Research Article

Threshold Dynamics for a Time-Periodic Viral Infection Model with Cell-to-Cell Transmission and Drug Treatments

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1. Introduction

Recently, much attention and great effort have been paid on modelling of HIV, and many models have been proposed and studied on HIV spreading. Many earlier models of HIV infection models describe the interaction between virus and target cells by assuming that the infected cells produce virions instantaneously [1, 2]. However, research studies have been carried out to show that a latent period exists before the infected cells are activated to produce virus [3–5]. Therefore, it is reasonable to introduce the latent period into a model.

As we know, antiretroviral drugs can effectively suppress viral replication to a low level, but cannot eradicate the virus permanently. An important reason is that HIV provirus can reside in latently infected CD4+ T-cells, which can live longer and cannot be affected by antiretroviral drugs or immune responses, but can be activated to produce virus by relevant antigens [5]. Thereafter, motivated by this factor, many viral infection models with latent cells have been proposed and studied to describe this phenomena [6–13] and references therein. For example, Pankavich [6] proposed and studied the following viral infection model:

\[
\begin{align*}
T'(t) &= \lambda - d_T T - k(1 - \eta_r)TV, \\
L'(t) &= p(1 - \eta_p)kTV - (\alpha + d_L)L, \\
I'(t) &= (1 - p)(1 - \eta_p)kTV + \alpha L - d_I I, \\
V'(t) &= (1 - \eta_p)Nd_I I - d_V V(t), \\
V_{NI}'(t) &= \eta_p Nd_I I - d_V V_{NI}(t),
\end{align*}
\]

where \(T, L, I, V, \) and \(V_{NI} \) represent the concentration of uninfected target T-cells, latent cells, productively infected T-cells, infectious virions, and noninfectious virions at time \(t\), respectively. \(\lambda, k, \alpha, p\) and \(\eta\) are the production rate of T-cells, virus-to-cell infection rate, the activation rate of latent cells, and the fraction of infections leading to latency. \(d_T, d_L, d_I, \) and \(d_V\) are the death rate of susceptible T-cells, latent cells, actively infected T-cells, and virions, respectively. \(N\) denotes the burst rate of actively infected cells. \(\eta_r\) and \(\eta_p\) are the efficacies of RTIs (reverse transcriptase inhibitors) and PIs (protease inhibitors), respectively. The global dynamics of model (1) have been investigated in [6].

Notice that the drug efficacy in model (1) is assumed to be a constant coefficient. In fact, drugs are often administered for patients periodically. As we known, drug
concentration will reach a peak value within a very short time when a dose is administered, and the concentration down to a lower value as time goes and then reaches a peak value again when another dose is administrated [14–16]. Therefore, drug concentration may vary periodically during the dose interval. Moreover, only cell-free infection has been considered in earlier work; the cell-to-cell transmission was not considered in model (1). However, a recent research work has shown that cell-to-cell transmission may be one of the main infection mode which leads to a failed therapy and potentially contribute to viral persistence [17]. Because a better understanding of the viral dynamics is very significant in terms of applications, thus motivated by these arguments many viral infection models with cell-to-cell transmission have been proposed and studied [18–29] and references therein. Besides, drugs’ efficacy about cell-to-cell infection was not taken into consideration in model (1). However, the results obtained in [30] show that PIs can effectively block cell-to-cell spread of HIV by preventing cleavage of viral polyproteins into functional subunits leading to the formation of immature noninfectious virus particles, while RTIs are less effective inhibitors of HIV cell-to-cell spread compared to virus-to-cell infection. To the best of our knowledge, the time-periodic viral infection model with cell-to-cell infection and latency have not been studied. Hence, motivated by the abovementioned work and arguments, we consider the following time-periodic model with two infection modes:

\[
\begin{align*}
T'(t) &= \lambda - d_T T(t) - (1 - \eta_{rt}(t)) \frac{k_1 TV_I}{1 + m_1 V_I} - \left(1 - \eta_p^{(1)}(t)\right) \frac{k_2 TI}{1 + m_2 I}, \\
L'(t) &= p(1 - \eta_{rt}(t)) \frac{k_1 TV_I}{1 + m_1 V_I} + p \left(1 - \eta_p^{(1)}(t)\right) \frac{k_2 TI}{1 + m_2 I} - (\alpha + d_L)L, \\
I'(t) &= (1 - p)(1 - \eta_{rt}(t)) \frac{k_1 TV_I}{1 + m_1 V_I} + (1 - p) \left(1 - \eta_p^{(1)}(t)\right) \frac{k_2 TI}{1 + m_2 I} + \alpha L - d_I I, \\
V_I'(t) &= \left(1 - \eta_p^{(2)}(t)\right) N d_I I - d_v V_I(t), \\
V_{NI}'(t) &= \eta_p^{(2)}(t) N d_I I - d_v V_{NI}(t),
\end{align*}
\]

where \(k_2\) is the infection rate of productively infected T-cells. Assume \(\eta_{rt}(t), \eta_p^{(1)}(t), \eta_p^{(2)}(t)\): \(R \to [0, 1]\) are the efficiencies of RTIs and PIs, and we assume they are continuous and periodic in time \(t\) with a same period \(\omega\). Here, we considered two saturated incidence rates, where \(m_1\) and \(m_2\) are the saturation parameters and are positive constants.

