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A DELAYED HIV-1 MODEL WITH VIRUS WANING TERM

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Abstract. In this paper, we propose and analyze a delayed HIV-1 model with CTL immune response and virus waning. The two discrete delays stand for the time for infected cells to produce viruses after viral entry and for the time for $CD8^+$ T cell immune response to emerge to control viral replication. We obtain the positiveness and boundedness of solutions and find the basic reproduction number R_0. If $R_0 < 1$, then the infection-free steady state is globally asymptotically stable and the infection is cleared from the T-cell population; whereas if $R_0 > 1$, then the system is uniformly persistent and the viral concentration maintains at some constant level. The global dynamics when $R_0 > 1$ is complicated. We establish the local stability of the infected steady state and show that Hopf bifurcation can occur. Both analytical and numerical results indicate that if, in the initial infection stage, the effect of delays on HIV-1 infection is ignored, then the risk of HIV-1 infection (if persists) will be underestimated. Moreover, the viral load differs from that without virus waning. These results highlight the important role of delays and virus waning on HIV-1 infection.

1. **Introduction.** The disease, now known as the acquired immunodeficiency syndrome (AIDS), was first reported in 1981 in the *Morbidity and Mortality Weekly Report* under the title "*Pneumocystis* pneumonia–Los Angeles" [14]. Although the disease was first found in homosexual men and injection-drug users, the susceptible groups actually include transfusion recipients, persons with hemophilia [1], infants [2], females having sexual contacts with infected men [3], and so on. By 2010, more than 30 million people worldwide had died of AIDS (UNAIDS2010).

In 1984, the French group and researchers at the US National Institutes of Health published seminal papers to prove the outcome that the virus known as HIV was the cause of AIDS [9, 19]. HIV viruses are intracellular parasites that depend on the host cells to survive and replicate. Host cells include Langerhans, macrophages and dendritic cells, but most importantly, helper T cells (specially $CD4^+$ T-cells). $CD4^+$ T-cells can be damaged either directly by the virus or by immune responses

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to the virus [8, 20]. It is believed that CTLs, also known as $CD8^+$ T-cells or killer T-cells, are the main host immune factor that limits the virus replication in vivo, blocks up virus into target cells, and determines the viral load [21].

Mathematical modeling and analysis are needed for a deeper understanding of HIV infection and immune responses. In the past decades, many approaches have been developed to discuss the relation among target cells, infected cells, viral load and immune factors [6, 18, 22, 25, 27, 29, 31, 32]. Wang et al. [32] presented two HIV models to incorporate the CTL immune response. The difference between the models lied in the inclusion or omission of a virus loss term. They obtained conditions for the existence of one, two or three steady states, and analyzed the stability of these steady states.

Time delays also have been introduced into models to explore innovative insights of virus dynamics. In 1996, Herz et al. [12] firstly incorporated delay to characterize the time between the initial viral entry into a target cell and viral production. In Ref. [12], they obtained the explicit estimate of the viral load and the effects of the intracellular delay with respect to viral load change. Since then, many delayed within-host HIV models have been established [13, 15, 16, 17, 22, 27, 29, 31]. In particular, Pawelek et al. [22] proposed an HIV-1 model with two discrete delays. The delays stood for the time needed for infected cells to produce viruses after viral entry and for the time needed for CTL immune response to control viral replication. For this model, it is found that the basic reproduction ratio played an important role in determining the stability of the steady states, and that incorporating the intracellular delay did not change the stability results while introducing the immune response delay generated abundant dynamics such as sustainable oscillations.

For HIV models, viral load is a pivotal determinant of the infection outcome and is relevant to pathogenicity, disease stages and progression of disease. Since the loss of the virus was very little and could be combined into the virus clearance term [7], researchers thought that it was not important to consider the loss of virus in the infection process. Only a few researchers introduced the loss of virus into HIV models. It turned out that this loss term may play a crucial role in some patients and may also affect the virus dynamics [7, 11, 23, 32]. For example, in Ref. [32], Wang et al. found that the basic reproduction number, viral dynamics and infected equilibria of the model with the loss of virus could vary greatly compared with the case without loss of virus.

In this paper, we extend the classic model of virus dynamics to include CTL immune response, two delays, and virus loss. The rest of the paper is organized as follows. The model to be studied is proposed in Section 2. Section 3 is the main part of this paper, which concerns the mathematical analysis of the model. First, we show the solutions are positive and bounded. Then we obtain the dynamics of the model, which is determined by the basic reproduction number R_0. It is shown that if $R_0 < 1$ then the infection-free steady state is globally asymptotically stable whereas if $R_0 > 1$ then the system is permanent. The local stability of the infected steady state is also discussed. It turns out that Hopf bifurcation can occur. The effects of virus waning and delays are demonstrated in Section 4. The paper concludes with a short discussion. Though the presentation here is parallel to that of Pawelek et al. [22], some arguments are genuinely modified and more complicated. For example, on the one hand, there is a flaw in the proof of Theorem 2 in Pawelek et al. [22]. Fortunately, this can be corrected by modifying the arguments. On the other hand, unlike in [22], the unique infected steady state cannot be found

explicitly and its existence is established through rigorous analysis; moreover, our bifurcation study is aimed at a four dimensional complicated system rather than a three dimensional system.

2. **The model.** Our model is based on the model proposed by Pawelek et al. [22]. Their model involves four variables: uninfected target cells $T(t)$, productively infected cells $T^\star(t)$, free viruses $V(t)$, and effector cells $E(t)$. Compared with the model in [22], we consider adding a virus waning term $-n_k kVT$ into the third equation of the original model. Therefore, our model is given by

$$\begin{aligned} \frac{d}{dt}T(t) &= s - dT - kVT, \\ \frac{d}{dt}T^\star(t) &= k_1 V(t-\tau_1)T(t-\tau_1) - \delta T^\star - d_x E T^\star, \\ \frac{d}{dt}V(t) &= N\delta T^\star - cV - n_k kVT, \\ \frac{d}{dt}E(t) &= pT^\star(t-\tau_2) - d_E E. \end{aligned} \tag{1}$$

TABLE 1. The meanings of parameters in (1)

Parameter	Meaning
s	Source term for uninfected $CD4^+$ T-cells
d	Death rate of uninfected $CD4^+$ T-cells
k	Rate at which $CD4^+$ T-cells become infected with virus
k_1	Rate at which infected cells are generated by virus infecting target cells
δ	Death rate of infected $CD4^+$ T-cells
d_x	Rate at which infected cells are killed by effector cells
N	The total number of viruses produced by an infected cell in its lifespan
c	Death rate of virus
n_k	The loss rate of viruses
p	Rate at which effector cells are generated by infected cells
d_E	Death rate of $CD8^+$ T-cells

The two nonnegative constant time delays τ_1 and τ_2 in (1) are accountable for the time between viral entry and virus production and the time for $CD8^+$ cell immune response activation, respectively, i.e., infected $CD4^+$ T cells at time t were infected by viruses at time $t-\tau_1$ and the immune cells at time t were activated by infected $CD4^+$ T cells at time $t-\tau_2$, respectively. The meanings of the other parameters are summarized in Table 1. Here $k_1 = ke^{-\alpha\tau_1}$, where α $(d < \alpha < \delta)$ is the death rate of infected cells before virus production begins. Thus $e^{-\alpha\tau_1}$ is the probability of an infected cell surviving eclipse phase to generate virus. For more details about the background of the model, we refer to [22].

3. **Model analysis.**

3.1. **Initial conditions.** Denote $\tau = \max\{\tau_1, \tau_2\}$. Let $X = \mathcal{C}([-\tau, 0], \mathbb{R}^4)$ be the Banach space of all continuous functions from $[-\tau, 0]$ to $\mathbb{R}^4$ equipped with the supremum norm. By the standard theory of functional differential equations (see,

for example, Hale and Verduyn Lunel [10]), for any $\phi \in X$, model (1) has a unique solution

$$Y(t,\phi) = (T(t,\phi), T^\star(t,\phi), V(t,\phi), E(t,\phi))$$

on $[-\tau,\infty)$ satisfying $Y_0(\cdot,\phi) = \phi$. Here as usual, for $t \geq 0$, $Y_t(\cdot,\phi) \in X$ is defined by $Y_t(\theta,\phi) = Y(t+\theta,\phi)$ for $\theta \in [-\tau, 0]$. Moreover, for a solution of (1), we have

$$\begin{aligned}
T(t) &= T(0)e^{-\int_0^t (d+kV(\xi))d\xi} + \int_0^t s e^{-\int_\gamma^t (d+kV(\xi))d\xi} d\gamma,\\
T^\star(t) &= T^\star(0)e^{-\int_0^t (\delta + d_x E(\xi))d\xi}\\
&\quad + \int_0^t k_1 T(\gamma-\tau_1)V(\gamma-\tau_1)e^{-\int_\gamma^t (\delta+d_x E(\xi))d\xi} d\gamma,\\
V(t) &= V(0)e^{-\int_0^t (c+n_k kT(\xi))d\xi} + \int_0^t N\delta T^\star(\gamma) e^{-\int_\gamma^t (c+n_k kT(\xi))d\xi} d\gamma,\\
E(t) &= E(0)e^{-d_E t} + \int_0^t pT^\star(\gamma-\tau_2)e^{-d_E(t-\gamma)}d\gamma.
\end{aligned} \tag{2}$$

From the view of mathematical biology, we consider (1) with the initial conditions $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+$, where

$$X_+ = \{\phi \in X | \phi_i(\theta) \geq 0 \text{ for } \theta \in [-\tau, 0] \text{ and } i = 1,\, 2,\, 3,\, 4\}.$$

It follows from (2) that (1) is well-posed on X_+, that is, any solution with initial condition in X_+ will stay in X_+ forever. However, for the infection to start, there should be infected cells or viruses. Then, one can easily see from (2) again that every component for such solutions will be positive when $t > 2\tau$. In fact, obviously, $T(t) > 0$ for $t > 0$ from the first equation of (2). First, suppose $T^*(0) > 0$. Then, from the second equation of (2), we know that $T^*(t) > 0$ for $t \geq 0$. This, combined with the third and fourth equations of (2) imply that $V(0) > 0$ for $t > 0$ and $E(t) > 0$ for $t > \tau$, respectively. In summary, we have shown that the components are positive when $t > \tau$ if $T^*(0) > 0$. Now, suppose $V(0) > 0$. Then the third equation of (2) tells us that $V(t) > 0$ for $t \geq 0$. This, combined with the second equation of (2) and the fact that $T(t) > 0$ for $t > 0$, gives us $T^*(t) > 0$ for $t > \tau$. Similar arguments as those for the case of $T^*(0) > 0$ show that the components are positive when $t > 2\tau$. Therefore, without loss of generality, we only need to consider (1) with the initial conditions in $\hat{X}_+ = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+ | \phi_i(0) > 0, i = 1, 2, 3, 4\}$.

