GLOBAL STABILITY AND BACKWARD BIFURCATION OF A
GENERAL VIRAL INFECTION MODEL WITH VIRUS-DRIVEN
PROLIFERATION OF TARGET CELLS

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Abstract. In this paper, a general viral model with virus-driven proliferation
of target cells is studied. Global stability results are established by employing
the Lyapunov method and a geometric approach developed by Li and Mul-
downey. It is shown that under certain conditions, the model exhibits a global
threshold dynamics, while if these conditions are not met, then backward bi-
furcation and bistability are possible. An example is presented to provide some
insights on how the virus-driven proliferation of target cells influences the virus
dynamics and the drug therapy strategies.

1. Introduction. Many efforts have been recently made in mathematical model-
ing of in vivo dynamics of HIV-1, HBV, HCV and other viruses. Mathematical
modeling plays an important role in understanding the viral infection process [25]
as the resulting mathematical analysis and numerical simulations may shed light on
developing new antiviral drugs and designing optimal combination of therapies for
patients [10, 22, 28].

The standard in-host model is given by Nowak and May [24], which describes the
interactions among healthy target cells (T cells), infected virus-producing T cells
and free virus particles. The model takes the following form:

\[
\begin{align*}
T'(t) &= s - \mu_1 T - k_1 TV, \\
T_i'(t) &= k_1 TV - \mu_2 T_i, \\
V'(t) &= N\mu_2 T_i - \mu_3 V,
\end{align*}
\]

where \(T(t)\) denotes the concentration of healthy \(T\) cells at time \(t\), \(T_i(t)\) denotes the concentration of infected virus-producing \(T\) cells at time \(t\), and \(V(t)\) denotes the concentration of free virus particles at time \(t\); the positive constant \(s\) is the
recruitment rate of healthy \(T\) cells, and \(\mu_i > 0, i = 1, 2, 3\) are, respectively, the
mortality rates of healthy \(T\) cells, infected \(T\) cells and free virus particles; \(k_1 > 0\) is
the contact rate between healthy \(T\) cells and virus particles; \(N > 0\) is the average
number of virions budding out from a single infected target cell.

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ported by NSERC, Mprime and the Harrison McCain Young Scholar Award.
The standard model and its various modifications have been extensively studied in the literature (see [4, 5, 6, 23, 25, 26, 33, 35, 36] and the references therein). If the recruitment rate of healthy \( T \) cells is assumed to be a constant, then a threshold dynamics is usually observed: the viral load will be stabilized at the equilibrium level if the basic reproduction number is greater than unity, otherwise the virus will be cleared [5, 12]. The viral load exhibits oscillations if a logistic growth function is adopted to model the production of new healthy \( T \) cells by antigen or mitogen [18, 34]. The proliferation of healthy \( T \) cells in the presence of virus is often neglected in many in-host models. However, it is known that both \( CD8^+ \) and \( CD4^+ \) \( T \) cells specific to HIV can be directly stimulated, and that activated \( T \) cells can stimulate other \( CD8^+ \) and \( CD4^+ \) [11]. Taking this into account, we consider the following general model:

\[
\begin{align*}
T'(t) &= f(T,V) - k_1 h(T) g(V), \\
T_i'(t) &= k_1 h(T) g(V) - \mu_2 p(T_i), \\
V'(t) &= N \mu_2 p(T_i) - \mu_3 q(V) - k_2 h(T) g(V).
\end{align*}
\]

Here the function \( f(T,V) \) denotes the intrinsic growth rate of the healthy \( T \) cells, which includes the source of new \( T \) cells from the thymus, the natural mortality of cells and the stimulation of \( T \) cells to proliferate in the presence of virus. The incidence of new infections of \( T \) cells occurs at a rate \( k_1 h(T) g(V) \), which includes the rate of contact between free virions and healthy \( T \) cells as well as the probability of cell entry per contact. Infected cells die at the rate \( \mu_2 p(T_i) \), and prior to death, each infected cell produces \( N \) new virions. The natural death rate of free virions is \( \mu_3 q(V) \) and the term \( k_2 h(T) g(V) \) represents the loss of free infectious virions when they enter target cells, where \( k_2 \) is assumed to satisfy \( k_2 < N k_3 \). This term is neglected (i.e., \( k_2 = 0 \)) in [24, 25] by arguing that it can be absorbed into the death rate \( \mu_3 q(V) \). However, as suggested in [5, 9, 10, 27], this loss term may also play a role in HIV (HBV/HCV) dynamics.

For our general model (2), we make the following assumptions:

- **(H1)**: There exists a \( T > 0 \) such that \( f(T,0) = 0 \) and \( f(T,0)(T - T) < 0 \) for \( T \neq T, T > 0 \);
- **(H2)**: \( f \in C^1 \) is bounded from above, \( f(0,V) > 0 \) for all \( V \geq 0 \), and
  \[
  \frac{\partial f(T,V)}{\partial V} < k_1 h(T) g'(V) \quad \text{for all} \quad T, V > 0;
  \]
- **(H3)**: \( h, g, p, q \in C^1 \); \( h, g, p, q \) are strictly increasing on \([0, \infty)\) with \( h(0) = g(0) = p(0) = q(0) = 0 \), \( \lim_{x \to \infty} g(x) = \infty \), and \( g(\cdot)/q(\cdot) \) is nonincreasing on \((0, \infty)\), and there exist \( k_p, k_q > 0 \) such that \( p(T_i) \geq k_p T_i \) for \( T_i \geq 0 \) and \( q(V) \geq k_q V \) for \( V \geq 0 \).

Examples of functions satisfying the above assumptions include many widely used ones in the literature. For example, \( f(T,V) = s - \mu T + r T (1 - T/T_{max}) \) with \( s, \mu, r, T_{max} > 0 \) [25]; \( f(T,V) = s - \mu T + r T V/(C + V) \) with \( s, \mu, r, C > 0 \) [11], \( h(T) = T^m/(T^m + A_1) \), and \( g(V) = V^n/(V^n + A_2) \) with \( m, n, \tilde{m}, \tilde{n} > 0 \) and \( A_1, A_2 \geq 0 \) [5, 17, 21, 25].

We organize the rest of this paper as follows. Section 2 provides some preliminary results concerning the well-posedness of Model (2) as well as an explicit formula for the basic reproduction number. Our global stability results are presented in Section 3. In Section 4, we show that backward bifurcation can be induced by the virus-driven proliferation of target cells. An example is presented in Section 5 to illustrate
our analytical results and their biological implications. We conclude our work in Section 6.

2. Preliminary results.

Proposition 1. Consider System (2) with the initial condition
\[ T(0) > 0, \quad T_i(0) \geq 0, \quad V(0) > 0. \] (4)

If the assumptions (H1)-(H3) are satisfied, then System (2) has a unique solution, which is nonnegative for \( t \geq 0 \) and is ultimately bounded in \( \mathbb{R}_+^3 \). Moreover, \( T(t) > 0 \) for all \( t \geq 0 \).

Proof. We first show that \( T(t) > 0 \) for all \( t \geq 0 \). Assume to the contrary that \( T(t) > 0 \) for \( t \in (0, t_1) \) and \( T(t_1) = 0 \) for some \( t_1 > 0 \). Then it follows from the first equation of System (2) and (H3) that \( T'(t_1) = f(0, V) > 0 \). Hence, \( T(t) < 0 \) for \( t \in (t_1 - \epsilon_1, t_1) \), where \( \epsilon_1 > 0 \) is sufficiently small. This leads to a contradiction. Thus, \( T(t) > 0 \) for all \( t \geq 0 \).