Other parameters have the same meaning of model (1). For convenience, we denote \(\beta_1(t) = k_1 (1 - \eta_{rt}(t)), \beta_2(t) = k_1 (1 - \eta_p^{(1)}(t)), \) and \(a(t) = (1 - \eta_p^{(2)}(t))\). Since the last equation of model (2) is independent with the others. Thus, we will focus on the following reduced model:

\[
\begin{align*}
T'(t) &= \lambda - d_T T(t) - \beta_1(t) \frac{TV_I}{1 + m_1 V_I} - \beta_2(t) \frac{TI}{1 + m_2 I}, \\
L'(t) &= p\beta_1(t) \frac{TV_I}{1 + m_1 V_I} + p\beta_2(t) \frac{TI}{1 + m_2 I} - (\alpha + d_L)L, \\
I'(t) &= (1 - p)\beta_1(t) \frac{TV_I}{1 + m_1 V_I} + (1 - p)\beta_2(t) \frac{TI}{1 + m_2 I} + \alpha L - d_I I, \\
V_I'(t) &= N d_I a(t) I - d_v V_I(t).
\end{align*}
\]

This study is organized as follows. In Section 2, preliminary results and the definition of the basic reproduction number are studied. In Section 3, global extinction of the disease and the uniform persistence are investigated in terms of the basic reproduction number. The global asymptotic stability of the infection equilibrium to the corresponding
autonomous model are discussed by applying the method of Lyapunov functions. In Section 4, some numerical simulations are carried out. A brief conclusion and discussion ends the paper.

2. The Basic Reproduction Number

In this section, we investigate the definition of the basic reproduction number $R_0$ for model (3) according to the work [31, 32]. The following result shows that solutions of model (3) are bounded.

**Theorem 1.** The solutions $(T(t),L(t),I(t),V_1(t))$ of model (3) are uniformly and ultimately bounded, i.e., there exist an $M_1 > 0$ and $t^* > 0$ such that $(T(t),L(t),I(t),V_1(t)) \leq (M,M,M,M)$, for $t \geq t^*$.

**Proof.** From model (3), we can obtain that

$$
\frac{d(T+L+I)}{dt} = \lambda - d_T T - d_L L - d_I I \leq \lambda - \sigma (T+L+I),
$$

where $\sigma = \min\{d_T, d_L, d_I\}$. Thus, there exists $t_1$ such that $T+L+I \leq \lambda/\sigma$, for $t \geq t_1$. It follows from the last equation of model (3); we have, for $t \geq t_1$,

$$
\frac{dV_1}{dt} \leq ND_1 \cdot \max_{r \in [0,\omega]} \{a(t)\} \cdot \lambda/\sigma - d_I V_1,
$$

which implies that there exist $t^* \geq t_1$ such that $V_1(t) \leq ND_1 \cdot \max_{r \in [0,\omega]} \{a(t)\} \cdot \lambda/\sigma 1/d_I$, for $t \geq t^*$. Let

$$
M = \max_{r \in [0,\omega]} \left\{ \frac{\lambda/\sigma \cdot ND_1 \cdot \max_{r \in [0,\omega]} \{a(t)\} \cdot \lambda/\sigma 1/d_I} {d_I} \right\}.
$$

It then follows that $(T(t),L(t),I(t),V_1(t)) \leq (M,M,M,M)$, for $t \geq t^*$. Hence, the solutions of model (3) are uniformly and ultimately bounded. This finishes the proof.

Let $(\mathbb{R}^n, \mathbb{R}^n_+)$ be the standard ordered $n$-dimensional Euclidean space with a norm $\|\cdot\|$. For $u, v \in \mathbb{R}^n$, we write $u \succeq v$ if $u - v \in \mathbb{R}^n_+$, $u > v$ if $u - v \in \mathbb{R}^n_+/0$, and $u \succ v$ if $u - v \in \text{Int}(\mathbb{R}^n_+)$. Let $A(t)$ be a continuous, cooperative, irreducible, and $\omega$-periodic $n \times n$ matrix function and $\Phi_A(t)$ be the fundamental solution matrix of the following linear system:

$$
\frac{dx}{dt} = A(t)x.
$$

Let $r(\Phi_A(\omega))$ be the spectral radius of $\Phi_A(\omega)$. It follows from the Perron–Frobenius theorem that $r(\Phi_A(\omega))$ is the principal eigenvalue of $\Phi_A(\omega)$ in the sense that it is simple and admits an eigenvector $v^* \succ 0$. The following lemma comes from [33] which will be used for the discussion in the next section.

**Lemma 1** (see [33]). Let $\mu = 1/\omega \ln r(\Phi_A(\omega))$. Then, there exists a positive $\omega$-periodic function $v(t)$ such that $e^{\mu t}v(t)$ is a solution of (5).