Theorem 3.1. *Let $Y(t,\phi)$ be any solution of (1) with $\phi \in \hat{X}_+$. Then all $T(t)$, $T^\star(t)$, $V(t)$, and $E(t)$ are positive for all $t \geq 0$ and they are ultimately bounded. Moreover, there exists an $\epsilon > 0$ such that $\liminf_{t\to\infty} T(t) \geq \epsilon$.*

Proof. The positiveness of components of the solution of (1) with $\phi \in \hat{X}_+$ follows immediately from (2).

We first show the boundedness of solutions as follows. By (1), we have

$$\frac{d}{dt}T(t) \leq s - dT(t) \qquad \text{for } t \geq 0,$$

which implies that $\limsup_{t\to\infty} T(t) \leq s/d$. Next, consider

$$U_1(t) = T(t) + \frac{k}{k_1}T^\star(t+\tau_1).$$

Then $U_1(t) \geq 0$ for $t \geq 0$ and its derivative along the solution is

$$\frac{dU_1(t)}{dt} \leq s - dT(t) - \frac{\delta k}{k_1}T^\star(t+\tau_1) \leq s - mU_1(t),$$

where $m = \min\{d, \delta\}$. It follows that $\limsup_{t\to\infty} U_1(t) \le s/m$ and hence

$$\limsup_{t\to\infty} T^\star(t) \le \frac{k_1 s}{km}.$$

With this, one can easily show that

$$\limsup_{t\to\infty} V(t) \le \frac{N\delta k_1 s}{ckm} \quad \text{and} \quad \limsup_{t\to\infty} E(t) \le \frac{pk_1 s}{kmd_E}.$$

We now show that $T(t)$ is bounded away from zero. Given $\xi > 0$, there exists $t_0 > 0$ such that $V(t) \le N\delta k_1 s/(ckm) + \xi$ for $t > t_0$ since $\limsup_{t\to\infty} V(t) \le N\delta k_1 s/(ckm)$. Then it follows from the first equation of (1) that

$$\frac{d}{dt}T(t) \ge s - dT - k\left(\frac{N\delta k_1 s}{ckm} + \xi\right)T = s - \left[d + k\left(\frac{N\delta k_1 s}{ckm} + \xi\right)\right]T \quad \text{for } t > t_0.$$

Therefore, $\liminf_{t\to\infty} T(t) \ge s/[d + k(\frac{N\delta k_1 s}{ckm} + \xi)]$. As ξ is arbitrary, we immediately get $\liminf_{t\to\infty} T(t) \ge \epsilon = scm/(dcm + k_1 N\delta s)$. This finishes the proof. □

3.2. **Steady states.** Obviously, model (1) always has an infection-free steady state $E_0(T_0, 0, 0, 0)$, where $T_0 = \frac{s}{d}$. Moreover, one can easily observe that if a steady state is not infection-free then it must be an infected steady state, that is, every component is positive.

If $(\bar{T}, \bar{T}^*, \bar{V}, \bar{E})$ is an infected steady state of (1) then

$$\begin{aligned} s - d\bar{T} - k\bar{V}\bar{T} &= 0, && (3)\\ k_1\bar{V}\bar{T} - \delta\bar{T}^* - d_x\bar{E}\bar{T}^* &= 0, && (4)\\ N\delta\bar{T}^* - c\bar{V} - n_k k\bar{V}\bar{T} &= 0, && (5)\\ p\bar{T}^* - d_E\bar{E} &= 0. && (6) \end{aligned}$$

It follows from (5) and (6) respectively that

$$\bar{V} = \frac{N\delta\bar{T}^*}{c + n_k k\bar{T}} \tag{7}$$

and

$$\bar{E} = \frac{p\bar{T}^*}{d_E}. \tag{8}$$

Substituting them into (4) and noting $\bar{T}^* \neq 0$ produce

$$\bar{T}^* = \frac{\delta d_E[(Nk_1 - n_k k)\bar{T} - c]}{d_x p(c + n_k k\bar{T})}. \tag{9}$$

Substituting (9) into (7) and then substituting the resultant into (3), we can see that $\bar{T}$ is a positive zero of the following cubic polynomial

$$h(T) = A_0T^3 + B_0T^2 + C_0T + D_0, \tag{10}$$

where

$$\begin{aligned} A_0 &= dn_k^2k^2d_xp > 0,\\ B_0 &= (2dc - sn_kk)d_xpn_kk + N\delta^2kd_E(Nk_1 - n_kk),\\ C_0 &= (dc - 2sn_kk)cd_xp - N\delta^2ckd_E,\\ D_0 &= -sc^2d_xp < 0. \end{aligned}$$

Since $(\bar{T}, \bar{T}^*, \bar{V}, \bar{E})$ is an infected steady state, one can see that $Nk_1 - n_kk$ must be positive. Moreover, $\bar{T} < s/d$ and $\bar{T} > c/(Nk_1 - n_kk)$. Therefore, a necessary

condition for the existence of such a steady state is that $c/(Nk_1 - n_k k) < s/d$ or equivalently $R_0 > 1$, where

$$R_0 = \frac{(Nk_1 - n_k k)s}{cd}.$$

In fact, we have the following result.

Theorem 3.2. *If $R_0 > 1$ then (1) has a unique infected steady state E_1 $(\bar{T}, \bar{T}^*, \bar{V}, \bar{E})$, where $\bar{T}$ is the unique positive zero of $h(T)$ defined by (10) and $\bar{T}^*$, $\bar{V}$, $\bar{E}$ are given by (9), (7), and (8), respectively.*

Proof. It suffices to show that $h(T)$ has a unique positive zero, which is in the interval $(c/(Nk_1 - n_k k), s/d)$.

First, we show that $h(T)$ has a zero in $(c/(Nk_1 - n_k k), s/d)$. Indeed, note that

$$h\left(\frac{c}{Nk_1 - n_k k}\right) = -\frac{d_x p c^2 N^2 k_1^2 [s(Nk_1 - n_k k) - dc]}{(Nk_1 - n_k k)^3} < 0$$

and

$$h\left(\frac{s}{d}\right) = \frac{sN\delta^2 k d_E [s(Nk_1 - n_k k) - dc]}{d^2} > 0.$$

By the Intermediate Value Theorem, $h(T)$ has a zero in $(c/(Nk_1 - n_k k), s/d)$.

Next, we prove that $h(T)$ only has one positive zero. If $h(T)$ has a complex zero then we are done. So, we assume that all zeros of $h(T)$ are real. We claim that $h(T)$ has at least one negative zero. The claim is proved by distinguishing two cases. First, assume that $C_0 \geq 0$. In this case, we have $dc > 2sn_k k$ and hence $B_0 > 0$. It follows that the sum of the three zeros of $h(T)$ is $-\frac{B_0}{A_0} < 0$. Thus $h(T)$ must have a negative zero. Second, assume that $C_0 < 0$. Then we know that the sum of the products of any two zeros of $h(T)$ is $\frac{C_0}{A_0} < 0$ and again $h(T)$ must have a negative zero. This proves the claim. Now, by noting $h(0) < 0$, we can easily see that $h(T)$ either has a negative zero of multiplicity 2 or has two distinct negative zeros, which means that $h(T)$ can only have one positive zero. This completes the proof. □

We should mention that, in epidemiology, R_0 is called the basic reproduction number. In HIV within-host infection, R_0 stands for the average number of newly infected cells that arise from any one infected cell when introduced into a population of healthy target cells (Heffernan and Wahl [11]; Nowak and May [21]). R_0 determines whether a pathogen can successfully infect the body. Compared with the expression of the basic reproduction number in [22], R_0 here is delay-dependent as $k_1 = ke^{-\alpha\tau_1}$. Also, with the virus waning term, R_0 becomes smaller and this means that the HIV-1 virus is more difficult to infect the body.

In the following, we discuss the impact of the virus waning term on the position of the infected steady state. Before doing it, we obtain another relationship between $\bar{T}$ and $\bar{T}^*$. It follows from (3) that $\bar{V} = (s - d\bar{T})/(k\bar{T})$. Substituting this and (8) into (4) gives $d_x kp(\bar{T}^*)^2 + \delta d_E k\bar{T}^* - k_1 d_E(s - d\bar{T}) = 0$, which yields

$$\bar{T}^* = \frac{\sqrt{(\delta k d_E)^2 + 4d_x kpk_1 d_E(s - d\bar{T})} - \delta k d_E}{2kpd_x}. \tag{11}$$

Now, we are ready to consider the impact of the virus waning term. Differentiating $h(T) = 0$ with respect to n_k we can get

$$\frac{d\bar{T}}{dn_k} = -\frac{2dn_k k^2 d_x p\bar{T}^2 - (2sn_k k^2 d_x p + N\delta^2 k^2 d_E)\bar{T} - 2sckd_x p}{3A_0\bar{T}^2 + 2B_0\bar{T} + C_0}\bar{T}. \tag{12}$$

As $\bar{T} < s/d$, we can see that $2dn_k k^2 d_x p\bar{T}^3 < 2sn_k k^2 d_x p\bar{T}^2$ and hence the numerator of the right hand side of (12) is negative. On the other hand, we know that $h'(\bar{T}) > 0$, that is, $3A_0\bar{T}^2 + 2B_0\bar{T} + C_0 > 0$. Therefore, $\frac{d\bar{T}}{dn_k} > 0$ and this means that the level of uninfected target cells at the steady state increases when the ability of virus waning increases. Then, combining this with (11), (7), and (8), we obtain

$$\frac{d\bar{T}^*}{dn_k} = -\frac{dk_1 d_E}{\sqrt{(\delta k d_E)^2 + 4d_x pkk_1 d_E(s - d\bar{T})}}\frac{d\bar{T}}{dn_k} < 0, \tag{13}$$

$$\frac{d\bar{V}}{dn_k} = -\frac{s}{k\bar{T}^2}\frac{d\bar{T}}{dn_k} < 0, \tag{14}$$

$$\frac{d\bar{E}}{dn_k} = \frac{p}{d_E}\frac{d\bar{T}^*}{dn_k} < 0. \tag{15}$$

The above three expressions tell us that all levels of the productively infected cells, the free viruses and effector cells at the infected steady state will decrease when the ability of virus waning increases.

