mathematics

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Global Stability Analysis of a Latent HIV Model with Saturated Immunity, Dual General Incidence Rates and Multiple Time Delays

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Abstract

This paper formulates a latent HIV infection model with saturated immunity, two general infection rates (virus-to-cell and cell-to-cell transmission), and three time delays (infected cell activation delay, virus production delay, and immune response delay). The dynamical behaviors and equilibria stability of the model are theoretically analyzed. By constructing appropriate Lyapunov functions, sufficient conditions for the global asymptotic stability of the infection-free, immune-free, and coexistence equilibria are derived. All theoretical results are validated using numerical simulations. The simulation results reveal the difficulty of suppressing HIV infection for cases with a sufficiently large basic reproduction number. For patients with a high basic reproduction number, a single therapeutic strategy that only enhances the reversion rate of latently infected cells may not be effective.

Keywords: HIV model; global stability; time delays; latent; saturated immunity; general incidence rates

MSC: 92D30; 34K20

1. Introduction

Mathematical models serve as powerful tools to reveal the infection dynamics of infectious diseases and clarify their progression mechanisms [1]. They generate quantitative analytical results for research and provide theoretical guidance for clinicians to adjust medication plans tailored to individual patients.

During many viral infections, including human immunodeficiency virus (HIV) infection, a biological process known as the eclipse phase exists. It refers to the period from initial infection to the release of new virions. Many infectious diseases such as HIV infection are notoriously difficult to cure. One plausible reason is that infected $CD4^+$T cells can escape recognition and clearance by cytotoxic T lymphocytes (CTLs) during the eclipse phase. Chun et al. [2] argued that latent infection constitutes the main obstacle to eradicating the virus. After HIV invades resting $CD4^+$T cells, viral RNA may not be completely reverse-transcribed into complementary DNA [3]. Consequently, some latently infected cells can return to an uninfected state before the viral genome integrates into the genome of host lymphocytes [4].

Academic Editor: Snezhana Hristova

Received: 13 May 2026
Revised: 1 June 2026
Accepted: 8 June 2026
Published: 9 June 2026

To characterize these biological processes, a series of dynamical models have been developed in the previous literature. Rong et al. [5] established a four-dimensional model taking the eclipse phase of infected cells into consideration, and Bruno et al. [6] further explored the global stability of this baseline model.

The above classical model adopts the bilinear incidence rate to describe viral transmission [7,8]. In practice, it is hard to identify the true incidence rate for most infectious diseases. In recent years, many researchers have adopted general incidence rates in viral dynamic models [9–11]. Meanwhile, the CTL immune response plays a key role in regulating the pathogenesis of HIV infection. Given the complexity of immune responses, some nonlinear functional forms for immune responses have been proposed and developed. Typical forms include the bilinear term [7,12], the saturated CTL response [13,14], and the generalized form [15,16]. Considering the above factors, Wang et al. [17] constructed a mathematical HIV model with a general infection rate and saturated CTL immune response in 2021.

Cell-to-cell transmission is not taken into account in the above model. Studies [18,19] have demonstrated that $CD4^+T$ cells can be infected via two pathways: virus-to-cell transmission and cell-to-cell transmission. Virus-to-cell transmission describes the process where free HIV virions released from infected cells diffuse in the extracellular environment and then invade susceptible $CD4^+T$ cells. In contrast, cell-to-cell transmission refers to direct viral transmission between infected cells and their adjacent healthy cells, which does not rely on the extracellular environment. In fact, over 50% of HIV infections are established via direct cell-to-cell transmission [19]. Given that cell-to-cell transmission is more efficient than the free virion pathway, some studies have investigated viral infection models with cell-to-cell transmission [10,20].

When mathematically modeling viral infection dynamics, introducing time delays [21–23] is biologically necessary to characterize realistic physiological processes. These delays account for the fact that infected cells require a finite period to generate mature virions and that the immune system needs time for clonal expansion and differentiation. Accordingly, incorporating time delays into viral infection models can improve their biological rationality in describing infection progression and immune regulation.

Motivated by the above discussions, we establish a latent HIV infection model that incorporates saturated immunity, dual general incidence rates and three distinct time delays: infected cell activation delay, virus production delay, and immune response delay. We will study the effects of these delays on the global stability of the equilibria.

The remainder of this paper is organized as follows. Section 2 presents the notations, fundamental hypotheses and model formulation. In Section 3, preliminary results are provided, which mainly include the boundedness of solutions and the basic reproduction number. Section 4 analyzes the existence and uniqueness of all equilibria. In Section 5, we construct appropriate Lyapunov functions to derive sufficient conditions for the global asymptotic stability of the infection-free equilibrium, immune-free equilibrium and coexistence equilibrium. Numerical simulations are performed in Section 6 to verify analytical results. Finally, main results and several open problems are summarized in the last section.

2. Model Formulation

In this section, we first list all notations for state variables and time delays adopted in the whole paper. Then we formulate the improved HIV model. Finally, we present mathematical hypotheses for nonlinear incidence functions required for subsequent theoretical analysis.

2.1. Notations

All biological variables and time delays are defined below:

- $x(t)$: uninfected CD4$^+$T cells;
- $w(t)$: latently infected CD4$^+$T cells in eclipse phase;
- $y(t)$: productively infected CD4$^+$T cells;
- $v(t)$: free HIV virions;
- $z(t)$: cytotoxic T lymphocytes (CTLs);
- τ_1: infected cell activation delay;
- τ_2: virus production delay;
- τ_3: immune response delay.

2.2. Improved Model

We revisit two classical HIV models from existing literature, then establish our novel delayed HIV dynamic model, and present mathematical hypotheses for nonlinear incidence functions.

First, Rong et al. [5] proposed a four-dimensional HIV model considering the eclipse phase:

$$\begin{cases} x' = \lambda - dx - \beta xv + k_1 w, \\ w' = \beta xv - (u_1 + k_1)w, \\ y' = k_2 w - u_2 y, \\ v' = k_3 y - u_3 v, \end{cases} \tag{1}$$

where λ is the production rate of uninfected CD4$^+$T cells; d, u_1, u_2, u_3 represent natural mortality rates of corresponding cells and virions, respectively. β is virus-to-cell infection rate; k_1 denotes the reversion rate of latent infected cells; k_2 and k_3 are cell transition rate and virus production rate, respectively. Bruno et al. [6] completed the global stability analysis for this model.

Further considering generalized incidence and saturated CTLs immunity, Wang et al. [17] constructed the following model:

$$\begin{cases} x' = \lambda - dx - \beta x f(v), \\ y' = \beta x f(v) - u_2 y - pyz, \\ v' = ky - u_3 v, \\ z' = \dfrac{cyz}{1 + \varepsilon z} - u_4 z. \end{cases} \tag{2}$$

Combining dual transmission modes, three biological time delays and latent infection characteristics, we propose the improved HIV model:

$$\begin{cases} x' = \lambda - dx - \beta_1 x f_1(v) - \beta_2 x f_2(y) + k_1 w, \\ w' = \beta_1 x f_1(v) + \beta_2 x f_2(y) - (u_1 + k_1)w, \\ y' = k_2 w(t - \tau_1) - u_2 y - pyz, \\ v' = k_3 y(t - \tau_2) - u_3 v, \\ z' = \dfrac{cy(t - \tau_3)z(t - \tau_3)}{1 + \varepsilon z(t - \tau_3)} - u_4 z, \end{cases} \tag{3}$$

where β_1, β_2 stand for infection rates of two transmission pathways; p is the killing rate of CTLs to infected cells; c is CTLs proliferation rate; ε is immune saturation constant; and u_4 is death rate of CTLs. The meaning of the other parameters is the same as that in model (1).

The nonlinear incidence functions $f_1(v)$ for virus-to-cell transmission and $f_2(y)$ for cell-to-cell transmission are continuously differentiable and satisfy the following hypotheses for all $x \geq 0$:

$$f_i(0) = 0, \quad f_i'(x) > 0, \quad f_i''(x) \leq 0, \quad i = 1, 2.$$

These hypotheses are biologically reasonable. The conditions $f_i(0) = 0$ mean no infection occurs without infectious sources. The conditions $f_i'(x) > 0$ indicate that infection risk rises with the increase of infectious individuals or free viruses. The concave conditions $f_i''(x) \leq 0$ describe the saturation phenomenon of actual infection, which is consistent with real HIV transmission characteristics.

Based on the above concave hypotheses, we derive a critical inequality for later Lyapunov stability analysis:

$$xf_i'(x) \leq f_i(x) \leq xf_i'(0), \quad x \geq 0,\ i = 1, 2.$$

3. Preliminaries

Denote the Banach space of continuous functions $\varphi : [-\tau, 0] \to \mathbb{R}^5$ by C with the norm

$$\|\varphi\| = \sup_{-\tau \leq \theta \leq 0} |\varphi(\theta)|,$$

where $\tau = \max(\tau_1, \tau_2, \tau_3)$. The initial conditions of model (3) are

$$\begin{cases} x(\theta) = \varphi_1(\theta),\ w(\theta) = \varphi_2(\theta),\ y(\theta) = \varphi_3(\theta),\ v(\theta) = \varphi_4(\theta),\ z(\theta) = \varphi_5(\theta), \\ \varphi_i(\theta) \geq 0,\ \theta \in [-\tau, 0],\ \varphi_i(0) > 0 \quad (i = 1, 2, 3, 4, 5), \end{cases}$$

where $\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5 \in C([-\tau, 0], \mathbb{R}_+)$.

Under the hypotheses of model (3), by virtue of the continuity and local Lipschitz continuity of the right-hand side functions, based on the basic theory of functional differential equations (cf. Theorem 2.3 [24]), it follows that model (3) has a unique solution $(x(t), w(t), y(t), v(t), z(t))$.

According to the methods presented in [3], it is easy to obtain the nonnegativity of the solutions. We only focus on proving the boundedness of solutions of model (3). We will give the following basic results of model (3).

3.1. Boundedness of Solutions

Theorem 1. *There is an $M > 0$, for any positive solution $(x(t), w(t), y(t), v(t), z(t))$ of model (3), we have $x(t) < M, w(t) < M,\ y(t) < M,\ v(t) < M,\ z(t) < M$.*

Proof. Define the following function

$$N(t) = x(t) + w(t) + \frac{u_1}{2k_2} y(t + \tau_1) + \frac{u_1 u_2}{4k_2 k_3} v(t + \tau_1 + \tau_2) + \frac{u_1 p}{2k_2 c} z(t + \tau_1 + \tau_3).$$

Calculating the derivative of $N(t)$ along the solutions of model (3) yields

$$\begin{aligned} N'(t) = {} & \lambda - dx(t) - u_1 w(t) \\ & + \frac{u_1}{2k_2}[k_2 w(t) - u_2 y(t + \tau_1) - p y(t + \tau_1) z(t + \tau_1)] \\ & + \frac{u_1 u_2}{4k_2 k_3}[k_3 y(t + \tau_1) - u_3 v(t + \tau_1 + \tau_2)] \\ & + \frac{u_1 p}{2k_2 c}\left[\frac{c y(t + \tau_1) z(t + \tau_1)}{1 + \varepsilon z(t + \tau_1)} - u_4 z(t + \tau_1 + \tau_3)\right] \end{aligned}$$

$$\begin{aligned}
&\leqslant \lambda - d \cdot x(t) - \frac{u_1}{2} \cdot w(t) - \frac{u_2}{2} \cdot \frac{u_1}{2k_2} y(t+\tau_1) \\
&- u_3 \cdot \frac{u_1 u_2}{4k_2 k_3} v(t+\tau_1+\tau_2) - u_4 \cdot \frac{u_1 p}{2k_2 c} z(t+\tau_1+\tau_3) \\
&\leqslant \lambda - \min\left\{d, \frac{u_1}{2}, \frac{u_2}{2}, u_3, u_4\right\} N(t).
\end{aligned}$$

Denote $h = \min\{d, \frac{u_1}{2}, \frac{u_2}{2}, u_3, u_4\}$, we obtain

$$N'(t) \leqslant \lambda - hN(t).$$

Hence, $\lim\limits_{t\to+\infty} \sup N(t) \leqslant \frac{\lambda}{h}$. We conclude all solutions are ultimately bounded. Therefore, there exists an $M > 0$ such that $x(t) < M, w(t) < M, y(t) < M, v(t) < M, z(t) < M$. □

Define the following invariant set for model (3)

$$D = \{(x,\ w,\ y,\ v,\ z) \in R^5_+ |\ \ x(t), w(t), y(t), v(t), z(t) \leqslant M\}.$$

3.2. Calculation of the Basic Reproduction Number

Using the framework of the next generation matrix [25] and the definition of the reproduction number [26], we compute the basic reproduction number of model (3). The corresponding result is stated in the following theorem:

Theorem 2. *The basic reproduction number of model (3) is*

$$R_0 = \frac{k_2 x_0}{(u_1+k_1)u_2 u_3}[\beta_1 k_3 f_1'(0) + \beta_2 u_3 f_2'(0)],$$

where $x_0 = \frac{\lambda}{d}$.