Obviously, model (3) has a unique infection-free equilibrium $E_0 = (T_0, 0, 0, 0)$, where $T_0 = \lambda/d_T$. Linearizing (3) at $E_0$ yields that

$$
\begin{aligned}
L'(t) &= p\beta_2(t)T_0 I + p\beta_1(t)T_0 V_1 - (\alpha + d_L) L, \\
I'(t) &= (1 - p)\beta_2(t)T_0 I + (1 - p)\beta_1(t)T_0 V_1 + \alpha L - d_L I, \\
V_1'(t) &= Nd_1 a(t)I - d_v V_1(t).
\end{aligned}
$$

(6)

Define

$$
F = \begin{pmatrix} 
0 & p\beta_2(t)T_0 & p\beta_1(t)T_0 \\
0 & (1 - p)\beta_2(t)T_0 & (1 - p)\beta_1(t)T_0 \\
0 & 0 & 0
\end{pmatrix},
$$

(7)

and

$$
V = \begin{pmatrix} 
\alpha + d_L & 0 & 0 \\
0 & -d_L & 0 \\
0 & -Nd_1 a(t) & d_v
\end{pmatrix}.
$$

(8)

Then, system (6) can be written as

$$
\frac{dx}{dt} = (F(t) - V(t))x(t).
$$

(9)

Assume that $Y(t,s), t \geq s$, is the evolution operator of the following system:

$$
\frac{dy}{dt} = -V(t)y(t).
$$

(10)

Then, the $3 \times 3$ matrix $Y(t,s)$ satisfies

$$
\frac{dY(t,s)}{dt} = -V(t)Y(t,s), \quad \forall t \geq s, Y(s,s) = I
$$

is a $3 \times 3$ identity matrix.

Let $C_w$ be the ordered Banach space of all $\omega$-periodic functions from $\mathbb{R}$ to $\mathbb{R}^3$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_w^+ = \{ \phi \in C_w; \phi(t) \geq 0, \forall t \in \mathbb{R} \}$. Suppose $\phi(s) \in C_w^+$ is the initial distribution of infectious cells and virus in this periodic environment; then, $Y(t,s)\phi(s)$ is the rate of new infections produced by the infected cells and virus who were introduced at time $s$, and $Y(t,s)\phi(s)$ represents the distribution of those infected cells and virus who were newly infected at time $s$ and remain in the infected compartments at time $t$, for $t \geq s$. Hence,

$$
\psi(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds,
$$

(11)

is the distribution of accumulative new infections at time $t$ produced by all those infected cells and virus introduced before $t$.

Define the linear operator $\mathcal{L}: C_w \longrightarrow C_w$ as follows:

$$
[\mathcal{L}\phi](t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da,
$$

(12)

$\forall t \in \mathbb{R}, \phi \in C_w$.

It follows from the idea in [32] that the basic reproduction number $R_0$ of system (3) is defined as the spectral radius of $\mathcal{L}$, i.e.,
\[ R_0 = r(\mathcal{D}). \]  

Moreover, the local asymptotic stability of the infection-free equilibrium \( E_0 \) follows from [32].

**Theorem 2** (see [32]). The following statements are valid:

(i) \( R_0 < 1 \) if and only if \( r(\phi_{(F-V)}(\omega)) < 1 \)

(ii) \( R_0 = 1 \) if and only if \( r(\phi_{(F-V)}(\omega)) = 1 \)

(iii) \( R_0 > 1 \) if and only if \( r(\phi_{(F-V)}(\omega)) > 1 \)

Thus, infection-free equilibrium \( E_0 \) of (3) is asymptotically stable if \( R_0 < 1 \) and unstable if \( R_0 > 1 \).

### 3. The Threshold Dynamics

#### 3.1. Stability and Persistence of the Disease

In this section, we will investigate the global asymptotic stability of infection-free equilibrium and the disease persistence by regarding \( R_0 \) as a threshold parameter.

**Theorem 3.** If \( R_0 < 1 \), then the infection-free equilibrium \( E_0 \) is globally asymptotically stable, and it is unstable for \( R_0 > 1 \).

**Proof.** It follows from Theorem 2 that if \( R_0 < 1 \), then \( E_0 \) is locally asymptotically stable and \( E_0 \) is unstable when \( R_0 > 1 \). Hence, it is sufficient to show that \( E_0 \) is global attractor for \( R_0 < 1 \).

From the first equation of (3) and nonnegativity of the solutions, we then have \( dT/dt \leq \lambda - dT \), which implies that \( T \rightarrow T_0 \); there exists \( \epsilon \) such that \( T(t) \leq T_0 + \epsilon, t > T \).

Consider the following auxiliary system:

\[
\begin{align*}
L'(t) &= p \beta_1(t)(T_0 + \epsilon)I + p \beta_1(t)(T_0 + \epsilon)V_1 - (\alpha + d_1)L, \\
\bar{T}'(t) &= (1 - p) \beta_2(t)(T_0 + \epsilon)I + (1 - p) \beta_1(t)(T_0 + \epsilon)V_1 + \alpha L - d_1 \bar{I}, \\
V_1'(t) &= N d_2 N(t) - d_3 V_1(t),
\end{align*}
\]

which is equivalent to

\[
\begin{pmatrix}
\bar{L}' \\
\bar{T}' \\
V_1'
\end{pmatrix} = (\mathbf{F} - \mathbf{V})
\begin{pmatrix}
\bar{L} \\
\bar{T} \\
V_1
\end{pmatrix} + \varepsilon M(t)
\begin{pmatrix}
\bar{L} \\
\bar{T} \\
V_1
\end{pmatrix},
\]

where

\[
M(t) =
\begin{pmatrix}
0 & p \beta_2(t) & p \beta_1(t) \\
0 & (1 - p) \beta_2(t) & (1 - p) \beta_1(t) \\
0 & 0 & 0
\end{pmatrix}.
\]

It then follows from Lemma 1 that there exists a positive \( \omega \)-periodic function \( v(t) = (v_1(t), v_2(t), v_3(t)) \) such that \( e^{\mu t}v(t) \) is a solution of (14), where \( \mu = 1/\omega \ln(r(\phi_{+V}, \omega)) \).

