Global Stability of HIV Infection Model with Adaptive Immune Response and Distributed Time Delay

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Abstract

In this paper, we propose a mathematical model with five nonlinear differential equations describing the interactions between HIV, CD4\(^+\) T cells, and the adaptive immune response represented by cytotoxic T lymphocytes (CTL) cells and the antibodies. In addition, the lag between the time when the virus enters a cell and when the cell becomes infected is modeled by a distributed time delay. The global stability of the steady states of the model is determined by using the direct Lyapunov functional method.
1 Introduction

Human immunodeficiency virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS). Nowadays, HIV infection is an important and serious worldwide cause of mortality. Recently, many mathematical models (see [8, 11, 5, 4, 6, 2, 10, 1]) have been developed in order to understand the dynamics of HIV infection.

In this paper, we consider the following HIV infection model with adaptive immune response and distributed time delay governed by nonlinear differential equations:

\[
\begin{align*}
\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\
\dot{y}(t) &= \int_0^h f(\tau)e^{-m\tau}x(t-\tau)v(t-\tau)d\tau - ay(t) - py(t)z(t), \\
\dot{v}(t) &= ky(t) - \mu v(t) - qv(t)w(t), \\
\dot{w}(t) &= gv(t)w(t) - hw(t), \\
\dot{z}(t) &= cz(t) - bz(t),
\end{align*}
\]

(1)

where \(x(t), y(t), v(t), w(t)\) and \(z(t)\) denote the concentration of uninfected cells, infected cells, free virus particles, antibody response and CTL response at time \(t\), respectively.

The uninfected cells are produced at a constant \(\lambda\), die a rate \(dx\) and become infected by free virus at a rate \(\beta xv\). Infected cells are lost at a rate \(ay\) and are killed by the CTL response at a rate \(pyz\). Free viruses are produced by infected cells at a rate \(ky\), cleared at a rate \(uv\) and are neutralized by antibodies at a rate \(qv w\). Antibodies develop in response to free virus at a rate \(gw w\) and decay at a rate \(hw\). CTL cells expand in response to viral antigen derived from infected cells at a rate \(cyz\) and decay in the absence of antigenic stimulation at a rate \(bz\). Here, we assume that the uninfected cells are contacted by the virus particles at time \(t-\tau\) becomes infected cells at time \(t\), where \(\tau\) is a random variable with a probability distribution \(f(\tau)\) over the interval \([0, h]\) and \(h\) is limit superior of this delay. This probability distribution is assumed to be a positive and integrable function on \([0, h]\), and satisfying \(\int_0^h f(\tau)d\tau = 1\). The term \(e^{-m\tau}\) is the probability of surviving from time \(t-\tau\) to time \(t\), where \(m\) is the death rate for infected but not yet virus-producing cells.

The novelty of our study is that it incorporates both humoral and cellular responses and investigates the impact of the distributed delay on the dynamical behavior of HIV infection.

The rest of the paper is organized as follows. Section 2 deals with positivity and boundedness of solutions. The equilibria of the model and five threshold parameters are given in Section 3. In Section 4, we discuss the global stability of the equilibria. The paper ends with a conclusion in Section 5.
2 Positive and boundedness of solutions

In this section, we establish the positivity and boundedness of solutions of system (1). Let $C = C([-h, 0], \mathbb{R}^5)$ be the Banach space of continuous functions mapping the interval $[-h, 0]$ into $\mathbb{R}^5$ with the topology of uniform convergence. By the fundamental theory of functional differential equations [3], it is easy to show that there exists a unique solution $(x(t), y(t), v(t), w(t), z(t))$ of system (1) with initial data $(x_0, y_0, v_0, w_0, z_0) \in C$.

For biological reasons, we assume that the initial data for system (1) satisfy:

$$x_0(s) \geq 0, \quad y_0(s) \geq 0, \quad v_0(s) \geq 0, \quad w_0(s) \geq 0, \quad z_0(s) \geq 0, \quad \forall s \in [-h, 0]$$  \hspace{1cm} (2)

**Proposition 2.1** All solutions of system (1) subject to condition (2) remains non-negative and bounded for all $t \in [0, +\infty)$.

