CrossMark

Asymptotic behavior of HIV-1 epidemic model with infinite distributed intracellular delays

Nigar Ali and Gul Zaman[*]

*Correspondence:
gzaman@uom.edu.pk
Department of Mathematics,
University of Malakand,
Chakdara Dir (Lower), Khyber
Pakhtunkhawa, Pakistan

Abstract

In this study, asymptotic analysis of an HIV-1 epidemic model with distributed intracellular delays is proposed. One delay term represents the latent period which is the time when the target cells are contacted by the virus particles and the time the contacted cells become actively infected and the second delay term represents the virus production period which is the time when the new virions are created within the cell and are released from the cell. The infection free equilibrium and the chronic-infection equilibrium have been shown to be locally asymptotically stable by using Rouths Hurwiths criterion and general theory of delay differential equations. Similarly, by using Lyapunov functionals and LaSalle's invariance principle, it is proved that if the basic reproduction ratio is less than unity, then the infection-free equilibrium is globally asymptotically stable, and if the basic reproduction ratio is greater than unity, the chronic-infection equilibrium is globally asymptotically stable. Finally, numerical results with conclusion are discussed.

Keywords: HIV-1 epidemic model, Distributed delay, Unique positive solution, Stability analysis

Mathematics Subject Classification: 92D25, 49J15, 93D20, 91G20

Background

Human immunodeficiency virus (HIV-1) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS). The HIV-1 infection passes through three different phases, viz, the primary infection, chronic infection and acquired immunodeficiency syndrome (AIDS). In the primary infection, viral load experiences, a substantial increase to the peak level, followed by decline to the steady state, which is referred to as the viral set point. To control this infection, many scientists and researchers have been focusing on it, as there is no effective way to cure AIDS.

In the recent research, recombinant virus is used for controlling the infection of HIV-1 (see for example, Wagner and Hewlett 1999; Nolan 1997). Revilla and Garcya-Ramos (2003) established a 5-dimensional ordinary differential equation system to investigate the control of the infection by introducing a recombinant virus to fight the virus. Jiang et al. (2009), introduced a constant injection rate of the recombinant virus and presented various bifurcation patterns. A control strategy of the HIV-1 epidemic model was given

in Yu and Zou (2012). The following differential equations are standard and classic in-host model for HIV-1 infection:

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t),$$
$$\dot{y}(t) = \beta x(t)v(t) - ay(t), \qquad\qquad (1)$$
$$\dot{v}(t) = ky(t) - pv(t),$$

where $x(t)$, $y(t)$ and $v(t)$ represent the densities of uninfected cells, infected cells and the free virus cells, respectively at time t. λ represents the rate at which new target cells are generated, d is the specific death rate and β is the constant rate at which a T-cell is contacted by the virus. It is assumed that once cells are infected, they may die at rate a either due to the virus or the immune system, and in the mean time, each cell produces new virus particles at a rate k during their life, p is the death rate of virus cells.

Revilla and Garcya-Ramos (2003) extended the model (1) by adding a second virus which may cause the infected cells to have a second infection, called double-infection, leading to a modified model is given by

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t),$$
$$\dot{y}(t) = \beta x(t)v(t) - ay(t) - \alpha w(t)y(t),$$
$$\dot{z}(t) = aw(t)y(t) - bz(t), \qquad\qquad (2)$$
$$\dot{v}(t) = ky(t) - pv(t),$$
$$\dot{w}(t) = cz(t) - qw(t).$$

Here $w(t)$ and $z(t)$ represent genetically modified(recombinant) virus and double-infected cells, respectively. It is assumed that recombinant infected cells previously infected by the pathogen virus and turn them at rate α into doubly-infected cells. In the mean time recombinant are removed at a rate q. The doubly infected cells die at a rate of b and release recombinant at a rate c. In Revilla and Garcya-Ramos (2003), the authors analyzed the structure of equilibrium solutions and presented some simulations of the model (2). The global attractivity of the three concerned disease-free equilibria is presented in Shang (2015) by using Lyapunov functional theory. Jiang et al. (2009), presented the stability of all possible equilibrium solutions and bifurcations between these equilibria, as well as proved the existence of Hopf bifurcation. Yu and Zou (2012), modified the model (2) by incorporating a control parameter η to measure the injection rate of the recombinant for controlling/eliminating the HIV virus. Tian et al. (2014) introduced the time lag into the model (2). Since in real situation, time is needed for the virus to contact a target cell and then the contacted cells become actively affected. Keeping in view this time lag they modified the model (2), by using the idea of Zhu and Zou (2008, 2009), as follows

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t),$$
$$\dot{y}(t) = \beta e^{-a\tau}x(t-\tau)v(t-\tau) - ay(t) - \alpha w(t)v(t),$$
$$\dot{z}(t) = aw(t)y(t) - bz(t), \qquad\qquad (3)$$
$$\dot{v}(t) = ky(t) - pv(t),$$
$$\dot{w}(t) = cz(t) - qw(t),$$

where τ denotes the average time for a viral particle to go through the eclipse phase. Here a is the constant death rate for infected cells but which are not virus producing

cells yet. Therefore, $e^{-a\tau}$ is the probability of surviving in the time period from $t - \tau$ to t. The effect of intracellular delays on viral infection has been discussed in Culshaw et al. (2003), Herz et al. (1996), Mittler et al. (1999), Nelson et al. (2000), Nelson and Perelson (2002), Xu (2011), while the effect of different awareness campaign on the spread of random network has been investigated in Shang (2013).