Choose \( \tau > T \) and a real number \( \alpha_1 > 0 \) such that \((\bar{L}(\tau), \bar{T}(\tau), V_1(\tau))^T \leq \alpha_1 v(0)\), which implies that

\[
(\bar{L}(\tau), \bar{T}(\tau), V_1(\tau))^T \leq \alpha_1 e^{\mu(t-\bar{T})} v(t-\bar{T}), \quad t \geq \bar{T}.
\]

The comparison principle yields that

\[
(\bar{L}(t), \bar{T}(t), V_1(t))^T \leq \alpha_1 e^{\mu(t-\bar{T})} v(t-\bar{T}), \quad t \geq \bar{T}.
\]

Recall Theorem 2 that \( R_0 < 1 \) if and only if \( r(\phi_{(F-V)}(\omega)) < 1 \). Since the continuity of the spectrum for matrices [34], then choose \( \varepsilon > 0 \) small enough such that \( r(\phi_{(F-V)}(\omega) < 1 \), which implies that \( n < 0 \). Then, we have \((\bar{L}(t), \bar{T}(t), V_1(t))^T \rightarrow 0 \) as \( t \rightarrow \infty \). Furthermore, it follows from the first equation of model (3) and the theory of asymptotically periodic semiflows [35] that \( \lim_{t \rightarrow \infty} T(t) = T_0 \).

Thus, \( E_0 \) is globally attractive.

**Theorem 4.** If \( R_0 > 1 \), then there exists an \( \epsilon > 0 \) such that any solution \( (T(t), L(t), I(t), V_1(t)) \) of model (3) with initial values \((T(0), L(0), I(0), V_1(0)) = (T_0^0, L_0^0, I_0^0, V_1^0^0) \in \mathbb{R}_+ \times Int(\mathbb{R}_+^2)\); the solution of (3) satisfies \( \liminf T(t), L(t), I(t), V_1(t), t > T \).

**Proof.** Let

\[
X = \mathbb{R}_+^1,
\]

\[
X_0 = \mathbb{R}_+ \times Int(\mathbb{R}_+^2),
\]

\[
\partial X_0 = \frac{\partial X}{X_0}.
\]

Define Poincare map \( P: \mathbb{R}_+^1 \rightarrow \mathbb{R}_+^1 \), satisfying \( P(x_0) = u(x_0), \forall x_0 \in \mathbb{R}_+^1 \), with \( u(t, x_0) \) as the unique solution of (3) satisfying \( u(0, x_0^0) = x_0^0 \).

We first show that \( P \) is uniformly persistent with respect to \( (X_0^0, \partial X_0) \). It is easy to see that \( X \) and \( X_0 \) are positively invariant. Moreover, \( \partial X \) is a relatively closed set in \( X \). Recall Theorem 1 that the solutions of model (3) are uniformly and ultimately bounded; thus, the semiflow \( P \) is point dissipative on \( \mathbb{R}_+^1 \), and \( P: \mathbb{R}_+^1 \rightarrow \mathbb{R}_+^1 \) is compact. Consequently, it follows from [36] that the semiflow \( P \) admits a global attractor, which attracts every bounded set in \( \mathbb{R}_+^1 \).

Define

\[
M_0 = \left[ (T_0^0, L_0^0, I_0^0, V_1^0) \right. e \partial X_0 \times P^m((T_0^0, L_0^0, I_0^0, V_1^0), e \partial X_0, \forall m \geq 0),
\]

\[
(20)
\]
Then, we claim that $M_\delta = \{(T, 0, 0, 0) : T \geq 0\}$. In fact, it is obvious that $\{(T, 0, 0, 0) : T \geq 0\} \subseteq M_\delta$. For any $(T^0, L^0, I^0, V^0) \in \partial X_0/(\{(T, 0, 0, 0) : T \geq 0\}$, considering the following cases: (1) $I^0 = 0$, $V^0 = 0$, (2) $L^0 > 0$, $I^0 > 0$, $V^0 = 0$, (3) $L^0 > 0$, $I^0 > 0$, $V^0 > 0$, (4) $L^0 = I^0 = 0$, $V^0 > 0$, (5) $L^0 = V^0 = 0$, $I^0 > 0$, and (6) $L^0 > 0$, $I^0 = 0$, $V^0 = 0$. For case (1), we have $dL/dt|_{T=0} = p\beta_1(t)(T_0 - \epsilon)(1 + m_1T_0) - p\beta_2(t)(T_0 - \epsilon)(1 + m_2T_0)\langle \alpha + d_L\rangle L,$

\[ I'(t) \geq (1 - p)\beta_1(t)(T_0 - \epsilon)(1 + m_1T_0)V_1 + \beta_2(t)(T_0 - \epsilon)(1 + m_2T_0) + aL - d_IL, \]

\[ V_1'(t) = Nd_\alpha aL + d_\beta V_1(t). \]

Set

\[ M_\epsilon = \left( \begin{array}{ccc} 0 & \epsilon(1 + m_1T_0)p\beta_1(t) & \epsilon(1 + m_1T_0)p\beta_1(t) \\ \epsilon(1 + m_2T_0)(1 - p)\beta_2(t) & 0 & \epsilon(1 + m_2T_0)(1 - p)\beta_1(t) \\ 0 & 0 & 0 \end{array} \right). \]

Then, we claim that

\[ \limsup_{m \to \infty} d(P^m(x_0), E_0) \geq \delta_0. \]  

