Mathematical Analysis and Clinical Implications of an HIV Model with Adaptive Immunity

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In this paper, a mathematical model describing the human immunodeficiency virus (HIV) pathogenesis with adaptive immune response is presented and studied. The mathematical model includes six nonlinear differential equations describing the interaction between the uninfected cells, the exposed cells, the actively infected cells, the free viruses, and the adaptive immune response. The considered adaptive immunity will be represented by cytotoxic T-lymphocytes cells (CTLs) and antibodies. First, the global stability of the disease-free steady state and the endemic steady states is established depending on the basic reproduction number R_0, the CTL immune response reproduction number R_1^z, the antibody immune response reproduction number R_1^w, the antibody immune competition reproduction number R_2^w, and the CTL immune response competition reproduction number R_3^z. On the other hand, different numerical simulations are performed in order to confirm numerically the stability for each steady state. Moreover, a comparison with some clinical data is conducted and analyzed. Finally, a sensitivity analysis for R_0 is performed in order to check the impact of different input parameters.

1. Introduction

The human immunodeficiency virus (HIV) is a virus that gradually weakens the immune system since it targets the principal vital immune cells. It is considered as the main cause for several deadly diseases after the resulting acquired immunodeficiency syndrome (AIDS) is reached. With 36.7 million people living with HIV, 1.8 million people becoming newly infected with HIV, and more than 1 million deaths annually, HIV becomes a major global public health issue [1].

In the last decades, many mathematical models describing HIV dynamics were developed [2–11]. With the three main dynamics compartments that are free viruses, healthy CD4$^+$ T cells, and infected CD4$^+$ T cells, the first viral dynamics was presented and studied in [2]. Including the exposed cells as a new fourth compartment, a modified HIV viral model was tackled in [8]. More recently, the model describing HIV viral dynamics with another fifth compartment representing the cytotoxic T-lymphocytes (CTL) cells is formulated and studied in [9]. The authors study the global stability of the endemic states and illustrate the numerical simulations in order to show the numerical stability for each problem steady state. Notice that the adaptive immunity has two main arms that are cellular and humoral responses. The first one is mediated by CTL cells that play a crucial role in the infection by killing infected cells, while the second arm is mediated by the antibodies which are proteins that are produced by B cells and are specifically programmed to neutralize the viruses [12]. In this paper, we extend the recent work [9] by incorporating to the model this other main component of the adaptive immune response. The dynamics of the HIV infection model including these two arms of the adaptive immune response will be governed by the following nonlinear system of differential equations:

$$\begin{cases} \dot{x} = \lambda - d_1 x - \dfrac{k_1 xv}{x+v}, \\[2mm] \dot{s} = \dfrac{k_1 xv}{x+v} - d_2 s - k_2 s, \\[2mm] \dot{y} = k_2 s - d_3 y - pyz, \\[2mm] \dot{v} = ay - d_4 v - qvw, \\[2mm] \dot{w} = gvw - hw, \\[2mm] \dot{z} = cyz - bz. \end{cases} \tag{1}$$

With the initial conditions, $x(0) = x_0$, $s(0) = s_0$, $y(0) = y_0$, $v(0) = v_0$, $w(0) = w_0$, and $z(0) = z_0$. In this model, x, s, y, v, w, and z denote the concentration of uninfected cells, exposed cells, infected cells, free viruses, antibodies, and CTL cells, respectively. Susceptible host cells, CD4$^+$ T cells, are produced at a rate λ and die at a rate $d_1 x$ and become infected by virus at a rate $k_1 xv/(x+v)$. The exposed cells die at a rate $(d_2 + k_2)s$. The infected cells increase at rate $k_2 s$ and decay at rate $d_3 y$ and are killed by the CTL response at a rate pyz. Free viruses are produced by infected cells at a rate ay and decay at a rate $d_4 v$ and are killed by the antibodies at a rate qvw. Antibodies develop in response to free viruses at a rate gvw and decay at a rate hw. Finally, CTLs expand in response to viral antigen derived from infected cells at a rate cyz and decay in the absence of antigenic stimulation at a rate bz. Note that this model (1), includes the saturated rate, called the saturated mass action [11], which describes better the rate of viral infection. Such HIV viral dynamics is illustrated in Figure 1. The model (1) extends the recent work [9] by adding a new compartment which is the adaptive immune response. In addition to the mathematical analysis of this new model, we will compare our simulations with some clinical data and we will perform a sensitivity analysis of our parameters.

The rest of the paper is organized as follows. The analysis of the model is described in Section 2. In Section 3, we illustrate numerical simulations and compare the model solution to some clinical data. We conclude in the last section.

2. Analysis of the Model

2.1. Positivity and Boundedness. For the problems dealing with cell population evolution, the cell densities should remain nonnegative and bounded. In this section, we will establish the positivity and boundedness of solutions of the model (1). First of all, for biological reasons, the parameters x_0, s_0, y_0, v_0, w_0, and z_0 must be larger than or equal to 0. Hence, we have the following result:

Proposition 1. *For any initial conditions* $(x_0, s_0, y_0, v_0, w_0, z_0)$*, system (1) has a unique solution. Moreover, this solution is nonnegative and bounded for all* $t \geq 0$*.*

Proof. By the classical functional differential equations theory (see for instance [13], and the references therein), we can confirm that there is a unique local solution $(x(t), s(t), y(t), v(t), w(t), z(t))$ to system (1) in $[0, t_m)$.

We have the following:

$$\dot{x}\big|_{x=0} = \lambda \geq 0,$$

$$\dot{s}\big|_{y=0} = \frac{k_1 xv}{x+v} \geq 0,$$

$$\dot{y}\big|_{s=0} = k_2 s \geq 0, \tag{2}$$

$$\dot{v}\big|_{v=0} = ay \geq 0,$$

$$\dot{w}\big|_{w=0} = 0 \geq 0,$$

$$\dot{z}\big|_{z=0} = 0 \geq 0,$$

this shows the positivity of solutions for $t \in [0, t_m)$. For the boundedness of the solutions,

$$X = x + s + y + \frac{p}{c} z, \tag{3}$$

then, we have

$$\dot{X} = \lambda - d_1 x - d_2 s - d_3 y - \frac{bp}{c} z$$
$$\leq \lambda - \delta X, \tag{4}$$

where $\delta = \min(d_1, d_2, d_3, b)$. So,

$$X(t) \leq X(0) e^{-\delta t} + \frac{\lambda}{\delta} \left(1 - e^{-\delta t}\right)$$
$$\leq X(0) e^{-\delta t} + \frac{\lambda}{\delta}. \tag{5}$$

Similarly, let us consider

$$V = v + \frac{q}{g} w; \tag{6}$$

therefore,

$$\dot{V} = ay - d_4 v - \frac{hq}{g} w$$
$$\leq ay - \delta V, \tag{7}$$

where $\alpha = \min(d_4, h)$, then,

$$V(t) \leq V(0) + \frac{a}{\alpha} \|y\|_\infty, \tag{8}$$

this proves that the solutions $x(t)$, $s(t)$, $y(t)$, $v(t)$, $w(t)$, and $z(t)$ are bounded. Hence, every local solution can be prolonged up to any time $t_m > 0$, which means that the solution exists globally. □

2.2. Steady States. System (1) has an infection-free equilibrium $E_f = (\lambda/d_1, 0, 0, 0, 0, 0)$, corresponding to the
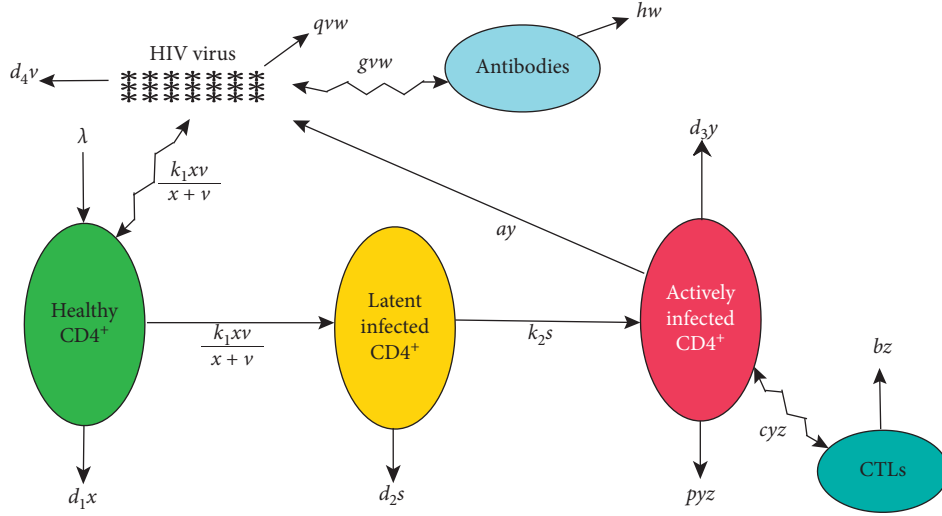
FIGURE 1: Schematic of the model under consideration.

maximal level of healthy CD4$^+$ T-cells. By simple calculation, the basic reproduction number of (1) is given by

$$R_0 = \frac{ak_1k_2}{d_3d_4(d_2 + k_2)} = k_1\frac{k_2}{d_2 + k_2} \times \frac{a}{d_3} \times \frac{1}{d_4},\qquad(9)$$

where $k_2/(d_2 + k_2)$ is the proportion of the exposed cells to become productively infected cells, a/d_3 is the number of free virus production by an infected cell, and $1/d_4$ is the average life of virus. From a biological point of view, R_0 stands for the average number of secondary infections generated by one infected cell when all cells are susceptibles. Depending on the value of this basic reproduction number R_0; in other words, depending on these three biological proportions, we will study the stability of the free-disease and the endemic equilibria. Indeed, it is easy to see that when $R_0 > 1$, system (1) has four of them. The first endemic equilibrium is $E_1 = (x_1, s_1, y_1, v_1, w_1, z_1)$, where

$$x_1 = \frac{\lambda}{d_1 + k_1(1 - (1/R_0))},$$

$$s_1 = \frac{\lambda k_1(1 - (1/R_0))}{(d_2 + k_2)(d_1 + k_1(1 - (1/R_0)))},$$

$$y_1 = \frac{\lambda d_4(R_0 - 1)}{ad_1 + ak_1(1 - (1/R_0))},\qquad(10)$$

$$v_1 = \frac{\lambda(R_0 - 1)}{d_1 + k_1(1 - (1/R_0))},$$

$$w_1 = 0,$$

$$z_1 = 0.$$

We define the antibody immune response reproduction number by

$$R_1^w = \frac{gv_1}{h} = \frac{g\lambda(R_0 - 1)}{d_1h + hk_1(1 - (1/R_0))},\qquad(11)$$

where $1/h$ is the average life of antibodies cells and v_1 is the number of free viruses at E_1. For the biological significance, R_1^w represents the average number of the antibodies activated by virus when the viral infection is successful in the absence of CTL immune response.

