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Analysis of an HIV-1 Infection Model with Delay Including Quiescent Cells and Cell-to-Cell Transmission

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Abstract: In this paper, we propose a model describing the transmission of HIV-1 infection by cell-free virus and cell-to-cell transfer mode under antiretroviral therapy. The model that we propose is derived from that proposed by Kouche et al. [1]. First, we consider the case without delay and we prove that the basic reproduction number of the model is the sum of the basic reproduction number of cell-free infection and that of cell-to-cell infection. We prove that when the basic reproduction number is less than one, the infection is cleared, and when it is greater than one, the endemic steady state is globally asymptotically stable. In the second part of the paper, we introduce an intracellular delay to take into account the incubation period of the infection. We give a complete stability analysis for both free and endemic steady states. Finally, we illustrate our study by some numerical simulations to evaluate the effects of time delay on the virus dynamics. Our analytical and computational results show that the intracellular delay has no effect on the quiescent cells but reduces the viral load.

Keywords: *HIV-1 infection; cell-to-cell transmission; delay; stability analysis; antiretroviral therapy.*

Mathematics Subject Classification (2020): 92B05, 92B99, 34C23, 93D30, 34D23.

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1 Introduction

In 1984, researchers discovered the primary causative viral agent of AIDS, called the human immunodeficiency virus type 1 (HIV-1). HIV-1 belongs to the family of retroviruses, whose genetic material is RNA. HIV-1 is transmitted by direct inoculation during unsafe sexual contact, transfusion of contaminated blood or blood products, sharing of contaminated needles [2–4].

There are two ways in which viruses move between cells, which are known as cell-free and cell-to-cell infections. In order to eradicate the virus, antiretroviral drug therapy (ART) involves the simultaneous administration of two or more antiviral drugs [5–8].

Recently, some clinical studies conducted *in vivo* showed that infections originating from cell-to-free virus decrease strongly in the presence of certain antiretrovirals, whereas infections involving cell-to-cell spread are markedly less sensitive to the drugs. Different mathematical models have been used to study the dynamics of HIV infection including these two transmission pathways [8].

In a previous paper, Kouche et al. [1] proposed the following model:

$$\begin{cases} \dfrac{dQ(t)}{dt} = \lambda + \rho T(t) - \alpha Q(t) - \mu_Q Q(t), \\ \dfrac{dT(t)}{dt} = \alpha Q(t) - (1-\eta)\gamma T(t) V_I(t) - \rho T(t) - \mu_T T(t), \\ \dfrac{dT^*(t)}{dt} = (1-\eta)\gamma T(t) V_I(t) - \mu_{T^*} T^*(t), \\ \dfrac{dV_I(t)}{dt} = \omega \mu_{T^*} \pi T^*(t) - \mu_V V_I(t), \end{cases} \tag{1}$$

which incorporated a class called quiescent cells Q, which are a class of $CD4^+$ cells of the immune system that cannot be infected by the virus. In this model, it was assumed that the immune system maintains activated the quiescent cells at a rate α and returns to the quiescent state at a rate ρ.

In this paper, our aim is to highlight the combined transmission effect of both cell-free and cell-to-cell virus spreadings through a new model derived from model (1) and including reverse transcriptase inhibitors (RTI) for both transmission pathways. We assume that the transmission spreads from infected cells and free virus to only activated cells through direct contact. Denote by Q the compartment of quiescent cells, T are the healthy activated cells, T^* are the infected cells, V_I is the free infectious virus and V_{NI} is the non infectious virus. Then the model we propose is

$$\begin{cases} \dfrac{dQ(t)}{dt} = \lambda + \rho T(t) - \alpha Q(t) - \mu_Q Q(t), \\ \dfrac{dT(t)}{dt} = \alpha Q(t) - (1-\eta_1)\gamma T(t) V_I(t) - (1-\eta_2)\beta T(t) T^*(t) - \rho T(t) - \mu_T T(t), \\ \dfrac{dT^*(t)}{dt} = (1-\eta_1)\gamma T(t) V_I(t) + (1-\eta_2)\beta T(t) T^*(t) - \mu_{T^*} T^*(t), \\ \dfrac{dV_I(t)}{dt} = \omega \mu_{T^*} \pi T^*(t) - \mu_V V_I(t), \\ \dfrac{dV_{NI}(t)}{dt} = (1-\omega)\mu_{T*} \pi T^*(t) - \mu_V V_{NI}(t), \end{cases} \tag{2}$$

where $t > 0$ is the time. λ is the rate at which new quiescent cells are produced. The death rates of quiescent cells, healthy cells, infected cells and virus are denoted by $\mu_Q, \mu_T, \mu_{T^*}, \mu_V$, respectively. As in model (1), we denote by α the activation rate

of Q cells and by ρ the rate of reversion to the quiescent state. β denotes the rate of transmission of the infection by cell-to-cell mode. π is the number of virions produced per one infected cell.

From a mathematical point of view, the use of RTIs will reduce the force of transmission of infection via cell-free and cell-to-cell channels through the parameters η_1 and η_2 which represent the drug effectiveness for both cell-free and cell-to-cell infections, respectively.

In Section 2, we compute the basic reproduction number R_0 of model (2) and we find that R_0 is the sum of the basic reproduction number R_{01} determined by cell-free virus infection and that determined by cell-to-cell infection R_{02}. Further, the local and global stability analysis of both free and endemic steady states is given in terms of R_0. In Section 3, we introduce a delay τ in model (2), which represents the incubation period of the infection. We give the local and global stability analysis of the delay model for both free and endemic steady states. In Section 4, we give some numerical simulations and determine the region of eradication of the infection with respect to the effectiveness of the RTIs drugs. Our simulation results demonstrate that the delay has no effect on the quiescent cells Q but reduces the peak of the viral load and expands the eradication region of the infection. Further, we find that the cell-to-cell infection is less sensitive to RTI drugs than the cell-free one, which allows us to think that cell-to-cell spread is probably an important factor which leads to therapy failure and contributes to the persistence of the viral load. Finally, we end the paper by a conclusion.

2 The ODE Model

2.1 Local stability of equilibria

Since the four first equations in system (2) do not depend on the last equation, the system can be reduced to the following one:

$$\begin{cases} \dfrac{dQ(t)}{dt} = \lambda + \rho T(t) - \alpha Q(t) - \mu_Q Q(t), \\ \dfrac{dT(t)}{dt} = \alpha Q(t) - (1-\eta_1)\gamma T(t) V_I(t) - \beta(1-\eta_2) T(t) T^*(t) - \rho T(t) - \mu_T T(t), \\ \dfrac{dT^*(t)}{dt} = (1-\eta_1)\gamma T(t) V_I(t) + \beta(1-\eta_2) T(t) T^*(t) - \mu_{T^*} T^*(t), \\ \dfrac{dV_I(t)}{dt} = \omega \mu_{T^*} \pi T^*(t) - \mu_V V_I(t). \end{cases} \tag{3}$$

We can see that system (3) has one free steady state $E_0 = (Q_0, T_0, 0, 0)$ given by

$$Q_0 = \frac{\lambda(\rho + \mu_T)}{\alpha\mu_T + \rho\mu_Q + \mu_Q\mu_T}, \quad T_0 = \frac{\alpha\lambda}{\alpha\mu_T + \rho\mu_Q + \mu_Q\mu_T}.$$

First, we compute the basic reproduction number R_0 of model (3) by using the method of the next-generation matrix [9]. Therefore

$$R_0 = R_{01} + R_{02},$$

where $R_{01} = \frac{\omega\pi(1-\eta_1)\gamma T_0}{\mu_V}$ and $R_{02} = \frac{\beta(1-\eta_2)T_0}{\mu_{T^*}}$ are the basic reproduction numbers corresponding to virus-to-cell infection and cell-to-cell transmission, respectively.