If it is not true, then we have

\[ \limsup_{m \to \infty} d(P^m(x_0), E_0) < \delta_0. \]

For some $x_0 \in X_0$ without loss of generality, we suppose that $\limsup / \liminf_{t \to \infty} \ cod(P^m(x_0), E_0) < \delta_0 \quad \forall m > 0$. Then, we can obtain that

\[ \|u(t, P^m(x_0)) - u(t, E_0)\| \leq \epsilon, \quad \forall t \in [0, \omega]. \]

For any $t \geq 0$, let $t = m\omega + t_1$, where $t_1 \in [0, \omega)$ and $m = [t/\omega]$, which is the greatest integer less than or equal to $t/\omega$. Then, we have

\[ \|u(t, P^m(x_0)) - u(t, E_0)\| \leq \|u(t_1, P^m(x_0)) - u(t_1, E_0)\| \leq \epsilon, \quad \forall t \in [0, \omega]. \]

Set $(T, L(t), I(t), V_1(t)) = u(t, x_0)$; then, we have $T_0 - \epsilon \leq t \leq T_0 + \epsilon, 0 \leq L \leq \epsilon, 0 \leq I < \epsilon$, and $0 \leq V_1 < \epsilon$, for $t \geq 0$. Then,

\[ T/1 + m_1V_1 > T_0 - \epsilon(1 + m_1T_0)/1 + m_1\epsilon = T_0 - \epsilon(1 + m_1T_0)/1 + m_1\epsilon \geq T_0 - \epsilon(1 + m_1T_0)/1 + m_2\epsilon = T_0 - \epsilon(1 + m_1T_0)/1 + m_2\epsilon \geq T_0 - \epsilon(1 + m_2T_0). \]

It follows from Theorem 2 that $r(\Phi_{F \rightarrow V}(\omega)) > 1$; then, we can select $\epsilon > 0$ small enough such that $r(\Phi_{F \rightarrow V}(\omega)) > 1$. It follows from Lemma 1 and the standard comparison principle that there exists a positive $\omega$-periodic function $\mathcal{P} = (\mathcal{P}_1, \mathcal{P}_2, \mathcal{P}_3, \mathcal{P}_4)$ such that $\mathcal{P}(\tau) \geq \mathcal{P}(\tau)e^{\omega\tau}$, where $\mathcal{P}(\tau) = (L(\tau), I(\tau), V_1(\tau), V_1(\tau))$ and $\mu_1 = 1/\omega \ln(\Phi_{F \rightarrow V}(\omega)) > 0$, which implies that $\lim/ \liminf_{t \to \infty} \mathcal{P}(\tau) > 0$, which is a contradiction in $M_\epsilon$ which converges to $E_0$, and hence, $E_0$ is an isolated in $M_\delta$. By Theorem 1.3.1 and Remark 1.3.1 in [35], we obtain that $P$ is uniformly persistent with respect to $(X_0, \partial X_0)$. It then follows from Theorem 3.1.1 in [35] that the solution of (3) is uniformly persistent.

Moreover, it follows from Theorem 1.3.6 in [35] that the Poincare map $P$ has a fixed point $(\tilde{T}(0), \tilde{L}(0), \tilde{I}(0), \tilde{V}_1(t)) \in X_0$. Then, we see that $\tilde{T}(0) > 0$. If not, suppose $\tilde{T}(0) = 0$, from the first equation of model (3), where $\tilde{T}(t)$ satisfies

\[ \frac{d\tilde{T}}{dt} \geq \lambda - d_T \tilde{T} - (\beta_1(t)V_1 + \beta_2(t)I)\tilde{T}. \]
It follows from the comparison theorem that

\[
\tilde{T}(t) \geq e^{-\int_0^t a(s)ds} \left( \tilde{T}(0) + \lambda \int_0^t e^{-\int_0^s a(\tau)d\tau} ds \right) = \lambda e^{-\int_0^t a(s)ds} \int_0^t e^{-\int_0^s a(\tau)d\tau} ds, \quad \forall t > 0, \tag{29}
\]

where \(a(t) = d_1 + \beta_1(t)V_1(t) + \beta_2(t)I(t)\). Then, we have

\[
\tilde{T}(n\omega) \geq e^{-\int_0^{n\omega} a(s)ds} \int_0^{n\omega} e^{-\int_0^\omega a(\tau)d\tau} ds > 0, \tag{30}
\]

The periodicity of \(\tilde{T}(t)\) implies \(\tilde{T}(0) = \tilde{T}(n\omega) = 0\), which is a contradiction. Thus, \(\tilde{T}(0) > 0\). Hence, \((\tilde{T}(0), \tilde{L}(0), \tilde{I}(0), \tilde{V}_1(0))\) is a positive \(\omega\)-periodic solution of model (3).

