GLOBAL DYNAMICS OF A LATENT HIV INFECTION MODEL WITH GENERAL INCIDENCE FUNCTION AND MULTIPLE DELAYS

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(Communicated by Gail Wolkowicz)

Abstract. In this paper, we propose a latent HIV infection model with general incidence function and multiple delays. We derive the positivity and boundedness of solutions, as well as the existence and local stability of the infection-free and infected equilibria. By constructing Lyapunov functionals, we establish the global stability of the equilibria based on the basic reproduction number. We further study the global dynamics of this model with Holling type-II incidence function through numerical simulations. Our results improve and generalize some existing ones. The results show that the prolonged time delay period of the maturation of the newly produced viruses may lead to the elimination of the viruses.

1. Introduction. Human immunodeficiency virus (HIV) continues to be a major global public health issue. According to the report by World Health Organization (WHO), an estimated 36.7 million people were living with HIV at the end of 2016 - with roughly 1.8 million new HIV infections in 2016 globally [1]. HIV incorporates into the host cell genome and can establish a latent form of HIV infection [40]. These latently infected cells decay slowly, can persist in patients for a long time and produce new virus when activated by relevant antigens [12]. Latently infected cells have been considered as a major obstacle to viral eradication [45]. They play a crucial role in maintaining a low steady state viral load during therapy [4]. To
better understand HIV infection and drug therapies, the basic three-dimensional viral infection model was proposed [3, 34, 35, 39, 41]. Furthermore, mathematical models that consider latently infected cell activation have been developed to describe this mechanism of the latent HIV infection [4, 10, 31, 39, 42, 46, 47].

Time delay is one of the key factors to study innovative insights of virus dynamics. To incorporate the intracellular phase of the virus life-cycle, Herz et al. [14] developed a model and showed that the delay can shorten the estimate for the half-life of free virus. Since then, mathematical models with time delay have been widely used in the study of the virus dynamics [5, 6, 9, 18–20, 23, 29, 38, 51, 53, 56, 57]. However, to our knowledge, there are few works to consider latent HIV infection model with time delay. Recently, Alshorman et al. [2] studied a latent HIV infection model with two time delays as follows:

\[
\begin{align}
\frac{dT}{dt} &= s - d_T T - \beta T V, \\
\frac{dL}{dt} &= k e^{-\delta_1 \tau_1} \beta T(t - \tau_1)V(t - \tau_1) - \delta L L - \alpha L, \\
\frac{dI}{dt} &= (1 - k) e^{-\delta_1 \tau_2} \beta T(t - \tau_2)V(t - \tau_2) - \delta I + \alpha L, \\
\frac{dV}{dt} &= N\delta I - cV,
\end{align}
\]

(1)

where \(T(t), L(t), I(t)\) and \(V(t)\) denote the concentrations of the uninfected CD4\(^+\) T cells, latently infected CD4\(^+\) T cells, productively infected CD4\(^+\) T cells and HIV virions in plasma at time \(t\), respectively. \(s\) is the generate rate of uninfected cells. \(d_T, \delta_L, \delta\) and \(c\) denote the death rates of the uninfected cells, latently infected cells, productively infected cells and virions, respectively. \(\beta\) is the infection rate of target cell by virus. A small fraction \((k)\) of infected cells is assumed to result in latency and the remaining fraction \((1 - k)\) becomes productively infected cells. Latently infected cells can be activated by their relevant antigens to become productively infected cells at a constant rate \(\alpha\). \(N\) is the total number of virions released by one infected cell in its lifespan. \(e^{-\delta_1 \tau_1}\) and \(e^{-\delta_1 \tau_2}\) describe the probability of latently and productively infected cells surviving the time \(\tau_1\) and \(\tau_2\), respectively. According to the viral life cycle, we have \(\tau_1 \leq \tau_2\). Alshorman et al. [2] established the local and global stability of equilibria for system (1). Wang et al. [55] further considered both the virus-to-cell infection and cell-to-cell transmission in system (1), and they also gave the proof of the local and global stability of equilibria as well as the persistence result.

It is well known that the mass action incidence is always used to model the infection incidence between the virus and target cells, which usually follow the predator-prey interaction in the mathematical modeling of virus dynamics [7]. However, the mass action incidence is insufficient to describe the infection process in detail, so some nonlinear transmission functions were adopted by many researchers. For example, Regoes et al. [44] used the sigmoidal incidence function \(T(V/\kappa)^p/(1+(V/\kappa)^p)\) where \(\kappa > 0\) and \(p > 1\), to model a nonlinear relationship between parasite dose and infection rate which was often observed in experiments [11, 27]. Song and Neumann [50] employed the saturated mass action incidence function \(TV^p/(1 + \alpha V^q)\) where \(p, q, \alpha > 0\), due to the saturation at high virus concentration in the modeling of HIV, HBV and HCV infections. Huang et al. [15] considered the general nonlinear incidence function \(F(T, V)\), which satisfies some conditions.
In reality, it has been realized that there is a time delay between initial viral entry into a cell and subsequent viral production. Nelson et al. [32] incorporated such intracellular delay into an HIV infection model. Furthermore, Nelson and Perelson [33] generalized the model in [32] by including the time delay between viral RNA transcription and viral release and maturation. Following the line of [15, 20, 33, 57], we also consider a discrete delay for the process of virus production. The model is given as follows:

\[
\begin{align*}
\frac{dT}{dt} &= s - d_T T - T f(V), \\
\frac{dL}{dt} &= k e^{-\delta_1 \tau_1} T(t - \tau_1) f(V(t - \tau_1)) - \delta_L L - \alpha L, \\
\frac{dI}{dt} &= (1 - k) e^{-\delta_1 \tau_2} T(t - \tau_2) f(V(t - \tau_2)) - \delta_I + \alpha L, \\
\frac{dV}{dt} &= N \delta e^{-\delta_2 \tau_3} I(t - \tau_3) - c V,
\end{align*}
\]

where \(\tau_3\) represents the maturation time of the newly produced viruses. The probability of survival of immature virions is given by \(e^{-\delta_2 \tau_3}\). Function \(f\) satisfies