**Proof.** From (1), we have

$$x(t) = x(0)e^{-\int_0^t (d+\beta_v(s))ds} + \lambda \int_0^t e^{\int_0^\xi (d+\beta_v(s))ds} d\xi$$  \hspace{1cm} (3)

$$y(t) = y(0)e^{-\int_0^t (a+pz(s))ds} + \int_0^t \beta e^{\int_0^\xi (a+pz(s))ds} \int_0^h f(\tau)e^{-m\tau v(\xi - \tau)}x(\xi - \tau)d\tau d\xi$$  \hspace{1cm} (4)

$$v(t) = v(0)e^{-\int_0^t (\mu + qw(s))ds} + k \int_0^t y(\xi)e^{\int_0^\xi (\mu + qw(s))ds} d\xi$$  \hspace{1cm} (5)

$$w(t) = w(0)e^{-\int_0^t (h - gw(s))ds}$$  \hspace{1cm} (6)

$$z(t) = z(0)e^{-\int_0^t (b - cy(s))ds}$$  \hspace{1cm} (7)

From (3), (6) and (7), we have $x(t) \geq 0$, $w(t) \geq 0$ and $z(t) \geq 0$ for all $t \in [0, +\infty)$.

Let $t \in [0, h]$, it is easy to show, from (4) and (5), that $y(t) \geq 0$ and $v(t) \geq 0$ for all $t \in [0, h]$. This method can be repeated to deduce non-negativity of $y$ and $v$ on the interval $[h, 2h]$ and then on successive intervals $[nh, (n+1)h], n \geq 2$, to include all positive times.

Next, we show the boundedness of solutions. Let

$$T(t) = x(t) + y(t) + \frac{a}{2k}v(t) + \frac{aq}{2kg}w(t) + \frac{p}{c}z(t) + \beta \int_0^h f(\tau) \int_{t-\tau}^t e^{-m(t-s)}x(s)v(s)ds d\tau.$$

We have

$$\dot{T}(t) = \lambda - dx(t) - \frac{a}{2}y(t) - \frac{a\mu}{2k}v(t) - \frac{aq h}{2g k}w(t) - \frac{pb}{c}z(t) - m\beta \int_0^h f(\tau) \int_{t-\tau}^t e^{-m(t-s)}x(s)v(s)ds d\tau.$$

Hence, $\dot{T}(t) \leq \lambda - \delta T(t)$ with $\delta = \min \{d, \frac{\mu}{2}, h, b, m\}$. So $T(t) \leq \max \{\frac{\lambda}{\delta}, T(0)\}$. and $T$ is bounded. Therefore, all variables of (1) are bounded. This completes the proof. \hfill \square
3 Equilibria and threshold parameters

In order to establish the global dynamics of system (1), we derive five threshold parameters, that are:

\[ R_0 = \frac{\lambda k \beta A}{ad \mu}, \]
\[ D_0 = \frac{\lambda k g A}{a \mu h}, \quad D_0^w = \frac{\lambda c A}{ab}, \]
\[ H_0^w = \frac{1}{R_0 + \frac{1}{D_0}}, \quad H_0^z = \frac{1}{H_0^w + \frac{1}{D_0}}, \]

where \( A = \int_0^h f(\tau) e^{-m\tau} d\tau. \)

The above threshold parameters \( R_0, D_0^w, D_0^z, H_0^w \) and \( H_0^z \) represent, respectively, the basic reproduction number, the basic defense number by antibody response, the basic defense number by CTL response, the half harmonic mean of \( R_0 \) and \( D_0^w \), and the half harmonic mean of \( R_0 \) and \( D_0^z \).