Clearly, if $R_0 > 1$, then system (3) has one positive endemic equilibrium $\overline{E} = \left(\overline{Q}, \overline{T}, \overline{T^*}, \overline{V_I}\right)$ with

$$\begin{aligned}
\overline{Q} &= \frac{\lambda\left(\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*} + \beta(1-\eta_2)\mu_V\right) + \rho\mu_V\mu_{T^*}}{\left(\alpha+\mu_Q\right)\left(\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*} + \beta(1-\eta_2)\mu_V\right)},\\
\overline{T} &= \frac{\mu_V\mu_{T^*}}{\left(\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*} + \beta(1-\eta_2)\mu_V\right)},\\
\overline{T^*} &= \frac{\alpha\lambda}{\mu_{T^*}\left(\alpha+\mu_Q\right)}\left(1-\frac{1}{R_0}\right), \quad \overline{V_I} = \frac{\alpha\lambda\omega\pi}{\mu_V\left(\alpha+\mu_Q\right)}\left(1-\frac{1}{R_0}\right).
\end{aligned}$$

The characteristic equation of system (3) around (Q, T, T^*, V_I) is given by

$$\begin{aligned}
P\left(\zeta\right) = \quad & \left(\zeta+\alpha+\mu_Q\right)\left[\left(\zeta+\left(1-\eta_1\right)\gamma V_I + \beta(1-\eta_2)T^* + \rho + \mu_T\right)\right.\\
& \times\left\{\left(\zeta-\beta(1-\eta_2)T+\mu_{T^*}\right)\left(\zeta+\mu_V\right) - \omega\pi\mu_{T^*}\left(1-\eta_1\right)\gamma T\right\}\\
& +\beta(1-\eta_2)T\left(\zeta+\mu_V\right)\left(\left(1-\eta_1\right)\gamma V_I + \beta(1-\eta_2)T^*\right)\\
& +\omega\pi\mu_{T^*}\left(1-\eta_1\right)\gamma T\left(\left(1-\eta_1\right)\gamma V_I + \beta(1-\eta_2)T^*\right)]\\
& -\alpha\rho\left\{\left(\zeta-\beta(1-\eta_2)T+\mu_{T^*}\right)\left(\zeta+\mu_V\right) - \omega\pi\mu_{T^*}\left(1-\eta_1\right)\gamma T\right\}.
\end{aligned} \tag{4}$$

Theorem 2.1

(i) If $R_0 < 1$, then the free equilibrium E_0 is locally asymptotically stable.

(ii) If $R_0 > 1$, then E_0 is unstable.

Proof. The characteristic polynomial $P\left(\zeta\right)$ at $E_0 = (Q_0, T_0, 0, 0)$ takes the form

$$\begin{aligned}
P\left(\zeta\right) =& \left\{\zeta^2 + \left(\alpha+\mu_Q+\rho+\mu_T\right)\zeta + \alpha\mu_T + \rho\mu_Q + \mu_Q\mu_T\right\}\\
& \times\left\{\zeta^2 + \mu_{T^*}\left(\frac{\mu_V}{\mu_{T^*}} + 1 - \frac{\beta(1-\eta_2)T_0}{\mu_{T^*}}\right)\zeta + \mu_V\mu_{T^*}\left(1-R_0\right)\right\}.
\end{aligned} \tag{5}$$

If $R_0 < 1$, we have $\left(1 - \dfrac{\beta(1-\eta_2)T_0}{\mu_{T^*}}\right) \geq (1-R_0) > 0$. Then all the coefficients of the two polynomials are positive, and by the Routh-Hurwitz theorem, we conclude that all roots of (5) have negative real parts. Hence E_0 is locally asymptotically stable.
If $R_0 > 1$, since

$$P\left(0\right) = \mu_V\mu_{T^*}\left(\left(\alpha+\mu_Q\right)\mu_T + \rho\mu_Q\right)\left(1-R_0\right) < 0,$$

further $P\left(\zeta\right) \to +\infty$ as $\zeta \to +\infty$, by continuity, we conclude that P has at least one positive real root. Thus E_0 is unstable. We now turn to prove the local stability of the endemic equilibrium $\overline{E}$.

Theorem 2.2 *Assume that*

$$(1-\eta_1)\gamma\omega\pi\mu_{T^*} + \beta(1-\eta_2)\mu_V > \beta\mu_{T^*}.$$

Then if $R_0 > 1$, the endemic equilibrium $\overline{E} = \left(\overline{Q}, \overline{T}, \overline{T^*}, \overline{V_I}\right)$ is locally asymptotically stable.

Proof. The characteristic polynomial $P\left(\zeta\right)$ at $\overline{E} = \left(\overline{Q}, \overline{T}, \overline{T}^*, \overline{V_I}\right)$ has the form

$$P\left(\zeta\right) = \zeta^4 + a_1\zeta^3 + a_2\zeta^2 + a_3\zeta + a_4,$$

where

$$
\begin{aligned}
a_1 = \; & \left[\alpha+\mu_Q+\rho+\mu_T+\left(\frac{\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V}{\mu_{T^*}\mu_V\left(\alpha+\mu_Q\right)}\right)\times\right. \\
& \left.\left(1-\frac{1}{R_0}\right)\right]+\left[\left(\mu_{T^*}+\mu_V-\beta\frac{\mu_{T^*}\mu_V}{\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*}+\beta(1-\eta_2)\mu_V}\right)\right], \\
a_2 = \; & \left[\left(\frac{\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V}{\mu_V\mu_{T^*}}\right)\left(1-\frac{1}{R_0}\right)+\mu_T\left(\alpha+\mu_Q\right)+\rho\mu_Q\right] \\
& +\left[\mu_{T^*}+\mu_V-\beta(1-\eta_2)\frac{\mu_{T^*}\mu_V}{\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*}+\beta(1-\eta_2)\mu_V}\right] \\
& \times\left[\alpha+\mu_Q+\rho+\mu_T+\left(\frac{\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V}{\mu_{T^*}\mu_V\left(\alpha+\mu_Q\right)}\right)\right. \\
& \left.\times\left(1-\frac{1}{R_0}\right)+\frac{\alpha\lambda\beta(1-\eta_2)}{\left(\alpha+\mu_Q\right)}\left(1-\frac{1}{R_0}\right)\right], \\
a_3 = \; & \left[\mu_{T^*}+\mu_V-\beta(1-\eta_2)\frac{\mu_{T^*}\mu_V}{\left(1-\eta_1\right)\gamma\omega\pi\mu_{T^*}+\beta(1-\eta_2)\mu_V}\right] \\
& \times\left[\left(\frac{\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V}{\mu_{T^*}\mu_V}\right)\left(1-\frac{1}{R_0}\right)+\mu_T\left(\alpha+\mu_Q\right)+\rho\mu_Q\right] \\
& +\left[\left(\frac{\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V+\alpha^2\lambda\beta(1-\eta_2)+\alpha\lambda\beta(1-\eta_2)\mu_Q}{\left(\alpha+\mu_Q\right)}\right)\times\right. \\
& \left.\left(1-\frac{1}{R_0}\right)\right], \\
a_4 = \; & \left(\alpha\lambda\omega\pi\left(1-\eta_1\right)\gamma\mu_{T^*}+\alpha\lambda\beta(1-\eta_2)\mu_V\right)\left(1-\frac{1}{R_0}\right).
\end{aligned}
$$

We prove that

$$\Delta_i>0, \qquad i=1,2,3,4,$$

where

$$\Delta_1=a_1,\Delta_2=a_1a_2-a_3,\Delta_3=a_3\Delta_2-a_1^2a_4,\Delta_4=a_4\Delta_3.$$

Thus, by the Routh-Hurwicz theorem, $\overline{E}$ is locally asymptotically stable.

2.2 Global dynamics of the model

In this section, we focus our attention on the global stability of both free and endemic steady states of system (3). We first prove the existence of a compact absorbing set for system (3). Define the set

$$G=\left\{(Q,T,T^*,V_I)\in\mathbb{R}_+^4:\,Q+T+T^*\leq\frac{\lambda}{\mu}\,\text{and}\,V_I\leq\frac{\lambda\omega\pi\mu_{T^*}}{\mu\mu_V}\right\},$$

where $\mu=\min\left(\mu_Q,\mu_T,\mu_{T^*}\right)$.

Proposition 2.1 *For any positive solution* $\left(Q\left(t\right),T\left(t\right),T^*\left(t\right),V_I\left(t\right)\right)$ *of system (3), we have*

(i) $\limsup_{t\to+\infty}F\left(t\right)\leq\frac{\lambda}{\mu},\limsup_{t\to+\infty}V_I\left(t\right)\leq\frac{\lambda\omega\pi\mu_{T^*}}{\mu\mu_V}$, *where* $F\left(t\right)=Q\left(t\right)+T\left(t\right)+T^*\left(t\right)$.

(ii) $\liminf_{t\to+\infty} Q(t) \geq m_1$, $\liminf_{t\to+\infty} T(t) \geq m_2$, *where*

$$m_1 = \frac{\lambda}{\alpha+\mu_Q}, \quad m_2 = \frac{\alpha\lambda}{(\alpha+\mu_Q)\left((1-\eta_1)\gamma\dfrac{\lambda\omega\pi\mu_{T^*}}{\mu\mu_V}+\dfrac{\lambda}{\mu}+\rho+\mu_T\right)}.$$

We now turn to prove the global stability of the free steady state E_0.

