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Dynamic analysis of a latent HIV infection model with CTL immune and antibody responses

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This paper develops a mathematical model to investigate the Human Immunodeficiency Virus (HIV) infection dynamics. The model includes two transmission modes (cell-to-cell and cell-free), two adaptive immune responses (cytotoxic T-lymphocyte (CTL) and antibody), a saturated CTL immune response, and latent HIV infection. The existence and local stability of equilibria are fully characterized by four reproduction numbers. Through sensitivity analyses, we assess the partial rank correlation coefficients of these reproduction numbers and identify that the infection rate via cell-to-cell transmission, the number of new viruses produced by each infected cell during its life cycle, the clearance rate of free virions, and immune parameters have the greatest impact on the reproduction numbers. Additionally, we compare the effects of immune stimulation and cell-to-cell spread on the model's dynamics. The findings highlight the significance of adaptive immune responses in increasing the population of uninfected cells and reducing the numbers of latent cells, infected cells, and viruses. Furthermore, cell-to-cell transmission is identified as a facilitator of HIV transmission. The analytical and numerical results presented in this study contribute to a better understanding of HIV dynamics and can potentially aid in improving HIV management strategies.

Keywords: HIV infection; cell-to-cell transmission; adaptive immune response; latent infection; local stability.

Mathematics Subject Classification 2020: 34D20, 92D30

1. Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by Human Immunodeficiency Virus (HIV) infection that can suppress T-cells in the human

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body which have a function to fight against infections [1]. According to the data released by the World Health Organization (WHO), more than 70 million people have been infected with HIV since it was first detected in 1981 [2]. Among them about 50% have died. As of 2022, AIDS is raging in almost every country on the planet, posing a huge threat to the safety of people's lives. Therefore, it is urgent to use knowledge of infectious disease dynamics to establish mathematical models to study HIV infection.

The fundamental model of HIV infection comprises uninfected cells, infected cells, and free viral particles [3]. The immune response plays a vital role in recognizing and eliminating pathogens and infected cells during the process of viral infection. As a result, more sophisticated models have been established to study the dynamic relationships between the immune response and the invading pathogens [4–6]. As an important branch of the immune system, CTL (cytotoxic T-lymphocyte) kills infected target cells by secreting various cytokines such as tumor necrosis factor, interferon, etc. It can also inhibit HIV reproduction through certain chemical chemokines. The CTL immune response was introduced in some of the early models [7, 8]. However, the stimulating effect of infected cells on immune cells is not a simple linear relationship; when the concentration of infected cells becomes sufficiently large a saturation state is reached. Thus it is of certain practical significance to incorporate this saturation effect into modeling. An SEIARV model with asymptomatic infection and saturation incidence rate is studied in [9]. In [10], Wang *et al.* considered saturated CTL immune response of the form $\frac{cyz}{1+qy}$, where $1+qy$ indicates the inhibitory effect of infected cells on the CTL immune response. In addition to the CTL immune response, neutralizing antibodies can bind specifically to viruses, causing them to lose the ability to infect host cells [11]. Extensions to the basic model were proposed by Wang and Zou [12] and Li and Xu [13], incorporating an additional class to account for antibody immune response.

The previously mentioned models focused solely on cell-free infection. Nevertheless, it has been observed that direct cell-to-cell transmission of HIV, potentially facilitated by virological synapses, is significantly more efficient compared to infection through free viral particles [14–16]. To gain insights into viral dynamics, mathematical models have been developed to incorporate cell-to-cell transmission. For example, Elaiw and Alshamrani showed that the inclusion of cell-to-cell transmission decreases the concentration of healthy $CD4^+$ T-cells and increases the concentrations of infected cells and free HIV particles [17]. In [18], a mathematical model with the two transmission modes for HIV-1 was proposed. It is found that if the basic reproduction number is greater than one, the infection can persist and Hopf bifurcation can occur at the positive equilibrium within certain ranges of parameter values. In [19], Guo *et al.* proposed a model including two intracellular delays in viral infection and production, in addition to the two transmission routes. They evaluated the effects of various viral spread modes, intracellular time delays and the immune responses on the infection dynamics.

In HIV, the viral genome is able to integrate into resting $CD4^+$ T-cells to produce a latent infection [20]. Latently infected $CD4^+$ T-cells have a prolonged lifespan and remain unaffected by antiretroviral drugs or immune responses. However, they can be triggered to release viruses upon stimulation by specific antigens [21]. In order to provide a more comprehensive explanation of biological phenomena, latent infection has also been incorporated into viral dynamics models. From a recently developed latent HIV infection model with cell-to-cell infection, Agosto *et al.* concluded that cell-to-cell infection could affect the establishment and persistence of latent infection in the resting $CD4^+$ T-cells [22]. The results in [23] suggest that although cell-to-cell transmission may have reduced susceptibility to HIV drugs, HIV latency represents a major reason for HIV persistence in patients on suppressive treatment. Therefore, the latent infection mechanism should be introduced into HIV models of both cell-to-cell infection and cell-free transmission.

Upon HIV entry into the human body, the immune system triggers two distinct branches of adaptive immune responses to combat the viral infection: the CTL immune response and the antibody immune response. Such adaptive immune responses have been incorporated into many viral infection models with the cell-free infection mode (see e.g. [5–9, 11, 12]). In particular, a saturated immune response is also considered in [10]. Experimental evidence suggests that direct cell-to-cell transmission of HIV is believed to be more efficient than infection by free virus particles [14, 15]. Furthermore, this mode of transmission may have implications for the establishment and persistence of latent infection in resting $CD4^+$ T-cells [22]. In recent studies, two modes of transmission, latent infection and CTL immunity, were taken into account in the modeling of HIV [2, 17]. But the antibody immune response was ignored.

Motivated by the aforementioned biological factors, we propose a comprehensive model that incorporates the key elements mentioned above: two transmission modes (cell-to-cell and cell-free), two types of adaptive immune responses (CTL and antibody), a saturated CTL immune response and latent infection. The model is described by the following system of ordinary differential equations:

$$\begin{cases} \dfrac{dT}{dt} = \lambda(T^* - T) - \beta_1 TV - \beta_2 TI, \\ \dfrac{dL}{dt} = \eta(\beta_1 TV + \beta_2 TI) - d_0 L - a_0 L, \\ \dfrac{dI}{dt} = (1-\eta)(\beta_1 TV + \beta_2 TI) - \delta I + a_0 L - \rho ZI, \\ \dfrac{dZ}{dt} = \dfrac{eIZ}{1+\alpha I} - bZ, \\ \dfrac{dV}{dt} = N\delta I - cV - qVA, \\ \dfrac{dA}{dt} = aVA - \delta_1 A. \end{cases} \tag{1}$$

Here T, L, I, Z, V, and A represent the concentrations of uninfected cells, latent cells, infected cells, CTL effectors, free viruses, and antibodies at time t, respectively. T^* is the equilibrium concentration of uninfected cells in the absence of viral infection. The constant λT^* is the generation rate of uninfected CD4$^+$ T-cells. Parameters β_1 and β_2 represent the infection rates via cell-free infection and cell-to-cell transmission, respectively. Parameters λ, δ, b, δ_1, and c are the decay rates of uninfected CD4$^+$ T-cells, infected CD4$^+$ T-cells, CTL cells, antibodies, and viruses, respectively. The parameter ρ is the rate at which infected cells are cleared by CTL cells. The constant q denotes the neutralization rate by antibody response. The antibody response is assumed to be stimulated at a rate a by the virus. Viral generation by productively infected CD4$^+$ T-cells leads to N new viruses by each infected cell during its lifetime. The average lifespan of an infected cell is $\frac{1}{\delta}$. Thus $N\delta$ is the viral production rate by an infected cell per unit time. Parameters d_0 and a_0 represent the mortality of latently infected cells and the activation rate from the latent to productive state, respectively. In the model, we assume that a fraction η $(0 < \eta < 1)$ of infected CD4$^+$ T-cells become latently infected and the remaining fraction $(1-\eta)$ become productively infected. We further assume that the cellular immune generation is $\frac{eIZ}{1+\alpha I}$, where $1+\alpha I$ represents the inhibitory effect of infected cells on CTL immune response. The parameter e is the proliferation rate of immune cells. It is easy to see that if $e \le b\alpha$ then $Z(t) \to 0$ as $t \to \infty$. As a result, we always assume that $e > b\alpha$ in the sequel.

The initial conditions for (1) are

$$0 \le T(0) \le T^*, \quad L(0) \ge 0, \quad I(0) \ge 0, \quad Z(0) \ge 0, \quad V(0) \ge 0, \quad A(0) \ge 0. \tag{2}$$

By the fundamental theory of ordinary differential equations, we can obtain the existence and uniqueness of solutions for $t \ge 0$ [24]. It is also straightforward to show that solutions are nonnegative. This can be verified by checking that the derivatives are greater than or equal to zero on the boundary of $\mathbb{R}^6_+$, for instance, if $T = 0$, then $\frac{dT}{dt} = \lambda T^* > 0$. Moreover, define

$$F(t) = T + L + I + \frac{\rho}{e}Z + \frac{1}{N}V + \frac{q}{aN}A.$$

A straightforward calculation yields

$$\begin{aligned} F'(t) &= \lambda(T^* - T) - d_0 L - \rho Z I + \frac{\rho Z I}{1+\alpha I} - \frac{\rho b}{e}Z - \frac{c}{N}V - \frac{\delta_1 q}{aN}A \\ &\le \lambda T^* - \lambda T - d_0 L - \frac{\rho b}{e}Z - \frac{c}{N}V - \frac{\delta_1 q}{aN}A \le \lambda T^* - \Gamma F, \end{aligned}$$

where $\Gamma = \min\{\lambda, d_0, \frac{\rho b}{e}, \frac{c}{N}, \frac{\delta_1 q}{aN}\}$. Then $\limsup_{t\to\infty} F(t) \le \frac{\lambda T^*}{\Gamma}$. This implies that the solutions of (1) are bounded. In fact, it is easy to see that

$$\Omega = \left\{ (T, L, I, Z, V, A) \in R^6_+ : T \le T^*, T + L + I + \frac{\rho}{e}Z + \frac{1}{N}V + \frac{q}{aN}A \le \frac{\lambda T^*}{\Gamma} \right\}$$

is attracting and positively invariant for system (1).

The objective of this study is to investigate the impact of various factors on the dynamics of cell and viral loads. In Sec. 2, the basic reproduction number, the immune reproduction numbers, and conditions on the existence of all kinds of equilibria are provided. Then the local stability of the equilibria is established in Sec. 3. Section 4 is devoted to the sensitivity analysis for the reproduction numbers. Section 5 provides numerical simulations, followed by brief discussion and conclusion in Sec. 6.