Furthermore, we introduce the CTL immune response reproduction number given by

$$R_1^z = \frac{cy_1}{b} = \frac{c\lambda d_4(R_0 - 1)}{abd_1 + abk_1(1 - (1/R_0))},\qquad(12)$$

where $1/b$ represents the average life of CTL cells and y_1 is the number of infected cells at E_1. Hence, R_1^z represents the mean of CTL immune cells activated by an infected cell when the viral infection is successful in the absence of the antibody immune response. The second endemic equilibrium is

$$E_2 = (x_2, s_2, y_2, v_2, w_2, z_2),\qquad(13)$$

where

$$x_2 = \frac{-abd_1 - abk_1 + \lambda cd_4 + \sqrt{A}}{2cd_1d_4},$$

$$s_2 = \frac{ak_1b(-abd_1 - abk_1 + \lambda cd_4 + \sqrt{A})}{cd_4(d_2 + k_2)(abd_1 - abk_1 + \lambda cd_4 + \sqrt{A})},$$

$$y_2 = \frac{b}{c},$$

$$v_2 = \frac{ab}{cd_4},$$

$$w_2 = 0,$$

$$z_2 = \frac{d_2((R_0 - 1)(-ak_1b + \lambda cd_4 + \sqrt{A}) - abd_1(R_0 + 1))}{p(abd_1 - ak_1b + \lambda cd_4 + \sqrt{A})},$$

$$\qquad(14)$$

with $A = (abk_1 - \lambda cd_4)^2 + a^2b^2d_1^2 + 2a^2b^2d_1k_1 + 2\lambda abcd_1d_4$.

We introduce the antibody immune competition reproduction number given by

$$R_2^w = \frac{gv_2}{h} = \frac{abg}{cd_4h},\qquad(15)$$

with $1/h$ represents the average life of antibodies and v_2 is the number of free viruses at E_2. For biological point of view, R_2^w

represents the average number of the antibodies activated by virus when the viral infection is successful in the absence of CTL response. The third endemic equilibrium is

$$E_3 = (x_3, s_3, y_3, v_3, w_3, z_3),\qquad(16)$$

where

$$x_3 = \frac{-d_1h - k_1h + \lambda g + \sqrt{B}}{2d_1g},$$

$$s_3 = \frac{k_1h(-d_1h - k_1h + \lambda g + \sqrt{B})}{g(d_2 + k_2)(d_1h - k_1h + \lambda g + \sqrt{B})},$$

$$y_3 = \frac{k_1k_2h(-d_1h - k_1h + \lambda g + \sqrt{B})}{d_3g(d_2 + k_2)(d_1h - k_1h + \lambda g + \sqrt{B})},$$

$$v_3 = \frac{h}{g},\qquad(17)$$

$$w_3 = \frac{d_4((R_0 - 1)(-k_1h + \lambda g + \sqrt{B}) - d_1h(R_0 + 1))}{q(d_1h - k_1h + \lambda g + \sqrt{B})},$$

$$z_3 = 0,$$

with $B = (hk_1 - \lambda g)^2 + d_1^2h^2 + 2k_1d_1h^2k_1 + 2\lambda gd_1h$.

We define the CTL immune competition reproduction number R_3^z of our model by

$$R_3^z = \frac{cy_3}{b} = \frac{ck_1k_2h(-d_1h - k_1h + \lambda g + \sqrt{B})}{bd_3g(d_2 + k_2)(d_1h - k_1h + \lambda g + \sqrt{B})},\qquad(18)$$

with $1/b$ represents the average life of CTL cells and y_3 is the number of infected cells at E_3. Hence, R_3^z represents the

average number of CTL immune cells activated by an infected cell when the viral infection is successful in the absence of the antibody immune response. The last endemic equilibrium is

$$E_4 = (x_4, y_4, v_4, w_4, z_4),\qquad(19)$$

where

$$x_4 = \frac{-d_1h - k_1h + \lambda g + \sqrt{B}}{2d_1g},$$

$$s_4 = \frac{k_1h(-d_1h - k_1h + \lambda g + \sqrt{B})}{g(d_2 + k_2)(d_1h - k_1h + \lambda g + \sqrt{B})},$$

$$y_4 = \frac{b}{c},$$

$$v_4 = \frac{h}{g},\qquad(20)$$

$$w_4 = \frac{abg - cd_4h}{chq} = \frac{d_4}{q}(R_2^w - 1),$$

$$z_4 = \frac{(ck_1k_2h - bd_3g(d_2 + k_2))(-k_1h + \lambda g + \sqrt{B}) - d_1h(ck_1k_2h + bd_3g(d_2 + k_2))}{pbg(d_2 + k_2)(d_1h - k_1h + \lambda g + \sqrt{B})},$$

$$= \frac{d_3}{p}(R_3^z - 1).$$

We observe that the second endemic state $E_2 = (x_2, y_2, v_2, w_2, z_2)$ exists when $R_1^z > 1$. We explain the existence of this endemic equilibrium E_2 as follows. We recall first that, in this state, both the free viruses and CTL cells are present. Assume that $R_0 > 1$, in the total absence of CTL immune response, the infected cell load per unit time is $\lambda d_4 (R_0 - 1)/(ad_1 + ak_1 (1 - (1/R_0)))$. Via the six equations of model (1), CTL cells are reproduced due to infected cells stimulated per unit time being $(c\lambda d_4 (R_0 - 1)/(ad_1 + ak_1 (1 - (1/R_0)))) = cy_1$. The CTL load during the lifespan of a CTL cell is $(c\lambda d_4 (R_0 - 1)/(abd_1 + abk_1 (1 - (1/R_0)))) = R_1^z$. If $(c\lambda d_4 (R_0 - 1)/(abd_1 + abk_1 (1 - (1/R_0)))) > 1$, we will have the existence of the endemic equilibrium $E2$. We observe also that the third endemic state $E_3 = (x_3, y_3, v_3, w_3, z_3)$ exists when $R_1^w > 1$. We explain the existence of this endemic equilibrium E_3 as follows. We recall first that, in this state, both of the free viruses and antibodies are present. Assume that $R_0 > 1$, in the total absence of the antibody immune response, the viral load per unit time is $\lambda (R_0 - 1)/(d_1 + k_1 (1 - (1/R_0)))$. Via the six equations of model (1), antibodies are reproduced due to free viruses stimulation per unit time is $(g\lambda (R_0 - 1)/(d_1 + k_1 (1 - (1/R_0)))) = gv_1$. The viral load during the lifespan of virion is $(g\lambda (R_0 - 1)/(d_1 h + hk_1 (1 - (1/R_0)))) = R_1^w$. If $(g\lambda (R_0 - 1)/(d_1 h + hk_1 (1 - (1/R_0)))) > 1$, we will have the existence of the endemic equilibrium $E3$. Similarly, one can see that $E_4 = (x_4, y_4, v_4, w_4, z_4)$ exists when $R_3^z > 1$ and $R_2^w > 1$.

2.3. Global Stability of the Disease-Free Equilibrium.

For the global stability of the disease-free equilibrium, we have the following result.

Proposition 2. *If $R_0 \leq 1$, then the endemic point E_f is globally asymptotically stable.*

Proof. Let the following Lyapunov functional be

$$\mathscr{L}(x, y, v, w, z) = s + \frac{d_2 + k_2}{k_2} y + \frac{d_3 (d_2 + k_2)}{ak_2} v + \frac{q}{g} \frac{d_3 (d_2 + k_2)}{ak_2} w + \frac{p}{c} \frac{d_2 + k_2}{k_2} z. \tag{21}$$

The time derivative is given by

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \dot{s} + \frac{d_2 + k_2}{k_2} \dot{y} + \frac{d_3 (d_2 + k_2)}{ak_2} \dot{v}$$

$$+ \frac{q}{g} \frac{d_3 (d_2 + k_2)}{ak_2} \dot{w} + \frac{p}{c} \frac{d_2 + k_2}{k_2} \dot{z},$$

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \frac{k_1 xv}{x + v} - (d_2 + k_2)s + \frac{d_2 + k_2}{k_2} (k_2 s - d_3 y)$$

$$- \frac{d_2 + k_2}{k_2} pyz$$

$$+ \frac{d_3 (d_2 + k_2)}{ak_2} (ay - d_4 v - qvw)$$

$$+ \frac{q}{g} \frac{d_3 (d_2 + k_2)}{ak_2} (gvw - hw)$$

$$+ \frac{p}{c} \frac{d_2 + k_2}{k_2} (cyz - bz),$$

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \frac{k_1 xv}{x + v} - \frac{d_3 d_2}{a} v - \frac{qh}{g} \frac{d_3 (d_2 + k_2)}{ak_2} w$$

$$- \frac{bp}{c} \frac{d_2 + k_2}{k_2} z,$$

$$\dot{\mathscr{L}}(x, y, s, v, w, z) \leq k_1 v - \frac{d_3 d_4 (d_2 + k_2)}{ak_2} v$$

$$\leq \frac{d_3 d_4 (d_2 + k_2)}{ak_2} (R_0 - 1)v. \tag{22}$$

If $R_0 < 1$, then $\dot{\mathscr{L}} \leq 0$. Moreover, $\dot{\mathscr{L}} \leq 0$ when $v = 0$. The largest compact invariant is

$$E = \{ (x, s, y, v, w, z) \mid v = 0 \}. \tag{23}$$

According to LaSalle's invariance principle [14], we have $\lim_{+\infty} v(t) = 0$. The limit system of equations is

$$\begin{cases} \dot{x} = \lambda - d_1 x, \\[2mm] \dot{s} = -d_2 s - k_2 s, \\[2mm] \dot{y} = k_2 s - d_3 y - pyz, \\[2mm] \dot{w} = -hw, \\[2mm] \dot{z} = cyz - bz. \end{cases} \tag{24}$$

We define

$$\mathscr{L}(x, s, y, w, z) = \frac{1}{x_0}\left(x - x_0 - x_0 \ln \frac{x}{x_0} \right) + s + \frac{d_2 + k_2}{k_2} y$$
$$+ \frac{q}{g} \frac{d_3(d_2 + k_2)}{ak_2} w + \frac{d_2 + k_2}{k_2} \frac{p}{c} z. \tag{25}$$

Since $x_0 = \lambda / d_1$, then

$$\dot{\mathscr{L}}(x, s, y, w, z) = d_1\left(2 - \frac{x}{x_0} - \frac{x_0}{x} \right) - \frac{d_3(d_2 + k_2)}{k_2} y$$
$$- \frac{q}{g} \frac{hd_3(d_2 + k_2)}{ak_2} w - \frac{d_2 + k_2}{k_2} \frac{pb}{c} z. \tag{26}$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$2 - \frac{x}{x_0} - \frac{x_0}{x} \leq 0. \tag{27}$$

Therefore, $\dot{\mathscr{L}} \leq 0$, and the equality holds if $x = x_0$ and $s = y = w = z = 0$, which complete the proof. □

2.4. Global Stability of Infection Steady States. In this subsection, attention is focused on the stability of the infection steady states.