Theorem 2.3 *If $R_0 < 1$, then the free steady state E_0 is globally asymptotically stable.*

Proof. We first prove that the set

$$B = \left\{(\phi,\psi,\theta,\xi) \in \mathbb{R}^4_+ : \phi \leq Q_0, \psi \leq T_0\right\}$$

is positively invariant for the system (3). Let $(Q(t), T(t), T^*(t), V_I(t))$ be a positive solution of system (3). As we have

$$\begin{aligned} \frac{dQ}{dt} &= \lambda + \rho T - \alpha Q - \mu_Q Q, \\ \frac{dT}{dt} &\leq \alpha Q - \rho T - \mu_T T. \end{aligned}$$

Define the linear cooperative system

$$\begin{aligned} \frac{d\widetilde{Q}}{dt} &= \lambda + \rho\widetilde{T} - \alpha\widetilde{Q} - \mu_Q\widetilde{Q}, \\ \frac{d\widetilde{T}}{dt} &= \alpha\widetilde{Q} - \rho\widetilde{T} - \mu_T\widetilde{T}. \end{aligned} \tag{6}$$

By the comparison principle, we have

$$Q(t) \leq \widetilde{Q}(t), \quad T(t) \leq \widetilde{T}(t) \tag{7}$$

for all $t > 0$. Further, since (6) is cooperative, it follows that $\widetilde{Q}(t) \leq Q_0$ and $\widetilde{T}(t) \leq T_0$ for all solution $(\widetilde{Q}, \widetilde{T})$ of system (6) such that $\widetilde{Q}(0) \leq Q_0$ and $\widetilde{T}(0) \leq T_0$. By inequality (7), we conclude that

$$Q(t) \leq Q_0, \quad T(t) \leq T_0$$

for all $t > 0$ such that $Q(0) \leq Q_0$ and $T(0) \leq T_0$. Define now the function

$$\varpi(t) = T^* + \frac{(1-\eta_1)\gamma}{\mu_V} T_0 V_I.$$

Since $R_0 < 1$, the derivative of ϖ along the trajectories of (3) gives

$$\begin{aligned} \frac{d\varpi}{dt} &= (1-\eta_1)\gamma T V_I + \beta(1-\eta_2)TT^* - \mu_{T^*}T^*(t) + \frac{\omega\pi(1-\eta_1)\gamma\mu_{T^*}}{\mu_V} T_0 T^* \\ &\quad - (1-\eta_1)\gamma T_0 V_I \\ &\leq \beta(1-\eta_2)T_0T^* - \mu_{T^*}T^*(t) + \frac{\omega\pi(1-\eta_1)\gamma\mu_{T^*}}{\mu_V} T_0 T^* \\ &= \mu_{T^*}(R_0-1)T^* < 0, \end{aligned} \tag{8}$$

ϖ is then a Lyapunov function on B. Define now the following set:

$$E = \left\{ (\phi, \psi, \theta, \xi) \in B : \frac{d\varpi}{dt}(\phi, \psi, \theta, \xi) = 0 \right\},$$

and denote by M the largest set in E which is invariant with respect to system (3). It is clear that $(Q_0, T_0, 0, 0) \in M$, and thus M is not empty. Let $(\phi, \psi, \theta, \xi) \in M$ and denote by $(Q(t), T(t), T^*(t), V_I(t))$ the corresponding solution. By the invariance of M, $\frac{d\varpi}{dt} = 0$, and by (8), $T^*(t) = 0$ for all $t > 0$. The fourth equation of (3) implies then that $V_I(t) \to 0$ as $t \to +\infty$ and hence $Q(t) \to Q_0$, $T(t) \to T_0$ as $t \to +\infty$. Now, by the invariance of M, $Q(t) = Q_0$, $T(t) = T_0$. Therefore, $M = \{E_0\}$. Finally, since E_0 is locally asymptotically stable, the LaSalle invariance principle [10] implies that E_0 is globally asymptotically stable. To prove the global stability of the endemic steady state $\overline{E}$, we use the method of the Lyapunov function. To this end, we define

$$\begin{aligned} A &= \alpha Q_0 > 0, \\ B &= \rho \overline{T} \frac{\overline{Q}}{m_1} - \rho m_2 \frac{\overline{Q}}{Q_0} - \alpha m_1 - \mu_T m_2 + \beta(1-\eta_2) M_1 \overline{T} + \mu_T \overline{T} + \frac{\alpha\lambda}{(\alpha+\mu_Q)} + \\ &\quad + \frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma\overline{T}^2}{m_2\mu_V(\alpha+\mu_Q)}, \\ C &= -\frac{\alpha\lambda}{(\alpha+\mu_Q)} - \frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma\overline{T}^2}{m_2\mu_V(\alpha+\mu_Q)} < 0. \end{aligned}$$

Theorem 2.4 *Assume that $R_0 > 1$. Then $\overline{E} = \left(\overline{Q}, \overline{T}, \overline{T^*}, \overline{V_I}\right)$ is globally asymptotically stable if*

$$\frac{-B - \sqrt{B^2 - 4AC}}{2A} \leq R_0 \leq \frac{-B + \sqrt{B^2 - 4AC}}{2A}.$$

Proof. Define the Lyapunov function as

$$\begin{aligned} L = &\left(Q - \overline{Q} - \overline{Q}\ln\frac{Q}{\overline{Q}}\right) + \left(T - \overline{T} - \overline{T}\ln\frac{T}{\overline{T}}\right) \\ &+ \left(T^* - \overline{T^*} - \overline{T}^*\ln\frac{T^*}{\overline{T^*}}\right) + \frac{(1-\eta_1)\gamma}{\mu_V}\overline{T}\left(V_I - \overline{V}_I - \overline{V}_I\ln\frac{V_I}{\overline{V}_I}\right). \end{aligned}$$

It follows from system (3) that

$$\begin{aligned} \dot{L} &= \dot{Q}\left(1 - \frac{\overline{Q}}{Q}\right) + \dot{T}\left(1 - \frac{\overline{T}}{T}\right) + \dot{T^*}\left(1 - \frac{\overline{T}^*}{T^*}\right) + \frac{(1-\eta_1)\gamma}{\mu_V}\overline{T}\dot{V_I}\left(1 - \frac{\overline{V_I}}{V_I}\right) \\ &= (\lambda + \rho T - \alpha Q - \mu_Q Q)\left(1 - \frac{\overline{Q}}{Q}\right) + (\alpha Q - (1-\eta_1)\gamma T V_I - \beta(1-\eta_2)TT^* \\ &\quad -\rho T - \mu_T T)\left(1 - \frac{\overline{T}}{T}\right) + ((1-\eta_1)\gamma T V_I + \beta(1-\eta_2)TT^* - \mu_{T^*}T^*) \\ &\quad \left(1 - \frac{\overline{T^*}}{T^*}\right) + \frac{(1-\eta_1)\gamma}{\mu_V}\overline{T}(\omega\mu_{T^*}\pi T^* - \mu_V V_I)\left(1 - \frac{\overline{V_I}}{V_I}\right), \end{aligned} \tag{9}$$

as

$$\lambda = (\alpha + \mu_Q)\overline{Q} - \rho\overline{T},$$

since $\overline{E}$ is a steady state of system (3) and $\mu_{T^*}\overline{T^*} = \dfrac{\mu_V}{\omega\pi}V_I$, and $\overline{T} = \dfrac{\mu_V\mu_{T^*}}{(1-\eta)\gamma\omega\pi\mu_{T^*}+\mu_V\beta}$, we obtain from the precedent equation that

$$\begin{aligned}\dot{L} &= -(\alpha+\mu_Q)Q\left(1-\frac{\overline{Q}}{Q}\right)^2+\alpha Q\left(2-\frac{\overline{T}}{T}-\frac{T}{\overline{T}}\right)\\ &\quad+\left(\frac{(1-\eta_1)\gamma\omega\pi\mu_{T^*}}{(1-\eta_1)\gamma\omega\pi\mu_{T^*}+\mu_V\beta(1-\eta_2)}-1\right)\mu_{T^*}T^*+(1-\eta_1)\gamma\overline{TV_I}\\ &\quad\left(3-\frac{TV_I\overline{T^*}}{\overline{TV_I}T^*}-\frac{T^*\overline{V_I}}{\overline{T^*}V_I}-\frac{\overline{T}}{T}\right)+\rho\overline{T}\frac{\overline{Q}}{Q}-\rho T\frac{\overline{Q}}{Q}\\ &\quad-\alpha Q+\alpha Q\frac{T}{\overline{T}}-\mu_T T+\beta(1-\eta_2)\overline{T}T^*+\mu_T\overline{T}-\beta(1-\eta_2)T\overline{T^*}+\mu_{T^*}\overline{T^*}\\ &\quad-2(1-\eta_1)\gamma\overline{TV_I}+(1-\eta_1)\gamma\overline{TV_I}\frac{\overline{T}}{T}.\end{aligned}\tag{10}$$

As

$$2-\frac{\overline{T}}{T}-\frac{T}{\overline{T}}\le 0,\quad 3-\frac{TV_I\overline{T^*}}{\overline{TV_I}T^*}-\frac{T^*\overline{V_I}}{\overline{T^*}V_I}-\frac{\overline{T}}{T}\le 0,$$

we obtain

$$\begin{aligned}\dot{L} &\le \rho\overline{T}\frac{\overline{Q}}{Q}-\rho T\frac{\overline{Q}}{Q}-\alpha Q+\alpha Q\frac{T}{\overline{T}}-\mu_T T+\beta(1-\eta_2)\overline{T}T^*+\mu_T\overline{T}\\ &\quad-\beta(1-\eta_2)T\overline{T^*}+\mu_{T^*}\overline{T^*}-2(1-\eta_1)\gamma\overline{TV_I}+(1-\eta_1)\gamma\overline{TV_I}\frac{\overline{T}}{T}.\end{aligned}\tag{11}$$