2. Reproduction Numbers and Equilibria

It is evident that system (1) possesses a unique infection-free equilibrium, denoted as $E_0 = (T_0, L_0, I_0, Z_0, V_0, A_0) = (T^*, 0, 0, 0, 0, 0)$. According to the method of next-generation matrix proposed by van den Driessche and Watmough [25], we define the matrices $\mathbb{F}$ and $\mathbb{V}$ as

$$\mathbb{F} = \begin{pmatrix} 0 & \eta\beta_2 T^* & \eta\beta_1 T^* \\ 0 & (1-\eta)\beta_2 T^* & (1-\eta)\beta_1 T^* \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbb{V} = \begin{pmatrix} d_0 + a_0 & 0 & 0 \\ -a_0 & \delta & 0 \\ 0 & -N\delta & c \end{pmatrix}.$$

The basic reproduction number, denoted as R_0, is defined as the spectral radius of the next-generation operator $\mathbb{F}\mathbb{V}^{-1}$. Note that

$$\mathbb{F}\mathbb{V}^{-1} = \begin{pmatrix} \dfrac{a_0\eta\beta_2 T^*}{(d_0+a_0)\delta} + \dfrac{a_0\eta\beta_1 T^* N}{(d_0+a_0)c} & \dfrac{\eta\beta_2 T^*}{\delta} + \dfrac{\eta\beta_1 T^* N}{c} & 0 \\ \dfrac{a_0(1-\eta)\beta_2 T^*}{(d_0+a_0)\delta} + \dfrac{a_0(1-\eta)\beta_1 T^* N}{(d_0+a_0)c} & \dfrac{(1-\eta)\beta_2 T^*}{\delta} + \dfrac{(1-\eta)\beta_1 T^* N}{c} & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Thus

$$\begin{aligned} R_0 = \rho(\mathbb{F}\mathbb{V}^{-1}) &= \frac{a_0 N\eta\beta_1 T^*}{c(d_0+a_0)} + \frac{(1-\eta)\beta_1 T^* N}{c} + \frac{(1-\eta)\beta_2 T^*}{\delta} + \frac{a_0\eta\beta_2 T^*}{\delta(d_0+a_0)} \\ &= R_{01} + R_{02}, \end{aligned}$$

where $R_{01} = \frac{a_0 N\eta\beta_1 T^*}{c(d_0+a_0)} + \frac{(1-\eta)\beta_1 T^* N}{c}$ and $R_{02} = \frac{(1-\eta)\beta_2 T^*}{\delta} + \frac{a_0\eta\beta_2 T^*}{\delta(d_0+a_0)}$. R_{01} and R_{02} are contributions to R_0 from the cell-free infection and cell-to-cell transmission, respectively. We also define the immune reproduction numbers,

$$R_1^c = \frac{R_0}{1 + \frac{(\beta_1 N\delta + \beta_2 c)b}{\lambda c(e - b\alpha)}},$$

$$R_1^a = \frac{R_0}{1 + \frac{(\beta_1 N\delta + \beta_2 c)\delta_1}{\lambda N\delta a}},$$

$$R_2^c = \frac{\frac{(e-b\alpha)\delta_1 c}{N\delta ab} R_{01} + R_{02}}{1 + \frac{\beta_1\delta_1(e-b\alpha) + \beta_2 ba}{\lambda a(e-b\alpha)}},$$

which come from the coming discussion on the existence and stability of other kinds of equilibria. The reproduction number of CTL immune response is denoted as R_1^c, while the reproduction number of the antibody immune response is represented by R_1^a. In biology, R_1^c represents the average number of CTL cells activated by infected cells when virus infection is successful but the antibody immune response has not been established, whereas R_1^a denotes the average number of antibodies activated by the virus when viral infection is successful but the CTL immune response has not been established. The value of R_2^c corresponds to the reproduction number of CTL immune competition, which quantifies the average number of CTL cells activated by infected cells when an established antibody immune response is present [26, 27].

After tedious calculations, we find that model (1) only has the following possible equilibria with the presence of infection.

(i) When $R_0 > 1$, system (1) has a unique CTL immune-free and antibody-free equilibrium $E_1 = (T_1, L_1, I_1, 0, V_1, 0)$, where

$$T_1 = \frac{T^*}{R_0}, \quad L_1 = \frac{\lambda\eta T^*}{d_0 + a_0}\left(1 - \frac{1}{R_0}\right),$$
$$I_1 = \frac{\lambda c(R_0 - 1)}{\beta_1 N\delta + \beta_2 c}, \quad V_1 = \frac{\lambda N\delta(R_0 - 1)}{\beta_1 N\delta + \beta_2 c}.$$

(ii) When $R_1^c > 1$ (which implies $R_0 > 1$), system (1) has a unique CTL immune-present and antibody-free equilibrium $E_2 = (T_2, L_2, I_2, Z_2, V_2, 0)$, where

$$T_2 = \frac{\lambda cT^*(e - b\alpha)}{\lambda c(e - b\alpha) + (\beta_1 N\delta + \beta_2 c)b},$$
$$L_2 = \frac{\lambda\eta T^*(\beta_1 N\delta + \beta_2 c)b}{(d_0 + a_0)[\lambda c(e - b\alpha) + (\beta_1 N\delta + \beta_2 c)b]}, \quad I_2 = \frac{b}{e - b\alpha},$$
$$Z_2 = \frac{\delta}{\rho}(R_1^c - 1), \quad V_2 = \frac{N\delta b}{c(e - b\alpha)}.$$

In this scenario, the infection transitions into a chronic phase with a persistent CTL immune response. However, the viral loads remain at such low levels that they are unable to trigger the activation of the antibody immune response.

(iii) When $R_1^a > 1$ (which implies $R_0 > 1$), system (1) has a unique antibody-present and CTL immune-free equilibrium $E_3 = (T_3, L_3, I_3, 0, V_3, A_3)$, where

$$T_3 = \frac{\lambda T^* N\delta a}{\lambda aN\delta + \beta_1 N\delta\delta_1 + \beta_2\delta_1(c + qA_3)},$$
$$L_3 = \frac{\lambda\eta T^*[\beta_1 N\delta\delta_1 + \beta_2\delta_1(c + qA_3)]}{(d_0 + a_0)[\lambda aN\delta + \beta_1 N\delta\delta_1 + \beta_2\delta_1(c + qA_3)]},$$
$$I_3 = \frac{(c + qA_3)\delta_1}{Na\delta}, \quad V_3 = \frac{\delta_1}{a}$$

and A_3 is the unique positive root of the quadratic equation given below:

$$\beta_2\delta_1 q^2 A_3^2 + q(2\beta_2\delta_1 c + \lambda a N\delta + \beta_1 N\delta\delta_1 - \lambda N a\delta R_{02})A_3 + c\lambda N\delta a R_0\left(\frac{1}{R_1^a} - 1\right) = 0.$$

This equilibrium suggests that the establishment of the antibody immune response occurs when there is viral production, while the presence of infected cells is insufficient to trigger the CTL immune response.

(iv) When $R_2^c > 1$ and $R_1^a > R_1^c$ (which also imply $R_0 > 1$), system (1) has a unique CTL and antibody immunity coexistence equilibrium $E_4 = (T_4, L_4, I_4, Z_4, V_4, A_4)$, where

$$T_4 = \frac{\lambda a T^*(e - b\alpha)}{\lambda a(e - b\alpha) + \beta_1\delta_1(e - b\alpha) + \beta_2 ba},$$

$$L_4 = \frac{\lambda\eta T^*[\beta_1\delta_1(e - b\alpha) + \beta_2 ba]}{(d_0 + a_0)[\lambda a(e - b\alpha) + \beta_1\delta_1(e - b\alpha) + \beta_2 ba]}, \quad I_4 = \frac{b}{e - b\alpha},$$

$$Z_4 = \frac{\delta}{\rho}(R_2^c - 1), \quad V_4 = \frac{\delta_1}{a}, \quad A_4 = \frac{1}{q}\left[\frac{N\delta ab}{(e - b\alpha)\delta_1} - c\right].$$

Biologically, even though both CTL and antibody immune responses are activated, the infection persists chronically.

The above are restated below as a result on the existence of equilibria.

Lemma 2.1. (i) *When $R_0 \le 1$, system (1) has only one equilibrium E_0.*

(ii) *When $R_0 > 1$, $R_1^c \le 1$, $R_1^a \le 1$ and either $R_2^c \le 1$ or $R_1^a \le R_1^c$, system (1) only has the two boundary equilibria E_0 and E_1.*

(iii) *When $R_1^c > 1$ and $R_1^a \le 1$, system (1) only has the three boundary equilibria E_0, E_1 and E_2.*

(iv) *When $R_1^a > 1$, $R_1^c \le 1$ and $R_2^c \le 1$, system (1) only has the three boundary equilibria E_0, E_1 and E_3.*

(v) *When $R_1^c > 1$, $R_1^a > 1$ and either $R_2^c \le 1$ or $R_1^a \le R_1^c$, system (1) only has the boundary equilibria E_0, E_1, E_2 and E_3.*

(vi) *When $R_1^a > R_1^c > 1$ and $R_2^c > 1$, besides the above four boundary equilibria, system (1) also has a unique interior equilibrium E_4.*

3. Local Stability

3.1. *Local stability of the infection-free equilibrium E_0*

Theorem 3.1. *The infection-free equilibrium E_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

Proof. The Jacobian matrix of system (1) at E_0 is

$$J(E_0) = \begin{pmatrix} -\lambda & 0 & -\beta_2 T_0 & 0 & -\beta_1 T_0 & 0 \\ 0 & -d_0 - a_0 & \eta\beta_2 T_0 & 0 & \eta\beta_1 T_0 & 0 \\ 0 & a_0 & (1-\eta)\beta_2 T_0 - \delta & 0 & (1-\eta)\beta_1 T_0 & 0 \\ 0 & 0 & 0 & -b & 0 & 0 \\ 0 & 0 & N\delta & 0 & -c & 0 \\ 0 & 0 & 0 & 0 & 0 & -\delta_1 \end{pmatrix}.$$

The characteristic equation of $J(E_0)$ is

$$\begin{aligned} &[(x + d_0 + a_0)(x + c)(x + \delta) - (x + d_0 + a_0)(1 - \eta)\beta_2 T_0(x + c) \\ &\quad - (x + d_0 + a_0)N\delta(1 - \eta)\beta_1 T_0 - a_0\eta\beta_2 T_0(x + c) \\ &\quad - a_0\eta\beta_1 T_0 N\delta](x + b)(x + \delta_1)(x + \lambda) = 0. \end{aligned} \tag{3}$$

There are three negative eigenvalues $x_1 = -\lambda$, $x_2 = -\delta_1$ and $x_3 = -b$. First suppose $R_0 < 1$. We show that if $x = a^* + ib^*$ is an eigenvalue, then the real part $a^* < 0$. By way of contradiction, suppose $a^* \geq 0$. We rewrite (3) as

$$\begin{aligned} 1 = &\frac{(1-\eta)\beta_2 T_0}{x+\delta} + \frac{N\delta(1-\eta)\beta_1 T_0}{(x+c)(x+\delta)} + \frac{a_0\eta\beta_2 T_0}{(x+\delta)(x+d_0+a_0)} \\ &+ \frac{a_0\eta\beta_1 T_0 N\delta}{(x+d_0+a_0)(x+c)(x+\delta)}. \end{aligned} \tag{4}$$

