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# A diffusion-based HIV model with inflammatory cytokines and adaptive immune impairment

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HIV continues to pose a critical threat to global public health, contributing to a high number of deaths worldwide. The virus predominantly attacks $CD4^+$T lymphocytes, which are essential for coordinating immune responses. A progressive decline in these cells is a hallmark of HIV pathogenesis. Recent research has underscored the role of inflammatory cytokines in promoting viral spread and exacerbating immune dysfunction. This study presents a spatially structured model of HIV infection incorporating the role of inflammatory cytokines. The model consists of six interacting components: healthy $CD4^+$ T cells, HIV-infected cells, inflammatory cytokines, free viral particles, cytotoxic T lymphocytes (CTLs), and antibodies. It accounts for both cell-free (virus-to-cell) and direct (cell-to-cell) modes of transmission. The model also captures the suppression of adaptive immune responses involving CTLs and B cells. Motivated by recent findings that immune and infected cells, as well as viruses, may migrate from high to low concentration areas, we introduce diffusion terms to represent spatial movement, resulting in a system of nonlinear partial differential equations. We first establish the model's mathematical well-posedness by proving the existence and boundedness of global solutions. A basic reproduction number $\mathcal{R}_0$ is derived, serving as a threshold parameter that governs the stability of two equilibria: the HIV-free equilibrium ($\mathcal{FE}$) and the HIV-persistent equilibrium ($\mathcal{PE}$). By constructing suitable Lyapunov functions and applying LaSalle's invariance principle, we demonstrate that $\mathcal{FE}$ is globally asymptotically stable when $\mathcal{R}_0 \leq 1$, while $\mathcal{PE}$ becomes globally stable if $\mathcal{R}_0 > 1$. Numerical simulations are performed to validate the analytical results, and a sensitivity analysis of $\mathcal{R}_0$ is carried out to evaluate the impact of critical model parameters.

KEYWORDS

**HIV infection, inflammatory cytokines, diffusion, cell-to-cell transmission, global stability, adaptive immune impairment, Lyapunov method**

## 1 Introduction

The human immunodeficiency virus (HIV), a fast-replicating retrovirus within the lentivirus genus, specifically targets and disrupts the functionality of critical immune cells, with a strong preference for $CD4^+$T cells. These immune cells play a vital role in regulating and coordinating immune defense mechanisms. Once HIV enters the body, it integrates its genetic material into the host genome, gradually depleting the number of $CD4^+$T cells. In a healthy individual, the $CD4^+$T cell count is typically around 1,000 cells per $mm^3$ of blood. As the infection progresses, these levels decline steadily, often without immediate symptoms. When the count falls below 200 cells/$mm^3$, the individual is considered to have developed acquired immunodeficiency syndrome (AIDS), a condition characterized by increased susceptibility to opportunistic infections and certain types of cancer [1, 2].

In the absence of appropriate antiretroviral therapy, the continuous weakening of the immune system can lead to severe complications and, ultimately, death. The adaptive immune response is vital in managing viral infections and operates primarily through two pathways: antibodies produced by B cells that neutralize HIV particles, and cytotoxic T lymphocytes (CTLs) that identify and destroy infected host cells. These coordinated responses work to inhibit viral replication and reduce the rate of disease advancement.

Mathematical modeling serves as an essential approach for exploring the complex interactions between viral infections and the host's immune defenses. By representing biological processes through mathematical equations, these models enable a deeper investigation into the factors that influence infection dynamics, the strength and limitations of immune responses, and the potential outcomes of various scenarios. This approach has greatly enhanced our comprehension of virus-immune system relationships and has become instrumental in guiding the design of effective treatments and shaping public health policies. A basic model for analyzing HIV dynamics was proposed by Nowak and Bangham [3], capturing the interactions between healthy $CD4^+T$ cells, infected cells, and free virus particles. Since its introduction, this foundational framework has been extended in various directions to incorporate the CTL response [4–9], the antibody-mediated immune response [10, 11], and more comprehensive formulations that include both CTL and antibody responses simultaneously [12–16].

Pyroptosis, unlike the controlled and non-inflammatory nature of apoptosis, is a pro-inflammatory programmed cell death mechanism closely linked to immune system activation and inflammatory responses. In HIV-infected individuals, Doitsh et al. [17] demonstrated that caspase-1, a cysteine-dependent protease, becomes activated and promotes the secretion of inflammatory mediators such as interleukin-1$\beta$ (IL-1$\beta$). These cytokines sustain a chronic inflammatory environment that draws in uninfected $CD4^+T$ cells, rendering them vulnerable to death. As a result, a destructive feedback loop is created in which infected $CD4^+T$ cells undergoing pyroptosis release inflammatory factors that drive the death of surrounding uninfected $CD4^+T$ cells, accelerating the decline of immune function [17]. Studies indicate that merely about 5% of $CD4^+T$ cell death is attributed to apoptosis triggered by caspase-3, whereas the majority are lost through pyroptosis, driven by caspase-1 activation [18].

Wang et al. [19] developed a mathematical model of HIV infection that incorporates the contribution of pyroptosis to $CD4^+T$ cell depletion. The model is given by a system of ordinary differential equations (ODEs) which describes the interaction of healthy $CD4^+T$ cells, productively infected cells, abortively infected cells, inflammatory cytokines, and free HIV particles. In this framework, the impact of inflammatory cytokines on the basic reproduction number is not considered. As a result, the model overlooks the potential rise in infection rates driven by cytokine-induced recruitment of $CD4^+T$ cells to inflamed areas, which could lead to an underestimation of the basic reproduction number.

Recent research has highlighted the role of cytokine-driven mechanisms in the accumulation of infected $CD4^+T$ cells and their impact on HIV dynamics [20]. Failing to account for the rise in viral infection caused by the higher concentration of $CD4^+T$ cells, which are attracted to inflamed regions by cytokines, could lead to an underestimation of the basic reproduction number [21]. Cytokine-induced viral infections can disturb the balance between cell renewal and viral replication, particularly through mechanisms such as pyroptosis [18]. The growth of the infected $CD4^+T$ cell population is shaped by two main pathways: (i) direct infection of healthy $CD4^+T$ cells through viral contact, and (ii) an increase in infection rates linked to the elevated presence of $CD4^+T$ cells in inflamed tissues, where cytokines actively recruit them (a process known as cytokine-enhanced viral infection). To capture the combined effects of these mechanisms, the following system of equations models the dynamics of HIV infection under cytokine influence [20]:

$$\begin{cases} \frac{dN(t)}{dt} = \delta - \varphi_N N(t) - \omega_1 N(t)B(t) - \omega_2 N(t)S(t), \\ \frac{dU(t)}{dt} = \omega_1 N(t)B(t) + \omega_2 N(t)S(t) - (\beta_1 + \varphi_U)\, U(t), \\ \frac{dS(t)}{dt} = \beta_2 U(t) - \varphi_S S(t), \\ \frac{dB(t)}{dt} = \mu U(t) - \varphi_B B(t). \end{cases} \tag{1}$$

Here, $N(t)$, $U(t)$, $S(t)$ and $B(t)$ represent the time-dependent concentrations of healthy $CD4^+T$ cells, $CD4^+T$ cells infected with HIV, inflammatory cytokines, and free HIV virions, respectively. The parameter $\delta$ represents the production rate of uninfected $CD4^+T$ cells. The term $\omega_1 NB$ corresponds to the rate at which $CD4^+T$ cells become infected through direct interaction with the virus, while $\omega_2 NS$ captures the cytokine-induced enhancement of infection. Cytokine and viral particle release from infected cells are modeled by the terms $\beta_2 U$ and $\mu U$, respectively. The expression $\varphi_\eta \eta$ denotes the natural death rate of a given compartment $\eta$, and $\beta_1 U$ specifically accounts for the loss of infected $CD4^+T$ cells through pyroptotic cell death. Various versions of this model have been developed to incorporate key biological aspects, including (i) time delays [8, 20, 22], (ii) cell-to-cell transmission [23–25], (iii) CTL response [26, 27], (iv) antibody response [28, 29], and (v) the combined effects of CTL and antibody responses [25, 30].

Model (Equation 1) and its aforementioned extension presume a homogeneous distribution of both cells and viruses, thereby ignoring their spatial movement and localized interactions. While this assumption simplifies analysis, it fails to account for the critical influence of spatial organization on viral behavior. In actual biological systems, the uneven distribution of infected and healthy cells, along with constraints on viral mobility, often creates spatial variability. This heterogeneity can significantly shape how infections emerge, spread, and are contained, influencing immune response and treatment outcomes. Phenomena such as clustering of infections, formation of infection hotspots, and restricted viral spread are examples of effects that uniform mixing models cannot represent. Therefore, integrating spatial dynamics into modeling frameworks offers a more realistic and nuanced understanding of viral infections and their progression. Brainard et al. [31] and Tattermusch and Bangham [32] highlighted that T cells are capable of moving along concentration gradients, typically from regions of higher density to lower density. More recent research has extended this idea, proposing that immune cells, infected cells, and viral particles may also undergo migration from areas of abundance to those with lower presence [see, for example, [33–41]].

Wang and Zhang [42] proposed a nonlocal partial differential equations (PDEs) model incorporating time delays to analyze the

role of pyroptosis in infection dynamics. Their framework includes both latent and actively infected cell populations. The infection process between healthy cells and the virus is modeled using a saturating function. Similarly, the influence of inflammatory cytokines on healthy $CD4^+T$ cells via pyroptosis is described by saturating function. In Wang et al. [43], the authors formulated a reaction-diffusion model that includes time-periodic parameters, spatial heterogeneity, and a latent infection stage to explore the role of pyroptosis in $CD4^+T$ cell loss during HIV infection. The model employs a Beddington-DeAngelis type functional response to characterize the formation rate of newly infected cells. The analysis focuses on threshold behavior governed by the basic reproduction number, providing insights into conditions for disease persistence or clearance. Wang et al. [44] introduced a partial differential equation model to investigate the effects of gasdermin D inhibition on pyroptosis in settings characterized by spatial and temporal heterogeneity. The framework includes both productively and abortively infected cell populations and accounts for the role of CTL response. The interaction between the virus and host cells is described using a general incidence function. Wang et al. [45] developed a periodic partial differential equation model to explore the dynamics of infected cell production, incorporating the heightened infection risk caused by cytokine-driven T cell migration to inflamed tissues. Their model also included the effect of necrosulfonamide, a pharmacological agent that inhibits pyroptosis. Wang and Feng [21] developed a partial differential equation model that incorporates spatial heterogeneity by introducing general functional forms to represent the dynamics of healthy $CD4^+T$ cell regeneration, virus-cell interactions, and cytokine-enhanced viral infection. However, in Wang and Feng [21], while the spatial dynamics of inflammatory cytokines and the virus are included, the movement of both healthy and infected $CD4^+T$ cells is omitted. Additionally, the immune response is not taken into account. In Chen et al. [46], the authors introduced a reaction-diffusion framework to study HIV dynamics, employing a general incidence function while accounting for cytokine-mediated enhancement of infection, CTL response, and the influence of time delay.

The models developed in Chen et al. [25] and Dahy et al. [30] assume that the presence of HIV and infected cells solely triggers CTL and antibody responses, overlooking the potential for immune suppression, commonly referred to as immune impairment. As noted in Lydyard et al. [47], HIV can weaken the immune system's functionality. Several studies have incorporated immune impairment into viral dynamics, focusing either on CTL dysfunction [e.g., [48–54]] or B-cell impairment [e.g., [54–57]]. More recently, AlShamrani et al. [58, 59] examined HIV dynamics by considering the impairment of both CTL and antibody responses. However, these studies did not consider the role of inflammatory cytokines. Although Song et al. [60] introduced CTL impairment alongside cytokine effects, it did not account for target cell population dynamics or the spatial mobility of viruses, infected cells and immune cells.

Accordingly, the objective of this work is to construct a comprehensive HIV infection model that captures several critical aspects of within-host viral dynamics. Specifically, the model aims to incorporate:

- the modulatory effects of pro-inflammatory cytokines, which play a key role in immune activation and disease progression;
- the functional impairment or exhaustion of both cytotoxic T lymphocyte (CTL) responses and antibody-mediated immunity, which are commonly observed in chronic HIV infection;
- the spatial mobility of viruses, infected cells, and various immune cell populations, allowing for a more realistic representation of cellular interactions and viral dissemination;
- and dual transmission mechanisms, encompassing both classical virus-to-cell infection and direct cell-to-cell viral spread.

By integrating these features, the proposed model seeks to provide deeper insights into HIV pathogenesis and to support the development of more effective therapeutic strategies.

We establish the well-posedness of the model by proving the existence and boundedness of global solutions, identify the equilibria and derive the basic reproduction number, and analyze the global asymptotic stability of the equilibria using appropriate Lyapunov functions and LaSalle's invariance principle. The theoretical findings are supported by detailed numerical simulations, and a sensitivity analysis of the basic reproduction number is conducted to assess the influence of key parameters.

