J. Math. Computer Sci., 32 (2024), 160–174

Online: ISSN 2008-949X

Journal of Mathematics and Computer Science

Journal Homepage: www.isr-publications.com/jmcs

A generalized fractional HIV-1 infection model with humoral immunity and highly active antiretroviral therapy

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Abstract

Highly active antiretroviral therapy (HAART) is a treatment that uses a combination of three or more drugs to treat human immunodeficiency virus type 1 (HIV-1). On the other hand, immunological memory is an important characteristic of humoral immunity. In this paper, we propose a mathematical model that takes into account immunological memory to describe the dynamics of HIV-1 infection in the presence of such therapy. We first show that the developed model is mathematically and biologically well posed. Furthermore, we discuss the existence of equilibrium points and their stability. Both effects of HAART and memory on the dynamical behavior of our proposed model are rigorously investigated. In addition, numerical simulations are presented to illustrate our analytical findings.

Keywords: Therapy, HIV-1 infection, humoral immunity, Hattaf fractional derivative, global stability.

2020 MSC: 26A33, 34A08, 65D05, 92B05, 93D30.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is a virus that infects immune cells, particularly $CD4^+$ T lymphocytes, resulting in a suppression of the immune system and leaving the body vulnerable to various infections and diseases. The last statistics of the World Health Organization (WHO) show that 38.4 million people living with HIV, where 650 000 people died from HIV-related causes and 1.5 million people acquired HIV [33]. Therefore, the world now faces significant challenges and must commit to provide effective prevention strategies and develop new treatments to control the HIV epidemic.

On the other hand, HIV-1 and human immunodeficiency virus type 2 (HIV-2) are two antigenic types of viruses that have numerous similarities in terms of genetic organization, modes of transmission, replication pathways, and clinical consequences. However, they exhibit significant differences in their epidemiology and clinical outcomes. Epidemiologically, HIV-2 is predominantly restricted to West Africa, while HIV-1 has achieved global dissemination, resulting in a less efficient transmission of HIV-2 between

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doi: 10.22436/jmcs.032.02.06

Received: 2023-05-07 *Revised:* 2023-07-08 *Accepted:* 2023-07-15

individuals compared to HIV-1. Clinically, the majority of individuals infected with HIV-2 demonstrates long-term non-progression, whereas most individuals infected with HIV-1 experience disease progression [24].

Highly active antiretroviral therapy (HAART) is a treatment strategy for HIV that uses a combination of three or more antiretroviral drugs. These drugs include protease inhibitors (PI) which block the production of viral protein precursors and prevent infected cells from producing virions, as well as reverse transcriptase inhibitors (RTI) which block the activity of reverse transcriptase and stop cell-to-cell transmission. The goal of HAART is to reduce the viral load in patients infected with HIV-1 to undetectable levels, which can improve immune system function and prevent the development of HIV-related complications. The drugs used in HAART target different stages of the HIV life cycle, making it more difficult for the virus to develop drug resistance. HAART has been shown to be highly effective in reducing the risk of HIV-1 transmission to others, controlling HIV and improving the quality of life of people living with HIV-1. In addition, several researches were interested to better understanding the dynamics of HIV-1 [8, 10, 12, 20, 25–28, 32, 34]. For example, Wang and Zhou [32] studied the global dynamics of a host model of HIV-1 infection incorporating long-term infected cells and four intracellular delays. Callaway and Perelson [8] studied the interaction between the immune system and the virus during chronic HIV-1 infection. A mathematical model describing the interactions between the virus and the host population with a focus on the impact of delay and diffusion on viral spread was investigated in [12]. Xu et al. [34] explored a mathematical model capturing the interaction between intracellular infection and humoral immunity, incorporating delays to account for lags in the immune response. Furthermore, Hlavacek et al. [20] investigated the dynamics of HIV dissociation from follicular dendritic cells (FDCs) during HAART.

Humoral immunity is one of the two forms of adaptive immune response, the other being cellular immunity. It is directed by antibodies, also called immunoglobulins, which are generated by the B cells of the immune system. Humoral immunity is characterized by two main features: specificity and immunological memory. Specificity refers to the ability of antibodies to associate with specific antigens, such as bacteria or viruses and to neutralize or eliminate them. Immunological memory refers to the ability of the immune system to remember antigens to which it has been previously exposed and to rapidly produce specific antibodies upon subsequent exposure to those same antigens. This characteristic allows humoral immunity to provide long-lasting protection against infectious diseases such as HIV-1. In this context of adaptive immunity, memory is a crucial characteristic which means that the immune system can remember the antigens that previously activated it and launch a more intense immune reaction when encountering the same antigen a second time. The classical integer derivative does not reflect this characteristic because it is a local operator unlike the fractional derivative operator [5]. Moreover, fractional-order models are more consistent with real phenomena than the integer-order models because the fractional derivatives enable the description of the memory and hereditary properties inherent in various materials and processes [30]. As a result, mathematical modeling of HIV-1 infection using fractional differential equations (FDEs) has attracted the attention of many researchers [7, 22, 29, 35]. In addition, in [21], a mathematical model proposed to investigate the dynamics of HIV-1 infection in $CD4^+$ T cells. A delayed-order fractional model including uninfected T-cells, infected T-cells and free HIV viruses have been studied and investigated in [23]. A fractional model for HIV was introduced and a generalized Euler homotopy analysis method was used to approximate the response studied in [2]. In [11], a multi-step differential transform method has been used to obtain an approximate response for the T-cell fractional system. In [3], a fractional model has been proposed and a finite difference method was used to solve the proposed fractional model. Therefore, fractional calculus offers new perspectives in understanding complex dynamics of biological systems that exhibit memory effects. However, accurately describing such systems remains a significant challenge for scientists. This challenge arises from the fact that classical fractional derivatives have singular kernels, limiting their ability to adequately capture the nonlocal nature of real-world dynamics [6]. To address this limitation and improve the characterization of nonlocal systems, novel fractional derivatives with nonsingular kernels have been proposed and implemented for practical applications. Notably, Hattaf [13] recently proposed a new definition of fractional derivative that generalizes fractional derivatives [1, 4, 9]

with non-singular kernels for both Caputo and Riemann-Liouville types.

The aim of this study is to propose a mathematical model that describes the dynamics of HIV-1 infection under highly active antiretroviral therapy. The proposed model takes into account the general incidence rate, the two classes of infected cells (long-lived infected cells and chronically infected cells) as well as both characteristics of the humoral immune response. The immunological memory is modeled using the new generalized Hattaf fractional (GHF) derivative [13]. Additionally, we utilize the numerical method developed in [14] to approximate the solution of proposed model.

The remainder of this paper is divided as follows. In Section 2, we recall some interesting preliminaries and formulas. The properties of the solutions and the existence conditions of the equilibrium points are discussed in Section 3. The global stability of the equilibria is studied in Section 4, while Section 5 provides numerical simulations to demonstrate the analytical results. We conclude with Section 6, which presents our conclusions.

2. Preliminary results

In this section, we remind some important definitions of the GHF derivative presented in the work [13].