Furthermore, we can obtain the basic reproduction number of model (31):

\[
R_0 = \left(1 - p\right) + \frac{ap}{\alpha + d_L} N \frac{(1 - \eta_{p}^{(2)}) \beta_1 T_0}{d_v} + \left(1 - p\right) + \frac{ap}{\alpha + d_L} \frac{\beta_2 T_0}{d_L} \tag{32}
\]

3.2. Analysis of the Autonomous Model. If there are no drug therapies, i.e., \(\eta_p(t) = \eta_{p}^{(1)}(t) = \eta_{p}^{(2)}(t) = 0\), or drug therapies are constant, then model (3) becomes an autonomous model. Without loss of generality, we assume drug therapy is constant. Then, model (3) leads to the following autonomous model:

\[
T'(t) = \lambda - d_1 T(t) - \frac{\beta_1 TV_1}{1 + m_1 V_1} - \frac{\beta_2 TI}{1 + m_2 I},
\]

\[
L'(t) = p \frac{\beta_1 TV_1}{1 + m_1 V_1} + p \frac{\beta_2 TI}{1 + m_2 I} - (\alpha + d_L) L,
\]

\[
I'(t) = (1 - p) \frac{\beta_1 TV_1}{1 + m_1 V_1} + (1 - p) \frac{\beta_2 TI}{1 + m_2 I} + aL - d_I I,
\]

\[
V_1'(t) = \bar{N}d_l \left(1 - \eta_{p}^{(2)}\right) I - d_v V_1(t),
\]

where \(\beta_1 = k_1 (1 - \eta_{p})\) and \(\beta_2 = k_2 (1 - \eta_{p}^{(1)})\). Clearly, model (31) has an infection-free equilibrium \(E_0 = (T_0, 0, 0, 0)\) with \(T_0 = \lambda/d_1\). Furthermore, we can obtain the basic reproduction number of model (31):

\[
R_0 = \left(1 - p\right) + \frac{ap}{\alpha + d_L} N \frac{(1 - \eta_{p}^{(2)}) \beta_1 T_0}{d_v} + \left(1 - p\right) + \frac{ap}{\alpha + d_L} \frac{\beta_2 T_0}{d_L} \tag{32}
\]

Next, we will show that there exists a unique infection equilibrium \(E^* = (T^*, L^*, I^*, V_1^*)\). For convenience, let \(f(T, V_1) = TV_1/1 + m_1 V_1\) and \(g(T, I) = TI/1 + m_2 I\). It is easy to see that \((T^*, L^*, I^*, V_1^*)\) satisfies the following equations:

\[
\lambda - d_1 T^* = \beta_1 T^* f(T^*, V_1^*) + \beta_2 g(T^*, I^*),
\]

\[
(1 - p)\beta_1 T^* f(T^*, V_1^*) + (1 - p)\beta_2 g(T^*, I^*) + aL^* = d_I I^*,
\]

\[
N \left(1 - \eta_{p}^{(2)}\right) d_I I^* = d_v V_1^*.
\]

\[
\left(33\right)
\]
Then, we can obtain

\[ T^* = \frac{1}{d_T} \left( \lambda - \frac{\alpha + d_L L^*}{p} \right), \]

\[ I^* = \frac{\alpha + d_L - p d_L L^*}{d_T p}, \]

\[ V_i^* = \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V}. \]

(34)

And \( L^* \) satisfies the following equation:

\[ \beta_1 f \left( \frac{1}{d_T} \left( \lambda - \frac{\alpha + d_L L^*}{p} \right), \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V} \right) + \]

\[ \beta_2 g \left( \frac{1}{d_T} \left( \lambda - \frac{\alpha + d_L L^*}{p} \right), \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V} \right) = \frac{\alpha + d_L L^*}{p}. \]

(35)

Since \( T^* > 0 \), which implies \( 0 < L^* < \lambda p / \alpha + d_L \), for \( L \in (0, \lambda p / \alpha + d_L) \), let

\[ H(L) = \beta_1 f \left( \frac{1}{d_T} \left( \lambda - \frac{\alpha + d_L L}{p} \right), \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V} \right) + \]

\[ \beta_2 g \left( \frac{1}{d_T} \left( \lambda - \frac{\alpha + d_L L}{p} \right), \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V} \right) - \frac{\alpha + d_L L}{p}, \]

(36)

Then, we have

\[ H(0) = 0, \]

\[ H \left( \frac{\lambda p}{\alpha + d_L} \right) = -\lambda < 0, \]

(37)

\[ H'(0) = \frac{\alpha + d_L}{p} (R_0 - 1) > 0 \quad \text{for} \quad R_0 > 1. \]

Thus, there exists a \( L^* \in (0, \lambda p / \alpha + d_L) \). Consequently, model (31) admits an infection equilibrium \( E^* = (T^*, L^*, I^*, V_i^*) \). Furthermore, by calculation, we have

\[ H'(L^*) = \frac{\alpha + d_L p}{pd_T} \frac{\partial f(T^*, V_i^*)}{dT} + \frac{N(1 - \eta_p(2)) (\alpha + d_L - p d_L)}{p d_V} \beta_1 \frac{\partial f(T^*, V_i^*)}{dV_i} - \]

\[ \frac{\alpha + d_L p}{pd_T} \frac{\partial g(T^*, I^*)}{dT} + \frac{\alpha + d_L - p d_L}{pd_T} \beta_2 \frac{\partial g(T^*, I^*)}{dI} - \frac{\alpha + d_L}{p}, \]

\[ = \frac{\alpha + d_L p}{pd_T} \beta_1 \frac{\partial f(T^*, V_i^*)}{dT} + \frac{V_i^*}{L^*} \beta_1 \frac{\partial f(T^*, V_i^*)}{dV_i} - \frac{\alpha + d_L}{p} \beta_2 \frac{\partial g(T^*, I^*)}{dI} - \]

\[ \frac{I^*}{L^*} \beta_2 \frac{\partial g(T^*, I^*)}{dI} - \frac{1}{L^*} (\beta_1 f(T^*, V_i^*) + \beta_2 g(T^*, I^*)) \]

\[ = \frac{\alpha + d_L}{pd_T} \left( \frac{\beta_1 V_i^*}{1 + m_1 V_i^*} + \frac{\beta_2 I^*}{1 + m_2 I^*} \right) - \frac{m_1 \beta_1 T^* (V_i^*)^2}{L^* (1 + m_1 V_i^*)^2} - \frac{m_2 \beta_2 T^* (I^*)^2}{L^* (1 + m_2 I^*)^2} < 0, \]