It is no difficult to show that the system (1) always a disease-free equilibrium \( E_0 \left( \frac{\lambda}{d}, 0, 0, 0, 0 \right) \), and four endemic equilibrium points:

\[ E_1 \left( \frac{\lambda}{d} \frac{1}{R_0}, \frac{\mu d}{k \beta} (R_0 - 1), \frac{d}{\beta} (R_0 - 1), 0, 0 \right), \]
\[ E_2 \left( \frac{\lambda}{d} H_0^z, \frac{b}{c}, \frac{kb}{\mu c}, 0, \frac{a}{p} (H_0^z - 1) \right), \]
\[ E_3 \left( \frac{\lambda}{d} H_0^w, \frac{h \mu}{k g} H_0^w, \frac{h}{g}, \frac{\mu}{q} (H_0^w - 1), 0 \right), \]
\[ E_4 \left( \frac{\lambda}{d} H_0^w, \frac{b}{c}, \frac{h}{g}, \frac{\mu}{q} \left( \frac{D_0^w}{D_0} - 1 \right), \frac{a}{p} \left( \frac{D_0^z}{D_0} H_0^w - 1 \right) \right). \]

As in [9], we remark that

**Remark 3.1**

1. If \( R_0 < 1 \), \( E_1 \) does not exists and \( E_1 = E_0 \) when \( R_0 = 1 \).

2. If \( H_0^z < 1 \), \( E_2 \) does not exists and \( E_2 = E_1 \) when \( H_0^z = 1 \).

3. If \( H_0^w < 1 \), \( E_3 \) does not exists and \( E_3 = E_1 \) when \( H_0^w = 1 \).

4. If \( \frac{D_0^z}{D_0} H_0^w < 1 \) or \( \frac{D_0^w}{D_0} < 1 \), \( E_2 \) does not exists. In addition, \( E_4 = E_3 \) if \( \frac{D_0^z}{D_0} H_0^w = 1 \), and \( E_4 = E_2 \) if \( \frac{D_0^w}{D_0} = 1 \).
4 Global Stability

In this section, we study the global stability of five equilibria \( E_i(x_i, y_i, v_i, w_i, z_i), \ i \in \{0, 1, 2, 3, 4\} \). Let the function \( F(s) = s - 1 - \ln(s) \), it is clear that \( F(s) \geq 0 \) for any \( s > 0 \) and \( F \) has the global minimum \( F(1) = 0 \). For each component \( s_i \) of \( E_i \), we define on \( \mathbb{R}^*_+ \) the following function

\[
\begin{aligned}
F_i(s) &= s_i F\left(\frac{s}{s_i}\right), \quad \text{if } s_i \neq 0 \\
F_i(s) &= s, \quad \text{if } s_i = 0.
\end{aligned}
\]

Therefore, we have the following main result.

**Theorem 4.1**

(i) If \( R_0 \leq 1 \), then \( E_0 \) is globally asymptotically stable.

(ii) \( R_0 > 1 \), \( H_0^z \leq 1 \) and \( H_0^w \leq 1 \), then \( E_1 \) is globally asymptotically stable.

(iii) \( H_0^z > 1 \) and \( \frac{D_0}{D_0^z} \leq 1 \), then \( E_2 \) is globally asymptotically stable.

(iv) If \( H_0^w > 1 \) and \( \frac{H_0^w D_0}{D_0^w} \leq 1 \), then \( E_3 \) is globally asymptotically stable.

(v) If \( \frac{D_0}{D_0^w} > 1 \) and \( \frac{H_0^w D_0}{D_0^w} > 1 \), then \( E_4 \) is globally asymptotically stable.

**Proof.** For each \( E_i \), we consider the following Lyapunov functional

\[
L_i = F_i(x) + \frac{1}{A} F_i(y) + \frac{\beta}{A} \int_0^h f(\tau)e^{-m\tau} \int_0^\tau F_i\left(x(t - \theta)v(t - \theta)\right) d\theta d\tau
+ m_i F_i(v) + m_i \frac{q}{g} F_i(w) + \frac{p}{cA} F_i(z),
\]

where \( m_i = \frac{a}{kA} \) when \( i \in \{0, 1, 3\} \), and \( m_i = \frac{2x_i m}{ky_i} \) when \( i \in \{2, 4\} \).