3.3. **Qualitative analysis.** The local stability of a steady state of (1) is obtained by linearization. After linearizing around a steady state, we obtain the characteristic equation

$$\left|\lambda I - \begin{pmatrix} -d - kV & 0 & -kT & 0 \\ k_1 V e^{-\lambda\tau_1} & -\delta - d_x E & k_1 T e^{-\lambda\tau_1} & -d_x T^\star \\ -n_k kV & N\delta & -c - n_k kT & 0 \\ 0 & pe^{-\lambda\tau_2} & 0 & -d_E \end{pmatrix}\right| = 0.$$

3.3.1. *The infection-free steady state E_0.*

Theorem 3.3. *The infection-free steady state E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The characteristic equation of (1) at the infection-free steady state E_0 is

$$(\lambda + d)(\lambda + d_E)[(\lambda + \delta)(\lambda + c + n_k kT_0) - N\delta k_1 T_0 e^{-\lambda\tau_1}] = 0. \tag{16}$$

Clearly, $\lambda = -d$ and $\lambda = -d_E$ are negative roots of (16). The remaining roots are given by the roots of the following equation

$$(\lambda + \delta)(\lambda + c + n_k kT_0) = N\delta k_1 T_0 e^{-\lambda\tau_1}. \tag{17}$$

Firstly, assume $R_0 < 1$. We claim that all roots of (17) have negative real parts. Suppose that this is not true and hence (17) has a root $\bar{\lambda}$ with a nonnegative real part. It follows from

$$(\bar{\lambda} + \delta)(\bar{\lambda} + c + n_k kT_0) = N\delta k_1 T_0 e^{-\bar{\lambda}\tau_1}$$

that

$$\delta(c + n_k kT_0) \le |(\bar{\lambda} + \delta)(\bar{\lambda} + c + n_k kT_0)| = |N\delta k_1 T_0 e^{-\bar{\lambda}\tau_1}| \le N\delta k_1 T_0,$$

which produces $R_0 > 1$, a contradiction. This proves the claim and hence the infection-free steady state E_0 is locally asymptotically stable if $R_0 < 1$.

Secondly, assume $R_0 > 1$. In this case, define $g(\lambda) = (\lambda + \delta)(\lambda + c + n_k kT_0) - N\delta k_1 T_0 e^{-\lambda\tau_1}$. Clearly, $g(0) = c\delta - \delta(Nk_1 - n_k k)T_0 = c\delta(1 - R_0) < 0$ if $R_0 > 1$ and $\lim_{\lambda\to\infty} g(\lambda) = \infty$. By the Intermediate Value Theorem, g has at least one positive zero. Therefore, the infection-free steady state E_0 is unstable when $R_0 > 1$. The proof is completed. □

In fact, the following result tells us that the infection-free steady state is globally stable if it is locally stable.

Theorem 3.4. *The infection-free steady state E_0 is globally asymptotically stable if $R_0 < 1$.*

Proof. Because of Theorem 3.3, it is sufficient to prove that E_0 is globally attractive, which is achieved by employing the technique of Lyapunov functionals. Consider the Lyapunov functional

$$W(t) = W_1(t) + W_2(t) + W_3(t),$$

where

$$\begin{aligned} W_1(t) &= T_0\left(\frac{T}{T_0} - \ln\frac{T}{T_0} - 1\right) + \frac{k + b_1 n_k k}{k_1} T^\star + b_1 V + b_2 E, \\ W_2(t) &= (k + b_1 n_k k)\int_{t-\tau_1}^{t} T(s)V(s)ds, \\ W_3(t) &= b_2 p \int_{t-\tau_2}^{t} T^\star(s)ds, \end{aligned}$$

with $b_1 = \frac{k}{c}T_0$ and $b_2 = \frac{k\delta(1-R_0)}{k_1 p}$ (> 0). Clearly, $W(t)$ is well-defined on $\hat{X}_+$ and $W(t) \geq 0$. Moreover, $W(t) = 0$ if and only if $T(t) = T_0$ and $T^\star(t) = V(t) = E(t) = 0$.

The derivative of W along solutions of (1) is

$$\begin{aligned} \left.\frac{dW}{dt}\right|_{(1)} &= \frac{dT}{dt} - \frac{T_0}{T}\frac{dT}{dt} + \frac{k + b_1 n_k k}{k_1}\frac{dT^\star}{dt} + b_1\frac{dV}{dt} + b_2 p(T^\star(t) - T^\star(t-\tau_2)) \\ &\quad + b_2\frac{dE}{dt} + (k + b_1 n_k k)(T(t)V(t) - T(t-\tau_1)V(t-\tau_1)) \\ &= (s - dT - kVT - s + dT_0) - \frac{T_0}{T}(s - dT - kVT) \\ &\quad + \frac{k + b_1 n_k k}{k_1}(k_1 T(t-\tau_1)V(t-\tau_1) - \delta T^\star(t) - d_x E T^\star) \\ &\quad + b_1(N\delta T^\star - cV - n_k kVT) + b_2(pT^\star(t-\tau_2) - d_E E) \\ &\quad + (k + b_1 n_k k)V(t)T(t) - (k + b_1 n_k k)T(t-\tau_1)V(t-\tau_1) \\ &\quad + b_2 pT^\star(t) - b_2 pT^\star(t-\tau_2) \\ &= -\frac{d}{T}(T - T_0)^2 - \frac{k + b_1 n_k k}{k_1} d_x E T^\star - b_2 d_E E + (kT_0 - b_1 c)V \\ &\quad + T^\star(t)\left(b_2 p + b_1 N\delta - \frac{(k + b_1 n_k k)\delta}{k_1}\right) \\ &= -\frac{d}{T}(T - T_0)^2 - \frac{k + b_1 n_k k}{k_1} d_x E T^\star - b_2 d_E E \\ &\leq 0. \end{aligned}$$

Observe that $\left.\frac{dW}{dt}\right|_{(1)} = 0$ if and only if $T(t) = T_0$ and $E(t) = 0$. In this case, using $T(t) = T_0$ in the first equation of (1), we get $V(t) = 0$. Substituting $E(t) = V(t) = 0$ into the second equation of (1), one obtains $T^\star(t) = 0$. Therefore, the maximal compact invariant set in $\{\left.\frac{dW}{dt}\right|_{(1)} = 0\}$ is the singleton E_0. By the LaSalle invariant principle (see, for example, Theorem 5.3.1 in Hale and Verduyn Lunel [10]), the infection-free steady state E_0 is globally attractive. This completes the proof. □

Theorems 3.3 and 3.4 imply that if $R_0 < 1$ then HIV viruses cannot establish infection. Since R_0 is smaller than the basic reproduction number in the case without virus waning, it is easier to eradicate the HIV infection with virus loss than without.

3.3.2. *Permanence when $R_0 > 1$.* Recall that when $R_0 > 1$ the infection-free steady state is unstable. In this case, to study the dynamics of (1), we first use the persistence theory developed by Smith and Zhao [28] for infinite dimensional systems [34] to prove that it is uniformly persistent.

Denote by $\{Q(t)\}_{t\geq 0}$ the family of solution operators associated with (1). The ω-limit set $\omega(x)$ of x consists of $y \in X_+$ such that there exists a sequence $\{t_n\}$ with $t_n \to \infty$ and $Q(t_n)x \to y$ as $n \to \infty$.

Theorem 3.5. *Assume $R_0 > 1$. Then system (1) is uniformly persistent, that is, there exists $\eta > 0$ such that $\liminf_{t\to\infty} T(t) \geq \eta$, $\liminf_{t\to\infty} T^\star(t) \geq \eta$, $\liminf_{t\to\infty} V(t) \geq \eta$, and $\liminf_{t\to\infty} E(t) \geq \eta$.*

Proof. Let $X_+^0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+ \mid \phi_2(0) > 0, \phi_3(0) > 0\}$. By the second and third equations of (2), it is easy to see that X_+^0 is positively invariant for $\{Q(t)\}$.

Denote $\partial X_+ = X_+ \setminus X_+^0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+ \mid \phi_2(0) = 0 \text{ or } \phi_3(0) = 0\}$, which is relatively closed in X_+. Define $M_\partial = \{\phi \in X_+ \mid Y_t(\cdot, \phi) \in \partial X_+ \text{ for } t \geq 0\}$. We claim that if $\phi \in M_\partial$ then $T^*(t, \phi) = V(t, \phi) = 0$ for $t \geq 0$. For simplicity of notation, we just use $Y(t)$ instead of $Y(t, \phi)$ for the solution through ϕ. By the definition of M_∂, we know that $T^*(t)V(t) = 0$ for $t \geq 0$. Then we have

$$\frac{dV^2}{dt} = 2V\frac{dV}{dt} = 2N\delta T^* V - 2cV^2 - 2n_k k V^2 T = -2V^2(c + n_k k T)$$

and hence $V^2(t) = V^2(0)e^{-2\int_0^t (c+n_k k T(s))ds}$. If $V(0) = 0$ then $V^2(t) = 0$ and hence $V(t) = 0$ for $t \geq 0$. This, together with the third equation of (1) will produce $T^*(t) = 0$ for $t \geq 0$. If $V(0) \neq 0$ then $V(t) \neq 0$ for $t \geq 0$ and hence $T^*(t) = 0$ since $T^*(t)V(t) = 0$ for $t \geq 0$. This, combined with the fact that $T(t) > 0$ for $t > 0$ and the second equation of (1), yields $V(t) = 0$ for $t \geq 0$. This proves the claim. Let $\Omega_0 = \bigcap_{x\in Y_0} \omega(x)$, where Y_0 is the global attractor of $\{Q(t)\}$ restricted to ∂X_+. We show that $\Omega_0 = \{E_0\}$. Actually, from $\Omega_0 \subseteq M_\partial$, the claim we just proved, and the first and fourth equations of (1), we have $\lim_{t\to\infty} E(t) = 0$ and $\lim_{t\to\infty} T(t) = T_0$. Therefore, $\{E_0\}$ is the isolated invariant set in X_+.

