a measure of the efficiency of the ART; if $\epsilon = 1$ HCV infection produces no productively-infected target cells, and ART has no effect and if $\epsilon = 0$, then ART is 100% effective. We will focus on the effects of RTI-based ART in this study. The parameter values in this model (1.1), are described in Table I.

Table I

Parameters description and Values

Para.	**Description**	**Source**
s	recruitment rate of uninfected hepatocytes	[19]
a	maximum proliferation rate	Estimated
d	death rate of uninfected target cells	Estimated
β	infection rate occurs at the transmissions	[19]
δ	clearance rate of infected hepatocytes	Estimated
p	number of virions an infected cell produces in its lifetime	[19]
c	viral clearance rate	Estimated
d_H	death rate of $CD4^+$ cells	[19]

The purpose of this paper is to study the stability and bifurcation of our model with delays. We investigate not only the local and global stability analysis of the steady state and the existence of the Hopf bifurcation also. The remainder of this paper is organized as follows: In Section 2, we determine the local stability analysis of an infected equilibrium, with permit delay time being positive. We demonstrate the global stability of the infected equilibrium in the

case of $\tau_2 < \tau_2^*$, when $R_0 > 1$. In order to support our theoretical results and stability analysis of equilibria, we provide some numerical simulation results in Section 3. Finally, we end with the conclusion in Section 4.

2. Stability analysis of DDE model

We adopt the following notation: $\mathbb{R}^4$ is a four-dimensional real Euclidean space with norm $|.|$. For $\tau > 0$, we denote by $C = C([-\tau, 0], \mathbb{R}^4_+)$, the Banach space of continuous functions from the interval $[-\tau, 0]$ into $\mathbb{R}^4_+$ with the topology of uniform convergence, where $\tau = \max\{\tau_1, \tau_2\}$. By the standard theory of functional differential equation [20, 21, 22], we know that for any $\phi \in C([-\tau, 0], \mathbb{R}^4_+)$, there exists a unique solution

$$Z(t, \phi) = (T(t, \phi), I(t, \phi), V(t, \phi), H(t, \phi))$$

of the delayed system (1.1), which satisfy $Z_0 = \phi$, where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathbb{R}^4_+$ with $\phi_i(\xi) \geq 0 : (\xi \in [-\tau, 0], \quad i = 1, ..., 4)$, and $\phi_1(0), \phi_2(0), \phi_3(0), \phi_4(0) > 0$. And the initial conditions are given by

$$T(\xi) = \phi_1(\xi), \quad I(\xi) = \phi_2(\xi), \quad V(\xi) = \phi_3(\xi), \quad H(\xi) = \phi_4(\xi). \tag{2.1}$$

Theorem 2.1. ([23]) *Let $Z(t, \phi)$ be a solution of the delayed system* (1.1) *with the initial conditions* (2.1). *Then for all $t \geq 0$, $T(t), I(t), V(t)$ and $H(t)$ are all non-negative and ultimately uniformly bounded at which the solution exists.*

2.1. Local stability analysis.

The model (1.1) has two steady states: the first, called the infection free equilibrium E^0 and the second one, called the chronic infection equilibrium $\hat{E}$. The steady state points are as follows:

$$E^0 = (T_0, I_0, V_0, H_0) = \frac{T_{max}}{2a}\left(a - d + \sqrt{(a-d)^2 + \frac{4as}{T_{max}}}, 0, 0, 0\right)$$

and

$$\hat{E} = (\hat{T}, \hat{I}, \hat{V}, \hat{H}) = \left(\frac{-D_2 + \sqrt{D_2^2 - 4D_1D_3}}{2D_1}, \frac{\hat{T}(A-1) + B}{\left(1 + \frac{\delta\alpha\gamma T_{max}}{a(d_H)}\right)}, \frac{p}{c}\hat{I}, \frac{\gamma}{d_H}\hat{I}\right).$$

where

$$D_1 = \frac{a}{T_{max}} + \frac{a}{T_{max}} \frac{(A-1)}{\left(1 + \frac{\delta\alpha\gamma T_{max}}{a(d_H)}\right)} + \frac{(1-\epsilon)\beta p(A-1)}{c\left(1 + \frac{\delta\alpha\gamma T_{max}}{a(d_H)}\right)},$$
$$D_2 = d - a + \frac{aB}{T_{max}\left(1 + \frac{\delta\alpha\gamma T_{max}}{a(d_H)}\right)} + \frac{(1-\epsilon)\beta pB}{c\left(1 + \frac{\delta\alpha\gamma T_{max}}{a(d_H)}\right)},$$
$$D_3 = -s,$$

$$A = \frac{(1-\epsilon)\beta p T_{max}}{ac},$$
$$B = T_{max} - \frac{\delta T_{max}}{a}.$$

Basic Reproduction Number: We computed the basic reproduction number of model using next generation matrix method and is given by

$$R_0 = \frac{a}{\delta}\left(1 - \frac{T_0}{T_{max}}\right) + \frac{(1-\epsilon)\beta T_0 p}{c\delta}. \tag{2.2}$$

It is apparent from the expression (2.2) that the basic reproduction number is independent of immune response parameters. It can be understood as the basic reproduction number is the number of newly infected cells produced by a single infected cell when introduced into completely healthy cells.

To determine the stability of the delayed model, we linearized system (1.1) around E^0 and obtained the characteristic equation as

$$\begin{vmatrix} -d + a - \frac{2aT_0}{T_{max}} - \lambda & -\frac{aT_0}{T_{max}} & -(1-\epsilon)\beta_0 & 0 \\ 0 & -\delta + a - \frac{aT_0}{T_{max}} - \lambda & (1-\epsilon)\beta T_0 e^{-\lambda\tau_1} & 0 \\ 0 & p & -c - \lambda & 0 \\ 0 & \gamma e^{-\lambda\tau_2} & 0 & -(d_H + V_H) - \lambda \end{vmatrix} = 0 \tag{2.3}$$

where λ is an eigenvalue of (2.3) around E^0 .

