Journal of Computational and Applied Mathematics 229 (2009) 313–323

Contents lists available at ScienceDirect

Journal of Computational and Applied Mathematics

journal homepage: www.elsevier.com/locate/cam

Stability analysis of an HIV/AIDS epidemic model with treatment☆

Liming Cai [a,b,*], Xuezhi Li [a], Mini Ghosh [c], Baozhu Guo [d]

[a] Department of Mathematics, Xinyang Normal University, Xinyang 464000, PR China
[b] Beijing Institute of Information Control, Beijing 100037, PR China
[c] School of Mathematics and Computer Application, Thapar University, Patiala-147004, India
[d] Academy of Mathematics and Systems Science, Academia Sinica, Beijing 100080, PR China

ARTICLE INFO

Article history:
Received 3 November 2007
Received in revised form 21 October 2008

Keywords:
HIV/AIDS
Basic reproduction number
Global stability
Time delay
Hopf bifurcation

ABSTRACT

An HIV/AIDS epidemic model with treatment is investigated. The model allows for some infected individuals to move from the symptomatic phase to the asymptomatic phase by all sorts of treatment methods. We first establish the ODE treatment model with two infective stages. Mathematical analyses establish that the global dynamics of the spread of the HIV infectious disease are completely determined by the basic reproduction number $\mathfrak{R}_0$. If $\mathfrak{R}_0 \leq 1$, the disease-free equilibrium is globally stable, whereas the unique infected equilibrium is globally asymptotically stable if $\mathfrak{R}_0 > 1$. Then, we introduce a discrete time delay to the model to describe the time from the start of treatment in the symptomatic stage until treatment effects become visible. The effect of the time delay on the stability of the endemically infected equilibrium is investigated. Moreover, the delay model exhibits Hopf bifurcations by using the delay as a bifurcation parameter. Finally, numerical simulations are presented to illustrate the results.

1. Introduction

AIDS has developed into a global pandemic since the first patients were identified in 1981. It is reported that 38.6 million people currently live with HIV-1 infection, 4.1 million people have been newly infected and 2.8 million AIDS deaths occurred in 2005 (http://www.unaids.org/epi/2005/index.asp). Viral transmission typically occurs following exposure to cell-associated virus through: (1) contaminated blood products or syringes, (2) sexual intercourse and (3) mother to child in utero, during birth, or through breastfeeding. An individual may advance through several infective stages before developing full blown AIDS [1]. Virus number in the blood is a major indicator of the disease stages. Sometimes these stages are meant to correspond to $CD4^+$ T-cell count ranges. In a normal healthy individual's peripheral blood, the level of $CD4^+$ T-cells is between 800 and 1200/mm^3 and once this number reaches 200 or below in an HIV infected patient, the person is classified as having AIDS. Without drug treatment, HIV-1 infection is nearly uniformly fatal within 5–10 years. With drug therapies, such as HAART (highly active antiretroviral therapy), treated individuals can live longer free of HIV-related symptoms [2]. In fact, worldwide, it is estimated that between 250,000 and 350,000 deaths were averted in 2005 as a result of increased treatment access (WHO/UNAIDS 2005).

Mathematical models have been used extensively in research into the epidemiology of HIV/AIDS to help improve our understanding of the major contributing factors to the pandemic. From the initial models of May and Anderson [3–5], various

☆ Supported by the National Natural Science Foundation of China and the Natural Science Foundation of Henan Province.
* Corresponding author at: Department of Mathematics, Xinyang Normal University, Xinyang 464000, PR China.
E-mail addresses: lmcai06@yahoo.com.cn (L. Cai), xzli66@mail2.xytc.edu.cn (X. Li), minighosh@thapar.edu (M. Ghosh), Bao-Zhu.Guo@wits.ac.za (B. Guo).

0377-0427/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cam.2008.10.067

refinements have been added into modelling frameworks, and specific issues have been addressed by researchers [6–14]. In [7], S. Blower shows that incidence rates of HIV will fall as more HIV-positive individuals gain access to treatment (HAART), but the underlying assumption is that treated individuals would change their behavior and the levels of risky behavior do not increase. In [6], M. Bachar shows that treatment without reduction of risky behavior may even increase the proportion of infected individuals. Treatment increases the expected available time for the transmission of HIV. It has been shown that many infected individuals – no matter whether they are treated or not – do not change their behavior despite their knowledge of the risks. In [9,2], according to clinical symptoms or viral load and CD4 + T cell count, 2–6 stages of infection before AIDS can be classified.

On the other hand, biological delay systems of one type or another have been considered by a number of authors, and we refer the reader to [15,16] for a general reference. Delay can arise for various practical reasons in epidemiology. For example, in the paper of Hethcote et al. [17], they considered model that the delay is introduced in the removed class to account for the period of temporary immunity. Culshaw and Ruan [18] consider the time delay between infection of a CD4+ T-cell and the emission of viral particles on a cellular level to investigate the effect of the time delay on the stability of the endemically infected equilibrium. Delay is also used to model the gestation lag, the incubation time for a infectious vector and the time delay in loss of vaccine, etc. These delay-differential equation systems often exhibit much more complicated dynamical behavior than those ordinary differential systems since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate.

In this paper, according to clinical symptoms, we shall first establish the ODE model with two infective stages before AIDS defined in [9,2]. i.e., the asymptomatic and the symptomatic phases. By all sorts of treatment methods, some individuals with the symptomatic phases can be transformed into asymptomatic individuals. By introducing discrete time delay (onset of treatment effects) to the model, we shall establish the delay differential equation model. One of our purpose is to investigate the effect the treatment on the long term dynamics of the disease. Our results show that treatment may result in the disease persisting or dying out, depending on parameter values. The other one is to investigate the effect of the time delay on the stability of the endemically infected equilibrium.

The organization of this paper is as follows: In the next section, the ODE model is presented and the basic reproduction number is obtained. In Section 3, equilibria and their stability are investigated, respectively. In Section 4, the delayed model is presented and dynamical behaviors are investigated, respectively. The paper ends with a discussion.

2. The ODE model and the basic reproduction number

To construct the model, we first divide the total population into a susceptible class of size S and an infectious class before the onset of AIDS and a full-blown AIDS group of size A which is removed from the active population. Based on the facts that the infectious period is very long ($\geq$ 10 years), we further consider several stages of the infectious period. For simplicity, we only consider two stages according to clinic stages and papers [9,2], i.e., the asymptomatic phase (I) and the symptomatic phase (J). Thus, we first establish the following model:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - c\beta(I + bJ)S - \mu S,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= c\beta(I + bJ)S - (\mu + k_1)I + \alpha J,\\
\frac{\mathrm{d}J}{\mathrm{d}t} &= k_1 I - (\mu + k_2 + \alpha)J,\\
\frac{\mathrm{d}A}{\mathrm{d}t} &= k_2 J - (\mu + d)A,
\end{aligned} \tag{2.1}$$

where, μK is the recruitment rate of the population, μ is the number of death rate constant. c is the average number of contacts of an individual per unit of time. β and $b\beta$ are probability of disease transmission per contact by an infective in the first stage and in the second stage, respectively. k_1 and k_2 are transfer rate constant from the asymptomatic phase I to the symptomatic phase J and from the symptomatic phase to the AIDS cases, respectively. α is treatment rate from the symptomatic phase J to the asymptomatic phase I. d is the disease-related death rate of the AIDS cases.