Now we prove that $W^s(E_0) \bigcap X_+^0 = \emptyset$, where $W^s(E_0)$ is the stable manifold of E_0. By way of contradiction, suppose that there exists a solution $(T(t), T^\star(t), V(t), E(t)) \in X_+^0$ such that

$$\lim_{t\to\infty} T(t) = T_0 \qquad \text{and} \qquad \lim_{t\to\infty} T^\star(t) = \lim_{t\to\infty} V(t) = \lim_{t\to\infty} E(t) = 0.$$

As $R_0 > 1$, there exists a sufficiently small $\varepsilon > 0$ such that

$$\frac{N\delta k_1(T_0 - \varepsilon)}{c + n_k k(T_0 + \varepsilon)} - \delta - d_x\varepsilon > 0.$$

For this ε, there exists a $\tilde{t} > 0$ such that $0 < T_0 - \varepsilon < T(t) < T_0 + \varepsilon$ and $E(t) < \varepsilon$ for all $t \geq \tilde{t}$. It follows from the second and third equations of (1) that, for $t \geq \tilde{t} + \tau$,

$$\frac{dT^\star(t)}{dt} \quad \geq \quad k_1(T_0 - \varepsilon)V(t - \tau_1) - \delta T^\star - d_x\varepsilon T^\star,$$

$$\frac{dV(t)}{dt} \geq N\delta T^\star - cV - n_k k(T_0+\varepsilon)V.$$

Since $\lim_{t\to\infty} T^\star(t) = \lim_{t\to\infty} V(t) = 0$, a standard comparison argument tells us that the solution $(T_1^\star(t), V_1(t))$ of the following monotone system

$$\begin{aligned} \frac{dT_1^\star(t)}{dt} &= k_1(T_0-\varepsilon)V_1(t-\tau_1) - \delta T_1^\star(t) - d_x\varepsilon T_1^\star(t), \\ \frac{dV_1(t)}{dt} &= N\delta T_1^\star(t) - cV_1 - n_k k(T_0+\varepsilon)V_1(t), \end{aligned} \tag{18}$$

for $t \geq \tilde{t}+\tau$ with the initial condition $(T_1^\star(t), V_1(t)) = (T^\star(t), V(t))$ for $t \in [\tilde{t}, \tilde{t}+\tau]$ satisfies $\lim_{t\to\infty} T_1^*(t) = \lim_{t\to\infty} V_1(t) = 0$, too. Then $\lim_{t\to\infty} U(t) = 0$, where $U(t) > 0$ is defined by

$$U(t) = T_1^\star(t) + k_1(T_0-\varepsilon)\int_{t-\tau_1}^{t} V_1(\xi)d\xi + \frac{k_1(T_0-\varepsilon)}{c+n_k k(T_0+\varepsilon)}V_1(t).$$

However, differentiating $U(t)$ with respect to time yields

$$\begin{aligned} \frac{dU(t)}{dt} &= -\delta T_1^\star(t) - d_x\varepsilon T_1^\star(t) + k_1(T_0-\varepsilon)V_1(t) \\ &\quad + \frac{N\delta k_1(T_0-\varepsilon)}{c+n_k k(T_0+\varepsilon)}T_1^\star(t) - (T_0-\varepsilon)k_1V_1(t) \\ &= \left[\frac{N\delta k_1(T_0-\varepsilon)}{c+n_k k(T_0+\varepsilon)} - \delta - d_x\varepsilon\right]T_1^\star(t). \end{aligned}$$

This implies that $U(t)$ goes to either infinity or a positive number as $t\to\infty$, a contradiction with $\lim_{t\to\infty} U(t) = 0$. Therefore, we have shown that $W^s(E_0)\bigcap X_+^0 = \emptyset$.

Define $\sigma : X_+ \to \mathbb{R}_+$ by $\sigma(\phi) = \min\{\phi_2(0), \phi_3(0)\}$ for $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+$. Clearly, $X_+^0 = \sigma^{-1}(0,\infty)$ and $\partial X_+ = \sigma^{-1}(0)$. Thus, by Theorem 3 of Smith and Zhao [28], we have $\liminf_{t\to\infty}(T^\star(t), V(t)) \geq (\eta_0, \eta_0)$ for some constant $\eta_0 > 0$. Then, by the fourth equation of (1), we can get $\liminf_{t\to\infty} E(t) \geq p\eta_0/d_E$. Then (1) is uniformly persistent with $\eta = \min\{\eta_0, p\eta_0/d_E, \epsilon\}$, where ϵ is the number obtained in Theorem 3.1 such that $\liminf_{t\to\infty} T(t) \geq \epsilon > 0$. This completes the proof. □

3.3.3. *The infected steady state.* Recall that the infected steady state E_1 exists only when $R_0 > 1$. Therefore, in the remaining of this section, we always assume that $R_0 > 1$. At the infected steady state E_1, the characteristic equation is

$$\begin{aligned} &[d_x d_E\bar{E}e^{-\lambda\tau_2} + (\delta + d_x\bar{E} + \lambda)(d_E+\lambda)]\left[(d+k\bar{V}+\lambda)(c+n_k k\bar{T}+\lambda)\right. \\ &\left.-n_k k\bar{V}k\bar{T}\right] = (d_E+\lambda)(d+\lambda)k_1\bar{T}N\delta e^{-\lambda\tau_1}. \end{aligned} \tag{19}$$

Here, we used the fact that $p\bar{T}^* = d_E\bar{E}$.

Generally, it is very difficult to analyze the distribution of roots of transcendental equations like (19) with many parameters. One approach is to first obtain a stable region in a subspace of the parameter space and then study the stability along each fibre with base being the obtained stable region. This has been used, for instance, by Wei and Ruan [33]. Remember that our focus is the effects of τ_1, τ_2, and n_k on the dynamics. The following result tells us that E_1 is locally stable in the (τ_1, n_k)-space.

Theorem 3.6. *Suppose $\tau_2 = 0$. Then the infected steady state E_1 of (1) is locally asymptotically stable.*

Proof. When $\tau_2 = 0$, equation (19) reduces to

$$\begin{aligned}&\left[d_x d_E \bar{E} + (\delta + d_x \bar{E} + \lambda)(d_E + \lambda)\right]\left[(d + k\bar{V} + \lambda)(c + n_k k\bar{T} + \lambda)\right.\\&\left.-n_k k^2 \bar{V}\bar{T}\right] = (d_E + \lambda)(d + \lambda)k_1 \bar{T} N\delta e^{-\lambda\tau_1}.\end{aligned} \tag{20}$$

We need to show that all roots of (20) have negative real parts. Note that the roots of (20) depend continuously on the parameters. It is sufficient to show that (20) has no roots on the imaginary axis and all roots of (20) have negative real parts for some parameters.

Firstly, we show that (20) has no nonnegative real roots. By way of contradiction, suppose (20) has a root $\lambda_0 \geq 0$. Then

$$(d_E + \lambda_0)(d + \lambda_0)k_1 \bar{T} N\delta e^{-\lambda_0\tau_1} \leq (d_E + \lambda_0)(d + \lambda_0)k_1 \bar{T} N\delta$$

and

$$\begin{aligned}&\left[d_x d_E \bar{E} + (\delta + d_x \bar{E} + \lambda_0)(d_E + \lambda_0)\right]\left[(d + k\bar{V} + \lambda_0)(c + n_k k\bar{T} + \lambda_0) - n_k k^2 \bar{V}\bar{T}\right]\\ >\ & (\delta + d_x \bar{E} + \lambda_0)(d_E + \lambda_0)(c + n_k k\bar{T} + \lambda_0)(d + \lambda_0)\\ \geq\ & (d_E + \lambda_0)(d + \lambda_0)(\delta + d_x \bar{E})(c + n_k k\bar{T}).\end{aligned}$$

Noting $(\delta + d_x \bar{E})(c + n_k k\bar{T}) = N\delta k_1 \bar{T}$, we obtain a contradiction to the assumption that λ_0 is a root of (20). This verified that (20) has no nonnegative real root.

Secondly, we claim that all roots of (20) have negative real parts when $R_0 > 1$ and is sufficiently small. Note that roots of (20) having nonnegative real parts are uniformly bounded. If the claim is not correct, then there exists a sequence of the parameters where $R_0(> 1) \to 1$ such that, by the result we just proved, for each set of the parameters there exists a pair of conjugate roots for (20). Without loss of generality, we assume that the sequence of the conjugate roots converges to $\alpha_0 \pm i\beta_0$, otherwise just consider a subsequence. Then $\alpha_0 \geq 0$ and $\alpha_0 \pm i\beta_0$ are roots of the characteristic equation (16) of the infection-free equilibrium. However, one can easily see that if $R_0 = 1$ then (16) has no roots with nonnegative real parts except the single root 0. Then $\alpha_0 = \beta_0 = 0$, which implies that 0 is a root of at least multiplicity 2 of (16), a contradiction. This proves the claim.