Proof. The basic reproduction number quantifies the average number of new infections generated by a single infected cell in the absence of any pre-existing infections. Obviously, the infection-free equilibrium of model (3) is $Q_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \frac{\lambda}{d}$.

Following the concept of the next generation matrix, the spectral radius of the matrix is

$$R_0 = \rho(FV^{-1}).$$

The nonlinear terms $\mathcal{F}$ and $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{pmatrix} \beta_1 x f_1(v) + \beta_2 x f_2(y) \\ 0 \\ 0 \end{pmatrix}, \mathcal{V} = \begin{pmatrix} (u_1+k_1)w \\ -k_2 w(t-\tau_1) + u_2 y + pyz \\ -k_3 y(t-\tau_2) + u_3 v \end{pmatrix}.$$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at Q_0 are

$$F = \begin{pmatrix} 0 & \beta_2 x_0 f_2'(0) & \beta_1 x_0 f_1'(0) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} u_1+k_1 & 0 & 0 \\ -k_2 & u_2 & 0 \\ 0 & -k_3 & u_3 \end{pmatrix}.$$

The basic reproduction number R_0 can be derived as the spectral radius of FV^{-1}. So,

$$R_0 = \frac{k_2 x_0}{(u_1+k_1)u_2 u_3}[\beta_1 k_3 f_1'(0) + \beta_2 u_3 f_2'(0)].$$

□

Notice that $R_0 = R_v + R_y$, where $R_v = \dfrac{\beta_1 x_0 k_2 k_3 f_1'(0)}{(u_1+k_1)u_2u_3}$, $R_y = \dfrac{\beta_2 x_0 k_2 f_2'(0)}{(u_1+k_1)u_2}$. Obviously, R_v is the contribution of virus-to-cell infection, and R_y accounts for cell-to-cell infection. Consequently, ignoring cell-to-cell spread leads to an underestimate of the basic reproduction number.

4. Existence and Properties of the Equilibria

In this section, we discuss the existence and uniqueness of equilibria of model (3). At any equilibrium, the following equations always hold:

$$\begin{cases} \lambda - dx - \beta_1 x f_1(v) - \beta_2 x f_2(y) + k_1 w = 0, \\ \beta_1 x f_1(v) + \beta_2 x f_2(y) - (u_1+k_1)w = 0, \\ k_2 w - u_2 y - pyz = 0, \\ k_3 y - u_3 v = 0, \\ \dfrac{cyz}{1+\varepsilon z} - u_4 z = 0. \end{cases} \tag{4}$$

(a) If $z = 0$ and $v = 0$,

Notice that $f_1(0) = 0$ and $f_2(0) = 0$. The infection-free equilibrium

$$Q_0 = (x_0, 0, 0, 0, 0) = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right)$$

always exists, which corresponds to virus extinction.

(b) If $z = 0$ and $v \neq 0$,

From the last equation in (4), setting $z = 0$, we derive the immune-free equilibrium $Q_1 = (\bar{x}_1, \bar{w}_1, \bar{y}_1, \bar{v}_1, 0)$. The existence and uniqueness of this equilibrium are given as below.

When $z = 0$, from the third and fourth equations of (4), we obtain

$$y = \frac{u_3}{k_3}v, \quad w = \frac{u_2 y}{k_2} = \frac{u_2 u_3}{k_2 k_3}v.$$

Adding the first and second equations of (4) yields

$$x = \frac{\lambda}{d} - \frac{u_1 w}{d} = \frac{\lambda}{d} - \frac{u_1 u_2 u_3}{d k_2 k_3}v.$$

From the biological perspective, we require $x > 0$, which implies $v < \dfrac{\lambda k_2 k_3}{u_1 u_2 u_3}$. Denote $v^0 = \dfrac{\lambda k_2 k_3}{u_1 u_2 u_3}$.

Substituting the expression of x into the second equation of (4), we introduce the following function:

$$F(v) = \frac{\lambda k_2 k_3}{u_2 u_3} \cdot \frac{G(v)}{d(u_1+k_1) + u_1 G(v)} - v, \tag{5}$$

where $G(v) = \beta_1 f_1(v) + \beta_2 f_2\left(\dfrac{u_3}{k_3}v\right)$. Since $f_i'(x) > 0$ and $f_i''(x) < 0$ $(i = 1, 2)$, we have $F''(v) < 0$. Consequently, $F(v)$ is concave for $0 \leq v \leq v^0$.

Clearly, $F(0) = 0$ and

$$F(v^0) = \frac{\lambda k_2 k_3}{u_1 u_2 u_3} \cdot \frac{-d(u_1 + k_1)}{d(u_1 + k_1) + u_1 G(v^0)} < 0.$$

By the properties of concave functions, the equation $F(v) = 0$ has a unique positive root in $(0, v^0)$ if and only if $F'(0) > 0$.

We have

$$F'(0) = \frac{\lambda k_2}{d(u_1 + k_1)u_2 u_3}\left[\beta_1 k_3 f_1'(0) + \beta_2 u_3 f_2'(0)\right] - 1 = R_0 - 1.$$

Hence, there exists a unique positive root $\bar{v} \in (0, v^0)$ of $F(v) = 0$ when $R_0 > 1$, and thus we obtain the unique immune-free equilibrium $Q_1 = (\bar{x}, \bar{w}, \bar{y}, \bar{v}, 0)$. This implies that the immune response is not activated.

(c) If $z \neq 0$,

Using the fourth equation in (4), we have $y = \frac{u_3}{k_3} v$. Combined with the last equation of (4) and $z \neq 0$, we get

$$z = \frac{cy - u_4}{\varepsilon u_4} = \frac{cu_3 v - k_3 u_4}{\varepsilon k_3 u_4}.$$

From biological considerations, $z > 0$ is required, so $v > \frac{k_3 u_4}{cu_3}$. Denote $v_0 = \frac{k_3 u_4}{cu_3}$.

From the second equation of (4),

$$w = \frac{\beta_1 x f_1(v) + \beta_2 x f_2\left(\frac{u_3}{k_3} v\right)}{u_1 + k_1}.$$

Substituting w into the first equation of (4) leads to

$$x = \frac{\lambda}{d + \frac{u_1}{u_1 + k_1}\left[\beta_1 f_1(v) + \beta_2 f_2\left(\frac{u_3}{k_3} v\right)\right]}.$$

From the third equation of (4), we obtain

$$w = \frac{u_2 y + pyz}{k_2}.$$

Summing the first two equations of (4) gives

$$\lambda - dx = u_1 w = \frac{u_1(u_2 + pz)y}{k_2},$$

and hence

$$x = \frac{\lambda}{d} - \frac{u_1(u_2 + pz)y}{k_2 d}.$$

Construct the following function:

$$S(v) = \frac{\lambda}{d + \frac{u_1}{u_1 + k_1}\left[\beta_1 f_1(v) + \beta_2 f_2\left(\frac{u_3}{k_3} v\right)\right]} - \left[\frac{\lambda}{d} - \frac{u_1 u_2 u_3 v}{d k_2 k_3} - \frac{u_1 p u_3 v}{d k_2 k_3} \cdot \frac{cu_3 v - bk_3}{b\varepsilon k_3}\right].$$

One can show that $S''(v) > 0$ for all $v > 0$ and $S(0) = 0$. Then $S(v) = 0$ admits a unique positive root if and only if $S'(0) < 0$ and $S(v_0) < 0$.

Direct calculation gives

$$S'(0) = \frac{u_1u_2u_3}{dk_2k_3}(1 - R_0) - \frac{u_1pu_3}{dk_2k_3\varepsilon}.$$

Thus $S'(0) < 0$ whenever $R_0 > 1$.
In addition, $S(v_0) < 0$ is equivalent to

$$S(v_0) = \frac{\lambda}{d + \frac{u_1}{u_1+k_1}\left[\beta_1 f_1(v_0) + \beta_2 f_2\left(\frac{u_3}{k_3}v_0\right)\right]} - \frac{\lambda k_2 c - u_1u_2u_4}{dk_2c} < 0,$$

which implies

$$(\lambda k_2 c - u_1u_2u_4)\left[\beta_1 f_1(v_0) + \beta_2 f_2\left(\frac{u_3}{k_3}v_0\right)\right] > (u_1 + k_1)u_2du_4.$$

Using the inequality $f_i(v) \le v f_i'(0)$, we further rewrite the above condition as

$$R_0 > 1 + \frac{u_1u_4}{c(u_1+k_1)u_3d}\left[\beta_1k_3f_1'(0) + \beta_2u_3f_2'(0)\right].$$

Denote

$$R_1 = 1 + \frac{u_1u_4}{c(u_1+k_1)u_3d}\left[\beta_1k_3f_1'(0) + \beta_2u_3f_2'(0)\right].$$

Therefore, when $R_0 > R_1$, there exists a unique positive root $\hat{v}$ of $S(v) = 0$, corresponding to the unique infection-immune coexistence equilibrium $Q_2 = (\hat{x}, \hat{w}, \hat{y}, \hat{v}, \hat{z})$. This means the immune response is successfully triggered.

The above conclusions are formulated into the following theorem:

Theorem 3. *The equilibria of model (3) are summarized below:*
(1) The infection-free equilibrium $Q_0 = (x_0, 0, 0, 0, 0)$ always exists.
(2) The immune-free equilibrium $Q_1 = (\bar{x}, \bar{w}, \bar{y}, \bar{v}, 0)$ exists when $R_0 > 1$.
(3) The infection-immune coexistence equilibrium $Q_2 = (\hat{x}, \hat{w}, \hat{y}, \hat{v}, \hat{z})$ exists when $R_0 > R_1 > 1$.

For convenience of the following discussion, we state a lemma below.

Lemma 1. *If $1 < R_0 < R_1$, then $\bar{y} \le \frac{u_4}{c}$.*

Proof. Let $F(v)$ be the function given by (5). Substitute $v_0 = \frac{k_3u_4}{cu_3}$ into the expression of $F(v)$, then

$$\begin{aligned} F(v_0) &= \frac{\lambda k_2k_3}{u_2u_3} \cdot \frac{G(v_0)}{d(u_1+k_1) + u_1G(v_0)} - v_0 \\ &= \frac{\lambda k_2k_3}{u_2u_3}\left[\frac{G(v_0)}{d(u_1+k_1) + u_1G(v_0)} - \frac{u_2u_4}{\lambda k_2c}\right] \\ &= \frac{k_3}{u_2u_3c\left[d(u_1+k_1) + u_1G(v_0)\right]}\left[(\lambda k_2c - u_1u_2u_4)G(v_0) - d(u_1+k_1)u_2u_4\right] \\ &\le \frac{k_3\left[(\lambda k_2c - u_1u_2u_4)G(v_0) - d(u_1+k_1)u_2u_4\right]}{u_2u_3c\left[d(u_1+k_1) + u_1G(v_0)\right]}. \end{aligned}$$

When $1 < R_0 < R_1$, the inequality

$$(\lambda k_2c - u_1u_2u_4)G(v_0) \le d(u_1+k_1)u_2u_4$$

holds, so $F(v_0) \leq 0$. Combining with the properties of $F(v)$, we conclude $\bar{v} \leq v_0$. Consequently,

$$\bar{y} - \frac{u_4}{c} = \frac{u_3\bar{v}}{k_3} - \frac{u_4}{c} = \frac{cu_3\bar{v} - k_3u_4}{ck_3} \leq \frac{cu_3v_0 - k_3u_4}{ck_3} = 0,$$

which yields $\bar{y} \leq \frac{u_4}{c}$. The proof is complete. □

5. Global Stability of the Equilibria

In this section, we investigate the global stability of the equilibria. For simplicity, we introduce the notation

$$X_{\tau_i} = X(t - \tau_i), \quad X \in \{y, v, z\},\ i = 1, 2, 3,$$

and define the function

$$H(x) = x - 1 - \ln x.$$

Theorem 4. *If $R_0 < 1$, then the infection-free equilibrium $Q_0 = (x_0, 0, 0, 0, 0)$ is globally asymptotically stable for all $\tau_1 \geq 0$, $\tau_2 \geq 0$ and $\tau_3 \geq 0$.*