For the first endemic equilibrium E_1, we have the following result.

Proposition 3. *If $R_0 > 1$, $R_1^z \leq 1$, and $R_1^w \leq 1$, then the endemic point E_1 is globally asymptotically stable.*

Proof. Let the following Lyapunov functional be

$$\mathscr{L}(x, s, y, v, w, z) = x - x_1 + \int_{x_1}^{x} \frac{(d_2 + k_2)s_1}{k_1 u v_1 / (u + v_1)} du + s - s_1$$
$$- s_1 \ln \frac{s}{s_1}$$
$$+ \frac{d_2 + k_2}{k_2}\left(y - y_1 - y_1 \ln \frac{y}{y_1} \right)$$
$$+ \frac{d_3(d_2 + k_2)}{ak_2}\left(v - v_1 - v_1 \ln \frac{v}{v_1} \right)$$
$$+ \frac{q}{g} \frac{d_3(d_2 + k_2)}{ak_2} w + \frac{p}{c} \frac{d_2 + k_2}{k_2} z. \tag{28}$$

we have then

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \dot{x} - (d_2 + k_2)s_1 \frac{x + v_1}{k_1 x v_1} \dot{x} + \dot{s} - \frac{s_1}{s} \dot{s}$$
$$+ \frac{d_2 + k_2}{k_2}\left(\dot{y} - \frac{y_1}{y} \dot{y} \right)$$
$$+ \frac{d_3(d_2 + k_2)}{ak_2}\left(\dot{v} - \frac{v_1}{v} \dot{v} \right)$$
$$+ \frac{q}{g} \frac{d_3(d_2 + k_2)}{ak_2} \dot{w} + \frac{p}{c} \frac{d_2 + k_2}{k_2} \dot{z}. \tag{29}$$

On the other hand, we have

$$\begin{cases} \lambda = d_1 x_1 + (d_2 + k_2)s_1, \\[2mm] \dfrac{k_1 x_1 v_1}{x_1 + v_1} = (d_2 + k_2)s_1, \\[2mm] \dfrac{s_1}{v_1} = \dfrac{d_3 d_4}{ak_2}, \\[2mm] \dfrac{y_1}{v_1} = \dfrac{d_4}{a}, \\[2mm] \dfrac{s_1}{y_1} = \dfrac{d_3}{k_2}. \end{cases} \tag{30}$$

Hence,

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \left(\lambda - d_1 x - \frac{k_1 xv}{x + v}\right)\left(1 - (d_2 + k_2)s_1 \frac{x + v_1}{k_1 xv_1}\right)$$

$$+ \frac{k_1 xv}{x + v} - (d_2 + k_2)s$$

$$- \frac{s_1}{s}\left(\frac{k_1 xv}{x + v} - (d_2 + k_2)s\right)$$

$$+ \frac{d_2 + k_2}{k_2}(k_2 s - d_3 y - pyz)$$

$$- \frac{d_2 + k_2}{k_2}\frac{y_1}{y}(k_2 s - d_3 y - pyz)$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}(ay - d_4 v - qvw)$$

$$- \frac{d_3(d_2 + k_2)}{ak_2}\frac{v_1}{v}(ay - d_4 v - qvw)$$

$$+ \frac{q}{g}\frac{d_3(d_2 + k_2)}{ak_2}(gvw - hw)$$

$$+ \frac{p}{c}\frac{d_2 + k_2}{k_2}(cyz - bz),$$

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \lambda - d_1 x - (d_2 + k_2)s_1 \frac{x + v_1}{k_1 xv_1}$$

$$\cdot \left(\lambda - d_1 x - \frac{k_1 xv}{x + v}\right)$$

$$- \frac{s_1}{s}\left(\frac{k_1 xv}{x + v}\right) + (d_2 + k_2)s_1$$

$$+ \frac{d_2 + k_2}{k_2}py_1 z + \frac{(d_2 + k_2)d_3}{k_2}y_1$$

$$- (d_2 + k_2)s\frac{y_1}{y} - \frac{d_3 d_4(d_2 + k_2)}{ak_2}v$$

$$+ \frac{(d_2 + k_2)d_3}{k_2}y_1 - (d_2 + k_2)s\frac{y_1}{y}$$

$$- \frac{d_3 d_4(d_2 + k_2)}{ak_2}v - \frac{qh}{g}\frac{d_3(d_2 + k_2)}{ak_2}w$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}v_1 qw - \frac{d_2 + k_2}{k_2}\frac{bp}{c}z.$$

(31)

Thus, this fact implies that

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \lambda - d_1 x - (d_2 + k_2)s_1 \frac{x + v_1}{k_1 xv_1}$$

$$\cdot \left(\lambda - d_1 x - \frac{k_1 xv}{x + v}\right) - \frac{s_1}{s}\frac{k_1 xv}{x + v} + d_2 s_1$$

$$- \frac{d_3 d_4(d_2 + k_2)}{ak_2}v - \frac{d_3(d_2 + k_2)}{k_2}\frac{v_1}{v}y$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}v_1 - \frac{qh}{g}\frac{d_3(d_2 + k_2)}{ak_2}w$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}qv_1 w + pz\left(y_1 - \frac{b}{c}\right).$$

(32)

Since

$$\begin{cases} \lambda - d_1 x = d_1 x_1 + (d_2 + k_2)s_1 - d_1 x, \\[2mm] \lambda - d_1 x - (d_2 + k_2)s_1 \frac{x + v_1}{k_1 xv_1}\left(\lambda - d_1 x - \frac{k_1 xv}{x + v}\right) \\[2mm] = d_1 x_1 \left(1 - \frac{x}{x_1} - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} + \frac{x + v_1}{x_1 + v_1}\right) \\[2mm] + (d_2 + k_2)s_1\left(1 - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} + \frac{v}{v_1}\frac{x + v_1}{x + v}\right) \\[2mm] - \frac{s_1}{s}\left(\frac{k_1 xv}{x + v}\right) + (d_2 + k_2)s_1 = -\frac{s_1}{s}\frac{xv}{x_1 v_1}\frac{x_1 + v_1}{x + v}(d_2 + k_2)s_1 \\[2mm] + (d_2 + k_2)s_1, \end{cases}$$

(33)

We have

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = d_1 x_1\left(1 - \frac{x}{x_1} - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} + \frac{x + v_1}{x_1 + v_1}\right)$$

$$+ (d_2 + k_2)s_1\left(1 - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} + \frac{v}{v_1}\frac{x + v_1}{x + v}\right)$$

$$+ (d_2 + k_2)s_1\left(1 - \frac{s_1}{s}\frac{xv}{x_1 v_1}\frac{x_1 + v_1}{x + v}\right)$$

$$+ (d_2 + k_2)s_1\left(1 - \frac{sy_1}{s_1 y} - \frac{v}{v_1}\right)$$

$$+ (d_2 + k_2)s_1\left(1 - \frac{v_1 y}{y_1 v}\right)$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}qw\left(v_1 - \frac{h}{g}\right)$$

$$+ pz\frac{d_2 + k_2}{k_2}\left(y_1 - \frac{b}{c}\right).$$

(34)

Therefore,

$$
\dot{\mathscr{L}} = -\frac{d_1 v_1}{x(x_1 + v_1)}(x - x_1)^2
$$

$$
+ (d_2 + k_2)s_1\left(-1 - \frac{v}{v_1} + \frac{v}{v_1}\frac{x + v_1}{x + v} + \frac{x + v}{x + v_1}\right)
$$

$$
+ (d_2 + k_2)s_1\left(5 - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} - \frac{s_1}{s}\frac{xv}{x_1 v_1}\frac{x_1 + v_1}{x + v}\right.
$$

$$
\left. - \frac{sy_1}{s_1 y} - \frac{yv_1}{y_1 v} - \frac{x + v}{x + v_1}\right)
$$

$$
+ \frac{d_3(d_2 + k_2)}{ak_2}\frac{h}{g}qw(R_1^w - 1) + \frac{d_2 + k_2}{k_2}\frac{b}{c}pz(R_1^z - 1),
$$

(35)

which implies that

$$
\dot{\mathscr{L}} = -\frac{d_1 v_1}{x(x_1 + v_1)}(x - x_1)^2
$$

$$
- (d_2 + k_2)s_1\left(\frac{x(v - v_1)^2}{v_1(x + v_1)(x + v)}\right)
$$

$$
+ (d_2 + k_2)s_1\left(5 - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} - \frac{s_1}{s}\frac{xv}{x_1 v_1}\frac{x_1 + v_1}{x + v}\right.
$$

$$
\left. - \frac{sy_1}{s_1 y} - \frac{yv_1}{y_1 v} - \frac{x + v}{x + v_1}\right)
$$

$$
+ \frac{d_3(d_2 + k_2)}{ak_2}\frac{h}{g}qw(R_1^w - 1) + \frac{d_2 + k_2}{k_2}\frac{b}{c}pz(R_1^z - 1).
$$

(36)

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$
5 - \frac{x_1}{x}\frac{x + v_1}{x_1 + v_1} - \frac{s_1}{s}\frac{xv}{x_1 v_1}\frac{x_1 + v_1}{x + v} - \frac{sy_1}{s_1 y} - \frac{yv_1}{y_1 v} - \frac{x + v}{x + v_1} \leq 0,
$$

(37)

and we know that $R_1^z < 1$ and $R_1^w < 1$, then $\dot{L} \leq 0$, and the equality holds when $x = x_1$, $y = y_1$, $v = v_1$, $w = w_1$, and $z = z_1$. By the LaSalle invariance principle [14], the endemic point E_1 is asymptotically stable when $R_0 > 1$.