Finally, we show that (20) has no roots on the imaginary axis. By way of contradiction, suppose for some parameter values (20) has a root iy_*. By the result in the first step, we can assume that $y_* > 0$. Then

$$\begin{aligned}&\left[(\delta + d_x \bar{E} + iy_*)(d_E + iy_*) + d_x d_E \bar{E}\right]\left[k\bar{V}(c + iy_*) + (c + n_k k\bar{T} + iy_*)\right.\\&\left.(d + iy_*)\right] = (d_E + iy_*)(d + iy_*)k_1 \bar{T} N\delta e^{-i\tau_1 y_*}.\end{aligned} \tag{21}$$

Note that the modulus of the right hand side of (21) is $|d_E + iy_*||d + iy_*|K_1 \bar{T} N\delta$. However, the modulus of the left hand side of (21) is strictly larger than $(\delta + d_x \bar{E})(c + n_k k\bar{T})|d_E + iy_*||d + iy_*| = |d_E + iy_*||d + iy_*|K_1 \bar{T} N\delta$ since

$$\begin{aligned}&|(\delta + d_x \bar{E} + iy_*)(d_E + iy_*) + d_x d_E \bar{E}|^2 - (\delta + d_x \bar{E})^2 |d_E + iy_*|^2\\ =\ & (y_*^2 - d_x d_E \bar{E})^2 + 2d_x d_E^2 \bar{E}(\delta + d_x \bar{E}) + (d_E y_*)^2\\ >\ & 0\end{aligned}$$

and

$$\begin{aligned}&|(d + iy_*)(c + n_k k\bar{T} + iy_*) + k\bar{V}(c + iy_*)|^2 - |(d + iy_*)(c + n_k k\bar{T} + iy_*)|^2\\ =\ & 2dc^2 k\bar{V} + k^2 \bar{V}^2 y_*^2 + 2dy_*^2 k\bar{V} + k^2 \bar{V}^2 c^2 + 2dn_k k^2 \bar{T}\bar{V}c + 2y_*^2 n_k k^2 \bar{T}\bar{V}\\ >\ & 0.\end{aligned}$$

Therefore, we get a contradiction and this finishes the proof. □

We should mention that the proof of Pawelek et al. [22, Theorem 2] has a flaw as 0 is a root of $(\lambda+\delta)(\lambda+c) = c\delta e^{-\lambda\tau_1}$. But they claim that this equation has no root with a nonnegative real part. The arguments here can be modified easily to correct the proof.

Based on Theorem 3.6, we can easily get the following result by employing similar arguments as those in the proof of Lemma 4 in Wei and Ruan [33].

Theorem 3.7. *For any $(\tau_1, n_k) \in \mathbb{R}^2_+$, there exists a $\tau_2(\tau_1, n_k) > 0$ such that when $\tau_2 \in [0, \tau_2(\tau_1, n_k))$ the infected steady state E_1 of (1) is locally asymptotically stable.*

The dynamics of (1) after $\tau_2 > \tau_2(\tau_1, n_k)$ may be complicated. As the case study below for $(\tau_1, n_k) = (0, 0)$ indicated, Hopf bifurcation can occur.

When $(\tau_1, n_k) = (0, 0)$, the characteristic equation (19) becomes

$$(\lambda^4 + \tilde{a}_1\lambda^3 + \tilde{a}_2\lambda^2 + \tilde{a}_3\lambda + \tilde{a}_4) + \tilde{a}_5(\lambda^2 + \tilde{a}_6\lambda + \tilde{a}_7)e^{-\lambda\tau_2} = 0, \tag{22}$$

where

$$\begin{aligned}
\tilde{a}_1 &= \delta + d_x\bar{E} + d_E + d + c + k\bar{V},\\
\tilde{a}_2 &= (\delta + d_x\bar{E})(d_E + d) + d_E(d + c) + dc + k\bar{V}(c + d_E + \delta + d_x\bar{E}),\\
\tilde{a}_3 &= d_E d(\delta + d_x\bar{E} + c) + ck\bar{V}(\delta + d_x\bar{E} + d_E) + d_E k\bar{V}(\delta + d_x\bar{E}),\\
\tilde{a_4} &= d_E ck\bar{V}(\delta + d_x\bar{E}),\\
\tilde{a_5} &= d_x d_E\bar{E},\\
\tilde{a}_6 &= d + c + k\bar{V},\\
\tilde{a}_7 &= dc + ck\bar{V}.
\end{aligned}$$

Since $\tilde{a}_4 + \tilde{a}_5\tilde{a}_7 > 0$, we know that $\lambda = 0$ is not a root of (22). Also, by Theorem 3.7, all roots of (22) have negative real parts when $\tau_2 = 0$. In the following, we determine whether the solution curve of the characteristic equation (22) crosses the imaginary axis.

Suppose that $i\omega$ $(\omega > 0)$ is a root of (22). By substituting $\lambda = i\omega$ into (22) and separating the real and imaginary parts, we obtain

$$\tilde{a}_1\omega^3 - \tilde{a}_3\omega = \tilde{a}_5[\tilde{a}_6\omega\cos(\omega\tau_2) - (\tilde{a}_7 - \omega^2)\sin(\omega\tau_2)], \tag{23}$$

$$\tilde{a}_2\omega^2 - \omega^4 - \tilde{a}_4 = \tilde{a}_5[(\tilde{a}_7 - \omega^2)\cos(\omega\tau_2) + \tilde{a}_6\omega\sin(\omega\tau_2)]. \tag{24}$$

Taking squares of the above two equations and adding the resultants, we have

$$\tilde{a}_5^2[(\tilde{a}_6\omega)^2 + (\tilde{a}_7 - \omega^2)^2] = (\tilde{a}_1\omega^3 - \tilde{a}_3\omega)^2 + (\tilde{a}_2\omega^2 - \omega^4 - \tilde{a}_4)^2 \tag{25}$$

or equivalently

$$F(y) = 0, \tag{26}$$

where $y = \omega^2$ and

$$\begin{aligned}
F(y) &= y^4 + (\tilde{a}_1^2 - 2\tilde{a}_2)y^3 + (\tilde{a}_2^2 + 2\tilde{a}_4 - 2\tilde{a}_1\tilde{a}_3 - \tilde{a}_5^2)y^2\\
&\quad + (\tilde{a}_3^2 + 2\tilde{a}_7\tilde{a}_5^2 - 2\tilde{a}_2\tilde{a}_4 - \tilde{a}_5^2\tilde{a}_6^2)y + (\tilde{a}_4^2 - \tilde{a}_5^2\tilde{a}_7^2).
\end{aligned}$$

If we know signs of the coefficients of $F(y)$, then we can employ the Descartes Rule of Signs to find out how many positive zeros $F(y)$ has. It is easy to verify that $\tilde{a}_1^2 - 2\tilde{a}_2 > 0$. But signs of the other coefficients of $F(y)$ are hard to tell. As a result, we make the following assumption.

(H) $\quad F(y) = 0$ has a unqiue positive root and it is simple, denoted by y^*.

One sufficient condition for (H) to hold is $\tilde{a}_2^2 + 2\tilde{a}_4 - 2\tilde{a}_1\tilde{a}_3 - \tilde{a}_5^2 > 0$, $\tilde{a}_3^2 + 2\tilde{a}_7\tilde{a}_5^2 - 2\tilde{a}_2\tilde{a}_4 - \tilde{a}_5^2\tilde{a}_6^2 > 0$, and $\tilde{a}_4 - \tilde{a}_5\tilde{a}_7 < 0$. It follows from (H) that the solution curve of

the characteristic equation (22) crosses the imaginary axis at $i\omega^* = i\sqrt{y^*}$. To find the critical values of τ, by (23) and (24), we get

$$\cos(\omega^*\tau_2) = \frac{(\tilde{a}_7-(\omega^*)^2)(\tilde{a}_2(\omega^*)^2-(\omega^*)^4-\tilde{a}_4)+\tilde{a}_6(\omega^*)^2(\tilde{a}_1(\omega^*)^2-\tilde{a}_3)}{\tilde{a}_5[(\tilde{a}_6\omega^*)^2+(\tilde{a}_7-(\omega^*)^2)^2]}, \tag{27}$$

$$\sin(\omega^*\tau_2) = \frac{\tilde{a}_6\omega^*(\tilde{a}_2(\omega^*)^2-(\omega^*)^4-\tilde{a}_4)-\omega^*(\tilde{a}_1(\omega^*)^2-\tilde{a}_3)(\tilde{a}_7-(\omega^*)^2)}{\tilde{a}_5[(\tilde{a}_6\omega^*)^2+(\tilde{a}_7-(\omega^*)^2)^2]}. \tag{28}$$

Let $\theta \in (0, 2\pi]$ be the unique number such that $\cos\theta$ and $\sin\theta$ are the right hand sides of (27) and (28), respectively. Define

$$\tau_{2,j} = \frac{\theta + 2j\pi}{\omega^*} \qquad \text{for } j \in \mathbb{N} = \{0, 1, 2 \ldots\}.$$

Then when $\tau_2 = \tau_{2,j}$, the characteristic equation (22) has a conjugate pair of roots $\pm i\omega^*$.