Then the modulus of the right-hand side of Eq. (4) satisfies

$$\begin{aligned} 1 = &\left|\frac{(1-\eta)\beta_2 T_0}{x+\delta} + \frac{N\delta(1-\eta)\beta_1 T_0}{(x+c)(x+\delta)} + \frac{a_0\eta\beta_2 T_0}{(x+\delta)(x+d_0+a_0)}\right. \\ &\left. + \frac{a_0\eta\beta_1 T_0 N\delta}{(x+d_0+a_0)(x+c)(x+\delta)}\right| \\ \leq &\left|\frac{(1-\eta)\beta_2 T_0}{x+\delta}\right| + \left|\frac{N\delta(1-\eta)\beta_1 T_0}{(x+c)(x+\delta)}\right| + \left|\frac{a_0\eta\beta_2 T_0}{(x+\delta)(x+d_0+a_0)}\right| \\ &+ \left|\frac{a_0\eta\beta_1 T_0 N\delta}{(x+d_0+a_0)(x+c)(x+\delta)}\right| \\ = &\left|\frac{(1-\eta)\beta_2 T_0}{x+\delta}\right| + \left|\frac{N(1-\eta)\beta_1 T_0}{x+c}\right|\left|\frac{\delta}{x+\delta}\right| + \left|\frac{a_0\eta\beta_2 T_0}{x+\delta}\right|\left|\frac{1}{x+d_0+a_0}\right| \\ &+ \left|\frac{a_0\eta\beta_1 T_0 N}{x+d_0+a_0}\right|\left|\frac{1}{x+c}\right|\left|\frac{\delta}{x+\delta}\right| \\ \leq &\frac{(1-\eta)\beta_2 T_0}{\delta} + \frac{N(1-\eta)\beta_1 T_0}{c} + \frac{a_0\eta\beta_2 T_0}{\delta(d_0+a_0)} + \frac{a_0\eta\beta_1 T_0 N}{(d_0+a_0)c} \\ = &R_0. \end{aligned}$$

This leads to a contradiction with $R_0 < 1$. Hence if $R_0 < 1$, all roots of Eq. (3) have negative real parts, indicating that E_0 is locally asymptotically stable. Now, let's assume that $R_0 > 1$. Note that the other three roots of (3) are the roots of $F(x) = 0$ with

$$F(x) = x^3 + t_1x^2 + t_2x + t_3,$$

where

$$\begin{aligned}
t_1 &= \delta + c + d_0 + a_0 - (1-\eta)\beta_2 T_0,\\
t_2 &= \delta c + d_0(\delta + c) + a_0(\delta + c) - (c + d_0 + a_0)(1-\eta)\beta_2 T_0\\
&\quad - N\delta(1-\eta)\beta_1 T_0 - a_0\eta\beta_2 T_0,\\
t_3 &= d_0\delta c + a_0\delta c - c(d_0 + a_0)(1-\eta)\beta_2 T_0 - (d_0 + a_0)N\delta(1-\eta)\beta_1 T_0\\
&\quad - a_0\eta\beta_2 T_0 c - a_0\eta\beta_1 T_0 N\delta.
\end{aligned}$$

It is clear that $F(0) = t_3 = (d_0 + a_0)\delta c(1 - R_0) < 0$ and $\lim_{x\to\infty} F(x) = \infty$. Thus $F(x)$ has at least one positive zero. Accordingly, the characteristic equation (3) has a positive eigenvalue and hence E_0 is unstable. □

3.2. *Local stability of the immune-free equilibrium* E_1

Theorem 3.2. *Suppose* $R_0 > 1$. *Then the CTL immune-free and antibody-free equilibrium* E_1 *is locally asymptotically stable if* $\max\{R_1^c, R_1^a\} < 1$ *and is unstable if* $\max\{R_1^c, R_1^a\} > 1$.

Proof. The characteristic equation at E_1 is

$$\begin{aligned}
&(x + \lambda + \beta_1 V_1 + \beta_2 I_1)(x + d_0 + a_0)(x + \delta)(x + c)(x - aV_1 + \delta_1)\\
&\quad \times \left(x - \frac{eI_1}{1 + \alpha I_1} + b\right)\\
&= (x + \lambda)(x - aV_1 + \delta_1)\left(x - \frac{eI_1}{1 + \alpha I_1} + b\right)\\
&\quad \times [(x + d_0 + a_0)(1-\eta)\beta_2 T_1(x + c) + (1-\eta)\beta_1 T_1 N\delta(x + d_0 + a_0)\\
&\quad + a_0\eta\beta_2 T_1(x + c) + a_0\eta\beta_1 T_1 N\delta]. \qquad (5)
\end{aligned}$$

There are two obvious eigenvalues: $x_4 = aV_1 - \delta_1$ and $x_5 = \frac{eI_1}{1+\alpha I_1} - b$. Recall

$$I_1 = \frac{\lambda c(R_0 - 1)}{\beta_1 N\delta + \beta_2 c}, \quad V_1 = \frac{\lambda N\delta(R_0 - 1)}{\beta_1 N\delta + \beta_2 c}.$$

If $\max\{R_1^c, R_1^a\} > 1$, then either $R_1^c > 1$ or $R_1^a > 1$. If $R_1^c > 1$, then $R_0 - 1 > \frac{(\beta_1 N\delta + \beta_2 c)b}{\lambda c(e - b\alpha)}$. Thus $I_1 > \frac{b}{e - b\alpha}$, which gives $x_5 > 0$. If $R_1^a > 1$ then $R_0 - 1 > \frac{(\beta_1 N\delta + \beta_2 c)\delta_1}{\lambda N\delta a}$. Thus $V_1 > \frac{\delta_1}{a}$, which implies $x_4 > 0$. Therefore, if $\max\{R_1^c, R_1^a\} > 1$

then $J(E_1)$ has a positive eigenvalue, which implies that E_1 is unstable. Now assume $\max\{R_1^c, R_1^a\} < 1$. Then similarly we have $V_1 < \frac{\delta_1}{a}$ and $I_1 < \frac{b}{e-b\alpha}$. Therefore, the two real eigenvalues x_4 and x_5 are negative. Subsequently, we demonstrate that the remaining roots of Eq. (5) possess negative real parts. Otherwise, let us assume that there exists a root x of (5) with a nonnegative real part. Dividing both sides of (5) by $(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+d_0+a_0)(x+\delta)(x+c)(x-aV_1+\delta_1)(x-\frac{eI_1}{1+\alpha I_1}+b)$ gives

$$1 = \frac{x+\lambda}{x+\lambda+\beta_1 V_1+\beta_2 I_1} \times \left[\frac{a_0\eta\beta_2 T_1}{(x+d_0+a_0)(x+\delta)} + \frac{a_0\eta\beta_1 T_1 N\delta}{(x+c)(x+d_0+a_0)(x+\delta)} + \frac{(1-\eta)\beta_2 T_1}{x+\delta} + \frac{(1-\eta)\beta_1 T_1 N\delta}{(x+c)(x+\delta)}\right].$$

Denote the right-hand side by Λ_1. In view of $T_1 = \frac{T^*}{R_0}$, we have

$$\begin{aligned}
|\Lambda_1| &= \left|\frac{(x+\lambda)a_0\eta\beta_2 T_1}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+d_0+a_0)(x+\delta)}\right. \\
&\quad + \frac{(x+\lambda)(1-\eta)\beta_1 T_1 N\delta}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+c)(x+\delta)} + \frac{(x+\lambda)(1-\eta)\beta_2 T_1}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+\delta)} \\
&\quad \left. + \frac{(x+\lambda)a_0\eta\beta_1 T_1 N\delta}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+c)(x+d_0+a_0)(x+\delta)}\right| \\
&\le \left|\frac{(x+\lambda)a_0\eta\beta_2 T_1}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+d_0+a_0)(x+\delta)}\right| \\
&\quad + \left|\frac{(x+\lambda)(1-\eta)\beta_1 T_1 N\delta}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+c)(x+\delta)}\right| + \left|\frac{(x+\lambda)(1-\eta)\beta_2 T_1}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+\delta)}\right| \\
&\quad + \left|\frac{(x+\lambda)a_0\eta\beta_1 T_1 N\delta}{(x+\lambda+\beta_1 V_1+\beta_2 I_1)(x+c)(x+d_0+a_0)(x+\delta)}\right| \\
&= \left|\frac{x+\lambda}{x+\lambda+\beta_1 V_1+\beta_2 I_1}\right| \times \left[\left|\frac{a_0\eta\beta_2 T_1}{x+d_0+a_0}\right|\left|\frac{1}{x+\delta}\right| + \left|\frac{(1-\eta)\beta_1 T_1 N}{x+c}\right|\left|\frac{\delta}{x+\delta}\right|\right. \\
&\quad \left. + \left|\frac{(1-\eta)\beta_2 T_1}{x+\delta}\right| + \left|\frac{a_0\eta\beta_1 T_1 N}{x+d_0+a_0}\right|\left|\frac{\delta}{x+\delta}\right|\left|\frac{1}{x+c}\right|\right] \\
&< \frac{a_0\eta\beta_2 T_1}{(d_0+a_0)\delta} + \frac{(1-\eta)\beta_1 T_1 N}{c} + \frac{(1-\eta)\beta_2 T_1}{\delta} + \frac{a_0\eta\beta_1 T_1 N}{(d_0+a_0)c} = \frac{R_0}{T^*}T_1 \\
&= 1.
\end{aligned}$$

This leads to a contradiction. Thus all roots of (5) have negative real parts. This proves that E_1 is locally asymptotically stable when $\max\{R_1^c, R_1^a\} < 1$. □

3.3. *Local stability of the infected equilibrium E_2*

Theorem 3.3. *Suppose $R_1^c > 1$. Then the CTL immune-present and antibody-free equilibrium E_2 is locally asymptotically stable when $R_1^a < R_1^c$ and unstable when $R_1^a > R_1^c$.*

Proof. The characteristic equation of $J(E_2)$ can be rewritten as

$$\begin{aligned}
&(x - aV_2 + \delta_1)(x + \lambda + \beta_1 V_2 + \beta_2 I_2)(x + c)(x + d_0 + a_0) \\
&\quad \times \left[(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1 + \alpha I_2)^2}\right] \\
&\quad = (x - aV_2 + \delta_1)(x + \lambda)x[a_0\eta\beta_1 T_2 N\delta + (x + d_0 + a_0)(1 - \eta)\beta_1 T_2 N\delta \\
&\quad + (x + c)a_0\eta\beta_2 T_2 + (x + c)(x + d_0 + a_0)(1 - \eta)\beta_2 T_2].
\end{aligned}$$