For the second endemic equilibrium E_2, we have the following result. □

Proposition 4. *If $R_0 > 1$, $R_1^z > 1$, and $R_2^w \leq 1$, then the endemic point E_2 is globally asymptotically stable.*

Proof. Let the following Lyapunov functional be

$$
\mathscr{L}(x, s, y, v, w, z) = x - x_2 - \int_{x_2}^{x}\frac{(d_2 + k_2)s_2}{k_1 u v_2/(u + v_2)}du + s
$$

$$
- s_2 - s_2\ln\frac{s}{s_2}
$$

$$
+ \frac{d_2 + k_2}{k_2}\left(y - y_2 - y_2\ln\frac{y}{y_2}\right)
$$

$$
+ \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}
$$

$$
\times\left(v - v_2 - v_2\ln\frac{v}{v_2}\right)
$$

$$
+ \frac{q}{g}\frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}w
$$

$$
+ \frac{p}{c}\frac{d_2 + k_2}{k_2}\left(z - z_2 - z_2\ln\frac{z}{z_2}\right),
$$

(38)

then, we have

$$
\dot{\mathscr{L}}(x, y, s, v, w, z) = \dot{x} - (d_2 + k_2)s_2\frac{x + v_2}{k_1 x v_2}\dot{x} + \dot{s} - \frac{s_2}{s}\dot{s}
$$

$$
+ \frac{d_2 + k_2}{k_2}\left(\dot{y} - \frac{y_2}{y}\dot{y}\right)
$$

$$
+ \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}\left(\dot{v} - \frac{v_2}{v}\dot{v}\right)
$$

$$
+ \frac{q}{g}\frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}\dot{w}
$$

$$
+ \frac{p}{c}\frac{d_2 + k_2}{k_2}\left(\dot{z} - \frac{z_2}{z}\dot{z}\right).
$$

(39)

We know that

$$
\begin{cases}
\lambda = d_1 x_2 + (d_2 + k_2)s_2, \\[2mm]
k_1 x_2 v_2 = (x_2 + v_2)(d_2 + k_2)s_2, \\[2mm]
\dfrac{s_2}{y_2} = \dfrac{d_3}{k_2} + \dfrac{pz_2}{k_2}, \\[2mm]
\dfrac{y_2}{v_2} = \dfrac{d_4}{a}, \\[2mm]
\dfrac{s_2}{v_2} = \dfrac{d_3 d_4}{ak_2} + \dfrac{d_4 pz_2}{ak_2},
\end{cases}
$$

(40)

so, we have

$$\dot{\mathscr{L}}(x, s, y, v, z) = \lambda - d_1 x - \frac{x_2}{x}\frac{x + v_2}{x_2 + v_2}(\lambda - d_1 x) + ((d_2 + k_2)s_2)\frac{v}{v_2}\frac{x_2 + v_2}{x + v} - (d_2 + k_2)s - \frac{s_2}{s}\left(\frac{k_1 xv}{x + v} - (d_2 + k_2)s\right)$$

$$+ \frac{d_2 + k_2}{k_2}(k_2 s - d_3 y - pyz) - \frac{d_2 + k_2}{k_2}\frac{y_2}{y}(k_2 s - d_3 y - pyz) + \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}$$

$$\times (ay - d_4 v - qvw) - \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}\frac{v_2}{v}(ay - d_4 v - qvw)$$

$$+ \frac{q}{g}\frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}(gvw - hw) + \frac{p}{c}\frac{d_2 + k_2}{k_2}(cyz - bz) - \frac{pz_2}{cz}\frac{d_2 + k_2}{k_2}(cyz - bz).$$

(41)

On the other hand, we have

$$\begin{cases} \lambda - d_1 x = (d_1 x_2 + d_2 + k_2)s_2 - d_1 x, \\[2mm] \lambda - d_1 x - (d_2 + k_2)s_2\dfrac{x + v_2}{k_1 xv_2}\left(\lambda - d_1 x - \dfrac{k_1 xv}{x + v}\right) = d_1 x_2\left(1 - \dfrac{x}{x_2} - \dfrac{x_2}{x}\dfrac{x + v_2}{x_2 + v_2} + \dfrac{x + v_2}{x_2 + v2}\right) \\[2mm] \quad + (d_2 + k_2)s_2\left(1 - \dfrac{x_2}{x}\dfrac{x + v_2}{x_2 + v_2} + \dfrac{v}{v_2}\dfrac{x + v_2}{x + v}\right) \\[2mm] \quad -\dfrac{s_2}{s}\left(\dfrac{k_1 xv}{x + v}\right) + (d_2 + k_2)s_2 = (d_2 + k_2)s_2\left(1 - \dfrac{s_2}{s}\dfrac{xv}{x_2 v_2}\dfrac{x_2 + v_2}{x + v}\right), \end{cases}$$

$$\begin{cases} \dfrac{(d_2 + k_2)d_3}{k_2}y_2 - (d_2 + k_2)s\dfrac{y_2}{y} - \dfrac{(d_2 + k_2)d_3 d_4}{ak_2}v \\[2mm] \quad = (d_2 + k_2)s_2\left(1 - \dfrac{s}{s_2}\dfrac{y_2}{y} - \dfrac{v}{v_2}\right) + \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2\dfrac{v}{v_2} - \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2, \\[2mm] \dfrac{d_4 d_3(d_2 + k_2)}{ak_2}v_2 - \dfrac{d_3(d_2 + k_2)}{k_2}\dfrac{v_2}{v}y = (d_2 + k_2)s_2\left(1 - \dfrac{y}{y_2}\dfrac{v_2}{v}\right) \\[2mm] \quad + \dfrac{(d_2 + k_2)}{k_2}pz_2 y\dfrac{v_2}{v} - \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2, \end{cases}$$

(42)

$$\begin{cases} \dfrac{(d_2 + k_2)pz_2}{ak_2}(ay - d_4 v) - \dfrac{(d_2 + k_2)pz_2}{ak_2}\dfrac{v_2}{v}(ay - d_4 v) = \dfrac{(d_2 + k_2)pz_2 y}{k_2} \\[2mm] \quad - \dfrac{(d_2 + k_2)pz_2 y_2}{k_2}\dfrac{v}{v_2} - \dfrac{(d_2 + k_2)pz_2 y}{k_2}\dfrac{v_2}{v} + \dfrac{(d_2 + k_2)pz_2 y_2}{k_2}, \\[2mm] \dfrac{(d_2 + k_2)pz_2}{ak_2}(ay - d_4 v) - \dfrac{(d_2 + k_2)pz_2}{ak_2}\dfrac{v_2}{v}(ay - d_4 v) - \dfrac{z_2}{z}\dfrac{p}{c}\dfrac{d_2 + k_2}{k_2}(cyz - bz) \\[2mm] \quad + \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2\dfrac{v}{v_2} - \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2 + \dfrac{(d_2 + k_2)}{k_2}pz_2 y\dfrac{v_2}{v} - \dfrac{(d_2 + k_2)}{k_2}pz_2 y_2 = 0. \end{cases}$$

This fact implies that

$$\dot{L} = -\frac{d_1 v_2}{x(x_2 + v_2)}(x - x_2)^2$$

$$- (d_2 + k_2)s_2\left(\frac{x(v - v_2)^2}{v_2(x + v_2)(x + v)}\right)$$

$$+ (d_2 + k_2)s_2\left(5 - \frac{x_2}{x}\frac{x + v_2}{x_2 + v_2} - \frac{s_2}{s}\frac{xv}{x_2v_2}\frac{x_2 + v_2}{x + v}\right. \quad (43)$$

$$\left. - \frac{sy_2}{s_2 y} - \frac{yv_2}{y_2 v} - \frac{x + v}{x + v_2}\right)$$

$$+ \frac{h}{g}\frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_2}{ak_2}qw(R_2^w - 1).$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$5 - \frac{x_2}{x}\frac{x + v_2}{x_2 + v_2} - \frac{s_2}{s}\frac{xv}{x_2v_2}\frac{x_2 + v_2}{x + v} - \frac{sy_2}{s_2 y} - \frac{yv_2}{y_2 v} - \frac{x + v}{x + v_2} \leq 0, \quad (44)$$

and we know that $R_2^w < 1$ which means that $\dot{L} \leq 0$, and the equality holds when $x = x_2$, $s = s_2$, $y = y_2$, $v = v_2$, $w = w_2$, and $z = z_2$. By the LaSalle invariance principle [14], the endemic point E_2 is asymptotically stable.

For the third endemic equilibrium E_3, we have the following result.   □

Proposition 5. *If $R_0 > 1$, $R_3^z \leq 1$, and $R_1^w > 1$, then the endemic point E_3 is globally asymptotically stable.*

Proof. Let the following Lyapunov functional be

$$\mathcal{L}(x, s, y, v, w, z) = x - x_3 - \int_{x_3}^{x}\frac{(d_2 + k_2)s_3}{k_1 uv_3/(u + v_3)}du + s$$

$$- s_3 - s_3 \ln\frac{s}{s_3}$$

$$+ \frac{d_2 + k_2}{k_2}\left(y - y_3 - y_3\ln\frac{y}{y_3}\right)$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}$$

$$\times\left(v - v_3 - v_3\ln\frac{v}{v_3}\right) + \frac{d_3(d_2 + k_2)}{ak_2}$$

$$\cdot\frac{q}{g}\left(w - w_3 - w_3\ln\frac{w}{w_3}\right)$$

$$+ \frac{p}{c}\frac{d_2 + k_2}{k_2}z.$$

$$(45)$$

Then, we have

$$\dot{\mathcal{L}}(x, s, y, v, w, z) = \dot{x} - (d_2 + k_2)s_3\frac{x + v_3}{k_1 xv_3}\dot{x} + \dot{s} - \frac{s_3}{s}\dot{s}$$

$$+ \frac{(d_2 + k_2)}{k_2}\left(\dot{y} - \frac{y_3}{y}\dot{y}\right)$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}\left(\dot{v} - \frac{v_3}{v}\dot{v}\right) + \frac{d_3(d_2 + k_2)}{ak_2}$$

$$\cdot\frac{q}{g}\left(\dot{w} - \frac{w_3}{w}\dot{w}\right) + \frac{p}{c}\dot{z};$$

$$(46)$$

this fact implies that

$$\dot{\mathcal{L}}(x, s, y, v, w, z) = \lambda - d_1 x - (d_2 + k_2)s_3\frac{x + v_3}{k_1 xv_3}$$

$$\cdot\left(\lambda - d_1 x - \frac{k_1 xv}{x + v}\right) - \frac{s_3}{s}\frac{k_1 xv}{x + v}$$

$$+ (d_2 + k_2)s_3$$

$$+ \frac{d_3(d_2 + k_2)}{k_2}y_3 - (d_2 + k_2)s\frac{y_3}{y}$$

$$- \frac{d_4 d_3(d_2 + k_2)}{ak_2}v$$

$$- \frac{d_3(d_2 + k_2)}{k_2}\frac{v_3}{v}y + \frac{d_3 d_4(d_2 + k_2)}{ak_2}v_3$$

$$- \frac{d_3(d_2 + k_2)}{ak_2}qw_3 v$$

$$+ \frac{d_3(d_2 + k_2)}{ak_2}qv_3 w_3$$

$$+ \frac{(d_2 + k_2)}{k_2}pz\left(y_3 - \frac{b}{c}\right).$$

$$(47)$$

We know that

$$\begin{cases} \lambda = d_1 x_3 + (d_2 + k_2)s_3, \\[2mm] k_1 x_3 v_3 = (x_3 + v_3)(d_2 + k_2)s_3, \\[2mm] \dfrac{s_3}{y_3} = \dfrac{d_3}{k_2}, \\[2mm] \dfrac{y_3}{v_3} = \dfrac{d_4}{a} + \dfrac{qw_3}{a}, \\[2mm] \dfrac{s_2}{v_2} = \dfrac{d_3 d_4}{ak_2} + \dfrac{d_3 qw_3}{ak_2}. \end{cases} \quad (48)$$