(H) For \(V \in \mathbb{R}_+\), \(f(V) \geq 0\) with equality if and only if \(V = 0\), \(f'(V) > 0\) and \(f''(V) \leq 0\).

It follows from assumption (H) and the mean value theorem that

\[
f'(V)V \leq f(V) \leq f'(0)V, \quad V \in \mathbb{R}_+.
\]

Clearly, the assumption is shared by many incidence functions in various literatures. For example, mass action incidence \(T f(V) = \beta TV\) [34, 39], Holling type-II incidence \(T f(V) = \frac{\beta TV}{1 + \alpha V}\) [21, 50].

The organization of this paper is as follows. In Section 2, we discuss the positivity, boundedness, and equilibria of system (2). In Section 3, we study the local stability of equilibria. In Section 4, we investigate the global stability of equilibria. To verify the theoretical results, an application and numerical simulations are given in Section 5. Finally, the paper ends with a conclusion in Section 6.

2. Positivity, boundedness and equilibria. Let \(X = C([-\tau, 0], \mathbb{R}_+^4)\) be the Banach space of continuous mapping from \([-\tau, 0]\) to \(\mathbb{R}_+^4\) equipped with the sup-norm \(\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|\), where \(\tau = \max\{\tau_1, \tau_2, \tau_3\}\). Define \(x(t) = (T(t), L(t), I(t), V(t))^T\) and \(x_i(\theta) = x(t + \theta)\) for \(\theta \in [-\tau, 0]\). The initial conditions are given by

\[
T(\theta) = \phi_1(\theta), \quad L(\theta) = \phi_2(\theta), \quad I(\theta) = \phi_3(\theta), \quad V(\theta) = \phi_4(\theta),
\]

\[
\phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad i = 1, 2, 3, 4.
\]

Let \(\phi = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in X\). Following from the standard theory of functional differential equations [13], we know that system (2) has a unique solution \(x(t, \phi)\) with initial conditions (4). We have the following result.

**Theorem 2.1.** The solutions of system (2) with initial conditions (4) are non-negative and uniformly bounded for all \(t \geq 0\).

**Proof.** See Appendix A for the proof. \(\square\)
It is easy to see that system (2) has an infection-free equilibrium \( E_0(T^0, 0, 0, 0) \), where \( T^0 = s/d_T \). By using the next generation method \([52]\), we derive the basic reproduction number \( R_0 \) as follows. First we define matrices \( F \) and \( V \) as

\[
F = \begin{pmatrix} 0 & kT^0 f'(0) e^{-\delta_1 \tau_1} & 0 \\ 0 & (1-k) T^0 f'(0) e^{-\delta_1 \tau_2} & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \alpha + \delta_L & 0 & 0 \\ -\alpha & \delta & 0 \\ 0 & -N \delta e^{-\delta_2 \tau_3} & c \end{pmatrix}.
\]

These expressions give

\[
FV^{-1} = \begin{pmatrix} kT^0 f'(0) e^{-\delta_1 \tau_1} \frac{\alpha N}{\alpha + \delta_L} e^{-\delta_2 \tau_3} & kT^0 f'(0) e^{-\delta_1 \tau_1} \frac{N e^{-\delta_2 \tau_3}}{c} \\ (1-k) T^0 f'(0) e^{-\delta_1 \tau_2} \frac{\alpha N}{\alpha + \delta_L} e^{-\delta_2 \tau_3} & (1-k) T^0 f'(0) e^{-\delta_1 \tau_2} \frac{N e^{-\delta_2 \tau_3}}{c} \\ 0 & 0 \end{pmatrix}.
\]

Then the basic reproduction number \( R_0 \) is defined as the spectral radius of \( FV^{-1} \).

Therefore,

\[
R_0 := \rho(FV^{-1}) = \frac{Ne^{-\delta_2 \tau_3} T^0 f'(0)}{c} \left( \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} + (1-k) e^{-\delta_1 \tau_2} \right).
\]

Note that \( R_0 \) is a decreasing function of the maturation time delay of the newly produced viruses \( \tau_3 \).

**Theorem 2.2.** If \( R_0 > 1 \), then system (2) has a unique infected equilibrium \( E^* = (T^*, L^*, I^*, V^*) \).

**Proof.** See Appendix B for the proof. \( \square \)

3. **Local stability.** In this section, we investigate the local stability of equilibria for system (2). For simplicity, we define

\[
\mathcal{H} = \frac{(1-k)(\alpha + \delta_L)e^{-\delta_1 \tau_2}}{(1-k)(\alpha + \delta_L)e^{-\delta_1 \tau_2} + \alpha k e^{-\delta_1 \tau_1}}.
\]

Then, we get

\[
0 < \mathcal{H} < 1, \quad c R_0 \mathcal{H} = N(1-k) T^0 f'(0) e^{-\delta_1 \tau_2} e^{-\delta_2 \tau_3},
\]

and

\[
c(\alpha + \delta_L)(1 - \mathcal{H}) R_0 = \alpha N k T^0 f'(0) e^{-\delta_1 \tau_1} e^{-\delta_2 \tau_3}.
\]

**Theorem 3.1.** (i): If \( R_0 < 1 \), then the infection-free equilibrium \( E_0 \) of system (2) is locally asymptotically stable; if \( R_0 > 1 \), then \( E_0 \) is unstable.