Similarly, we can show that \( T_i(t), V(t) \) are nonnegative for \( t > 0 \). If \( T_i(0) = 0 \), then \( T_i'(0) = k_1 h(T(0)) g(V(0)) > 0 \). Therefore, for any given \( T_i(0) \geq 0 \), there exists \( \bar{t} > 0 \) such that \( T_i(t) > 0 \) for \( t \in (0, \bar{t}) \). Assume to the contrary that there exists \( t_2 > 0 \) such that \( T_i(t), V(t) > 0 \) for \( t \in (0, t_2) \) with either (i) \( T_i(t_2) = 0, V(t_2) \geq 0 \) and \( T_i'(t_2) < 0 \); or (ii) \( T_i(t_2) \geq 0, V(t_2) = 0 \) and \( V'(t_2) < 0 \). In case (i), the second equation of (2) reads as \( T_i'(t_2) = k_1 h(T(t_2)) g(V(t_2)) \geq 0 \), a contradiction. In case (ii), the third equation of (2) reads as \( V'(t_2) = N \mu_2 p(T_i(t_2)) \geq 0 \), a contradiction. Therefore, \( T_i(t), V(t) \) are nonnegative for all \( t > 0 \).

Next we show the solution is ultimately bounded. Condition (3) in (H2) yields

\[ \int_0^V \frac{\partial f(T, V)}{\partial V} dV < \int_0^V k_1 h(T) g(V) dV \quad \text{for} \quad V > 0. \]

Thus, \( f(T, V) - f(T, 0) - k_1 h(T) g(V) < 0 \) for \( V > 0 \). Note that \( f(\overline{T}, 0) = 0 \) and \( g(0) = 0 \), we have

\[ f(T, V) - k_1 h(T) g(V) \leq 0 \quad \text{for all} \quad V \geq 0. \] (5)

This, together with the first equation of (2), implies that \( \limsup_{t \to \infty} T(t) \leq \overline{T} \). Set \( s = \max_{T,V \geq 0} f(T, V) > 0 \) and \( \sigma = \min\{s/\overline{T}, \mu_2 k_p/2, \mu_3 k_q\} \). It follows from (2) that

\[ (T(t) + T_i(t) + \frac{1}{2N} V(t))' \leq s - \frac{\mu_3}{2} k_p T_i(t) - \frac{\mu_3}{2N} k_q V(t) \]
\[ \leq 2s - \frac{s}{\overline{T}} T(t) - \frac{\mu_2}{2} k_p T_i(t) - \frac{\mu_3}{2N} k_q V(t) \]
\[ \leq 2s - \sigma(T(t) + T_i(t) + \frac{1}{2N} V(t)). \]

Thus

\[ \limsup_{t \to \infty} \left( T(t) + T_i(t) + \frac{1}{2N} V(t) \right) \leq \frac{2s}{\sigma}. \]

Therefore, the solution \((T(t), T_i(t), V(t))\) is ultimately bounded in \( \mathbb{R}_+^3 \). \( \square \)

The above analysis shows that the omega limit sets of System (2) are contained in the following positively invariant region:

\[ \Gamma = \left\{ (T, T_i, V) \in \mathbb{R}_+^3 : T \leq \overline{T}, T + T_i + \frac{1}{2N} V \leq \frac{2s}{\sigma} \right\}. \]
It is clear that System (2) admits a unique infection free equilibrium (IFE) \( E_0 = (T, 0, 0) \). An infection persistent equilibrium (IFE) \( E^* = (T^*, T^*_1, V^*) \) is a positive solution to the following equations

\[
\begin{align*}
    f(T^*, V^*) &= k_1 h(T^*) g(V^*), \\
    k_1 h(T^*) g(V^*) &= \mu_2 p(T^*_1), \\
    N \mu_2 p(T^*_1) &= \mu_3 q(V^*). \\
\end{align*}
\]

(6)

Making use of the next generation method developed in [31], we obtain the basic reproduction number \( R_0 \) for System (2):

\[
    R_0 = \frac{Nk_1 - k_2}{\mu_3} h(T) \lim_{V \to 0} \frac{g(V)}{q(V)}. 
\]

(7)

By L’Hôpital’s Rule, \( R_0 \) can be written as

\[
    R_0 = \frac{Nk_1 - k_2}{\mu_3} h(T) \frac{g'(0)}{q'(0)}. 
\]

3. Global dynamics of System (2). We first show that the IFE is locally asymptotically stable if \( R_0 < 1 \). The characteristic equation associated with the linearization of System (2) at the IFE \( E_0 \) is

\[
    \left( \lambda - \frac{\partial f(T, 0)}{\partial T} \right) (\lambda^2 + a_1 \lambda + a_0) = 0, 
\]

(8)

where \( a_1 = \mu_2 p'(0) + \mu_3 q'(0) + k_2 h(T) g'(0), a_0 = \mu_2 \mu_3 p'(0) q'(0) (1 - R_0) \). One eigenvalue is \( \lambda_1 = \frac{\partial f(T, 0)}{\partial T} < 0 \) (by (H1)). The other two eigenvalues, denoted by \( \lambda_2, \lambda_3 \), are the roots of \( \lambda^2 + a_1 \lambda + a_0 = 0 \). It follows from (H3) that \( p'(0) > 0, q'(0) > 0, g'(0) > 0 \) and \( h(T) > 0 \), thus \( a_1 > 0 \). Therefore, if \( R_0 < 1 \), then all eigenvalues of (8) have negative real parts; if \( R_0 > 1 \), then the characteristic equation (8) has one positive eigenvalue and two negative eigenvalues.

**Lemma 3.1.** Assume that (H1)-(H3) are satisfied. If \( R_0 < 1 \), then \( E_0 \) is locally asymptotically stable; If \( R_0 > 1 \), then \( E_0 \) is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.

In addition, by constructing a suitable Lyapunov function, we can show that \( E_0 \) is globally asymptotically stable in \( \Gamma \) if \( R_0 \leq 1 \).

**Theorem 3.2.** Assume that (H1)-(H3) are satisfied. If \( R_0 \leq 1 \), then the IFE \( E_0 \) of System (2) is globally asymptotically stable in \( \Gamma \); If \( R_0 > 1 \), then \( E_0 \) is unstable, all solutions starting on the invariant \( T \)-axis approach \( E_0 \) along the \( T \)-axis, and System (2) is uniformly persistent in \( \Gamma \setminus \{ T \text{-axis} \} \).

**Proof.** Define a Lyapunov function \( L \) as

\[
    L = T_i + \frac{V}{N}. 
\]

(9)

Then the derivative of \( L \) along the solutions of (2) is

\[
    L'(T, V) = \frac{Nk_1 - k_2}{N} h(T) g(V) - \frac{\mu_3}{N} q(V) \\
    = \frac{\mu_3 q(V)}{N} \left( \frac{(Nk_1 - k_2) h(T) g(V)}{\mu_3 q(V)} - 1 \right). 
\]

(10)
By (H3), we have \( h(T) \leq h(T) \) in \( \Gamma \) and \( g(V)/q(V) \leq \lim_{V \to 0} g(V)/q(V) \), and hence

\[
L'(2) \leq \frac{\mu_3 g(V)}{N} \left( \lim_{V \to 0} \frac{(Nk_1 - k_2)h(T)g(V)}{\mu_3 q(V)} - 1 \right) = \frac{\mu_3 g(V)}{N}(R_0 - 1).
\]

Therefore, \( L'(2) \leq 0 \) if \( R_0 \leq 1 \). Moreover, \( L'(2) = 0 \) if and only if \( V = 0 \) or if \( R_0 = 1 \) and \( T = \bar{T} \). The maximum invariant set in \( \{(T,T_i,V) \in \Gamma : L'(2) = 0\} \) is \( \{E_0\} \). Lyapunov-LaSalle Invariance Principle \([8, 13]\) implies that all solutions in \( \Gamma \) converge to \( E_0 \). Thus \( E_0 \) is globally asymptotically stable.

Now we assume that \( R_0 > 1 \). By (10), if \( (T(0),T_i(0),V(0)) \in \hat{\Gamma} \) is in a small neighborhood of \( E_0 \), then along the solution through \( (T(0),T_i(0),V(0)) \), \( L'(2) > 0 \). Hence the solution leaves this neighborhood. Solutions on the positively invariant \( \Gamma \)-axis satisfy \( T'(t) = f(T,0) \). Thus \( T(t) \to \bar{T} \) as \( t \to \infty \), that is all solutions converge to \( E_0 \) along the \( T \)-axis. The uniform persistence result in \([7]\) and a similar argument as in the proof of Proposition 3.2 in \([14]\) lead to the instability of \( E_0 \) and the uniform persistence of System (2).