(38)
which implies that \( H(L) \) is decreasing at each of its root. If there exists more than one root of \( H(L) = 0 \), then it must
exists a root \( \hat{L} \) such that \( H'(\hat{L}) \geq 0 \), which leads to a contradiction. Hence, we claim that there exists a unique
infection equilibrium \( E^* = (T^*, L^*, I^*, V^*_I) \) for \( \mathcal{R}_0 > 1 \).

By constructing suitable Lyapunov functions, we can show that the corresponding infection-free equilibrium \( E_0 \)
and infection equilibrium \( E^* \) of model (31) are globally asymptotically stable.

**Theorem 5.** If \( \mathcal{R}_0 \leq 1 \), then the infection-free equilibrium \( E_0 \)
of model (31) is globally asymptotically stable.

**Proof.** Define

\[
U(t) = Y \left( T - T^* - T^*_t \ln \frac{T}{T^*} \right) + \frac{\alpha}{\alpha + d_L} \left( I - L^* - L^*_t \ln \frac{L}{L^*} \right)
\]

\[
\leq Y \left( T - T^* - T^*_t \ln \frac{T}{T^*} \right) + \frac{\alpha}{\alpha + d_L} \left( I - L^* - L^*_t \ln \frac{L}{L^*} \right)
\]

\[= Y \left( T - T^* - T^*_t \ln \frac{T}{T^*} \right) \left( \frac{d_I}{N(1 - \eta_0^{(3)})} \right) (\mathcal{R}_0 - 1).
\]

Clearly, if \( \mathcal{R}_0 \leq 1 \), then \( U(t) \leq 0 \). Moreover, by LaSalle’s invariance principle, one can easily show that the infection-free equilibrium \( E_0 \) is globally asymptotically stable. \( \square \)

**Theorem 6.** If \( \mathcal{R}_0 > 1 \), then the infection equilibrium \( E^* \) of model (31) is globally asymptotically stable.

**Proof.** Define

\[
G(t) = Y \left( T - T^* - T^*_t \ln \frac{T}{T^*} \right) + \frac{\alpha}{\alpha + d_L} \left( I - L^* - L^*_t \ln \frac{L}{L^*} \right)
\]

\[+ I - I^* - I^*_t \ln \frac{I}{I^*} + Y \frac{\beta_1 f(T^*, V^*_I)}{N(1 - \eta_0^{(3)})d_I} \left( V_I - V^*_I \ln \frac{V_I}{V^*_I} \right).
\]

where \( Y = (\alpha p / \alpha + d_L + (1 - p)) \). Then, combining (33) and by a tedious computation yields

\[
G'(t) = d_I T^* \left( 1 - \frac{T^*}{T} \right) \left( 1 - \frac{T^*}{T^*} \right) + \frac{\alpha p}{\alpha + d_L} \beta_1 f(T^*, V^*_I)
\]

\[\times \left[ 4 - \frac{T^*}{T} \cdot \frac{L^*}{L^*} - \frac{V^*_I}{I^*} \cdot \frac{V_I}{V_I} \cdot \frac{f(T, V_I) L^*}{f(T^*, V^*_I) L} \cdot \frac{V_I}{V_I} \cdot \frac{T^* f(T, V_I)}{T f(T^*, V^*_I)} \right]
\]

\[+ (1 - p) \beta_1 f(T^*, V^*_I) \left[ 3 - \frac{T^*}{T} \cdot \frac{V^*_I}{V_I} - I^* \cdot \frac{f(T, V_I)}{f(T^*, V^*_I)} \right] \frac{V_I}{V_I} \]

\[+ \frac{\alpha p}{\alpha + d_L} \beta_2 g(T^*, I^*) \left[ 3 - \frac{T^*}{T} - \frac{L^*}{L^*} - \frac{g(T, I)}{g(T^*, I^*)} \right] \frac{T^* g(T, I)}{T g(T^*, I^*)} - \frac{I}{I^*}
\]

\[+ (1 - p) \beta_2 g(T^*, I^*) \left[ 2 - \frac{T^* - g(T, I) I^*}{g(T^*, I^*)} + \frac{T^* g(T, I)}{T g(T^*, I^*)} - I \right] \frac{T}{T^*}.
\]
\begin{align*}
&= d_T T^* Y \left( 1 - \frac{T^*}{T} \right) \left( 1 - \frac{T}{T^*} \right) + Y \beta_1 f(T^*, V_i^*) \left[ \varphi \left( \frac{T^*}{T} \right) + \varphi \left( \frac{T f(T^*, V_i^*) V_i}{T^* f(T, V_i^*) V_i} \right) + \varphi \left( \frac{V_i^* I}{V_i} \right) - \frac{m_1 (V_i - V_i^*)^2}{V_i (1 + m_1 V_i^*)(1 + m_1 V_i)} \right] \\
&\quad + \frac{\alpha}{\alpha + d_L} \beta_2 f(T^*, V_i^*) \left[ \varphi \left( \frac{I^* L}{I L^*} \right) + \varphi \left( \frac{f(T, V_i)L^*}{f(T^*, V_i^*)} \right) \right] + (1 - p) \beta_2 f(T^*, V_i^*) \\
&\quad \times \varphi \left( \frac{I^* f(T, V_i)}{I f(T^*, V_i^*)} \right) + Y \beta_2 g(T^*, I^*) \varphi \left( \frac{T^*}{T} \right) + \varphi \left( \frac{T g(T^*, I^*) I}{T^* g(T, I^*)} \right) - \frac{m_2 (I - I^*)^2}{I^* (1 + m_2 I)(1 + m_2 I^*)} \\
&\quad + \frac{\alpha}{\alpha + d_L} \beta_3 g(T^*, I^*) \left[ \varphi \left( \frac{g(T, I)L^*}{g(T^*, I^*)} \right) + \varphi \left( \frac{I^*}{I L^*} \right) \right] \\
&\quad + (1 - p) \beta_3 g(T^*, I^*) \varphi \left( \frac{g(T, I)}{g(T^*, I^*)} \right) \leq 0,
\end{align*}