We see that (2.3) has an eigenvalue $\lambda = -(d_H) < 0$, we also consider that $\hat{E}$ satisfies system (1.1) so $a\left(1 - \frac{T_0}{T_{max}}\right) = d - \frac{s}{T_0}$. And using the previous fact we can rewrite the factors of the characteristic equation (2.3) as

$$\lambda = a - d - \frac{2aT_0}{T_{max}} = -\left(\frac{s}{T_0} + \frac{aT_0}{T_{max}}\right)$$

which have a negative eigenvalue and other eigenvalues are determined by

$$\lambda^2 + \lambda\left(c + \delta + \frac{aT_0}{T_{max}} - a\right) + c\delta\left(1 - R_0 e^{-\lambda\tau_1}\right) = 0. \tag{2.4}$$

Theorem 2.2. *The infection free steady state of model* (1.1) *is locally asymptotically stable when* $R_0 < 1$ *and unstable when* $R_0 > 1$.

Proof. The characteristic equation (2.4) at the infection free steady state can be rewritten as

$$\left(\lambda + \delta + \frac{aT_0}{T_{max}} - a\right)(\lambda + c) = c\delta R_0 e^{-\lambda\tau_1}. \tag{2.5}$$

If the eigenvalue of λ in (2.4) has a non-negative real part, then the modulus of the LHS of (2.4) satisfies,

$$\left|\left(\lambda + \delta + \frac{aT_0}{T_{max}} - a\right)(\lambda + c)\right| \geq c\delta, \tag{2.6}$$

while the modulus of the RHS of (2.4) satisfies $|c\delta R_0 e^{-\lambda\tau_1}| < |c\delta R_0| < c\delta$.

This leads to a contradiction of (2.4). Thus, all the eigenvalues of (2.4) have negative real part and hence the infected free steady state of the model (1.1) is locally asymptotically stable when $R_0 < 1$.

For $R_0 > 1$, we define

$$\Psi_1(\lambda) = \left(\lambda + \delta + \frac{aT_0}{T_{max}} - a\right)(\lambda + c) - c\delta R_0 e^{-\lambda\tau_1}.$$

It is clear that $\Psi_1(0) < 0$ and $\Psi_1(\lambda) \to \infty$ as $\lambda \to \infty$. By the continuity, we know that, there exists at least one positive root when $R_0 > 1$. Thus, the infection free steady state of the model (1.1) is unstable when $R_0 > 1$. □

From biological point of view, it can be understand from the above result that on the onset of infection if $R_0 < 1$, (i.e. number of new infections on average is less than one) then the infection will not keep on increasing further and the system will settle to infection-free equilibrium point.

Now, we have to ascertain the stability of $\hat{E}(\hat{T}, \hat{I}, \hat{V}, \hat{H})$ and so the linearized system (1.1) at $\hat{E}$ and obtain the characteristic equation:

$$\begin{vmatrix} a_{11}-\lambda & -\frac{a\hat{I}}{T_{max}} & -(1-\epsilon)\beta\hat{T} & 0 \\ (1-\epsilon)\beta\hat{V}e^{-\lambda\tau_1}-\frac{a\hat{I}}{T_{max}} & a_{22}-\lambda & (1-\epsilon)\beta\hat{T}e^{-\lambda\tau_1} & -\delta\alpha\hat{I} \\ 0 & p & -c-\lambda & 0 \\ 0 & \gamma e^{-\lambda\tau_2} & 0 & -(d_H)-\lambda \end{vmatrix} = 0,$$

where

$$a_{11} = a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}$$

and

$$a_{22} = a - \delta - \frac{2a\hat{I}}{T_{max}} - \frac{a\hat{T}}{T_{max}} - \delta\alpha\hat{H}.$$

Thus, the characteristic equation as follows:

$$\begin{aligned} L(\lambda,\tau_1,\tau_2) &= \lambda^4 + p_1\lambda^3 + p_2\lambda^2 + p_3\lambda + p_4 + e^{-\lambda\tau_1}(q_1\lambda^2 + q_2\lambda + q_3) \\ &\quad + e^{-\lambda\tau_2}(r_1\lambda^2 + r_2\lambda + r_3) \\ &= 0, \end{aligned} \tag{2.7}$$

where $p_i = p_i(\tau_1,\tau_2),\ q_i = q_i(\tau_1,\tau_2), r_i = r_i(\tau_1,\tau_2)$, and

$$\begin{aligned} p_1 = a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V} \\ + a - \delta - \frac{2a\hat{I}}{T_{max}} - \frac{a\hat{T}}{T_{max}} - \delta\alpha\hat{H} + c + d_H, \end{aligned}$$

$$\begin{aligned} p_2 = \Bigg\{ &\left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}\right)\left(a - \delta - \frac{2a\hat{I}}{T_{max}} - \frac{a\hat{T}}{T_{max}} - \delta\alpha\hat{H}\right) \\ &+ \left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V} + a - \delta - \frac{2a\hat{I}}{T_{max}} - \frac{a\hat{T}}{T_{max}} - \delta\alpha\hat{H}\right) \\ &\times (c + d_H) + c(d_H + \beta_H V_H) - \frac{a^2\hat{T}\hat{I}}{T_{max}^2}\Bigg\}, \end{aligned}$$

$$p_3 = \left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}\right)\left(a-\delta-\frac{2a\hat{I}}{T_{max}}-\frac{a\hat{T}}{T_{max}}-\delta\alpha\hat{H}\right)$$
$$\times (c + d_H + \beta_H V_H)$$
$$+ c\left(a-d-\frac{2a\hat{T}}{T_{max}}-\frac{a\hat{I}}{T_{max}}-(1-\epsilon)\beta\hat{V}+a-\delta-\frac{2a\hat{I}}{T_{max}}-\frac{a\hat{T}}{T_{max}}-\delta\alpha\hat{H}\right)$$
$$-\frac{a^2\hat{T}\hat{I}}{T_{max}^2}-\frac{(1-\epsilon)\beta\hat{T}a\hat{I}p}{T_{max}},$$

$$p_4 = \left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}\right)\left(a-\delta-\frac{2a\hat{I}}{T_{max}}-\frac{a\hat{T}}{T_{max}}-\delta\alpha\hat{H}\right)$$
$$\times c(d_H + \beta_H V_H) - \frac{a^2\hat{T}\hat{I}}{T_{max}^2}c(d_H) - \frac{(1-\epsilon)\beta\hat{T}a\hat{I}p}{T_{max}}(d_H),$$