Therefore, there is an eigenvalue $x_6 = aV_2 - \delta_1$ and the others satisfy

$$\begin{aligned}
&(x + c)(x + \lambda + \beta_1 V_2 + \beta_2 I_2)(x + d_0 + a_0)\left[(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1 + \alpha I_2)^2}\right] \\
&\quad = (x + \lambda)x[a_0\eta\beta_1 T_2 N\delta + (x + d_0 + a_0)(1 - \eta)\beta_1 T_2 N\delta + (x + c)a_0\eta\beta_2 T_2 \\
&\quad + (x + c)(x + d_0 + a_0)(1 - \eta)\beta_2 T_2]. \qquad (6)
\end{aligned}$$

If $R_1^a > R_1^c$ then from $V_2 = \frac{N\delta b}{c(e - b\alpha)}$ we can obtain $V_2 > \frac{\delta_1}{a}$ and hence $x_6 > 0$. This means that E_2 is unstable if $R_1^a > R_1^c$. Now assume that $R_1^a < R_1^c$. Then similarly we can obtain $V_2 < \frac{\delta_1}{a}$ so x_6 is a negative eigenvalue. Now, we demonstrate that all the remaining eigenvalues possess negative real parts. By way of contradiction, suppose that $x = a^* + ib^*$ is an eigenvalue with $a^* \geq 0$. We rewrite (6) as

$$\begin{aligned}
1 = \frac{x + \lambda}{x + \lambda + \beta_1 V_2 + \beta_2 I_2}\Bigg\{ &\frac{a_0\eta\beta_1 T_2 N\delta x}{(x + d_0 + a_0)(x + c)\left[(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right]} \\
&+ \frac{(1 - \eta)\beta_1 T_2 N\delta x}{(x + c)\left[(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right]} \\
&+ \frac{a_0\eta\beta_2 T_2 x}{(x + d_0 + a_0)\left[(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right]} + \frac{(1 - \eta)\beta_2 T_2 x}{(x + \delta + \rho Z_2)x + \frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}}\Bigg\}.
\end{aligned}$$

Denote the right-hand side by Λ_2. If $a^* = b^* = 0$, then $\Lambda_2 = 0$, a contradiction to $1 = \Lambda_2$. So we assume $a^{*2} + b^{*2} > 0$. Using $Z_2 = \frac{\delta}{\rho}(R_1^c - 1) = \frac{\delta}{\rho}(\frac{T_2}{T^*}R_0 - 1)$,

we have

$$
\begin{aligned}
|\Lambda_2| = &\left| \frac{a_0\eta\beta_1 T_2 N\delta x(x+\lambda)}{(x+d_0+a_0)(x+c)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right. \\
&+ \frac{(1-\eta)\beta_1 T_2 N\delta x(x+\lambda)}{(x+c)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)} \\
&+ \frac{a_0\eta\beta_2 T_2 x(x+\lambda)}{(x+d_0+a_0)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)} \\
&\left.+ \frac{(1-\eta)\beta_2 T_2 x(x+\lambda)}{\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right| \\
\le &\left| \frac{a_0\eta\beta_1 T_2 N\delta x(x+\lambda)}{(x+d_0+a_0)(x+c)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right| \\
&+ \left| \frac{(1-\eta)\beta_1 T_2 N\delta x(x+\lambda)}{(x+c)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right| \\
&+ \left| \frac{a_0\eta\beta_2 T_2 x(x+\lambda)}{(x+d_0+a_0)\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right| \\
&+ \left| \frac{(1-\eta)\beta_2 T_2 x(x+\lambda)}{\left[(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}\right](x+\lambda+\beta_1 V_2+\beta_2 I_2)}\right| \\
= &\left| \frac{x+\lambda}{x+\lambda+\beta_1 V_2+\beta_2 I_2}\right| \times \left| \frac{x}{(x+\delta+\rho Z_2)x+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2}}\right| \\
&\times \left\{ \left| \frac{a_0\eta\beta_1 T_2 N\delta}{(x+d_0+a_0)(x+c)}\right| + \left| \frac{(1-\eta)\beta_1 T_2 N\delta}{x+c}\right| + \left| \frac{a_0\eta\beta_2 T_2}{x+d_0+a_0}\right| \right. \\
&\left. + |(1-\eta)\beta_2 T_2| \right\} \\
= &\left| \frac{x+\lambda}{x+\lambda+\beta_1 V_2+\beta_2 I_2}\right| \times \left| \frac{1}{x+\delta+\rho Z_2+\frac{eZ_2\rho I_2}{(1+\alpha I_2)^2 x}}\right| \\
&\times \left\{ \left| \frac{a_0\eta\beta_1 T_2 N\delta}{(x+d_0+a_0)(x+c)}\right| + \left| \frac{(1-\eta)\beta_1 T_2 N\delta}{x+c}\right| + \left| \frac{a_0\eta\beta_2 T_2}{x+d_0+a_0}\right| \right. \\
&\left. + |(1-\eta)\beta_2 T_2| \right\}
\end{aligned}
$$

$$
\begin{aligned}
&\leq \frac{1}{\delta+\rho Z_2}\times\left\{\left|\frac{a_0\eta\beta_1T_2N\delta}{(x+d_0+a_0)(x+c)}\right|+\left|\frac{(1-\eta)\beta_1T_2N\delta}{x+c}\right|+\left|\frac{a_0\eta\beta_2T_2}{x+d_0+a_0}\right|\right.\\
&\quad\left.+|(1-\eta)\beta_2T_2|\right\}\\
&< \frac{a_0\eta\beta_1T_2N\delta}{(d_0+a_0)c(\delta+\rho Z_2)}+\frac{(1-\eta)\beta_1T_2N\delta}{c(\delta+\rho Z_2)}+\frac{a_0\eta\beta_2T_2}{(d_0+a_0)(\delta+\rho Z_2)}+\frac{(1-\eta)\beta_2T_2}{\delta+\rho Z_2}\\
&= \left[\frac{a_0\eta\beta_1T^*N}{(d_0+a_0)c}+\frac{(1-\eta)\beta_1T^*N}{c}+\frac{a_0\eta\beta_2T^*}{(d_0+a_0)\delta}+\frac{(1-\eta)\beta_2T^*}{\delta}\right]\frac{1}{R_0}\\
&= 1.
\end{aligned}
$$

This leads to a contradiction. Thus E_2 is locally asymptotically stable when $R_1^a < R_1^c$. □

3.4. *Local stability of the infected equilibrium E_3*

Theorem 3.4. *Suppose $R_1^a > 1$. Then the antibody-present and CTL immune-free equilibrium E_3 is locally asymptotically stable when $R_2^c < 1$ and unstable when $R_2^c > 1$.*

Proof. The characteristic equation at E_3 is

$$
\begin{aligned}
&(x+\lambda+\beta_1V_3+\beta_2I_3)(x+d_0+a_0)[qV_3aA_3+x(x+c+qA_3)](x+\delta)\\
&\quad\times\left(x-\frac{eI_3}{1+\alpha I_3}+b\right)\\
&\quad=(x+\lambda)\left(x-\frac{eI_3}{1+\alpha I_3}+b\right)\{(x+d_0+a_0)(1-\eta)\beta_1T_3N\delta x+a_0\eta\beta_2T_3\\
&\quad\times[qV_3aA_3+x(x+c+qA_3)]+a_0\eta\beta_1T_3N\delta x+(1-\eta)\beta_2T_3\\
&\quad\times[qV_3aA_3+x(x+c+qA_3)](x+d_0+a_0)\}.
\end{aligned}
$$

Thus there is an eigenvalue $x_7=\frac{eI_3}{1+\alpha I_3}-b=\frac{e\delta_1(c+qA_3)}{N\delta a+(c+qA_3)\delta_1\alpha}-b$ and the others satisfy

$$
\begin{aligned}
&(x+\lambda+\beta_1V_3+\beta_2I_3)(x+d_0+a_0)[qV_3aA_3+x(x+c+qA_3)](x+\delta)\\
&\quad=(x+\lambda)\{(x+d_0+a_0)(1-\eta)\beta_1T_3N\delta x+a_0\eta\beta_2T_3[qV_3aA_3+x(x+c+qA_3)]\\
&\qquad+a_0\eta\beta_1T_3N\delta x+(1-\eta)\beta_2T_3[qV_3aA_3+x(x+c+qA_3)](x+d_0+a_0)\}.
\end{aligned}
\tag{7}
$$

With the help of system (1), we have

$$\begin{aligned} c + qA_3 &= \frac{cR_0}{T^*}T_3 + \frac{(1-\eta)\beta_2 T_3 qA_3}{\delta} + \frac{a_0\eta\beta_2 T_3 qA_3}{(d_0+a_0)\delta} \\ &= \frac{T_3}{T^*}(cR_0 + R_{02}qA_3) \\ &= \frac{\frac{T_3}{T^*}R_{01}c}{1-\frac{T_3}{T^*}R_{02}} \\ &= \frac{\lambda N\delta a R_{01}c}{\lambda N\delta a(1-R_{02}) + \beta_1 N\delta\delta_1 + \beta_2\delta_1(c+qA_3)}, \end{aligned}$$

which yields that

$$c + qA_3 = \frac{\begin{array}{c}\lambda N\delta a(R_{02}-1) - \beta_1 N\delta\delta_1 \\ + \sqrt{[\lambda N\delta a(1-R_{02}) + \beta_1 N\delta\delta_1]^2 + 4\beta_2\delta_1\lambda N\delta a R_{01}c}\end{array}}{2\beta_2\delta_1}.$$

We can obtain $c + qA_3 > \frac{N\delta ab}{\delta_1(e-b\alpha)}$ if $R_2^c = \frac{\frac{(e-b\alpha)\delta_1 c}{N\delta ab}R_{01} + R_{02}}{1+\frac{\beta_1\delta_1(e-b\alpha)+\beta_2 ba}{\lambda a(e-b\alpha)}} > 1$. Therefore, $x_7 > 0$ if $R_2^c > 1$, which means that E_3 is unstable if $R_2^c > 1$. Suppose $R_2^c < 1$. Then $x_7 < 0$. We establish that the remaining roots of Eq. (7) exhibit negative real parts. Otherwise, suppose that (7) has a root $x = a^* + ib^*$ with $a^* \geq 0$. Dividing both sides of (7) by $(x+\lambda+\beta_1 V_3+\beta_2 I_3)(x+d_0+a_0)[qV_3 aA_3 + x(x+c+qA_3)](x+\delta)$ yields

$$\begin{aligned} 1 = \frac{x+\lambda}{x+\lambda+\beta_1 V_3+\beta_2 I_3}\Bigg\{ &\frac{(1-\eta)\beta_1 T_3 N\delta x}{[qV_3 aA_3 + x(x+c+qA_3)](x+\delta)} + \frac{(1-\eta)\beta_2 T_3}{x+\delta} \\ &+ \frac{a_0\eta\beta_1 T_3 N\delta x}{(x+d_0+a_0)[qV_3 aA_3 + x(x+c+qA_3)](x+\delta)} + \frac{a_0\eta\beta_2 T_3}{(x+d_0+a_0)(x+\delta)}\Bigg\}. \end{aligned}$$