Next, we determine how the solution curve of the eigenvalues crosses the imaginary axis. Let $\lambda(\tau)$ be a solution curve with $\lambda(\tau_{2,j}) = i\omega^*$. We need to find $\text{sign}(\frac{d\text{Re}(\lambda)}{d\tau_2}|_{\tau_2=\tau_{2,j}})$. Taking derivative of (22) with respect to τ_2, we know

$$[4\lambda^3 + 3\tilde{a}_1\lambda^2 + 2\tilde{a}_2\lambda + \tilde{a}_3]\frac{d\lambda}{d\tau_2} + \tilde{a}_5(2\lambda + \tilde{a}_6)e^{-\lambda\tau_2}\frac{d\lambda}{d\tau_2}$$
$$-\tilde{a}_5(\lambda^2 + \tilde{a}_6\lambda + \tilde{a}_7)e^{-\lambda\tau_2}\left(\tau_2\frac{d\lambda}{d\tau_2} + \lambda\right) = 0.$$

With $e^{\lambda\tau_2} = -\frac{\tilde{a}_5(\lambda^2+\tilde{a}_6\lambda+\tilde{a}_7)}{\lambda^4+\tilde{a}_1\lambda^3+\tilde{a}_2\lambda^2+\tilde{a}_3\lambda+\tilde{a}_4}$, we see that

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = -\frac{4\lambda^3 + 3\tilde{a}_1\lambda^2 + 2\tilde{a}_2\lambda + \tilde{a}_3}{\lambda(\lambda^4 + \tilde{a}_1\lambda^3 + \tilde{a}_2\lambda^2 + \tilde{a}_3\lambda + \tilde{a}_4)} + \frac{2\lambda + \tilde{a}_6}{\lambda(\lambda^2 + \tilde{a}_6\lambda + \tilde{a}_7)} - \frac{\tau_2}{\lambda}.$$

In particular, this gives

$$\begin{aligned}
&\text{sign}\left(\frac{d\text{Re}(\lambda)}{d\tau_2}\Big|_{\tau_2=\tau_{2,j}}\right)\\
=\ &\text{sign}\left(\text{Re}\left(\frac{d\lambda}{d\tau_2}\right)^{-1}\Big|_{\tau_2=\tau_{2,j}}\right)\\
=\ &\text{sign}\left(\frac{4\omega^{*6} + 3\omega^{*4}(\tilde{a}_1^2 - 2\tilde{a}_2) + 2\omega^{*2}(\tilde{a}_2^2 + 2\tilde{a}_4 - 2\tilde{a}_1\tilde{a}_3) + \tilde{a}_3^2 - 2\tilde{a}_2\tilde{a}_4}{\omega^{*2}(\tilde{a}_3 - \tilde{a}_1\omega^{*2})^2 + (\tilde{a}_4 - \tilde{a}_2\omega^{*2} + \omega^{*4})^2}\right.\\
&\left.+\frac{2(\tilde{a}_7 - \omega^{*2}) - \tilde{a}_6^2}{\tilde{a}_6^2\omega^{*2} + (\tilde{a}_7 - \omega^{*2})^2}\right)\\
=\ &\text{sign}\left(\frac{F'(y^*)}{\tilde{a}_5^2[\tilde{a}_6^2\omega^{*2} + (\tilde{a}_7 - \omega^{*2})^2]}\right)\\
=\ &\text{sign}\left(F'(y^*)\right).
\end{aligned}$$

Since $F'(y^*) > 0$ by (H), this verifies the transversality condition for Hopf bifurcation and hence we have established the following result.

Theorem 3.8. *Suppose $n_k = \tau_1 = 0$ and (H) holds. Then the infected steady state E_1 of (1) is locally asymptotically stable when $\tau_2 \in [0, \tau_{2,0})$. Moreover, a Hopf bifurcation occurs at the infected steady state when $\tau_2 = \tau_{2,j}$, $j \in \mathbb{N}$.*

Finally, adopting the idea from Wei and Ruan [33], we study the effect of the virus waning in the case where $\tau_1 = 0$. When $\tau_1 = 0$, the characteristic equation (19) reduces to

$$(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4) + a_5(\lambda^2 + a_6\lambda + a_7)e^{-\lambda\tau_2} = 0, \tag{29}$$

where $a_1 = \tilde{a}_1 + n_k k\bar{T}$, $a_2 = \tilde{a}_2 + n_k k\bar{T}(d_E + d)$, $a_3 = \tilde{a}_3 + d_E d n_k k\bar{T}$, $a_4 = \tilde{a}_4$, $a_5 = \tilde{a}_5$, $a_6 = \tilde{a}_6 + n_k k\bar{T}$, and $a_7 = \tilde{a}_7 + d n_k k\bar{T}$. We concern with whether n_k will stabilize E_1 or not. As a result, we assume that $\tau_2 \in (\tau_{2,0}, \tau_{2,1})$. In this case, E_1 is unstable and all the eigenvalues of the characteristic equation (22) have negative real parts except one pair with positive real parts.

Fix τ_2 as above and regard n_k as a parameter in (29). One can easily see that $\lambda = 0$ is not a root of (29) since $a_4 + a_5 a_7 > 0$. Suppose that $i\omega$ ($\omega > 0$) is a purely imaginary root of (29). Substituting $\lambda = i\omega$ into (29) and separating the real and imaginary parts, we obtain

$$\begin{aligned} a_5[a_6\omega\cos(\omega\tau_2) - (a_7 - \omega^2)\sin(\omega\tau_2)] &= a_1\omega^3 - a_3\omega, \\ a_5[(a_7 - \omega^2)\cos(\omega\tau_2) + a_6\omega\sin(\omega\tau_2)] &= a_2\omega^2 - \omega^4 - a_4. \end{aligned} \tag{30}$$

Squaring the two equations of (30) and summing up the resultants lead to

$$a_5^2[(a_6\omega)^2 + (a_7 - \omega^2)^2] = (a_1\omega^3 - a_3\omega)^2 + (a_2\omega^2 - \omega^4 - a_4)^2, \tag{31}$$

or

$$F(n_k, \omega^2) = 0,$$

where

$$\begin{aligned} F(n_k, y) \quad = \quad & y^4 + (a_1^2 - 2a_2)y^3 + (a_2^2 + 2a_4 - 2a_1a_3 - a_5^2)y^2 \\ & + (a_3^2 + 2a_7a_5^2 - 2a_2a_4 - a_5^2a_6^2)y + (a_4^2 - a_5^2a_7^2). \end{aligned}$$

Lemma 3.9. *Under the assumption (H), $F(n_k, y) = 0$ has at least one positive solution.*

Proof. Note that $F(0, y) = F(y)$, where F is defined on Page 146. It is not difficult to see that $F(0) < 0$ and hence $F(0, 0) = F(0) < 0$. Now, we have

$$\begin{aligned} & F(n_k, 0) \\ = \quad & a_4^2 - a_5^2a_7^2 = (a_4 + a_5a_7)(a_4 - a_5a_7) \\ = \quad & d_E^2[ck\bar{V}(\delta + d_x\bar{E}) + d_x\bar{E}(dc + dn_kk\bar{T} + ck\bar{V})][ck\bar{V}\delta - d_x\bar{E}d(c + n_kk\bar{T})]. \end{aligned}$$

So the sign of $F(n_k, 0)$ is the same as that of $ck\bar{V}\delta - d_x\bar{E}d(c + n_kk\bar{T}) = \bar{T}^*[d_EN\delta^2ck - dd_xp(c + n_kk\bar{T})^2]/[d_E(c + n_kk\bar{T}]$ or that of $d_EN\delta^2ck - dd_xp(c + n_kk\bar{T})^2$. Here we used both (7) and (8). Since $\frac{d\bar{T}}{dn_k} > 0$ we know that $d_EN\delta^2ck - dd_xp(c + kn_k\bar{T})^2$ is decreasing with respect to n_k. This combined with $F(0, 0) < 0$ implies that $F(n_k, 0) < 0$. Then we can easily get the required result by applying the Intermediate Value Theorem as $\lim_{y\to\infty} F(n_k, y) = \infty$. □

With Lemma 3.9, we can see that $F(n_k, y) = 0$ can have at least one but at most three positive solutions. Denote these possible solutions by $y_i(n_k)$, $i \in \mathbb{N}_{n_k} \subseteq \{1, 2, 3\}$. Let $w_i(n_k) = \sqrt{y_i(n_k)}$ for $i \in \mathbb{N}_{n_k}$. To find the critical values of n_k, similarly as in the discussion before Theorem 3.8, we get

$$\cos(\omega^*\tau_2) = \frac{(a_7 - (\omega^*)^2)(a_2(\omega^*)^2 - (\omega^*)^4 - a_4) + a_6(\omega^*)^2(a_1(\omega^*)^2 - a_3)}{a_5[(a_6\omega^*)^2 + (a_7 - (\omega^*)^2)^2]}, \tag{32}$$

$$\sin(\omega^*\tau_2) = \frac{a_6\omega^*(a_2(\omega^*)^2 - (\omega^*)^4 - a_4) - \omega^*(a_1(\omega^*)^2 - a_3)(a_7 - (\omega^*)^2)}{a_5[(a_6\omega^*)^2 + (a_7 - (\omega^*)^2)^2]}, \tag{33}$$

where $\omega^* \in \{\omega_i(n_k)|i \in \mathbb{N}_{n_k}\}$. Let $\theta_i(n_k) \in (0, 2\pi]$ be the unique number such that $\cos\theta_i(n_k)$ and $\sin\theta_i(n_k)$ are the right hand sides of (32) and (33), respectively. Denote

$$n_k^* = \min\{n_k > 0|n_k \text{ is a solution to } w_i(n_k)\tau_2 = \theta_i(n_k) \text{ for } i \in \mathbb{N}_{n_k}\}.$$

Then one can easily obtain the following result.

Theorem 3.10. *Suppose (H) holds, $\tau_1 = 0$, and $\tau_2 \in (\tau_{2,0}, \tau_{2,1})$. If $\alpha'(n_k^*) < 0$ then the infected steady state E_1 of (1) is unstable for $n_k \in [0, n_k^*)$ and will become stable when $n_k > n_k^*$ and is close to n_k^*, where $\alpha(n_k)+i\omega(n_k)$ is the root of (29) satisfying $\alpha(n_k^*) = 0$ and $\omega(n_k^*) = w_i(n_k^*)$ for the $w_i(n_k^*)$ corresponding to n_k^*. Moreover, Hopf bifurcation occurs at the infected steady state E_1 when $n_k = n_k^*$.*