Let $\epsilon>0$ be chosen later. Proposition 2.1 implies that there is $T_\epsilon>0$ such that

$$\begin{gathered}m_1^\epsilon=m_1-\epsilon\le Q(t)\le Q_0+\epsilon=Q_0^\epsilon,\\ m_2^\epsilon=m_2-\epsilon\le T(t)\le T_0+\epsilon=T_0^\epsilon,\\ T^*(t)\le M_1+\epsilon=M_1^\epsilon,\quad t\ge T_\epsilon.\end{gathered}\tag{12}$$

By (11) and (12), we obtain

$$\begin{aligned}\dot{L} &\le \rho\overline{T}\frac{\overline{Q}}{m_1^\epsilon}-\rho m_2^\epsilon\frac{\overline{Q}}{Q_0^\epsilon}-\alpha m_1^\epsilon+\alpha Q_0^\epsilon\frac{T_0^\epsilon}{\overline{T}}-\mu_T m_2^\epsilon\\ &\quad+\beta(1-\eta_2)M_1^\epsilon\overline{T}+\mu_T\overline{T}+\mu_{T^*}\overline{T^*}+\frac{1}{m_2^\epsilon}(1-\eta_1)\gamma\overline{T}^2\overline{V_I}.\end{aligned}\tag{13}$$

Since $\dfrac{T_0}{\overline{T}}=R_0$ and $(1-\eta_1)\gamma\overline{TV_I}=\dfrac{(1-\eta)\alpha\lambda\omega\pi\gamma}{\mu_V(\alpha+\mu_Q)}\overline{T}\left(1-\dfrac{1}{R_0}\right)$, we can derive from (13) that

$$\begin{aligned}\dot{L} &\le \rho\overline{T}\frac{\overline{Q}}{m_1^\epsilon}-\rho m_2^\epsilon\frac{\overline{Q}}{Q_0^\epsilon}-\alpha m_1^\epsilon+\alpha Q_0^\epsilon\left(R_0+\frac{\epsilon}{\overline{T}}\right)-\mu_T m_2^\epsilon+(1-\eta_2)\beta M_1^\epsilon\overline{T}\\ &\quad+\mu_T\overline{T}+\frac{\alpha\lambda}{(\alpha+\mu_Q)}\left(1-\frac{1}{R_0}\right)+\frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma\overline{T^2}}{m_2^\epsilon\mu_V(\alpha+\mu_Q)}\left(1-\frac{1}{R_0}\right)\\ &\le \tfrac{1}{R_0}\left[\alpha Q_0^\epsilon R_0\left(R_0+\frac{\epsilon}{\overline{T}}\right)+\left(\rho\overline{T}\frac{\overline{Q}}{m_1^\epsilon}-\rho m_2^\epsilon\frac{\overline{Q}}{Q_0^\epsilon}-\alpha m_1^\epsilon-\mu_T m_2^\epsilon+(1-\eta_2)\beta M_1^\epsilon\overline{T}\right.\right.\\ &\quad\left.\left.+\mu_T\overline{T}+\frac{\alpha\lambda}{(\alpha+\mu_Q)}+\frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma\overline{T^2}}{m_2^\epsilon\mu_V(\alpha+\mu_Q)}\right)R_0-\frac{\alpha\lambda}{(\alpha+\mu_Q)}-\frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma\overline{T^2}}{m_2^\epsilon\mu_V(\alpha+\mu_Q)}\right].\end{aligned}$$

By the hypothesis of Theorem 2.4, we have $AR_0^2 + BR_0 + C < 0$. Then we can choose $\epsilon > 0$ small enough so that

$$\dot{L} \leq 0$$

for $t \geq T_\epsilon$. Further, by (10), $\dot{L} = 0$ if and only if $Q = \overline{Q}$, $T = \overline{T}$, $T^* = \overline{T^*}$, $V_I = \overline{V_I}$, the LaSalle invariance principle [10] implies that $\overline{E}$ is globally asymptotically stable.

3 The Delay Model

To take into account the incubation period of the infection, we modify, in this section, the model (3) by introducing a discrete delay τ by assuming that cells become infected τ times after initial infection. To this end, we propose the following system:

$$\begin{cases} \dfrac{dQ(t)}{dt} &= \lambda + \rho T(t) - \alpha Q(t) - \mu_Q Q(t), \\ \dfrac{dT(t)}{dt} &= \alpha Q(t) - (1-\eta_1)\gamma T(t) V_I(t) - \beta(1-\eta_2) T(t) T^*(t) - \rho T(t) - \mu_T T(t), \\ \dfrac{dT^*(t)}{dt} &= e^{-\tau m}(1-\eta_1)\gamma T(t-\tau) V_I(t-\tau) + e^{-\tau m}\beta(1-\eta_2) T(t-\tau) T^*(t-\tau) \\ & \quad -\mu_{T^*} T^*(t), \\ \dfrac{dV_I(t)}{dt} &= \omega \mu_{T^*} \pi T^*(t) - \mu_V V_I(t) \end{cases} \tag{14}$$

with the initial conditions

$$\begin{aligned} &Q(\theta) = \phi_1(\theta), \quad T(\theta) = \phi_2(\theta), \quad T^*(\theta) = \phi_3(\theta), \\ &V_I(\theta) = \phi_4(\theta), \quad \theta \in [-\tau, 0], \end{aligned} \tag{15}$$

where $\phi_i \in C([-\tau, 0], \mathbb{R}_+)$ with $\phi_i(0) > 0$, $i = 1, 2, 3, 4$. It is well known by the theory of functional differential equations [11] that system (14)-(15) has a unique positive solution $(Q(t), T(t), T^*(t), V_I(t))$ defined for all $t > 0$. As in the ODE model, it is easy to see that system (14) has one free steady state $E_0 = (Q_0, T_0, 0, 0)$,

$$Q_0 = \frac{\lambda(\rho + \mu_T)}{\alpha\mu_T + \rho\mu_Q + \mu_Q\mu_T}, \qquad T_0 = \frac{\alpha\lambda}{\alpha\mu_T + \rho\mu_Q + \mu_Q\mu_T}.$$

The basic reproduction number is then given by (see [12])

$$R_0 = \frac{\beta(1-\eta_2)\mu_V e^{-\tau m} + \omega\pi\mu_{T^*}(1-\eta_1)\gamma e^{-m\tau}}{\mu_{T^*}\mu_V} T_0. \tag{16}$$

If $R_0 > 1$, system (14) has the endemic steady state $\overline{E} = \left(\overline{Q}, \overline{T}, \overline{T^*}, \overline{V_I}\right)$ given by

$$\begin{aligned} \overline{Q} &= \frac{\lambda\left(\omega\pi\mu_{T^*}(1-\eta_1)\gamma e^{-\tau m} + \beta(1-\eta_2)\mu_V e^{-\tau m}\right) + \rho\mu_{T^*}\mu_V}{(\alpha+\mu_Q)\left(\omega\pi\mu_{T^*}(1-\eta_1)\gamma e^{-\tau m} + \beta(1-\eta_2)\mu_V e^{-\tau m}\right)}, \\ \overline{T} &= \frac{\mu_{T^*}\mu_V}{\omega\pi\mu_{T^*}(1-\eta_1)\gamma e^{-\tau m} + \beta(1-\eta_2)\mu_V e^{-\tau m}}, \\ \overline{T^*} &= \frac{\alpha\lambda e^{-\tau m}}{\mu_{T^*}(\alpha+\mu_Q)}\left(1 - \frac{1}{R_0}\right), \quad \overline{V_I} = \frac{\alpha\lambda\omega\pi e^{-\tau m}}{\mu_V(\alpha+\mu_Q)}\left(1 - \frac{1}{R_0}\right). \end{aligned} \tag{17}$$

3.1 Local stability of equilibria

3.1.1 Local stability of the free equilibrium

The characteristic equation of system (14) around $E = (Q, T, T^*, V_I)$ is

$$\begin{aligned} P(\zeta) &= [(\zeta+\alpha+\mu_Q)(\zeta+(1-\eta_1)\gamma V_I+\beta(1-\eta_2)T^*+\rho+\mu_T)-\alpha\rho] \\ &\quad \times\left[\left(\zeta-\beta(1-\eta_2)Te^{-\tau m}e^{-\zeta\tau}+\mu_{T^*}\right)(\zeta+\mu_V)-\omega\pi\mu_{T^*}(1-\eta_1)\gamma Te^{-\tau m}e^{-\zeta\tau}\right] \\ &\quad +(\zeta+\alpha+\mu_Q)\left\{\beta(1-\eta_2)T\left((1-\eta_1)\gamma V_I e^{-m\tau}e^{-\zeta\tau}+\beta(1-\eta_2)T^*e^{-\tau m}e^{-\zeta\tau}\right)\right. \\ &\quad \left.(\zeta+\mu_V)+\omega\pi\mu_{T^*}(1-\eta_1)\gamma T\left((1-\eta_1)\gamma V_I e^{-m\tau}e^{-\zeta\tau}+\beta(1-\eta_2)T^*e^{-\tau m}e^{-\zeta\tau}\right)\right\}. \end{aligned} \tag{18}$$