Since the variable A of system (2.1) does not appear in the first three equation, in the subsequent analysis, we only consider the subsystem:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - c\beta(I + bJ)S - \mu S,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= c\beta(I + bJ)S - (\mu + k_1)I + \alpha J,\\
\frac{\mathrm{d}J}{\mathrm{d}t} &= k_1 I - (\mu + k_2 + \alpha)J.
\end{aligned} \tag{2.2}$$

It follows from system (2.2) that

$$\begin{aligned}(S+I+J)' &= \mu K - \mu(S+I+J) - k_2 J\\ &\le \mu[K-(S+I+J)].\end{aligned}$$

Then

$$\lim_{t\to\infty} \sup(S+I+J) \le K.$$

Thus the feasible region for system (2.2) is

$$\Gamma = \{(S,I,J) : S+I+J \le K, S>0, I\ge 0, J\ge 0\}.$$

Let $Int\,\Gamma$ denote the interior of Γ. It is easy to verify that the region Γ is a positively invariant with respect to system (2.2). In the following, we will investigate dynamic behavior of system (2.2) on Γ. Now, we firstly investigate the basic reproduction number of system (2.2) by the method of next generation matrix formulated in [19].

It is easy to see that system (2.2) has always a disease-free equilibrium, $E_0 = (K, 0, 0)$.

Let $x = (I, J, S)^T$. System (2.2) can be written as

$$x' = \mathcal{F}(x) - \mathcal{V}(x), \tag{2.3}$$

where

$$\mathcal{F}(x) = \begin{pmatrix} c\beta S(I+bJ)\\ 0\\ 0\end{pmatrix}, \quad \mathcal{V}(x) = \begin{pmatrix} (\mu+k_1)I - \alpha J\\ -k_1 I + (\mu+k_2+\alpha)J\\ -\mu K + c\beta S(I+bJ) + \mu S\end{pmatrix}.$$

The Jacobian matrices of $\mathcal{F}(x)$ and $\mathcal{V}(x)$ at the disease-free equilibrium E_0 are, respectively,

$$D\mathcal{F}(E_0) = \begin{pmatrix} F & 0\\ 0 & 0\end{pmatrix}, \quad D\mathcal{V}(E_0) = \begin{pmatrix} V & 0\\ c\beta K & c\beta bK\end{pmatrix},$$

where,

$$F = \begin{pmatrix} c\beta K & cb\beta K\\ 0 & 0\end{pmatrix}, \quad V = \begin{pmatrix} \mu+k_1 & -\alpha\\ -k_1 & \mu+k_2+\alpha\end{pmatrix}.$$

FV^{-1} is the next generation matrix of system (2.2). It follows that the spectral radius of matrix FV^{-1} is

$$\rho(FV^{-1}) = \frac{c\beta K(\mu+k_2+\alpha+bk_1)}{(\mu+k_1)(\mu+k_2)+\mu\alpha}. \tag{2.4}$$

According to [19, Theorem 2], the basic reproduction number of system (2.2) is

$$\mathfrak{R}_0 = \frac{c\beta K(\mu+k_2+\alpha+bk_1)}{(\mu+k_1)(\mu+k_2)+\mu\alpha}. \tag{2.5}$$

3. Equilibria and their stability

Except for a disease-free equilibrium $E_0 = (K, 0, 0)$, by straightforward computation, system (2.2) has the unique positive equilibrium $E^*(S^*, I^*, J^*)$ for $\mathfrak{R}_0 > 1$, where

$$S^* = \frac{(\mu+k_1)(\mu+k_2)+\alpha\mu}{c\beta(\mu+k_2+\alpha+bk_1)}, \quad I^* = \frac{(\mu+k_2+\alpha)\mu K}{(\mu+k_1)(\mu+k_2)+\alpha\mu}\left(1-\frac{1}{\mathfrak{R}_0}\right), \quad J^* = \frac{k_1}{\mu+k_2+\alpha} I^*.$$

We first investigate the local geometric properties of the equilibria of system (2.2). Linearizing system (2.2) at equilibrium $E_0(K, 0, 0)$, we obtain the characteristic equation about E_0.

$$(\lambda+\mu)(\lambda^2 + a_1\lambda + a_2) = 0, \tag{3.1}$$

where

$$\begin{aligned} a_1 &= \mu + k_1 + \mu + k_2 + \alpha - c\beta K,\\ a_2 &= (\mu+k_1)(\mu+k_2) + \alpha\mu - c\beta K(\mu+k_2+\alpha+bk_1).\end{aligned} \tag{3.2}$$

Clearly, one root of the characteristic equation (3.1) is $\lambda_1 = -\mu$. The other two roots are determined by the quadratic equation

$$\lambda^2 + a_1\lambda + a_2 = 0. \tag{3.3}$$

If $\Re_0 < 1$, then

$$(\mu + k_1)(\mu + k_2) + \alpha\mu - c\beta K(\mu + k_2 + \alpha + bk_1) > 0. \tag{3.4}$$

Thus, from (3.4) we have $a_2 > 0$. It follows from

$$(\mu + k_1)(\mu + k_2) + \alpha(\mu + k_1) > (\mu + k_1)(\mu + k_2) + \alpha\mu > c\beta K(\mu + k_2 + \alpha + bk_1)$$

that $(\mu + k_1)(\mu + k_2 + \alpha) > c\beta K(\mu + k_2 + \alpha + bk_1)$. Therefore, we have

$$\mu + k_1 > c\beta K(1 + bk_1/(\mu + k_2 + \alpha)) > c\beta K.$$

Thus $a_1 > 0$ and all roots of the Eq. (3.3) have negative real parts if and only if $\Re_0 < 1$. So, E_0 is locally asymptotically stable for $\Re_0 < 1$. If $\Re_0 = 1$, one eigenvalue of (3.1) is 0 and it is simple. If $\Re_0 > 1$, the characteristic equation (3.1) has positive eigenvalue. So, E_0 is thus unstable with $dimW^s(E_0) = 2$ and $dimW^u(E_0) = 1$. We first establish the following result for E_0.