Definition 2.1 ([13]). Let $\alpha \in [0,1)$, $\beta, \gamma > 0$, and $f \in H^1(a,b)$. The GHF derivative of order α in Caputo sense of the function $f(t)$ with respect to the weight function $w(t)$ is defined as follows:

$$ {}^{C}D^{\alpha,\beta,\gamma}_{a,t,w} f(t) = \frac{N(\alpha)}{1-\alpha}\frac{1}{w(t)}\int_a^t E_\beta[-\mu_\alpha(t-\tau)^\gamma]\frac{d}{d\tau}(wf)(\tau)d\tau, $$

where $w \in C^1(a,b)$, $w, w' > 0$ on $[a,b]$, $N(\alpha)$ is a normalization function such that $N(0) = N(1) = 1$, $\mu_\alpha = \dfrac{\alpha}{1-\alpha}$, and $E_\beta(t) = \displaystyle\sum_{k=0}^{+\infty} \frac{t^k}{\Gamma(\beta k+1)}$ is the Mittag-Leffler function of parameter β.

Let us denote ${}^{C}D^{\alpha,\beta,\beta}_{a,t,w}$ by $\mathcal{D}^{\alpha,\beta}_{a,w}$. The generalized fractional integral associated to $\mathcal{D}^{\alpha,\beta}_{a,w}$ is provided by the following definition.

Definition 2.2 ([13]). The generalized fractional integral operator associated to $\mathcal{D}^{\alpha,\beta}_{a,w}$ is defined by

$$ \mathcal{I}^{\alpha,\beta}_{a,w} f(t) = \frac{1-\alpha}{N(\alpha)} f(t) + \frac{\alpha}{N(\alpha)}\, {}^{RL}\mathcal{I}^{\beta}_{a,w} f(t), $$

where ${}^{RL}\mathcal{I}^{\beta}_{a,w}$ is the standard weighted Riemann-Liouville fractional integral of order β given by

$$ {}^{RL}\mathcal{I}^{\beta}_{a,w} f(t) = \frac{1}{\Gamma(\beta)}\frac{1}{w(t)}\int_a^t (t-\tau)^{\beta-1} w(\tau) f(\tau) dx. $$

Theorem 2.3 ([15]). *Let $\alpha \in [0,1)$, $\beta > 0$ and $f \in H^1(a,b)$. Then we have the following properties:*

$$ \mathcal{I}^{\alpha,\beta}_{a,w}\left(\mathcal{D}^{\alpha,\beta}_{a,w} f\right)(t) = f(t) - \frac{w(a)f(a)}{w(t)} \quad \textit{and} \quad \mathcal{D}^{\alpha,\beta}_{a,w}\left(\mathcal{I}^{\alpha,\beta}_{a,w} f\right)(t) = f(t) - \frac{w(a)f(a)}{w(t)}. $$

3. Model formulation and basic properties

3.1. Model formulation

In this section, we first propose a mathematical model for HIV-1 infection with GHF derivative, general incidence rate and humoral immune response. The dynamics of this model is governed by the following

nonlinear system of FDEs:

$$\begin{cases} D_{0,1}^{\alpha,\beta} U = \lambda - d_1 U(t) - (1-\varepsilon) f\big(U(t), V(t)\big) V(t), \\ D_{0,1}^{\alpha,\beta} I = (1-\rho)(1-\varepsilon) f\big(U(t), V(t)\big) V(t) - d_2 I(t), \\ D_{0,1}^{\alpha,\beta} C = \rho(1-\varepsilon) f\big(U(t), V(t)\big) V(t) - d_3 C(t), \\ D_{0,1}^{\alpha,\beta} V = N_1(1-\eta_1) d_2 I(t) + N_2(1-\eta_2) d_3 C(t) - d_4 V(t) - b V(t) W(t), \\ D_{0,1}^{\alpha,\beta} W = a V(t) W(t) - d_5 W(t), \end{cases} \tag{3.1}$$

where $U(t)$, $I(t)$, $C(t)$, $V(t)$, and $W(t)$ represent the concentrations of uninfected cells, long-lived infected cells, chronically infected cells, free virus particles, and antibodies at time t, respectively. λ is the source term for uninfected cells. ε is the efficacy of the therapy. d_1, d_2, d_3, d_4, and d_5 are the death rates of uninfected cells, long-infected cells, chronically infected cells, virus, and antibodies, respectively. The fractions ρ and $(1-\rho)$ are the probabilities that, an uninfected cell will become either chronically infected or long-lived infected. $\bar{N}_1 = N_1(1-\eta_1)$ and $\bar{N}_2 = N_2(1-\eta_2)$, where N_1 and N_2 are the average numbers of virions produced in the lifetime of long-lived and chronically infected cells, respectively, as well as η_1 and η_2 are the efficacy of the therapy. Finally, a is the rate at which antibodies develop in response to free virus and b is the rate of neutralization of free HIV particles by antibodies. The flow diagram of the model is shown in Figure 1.

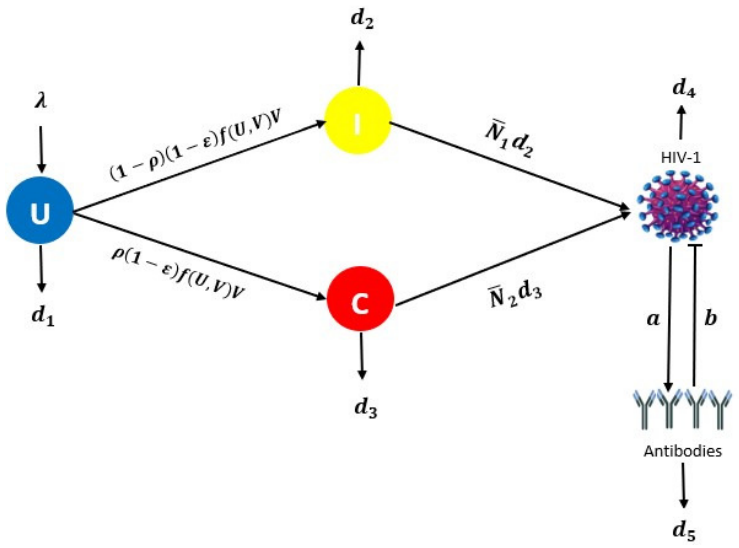

Figure 1: The flowchart representing the dynamics of model (3.1).

In this study, we assume that the general incidence function $f(U,V)$ is continuously differentiable in the interior of R_+^2 and satisfies the following assumptions:

(H_1) $f(0,V) = 0$, for all and $V \geqslant 0$;
(H_1) $\frac{\partial f(U,V)}{\partial U} > 0$ for all $U > 0$ and $V \geqslant 0$;
(H_1) $\frac{\partial f(U,V)}{\partial V} \leqslant 0$ for all $U \geqslant 0$ and $V \geqslant 0$.