Note that the uniform persistence, together with uniform boundedness of solutions in \( \hat{\Gamma} \), implies the existence of the IPE of System (2) \([1, Theorem 2.8.6]\). To obtain the uniqueness of IPE \( E^* = (T^*, T_i^*, V^*) \), we need another assumption

\[(H4)\] \( f(T,V) \) is strictly decreasing in \( T \in [0, \infty) \).

Lemma 3.3. Assume that (H1)-(H4) are satisfied. Then \( \Gamma \) is positively invariant and absorbing with respect to System (2); namely, all solutions with nonnegative initial conditions enter \( \Gamma \) in finite time, and all omega limit sets are contained in \( \Gamma \).

Proof. We only need to show that all solutions enter \( \Omega = \{(T,T_i,V) \in \mathbb{R}^3_+ : T \leq \bar{T}\} \) in finite time. Suppose to the contrary that there exist a \( t_1 > 0 \) and a solution \( T(t) \) with \( T(t) > \bar{T} \) for all \( t > t_1 \). It then follows from (5) that

\[
T'(t) = f(T,V) - k_1 h(T)g(V) < f(\bar{T},V) - k_1 h(\bar{T})g(V) \leq 0 \quad \text{for all} \ t > t_1,
\]

which shows that \( T(t) \to -\infty \) as \( t \to \infty \). This is a contradiction. Thus, there must exist a \( t_2 > t_1 \) such that \( T(t_2) \leq \bar{T} \). Similar arguments can be used to show that all solutions \( (T,T_i,V) \) satisfy \( T + T_i + V/(2N) \leq 2s/\sigma \) in finite time. Thus \( \Gamma \) is absorbing in \( \mathbb{R}^3_+ \) with respect to System (2).

Next, we establish the uniqueness of the IPE. Define

\[
F(T,V) = f(T,V) - k_1 h(T)g(V), \ G(T,V) = h(T)g(V) - \frac{\mu_3}{Nk_1 - k_2}q(V).
\]

Then \( F(0,V) = f(0,V) > 0 \) for all \( V \geq 0 \), and \( F(\bar{T},0) = f(\bar{T},0) - k_1 h(\bar{T})g(0) = 0 \). By (3), we have \( \partial F(T,V)/\partial V < 0 \) for all \( T, V > 0 \). Thus, \( F(T,V) < 0 \) for all \( V > 0 \), and hence \( F(0,V)F(\bar{T},V) < 0 \) for \( V > 0 \). It follows from (H3)-(H4) that \( F(T,V) \) is strictly decreasing in \( T \). Therefore, the equation \( F(T,V) = 0 \) can be uniquely solved for \( T \in (0, \bar{T}) \) as a function of \( V \). That is, there exists a function \( T = \phi(V) \) such that

\[
F(\phi(V), V) = f(\phi(V), V) - k_1 h(\phi(V))g(V) = 0.
\]
Note that $\partial F(T,V)/\partial V < 0$ and $\partial F(T,V)/\partial T < 0$ for all $T, V > 0$. Then
\[
\phi'(V) = -\frac{\partial F(T,V)/\partial V}{\partial F(T,V)/\partial T} < 0 \quad \text{for all } T, V > 0.
\]
Moreover, we obtain $\lim_{V \to \infty} \phi(V) = 0$ due to $\lim_{V \to \infty} g(V) = \infty$, $h$ is strictly increasing on $[0, \infty)$ and $h(0) = 0$.

Solving $G(T,V) = 0$ for $T$ gives
\[
T = h^{-1}\left(\frac{\mu_3}{Nk_1 - k_2} \frac{q(V)}{g(V)}\right) =: \varphi(V),
\]
which is strictly increasing since $h$ is strictly increasing and $q/g$ is nondecreasing.

By the monotonicity of $\phi$ and $\varphi$, and note that $\lim_{V \to \infty} \phi(V) = 0$, it follows that the curves $T = \phi(V)$ and $T = \varphi(V)$ have a unique intersection point $(T^*, V^*)$ with $T^*, V^* > 0$ if and only if $\phi(0) > \varphi(0)$. Note that
\[
R_0 > 1 \quad \text{if and only if} \quad h(T) > \frac{\mu_3}{Nk_1 - k_2} \lim_{V \to 0} \frac{q(V)}{g(V)}.
\]
It then follows from $\phi(0) = T$, $h(\varphi(0)) = \frac{\mu_3}{Nk_1 - k_2} \lim_{V \to 0} \frac{q(V)}{g(V)}$, and the monotonicity of $h$ that $\phi(0) > \varphi(0)$ if and only if $R_0 > 1$. Therefore, (6) has a unique positive solution $(T^*, V^*)$ if and only if $R_0 > 1$. Consequently, System (2) has a unique IPE $E^* = (T^*, T_i^*, V^*)$ with $T_i^* = p^{-1}(k_1 h(T^*) g(V^*)/\mu_2)$ if $R_0 > 1$.

Next, we investigate the stability of the IPE $E^*$. The characteristic equation associated with the linearization of System (2) at $E^*$ is
\[
\lambda^3 + b_2 \lambda^2 + b_1 \lambda + b_0 = 0,
\]
where
\[
b_2 = \alpha + \mu_2 p'(T_i^*) + \mu_3 q'(V^*) + k_2 h(T^*) g'(V^*),
\]
\[
\alpha = k_1 h'(T^*) g(V^*) - \frac{\partial f(T^*, V^*)}{\partial T},
\]
\[
b_1 = \alpha (\mu_2 p'(T_i^*) + \mu_3 q'(V^*)) - k_2 h(T^*) g'(V^*) \frac{\partial f(T^*, V^*)}{\partial T}
\]
\[
+ k_2 h'(T^*) g(V^*) \frac{\partial f(T^*, V^*)}{\partial V},
\]
\[
b_0 = (Nk_1 - k_2) h'(T^*) g(V^*) \mu_2 p'(T_i^*) \left( k_1 h(T^*) g'(V^*) - \frac{\partial f(T^*, V^*)}{\partial V} \right)
\]
\[
+ \alpha \mu_2 \mu_3 p'(T_i^*) q'(V^*) \left( 1 - \frac{(Nk_1 - k_2) h(T^*) g'(V^*)}{\mu_3 q'(V^*)} \right).
\]
By (H3)-(H4), $\alpha > 0, b_2 > 0$. If $\partial f(T^*, V^*)/\partial V \geq 0$, then $b_1 > 0$. Note that $g'(V)/q(V)$ is nonincreasing on $(0, \infty)$, thus $(g/q)'(V^*) \leq 0$, which implies $g'(V^*)/q(V^*) \leq g(V^*)/(q(V^*)$. Hence,
\[
\frac{(Nk_1 - k_2) h(T^*) g'(V^*)}{\mu_3 q'(V^*)} \leq \frac{(Nk_1 - k_2) h(T^*) g(V^*)}{\mu_3 g(V^*)} = 1.
\]
By (3), $k_1 h(T^*) g'(V^*) - \partial f(T^*, V^*)/\partial V > 0$ and hence $b_0 > 0$. If $\partial f(T^*, V^*)/\partial V \geq 0$, then it follows from (H3)-(H4) that
\[
b_2 b_1 - b_0 > \mu_2 p'(T_i^*) Nk_1 h(T^*) g'(V^*) (\alpha - k_1 h'(T^*) g(V^*))
\]
\[
= - \frac{\partial f(T^*, V^*)}{\partial T} \mu_2 p'(T_i^*) Nk_1 h(T^*) g'(V^*) > 0.
\]
The Routh-Hurwitz stability criterion implies that all roots of the characteristic equation (12) have negative real parts, and we have the following result.

**Theorem 3.4.** Assume that (H1)-(H4) are satisfied. If $R_0 > 1$, then System (2) has a unique IPE $E^* = (T^*, T_1^*, V^*)$, which is locally asymptotically stable provided that $\partial f(T^*, V^*)/\partial V \geq 0$.