This paper focuses on the dynamical behavior of the system with delays and studies their equilibrium solutions with bifurcations. This study extends the work presented in Tian et al. (2014) by incorporating two distributed intracellular delays. In the proposed model one delay term represents the latent period which is the time that the target cells are contacted by the virus particles and the time the contacted cells become actively infected. While the second delay term represents the virus production period which means the time during when new virions are created within the cell and are released from the cell. The proposed model becomes

$$
\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - (1 - n_{rt})\beta x(t)v(t), \\
\dot{y}(t) &= (1 - n_{rt})\beta \int_0^\infty e^{-m\tau} f_1(\tau) x(t - \tau)v(t - \tau)d\tau - ay(t) - \alpha w(t)y(t), \\
\dot{z}(t) &= aw(t)y(t) - bz(t), \\
\dot{v}(t) &= (1 - n_p)k \int_0^\infty f_2(\tau)y(t - \tau)d\tau - pv(t), \\
\dot{w}(t) &= cz(t) - qw(t).
\end{aligned}
\tag{4}
$$

The measure of the efficacies of the protease inhibitor and the reverse transcriptase inhibitor are denoted by n_p and n_{rt}, respectively. It is also assumed that the infected cells become productively infected τ units later, where τ is distributed according to the probability distribution $f_1(\tau)$. The recruitment of virus producing cells at time t is given by the number of the cells that were infected at time $t - \tau$ and are still alive at time t. Here m is the constant death rate for infected cells but which are not virus producing cells as yet. Therefore, $e^{-m\tau}$ is the probability of surviving in the time period from $t - \tau$ to t. Also it is assumed that τ units later the virus penetrated into the cell at time t, where τ is distributed according to the probability distribution $f_2(\tau)$. The probability distribution functions like $f_1(\tau) = \delta(t - \tau_1)$, $f_2(\tau) = \delta(\tau)$ or $f_1(\tau) = \delta(\tau)$, $f_2(\tau) = \delta(t - \tau_2)$, are proposed. After some manipulation our proposed model in general form can be written as follows:

$$
\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \widetilde{\beta} x(t)v(t), \\
\dot{y}(t) &= \widetilde{\beta} \int_0^\infty e^{-m_1\tau} f_1(\tau) x(t - \tau)v(t - \tau)d\tau - ay(t) - \alpha w(t)y(t), \\
\dot{z}(t) &= aw(t)y(t) - bz(t), \\
\dot{v}(t) &= \widetilde{k} \int_0^\infty e^{-m_2\tau} f_2(\tau)y(t - \tau)d\tau - pv(t), \\
\dot{w}(t) &= cz(t) - qw(t),
\end{aligned}
\tag{5}
$$

where $\widetilde{\beta} = (1 - n_{rt})\beta$ and $\widetilde{k} = (1 - n_p)k$. The term $e^{-m_2\tau}$ is the probability of surviving from time $t - \tau$ to time t, where m_2 is the death rate of infected but not yet virus-producing cells. In the system (5), the delay kernel is assumed to be piecewise continuous to

satisfy $\int_0^\infty f_i(\tau)d\tau = 1$ and $\int_0^\infty \tau f_i(\tau)d\tau < 1, i = 1, 2$. The initial conditions for the system (5) become

$$x(\zeta) = \psi_1(\zeta), y(\zeta) = \psi_2(\zeta), z(\zeta) = \psi_3(\zeta), v(\zeta) = \psi_4(\zeta), w(\zeta) = \psi_5(\zeta), \zeta \in [-\infty, 0].$$

$$(6)$$

Here $(\psi_1, \psi_2, \psi_3, \psi_4, \psi_5) \in C[(-\infty, 0), R^5]$ be the space of continuous functions mapping the interval $(-\infty, 0]$ into R^5, where $\psi_i(\zeta) \geq 0, i = 1, 2, \ldots, 5$ and $R^5 = \{(x_1, x_2, x_3, x_4, x_5); x_i \geq 0, i = 1, 2, \ldots, 5\}$.

According to the fundamental theory of functional differential equations (Kuang 1993), the system (5) admits a unique solution of $(x(t), y(t), v(t), z(t), w(t))$ and satisfies the initial conditions (6). It is easy to show that all solutions of the system (5) with initial conditions (6) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

The rest of the paper is organized as follows: In "Positivity and well-posdeness of the solution" section, we address the well-posedness of the model by proving the positivity and boundedness of solutions. We also identify the basic reproduction number R_0 which determines whether there is or not an uninfected equilibrium. In "Local behavior of the proposed model" section, local stability has been discussed and it is proved that disease free equilibrium is locally stable if $R_0 < 1$ and chronic-infection equilibrium is locally stable if $R_0 > 1$. "Global behavior of the proposed model" section is dedicated to the global stability of the proposed model. Numerical simulations and discussion are presented in "Numerical simulation" section. Finally, conclusion is given in "Conclusion and discussion" section.

Positivity and well-posdeness of the solution

In this section, we will discuss positivity and boundedness of the solution. The following theorem gives boundedness and positivity of the solution.

Theorem 1 *All solutions of the system* (5) *remain non-negative, provided the given conditions are non-negative and bounded.*

Proof 1 By using variation of parameter formulae, we get the following solution of the system (5)

$$x(t) = x(0)e^{-\int_0^t (d+\widetilde{\beta}v(\zeta))d\zeta} + \lambda \int_0^t e^{-\int_\eta^t (d+\widetilde{\beta}v(\zeta))d\zeta} d\eta,$$

$$y(t) = y(0)e^{-\int_0^t (a+\alpha w(\zeta))d\zeta} + \widetilde{\beta} \int_0^t e^{-\int_\eta^t (a+\alpha w(\zeta))d\zeta} \int_0^\infty e^{-m_1\tau}f_1(\tau)x(t-\tau)v(t-\tau)d\tau d\eta,$$

$$z(t) = z(0)e^{-bt} + \int_0^t \alpha w(t)y(t)e^{-\int_\eta^t b(t-\zeta)d\zeta}d\eta,$$

$$v(t) = v(0)e^{-pt} + \widetilde{k} \int_0^t e^{-p(t-\eta)} \int_0^\infty e^{-m_2\tau}f_2(\tau)y(t-\tau)d\tau d\eta,$$

$$w(t) = w(0)e^{-\widetilde{k}t} + c \int_0^t z(\eta)e^{-\widetilde{k}(t-\eta)}d\eta.$$

Which shows the positivity of the solution of each solution $x(t), y(t), v(t), z(t)$ and $w(t)$.