Proof. We construct the following Lyapunov functional:

$$\begin{aligned} L(t) \quad = \quad & x_0 H\left(\frac{x}{x_0}\right) + \frac{k_1}{2(d+u_1)x_0}\left[(x - x_0) + w\right]^2 + w + \frac{u_1 + k_1}{k_2}y + \frac{\beta_1 x_0 f_1'(0)}{u_3}v \\ & + \frac{(u_1 + k_1)p}{k_2c}z + (u_1 + k_1)\int_0^{\tau_1} w(t - \tau)\,d\tau + \frac{\beta_1 x_0 f_1'(0)}{u_3}k_3\int_0^{\tau_2} y(t - \tau)\,d\tau \\ & + \frac{(u_1 + k_1)p}{k_2}\int_0^{\tau_3} \frac{y(t - \tau)z(t - \tau)}{1 + \varepsilon z(t - \tau)}\,d\tau. \end{aligned}$$

Calculating the derivative of $L(t)$ along the solutions of system (3), we get

$$\begin{aligned} L'(t) = & \frac{x - x_0}{x}\left[\lambda - dx - \beta_1 x f_1(v) - \beta_2 x f_2(y) + k_1 w\right] \\ & + \frac{k_1}{(d+u_1)x_0}\left[(x - x_0) + w\right]\left[\lambda - dx - u_1 w\right] + \left[\beta_1 x f_1(v) + \beta_2 x f_2(y) - (u_1 + k_1)w\right] \\ & + \frac{u_1 + k_1}{k_2}\left[k_2 w_{\tau_1} - u_2 y - pyz\right] + \frac{\beta_1 x_0 f_1'(0)}{u_3}\left[k_3 y_{\tau_2} - u_3 v\right] \\ & + \frac{(u_1 + k_1)p}{k_2}\left[\frac{y_{\tau_3} z_{\tau_3}}{1 + \varepsilon z_{\tau_3}} - \frac{u_4}{c}z\right] + (u_1 + k_1)\left[w - w_{\tau_1}\right] \\ & + \frac{\beta_1 x_0 f_1'(0)}{u_3}k_3\left[y - y_{\tau_2}\right] + \frac{(u_1 + k_1)p}{k_2}\left[\frac{yz}{1 + \varepsilon z} - \frac{y_{\tau_3} z_{\tau_3}}{1 + \varepsilon z_{\tau_3}}\right]. \end{aligned}$$

Note that $\lambda = dx_0$ and

$$\frac{k_1 w(x - x_0)}{x} = -\frac{k_1 w(x - x_0)^2}{xx_0} + \frac{k_1 w(x - x_0)}{x_0}.$$

Substituting this relation yields

$$\begin{aligned} L'(t) \quad = \quad & -\frac{(x - x_0)^2}{xx_0}\left(dx_0 + k_1 w + \frac{dk_1}{d + u_1}x\right) - \frac{k_1 u_1}{(d+u_1)x_0}w^2 + x_0(\beta_1 f_1(v) + \beta_2 f_2(y)) \\ & - \frac{(u_1 + k_1)u_2}{k_2}y - \beta_1 x_0 f_1'(0)v + \frac{\beta_1 x_0 f_1'(0)k_3}{u_3}y - \frac{(u_1 + k_1)pu_4}{k_2c}z - \frac{\varepsilon(u_1 + k_1)pyz^2}{k_2(1 + \varepsilon z)}. \end{aligned}$$

Since $f_1(v) \le v f_1'(0)$ and $f_2(y) \le y f_2'(0)$, we further obtain

$$\begin{aligned} L'(t) \quad \le \quad & -\frac{(x-x_0)^2}{xx_0}\left(dx_0 + k_1 w + \frac{dk_1}{d+u_1}x\right) - \frac{k_1 u_1}{(d+u_1)x_0}w^2 - \beta_1 x_0\left(v f_1'(0) - f_1(v)\right) \\ & -\frac{(u_1+k_1)u_2}{k_2}(1-R_0)y - \frac{(u_1+k_1)pu_4}{k_2 c}z - \frac{\varepsilon(u_1+k_1)pyz^2}{k_2(1+\varepsilon z)}. \end{aligned}$$

From the given hypotheses, we have $v f_1'(0) - f_1(v) \ge 0$. If $R_0 < 1$, then $L'(t) \le 0$, and $L'(t) = 0$ holds if and only if $x = x_0$, $w = 0$, $y = 0$, $z = 0$. From the fourth equation of model (3), the set $\mathbb{M} = \{Q_0\}$ is the largest invariant subset of $L'(t) = 0$. By LaSalle's invariance principle, we conclude that the infection-free equilibrium $Q_0 = (x_0, 0, 0, 0, 0)$ is globally asymptotically stable. This completes the proof. □

Theorem 5. *If $1 < R_0 < R_1$ and $k_1 < \frac{d\bar{x}}{\bar{w}}$, then the immune-free equilibrium $Q_1 = (\bar{x}, \bar{w}, \bar{y}, \bar{v}, 0)$ is globally asymptotically stable for all $\tau_1 \ge 0$, $\tau_2 \ge 0$ and $\tau_3 \ge 0$.*

Proof. Define a Lyapunov functional

$$\begin{aligned} L(t) \quad = \quad & \bar{x}H(\frac{x}{\bar{x}}) + \frac{k_1}{2(d+u_1)\bar{x}}[(x-\bar{x}) + (w-\bar{w})]^2 + \bar{w}H(\frac{w}{\bar{w}}) + \frac{\beta_1\bar{x}f_1(\bar{v}) + \beta_2\bar{x}f_2(\bar{y})}{k_2\bar{w}}\bar{y}H(\frac{y}{\bar{y}}) \\ & + \frac{\beta_1\bar{x}f_1(\bar{v})}{k_3\bar{y}}\bar{v}H(\frac{v}{\bar{v}}) + \frac{(u_1+k_1)p}{k_2 c}z + [\beta_1\bar{x}f_1(\bar{v}) + \beta_2\bar{x}f_2(\bar{y})]\int_0^{\tau_1} H\left(\frac{w(t-\tau)}{\bar{w}}\right)d\tau \\ & + \beta_1\bar{x}f_1(\bar{v})\int_0^{\tau_2} H\left(\frac{y(t-\tau)}{\bar{y}}\right)d\tau + \frac{(u_1+k_1)p}{k_2}\int_0^{\tau_3} H\left(\frac{y(t-\tau)z(t-\tau)}{1+\varepsilon z(t-\tau)}\right)d\tau. \end{aligned}$$

Calculating the derivative of $L(t)$ along the solutions of model (3), we have

$$\begin{aligned} L'(t) = & \left(1-\frac{\bar{x}}{x}\right)[\lambda - dx - \beta_1 x f_1(v) - \beta_2 x f_2(y) + k_1 w] \\ & + \frac{k_1}{(d+u_1)\bar{x}}[(x-\bar{x}) + (w-\bar{w})][\lambda - dx - u_1 w] \\ & + \left(1-\frac{\bar{w}}{w}\right)[\beta_1 x f_1(v) + \beta_2 x f_2(y) - (u_1+k_1)w] \\ & + \frac{\beta_1\bar{x}f_1(\bar{v})}{k_2\bar{w}}\left(1-\frac{\bar{y}}{y}\right)[k_2 w_{\tau_1} - u_2 y - pyz] \\ & + \frac{\beta_2\bar{x}f_2(\bar{y})}{k_2\bar{w}}\left(1-\frac{\bar{y}}{y}\right)[k_2 w_{\tau_1} - u_2 y - pyz] + \frac{\beta_1\bar{x}f_1(\bar{v})}{k_3\bar{y}}\left(1-\frac{\bar{v}}{v}\right)[k_3 y_{\tau_2} - u_3 v] \\ & + \frac{(u_1+k_1)p}{k_2 c}\left[\frac{c y_{\tau_3} z_{\tau_3}}{1+\varepsilon z_{\tau_3}} - u_4 z\right] + [\beta_1\bar{x}f_1(\bar{v}) + \beta_2\bar{x}f_2(\bar{y})]\left[H\left(\frac{w}{\bar{w}}\right) - H\left(\frac{w_{\tau_1}}{\bar{w}}\right)\right] \\ & + \beta_1\bar{x}f_1(\bar{v})\left[H\left(\frac{y}{\bar{y}}\right) - H\left(\frac{y_{\tau_2}}{\bar{y}}\right)\right] + \frac{(u_1+k_1)p}{k_2}\left[\frac{yz}{1+\varepsilon z} - \frac{y_{\tau_3} z_{\tau_3}}{1+\varepsilon z_{\tau_3}}\right]. \end{aligned}$$

At the immune-free equilibrium Q_1, the following relations hold:

$$\begin{aligned} & \lambda = d\bar{x} + \beta_1\bar{x}f_1(\bar{v}) + \beta_2\bar{x}f_2(\bar{y}) - k_1\bar{w}, \\ & \lambda = d\bar{x} + u_1\bar{w}, \\ & u_1 + k_1 = \frac{\beta_1\bar{x}f_1(\bar{v}) + \beta_2\bar{x}f_2(\bar{y})}{\bar{w}}, \\ & u_2 = \frac{k_2\bar{w}}{\bar{y}}, \\ & u_3 = \frac{k_3\bar{y}}{\bar{v}}, \end{aligned}$$

$$k_1(w-\bar{w})\left(1-\frac{\bar{x}}{x}\right)=-\frac{k_1(w-\bar{w})(x-\bar{x})^2}{x\bar{x}}+\frac{k_1(w-\bar{w})(x-\bar{x})}{\bar{x}}.$$

Substituting these into $L'(t)$ and simplifying, we have

$$\begin{aligned}
L'(t) &= -\frac{(x-\bar{x})^2}{x\bar{x}}[d\bar{x}+k_1(w-\bar{w})+\frac{dk_1}{(d+u_1)}x]-\frac{k_1u_1}{(d+u_1)\bar{x}}(w-\bar{w})^2\\
&+\beta_1\bar{x}f_1(\bar{v})[1-\frac{\bar{x}}{x}-\frac{xf_1(v)}{\bar{x}f_1(\bar{v})}+\frac{f_1(v)}{f_1(\bar{v})}]+\beta_2\bar{x}f_2(\bar{y})[1-\frac{\bar{x}}{x}-\frac{xf_2(y)}{\bar{x}f_2(\bar{y})}+\frac{f_2(y)}{f_2(\bar{y})}]\\
&+\beta_1\bar{x}f_1(\bar{v})[1-\frac{w}{\bar{w}}-\frac{\bar{w}xf_1(v)}{w\bar{x}f_1(\bar{v})}+\frac{xf_1(v)}{\bar{x}f_1(\bar{v})}]+\beta_2\bar{x}f_2(\bar{y})[1-\frac{w}{\bar{w}}-\frac{\bar{w}xf_2(y)}{w\bar{x}f_2(\bar{y})}+\frac{xf_2(y)}{\bar{x}f_2(\bar{y})}]\\
&+\beta_1\bar{x}f_1(\bar{v})[1-\frac{y}{\bar{y}}-\frac{w_{\tau_1}\bar{y}}{\bar{w}y}+\frac{w_{\tau_1}}{\bar{w}}]-\beta_1\bar{x}f_1(\bar{v})(y-\bar{y})\frac{pz}{k_2\bar{w}}\\
&+\beta_2\bar{x}f_2(\bar{y})[1-\frac{y}{\bar{y}}-\frac{w_{\tau_1}\bar{y}}{\bar{w}y}+\frac{w_{\tau_1}}{\bar{w}}]-\beta_2\bar{x}f_2(\bar{y})(y-\bar{y})\frac{pz}{k_2\bar{w}}\\
&+\beta_1\bar{x}f_1(\bar{v})[1-\frac{v}{\bar{v}}-\frac{y_{\tau_2}\bar{v}}{\bar{y}v}+\frac{y_{\tau_2}}{\bar{y}}]+\frac{(u_1+k_1)p}{k_2}[\frac{y_{\tau_3}z_{\tau_3}}{1+\varepsilon z_{\tau_3}}-\frac{u_4}{c}z]\\
&+\beta_1\bar{x}f_1(\bar{v})[\frac{w}{\bar{w}}-\frac{w_{\tau_1}}{\bar{w}}-\ln\frac{w}{\bar{w}}+\ln\frac{w_{\tau_1}}{\bar{w}}]+\beta_2\bar{x}f_2(\bar{y})[\frac{w}{\bar{w}}-\frac{w_{\tau_1}}{\bar{w}}-\ln\frac{w}{\bar{w}}+\ln\frac{w_{\tau_1}}{\bar{w}}]\\
&+\beta_1\bar{x}f_1(\bar{v})[\frac{y}{\bar{y}}-\frac{y_{\tau_2}}{\bar{y}}-\ln\frac{y}{\bar{y}}+\ln\frac{y_{\tau_2}}{\bar{y}}]+\frac{(u_1+k_1)p}{k_2}[\frac{yz}{1+\varepsilon z}-\frac{y_{\tau_3}z_{\tau_3}}{1+\varepsilon z_{\tau_3}}].
\end{aligned}$$