First, we prove (i). For \( i = 0 \), we get

\[
\frac{dL_0}{dt} = (1 - \frac{x_0}{x})[\lambda - dx(t) - \beta x(t)v(t)] + \frac{\beta}{A} \int_0^h f(\tau)e^{-m\tau} x(t - \tau)v(t - \tau)d\tau
- \frac{a}{A} y(t) - \frac{p}{A} y(t)z(t) + \frac{\beta}{A} \int_0^h f(\tau)e^{-m\tau} [x(t)v(t) - x(t - \tau)v(t - \tau)]d\tau
+ \frac{a}{kA} [ky(t) - \mu v(t) - qv(t)w(t)] + \frac{aq}{kAg} [qv(t)w(t) - hw(t)] + \frac{p}{cA} [cy(t)z(t) - bz(t)].
\]

Since \( x_0 = \frac{\lambda}{d} \), we have that

\[
\frac{dL_0}{dt} = -\frac{d}{x}(x - x_0)^2 + (\beta x_0 - \frac{a\mu}{kA})v - \frac{aqh}{kAg}w - \frac{bp}{cA}z.
\]

\[
= -\frac{d}{x}(x - x_0)^2 - \frac{a\mu}{kA}(1 - R_0)v - \frac{aqh}{kAg}w - \frac{bp}{cA}z.
\]
If $R_0 \leq 1$ then $\frac{dL_0}{dt} \leq 0$.

\[ \frac{dL_0}{dt} = 0 \Rightarrow x = x_0, w = 0, z = 0. \] Using (1), we have $v = 0$ and $y = 0$. By LaSalle’s invariance principle, we have $E_0$ is globally asymptotically stable.

For $i \neq 0$ we have

\[
\frac{dL_i}{dt} = (1 - \frac{x_i}{x})[\lambda - dx(t) - \beta x(t)v(t)]
\]
\[+ (1 - \frac{y_i}{y})[\frac{\beta}{A}\int_0^h f(\tau)e^{-\mu_\tau x(t-\tau)v(t-\tau)}d\tau - \frac{\kappa y(t)}{A} - \frac{p}{A}y(t)z(t)]
\]
\[+ \frac{\beta}{A}\int_0^h f(\tau)e^{-\mu_\tau x(t-\tau)v(t-\tau)}d\tau - x_i v_i l n(\frac{x(t-\tau)v(t-\tau)}{x v})] d\tau
\]
\[+ m_i (1 - \frac{v_i}{v}) [y(t) - \mu v(t) - qv(t)w(t)] + m_i \frac{q}{g} (1 - \frac{w_i}{w}) [gv(t)w(t) - hw(t)]
\]
\[+ \frac{p}{cA} (1 - \frac{z_i}{z}) [cy(t)z(t) - bz(t)].
\]

Using the fact that $\lambda = dx_i + \beta x_i v_i$, we have

\[
\frac{dL_i}{dt} = -\frac{d}{x}(x - x_i)^2 + \beta x_i v_i - \beta x_i v_i \frac{x_i}{x} - \frac{\beta}{A}\int_0^h f(\tau)e^{-\mu_\tau x(t-\tau)v(t-\tau)}\frac{y_i}{y} d\tau
\]
\[+ \frac{\beta x_i v_i}{A} \int_0^h f(\tau)e^{-\mu_\tau} l n(\frac{x(t-\tau)v(t-\tau)}{x v})] d\tau - m_i k y_i - m_i[\mu v_i + \frac{h q w_i}{g}]
\]
\[+ \frac{1}{A}[a y_i + \frac{p b}{c} z_i] + [-\frac{a}{A} + m_i k - \frac{p z_i}{A}] y + [\beta x_i - m_i \mu - q m_i w_i] v + q m_i[\frac{v_i}{v} - \frac{h}{g}] w
\]
\[+ \frac{p}{A}[y_i - \frac{b}{c}] z.
\]

Using the relation: $l n(\frac{x(t-\tau)v(t-\tau)}{x v})] = ln(\frac{x(t-\tau)v(t-\tau)}{x_i v_i y_i}) + ln(\frac{z_i}{x}) + ln(\frac{v_i}{v y_i})$, we obtain

\[
\frac{dL_i}{dt} = -\frac{d}{x}(x - x_i)^2 + \beta x_i v_i - \beta x_i v_i \frac{x_i}{x} + \beta x_i v_i \frac{x_i}{x}
\]
\[- \frac{\beta x_i v_i}{A} \int_0^h f(\tau)e^{-\mu_\tau} l n(\frac{x(t-\tau)v(t-\tau)}{x v})] d\tau + \frac{1}{A}[a y_i + \frac{p b}{c} z_i]
\]
\[- m_i k y_i + m_i[\mu v_i + \frac{h q w_i}{g}] + \beta x_i v_i l n(\frac{v_i}{v y_i})
\]
\[+ [-\frac{a}{A} + m_i k - \frac{p z_i}{A}] y + [\beta x_i - m_i \mu - q m_i w_i] v + q m_i[\frac{v_i}{v} - \frac{h}{g}] w + \frac{p}{A}[y_i - \frac{b}{c}] z.
\]