## 2 Model construction

We formulate a reaction-diffusion model based on partial differential equations to describe the variation of the concentrations of six compartments with respect to spatial location $\varkappa$ and time $t$; healthy $CD4^+T$ cells $N(\varkappa,t)$, HIV-infected $CD4^+T$ cells $U(\varkappa,t)$, inflammatory cytokines $S(\varkappa,t)$, free HIV particles $B(\varkappa,t)$, Cytotoxic T Lymphocytes (CTLs) $M(\varkappa,t)$, and antibodies $H(\varkappa,t)$.

$$\begin{cases} \frac{\partial N(\varkappa,t)}{\partial t} = D_N \quad N(\varkappa,t) + \delta - \varphi_N N(\varkappa,t) - \omega_1 N(\varkappa,t)B(\varkappa,t) \\ \qquad -\omega_2 N(\varkappa,t)S(\varkappa,t) - \omega_3 N(\varkappa,t)U(\varkappa,t), \\ \frac{\partial U(\varkappa,t)}{\partial t} = D_U \quad U(\varkappa,t) + \omega_1 N(\varkappa,t)B(\varkappa,t) + \omega_2 N(\varkappa,t)S(\varkappa,t) \\ \qquad +\omega_3 N(\varkappa,t)U(\varkappa,t) - (\beta_1 + \varphi_U)\, U(\varkappa,t) - \ {}_1U(\varkappa,t) \\ \qquad M(\varkappa,t), \\ \frac{\partial S(\varkappa,t)}{\partial t} = D_S \quad S(\varkappa,t) + \beta_2 U(\varkappa,t) - \varphi_S S(\varkappa,t), \\ \frac{\partial B(\varkappa,t)}{\partial t} = D_B \quad B(\varkappa,t) + \mu U(\varkappa,t) - \varphi_B B(\varkappa,t) - \ {}_2B(\varkappa,t) \\ \qquad H(\varkappa,t), \\ \frac{\partial M(\varkappa,t)}{\partial t} = D_M \quad M(\varkappa,t) + \xi U(\varkappa,t) - \varphi_M M(\varkappa,t) - \lambda_1 U(\varkappa,t) \\ \qquad M(\varkappa,t), \\ \frac{\partial H(\varkappa,t)}{\partial t} = D_H \quad H(\varkappa,t) + \psi B(\varkappa,t) - \varphi_H H(\varkappa,t) - \lambda_2 B(\varkappa,t) \\ \qquad H(\varkappa,t), \end{cases} \tag{2}$$

where $\varkappa = (\varkappa_1, \varkappa_2, ..., \varkappa_\ell) \in \Lambda$, and $t > 0$. The spatial region $\Lambda \subset \mathbb{R}^\ell$, is a connected, bounded domain, and has a smooth boundary $\partial\Lambda$, where $\ell$ is an integer such that $\ell \geq 1$. The diffusion coefficient $D_{\mathcal{G}}$ is positive for each $\mathcal{G}$ in the set $\{N, U, S, B, M, H\}$. The Laplace operator, represented by , is defined as $\frac{\partial^2}{\partial \varkappa^2}$. The infection rate resulting from cellular infection is $\omega_3 NU$. The terms $\xi U$ and $\psi B$ represent the rates at which CTLs and antibodies proliferate, respectively, from infected cells and free HIV particles. The rate at which infected cells are killed by CTLs is denoted as

$_1UM$, whereas free HIV particles are neutralized by antibodies at rate $_2BH$. The rates at which CTL and antibody immunities are impaired are labeled as $\lambda_1 UM$ and $\lambda_2 BH$, respectively. The natural death rates associated with CTLs and antibodies are represented by $\varphi_M$ and $\varphi_H$, respectively. As previously outlined in Section 1, all other parameters share an identical biological interpretation.

In the following, the initial conditions, as well as the homogeneous Neumann boundary conditions adopted for system (Equation 2), are given as:

$$\begin{cases} N(\varkappa,0)=\mathcal{I}_1(\varkappa), \quad U(\varkappa,0)=\mathcal{I}_2(\varkappa), \quad S(\varkappa,0)=\mathcal{I}_3(\varkappa), \\ B(\varkappa,0)=\mathcal{I}_4(\varkappa), \quad M(\varkappa,0)=\mathcal{I}_5(\varkappa), \quad H(\varkappa,0)=\mathcal{I}_6(\varkappa), \quad \varkappa\in\bar{\Lambda}. \end{cases} \tag{3}$$

$$\begin{cases} \frac{\partial N}{\partial \vec{\mathcal{Z}}}=\frac{\partial U}{\partial \vec{\mathcal{Z}}}=\frac{\partial S}{\partial \vec{\mathcal{Z}}}=\frac{\partial B}{\partial \vec{\mathcal{Z}}}=\frac{\partial M}{\partial \vec{\mathcal{Z}}}=\frac{\partial H}{\partial \vec{\mathcal{Z}}}=0, \quad t>0, \quad \varkappa\in\partial\Lambda. \end{cases} \tag{4}$$

Here, the functions $\mathcal{I}_j(\varkappa)$, for $j = 1,...,6$, are both continuous and non-negative. Meanwhile, $\frac{\partial}{\partial \vec{\mathcal{Z}}}$ represents the outward normal derivative on the boundary $\partial\Lambda$. The boundary conditions (Equation 4) ensure that all populations are prohibited from traversing the isolated boundary $\partial\Lambda$ [61].

Remark 1. The mathematical model developed in Hattaf [6] incorporates CTL immune responses and considers the spatial mobility of both immune cells and viruses. However, it omits several key immunological factors, such as the contribution of antibody-mediated immunity, the regulatory role of pro-inflammatory cytokines, and the potential dysfunction or exhaustion of CTL response that may occur during chronic infection. Conversely, the study by Hajhouji et al. [62] focuses on the antibody response in the context of HIV dynamics but does not include CTL-mediated immunity, cytokine-driven inflammation, or the spatial migration of immune cells and viral particles. Together, these limitations highlight the need for more comprehensive models that integrate multiple layers of the immune system and spatial effects to better capture the complexity of HIV pathogenesis. These limitations have been addressed in the present model, which incorporates both CTL and antibody-mediated immune responses, accounts for the effects of pro-inflammatory cytokines, and includes the mobility of immune cells and viruses. By integrating these critical biological factors, our model offers a more comprehensive framework for analyzing HIV infection dynamics and immune system interactions.

## 3 Characteristics of solutions

The following result addresses the existence, uniqueness, non-negativity, and boundedness of solutions for model (Equation 2), which describe the densities of healthy CD4$^+$T cells, HIV-infected CD4$^+$T cells, inflammatory cytokines, free HIV particles, CTLs, and antibodies.

**Lemma 1.** Let the assumption $D_N = D_U = D_S = D_B = D_M = D_H = \hat{D}$ hold true. For any initial function $\mathcal{I} = (\mathcal{I}_1,\mathcal{I}_2,\mathcal{I}_3,\mathcal{I}_4,\mathcal{I}_5,\mathcal{I}_6)^T \in \mathcal{Y}_+$ satisfying the initial conditions (Equation 3), model (Equation 2) has a unique, non-negative and bounded solution $(N(\varkappa,t),U(\varkappa,t),S(\varkappa,t),B(\varkappa,t),M(\varkappa,t),H(\varkappa,t)$ defined on $\bar{\Lambda}\times[0,+\infty)$.

**Proof**. Let $\mathcal{Y} = BUC(\bar{\Lambda},\mathbb{R}^6$ be defined as the set of all functions from $\bar{\Lambda}$ to $\mathbb{R}^6$ that are both bounded and uniformly continuous, with the norm $\|\phi\|_{\mathcal{Y}} = \sup_{\varkappa\in\bar{\Lambda}}|\phi(\varkappa)|$. We denote the positive cone $\mathcal{Y}_+ = BUC(\bar{\Lambda},\mathbb{R}^6_+ \subset\mathcal{Y}$ which establishes a partial order on $\mathcal{Y}$. This characterization demonstrates that the space $(\mathcal{Y},\|\cdot\|_{\mathcal{Y}}$ forms a Banach lattice [63, 64].

Concerning every initial data $\mathcal{I} = (\mathcal{I}_1,\mathcal{I}_2,\mathcal{I}_3,\mathcal{I}_4,\mathcal{I}_5,\mathcal{I}_6)^T \in \mathcal{Y}_+$, we define $K = (K_1,K_2,K_3,K_4,K_5,K_6)^T : \mathcal{Y}_+ \to \mathcal{Y}$ as follows:

$$\begin{cases} K_1(\mathcal{I})(\varkappa)=\delta-\varphi_N\mathcal{I}_1(\varkappa)-\omega_1\mathcal{I}_1(\varkappa)\mathcal{I}_4(\varkappa)-\omega_2\mathcal{I}_1(\varkappa)\mathcal{I}_3(\varkappa) \\ \qquad -\omega_3\mathcal{I}_1(\varkappa)\mathcal{I}_2(\varkappa), \\ K_2(\mathcal{I})(\varkappa)=\omega_1\mathcal{I}_1(\varkappa)\mathcal{I}_4(\varkappa)+\omega_2\mathcal{I}_1(\varkappa)\mathcal{I}_3(\varkappa)+\omega_3\mathcal{I}_1(\varkappa)\mathcal{I}_2(\varkappa)- \\ \qquad (\beta_1+\varphi_U+\ _1\mathcal{I}_5(\varkappa)\ \mathcal{I}_2(\varkappa), \\ K_3(\mathcal{I})(\varkappa)=\beta_2\mathcal{I}_2(\varkappa)-\varphi_S\mathcal{I}_3(\varkappa), \\ K_4(\mathcal{I})(\varkappa)=\mu\mathcal{I}_2(\varkappa)-\varphi_B\mathcal{I}_4(\varkappa)-\ _2\mathcal{I}_4(\varkappa)\mathcal{I}_6(\varkappa), \\ K_5(\mathcal{I})(\varkappa)=\xi\mathcal{I}_2(\varkappa)-\varphi_M\mathcal{I}_5(\varkappa)-\lambda_1\mathcal{I}_2(\varkappa)\mathcal{I}_5(\varkappa), \\ K_6(\mathcal{I})(\varkappa)=\psi\mathcal{I}_4(\varkappa)-\varphi_H\mathcal{I}_6(\varkappa)-\lambda_2\mathcal{I}_4(\varkappa)\mathcal{I}_6(\varkappa). \end{cases}$$

We observe that $K$ is locally Lipschitz on $\mathcal{Y}_+$, which is a fact straightforward to verify (see Corollary 4 in Martin and Smith [65]). System (Equation 2) subject to initial conditions (Equation 3) and boundary conditions (Equation 4) can be reformulated as the following abstract functional differential equation:

$$\begin{cases} \frac{d\mathcal{L}}{dt}=\Gamma\mathcal{L}+H(\mathcal{L}),\ t>0, \\ \mathcal{L}(0)=\mathcal{I}\in\mathcal{Y}_+, \end{cases}$$

where $\mathcal{L} = (N,U,S,B,M,H)^T$ and $\Gamma\mathcal{L} = (D_N\ N, D_U\ U, D_S\ S, D_B\ B, D_M\ M, D_H\ H)^T$. One can prove that

$$\lim_{\upsilon\to0^+}\frac{1}{\upsilon}\mathrm{dist}\left(\mathcal{I}(0)+\upsilon K(\mathcal{I}),\mathcal{Y}_+\right)=0, \text{ for every } \mathcal{I}\in\mathcal{Y}_+.$$

Follows the work of Xu and Xu [63], Zhang and Xu [64], and Smith [66], we deduce that for any $\mathcal{I}\in\mathcal{Y}_+$, system (Equation 2) subject to (Equations 3, 4) possesses a unique non-negative mild solution $(N(\varkappa,t),U(\varkappa,t),S(\varkappa,t),B(\varkappa,t),M(\varkappa,t),H(\varkappa,t)$. This solution is defined on $\bar{\Lambda}\times[0,\mathcal{T}_M)$, where $[0,\mathcal{T}_M)$ is the maximal time interval over which the solution remains in existence. Furthermore, this solution constitutes a classical solution to the problem at hand.

To confirm that the solutions have a bounded nature, we introduce

$$\mathcal{P}(\varkappa,t)=N(\varkappa,t)+U(\varkappa,t)+\frac{\beta_1+\varphi_U}{2\beta_2}S(\varkappa,t) + \frac{\beta_1+\varphi_U}{4\mu}B(\varkappa,t)+\frac{\beta_1+\varphi_U}{8\xi}M(\varkappa,t)+\frac{\varphi_B(\beta_1+\varphi_U)}{8\mu\psi}H(\varkappa,t).$$

Based on the fact that $D_N = D_U = D_S = D_B = D_M = D_H = \hat{D}$, using system (Equation 2) we derive

$$\frac{\partial\mathcal{P}(\varkappa,t)}{\partial t}-\hat{D}\ \mathcal{P}(\varkappa,t)=\delta-\varphi_N N(\varkappa,t)-\frac{\beta_1+\varphi_U}{8}U(\varkappa,t) - \frac{\varphi_S(\beta_1+\varphi_U)}{2\beta_2}S(\varkappa,t) - \frac{\varphi_B(\beta_1+\varphi_U)}{8\mu}B(\varkappa,t)-\frac{\varphi_M(\beta_1+\varphi_U)}{8\xi}M(\varkappa,t)$$

$$
\begin{aligned}
&-\frac{\varphi_B\varphi_H\left(\beta_1+\varphi_U\right)}{8\mu\psi}H(\varkappa,t)-\quad{}_1+\frac{\lambda_1\left(\beta_1+\varphi_U\right)}{8\xi}\quad U(\varkappa,t)M(\varkappa,t)\\
&-\frac{\beta_1+\varphi_U}{4\mu}\quad{}_2+\frac{\varphi_B\lambda_2}{2\psi}\quad B(\varkappa,t)H(\varkappa,t)\\
&<\delta-\varphi_N N(\varkappa,t)-\frac{\beta_1+\varphi_U}{8}U(\varkappa,t)-\frac{\varphi_S\left(\beta_1+\varphi_U\right)}{2\beta_2}S(\varkappa,t)\\
&-\frac{\varphi_B\left(\beta_1+\varphi_U\right)}{8\mu}B(\varkappa,t)-\frac{\varphi_M\left(\beta_1+\varphi_U\right)}{8\xi}M(\varkappa,t)\\
&-\frac{\varphi_B\varphi_H\left(\beta_1+\varphi_U\right)}{8\mu\psi}H(\varkappa,t)\\
&\leq\delta-\varpi\quad N(\varkappa,t)+U(\varkappa,t)+\frac{\beta_1+\varphi_U}{2\beta_2}S(\varkappa,t)+\frac{\beta_1+\varphi_U}{4\mu}B(\varkappa,t)\\
&+\frac{\beta_1+\varphi_U}{8\xi}M(\varkappa,t)+\frac{\varphi_B\left(\beta_1+\varphi_U\right)}{8\mu\psi}H(\varkappa,t)\quad=\delta-\varpi\mathcal{P}\left(\varkappa,t\right),
\end{aligned}
$$

where $\varpi = \min\{\varphi_N, \frac{\beta_1+\varphi_U}{8}, \varphi_S, \frac{\varphi_B}{2}, \varphi_M, \varphi_H\}$. Consequently, $\mathcal{P}(\varkappa,t)$ fulfills the subsequent system

$$
\begin{cases}
\frac{\partial\mathcal{P}(\varkappa,t)}{\partial t}-\hat{D}\quad\mathcal{P}\left(\varkappa,t\right)\leq\delta-\varpi\mathcal{P}\left(\varkappa,t\right),\\
\mathcal{P}\left(\varkappa,0\right)=\mathcal{I}_1(\varkappa)+\mathcal{I}_2(\varkappa)+\frac{\beta_1+\varphi_U}{2\beta_2}\mathcal{I}_3(\varkappa)+\frac{\beta_1+\varphi_U}{4\mu}\mathcal{I}_4(\varkappa)\\
\qquad+\frac{\beta_1+\varphi_U}{8\xi}\mathcal{I}_5(\varkappa)+\frac{\varphi_B(\beta_1+\varphi_U)}{8\mu\psi}\mathcal{I}_6(\varkappa)\geq 0,\\
\frac{\partial\mathcal{P}}{\partial\vec{\mathcal{Z}}}=0.
\end{cases}
$$