From a biological point of view, all three assumptions are reasonable and consistent with reality. For more details on the biological significance of these three assumptions, we refer the reader to the following works [16, 31]. It is easy to check that a class of functions $f(U,V)$ satisfying (H_1)-(H_3) includes some common nonlinear incidence functions such as $f(U,V) = \frac{kU}{1+c_1V}$, $f(U,V) = \frac{kU}{1+c_2U+c_1V}$, and $f(U,V) = \frac{kU}{1+c_2U+c_1V+c_3UV}$ for $k, c_1, c_2, c_3 > 0$. For biological reasons, we assume that the initial conditions of model (3.1) satisfy:

$$U(0) = \phi_1(0) \geqslant 0, \quad I(0) = \phi_2(0) \geqslant 0, \quad C(0) = \phi_3(0) \geqslant 0, \quad V(0) = \phi_4(0) \geqslant 0, \quad W(0) = \phi_5(0) \geqslant 0. \tag{3.2}$$

It is important to note that the model presented by system (3.1) includes several cases existing in the literature. For instance, we obtain

- model of Callaway and Perelson [8] with chronically infected cells, when we ignore the role of humoral immunity, $\eta_1 = \eta_2 = 0$, $\alpha = \beta = 1$, and $f(U, V) = kU$;
- model without intracellular delay presented in [32], when the role of humoral immunity is negliged, $\alpha = \beta = 1$, and $f(U, V) = kU$.

3.2. Basic properties

As model (3.1) describes the population's evolution, it is necessary to demonstrate that the solutions remain non-negative and bounded for all time. These characteristics indicate the presence of global solutions.

Theorem 3.1. *For any initial conditions satisfying* (3.2)*, system* (3.1) *has a unique solution on* $[0, \infty)$*. Moreover, this solution remains non-negative and bounded for all* $t \geqslant 0$*.*

Proof. First, system (3.1) can be written as follows:

$$\begin{cases} D_{0,1}^{\alpha,\beta} X(t) = F(X(t)), \\ X(0) = X_0, \end{cases} \tag{3.3}$$

where $X(t) = \big(U(t), I(t), C(t), V(t), W(t)\big)^T$, $X_0 = \big(U(0), I(0), C(0), V(0), W(0)\big)^T$, and

$$F\big(X(t)\big) = \begin{pmatrix} \lambda - d_1 U(t) - (1-\varepsilon) f\big(U(t), V(t)\big) V(t) \\ (1-\varepsilon)(1-\rho) f\big(U(t), V(t)\big) V(t) - d_2 I(t) \\ \rho(1-\varepsilon) f\big(U(t), V(t)\big) V(t) - d_3 C(t) \\ \bar{N}_1 d_2 I(t) + \bar{N}_2 d_3 C(t) - d_4 V(t) - b V(t) W(t) \\ a V(t) W(t) - d_5 W(t) \end{pmatrix}.$$

The conditions given in [17] are clearly satisfied by $X(t)$, which implies the existence of a unique local solution for the initial value problem (3.3).

However, and in accordance with (3.1), we have

$$\begin{aligned} D_{0,1}^{\alpha,\beta} U(t) \,|_{U=0} &= \lambda \geqslant 0, \\ D_{0,1}^{\alpha,\beta} I(t) \,|_{I=0} &= (1-\rho)(1-\varepsilon) f\big(U(t), V(t)\big) V(t) \geqslant 0, \\ D_{0,1}^{\alpha,\beta} C(t) \,|_{C=0} &= \rho(1-\varepsilon) f\big(U(t), V(t)\big) V(t) \geqslant 0, \\ D_{0,1}^{\alpha,\beta} V(t) \,|_{V=0} &= \bar{N}_1 d_2 I(t) + \bar{N}_2 d_3 C(t) \geqslant 0, \\ D_{0,1}^{\alpha,\beta} W(t) \,|_{W=0} &= 0 \geqslant 0. \end{aligned}$$

Hence, $U(t), I(t), C(t), V(t)$, and $W(t)$ are nonnegative for all $t \geqslant 0$.

Next, we prove the boundedness of solutions. We consider the following function

$$T(t) = \frac{-\lambda}{\delta_1} + S_1(t),$$

where $S_1(t) = U(t) + I(t) + C(t)$ and $\delta_1 = \min\{d_1, d_2, d_3\}$. Taking the fractional-order derivative of $T(t)$ and from model (3.1), we have

$$D_{0,1}^{\alpha,\beta} T(t) = \lambda - d_1 U(t) - d_1 I(t) - d_3 C(t) \leqslant \lambda - \delta_1 S_1(t) = -\delta_1 T(t).$$

According to Corollary 1 in [18], we obtain

$$T(t) \leqslant T(0)E_\beta\left(\frac{-\alpha\delta_1 t^\beta}{N(\alpha)+\delta_1(1-\alpha)}\right).$$

Then

$$S_1(t) \leqslant S_1(0)E_\beta\left(\frac{-\alpha\delta_1 t^\beta}{N(\alpha)+\delta_1(1-\alpha)}\right)+\frac{\lambda}{\delta_1}\left[1-E_\beta\left(\frac{-\alpha\delta_1 t^\beta}{N(\alpha)+\delta_1(1-\alpha)}\right)\right].$$

Hence,

$$S_1(t) \leqslant S_1(0)+\frac{\lambda}{\delta_1}=\kappa_1.$$

Consequently, we can conclude that U, I, and C are bounded. To show the boundness of V and W, we set

$$H(t)=\frac{-\kappa_2}{\delta_2}+S_2(t),$$

where $S_2(t)=V(t)+\frac{b}{a}W(t)$, $\delta_2=\min\{d_4,d_5\}$, and $\kappa_2=\frac{\max\left(\bar{N}_1 d_2+\bar{N}_2 d_3\right)\kappa_1}{\delta_2}$. It follows from model (3.1) that

$$D_{0,1}^{\alpha,\beta}H(t)=\bar{N}_1 d_2 I(t)+\bar{N}_2 d_3 C(t)-d_4 V(t)-\frac{b d_5}{a}W(t)\leqslant \kappa_2-\delta_2 S_2(t)=-\delta_2 H(t).$$

Similarly to above, we have

$$H(t) \leqslant H(0)E_\beta\left(\frac{-\alpha\delta_1 t^\beta}{N(\alpha)+\delta_1(1-\alpha)}\right).$$

Then

$$S_2(t) \leqslant S_2(0)E_\beta\left(\frac{-\alpha\delta_2 t^\beta}{N(\alpha)+\delta_2(1-\alpha)}\right)+\frac{\kappa_2}{\delta_2}\left[1-E_\beta\left(\frac{-\alpha\delta_2 t^\beta}{N(\alpha)+\delta_2(1-\alpha)}\right)\right].$$

Hence,

$$S_2(t) \leqslant S_2(0)+\frac{\kappa_2}{\delta_2}.$$

Therefore, we conclude that V and W are bounded. This completes the proof.