Theorem 3.1 *1. If $R_0 < 1$, the free steady state E_0 is locally asymptotically stable for all $\tau \geq 0$.*

2. If $R_0 > 1$, E_0 is unstable for all $\tau \geq 0$.

Proof. At $E_0 = (Q_0, T_0, 0, 0)$, the characteristic equation (18) takes the form

$$\begin{aligned} P(\zeta) &= \left[\zeta^2+(\alpha+\mu_Q+\rho+\mu_T)\zeta+\alpha\mu_T+\rho\mu_Q+\mu_Q\mu_T\right]\times \\ &\quad \left[\left(\zeta-\beta(1-\eta_2)T_0e^{-\tau m}e^{-\zeta\tau}+\mu_{T^*}\right)(\zeta+\mu_V)-\omega\pi\mu_{T^*}(1-\eta_1)\gamma T_0e^{-\tau m}e^{-\zeta\tau}\right] \\ &= 0. \end{aligned}$$

All the coefficients of the polynomial

$$\zeta^2+(\alpha+\mu_Q+\rho+\mu_T)\zeta+\alpha\mu_T+\rho\mu_Q+\mu_Q\mu_T=0 \tag{19}$$

are positive, then by the Routh-Hurwitz theorem, we conclude that the equation (19) has two roots with negative real parts. The other roots are determined by the solutions of the quadratic polynomial

$$\zeta^2+\mu_{T^*}\left(\frac{\mu_V}{\mu_{T^*}}+1-\frac{\beta(1-\eta_2)\mu_V T_0e^{-\tau m}}{\mu_{T^*}\mu_V}e^{-\zeta\tau}\right)\zeta+\mu_{T^*}\mu_V\left(1-R_0e^{-\zeta\tau}\right)=0. \tag{20}$$

Substituting $\tau = 0$ into equation (20), we obtain

$$\zeta^2+\mu_{T^*}\left(\frac{\mu_V}{\mu_{T^*}}+1-\frac{\beta(1-\eta_2)\mu_V T_0}{\mu_{T^*}\mu_V}\right)\zeta+\mu_{T^*}\mu_V\left(1-R_0\right)=0. \tag{21}$$

If $R_0 < 1$, all the coefficients of equation (21) are positive. Then equation (21) has two roots with negative real parts.

In the case $\tau > 0$, assume that the equation (20) has two purely imaginary roots $\zeta = ix(\tau)$ $(x > 0)$. Separating real and imaginary parts yields

$$\begin{aligned} x\beta(1-\eta_2)T_0e^{-\tau m}\sin(x(\tau)\tau)+\mu_{T^*}\mu_V R_0\cos(x(\tau)\tau) &= \mu_V\mu_{T^*}-x^2, \\ x\beta(1-\eta_2)T_0e^{-\tau m}\cos(x(\tau)\tau)-\mu_{T^*}\mu_V R_0\sin(x(\tau)\tau) &= (\mu_V+\mu_{T^*})x. \end{aligned}$$

Squaring and adding the two equations give

$$x^4+\mu_{T^*}^2\left(\frac{\mu_V^2}{\mu_{T^*}^2}+1-\left(\frac{\beta(1-\eta_2)\mu_V T_0e^{-\tau m}}{\mu_V\mu_{T^*}}\right)^2\right)x^2+\left(\mu_V\mu_{T^*}\right)^2\left(1-R_0^2\right)=0. \tag{22}$$

If $R_0 < 1$, then $1 - \left(\frac{\beta(1-\eta_2)\mu_V T_0 e^{-\tau m}}{\mu_V \mu_{T^*}}\right)^2 > \left(1 - R_0^2\right) > 0$, so equation (22) cannot have positive roots and equation (20) cannot have a purely imaginary root. By the general theory of delay differential equations, all roots of (20) have negative real parts provided that $R_0 < 1$ and E_0 is locally asymptotically stable for $\tau > 0$.

If $R_0 > 1$, let $f(\zeta) = \zeta^2 + \left(\mu_V + \mu_{T^*} - \beta(1-\eta_2)T_0 e^{-\tau m} e^{-\zeta\tau}\right)\zeta + \mu_{T^*}\mu_V\left(1 - R_0 e^{-\zeta\tau}\right)$. Since $f(0) = \mu_{T^*}\mu_V(1 - R_0) < 0$ and $f(\zeta) \to +\infty$ as $\zeta \to +\infty$, by continuity, we conclude that $f(\zeta) = 0$ has at least one positive real root. Thus E_0 is unstable.

3.1.2 Local stability of the endemic equilibrium

We now turn to prove the local stability of the endemic steady state $\overline{E}$. At $\overline{E}$, the characteristic equation (18) of system (14) is reduced to the following form:

$$P(\zeta) + Q(\zeta)e^{-\zeta\tau} = 0, \tag{23}$$

where

$$P(\zeta) = \zeta^4 + a_3\zeta^3 + a_2\zeta^2 + a_1\zeta + a_0, \qquad Q(\zeta) = b_3\zeta^3 + b_2\zeta^2 + b_1\zeta + b_0 \tag{24}$$

with

$$\begin{aligned}
a_3 = {} & \alpha + \mu_Q + \rho + \mu_T + \mu_{T^*} + \mu_V + \frac{\alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}}{\mu_{T^*}\mu_V(\alpha+\mu_Q)}\left(1 - \frac{1}{R_0}\right), \\
a_2 = {} & \frac{\alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}}{\mu_{T^*}\mu_V}\left(1 - \frac{1}{R_0}\right) + (\alpha+\mu_Q)\mu_T + \rho\mu_Q + \mu_{T^*}\mu_V \\
& + \left(\alpha + \mu_Q + \rho + \mu_T + \frac{\alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}}{\mu_{T^*}\mu_V(\alpha+\mu_Q)}\left(1 - \frac{1}{R_0}\right)\right)(\mu_{T^*} + \mu_V), \\
a_1 = {} & \left(\frac{\alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}}{\mu_{T^*}\mu_V}\left(1 - \frac{1}{R_0}\right) + (\alpha+\mu_Q)\mu_T + \rho\mu_Q\right)(\mu_{T^*} + \mu_V) \\
& + (\alpha + \mu_Q + \rho + \mu_T)\mu_{T^*}\mu_V + \frac{\alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}}{(\alpha+\mu_Q)}\left(1 - \frac{1}{R_0}\right), \\
a_0 = {} & \alpha\lambda(\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V)e^{-\tau m}\left(1 - \frac{1}{R_0}\right) \\
& + ((\alpha+\mu_Q)\mu_T + \rho\mu_Q)\mu_{T^*}\mu_V, \\
b_3 = {} & -\frac{\beta(1-\eta_2)\mu_{T^*}\mu_V}{\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V}, \\
b_2 = {} & -\mu_{T^*}\mu_V - \frac{(\alpha+\mu_Q+\rho+\mu_T)\beta(1-\eta_2)\mu_{T^*}\mu_V}{\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V},
\end{aligned} \tag{25}$$

$$\begin{aligned}
b_1 = {} & -(\alpha + \mu_Q + \rho + \mu_T)\mu_{T^*}\mu_V - \frac{((\alpha+\mu_Q)\mu_T + \rho\mu_Q)\beta(1-\eta_2)\mu_{T^*}\mu_V}{\omega\pi(1-\eta_1)\gamma\mu_{T^*} + \beta(1-\eta_2)\mu_V}, \\
b_0 = {} & -((\alpha+\mu_Q)\mu_T + \rho\mu_Q)\mu_{T^*}\mu_V.
\end{aligned} \tag{26}$$

From Theorem 2.2, we know that if $R_0 > 1$ and $\tau = 0$, $\overline{E}$ is locally asymptotically stable. To investigate the stability of equation (23), we will apply the following version of the main theorem of Cooke and Van den Driessche [13].