Theorem 3.1. *If $\Re_0 < 1$, the disease-free equilibrium E_0 of system (2.2) is locally asymptotically stable. If $\Re_0 = 1$, E_0 is locally stable. If $\Re_0 > 1$, E_0 is a saddle point with $dimW^s(E_0) = 2$ and $dimW^u(E_0) = 1$.*

Let $w = \mu + k_1, \quad v = \mu + k_2$. Linearizing system (2.2) about the positive equilibrium E^* gives the following Jacobian matrix

$$\frac{\partial f}{\partial x}(E^*) = \begin{bmatrix} -\dfrac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} - \mu & -c\beta S^* & -bc\beta S^* \\ \dfrac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} & c\beta S^* - w & bc\beta S^* + \alpha \\ 0 & k_1 & -(v + \alpha) \end{bmatrix}, \tag{3.5}$$

with $c\beta(I^* + bJ^*) = \frac{(wv+\alpha\mu)I^*}{(v+\alpha)S^*}$.

The second additive compound matrix $\partial f^{[2]}/\partial x(E^*)$ of $J(E^*)$ is given by

$$\frac{\partial f^{[2]}}{\partial x}(E^*) = \begin{bmatrix} \begin{pmatrix} -\mu - \dfrac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} \\ +c\beta S^* - w \end{pmatrix} & bc\beta S^* + \alpha & bc\beta S^* \\ k_1 & \begin{pmatrix} -\mu - \dfrac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} \\ -v - \alpha \end{pmatrix} & -c\beta S^* \\ 0 & \dfrac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} & \begin{pmatrix} c\beta S^* - w \\ -v - \alpha \end{pmatrix} \end{bmatrix} \tag{3.6}$$

To demonstrate the local stability of the positive equilibrium E^*, we need the following lemma.

Lemma 3.1 (*[20,21]*). *Let M be a 3×3 real matrix. If $tr(M)$, $det(M)$ and $det(M^{[2]})$ are all negative, then all of the eigenvalues of M have negative real part.*

Theorem 3.2. *The positive equilibrium E^* of system (2.2) is locally asymptotically stable if $\Re_0 > 1$.*

Proof. It follows from $w > c\beta S^*$ that $tr(\partial f/\partial x)(E^*) = -\mu - \frac{(wv+\alpha\mu)I^*}{(v+\alpha)S^*} + c\beta S^* - w - v - \alpha < 0$. It follows from (3.5) that the determinant of $(\partial f/\partial x)(E^*)$ is given by

$$det\left(\frac{\partial f}{\partial x}(E^*)\right) = -\frac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*}(v + \alpha + k_1 b)c\beta S^* < 0. \tag{3.7}$$

Computing directly, taking the determinant of $\frac{\partial f^{[2]}}{\partial x}$ as it appears in Eq. (3.6) gives

$$\begin{aligned} det\left(\frac{\partial f^{[2]}}{\partial x}(E^*)\right) = &-(v + \alpha + w - c\beta S^*)\left[\left(\mu + \frac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*}\right)^2 + \left(\mu + \frac{(wv + \alpha\mu)I^*}{(v + \alpha)S}\right)(w - c\beta S^*)\right] \\ &- (v + \alpha)^2\left(\mu + \frac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*}\right) - \mu(w - c\beta S^*)(v + \alpha) - \frac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} \\ &\times \left[c\beta S^*\left(\mu + \frac{(wv + \alpha\mu)I^*}{(v + \alpha)S^*} + w - c\beta S^*\right)\right] - \frac{\alpha k_1(wv + \alpha\mu)I^*}{(v + \alpha)S^*} < 0. \end{aligned} \tag{3.8}$$

Noting that if $\Re_0 > 1$, then $w - c\beta S^* > 0$. Thus, $det(\frac{\partial f^{[2]}}{\partial x}(E^*)) < 0$. Hence, the result follows from Lemma 3.1.

This completes the proof of Theorem 3.2. □

We are now in a position to investigate the global stability of the disease-free equilibrium E_0 when $\Re_0 \leq 1$. Consider the following Lyapunov function $L = (\mu + k_2 + \alpha + bk_1)I + (b(\mu + k_1) + \alpha)J$. Thus, if $\Re_0 \leq 1$, we have

$$\begin{aligned}\frac{dL}{dt} &= (\mu + k_2 + \alpha + bk_1)\frac{dI}{dt} + (b(\mu + k_1) + \alpha)\frac{dJ}{dt}\\ &= [(\mu + k_2 + \alpha + bk_1)c\beta S - ((\mu + k_1)(\mu + k_2) + \alpha\mu)](I + bJ)\\ &\leq [(\mu + k_2 + \alpha + bk_1)c\beta K - ((\mu + k_1)(\mu + k_2) + \alpha\mu)](I + bJ)\\ &= [((\mu + k_1)(\mu + k_2) + \alpha\mu)](\Re_0 - 1)(I + bJ)\\ &\leq \rho((\mu + k_1)(\mu + k_2) + \alpha\mu)(\Re_0 - 1)L\\ &\leq 0,\end{aligned} \tag{3.9}$$

where $\rho = \min\{\frac{1}{\mu+k_2+\alpha+bk_1}, \frac{b}{\alpha+b(\mu+k_1)}\}$.

The maximal compact invariant set in $\{(S, I, J) \in \Gamma : dL/dt = 0\}$ is the singleton $\{E_0\}$ when $\Re_0 \leq 1$. The global stability of E_0 follows from the LaSalle invariance principle [22].

From the above discussion, we have the following conclusion:

Theorem 3.3. *If $\Re_0 \leq 1$, then the infection-free equilibrium E_0 is globally stable in Γ. If $\Re_0 > 1$, then E_0 is unstable.*

Next, we deal with the uniform persistence of system (2.2).

Theorem 3.4. *If $\Re_0 > 1$, then system (2.2) is uniformly persistent in Int Γ, i.e., there exists a constant $0 < \eta < 1$ (independent of initial conditions), such that any solution $(S(t), I(t), J(t))$ of (2.2) satisfying $\liminf_{t\to+\infty} S(t) > \eta$, $\liminf_{t\to+\infty} I(t) > \eta$, and $\liminf_{t\to+\infty} J(t) > \eta$.*

Proof. We shall apply [23, Theorem 4.6] to show this result. To do so, we choose $X = \Omega, X_1 = int\,\Omega, X_2 = bd(\Omega)$. Similar to the [11, proof of Lemma 3.5], it is easy to obtain that $Y_2 = \{(S, 0, 0) : 0 < S \leq K\}$, $\Omega_2 = \bigcup_{y\in Y_2} \omega(y) = \{E_0\}$, and $\{E_0\}$ is a isolated compact invariant set in X. Furthermore, let $M = \{E_0\}$, we have M is an acyclic isolated covering of Ω_2.