$$q_1 = \frac{a\hat{T}}{T_{max}}(1-\epsilon)\beta\hat{V} - (1-\epsilon)\beta p\hat{T},$$

$$q_2 = \frac{a\hat{T}}{T_{max}}(c + d_H)(1-\epsilon)\beta\hat{V} + (1-\epsilon)^2\beta^2\hat{V}\hat{T}p$$
$$-(1-\epsilon)\beta\hat{T}p\left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V} + d_H + \beta_H V_H\right),$$

$$q_3 = (1-\epsilon)\beta\hat{V}\frac{a\hat{T}}{T_{max}}c(d_H) + (1-\epsilon)^2\beta^2\hat{V}\hat{T}p$$
$$-(1-\epsilon)\beta\hat{T}p\left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}\right)(d_H),$$

$$r_1 = \delta\alpha\gamma\hat{I},$$

$$r_2 = \delta\alpha\gamma\hat{I}\left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V} + c\right),$$

$$r_3 = \delta\alpha\gamma\hat{I}\left(a - d - \frac{2a\hat{T}}{T_{max}} - \frac{a\hat{I}}{T_{max}} - (1-\epsilon)\beta\hat{V}\right) \times c.$$

For $\tau_1 = \tau_2 = 0$ the above equation (2.7) becomes as follows

$$\lambda^4 + \lambda^3 p_1 + \lambda^2(p_2 + q_1 + r_1) + \lambda(p_3 + q_2 + r_2) + (p_4 + q_3 + r_3) = 0. \quad (2.8)$$

Since $R_0 > 1$, by Routh-Hurwitz criteria, the corresponding system without delay is locally asymptotically stable around the chronic infection equilibrium if following conditions are satisfied:

(1) $p_1 > 0,\ p_3 + q_2 + r_2 > 0$ and $p_4 + q_3 + r_3 > 0$,
(2) $p_1(p_2 + q_1 + r_1)(p_3 + q_2 + r_2) > (p_3 + q_2 + r_2)^2 + p_1^2(p_4 + q_3 + r_3)$.

To determine the local stability $\hat{E}$ of (1.1), for various delays, we need to show that the distribution of zeros of the characteristic equation (2.7) for τ_1 and τ_2. In contrast to the transcendental equation with one delay in [24] the parameters of equation (2.7) depend on two delays. Therefore, it is necessary to reformulate the stability switch criteria for (2.7). However, we suppose hereafter $\tau_1 = \bar{\tau}$ to simplify the study and the general case can be treated in the same manner.

When $\bar{\tau} = 0$, the characteristic equation (2.7) becomes

$$L(\lambda, \tau_2) = G_1(\lambda, \tau_2) + e^{-\lambda\tau_2} G_2(\lambda, \tau_2) = 0, \tag{2.9}$$

where

$$\begin{aligned} G_1(\lambda, \tau_2) &= \lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_3\lambda + k_4, \\ G_2(\lambda, \tau_2) &= m_1\lambda^2 + m_2\lambda + m_3, \end{aligned}$$

for

$$k_1 = p_1, \quad k_2 = p_2 + q_1, \quad k_3 = p_3 + q_2, \quad k_4 = p_4 + q_3,$$

$$m_1 = r_1, \quad m_2 = r_2, \quad m_3 = r_3.$$

Let $\lambda = i\omega^*$ $(\omega^* > 0)$ be a root of (2.9), and separating the real and imaginary parts, we have

$$\begin{aligned} \omega^{*4} - \omega^{*2}k_2^* + k_4^* &= (m_1\omega^{*2} - m_3)\ \cos(\omega^*\tau_2) \\ &\quad -m_2\ \omega^*\ \sin(\omega^*\tau_2) \end{aligned} \tag{2.10}$$

and

$$\begin{aligned} \omega^* k_3^* - \omega^{*3}k_1^* &= (m_1\omega^{*2} - m_3)\ \sin(\omega^*\tau_2) \\ &\quad +m_2\ \omega^*\ \cos(\omega^*\tau_2). \end{aligned} \tag{2.11}$$

Squaring and adding both equations of (2.10) and (2.11), we can obtain the following eight-degree equation for ω^*:

$$\begin{aligned} &\omega^{*8} + \omega^{*6}(k_1^{*2} - 2k_2^*) + \omega^{*4}(k_2^{*2} - m_1^2 + 2k_4^* - 2k_1^*k_3^*) \\ &+ \omega^{*2}(k_3^{*2} - 2k_2^*k_4^* - m_2^2) + k_4^{*2} - m_3^2 = 0. \end{aligned} \tag{2.12}$$

Putting $\omega^{*2} = u^{**}$ into (2.12), we can obtain the following equation:

$$F(u^{**}) = u^{**4} + A_1^* u^{**3} + A_2^* u^{**2} + A_3^* u^{**} + A_4^* = 0, \tag{2.13}$$

where

$$\begin{aligned} A_1^* &= k_1^{*2} - 2k_2^*, \\ A_2^* &= k_2^{*2} - m_1^2 + 2k_4^* - 2k_1^* k_3^*, \\ A_3^* &= k_3^{*2} - 2k_2^* k_4^* - m_2^2, \\ A_4^* &= k_4^{*2} - m_3^2. \end{aligned}$$

Taking derivative with respect to u^{**} of equation (2.13), we get

$$\dot{F}(u^{**}) = 4u^{**3} + 3u^{**2}A_1^* + 2u^{**}A_2^* + A_3^* = 0. \tag{2.14}$$

It is easy to verify that the coefficients in the above equation (2.14) are all positive and hence $\dot{F}(u^{**}) > 0$. By Descartes rule of signs, equation (2.13) has positive root u^{**} and thus equation (2.12) has a pair of purely imaginary roots $i\omega^*$. From equation (2.10) and (2.11), we obtain

$$\tau_2^* = \frac{1}{\omega^*} \arccos\left(\frac{(\omega^{*4} - \omega^{*2}k_2^* + k_4^*)(\omega^{*2}m_1 - m_3) + (\omega^{*2}k_3^* - \omega^{*4}k_1^*)m_2}{(\omega^{*2}m_1 - m_3)^2 + \omega^{*2}m_2^2}\right) + \frac{2j\pi}{\omega^*},$$

where $j = 0, 1, 2, \ldots$. Therefore $\hat{E}$ is stable for $\tau_2 \in [0, \tau_2^*)$ and unstable when $\tau_2 > \tau_2^*$.