Denote the right-hand side by Λ_3. If $a^* = b^* = 0$, then according to $c + qA_3 = \frac{\frac{T_3}{T^*}R_{01}c}{1-\frac{T_3}{T^*}R_{02}} > 0$, we can derive $R_{02} < \frac{T^*}{T_3}$. Therefore,

$$\begin{aligned} |\Lambda_3| &= \frac{\lambda}{\lambda+\beta_1 V_3+\beta_2 I_3}\left[\frac{(1-\eta)\beta_2 T_3}{\delta} + \frac{a_0\eta\beta_2 T_3}{(d_0+a_0)\delta}\right] \\ &= \frac{\lambda}{\lambda+\beta_1 V_3+\beta_2 I_3}\frac{R_{02}T_3}{T^*} \\ &= \frac{\lambda}{\frac{\lambda T^*}{T_3}}\frac{R_{02}T_3}{T^*} \\ &= R_{02}\frac{T_3^2}{T^{*2}} < \frac{T_3}{T^*} \\ &< 1. \end{aligned}$$

This leads to a contradiction. Now assume $a^{*2} + b^{*2} > 0$. Then

$$
\begin{aligned}
|\Lambda_3| &\le \left|\frac{x+\lambda}{x+\lambda+\beta_1 V_3+\beta_2 I_3}\right| \times \left\{\left|\frac{(1-\eta)\beta_1 T_3 N\delta x}{[qV_3 aA_3 + x(x+c+qA_3)](x+\delta)}\right|\right. \\
&\quad + \left|\frac{(1-\eta)\beta_2 T_3}{x+\delta}\right| + \left|\frac{a_0\eta\beta_1 T_3 N\delta x}{(x+d_0+a_0)[qV_3 aA_3 + x(x+c+qA_3)](x+\delta)}\right| \\
&\quad \left. + \left|\frac{a_0\eta\beta_2 T_3}{(x+d_0+a_0)(x+\delta)}\right|\right\} \\
&< \left[\left|\frac{(1-\eta)\beta_1 T_3 N\delta}{x+\delta}\right| + \left|\frac{a_0\eta\beta_1 T_3 N\delta}{(x+d_0+a_0)(x+\delta)}\right|\right] \times \left|\frac{x}{qV_3 aA_3 + x(x+c+qA_3)}\right| \\
&\quad + \left|\frac{a_0\eta\beta_2 T_3}{(x+d_0+a_0)(x+\delta)}\right| + \left|\frac{(1-\eta)\beta_2 T_3}{x+\delta}\right| \\
&= \left[\left|\frac{(1-\eta)\beta_1 T_3 N\delta}{x+\delta}\right| + \left|\frac{a_0\eta\beta_1 T_3 N\delta}{(x+d_0+a_0)(x+\delta)}\right|\right] \times \left|\frac{1}{\frac{qV_3 aA_3}{x} + x + c + qA_3}\right| \\
&\quad + \left|\frac{a_0\eta\beta_2 T_3}{(x+d_0+a_0)(x+\delta)}\right| + \left|\frac{(1-\eta)\beta_2 T_3}{x+\delta}\right| \\
&\le \left|\frac{(1-\eta)\beta_1 T_3 N\delta}{x+\delta}\right| \times \left|\frac{1}{c+qA_3}\right| + \left|\frac{a_0\eta\beta_1 T_3 N\delta}{(x+d_0+a_0)(x+\delta)}\right| \times \left|\frac{1}{c+qA_3}\right| \\
&\quad + \left|\frac{a_0\eta\beta_2 T_3}{(x+d_0+a_0)(x+\delta)}\right| + \left|\frac{(1-\eta)\beta_2 T_3}{x+\delta}\right| \\
&< \frac{(1-\eta)\beta_1 T_3 N}{c+qA_3} + \frac{a_0\eta\beta_2 T_3}{(d_0+a_0)\delta} + \frac{a_0\eta\beta_1 T_3 N}{(d_0+a_0)(c+qA_3)} + \frac{(1-\eta)\beta_2 T_3}{\delta} \\
&= \frac{(1-\eta)\beta_1 T^* N}{cR_0 + R_{02}qA_3} + \frac{a_0\eta\beta_2 T^* T_3}{(d_0+a_0)\delta T^*} + \frac{a_0\eta\beta_1 T^* N}{(d_0+a_0)(cR_0 + R_{02}qA_3)} \\
&\quad + \frac{(1-\eta)\beta_2 T^* T_3}{\delta T^*} \\
&= \frac{cR_{01}}{cR_0 + R_{02}qA_3} + \frac{R_{02}T_3}{T^*} = \frac{cR_{01}}{cR_0 + R_{02}qA_3} + \frac{(c+qA_3)R_{02}}{cR_0 + R_{02}qA_3} = 1.
\end{aligned}
$$

This also leads to a contradiction. Therefore, E_3 is locally asymptotically stable when $R_2^c < 1$. □

3.5. *Local stability of the infected equilibrium E_4*

Theorem 3.5. *Suppose $R_1^a > R_1^c$ and $R_2^c > 1$. Then the CTL and antibody immunity coexistence equilibrium E_4 is locally asymptotically stable.*

Proof. The characteristic equation at E_4 is

$$\begin{aligned}
&(x+\lambda+\beta_1 V_4+\beta_2 I_4)(x+d_0+a_0)[qV_4aA_4+x(x+c+qA_4)]\\
&\quad\times\left[(x+\delta+\rho Z_4)x+\frac{eZ_4\rho I_4}{(1+\alpha I_4)^2}\right]\\
&=(x+\lambda)\{(x+d_0+a_0)(1-\eta)\beta_1 T_4 N\delta x^2+a_0\eta\beta_2 T_4 x[qV_4aA_4\\
&\quad+x(x+c+qA_4)]+a_0\eta\beta_1 T_4 N\delta x^2+(1-\eta)\beta_2 T_4 x[qV_4aA_4\\
&\quad+x(x+c+qA_4)](x+d_0+a_0)\}. \qquad (8)
\end{aligned}$$

Let $g=(x+\delta+\rho Z_4)x+\frac{eZ_4\rho I_4}{(1+\alpha I_4)^2}$. We establish that all the roots of Eq. (8) exhibit negative real parts. If this were not the case, there would exist a root $x=a^*+ib^*$ with a nonnegative real part. Dividing both sides of (8) by $(x+\lambda+\beta_1V_4+\beta_2I_4)(x+d_0+a_0)[qV_4aA_4+x(x+c+qA_4)]g$ gives us

$$\begin{aligned}
1=&\frac{x+\lambda}{x+\lambda+\beta_1V_4+\beta_2I_4}\times\left\{\frac{a_0\eta\beta_2T_4x}{(x+d_0+a_0)g}+\frac{(1-\eta)\beta_2T_4x}{g}\right.\\
&\left.+\frac{(1-\eta)\beta_1T_4N\delta x^2}{[qV_4aA_4+x(x+c+qA_4)]g}+\frac{a_0\eta\beta_1T_4N\delta x^2}{(x+d_0+a_0)[qV_4aA_4+x(x+c+qA_4)]g}\right\}.
\end{aligned}$$

Let the right-hand side be Λ_4. If $a^*=b^*=0$, then we have $\Lambda_4=0$, which leads to a contradiction. Now assume $a^{*2}+b^{*2}>0$. Then we have

$$\begin{aligned}
|\Lambda_4|\le&\left|\frac{x+\lambda}{x+\lambda+\beta_1V_4+\beta_2I_4}\right|\times\left\{\left|\frac{(1-\eta)\beta_1T_4N\delta x^2}{[qV_4aA_4+x(x+c+qA_4)]g}\right|\right.\\
&+\left|\frac{a_0\eta\beta_2T_4x}{(x+d_0+a_0)g}\right|+\left|\frac{a_0\eta\beta_1T_4N\delta x^2}{(x+d_0+a_0)[qV_4aA_4+x(x+c+qA_4)]g}\right|\\
&\left.+\left|\frac{(1-\eta)\beta_2T_4x}{g}\right|\right\}\\
\le&\left\{\left[|(1-\eta)\beta_1T_4N\delta|+\left|\frac{a_0\eta\beta_1T_4N\delta}{x+d_0+a_0}\right|\right]\times\left|\frac{x}{qV_4aA_4+x(x+c+qA_4)}\right|\right.\\
&\left.+\left|\frac{a_0\eta\beta_2T_4}{x+d_0+a_0}\right|+|(1-\eta)\beta_2T_4|\right\}\times\left|\frac{x}{(x+\delta+\rho Z_4)x+\frac{eZ_4\rho I_4}{(1+\alpha I_4)^2}}\right|\\
=&\left\{\left[|(1-\eta)\beta_1T_4N\delta|+\left|\frac{a_0\eta\beta_1T_4N\delta}{x+d_0+a_0}\right|\right]\times\left|\frac{1}{\frac{qV_4aA_4}{x}+x+c+qA_4}\right|\right.\\
&\left.+\left|\frac{a_0\eta\beta_2T_4}{x+d_0+a_0}\right|+|(1-\eta)\beta_2T_4|\right\}\times\left|\frac{1}{x+\delta+\rho Z_4+\frac{eZ_4\rho I_4}{(1+\alpha I_4)^2x}}\right|
\end{aligned}$$

$$
\begin{aligned}
&\leq \left\{ \left[|(1-\eta)\beta_1 T_4 N\delta| + \left| \frac{a_0\eta\beta_1 T_4 N\delta}{x+d_0+a_0} \right| \right] \times \frac{1}{c+qA_4} + \left| \frac{a_0\eta\beta_2 T_4}{x+d_0+a_0} \right| \right. \\
&\quad \left. + |(1-\eta)\beta_2 T_4| \right\} \times \frac{1}{\delta+\rho Z_4} \\
&< \frac{(1-\eta)\beta_1 T_4 N\delta}{(c+qA_4)(\delta+\rho Z_4)} + \frac{a_0\eta\beta_1 T_4 N\delta}{(d_0+a_0)(\delta+\rho Z_4)(c+qA_4)} + \frac{a_0\eta\beta_2 T_4}{(d_0+a_0)(\delta+\rho Z_4)} \\
&\quad + \frac{(1-\eta)\beta_2 T_4}{\delta+\rho Z_4} \\
&= \left[\frac{a_0\eta\beta_1 T^* N}{d_0+a_0} + \frac{a_0\eta\beta_2 T^*(c+qA_4)}{(d_0+a_0)\delta} + (1-\eta)\beta_1 T^* N \right. \\
&\quad \left. + \frac{(1-\eta)\beta_2 T^*(c+qA_4)}{\delta} \right] \frac{1}{R_0 c + R_{02} q A_4} \\
&= 1.
\end{aligned}
$$

This again leads to a contradiction. Thus E_4 is locally asymptotically stable. □

4. Sensitivity Analysis

To assess the impact of parameters on the reproduction numbers, we perform a sensitivity analysis [28] on them. For this purpose, we employ the Latin hypercube sampling (LHS) method and the partial rank correlation coefficients (PRCCs) method. The used parameter values, taken from [2, 21, 29–32], are listed in Table 1.