Consider a solution, $\mathcal{P}(t)$, for the following ordinary differential equation:

$$
\begin{cases}
\frac{d\mathcal{P}(t)}{dt}=\delta-\varpi\mathcal{P}(t),\\
\mathcal{P}(0)=\max\limits_{\varkappa\in\bar{\Lambda}}\mathcal{P}(\varkappa,0).
\end{cases}
$$

This results in $\mathcal{P}(t)\leq\max\left\{\frac{\delta}{\varpi},\max\limits_{\varkappa\in\bar{\Lambda}}\mathcal{P}(\varkappa,0)\right.$. With reference to the comparison principle (refer to Protter and Weinberger [67]), we find that $\mathcal{P}(\varkappa,t)\leq\mathcal{P}(t)$. From this, we derive

$$
\mathcal{P}(\varkappa,t)\leq\max\left\{\frac{\delta}{\varpi},\max_{\varkappa\in\bar{\Lambda}}\mathcal{P}(\varkappa,0)\right.,
$$

which demonstrates that $N(\varkappa,t)$, $U(\varkappa,t)$, $S(\varkappa,t)$, $B(\varkappa,t)$, $M(\varkappa,t)$, and $H(\varkappa,t)$ are bounded on $\bar{\Lambda}\times[0,\mathcal{T}_M)$. According to the standard theory for semi-linear parabolic systems, we infer that $\mathcal{T}_M=+\infty$ [68]. The solution $\left(N(\varkappa,t),U(\varkappa,t),S(\varkappa,t),B(\varkappa,t),M(\varkappa,t),H(\varkappa,t)\right.$ exists and is uniquely determined and non-negative for all $\varkappa\in\Lambda$, $t>0$.

## 4 Equilibria and basic reproduction number

In this section, we assess the equilibria and identify the threshold parameter necessary to confirm their existence. The results are outlined in the subsequent lemma:

**Lemma 2.** Considering system (Equation 2), a basic reproduction number

$$
\mathcal{R}_0=\frac{\delta\left(\mu\varphi_S\omega_1+\varphi_B\left(\beta_2\omega_2+\varphi_S\omega_3\right)\right)}{\varphi_N\varphi_S\varphi_B\left(\beta_1+\varphi_U\right)}>0
$$

can be identified, which fulfills the following statements:

1. The system ensures that it consistently achieves an HIV-free equilibrium, labeled as $\mathcal{FE}=(N_0,0,0,0,0,0)$, $N_0=\delta/\varphi_N$.
2. The system also maintains an HIV-persistent equilibrium, labeled as $\mathcal{PE}=\left(\bar{N},\bar{U},\bar{S},\bar{B},\bar{M},\bar{H}\right.$, in the case of $\mathcal{R}_0>1$.

**Proof**. The basic reproduction number, $\mathcal{R}_0$, is computed through the next-generation matrix technique described in van den Driessche and Watmough [69]. To accomplish this, we can represent the right-hand side of system (Equation 2) as $\mathcal{J}_1-\mathcal{J}_2$ with

$$
\mathcal{J}_1=\begin{pmatrix}\omega_1NB+\omega_2NS+\omega_3NU\\0\\0\end{pmatrix},
$$

$$
\mathcal{J}_2=\begin{pmatrix}\left(\beta_1+\varphi_U\right)U+\quad{}_1UM\\-\beta_2U+\varphi_SS\\-\mu U+\varphi_BB+\quad{}_2BH\end{pmatrix}.
$$

System (Equation 2) consistently exhibits an HIV-free equilibrium $\mathcal{FE}=(N_0,0,0,0,0,0)$, where $N_0=\frac{\delta}{\varphi_N}$.

Upon computing the Jacobian matrices, $\mathcal{J}_1$ and $\mathcal{J}_2$, at the equilibrium $\mathcal{FE}$, we find

$$
J_1=\begin{pmatrix}\omega_3N_0&\omega_2N_0&\omega_1N_0\\0&0&0\\0&0&0\end{pmatrix},\ J_2=\begin{pmatrix}\beta_1+\varphi_U&0&0\\-\beta_2&\varphi_S&0\\-\mu&0&\varphi_B\end{pmatrix}.
$$

Note that, the next generation matrix is in the following form:

$$
J_1J_2^{-1}=\begin{pmatrix}\frac{N_0(\mu\varphi_S\omega_1+\varphi_B(\beta_2\omega_2+\varphi_S\omega_3))}{\varphi_S\varphi_B(\beta_1+\varphi_U)}&\frac{N_0\omega_2}{\varphi_S}&\frac{N_0\omega_1}{\varphi_B}\\0&0&0\\0&0&0\end{pmatrix}.
$$

The basic reproduction number $\mathcal{R}_0$ is determined by the spectral radius of the matrix product $J_1J_2^{-1}$, expressed as:

$$
\mathcal{R}_0=\frac{N_0\left(\mu\varphi_S\omega_1+\varphi_B\left(\beta_2\omega_2+\varphi_S\omega_3\right)\right)}{\varphi_S\varphi_B\left(\beta_1+\varphi_U\right)}=\mathcal{R}_{0B}+\mathcal{R}_{0S}+\mathcal{R}_{0U},\quad(5)
$$

where

$$
\mathcal{R}_{0B}=\frac{N_0\mu\omega_1}{\varphi_B\left(\beta_1+\varphi_U\right)},\quad\mathcal{R}_{0S}=\frac{N_0\beta_2\omega_2}{\varphi_S\left(\beta_1+\varphi_U\right)},\quad\mathcal{R}_{0U}=\frac{N_0\omega_3}{\beta_1+\varphi_U}.
$$

To clarify, the contributions of viral and cellular infections are represented, respectively, by $\mathcal{R}_{0B}$ and $\mathcal{R}_{0U}$, whereas $\mathcal{R}_{0S}$ denotes the influence of inflammatory cytokines.

To identify the additional equilibrium beyond $\mathcal{FE}$, we assume $(N,U,S,B,M,H)$ represents any equilibrium that fulfills the following equations:

$$
\begin{aligned}
0&=\delta-\varphi_NN-\omega_1NB-\omega_2NS-\omega_3NU,&(6)\\
0&=\omega_1NB+\omega_2NS+\omega_3NU-\left(\beta_1+\varphi_U\right)U-\quad{}_1UM,&(7)\\
0&=\beta_2U-\varphi_SS,&(8)\\
0&=\mu U-\varphi_BB-\quad{}_2BH,&(9)\\
0&=\xi U-\varphi_MM-\lambda_1UM,&(10)\\
0&=\psi B-\varphi_HH-\lambda_2BH.&(11)
\end{aligned}
$$

Referring to Equations 10, 11, we derive

$$
M=\frac{\xi U}{\varphi_M+\lambda_1U},\quad H=\frac{\psi B}{\varphi_H+\lambda_2B}.\quad(12)
$$

Replacing the values from Equation 12 in Equation 9, we obtain

$$U = \frac{\varphi_H \varphi_B B + (\lambda_2 \varphi_B + \ {}_2\psi)\, B^2}{\mu\,(\varphi_H + \lambda_2 B)}. \tag{13}$$

By substituting the expression from Equation 13 into Equation 12, we yield

$$M = \frac{\xi\,\left(\varphi_H \varphi_B B + (\lambda_2 \varphi_B + \ {}_2\psi)\, B^2\right.}{\varphi_M \mu\,(\varphi_H + \lambda_2 B) + \lambda_1\left(\varphi_H \varphi_B B + (\lambda_2 \varphi_B + \ {}_2\psi)\, B^2\right.}. \tag{14}$$

Replacing the values from Equation 13 in Equation 8 gives

$$S = \frac{\beta_2\,\left(\varphi_H \varphi_B B + (\lambda_2 \varphi_B + \ {}_2\psi)\, B^2\right.}{\mu \varphi_S\,(\varphi_H + \lambda_2 B)}. \tag{15}$$

From Equations 6, 7, we get

$$\delta - \varphi_N N = (\beta_1 + \varphi_U)\, U + \ {}_1 UM. \tag{16}$$

Substituting from Equations 13, 14 into Equation 16, we get

$$\begin{aligned} N \quad &= \tfrac{1}{\varphi_N}\left(\delta - \tfrac{(\beta_1+\varphi_U)(\psi_{\varrho 2} B + \varphi_B(\varphi_H+\lambda_2 B))B}{\mu(\varphi_H+\lambda_2 B)}\right. \\ &+ \left.\tfrac{\xi_{\varrho 1}(\psi_{\varrho 2} B + \varphi_B(\varphi_H+\lambda_2 B))^2 B^2}{\mu(\varphi_H+\lambda_2 B)(\mu\varphi_M(\varphi_H+\lambda_2 B)+\lambda_1(\psi_{\varrho 2} B+\varphi_B(\varphi_H+\lambda_2 B))B)}\right) . \end{aligned} \tag{17}$$

Substituting from Equations 13–15, 17 into Equation 7, we get

$$\begin{aligned} &\frac{B\left(A_5 B^5 + A_4 B^4 + A_3 B^3 + A_2 B^2 + A_1 B + A_0\right)}{\varphi_N \varphi_S \mu^2 (\mu\varphi_M \varphi_H + (\lambda_2 \mu \varphi_M + \lambda_1 \varphi_B \varphi_H) B + \lambda_1(\lambda_2 \varphi_B + \psi_{\varrho 2}) B^2\ (\varphi_H + \lambda_2 B)^2} \\ &= 0, \end{aligned} \tag{18}$$

where

$$\begin{aligned} A_5 = {} & (\lambda_1(\beta_1 + \varphi_U) - \xi_{\varrho 1})\,(\lambda_2 \varphi_B + \psi_{\varrho 2})^2\,(\lambda_2\,(\beta_2 \varphi_B \omega_2 \\ & + \varphi\ {}_S\,(\mu\omega_1 + \varphi_B \omega_3)) + \psi_{\varrho 2}\,(\beta_2 \omega_2 + \varphi_S \omega_3))\,, \end{aligned}$$

$$\begin{aligned} A_4 = {} & (\lambda_2 \varphi_B + \psi_{\varrho 2})(-\varphi_H \psi_{\varrho 2}(\xi_{\varrho 1} - \lambda_1 \varphi_U)(3\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \\ & 3\varphi_B \omega_3)) \\ & + \mu\lambda_2^2(\xi \varphi_N \varphi_S \varphi_B\ {}_1 + \varphi_U \varphi_M(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & + \lambda_1(\varphi_N \varphi_U \varphi_S \varphi_B \\ & - \delta(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)))) + \lambda_2(\mu\varphi_U \varphi_M \psi_{\varrho 2}(\beta_2 \omega_2 \\ & + \varphi_S \omega_3) + \xi_{\varrho 1}(\mu \varphi_N \varphi_S \psi_{\varrho 2} \\ & - 3\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3))) + \lambda_1(\mu\psi\ {}_2(\varphi_S \\ & (\varphi_N \varphi_U - \delta\omega_3) - \beta_2 \delta\omega_2) \\ & + 3\varphi_U \varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)))) + \beta_1(\lambda_2 \mu\varphi_M \\ & (\psi_{\varrho 2}(\beta_2 \omega_2 + \varphi_S \omega_3) \\ & + \lambda_2(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3))) + \lambda_1(\varphi_H \psi_{\varrho 2}(3\beta_2 \varphi_B \omega_2 \\ & + \varphi_S(\mu\omega_1 + 3\varphi_B \omega_3)) \\ & + \lambda_2^2 \mu \varphi_N \varphi_S \varphi_B + \lambda_2(3\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & + \mu\varphi_N \varphi_S \psi_{\varrho 2})))), \end{aligned}$$