When $\tau_2 > 0$ we show the existence of bifurcating periodic solutions. We already proved that the characteristic equation (2.9) has a purely imaginary eigenvalues $i\omega^*$, now we shall verify the transversality condition only.

Differentiating (2.9) with respect to τ_2, we get

$$\left\{(4\lambda^3 + 3\lambda^2 k_1^* + 2\lambda k_2^* + k_3^*) + e^{-\lambda\tau_2}(2\lambda m_1 + m_2) - \tau_2 e^{-\lambda\tau_2}(m_1\lambda^2 + m_2\lambda + m_3)\right\}\frac{d\lambda}{d\tau_2} = \lambda e^{-\lambda\tau_2}(m_1\lambda^2 + m_2\lambda + m_3)$$

which implies

$$\begin{aligned} &\left(\frac{d\lambda}{d\tau_2}\right)^{-1} \\ &= \frac{4\lambda^3 + 3\lambda^2 k_1^* + 2\lambda k_2^* + k_3^*}{\lambda e^{-\lambda\tau_2}(m_1\lambda^2 + m_2\lambda + m_3)} + \frac{2\lambda m_1 + m_2}{\lambda(m_1\lambda^2 + m_2\lambda + m_3)} - \frac{\tau_2}{\lambda} \\ &= \frac{4\lambda^3 + 3\lambda^2 k_1^* + 2\lambda k_2^* + k_3^*}{-\lambda(\lambda^4 + k_1^*\lambda^3 + k_2^*\lambda^2 + k_3^*\lambda + k_4^*)} + \frac{2\lambda m_1 + m_2}{\lambda(m_1\lambda^2 + m_2\lambda + m_3)} - \frac{\tau_2}{\lambda} \\ &= \frac{3\lambda^4 + 2k_1^*\lambda^3 + k_2^*\lambda^2 - k_4^*}{-\lambda^2(\lambda^4 + k_1^*\lambda^3 + k_2^*\lambda^2 + k_3^*\lambda + k_4^*)} + \frac{\lambda^2 m_1 - m_3}{\lambda^2(m_1\lambda^2 + m_2\lambda + m_3)} - \frac{\tau_2}{\lambda}. \end{aligned}$$

Therefore,

$$
\begin{aligned}
\Xi &= sign\left\{Re\left(\frac{3\lambda^4+2k_1^*\lambda^3+k_2^*\lambda^2-k_4^*}{-\lambda^2(\lambda^4+k_1^*\lambda^3+k_2^*\lambda^2+k_3^*\lambda+k_4^*)}\right.\right.\\
&\quad\left.\left.+\frac{\lambda^2 m_1-m_3}{\lambda^2(m_1\lambda^2+m_2\lambda+m_3)}-\frac{\tau_2}{\lambda}\right)\right\}_{\lambda=i\omega_0^*}\\
&= sign\left\{Re\left(\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)+i(-2\omega_0^{*3}k_1^*)}{\omega_0^{*2}(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)+i(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}\right.\right.\\
&\quad\left.\left.+\frac{m_1\omega_0^{*2}+m_3}{\omega_0^{*2}(m_3-m_1\omega_0^{*2})+i(m_2\omega_0^*)}-\frac{\tau_2}{i\omega_0^*}\right)\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)-2\omega_0^{*3}k_1^*(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}{(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)^2+(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)^2}\right.\\
&\quad\left.+\frac{(m_1\omega_0^{*2}+m_3)(m_3-m_1\omega_0^{*2})}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right.\\
&\quad\left.+\frac{(m_1\omega_0^{*2}+m_3)(m_3-m_1\omega_0^{*2})-2\omega_0^{*3}k_1^*(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{3\omega_0^{*8}+(k_1^{*2}-2k_2)\omega_0^{*6}+(k_2^{*2}-2k_1^*k_3^*+2k_4^*-m_1^2)\omega_0^{*4}+k_4^{*2}-m_3^2}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}.
\end{aligned}
$$

As $k_1^{*2}-2k_2^*$, $k_2^{*2}-2k_1^*k_3^*+2k_4^*-m_1^2$ and $k_4^{*2}-m_3^2$ are both positive by virtue of equation (2.12), we have

$$\left(\frac{dRe(\lambda)}{d\tau_2}\right)\Big|_{\omega^*=\omega_0^*,\tau_2=\tau_2^*}>0.$$

Therefore the transversality condition holds and hence Hopf bifurcation occurs at $\omega^*=\omega_0^*,\tau_2=\tau_2^*$.

Moreover the infected equilibrium $\hat{E}$ is stable when $\tau_2\in[0,\tau_2^*)$ and unstable when $\tau_2>\tau_2^*$. τ_2 is the Hopf bifurcation value, which means that periodic solutions will bifurcate from this infected equilibrium as τ_2 passes through the critical value τ_2^*.

2.2. **Global stability analysis.** In this section, we prove that E^0 of (1.1) is globally asymptotically stable when $R_0<1$, and so is $\hat{E}$ of (1.1) is provided that $R_0>1$. Therefore, the model (1.1) demonstrates global dynamics. We shall achieve our goal with the global asymptotic stability of E^0 of (1.1) under $R_0<1$.