Hence, we have

$$\begin{aligned}
L'(t) &= -\frac{(x-\bar{x})^2}{x\bar{x}}\left[(d\bar{x}-k_1\bar{w})+k_1w+\frac{dk_1}{(d+u_1)}x\right]-\frac{k_1u_1}{(d+u_1)\bar{x}}(w-\bar{w})^2\\
&+\beta_1\bar{x}f_1(\bar{v})\left[5-\frac{\bar{x}}{x}-\frac{\bar{w}xf_1(v)}{w\bar{x}f_1(\bar{v})}-\frac{w_{\tau_1}\bar{y}}{\bar{w}y}-\frac{y_{\tau_2}\bar{v}}{\bar{y}v}-\ln\frac{w}{\bar{w}}-\ln\frac{y}{\bar{y}}+\ln\frac{w_{\tau_1}}{\bar{w}}+\ln\frac{y_{\tau_2}}{\bar{y}}-\frac{vf_1(\bar{v})}{\bar{v}f_1(v)}\right]\\
&+\beta_1\bar{x}f_1(\bar{v})\left[-1-\frac{v}{\bar{v}}+\frac{f_1(v)}{f_1(\bar{v})}+\frac{vf_1(\bar{v})}{\bar{v}f_1(v)}\right]\\
&+\beta_2\bar{x}f_2(\bar{y})\left[4-\frac{\bar{x}}{x}-\frac{\bar{w}xf_2(y)}{w\bar{x}f_2(\bar{y})}-\frac{w_{\tau_1}\bar{y}}{\bar{w}y}-\ln\frac{w}{\bar{w}}+\ln\frac{w_{\tau_1}}{\bar{w}}-\frac{yf_2(\bar{y})}{\bar{y}f_2(y)}\right]\\
&+\beta_2\bar{x}f_2(\bar{y})\left[-1-\frac{y}{\bar{y}}+\frac{f_2(y)}{f_2(\bar{y})}+\frac{yf_2(\bar{y})}{\bar{y}f_2(y)}\right]+\frac{(u_1+k_1)p}{k_2}z\left(\bar{y}-\frac{u_4}{c}\right)-\frac{\varepsilon(u_1+k_1)pyz^2}{k_2(1+\varepsilon z)}\\
&= -\frac{(x-\bar{x})^2}{x\bar{x}}\left[(d\bar{x}-k_1\bar{w})+k_1w+\frac{dk_1}{(d+u_1)}x\right]-\frac{k_1u_1}{(d+u_1)\bar{x}}(w-\bar{w})^2\\
&-\beta_1\bar{x}f_1(\bar{v})\left[H\left(\frac{\bar{x}}{x}\right)+H\left(\frac{\bar{w}xf_1(v)}{w\bar{x}f_1(\bar{v})}\right)+H\left(\frac{w_{\tau_1}\bar{y}}{\bar{w}y}\right)+H\left(\frac{y_{\tau_2}\bar{v}}{\bar{y}v}\right)+H\left(\frac{vf_1(\bar{v})}{\bar{v}f_1(v)}\right)\right]\\
&-\beta_1\bar{x}f_1(\bar{v})\left[\frac{f_1(v)}{f_1(\bar{v})}-\frac{v}{\bar{v}}\right]\left[\frac{f_1(\bar{v})}{f_1(v)}-1\right]\\
&-\beta_2\bar{x}f_2(\bar{y})\left[H\left(\frac{\bar{x}}{x}\right)+H\left(\frac{\bar{w}xf_2(y)}{w\bar{x}f_2(\bar{y})}\right)+H\left(\frac{w_{\tau_1}\bar{y}}{\bar{w}y}\right)+H\left(\frac{yf_2(\bar{y})}{\bar{y}f_2(y)}\right)\right]\\
&-\beta_2\bar{x}f_2(\bar{y})\left[\frac{f_2(y)}{f_2(\bar{y})}-\frac{y}{\bar{y}}\right]\left[\frac{f_2(\bar{y})}{f_2(y)}-1\right]\\
&-\frac{\varepsilon(u_1+k_1)pyz^2}{k_2(1+\varepsilon z)}+\frac{(u_1+k_1)p}{k_2}z\left(\bar{y}-\frac{u_4}{c}\right).
\end{aligned}$$

Note that $f_1'(v)\geq 0$, so $f_1(v)$ is increasing with respect to v. In addition, the function $\frac{f_1(v)}{v}$ is decreasing with respect to v. Consequently,

$$\left(\frac{f_1(v)}{f_1(\bar{v})}-\frac{v}{\bar{v}}\right)\left(\frac{f_1(\bar{v})}{f_1(v)}-1\right)\geq 0.$$

The same argument gives

$$\left(\frac{f_2(y)}{f_2(\bar{y})}-\frac{y}{\bar{y}}\right)\left(\frac{f_2(\bar{y})}{f_2(y)}-1\right)\geq 0.$$

By Lemma 1, $\bar{y}<\frac{u_4}{c}$ whenever $1<R_0<R_1$. Thus, if $1<R_0<R_1$ and $k_1<\frac{d\bar{x}}{\bar{w}}$, we obtain $L'(t)\leq 0$. $L'(t)=0$ holds if and only if $x=\bar{x}$, $w=\bar{w}$, $y=\bar{y}$, $v=\bar{v}$ and $z=0$. By LaSalle's invariance principle, we conclude that the immune-free equilibrium $Q_1=(\bar{x},\bar{w},\bar{y},\bar{v},0)$ is globally asymptotically stable. This completes the proof. □

Theorem 6. *If $R_0>R_1>1$, $k_1<\frac{d\hat{x}}{\hat{w}}$ and $\tau_3=0$, then the infection-immune coexistence equilibrium $Q_2=(\hat{x},\hat{w},\hat{y},\hat{v},\hat{z})$ is globally asymptotically stable for all $\tau_1\geq 0,\tau_2\geq 0$.*

Proof. Define a Lyapunov functional

$$\begin{aligned}L(t) &= \hat{x}H(\frac{x}{\hat{x}})+\frac{k_1}{2(d+u_1)\hat{x}}[(x-\hat{x})+(w-\hat{w})]^2+\hat{w}H(\frac{w}{\hat{w}})\\ &+\frac{\beta_1\hat{x}f_1(\hat{v})+\beta_2\hat{x}f_2(\hat{y})}{k_2\hat{w}}\hat{y}H(\frac{y}{\hat{y}})+\frac{\beta_1\hat{x}f_1(\hat{v})}{k_3\hat{y}}\hat{v}H(\frac{v}{\hat{v}})+\frac{(u_1+k_1)(1+\varepsilon\hat{z})p}{k_2c}\hat{z}H(\frac{z}{\hat{z}})\\ &+[\beta_1\hat{x}f_1(\hat{v})+\beta_2\hat{x}f_2(\hat{y})]\int_0^{\tau_1}H\left(\frac{w(t-\tau)}{\hat{w}}\right)d\tau+\beta_1\hat{x}f_1(\hat{v})\int_0^{\tau_2}H\left(\frac{y(t-\tau)}{\hat{y}}\right)d\tau.\end{aligned}$$

Calculating the derivative of $L(t)$ along the solutions of model (3), we have

$$\begin{aligned}L'(t) &= (1-\frac{\hat{x}}{x})[\lambda-dx-\beta_1xf_1(v)-\beta_2xf_2(y)+k_1w]\\ &+\frac{k_1}{(d+u_1)\hat{x}}[(x-\hat{x})+(w-\hat{w})][\lambda-dx-u_1w]\\ &+(1-\frac{\hat{w}}{w})[\beta_1xf_1(v)+\beta_2xf_2(y)-(u_1+k_1)w]\\ &+\frac{\beta_1\hat{x}f_1(\hat{v})}{k_2\hat{w}}(1-\frac{\hat{y}}{y})[k_2w_{\tau_1}-u_2y-pyz]\\ &+\frac{\beta_2\hat{x}f_2(\hat{y})}{k_2\hat{w}}(1-\frac{\hat{y}}{y})[k_2w_{\tau_1}-u_2y-pyz]+\frac{\beta_1\hat{x}f_1(\hat{v})}{k_3\hat{y}}(1-\frac{\hat{v}}{v})[k_3y_{\tau_2}-u_3v]\\ &+\frac{(u_1+k_1)(1+\varepsilon\hat{z})p}{k_2c}(1-\frac{\hat{z}}{z})[\frac{cyz}{1+\varepsilon z}-u_4z]\\ &+[\beta_1\hat{x}f_1(\hat{v})+\beta_2\hat{x}f_2(\hat{y})][H(\frac{w}{\hat{w}})-H(\frac{w_{\tau_1}}{\hat{w}})]+\beta_1\hat{x}f_1(\hat{v})[H(\frac{y}{\hat{y}})-H(\frac{y_{\tau_2}}{\hat{y}})].\end{aligned}$$

At the infection-immune coexistence equilibrium Q_2, we have the following equations

$$\begin{aligned}&\lambda=d\hat{x}+\beta_1\hat{x}f_1(\hat{v})+\beta_2\hat{x}f_2(\hat{y})-k_1\hat{w},\\ &\lambda=d\hat{x}+u_1\hat{w},\\ &u_1+k_1=\frac{\beta_1\hat{x}f_1(\hat{v})+\beta_2\hat{x}f_2(\hat{y})}{\hat{w}},\\ &u_2=\frac{k_2\hat{w}}{\hat{y}}-p\hat{z},\\ &u_3=\frac{k_3\hat{y}}{\hat{v}},\\ &u_4=\frac{c\hat{y}}{1+\varepsilon\hat{z}},\\ &k_1(w-\hat{w})\left(1-\frac{\hat{x}}{x}\right)=-\frac{k_1(w-\hat{w})(x-\hat{x})^2}{x\hat{x}}+\frac{k_1(w-\hat{w})(x-\hat{x})}{\hat{x}}.\end{aligned}$$