Proposition 3.1 *Assume that P and Q are analytic functions in the right half-plane $Re(\zeta) > 0$ and satisfy the following conditions:*

1. *$P(\zeta)$ and $Q(\zeta)$ have no common imaginary roots;*
2. *$\overline{P(-iy)} = P(iy)$, $\overline{Q(-iy)} = Q(iy)$ for all $y \in \mathbb{R}$;*

3. $P(0) + Q(0) \neq 0$;

4. $\limsup_{|\zeta| \longrightarrow \infty,\, Re(\zeta) \geq 0} (|Q(\zeta)/P(\zeta)|) < 1$;

5. $F(y) \equiv |P(iy)|^2 - |Q(iy)|^2$ *for the real* y *has at most a finite number of real roots.*

Then the following statements are true:

1. *If the equation* $F(\zeta) = 0$ *has no positive roots, then if (23) is stable at* $\tau = 0$*, it remains stable for all* $\tau \geq 0$*, whereas if it is unstable at* $\tau = 0$*, it remains unstable for all* $\tau \geq 0$.

2. *If the equation* $F(\zeta) = 0$ *has at least one positive root and each root is simple, in this case, as* τ *increases, stability switches may occur. There exists a positive number* τ^* *such that (23) is unstable for all* $\tau > \tau^*$*. As* τ *varies from* 0 *to* τ^**, at most a finite number of stability switches may occur.*

Theorem 3.2 *Under the hypothesis of Theorem 2.2, if* $R_0 > 1$*, the endemic steady state* $\overline{E}$ *is locally asymptotically stable for all* $\tau \geq 0$.

Proof. From Theorem 2.2, we know that if $R_0 > 1$, the infected equilibrium $\overline{E}$ is locally asymptotically stable for $\tau = 0$. To show the stability of the equilibrium $\overline{E}$, we need to analyze the existence of positive roots of the following equation:

$$F(\zeta) = y^8 + A_1 y^6 + A_2 y^4 + A_3 y^2 + A_4, \tag{27}$$

where

$$A_1 = a_3^2 - 2a_2 - b_3^2, \quad A_2 = a_2^2 + 2a_0 - 2a_3 a_1 - b_2^2 + 2b_3 b_1,$$
$$A_3 = a_1^2 - 2a_2 a_0 + 2b_2 b_0 - b_1^2, \quad A_4 = a_0^2 - b_0^2.$$

Clearly, equation (27) has no positive real roots if A_1, A_2, A_3 and A_4 are all positive. The coefficients of $F(\zeta)$ are non-negative. Thus equation (27) has no positive real roots. By Theorem 2.2 and Proposition 3.1, the endemic steady state $\overline{E}$ is locally asymptotically stable for all $\tau \geq 0$.

3.2 Global stability

3.2.1 Global stability of the free equilibrium

In this section, we focus our attention on the global stability of both free and endemic steady states of system (14). Define the set

$$G = \left\{ (Q, T, T^*, V_I) \in \mathbb{R}^4_+ : Q + T + T^* \leq \frac{\lambda e^{-\tau m}}{\mu} \quad \text{and} \quad V_I \leq \frac{\lambda \omega \pi \mu_{T^*} e^{-\tau m}}{\mu \mu_V} \right\},$$

where $\mu = \min(\mu_Q, \mu_T, \mu_{T^*})$. Arguing as in Proposition (2.1), we can prove the following result.

Proposition 3.2 *For any positive solution* $(Q(t), T(t), T^*(t), V_I(t))$ *of system (14), we have the following two assertions:*

1. $\limsup_{t \to +\infty} F(t) \leq M_1, \qquad \limsup_{t \to +\infty} V_I(t) \leq M_2,$

2. $\liminf_{t\to+\infty} Q(t) \geq m_1, \liminf_{t\to+\infty} T(t) \geq m_2$, *where*

$$\begin{array}{l} F(t) = Q(t) + T(t) + e^{m\tau}T^*(t+\tau), M_1 = \frac{\lambda e^{-m\tau}}{\mu}, \\ M_2 = \frac{\lambda\omega\pi\mu_{T^*}e^{-m\tau}}{\mu\mu_V}, m_1 = \frac{\lambda}{\alpha+\mu_Q}, m_2 = \frac{\alpha m_1}{\beta M_1+(1-\eta)\gamma M_2+\rho+\mu_T}. \end{array} \tag{28}$$

We have the following stability result about E_0.

Theorem 3.3 *If $R_0 < 1$, then the free steady state E_0 of system (14) is globally asymptotically stable for all $\tau \geq 0$.*

Proof. Define the set

$$S = \left\{(\phi_1, \phi_2, \phi_3, \phi_4) \in C\left([-\tau, 0], \mathbb{R}^4_+\right) : \phi_1 \leq Q_0,\ \phi_2 \leq T_0\right\},$$

and let $(Q(t), T(t), T^*(t), V_I(t))$ be a positive solution of system (14). By the comparison principle,

$$Q(t) \leq Q_0, \quad T(t) \leq T_0$$

for all $t \geq 0$ such that $Q(0) \leq Q_0$ and $T(0) \leq T_0$. Thus S is a positively invariant set for system (14). Define the following Lyapunov function:

$$\begin{array}{rcl} U(t) & = & T^*(t) + \frac{(1-\eta_1)\gamma e^{-m\tau}}{\mu_V} T_0 V_I(t) \\ & & +(1-\eta_1)\gamma e^{-m\tau}\int_{t-\tau}^{t} T(s)V_I(s)ds + \beta(1-\eta_2)e^{-m\tau}\int_{t-\tau}^{t} T(s)T^*(s)ds. \end{array}$$

The derivatives of $U(t)$ along the trajectories of (14) give, since $R_0 < 1$,

$$\begin{array}{rcl} \frac{dU}{dt}(t) & = & -\mu_{T^*}T^*(t) + \frac{\omega\pi(1-\eta_1)\gamma\mu_{T^*}e^{-m\tau}}{\mu_V} T_0 T^*(t) - (1-\eta_1)\gamma e^{-m\tau} T_0 V_I(t) \\ & & +(1-\eta_1)\gamma e^{-m\tau} T(t) V_I(t) + \beta(1-\eta_2)e^{-m\tau} T(t) T^*(t) \\ & \leq & \beta(1-\eta_2)e^{-m\tau} T_0 T^*(t) + \frac{\omega\pi(1-\eta_1)\gamma\mu_{T^*}e^{-m\tau}}{\mu_V} T_0 T^*(t) - \mu_{T^*} T^*(t) \\ & = & \mu_{T^*}(R_0 - 1) T^*(t) < 0. \end{array} \tag{29}$$

U is then a Lyapunov function. Define now the set

$$E = \left\{(\phi, \psi, \theta, \xi) \in S : \frac{dU}{dt}(\phi, \psi, \theta, \xi) = 0\right\},$$

and denote by M the largest set in E, which is invariant with respect to system (14). It is clear that $(Q_0, T_0, 0, 0) \in M$, M is not empty. Let $(\phi, \psi, \theta, \xi) \in M$ and denote by $(Q(t), T(t), T^*(t), V_I(t))$ the corresponding solution. By the invariance of M, $(Q(t), T(t), T^*(t), V_I(t) \in M$ for all $t > 0$, thus $\frac{dU}{dt} = 0$ and, by (29), $T^*(t) = 0$ for all $t > 0$. The last equation of (14) implies then that $V_I(t) \to 0$ as $t \to +\infty$ and hence $Q(t) \to Q_0$ and $T(t) \to T_0$ as $t \to +\infty$. Now, by the invariance of M, $Q(t) = Q_0$, $T(t) = T_0$ for all $t > 0$. Therefore

$$M = \{E_0 = (Q_0, T_0, 0, 0)\}.$$

Finally, since E_0 is locally asymptotically stable, by the LaSalle invariance principle, E_0 is globally asymptotically stable.

3.2.2 Global stability of the endemic equilibrium

The following theorem assures the global stability of the endemic steady state $\overline{E}$.

Theorem 3.4 *Assume that $R_0 > 1$ and let*

$$\begin{aligned}
A = &\quad \alpha Q_0 > 0,\\
B = &\quad \rho\overline{T}\frac{\overline{Q}}{m_1^\epsilon} - \rho m_2^\epsilon \frac{\overline{Q}}{Q_0^\epsilon} - \alpha m_1^\epsilon - \mu_T m_2^\epsilon + \beta(1-\eta_2)M_1^\epsilon \overline{T}\\
&\quad +\mu_T\overline{T} + \frac{\alpha\lambda}{\alpha+\mu_Q} + \frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_V(\alpha+\mu_Q)} + \frac{\alpha\lambda\beta(1-\eta_2)e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_{T^*}(\alpha+\mu_Q)},\\
C = &\quad -\frac{\alpha\lambda}{\alpha+\mu_Q} - \frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_V(\alpha+\mu_Q)} - \frac{\alpha\lambda\beta(1-\eta_2)e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_{T^*}(\alpha+\mu_Q)} < 0.
\end{aligned}$$

Then if

$$\frac{-B+\sqrt{B^2-4AC}}{2A} \le R_0 \le \frac{-B+\sqrt{B^2-4AC}}{2A},$$

the endemic steady state $\overline{E}$ of system (14) is globally asymptotically stable for all $\tau \ge 0$.