Next, we show the boundedness of the solution. We define

$$D(t) = c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)x(t-\tau)d\tau d\tau + c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t)d\tau$$

$$+ c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)z(t)d\tau + \frac{ac}{2}v(t+\tau) + \frac{b\widetilde{k}}{2}\int_0^\infty e^{-m_2\tau}f_2(\tau)w(t)d\tau.$$

Calculating the derivative and using the system (5), we have

$$\frac{dD(t)}{dt} = c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)\Big(\lambda - dx(t-\tau) - \widetilde{\beta}x(t-\tau)v(t-\tau)\Big)d\tau d\tau$$

$$+ c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\Big(\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)\widetilde{\beta}x(t-\tau)v(t-\tau)d\tau - ay(t) - \alpha w(t)y(t)\Big)d\tau$$

$$+ c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\Big(aw(t)y(t) - bz(t)\Big)d\tau + \frac{ac}{2}\Big(\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t)d\tau$$

$$- pv(t+\tau)\Big)d\tau + \frac{b\widetilde{k}}{2}\int_0^\infty e^{-m_2\tau}f_2(\tau)\Big(cz(t) - qw(t)\Big)d\tau$$

$$= \lambda c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau d\tau - \Big[dc\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)$$

$$x(t-\tau)d\tau d\tau + \frac{a}{2}c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t)d\tau + \frac{b}{2}c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)z(t)d\tau$$

$$+ q\frac{b\widetilde{k}}{2}\int_0^\infty e^{-m_2\tau}f_2(\tau)w(t)d\tau + p\frac{ac}{2}v(t)\Big]$$

$$\le \lambda c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau d\tau$$

$$- \epsilon D(t)\begin{cases} < 0, & \text{for } D(t) > \frac{\lambda c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau d\tau}{\epsilon}, \\ > 0, & \text{for } D(t) < \frac{\lambda c\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau d\tau}{\epsilon}. \end{cases}$$

where $\epsilon = \min\{d, \frac{a}{2}, \frac{b}{2}, q, p\}$. This implies that $D(t)$ is bounded. Thus all the solutions $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ are bounded.

In order to study the asymptotic behavior of the proposed model, we use Zaman (2011). The model (5) has three possible equilibria, disease-free equilibrium $E_0(x_0, y_0, z_0, v_0, w_0)$, single-infection equilibrium $E_1(x_1, y_1, z_1, v_1, w_1)$ and double-infection equilibrium $E_2(x_2, y_2, z_2, v_2, w_2)$ which are given below,

$$E_0 = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right),$$

$$E_1 = \left(\frac{ap}{\widetilde{k}\widetilde{\beta}M_1M_2}, \frac{\lambda\widetilde{\beta}\widetilde{k}M_1M_2 - apd}{a\widetilde{\beta}\widetilde{k}}, 0, \frac{\lambda\widetilde{\beta}\widetilde{k}M_1M_2 - apd}{a\widetilde{\beta}p}, 0\right),$$

$$E_2 = \left(\frac{\lambda\alpha cp}{d\alpha cp + \widetilde{\beta}b\widetilde{k}q}, \frac{qb}{\alpha c}, \frac{q(\alpha\widetilde{\beta}\lambda c\widetilde{k}M_1M_2 - \widetilde{\beta}ab\widetilde{k}q - a\alpha cdp)}{ac(\widetilde{\beta}b\widetilde{k}q + \alpha cdp)}, \frac{\widetilde{k}qb}{\alpha cp},\right.$$

$$\left.\frac{\widetilde{k}qb}{\alpha cp}, \frac{\alpha\widetilde{\beta}\lambda c\widetilde{k}M_1M_2 - \widetilde{\beta}ab\widetilde{k}q - a\alpha cdp}{\alpha(\widetilde{\beta}b\widetilde{k}q + \alpha cdp)}\right),$$

where $M_i = \int_0^\infty e^{-m_i\tau}f_i(\tau)d\tau, (i = 1, 2)$.

The steady state with the pathogen presence is possible when the equilibrium density of the pathogen is greater than zero ($v_1 > 0$). This leads to a condition for invasion of the pathogen. Therefore, we can define

$$R_0 = \frac{\lambda \widetilde{\beta} \, \widetilde{k} \int_0^\infty e^{-m_1 \tau} f_1(\tau) d\tau \int_0^\infty e^{-m_2 \tau} f_2(\tau) d\tau}{apd} > 0.$$

Here, R_0 is called the basic reproduction ratio of model which represents the average number of secondary virus produced from a single virus for system (5). Noting that $\int_0^\infty \tau f_i(\tau) d\tau = 1$ and if $m_i > 0 (i = 1, 2)$, then $\int_0^\infty e^{-m_i \tau} f_i(\tau) d\tau < 1$. It is clear that increasing either of the delay may decrease the basic reproduction ratio R_0.

It turns out that the value of R_0 determines the existence of the single-infection equilibrium, that is E_1 exists if and only if $R_0 > 1$. For the third equilibrium to exist, the density of the recombinant virus must be greater than zero ($w_2 > 0$) and this leads to the condition

$$R_2 = \frac{\alpha cdp}{\widetilde{\beta} b \widetilde{k} q}(R_0 - 1).$$

Hence, $R_2 > 1$ if and only if $R_0 > R_1$, where $R_1 = 1 + \frac{\widetilde{\beta} b \widetilde{k} q}{\alpha cdp}$.

To analyze the stability of the equilibria, we need to calculate the characteristic equation of the Jacobian matrix of the system (5) at equilibrium point $E(\bar{x}, \bar{y}, \bar{z}, \bar{v}, \bar{w})$ as below

$$det[\eta I - J] = det \begin{pmatrix} \eta + d + \widetilde{\beta}\bar{v} & 0 & 0 & \widetilde{\beta}\bar{x} & 0 \\ -\bar{v}\widetilde{\beta}N_1(\eta) & \eta + a + \alpha\bar{w} & 0 & -\bar{x}\widetilde{\beta}N_1(\eta) & \bar{y}\alpha \\ 0 & -\bar{w}\alpha & \eta + b & 0 & -\bar{y}\alpha \\ 0 & -\widetilde{k}N_2(\eta) & 0 & \eta + p & 0 \\ 0 & 0 & -c & 0 & \eta + q \end{pmatrix} = 0.$$

where $N_i(\eta) = \int_0^\infty e^{-m_i \tau} e^{-\eta \tau} f_i(\tau) d\tau, (i = 1, 2)$.