For completeness, similarly as before, differentiating (29) with respect to n_k and evaluating at $n_k = n_k^*$, we can obtain

$$\alpha'(n_k^*) = -\frac{AC + BD}{C^2 + D^2},$$

where

$$\begin{aligned}
A &= -\omega^2\frac{da_2}{dn_k} + \frac{da_4}{dn_k} + [(a_7 - \omega^2)\cos\omega\tau_2 + a_6\omega\sin\omega\tau_2]\frac{da_5}{dn_k} \\
&\quad + a_5\omega\sin\omega\tau_2\frac{da_6}{dn_k} + a_5\cos\omega\tau_2\frac{da_7}{dn_k}, \\
B &= -\omega^3\frac{da_1}{dn_k} + \omega\frac{da_3}{dn_k} + [-(a_7 - \omega^2)\sin\omega\tau_2 + a_6\omega\cos\omega\tau_2]\frac{da_5}{dn_k} \\
&\quad + a_5\omega\cos\omega\tau_2\frac{da_6}{dn_k} - a_5\sin\omega\tau_2\frac{da_7}{dn_k}, \\
C &= -3a_1\omega^2 + a_3 + a_5\left[(\tau_2\omega^2 + a_6 - a_7\tau_2)\cos\omega\tau_2 + \omega(2 - a_6\tau_2)\sin\omega\tau_2\right], \\
D &= -4\omega^3 + 2a_2\omega + a_5\left[\omega(2 - a_6\tau_2)\cos\omega\tau_2 - (\tau_2\omega^2 + a_6 - a_7\tau_2)\sin\omega\tau_2\right],
\end{aligned}$$

with

$$\begin{aligned}
\frac{da_1}{dn_k} &= k\bar{T} + n_k k\frac{d\bar{T}}{dn_k} + k\frac{d\bar{V}}{dn_k} + d_x\frac{d\bar{E}}{dn_k}, \\
\frac{da_2}{dn_k} &= (d + d_E)\left(k\bar{T} + n_k k\frac{d\bar{T}}{dn_k}\right) + k(c + d_E + \delta + d_x\bar{E})\frac{d\bar{V}}{dn_k} \\
&\quad + d_x(d + d_E + k\bar{V})\frac{d\bar{E}}{dn_k}, \\
\frac{da_3}{dn_k} &= d_E d\left(k\bar{T} + n_k k\frac{d\bar{T}}{dn_k} + d_x\frac{d\bar{E}}{dn_k}\right) + d_x k\bar{V}(c + d_E)\frac{d\bar{E}}{dn_k} \\
&\quad + k\frac{d\bar{V}}{dn_k}[c(\delta + d_x\bar{E} + d_E) + d_E(\delta + d_x\bar{E})], \\
\frac{da_4}{dn_k} &= d_E ck\left[(\delta + d_x\bar{E})\frac{d\bar{V}}{dn_k} + d_x\bar{V}\frac{d\bar{E}}{dn_k}\right] < 0, \\
\frac{da_5}{dn_k} &= d_x d_E\frac{d\bar{E}}{dn_k} < 0, \\
\frac{da_6}{dn_k} &= k\bar{T} + n_k k\frac{d\bar{T}}{dn_k} + k\frac{d\bar{V}}{dn_k},
\end{aligned}$$

$$\frac{da_7}{dn_k} = d\left(k\bar{T} + n_k k\frac{d\bar{T}}{dn_k}\right) + ck\frac{d\bar{V}}{dn_k},$$

all evaluated at $n_k = n_k^*$.

4. **Numerical simulations.** In Section 3, we discussed the stability of the two steady states under some conditions. In this section, with different sets of parameter values during primary HIV-1 infection, we explore the vial dynamics with/without virus waning or delays.

The parameter values given in Table 2 are mainly from [5, 24, 30]. In particular,

TABLE 2. Five sets of parameter values used in numerical simulations

Parameter	Data 1	Data 2	Data 3	Data 4	Range	Refs.
s cells ml-day^{-1}	200	65	46	170	0-10^4	[26, 32]
d day^{-1}	0.02	0.0065	0.0046	0.017	0.0001-0.2	[4]
$k \times 10^{-6}$ml viron-day^{-1}	0.36	0.64	4.8	0.63	10^{-8}-0.5	[6, 26]
δ day^{-1}	0.53	0.3	0.1	0.3	0.00019-1.4	[5, 32]
$d_x \times 10^{-4}$ml viron-day^{-1}	8.8	3.7	9.4	1.0	0.0001-4.048	[5, 22]
N viron-cells^{-1}	6167	2374	1261	3360	6.25-23599.9	[5, 32]
c day^{-1}	3	3	3	3	0.081-36	[5, 32]
p day^{-1}	0.4	0.3	0.02	0.09	0.0051-3.912	[5]
d_E day^{-1}	0.41	1.81	0.81	0.45	0.004-8.087	[5]
τ_1	0.4	0.1	0.5	0.1	≤ 1.5	[24]
τ_2	8.5	9.2	16.1	7.0	7-32	[5, 22]

the values of d, k and s are the same as those in Refs. [5, 30]. It is unclear about the precise values of the intracellular time delay τ_1 and the immune delay τ_2. So we assume that $\tau_1 \leq 1.5$ days and $\tau_2 \leq 30$ days according to Refs. [5, 24]. Similarly, we assume that k_1 is equal to k since k is a good approximation of k_1 when both α and τ_1 are small enough.

For the purpose of simulation, we take the initial state with $T_0 = 10^4$ cell/ml, $T^* = 0$ cell/ml, $V = 10^{-6}$ RNA copies/ml, $E_0 = 0$ cell/ml.

First, we study the effect of virus waning in the virus dynamics. Fig. 1 shows the effect for data 1. When n_k equals to 1, the virus curve is almost the same as that when there is no virus waning ($n_k = 0$). But if n_k equals to 10, then the virus curve differs greatly from that with smaller virus waning ($n_k = 1$) and has the first smaller peak value at the infection time 68–72 days. Note that even with the virus waning term, oscillation of virus curve is sustained. Based on data 2, Fig. 2 indicates the same phenomenon for the first peak values at the infection time 37–41 days. But the differences among the virus concentrations become smaller (about 200 ml) after 300 days. Similar observations can be made by using data 3 with $n_k = 0$, 1, 10. Further increasing n_k to 20, we can see that the three curves seem to coincide when the infection time is larger than 150 days, *i.e.*, the effects of the virus waning almost disappear since the infection time is 150 days.

Second, we use data 4 to illustrate how time delays affect the virus dynamics. In the left figure of Fig. 3, we fix the intracellular delay τ_1 to be the best fit value and increase the immune delay τ_2 from the best fit value to 30. We find that, with the virus waning, the immune delay does not affect the magnitude of the viral peak and the time to reach the peak. This is due to the tiny values of the killing rate d_x and the production rate p of immune cells. Around the viral peak, a high

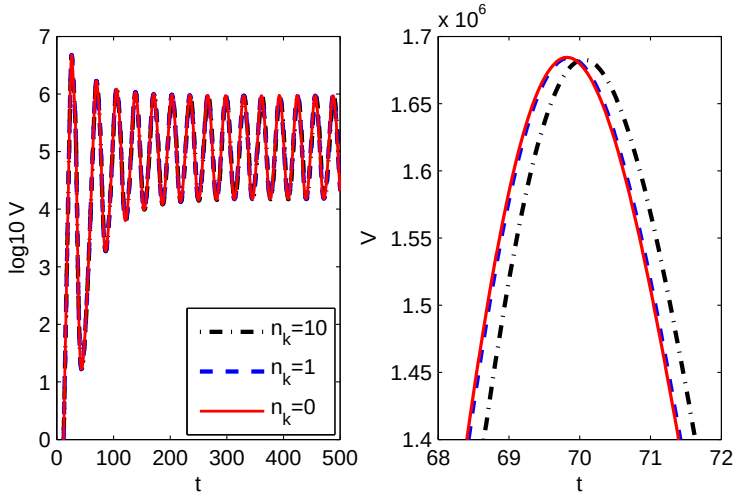

FIGURE 1. The virus curves for data 1 with $n_k = 0$, 1, and 10

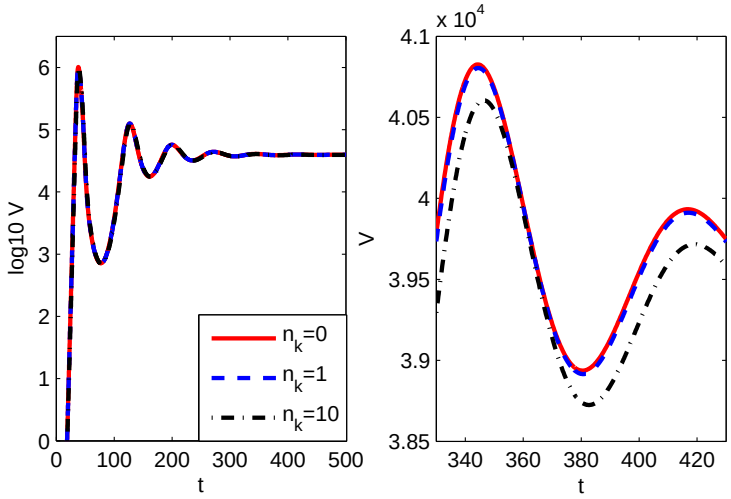

FIGURE 2. The virus curves for data 2 with $n_k = 0$, 1, 10

level of infected cells activates a large number of immune cells which leads to an effective killing of infected cells [22]. When fixing the immune delay and changing the intracellular delay, we obtain that the time to achieve the viral peak is postponed and the magnitude of the viral peak is lowered as the intracellular delay is increased (see the right figure of Fig. 3). This result agrees with that in Pawelek et al. [22] for a delay HIV-1 infection model.

Third, demonstrated by Theorem 3.8, we obtain that the stability of the infected steady state E_1 varies as the immune delay varies. Fig. 4 illustrates that E_1 is locally asymptotically stable, while Fig. 5 displays the asymptotically stable bifurcated periodic solution. Concerning with both the local dynamics near the critical point and the dynamics when the immune delay is far away from the critical point, we obtain the bifurcation diagram for immune delay $\tau_2 \in [0, 30]$ (see Fig. 6).