(ii): If \( R_0 > 1 \), then the infected equilibrium \( E^* \) of system (2) is locally asymptotically stable.

**Proof.** The characteristic equation of system (2) at \( E_0 \) is given by

\[
(\lambda + d_T) [ (\lambda + \alpha + \delta_L)(\lambda + \delta)(\lambda + c) \\
- (\lambda + \alpha + \delta_L) N \delta (1-k) e^{-\delta_1 \tau_2} T^0 f'(0) e^{-\delta_2 \tau_3} e^{-\lambda (\tau_2 + \tau_3)} \\
- \alpha N \delta k e^{-\delta_1 \tau_1} T^0 f'(0) e^{-\delta_2 \tau_3} e^{-\lambda (\tau_1 + \tau_3)} ] = 0.
\]
We see that equation (5) has an eigenvalue \( \lambda_1 = -d_T < 0 \), and other eigenvalues are determined by
\[
(\lambda + \alpha + \delta_L) [(\lambda + \delta)(\lambda + c) - c\delta R_0 \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)}] = c\delta(\alpha + \delta_L)(1 - \mathcal{H}) \mathcal{R}_0 e^{-\lambda(\tau_1 + \tau_3)}, \tag{6}
\]

For the case \( \mathcal{R}_0 < 1 \). If \( \text{Re}(\lambda) \geq 0 \), then the left hand side of equation (6) satisfies
\[
|\lambda + \alpha + \delta_L||(\lambda + \delta)(\lambda + c) - c\delta \mathcal{R}_0 \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)}| \\
\geq (\alpha + \delta_L)||(\lambda + \delta)(\lambda + c)| - |c\delta \mathcal{R}_0 \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)}|| \\
\geq (\alpha + \delta_L)\delta(1 - \mathcal{R}_0 \mathcal{H}) \\
> (\alpha + \delta_L)\delta(1 - \mathcal{H}), \tag{7}
\]
and the right hand side of equation (6) satisfies
\[
|c\delta(\alpha + \delta_L)(1 - \mathcal{H}) \mathcal{R}_0 e^{-\lambda(\tau_1 + \tau_3)}| < c\delta(\alpha + \delta_L)(1 - \mathcal{H}). \tag{8}
\]

Note that equation (6) and inequalities (7), (8) imply a contradiction. Thus, all eigenvalues of equation (5) have negative real parts when \( \mathcal{R}_0 < 1 \), yielding that \( E_0 \) is locally asymptotically stable.

For the case \( \mathcal{R}_0 > 1 \). The characteristic equation (6) can be written as the following equation
\[
\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,
\]
where
\[
a_1 = c + \delta + \delta_L + \alpha, \\
a_2 = c\delta + (\alpha + \delta_L)(c + \delta) - (1 - k)N\delta \tau T^0 f'(0) e^{-\delta_1 \tau_2} e^{-\delta_2 \tau_3} e^{-\lambda(\tau_2 + \tau_3)}, \\
a_3 = c\delta(\alpha + \delta_L) - (\alpha + \delta_L)(1 - k)N\delta T^0 f'(0) e^{-\delta_1 \tau_2} e^{-\delta_2 \tau_3} e^{-\lambda(\tau_2 + \tau_3)} \\
- \alpha N k d T^0 f'(0) e^{-\delta_1 \tau_1} e^{-\delta_2 \tau_3} e^{-\lambda(\tau_1 + \tau_3)}.
\]
Define
\[
P(\lambda) := \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3.
\]
Since \( P(0) = c\delta(\alpha + \delta_L)(1 - \mathcal{R}_0) < 0 \) and \( P(\infty) = +\infty \), we know that \( P(\lambda) = 0 \) has at least one positive eigenvalue. This yields that equation (5) has a positive eigenvalue when \( \mathcal{R}_0 > 1 \), and thus \( E_0 \) is unstable.

Next, we prove the second part of this theorem. The characteristic equation of system (2) at \( E^* \) is given by
\[
(\lambda + \alpha + \delta_L) \left( \frac{\lambda + d_T + f(V^*)}{(\lambda + d_T + f(V^*) N)(\lambda + \delta)(\lambda + c) T^0 f'(0) - c\delta \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)}} \right) = c\delta(\alpha + \delta_L)(1 - \mathcal{H}) e^{-\lambda(\tau_1 + \tau_3)}. \tag{9}
\]