Local behavior of the proposed model

In this section, we find the local stability of the system (5).

Theorem 2 *When $R_0 < 1$, then the disease-free equilibrium E_0 is locally asymptotically stable while for $R_0 > 1$, E_0 becomes unstable and the single-infection equilibrium E_1 occurs.*

Proof 2 The characteristic equation of the Jacobian matrix of the linearized system corresponding to the system (5) at $E_0(\frac{\lambda}{d}, 0, 0, 0, 0)$ is given by

$$det[\eta I - J(E_0)] = (b + \eta)(d + \eta)(q + \eta)\left[(a + \eta)(p + \eta) - \frac{\lambda}{d}\widetilde{\beta}\widetilde{k}N_1(\eta)N_2(\eta)\right] = 0.$$

The three roots of the characteristic equation $\eta_1 = -b$, $\eta_2 = -d$ and $\eta_3 = -q$ are negative and the remaining two roots are given by the following equation

$$(a + \eta)(p + \eta) - \frac{\lambda}{d}\widetilde{\beta}\widetilde{k}N_1(\eta)N_2(\eta) = 0. \tag{7}$$

Let us rewrite the above equation

$$g(\eta) = (a + \eta)(p + \eta) - \frac{\lambda}{d}\widetilde{\beta}\widetilde{k}N_1(\eta)N_2(\eta). \tag{8}$$

Noting that $|N_i(\eta)| \leq 1, (i = 1, 2)$.

Let us assume $g(0) = ap(1 - R_0) < 0$ and $\lim_{\eta \to \infty} g(\eta) = +\infty$. By the continuity of $g(\eta)$ there exist at least one positive root of $g(\eta) = 0$. Thus, the infection-free equilibrium E_0 is unstable if $R_0 > 1$.

If we choose the direct delta function $f_i(\tau) = \delta(t), (i = 1, 2)$ then we obtain $N_i(\eta) = 1, (i = 1, 2)$. In this case Eq. (7) becomes

$$\eta^2 + (a + p)\eta + ap(1 - R_0) = 0. \tag{9}$$

Thus, if $R_0 < 1$, then Eq. (8) has two negative roots. Hence the equilibrium E_0 is locally asymptotically stable when $f_i(\tau) = \delta(t), (i = 1, 2)$.

If $i\nu(\nu > 0)$ is a solution of Eq. (7), it follows that

$$-\nu^2 + (a + p)\nu i + ap - \widetilde{k}\widetilde{\beta}\frac{\lambda}{d}N_1(i\nu)N_2(i\nu) = 0,$$

which yields

$$\nu^4 + (a^2 + p^2)\eta^2 + (ap)^2 - \left(\widetilde{k}\widetilde{\beta}\frac{\lambda}{d}\right)^2 |N_1(i\nu)|^2|N_2(i\nu)|^2 = 0. \tag{10}$$

We note that for $(i = 1, 2)$,

$$|N_i(i\nu)| = \left| \int_0^\infty e^{-m_i\tau}\left(\cos(i\nu\tau) - \sin(i\nu\tau)\right)f_i(\tau)d\tau \right| \leq \int_0^\infty e^{-m_i\tau}f_i(\tau)d\tau. \tag{11}$$

Therefore, we have

$$(ap)^2 - \left(\widetilde{k}\widetilde{\beta}\frac{\lambda}{d}\right)^2 |N_1(i\nu)|^2|N_2(i\nu)|^2 \geq (ap)^2(1 - R_0^2).$$

Hence, if $R_0 < 1$, then Eq. (10) has no positive roots. Therefore, by the general theory on characteristic equations of delay differential equations (Kuang 1993) (Theorem 3.4.1), it is clear that E_0 is always locally asymptotically stable for $f_i(\tau) = \delta(t), (i = 1, 2)$, if $R_0 < 1$.

Theorem 3 *For $1 < R_0 < R_1$ the single infection-free equilibrium E_1 is locally asymptotically stable, while E_1 becomes unstable for $R_0 > R_1$ and recombinant virus may persist.*

Proof 3 The characteristic equation corresponding to the Jacobian matrix of the linearized system of the system (5), is given by

$$det[\eta I - J(E_1)] = ((b + \eta)(q + \eta) - \alpha y_1 c)\left[(d + \widetilde{\beta}\nu_1 + \eta)\widetilde{k}\widetilde{\beta}x_1N_1(\eta)N_2(\eta) - (\widetilde{\beta})^2 x_1 k\nu_1 N_1(\eta)N_2(\eta) \right.$$

$$\left. - (d + \widetilde{\beta}\nu_1 + \eta)(a + \eta)(p + \eta) \right] = 0.$$

We can write the equation in the form $P_1(\eta)P_2(\eta) = 0$, where

$P_1(\eta) = (b + \eta)(q + \eta) - \alpha y_1 c,$

$P_2(\eta) = (d + \widetilde{\beta}v_1 + \eta)\widetilde{k}\widetilde{\beta}x_1 N_1(\eta)N_2(\eta) - (\widetilde{\beta})^2 x_1\widetilde{k}v_1 N_1(\eta)N_2(\eta) - (d + \widetilde{\beta}v_1 + \eta)(a + \eta)(p + \eta).$