The Jacobian matrix $J$ associated with a general solution $(T(t), T_1(t), V(t))$ to (2) is

$$J = \begin{pmatrix} J_{11} & 0 & \frac{\partial f(T, V)}{\partial V} - k_1 h(T)g'(V) \\ k_1 h'(T)g(V) & -\mu_2 p'(T_1) & k_1 h(T)g'(V) \\ -k_2 h'(T)g(V) & N\mu_2 p'(T_1) & -\mu_3 q'(V) - k_2 h(T)g'(V) \end{pmatrix},$$

where $J_{11} = \partial f(T, V)/\partial T - k_1 h'(T)g(V)$.

The assumptions (H2) and (H3) imply that System (2) is competitive with respect to the cone \( \{(x, y, z) \in \mathbb{R}^3 : x, z \geq 0, y \leq 0\} \) [30]. It then follows from the uniform persistence of System (2) (Theorem 3.2) that the omega limit set of a solution with initial condition satisfying (4) cannot contain a point on the $T$-axis if $R_0 > 1$. By Theorem 3.4, there is only one equilibrium $E^*$ which is not on the $T$-axis. The generalized Poincaré-Bendixson theorem for three dimensional competitive systems implies that the omega limit set of every solution with initial condition (4) either contains the unique IPE $E^*$ or is a nontrivial periodic orbit.

Next we adopt the geometric approach developed by Li and Muldowney [15, 16] to establish the global stability of the IPE $E^*$. To this end, we first briefly introduce this approach. Consider a system of ordinary differential equations

$$x' = \mathcal{F}(x), \quad x \in U, \quad \mathcal{F} \in C^1,$$

where $U$ is an open set in $\mathbb{R}^n$. Denote by $x(t, x_0)$ the solution of (13) satisfying $x(0, x_0) = x_0$. A subset $K$ is said to be absorbing in $U$ if $x(t, K) \subset K$ for each compact set $K \subset U$ when $t$ is sufficiently large. The second compound equation is

$$z'(t) = \frac{\partial \mathcal{F}^{[2]}}{\partial x}(x(t, x_0))z(t),$$

where $\frac{\partial \mathcal{F}^{[2]}}{\partial x}$ is the second additive compound matrix of the Jacobian matrix $\frac{\partial \mathcal{F}}{\partial x}$ [20]. Let $|\cdot|$ denote a vector norm in $\mathbb{R}^n$ and the induced matrix norm in $\mathbb{R}^{n \times n}$. For $A \in \mathbb{R}^{n \times n}$, $\xi(A) = \lim_{h \to 0^+} (|I + hA| - 1)/h$ defines the Lozinskii measure [3]. Let $Q(x) \in C^1$ be an $m \times m$ matrix-valued function and suppose $Q^{-1}(x)$ exists for $x \in U$, where $m = (n - 1)/2$. Define a quantity $\bar{q}_2$ as

$$\bar{q}_2 = \limsup_{t \to \infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \xi(M(x(s, x_0))) ds,$$

where $K$ denotes a compact absorbing set in $U$, $M = Q \hat{Q}^{-1} + Q \frac{\partial \mathcal{F}^{[2]}}{\partial x} Q^{-1}$ with $Q \hat{Q}$ obtained by replacing each entry $q_{ij}$ of $Q$ with its derivative in the direction of $\mathcal{F}$. The following result from [15, 16] will be employed to establish the global stability of $E^*$ when $R_0 > 1$.

**Lemma 3.5.** Let $U \subset \mathbb{R}^n$ be a simply connected region. Assume that System (13) has a compact absorbing set $K \subset U$ admitting a unique equilibrium $\bar{x} \in U$. Then the unique equilibrium $\bar{x}$ is globally asymptotically stable in $U$ if there exist a function $Q(x)$ and a Lozinskii measure $\xi$ such that $\bar{q}_2 < 0$.
Clearly, $\Gamma$ is a simply connected region in $\mathbb{R}^3$. By Theorem 3.4, System (2) has a unique IPE $E^*$ in $\Gamma$ if $R_0 > 1$. The uniform persistence of System (2), together with the boundedness of solutions given in Proposition 1, implies the existence of a compact absorbing set $K \subset \Gamma$ [2, 32]. Therefore, by Lemma 3.5, we only need to show that there exist a matrix-valued function $Q(x)$ and a Lozinski measure $\xi$ such that $\bar{q}_2 < 0$.

The second additive compound matrix $J^{[2]}$ is

$$
J^{[2]} = \begin{pmatrix}
J_{11} & k_1 h'(T)V g'(V) - \frac{\partial f(T, V)}{\partial V} + k_1 h(T)g'(V) & 0 \\
k_{12}h'(T)V g(V) & k_1 h'(T)V g(V) \\
J_{33} & \end{pmatrix},
$$

where

$$
J_{11} = \frac{\partial f(T, V)}{\partial T} - k_1 h'(T)V g(V) - \mu_2 p'(T),
$$

$$
J_{22} = \frac{\partial f(T, V)}{\partial T} - k_1 h'(T)V g(V) - \mu_3 q'(V) - k_2 h(T)g'(V),
$$

$$
J_{33} = -\mu_2 p'(T) - \mu_3 q'(V) - k_2 h(T)g'(V).
$$

Take $Q = \text{diag}\{1, T_i/V, T_i/V\}$. Then

$$
M = QfQ^{-1} + QJ^{[2]}Q^{-1} = \begin{pmatrix}
M_{11} & M_{12} \\
M_{21} & M_{22}
\end{pmatrix},
$$

where

$$
M_{11} = J_{11}, \quad M_{12} = \frac{V}{T_i} (k_1 h(T)V g'(V), -\frac{\partial f(T, V)}{\partial V} + k_1 h(T)g'(V)),
$$

$$
M_{21} = \frac{T_i}{V} \begin{pmatrix}
N \mu p'(T_i) \\
k_2 h'(T)V g(V)
\end{pmatrix}, \quad M_{22} = \begin{pmatrix}
J_{22} + \frac{T_i}{V} \frac{\partial V}{\partial T} & \frac{\partial V}{\partial T} & 0 \\
k_1 h'(T)V g(V) & \frac{T_i}{V} & J_{33} + \frac{T_i}{V} \frac{\partial V}{\partial T}
\end{pmatrix}.
$$

For $(u, v, w) \in \mathbb{R}^3$, define $|(u, v, w)| = \max\{|u|, |v| + |w|\}$ and let $\xi$ be the corresponding Lozinski measure. Then according to [19], we have

$$
\xi(M) \leq \max\{g_1, g_2\},
$$

(15)

with $g_1 = \xi_1(M_{11}) + |M_{21}|$ and $g_2 = |M_{21}| + \xi_1(M_{22})$, where $|M_{21}|$ and $|M_{22}|$ are the matrix norms with respect to the $l_1$ vector norm, and $\xi_1$ is the Lozinski measure with respect to the $l_1$ matrix norm. Thus,

$$
\xi_1(M_{11}) = J_{11}, \quad |M_{21}| = \max\left\{N \mu p'(T_i) \frac{T_i}{V}, k_2 h'(T)V g(V) \frac{T_i}{V}\right\}.
$$

Assume that $\partial f(T, V)/\partial V \geq 0$ for all $T, V \geq 0$. It then follows from (3) that

$$
0 \leq -\frac{\partial f(T, V)}{\partial V} + k_1 h(T)g'(V) \leq k_1 h(T)g'(V),
$$
and hence $|M_{12}| = k_1 h(T) g'(V) V / T_i$. Following the same fashion as in [3], we calculate $\xi_1(M_{22})$ as

$$\xi_1(M_{22}) = \max \left\{ \frac{T'_i}{T_i} - \frac{V'}{V} + J_{22} + k_1 h'(T) g(V), \quad \frac{T'_i}{T_i} - \frac{V'}{V} + J_{33} \right\}$$

$$= \frac{T'_i}{T_i} - \frac{V'}{V} - \mu_3 g'(V) - k_2 h(T) g'(V) + \max \left\{ \frac{\partial f(T, V)}{\partial T}, -\mu_2 p'(T_i) \right\}$$

$$= \frac{T'_i}{T_i} - \frac{V'}{V} - \mu_3 g'(V) - k_2 h(T) g'(V) - \min \{ \delta, \mu_2 p'(T_i) \},$$

where

$$\delta = -\max_{T \in [0, T]} \frac{\partial f(T, V)}{\partial T} > 0. \quad (16)$$