From the second equation of system (2), we have
\[
L^* = \frac{k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} T^* f(V^*).
\]
It follows from the third equation of system (2) that
\[
\delta I^* = (1 - k) e^{-\delta_1 \tau_2} T^* f(V^*) + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} T^* f(V^*).
\]
Thus, 
\[
\frac{c}{N} e^{\delta_1 \tau_3} V^* = \left( (1 - k)e^{-\delta_1 \tau_2} + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} \right) T^* f(V^*) 
\geq \left( (1 - k)e^{-\delta_1 \tau_2} + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} \right) T^* f'(V^*) V^*.
\]
This gives that 
\[
1 \geq \frac{N \left( (1 - k)e^{-\delta_1 \tau_2} + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} \right) e^{\delta_2 \tau_3}}{c e^{\delta_2 \tau_3}} T^* f'(V^*)
\]
that is
\[
1 \geq \frac{\mathcal{R}_0 T^* f'(V^*)}{T^0 f'(0)}.
\]
If \( \text{Re}(\lambda) \geq 0 \), by using the above inequality, then we have 
\[
\left| (\lambda + \alpha + \delta_L) \left( \frac{\lambda + d_T + f(V^*)}{(\lambda + d_T)T^* f'(V^*)} + \frac{\alpha + \delta L}{\lambda + \alpha + \delta L} \right) \mathcal{R}_0 (\lambda + \delta)(\lambda + c)T^0 f'(0) - c\delta \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)} \right| \]
\[
> (\alpha + \delta L) \left| (\lambda + \delta)(\lambda + c) - |c\delta \mathcal{H} e^{-\lambda(\tau_2 + \tau_3)}| \right|
\]
\[
\geq (\alpha + \delta L) |(\lambda + \delta)(\lambda + c) - c\delta \mathcal{H}| \]
\[
\geq (\alpha + \delta L) c\delta (1 - \mathcal{H}), \quad (10)
\]
and 
\[
|c\delta (\alpha + \delta L)(1 - \mathcal{H}) e^{-\lambda(\tau_1 + \tau_3)}| \leq c\delta (\alpha + \delta L)(1 - \mathcal{H}). \quad (11)
\]
Note that equation (9) and inequalities (10), (11) imply a contradiction. Therefore, the infected equilibrium \( E^* \) is locally asymptotically stable when \( \mathcal{R}_0 > 1 \). \( \square \)

4. Global stability. In this section, we study the global stability of equilibria for system (2) with the help of the method of Lyapunov functionals (also called the Lyapunov’s second method), which is an effctive tool to prove the global stability for the system of delay differential equations. McCluskey [25, 26] and Huang et al. [16] developed a class of Lyapunov functionals to investigate the global stability of delay epidemiological models. This method of Lyapunov functionals construction has been used to study the global stability of epidemic models with bounded delay [15, 17, 24] and infinite delay [18, 36, 37, 57]. Let 
\[
g(x) = x - 1 - \ln x, \quad x > 0.
\]
The function \( g(x) \geq 0 \) for any \( x > 0 \) and \( g(x) = 0 \) if and only if \( x = 1 \).

**Theorem 4.1.** If \( \mathcal{R}_0 < 1 \), then the infection-free equilibrium \( E_0 \) is globally asymptotically stable.

**Proof.** Define a Lyapunov functional 
\[
U(t) = \frac{\alpha}{\alpha + \delta_L} L(t) + I(t) + \frac{1}{N} e^{\delta_2 \tau_3} V(t) + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} \int_{t-\tau_1}^{t} T(\theta) f(V(\theta)) d\theta \]
\[
+ (1 - k) e^{-\delta_1 \tau_2} \int_{t-\tau_2}^{t} T(\theta) f(V(\theta)) d\theta + \delta \int_{t-\tau_3}^{t} I(\theta) d\theta.
\]
Then for large \( t > 0 \) the time derivative of \( U(t) \) along solutions of system (2) is
Define a Lyapunov functional where
\[ W(t) = W_1(t) + W_2(t), \]
where
\[ W_1(t) = (A + B)T^* g \left( \frac{T(t)}{T^*} \right) + \frac{\alpha}{\alpha + \delta_L} L^* g \left( \frac{L(t)}{L^*} \right) + I^* g \left( \frac{I(t)}{I^*} \right) + \frac{1}{N} e^{\delta_{\tau_3}} V^* g \left( \frac{V(t)}{V^*} \right), \]
and
\[ W_2(t) = AT^* f(V^*) \int_{t-\tau_2}^{t} g \left( \frac{T(\theta)f(V(\theta))}{T^*f(V^*)} \right) d\theta + BT^* f(V^*) \int_{t-\tau_3}^{t} g \left( \frac{T(\theta)f(V(\theta))}{T^*f(V^*)} \right) d\theta + \delta I^* \int_{t-\tau_3}^{t} g \left( \frac{I(\theta)}{I^*} \right) d\theta. \]

Hence, the largest invariant set in \( \{ T, L, I, V \} \frac{dU}{dt} = 0 \) is the singleton \( \{ E_0 \} \). Using LaSalle’s Invariance Principle, the infection-free equilibrium \( E_0 \) is globally asymptotically stable.

**Theorem 4.2.** If \( \mathcal{R}_0 > 1 \), then the infected equilibrium \( E^* \) is globally asymptotically stable.

**Proof.** For brevity, we denote
\[ A = \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 t}, \quad B = (1-k)e^{-\delta_1 t}. \]

Observe that \( dU \frac{dt}{dt} = 0 \) if and only if \( V = 0 \). Hence, the last inequality following from Theorem 2.1. By hypothesis (H), we can obtain
\[ \frac{dU}{dt} \leq \frac{c}{N} e^{\delta_{\tau_3}} V \left[ \frac{N e^{-\delta_{\tau_3}}}{c} \left( \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 t} + (1-k)e^{-\delta_1 t} \right) \lim_{V \to 0^+} \frac{f(V)}{V} - 1 \right] \]
\[ \leq \frac{c}{N} e^{\delta_{\tau_3}} V (\mathcal{R}_0 - 1). \]