Now $P_1(\eta)$ can be written as

$P_1(\eta) = \eta^2 + (b + q)\eta + bq(1 - R_2),$

which shows that $P_1(\eta) = 0$ has two roots with negative real parts iff $R_2 < 1$ (i.e $R_0 < R_1$ or one positive and one negative if $R_2 > 1$ (i.e $R_0 > R_1$, which shows that the single infection free equilibrium E_1 is unstable. $P_2(\eta) = 0$ also can be written as

$$\eta^3 + a_2(\tau)\eta^2 + a_1(\tau)\eta + a_0(\tau) + (b_1\eta + b_2)N_1(\eta)N_2(\eta) = 0, \tag{12}$$

where

$a_2(\tau) = a + p + d + \widetilde{\beta}v_1,$

$a_1(\tau) = (a + p)(d + \widetilde{\beta}v_1) + ap,$

$a_0(\tau) = ap(d + \widetilde{\beta}v_1),$

$b_1(\tau) = -\widetilde{k}\widetilde{\beta}x_1,$

$b_0(\tau) = -d\widetilde{k}\widetilde{\beta}x_1.$

When $f_i(\tau) = \delta(\tau)$, we have $N_i(\eta) = 1 (i = 1, 2)$. In this case Eq. (12) becomes

$$\eta^3 + a_2(\tau)\eta^2 + (a_1(\tau) + b_1(\tau))\eta + a_0(\tau) + b_2(\tau) = 0, \tag{13}$$

By applying the Routh-Hurwitz criterion (Gantmacher 1959), we know that all the roots of (13) have negative real parts if $R_0 > 1$, because

$a_2(\tau) = a + p + d + d(R_0 - 1) > 0,$

$a_1(\tau) + b_1(\tau) = (a + p)(d + d(R_0 - 1)) > 0,$

$a_0(\tau) + b_2(\tau) = apd(R_0 - 1) > 0.$

Finally, we have

$a_2(a_1 + b_1) - (a_0 + b_2) = \big(dR_0\big(a^2 + (a + p)(p + dR_0) + apd\big) > 0.$

Therefore, the equilibrium E_1 is locally asymptotically stable when $f_i(\tau) = \delta(\tau)(i = 1, 2)$.

If iv for $v > 0$ is a solution of Eq. (13), then it follows that

$$-iv^3 + a_2(\tau)v^2 + a_1(\tau)iv + a_0(\tau) + (b_1 iv + b_2)N_1(iv)N_2(iv) = 0. \tag{14}$$

After some simplification, we get

$$v^6 + (a_2^2 - 2a_1)v^4 + (a_1^2 - 2a_0 a_2)v^2 + a_0^2 - (b_2^2 + b_1^2 v^2)|N_1(iv)|^2|N_2(iv)|^2 = 0, \tag{15}$$

where

$$a_2^2 - 2a_1 = (d + \widetilde{\beta}v_1)^2 + a^2 + p^2 > 0,$$

$$a_1^2 - 2a_0 a_2 - b_1^2|N_1(iv)|^2|N_2(iv)|^2 = (d + \beta v_1)^2(a^2 + p^2) + a^2 p^2 - (\widetilde{k}\widetilde{\beta}x_1)|N_1(iv)|^2|N_2(iv)|^2$$

$$\geq (a^2 + p^2)(d + \widetilde{\beta}v_1)^2,$$

$$(a_0^2 - b_2^2)|N_1(iv)|^2|N_2(iv)|^2 = (a^2 + p^2)(ap(d + \widetilde{\beta}v_1))^2 - (d\widetilde{k}\widetilde{\beta}x_1)^2|N_1(iv)|^2|N_2(iv)|^2$$

$$\geq ap\widetilde{\beta}v_1\left[ap(d + \widetilde{\beta}v_1) + dk\widetilde{\beta}x_1|N_1(iv)|^2|N_2(iv)|^2\right].$$

Hence if $R_0 > 1$, then the Eq. (15) has no positive roots. So by the general theory of characteristic equations of delay differential equations (Kuang 1993), the chronic infection equilibrium E_1 is locally asymptotically stable when $f_i(\tau) = \delta(\tau), (i = 1, 2)$.

Global behavior of the proposed model

In this section, we study the global behavior of the system (5). To do this we will use Lyapunove functionals theory and Lasali's invariance principle.

Theorem 4 *The disease-free equilibrium E_0 is globally asymptotically stable when $R_0 < 1$.*

Proof 4 Let $\big(x(t), y(t), z(t), v(t), w(t)\big)$ be any positive solution of the system (5) with initial conditions (6). Consider the Lyapunove functional

$$L_{E_0}(t) = L_1(t) + L_2(t), \tag{16}$$

where

$$L_1(t) = x(t) - x_0 - \ln\frac{x(t)}{x_0} + r_1 y(t) + r_1 z(t) + r_2 v(t) + r_1\frac{b}{c}w(t),$$

$$L_2(t) = r_1\widetilde{\beta}\int_0^\infty f_1(\tau)e^{-m_1\tau}\int_{t-\tau}^t x(\theta)v(\theta)d\theta d\tau + r_2\widetilde{k}\int_0^\infty f_2(\tau)e^{-m_2\tau} \times \int_{t-\tau}^t y(\theta)d\theta d\tau$$

with $r_1 = \frac{1}{\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau}$ and $r_2 = \frac{1}{\widetilde{k}\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau\int_0^\infty e^{-m_2\tau}f_2(\tau)d\tau}$.

By taking derivative of $L_1(t)$ along the positive solution of the system (5), we have

$$\frac{dL_1(t)}{dt} = \left(x(t) - \frac{x}{x_0}\right)\left(\lambda - dx(t) - \widetilde{\beta}x(t)v(t)\right) + r_1\left(\widetilde{\beta}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau\right.$$
$$\left. - ay(t) - \alpha w(t)y(t)\right) + r_1\left(aw(t)y(t) - bz(t)\right)$$
$$+ r_2\left(\widetilde{k}\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - pv(t)\right) + r_1\frac{b}{c}\left(cz(t) - qw(t)\right).$$

On substituting $\lambda = dx_0$, and simplifying, we get

$$\frac{dL_1(t)}{dt} = \frac{(x(t)-x_0)^2}{x} - \widetilde{\beta}x(t)v(t) + r_1\left(\widetilde{\beta}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau\right.$$
$$\left. - ay(t) - \alpha w(t)y(t)\right) + r_1\left(aw(t)y(t) - bz(t)\right) + r_2\widetilde{k}\left(\int_0^\infty f_2(\tau)\right.$$
$$\left. \times e^{-m_2\tau}y(t-\tau)d\tau - pv(t)\right) + r_1\frac{b}{c}\left(cz(t) - qw(t)\right),$$
$$= \frac{-d(x(t)-x_0)^2}{x} - \widetilde{\beta}x(t)v(t) + r_1\left(\widetilde{\beta}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau\right)$$
$$- r_1 ay(t) + r_2\widetilde{k}\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - r_1\frac{bq}{c}w(t) + r_2 p(R_0 - 1)v(t)$$
$$- r_1\frac{bq}{c}w(t). \tag{17}$$