In this section, we study the existence of equilibria in (3.1). It is clear that system (3.1) has one disease-free equilibrium $E_0(U_0,0,0,0,0)$, where $U_0=\frac{\lambda}{d_1}$. Therefore, the basic reproduction number of the model (3.1) is given by

$$R_0=\frac{(1-\varepsilon)\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)f\left(\frac{\lambda}{d_1},0\right)}{d_4}.$$

In the biological context, R_0 represents the average number of secondary infections caused by a single infected cell during the period of infection when all cells are initially uninfected. The remaining equilibria of system (3.1) satisfy the following algebraic equations

$$\begin{aligned}
\lambda-d_1U-(1-\varepsilon)f(U,V)V&=0,\\
(1-\varepsilon)(1-\rho)f(U,V)V-d_2I&=0,\\
\rho(1-\varepsilon)f(U,V)V-d_3C&=0,\\
\bar{N}_1 d_2 I+\bar{N}_2 d_3 C-d_4V-bVW&=0,\\
aVW-d_5W&=0.
\end{aligned}\tag{3.4}$$

The last equation of (3.4) implies that either $W = 0$ or $V = \frac{d_5}{a}$. Each of these scenarios will result in one of the other equilibria. First, when $W = 0$ and from (3.4), we have $I_1 = \frac{(1-\rho)(\lambda - d_1 U_1)}{d_2}$, $C_1 = \frac{\rho(\lambda - d_1 U_1)}{d_3}$, $V_1 = \frac{(\lambda - d_1 U_1)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}{d_4}$, and $f\left(U, \frac{(\lambda - d_1 U)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}{d_4}\right) = \frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}$. As a result of $V \geqslant 0$, we have $U \leqslant \frac{\lambda}{d_1}$. Now, we define a function G_1 on the interval $\left[0, \frac{\lambda}{d_1}\right]$ as follows

$$G_1(U) = f\left(U, \frac{(\lambda - d_1 U)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}{d_4}\right) - \frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}.$$

Then, we have

$$\begin{aligned} G_1(0) &= -\frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)} < 0, \\ G_1\left(\frac{\lambda}{d_1}\right) &= \frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}(R_0 - 1), \\ G_1'(U) &= \frac{\partial f}{\partial U} - \frac{d_1}{d_4}\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)\frac{\partial f}{\partial V} > 0. \end{aligned}$$

When $R_0 > 1$, we deduce that system (3.4) admits a unique infection equilibrium without immunity $E_1(U_1, I_1, C_1, V_1, 0)$, where $U_1 \in \left(0, \frac{\lambda}{d_1}\right)$, $I_1 = \frac{(1-\rho)(\lambda - d_1 U_1)}{d_2}$, $C_1 = \frac{\rho(\lambda - d_1 U_1)}{d_3}$ and $V_1 = \frac{(\lambda - d_1 U_1)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}{d_4}$. For the case when $W \neq 0$, we find $V = \frac{d_5}{a}$. Since W represents the number of antibody immune cells, we need to have $W \geqslant 0$. So, $W = \frac{a(\lambda - d_1 U_2)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}{b d_4} - \frac{d_4 d_5}{b d_5} \geqslant 0$. This condition leads to $U \leqslant \frac{\lambda}{d_1} - \frac{d_4 d_5}{a d_1\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}$. Let us consider

$$G_2(U) = f\left(U, \frac{d_5}{a}\right) - \frac{a(\lambda - d_1 U)}{d_5(1-\varepsilon)}.$$

Then, we have $G_2(0) = -\frac{a\lambda}{d_5(1-\varepsilon)} < 0$ and $G_2'(U) = \frac{\partial f}{\partial U} + \frac{a d_1}{d_5(1-\varepsilon)} > 0$. In addition to the threshold parameter R_0, we define another threshold parameter called the reproduction number for humoral immunity as follows

$$R_1^W = \frac{a V_1}{d_5},$$

where $\frac{1}{d_5}$ is the average life span of antibodies and V_1 is the quantity of viruses at the steady state E_1. Therefore, the number R_1^W biologically represents the average number of antibodies activated by viral particles [19].

Note that when $R_1^W > 1$, then $V_1 > \frac{d_5}{a}$ and $U_1 < \frac{\lambda}{d_1} - \frac{d_4 d_5}{a d_1\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}$ and we have

$$\begin{aligned} G_2\left(\frac{\lambda}{d_1} - \frac{d_4 d_5}{a d_1\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}\right) &= f\left(\frac{\lambda}{d_1} - \frac{d_4 d_5}{a d_1\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)}, \frac{d_5}{a}\right) - \frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)} \\ &> f(U_1, V_1) - \frac{d_4}{(1-\varepsilon)\left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)} = 0. \end{aligned}$$

Therefore, the model (3.1) admits a unique infection equilibrium with humoral immunity, $E_2(U_2, I_2, C_2, V_2, W_2)$, where $U_2 \in \left(0, \frac{\lambda}{d_1} \frac{d_4 d_5}{a d_1 \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)}\right)$, $I_2 = \frac{(1-\rho)(\lambda - d_1 U_2)}{d_2}$, $C_2 = \frac{\rho(\lambda - d_1 U_2)}{d_3}$, and $W_2 = \frac{a(\lambda - d_1 U_2)\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)}{b d_4} - \frac{d_4 d_5}{b d_5}$. □

Summarizing the above discussions, we get the following theorem.

Theorem 3.2.

(i) *If* $R_0 \leqslant 1$, *then the model* (3.1) *always has one disease-free equilibrium* $E_0\left(U_0, 0, 0, 0, 0\right)$, *where* $U_0 = \frac{\lambda}{d_1}$.

(ii) *If* $R_1^W \leqslant 1 < R_0$, *then the model* (3.1) *has an infection equilibrium without humoral immunity* $E_1\left(U_1, I_1, C_1, V_1, 0\right)$, *where* $U_1 \in \left(0, \frac{\lambda}{d_1}\right)$, $I_1 = \frac{(1-\rho)(\lambda - d_1 U_1)}{d_2}$, $C_1 = \frac{\rho(\lambda - d_1 U_1)}{d_3}$, *and*

$$V_1 = \frac{(\lambda - d_1 U_1)\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)}{d_4}.$$

(iii) *If* $R_1^W > 1$, *then the model* (3.1) *has an infection equilibrium with humoral immunity* $E_2\left(U_2, I_2, C_2, V_2, W_2\right)$, *where* $U_2 \in \left(0, \frac{\lambda}{d_1} - \frac{d_4 d_5}{a d_1 \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)}\right)$, $I_2 = \frac{(1-\rho)(\lambda - d_1 U_2)}{d_2}$, $C_2 = \frac{\rho(\lambda - d_1 U_2)}{d_3}$, $V_2 = \frac{d_5}{a}$, *and* $W_2 = \frac{a(\lambda - d_1 U_2)\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)}{b d_5} - \frac{d_4 d_5}{b d_5}$.

4. Mathematical analysis

In this section, we study the global stability of the three equilibria of model (3.1) by constructing suitable Lyapunov functions. We first investigate the global stability of the disease-free equilibrium.

Lemma 4.1. *Let* f *be a continuous function and* U *be a continuously differentiable function. For any constants* $U^*, V^* \geqslant 0$ *and any function* F *defined by*

$$F(t) = \int_{U^*}^{U(t)} g(x)dx,$$

where $g(x) = 1 - \frac{f(U^*, V^*)}{f(x, V^*)}$, *we have following inequality:*

$$D_{0,1}^{\alpha,\beta} F(t) \leqslant \left(1 - \frac{f(U^*, V^*)}{f(U(t), V^*)}\right) D_{0,1}^{\alpha,\beta} U(t). \tag{4.1}$$

Proof. It is not hard to see that g is an increasing function. By applying the first result of Theorem 1 in [15] and using the definition of GHF derivative, we obtain the following inequality

$$D_{0,1}^{\alpha,\beta} F(t) \leqslant g(U) D_{0,1}^{\alpha,\beta} U(t) = \left(1 - \frac{f(U^*, V^*)}{f(U(t), V^*)}\right) D_{0,1}^{\alpha,\beta} U(t).$$

This proves (4.1). □

Theorem 4.2. *The disease-free equilibrium* E_0 *is globally stable for* $R_0 \leqslant 1$.