So, we have

$$
\begin{cases}
\lambda - d_1 x = d_1 x_3 + (d_2 + k_2)s_3 - d_1 x, \\[2ex]
\lambda - d_1 x - (d_2 + k_2)s_3 \dfrac{x + v_3}{k_1 x v_3}\left(\lambda - d_1 x - \dfrac{k_1 x v}{x + v}\right) = d_1 x_3\left(1 - \dfrac{x}{x_3} - \dfrac{x_3}{x}\dfrac{x + v_3}{x_3 + v_3} + \dfrac{x + v_3}{x_3 + v_3}\right) \\[2ex]
\qquad + (d_2 + k_2)s_3\left(1 - \dfrac{x_3}{x}\dfrac{x + v_3}{x_3 + v_3} + \dfrac{v}{v_3}\dfrac{x + v_3}{x + v}\right) \\[2ex]
\qquad - \dfrac{s_3}{s}\left(\dfrac{k_1 x v}{x + v}\right) + (d_2 + k_2)s_3 = (d_2 + k_2)s_3\left(1 - \dfrac{s_3}{s}\dfrac{x v}{x_3 v_3}\dfrac{x_3 + v_3}{x + v}\right), \\[2ex]
\dfrac{(d_2 + k_2)d_3}{k_2}y_3 - (d_2 + k_2)s\dfrac{y_3}{y} = (d_2 + k_2)s_3\left(1 - \dfrac{s}{s_3}\dfrac{y_3}{y}\right), \\[2ex]
-\dfrac{d_3 d_4 (d_2 + k_2)}{a k_2}v - \dfrac{d_3(d_2 + k_2)}{k_2}\dfrac{v_3}{v}y + \dfrac{d_3 d_4 (d_2 + k_2)}{a k_2}v_3 - \dfrac{d_3(d_2 + k_2)}{a k_2}q w_3 v + \dfrac{d_3(d_2 + k_2)}{a k_2}q v_3 w_3 \\[2ex]
\qquad = (d_2 + k_2)s_3\left(1 - \dfrac{v}{v_3} - \dfrac{v_3}{v}\dfrac{y}{y_3}\right).
\end{cases}
\tag{49}
$$

Then, we have

$$
\begin{aligned}
\dot{L} = {} & -\frac{d_1 v_3}{x(x_3 + v_3)}(x - x_3)^2 \\[2ex]
& - (d_2 + k_2)s_3\left(\frac{x(v - v_3)^2}{v_3(x + v_3)(x + v)}\right) \\[2ex]
& + (d_2 + k_2)s_3\left(5 - \frac{x_3}{x}\frac{x + v_3}{x_3 + v_3} - \frac{s_3}{s}\frac{x v}{x_3 v_3}\frac{x_3 + v_3}{x + v}\right. \\[2ex]
& \left. \qquad - \frac{s y_3}{s_3 y} - \frac{y v_3}{y_3 v} - \frac{x + v}{x + v_3}\right), \\[2ex]
& + \frac{b}{c}\frac{d_2 + k_2}{k_2}pz(R_3^z - 1).
\end{aligned}
\tag{50}
$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$
5 - \frac{x_3}{x}\frac{x + v_3}{x_3 + v_3} - \frac{s_3}{s}\frac{x v}{x_3 v_3}\frac{x_3 + v_3}{x + v} - \frac{s y_3}{s_3 y} - \frac{y v_3}{y_3 v} - \frac{x + v}{x + v_3} \le 0,
\tag{51}
$$

and we know that $R_3^z < 1$, then $\dot{L} \le 0$, and the equality holds when $x = x_3$, $s = s_3$, $y = y_3$, $v = v_3$, $w = w_3$, and $z = z_3$. By the LaSalle invariance principle [14], the endemic point E_3 is asymptotically stable when $R_0 > 1$.

Finally, for the last endemic equilibrium E_4, we have the following result. □

Proposition 6. *If $R_0 > 1$, $R_3^z > 1$, and $R_2^w > 1$, then the endemic point E_4 is globally asymptotically stable.*

Proof. Let the following Lyapunov functional be

$$
\begin{aligned}
\mathscr{L}(x, s, y, v, w, z) = {} & x - x_4 - \int_{x_4}^{x}\frac{(d_2 + k_2)s_4}{k_1 u v_4/(u + v_4)}du + s \\[2ex]
& - s_4 - s_4 \ln\frac{s}{s_4} \\[2ex]
& + \frac{d_2 + k_2}{k_2}\left(y - y_4 - y_4 \ln\frac{y}{y_4}\right) \\[2ex]
& + \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{a k_2} \\[2ex]
& \times\left(v - v_4 - v_4 \ln\frac{v}{v_4}\right) \\[2ex]
& + \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{a k_2} \\[2ex]
& \cdot \frac{q}{g}\left(w - w_4 - w_4 \ln\frac{w}{w_4}\right) \\[2ex]
& + \frac{p}{c}\frac{d_2 + k_2}{k_2}\left(z - z_4 - z_4 \ln\frac{z}{z_4}\right).
\end{aligned}
\tag{52}
$$

Then, we have

$$\dot{\mathscr{L}}(x, s, y, v, w, z) = \lambda - d_1 x - (d_2 + k_2)s_4 \frac{x + v_4}{k_1 x v_4}$$

$$\cdot \left(\lambda - d_1 x - \frac{k_1 xv}{x + v} \right) - \frac{s_4}{s} \frac{k_1 xv}{x + v}$$

$$+ (d_2 + k_2)s_4$$

$$+ \frac{d_3(d_2 + k_2)}{k_2} y_4 - (d_2 + k_2)\frac{y_4}{y} s$$

$$- \frac{d_3 d_4(d_2 + k_2) + d_4(d_2 + k_2)pz_4}{ak_2} v$$

$$- \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{k_2} \frac{v_4}{v} y$$

$$+ \frac{d_3 d_4(d_2 + k_2) + d_4(d_2 + k_2)pz_4}{ak_2} v_4$$

$$- \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{ak_2} qw_4 v$$

$$+ \frac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{ak_2} qv_4 w_4$$

$$+ \frac{(d_2 + k_2)}{k_2} pz_4 y_4.$$

$$(53)$$

We know that

$$\begin{cases} \lambda = d_1 x_4 + (d_2 + k_2)s_4, \\[2mm] k_1 x_4 v_4 = (x_4 + v_4)(d_2 + k_2)s_4, \\[2mm] \dfrac{s_4}{y_4} = \dfrac{d_3}{k_2} + \dfrac{pz_4}{k_2}, \\[2mm] \dfrac{y_4}{v_4} = \dfrac{d_4}{a} + \dfrac{qw_4}{a}, \\[2mm] \dfrac{s_4}{v_4} = \dfrac{d_3 d_4}{ak_2} + \dfrac{d_4 pz_2}{ak_2} + \dfrac{d_3 qw_4}{ak_2} + \dfrac{pqz_4 w_4}{ak_2}, \end{cases}$$

$$(54)$$

then,

$$\begin{cases} \lambda - d_1 x = (d_1 x_4 + d_2 + k_2)s_4 - d_1 x, \\[3mm] \lambda - d_1 x - (d_2 + k_2)s_4 \dfrac{x + v_4}{k_1 x v_4}\left(\lambda - d_1 x - \dfrac{k_1 xv}{x + v} \right) \\[3mm] \quad = d_1 x_4 \left(1 - \dfrac{x}{x_4} - \dfrac{x_4}{x}\dfrac{x + v_4}{x_4 + v_4} + \dfrac{x + v_4}{x_4 + v4} \right) \\[3mm] \quad + (d_2 + k_2)s_4 \left(1 - \dfrac{x_4}{x}\dfrac{x + v_4}{x_4 + v_4} + \dfrac{v}{v_4}\dfrac{x + v_4}{x + v} \right) \\[3mm] \quad - \dfrac{s_4}{s}\left(\dfrac{k_1 xv}{x + v} \right) + (d_2 + k_2)s_4 = (d_2 + k_2)s_4 \\[3mm] \quad \left(1 - \dfrac{s_4}{s}\dfrac{xv}{x_4 v_4}\dfrac{x_4 + v_4}{x + v} \right), \end{cases}$$

$$\begin{cases} \dfrac{d_3(d_2 + k_2)}{k_2} y_4 + \dfrac{d_2 + k_2}{k_2} py_4 z_4 - (d_2 + k_2)\dfrac{y_4}{y} s \\[3mm] \quad = (d_2 + k_2)s_4 \left(1 - \dfrac{y_4}{y}\dfrac{s}{s_4} \right), \\[3mm] \quad - \dfrac{d_3 d_4(d_2 + k_2) + d_4(d_2 + k_2)pz_4}{ak_2} v \\[3mm] \quad - \dfrac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{k_2}\dfrac{v_4}{v} y \\[3mm] \quad + \dfrac{d_3 d_4(d_2 + k_2) + d_4(d_2 + k_2)pz_4}{ak_2} v_4 \\[3mm] \quad - \dfrac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{ak_2} qw_4 v \\[3mm] \quad + \dfrac{d_3(d_2 + k_2) + (d_2 + k_2)pz_4}{ak_2} qv_4 w_4 \\[3mm] \quad = (d_2 + k_2)s_4 \left(1 - \dfrac{v_4}{v}\dfrac{y}{y_4} - \dfrac{v}{v_4} \right). \end{cases}$$

$$(55)$$

TABLE 1: Parameters and their symbols and default values used in the suggested HIV model.