For $i = 1$, we have $m_1 = \frac{q}{k A}, [\frac{1}{A}[a y_1 + \frac{p b}{c} z_1] = m_1[\mu v_1 + \frac{h q w_1}{g}] = m_1 k y_1 = \beta x_1 v_1$, and $[-\frac{a}{A} + m_i k - \frac{p z_i}{A}] = [\beta x_1 - m_i \mu - q m_i w_1] = 0$, then

\[
\frac{dL_1}{dt} = -\frac{d}{x}(x - x_1)^2 - \beta x_1 v_1 F(\frac{x_1}{x}) - \frac{\beta x_1 v_1 A}{A} \int_0^h f(\tau)e^{-\mu_\tau} F(\frac{y_1 (x(t-\tau)v(t-\tau))}{x_1 v_1}) d\tau
\]
\[- \beta x_1 v_1 F(\frac{v_i}{v y_1}) - \frac{aq}{k A} (\frac{d g + h \beta}{gb}) (1 - H_0) w - \frac{p}{A} (\frac{\mu c d + b k \beta}{k \beta c}) (1 - H_0) z.
\]
Since $F(s) \geq 0$, $\forall s > 0$ and $H_0^w \leq 1$, $H_0^w \leq 1$ then $\frac{dL_1}{dt} \leq 0$.
If $\frac{dL_1}{dt} = 0$. Then $x = x_1$, and $v_1y = vy_1$. And from first equation of (1) we have $v = v_1$, and thereafter $y = y_1$. And from the other equation of (1) we have $w = 0$ and $z = 0$. By LaSalle’s invariance principle [7], we have $E_1$ is globally asymptotically stable.

If $i = 2$, we get $m_2 = \frac{\beta xy_2}{ky_2}, \frac{1}{\lambda}[ay_2 + pb \cdot z_2] = m_2[\mu v_2 + \frac{hw_2}{g}] = \beta x_2v_2$, and $[\frac{a}{A} + m_2k - \frac{\mu^2}{A}] = [\beta x_2 - m_2\mu - qm_2w_2] = \frac{\mu}{A}[y_2 - \frac{k}{c}] = 0$, then

$$\frac{dL_2}{dt} = -\frac{d}{x} \frac{(x - x_2)^2}{x} - \beta x_2v_2F(\frac{x_2}{x}) - \frac{\beta x_2v_2}{\lambda} \int_0^h f(\tau)e^{-m\tau}\frac{y_2x(t - \tau)v(t - \tau)}{x_2v_2}d\tau$$

$$- \beta x_2v_2 \frac{v_2y}{vy_2} - \frac{g\beta x_2v_2h}{gky_2}[1 - \frac{D^w_0}{D^w_0}].$$

Since $F(s) \geq 0$, $\forall s > 0$ and $\frac{D^w_0}{D^w_0} \leq 1$ then $\frac{dL_2}{dt} \leq 0$.
If $\frac{dL_2}{dt} = 0$. Then $x = x_2$ and $v_2y = vy_2$. And from first equation of (1) we have $v = v_2$ and from the other equation of (1) we have $y = y_2$, $w = 0$ and $z = z_2$. By LaSalle’s invariance principle, $E_2$ is globally asymptotically stable.