Figure 1: The results show that the infection-free equilibrium $E_0$ is globally asymptotically stable when $R_0 < 1.$
where $\phi(x) = 1 + \ln x - x$ with maximum value $\phi(1) = 0$ for $x > 0$. Then, it follows from the LaSalle's invariance principle that one can show $E^*$ is globally asymptotically stable. This completes the proof. □

Remark 1. It follows from the above analysis of the model that the saturated incidence rates $V_I/1 + m_1V_I$ and $I/1 + m_2I$ can be extended to a more general form $f(V)$ and $g(I)$ with some conditions as in [27]. Thus, the saturated incidence rates of model (3) can be regarded as a special case.

4. Numerical Simulations

In this section, some numerical simulations are carried out to explain the obtained theoretical results. Most of these parameter values are taken from [6, 13].

**Case 1.** Let $\lambda = 100$, $d_T = 0.02$, $k_1 = 2.4 \times 10^{-6}$, $k_2 = 1.5 \times 10^{-4}$, $\alpha = 0.1$, $N = 1500$, $p = 0.01$, $d_V = 23$, $d_l = 0.4$, $m_1 = 0.01$, $m_2 = 0.01$, $\eta_{rt} = 0.6 - 0.3\cos(\pi t/12)$, $\eta_{r}^{(1)} = 0.7 - 0.2\cos(\pi t/12)$, and $\eta_{r}^{(2)} = 0.6 - 0.25\cos(\pi t/12)$; then, we have $R_0 = 0.7875 < 1$. The simulation shows that the infection-free equilibrium $E_0 = (5000, 0, 0, 0)$ is globally asymptotically stable, which implies disease dies out. Figure 1 validates the above analysis.

**Case 2.** Let $\lambda = 100$, $d_T = 0.02$, $k_1 = 2.4 \times 10^{-4}$, $k_2 = 1 \times 10^{-4}$, $\alpha = 0.1$, $N = 2000$, $p = 0.01$, $d_V = 23$, $d_l = 0.4$, $m_1 = 0.01$, $m_2 = 0.01$, $\eta_{rt} = 0.6 - 0.3\cos(\pi t/12)$, $\eta_{r}^{(1)} = 0.7 - 0.2\cos(\pi t/12)$, and $\eta_{r}^{(2)} = 0.6 - 0.25\cos(\pi t/12)$; then, we have $R_0 = 17.0641 > 1$. The theoretical results show that the model admits a positive
periodic solution and disease keeps persistent in the host. Figure 2 confirms this conclusion.

Figure 3 shows the impact of cell-to-cell transmission \((k_2)\) on the dynamics of model (3). This shows that the existence of cell-to-cell transmission is benefit for viral infection.

Figure 4 shows that the effects of PIs on the dynamics of the model by blocking cell-to-cell transmission, and the other parameters are the same with Figure 2. By varying the drug efficacy \(\eta_p^{(1)}\) of PIs for blocking cell-to-cell transmission from the baseline value \(\eta_p^{(1)} = 0.7 - 0.2\cos(\pi t/12)\) to 50\% and 0\%, the numerical results imply that the peak level of the density of latent cell, infected cells, and viral load decrease under PIs’ blocking cell-to-cell transmission. This implies that increase of the efficacy of PIs for blocking cell-to-cell transmission may contribute to weakening the severity of the viral infection.
Summary and Discussion

In this study, a time-periodic viral infection model with cell-cell transmission was investigated. We have shown that the infection-free equilibrium $E_0$ is globally asymptotically stable if $R_0 < 1$ which implies that infection will be eradicated, and the infection will persist when $R_0 > 1$.

Furthermore, for the corresponding autonomous model, we have shown that the corresponding equilibria are globally asymptotically stable by applying the method of Lyapunov function. The results imply that cell-to-cell transmission existing may contribute to viral persistence and be a barrier to curing the viral infection. At the same time, increasing the efficacy of PIs for blocking cell-to-cell transmission is beneficial to weakening the severity of the viral infection.

Note that only a constant recruitment of uninfected T-cells has been considered in our model. However, T-cells can also be created by proliferation of existing T-cells with a logistic form instead of a constant recruitment [19] and the incidence rates can be a more general form $f(V)$ and $g(I)$ [27], which formulated a further work. Furthermore, immune response and dynamics of the drug are also a good choice to extend the current work, which will be another future work.

Data Availability

All the data used to support the study are included in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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