It is obvious that \( \frac{dU}{dt} \leq 0 \) when \( \mathcal{R}_0 < 1 \). Observe that \( \frac{dU}{dt} = 0 \) if and only if \( V = 0 \). Using LaSalle’s Invariance Principle, the infection-free equilibrium \( E_0 \) is globally asymptotically stable. \( \square \)
Then we have
\[
\frac{dW_1}{dt} = \frac{-d_T(A + B)}{T} (T - T^*)^2 + 3(A + B)T^* f(V^*) - (A + B)T f(V) \\
- (A + B)T^* f(V^*) \frac{T^*}{T} + (A + B)T^* f(V^*) \frac{f(V)}{f(V^*)} \\
+ AT(t - \tau_1)f(V(t - \tau_1)) - AL \frac{T(t - \tau_1)f(V(t - \tau_1))}{L} + \alpha L^* \\
+ BT(t - \tau_2)f(V(t - \tau_2)) - BL \frac{T(t - \tau_2)f(V(t - \tau_2))}{L} + \delta I^* - \delta I \\
- \alpha I^* \frac{L}{L} + \delta I(t - \tau_3) - \delta V^* \frac{I(t - \tau_3)}{V^*} + \frac{c}{N} e^{\delta \tau_3} V^* - \frac{c}{N} e^{\delta \tau_3} V.
\]
Applying
\[
\alpha L^* = AT^* f(V^*), \quad \delta I^* = (A + B)T^* f(V^*) = \frac{c}{N} e^{\delta \tau_3} V^*, \quad \frac{c}{N} e^{\delta \tau_3} = \delta I^* \frac{1}{V^*},
\]
we get
\[
\frac{dW_1}{dt} = \frac{-d_T(A + B)}{T} (T - T^*)^2 + 3(A + B)T^* f(V^*) - (A + B)T f(V) \\
- (A + B)T^* f(V^*) \frac{T^*}{T} + (A + B)T^* f(V^*) \frac{f(V)}{f(V^*)} \\
- AT^* f(V^*) \frac{T(t - \tau_1)f(V(t - \tau_1))}{T^* f(V^*) L^*} + AT(t - \tau_1)f(V(t - \tau_1)) \\
+ BT(t - \tau_2)f(V(t - \tau_2)) - BT^* f(V^*) \frac{T(t - \tau_2)f(V(t - \tau_2))}{T^* f(V^*) I^*} - \delta I \\
- AT^* f(V^*) \frac{I^* L}{L I^*} + \delta I(t - \tau_3) - (A + B)T^* f(V^*) \frac{V}{V^*} \\
- (A + B)T^* f(V^*) \frac{V^* I(t - \tau_3)}{V^* I^*}.
\]
Next, we have
\[
\frac{dW_2}{dt} = AT f(V) - AT(t - \tau_1)f(V(t - \tau_1)) \\
+ AT^* f(V^*) \ln \frac{T(t - \tau_1)f(V(t - \tau_1))}{T f(V)} + BT f(V) \\
- BT(t - \tau_2)f(V(t - \tau_2)) + BT^* f(V^*) \ln \frac{T(t - \tau_2)f(V(t - \tau_2))}{T f(V)} \\
+ \delta I - \delta I(t - \tau_3) + (A + B)T^* f(V^*) \ln \frac{I(t - \tau_3)}{I^*}.
\]
Thus,
\[
\frac{dW}{dt} = \frac{dW_1}{dt} + \frac{dW_2}{dt} \\
= \frac{-d_T(A + B)}{T} (T - T^*)^2 + 3(A + B)T^* f(V^*) \\
- (A + B)T^* f(V^*) \frac{T^*}{T} + (A + B)T^* f(V^*) \frac{f(V)}{f(V^*)} \\
- AT^* f(V^*) \frac{T(t - \tau_1)f(V(t - \tau_1))L^*}{T^* f(V^*) L} + AT^* f(V^*)
\]
the number of virions increases. Then system (2) becomes

\[-BT^* f(V^*) \frac{T(t - \tau_2) f(V(t - \tau_2)) I^*}{T^* f(V^*) I} - AT^* f(V^*) \frac{I^* L}{I L^*} \]

\[-(A + B) T^* f(V^*) \frac{V}{V^*} - (A + B) T^* f(V^*) \frac{V^* I(t - \tau_3)}{V I^*} \]

\[+ AT^* f(V^*) \ln \frac{T(t - \tau_1) f(V(t - \tau_1))}{T f(V)} + (A + B) T^* f(V^*) \ln \frac{I(t - \tau_3)}{I} \]

\[+ BT^* f(V^*) \ln \frac{T(t - \tau_2) f(V(t - \tau_2))}{T f(V)} \]

\[= - \frac{d_T (A + B)}{T} (T - T^*)^2 - AT^* f(V^*) \left( g \left( \frac{V}{V^*} \right) - g \left( \frac{f(V)}{f(V^*)} \right) \right) \]

\[- AT^* f(V^*) \left( g \left( \frac{T^*}{T} \right) + g \left( \frac{T(t - \tau_1) f(V(t - \tau_1)) L^*}{T^* f(V^*) L} \right) \right) \]

\[+ g \left( \frac{I^* L}{I L^*} \right) + g \left( \frac{V^* I(t - \tau_3)}{V I^*} \right) \] \[- BT^* f(V^*) \left( g \left( \frac{V}{V^*} \right) - g \left( \frac{f(V)}{f(V^*)} \right) \right) \]

\[- BT^* f(V^*) g \left( \frac{T(t - \tau_2) f(V(t - \tau_2)) I^*}{T^* f(V^*) I} \right) \].