Substituting these into $L'(t)$ and simplifying, we have

$$\begin{aligned}
L'(t) &= -\frac{(x-\hat{x})^2}{x\hat{x}}[d\hat{x}+k_1(w-\hat{w})+\frac{dk_1}{(d+u_1)}x]-\frac{k_1u_1}{(d+u_1)\hat{x}}(w-\hat{w})^2\\
&+\beta_1\hat{x}f_1(\hat{v})[1-\frac{\hat{x}}{x}-\frac{xf_1(v)}{\hat{x}f_1(\hat{v})}+\frac{f_1(v)}{f_1(\hat{v})}]+\beta_2\hat{x}f_2(\hat{y})[1-\frac{\hat{x}}{x}-\frac{xf_2(y)}{\hat{x}f_2(\hat{y})}+\frac{f_2(y)}{f_2(\hat{y})}]\\
&+\beta_1\hat{x}f_1(\hat{v})[1-\frac{w}{\hat{w}}-\frac{\hat{w}xf_1(v)}{w\hat{x}f_1(\hat{v})}+\frac{xf_1(v)}{\hat{x}f_1(\hat{v})}]+\beta_2\hat{x}f_2(\hat{y})[1-\frac{w}{\hat{w}}-\frac{\hat{w}xf_2(y)}{w\hat{x}f_2(\hat{y})}+\frac{xf_2(y)}{\hat{x}f_2(\hat{y})}]\\
&+\beta_1\hat{x}f_1(\hat{v})[1-\frac{y}{\hat{y}}-\frac{w_{\tau_1}\hat{y}}{\hat{w}y}+\frac{w_{\tau_1}}{\hat{w}}]-\frac{\beta_1\hat{x}f_1(\hat{v})p}{k_2\hat{w}}(y-\hat{y})(z-\hat{z})\\
&+\beta_2\hat{x}f_2(\hat{y})[1-\frac{y}{\hat{y}}-\frac{w_{\tau_1}\hat{y}}{\hat{w}y}+\frac{w_{\tau_1}}{\hat{w}}]-\frac{\beta_2\hat{x}f_2(\hat{y})p}{k_2\hat{w}}(y-\hat{y})(z-\hat{z})\\
&+\beta_1\hat{x}f_1(\hat{v})[1-\frac{v}{\hat{v}}-\frac{y_{\tau_2}\hat{v}}{\hat{y}v}+\frac{y_{\tau_2}}{\hat{y}}]+\frac{(u_1+k_1)(1+\varepsilon\hat{z})p}{k_2}(z-\hat{z})[\frac{y}{1+\varepsilon z}-\frac{\hat{y}}{1+\varepsilon\hat{z}}]\\
&+\beta_1\hat{x}f_1(\hat{v})[\frac{w}{\hat{w}}-\frac{w_{\tau_1}}{\hat{w}}-\ln\frac{w}{\hat{w}}+\ln\frac{w_{\tau_1}}{\hat{w}}]\\
&+\beta_2\hat{x}f_2(\hat{y})[\frac{w}{\hat{w}}-\frac{w_{\tau_1}}{\hat{w}}-\ln\frac{w}{\hat{w}}+\ln\frac{w_{\tau_1}}{\hat{w}}]\\
&+\beta_1\hat{x}f_1(\hat{v})[\frac{y}{\hat{y}}-\frac{y_{\tau_2}}{\hat{y}}-\ln\frac{y}{\hat{y}}+\ln\frac{y_{\tau_2}}{\hat{y}}].
\end{aligned}$$

Hence, we have

$$\begin{aligned}
L'(t) &= -\frac{(x-\hat{x})^2}{x\hat{x}}[(d\hat{x}-k_1\hat{w})+k_1w+\frac{dk_1}{(d+u_1)}x]-\frac{k_1u_1}{(d+u_1)\hat{x}}(w-\hat{w})^2\\
&+\beta_1\hat{x}f_1(\hat{v})[5-\frac{\hat{x}}{x}-\frac{\hat{w}xf_1(v)}{w\hat{x}f_1(\hat{v})}-\frac{w_{\tau_1}\hat{y}}{\hat{w}y}-\frac{y_{\tau_2}\hat{v}}{\hat{y}v}-\ln\frac{w}{\hat{w}}-\ln\frac{y}{\hat{y}}+\ln\frac{w_{\tau_1}}{\hat{w}}+\ln\frac{y_{\tau_2}}{\hat{y}}\\
&-\frac{vf_1(\hat{v})}{\hat{v}f_1(v)}]+\beta_1\hat{x}f_1(\hat{v})[-1-\frac{v}{\hat{v}}+\frac{f_1(v)}{f_1(\hat{v})}+\frac{vf_1(\hat{v})}{\hat{v}f_1(v)}]\\
&+\beta_2\hat{x}f_2(\hat{y})[4-\frac{\hat{x}}{x}-\frac{\hat{w}xf_2(y)}{w\hat{x}f_2(\hat{y})}-\frac{w_{\tau_1}\hat{y}}{\hat{w}y}-\ln\frac{w}{\hat{w}}+\ln\frac{w_{\tau_1}}{\hat{w}}-\frac{yf_2(\hat{y})}{\hat{y}f_2(y)}]\\
&+\beta_2\hat{x}f_2(\hat{y})[-1-\frac{y}{\hat{y}}+\frac{f_2(y)}{f_2(\hat{y})}+\frac{yf_2(\hat{y})}{\hat{y}f_2(y)}]-\frac{\varepsilon(u_1+k_1)py(z-\hat{z})^2}{k_2(1+\varepsilon z)}\\
&= -\frac{(x-\hat{x})^2}{x\hat{x}}[(d\hat{x}-k_1\hat{w})+k_1w+\frac{dk_1}{(d+u_1)}x]-\frac{k_1u_1}{(d+u_1)\hat{x}}(w-\hat{w})^2\\
&-\beta_1\hat{x}f_1(\hat{v})[H(\frac{\hat{x}}{x})+H(\frac{\hat{w}xf_1(v)}{w\hat{x}f_1(\hat{v})})+H(\frac{w_{\tau_1}\hat{y}}{\hat{w}y})+H(\frac{y_{\tau_2}\hat{v}}{\hat{y}v})+H(\frac{vf_1(\hat{v})}{\hat{v}f_1(v)})]\\
&-\beta_1\hat{x}f_1(\hat{v})[\frac{f_1(v)}{f_1(\hat{v})}-\frac{v}{\hat{v}}][\frac{f_1(\hat{v})}{f_1(v)}-1]\\
&-\beta_2\hat{x}f_2(\hat{y})[H(\frac{\hat{x}}{x})+H(\frac{\hat{w}xf_2(y)}{w\hat{x}f_2(\hat{y})})+H(\frac{w_{\tau_1}\hat{y}}{\hat{w}y})+H(\frac{yf_2(\hat{y})}{\hat{y}f_2(y)})]\\
&-\beta_2\hat{x}f_2(\hat{y})[\frac{f_2(y)}{f_2(\hat{y})}-\frac{y}{\hat{y}}][\frac{f_2(\hat{y})}{f_2(y)}-1]\\
&-\frac{\varepsilon(u_1+k_1)py(z-\hat{z})^2}{k_2(1+\varepsilon z)}.
\end{aligned}$$

Note that $f_1'(v)\geq 0$, so $f_1(v)$ is increasing with respect to v. In addition, the function $\frac{f_1(v)}{v}$ is decreasing with respect to v. Consequently,

$$[\frac{f_1(v)}{f_1(\hat{v})}-\frac{v}{\hat{v}}][\frac{f_1(\hat{v})}{f_1(v)}-1]\geq 0.$$

Similarly,

$$[\frac{f_2(y)}{f_2(\hat{y})} - \frac{y}{\hat{y}}][\frac{f_2(\hat{y})}{f_2(y)} - 1] \geq 0.$$

Hence, when $R_0 > R_1 > 1, k_1 < \frac{d\hat{x}}{\hat{w}}$ and $\tau_3 = 0$, then $L'(t) \leq 0$. $L'(t) = 0$ if and only if $x = \hat{x}, w = \hat{w}, y = \hat{y}, v = \hat{v}, z = \hat{z}$. By LaSalle's invariance principle, the infection-immune coexistence equilibrium $Q_2 = (\hat{x}, \hat{w}, \hat{y}, \hat{v}, \hat{z})$ is globally asymptotically stable. This completes the proof. □

6. Numerical Simulations

In this section, numerical simulations are carried out to validate the previous theoretical results. The saturated incidence functions $f_1(v) = \frac{v}{1+a_1v}$ and $f_2(y) = \frac{y}{1+a_2y}$ satisfying the required assumptions are adopted in model (3). The specific model is presented as follows:

$$\begin{cases} x' = \lambda - dx - \frac{\beta_1 xv}{1+a_1v} - \frac{\beta_2 xy}{1+a_2y} + k_1 w, \\ w' = \frac{\beta_1 xv}{1+a_1v} + \frac{\beta_2 xy}{1+a_2y} - (u_1 + k_1)w, \\ y' = k_2 w(t-\tau_1) - u_2 y - pyz, \\ v' = k_3 y(t-\tau_2) - u_3 v, \\ z' = \frac{cy(t-\tau_3)z(t-\tau_3)}{1+\varepsilon z(t-\tau_3)} - u_4 z. \end{cases} \tag{6}$$

Baseline parameters for numerical simulations are summarized in Table 1, most of which are derived from clinical trial data. We choose β_1 as the varying parameter to examine the basic reproduction number R_0 and verify the theorems in Section 5.

Table 1. Descriptions and values of parameters used for simulations.

Parameters	Descriptions	Values	References
λ	Recruitment rate of uninfected CD4$^+$T cells	10	[10,27]
d	Death rate of uninfected CD4$^+$T cells	0.1	[28,29]
β_1	Infection rate via virus-to-cell transmission	0.001	[11]
β_2	Infection rate via cell-to-cell transmission	0.001	[11]
a_1	Saturation constant for virus-to-cell infection	0.1	[10]
a_2	Saturation constant for cell-to-cell infection	0.2	[10]
k_1	Reversion rate of latently infected cells	0.02	[6]
k_2	Transition rate from latent to productive infection	0.8	[27]
k_3	Viral production rate	2	[28]
p	Killing rate of infected cells by CTLs	0.2	[10]
u_1	Death rate of latently infected cells	0.6	[28]
u_2	Death rate of productively infected cells	2	[28]
u_3	Death rate of free HIV virions	2	[10]
u_4	Death rate of CTLs	1	[29]
c	Proliferation rate of CTLs	0.5	[11]
ε	Saturation constant for CTLs	0.5	[28]
τ_1	Infected cell activation delay	1	Assumed
τ_2	Virus production delay	1	Assumed
τ_3	Immune response delay	1	Assumed

To verify Theorem 4, we choose $\beta_1 = 0.003$. A simple calculation gives $R_0 = 0.266 < 1$. As illustrated in Figure 1a, we conduct numerical simulations to explore how the infected cell activation delay τ_1 affects the dynamics of uninfected cells x, virions v and CTLs z when $\tau_2 = \tau_3 = 1$. Increasing τ_1 reduces the number of uninfected cells and increases the number of virions. All variables quickly reach steady states: the virus is gradually cleared, the immune response cannot be activated, and the infection-free equilibrium is

stable. Similar behaviors are observed in Figure 1b, where we vary the virus production delay τ_2 and set $\tau_1 = \tau_3 = 1$. Interestingly, in Figure 1c with $\tau_1 = \tau_2 = 1$, we adopt the immune response delay τ_3 as the parameter. Compared with Figure 1a,b, the parameter τ_3 has little effect on the dynamics of uninfected cells x and virions v in Figure 1c. As shown in Figure 1, when $R_0 = 0.266 < 1$, the infection-free equilibrium $Q_0 = (100, 0, 0, 0, 0)$ is globally asymptotically stable for all time delays. The virus is eventually eliminated, and the disease vanishes.