If $g(x) = x$, $p(x) = x$, then by (H3), we have $g'(V) \geq q(V) / V$ for $V \in (0, \infty)$. Thus it follows from System (2) that

$$\frac{T'_i}{T_i} = k_1 h(T) \frac{V}{T_i} - \mu_2, \quad \frac{V'}{V} \geq N \frac{T_i}{T_i} - \mu_3 g'(V) - k_2 h(T).$$

This shows

$$g_1 \leq \frac{T'_i}{T_i} - \delta, \quad g_2 \leq \frac{T'_i}{T_i} + k_2 h'(T) T_i - \min \{ \delta, \mu_2 \}. \quad (17)$$

Therefore

$$\xi(M) \leq \max \{ g_1, g_2 \} \leq \frac{T'_i}{T_i} + k_2 h'(T) T_i - \eta, \quad (18)$$

where

$$\eta = \min \{ \delta, \mu_2 \} > 0. \quad (18)$$

Let $(T(t), T_i(t), V(t))$ be any solution starting in the compact absorbing set $K \subset \hat{\Gamma}$ and let $\tilde{t}$ be sufficiently large such that $(T(t), T_i(t), V(t)) \in K$ for all $t \geq \tilde{t}$. Then along each solution $(T(t), T_i(t), V(t))$ with $(T(0), T_i(0), V(0)) \in K$, for $t > \tilde{t}$, we have

$$\frac{1}{t} \int_0^t \xi(M) ds \leq \frac{1}{t} \int_0^t \xi(M) ds + \frac{1}{t} \ln \frac{T_i(t)}{T_i(\tilde{t})} + \frac{1}{t} \int_{\tilde{t}}^t k_2 h'(T) T_i dt - \frac{t - \tilde{t}}{t} \eta. \quad (19)$$

Denote

$$m_1 = \max_{T \in [0, T]} h'(T) > 0, \quad m_2 = \max_{V \in [0, \infty]} f(0, V) \quad (20)$$

By (H4) and $\partial f(T, V) / \partial V \geq 0$, we further have

$$\frac{1}{t} \int_{\tilde{t}}^t k_2 h'(T) T_i dt = \frac{k_2 m_1}{\mu_2} \int_{\tilde{t}}^t f(T, V) dt \leq \frac{k_2 m_1 m_2 t - \tilde{t}}{\mu_2}.$$

Thus

$$\frac{1}{t} \int_0^t \xi(M) ds \leq \frac{1}{t} \int_0^t \xi(M) ds + \frac{1}{t} \ln \frac{T_i(t)}{T_i(\tilde{t})} + \frac{t - \tilde{t}}{t} \left( \frac{k_2 m_1 m_2}{\mu_2} - \eta \right).$$

Consequently, if

$$k_2 m_1 m_2 < \mu_2 \eta, \quad (21)$$

then by the boundedness of $T_i$ and the uniform persistence of System (2), we obtain $\bar{q}_2 < 0$. The above analysis and Lemma 3.3 immediately give the following result.
Theorem 3.6. Assume that (H1)-(H4) are satisfied. For System (2) with initial conditions satisfying (4), if $R_0 > 1$, then the omega limit set either contains the unique IPE $E^*$ or is a nontrivial periodic orbit. In addition, if $g(x) = x, p(x) = x$, then System (2) reduces to the model considered in [5]; if $f(T, V) = s - \mu_1 T + rTV/(C + V)$, and $h(x) = g(x) = p(x) = q(x) = x$, then System (2) reduces to the model considered in [29].

Remark 1. System (2) includes the models considered in [5] and [29] as special cases: if $f(T, V)$ and $h(x) = g(x) = p(x) = q(x) = x$, then System (2) reduces to the model considered in [5]; if $f(T, V) = s - \mu_1 T + rTV/(C + V)$, and $h(x) = g(x) = p(x) = q(x) = x$, then System (2) reduces to the model considered in [29].

If $k_2 = 0$ in System (2), then the global stability of the IPE $E^*$ can be proved by constructing a Lyapunov function.

Theorem 3.7. Consider System (2) with $k_2 = 0$ and (H1)-(H4). If $R_0 > 1$, then there exists a unique IPE $E^* = (T^*, T^*_{\circ}, V^*)$, which is globally asymptotically stable in int$(\mathbb{R}^+_0)$ provided that $\partial f(T^*, V^*)/\partial V \geq 0$ and

$$(f(T, V) - f(T^*, V^*))(T - T^*) \leq 0 \quad \text{for all } T, V \geq 0.$$  \hspace{1cm} (22)

Proof. The existence and uniqueness of $E^*$ and its local stability follow from Theorem 3.4. By Lemma 3.3, it suffices to show that $E^*$ is globally attractive in $\Gamma$. Define a Lyapunov function $L$ in $\Gamma$ as

$L(T, T_1, V) = N \int_{T_1}^{T} h(s) - h(T^*) \, ds + N \int_{T_1}^{T} p(s) - p(T^*) \, ds + \int_{V^*}^{V} g(s) - g(V^*) \, ds.$

Calculating the time derivative of $L$ along the positive solutions of System (2), we obtain

$L'(T) = N(1 - h(T^*)/h(T))(f(T, V) - k_1 h(T) g(V))$

$\quad + N(1 - p(T^*)/p(T^*)) (k_1 h(T) g(V) - \mu_2 p(T_1))$

$\quad + (1 - g(V^*)/g(V)) (N \mu_2 p(T_1) - \mu_3 q(V))$

$= N f(T, V)(1 - h(T^*)/h(T)) + N k_1 h(T^*) g(V) - N k_1 h(T) g(V) \frac{p(T^*)}{p(T^*_1)}$

$\quad + N \mu_2 p(T^*_1) - \mu_3 q(V) - N \mu_2 p(T_1) \frac{g(V^*)}{g(V)} + \mu_3 q(V) \frac{g(V^*)}{g(V)}.$

Note that $N f(T^*, V^*) = N k_1 h(T^*) g(V^*) = N \mu_2 p(T^*_1) = \mu_3 q(V^*)$. Thus,

$L'(T) = N f(T, V)(1 - h(T^*)/h(T)) + \mu_3 q(V^*) \frac{g(V)}{g(V^*)}$

$\quad - \mu_3 q(V^*) \frac{p(T^*) h(T) g(V)}{p(T^*_1) h(T^*) g(V^*)} + \mu_3 q(V^*) - \mu_3 q(V^*) \frac{g(V)}{q(V^*)}$.
the monotonicity of $T$.

Note also that $g(T)$ is strictly increasing on $[0, \infty)$, and $g(\cdot)/q(\cdot)$ is nonincreasing on $(0, \infty)$, we have

$$
\left(\frac{g(V^*)}{g(V)} - 1\right) \left(\frac{q(V)}{q(V^*)} - \frac{g(V)}{g(V^*)}\right) \leq 0.
$$

Note also that

$$
\frac{p(T^*_i) h(T) g(V)}{p(T_i) h(T^*) g(V^*)} + \frac{g(V^*) p(T_i)}{g(V) p(T^*_i)} + \frac{h(T^*)}{h(T)} - 3 \geq 0,
$$

and the equality holds if and only if $h(T) = h(T^*)$ and $g(V^*)/g(V) = p(T^*_i)/p(T_i)$. The monotoncity of $h$ and (22) imply that

$$
(f(T, V) - f(T^*, V^*))(1 - \frac{h(T^*)}{h(T)}) \leq 0.
$$

Therefore, $\mathcal{L} \leq 0$ for all $(T, T_i, V) \in \tilde{\Gamma}$, and $\mathcal{L} = 0$ only if

$$
T = T^*, \quad \frac{g(V^*)}{g(V)} = \frac{p(T^*_i)}{p(T_i)}.
$$

Let $\mathcal{B}$ be the largest invariant subset of $\{\mathcal{L} = 0\}$. Along a solution in $\mathcal{B}$, we have $T = T^*$ and $T'(t) = 0$, that is $f(T^*, V) = k_i h(T^*) g(V)$. By (3), (23) and the monotonicity of $p$, we obtain $V = V^*, T_i = T^*_i$. Hence, $\mathcal{B} = \{E^*\}$. The global attractivity of $E^*$ follows from the Lyapunov-LaSalle Invariance Principle [8, 13].