Proof. To study the global stability of E_0, we consider the following Lyapunov functional

$$L_0(U,I,C,V,W) = \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(U-U_0-\int_{U_0}^{U}\frac{f(U_0,0)}{f(s,0)}ds\right)+\bar{N}_1 I+\bar{N}_2 C+V+\frac{b}{a}W.$$

Applying Lemma 4.1 and Corollary 2 of [15], we get

$$D_{0,1}^{\alpha,\beta}L_0 \leqslant \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(1-\frac{f(U_0,0)}{f(U,0)}\right)D_{0,1}^{\alpha,\beta}U+\bar{N}_1 D_{0,1}^{\alpha,\beta}I+\bar{N}_2 D_{0,1}^{\alpha,\beta}C+D_{0,1}^{\alpha,\beta}V+\frac{b}{a}D_{0,1}^{\alpha,\beta}W,$$

then,

$$\begin{aligned}
D_{0,1}^{\alpha,\beta}L_0 &\leqslant \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(1-\frac{f(U_0,0)}{f(U,0)}\right)\left(d_1U_0-d_1U-(1-\varepsilon)f(U,V)V\right)\\
&\quad+\bar{N}_1\left[(1-\rho)(1-\varepsilon)f(U,V)V-d_2I\right]+\bar{N}_2\left(\rho(1-\varepsilon)f(U,V)V-d_3C\right)\\
&\quad+\left(\bar{N}_1 d_2 I_{\tau_3}+\bar{N}_2 d_3 C_{\tau_4}-d_4V-bVW\right)+\frac{b}{a}\left(aVW-d_5W\right)\\
&\leqslant d_1U_0\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(1-\frac{U}{U_0}\right)\left(1-\frac{f(U_0,0)}{f(U,0)}\right)+d_4\left(\frac{f(U,V)}{f(U_0,0)}R_0-1\right)V-\frac{b}{a}d_5W.
\end{aligned}$$

This leads to the following inequality

$$D_{0,1}^{\alpha,\beta}L_0 \leqslant d_1U_0\left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(1-\frac{U}{U_0}\right)\left(1-\frac{f(U_0,0)}{f(U,0)}\right)+d_4\left(R_0-1\right)V.$$

Since the function $f(U,V)$ is strictly monotonically increasing with respect to U, we have

$$\left(1-\frac{U}{U_0}\right)\left(1-\frac{f(U_0,0)}{f(U,0)}\right)\leqslant 0.$$

Hence, $D_{0,1}^{\alpha,\beta}L_0 \leqslant 0$ if $R_0 \leqslant 1$. As a result, the condition (ii) of Theorem 5 of [14] is satisfied. Therefore, the disease-free equilibrium E_0 of model (3.1) is globally stable whenever $R_0 \leqslant 1$.

Now, we establish the global stability of the humoral immunity infection equilibrium E_1. To do this, we assume that $R_0 > 1$ and the incidence function f satisfy the following hypothesis:

(H_4)
$$\left(1-\frac{f(U,V)}{f(U,V_i)}\right)\left(\frac{f(U,V_i)}{f(U,V)}-\frac{V}{V_i}\right)\leqslant 0, \quad \text{for } i=1,2.$$

It is not difficult to see that (H_4) is satisfied for the Beddington-DeAngelis functional response, the Crowley-Martin functional response, and the Hattaf-Yousfi functional response. In addition, (H_4) is also satisfied when $f(U,V)V$ is monotonically increasing function with respect to V. □

Theorem 4.3. *Assume that* (H_4) *holds for* E_1. *If* $R_1^W \leqslant 1 < R_0$, *then the infection equilibrium without humoral immunity* E_1 *is globally asymptotically stable.*

Proof. Constructing a Lyapunov functional L_1 as follows:

$$\begin{aligned}
L_1(U,I,C,V,W) &= \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(U-U_1-\int_{U_1}^{U}\frac{f(U_1,V_1)}{f(s,V_1)}ds\right)+\bar{N}_1 I_1\Phi\left(\frac{I}{I_1}\right)\\
&\quad+\bar{N}_2 C_1\Phi\left(\frac{C}{C_1}\right)+V_1\Phi\left(\frac{V}{V_1}\right)+\frac{b}{a}W,
\end{aligned}$$

where $\Phi(x) = x - 1 - \ln(x)$ for $x > 0$. Note that $\Phi(x) = 0$ if and only if $x = 1$. Applying Lemma 4.1 and Corollary 2 of [15], we get

$$D_{0,1}^{\alpha,\beta} L_1 \leqslant \left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)\left(1 - \frac{f(U_1,V_1)}{f(U,V_1)}\right) D_{0,1}^{\alpha,\beta} U + \bar{N}_1\left(1 - \frac{I_1}{I}\right) D_{0,1}^{\alpha,\beta} I$$
$$+ \bar{N}_2\left(1 - \frac{C_1}{C}\right) D_{0,1}^{\alpha,\beta} C + \left(1 - \frac{V_1}{V}\right) D_{0,1}^{\alpha,\beta} V + \frac{b}{a} D_{0,1}^{\alpha,\beta} W.$$

At the equilibrum point E_1, we have

$$(1-\varepsilon) f(U_1,V_1) V_1 = \lambda - d_1 U_1, \qquad (1-\varepsilon)(1-\rho) f(U_1,V_1) V_1 = d_2 I_1,$$
$$\rho(1-\varepsilon) f(U_1,V_1) V_1 = d_3 C_1, \qquad \bar{N}_1 d_2 I + \bar{N}_2 d_3 C = d_4 V_1.$$

Hence,

$$D_{0,1}^{\alpha,\beta} L_1 = \left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)\left(1 - \frac{f(U_1,V_1)}{f(U,V_1)}\right)\left(d_1 U_1 - d_1 U + (1-\varepsilon) f(U_1,V_1) V_1 - (1-\varepsilon) f(U,V) V\right)$$
$$+ \bar{N}_1\left(1 - \frac{I_1}{I}\right)\left((1-\rho)(1-\varepsilon) f(U,V) V - d_2 I\right) + \bar{N}_2\left(1 - \frac{C_1}{C}\right)\left(\rho(1-\varepsilon) f(U,V) V - d_3 C\right)$$
$$+ \left(1 - \frac{V_1}{V}\right)\left(\bar{N}_1 d_2 I + \bar{N}_2 d_3 C - d_4 V - bVW\right) + \frac{b}{a}\left(aVW - d_5 W\right).$$