| Parameters	Units	Meaning	Value	References
Λ	cells μl^{-1} day^{-1}	Source rate of CD4$^+$ T cells	$[0, 10]$	[15]
k_1	μl virion^{-1} day^{-1}	Average of infection	$[2.5 \times 10^{-4}, 0.5]$	[9]
d_1	day^{-1}	Decay rate of healthy cells	0.0139	[9]
d_2	day^{-1}	Death rate of exposed CD4$^+$ T cells	0.0495	[9]
k_2	day^{-1}	The rate that exposed cells become infected CD4$^+$ T cells	1.1	[9]
d_3	day^{-1}	Death rate of infected CD4$^+$ T cells, not by CTL killing	0.5776	[9]
a	day^{-1}	The rate of production the virus by infected CD4$^+$ T cells	$[2, 1250]$	[9]
d_4	day^{-1}	Clearance rate of virus	$[0.3466, 2.4]$	[9]
Q	μl virion days^{-1}	Killing rate of antibody	0.5	[16]
G	μl virion days^{-1}	Activation rate CTL cells	$10^{-11}, 10^{-4}$	[16]
H	day^{-1}	Death rate of antibody	0.1	[16]
P	μl cell^{-1} day^{-1}	Clearance rate of infection	0.0024	[17]
C	cells cell^{-1} day^{-1}	Activation rate CTL cells	0.15	[17]
b	day^{-1}	Death rate of CTL cells	0.5	[17]
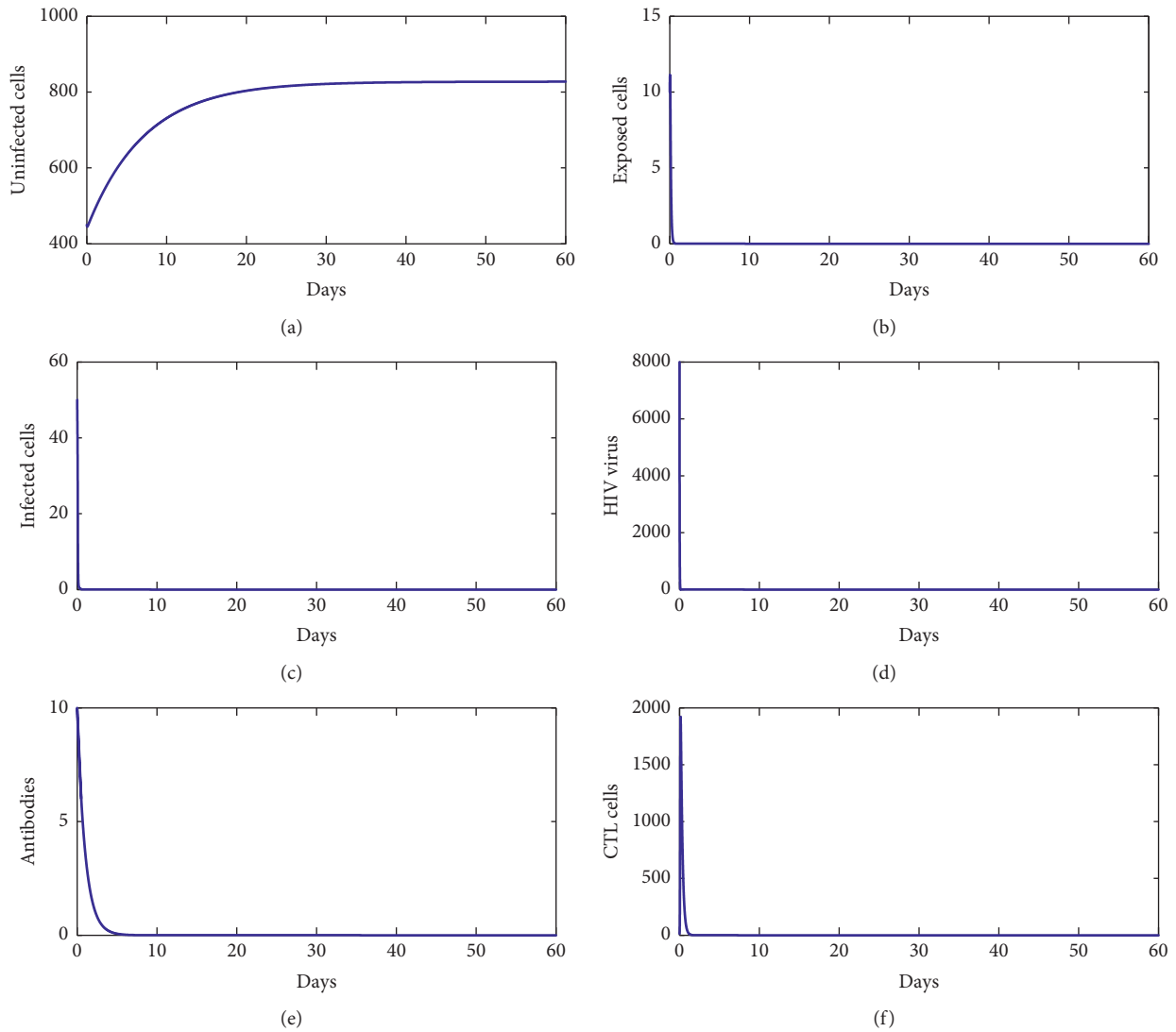
FIGURE 2: The behavior of the disease for $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.04$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 2$, $d_4 = 0.6$, $q = 0.05$, $g = 10^{-11}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.
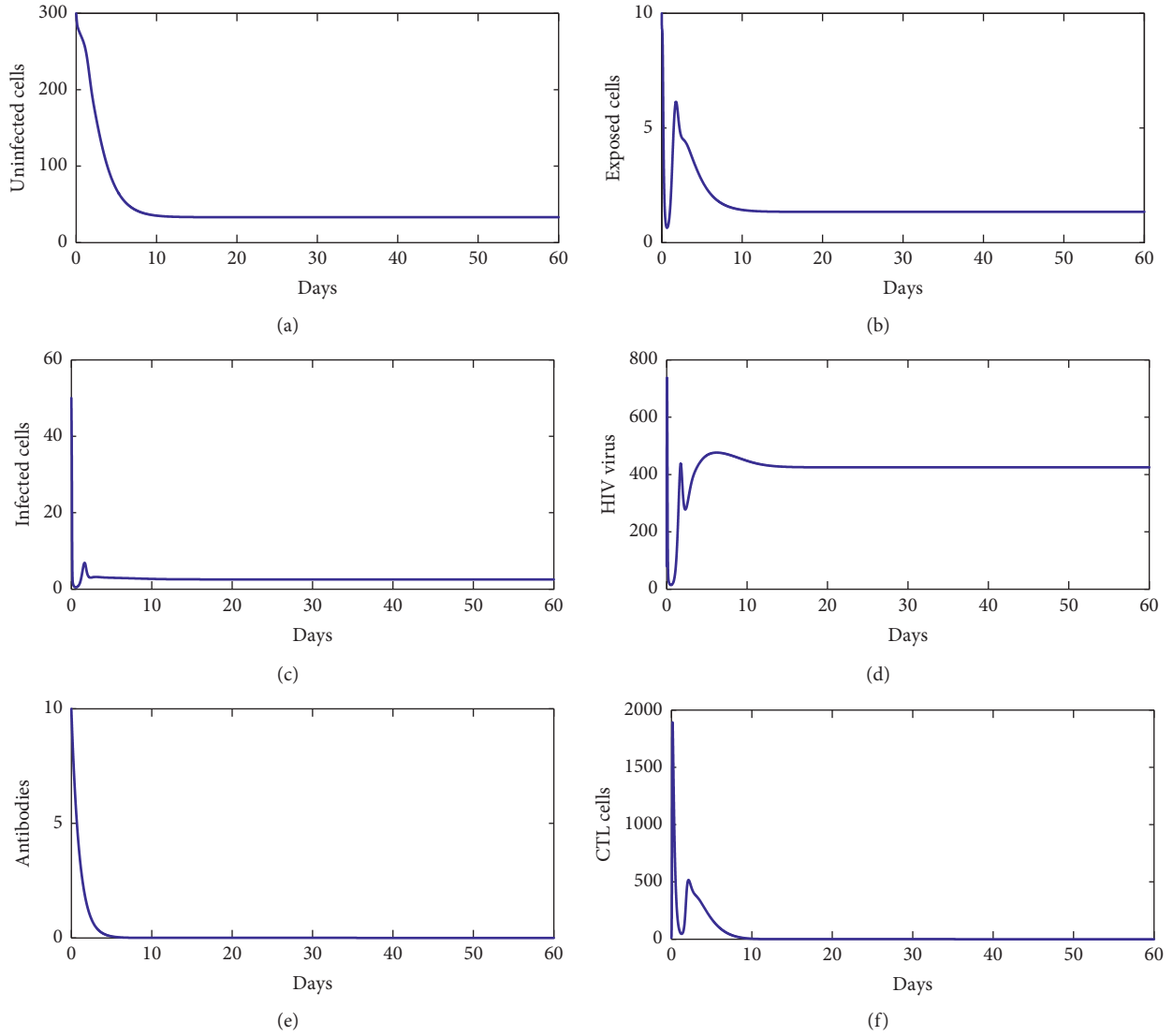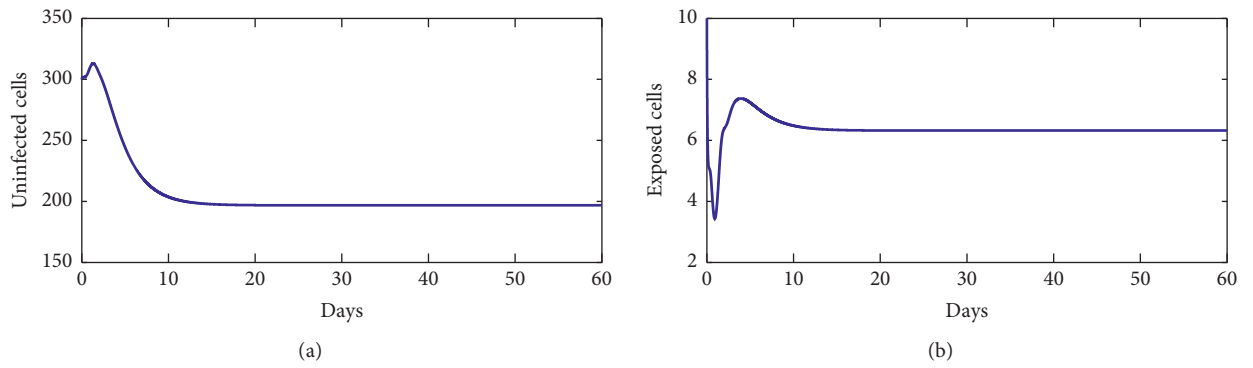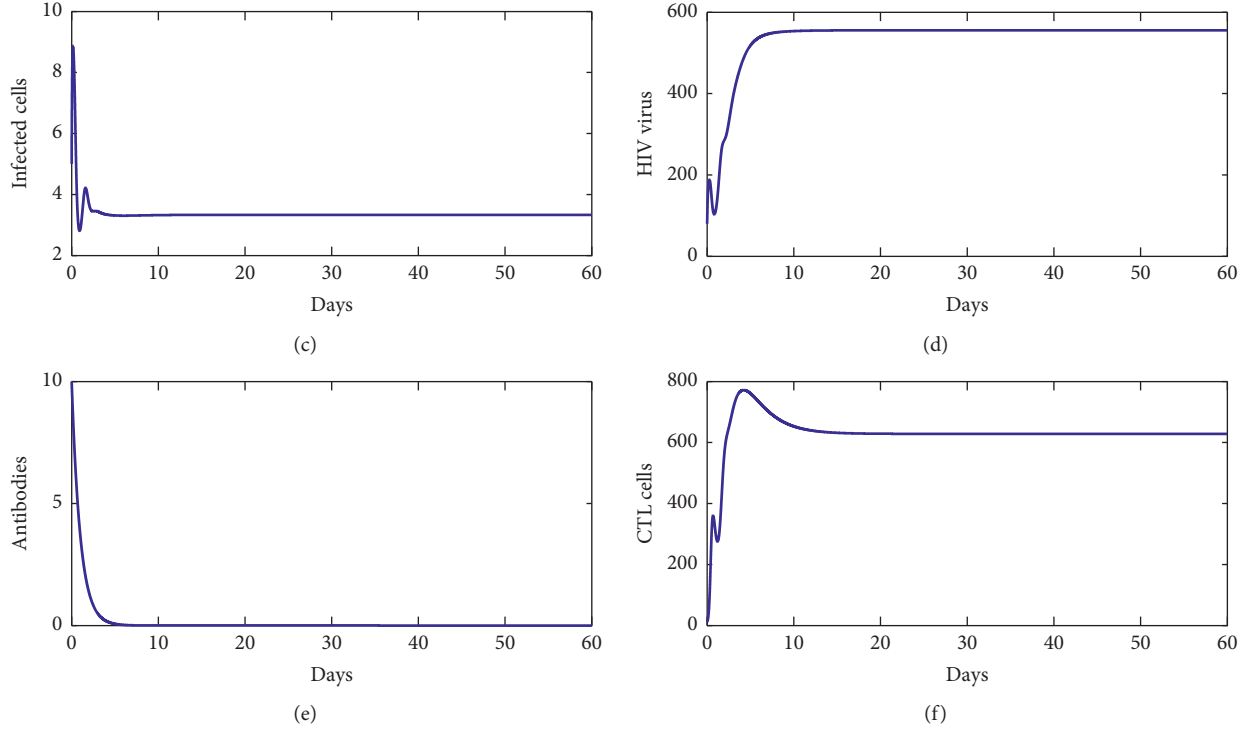
(a)

(b)

(c)

(d)

(e)

(f)

Figure 3: The behavior of the disease for $\lambda = 2$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 100$, $d_4 = 0.6$, $q = 0.05$, $g = 10^{-11}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.