Proof. Define the Lyapunov function L as follows:

$$\begin{aligned}
L(t) =& e^{-m\tau}\left(Q(t)-\overline{Q}-\overline{Q}\ln\frac{Q(t)}{\overline{Q}}\right) + e^{-m\tau}\left(T(t)-\overline{T}-\overline{T}\ln\frac{T(t)}{\overline{T}}\right)\\
&+\left(T^*(t)-\overline{T^*}-\overline{T^*}\ln\frac{T^*(t)}{\overline{T^*}}\right) + \frac{e^{-m\tau}(1-\eta_1)\gamma}{\mu_V}\overline{T}\left(V_I(t)-\overline{V_I}-\overline{V_I}\ln\frac{V_I(t)}{\overline{V_I}}\right)\\
&+(1-\eta_1)\gamma e^{-m\tau}\int_{t-\tau}^{t}\left[T(s)V_I(s)-\overline{TV_I}-\overline{TV_I}\ln\frac{T(s)V_I(s)}{\overline{TV_I}}\right]ds\\
&+\beta(1-\eta_2)e^{-\tau m}\int_{t-\tau}^{t}\left[T(s)T^*(s)-\overline{TT^*}-\overline{TT^*}\ln\frac{T(s)T^*(s)}{\overline{TT^*}}\right].
\end{aligned}$$

Then

$$\begin{aligned}
\frac{dL(t)}{dt} =& e^{-m\tau}(\lambda+\rho T-\alpha Q-\mu_Q Q)\left(1-\frac{\overline{Q}}{Q}\right)\\
&+e^{-m\tau}\left(\alpha Q-(1-\eta_1)\gamma TV_I-\beta(1-\eta_2)TT^*-\rho T-\mu_T T\right)\left(1-\frac{\overline{T}}{T}\right)\\
&+\left((1-\eta_1)\gamma e^{-m\tau}T(t-\tau)V_I(t-\tau)+\beta(1-\eta_2)e^{-\tau m}T(t-\tau)T^*(t-\tau)-\mu_{T^*}T^*\right)\\
&\times\left(1-\frac{\overline{T^*}}{T^*}\right)+\frac{e^{-m\tau}(1-\eta_1)\gamma}{\mu_V}\overline{T}\left(\omega\mu_{T^*}\pi T^*-\mu_V V_I\right)\left(1-\frac{\overline{V_I}}{V_I}\right)\\
&+(1-\eta_1)\gamma e^{-m\tau}\left[TV_I-T(t-\tau)V_I(t-\tau)+\overline{TV_I}\ln\frac{T(t-\tau)V_I(t-\tau)}{TV_I}\right]\\
&+\beta(1-\eta_2)e^{-\tau m}\left[TT^*-T(t-\tau)T^*(t-\tau)+\overline{TT^*}\ln\frac{T(t-\tau)T^*(t-\tau)}{TT^*}\right].
\end{aligned}$$

Now $\lambda = (\alpha+\mu_Q)\overline{Q} - \rho\overline{T}$ and $2-\frac{\overline{T}}{T}-\frac{T}{\overline{T}} \le 0$.

Let $\epsilon > 0$ be chosen later. By Proposition 3.2, there is $T_\epsilon > 0$ such that for all $t > T_\epsilon$ and from the hypotheses of the theorem, $AR_0^2 + BR_0 + C < 0$. We can then choose $\epsilon > 0$

small enough so that

$$\frac{e^{-m\tau}}{R_0}\left[\alpha Q_0^\epsilon R_0\left(R_0+\frac{\epsilon}{\overline{T}}\right)+\left(\rho\overline{T}\frac{\overline{Q}}{m_1^\epsilon}-\rho m_2^\epsilon\frac{\overline{Q}}{Q_0^\epsilon}-\alpha m_1^\epsilon-\mu_T m_2^\epsilon+\beta(1-\eta_2)M_1^\epsilon\overline{T}\right.\right.$$
$$\left.+\mu_T\overline{T}+\frac{\alpha\lambda}{\alpha+\mu_Q}+\frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_V\left(\alpha+\mu_Q\right)}+\frac{\alpha\lambda\beta(1-\eta_2)e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_{T^*}\left(\alpha+\mu_Q\right)}\right)R_0$$
$$\left.-\frac{\alpha\lambda}{\alpha+\mu_Q}-\frac{\alpha\lambda\omega\pi(1-\eta_1)\gamma e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_V\left(\alpha+\mu_Q\right)}-\frac{\alpha\lambda\beta(1-\eta_2)e^{-\tau m}\overline{T}^2}{m_2^\epsilon\mu_{T^*}\left(\alpha+\mu_Q\right)}\right]\leq 0$$

for $t > T_\epsilon$. Further, $\frac{dL(t)}{dt} = 0$ if and only if $Q = \overline{Q}$, $T = \overline{T}$, $T^* = \overline{T^*}$, $V_I = \overline{V_I}$, then by the LaSalle invariance principle, $\overline{E}$ is globally asymptotically stable.

4 Numerical Simulations

In this section, we perform some numerical simulations to illustrate our stability results and to examine the effect of time delay and the efficacy of RTI treatments on the viral load. The parameters of the model are given in Table 1 [1, 14, 15]. We begin first with

Parameters	Meaning	Values
α	Activation rate of Q cells (day^{-1})	0.042
λ	Rate of Q cells production (ml^{-1})	10^4
μ_{T^*}	Death rate of T^* cells (day^{-1})	0.67
π	Number of virions per T^* cell	104
μ_T	Death rate of T cells (day^{-1})	0.12
$\eta_{1,2}$	Efficiency of treatment	$[0, 1]$
γ	Infection rate of cells per virion (mm^{3}day^{-1})	0.05×10^{-3}
β	Infection rate by cell-to-cell transmission	2×10^{-5} (cell day)$^{-1}$
μ_Q	Death rate of Q cells (day^{-1})	0.00014
μ_V	Clearance of free virion (day^{-1})	30
ρ	Rate of reversion to the quiescent state (day^{-1})	0.017
ω	Proportion of non-infectious virions	0.2
τ	Incubation period of the infection	$0.2 - 2$ days
m	Fractional of cells surviving incubation period	0.05 days

Table 1: Parameters and values of model (19)

the non delay case $\tau = 0$. In Figure 1, we have plotted the solutions of system (3) in the case of absence of the treatment, i.e., $\eta_1 = \eta_2 = 0$, which corresponds to the value of the basic reproduction number $R_0 = 5.39 > 1$. Since $\mu_V > \mu_{T^*}$, the condition of Theorem 2.2 is satisfied and the endemic equilibrium E^* is locally asymptotically stable. Under RTI treatment if we increase both the efficacy of the RTI inhibiting the virus-to-cell and cell-to-cell infections to the values $\eta_1 = 0.8$, $\eta_2 = 0.84$ which correspond to the value of the basic reproduction number $R_0 = 0.97 < 1$, then by Theorem 2.1, the free steady state E_0 is locally asymptotically stable and the infection is cleared (see Figure 2). In Figure 3, we have plotted the region (in red) for which $R_0 < 1$, which corresponds to the eradication of the infection. We can observe that the infection is cleared when the

efficacy of the RTI corresponding to the virus-to-cell and cell-to-cell channels is greater than 0.66 and 0.6, respectively.

In the delay case, we consider a different level of therapy intervention with different values of the delay. Since the incubation time of the infection is between 0.5 to 2 days [15], we run our simulations with the following values: $\tau = 0.4,\ 0.8,\ 1.3,\ 1.8$.

Case 1: In the first case, we assume that the effect of drugs efficiency is $\eta_1 = \eta_2 = 0.45$. In Figure 4, we have plotted solutions of system (14) with the following values of the delay: $\tau = 0.2$, $\tau = 0.8$, $\tau = 1.3$, $\tau = 1.8$.

Case 2: In this case, we keep the value of $\eta_1 = 0.45$ fixed and we increase the value of $\eta_2 = 0.8$. The corresponding solutions with different values of the delay are plotted in Figure 5.

Case 3: Here we fix the value of $\eta_2 = 0.45$ and we increase $\eta_1 = 0.8$. The corresponding solutions are plotted in Figure 6.

Case 4: In the last case, we increase the efficiency of RTI treatment for both virus-to-cell and cell-to-cell infections to the values $\eta_1 = \eta_2 = 0.8$. The solutions are plotted in Figure 7.

Numerical simulations show that the increase of the delay time will decrease the peak of viral load and increase the number of activated T-cells. Further, the delay seems to have no effect on the number of quiescent cells. Since the basic reproduction number of the delay model is multiplied by a factor equal to $e^{-m\tau}$ with respect to that of the non delayed model, we conclude that the region of eradication of the infection is more large than that without delay. Figures 5 and 6 show that the increase of efficiency of the RTI treatments for either virus-to-cell or cell-to-cell transmission mode will reduce the viral load and the number of infected cells T^* but is not sufficient to eradicate the infection. In Figure 7, where we have increased the efficiency of treatments for both virus-to-cell and cell-to-cell routes, we observe that the infection is cleared.