4. Backward bifurcation induced by virus-driven proliferation of target cells. In this section, we restrict our attention to System (2) with $h(x) = g(x) = p(x) = q(x) = x$. Then System (2) reduces to

$$
T'(t) = f(T, V) - k_1 TV,
$$

$$
T_i'(t) = k_1 TV - \mu_2 T_i,
$$

$$
V'(t) = N \mu_2 T_i - \mu_3 V - k_2 TV.
$$

(24)

The basic reproduction number $R_0$ defined in (7) reads as

$$
R_0 = \frac{(N k_1 - k_2) \bar{T}}{\mu_3}.
$$

If $R_0 > 1$, assumptions (H1)-(H2) ensure the existence and uniqueness of the IPE $E^*$. Applying Theorems 3.2 and 3.6 to System (24), we have the following result.

**Corollary 1.** Assume that $f(T, V)$ satisfies (H1)-(H2). If $R_0 \leq 1$, then the IFE $E_0$ of System (24) is globally asymptotically stable in $\mathbb{R}_+^3$. If $R_0 > 1$, then $E_0$ is unstable, System (24) is uniformly persistent in $\mathbb{R}_+^3 \backslash \{T\text{-axis}\}$, and there exists a unique IPE $E^*$. In addition, if $f(T, V)$ satisfies (H4), $\partial f(T, V)/\partial V \geq 0$ for all
$T,V \geq 0$ and $k_2m_2 < \mu_2\eta$, where $\eta$ and $m_2$ are defined in (18) and (20), respectively, then $E^*$ is globally asymptotically stable in $\text{int}(\mathbb{R}^3_+)$.

The above result shows that if (3) holds, then the model exhibits the same threshold dynamics as the standard in-host model does. This implies that the virus-driven proliferation of target cells does not affect the viral dynamics structurally. In the sequel we assume that (3) is not satisfied. As we shall show that System (24) undergoes a backward bifurcation, and thus the virus-driven proliferation of target cells has an impact on the viral dynamics.

We first make the following assumptions on $f(T,V)$.

**B1:** $f \in \mathbf{C}^1$ is bounded from above and satisfies (H1) and (H4), $f(0,V) > 0$, $\partial f_T(T,V)/\partial V \geq 0$ for all $T,V \geq 0$. Moreover, there exists $\mathcal{M} > 0$ such that $f(\mathcal{M},V) < k_1\mathcal{M}V$ for all $V \geq 0$.

**B2:** $f(T,V)$ is strictly concave down in $V$ and $\partial f(T^*,0)/\partial V > k_1T^*$, where $T^* = \mu_3/(Nk_1 - k_2) > 0$.

We remark that (25) implies $\mathcal{M} \geq \mathcal{T}$ since $f(\mathcal{T},0) = 0$ and $f(T,V) - k_1TV$ is decreasing in $T$. Similar to the proofs of Proposition 1 and Lemma 3.3, we can show that the omega limit sets of System (24) are contained in the following positively invariant region

$$\Gamma = \{ (T,T_i,V) \in \mathbb{R}^3_+ : T \leq \mathcal{M}, T + T_i + \frac{1}{2N}V \leq \frac{2s}{\bar{s}} \},$$

where $s = \max_{T,V \geq 0} f(T,V) > 0$ and $\bar{s} = \min\{s/\mathcal{M}, \mu_2/2, \mu_3\}$.

If System (24) has an IPE $E^* = (T^*, T_i^*, V^*)$, then we must have $T^* = \mu_3/(Nk_1 - k_2), V^*$ is a positive root of

$$f(T^*,V) = k_1T^*V. \tag{26}$$

and $T_i^* = k_1T^*V^*/\mu_2$. The existence of the IPE can be analyzed geometrically through examining the intersections of $h_1(V) = f(T^*,V)$ and $h_2(V) = k_1T^*V$.

If $R_0 < 1$, that is $\mathcal{T} < T^*$, then (H1) implies that $f(T^*,0) < 0$. Since $f(T,V)$ is bounded from above and $\partial f(T,V)/\partial V \geq 0$, we have $\lim_{V \to \infty} \partial f(T,V)/\partial V = 0$. This, together with (B2), shows that there exists a unique $\tilde{V} > 0$ such that $\partial f(T^*,\tilde{V})/\partial V = k_1T^*$. Define

$$R_1 = \frac{R_0f(T^*,\tilde{V})}{k_1\tilde{V}}. \tag{27}$$

Then we have three cases to consider for $R_0 < 1$. Case (a): $R_1 < 1$, that is $f(T^*,\tilde{V}) < k_1T^*\tilde{V}$. Then (26) has no positive root (Figure 1(i)). Case (b): $R_1 = 1$, that is $f(T^*,\tilde{V}) = k_1T^*\tilde{V}$. Then (26) has a unique positive root $\tilde{V}$ (Figure 1(ii)). Case (c): $R_1 > 1$, that is $f(T^*,\tilde{V}) > k_1T^*\tilde{V}$. Then (26) has two positive roots $V_1^*$ and $V_2^*$ with $V_2^* > V_1^*$ (Figure 1(iii)). We further have

$$\frac{\partial f(T^*,V_1^*)}{\partial V} > k_1T^*, \quad \frac{\partial f(T^*,V_2^*)}{\partial V} < k_1T^*. \tag{28}$$

If $R_0 = 1$, that is $\mathcal{T} = T^*$, then $f(T^*,0) = 0$. It then follows from (B2) that (26) has a unique positive root (Figure 1(iv)).

If $R_0 > 1$, that is $\mathcal{T} > T^*$, then $f(T^*,0) > 0$, and hence (26) has a unique positive root since $f(T,V)$ is concave down in $V$ (Figure 1(v)).
Figure 1. The determination of the number of intersections of \( h_1 \) and \( h_2 \) in the first quadrant.

**Proposition 2.** Consider System (24) with (B1)-(B2).

(i) If \( R_0 < 1 \) and \( R_1 < 1 \), then the IFE \( E_0 \) is the only equilibrium.
(ii) If \( R_0 < 1 \) and \( R_1 > 1 \), then there are three equilibria: the IFE \( E_0 \) and two IPEs, which we denote by \( E^*_1 = (T^*, T^*_1, V^*_1) \) and \( E^*_2 = (T^*, T^*_2, V^*_2) \) satisfying \( V^*_2 > V^*_1 \).
(iii) If either \( R_0 < 1 \) and \( R_1 = 1 \) or \( R_0 \geq 1 \), then there are two equilibria: the IFE \( E_0 \) and a unique IPE \( E^* \).

Next we study the stability of the equilibria of System (24). The characteristic equation of System (24) at \( E_0 \) is given as follows

\[
\left( \lambda - \frac{\partial f(T, 0)}{\partial T} \right) \left( \lambda^2 + \left( \mu_2 + \mu_3 + k_2 T \right) \lambda + \mu_2 (\mu_3 + k_2 T) (1 - R_0) \right) = 0.
\]
As a consequence of a straightforward analysis on the distribution of the eigenvalues, we have the following result.

**Lemma 4.1.** Assume that (B1) is satisfied. If \( R_0 < 1 \), then \( E_0 \) is asymptotically stable. If \( R_0 > 1 \), then \( E_0 \) is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.

If \( R_0 < 1 \) and \( R_1 < 1 \), then it follows from (B2) and the definition of \( \tilde{V} \) that
\[
\frac{\partial f(T^*, V)}{\partial V} > k_1 T^* \quad \text{for} \quad 0 \leq V < \tilde{V}, \quad \text{and} \quad \frac{\partial f(T^*, V)}{\partial V} < k_1 T^* \quad \text{for} \quad V > \tilde{V}.
\]

Thus, we have \( \max_{V \geq 0} \{ f(T^*, V) - k_1 T^* V \} = f(T^*, \tilde{V}) - k_1 T^* \tilde{V} < 0 \). This, together with the first equation of (24) and (B1), implies that
\[
\limsup_{t \to \infty} T(t) < T^*.
\]

Let \( L = T_i + V/N \), then
\[
L'_{(24)} = \frac{\mu_3 V}{N} - \frac{(Nk_1 - k_2) T - 1}{\mu_3} - \frac{(Nk_1 - k_2) T^* - 1}{\mu_3} = 0.
\]

The maximum invariant set in \( \{(T, T_i, V) \in \Gamma : L'_{(24)} = 0\} \) is \( \{E_0\} \). Similar as the proof of Theorem 3.2, we arrive at the following result.