$$\begin{aligned} A_3 = {} & -\lambda_2^3 \mu^2 \varphi_M(\beta_2 \delta \varphi_B \omega_2 + \delta\varphi_S(\mu\omega_1 + \varphi_B \omega_3) - \varphi_N \varphi_U \varphi_S \varphi_B) \\ & + \lambda_2 \varphi_H(2\mu\varphi_U \varphi_M \psi_{\varrho 2}(2\beta_2 \varphi_B \omega_2 \\ & + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) - \xi \varphi_B\ {}_1(3\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 \\ & + \varphi_B \omega_3)) - 4\mu\varphi_N \varphi_S \psi_{\varrho 2}) \\ & + \lambda_1(3\varphi_U \varphi_B^2 \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) - 2\mu\psi\ {}_2 \\ & (2\beta_2 \delta \varphi_B \omega_2 + \delta\varphi_S(\mu\omega_1 + 2\varphi_B \omega_3) \\ & - 2\varphi_N \varphi_U \varphi_S \varphi_B))) + \varphi_H \psi_{\varrho 2}(\mu\varphi_U \varphi_M \psi_{\varrho 2}(\beta_2 \omega_2 + \varphi_S \omega_3) \\ & + \xi_{\varrho 1}(\mu\varphi_N \varphi_S \psi_{\varrho 2} \\ & - \varphi_B \varphi_H(3\beta_2 \varphi_B \omega_2 + \varphi_S(2\mu\omega_1 + 3\varphi_B \omega_3))) + \\ & \lambda_1(\mu\psi\ {}_2(\varphi_S(\varphi_N \varphi_U - \delta\omega_3) - \beta_2 \delta\omega_2) \\ & + \varphi_U \varphi_B \varphi_H(3\beta_2 \varphi_B \omega_2 + \varphi_S(2\mu\omega_1 + 3\varphi_B \omega_3)))) \\ & + \mu\lambda_2^2(\mu\varphi_M \psi_{\varrho 2}(\varphi_N \varphi_U \varphi_S - \delta(\beta_2 \omega_2 + \varphi_S \omega_3)) \\ & + 3\varphi_B \varphi_H(\varphi_U \varphi_M(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & + \xi \varphi_N \varphi_S \varphi_B\ {}_1 + \lambda_1(\varphi_N \varphi_U \varphi_S \varphi_B \\ & - \delta(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3))))) + \beta_1(\lambda_2^3 \mu^2 \varphi_N \varphi_S \varphi_B \varphi_M + \\ & \mu\lambda_2^2(\mu\varphi_N \varphi_S \varphi_M \psi_{\varrho 2} \\ & + 3\varphi_B \varphi_H(\varphi_M(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) + \lambda_1 \varphi_N \varphi_S \varphi_B)) \\ & + \lambda_2 \varphi_H(2\mu\varphi_M \psi_{\varrho 2}(2\beta_2 \varphi_B \omega_2 \\ & + \varphi_S(\mu\omega_1 + 2\varphi_B \omega_3)) + \lambda_1 \varphi_B(3\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 \\ & + \varphi_B \omega_3)) + 4\mu\varphi_N \varphi_S \psi_{\varrho 2})) \\ & + \psi_{\varrho 2} \varphi_H(\mu\varphi_M \psi_{\varrho 2}(\beta_2 \omega_2 + \varphi_S \omega_3) + \lambda_1(\varphi_B \varphi_H(3\beta_2 \varphi_B \omega_2 \\ & + \varphi_S(2\mu\omega_1 + 3\varphi_B \omega_3)) + \mu\varphi_N \varphi_S \psi_{\varrho 2}))), \end{aligned}$$

$$\begin{aligned} A_2 = {} & \varphi_H(\lambda_2 \mu(2\mu\varphi_M \psi_{\varrho 2}(\varphi_N \varphi_U \varphi_S - \delta(\beta_2 \omega_2 + \varphi_S \omega_3)) \\ & + 3\varphi_B \varphi_H(\xi \varphi_N \varphi_S \varphi_B\ {}_1 \\ & + \varphi_U \varphi_M(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) + \lambda_1(\varphi_N \varphi_U \varphi_S \varphi_B \\ & - \delta(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3))))) \\ & + \varphi_H(\mu\varphi_U \varphi_M \psi_{\varrho 2}(2\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + 2\varphi_B \omega_3)) - \\ & \xi \varphi_B\ {}_1(\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & - 2\mu\varphi_N \varphi_S \psi_{\varrho 2}) + \lambda_1(\varphi_U \varphi_B^2 \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & - \mu\psi\ {}_2(2\beta_2 \delta \varphi_B \omega_2 + \delta\varphi_S(\mu\omega_1 + 2\varphi_B \omega_3) - 2\varphi_N \varphi_U \varphi_S \varphi_B))) \\ & + \beta_1(\lambda_2 \mu(3\varphi_B \varphi_H(\varphi_M(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & + \lambda_1 \varphi_N \varphi_S \varphi_B) + 2\mu\varphi_N \varphi_S \varphi_M \psi_{\varrho 2}) \\ & + \varphi_H(\lambda_1 \varphi_B(\varphi_B \varphi_H(\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + \varphi_B \omega_3)) \\ & + 2\mu\varphi_N \varphi_S \psi_{\varrho 2}) \\ & + \mu\varphi_M \psi_{\varrho 2}(2\beta_2 \varphi_B \omega_2 + \varphi_S(\mu\omega_1 + 2\varphi_B \omega_3))) \\ & + 3\lambda_2^2 \mu^2 \varphi_N \varphi_S \varphi_B \varphi_M) \\ & - 3\lambda_2^2 \mu^2 \varphi_M(\beta_2 \delta \varphi_B \omega_2 + \delta\varphi_S(\mu\omega_1 + \varphi_B \omega_3) - \varphi_N \varphi_U \varphi_S \varphi_B)), \end{aligned}$$

$$\begin{aligned} A_1 = {} & \mu\varphi_H^2(\xi \varphi_N \varphi_S \varphi_H \varphi_B^2\ {}_1 + \mu\varphi_S \varphi_M \varphi_H \varphi_B \omega_1(\beta_1 + \varphi_U) \\ & + \mu\varphi_N \varphi_S \varphi_M \psi_{\varrho 2}(\beta_1 + \varphi_U) \\ & - (3\lambda_2 \mu\varphi_M + \lambda_1 \varphi_B \varphi_H)(\beta_2 \delta \varphi_B \omega_2 - \beta_1 \varphi_N \varphi_S \varphi_B \\ & + \delta\varphi_S(\mu\omega_1 + \varphi_B \omega_3) - \varphi_N \varphi_U \varphi_S \varphi_B) \\ & - \beta_2 \varphi_M \omega_2(\delta\mu\psi\ {}_2 - \varphi_B^2 \varphi_H(\beta_1 + \varphi_U)) - \varphi_S \varphi_M \omega_3(\delta\mu\psi\ {}_2 \\ & - \varphi_B^2 \varphi_H(\beta_1 + \varphi_U))), \end{aligned}$$

$$A_0 = \varphi_N \varphi_S \varphi_B \varphi_M \mu^2 \varphi_H^3\,(\beta_1 + \varphi_U)\,(1 - \mathcal{R}_0),$$

where $\mathcal{R}_0$ is outlined in Equation 5. According to Equation 18, it follows that

1. If $B = 0$, then based on Equations 12–15, 17 we deduce the HIV-free equilibrium, $\mathcal{FE} = (N_0, 0, 0, 0, 0, 0)$, with $N_0 = \delta/\varphi_N$.
2. If $B = 0$, the equation $A_5B^5+A_4B^4+A_3B^3+A_2B^2+A_1B+A_0 = 0$ holds. In this context, we introduce a function $\Omega(B)$ on $[0, \infty)$ as:

$$\Omega(B) = A_5B^5 + A_4B^4 + A_3B^3 + A_2B^2 + A_1B + A_0.$$

We have $\Omega(0) = \varphi_N\varphi_S\varphi_B\varphi_M\mu^2\varphi_H^3(\beta_1 + \varphi_U)(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$, and $\lim_{B\to\infty} \Omega(B) = \infty$, which indicates that $\Omega$ possesses a positive real root, $\bar{B}$. By substituting the expressions from Equations 13, 15 into Equation 6, we get

$$\bar{N} = \frac{\delta}{\varphi_N + \omega_1\bar{B} + \omega_2\bar{S} + \omega_3\bar{U}},$$

where

$$\bar{U} = \frac{\varphi_H\varphi_B\bar{B} + (\lambda_2\varphi_B + {}_2\psi)\bar{B}^2}{\mu(\varphi_H + \lambda_2\bar{B}},$$

$$\bar{S} = \frac{\beta_2(\varphi_H\varphi_B\bar{B} + (\lambda_2\varphi_B + {}_2\psi)\bar{B}^2}{\mu\varphi_S(\varphi_H + \lambda_2\bar{B}},$$

$$\bar{M} = \frac{\xi(\varphi_H\varphi_B\bar{B} + (\lambda_2\varphi_B + {}_2\psi)\bar{B}^2}{\varphi_M\mu(\varphi_H + \lambda_2\bar{B} + \lambda_1(\varphi_H\varphi_B\bar{B} + (\lambda_2\varphi_B + {}_2\psi)\bar{B}^2},$$

$$\bar{H} = \frac{\psi\bar{B}}{\varphi_H + \lambda_2\bar{B}}.$$

It is evident that the existence of the HIV-persistent equilibrium, $\mathcal{PE} = (\bar{N}, \bar{U}, \bar{S}, \bar{B}, \bar{M}, \bar{H}$ , is confirmed when $\mathcal{R}_0 > 1$.

## 5 Global stability investigation

This section focuses on exploring the global asymptotic stability of all equilibria through the technique of the Lyapunov method. Take the function $\Upsilon_j(N, U, S, B, M, H)$ into consideration, and let $\hat{\Upsilon}_j(t)$ be defined as follows:

$$\hat{\Upsilon}_j(t) = \int_\Lambda \Upsilon_j(\varkappa, t)\,\mathrm{d}\varkappa, \quad j = 0, 1.$$

Assume that $\Theta_j$ is the largest invariant subset of $\Theta_j$, where

$$\Theta_j = \left\{(N, U, S, B, M, H) : \frac{d\hat{\Upsilon}_j}{dt} = 0\right\}, \quad j = 0, 1.$$

The inequality relating the arithmetic and geometric means will be employed in the analysis as follows:

$$\frac{\mathcal{G}_1 + \mathcal{G}_2 + \ldots + \mathcal{G}_n}{n} \geq \sqrt[n]{(\mathcal{G}_1)(\mathcal{G}_2)\ldots(\mathcal{G}_n)}. \tag{19}$$

We introduce a function $\Psi(\upsilon)$ as follows:

$$\Psi(\upsilon) = \upsilon - 1 - \ln\upsilon.$$

According to the Numann boundary conditions (Equation 4), along with the Divergence Theorem, they lead to the conclusion that

$$0 = \int_{\partial\Lambda} \nabla\mathcal{G}\cdot\vec{\mathcal{Z}}\,\mathrm{d}\varkappa = \int_\Lambda \mathrm{div}(\nabla\mathcal{G})\,\mathrm{d}\varkappa = \int_\Lambda \mathcal{G}\,\mathrm{d}\varkappa,$$

$$0 = \int_{\partial\Lambda} \frac{1}{\mathcal{G}}\nabla\mathcal{G}\cdot\vec{\mathcal{Z}}\,\mathrm{d}\varkappa = \int_\Lambda \mathrm{div}(\frac{1}{\mathcal{G}}\nabla\mathcal{G})\,\mathrm{d}\varkappa =$$

$$\int_\Lambda \frac{\mathcal{G}}{\mathcal{G}} - \frac{\|\nabla\mathcal{G}\|^2}{\mathcal{G}^2}\,\mathrm{d}\varkappa,$$

$$\int_\Lambda \mathcal{G}\;\mathcal{G}\,\mathrm{d}\varkappa = -\int_\Lambda \|\nabla\mathcal{G}\|^2\,\mathrm{d}\varkappa + \int_{\partial\Lambda} \mathcal{G}\frac{\partial\mathcal{G}}{\partial\vec{\mathcal{Z}}}\,\mathrm{d}\varkappa,$$

for $\mathcal{G} \in \{N, U, S, B, M, H\}$. As a consequence, we arrive at

$$\int_\Lambda \mathcal{G}\,\mathrm{d}\varkappa = 0,$$

$$\int_\Lambda \frac{\mathcal{G}}{\mathcal{G}}\,\mathrm{d}\varkappa = \int_\Lambda \frac{\|\nabla\mathcal{G}\|^2}{\mathcal{G}^2}\,\mathrm{d}\varkappa,$$

$$\int_\Lambda \mathcal{G}\;\mathcal{G}\,\mathrm{d}\varkappa = -\int_\Lambda \|\nabla\mathcal{G}\|^2\,\mathrm{d}\varkappa. \tag{20}$$

The input notation is omitted for the purpose of simplicity, i.e., $(N, U, S, B, M, H) = \big(N(\varkappa, t), U(\varkappa, t), S(\varkappa, t), B(\varkappa, t), M(\varkappa, t), H(\varkappa, t)\big)$ .