Theorem 2.3. *If $R_0<1$, then the infection free equilibrium E^0 of* (1.1) *is indeed globally asymptotically stable.*

Proof. We consider a Lyapunov functional $W_1(t)$ as follows,

$$W_1(t) = T - T_0 \ln \frac{T}{T_0} + I + \frac{(1-\epsilon)\beta}{c} T_0 V + \frac{\delta}{\gamma}(1-R_0)H + (1-\epsilon)\beta \int_{-\tau_1}^{0} T(t+\sigma)V(t+\sigma)d\sigma + \frac{\delta}{\gamma}(1-R_0)\gamma \int_{-\tau_2}^{0} I(t+\sigma)d\sigma.$$

Calculating the time derivative of $W_1(t)$ along positive solutions of (1.1), we have

$$\begin{aligned}
\frac{dW_1}{dt} &= \left(1-\frac{T_0}{T}\right)\frac{dT}{dt} + \frac{dI}{dt} + \frac{(1-\epsilon)\beta}{c}T_0\frac{dV}{dt} + \frac{\delta}{\gamma}(1-R_0)\frac{dH}{dt} \\
&\quad +(1-\epsilon)\beta(T(t)V(t) - T(t-\tau_1)V(t-\tau_1)) \\
&\quad +\frac{\delta}{\gamma}(1-R_0)\gamma(I(t) - I(t-\tau_2)) \\
&= (T-T_0)\left(\frac{s}{T} - d + a\left(1-\frac{T+I}{T_{max}}\right) - (1-\epsilon)\beta TV\right) \\
&\quad -\delta I - \delta\alpha HI + aI\left(1-\frac{T+I}{T_{max}}\right)\frac{(1-\epsilon)\beta}{c}T_0[pI - cV] \\
&\quad + \left(\frac{d}{\gamma}\right)\left(1-\frac{\hat{H}}{H}\right)\frac{dH}{dt} + (1-\epsilon)\beta TV \\
&\quad -\frac{\delta}{\gamma}(1-R_0)(d_H H) + \delta(1-R_0)I. \qquad (2.15)
\end{aligned}$$

Using the infection-free equilibrium condition of model (1.1), $a-d = \frac{aT_0}{T_{max}} - \frac{s}{T_0}$ in (2.15), then we get

$$\begin{aligned}
\frac{dW_1}{dt} &= -s\frac{(T-T_0)^2}{TT_0} - \frac{a}{T_{max}}(T-T_0)^2 - \frac{a}{T_{max}}I(T-T_0) - (1-\epsilon)\beta(T-T_0)V \\
&\quad - \delta I - \delta\alpha HI + aI - \frac{aIT}{T_{max}} - \frac{aI^2}{T_{max}} + \frac{(1-\epsilon)\beta}{c}T_0 pI - (1-\epsilon)\beta T_0 V \\
&\quad + (1-\epsilon)\beta T(t)V(t) - \frac{\delta}{\gamma}(1-R_0)(d_H H) + \delta(1-R_0) \\
&\quad + \frac{a}{T_{max}}IT_0 - \frac{a}{T_{max}}IT_0, \\
&= -s\frac{(T-T_0)^2}{TT_0} - \frac{a}{T_{max}}((T-T_0)+I)^2 \\
&\quad + I\left(a\left(1-\frac{T_0}{T_{max}}\right) + \frac{(1-\epsilon)\beta}{c}T_0 p - \delta\right) + \delta(1-R_0).
\end{aligned}$$

Note that,

$$a\left(1-\frac{T_0}{T_{max}}\right)+\frac{(1-\epsilon)\beta}{c}T_0p-\delta=\delta(1-R_0)\leq 0.$$

Since $R_0<1$, we have

$$\begin{aligned}\frac{dW_1}{dt}&=-\left(s\frac{(T-T_0)^2}{TT_0}-\frac{a}{T_{max}}((T-T_0)+I)^2+2\delta(1-R_0)\right)\\&\leq 0.\end{aligned}$$

Hence if $R_0<1$, then $\frac{dW_1}{dt}\leq 0$. Therefore, the maximal compact invariant set in $\left\{\frac{dW_1}{dt}=0\right\}$ is the singleton E^0. By the LaSalle invariance principle for delay systems [25], the infection free equilibrium of (1.1) is globally attracting. In previous section, we proved that the infection free equilibrium is locally asymptotically stable when $R_0<1$. Therefore, the disease free equilibrium of model (1.1) is globally asymptotically stable when $R_0<1$. □

Determining the global convergence to the infected equilibrium or uniform persistence of solutions is important in understanding the threshold dynamics in the viral systems. The uniform persistence of system (1.1) can be shown by using the persistence theory in [26], for infinite dimensional systems, as in the proof of [27] (Theorem 4.1) or [28] (Theorem 5). We present this result in the following theorem and omit the proof.

Theorem 2.4. *If $R_0>1$, then the system* (1.1) *is uniformly persistent, that is, there is a constant $\gamma_0>0$ such that $\liminf_{t\to\infty}T(t)\geq\gamma_0$, $\liminf_{t\to\infty}I(t)\geq\gamma_0$, $\liminf_{t\to\infty}V(t)\geq\gamma_0$ and $\liminf_{t\to\infty}H(t)\geq\gamma_0$.*

Theorem 2.5. *If the basic reproductive number satisfies $R_0>1$, then the chronic infection equilibrium $\hat{E}$ of model* (1.1) *is globally attracting.*

Proof. We define a Lyapunov functional $W_2(t)$ as follows,

$$\begin{aligned}W_2(t)=&\left(T-\hat{T}\ln\frac{T}{\hat{T}}\right)+\left(I-\hat{\hat{I}}\ln\frac{I}{\hat{I}}\right)+\frac{(1-\epsilon)\beta\hat{T}}{c}\left(V-\hat{V}\ln\frac{V}{\hat{V}}\right)\\&\times\left(\frac{d}{\gamma}\right)\left(H-\hat{H}\ln\frac{H}{\hat{H}}\right)+(1-\epsilon)\beta\hat{T}\hat{V}\int_{-\tau_1}^{0}g\left(\frac{T(t+\sigma)V(t+\sigma)}{\hat{T}\hat{V}}\right)d\sigma\\&\times\left(\frac{d}{\gamma}\right)\gamma\hat{I}\int_{-\tau_2}^{0}g\left(\frac{I(t+\sigma)}{\hat{I}}\right)d\sigma,\end{aligned}$$

where, $u(x) = x - 1 - \ln x$, and the function $g(x) \geq 0$, for all $x \in (0, \infty)$ and $u(x) = 0$, if and only if $x = 1$. Note that $\hat{E}$ of (1.1) satisfies