Now we only need to show that $\{E_0\}$ is a weak repeller for X_1. Suppose that there exists a positive orbit $(S(t), I(t), J(t))$ of (2.2) such that

$$\lim_{t\to+\infty} S(t) = K, \quad \lim_{t\to+\infty} I(t) = 0, \quad \lim_{t\to+\infty} J(t) = 0.$$

Since $\Re_0 > 1$, there exists a small enough $\varepsilon > 0$, such that

$$c\beta(K - \varepsilon)(\mu + k_2 + \alpha + bk_1) > (\mu + k_1)(\mu + k_2) + \alpha\mu. \tag{3.10}$$

From (2.2), we choose $t_0 > 0$ large enough such that when $t \geq t_0$, we have

$$\begin{aligned}\frac{dI}{dt} &> [bc\beta(K - \varepsilon)]J - [\mu + k_1 - c\beta(K - \varepsilon)]I,\\ \frac{dJ}{dt} &= k_1 I - (\mu + k_2 + \alpha)J.\end{aligned} \tag{3.11}$$

Consider the following matrix M_ε defined by

$$M_\varepsilon = \begin{pmatrix} -[\mu + k_1 - c\beta(K - \varepsilon)] & bc\beta(K - \varepsilon) + \alpha \\ k_1 & -(\mu + k_2 + \alpha) \end{pmatrix}.$$

Since M_ε admits a positive off-diagonal element, the Perron–Frobenius Theorem implies that there is a positive eigenvector $v = (v_1, v_2)$ for the maximum eigenvalue λ^* of M_ε. From (3.10), we see that the maximum eigenvalue λ^* is positive. Let us consider the following system:

$$\begin{aligned}\frac{du_1}{dt} &= [bc\beta(K - \varepsilon)]u_2 - [\mu + k_1 - c\beta(K - \varepsilon)]u_1,\\ \frac{du_2}{dt} &= k_1 u_1 - (\mu + k_2 + \alpha)u_2.\end{aligned} \tag{3.12}$$

Let $u(t) = (u_1(t), u_2(t))$ be a solution of (3.12) through (lv_1, lv_2) at $t = t_0$, where $l > 0$ satisfies $lv_1 < I(t_0), lv_2 < J(t_0)$. Since the semiflow of (3.12) is monotone and $M_\varepsilon v > 0$, it follows that $u_i(t)$ are strictly increasing and $u_i(t) \to +\infty$ as $t \to +\infty$, contradicting the eventual boundedness of positive solutions of system (2.2). Thus, E_0 is weak repeller for X_1. This completes the proof of Theorem 3.4.

Now we investigate the global stability of the infectious steady state. To do this, we apply Theorem 4.1 of [24] to show the system (2.2) has no periodic solutions, homoclinic loops and oriented phase polygons inside the invariant region. For its applications, we refer the reader to [25,26].

Set

$$\Gamma_1 = \left\{(S,I,J) \in \Gamma : S + I + \frac{\mu + k_2}{\mu} J > K\right\},$$
$$\Gamma^* = \left\{(S,I,J) \in \Gamma : S + I + \frac{\mu + k_2}{\mu} J = K\right\},$$
$$\Gamma_2 = \left\{(S,I,J) \in \Gamma : S + I + \frac{\mu + k_2}{\mu} J < K\right\}.$$

Thus, Γ_1, Γ^*, Γ_2 are pairwise disjoint subject of Γ, and $\Gamma = \Gamma_1 \cup \Gamma^* \cup \Gamma_2$. Let $N_1 = S + I + J$, $(S,I,J) \in \Gamma$. From system (2.2), the equation for the total population N_1 is

$$\frac{\mathrm{d}N_1}{\mathrm{d}t} = \mu K - \mu N_1 - k_2 J. \tag{3.13}$$

Obviously, in Γ_1, Γ^*, Γ_2, we have $\frac{\mathrm{d}N_1}{\mathrm{d}t} > 0$, $\frac{\mathrm{d}N_1}{\mathrm{d}t} = 0$, $\frac{\mathrm{d}N_1}{\mathrm{d}t} < 0$, respectively. It follows that Γ^* is a positively invariant set in Γ.

Theorem 4.1 of Busenberg and van den Driessche [24] are stated as follows.

Let $g(S,I,J) = \{g_1(S,I,J), g_2(S,I,J), g_3(S,I,J)\}$ be a vector field which is piecewise smooth on Γ^*, and which satisfies the conditions $g \cdot f = 0$ and $(\mathrm{curl}\, g) \cdot (1,1,1) < 0$ in the interior of Γ^*, where $f = (f_1, f_2, f_3)$ is a Lipschitz continuous field in the interior of Γ^* and

$$\mathrm{curl}\, g := \det \begin{pmatrix} \vec{i} & \vec{j} & \vec{k} \\ \dfrac{\partial}{\partial S} & \dfrac{\partial}{\partial I} & \dfrac{\partial}{\partial J} \\ g_1 & g_2 & g_3 \end{pmatrix}.$$

Then the differential equation system $\mathrm{d}S/\mathrm{d}t = f_1$, $\mathrm{d}I/\mathrm{d}t = f_2$, $\mathrm{d}J/\mathrm{d}t = f_3$ has no periodic solutions, homoclinic loops and oriented phase polygons in Γ^*.

Thus, we can state the following theorem.

Theorem 3.5. *The system (2.2) has no periodic solutions, homoclinic loops and oriented phase polygons inside the invariant region Γ^*.*

Proof. Let f_1, f_2 and f_3 denote the right hand side of system (2.2), respectively. Now we use the relation $S + I + \frac{\mu+k_2}{\mu} J = K$ to rewrite them in the equivalent forms:

$$\begin{aligned}
f_1(S,I) &= \mu K - c\beta \left[I + b(K - S - I)\frac{\mu}{\mu + k_2}\right] S - \mu S,\\
f_1(S,J) &= \mu K - c\beta S \left[K - S - \frac{\mu + k_2}{\mu} J + bJ\right] - \mu S,\\
f_2(S,I) &= c\beta S \left[I + b(K - S - I)\frac{\mu}{\mu + k_2}\right] - (\mu + k_1) I + \alpha(K - S - I)\frac{\mu}{\mu + k_2},\\
f_2(I,J) &= c\beta(I + bJ)\left(K - I - \frac{\mu + k_2}{\mu} J\right) - (\mu + k_2) I + \alpha J,\\
f_3(S,J) &= k_1 \left(K - S - \frac{\mu + k_2}{\mu} J\right) - (\mu + k_2 + \alpha) J,\\
f_3(I,J) &= k_1 I - (\mu + k_2 + \alpha) J.
\end{aligned} \tag{3.14}$$

Let $g = (g_1, g_2, g_3)$ be a vector field, where

$$\begin{aligned}
g_1 &= \frac{f_3(S,J)}{SJ} - \frac{f_2(S,I)}{SI} = -\frac{k_1(K - S)}{SJ} - \frac{k_1 k_2 + \mu(k_2 + \alpha)}{\mu S} - \frac{\mu(bc\beta S + \alpha)(K - S - I)}{(\mu + k_2) SI} - c\beta,\\
g_2 &= \frac{f_1(S,I)}{SI} - \frac{f_3(I,J)}{IJ} = \frac{\mu(K - S)}{SI} - c\beta - \frac{b\mu c\beta(K - S - I)}{(\mu + k_2) I} - \frac{k_1}{J} + \frac{\mu + k_2 + \alpha}{I},\\
g_3 &= \frac{f_2(I,J)}{IJ} - \frac{f_1(S,J)}{SJ} = c\beta\left(\frac{1}{J} + \frac{b}{I}\right)\left(K - I - \frac{\mu + k_2}{\mu} J\right) - \frac{k_1}{J} + \frac{\alpha}{I} - \frac{\mu K}{SJ} + \frac{c\beta K - c\beta S}{J} + b - \frac{\mu + k_2}{\mu}.
\end{aligned}$$