(a)

(b)

Figure 4: Continued.

(c)

(d)

(e)

(f)

FIGURE 4: The behavior of the disease for $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 100$, $d_4 = 0.6$, $q = 0.05$, $g = 10^{-11}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.

This fact implies that

$$\dot{\mathcal{L}}(x, s, y, v, w, z) = -\frac{d_1 v_4}{x(x_4 + v_4)}(x - x_4)^2$$

$$- (d_2 + k_2)s_4\left(\frac{x(v - v_4)^2}{v_4(x + v_4)(x + v)}\right)$$

$$+ (d_2 + k_2)s_4\left(5 - \frac{x_4}{x}\frac{x + v_4}{x_4 + v_4}\right.$$

$$\left. - \frac{s_4}{s}\frac{xv}{x_4 v_4}\frac{x_4 + v_4}{x + v} - \frac{sy_4}{s_4 y} - \frac{yv_4}{y_4 v} - \frac{x + v}{x + v_4}\right).$$

(56)

Since the arithmetic mean is greater than or equal to the geometric mean, it follows that

$$5 - \frac{x_4}{x}\frac{x + v_4}{x_4 + v_4} - \frac{s_4}{s}\frac{xv}{x_4 v_4}\frac{x_4 + v_4}{x + v} - \frac{sy_4}{s_4 y} - \frac{yv_4}{y_4 v} - \frac{x + v}{x + v_4} \leq 0,$$

(57)

which means that $\dot{\mathcal{L}} \leq 0$, and the equality holds when $x = x_4$, $s = s_4$, $y = y_4$, $v = v_4$, $w = w_4$, and $z = z_4$. By the LaSalle invariance principle [14], the endemic point E_4 is globally asymptotically stable when $R_0 > 1$. □

3. Numerical Results

For our numerical simulations, system (1) is solved using the Runge–Kutta method iterative scheme. The numerical ranges of our parameters are given in Table 1. Figure 2 shows the behavior of disease during the first 60 days of observation. From this figure, we observe that the solution converges to the point $E_f = (827.22, 0, 0, 0, 0, 0)$. With these chosen parameters, we have $R_0 = 0.22 < 1$, which proves that E_f is stable. This supports our theoretical findings. Figure 3 shows the behavior of the disease during 60 first days. From this figure, we observe that the solution of (1) converges towards the point $E_1 = (33.17, 1.33, 2.54, 4.24 \times 10^2, 0, 0)$. With these chosen parameters, we have $R_0 = 13.81 > 1$, $R_1^z = 7.64 \times 10^{-1} < 1$, and $R_1^w = 4.24 \times 10^{-8} < 1$. This fact supports that E_1 is stable. Figure 4 shows the behavior of disease during 60 days. We observe that the solution of (1) converges towards the endemic point $E_2 = (1.96 \times 10^2, 6.32, 3.33, 5.55 \times 10^2, 0, 6.28 \times 10^2)$. In this figure, we have $R_0 = 13.81 > 1$, $R_1^z = 3.81 > 1$, and $R_2^w = 5.55 \times 10^{-8} < 1$, which supports the fact that E_2 is stable. Figure 5 shows the behavior of disease during the first 60 days of observation. We clearly see that the solution of (1) converges towards the endemic point $E_3 = (32.07, 1.35, 2.57, 1000, 4.45, 0)$. With the chosen parameters, we have $R_0 = 2.39 \times 10^2 > 1$, $R_3^z = 0.77 < 1$, and $R_1^w = 9.61 > 1$; this supports the stability of E_3. In addition, Figure 6 shows the behavior of disease for the first 60 days. We remark that the solution converges towards the last endemic point $E_4 = (1.77 \times 10^2, 6.55,$
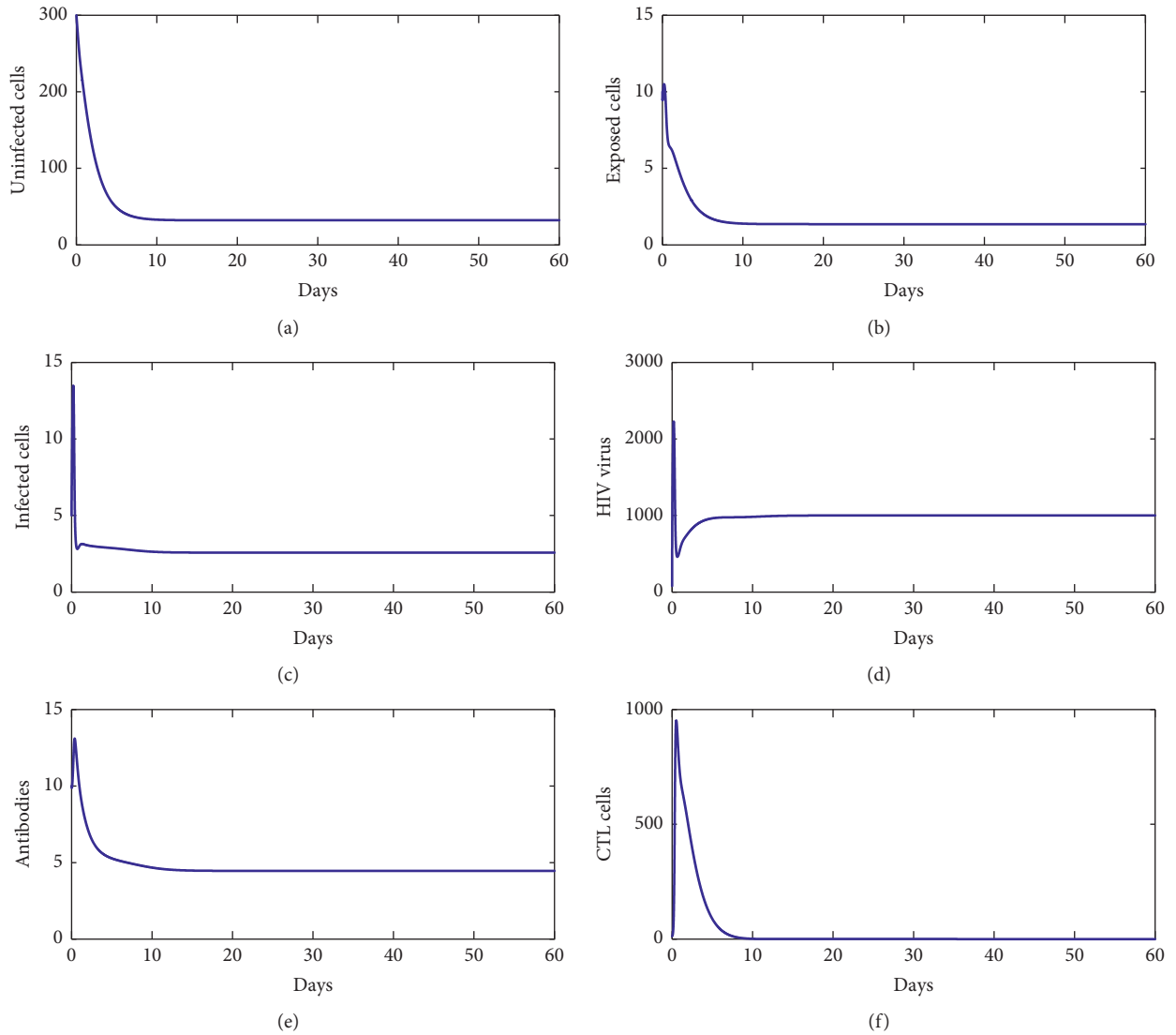
Figure 5: The behavior of the disease for $\lambda = 2$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 500$, $d_4 = 0.6$, $q = 0.05$, $g = 10^{-4}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.
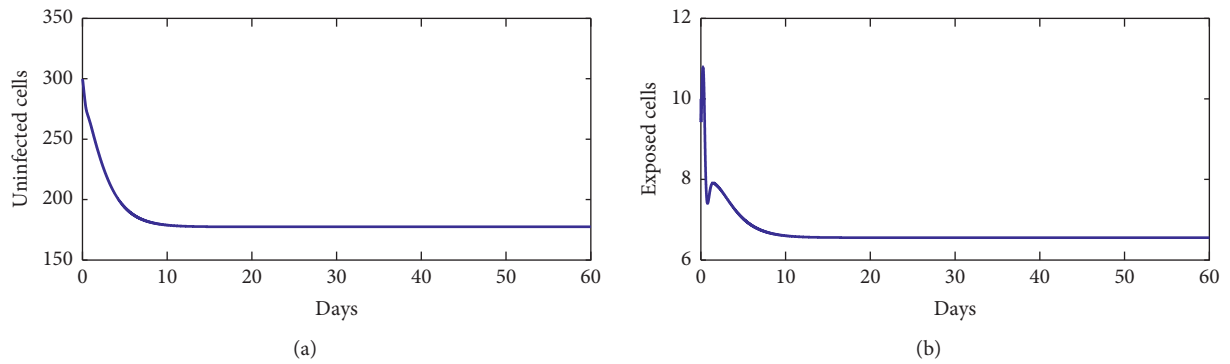

Figure 6: Continued.