By taking the derivative of $L_2(t)$, we get

$$\frac{dL_2(t)}{dt} = r_1\widetilde{\beta}\int_0^\infty f_1(\tau)e^{-m_1\tau}\Big(x(t)v(t) - x(t-\tau)v(t-\tau)\Big)d\tau + r_2\widetilde{k}\int_0^\infty f_2(\tau)e^{-m_2\tau}$$

$$\times \Big(y(t) - y(t-\tau)\Big)d\tau. \tag{18}$$

Taking derivative of Eq. (16) and using Eqs. (17) and (18) and simplifying, we get

$$\frac{dL_{E_0}(t)}{dt} = -d\frac{(x(t)-x_0)^2}{x} + \frac{p(R_0-1)v(t)}{\widetilde{k}\int_0^\infty f_1(\tau)e^{-m_1\tau}d\tau \int_0^\infty f_2(\tau)e^{-m_2\tau}d\tau} - r_1\frac{bq}{c}w(t). \tag{19}$$

If $R_0 \leq 1$, it follows from Eq. (19) that $\frac{d}{dt}V_{E_0}(t) \leq 0$. Moreover, the equality also holds if $x_0 = \frac{\lambda}{d}$, $y(t) = 0$, $z(t) = 0$, $v(t) = 0$, $w(t) = 0$. Hence by LaSalle's invariance principle (see LaSalle (1976)), we conclude that E_0 is globally asymptotically stable when $R_0 < 1$.

Theorem 5 *If $1 < R_0 < R_1$, then the single infection free equilibrium E_1 is globally asymptotically stable, implying that the recombinant virus cannot survive but the pathogen virus can exist.*

Proof 5 Let $(x(t), y(t), z(t), v(t), w(t))$ be any positive solution of the system (5) with initial conditions (6). Let us consider the Lyapunove functional

$$V_1(t) = \big(x(t)-x_1\ln x(t)\big)+r_1\big(y(t)-y_1\ln y(t)\big)+r_2\big(v(t)-\ln v(t)\big)+r_1z(t)+r_1\frac{b}{c}w(t), \tag{20}$$

where r_1 and r_2 are discussed in the previous theorem. Now taking derivative of $V_1(t)$, we get

$$\frac{dV_1(t)}{dt} = \Big(1-\frac{x_1}{x}\Big)\Big(\lambda - dx(t) - \widetilde{\beta}x(t)v(t)\Big) + r_1\Big(1-\frac{y_1}{y}\Big)\Big(\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau x(t-\tau)v(t-\tau)$$

$$- ay(t) - \alpha w(t)y(t)\Big) + r_1\Big(aw(t)y(t) - bz(t)\Big)$$

$$+ r_2\Big(1-\frac{v_1}{v}\Big)\Big(\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t-\tau)d\tau - pv(t)\Big) + r_1\frac{b}{c}\Big(cz(t) - qw(t)\Big).$$

Using $\lambda = dx_1 - \widetilde{\beta}x_1v_1$ in the above equation, we have

$$\frac{dV_1(t)}{dt} = -\frac{(x(t)-x_1)^2}{x} - \widetilde{\beta}x(t)v(t) + \widetilde{\beta}x_1v_1\Big(1-\frac{x_1}{x}\Big) + r_1\widetilde{\beta}\int_0^\infty e^{-m\tau}f_1(\tau)d\tau x(t-\tau)d\tau$$

$$- r_1\frac{\widetilde{\beta}y_1}{y}\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau x(t-\tau)v(t-\tau)v(t-\tau)d\tau - r_1ay(t)$$

$$+ \widetilde{\beta}x_1v_1 + r_2\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)d\tau y(t-\tau) - r_2\widetilde{k}\frac{v_1}{v(t)}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t-\tau)d\tau$$

$$+ \widetilde{\beta}x_1v_1 + r_1(\alpha y_1 - \frac{bq}{c})w(t). \tag{21}$$

Let us define

$$
V_{E_1}(t) = V_1(t) + r_1\widetilde{\beta} \int_0^\infty e^{-m_1\tau} f_1(\tau) \int_{t-\tau}^t \left[x(\rho)v(\rho) - x_1 v_1 - xv \ln \frac{x(\rho)v(\rho)}{x_1 v_1} \right] d\rho d\tau
$$
$$
+ r_2\widetilde{k} \int_0^\infty e^{-m_2\tau} f_2(\tau) \int_{t-\tau}^t \left[y(\rho) - y_1 - y_1 \ln \frac{y(\rho)}{y_1} \right] d\rho d\tau. \tag{22}
$$