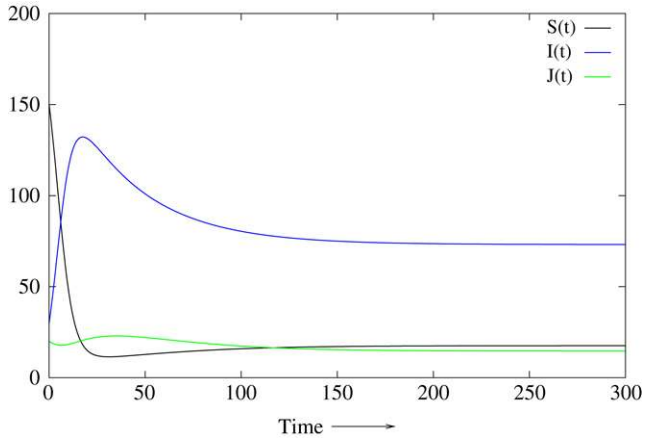

Fig. 1. Variation of S, I and J with time for the parameter values $K = 120$, $\beta_1 = 0.0005$, $b = 0.3$, $\mu = 0.02$, $c = 3$, $k_1 = 0.01$, $k_2 = 0.02$, $\alpha = 0.01$ when $\Re_0 = 6.814286$.

Clearly, $g \cdot f = 0$ on Γ^*, since the alternate forms of f_1, f_2 and f_3 are equivalent on Γ^*. Using the normal vector $\mathbf{n} = \left(\frac{1}{K}, \frac{1}{K}, \frac{\mu+k_2}{\mu K}\right)$ to Γ^*, it can be shown that the expression

$$(\text{curl } g) \cdot \mathbf{n} = -\frac{bc\beta}{I^2} + \frac{bc\beta}{I^2K}\left(S + I + \frac{\mu + k_2}{\mu}J\right) - \frac{k_1}{SJ^2} - \frac{\mu}{S^2J} - \frac{\mu + k_2}{S^2I} - \frac{bc\beta}{I^2} - \frac{\alpha}{SI^2} < 0, \tag{3.15}$$

since $S + I + \frac{\mu+k_2}{\mu}J = K$. Thus, by Theorem 4.1 in [24], the system (2.2) has no periodic solutions, homoclinic loops and oriented phase polygons inside the invariant region Γ^*. This completes the proof. □

Theorem 3.6. *If $\Re_0 > 1$, then the infected equilibrium E^* of system (2.2) is globally asymptotically stable.*

Proof. Notice that Γ^* is positively invariant subset of Γ, it follows from Theorem 3.4 that the $\omega - limit$ set of each solution of system (2.2) must be a single point in Γ^*. This implies that if E_0 is unstable (which occurs by Theorem 3.1), then E^* exists in Γ^* and it is globally asymptotically stable. This completes the proof. □

Remark. Numerical simulation in Fig. 1 verifies Theorem 3.6, where system goes to steady state solution for $\Re_0 > 1$.

4. The model with time delay

In this section, by introducing time delay to model (2.2), we investigate the effect of the time delay on the stability of the endemically infected equilibrium. Let τ be the time from the start of treatment in the symptomatic stage (J) until the treatment effects become visible. Thus, we consider the following model

$$\begin{aligned}
\frac{dS(t)}{dt} &= \mu K - c\beta(I(t) + bJ(t))S(t) - \mu S(t),\\
\frac{dI(t)}{dt} &= c\beta(I(t) + bJ(t))S(t) - (\mu + k_1)I(t) + \alpha J(t-\tau),\\
\frac{dJ(t)}{dt} &= k_1 I(t) - (\mu + k_2)J(t) - \alpha J(t-\tau),
\end{aligned} \tag{4.1}$$

with the initial values

$$S(0) = S_0, \quad I(0) = 0, \quad J(\theta) = J_0, \quad \theta \in [-\tau, 0].$$

All parameters are the same as in system (2.1) except that the constant τ represents the length of the delay in days.

System (4.1) has always the disease-free equilibrium $E_0(K, 0, 0)$ and the unique infected equilibrium $E^*(S^*, I^*, J^*)$ as in system (2.2) without delay. It is easily shown that E_0 is globally stable for $\Re_0 \leq 1$. Moreover, since the disease-free equilibrium E_0 is unstable when $\tau = 0$ and $\Re_0 > 1$, incorporation of a delay will not change the instability. Thus, E_0 is unstable for $\tau > 0$, $\Re_0 > 1$.

Now we mainly investigate the effect of the time delay on the stability of the endemically infected equilibrium. To do this, the characteristic equation corresponding to the Jacobian matrix of the linearized system of (4.1) at the equilibrium E^* is

$$\begin{vmatrix} \lambda + \dfrac{mI^*}{S^*} + \mu & c\beta S^* & bc\beta S^* \\ -\dfrac{mI^*}{S^*} & \lambda + \mu + k_1 - c\beta S^* & -bc\beta S^* - \alpha e^{-\lambda\tau} \\ 0 & k_1 & \lambda + \mu + k_2 + \alpha e^{-\lambda\tau} \end{vmatrix} = 0, \tag{4.2}$$

with $c\beta(I^* + bJ^*) = \frac{mI^*}{S^*}$, $m = \frac{(\mu+k_1)(\mu+k_2)+\alpha\mu}{\mu+k_2+\alpha}$.

Eq. (4.2) can be reduced to

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0. \tag{4.3}$$

where

$$\begin{aligned}
&P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3,\\
&Q(\lambda) = b_1\lambda^2 + b_2\lambda + b_3,\\
&a_1 = \mu + k_1 - c\beta S^* + \mu + mI^*/S^* + \mu + k_2 > 0,\\
&a_2 = (\mu + mI^*/S^*)(\mu + k_1) - c\beta\mu S^* + (\mu + k_2)(\mu + k_1 - c\beta S^* + \mu + mI^*/S^*) - k_1 bc\beta S^*,\\
&a_3 = (\mu + k_2)[(\mu + mI^*/S^*)(\mu + k_1) - c\beta\mu S^*] - k_1 bc\beta mI^* - k_1 bc\beta S^*(\mu + mI^*/S^*),\\
&b_1 = \alpha,\\
&b_2 = \alpha(\mu + k_1 - c\beta S^* + \mu + mI^*/S^*) - \alpha k_1,\\
&b_3 = \alpha\mu(\mu + mI^*/S^* - c\beta S^*).
\end{aligned}$$

To proceed, we consider Eq. (4.3) with $\tau = 0$. It follows from Theorem 3.2 that all the roots of

$$\begin{aligned}
&P(\lambda) + Q(\lambda) = 0,\\
&\Rightarrow \lambda^3 + (a_1 + b_1)\lambda^2 + (a_2 + b_2)\lambda + a_3 + b_3 = 0
\end{aligned} \tag{4.4}$$

have negative real parts. By Rouchĕ's [27, Theorem 9.17.4] and the continuity in τ, the transcendental equation (4.3) has roots with positive real parts if and only if it has purely imaginary roots. We shall determine if (4.3) has purely imaginary roots, from which we then shall be able to find conditions for all eigenvalues to have negative real parts.