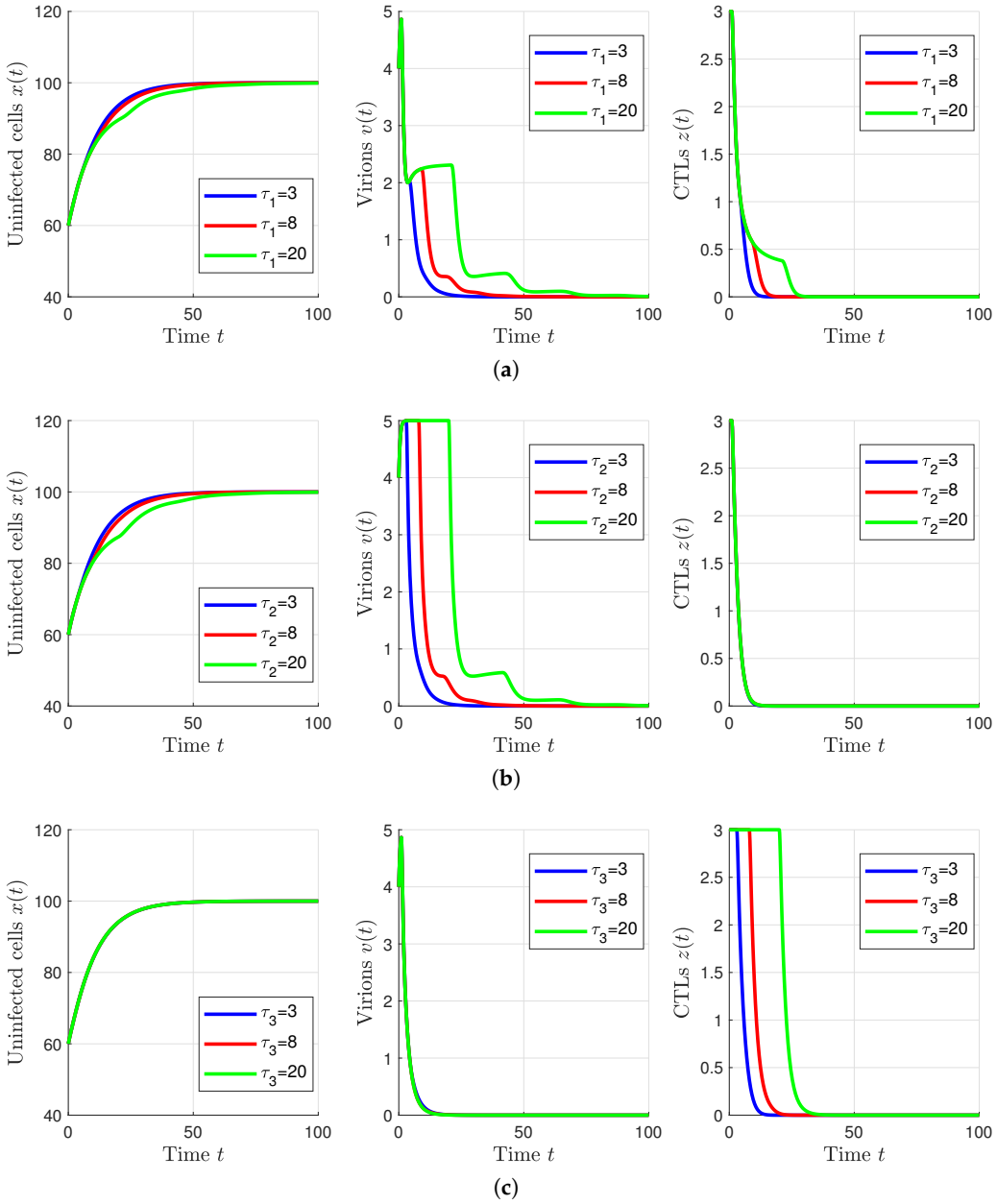

Figure 1. When the basic reproduction number $R_0 = 0.266 < 1$, the infection-free equilibrium Q_0 is globally asymptotically stable for all time delays. The virus will eventually die out, and the disease will disappear. (**a**) The effect of the infected cell activation delay τ_1 on dynamics of x, v and z when $\beta_1 = 0.003$. (**b**) The effect of the virus production delay τ_2 on dynamics of x, v and z when $\beta_1 = 0.003$. (**c**) The effect of the immune response delay τ_3 on dynamics of x, v and z when $\beta_1 = 0.003$.

To verify the stability of the immune-free equilibrium in Theorem 5, we keep other parameters unchanged as shown in Table 1 and take $\beta_1 = 0.02$. The corresponding calculations yield $R_0 = 1.3977$, $R_1 = 1.4193$, $k_1 = 0.02$, $\frac{d\bar{x}}{\bar{w}} = 2.5577$. All conditions specified in

Theorem 5 are met. Similar to Figure 1, we carry out numerical simulations to examine the impacts of time delays on the dynamics of uninfected cells x, virions v and CTLs z. As presented in Figure 2, the immune-free equilibrium $Q_1 = (81.0019, 3.1670, 1.2657, 1.2647, 0)$ is globally asymptotically stable for all time delays. The immune response becomes exhausted and fails to activate, resulting in persistent infection.

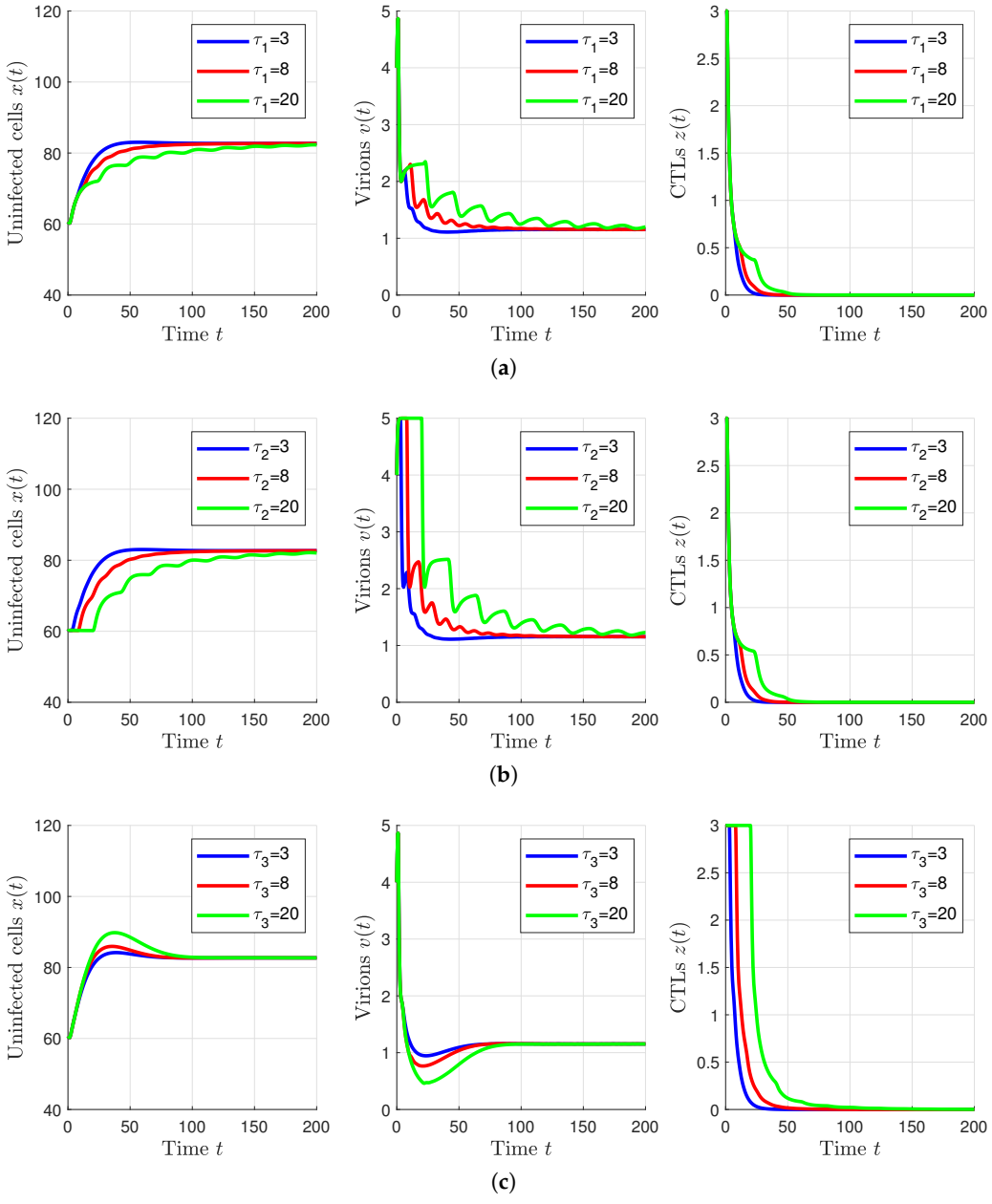

Figure 2. When the basic reproduction number satisfies $1 < R_0 = 1.3977 < R_1 = 1.4193$ and the corresponding condition in Theorem 5 holds, the immune-free equilibrium Q_1 is globally asymptotically stable for all time delays. The immune response is exhausted and cannot be activated, leading to persistent infection. (**a**) The effect of the infected cell activation delay τ_1 on dynamics of x, v and z when $\beta_1 = 0.02$. (**b**) The effect of the virus production delay τ_2 on dynamics of x, v and z when $\beta_1 = 0.02$. (**c**) The effect of the immune response delay τ_3 on dynamics of x, v and z when $\beta_1 = 0.02$.

We set $\beta_1 = 0.05$ and $\tau_3 = 0$ to verify Theorem 6. The corresponding parameter values are $R_0 = 3.3943$, $R_1 = 2.0183$, $k_1 = 0.02$ and $\frac{d\hat{x}}{\hat{w}} = 0.4783$. All conditions of Theorem 6 hold. Consequently, the infection-immune coexistence equilibrium $Q_2 = (44.3535, 9.2742, 3.2848, 3.2871, 1.2873)$ is globally asymptotically stable for any τ_1

and τ_2. As can be seen in Figure 3, although the immune response is activated, the virus persists and maintains stable coexistence with the immune response in the long term.

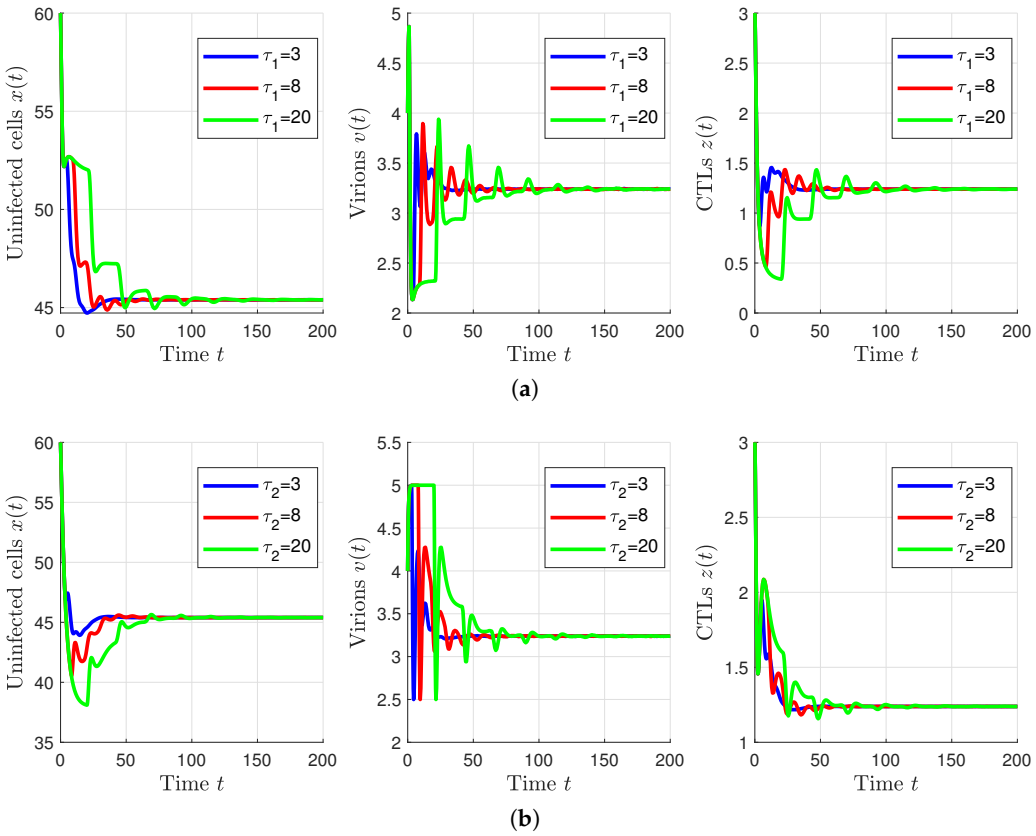

Figure 3. When the basic reproduction number $R_0 = 3.3943 > R_1 = 2.0183 > 1, \tau_3 = 0$ and the corresponding condition in Theorem 6 holds, the immune-free coexistence equilibrium Q_2 is globally asymptotically stable for all τ_1 and τ_2. The immune response is activated, and the virus and immune response coexist stably in the long term. (**a**) The effect of the infected cell activation delay τ_1 on dynamics of x, v and z when $\beta_1 = 0.05$. (**b**) The effect of the virus production delay τ_2 on dynamics of x, v and z when $\beta_1 = 0.05$.

Furthermore, when the restrictive condition $\tau_3 = 0$ in Theorem 6 is violated, numerical simulations show that the infection-immune coexistence equilibrium remains stable even if the time delay rises to a sufficiently large magnitude. All parameter values are the same as those in Figure 3, and we take $\tau_3 = 50,\ 80$ and 200, setting $\tau_1 = \tau_2 = 1$. As can be seen in Figure 4, the infection-immune coexistence equilibrium Q_2 remains stable. It appears that the time delay τ_3 does not destabilize this equilibrium. However, a complete theoretical proof to verify this conclusion is non-trivial and is left for further investigation.