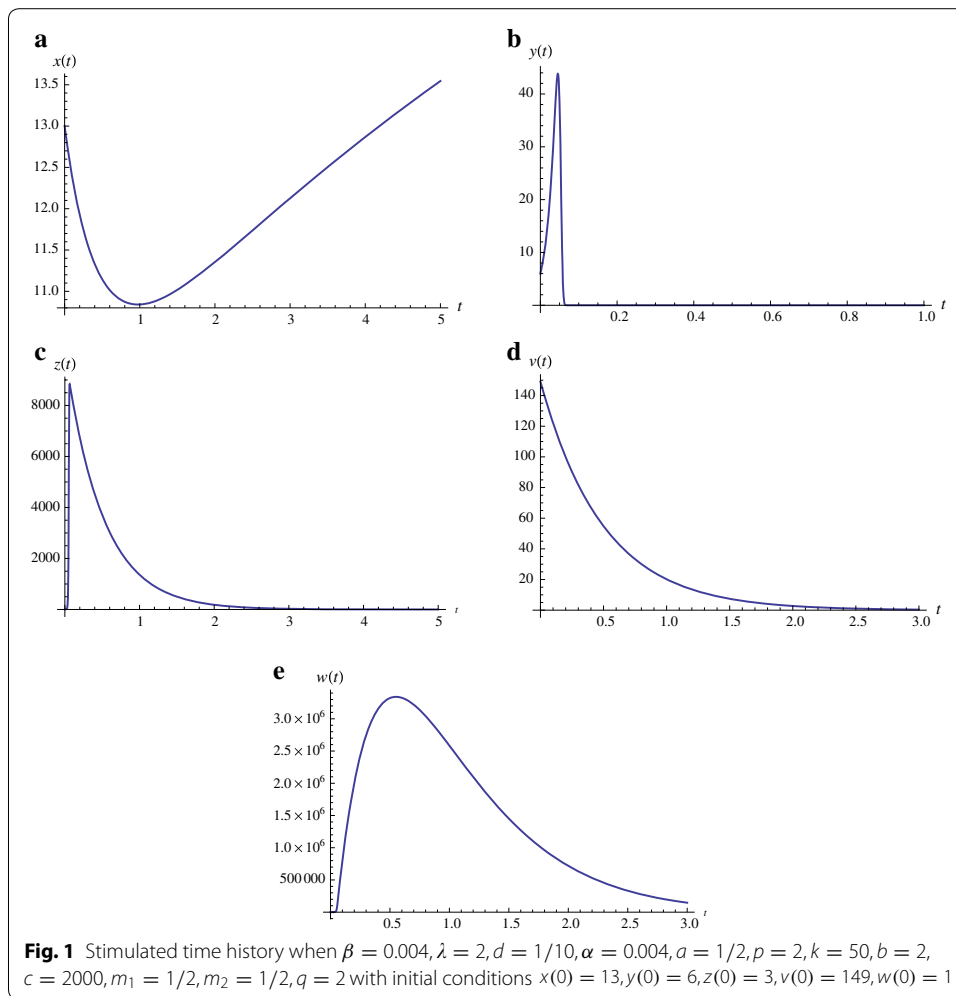Taking derivative of Eq. (22) and using Eq. (21), we get

$$
\frac{dV_{E_1}(t)}{dt} = -\frac{(x(t)-x_1)^2}{x} - \widetilde{\beta}x(t)v(t) + \widetilde{\beta}x_1 v_1 \left(1 - \frac{x_1}{x}\right) + r_1\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)d\tau x(t-\tau)d\tau
$$
$$
- r_1\frac{\widetilde{\beta}y_1}{y}\int_0^\infty e^{-m_1\tau}f_1(\tau)x(t-\tau)v(t-\tau)d\tau - r_1 a y(t)
$$
$$
+ \widetilde{\beta}x_1 v_1 + r_2\widetilde{k}\int_0^\infty e^{-\tau}f_2(\tau)d\tau y(t-\tau) - r_2\widetilde{k}\frac{v_1}{v(t)}\int_0^\infty e^{-m_2\tau}f_2(\tau)y(t-\tau)d\tau
$$
$$
+ \widetilde{\beta}x_1 v_1 + r_1\left(\alpha y_1 - \frac{bq}{c}\right)w(t) + r_1\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)\Big[x(t)v(t) - x(t-\tau)v(t-\tau)
$$
$$
+ x_1 v_1 \ln \frac{x(t-\tau)v(t-\tau)}{x(t)v(t)}\Big]d\rho d\tau + r_2\widetilde{k}\int_0^\infty e^{-m_2\tau}f_2(\tau)\Big[y(t) - y(t-\tau) + y_1 \ln \frac{y(t-\tau)}{y(t)}\Big]
$$
$$
= -\frac{(x(t)-x_1)^2}{x} + \widetilde{\beta}x_1 v_1\left(1 - \frac{x_1}{x}\right) - r_1\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)\ln\frac{x(t-\tau)v(t-\tau)}{x_1 v_1 y(t)}d\tau + \widetilde{\beta}x_1 v_1
$$
$$
- r_2\widetilde{k}y_1\int_0^\infty e^{-m_2\tau}f_2(\tau)\ln\frac{v_1 y(t-\tau)}{y_1 v(t)}d\tau + \widetilde{\beta}x_1 v_1 - r_1\widetilde{\beta}\int_0^\infty e^{-m_1\tau}f_1(\tau)
$$
$$
\times \ln \frac{x(t-\tau)v(t-\tau)}{x(t)v(t)}d\tau + r_2\widetilde{k}y_1\int_0^\infty e^{-m_2\tau}f_2(\tau)\ln\frac{y(t-\tau)}{y(t)}d\tau + r_1\left(\alpha y_1 - \frac{bq}{c}\right)w(t),
$$
$$
= -\frac{(x(t)-x_1)^2}{x} + \widetilde{\beta}x_1 v_1\left(1 - \frac{x_1}{x} - \frac{x}{x_1}\right) - r_1\widetilde{\beta}x_1 v_1\int_0^\infty e^{-m_1\tau}f_1(\tau)\Big[\frac{y_1 x(t-\tau)v(t-\tau)}{x_1 v_1 y(t)}
$$
$$
- 1 - \ln\frac{y_1 x(t-\tau)v(t-\tau)}{x_1 v_1 y(t)}\Big]d\tau - r_2\widetilde{k}y_1\int_0^\infty e^{-m_2\tau}f_2(\tau)\Big[\frac{v_1 y(t-\tau)}{y_1 v(t)} - 1 - \ln\frac{v_1 y(t-\tau)}{y_1 v(t)}\Big]d\tau
$$
$$
- \frac{\alpha r_1 pd}{\widetilde{\beta}\widetilde{k}}(R_1 - R_0)w(t). \tag{23}
$$

If $R_0 \le R_1$, it follows from Eq. (23) that $\frac{dV_{E_1}(t)}{dt} \le 0$ for $x_1, y_1, v_1 > 0$. Also equality holds when $x = x_1$ and $y = y_1$, $v = v_1$, $z = 0$ and $w = 0$. Thus the solutions limit to the largest invariant subset of $\frac{dV_{E_1}}{dt} = 0$. Then, by LaSalle's invariance principle (LaSalle 1976), we conclude that E_1 is globally asymptotically stable. This complete the proof.