Let $\lambda = \eta(\tau) + i\omega(\tau)(\omega > 0)$ be the eigenvalue of the characteristic equation (4.3), where $\eta(\tau)$ and $\omega(\tau)$ depend on the delay τ. Since the endemic equilibrium E^* of the ODE model is stable, it follows that $\eta(0) < 0$ when $\tau = 0$. By continuity, if $\tau > 0$ is sufficiently small, we still have $\eta(\tau) < 0$ and E^* is still stable. For $\eta(\tau_0) = 0$ for certain value $\tau_0 > 0$ (so that $\lambda = i\omega(\tau_0)$ is purely imaginary root of (4.3)), the positive equilibrium E^* loses stability and eventually becomes unstable when $\eta(\tau)$ becomes positive. In other words, if such $\omega(\tau_0)$ does not exist, that is, if the characteristic equation (4.3) does not have purely imaginary roots for all delay, then the positive equilibrium E^* is always stable. When $\Re_0 > 1$ and $\tau > 0$, assuming $\lambda = i\omega$ with $\omega > 0$ and substituting in (4.3) gives

$$-i\omega^3 - a_1\omega^2 + ia_2\omega + a_3 + (-b_1\omega^2 + b_2 i\omega + b_3)(\cos\omega\tau - i\sin\omega\tau) = 0. \tag{4.5}$$

Separating the real and imaginary parts, we have

$$\begin{aligned}
&a_1\omega^2 - a_3 = (b_3 - b_1\omega^2)\cos\omega\tau + b_2\omega\sin\omega\tau,\\
&\omega^3 - a_2\omega = b_2\omega\cos\omega\tau - (b_3 - b_1\omega^2)\sin\omega\tau.
\end{aligned} \tag{4.6}$$

Adding up squares of both the equations, we obtain

$$\omega^6 + (a_1^2 - 2a_2 - b_1^2)\omega^4 + (a_2^2 - b_2^2 - 2a_1a_3 + 2b_1b_3)\omega^2 + a_3^2 - b_3^2 = 0.$$

Let

$$u = \omega^2, \quad \gamma_1 = a_1^2 - 2a_2 - b_1^2, \quad \gamma_2 = a_2^2 - b_2^2 - 2a_1a_3 + 2b_1b_3, \quad \gamma_3 = a_3^2 - b_3^2.$$

Thus, we have

$$G(u) = u^3 + \gamma_1 u^2 + \gamma_2 u + \gamma_3 = 0. \tag{4.7}$$

It is easily shown that if $\gamma_2 > 0$ and $\gamma_3 \geq 0$, then Eq. (4.7) has no positive roots. This implies that there is no ω such that $i\omega$ is an eigenvalue of the characteristic equation (4.3). By Rouchĕ's Theorem, the real parts of all the eigenvalues of (4.3) are negative for all delay $\tau \geq 0$.

Therefore, we have the following results

Theorem 4.1. *If $\Re_0 > 1$ and $\gamma_2 > 0, \gamma_3 \geq 0$, then the unique infected equilibrium E^* is asymptotically stable for all delay $\tau \geq 0$.*

We notice that if $\gamma_3 < 0$, then it follows from (4.7) that $G(0) = \gamma_3 < 0$ and $\lim_{u\to\infty} G(u) = \infty$. Thus, there is at least a positive root satisfying Eq. (4.7). So, the characteristic equation (4.3) has at least a pair of purely imaginary roots of the form $\pm i\omega_0$. Eliminating $sin\tau\omega$ from (4.6), we obtain

$$\cos\omega\tau = \frac{(a_1\omega^2 - a_3)(b_3 - b_1\omega^2) + (\omega^3 - a_2\omega)b_2\omega}{(b_3 - b_1\omega^2)^2 + (b_2\omega)^2}. \tag{4.8}$$

Therefore, τ_n^* corresponding to ω_0 is given by

$$\tau_n^* = \frac{1}{\omega_0}\arccos\left[\frac{(a_1\omega_0^2 - a_3)(b_3 - b_1\omega_0^2) + (\omega_0^3 - a_2\omega_0)b_2\omega_0}{(b_3 - b_1\omega_0^2)^2 + (b_2\omega_0)^2}\right] + \frac{2n\pi}{\omega_0}. \tag{4.9}$$

For $\tau = 0$, it follows from Theorem 3.2 that the positive equilibrium E^* is stable when $\Re_0 > 1$. Hence, by Butler's Lemma [28], E^* remains stable for $\tau < \tau_0$ where $\tau_0 = \tau_0^*$ as $n = 0$.

From the above discussion, if the characteristic equation (4.3) has a pair of purely imaginary roots, then by Rouchĕ's Theorem and the continuity in τ, the transcendental equation (4.3) has roots with positive real parts. Hence E^* lose its stability. By Cooke and van den Driessche's Theorem [29], the periodic solutions may happen. To do this, we verify that the following conditions hold:

$$\left.\frac{\mathrm{d}(Re\lambda)}{\mathrm{d}\tau}\right|_{\tau=\tau_0} > 0.$$

Differentiating Eq. (4.3) with respect to τ, we have

$$[(3\lambda^2 + 2a_1\lambda + a_2) + \mathrm{e}^{-\lambda\tau}(2b_1\lambda + b_2) - \tau\mathrm{e}^{-\lambda\tau}(b_1\lambda^2 + b_2\lambda + b_3)]\frac{\mathrm{d}\lambda}{\mathrm{d}\tau} = \lambda\mathrm{e}^{-\lambda\tau}(b_1\lambda^2 + b_2\lambda + b_3).$$

This gives

$$\begin{aligned}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right)^{-1} &= \frac{3\lambda^2 + 2a_1\lambda + a_2}{\lambda\mathrm{e}^{-\lambda\tau}(b_1\lambda^2 + b_2\lambda + b_3)} + \frac{2b_1\lambda + b_2}{\lambda(b_1\lambda^2 + b_2\lambda + b_3)} - \frac{\tau}{\lambda}\\ &= \frac{3\lambda^2 + 2a_1\lambda + a_2}{-\lambda(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3)} + \frac{2b_1\lambda + b_2}{\lambda(b_1\lambda^2 + b_2\lambda + b_3)} - \frac{\tau}{\lambda}\\ &= \frac{2\lambda^3 + a_1\lambda - a_3}{-\lambda^2(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3)} + \frac{b_1\lambda^2 - b_3}{\lambda^2(b_1\lambda^2 + b_2\lambda + b_3)} - \frac{\tau}{\lambda}.\end{aligned}$$