One interesting phenomenon in the model (6) is that parameter k_1 $(0 < k_1 < 1)$ describes the rate at which latently infected cells revert to the uninfected state. For sufficiently small values of k_1, such as $k_1 = 0$, the conditions $k_1 < \frac{d\bar{x}}{\bar{w}}$ and $k_1 < \frac{d\hat{x}}{\hat{w}}$ in Theorems 5 and 6 are trivially satisfied. Note that the basic reproduction number R_0 is a decreasing function of k_1. Therefore, we investigate whether these restrictive conditions can be replaced by the conditions associated with R_0. By taking k_1 as a varying parameter and increasing it from 0 to a sufficiently large value (e.g., $k_1 = 1$), numerical simulations show that if the corresponding equilibria exist, the parameter k_1 is always smaller than d multiplied by the ratio of uninfected cells to latently infected cells, which means the above two constraints always hold.

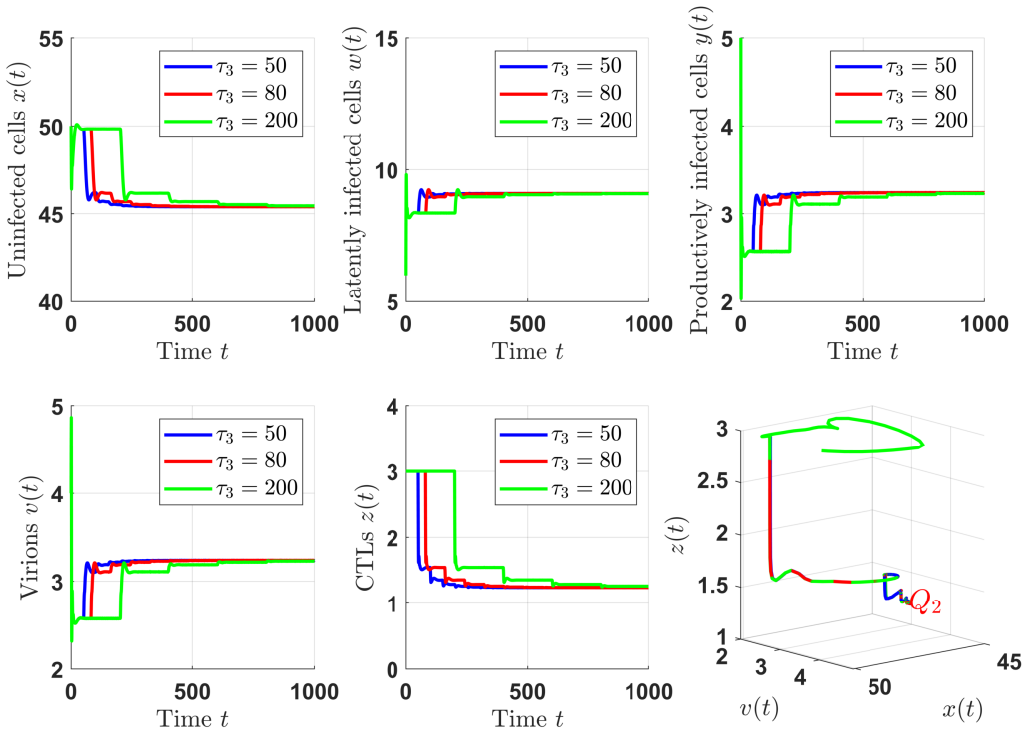

Figure 4. When the restrictive condition $\tau_3 = 0$ in Theorem 6 is violated, numerical simulations show that the infection-immune coexistence equilibrium Q_2 remains stable.

These observations further imply that the stability conditions derived in Theorems 5 and 6 might be relaxed to the simpler criteria $1 < R_0 < R_1$ and $1 < R_1 < R_0$ $(\tau_3 = 0)$, suggesting that the actual parameter range for global asymptotic stability is wider than our theoretical conditions indicate. This result is consistent with the findings in [6].

In other words, the constraints $k_1 < \frac{d\bar{x}}{\bar{w}}$ and $k_1 < \frac{d\hat{x}}{\hat{w}}$ in Theorems 5 and 6 may be further relaxed or even removed. Figure 5 illustrates the existence and global asymptotic stability regions of the three equilibria under the relaxed conditions in the R_1-R_0 parameter plane. However, constructing suitable Lyapunov functions or adopting other approaches to verify this conclusion remains a challenging open problem.

To further explore the effect of k_1 on equilibrium stability, we perform a analysis with k_1 chosen as the parameter. All other parameters remain unchanged as listed in Table 1, and we set $\beta_1 = 0.025$. When $k_1 = 0$, calculations show that the infection-immune coexistence equilibrium Q_2 is globally asymptotically stable. Recall that R_0 is a decreasing function of k_1. As k_1 increases beyond the critical threshold ($R_0 = R_1$), the equilibrium Q_2 no longer exists and Q_1 becomes globally asymptotically stable. If k_1 continues to rise to another threshold such that $R_0 < 1$, Q_1 disappears and the infection-free equilibrium Q_0 is globally asymptotically stable. As illustrated in Figure 6, starting from $R_0 > 1$ at $k_1 = 0$, a small initial value of R_0 implies that increasing k_1 will sharply reduce R_0 to below 1, thereby resulting in disease elimination. Notably, when the initial R_0 is large, it declines slowly with the increase of k_1, as shown in Figure 7.

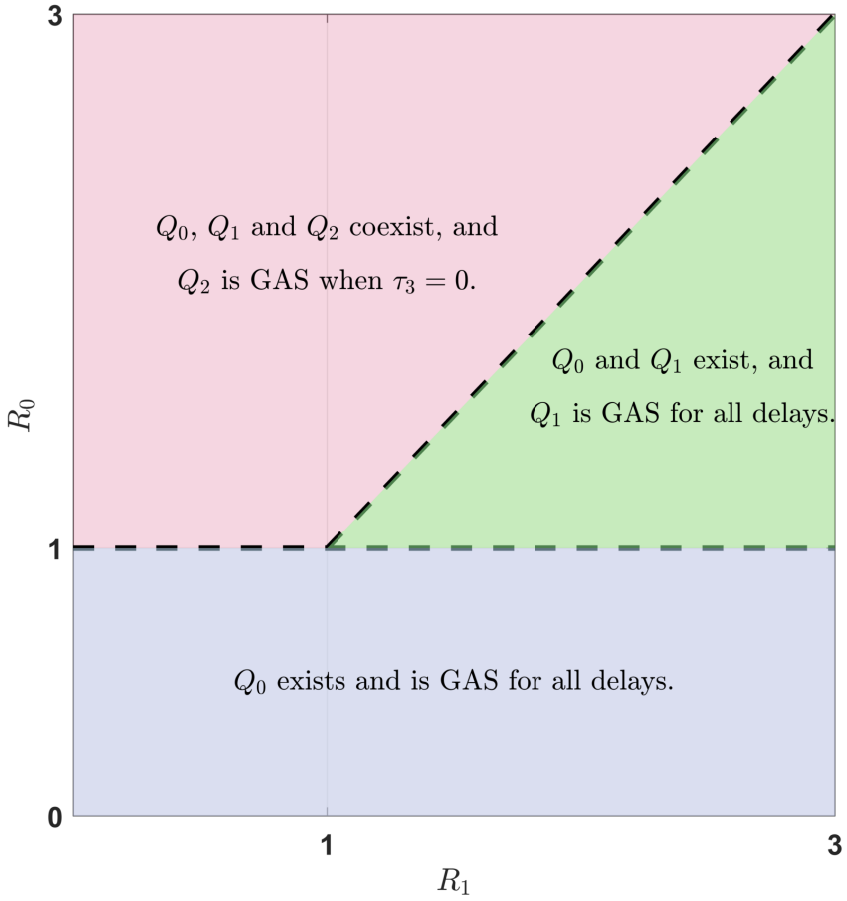

Figure 5. The existence and global asymptotic stability regions of equilibria under relaxed conditions. The pink, green and blue areas denote the parameter domains where Q_2, Q_1 and Q_0 are globally asymptotically stable (GAS), respectively.

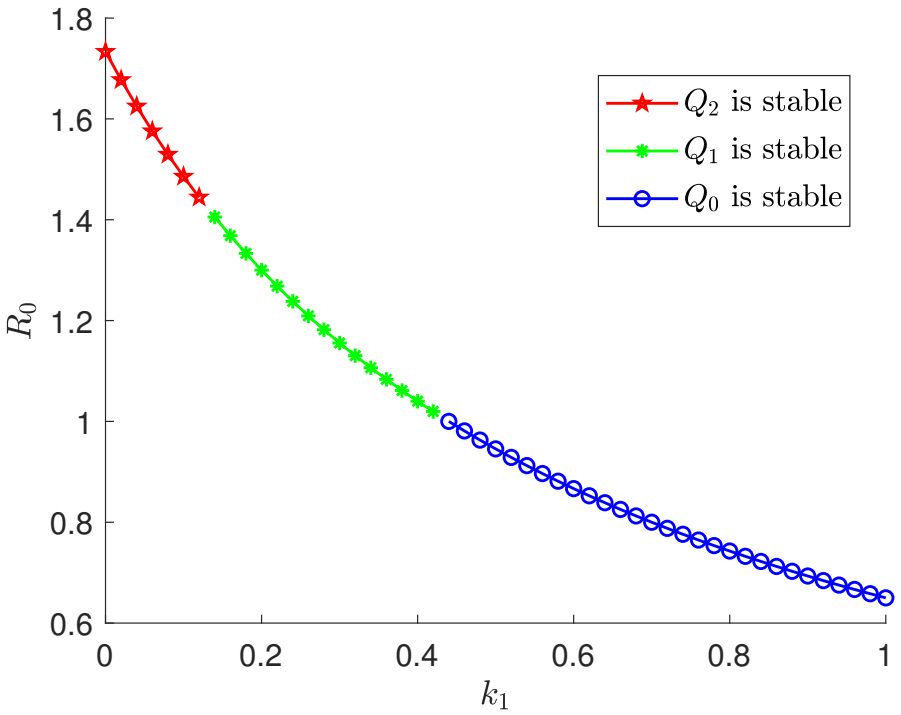

Figure 6. Stability transition diagram of equilibria with k_1 as the varying parameter under a low initial value of R_0. ★, $*$ and ○ represent the stable infection-immune coexistence equilibrium, immune-free equilibrium and infection-free equilibrium, respectively.

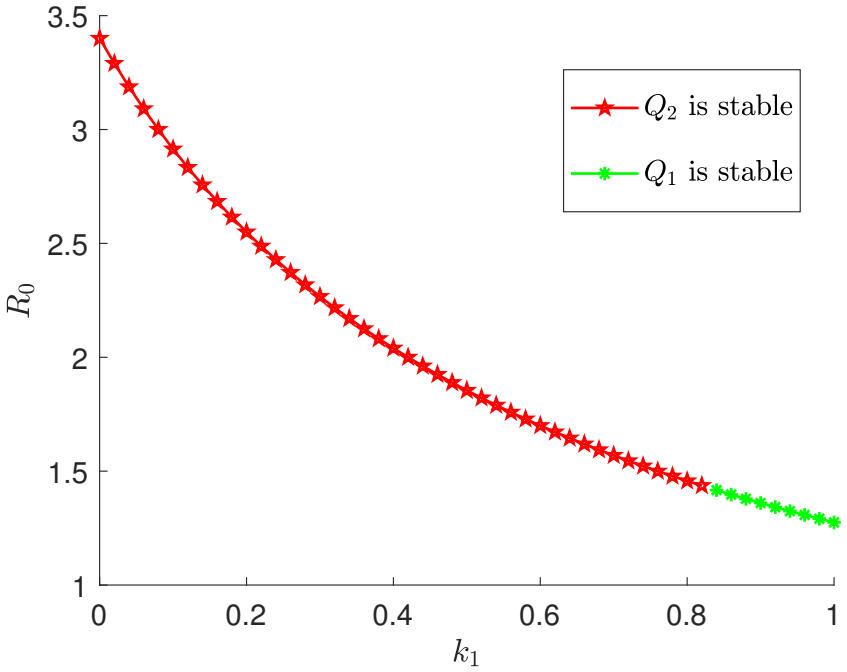

Figure 7. Stability transition diagram of equilibria with k_1 as the varying parameter under a high initial value of R_0. ★ and $*$ represent the infection-immune coexistence equilibrium and the immune-free equilibrium, which are stable respectively.