Applying proposition A.1 of Sigdel and McCluskey [48], we get

\[g \left( \frac{f(V)}{f(V^*)} \right) \leq g \left( \frac{V}{V^*} \right).\]

The above arguments show that \( \frac{dW}{dt} \leq 0 \). The largest invariant set where \( \frac{dW}{dt} = 0 \) is the singleton \( \{ E^* \} \). Again by LaSalle’s Invariance Principle, the infected equilibrium \( E^* \) is globally asymptotically stable. \( \square \)

5. Application. In this section, we give an application of the above results. We also present some numerical simulations.

Example 1. Suppose \( f(V) = \frac{\beta V}{1 + \alpha_1 V} \) (\( \alpha_1 \geq 0 \)), where \( \frac{1}{1 + \alpha_1 V} \) measures the crowding effect from the behavioral change of the uninfected CD4$^+$ T cells when the number of virions increases. Then system (2) becomes

\[
\begin{align*}
\frac{dT}{dt} &= s - d_T T - \frac{\beta T V}{1 + \alpha_1 V}, \\
\frac{dL}{dt} &= k e^{-\delta_1 \tau_1} \frac{\beta T(t - \tau_1) V(t - \tau_1)}{1 + \alpha_1 V(t - \tau_1)} - \delta_L L - \alpha L, \\
\frac{dI}{dt} &= (1 - k) e^{-\delta_1 \tau_2} \frac{\beta T(t - \tau_2) V(t - \tau_2)}{1 + \alpha_1 V(t - \tau_2)} - \delta I + \alpha L, \\
\frac{dV}{dt} &= N \delta e^{-\delta_2 \tau_3} I(t - \tau_3) - c V.
\end{align*}
\]

Straightforward calculation yields

\[ R_0 = \frac{s N \beta e^{-\delta_2 \tau_3}}{cd_T} \left( (1 - k) e^{-\delta_1 \tau_2} + \frac{\alpha k}{\alpha + \delta_L} e^{-\delta_1 \tau_1} \right). \]
System (12) always has an infection-free equilibrium $E_0 = (T^0_0, 0, 0, 0)$. If $R_0 > 1$, then system (12) possesses a unique infected equilibrium $E^* = (T^*, L^*, I^*, V^*)$, where

$$T^* = \frac{s(\beta + \alpha_1 d \tau R_0)}{d_T(\beta + \alpha_1 d \tau R_0)}; \quad L^* = \frac{sk\beta e^{-\delta_1 \tau_1}}{(\alpha + \delta_L)(\beta + \alpha_1 d \tau R_0)(R_0 - 1)},$$

$$I^* = \frac{c d_T e^{\delta_2 \tau_2}}{N\delta(\beta + \alpha_1 d \tau R_0)(R_0 - 1)}; \quad V^* = \frac{d_T}{\beta + \alpha_1 d \tau R_0}(R_0 - 1).$$

Applying Theorems 4.1 and 4.2 to system (12), we have the following results.

**Table 1. List of parameters**

| Parameters | Data1 | Data2 | Data3 | Source |
|------------|-------|-------|-------|--------|
| $s$ (cells ml$^{-1}$ day$^{-1}$) | $10^4$ | $10^4$ | $10^4$ | [4] |
| $d_T$ (day$^{-1}$) | 0.01 | 0.01 | 0.01 | [30] |
| $\beta$ (ml virion$^{-1}$ day$^{-1}$) | $2.4 \times 10^{-8}$ | $2.4 \times 10^{-8}$ | $2.4 \times 10^{-8}$ | [43] |
| $\alpha_1$ | 0.00001 | 0.00001 | 0.00001 | Assumed |
| $k$ | $1.5 \times 10^{-4}$ | 0.001 | 0.001 | [2, 4] |
| $\delta_1$ (day$^{-1}$) | 0.05 | 0.05 | 0.05 | [2] |
| $\delta_L$ (day$^{-1}$) | 0.004 | 0.004 | 0.004 | [4] |
| $\alpha$ (day$^{-1}$) | 0.01 | 0.01 | 0.01 | [28] |
| $\delta$ (day$^{-1}$) | 0.7 | 1 | 1 | [4, 22] |
| $N$ (virions cell$^{-1}$) | 100 | 2000 | 2000 | [4, 47] |
| $c$ (day$^{-1}$) | 13 | 23 | 23 | [4, 45] |
| $\tau_1$ | 0.3 | 0.3 | 0.3 | [2] |
| $\tau_2$ | 0.6 | 0.6 | 0.6 | [2] |
| $\tau_3$ | 0.6 | 0.6 | Assumed | [41] |

**Theorem 5.1.**

(i) If $R_0 < 1$, then the infection-free equilibrium $E_0$ of system (12) is globally asymptotically stable;

(ii) If $R_0 > 1$, then the infected equilibrium $E^*$ of system (12) is globally asymptotically stable.

The parameter values are listed in Table 1. For simulation, we take the initial values with $T(\theta) = 8 \times 10^5$ cells ml$^{-1}$, $V(\theta) = 0.005$ virions ml$^{-1}$, $L(\theta) = 0$ and $I(\theta) = 0$ for $\theta \in [-\tau, 0]$.