(c)

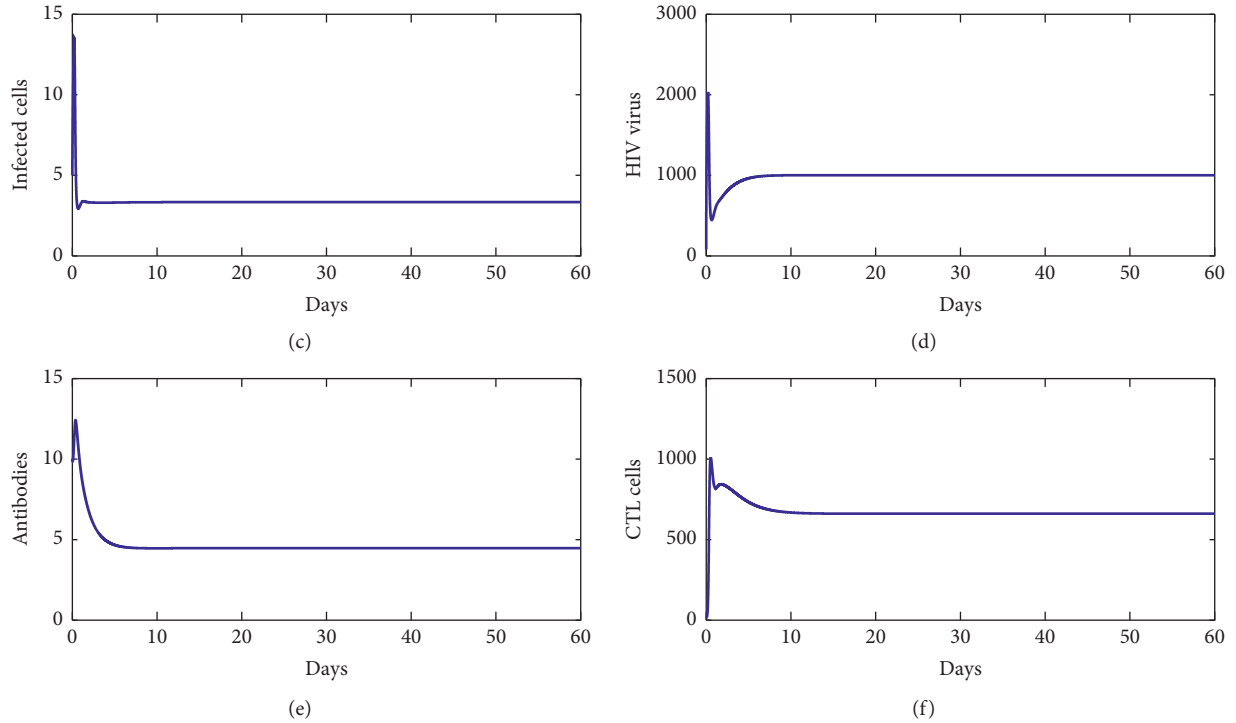

(d)

(e)

(f)

FIGURE 6: The behavior of the disease for $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 800$, $d_4 = 0.6$, $q = 0.5$, $g = 10^{-4}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.

$3.33, 1000, 4.46, 6.61 \times 10^2$). With the used parameters, we have $R_0 = 75.31 > 1$, $R_3^z = 3.74 > 1$, and $R_2^w = 3.03 > 1$; this confirms the theoretical result concerning the stability of E_4.

3.1. Comparison with the Clinical Data. First, define the following objective function:

$$J = \frac{1}{n} \sum_{i=1}^{n} \log \left(v(t_i) - \log \left(\widehat{v}(t_i) \right) \right)^2, \qquad (58)$$

where $v(t_i)$ represents the virus concentration at time t_i using the mathematical model (1) and $\widehat{v}(t_i)$ represents the virus concentration clinical data at time t_i [18].

The numerical simulations are performed and compared to three patients' data picked from [18]. The data were from the University of Washington study [7] and from the Aaron Diamond AIDS Research Center (see Table 2).

In Figure 7, the dots show the evolution of the infection during the first 120 days for the first patient [18], while the solid curve represents the numerical simulation of our suggested model. The error between the numerical simulation and the clinical data is approximately $J \approx 2.378 \times 10^{-1}$ which indicates that the numerical simulation is a good approximation of the clinical data. Figures 8 and 9 show a comparison between the clinical data (dots) and the mathematical model (solid line), and the error is approximately $J \approx 8.43 \times 10^{-2}$ and $J \approx 1.64 \times 10^{-1}$, respectively. These three results indicate that our mathematical model can fit the clinical data of different patients for the first days of observations. However, the limit of our model is to predict a long time behavior of the infection disease.

TABLE 2: The used clinical data [18] for Figure 7 (A), for Figure 8 (B), and for Figure 9 (C).

Clinical day test	Viral load (virions per μl)
A	
22	27.7
43	210
78	85.9
106	81.1
B	
0	228.8
2	599.2
14	169.6
21	93.7
42	165.6
98	127
C	
0	1350.6
9	337.2
12	340.6
16	202.3
19	169.7
23	141.4
26	56.48
30	182.75
50	267
60	182.7

3.2. Sensitivity Analysis. Using the method outlined in [19], we perform a sensitivity analysis using partial rank correlation coefficients (PRCC) to identify the main drivers of the basic reproduction number R_0. Parameters were tested within the ranges given in Table 1.
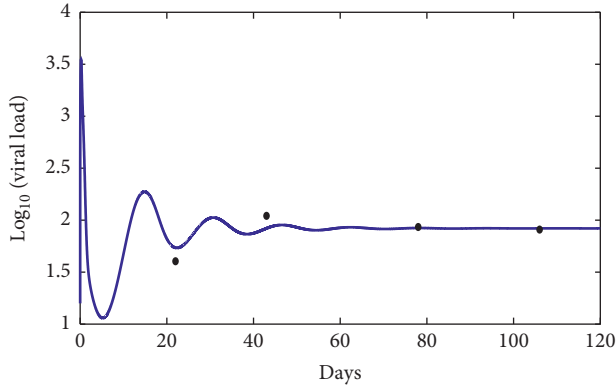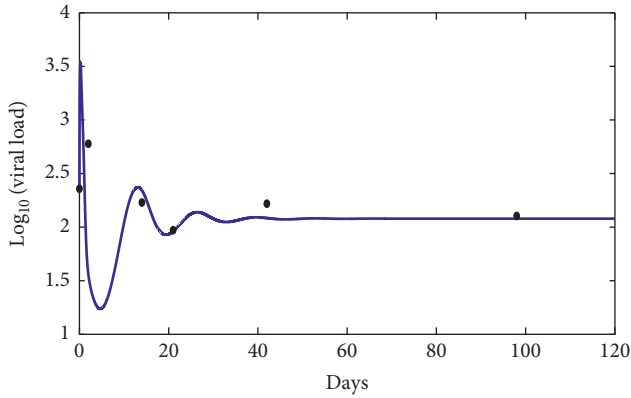
FIGURE 7: Comparison between the mathematical model (solid line) and the clinical data of the first patient [18] (dots). The used parameters for the model are $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 850$, $d_4 = 0.6$, $q = 0.5$, $g = 1.2 \times 10^{-3}$, $h = 0.1$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.
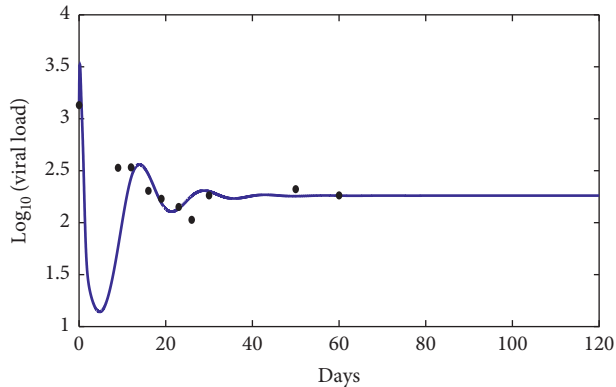

FIGURE 8: Comparison between the mathematical model (solid line) and the clinical data of the fifth patient [18] (dots). The used parameters for the model are $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 650$, $d_4 = 0.6$, $q = 0.5$, $g = 10^{-3}$, $h = 0.12$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.

FIGURE 9: Comparison between the mathematical model (solid line) and the clinical data of the seventh patient [18] (dots). The used parameters for the model are $\lambda = 10$, $d_1 = 0.0139$, $k_1 = 0.05$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 600$, $d_4 = 0.6$, $q = 0.5$, $g = 10^{-3}$, $h = 0.182$, $p = 0.0024$, $c = 0.15$, and $b = 0.5$.
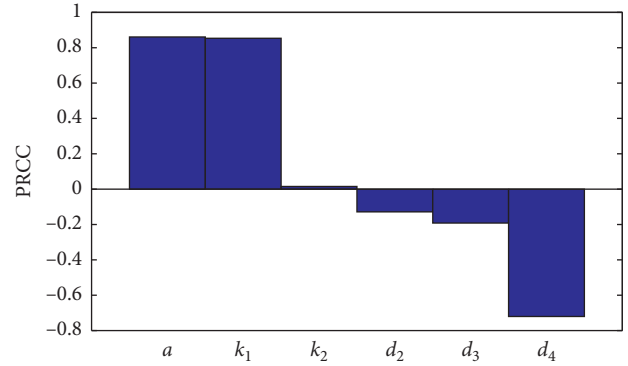

FIGURE 10: Sensitivity analysis of R_0 to different input parameters of the model.

In Figure 10, we observe that a and k_1 is highly positively correlated with R_0. However, d_4 has a strong negative correlation with R_0. The other parameters k_2, d_2, and d_3 present a weak correlation with R_0. From the biological point of view, the sensitivity analysis shows that an increase of production rate of the virus by infected cells a or an increase of the infection rate k_1 leads to an increase of the basic reproduction number R_0. However, an increase in the clearance rate of virus d_4 leads to a significant decease of the basic reproduction number R_0.

4. Conclusion

In this paper, we have presented and studied a mathematical model describing HIV viral infection with saturated rate in the presence of the adaptive immune response. This adaptive immunity is represented by CTL immune response and antibodies. By using suitable Lyapunov functionals, the global stability of each equilibrium has been established. More precisely, the disease-free equilibrium is globally asymptotically stable when the basic reproduction number is below unity ($R_0 \leq 1$). Also, the endemic steady state E_1 is globally asymptotically stable when $R_0 \geq 1$, $R_1^z \leq 1$, and $R_1^w \leq 1$. In presence of the adaptive immune response governed by competition between CTL and antibody responses, system (1) admits three infection steady states. The first infection steady state E_2 is with only the presence of CTL response which is globally asymptotically stable if $R_1^z \geq 1$ and $R_2^w \leq 1$. The second infection steady state E_3 is with only the presence of the antibody response which is globally asymptotically stable if $R_1^w \geq 1$ and $R_3^z \leq 1$. The third infection steady state is E_4 with the activation of the antibodies and the CTL response at the same time. In this case, this equilibrium E_4 is globally asymptotically stable when $R_2^w \geq 1$ and $R_3^z \geq 1$. In addition, different numerical simulations are performed in order to confirm the theoretical findings and to show that the adaptive immune response is responsible to reduce the viral load, increase the uninfected cells, and decrease the infected cells. Moreover, a comparison with some clinical data shows that our suggested model can be considered as a good approximation of the clinical tests especially for the first days of observation.

Data Availability

Conflicts of Interest

Acknowledgments

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