**Theorem 1.** The HIV-free equilibrium $\mathcal{FE}$ exhibits global asymptotic stability when $\mathcal{R}_0 \leq 1$.

**Proof.** Introduce a Lyapunov function $\Upsilon_0(\varkappa, t)$ as follows:

$$\Upsilon_0(\varkappa, t) = N_0\Psi\left(\frac{N}{N_0}\right) + U + \frac{\omega_2N_0}{\varphi_S}S + \frac{\omega_1N_0}{\varphi_B}B + \frac{1}{2\xi}M^2 + \frac{{}_2\omega_1N_0}{2\psi\varphi_B}H^2.$$

It is evident that $\hat{\Upsilon}_0(N, U, S, B, M, H) > 0$ for all positive values of $N, U, S, B, M, H$, and $\hat{\Upsilon}_0(N_0, 0, 0, 0, 0, 0) = 0$. The derivative $\frac{\partial\Upsilon_0}{\partial t}$ is computed along the solutions of model (Equation 2) as:

$$\begin{aligned}
\frac{\partial\Upsilon_0}{\partial t} &= \left(1 - \frac{N_0}{N}\right)(D_N N + \delta - \varphi_N N - \omega_1 NB - \omega_2 NS - \omega_3 NU) \\
&+ D_U U + \omega_1 NB + \omega_2 NS + \omega_3 NU - (\beta_1 + \varphi_U)U - {}_1UM \\
&+ \frac{\omega_2N_0}{\varphi_S}(D_S S + \beta_2 U - \varphi_S S) + \frac{\omega_1N_0}{\varphi_B}(D_B B + \mu U \\
&- \varphi_B B - {}_2BH) + \frac{{}_1M}{\xi} \\
&(D_M M + \xi U - \varphi_M M - \lambda_1 UM) \\
&+ \frac{{}_2\omega_1N_0H}{\psi\varphi_B}(D_H H + \psi B - \varphi_H H - \lambda_2 BH) \\
&= (\delta - \varphi_N N)\left(1 - \frac{N_0}{N}\right) + \omega_3N_0U - (\beta_1 + \varphi_U)U \\
&+ \frac{\omega_2\beta_2N_0}{\varphi_S}U \\
&+ \frac{\omega_1\mu N_0}{\varphi_B}U - \frac{{}_1\varphi_M}{\xi}M^2 - \frac{{}_1\lambda_1}{\xi}UM^2 - \frac{{}_2\omega_1\varphi_HN_0}{\psi\varphi_B}H^2 \\
&- \frac{{}_2\omega_1\lambda_2N_0}{\psi\varphi_B}BH^2 + D_N\left(1 - \frac{N_0}{N}\right)N + D_U U \\
&+ \frac{\omega_2N_0D_S}{\varphi_S}S \\
&+ \frac{\omega_1N_0D_B}{\varphi_B}B + \frac{{}_1MD_M}{\xi}M + \frac{{}_2\omega_1N_0HD_H}{\psi\varphi_B}H.
\end{aligned}$$

By setting $N_0 = \delta/\varphi_N$, we deduce that

$$\frac{\partial\Upsilon_0}{\partial t} = -\frac{\varphi_N(N - N_0)^2}{N} + (\beta_1 + \varphi_U)(\mathcal{R}_0 - 1)U -$$
$$\frac{1}{\xi}(\varphi_M + \lambda_1 U)M^2$$

$$
\begin{aligned}
&- \frac{{}_2\omega_1 N_0}{\psi\varphi_B}\left(\varphi_H + \lambda_2 B\right) H^2 + D_N \quad 1 - \frac{N_0}{N} \qquad N \\
&+ D_U \quad U \\
&+ \frac{\omega_2 N_0 D_S}{\varphi_S} \quad S + \frac{\omega_1 N_0 D_B}{\varphi_B} \quad B + \frac{{}_1D_M}{\xi} M \quad M + \\
&\frac{{}_2\omega_1 N_0 D_H}{\psi\varphi_B} H \quad H.
\end{aligned}
$$

As a result, we evaluate $\frac{d\hat{\Upsilon}_0}{dt}$ as follows:

$$
\begin{aligned}
\frac{d\hat{\Upsilon}_0}{dt} = &-\varphi_N \int_\Lambda \frac{(N - N_0)^2}{N}\, \mathrm{d}\varkappa + (\beta_1 + \varphi_U)(\mathcal{R}_0 - 1) \\
&\int_\Lambda U\, \mathrm{d}\varkappa - \frac{{}_1\varphi_M}{\xi} \int_\Lambda M^2\, \mathrm{d}\varkappa \\
&- \frac{{}_1\lambda_1}{\xi} \int_\Lambda UM^2\, \mathrm{d}\varkappa - \frac{{}_2\omega_1\varphi_H N_0}{\psi\varphi_B} \int_\Lambda H^2\, \mathrm{d}\varkappa - \frac{{}_2\omega_1\lambda_2 N_0}{\psi\varphi_B} \\
&\int_\Lambda BH^2\, \mathrm{d}\varkappa \\
&+ D_N \int_\Lambda \quad 1 - \frac{N_0}{N} \qquad N\, \mathrm{d}\varkappa + D_U \int_\Lambda \quad U\, \mathrm{d}\varkappa + \frac{\omega_2 N_0 D_S}{\varphi_S} \\
&\int_\Lambda \quad S\, \mathrm{d}\varkappa \\
&+ \frac{\omega_1 N_0 D_B}{\varphi_B} \int_\Lambda \quad B\, \mathrm{d}\varkappa + \frac{{}_1D_M}{\xi} \int_\Lambda M \quad M\, \mathrm{d}\varkappa + \frac{{}_2\omega_1 N_0 D_H}{} \\
&\int_\Lambda H \quad H\, \mathrm{d}\varkappa. \qquad (21)
\end{aligned}
$$

Through the use of equality (Equation 20), Equation 21 takes the following form:

$$
\begin{aligned}
\frac{d\hat{\Upsilon}_0}{dt} = &-\varphi_N \int_\Lambda \frac{(N - N_0)^2}{N}\, \mathrm{d}\varkappa + (\beta_1 + \varphi_U)(\mathcal{R}_0 - 1) \int_\Lambda U\, \mathrm{d}\varkappa \\
&- \frac{{}_1\varphi_M}{\xi} \int_\Lambda M^2\, \mathrm{d}\varkappa \\
&- \frac{{}_1\lambda_1}{\xi} \int_\Lambda UM^2\, \mathrm{d}\varkappa - \frac{{}_2\omega_1\varphi_H N_0}{\psi\varphi_B} \int_\Lambda H^2\, \mathrm{d}\varkappa - \frac{{}_2\omega_1\lambda_2 N_0}{\psi\varphi_B} \\
&\int_\Lambda BH^2\, \mathrm{d}\varkappa \\
&- D_N N_0 \int_\Lambda \frac{\|\nabla N\|^2}{N^2}\, \mathrm{d}\varkappa - \frac{{}_1D_M}{\xi} \int_\Lambda \|\nabla M\|^2\, \mathrm{d}\varkappa \\
&- \frac{{}_2\omega_1 N_0 D_H}{\psi\varphi_B} \int_\Lambda \|\nabla H\|^2\, \mathrm{d}\varkappa.
\end{aligned}
$$

Therefore, $\frac{d\hat{\Upsilon}_0}{dt} \leq 0$ for all $N, U, M, H, B > 0$ under the condition that $\mathcal{R}_0 \leq 1$. Equality $\frac{d\hat{\Upsilon}_0}{dt} = 0$ is achieved in the case when $(N, U, B, M, H) = (N_0, 0, 0, 0, 0)$. The solutions of system (Equation 2) converge to $\Theta_0$. The elements of $\Theta_0$ satisfy $(N, U, B, M, H) = (N_0, 0, 0, 0, 0)$. At this point, $\frac{\partial S}{\partial t} = \frac{\partial Y}{\partial t} = \quad S = Y = 0$. The first equation of system (Equation 2) simplifies to

$$
0 = \frac{\partial N}{\partial t} = \delta - \varphi_N N_0 - \omega_2 N_0 S.
$$

From this $S = 0$, leading to $\Theta_0 = \{\mathcal{FE}\}$. By applying the Lyapunov-LaSalle asymptotic stability theorem [70], it is concluded that the equilibrium $\mathcal{FE}$ is globally asymptotically stable.

**Theorem 2.** The HIV-persistent equilibrium $\mathcal{PE}$ achieves global asymptotic stability when $\mathcal{R}_0 > 1$.

**Proof.** Define a function $\Upsilon_1(\varkappa, t)$ as:

$$
\begin{aligned}
\Upsilon_1(\varkappa, t) = &\bar{N}\Psi \quad \frac{N}{\bar{N}} \quad + \bar{U}\Psi \quad \frac{U}{\bar{U}} \quad + \frac{\omega_2\bar{N}}{\varphi_S}\bar{S}\Psi \quad \frac{S}{\bar{S}} \quad + \frac{\omega_1\bar{N}}{\varphi_B + \quad {}_2\bar{H}} \\
&\bar{B}\Psi \quad \frac{B}{\bar{B}} \\
&+ \frac{1}{2\left(\xi - \lambda_1\bar{M}\right.} \left(M - \bar{M}\right.^2 + \frac{{}_2\omega_1\bar{N}}{2\left(\psi - \lambda_2\bar{H}\right)\left(\varphi_B + \quad {}_2\bar{H}\right.} \\
&\left(H - \bar{H}\right.^2.
\end{aligned}
$$

Equations 10, 11 indicate that $\xi - \lambda_1\bar{M} = \frac{\varphi_M\bar{M}}{\bar{U}} > 0$ and $\psi - \lambda_2\bar{H} = \frac{\varphi_H\bar{H}}{\bar{B}} > 0$. The computation of $\frac{\partial\Upsilon_1}{\partial t}$ yields

$$
\begin{aligned}
\frac{\partial\Upsilon_1}{\partial t} = &\quad 1 - \frac{\bar{N}}{N} \quad (D_N \quad N + \delta - \varphi_N N - \omega_1 NB - \omega_2 NS - \omega_3 NU) \\
&+ \quad 1 - \frac{\bar{U}}{U} \quad (D_U \quad U + \omega_1 NB + \omega_2 NS + \omega_3 NU - (\beta_1 + \varphi_U) \\
&U - \quad {}_1UM) \\
&+ \frac{\omega_2\bar{N}}{\varphi_S} \quad 1 - \frac{\bar{S}}{S} \quad (D_S \quad S + \beta_2 U - \varphi_S S) \\
&+ \frac{\omega_1\bar{N}}{\varphi_B + \quad {}_2\bar{H}} \quad 1 - \frac{\bar{B}}{B} \quad (D_B \quad B + \mu U - \varphi_B B - \quad {}_2BH) \\
&+ \frac{1}{\xi - \lambda_1\bar{M}} \left(M - \bar{M}\right. \quad (D_M \quad M + \xi U - \varphi_M M - \lambda_1 UM) \\
&+ \frac{{}_2\omega_1\bar{N}}{\left(\psi - \lambda_2\bar{H}\right)\left(\varphi_B + \quad {}_2\bar{H}\right.} \left(H - \bar{H}\right. \quad (D_H \quad H + \psi B - \varphi_H H \\
&-\lambda_2 BH) \\
= &\left(\delta - \varphi_N N\right) \quad 1 - \frac{\bar{N}}{N} \quad + \omega_1\bar{N}B + \omega_3\bar{N}U - (\beta_1 + \varphi_U) \\
&\left(U - \bar{U}\right. \\
&- \quad {}_1M\left(U - \bar{U}\right. \quad - \omega_1\frac{NB\bar{U}}{U} - \omega_2\frac{NS\bar{U}}{U} - \omega_3 N\bar{U} + \frac{\omega_2\beta_2\bar{N}}{\varphi_S}U \\
&- \frac{\omega_2\beta_2\bar{N}}{\varphi_S}\frac{U\bar{S}}{S} + \omega_2\bar{N}\bar{S} + \frac{\omega_1\mu\bar{N}}{\varphi_B + \quad {}_2\bar{H}}U - \frac{\omega_1\varphi_B\bar{N}}{\varphi_B + \quad {}_2\bar{H}}\left(B - \bar{B}\right. \\
&- \frac{{}_2\omega_1\bar{N}}{\varphi_B + \quad {}_2\bar{H}}H\left(B - \bar{B}\right. \quad - \frac{\omega_1\mu\bar{N}}{\varphi_B + \quad {}_2\bar{H}}\frac{\bar{B}U}{B} \\
&+ \frac{1}{\xi - \lambda_1\bar{M}} \left(M - \bar{M}\right. \quad (\xi U - \varphi_M M - \lambda_1 UM) \\
&+ \frac{{}_2\omega_1\bar{N}}{\left(\psi - \lambda_2\bar{H}\right)\left(\varphi_B + \quad {}_2\bar{H}\right.} \left(H - \bar{H}\right. \quad (\psi B - \varphi_H H - \lambda_2 BH) \\
&+ D_N \quad N \quad 1 - \frac{\bar{N}}{N} \quad + D_U \quad 1 - \frac{\bar{U}}{U} \qquad U + \frac{\omega_2\bar{N}D_S}{\varphi_S} \\
&1 - \frac{\bar{S}}{S} \qquad S \\
&+ \frac{\omega_1\bar{N}D_B}{\varphi_B + \quad {}_2\bar{H}} \quad 1 - \frac{\bar{B}}{B} \qquad B + \frac{{}_1D_M}{\xi - \lambda_1\bar{M}} \left(M - \bar{M}\right. \qquad M \\
&+ \frac{{}_2\omega_1\bar{N}D_H}{\left(\psi - \lambda_2\bar{H}\right)\left(\varphi_B + \quad {}_2\bar{H}\right.} \left(H - \bar{H}\right. \qquad H.
\end{aligned}
$$

The equilibrium conditions associated with $\mathcal{PE}$ indicate that

$$
\delta = \varphi_N\bar{N} + \omega_1\bar{N}\bar{B} + \omega_2\bar{N}\bar{S} + \omega_3\bar{N}\bar{U},
$$

$$\omega_1\bar{N}\bar{B}+\omega_2\bar{N}\bar{S}+\omega_3\bar{N}\bar{U}=\left(\beta_1+\varphi_U+\ {}_1\bar{M}\ \ \bar{U},\right.$$
$$\bar{S}=\frac{\beta_2\bar{U}}{\varphi_S},\qquad \bar{B}=\frac{\mu\bar{U}}{\varphi_B+\ {}_2\bar{H}},$$
$$\xi\bar{U}=\varphi_M\bar{M}+\lambda_1\bar{U}\bar{M},\qquad \psi\bar{B}=\varphi_H\bar{H}+\lambda_2\bar{B}\bar{H}.$$