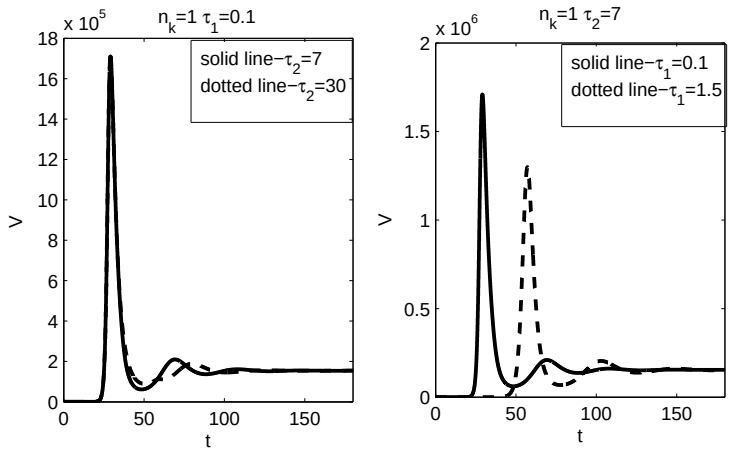

FIGURE 3. The effects of delays on the virus dynamics for data 4

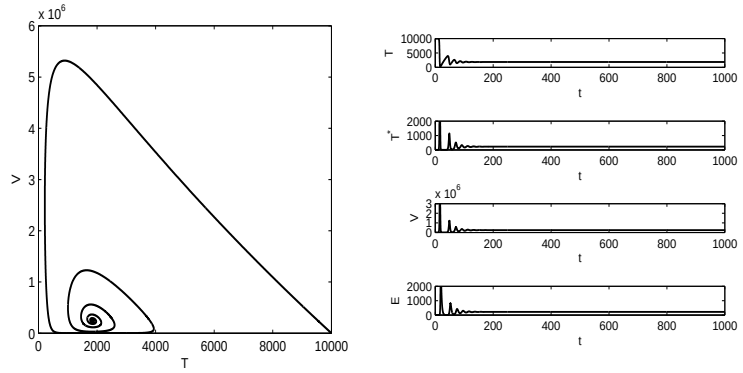

FIGURE 4. Phase portrait of system (1) with $n_k = \tau_1 = 0$ and $\tau_2 = 2.5$ for data 1

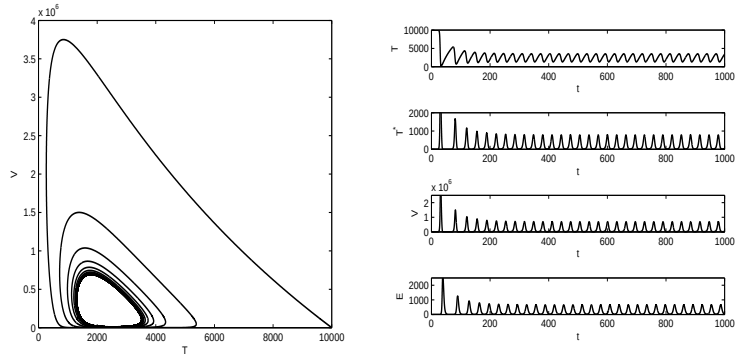

FIGURE 5. Phase portrait of system (1) with $n_k = \tau_1 = 0$ and $\tau_2 = 6.5$ for data 1

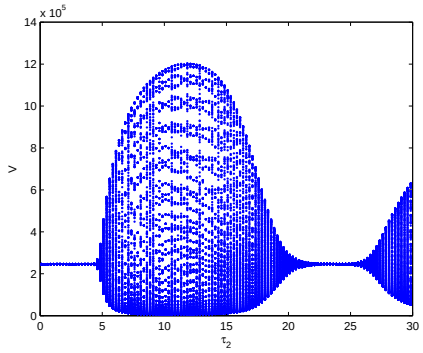

FIG. 6. Bifurcation diagram when $n_k = \tau_1 = 0$ and $\tau_2 \in [0, 30]$ for data 1

Moreover, we consider the combined effects of delays and virus waning, which is demonstrated in Fig. 7. When n_k equals to 1 (see the left figure in Fig. 7), the curve oscillates more severely in the case of delays than in the case of without delays for the infection time less than 300 days. But in the following stage, the two curves seem to coincide and stabilize. The result when n_k equals to 10 is analogous (see the right figure in Fig. 7).

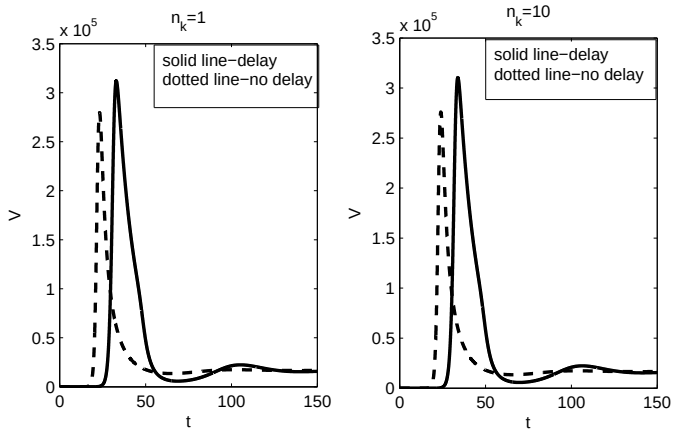

FIG. 7. Virus dynamics for data 3 with/without delays: $n_k = 1$ (left) and $n_k = 10$ (right)

Finally, we pay close attention to the effect of the virus waning term n_k. Since we do not know the exact number of viruses which are needed to contact a healthy $CD4^+$ T cell and make a healthy $CD4^+$ T cell become infective, we limit the range of n_k to $0 - 10$. We also adopt a set of parameter values from ranges of parameter values in Table 2 as follows: $s = 80, d = 0.0002, k = 0.00036, \delta = 0.083, d_x = 0.00088, N = 50, c = 36, p = 0.4, d_E = 0.41$. We take the initial state with $T_0 = 10^3$ cell/ml, $T^* = 1$ cell/ml, $V = 1$ RNA copies/ml, $E_0 = 1$ cell/ml.

Fig. 8 illustrates that the infected steady state is locally asymptotically stable when n_k equals to 10, and when n_k equals to 0 or 1, the solution curve of model (1)

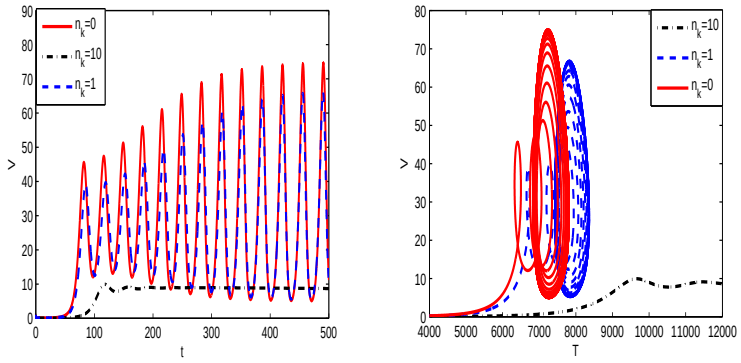

FIGURE 8. Phase portrait of system (1) with $\tau_1 = 0$, $\tau_2 = 6.5$ for $n_k = 0$, 1, 10

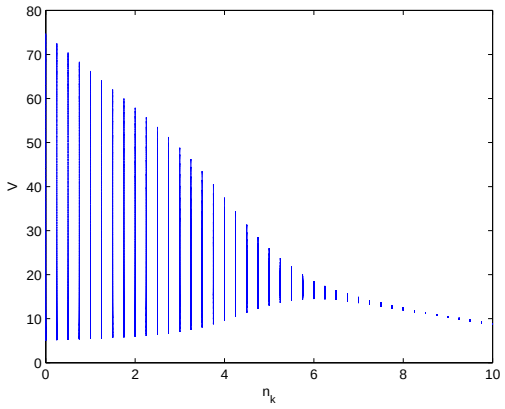

FIG. 9. Bifurcation diagram when $\tau_1 = 0$, $\tau_2 = 6$ and $n_k \in [0, 10]$

approaches a periodic oscillation. Fig. 9 shows the bifurcation diagram for $n_k \in [0, 10]$.

To conclude this section, we mention that the effects of the immune delay and the virus waning on the stability of the infected steady state are contrary. Precisely, the stability of the infected steady state weakens as the immune delay increases while the stability of the infected steady sate strengthens as the virus waning increases (see Fig. 10).

5. **Discussion.** In this paper, we have proposed and analyzed a model for HIV-1 transmission by incorporating two discrete delays, CTL response, and virus waning. The delays represent the times for infected cells to produce viruses after viral entry and for the emergence of $CD8^+$ T cell immune response to control viral replication.

We firstly showed that any solution of the model with the given initial condition is positive and ultimately bounded. Then we obtained the basic reproduction number R_0, an important threshold in disease control. The infection-free steady state is locally and globally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$. This means that if $R_0 < 1$ then the disease cannot outbreak since one infected cell can

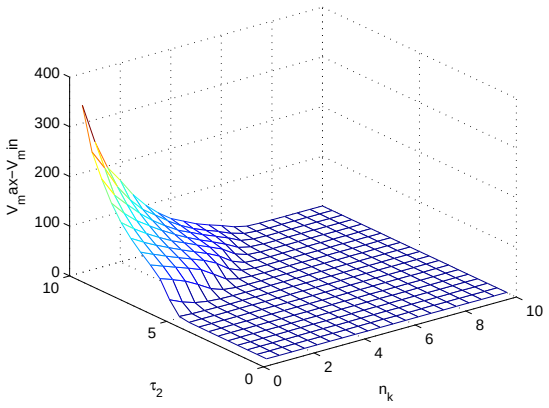

FIG. 10. Virus dynamics when $\tau_1 = 0$, $\tau_2, n_k \in [0, 10]$.

not produce enough infectious virus particles to infect target cells in its lifetime. We also showed that the model is uniformly persistent if $R_0 > 1$ and studied the local stability of the infected steady state under some additional conditions. Finally, we illustrate the effects of delays and virus waning with numerical simulations.

Our numerical results show some interesting dynamics of the model with virus waning. There is little differences between the virus loads when n_k equals 0 and 1, but large difference occurs when n_k is increased to 10. Also increasing n_k will lower the peak value of the virus load. In the initial infection stage, the virus load curve oscillates more severely in the case of delays than in the case of without delays, but then, in the later stage, the difference disappears and the virus loads stabilize at the same level. We also find that the immune delay does not affect the magnitude of the viral peak and the time to reach the peak. But with the intracellular delay increasing, the time to achieve the viral peak is postponed and the magnitude of the viral peak becomes smaller. This may suggest that the effect of the intracellular delay is far more important than that of the immune delay.

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