Using the parameter values from Data1 in Table 1, we get $R_0 = 0.1781 < 1$. According to Theorem 5.1, the infection-free equilibrium $E_0(10^0, 0, 0, 0)$ is globally asymptotically stable (see Fig. 1). Using the parameter values from Data2 in Table 1, we obtain $R_0 = 2.0126 > 1$, and the infected equilibrium $E^*(9.0262 \times 10^2, 68.5219, 944.7647, 8.1662 \times 10^4)$ is globally asymptotically stable demonstrated by Theorem 5.1 (see Fig. 2). Using the parameter values from Data2 except $\tau_3$ in Table 1, we can see that $R_0(\tau_3)$ is an exponentially decreasing function of $\tau_3$ (see Fig. 3). There exists a critical value $\tau_3^*$ satisfying $R_0(\tau_3^*) = 1$. When $\tau_3 > \tau_3^*$, $R_0 < 1$. It means that the prolonged time delay period of the maturation of the newly produced viruses ($\tau_3$) may lead to the elimination of the viruses. Using the parameter values from Data2 in Table 1, we found there is a delay in the appearance...
Figure 1. The solution converges to the infection-free equilibrium $E_0(10^6, 0, 0, 0)$ when $R_0 = 0.1781 < 1$. The parameter values are taken from Data1 in Table 1.

Figure 2. The solution converges to the infected equilibrium $E^*(9.0262 \times 10^5, 68.5219, 944.7647, 8.1662 \times 10^4)$ when $R_0 = 2.0126 > 1$. The parameter values are taken from Data2 in Table 1.

of peaks of target cells, latently infected cells, productively infected cells, and viral loads when the delay $\tau_3$ increases (see Fig. 4). Besides, we found that the first peaks of productively infected cells and viral loads obviously become smaller with the increase of $\tau_3$. Using the parameter values from Data3 in Table 1 and let $\tau_3 = 80$, ...
we have $R_0 = 0.9098 < 1$ and the solution converges to $E_0(10^6, 0, 0, 0)$ (see Fig. 5). Note that the only difference between Data2 and Data3 is the value of $\tau_3$.

6. **Conclusion.** In this paper, we propose a latent HIV infection model with general incidence function and multiple delays. It is generally difficult to study the global properties of delayed models arising in biology and medicine. However, the global stability of some delayed models could be achieved thanks to direct Lyapunov method. The basic reproduction number $R_0$ is obtained to determine the threshold properties. If $R_0 < 1$, then the infection-free equilibrium $E_0$ is globally asymptotically stable. If $R_0 > 1$, then the infected equilibrium $E^*$ is globally asymptotically stable.
Our model includes some existing literatures as special cases. For the case \( f(V) = \beta V \) and \( \tau_3 = 0 \), system (2) is similar to that considered by Alshorman et al. [2]. For the case \( f(V) = \beta V \) and \( \tau_1 = \tau_2 = \tau_3 = 0 \), system (2) is similar to that considered by Callaway and Perelson [4].

When the target-cell dynamics modelled by the logistic equation, we known that Hopf bifurcations can occur in within-host models without intracellular delay (see, for instance, De Leenheer and Smith [8] and Wang and Li [54]). Li and Shu [20] and Yang et al. [57] showed that the occurrence of Hopf bifurcation in within-host models depends on the target-cell dynamics, not on intracellular delays. Our results show that no Hopf bifurcations occur by introducing intracellular delays into the system (2). Numerical simulations are performed to illustrate the special model with Holling type-II incidence function. The results show that an increase of the maturation time of the newly produced viruses may bring the infection under control eventually. Since the complete blockage of the production of new viruses is impossible, we could provide an alternative strategy that the new drug design and development should consider how to extend the maturation delay of the newly produced viruses.

Appendix A. Proof of Theorem 2.1. System (2) can be written as \( \dot{x}(t) = F(x_i) \), where

\[
F(\phi) = \begin{pmatrix}
    s - dT\phi_1(0) - \phi_1(0)f(\phi_4(0)) \\
    ke^{-\delta_1\tau_1}\phi_1(-\tau_1)f(\phi_4(-\tau_1)) - (\alpha + \delta_L)\phi_2(0) \\
    (1-k)e^{-\delta_1\tau_2}\phi_1(-\tau_2)f(\phi_4(-\tau_2)) - \delta\phi_3(0) + \alpha\phi_2(0) \\
    N\delta e^{-\delta_2\tau_3}\phi_3(-\tau_3) - c\phi_4(0)
\end{pmatrix}.
\]

It is clear that for any \( \phi \in X \), \( \phi_i(0) = 0 \) for some \( i \), we get \( F_i(\phi) \geq 0 \). Using Theorem 2.1 in [49, Chapter 5] for \( t \geq 0 \), we know that \( x(t, \phi) \geq 0 \) for all \( t \geq 0 \) in its maximal interval of existence.
To show the boundedness of the solutions, we first see that
\[
\frac{dT}{dt} \leq s - d_T T.
\]
This implies that \( \limsup_{t \to +\infty} T(t) = s/d_T \). Next, we prove the boundedness of \( L(t) \).
Define
\[
K(t) = T(t) + \frac{1}{k} e^{\delta_1 \tau_1} L(t + \tau_1).
\]
Then, the derivative of \( K(t) \) with respect to time \( t \) along the solutions of system (2) yields
\[
\frac{dK}{dt} = s - d_T T - T f(V) + T f(V) - \frac{\alpha + \delta L}{k} e^{\delta_1 \tau_1} L(t + \tau_1).
\]
This implies that \( \limsup_{t \to +\infty} K(t) \leq \frac{s}{d_T} \). It follows from
the positivity of \( T(t) \) that \( \limsup_{t \to +\infty} L(t) \leq \frac{s k}{d_T} e^{-\delta_1 \tau_1} \).
Similarly, by using \( \tilde{K}(t) = T(t) + \frac{1}{1 - k} e^{\delta_1 \tau_2} I(t + \tau_2) \), we can get
\[
\limsup_{t \to +\infty} I(t) \leq \frac{s (1 - k) \tilde{d} e^{-\delta_1 \tau_2} + \alpha k e^{-\delta_1 \tau_1}}{\delta \tilde{d}} := M_1,
\]
where \( \tilde{d} = \min\{d_T, \alpha + \delta L\} \). Then, from the fourth equation of system (2), we obtain
\[
\limsup_{t \to +\infty} V(t) \leq \frac{e^{-\delta_2 \tau_3} s N \delta ((1 - k) \tilde{d} e^{-\delta_1 \tau_2} + \alpha k e^{-\delta_1 \tau_1})}{\delta \tilde{d}} := M_2.
\]