Then

$$\begin{aligned} D_{0,1}^{\alpha,\beta} L_1 &\leqslant d_1 U_1 \left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)\left(1 - \frac{U}{U_1}\right)\left(1 - \frac{f(U_1,V_1)}{f(U,V_1)}\right) \\ &+ \left(\bar{N}_1 d_2 I_1 + \bar{N}_2 d_3 C_1\right)\left(1 - \frac{f(U,V)}{f(U,V_1)}\right)\left(\frac{f(U,V_1)}{f(U,V)} - \frac{V}{V_1}\right) \\ &- \bar{N}_1 d_2 I_1 \left(-4 + \frac{f(U_1,V_1)}{f(U,V_1)} + \frac{f(U,V) V I_1}{f(U_1,V_1) V_1 I} + \frac{f(U,V_1)}{f(U,V)} + \frac{I V_1}{I_1 V}\right) \\ &- \bar{N}_2 d_3 C_1 \left(-4 + \frac{f(U_1,V_1)}{f(U,V_1)} + \frac{f(U,V) V C_1}{f(U_1,V_1) V_1 C} + \frac{f(U,V_1)}{f(U,V)} + \frac{C V_1}{C_1 V}\right) + \frac{b d_5}{a}(R_1^W - 1) W, \\ &\leqslant d_1 U_1 \left(\bar{N}_1(1-\rho) + \rho\bar{N}_2\right)\left(1 - \frac{U}{U_1}\right)\left(1 - \frac{f(U_1,V_1)}{f(U,V_1)}\right) \\ &+ \left(\bar{N}_1 d_2 I_1 + \bar{N}_2 d_3 C_1\right)\left(1 - \frac{f(U,V)}{f(U,V_1)}\right)\left(\frac{f(U,V_1)}{f(U,V)} - \frac{V}{V_1}\right) \\ &- \bar{N}_1 d_2 I_1 \left(\Phi\left(\frac{f(U_1,V_1)}{f(U,V_1)}\right) + \Phi\left(\frac{f(U,V) V I_1}{f(U_1,V_1) V_1 I}\right) + \Phi\left(\frac{f(U,V_1)}{f(U,V)}\right) + \Phi\left(\frac{I V_1}{I_1 V}\right)\right) \\ &- \bar{N}_2 d_3 C_1 \left(\Phi\left(\frac{f(U_1,V_1)}{f(U,V_1)}\right) + \Phi\left(\frac{f(U,V) V C_1}{f(U_1,V_1) V_1 C}\right) + \Phi\left(\frac{f(U,V_1)}{f(U,V)}\right) + \Phi\left(\frac{C V_1}{C_1 V}\right)\right) + \frac{b d_5}{a}(R_1^W - 1) W. \end{aligned}$$

Since the function $f(U,V)$ is strictly monotonically increasing with respect to U, we have

$$\left(1 - \frac{U}{U_1}\right)\left(1 - \frac{f(U_1,V_1)}{f(U,V_1)}\right) \leqslant 0.$$

Hence, $D_{0,1}^{\alpha,\beta} L_1 \leqslant 0$ if $R_1^W \leqslant 1$. As a result, the condition (ii) of Theorem 5 of [14] is satisfied. Therefore, the infection equilibrium without humoral immunity E_1 of model (3.1) is globally stable whenever $R_1^W \leqslant 1$. □

Theorem 4.4. *Assume that* (H_4) *holds for* E_2. *If* $R_1^W > 1$, *then the infection equilibrium with humoral immunity* E_2 *is globally asymptotically stable.*

Proof. Construct a Lyapunov functional L_2 as follows:

$$L_2(U,I,C,V,W) = (\bar{N}_1(1-\rho)+\rho\bar{N}_2)\left(U-U_2-\int_{U_2}^{U}\frac{f(U_2,V_2)}{f(s,V_2)}ds\right)+\bar{N}_1 I_2\Phi\left(\frac{I}{I_2}\right)$$
$$+\bar{N}_2 C_2\Phi\left(\frac{C}{C_2}\right)+V_2\Phi\left(\frac{V}{V_2}\right)+\frac{b}{a}W_2\Phi\left(\frac{W}{W_2}\right).$$

Applying Lemma 4.1 and Corollary 2 of [15], we get

$$D_{0,1}^{\alpha,\beta}L_2 \leqslant \left(\bar{N}_1(1-\rho)+\rho\bar{N}_2\right)\left(1-\frac{f(U_2,V_2)}{f(U,V_2)}\right)D_{0,1}^{\alpha,\beta}U+\bar{N}_1\left(1-\frac{I_2}{I}\right)D_{0,1}^{\alpha,\beta}I$$
$$+\bar{N}_2\left(1-\frac{C_2}{C}\right)D_{0,1}^{\alpha,\beta}C+\left(1-\frac{V_2}{V}\right)D_{0,1}^{\alpha,\beta}V+\frac{b}{a}\left(1-\frac{W_2}{W}\right)D_{0,1}^{\alpha,\beta}W.$$

At the equilibrum point E_2, we have

$$\begin{aligned}(1-\varepsilon)f(U_2,V_2)V_2 &= \lambda-d_1U_2,\\ (1-\varepsilon)(1-\rho)f(U_2,V_2)V_2 &= d_2I_2,\\ \rho(1-\varepsilon)f(U_2,V_2)V_2 &= d_3C_2,\\ \bar{N}_1d_2I+\bar{N}_2d_3C &= d_4V_2+bV_2W_2,\\ aV_2W_2 &= d_5W_2.\end{aligned}$$

Hence,

$$D_{0,1}^{\alpha,\beta}L_2 \leqslant d_1U_2(\bar{N}_1(1-\rho)+\rho\bar{N}_2)\left(1-\frac{U}{U_2}\right)\left(1-\frac{f(U_2,V_2)}{f(U,V_2)}\right)$$
$$+(\bar{N}_1d_2I_2+\bar{N}_2d_3C_2)\left(1-\frac{f(U,V)}{f(U,V_2)}\right)\left(\frac{f(U,V_2)}{f(U,V)}-\frac{V}{V_2}\right)$$
$$-\bar{N}_1d_2I_2\left(-3+\frac{f(U_2,V_2)}{f(U,V_2)}+\frac{f(U,V)VI_2}{f(U,V_2)V_2I}+\frac{IV_2}{I_2V}\right)$$
$$-\bar{N}_2d_3C_2\left(-3+\frac{f(U_2,V_2)}{f(U,V_2)}+\frac{f(U,V)VC_2}{f(U,V_2)V_2C}+\frac{CV_2}{C_2V}\right).$$

We have

$$\left(3-\frac{f(U_2,V_2)}{f(U,V_2)}-\frac{f(U,V)VI_2}{f(U_2,V_2)V_2I}-\frac{IV_2}{I_2V}\right)\leqslant 0,$$

and

$$\left(3-\frac{f(U_2,V_2)}{f(U,V_2)}-\frac{f(U,V)VC_2}{f(U_2,V_2)V_2C}-\frac{CV_2}{C_2V}\right)\leqslant 0.$$

Since the function $f(U,V)$ is strictly monotonically increasing with respect to U, we have

$$\left(1-\frac{U}{U_2}\right)\left(1-\frac{f(U_2,V_2)}{f(U,V_2)}\right)\leqslant 0,$$

and according to the hypothesis (H_4), we have the following inequality:

$$\left(1-\frac{f(U,V)}{f(U,V_2)}\right)\left(\frac{f(U,V_2)}{f(U,V)}-\frac{V}{V_2}\right)\leqslant 0.$$

Therefore, we have $D_{0,1}^{\alpha,\beta}L_2 \leqslant 0$ if $R_1^W > 1$. It follows from the condition (ii) of Theorem 5 of [14] that the infection equilibrium E_2 with humoral immunity is globally stable when $R_1^W > 1$. □

5. Numerical analysis

In this section, we validate our theoretical results by numerical simulations.