In order to quantify infection sensitivity to drugs, we use the transmission index T_x which is defined as the fraction of cells infected in the presence of drugs $T_\eta^*(t)$ divided by the fraction of cells infected in the absence of drugs $T^*(t)$. Thus $T_x = \dfrac{T_\eta^*(t)}{T^*(t)}$.

T_x has two important limiting regimes: $T_x \simeq 0$, which means that few viruses infect each cell, the infection is sensitive to the effect of the drugs, whereas in the case $T_x \simeq 1$, many viruses infect each cell and the infection is insensitive. At the quasi-steady-state assumption (as $t \to +\infty$), we can simplify T_x as $T_x \simeq \dfrac{\overline{T_\eta^*}}{\overline{T^*}}$,

where $\overline{T_\eta^*}$ and $\overline{T^*}$ are, respectively, the steady states of infection cells in the presence and in the absence of drugs. By (17), we have

$$T_x \simeq \frac{\left(1 - \dfrac{1}{R_0(\eta)}\right)}{\left(1 - \dfrac{1}{R_0}\right)}$$

with

$$\begin{aligned} R_0(\eta) &= \frac{(1-\eta_2)\beta\mu_V e^{-\tau m} + \omega\pi\mu_{T^*}(1-\eta_1)\gamma e^{-m\tau}}{\mu_{T^*}\mu_V} T_0, \\ R_0 &= \frac{\beta(1-\eta_2)\mu_V e^{-\tau m} + \omega\pi\mu_{T^*}\gamma e^{-m\tau}}{\mu_{T^*}\mu_V} T_0. \end{aligned} \tag{30}$$

In Figure 8, we have plotted on the right the transmission index T_x with respect to η_2 for different values of η_1 and on the left, we have plotted T_x with respect to η_1 for different values of η_2. We observe that infections originating from cell-free virus decrease strongly in the presence of drugs, whereas the other plot shows that infections involving cell-to-cell spread are markedly less sensitive to the drugs. The simulations in Figure 8 suggested that cell-to-cell infection permits viral replication even under the anti-retroviral therapy. As pointed out in other clinical studies [14], cell-to-cell spread leads to therapy failure and potentially contributes to viral persistence and hence is a barrier to curing HIV infection.

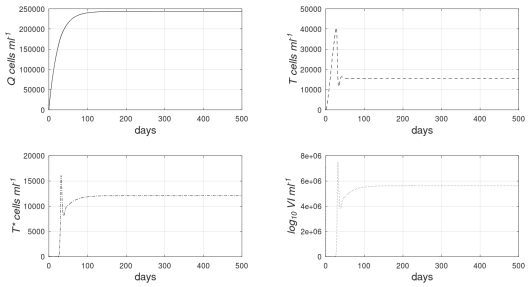

Figure 1: Simulation of solutions of model (3) in the absence of drugs $\eta_1 = \eta_2 = 0$: in this case, $R_0 = 5.36 > 1$, by Theorem 2.2 the endemic steady state E^* is globally stable.

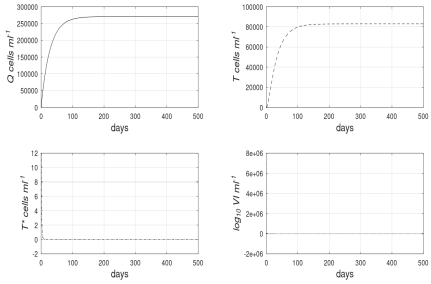

Figure 2: Simulation of solutions of model (3) without delay, where we have taken $\eta_1 = 0.8$ and $\eta_2 = 0.84$: in this case, $R_0 = 0.97 < 1$, by Theorem 2.1, the free steady state E_0 is globally stable and the infection is cleared.

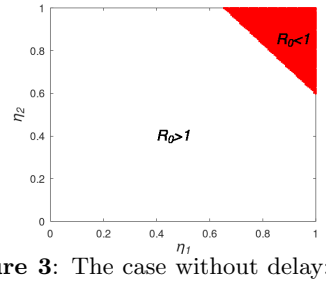

Figure 3: The case without delay: in red is the region of eradication of the infection.

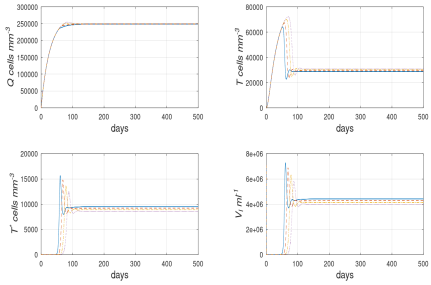

Figure 4: Solutions of system 14 for $\eta_1 = 0.45$, $\eta_2 = 0.45$, $\tau = 0.4$ in solid line (-); $\tau = 0.8$ in dashed line (–); $\tau = 1.3$ in dash-dotted line (-.); $\tau = 1.8$ in dotted line (:).

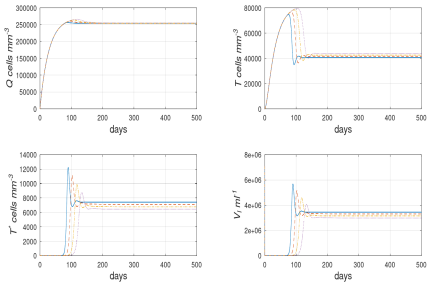

Figure 5: $\eta_1 = 0.45$, $\eta_2 = 0.8$, $\tau = 0.4$ in solid line (-); $\tau = 0.8$ in dashed line (–); $\tau = 1.3$ in dash-dotted line (-.); $\tau = 1.8$ in dotted line (:).

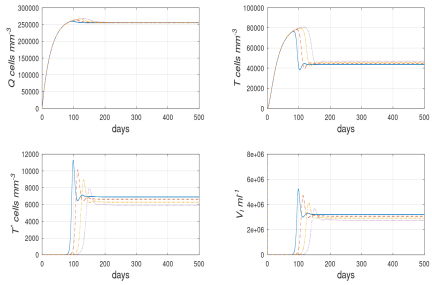

Figure 6: $\eta_1 = 0.8$, $\eta_2 = 0.45$, $\tau = 0.4$ in solid line (-); $\tau = 0.8$ in dashed line (–); $\tau = 1.3$ in dash-dotted line (-.); $\tau = 1.8$ in dotted line (:).

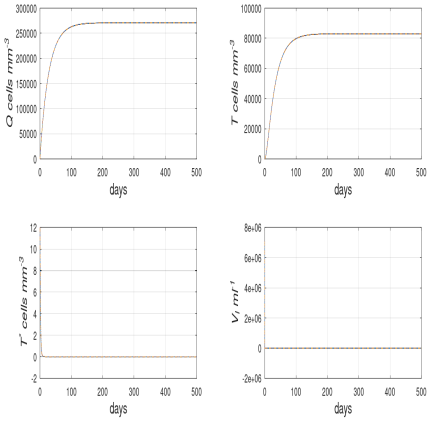

Figure 7: $\eta_1 = 0.8$, $\eta_2 = 0.8$, $\tau = 0.4$ in solid line (-); $\tau = 0.8$ in dashed line (–); $\tau = 1.3$ in dash-dotted line (-.); $\tau = 1.8$ in dotted line (:).

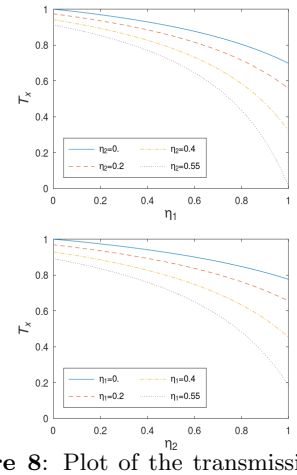

Figure 8: Plot of the transmission index T_x: on the right with respect to η_2 and on the left with respect to η_1, here we have taken $\tau = 2$.

5 Conclusion

This study presents a model incorporating quiescent cells to describe HIV-1 transmission, with an intracellular time delay to account for the role of the non-activated immune system. It demonstrates that the basic reproduction number R_0 is the sum of virus-to-cell and cell-to-cell transmission contributions. The analysis shows that when $R_0 < 1$, the infection is cleared, while for $R_0 > 1$, the endemic steady state is globally asymptotically stable [16].

Numerical simulations indicate that increasing intracellular delay reduces viral load and enhances activated T cells without significantly affecting quiescent cells. Antiretroviral drugs (RTIs) effectively decrease cell-free virus infections but are less effective against cell-to-cell transmission, which can transfer multiple virions simultaneously.

The simulations reveal that improving RTI efficiency to block cell-free infections has

only a limited impact on overall HIV infection. Thus, targeting both transmission pathways, virus-to-cell and cell-to-cell, is crucial. The study suggests that cell-to-cell transmission plays a key role in viral spread and should be a primary focus in future vaccination strategies for better effectiveness.

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