To conduct the sensitivity analysis, we calculate the PRCCs between the four reproduction numbers and each parameter, as shown in Fig. 1. The sign of the PRCC denotes whether the input variable exhibits a positive or negative correlation with the output variable [33]. Additionally, the magnitude of the PRCC indicates the strength of the relationship between each input parameter and the output variable. Specifically, a PRCC value greater than 0.4 indicates a strong correlation, while a value between 0.2 and 0.4 suggests a moderate correlation. Conversely, a PRCC value below 0.2 indicates a weak correlation [19].

Table 1. Parameter values.

Parameter	Value	Parameter	Value
e	0.2 day^{-1}	a	0.003 μL · day^{-1}
N	2000 virions/cell	b	0.1 day^{-1}
β_1	2.4×10^{-8} μL · day^{-1}	δ	1 day^{-1}
β_2	1×10^{-6} μL · day^{-1}	η	0.05
λ	0.01 day^{-1}	c	23 day^{-1}
a_0	0.1 day^{-1}	δ_1	10 day^{-1}
d_0	0.001 day^{-1}	α	0.01
T^*	10^6 cells/mm^3	ρ	0.0024 μL · day^{-1}

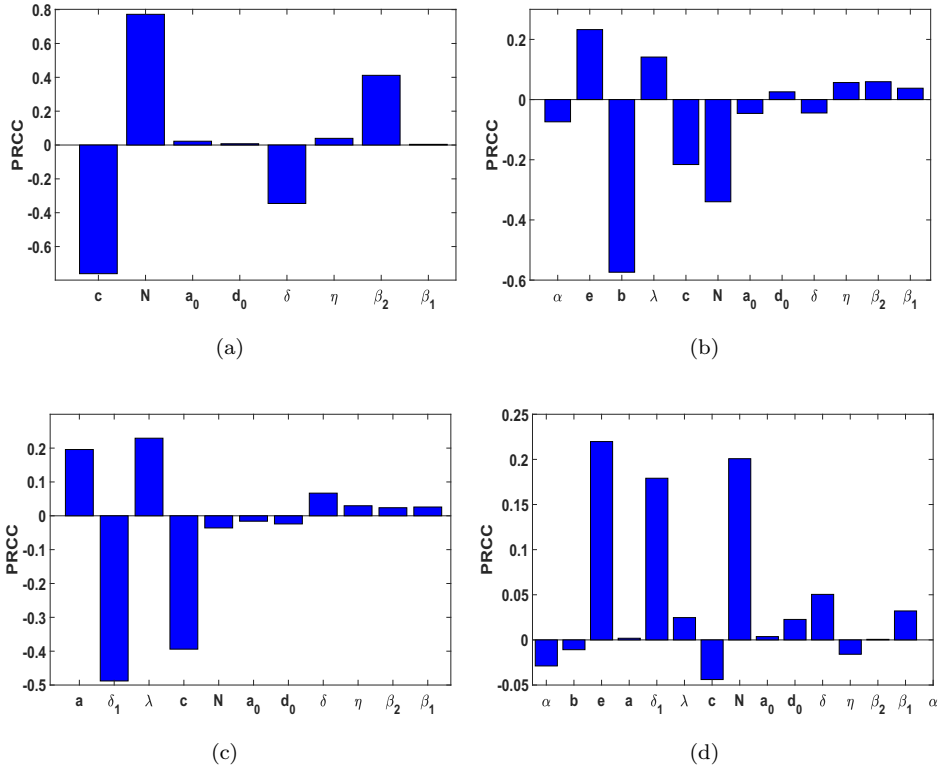

Fig. 1. The sensitivity analyses of the four reproduction numbers: (a) R_0, (b) R_1^c, (c) R_1^a and (d) R_2^c.

Based on these guidelines, we observe from Fig. 1(a) that the parameters with the most significant influence on R_0 are c, N, δ, and β_2. Similarly, for the reproduction number R_1^c, the influences of c, N, and e are similar, while b exhibits the highest significance, as depicted in Fig. 1(b). Figure 1(c) demonstrates that R_1^a is greatly correlated with δ, c, and λ. Similarly, by referring to Fig. 1(d), we can determine the relationships between R_2^c and each parameter.

5. Numerical Simulations

Numerical simulations are performed in this section to illustrate and extend the theoretical results for model (1).

5.1. *Local stability*

First, we choose $N = 800$, $\eta = 0.4$, $e = 0.000011$, $a = 0.00002$, $\alpha = 0.0001$, $q = 0.1$, and the remaining parameters are the same as those in Table 1. In this case, $R_0 = 1.69$, $R_1^c = 0.19$, and $R_1^a = 0.79$. By Theorem 3.2, the CTL immune-free and

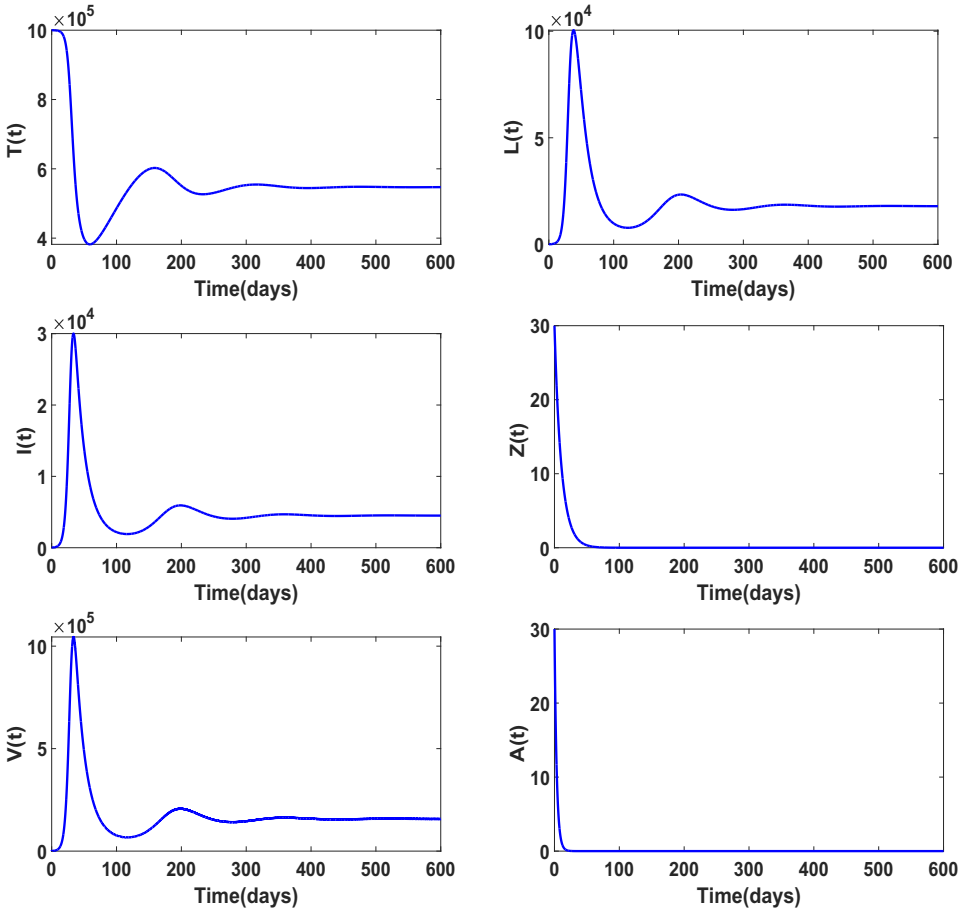

Fig. 2. Solutions of system (1) converge to the CTL immune-free and antibody-free equilibrium when $R_0 > 1$ and $\max\{R_1^c, R_1^a\} < 1$. Initial condition is: $(T(0), L(0), I(0), Z(0), V(0), A(0)) = (10^6, 20, 30, 30, 50, 30)$.

antibody-free equilibrium $E_1 = (547135, 17904, 4501, 0, 156748, 0)$ is locally asymptotically stable. See Fig. 2.

Next, we choose $e = 0.2$, $b = 0.8$, $a = 0.00002$, $q = 0.1$, and the remaining parameters are the same as those in Table 1. In this case, $R_0 = 2.74$, $R_1^c = 2.73$, and $R_1^a = 0.68$. By Theorem 3.3, the CTL immune-present and antibody-free equilibrium $E_2 = (998765, 6, 4, 867, 362, 0)$ is locally asymptotically stable. See Fig. 3.

We now change e, b, a, and δ_1 to $e = 0.0003$, $b = 0.1$, $a = 0.001$, and $\delta_1 = 1$. The other values are the same as those for Fig. 3. We obtain that $R_0 = 2.74$, $R_1^a = 2.69$, and $R_2^c = 0.97$. By Theorem 3.4, the antibody-present and CTL immune-free equilibrium $E_3 = (952425, 235, 475, 0, 999, 9280)$ is locally asymptotically stable. See Fig. 4.

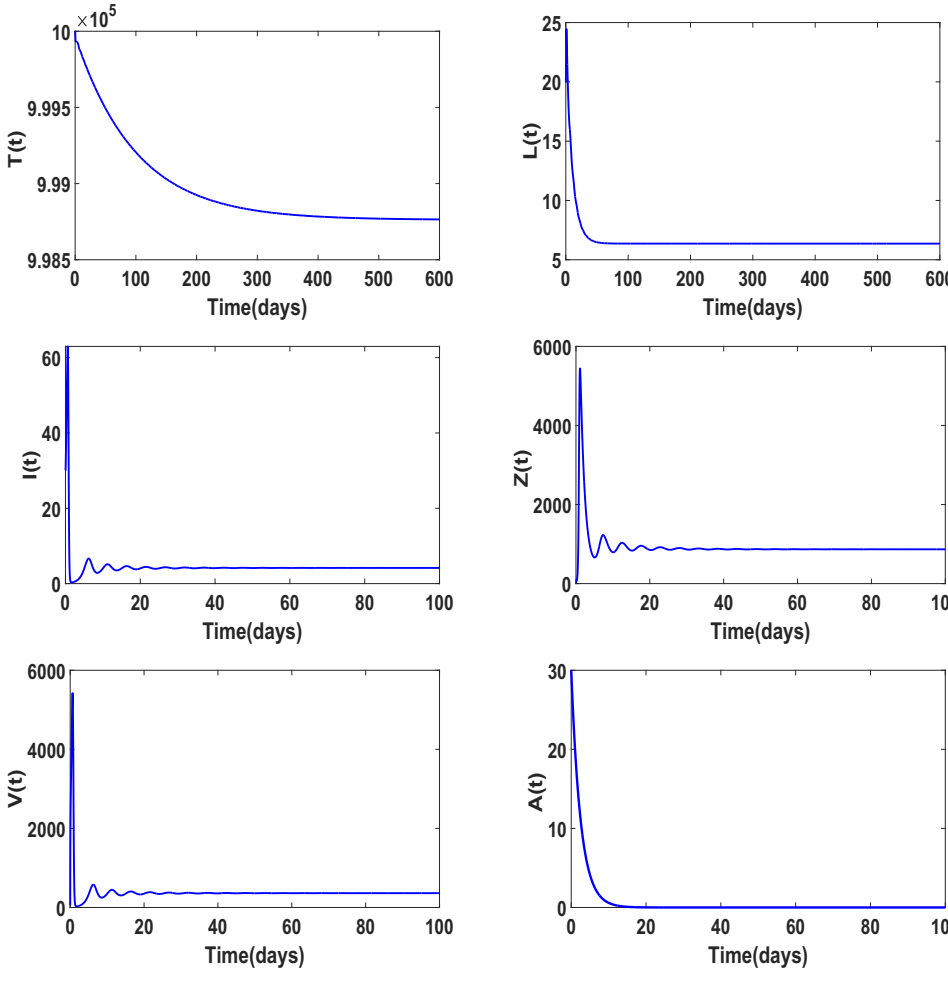

Fig. 3. Solutions of system (1) converge to the CTL immune-present and antibody-free equilibrium when $R_1^c > 1$ and $R_1^a < R_1^c$. Initial condition is: $(T(0), L(0), I(0), Z(0), V(0), A(0)) = (10^6, 20, 30, 30, 50, 30)$.