Thus

$$\begin{aligned}\mathrm{sign}\left\{\frac{d(Re\lambda)}{d\tau}\right\}_{\lambda=i\omega_0} &= \mathrm{sign}\left\{Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\}_{\lambda=i\omega_0}\\ &= \mathrm{sign}\left\{Re\left[\frac{2\lambda^3 + a_1\lambda - a_3}{-\lambda^2(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3)} + \frac{b_1\lambda^2 - b_3}{\lambda^2(b_1\lambda^2 + b_2\lambda + b_3)} - \frac{\tau}{\lambda}\right]\right\}_{\lambda=i\omega_0}\\ &= \frac{1}{\omega_0^2}\mathrm{sign}\left[\frac{(a_3 + a_1\omega_0^2)(a_1\omega_0^2 - a_3) + 2\omega_0^3(\omega_0^3 - a_2\omega_0)}{(a_1\omega_0^2 - a_3)^2 + (\omega_0^3 - a_2\omega_0)^2} + \frac{(b_1\omega_0^2 + b_3)(b_3 - b_1\omega_0^2)}{(b_3 - b_1\omega_0^2)^2 + (b_2\omega_0)^2}\right]\\ &= \frac{1}{\omega_0^2}\mathrm{sign}\left[\frac{(a_3 + a_1\omega_0^2)(a_1\omega_0^2 - a_3) + 2\omega_0^3(\omega_0^3 - a_2\omega_0) + (b_1\omega_0^2 + b_3)(b_3 - b_1\omega_0^2)}{(b_3 - b_1\omega_0^2)^2 + (b_2\omega_0)^2}\right]\\ &= \frac{1}{\omega_0^2}\mathrm{sign}\left[\frac{2\omega_0^6 + (a_1^2 - 2a_2 - b_1^2)\omega_0^4 + (b_3^2 - a_3^2)}{(b_3 - b_1\omega_0^2)^2 + (b_2\omega_0)^2}\right].\end{aligned}$$

Notice that if $\gamma_1 = a_1^2 - 2a_2 - b_1^2 > 0$ and $\gamma_3 = a_3^2 - b_3^2 < 0$, then we have

$$\left.\frac{\mathrm{d}(Re\lambda)}{\mathrm{d}\tau}\right|_{\tau=\tau_0,\omega=\omega_0} > 0.$$

This will signify that there exists at least one eigenvalue with positive real part for $\tau > \tau_0$. The conditions for Hopf bifurcation [30] are then satisfied yielding the required periodic solution at $\omega = \omega_0, \tau = \tau_0$.

From the above analyses, we can obtain the following result:

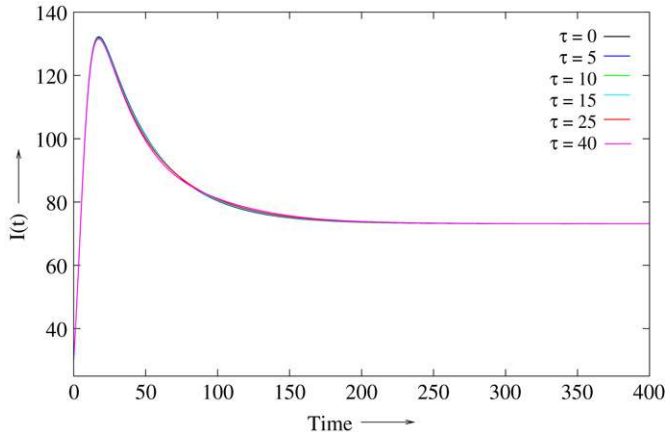

Fig. 2. Variation of I with time for different delay where other parameter values are $K = 120$, $\beta_1 = 0.0005$, $b = 0.3$, $\mu = 0.02$, $c = 3$, $k_1 = 0.01$, $k_2 = 0.02$, $\alpha = 0.01$ and $\Re_0 = 6.814286$.

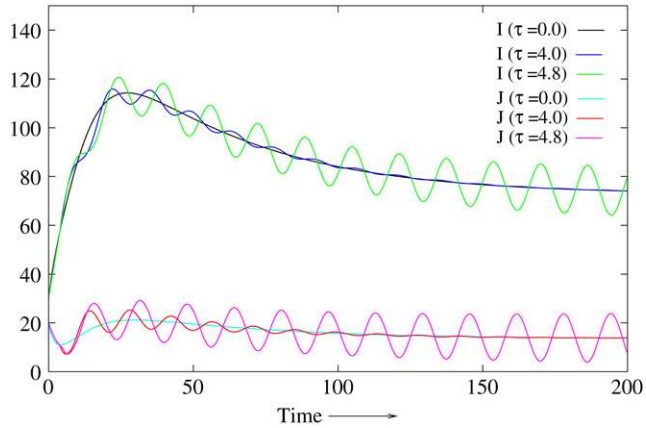

Fig. 3. Variation of I and J with time for delay parameter $\tau = 0$, $\tau < \tau_n^*$ and $\tau > \tau_n^*$ where other parameter values are $K = 120$, $\beta_1 = 0.0003$, $b = 0.3$, $\mu = 0.02$, $c = 3$, $k_1 = 0.08$, $k_2 = 0.01$, $\alpha = 0.4$ and $\Re_0 = 4.457455$ and $\tau_n^* = 4.745229$ (for $n = 0$).

Theorem 4.2. *If $\Re_0 > 1$ and $\gamma_1 > 0$, $\gamma_3 < 0$, the infected equilibrium E^* remains stable for $\tau < \tau_0$ and unstable when $\tau > \tau_0$, a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from E^* as τ passes through the critical value τ_0, where $\tau_0 = \tau_0^*$ as $n = 0$, τ_0^* is defined in (4.9).*

Numerical simulations also verify that Theorems 4.1 and 4.2 hold, which is demonstrated in Figs. 2 and 3, respectively. System (4.1) is simulated for different length of delay and Fig. 2 is showing the variation of $I(t)$ with time for delay ranging between 0 and 40. It is clear from the plot that there is minor change in the $I(t)$ as time progresses but there is no effect of delays on the steady state solution for the set of parameters satisfying $\Re_0 > 1$, $\gamma_2 > 0$, $\gamma_3 \geq 0$. Fig. 3 is showing both steady state and stable oscillation in the system which occurs for the delay $\tau < \tau_0^*$ and $\tau > \tau_0^*$, respectively, for the set of parameters satisfying $\Re_0 > 1$, $\gamma_2 > 0$, $\gamma_3 < 0$. It is observed that Hopf bifurcation occurs at $\tau = \tau_0^* = 4.745229$ where the stable equilibrium gives way to stable oscillations and it continues until high value of τ.