**Lemma 4.2.** Assume that (B1)–(B2) are satisfied. If \( R_0 < 1 \) and \( R_1 < 1 \), then the IFE \( E_0 \) of System (24) is globally asymptotically stable in \( \mathbb{R}_+^3 \).

The characteristic equation associated with the linearization of System (24) at an IPE \( E^* = (T^*, T^*_i, V^*) \) is
\[
\lambda^3 + c_2 \lambda^2 + c_1 \lambda + c_0 = 0,
\]
where
\[
c_2 = -\frac{\partial f(T^*, V^*)}{\partial T} + k_1 V^* + \mu_2 + \mu_3 + k_2 T^* > 0,
\]
\[
c_1 = (\mu_2 + \mu_3)\left(-\frac{\partial f(T^*, V^*)}{\partial T} + k_1 V^* - k_2 T^* \frac{\partial f(T^*, V^*)}{\partial T} + k_2 V^* \frac{\partial f(T^*, V^*)}{\partial V}\right) > 0,
\]
\[
c_0 = \mu_2 V^* (Nk_1 - k_2) (k_1 T^* - \frac{\partial f(T^*, V^*)}{\partial V}).
\]

Obviously,
\[
c_2 c_1 - c_0 > (\mu_2 + \mu_3)^2 (\frac{\partial f(T^*, V^*)}{\partial T} + k_1 V^*) - \mu_2 \mu_3 k_1 V^* > \mu_2 \mu_3 k_1 V^* > 0.
\]

If \( R_0 < 1 \) and \( R_1 = 1 \), then there is a unique IPE \( E^* = (T^*, T^*_i, V^*) \) and \( \partial f(T^*, V^*)/\partial V = k_1 T^* \). Thus, \( c_0 = 0 \), which implies that one eigenvalue is 0, the other two eigenvalues have negative real parts. Therefore, \( E^* \) is locally stable, at which a saddle-node bifurcation occurs.

If \( R_0 < 1 \) and \( R_1 > 1 \), then there are two IPEs \( E^*_1 = (T^*, T^*_i, V^*_1) \) and \( E^*_2 = (T^*, T^*_2, V^*_2) \) with \( V^*_2 > V^*_1 \). By (28), we know \( c_0(V^*_1) < 0 \) and \( c_0(V^*_2) > 0 \). It then follows from the Routh-Hurwitz stability criterion that \( E^*_2 \) is locally asymptotically stable and \( E^*_1 \) is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.

If \( R_0 \geq 1 \), then there is a unique IPE \( E^* = (T^*, T^*_i, V^*) \) with \( \partial f(T^*, V^*)/\partial V < k_1 T^* \). Thus, \( c_0 > 0 \), and hence \( E^* \) is locally asymptotically stable. Moreover, the
global stability of $E^*$ can be obtained from the same geometric approach as in the proof of Theorem 3.6.

Summarizing the discussion above, we have the following result.

**Theorem 4.3.** Consider System (24) with (B1)-(B2).

(i) If $R_0 < 1$ and $R_1 < 1$, then the IFE $E_0$ is globally asymptotically stable in $\mathbb{R}^2_+$. 
(ii) If $R_0 < 1$ and $R_1 = 1$, then the IFE $E_0$ is locally asymptotically stable, and the unique IPE $E^*$ is locally stable, at which a saddle-node bifurcation occurs.
(iii) If $R_0 < 1$ and $R_1 > 1$, then both the IFE $E_0$ and the IPE $E^*_2$ are locally asymptotically stable, and the IPE $E^*_1$ is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.
(iv) If $R_0 = 1$, then the IFE $E_0$ is locally stable, at which a transcritical bifurcation occurs, and the unique IPE $E^*$ is locally asymptotically stable.
(v) If $R_0 > 1$, the IFE $E_0$ is unstable, and the unique IPE $E^*$ is locally asymptotically stable. In addition, all solutions in int($\mathbb{R}^3_+$) with initial conditions satisfying (4) converge to $E^*$ provided that $k_2m_2 < \mu_2\eta$, where $\eta$ and $m_2$ are defined in (18) and (20), respectively.

5. **An example: Data fitting, numerical simulations and drug therapies.**

Let $f(T,V) = s - \mu_1 T + rTV/(c + V)$, and $h(x) = g(x) = p(x) = q(x) = x$. Then System (2) reduces to the following system:

$$
\begin{align*}
T'(t) &= s - \mu_1 T(t) + \frac{rT(t)V(t)}{c + V(t)} - k_1 T(t)V(t), \\
T_i'(t) &= k_1 T(t)V(t) - \mu_2 T_i(t), \\
V'(t) &= N \mu_2 T_i(t) - \mu_3 V(t) - k_2 T(t)V(t).
\end{align*}
$$

(31)

Here the term $rT(t)V(t)/(c + V(t))$ represents the virus-driven proliferation of $T$ cells, $r$ is the maximal proliferation rate satisfying $0 \leq r < \mu_1$, and $c$ is the half saturation constant of the virus-driven proliferation process [11].

Clearly, System (31) admits a unique IFE $E_0 = (s/\mu_1, 0, 0)$. If $V^*$ is a positive root of

$$
V^2 + (c + \frac{\mu_1 - r}{k_1})V + \frac{\mu_1 c}{k_1} = 0,
$$

then $E^* = (T^*, T_i^*, V^*)$ is an IPE with $T^* = \mu_3/(Nk_1 - k_2)$, and $T_i^* = k_1 T^* V^*/\mu_2$. The basic reproduction number defined in (7) is given by

$$
R_0 = \frac{(Nk_1 - k_2)s}{\mu_1 \mu_3}.
$$

Obviously, assumptions (H1) and (H3)-(H4) are satisfied with $T^* = s/\mu_1$. If $r \leq k_1 c$, then (H2) holds. By Theorems 3.2 and 3.6, we have

**Theorem 5.1.** Assume that (D1): $r \leq k_1 c$ is satisfied.

(i) If $R_0 \leq 1$, then System (31) admits a unique equilibrium, the IFE $E_0$, which is globally asymptotically stable in $\mathbb{R}^3_+$.
(ii) If $R_0 > 1$, then $E_0$ becomes unstable, and there is a unique IPE $E^*$, which is locally asymptotically stable. Moreover, if $k_2 s \leq \mu_2 \min\{\mu_1 - r, \mu_2\}$ holds, then all solutions in int($\mathbb{R}^3_+$) with initial conditions satisfying (4) converge to $E^*$. 

Next, we assume that \( r > k_1 c \), then assumptions (B1)-(B2) hold with \( \mathcal{M} = s/(\mu_1 - r) \). If \( R_0 < 1 \), then we can easily calculate \( \dot{V} = \sqrt{r c/k_1 - c} \), and obtain

\[
R_1 = \frac{\mu_1 R_0 - \mu_1 + r - \sqrt{r c/k_1}}{\sqrt{r c/k_1} - c}.
\]

Note that it is easy to show that \( R_1 < 1 \) if and only if \( R_0 < 1 - a \), where

\[
a = \left( \frac{\sqrt{r} - \sqrt{k_1 c}}{\mu_1} \right) < 1.
\]

Applying Theorem 4.3 to System (31), we have the following result.

**Theorem 5.2.** Assume that (D2): \( r > k_1 c \) holds, and let \( a \in (0, 1) \) be the constant defined in (32).

(i) If \( R_0 < 1 - a \), then the IFE \( E_0 \) is globally asymptotically stable in \( \mathbb{R}^4_+ \).

(ii) If \( R_0 = 1 - a \), then \( E_0 \) is locally asymptotically stable, and the unique IPE \( E^* \) is locally stable, at which a saddle-node bifurcation occurs.