$$\begin{aligned} a - d &= -\frac{s}{\hat{T}} + (1-\epsilon)\beta\hat{V} + \frac{a}{T_{max}}(\hat{T} + \hat{I}), \\ a - \delta &= -\frac{(1-\epsilon)\beta\hat{T}\hat{V}}{\hat{I}} + \frac{a}{T_{max}}(\hat{T} + \hat{I}) + \delta\alpha\hat{H}, \\ & c\hat{V} = p\hat{I}, \\ & \gamma\hat{I} - (d_H)\hat{H} = 0 \end{aligned} \tag{2.16}$$

and directly calculate the time derivative of $W_2(t)$ along a positive solutions of (1.1) to obtain,

$$\begin{aligned} &\frac{dW_2}{dt} \\ &= \left(1 - \frac{\hat{T}}{T}\right)\frac{dT}{dt} + \left(1 - \frac{\hat{I}}{I}\right)\frac{dI}{dt} + \frac{(1-\epsilon)\beta\hat{T}}{c}\left(1 - \frac{\hat{V}}{V}\right)\frac{dV}{dt} \\ &\quad + \left(\frac{d}{\gamma}\right)\left(1 - \frac{\hat{H}}{H}\right)\frac{dH}{dt} \\ &\quad + (1-\epsilon)\beta\hat{T}\hat{V}\left\{\frac{T(t)V(t)}{\hat{T}\hat{V}} - \frac{T(t-\tau_1)V(t-\tau_1)}{\hat{T}\hat{V}} + \ln\frac{T(t-\tau_1)V(t-\tau_1)}{TV}\right\} \\ &\quad + \left(\frac{d}{\gamma}\right)\gamma\hat{I}\left\{\frac{I}{\hat{I}} - \frac{I(t-\tau_2)}{\hat{I}} + \ln\frac{I(t-\tau_2)}{I}\right\} \\ &= \left(T - \hat{T}\right)\left(\frac{s}{T} - d + a\left(1 - \frac{T+I}{T_{max}}\right) - (1-\epsilon)\beta TV\right) \\ &\quad + \left(I - \hat{I}\right)\left(\frac{(1-\epsilon)\beta T(t-\tau_1)V(t-\tau_1)}{I} - \delta - \delta\alpha H + a\left(1 - \frac{T+I}{T_{max}}\right)\right) \\ &\quad + \frac{(1-\epsilon)\beta\hat{T}}{c}\left(1 - \frac{\hat{V}}{V}\right)(pI - cV) + \left(\frac{d}{\gamma}\right)\left(1 - \frac{\hat{H}}{H}\right) \\ &\quad \times (\gamma I(t-\tau_2) - (d_H H) + (1-\epsilon)\beta TV - (1-\epsilon)\beta T(t-\tau_1)V(t-\tau_1) \\ &\quad + (1-\epsilon)\beta\hat{T}\hat{V}\ln\frac{T(t-\tau_1)V(t-\tau_1)}{TV} + \left(\frac{d}{\gamma}\right)\gamma\hat{I}\left(\frac{I}{\hat{I}}\right) - (d)I(t-\tau_2) \\ &\quad + \left(\frac{d}{\gamma}\right)\ln\left(\frac{I(t-\tau_2)}{I}\right). \end{aligned} \tag{2.17}$$

By using (2.16), the above equation (2.17) becomes

$$\begin{aligned}
\frac{dW_2}{dt} &= -\frac{s(T-\hat{T})^2}{T\hat{T}} - \frac{a}{T_{max}}((T-\hat{T})+(I-\hat{I}))^2 - (1-\epsilon)\beta TV \\
&\quad + (1-\epsilon)\beta\hat{T}V + (1-\epsilon)\beta\hat{V}T - (1-\epsilon)\beta\hat{V}\hat{T} \\
&\quad + (1-\epsilon)\beta V(t-\tau_1)T(t-\tau_1) - \frac{(1-\epsilon)\beta V(t-\tau_1)T(t-\tau_1)\hat{I}}{I} \\
&\quad - \frac{(1-\epsilon)\beta\hat{V}\hat{T}I}{\hat{I}} + (1-\epsilon)\beta\hat{V}\hat{T} - \delta\alpha(H-\hat{H}) \\
&\quad + \frac{(1-\epsilon)\beta\hat{T}}{c}pI - \frac{(1-\epsilon)\beta\hat{T}\hat{V}}{cV}pI - \frac{(1-\epsilon)\beta\hat{T}}{c}cV \\
&\quad + \frac{(1-\epsilon)\beta\hat{T}}{c}c\hat{V} + \left(\frac{d}{\gamma}\right)\left(\gamma I(t-\tau_2) - \frac{\gamma I(t-\tau_2)\hat{H}}{H} - (d_H)(H-\hat{H})\right) \\
&\quad + (1-\epsilon)\beta TV - (1-\epsilon)\beta T(t-\tau_1)V(t-\tau_1) \\
&\quad + (1-\epsilon)\beta\hat{T}\hat{V}\ln\frac{T(t-\tau_1)V(t-\tau_1)}{TV} + \left(\frac{d}{\gamma}\right)\gamma\hat{I}\left(\frac{I}{\hat{I}}\right) \\
&\quad - (d)I(t-\tau_2) + \left(\frac{d}{\gamma}\right)\ln\left(\frac{I(t-\tau_2)}{I}\right) \\
&= -\frac{s(T-\hat{T})^2}{T\hat{T}} - \frac{a}{T_{max}}((T-\hat{T})+(I-\hat{I}))^2 + (1-\epsilon)\beta\hat{V}T \\
&\quad - \frac{(1-\epsilon)\beta V(t-\tau_1)T(t-\tau_1)\hat{I}}{I} - \frac{(1-\epsilon)\beta\hat{V}\hat{T}I}{\hat{I}} + (1-\epsilon)\beta\hat{V}\hat{T} \\
&\quad - \delta\alpha(H-\hat{H}) + \frac{(1-\epsilon)\beta\hat{T}}{c}pI - \frac{(1-\epsilon)\beta\hat{T}\hat{V}}{cV}pI \\
&\quad \times\left(-\frac{(1-\epsilon)\beta\hat{T}}{c}c + (1-\epsilon)\beta\hat{T}\right)V + \left(\frac{(1-\epsilon)\beta\hat{T}}{c}c - (1-\epsilon)\beta\hat{T}\right)\hat{V} \\
&\quad - \left(\frac{d}{\gamma}\right)\left(\frac{\gamma I(t-\tau_2)\hat{H}}{H}\right) + (1-\epsilon)\beta\hat{T}\hat{V}\ln\frac{T(t-\tau_1)V(t-\tau_1)}{TV} \\
&\quad + \left(\frac{d}{\gamma}\right)\gamma\hat{I}\left(\frac{I}{\hat{I}}\right) + \left(\frac{d}{\gamma}\right)\ln\left(\frac{I(t-\tau_2)}{I}\right) \\
&\leq -\frac{s(T-\hat{T})^2}{T\hat{T}} - \frac{a}{T_{max}}((T-\hat{T})+(I-\hat{I}))^2 - \gamma\hat{I}\frac{(I-\hat{I})^2}{I\hat{I}} \\
&\quad + \left(\gamma\hat{I} - (d_H)\hat{H}\right)\frac{(I-\hat{I})^2}{I\hat{I}} - (d_H)\hat{I}\left(2 + g\left(\frac{\hat{I}H}{\hat{H}I}\right) + g\left(\frac{I(t-\tau_2)\hat{H}}{H\hat{I}}\right)\right) \\
&\quad - (1-\epsilon)\beta\hat{T}\hat{V}\left\{2 + g\left(\frac{\hat{T}}{T}\right) + g\left(\frac{T(t-\tau_1)V(t-\tau_1)\hat{I}}{\hat{T}\hat{V}I}\right) + g\left(\frac{\hat{V}I}{\hat{I}V}\right)\right\} \\
&\leq 0. \qquad (2.18)
\end{aligned}$$