Furthermore, with $e = 0.2$, $b = 0.8$, $a = 0.004$, and the other parameter values being the same as those for Fig. 4, we have $R_0 = 2.74$, $R_2^c = 2.25$, $R_1^c = 2.68$, and $R_1^a = 2.74$. By Theorem 3.5, the CTL and antibody immunity coexistence equilibrium $E_4 = (999002, 4, 4, 598, 249, 91)$ is locally asymptotically stable. See Fig. 5.

5.2. *Effect of e and a on the dynamics of system* (1)

By conducting the sensitivity analysis (as shown in Fig. 1), we can qualitatively discern the positive and negative effects of parameters on the four reproduction

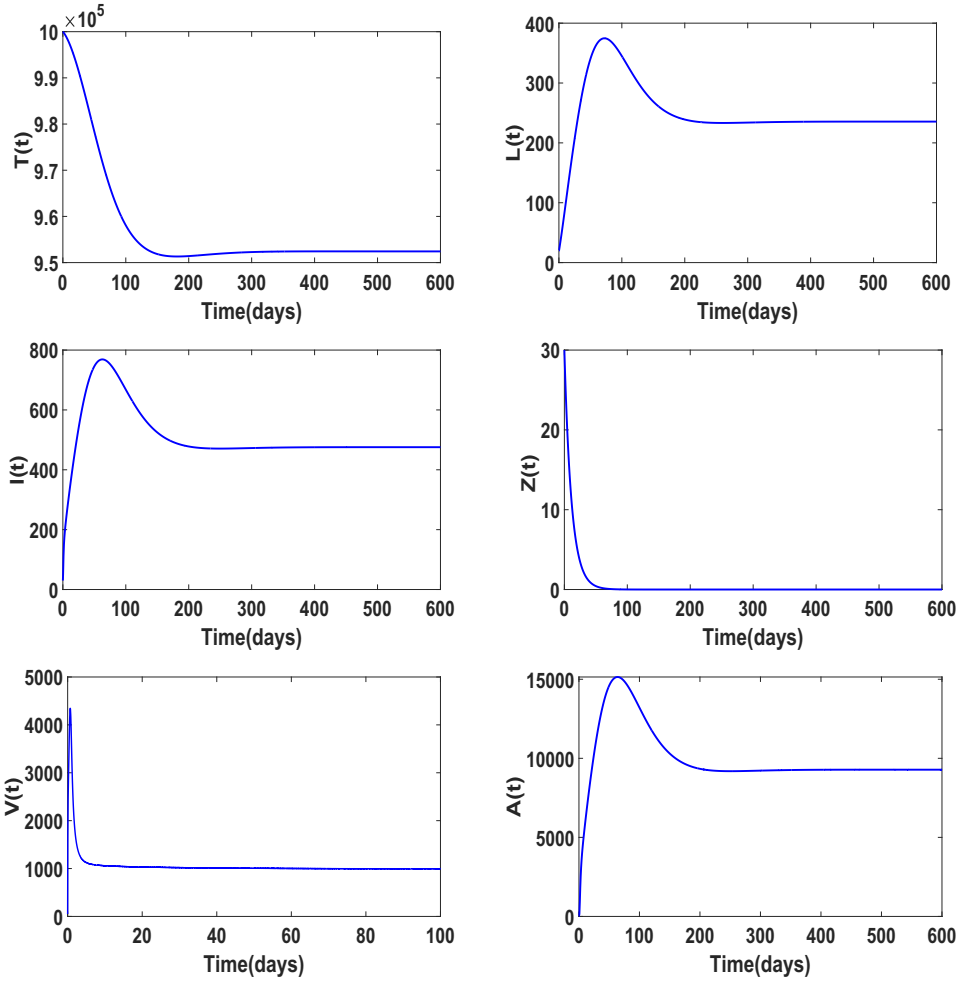

Fig. 4. Solutions of system (1) converge to the antibody-present and CTL immune-free equilibrium when $R_1^a > 1$ and $R_2^c < 1$. Initial condition is: $(T(0), L(0), I(0), Z(0), V(0), A(0)) = (10^6, 20, 30, 30, 50, 30)$.

numbers, as well as quantitatively evaluate the magnitude of these effects. Nevertheless, the influence of sensitive parameters on the dynamic behavior of the population remains uncertain. To address this, we will examine the influence of the sensitive parameters e and a on the dynamics of system (1) through numerical simulations.

First, we observe that though the activation of CTL immune response alone may not be sufficient to eradicate the virus, the size of uninfected cells increases with enhanced CTL activity. Additionally, as the parameter e increases, the levels of latent cells, infected cells, and viruses reach lower stabilized levels (see Fig. 6). On the other hand, neutralizing antibodies specifically bind to viruses, leading to

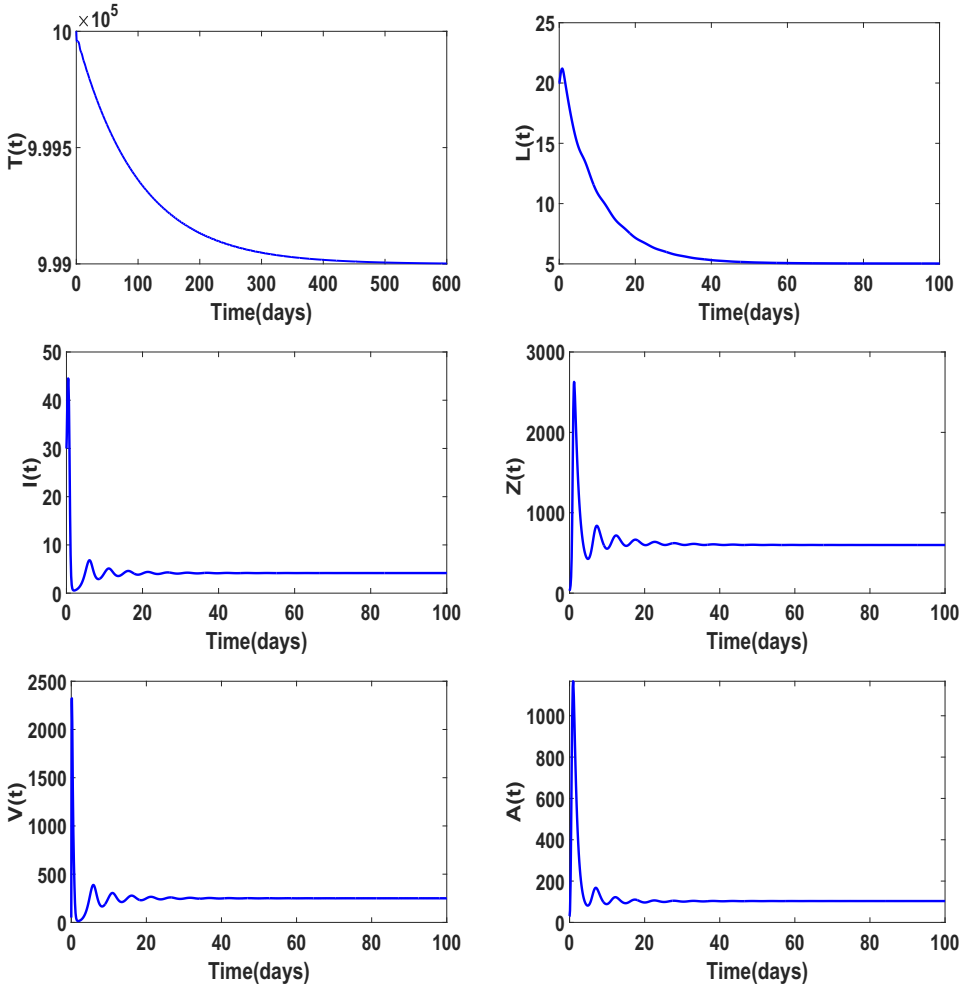

Fig. 5. Solutions of system (1) converge to the CTL and antibody immune coexistence equilibrium when $R_2^c > 1$ and $R_1^a > R_1^c$. Initial condition is: $(T(0), L(0), I(0), Z(0), V(0), A(0)) = (10^6, 20, 30, 30, 50, 30)$.

a significant reduction in the viral population as the parameter a increases (see Fig. 7). These findings indicate that both CTL immunity and antibody immunity play crucial roles in increasing the population of uninfected cells and decreasing the numbers of latent cells, infected cells, and viruses.

Moreover, Fig. 6 illustrates the competitive nature of adaptive immune responses, where the antibody immune response diminishes to zero when the CTL immune response is at a high level. This suggests that there is a competitive relationship between the two immune responses, with the CTL immune response exerting a stronger influence. Consequently, the CTL immune response is indispensable in shaping the dynamics of viral infection.