From this, we find

$$\begin{aligned}\frac{\partial\Upsilon_1}{\partial t}=&\left(\varphi_N\bar{N}-\varphi_N N\quad 1-\frac{\bar{N}}{N}\right.+\left(\omega_1\bar{N}\bar{B}+\omega_2\bar{N}\bar{S}\right.\\&+\omega_3\bar{N}\bar{U}\quad 1-\frac{\bar{N}}{N}\\&+\omega_1\bar{N}B+\omega_3\bar{N}U-(\beta_1+\varphi_U)\left(U-\bar{U}\right.\\&-\ {}_1M\left(U-\bar{U}\right.-\omega_1\bar{N}\bar{B}\frac{NB\bar{U}}{\bar{N}\bar{B}U}\\&-\omega_2\bar{N}\bar{S}\frac{NS\bar{U}}{\bar{N}\bar{S}U}-\omega_3\bar{N}\bar{U}\frac{N}{\bar{N}}+\frac{\omega_2\beta_2\bar{N}}{\varphi_S}U-\omega_2\bar{N}\bar{S}\frac{U\bar{S}}{\bar{U}S}\\&+\omega_2\bar{N}\bar{S}\\&+\frac{\omega_1\mu\bar{N}}{\varphi_B+\ {}_2\bar{H}}U-\frac{\omega_1\varphi_B\bar{N}}{\varphi_B+\ {}_2\bar{H}}\left(B-\bar{B}\right.-\frac{{}_2\omega_1\bar{N}}{\varphi_B+\ {}_2\bar{H}}\\&H\left(B-\bar{B}\right.-\omega_1\bar{N}\bar{B}\frac{\bar{B}U}{B\bar{U}}\\&+\frac{{}_1\left(M-\bar{M}\right.}{\xi-\lambda_1\bar{M}}\left(\xi U-\varphi_M M-\lambda_1 UM-\xi\bar{U}+\varphi_M\bar{M}\right.\\&+\lambda_1\bar{U}\bar{M}-\lambda_1 U\bar{M}+\lambda_1 U\bar{M}\\&+\frac{{}_2\omega_1\bar{N}\left(H-\bar{H}\right.}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\left(\psi B-\varphi_H H-\lambda_2 BH-\psi\bar{B}\right.\\&+\varphi_H\bar{H}+\lambda_2\bar{B}\bar{H}-\lambda_2 B\bar{H}+\lambda_2 B\bar{H}\\&+D_N\quad N\quad 1-\frac{\bar{N}}{N}\quad+D_U\quad 1-\frac{\bar{U}}{U}\qquad U+\frac{\omega_2\bar{N}D_S}{\varphi_S}\\&1-\frac{\bar{S}}{S}\qquad S+\frac{\omega_1\bar{N}D_B}{\varphi_B+\ {}_2\bar{H}}\\&\times\quad 1-\frac{\bar{B}}{B}\qquad B+\frac{{}_1D_M}{\xi-\lambda_1\bar{M}}\left(M-\bar{M}\right.\qquad M\\&+\frac{{}_2\omega_1\bar{N}D_H}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\left(H-\bar{H}\right.\qquad H.\end{aligned}$$

Simplifying, we arrive at

$$\begin{aligned}\frac{\partial\Upsilon_1}{\partial t}=&-\frac{\varphi_N\left(N-\bar{N}\right.^2}{N}+\left(\omega_1\bar{N}\bar{B}+\omega_2\bar{N}\bar{S}+\omega_3\bar{N}\bar{U}\right.\quad 1-\frac{\bar{N}}{N}\\&+\omega_1\bar{N}B+\omega_3\bar{N}U\\&-(\beta_1+\varphi_U)\left(U-\bar{U}\right.-\ {}_1M\left(U-\bar{U}\right.+\ {}_1\bar{M}\left(U-\bar{U}\right.\\&-\ {}_1\bar{M}\left(U-\bar{U}\right.\\&-\omega_1\bar{N}\bar{B}\frac{NB\bar{U}}{\bar{N}\bar{B}U}-\omega_2\bar{N}\bar{S}\frac{NS\bar{U}}{\bar{N}\bar{S}U}-\omega_3\bar{N}\bar{U}\frac{N}{\bar{N}}+\frac{\omega_2\beta_2\bar{N}}{\varphi_S}U\\&-\omega_2\bar{N}\bar{S}\frac{U\bar{S}}{\bar{U}S}\\&+\omega_2\bar{N}\bar{S}+\frac{\omega_1\mu\bar{N}}{\varphi_B+\ {}_2\bar{H}}U-\frac{\omega_1\varphi_B\bar{N}}{\varphi_B+\ {}_2\bar{H}}\left(B-\bar{B}\right.-\frac{{}_2\omega_1\bar{N}}{\varphi_B+\ {}_2\bar{H}}\\&H\left(B-\bar{B}\right.\\&+\frac{{}_2\omega_1\bar{N}}{\varphi_B+\ {}_2\bar{H}}\bar{H}\left(B-\bar{B}\right.-\frac{{}_2\omega_1\bar{N}}{\varphi_B+\ {}_2\bar{H}}\bar{H}\left(B-\bar{B}\right.-\omega_1\bar{N}\bar{B}\frac{\bar{B}U}{B\bar{U}}\\&+\ {}_1\left(M-\bar{M}\right)\left(U-\bar{U}\right.-\frac{{}_1\left(\varphi_M+\lambda_1 U\right)}{\xi-\lambda_1\bar{M}}\left(M-\bar{M}\right.^2\\&+\frac{{}_2\omega_1\bar{N}\left(H-\bar{H}\right.}{\varphi_B+\ {}_2\bar{H}}\left(B-\bar{B}\right.\\&-\frac{{}_2\omega_1\bar{N}\left(\varphi_H+\lambda_2 B\right)}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\left(H-\bar{H}\right.^2+D_N\quad N\quad 1-\frac{\bar{N}}{N}\\&+D_U\quad 1-\frac{\bar{U}}{U}\qquad U+\frac{\omega_2\bar{N}D_S}{\varphi_S}\quad 1-\frac{\bar{S}}{S}\qquad S+\frac{\omega_1\bar{N}D_B}{\varphi_B+\ {}_2\bar{H}}\\&1-\frac{\bar{B}}{B}\qquad B\\&+\frac{{}_1D_M}{\xi-\lambda_1\bar{M}}\left(M-\bar{M}\right.\qquad M+\frac{{}_2\omega_1\bar{N}D_H}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\\&\left(H-\bar{H}\right.\qquad H.\end{aligned}\tag{22}$$

In this way, Equation 22 is rewritten in the form

$$\begin{aligned}\frac{\partial\Upsilon_1}{\partial t}=&-\frac{\varphi_N\left(N-\bar{N}\right.^2}{N}+\left(\omega_1\bar{N}\bar{B}+\omega_2\bar{N}\bar{S}+\omega_3\bar{N}\bar{U}\right.\quad 1-\frac{\bar{N}}{N}\\&+\omega_3\bar{N}U-\left(\beta_1+\varphi_U+\ {}_1\bar{M}\right)\left(U-\bar{U}\right.-\omega_1\bar{N}\bar{B}\frac{NB\bar{U}}{\bar{N}\bar{B}U}\\&-\omega_2\bar{N}\bar{S}\frac{NS\bar{U}}{\bar{N}\bar{S}U}\\&-\omega_3\bar{N}\bar{U}\frac{N}{\bar{N}}+\frac{\omega_2\beta_2\bar{N}}{\varphi_S}U-\omega_2\bar{N}\bar{S}\frac{U\bar{S}}{\bar{U}S}+\omega_2\bar{N}\bar{S}+\frac{\omega_1\mu\bar{N}}{\varphi_B+\ {}_2\bar{H}}U\\&+\omega_1\bar{N}\bar{B}\\&-\omega_1\bar{N}\bar{B}\frac{\bar{B}U}{B\bar{U}}-\frac{{}_1\left(\varphi_M+\lambda_1 U\right)\left(M-\bar{M}\right.^2}{\xi-\lambda_1\bar{M}}-\\&\frac{{}_2\omega_1\bar{N}\left(\varphi_H+\lambda_2 B\right)\left(H-\bar{H}\right.^2}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\\&+D_N\quad N\quad 1-\frac{\bar{N}}{N}\quad+D_U\quad 1-\frac{\bar{U}}{U}\qquad U+\frac{\omega_2\bar{N}D_S}{\varphi_S}\\&1-\frac{\bar{S}}{S}\qquad S\\&+\frac{\omega_1\bar{N}D_B}{\varphi_B+\ {}_2\bar{H}}\quad 1-\frac{\bar{B}}{B}\qquad B+\frac{{}_1D_M}{\xi-\lambda_1\bar{M}}\left(M-\bar{M}\right.\qquad M\\&+\frac{{}_2\omega_1\bar{N}D_H}{\left(\psi-\lambda_2\bar{H}\right)\left(\varphi_B+\ {}_2\bar{H}\right.}\left(H-\bar{H}\right.\qquad H.\end{aligned}$$

Since we have

$$\frac{\omega_1\mu\bar{N}}{\varphi_B+\ {}_2\bar{H}}\bar{U}+\frac{\omega_2\beta_2\bar{N}}{\varphi_S}\bar{U}+\omega_3\bar{N}\bar{U}-\left(\beta_1+\varphi_U+\ {}_1\bar{M}\ \ \bar{U}\right.$$
$$\frac{U}{\bar{U}}=0.$$

This results in the following form

$$\begin{aligned}\frac{\partial\Upsilon_1}{\partial t}=&-\frac{\varphi_N\left(N-\bar{N}\right.^2}{N}+\left(\omega_1\bar{N}\bar{B}+\omega_2\bar{N}\bar{S}+\omega_3\bar{N}\bar{U}\right.\quad 2-\frac{\bar{N}}{N}\\&-\omega_1\bar{N}\bar{B}\frac{NB\bar{U}}{\bar{N}\bar{B}U}\\&-\omega_2\bar{N}\bar{S}\frac{NS\bar{U}}{\bar{N}\bar{S}U}-\omega_3\bar{N}\bar{U}\frac{N}{\bar{N}}-\omega_2\bar{N}\bar{S}\frac{U\bar{S}}{\bar{U}S}+\omega_2\bar{N}\bar{S}+\omega_1\bar{N}\bar{B}\\&-\omega_1\bar{N}\bar{B}\frac{\bar{B}U}{B\bar{U}}\end{aligned}$$

$$
\begin{aligned}
&- \frac{{}_1(\varphi_M + \lambda_1 U)\left(M - \bar{M}\right)^2}{\xi - \lambda_1 \bar{M}} - \\
&\frac{{}_2\omega_1 \bar{N}(\varphi_H + \lambda_2 B)\left(H - \bar{H}\right)^2}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)} \\
&+ D_N \quad N \quad 1 - \frac{\bar{N}}{N} \quad + D_U \quad 1 - \frac{\bar{U}}{U} \qquad U + \frac{\omega_2 \bar{N} D_S}{\varphi_S} \\
&\quad 1 - \frac{\bar{S}}{S} \qquad S \\
&+ \frac{\omega_1 \bar{N} D_B}{\varphi_B + {}_2\bar{H}} \quad 1 - \frac{\bar{B}}{B} \qquad B + \frac{{}_1D_M}{\xi - \lambda_1 \bar{M}} \left(M - \bar{M} \quad M\right. \\
&+ \frac{{}_2\omega_1 \bar{N} D_H}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)} \left(H - \bar{H} \quad H\right. \\
&= - \frac{\left(\varphi_N + \omega_3 \bar{U}\right)\left(N - \bar{N}\right)^2}{N} \\
&\quad + \omega_1 \bar{N} \bar{B} \quad 3 - \frac{\bar{N}}{N} - \frac{N\bar{B}\bar{U}}{\bar{N}\bar{B}U} - \frac{\bar{B}U}{B\bar{U}} \\
&+ \omega_2 \bar{N} \bar{S} \quad 3 - \frac{\bar{N}}{N} - \frac{N\bar{S}\bar{U}}{\bar{N}\bar{S}U} - \frac{U\bar{S}}{\bar{U}S} \\
&\quad - \frac{{}_1(\varphi_M + \lambda_1 U)\left(M - \bar{M}\right)^2}{\xi - \lambda_1 \bar{M}} \\
&- \frac{{}_2\omega_1 \bar{N}(\varphi_H + \lambda_2 B)\left(H - \bar{H}\right)^2}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)} + D_N \quad N \quad 1 - \frac{\bar{N}}{N} \\
&\quad + D_U \quad 1 - \frac{\bar{U}}{U} \qquad U \\
&+ \frac{\omega_2 \bar{N} D_S}{\varphi_S} \quad 1 - \frac{\bar{S}}{S} \qquad S + \frac{\omega_1 \bar{N} D_B}{\varphi_B + {}_2\bar{H}} \quad 1 - \frac{\bar{B}}{B} \qquad B \\
&+ \frac{{}_1D_M}{\xi - \lambda_1 \bar{M}} \left(M - \bar{M} \quad M + \frac{{}_2\omega_1 \bar{N} D_H}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)}\right. \\
&\quad \left(H - \bar{H} \quad H.\right.
\end{aligned}
$$