(iii) If \( 1 - a < R_0 < 1 \), then besides \( E_0 \), System (31) admits two IPE \( E^*_1 = (T^*_1, T^*_1, V^*_1) \) and \( E^*_2 = (T^*_2, T^*_2, V^*_2) \) with \( V^*_1 < V^*_2 \). Both \( E_0 \) and \( E^*_2 \) are locally asymptotically stable, and \( E^*_1 \) is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.

(iv) If \( R_0 = 1 \), then the IFE \( E_0 \) is locally stable, at which a transcritical bifurcation occurs, and there exists an IPE \( E^* \), which is locally asymptotically stable.

(v) If \( R_0 > 1 \), then the IFE \( E_0 \) is unstable, and there exists a unique IPE \( E^* \), which is locally asymptotically stable. Moreover, if \( k_2 a \leq \mu_2 \min\{\mu_1 - r, \mu_2\} \) holds, then all solutions in int(\( \mathbb{R}^4_+ \)) with initial conditions satisfying (4) converge to \( E^* \).

The above theorem implies that a backward bifurcation occurs at \( R_0 = 1 \) and bistability occurs when \( R_0 \in (1-a, 1) \). A bifurcation diagram is plotted in Figure 2.

We next use numerical simulations to illustrate our analytical results. We first fit System (31) to the data of patient 102 reported in [26] (See Figure 3). The fitted parameter values are: \( s = 100 \text{ mm}^{-3} \cdot \text{day}^{-1}, \mu_1 = 3.96 \times 10^{-2} \text{day}^{-1}, r = 2.3 \times 10^{-3} \text{day}^{-1}, c = 166.57 \text{ ml}^{-1}, k_1 = 3.0 \times 10^{-5} \text{ml} \cdot \text{day}^{-1}, k_2 = 0.3873 \text{ day}^{-1}, N = 1500 \text{ mm}^3 \cdot \text{ml}^{-1}, \mu_3 = 4 \text{ day}^{-1}, k_2 = 9.9933 \times 10^{-4} \text{mm}^3 \cdot \text{day}^{-1} \) and the initial condition is \( T(0) = 4099.1 \text{ mm}^{-3}, T_i(0) = 593.7 \text{ mm}^{-3}, V(0) = 610000 \text{ ml}^{-1} \). Note that for this set of parameters, \( r = 2.3 \times 10^{-3} < k_1 c = 5 \times 10^{-3} \). The resulting basic reproduction number \( R_0 \approx 27.78 > 1 \) and the solution converges to the IPE \( E^* = (90.91, 249.44, 35424) \). Hence, the infection persists and the viral load \( V(t) \) maintains at the level of \( V^* \approx 35424 \) virons per ml.

To reduce the viral load, it is common to apply antiretroviral therapies using reverse transcriptase inhibitors (RTIs). Denote the efficacy of the RTIs by \( n_{rt} \), then the infection rate \( k_1 \) is reduced to \( k'_1 = k_1(1-n_{rt}) \), and hence System (31) reads as

\[
T'(t) = s - \mu_1 T(t) + \frac{rT(t)V(t)}{c + V(t)} - k_1(1-n_{rt})T(t)V(t),
\]

\[
T'_1(t) = k_1(1-n_{rt})T(t)V(t) - \mu_2 T_1(t),
\]

\[
V'(t) = N(\mu_2 T_1(t) - \mu_3 V(t) - k_2 T(t)V(t)).
\]

As \( n_{rt} \) increases, the effective infective rate \( k'_1 \) decreases from \( k_1 \), therefore, \( R_0 \) decreases, and there exists a critical value of \( n_{c1,rt} \) at which \( R_0 = 1 \). In the meantime,
it is likely that the assumption (D2) holds and Theorem 5.2 applies. Thus, there exists another critical value of $n_{c,rt}$ at which $R_0 = 1 - a$. Take parameter values as: $s = 100 \text{ mm}^{-3} \cdot \text{day}^{-1}$, $\mu_1 = 3.96 \times 10^{-2} \text{day}^{-1}$, $r = 0.03 \text{ day}^{-1}$, $c = 10 \text{ ml}^{-1}$, $k_1 = 3.0 \times 10^{-5} \text{ml} \cdot \text{day}^{-1}$, $\mu_2 = 0.3873 \text{ day}^{-1}$, $N = 200 \text{ mm}^3 \cdot \text{ml}^{-1}$, $\mu_3 = 4 \text{ day}^{-1}$, $k_2 = 9.9933 \times 10^{-4} \text{mm}^3 \cdot \text{day}^{-1}$, then $n_{c,1,rt} \approx 0.5694$ and $n_{c,2,rt} = 0.75$. As shown in Figure 4, we find $R_0 > 1$ for $n_{rt} \in [0, 0.5694)$ and $1 - a < R_0 < 1$ for $n_{rt} \in (0.5694, 0.75)$ and $R_0 < 1 - a$ for $n_{rt} \in (0.75, 1]$. Due to the existence of a backward bifurcation and the resulting bistability for $R_0 \in (1 - a, 1)$, the virus may not be completely eradicated even if $R_0$ is less than 1. Suppose that the drug therapy starts at day 200 at which the viral load of the
patient is near the equilibrium level, as indicated in Figure 5, the equilibrium viral load drops as the efficacy \( n_{rt} \) increases, but the virus persists until the efficacy is increased to \( n_{c,rt} = 0.68 \) at which the viral load quickly drops to zero. We notice that as \( n_{rt} \) increases, the equilibrium viral load drops, and more damped oscillations are observed and as \( n_{rt} \) reaches a critical value, \( n_{rt} = n_{c,rt} = 0.68 \), a complete clearance of virus is achieved. Note that such a critical value \( n_{c,rt} \) is less than \( n_{c,2,rt} \) and the value is initial condition dependent and also depends on the time when the drug therapy starts. To completely clear the virus from the host, it is required that therapies either lower \( R_0 \) to be less than \( 1 - a \) or shift the viral load to the basin of attraction of the infection free equilibrium.

Figure 4. The plot of the basic reproduction number \( R_0 \) of System (33) versus the efficacy of the RTIs, \( n_{rt} \).

Figure 5. The viral dynamics under different drug therapy efficacy. Initial condition is \((T(0), T_i(0), V(0)) = (1000, 50, 500)\). The drug therapy starts at \( t = 200 \).
6. Summary and discussion. In this paper, we have incorporated the virus-driven proliferation of target cells into a general viral infection model (2). We have shown that this general model exhibits a threshold dynamics under the assumptions (H1)-(H3): if \( R_0 \leq 1 \), then the infection free equilibrium \( E_0 \) is globally stable (Theorem 3.2), whereas if \( R_0 > 1 \), then \( E_0 \) becomes unstable and there exists a unique infection persistent equilibrium \( E^* = (T^*, T^*_i, V^*) \), which is locally stable provided that (H4) and \( \partial f(T^*, V^*)/\partial V \geq 0 \) are further satisfied (Theorem 3.4). If some additional conditions are satisfied, then \( E^* \) attracts all positive solutions (Theorem 3.6). The more interesting dynamics occurs when the assumption (H2) is not satisfied. In that case, we have shown that a backward bifurcation occurs (Theorem 5.2). As such a backward bifurcation does not occur in the corresponding model where the virus-driven proliferation of target cells is ignored, we conclude that the backward bifurcation is induced by the virus-driven proliferation of target cells.

An example, System (31), has been given to demonstrate our analytical results. Essentially if \( r \leq k_1 c \) and \( R_0 > 1 \), then the virus persists. Drug therapies such as the use of RTIs aiming to control the viral infection can reduce the value of the infection rate \( k_1 \) such that \( r > k_1 c \) and thus the result of Theorem 5.2 applies. As a consequence, a backward bifurcation occurs. The efficacy of the RTIs should be high enough such that either \( R_0 < 1 - a \) or the solution is shifted to the basin of attraction of the infection free equilibrium. Our analysis and numerical simulations suggest that simply reducing the basic reproduction number below unity may not be enough to successfully clear the viral infection and there exists an initial condition dependent critical value for the efficacy of drug therapy, above which the viral infection can be cleared. This implies that the virus-driven proliferation of target cells does play an important role and thus cannot be neglected.

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