Numerical simulation

In this section, we present numerical simulation. We use Runge–Kutta order four method to find numerical results. For our numerical simulation we used parameters values $\beta = 0.004$ (estimated), $\lambda = 2$ (Philips 1996), $d = 1/10$ (Philips 1996), $\alpha = 0.004$, (estimated), $a = 1/2$ (estimated), $p = 2$ (Philips 1996), $k = 50$ (Hass 1999), $b = 2$ (Schnell et al. 1997), $c = 2000$ (Schnell et al. 1997), $m_1 = 1/2 = m_2 = 1/2$ (assumed), $q = 2$ (assumed) with initial conditions $x(0) = 13, y(0) = 6, z(0) = 3, v(0) = 149, w(0) = 1$. Our numerical results show that, by using continuous delays in latent and virus production periods, then the number of healthy cells increases and the virus load reduces as shown by Figure 1a and d, respectively. Figure 1b shows that the number of infected cells decreases due to reducing the viral load by postponing the production period of infected cells. Figure 1d shows that the number of double infected cells increases which release the recombinant virus to fight with pathogens virus. Figure 1e the shows that recombinant virus are decreasing with the passage of time.

Fig. 1 Stimulated time history when $\beta = 0.004, \lambda = 2, d = 1/10, \alpha = 0.004, a = 1/2, p = 2, k = 50, b = 2,$ $c = 2000, m_1 = 1/2, m_2 = 1/2, q = 2$ with initial conditions $x(0) = 13, y(0) = 6, z(0) = 3, v(0) = 149, w(0) = 1$

Conclusion and discussion

In this work, we presented the asymptotic analysis of an HIV-1 epidemic model by incorporating distributed intracellular delays. Our one delay term used for latent period and the second one used for virus production period. From the corresponding characteristic equations, it was shown that if the basic reproduction ratio is less than unity, the infection-free equilibrium is locally asymptotically stable. We also proved that the chronic-infection equilibrium exists and is locally asymptotically stable if the basic reproduction ratio is greater than one. Similarly, the global stability of the infection-free equilibrium and the chronic-infection equilibrium of the proposed model have been completely established under certain conditions. It is clear from these results that intracellular delays describing the latent period and viral production period have great effect on the stability of feasible equilibria and therefore, do not induce periodic oscillations. Numerical results of our proposed model represented that continuous delays in latent period and virus production period can help in reducing the load of pathogen virus due which the number of infected cells reduced and CD4+ cells are increased.

Authors' contributions

All authors contributed to the formulation of the model, discussion of results and wrote the paper. Both authors read and approved the final manuscript.

References

Culshaw RV, Ruan S, Webb G (2003) A mathematical model of cell-to-cell HIV-1 that include a time delay. J Math Biol 46:425–444

Gantmacher F (1959) The theory of matrices, vol 2. Chelsea, New York

Hass AT (1999) Population biology of HIV infection: viral and CD4+ T cell demography and dynamics in lymphatic tissues. Ann Rev Immunol 17:625

Herz AVM, Bonhoeffer S, Anderson RM, May RM, Nowak MA (1996) Viral dynamics in vivo: limitations on estimates of intracellular delay and virus decay. Proc Natl Acad Sci USA 93:7247–7251

Jiang X, Yu P, Yuan Z, Zou X (2009) Dynamics of an HIV-1 therapy model of fighting a virus with another virus. J Biol Dyn 3:387–409

Kuang Y (1993) Delay differential equations with applications in population dynamics. Academic Press, New York

LaSalle J (1976) The stability of dynamical systems. SIAM, Philadelphia

Mittler JE, Markowitz B, Ho DD, Perelson AS (1999) Improved estimates for HIV-1 clearance rate and intracellular delay. AIDS 13:1415–1417

Nelson PW, Perelson AS (2002) Mathematical analysis of delay differential equation models of HIV-1 infection. Math Biosci 179:73–94

Nelson PW, Murray JD, Perelson AS (2000) A model of HIV-1 pathogenesis that includes an intracellular delay. Math Biosci 163:201–215

Nolan G (1997) Harnessing viral devices as pharmaceuticals: fighting HIV-1s fire with fire. Cell 90:821–824

Philips BN (1996) Reduction of HIV concentration during acute infection: independent from a specific immune response. Science 271(5248):497–499

Revilla T, Garcya-Ramos G (2003) Fighting a virus with a virus: a dynamic model for HIV-1 therapy. Math Biosci 185:191–203

Schnell MH, Johnson E, Buonocore L, Rosc JK (1997) Construction of a novel virus that targets HIV first infected and control HIV first infection. Cell 90(5):849–57

Shang Y (2013) Modeling epidemic spread with awareness and heterogeneous transmission rates in networks. J Biol Phys 39(3):489–500

Shang Y (2015) Global stability of disease-free equilibria in a two-group SI model with feedback control. Nonlinear Anal Model Control 20(4):501–508

Tian Y, Bai Y, Yu P (2014) Impact of delay on HIV-1 dynamics of fighting a virus with an other virus. Math Biosci Eng Oct;11(5):1181–1198

Wagner E, Hewlett M (1999) Basic virology. Blackwell, New York

Xu R (2011) Global dynamics of an HIV-1 infection model with distributed intracellular delays. Comput Math Appl 61(9):2799–2805

Yu P, Zou X (2012) Bifurcation analysis on an HIV-1 model with constant injection of recombinant. Int J Bifurcation Chaos 22(3):1250062

Zaman G (2011) Qualitative behavior of giving up smoking model. Bull Malays Math Sci Soc 34(2):403–4015

Zhu H, Zou X (2008) Impact of delays in cell infection and virus production on HIV-1 dynamics. Math Med Biol 25:99–112

Zhu H, Zou X (2009) Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay. Discrete Contin Dyn Syst B 12:511–524