If $i = 3$, we have $m_3 = \frac{\alpha}{kA}, \frac{1}{\lambda}[ay_3 + \frac{pb}{c}z_3] = m_3[\mu v_3 + \frac{hw_3}{g}] = \beta x_3v_3$, and $[\frac{a}{A} + m_3k - \frac{\mu^2}{A}] = [\beta x_3 - m_3\mu - qm_3w_3] = qm_3\lbrack v_3 - \frac{k}{g} \rbrack = 0$, then

$$\frac{dL_3}{dt} = -\frac{d}{x} \frac{(x - x_3)^2}{x} - \beta x_3v_3F(\frac{x_3}{x}) - \frac{\beta x_3v_3}{A} \int_0^h f(\tau)e^{-m\tau}\frac{y_3x(t - \tau)v(t - \tau)}{x_3v_3}d\tau$$

$$- \beta x_3v_3 \frac{v_3y}{vy_3} - \frac{pb}{Ac}[1 - \frac{H_0^w D^w_0}{D^w_0}].$$

Since $F(s) \geq 0$, $\forall s > 0$ and $\frac{H_0^w D^w_0}{D^w_0} \leq 1$ then $\frac{dL_3}{dt} \leq 0$.
If $\frac{dL_3}{dt} = 0$. Then $x = x_3$ and $v_3y = vy_3$. As above, we have $y = y_3$, $v = v_3$, $w = w_3$ and $z = 0$. By LaSalle’s invariance principle, $E_3$ is globally asymptotically stable.

If $i = 4$, we have $m_4 = \frac{\beta xy_4}{ky_4}, \frac{1}{\lambda}[ay_4 + \frac{pb}{c}z_4] = m_4[\mu v_4 + \frac{hw_4}{g}] = \beta x_4v_4$, and $[\frac{a}{A} + m_4k - \frac{\mu^2}{A}] = [\beta x_4 - m_4\mu - qm_4w_4] = qm_4\lbrack v_4 - \frac{k}{c} \rbrack = \frac{\mu}{A}[y_4 - \frac{k}{c}] = 0$, then

$$\frac{dL_4}{dt} = -\frac{d}{x} \frac{(x - x_4)^2}{x} - \beta x_4v_4F(\frac{x_4}{x}) - \frac{\beta x_4v_4}{A} \int_0^h f(\tau)e^{-m\tau}\frac{y_4x(t - \tau)v(t - \tau)}{x_4v_4}d\tau$$

$$- \beta x_4v_4 \frac{v_4y}{vy_4}.$$

Since $F(s) \geq 0$, $\forall s > 0$, then $\frac{dL_4}{dt} \leq 0$. If $\frac{dL_4}{dt} = 0$. Then $x = x_4$ and $vy = vy_4$. As above, we have $y = y_4$, $w = w_4$ and $z = z_4$. By LaSalle’s invariance principle, $E_4$ is globally asymptotically stable. This completes the proof of the theorem. ■

5 Conclusion

In this work, we have proposed a mathematical model with distrusted delay time and both humoral and cellular immune responses. The global stability of equilibria is completely
determined by five thresholds parameters. More precisely, we have proved that when $R_0 \leq 1$, the disease-free equilibrium $E_0$ is globally asymptotically stable. When $R_0 > 1$, four endemic equilibria appear that are: the immune-free equilibrium $E_1$ which is globally asymptotically stable if $H_0^z \leq 1$ and $H_0^w \leq 1$; the endemic equilibrium with CTL response $E_2$ which is globally asymptotically stable if $H_0^\delta > 1$ and $\frac{D_0^w}{D_0^z} \leq 1$; the endemic equilibrium with antibody response $E_3$ which is globally asymptotically stable if $H_0^w > 1$ and $\frac{H_0^w D_0^w}{D_0^z} \leq 1$; the endemic equilibrium with both CTL and antibody responses $E_4$ that is globally asymptotically stable if $\frac{D_0^w}{D_0^z} > 1$ and $\frac{H_0^w D_0^w}{D_0^z} > 1$.

From our main result, we conclude that the time distributed delay plays an important role to control the concentration of viral load by reducing the basic number $R_0$ (see (8)). In addition, this $R_0$ is independent of the immune parameters that are $b$, $c$, $p$, $g$, $h$ and $q$, which means that the adaptive immune response is unable to eliminate the virus, but it can reduce the concentration of viral load and increase the concentration of healthy $CD4^+$ cells, which can see by comparing the components of the viral load and those of the concentration of $CD4^+$ before and after the activation of both CTL and antibody immune response.

References


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