Let $t_n = nh$, where $n \in \mathbb{N}$ and h is the time step of discretization. Based on the method [14] that includes the classical Euler numerical scheme, we obtain the following discrete model:

$$\begin{cases} U(t_{n+1}) = U(t_0) + \dfrac{1-\alpha}{N(\alpha)} f_1\big(t_n, U(t_n)\big) + \dfrac{\alpha h^\beta}{N(\alpha)\Gamma(\beta+1)} \mathcal{A}^\beta_{n,1}, \\ I(t_{n+1}) = I(t_0) + \dfrac{1-\alpha}{N(\alpha)} f_2\big(t_n, I(t_n)\big) + \dfrac{\alpha h^\beta}{N(\alpha)\Gamma(\beta+1)} \mathcal{A}^\beta_{n,2}, \\ C(t_{n+1}) = C(t_0) + \dfrac{1-\alpha}{N(\alpha)} f_3\big(t_n, C(t_n)\big) + \dfrac{\alpha h^\beta}{N(\alpha)\Gamma(\beta+1)} \mathcal{A}^\beta_{n,3}, \\ V(t_{n+1}) = V(t_0) + \dfrac{1-\alpha}{N(\alpha)} f_4\big(t_n, V(t_n)\big) + \dfrac{\alpha h^\beta}{N(\alpha)\Gamma(\beta+1)} \mathcal{A}^\beta_{n,4}, \\ W(t_{n+1}) = W(t_0) + \dfrac{1-\alpha}{N(\alpha)} f_5\big(t_n, W(t_n)\big) + \dfrac{\alpha h^\beta}{N(\alpha)\Gamma(\beta+1)} \mathcal{A}^\beta_{n,5}, \end{cases} \tag{5.1}$$

with $\mathcal{A}^\beta_{n,j} = \sum_{i=0}^{n} f_j\big(t_i, X(t_i)\big)\Big((n-i+1)^\beta - (n-i)^\beta\Big)$, $N(\alpha)$ is the normalization function defined by:

$$N(\alpha) = 1 - \alpha + \frac{\alpha}{\Gamma(\alpha)},$$

$f(U,V) = \dfrac{\kappa_1 U}{1+\kappa_2 V}$, and

$$\begin{aligned} f_1\big(t_n, U(t_n)\big) &= \lambda - d_1 U(t_n) - (1-\varepsilon)\frac{\kappa_1 U(t_n) V(t_n)}{1+\kappa_2 V(t_n)}, \\ f_2\big(t_n, I(t_n)\big) &= (1-\rho)(1-\varepsilon)\frac{\kappa_1 U(t_n) V(t_n)}{1+\kappa_2 V(t_n)} - d_2 I(t_n), \\ f_3\big(t_n, C(t_n)\big) &= \rho(1-\varepsilon)\frac{\kappa_1 U(t_n) V(t_n)}{1+\kappa_2 V(t_n)} - d_3 C(t_n), \\ f_4\big(t_n, V(t_n)\big) &= N_1(1-\eta_1) d_2 I(t_n) + N_2(1-\eta_2) d_3 C(t_n) - d_4 V(t_n) - b V(t_n) W(t_n), \\ f_5\big(t_n, W(t_n)\big) &= a V(t_n) W(t_n) - d_5 W(t_n). \end{aligned}$$

For numerical simulations we choose the time interval $[0, 500]$ with a step size $h = 0.1$. Also, we take $N_1 = 10$, $N_2 = 2.11$, $\rho = 0.195$, $\varepsilon = 0.5$, $b = 0.001$, and $\beta = 1$.

First, system (3.1) cannot be solved analytically. Based on the numerical method [14], we approximate the solution of (3.1). Therefore, we chose $\lambda = 1000$, $\kappa_1 = 8 \times 10^{-7}$, $\kappa_2 = 0.01$, $d_2 = 0.95$, $d_3 = 0.5$, $d_4 = 0.4$, and $d_5 = 0.6$. By computation we find that $R_0 = 0.8461$. In this case, we remark that the solution of our system converges to the disease-free equilibrium $E_0(10^5, 0, 0, 0, 0)$ which means that the HIV-1 is cleared and the infection dies out and also indicates limited success of HAART used to treat HIV-1. Figure 2 illustrates this observation for different values of α.

Second, in the absence of humoral immunity, we take $\lambda = 1000$, $\kappa_1 = 8 \times 10^{-5}$, $\kappa_2 = 0.0001$, $d_3 = 0.2$, $d_4 = 0.8$, and $d_5 = 0.9$. By computation, we have $R_0 = 4.2307$ and $R_1 = 0.9$. In this case, the solution of (3.1) converges to the infection equilibrium without humoral immunity $E_1(2.3838 \times 10^4, 6.4666 \times 10^2, 7.43340 \times 10^2, 8.069 \times 10^2, 0)$. Figure 3 illustrates this observation for different values of α.

Finally, in the presence of humoral immunity, we select $d_2 = 0.3$, $d_5 = 0.72$, $a = 0.002$ and we keep the same values of the other parameters as the second case. In this case we have $R_1^W = 4.2307 > 1$. Therefore, the solution of system (3.1) converges to the infection equilibrium with humoral immunity $E_2(4.1718 \times 10^3, 1.5559 \times 10^2, 5.6529 \times 10, 3.601 \times 10^2, 5.626 \times 10^3)$, which means that HIV-1 persists and

the infection becomes chronic. Additionally, HAART is no longer effective in preventing HIV replication, leading to a condition known as drug resistance. Figure 4 illustrates this observation for different values of α. Therefore, Figures 2,3, and 4 demonstrate that higher values of α lead to faster stabilization of the curves, while the shape of the trajectories remains the same. Moreover, it is evident that decreasing the order of β requires more time to achieve stability.