5. Discussion

In this paper, we have considered an HIV/AIDS treatment model. According to papers [9,2], the period of infection is divided into the asymptomatic and the symptomatic phases. By all sorts of treatment methods, individuals with the symptomatic phases can be transformed into asymptomatic individuals. The dynamics behavior of the ODE treatment model (2.2) can be determined by its basic reproduction number $\Re_0$, i.e., If $\Re_0 \leq 1$, the disease-free equilibrium is globally stable. If $\Re_0 > 1$, the disease persists and the unique endemic equilibrium is globally asymptotically stable. To explain that treatment may result in the disease persisting or in the disease dying out, depending on parameter value, we differentiate the expressions corresponding to $\Re_0$ with respect to treatment rate α. Thus we have

$$\operatorname{sgn}\left(\frac{\partial \Re_0}{\partial \alpha}\right) = \operatorname{sgn}\left(\frac{c\beta K}{\mu} - \Re_0\right). \tag{5.1}$$

From (2.5), it follows that if all other parameters are held fixed, then $\lim_{\alpha\to\infty}\Re_0 = \frac{c\beta K}{\mu}$. So, for control of disease in a population, it is generally accepted that it is desirable for $\Re_0$ to be as small as possible. Particularly, it is desired, if possible, for $\Re_0$ to be less than one. By considering (5.1), it is clear that it is possible that in the absence of treatment i.e., $\alpha = 0$ to have $\frac{c\beta K}{\mu} < 1 < \Re_0$. In this case, $\frac{\partial\Re_0}{\partial\alpha} < 0$, and if α can be made sufficiently large, then $\Re_0$ will become less than one. This means that in some situations, it is possible that treatment can be used to make E_0 stable when it would be unstable in the absence of treatment. On the other hand, if $\Re_0 < 1 < \frac{c\beta K}{\mu}$, then by making α sufficiently large, E_0 can be switched from stable to unstable, causing the disease to persistence in the population when it otherwise would have died out. For the treatment model (4.1) with time delay, Theorem 4.1 shows that if the parameters satisfy $\gamma_2 > 0$, $\gamma_3 > 0$, then the infected equilibrium E^* is asymptotically stable for all delay values, i.e., independent of the delay. However, if $\gamma_1 > 0$, $\gamma_3 < 0$ the delay can induce oscillations in system. Biologically, this means that there is a critical value for the treatment-induced delay τ_0. which determines the stability of the infected equilibrium E^*. That is, the infected equilibrium E^* is asymptotically stable when antiretroviral drugs on average show positive effects in patients within less than time delay τ_0. As soon as it takes more than time delay τ_0 for the patients to feel better, the infected equilibrium E^* loses its stability.

Acknowledgments

We are very grateful to the anonymous referee and the editor (Prof. B. Sommeijer) for their careful reading, constructive criticisms, helpful comments and suggestions, which have helped us to improve the presentation of this work significantly.

References

[1] J.A. Levy, Pathogenesis of human immunodeficiency virus infection, Microbiol. Rev. 57 (1993) 183–289.
[2] C.A. Stoddart, R.A. Reyes, Models of HIV-1 disease: A review of current status, Drug Discovery Today: Disease Models 3 (1) (2006) 113–119.
[3] R.M. Anderson, The role of mathematical models in the study of HIV transmission and the epidemiology of AIDS, J. AIDS. 1 (1988) 241–256.
[4] R.M. Anderson, G.F. Medly, R.M. May, A.M. Johnson, A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS, IMA J. Math. Appl. Med. Biol. 3 (1986) 229–263.
[5] R.M. May, R.M. Anderson, Transmission dynamics of HIV infection, Nature 326 (1987) 137–142.
[6] M. Bachar, A. Dorfmayr, HIV treatment models with time delay, C. R. Biologies 327 (2004) 983–994.
[7] S. Blower, Calculating the consequences: HAART and risky sex, AIDS 15 (2001) 1309–1310.
[8] C. Connell McCluskey, A model of HIV/AIDS with staged progression and amelioration, Math. Biosci. 181 (2003) 1–16.
[9] H.W. Hethcote, J.W. Van Ark, Modelling HIV Transmission and AIDS in the United States, in: Lect. Notes Biomath., vol. 95, Springer, Berlin, 1992.
[10] Y.-H. Hsieh, C.H. Chen, Modelling the social dynamics of a sex industry: Its implications for spread of HIV/AIDS, Bull. Math. Biol. 66 (2004) 143–166.
[11] P.D. Leenheer, H.L. Smith, Virus dynamics: A global analysis, SIAM J. Appl. Math. 63 (2003) 1313–1327.
[12] A.S. Perelson, P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41 (1) (1999) 3–44.
[13] L. Wang, M.Y. Li, Mathematical analysis of the global dynamics of a model for HIV infection of $CD4^+$ T-cells, Math. Biosci. 200 (2006) 44–57.
[14] K. Wang, W. Wang, X. Liu, Viral infection model with periodic lytic immune response, Chaos Solitons Fractals 28 (1) (2006) 90–99.
[15] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, London, 1993.
[16] Z. Ma, Y. Zhou, W. Wang, Z. Jin, Mathematical models and dynamics of infectious diseases, China Science Press, Beijing, 2004.
[17] H.W. Hethcote, M.A. Lewis, P. van den Driessche, An epidemiological model with a delay and a nonlinear incidence rate, J. Math. Biol. 27 (1989) 49–64.
[18] R.V. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of CD4+ T-cells, Math. Biosci. 165 (2000) 27–39.
[19] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (2002) 29–48.
[20] J. Arino, C.C. McCluskey, P. van den Driessche, Global results for an epidemic model with vaccination that exhibits backward bifurcation, SIAM J. Appl. Math. 64 (2003) 260–276.
[21] C.C. McCluskey, P. van den Driessche, Global analysis of two tuberculosis models, J. Dyn. Diff. Equ. 16 (2004) 139–166.
[22] J.P. LaSalle, The Stability of Dynamical Systems, in: Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, PA, 1976.
[23] R.H. Thieme, Persistence under relaxed point-dissipativity (with application to an endemic model), SIAM J. Math. Anal. 24 (1993) 407–435.
[24] S. Busenberg, P. van den Driessche, Analysis of a disease transmission model in a population with varying size, J. Math. Biol. 28 (1990) 257–270.
[25] S.M. Moghadas, A.B. Gumel, A mathematical study of a model for childhood diseases with non-permanent immunity, J. Comput. Appl. Math. 157 (2003) 347–363.
[26] J. Li, Z. Ma, Qualitative analyses of SIS epidemic model with vaccination varying total population, Math. Comput. Modelling 35 (2002) 1235–1243.
[27] J. Dieudonne, Foundations of Modern Analysis, Academic Press, New York, 1960.
[28] L.H. Erbe, V.S.H. Rao, H. Freedman, Three-species food chain models with mutual interference and time delays, Math. Biosci. 80 (1986) 57–80.
[29] K.L. Cooke, P. van den Driessche, On zeroes of some transcendental equations, Funkcial. Ekvac. 29 (1986) 77–90.
[30] J.K. Hale, Theory of Functional Differential Equations, Springer, New York, 1997.