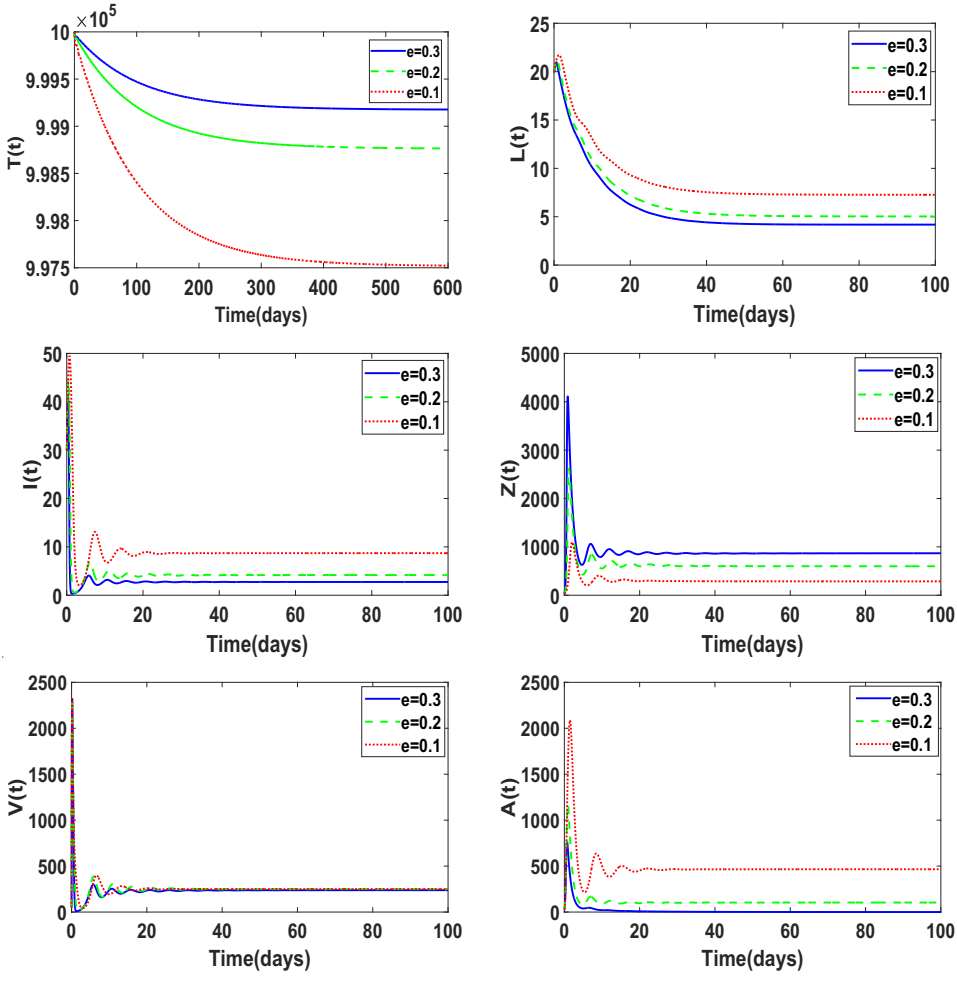

Fig. 6. The effect of e on the dynamics of the model with the same values for the other parameters and initial condition as those for Fig. 5.

Overall, these results shed light on the intricate interactions between the immune responses and the viral dynamics, emphasizing the significance of both CTL and antibody immunities in controlling the infection.

5.3. *Effect of β_2 on viruses and infected cells*

To examine the impact of cell-to-cell transmission, numerical simulations are conducted to assess its contribution throughout the infection process. Initially, we set β_2 to zero to compare HIV infection in the absence of cell-to-cell transmission with infection involving both transmission routes ($\beta_2 = 0$ and $\beta_2 = 1 \times 10^{-6}$). The results clearly indicate that cell-to-cell transmission plays a favorable role in HIV transmission (refer to Fig. 8).

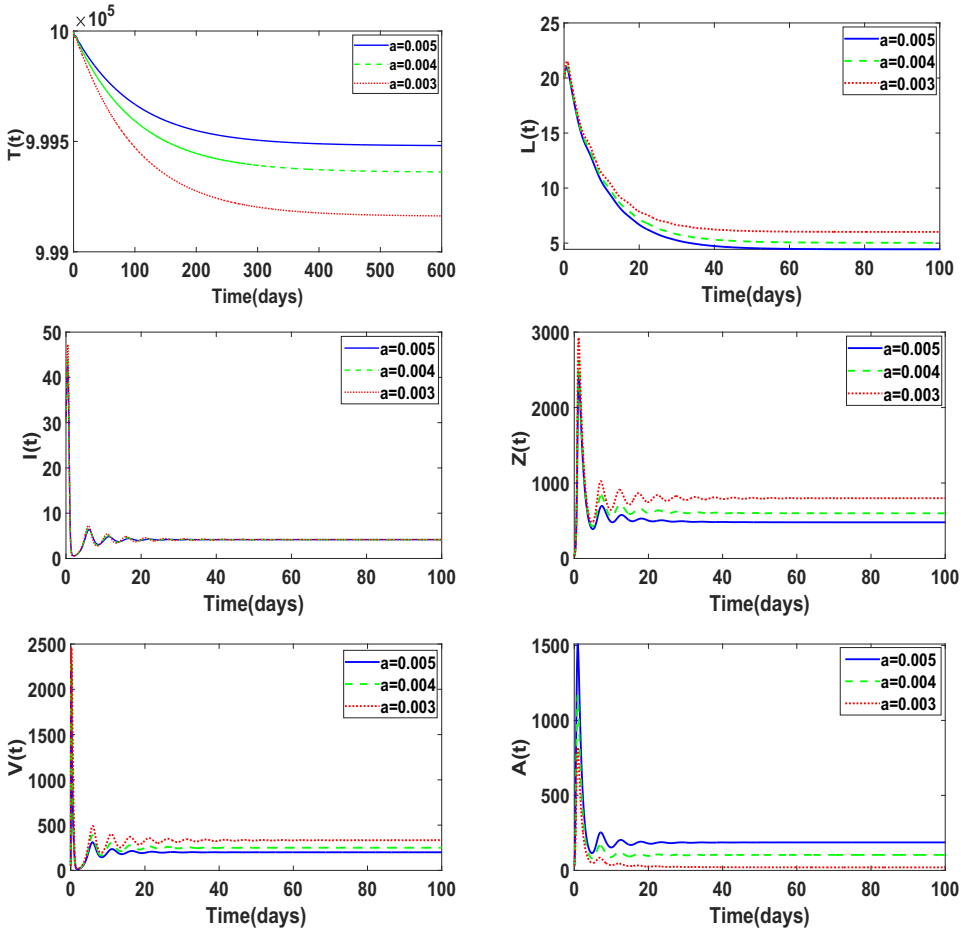

Fig. 7. The effect of a on the dynamics of the model with the same values for the other parameters and initial condition as those for Fig. 5.

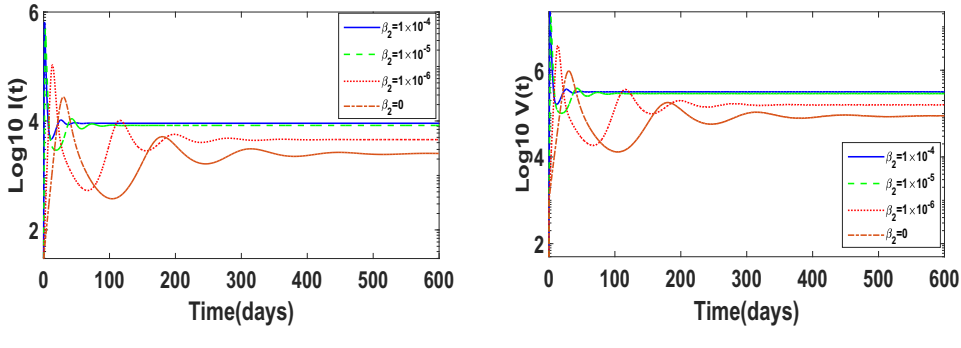

Fig. 8. The effect of β_2 on the dynamics of the model with the same values for the other parameters and initial condition as those for Fig. 2.

Subsequently, we increased β_2 to examine the variations in peak levels of infected cells and viruses, as well as the time required to reach these peak levels ($\beta_2 = 1 \times 10^{-6}$, $\beta_2 = 1 \times 10^{-5}$, and $\beta_2 = 1 \times 10^{-4}$). Our findings reveal that as β_2 increases, infected cells and viruses reach their peak levels more rapidly. Moreover, the peak levels themselves also become higher with increasing β_2. This finding underscores the significance of considering cell-to-cell transmission in the study of HIV infection dynamics, emphasizing its importance and suggesting that it should not be overlooked.

6. Discussion and Conclusion

Several previous HIV infection models have primarily focused on the cell-free infection mode, often neglecting latent infection [5, 6]. Furthermore, the consideration of adaptive immune responses has predominantly focused on either CTLs or antibodies, with few studies exploring the coexistence of both immune responses [2, 17]. The novelty of this research lies in the construction of a mathematical model that encompasses two distinct modes of infection, two types of immune responses, and latent infection. The model also incorporates a saturated CTL immune response, thereby introducing additional intricacies to the analysis.

The mathematical model presented in this study has been rigorously analyzed, ensuring that the solutions are nonnegative and bounded. We show that this model has five possible equilibria: infection-free equilibrium E_0, CTL immune-free and antibody-free equilibrium E_1, CTL immune-present and antibody-free equilibrium E_2, antibody-present and CTL immune-free equilibrium E_3, and CTL and antibody immune coexistence equilibrium E_4. In addition, the existence of these equilibria is determined by four threshold parameters, which are the basic reproduction number R_0 and the immune reproduction numbers R_1^c, R_1^a, and R_2^c. They also characterize the local characteristics of the model.

As we know, the basic reproductive number of the system plays a key role in predicting whether the infection will persist. By the explicit expression of R_0, it consists of the contributions of the two transmission routes. Figure 1(a) shows that β_2 has a strong positive correlation with R_0. And Fig. 8 shows that cell-to-cell transmission is beneficial for HIV transmission and the time to reach the peak level of virus is shorter. Therefore, it is crucial to consider the transmission of the virus through the cell-to-cell route as a fundamental factor in the study of HIV infection.

Antiretroviral drugs have the ability to inhibit infection, resulting in a reduction in the values of β_1 and β_2, which can potentially lower the basic reproduction number to below 1. Immune therapy, on the other hand, can enhance the activation of both CTL and antibody responses, leading to an increase in the values of e and a, respectively. While the activation of immune responses may not have a direct impact on the basic reproduction number R_0, it can indirectly decrease its value by enhancing the clearance of infected cells and viruses (as depicted in Fig. 1(a)). Moreover, this can also influence other immune-related reproduction numbers and

contribute to the stability of the corresponding equilibria (as shown in Figs. 1(b)–1(d)). The impact of CTL stimulation on reducing the concentration of infected cells and increasing the level of uninfected cells is more pronounced, as observed in Figs. 6 and 7. Similarly, a higher rate of antibody immunity generation can significantly decrease the number of viruses. Notably, the last graph in Fig. 6 suggests a competitive relationship between CTL and antibody immune responses.

In this paper, our focus was primarily on analyzing the local dynamics of Eq. (1). Exploring the global dynamics poses a very challenging task, which we consider as a future work. Additionally, there are several extensions that can be made to the model. For instance, incorporating time delays that account for the integration of viral DNA into host cell DNA and incorporating logistic growth dynamics in the viral infection process can provide a more realistic description of the dynamic evolution of viruses and normal cells [19, 34, 35]. This paper only considers the immune response caused by the virus and does not take into account the effects of drug treatment on infected individuals. The model can also consider the impact of treatment strategies, e.g. combined antiretroviral treatment strategies, optimal control strategies while calculating the associated costs using optimal control theory [36].

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