Differentiating with respect to time $\hat{\Upsilon}_1(t)$ and utilizing equality (Equation 20) gives

$$
\begin{aligned}
\frac{d\hat{\Upsilon}_1}{dt} &= -\left(\varphi_N + \omega_3 \bar{U}\right. \int_\Lambda \frac{\left(N - \bar{N}\right)^2}{N} \, \mathrm{d}\varkappa + \omega_1 \bar{N} \bar{B} \\
&\quad \int_\Lambda \quad 3 - \frac{\bar{N}}{N} - \frac{N\bar{B}\bar{U}}{\bar{N}\bar{B}U} - \frac{\bar{B}U}{B\bar{U}} \quad \mathrm{d}\varkappa \\
&\quad + \omega_2 \bar{N} \bar{S} \int_\Lambda \quad 3 - \frac{\bar{N}}{N} - \frac{N\bar{S}\bar{U}}{\bar{N}\bar{S}U} - \frac{U\bar{S}}{\bar{U}S} \quad \mathrm{d}\varkappa - \frac{1}{\xi - \lambda_1 \bar{M}} \\
&\quad \int_\Lambda (\varphi_M + \lambda_1 U)\left(M - \bar{M}\right)^2 \, \mathrm{d}\varkappa \\
&\quad - \frac{{}_2\omega_1 \bar{N}}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)} \int_\Lambda (\varphi_H + \lambda_2 B)\left(H - \bar{H}\right)^2 \, \mathrm{d}\varkappa \\
&\quad - D_N \bar{N} \int_\Lambda \frac{\|\nabla N\|^2}{N^2} \, \mathrm{d}\varkappa \\
&\quad - D_U \bar{U} \int_\Lambda \frac{\|\nabla U\|^2}{U^2} \, \mathrm{d}\varkappa - \frac{\omega_2 \bar{N} D_S \bar{S}}{\varphi_S} \int_\Lambda \frac{\|\nabla S\|^2}{S^2} \, \mathrm{d}\varkappa \\
&\quad - \frac{\omega_1 \bar{N} D_B \bar{B}}{\varphi_B + {}_2\bar{H}} \int_\Lambda \frac{\|\nabla B\|^2}{B^2} \, \mathrm{d}\varkappa \\
&\quad - \frac{{}_1D_M}{\xi - \lambda_1 \bar{M}} \int_\Lambda \|\nabla M\|^2 \, \mathrm{d}\varkappa - \frac{{}_2\omega_1 \bar{N} D_H}{\left(\psi - \lambda_2 \bar{H}\right)\left(\varphi_B + {}_2\bar{H}\right)} \\
&\quad \int_\Lambda \|\nabla H\|^2 \, \mathrm{d}\varkappa.
\end{aligned}
$$

Employing the inequality between the arithmetic and geometric means, as presented in Equation 19, we obtain

$$
3 \leq \frac{\bar{N}}{N} + \frac{N\bar{B}\bar{U}}{\bar{N}\bar{B}U} + \frac{\bar{B}U}{B\bar{U}}, \qquad 3 \leq \frac{\bar{N}}{N} + \frac{N\bar{S}\bar{U}}{\bar{N}\bar{S}U} + \frac{U\bar{S}}{\bar{U}S}.
$$

At this stage, we guarantee that $\frac{d\hat{\Upsilon}_1}{dt} \leq 0$ for all positive values of $N, U, S, B, M, H$ when $\mathcal{R}_0 > 1$. Meanwhile, $\frac{d\hat{\Upsilon}_1}{dt} = 0$ when $(N, U, S, B, M, H) = \left(\bar{N}, \bar{U}, \bar{S}, \bar{B}, \bar{M}, \bar{H}\right.$. The solutions of model (Equation 2) approach $\Theta_1 = \{\mathcal{PE}\}$. By applying Lyapunov-LaSalle asymptotic stability theorem, we conclude that $\mathcal{PE}$ attains global asymptotic stability.

Remark 2. Exploring memory effects within our model through the use of fractional differential equations (FDEs) represents a valuable avenue for future investigation [71, 72]. FDEs are particularly well-suited for capturing systems characterized by memory and non-local interactions–features that are highly relevant in both biological [73] and epidemiological contexts. Recent studies have demonstrated that the Lyapunov method is an effective analytical tool for evaluating the global stability of fractional-order systems [73, 74]. The Lyapunov functions constructed in this section lay the groundwork for future analysis of the stability properties in a fractional-order HIV-1 model.

# 6 Numerical simulations

This section focuses on performing numerical simulations to explore the theoretical findings of our study. Furthermore, a detailed sensitivity analysis will be conducted for each parameter. To solve the system of PDEs, we employed MATLAB's built-in PDEPE solver, which is designed for one-dimensional parabolic and elliptic PDEs. The PDEPE solver utilizes a spatial discretization based on the Galerkin or Petrov–Galerkin method, converting the PDE system into a set of ODEs. These ODEs are then solved using the ode15s solver, a variable-order, implicit numerical integrator well-suited for stiff problems. This method offers a robust and efficient approach for numerically approximating the dynamics of the model over time and space.

## 6.1 Stability of equilibrium points

Here, we undertake a numerical investigation into the global stability of all equilibria. To achieve this, a time step size of 0.1 is applied for $t > 0$, and the domain $\Lambda$, defined as $\Lambda = [0, 2]$, is used with a step size of 0.02. Based on Theorems 1 and 2 which ensure the global stability of both equilibria, convergence is guaranteed irrespective of the initial values. Therefore, the initial conditions for

TABLE 1 The values of the model's parameters.

| Parameter | Description | Value | Source |
|---|---|---|---|
| $\delta$ | Natural production rate of uninfected CD4$^+$T cells | 10 | [77] |
| $\omega_1$ | Rate of infection of CD4$^+$T cells due to direct interaction with free virus particles | Varied | |
| $\omega_2$ | Rate of cytokine-induced enhancement of viral infection | Varied | |
| $\omega_3$ | Rate of infection of CD4$^+$T cells through cell-to-cell (synaptic) transmission | Varied | |
| $\beta_1$ | Rate of pyroptosis-induced death of infected CD4$^+$T cells | 0.1 | [26] |
| $\beta_2$ | Rate of cytokine release from infected CD4$^+$T cells | 0.1 | [30] |
| $_1$ | Rate at which infected CD4$^+$T cells are killed by CTLs | 0.001 | [26] |
| $_2$ | Rate at which free HIV particles are neutralized by antibodies | 0.1 | [57] |
| $\mu$ | Rate of viral particle release from infected CD4$^+$T cells | 3 | [57] |
| $\xi$ | Rate of CTL proliferation in response to infected CD4$^+$T cells | 0.5 | [78] |
| $\psi$ | Rate of antibody proliferation in response to free HIV particles | 0.2 | [57] |
| $\lambda_1$ | Rate of CTL impairment due to interaction with infected CD4$^+$T cells | 0.001 | [58] |
| $\lambda_2$ | Rate of antibody impairment due to interaction with free HIV particles | 0.001 | [58] |
| $\varphi_N$ | Natural death rate of uninfected CD4$^+$T cells | 0.01 | [77] |
| $\varphi_U$ | Natural death rate of infected CD4$^+$T cells | 0.75 | [26] |
| $\varphi_S$ | Natural degradation rate of inflammatory cytokines | 0.1 | [26] |
| $\varphi_B$ | Natural degradation rate of free HIV particles | 1 | [57] |
| $\varphi_M$ | Natural death rate of cytotoxic T lymphocytes (CTLs) | 0.2 | [78, 79] |
| $\varphi_H$ | Natural death rate of antibodies | 0.01 | [57] |
| $D_N$ | Diffusion coefficient of uninfected CD4$^+$T cells | 0.1 | Assumed |
| $D_U$ | Diffusion coefficient of infected CD4$^+$T cells | 0.1 | Assumed |
| $D_S$ | Diffusion coefficient of inflammatory cytokines | 0.01 | Assumed |
| $D_B$ | Diffusion coefficient of free HIV particles | 0.01 | Assumed |
| $D_M$ | Diffusion coefficient of cytotoxic T lymphocytes (CTLs) | 0.2 | Assumed |
| $D_H$ | Diffusion coefficient of antibodies | 0.2 | Assumed |

system (Equation 2) are chosen randomly as follows:

$$\begin{aligned}
&N(\varkappa,0) = 500\left[1+0.1\cos^2(\pi\varkappa)\right],\\
&U(\varkappa,0) = 3\left[1+0.2\cos^2(\pi\varkappa)\right],\\
&S(\varkappa,0) = 3\left[1+0.2\cos^2(\pi\varkappa)\right], \quad B(\varkappa,0) = 2\left[1+0.2\cos^2(\pi\varkappa)\right],\\
&M(\varkappa,0) = 8\left[1+0.2\cos^2(\pi\varkappa)\right],\\
&H(\varkappa,0) = 30\left[1+0.2\cos^2(\pi\varkappa)\right], \quad \varkappa\in[0,2].
\end{aligned} \tag{23}$$

Additionally, we apply the homogeneous Neumann boundary conditions:

$$\frac{\partial N}{\partial\vec{\mathcal{Z}}} = \frac{\partial U}{\partial\vec{\mathcal{Z}}} = \frac{\partial S}{\partial\vec{\mathcal{Z}}} = \frac{\partial B}{\partial\vec{\mathcal{Z}}} = \frac{\partial M}{\partial\vec{\mathcal{Z}}} = \frac{\partial H}{\partial\vec{\mathcal{Z}}} = 0, \quad t>0, \quad \varkappa = 0,2. \tag{24}$$

For numerical calculations, $\omega_1$, $\omega_2$, and $\omega_3$ are varied, whereas the other parameters are kept constant as specified in Table 1. Those parameters are sourced from existing literature, except for the diffusion coefficients, which are predetermined.

Therefore, the following cases arise:

**Case 1.** Assigning $\omega_1 = \omega_2 = \omega_3 = 0.0001$, the basic reproduction number $\mathcal{R}_0$ is calculated to be 0.59, which is less than unity. In accordance with Theorem 1, the equilibrium point $\mathcal{FE} = (1000, 0, 0, 0, 0, 0)$ demonstrates global asymptotic stability, as depicted in Figure 1. This finding indicates the successful clearance of HIV infection from the human body, highlighting the conditions under which the virus cannot persist.

**Case 2.** The values $\omega_1 = 0.0004$, $\omega_2 = 0.0006$, and $\omega_3 = 0.0005$ are assigned. With these parameters, the basic reproduction number, $\mathcal{R}_0$, is determined to be 2.7, exceeding unity. Theorem 2 confirms that the equilibrium point $\mathcal{PE} = (641.9, 4.16, 4.16, 2.5, 10.2, 39.98)$ exhibits global asymptotic stability, as depicted in Figure 2. This analysis reflects the ability of the virus to maintain a stable presence in the human body under this condition and cause chronic infection, highlighting the persistence of HIV infection.

## 6.2 Sensitivity analysis

The main objective of this subsection is to discuss the sensitivity analysis of model (Equation 2). Specifically, the analysis aims to assess the impact of various parameters on the advancement of HIV infection in a host, offering insights that can be useful for the development of novel antiviral therapies. The sensitivity index will be determined by employing partial derivatives to examine how variables fluctuate in accordance to parameter changes. The following formula represents the normalized forward sensitivity index of $\mathcal{R}_0$ in relation to the parameter:

$$Q_\tau = \frac{\tau}{\mathcal{R}_0}\times\frac{\partial\mathcal{R}_0}{\partial\tau}. \tag{25}$$

Here, $\tau$ accounts for a specified parameter. The values of $Q_\tau$ range from $-1$ to 1, with a positive $Q_\tau$ indicating a positive correlation and a negative value reflecting a negative correlation. The absolute value of $Q_\tau$ signifies the level of sensitivity: values

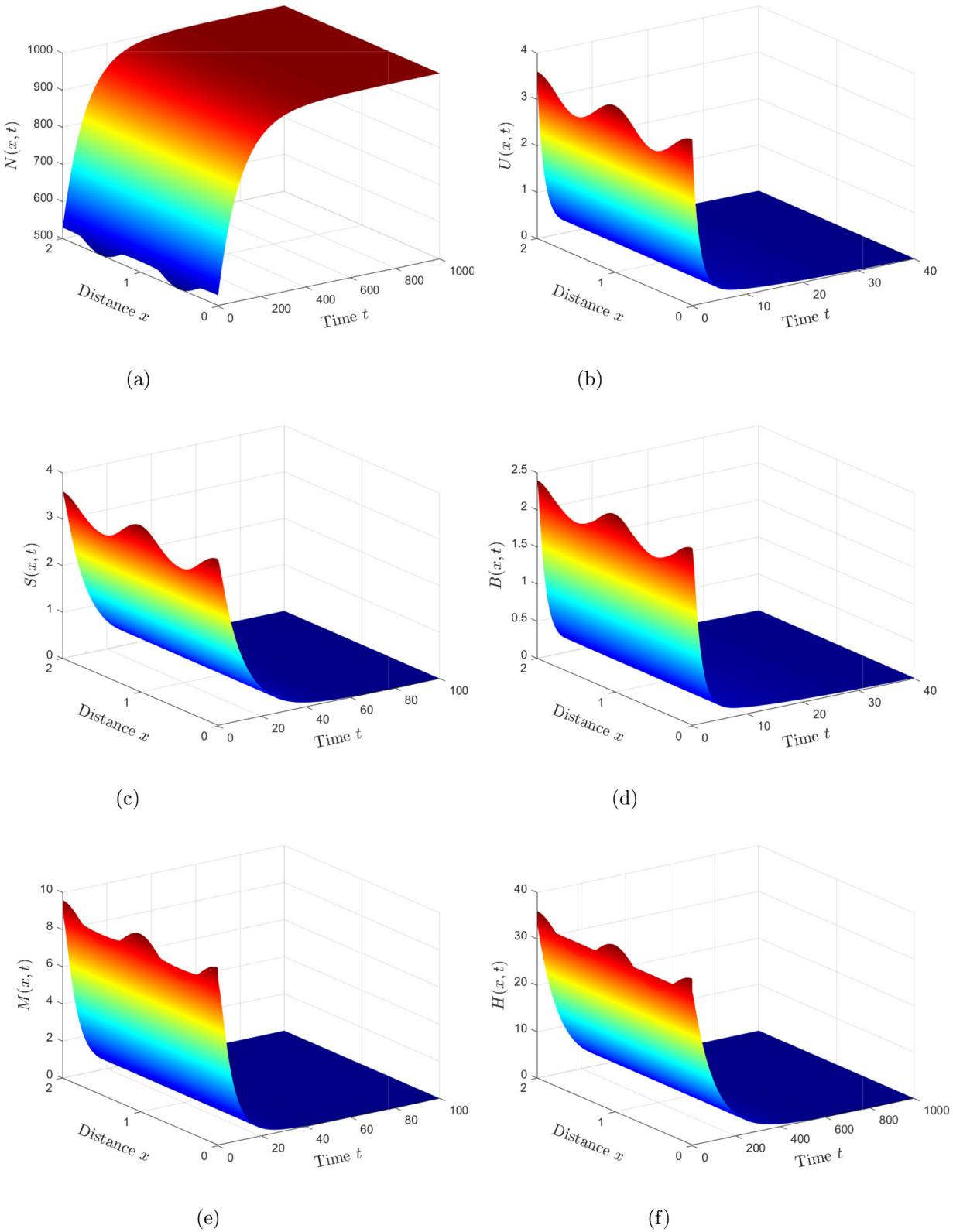


FIGURE 1
Numerical simulations reveal that the solution of system (Equation 2) stabilizes at the HIV-free equilibrium $\mathcal{FE} = (1000, 0, 0, 0, 0, 0)$ when $\mathcal{R}_0 \leq 1$ (Case 1). **(a)** Healthy CD4$^+$T cells. **(b)** HIV-infected CD4$^+$T cells. **(c)** Inflammatory cytokines. **(d)** Free HIV particles. **(e)** CTLs. **(f)** Antibodies.