Thus $\frac{dW_2}{dt} \leq 0$. Let $\Gamma = \left\{(T, I, V, E) : \frac{dW_2}{dt} = 0\right\}$ and $\hat{E}$ be the largest invariant set in Γ. Note that $\frac{dW_2}{dt} = 0$ if and only if $T = \hat{T}$, $\hat{I}T(t-\tau_1)V(t-\tau_1) = I\hat{T}\hat{V}$, $I\hat{V} = \hat{I}V$, $I\hat{H} = \hat{I}H$ and $I(t-\tau_2)\hat{H} = H\hat{I}$. Therefore, the maximal compact invariant set in $\left\{\frac{dW_2}{dt} = 0\right\}$ is the singleton $\hat{E}$. By the LaSalle invariance principle for delay systems [25], the chronic infection equilibrium of (1.1) is globally attracting. In previous section, we proved that the chronic infection equilibrium of model (1.1) is locally asymptotically stable when $R_0 > 1$. Therefore, the chronic infection equilibrium of model (1.1) is globally asymptotically stable when $R_0 > 1$. □

3. Numerical simulations

In this section, we illustrate some simulation results performed to validate the analytical results of model (1.1) using Maple. We present some such examples using different levels of therapy intervention. In spite of what seems to be observe restrictions to the applicability of the model (1.1), there are still some interesting findings illustrated by the following cases.

Fix the parameters

$$\begin{aligned} s &= 4365, & \beta &= 4.1 \times 10^{-6}, \\ \delta &= 3, & \beta_H &= 7.3 \times 10^{-8}, \\ p &= 13.48, & T_{max} &= 4.106 \times 10^{8}, \\ d &= 1.06 \times 10^{-3}, & c &= 2.06, \\ d_H &= 9 \times 10^{-3}, & \alpha &= 5 \times 10^{-3}, \\ \gamma &= 2 \times 10^{-8}, & V_H &= 1 \times 10^{6}, \\ a &= 3, & \epsilon &= 0.85. \end{aligned}$$

We obtain the characteristic equation for the above system (1.1) consider for the following cases.

Case 1: We obtain the characteristic equation for $\epsilon = 0.85$ as follows:

$$\begin{aligned} &\lambda^4 - 5.506603785 \times 10^5 \lambda^3 + 1.117238907 \times 10^9 \lambda^2 + 4.102776713 \times 10^9 \lambda \\ &\quad + 1.900088900 \times 10^9 + e^{-21\lambda}(40.8218758\lambda^2 - 2.239588860 \times 10^7 \lambda \\ &\quad - 4.613570376 \times 10^7) = 0. \end{aligned} \tag{3.1}$$

For $\epsilon = 0.85$, $\tau_1 = 0$ and $\tau_2 = 3$ weeks (21 days). Hence the above equation (3.1) is stable when $\tau_2 > 0$. It can be shown from the following Figure 1.

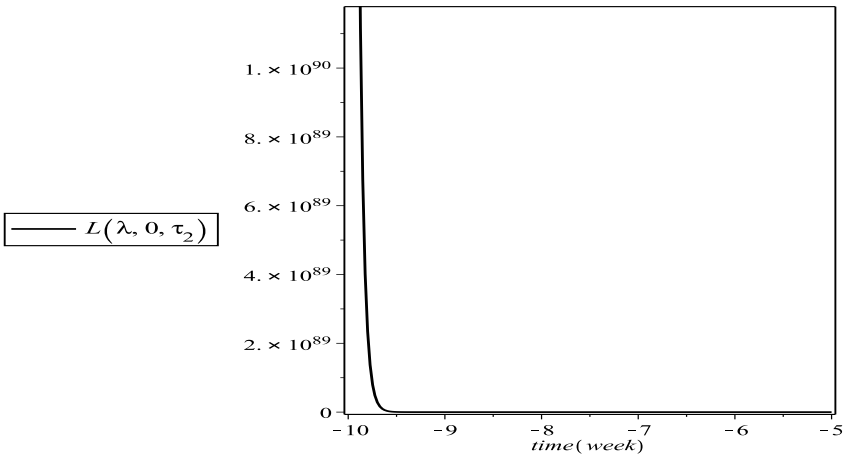

Figure 1

Case 2: For $\epsilon = 0.90$, $\tau_1 = 0$ and $\tau_2 = 2$ weeks (14 days), we depict the characteristic equation as follows:

$$\lambda^4 - 2.451892421 \times 10^5\lambda^3 + 3.310058143 \times 10^8\lambda^2 + 1.214847951 \times 10^9\lambda + 5.625044666 \times 10^8 + e^{-14\lambda}(27.1892787\lambda^2 - 6.629628711 \times 10^6\lambda - 1.365715053 \times 10^7) = 0. \tag{3.2}$$

Hence the above system (3.2) is stable when $\tau_2 > 0$. It can be shown from the following Figure 2.