Hence the solutions of system (2) are bounded, and the positive invariant set of system (2) can be given by
\[
\Omega = \{ (T, L, I, V) \in X : 0 < T < \frac{s}{d_T}, 0 < L < \frac{s k e^{-\delta_1 \tau_1}}{d_T}, 0 \leq I \leq M_1, 0 \leq V \leq M_2 \}.
\]

Appendix B. Proof of Theorem 2.2. To find the infected equilibrium, we set
\[
\begin{cases}
  s - d_T T - T f(V) = 0, \\
  k e^{-\delta_1 \tau_1} T f(V) - (\alpha + \delta L) L = 0, \\
  (1 - k) e^{-\delta_1 \tau_2} T f(V) - \delta I + \alpha L = 0, \\
  N \delta e^{-\delta_2 \tau_3} I - c V = 0.
\end{cases}
\tag{13}
\]
After some computations, we have
\[
\frac{s}{d_T} - \frac{\alpha + \delta L}{k} e^{\delta_1 \tau_1} L, \quad V = \frac{N \delta e^{-\delta_2 \tau_3} I}{c},
\]
and
\[
I = \frac{(1 - k) (\alpha + \delta L) e^{\delta_1 (\tau_1 - \tau_2)} + \alpha k}{\delta k} L.
\]
Substituting the above equalities into the second equation in (13), we get
\[
\frac{s}{d_T} - \frac{\alpha + \delta L}{k} e^{\delta_1 \tau_1} L \left( \frac{N e^{-\delta_2 \tau_3} ((1 - k) (\alpha + \delta L) e^{\delta_1 (\tau_1 - \tau_2)} + \alpha k) L}{ck} \right) = \frac{\alpha + \delta L}{k} e^{\delta_1 \tau_1} L.
\]
Define
\[ P(L) = s - \frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} L \left( \frac{Ne^{-\delta_2 \tau_3}((1 - k)(\alpha + \delta_L)e^{\delta_1(\tau_1 - \tau_2)} + ak)}{ck} \right) \]

It is obvious that \( P \left( \frac{k}{\alpha + \delta_L} e^{\delta_1 \tau_1} \right) = -s < 0 \) and \( P(0) = 0 \). Then, we have
\[ P'(0) = N T_0 e^{-\delta_2 \tau_3}((1 - k)(\alpha + \delta_L)e^{\delta_1(\tau_1 - \tau_2)} + ak) \frac{f'(0)}{ck} - \frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} \]

Therefore, if \( R_0 > 1 \), then \( P(L) \) is positive for sufficiently small \( L \), and thus there exists an infected equilibrium \( E^* = (T^*, L^*, I^*, V^*) \). Note that \( L^* < \frac{sk}{(\alpha + \delta_L)e^{\delta_1 \tau_1}} \), which ensures \( T^* > 0 \).

We now prove that \( E^* \) is the unique infected equilibrium of system (2). Using
\[ \frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} = \frac{Ne^{-\delta_2 \tau_3}((1 - k)(\alpha + \delta_L)e^{\delta_1(\tau_1 - \tau_2)} + ak)}{ck} \]

and hypothesis (H), we have
\[ P'(L^*) = -\frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} f(V^*) - \frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} \]
\[ + \frac{Ne^{-\delta_2 \tau_3}((1 - k)(\alpha + \delta_L)e^{\delta_1(\tau_1 - \tau_2)} + ak)}{ck} T^* f'(V^*) \]
\[ = \frac{Ne^{-\delta_2 \tau_3}((1 - k)(\alpha + \delta_L)e^{\delta_1(\tau_1 - \tau_2)} + ak)}{ck} \]
\[ \times \left( V^* f'(V^*) - f(V^*) \right) \]
\[ - \frac{\alpha + \delta_L}{k} e^{\delta_1 \tau_1} f(V^*) \]
\[ < 0. \]

This means that \( P \) is strictly decreasing at each of its zeros.

Assume there exists more than one infected equilibrium. We conclude that there must exist an equilibrium \( E^{**} = (T^{**}, L^{**}, I^{**}, V^{**}) \) such that \( P'(L^{**}) \geq 0 \) contradicting the calculation above. Thus, we claim that if \( R_0 > 1 \), then system (2) has a unique infected equilibrium \( E^* \).

Acknowledgments. We would like to thank the editor and anonymous reviewers for their helpful comments and suggestions.

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Received August 2017; revised January 2018.