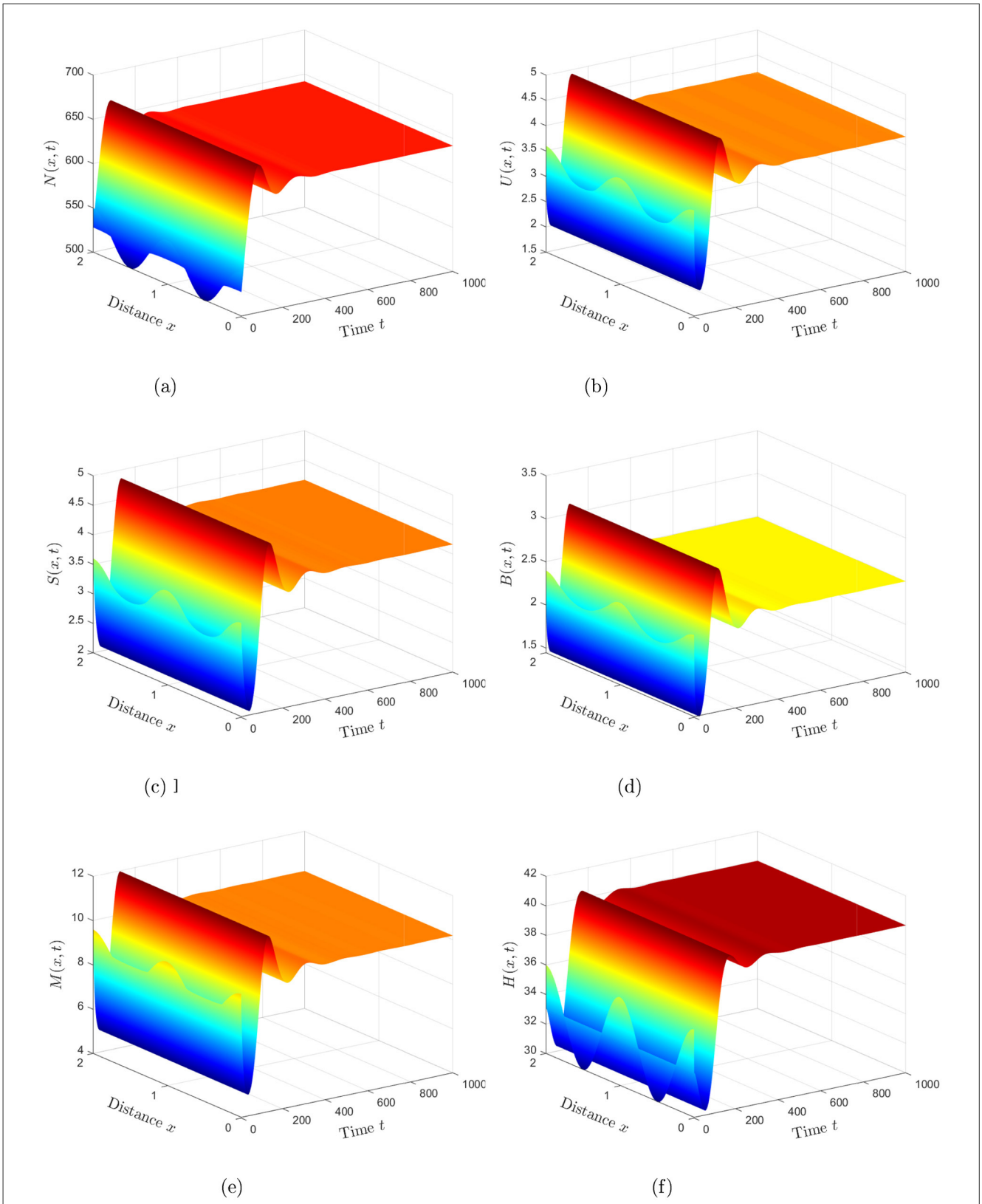


FIGURE 2
Numerical simulations reveal that the solution of system (Equation 2) stabilizes at the HIV-persistent equilibrium $\mathcal{PE} = (641.9, 4.16, 4.16, 2.5, 10.2, 39.98)$ when $\mathcal{R}_0 > 1$ (Case 2). **(a)** Healthy CD4$^+$T cells. **(b)** HIV-infected CD4$^+$T cells. **(c)** Inflammatory cytokines. **(d)** Free HIV particles. **(e)** CTLs. **(f)** Antibodies.

close to zero imply a minimal effect, whereas values near one point to a strong impact [75]. The sensitivity indices for $\mathcal{R}_0$ were computed using Equation 25 by applying the parameter values provided in Table 1, including $\omega_1 = 0.0004$, $\omega_2 = 0.0006$, and $\omega_3 = 0.0005$. The calculated sensitivity indices, derived from these values, are summarized in Table 2. The sensitivity indices of

TABLE 2 Quantifying parameters' influence on $\mathcal{R}_0$ in model (Equation 2): sensitivity index.

| Parameter $\tau$ | Value of $Q_\tau$ | Parameter $\tau$ | Value of $Q_\tau$ | Parameter $\tau$ | Value of $Q_\tau$ |
|---|---|---|---|---|---|
| $\delta$ | 1 | $\omega_3$ | 0.217 | $\varphi_U$ | −0.882 |
| $\varphi_N$ | −1 | $\mu$ | 0.522 | $\varphi_S$ | −0.261 |
| $\omega_1$ | 0.522 | $\beta_1$ | −0.118 | $\varphi_B$ | −0.522 |
| $\omega_2$ | 0.261 | $\beta_2$ | 0.261 | | |

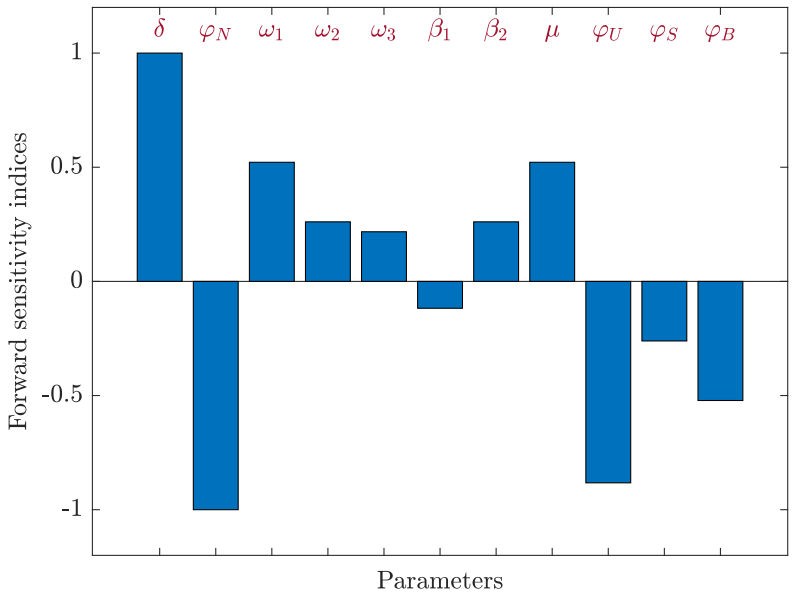


FIGURE 3
Assessment of parameter influence on $\mathcal{R}_0$ in system (Equation 2) using forward sensitivity analysis.

$\mathcal{R}_0$, as demonstrated in Table 2 and Figure 3, shed light on the varying influences of each parameter. From these, it is apparent that parameters $\delta$, $\omega_1$, $\omega_2$, $\omega_3$, $\mu$, and $\beta_2$ exhibit positive index values. This indicates that an increase in the values of these parameters is linked to a higher $\mathcal{R}_0$ value, leading to a greater level of HIV endemicity. In contrast, the parameters $\varphi_N$, $\beta_1$, $\varphi_U$, $\varphi_S$, and $\varphi_B$ show negative sensitivity indices, meaning that as their values rise, $\mathcal{R}_0$ decreases. Among all the parameters, the most influential are $\delta$, $\omega_1$, and $\mu$, while $\omega_2$, $\omega_3$, and $\beta_2$ have relatively minor impacts. Moreover, the parameters related to CTL and antibody responsiveness, $\xi$ and $\psi$, seem to have no impact on $\mathcal{R}_0$.

## 7 Conclusion and discussion

This study proposed and investigated a within-host HIV infection model that integrates both the influence of inflammatory cytokines and the weakening of adaptive immune responses (CTL and antibody). The framework comprises six biologically relevant compartments and incorporates two modes of viral transmission: traditional virus-to-cell spread and direct cell-to-cell contact. By introducing diffusion terms, the model also captures spatial movement of immune and infected cells, as well as free viral particles—a feature supported by recent biological findings. We conducted a thorough mathematical analysis, establishing the existence and boundedness of global solutions, ensuring the model's well-posedness. A key threshold parameter, the basic reproduction number $\mathcal{R}_0$, was derived and found to dictate the system's long-term behavior. Specifically, the model predicts global stability of the HIV-free equilibrium when $\mathcal{R}_0 \leq 1$ and global stability of HIV-persistent equilibrium when $\mathcal{R}_0 > 1$. These analytical results were supported by numerical simulations that also revealed how variations in key parameters affect disease progression. Further, sensitivity analysis of $\mathcal{R}_0$ helped identify the most influential factors in viral persistence and immune control.

An important challenge in controlling HIV infection lies in reducing the basic reproduction number $\mathcal{R}_0$ to a value less than or equal to one, thereby preventing sustained transmission. One effective strategy involves the use of antiviral therapies aimed at interrupting different modes of viral spread. To capture this therapeutically induced suppression, we introduce parameters $0 \leq \epsilon_i \leq 1$, for $i = 1, 2$, where $\epsilon_1$ represents the efficacy of treatment in inhibiting cell-free virus transmission, and $\epsilon_2$ accounts for the suppression of cell-to-cell viral transfer. In addition to standard antiretroviral therapies, we also consider the role of Necrosulfonamide (NSA), a selective inhibitor of pyroptosis, a highly inflammatory form of programmed cell death that exacerbates immune depletion in HIV-positive individuals

[76]. The parameter $\epsilon_3 \in [0,1]$ is used to denote the therapeutic effectiveness of NSA in curbing inflammation-driven cell death. Under these assumptions, the modified expression for the basic reproduction number becomes:

$$\mathcal{R}_0 = \frac{\delta\left(\mu\varphi_S(1-\epsilon_1)\omega_1 + \varphi_B\left(\beta_2(1-\epsilon_2)\omega_2 + \varphi_S(1-\epsilon_3)\omega_3\right.\right.}{\varphi_N\varphi_S\varphi_B\left(\beta_1+\varphi_U\right)}.$$

It is evident from this formulation that $\mathcal{R}_0$ is a monotonically decreasing function of the drug efficacy parameters $\epsilon_1$, $\epsilon_2$, $\epsilon_3$. Hence, by appropriately increasing the effectiveness of these interventions, through optimal drug combinations or dosing strategies, it is theoretically possible to drive $\mathcal{R}_0 \leq 1$, thereby achieving infection control or even eradication within the modeled population.

Future extensions of this model could involve incorporating more detailed biological mechanisms, such as latent viral reservoirs, time delays, and stochastic variations in immune responses, as well as clinical interventions including antiretroviral therapy (ART) and anti-inflammatory treatments targeting cytokine activity. Formulating the model as a nonlinear control system, with antiviral drug efficacy treated as a control input, also presents a promising avenue for optimizing treatment strategies-balancing therapeutic effectiveness with minimized drug costs and side effects. Moreover, integrating fractional differential equations may offer a more realistic representation of immunological memory. The inclusion of individual-level data could further enhance model accuracy and support more personalized predictions of treatment outcomes. Clinically, a better understanding of cytokine-induced inflammation and the spatial distribution of immune and infected cells may aid in developing novel therapeutic strategies aimed at preserving immune function and reducing chronic immune activation in HIV-positive individuals.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

NA: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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