Finally, we perform a sensitivity analysis using the Partial Rank Correlation Coefficient (PRCC) method to examine the impact of parameters on R_0. Latin Hypercube Sampling (LHS) is employed to compute PRCC values based on 20,000 simulations, where each parameter is uniformly sampled from 0.5 to 4 times its baseline value. As shown in Figure 8, $\lambda, \beta_1, \beta_2, k_2$ and k_3 are positively correlated with R_0, indicating that interventions targeting these factors could effectively limit disease spread. Conversely, clearance and death rate parameters (d, u_1, u_2, u_3) exhibit strong negative correlations with R_0, highlighting their potential as therapeutic targets. Notably, k_1 shows negligible influence on R_0.

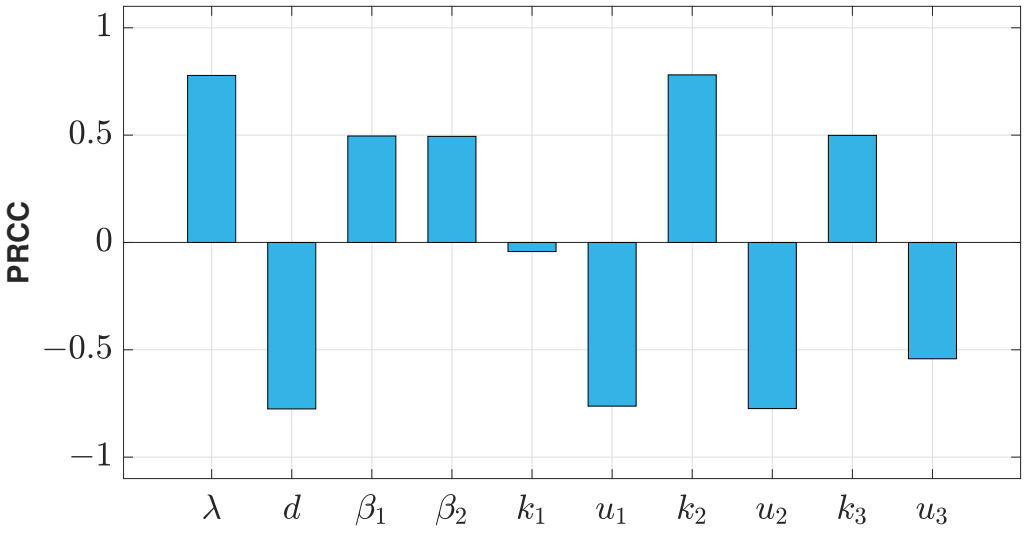

Figure 8. Partial rank correlation coefficient (PRCC) values between the basic reproduction number R_0 and the model parameters.

7. Conclusions and Open Problems

This paper presents an improved HIV model combining dual transmission modes, three biological time delays and latent infection characteristics. We first establish the

boundedness of solutions, and analyze the existence and uniqueness of the equilibria associated with the basic reproduction number. By constructing suitable Lyapunov functions, we derive sufficient conditions for the global asymptotic stability of the infection-free equilibrium, the immune-free equilibrium and the infection-immune coexistence equilibrium, respectively.

We note that both virus-to-cell and cell-to-cell infections contribute to the basic reproduction number of the model. Consequently, neglecting the cell-to-cell transmission pathway will result in an underestimation of the threshold value of the basic reproduction number. When the basic reproduction number is less than one, the virus will eventually die out completely, regardless of time delays. If transmissibility remains at a moderate level and certain conditions are met, the immune-inactive state will stay stable for all time delays, meaning the immune response is exhausted and fails to activate. When the disease spreads intensely and relevant requirements are satisfied, the virus and immune responses can coexist steadily. Numerical simulations are carried out to validate the analytical results.

Compared with the classical latent HIV model (1), the extended model (3) incorporates an immune response component and further enriches the original modeling framework. Mathematically, a novel equilibrium associated with immune exhaustion emerges, which characterizes the state of failed immune activation and better conforms to real biological observations. Furthermore, unlike the existing models in (1) and (2), the present work adopts two general nonlinear incidence functions to improve the versatility of the classical models, which can be applied to broader viral infection research scenarios.

Meanwhile, we perform numerical simulations to plot the stability transition diagram of equilibria, taking k_1 (the reversion rate of latently infected cells) as the parameter, and conduct sensitivity analysis with respect to $\mathcal{R}_0$. As illustrated in Figures 7 and 8, when R_0 exceeds a certain threshold, the infection cannot be eradicated even if k_1 is sufficiently large. This result highlights the challenge of suppressing HIV infection under such circumstances. For patients with a high basic reproduction number, a single therapeutic strategy that only enhances parameter k_1 may not be effective.

It remains an open problem to relax the conditions in Theorems 5 and 6 by means of suitable Lyapunov functions or other geometric methods. To gain further insight into HIV infection dynamics, reaction-diffusion theory, optimal control and other approaches can be adopted for model improvement.

Author Contributions: Methodology, Y.J. and Y.Z.; software, Y.J.; validation, Y.Z., Y.S. and T.W.; writing—original draft preparation, Y.J.; writing—review and editing, T.W. and Z.Q.; funding acquisition, Y.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Fundamental Research Funds for the Central Universities of China (3142020024).

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Lewin, S.; Walters, T.; Locarnini, S. Hepatitis B treatment: Rational combination chemotherapy based on viral kinetic and animal model studies. *Antivir. Res.* **2002**, *55*, 381–396. [CrossRef]
2. Chun, T.W.; Stuyver, L.; Mizell, S.B.; Ehler, L.A.; Mican, J.A.M.; Baseler, M.; Lloyd, A.L.; Nowak, M.A.; Fauci, A.S. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 13193–13197. [CrossRef]
3. Zack, J.A.; Arrigo, S.J.; Weitsman, S.R.; Go, A.S.; Haislip, A.; Chen, I.S. HIV-1 entry into quiescent primary lymphocytes: Molecular analysis reveals a labile latent viral structure. *Cell* **1990**, *61*, 213–222. [CrossRef]

4. Essunger, P.; Perelson, A.S. Modeling HIV infection of CD4$^+$ T-cell subpopulations. *J. Theor. Biol.* **1994**, *170*, 367–391. [CrossRef] [PubMed]
5. Rong, L.; Gilchrist, M.A.; Feng, Z.; Perelson, A.S. Modeling within-host HIV-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility. *J. Theor. Biol.* **2007**, *247*, 804–818. [CrossRef]
6. Buonomo, B.; Vargas-De-León, C. Global stability for an HIV-1 infection model including an eclipse stage of infected cells. *J. Math. Anal. Appl.* **2012**, *385*, 709–720. [CrossRef] [PubMed]
7. Nowak, M.A.; May, R.M. *Virus Dynamics*; Oxford University Press: Oxford, UK, 2000; pp. 16–26.
8. Guan, X.; Dong, Y.; Wang, H. Global stability of an HIV infection model with follicular dendritic cells. *Appl. Math. Lett.* **2026**, *178*, 109936. [CrossRef]
9. Hattaf, K.; Yousfi, N.; Tridane, A. Mathematical analysis of a virus dynamics model with general incidence rate and cure rate. *Nonlinear Anal.-Real World Appl.* **2012**, *13*, 1866–1872. [CrossRef]
10. AlShamrani, N.H. Stability of a general adaptive immunity HIV infection model with silent infected cell-to-cell spread. *Chaos Solitons Fractals* **2021**, *150*, 110422. [CrossRef]
11. Chen, C.; Zhou, Y.; Ye, Z. Stability and optimal control of a cytokine-enhanced general HIV infection model with antibody immune response and CTLs immune response. *Comput. Methods Biomech. Biomed. Eng.* **2024**, *27*, 2199–2230. [CrossRef]
12. Baleanu, D.; Jajarmi, A.; Sajjadi, S.S.; Mozyrska, D. A new fractional model and optimal control of a tumor-immune surveillance with non-singular derivative operator. *Chaos* **2019**, *29*, 083127. [CrossRef]
13. Gomez-Acevedo, H.; Li, M.Y.; Jacobson, S. Multi-stability in a model for CTL response to HTLV-1 infection and its implications to HAM/TSP development and prevention. *Bull. Math. Biol.* **2010**, *72*, 681–696. [CrossRef]
14. Chen, C.; Zhou, Y. Dynamic analysis of HIV model with a general incidence, CTLs immune response and intracellular delays. *Math. Comput. Simul.* **2023**, *212*, 159–181. [CrossRef]
15. Yuan, Z.; Zou, X. Global threshold dynamics in an HIV virus model with nonlinear infection rate and distributed invasion and production delays. *Math. Biosci. Eng.* **2013**, *10*, 483–498. [CrossRef] [PubMed]
16. Guo, K.; Guo, S. Lyapunov functionals for a general time-delayed virus dynamic model with different CTL responses. *Chaos* **2024**, *34*, 053138. [CrossRef]
17. Wang, A.; Li, M.Y. Viral dynamics of HIV-1 with CTL immune response. *Discret. Contin. Dyn. Syst. Ser. B* **2021**, *26*, 2257–2272. [CrossRef]
18. Sato, H.; Orenstein, J.; Dimitrov, D.; Martin, M. Cell-to-cell spread of HIV-1 occurs within minutes and may not involve the participation of virus particles. *Virology* **1992**, *186*, 712–724. [CrossRef]
19. Iwami, S.; Takeuchi, J.S.; Nakaoka, S.; Mammano, F.; Clavel, F.; Inaba, H.; Kobayashi, T.; Misawa, N.; Aihara, K.; Koyanagi, Y.; et al. Cell-to-cell infection by HIV contributes over half of virus infection. *eLife* **2015**, *4*, 08150. [CrossRef] [PubMed]
20. Sadki, M.; Harroudi, S.; Allali, K. Local and global stability of an HCV viral dynamics model with two routes of infection and adaptive immunity. *Comput. Methods Biomech. Biomed. Eng.* **2024**, *27*, 1510–1537. [CrossRef]
21. Canabarro, A.A.; Gleria, I.M.; Lyra, M.L. Periodic solutions and chaos in a non-linear model for the delayed cellular immune response. *Phys. A* **2004**, *342*, 234–241. [CrossRef]
22. Wang, Z.P.; Xu, R. Stability and Hopf bifurcation in a viral infection model with nonlinear incidence rate and delayed immune response. *Commun. Nonlinear Sci. Numer. Simul.* **2012**, *17*, 964–978. [CrossRef]
23. Huang, G.; Ma, W.; Takeuchi, Y. Global analysis for delay virus dynamics model with Beddington-DeAngelis functional response. *Appl. Math. Lett.* **2011**, *24*, 1199–1203. [CrossRef]
24. Hale, J.K.; Lunel, S.M.V. *Introduction to Functional Differential Equations*; Springer: New York, NY, USA, 2013; pp. 39–44.
25. Diekmann, O.; Heesterbeek, J.A.P.; Metz, J.A.J. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.* **1990**, *28*, 365–382. [CrossRef] [PubMed]
26. van den Driessche, P.; Watmough, J. Reproduction numbers and sub-threshold endemic equilibra for compartmental models of disease transmission. *Math. Biosci.* **2002**, *180*, 29–48. [CrossRef] [PubMed]
27. Wang, Y.; Zhou, Y.; Brauer, F.; Heffernan, J.M. Viral dynamics model with CTL immune response incorporating antiretroviral therapy. *J. Math. Biol.* **2013**, *67*, 901–934. [CrossRef] [PubMed]
28. Xu, J.; Huang, G. Global stability and bifurcation analysis of a virus infection model with nonlinear incidence and multiple delays. *Fractal Fract.* **2023**, *7*, 583. [CrossRef]
29. Stafford, M.A.; Corey, L.; Cao, Y.Z.; Daar, E.S.; Ho, D.D.; Perelson, A.S. Modeling plasma virus concentration during primary HIV infection. *Mathematics* **2000**, *203*, 285–301. [CrossRef]