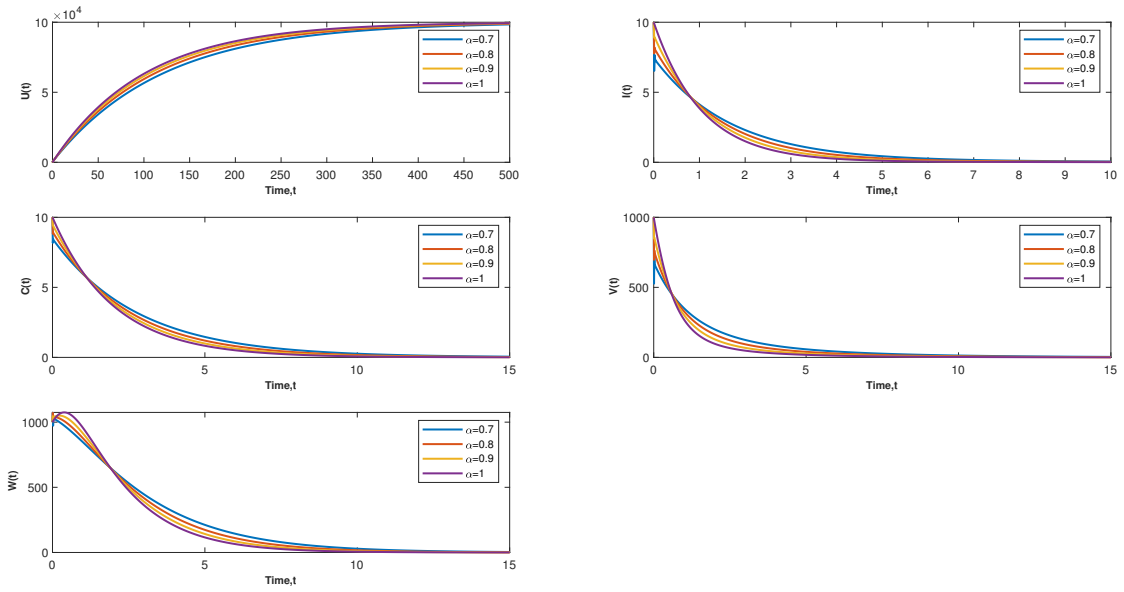

Figure 2: Stability of the disease-free equilibrium E_0 for different values of α.

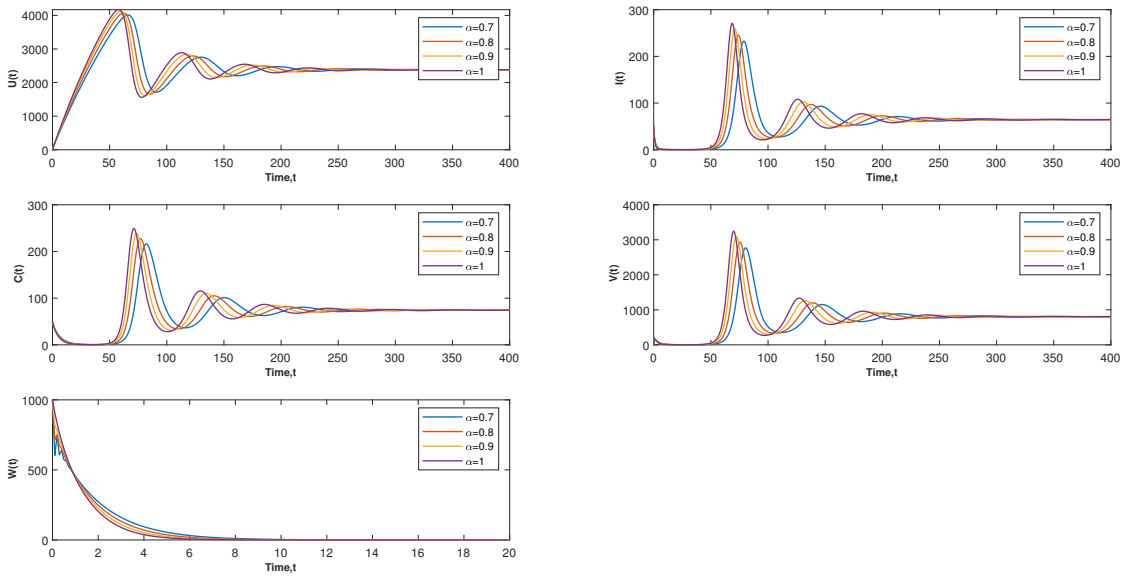

Figure 3: Stability of the infection equilibrium without humoral immunity E_1 for different values of α.

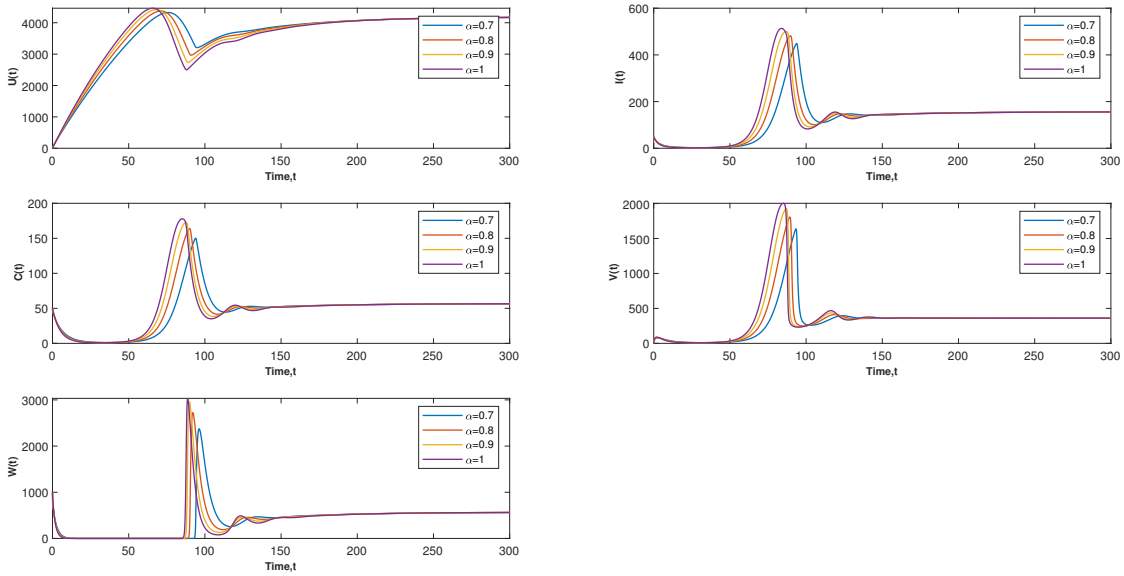

Figure 4: Stability of the infection equilibrium with humoral immunity E_2 for different values of α.

6. Conclusions

In this paper, we have proposed and investigated a mathematical model governed by a nonlinear system of FDEs with GHF derivative which describes the dynamics of HIV-1 infection with long-lived infected cells under highly active antiretroviral therapy and humoral immunity. We have derived two threshold parameters in order to fully characterize the dynamical behaviors of model. These parameters are the basic reproduction number R_0 and the reproduction numbers for humoral immunity R_1^W. More precisely, the disease-free equilibrium is globally stable if $R_0 \leqslant 1$, which biologically means that the HIV-1 is cleared and the infection dies out. When $R_0 > 1$, the disease-free equilibrium becomes unstable and two infection steady states are appeared which are: (i) the infection equilibrium without humoral immunity which is globally stable if $R_1^W \leqslant 1$; and (ii) the infection equilibrium with humoral immunity which is globally stable if $R_1^W > 1$. Biologically, this implies that the HIV-1 persists and the infection becomes chronic.

From the analytical and numerical results presented above, we can conclude that the order of the GHF derivative does not affect the stability of the three equilibria. However, it may have an impact on the time required to reach these equilibria. Specifically, increasing the order of the GHF derivative α leads to a faster convergence of the solutions to the equilibrium points.

Acknowledgments

The authors thank the editor and anonymous referees for their helpful comments and suggestions that greatly improved the quality of this paper.

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