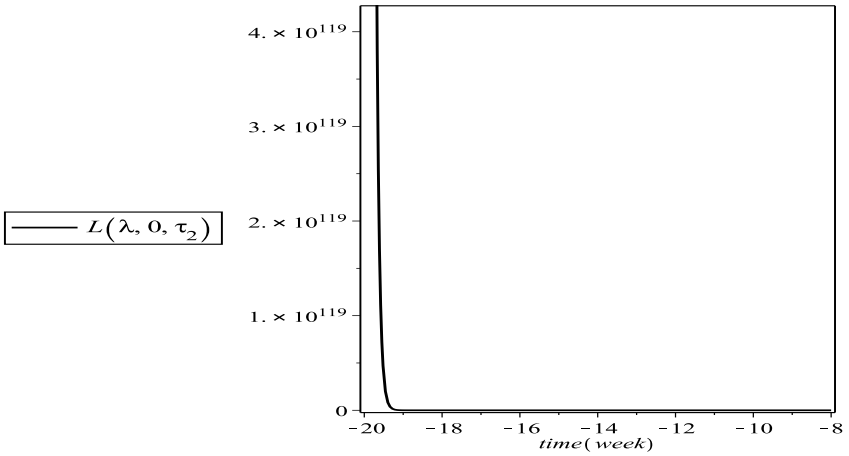

Figure 2

Case 3: For $\epsilon = 0.95$, $\tau_1 = 0$ and $\tau_2 = 1$ week, 3 days (10 days), we obtain the characteristic equation as follows:

$$\begin{aligned}\lambda^4 - 61634.99476\lambda^3 + 4.136395210 \times 10^7\lambda^2 + 1.515594467 \times 10^8\lambda \\ + 7.013121938 \times 10^7 + e^{-10\lambda}(6.317921546 \times 10^7\lambda^2 \\ - 8.263763638 \times 10^5\lambda - 1.702392839 \times 10^6) = 0. \qquad (3.3)\end{aligned}$$

Hence the above system (3.3) is stable when $\tau_2 > 0$. It can be shown from the following Figure 3.

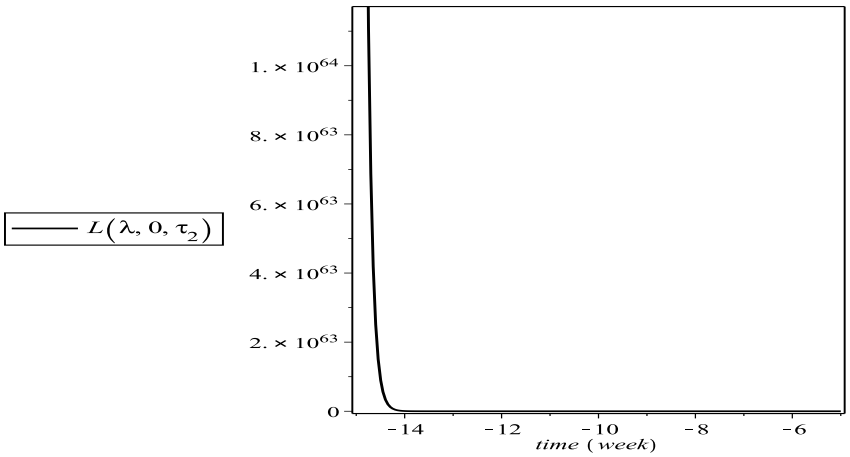

Figure 3

Letting $\tau_1 = 0$, $\tau_2 > 0$ all the characteristic roots of the characteristic equation of the HIV co-infection model on HCV dynamics have negative real parts. (see Fig 1, 2, 3). It is also verified that the steady state $\hat{E}(\hat{T}, \hat{I}, \hat{V}, \hat{H})$ of the HIV co-infection on HCV is stable in the following three cases:

(i) $\bar{\tau} = 0$ and $\tau_2 \in [0, \tau_2^*), \tau_2 = 3$weeks (21 days) for $\epsilon = 0.85$;
(ii) $\bar{\tau} = 0$ and $\tau_2 \in [0, \tau_2^*), \tau_2 = 2$weeks (14 days) for $\epsilon = 0.90$;
(iii) $\bar{\tau} = 0$ and $\tau_2 \in [0, \tau_2^*), \tau_2 = 1$week and 3 days (10days) for $\epsilon = 0.95$.

From the above figures, finally we can easily shown that the drug period plays an important role in the disease spread and that the disease may be controlled by the consuming level of therapy intervention in the drug period (that is, The high amount of therapy can reducing the infection at the small level of period).

4. Conclusion

In this paper, we have proposed and analyzed a model of delayed immunological impact of HIV co-infection on HCV. The model results presented here

give a theoretical demonstration of the effect that HIV coinfection can have on the course of HCV infection. We examined the local stability analysis our model (1.1), which is based upon the reproduction ratio number $R_0 < 1$ and $R_0 > 1$.

Additionally, we showed that global asymptotic stability of the infected equilibrium in the presence of immune delay. Additionally, our findings have demonstrated that the drug period plays an important role in the disease spread and the disease may be controlled by shortening that drug period. The positive immune delay, τ_2 is able to destabilize the infected steady state.

We showed that for this simplified model (1.1), the chronic infection equilibrium is locally asymptotically stable for $\tau_2 < \tau_2^*$ and bifurcation leads when $\tau_2 = \tau_2^*$. By the result, the immune delay τ_2 as a bifurcation parameter, a sufficient condition has been established for existence of Hopf bifurcation at the infected equilibrium.

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