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EDITED BY

Khalid Hattaf,
Centre Régional des Métiers de l'Éducation et
de la Formation (CRMEF), Morocco

REVIEWED BY

Anthony O'Hare,
University of Stirling, United Kingdom
Ahmed Mohsen,
University of Baghdad, Iraq

*CORRESPONDENCE

Ahmed M. Elaiw
✉ aelaiwksu.edu.sa@kau.edu.sa

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Dynamics and stability of a within-host HIV-HBV co-infection model with time delays

Ahmed M. Elaiw^{1*}, Abdulaziz S. Alhmadi^{1,2} and Aatef D. Hobiny¹

¹Department of Mathematics, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia,

²Department of General Studies, Technical College, Technical and Vocational Training Corporation, Jeddah, Saudi Arabia

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) co-infection is common due to their shared transmission routes. Understanding their interaction within host cells is key to improving treatment strategies. Mathematical models are crucial tools for analyzing within-host viral dynamics and informing therapeutic interventions. This study presents a mathematical framework designed to investigate the interactions and progression of HIV-HBV co-infection within a host. The model captures the distinct biological characteristics of the two viruses: HBV primarily infects liver cells (hepatocytes), while HIV targets CD4⁺ T cells and can also infect hepatocytes. A system of seven non-linear delay differential equations (DDEs) is formulated to represent the dynamic interactions among uninfected and virus-infected hepatocytes, uninfected and HIV-infected CD4⁺T cells, as well as circulating HIV and HBV particles. The model incorporates two biologically significant time delays: the first represents the latency between the initial infection and the onset of productive infection in host cells, while the second accounts for the maturation duration of newly produced virions before they become infectious. The model's mathematical consistency is verified by showing that its solutions remain bounded and non-negative throughout the system's dynamics. Equilibrium points and their associated threshold parameters are identified, with conditions for existence and stability rigorously derived. Global stability of the equilibria is established through the application of carefully designed Lyapunov functionals in conjunction with Lyapunov-LaSalle asymptotic stability theorem, ensuring a rigorous and comprehensive analysis of the system's long-term behavior. The theoretical findings are corroborated by numerical simulations. We conducted a sensitivity analysis of the basic reproduction numbers, R_0 for HIV and R_1 for HBV. The effects of antiviral treatment and time delays on the HIV-HBV co-dynamics are discussed. Minimum efficacy thresholds for anti-HIV and anti-HBV therapies are Determined, and when drug effectiveness surpasses these levels, the model predicts the full elimination of both viruses from the host. Additionally, the length of the time delay interval plays a role similar to that of antiviral treatment, suggesting a potential strategy for developing drug therapies aimed at extending the time delay period. The results of this study highlight the importance of incorporating time delays in models of dual viral infection and support the development of treatment strategies that enhance therapeutic outcomes by extending these delays.

KEYWORDS

HIV, HBV, co-infection, time delay, global dynamics, Lyapunov stability

1 Introduction

Two deadly viruses for the human body are the human immunodeficiency virus (HIV) and hepatitis B virus (HBV). In several patients, co-infection with these two viruses occurs because they share common transmission routes, such as blood transfusions, use of contaminated syringes, unprotected sexual intercourse, and others [1]. It is estimated that 8% to 10% of people diagnosed with HIV are also infected with HBV worldwide, making it important to study the co-infection of these two viruses. The co-infection with both viruses may increase the symptoms of each disease. This is due to the weakening and deterioration of the patient's immune system and the difficulty of determining effective treatments for both viruses [2, 3]. HIV is a single-stranded RNA virus that primarily infects CD4⁺ T cells, which are key components of the adaptive immune system. Over time, if left untreated, the number of CD4⁺ T cells declines, eventually leading to a disease called acquired immunodeficiency syndrome (AIDS) [4]. AIDS infection exposes the patient to opportunistic diseases and cancers. Besides infecting CD4⁺ T cells, HIV is also capable of invading other immune cells like dendritic cells and macrophages, resulting in their reduction and impaired function. The HIV also has the ability to infect different liver cells, including hepatocytes, Kupffer cells, and infiltrating T cells [5, 6]. HBV is a double-stranded DNA virus that primarily targets liver cells (hepatocytes) [7]. Over time, if left untreated, this infection can lead to chronic hepatitis, which may progress to cirrhosis and hepatocellular carcinoma.

Studying the interactions between viruses and target cells within the host, as well as immune responses, through laboratory experiments is not only difficult but also expensive. Therefore, mathematical modeling and simulation have become essential and important tools for understanding the dynamics of viruses within the host, as well as the role of the immune system in combating them. Furthermore, mathematical models may help design appropriate therapeutic strategies. In [8, 9], the basic models of HIV and hepatitis B virus (HBV) infection, respectively, have been formulated. These models consist of three main compartments: uninfected target cells (CD4⁺ T cells for HIV and hepatocytes for HBV), infected cells, and free viral particles. To take into account different biological phenomena not covered by these basic models, various extensions and generalizations have been made. One of the most important of these phenomena is the time delay during biological reactions. Examples of time delays include the time delay until a cell becomes infected, the time required for activation of the virus released from the cells, and the delay in the immune response. Time delays contribute to the development of accurate models that help understand the evolution of the virus within the host. Numerous studies have explored the incorporation of time delays into HIV single-infection models (see, e.g., [10–16]). On the other hand, HBV single-infection models with delay have also been formulated in some studies (e.g., [17–20]).

Mathematical modeling of HIV and hepatitis B virus co-infection at the population level has received considerable attention from researchers. These models play an important role in understanding patterns of infectious disease transmission within populations. These models may also play a significant role in formulating epidemic control strategies. Therefore, several

mathematical models have been developed for the coinfection of HBV and HIV (see, e.g., [3, 21–26]). In contrast, within-host models that examine the biological interactions and co-dynamics of HIV and HBV at the cellular level are relatively scarce. To our knowledge, only a limited number of studies, notably [27, 28], have addressed the within-host interplay between these two viruses. This highlights a significant gap in the literature, underscoring the need for more comprehensive investigations into their intracellular co-infection dynamics.

The HIV-HBV co-infection model proposed by [28] is formulated as follows:

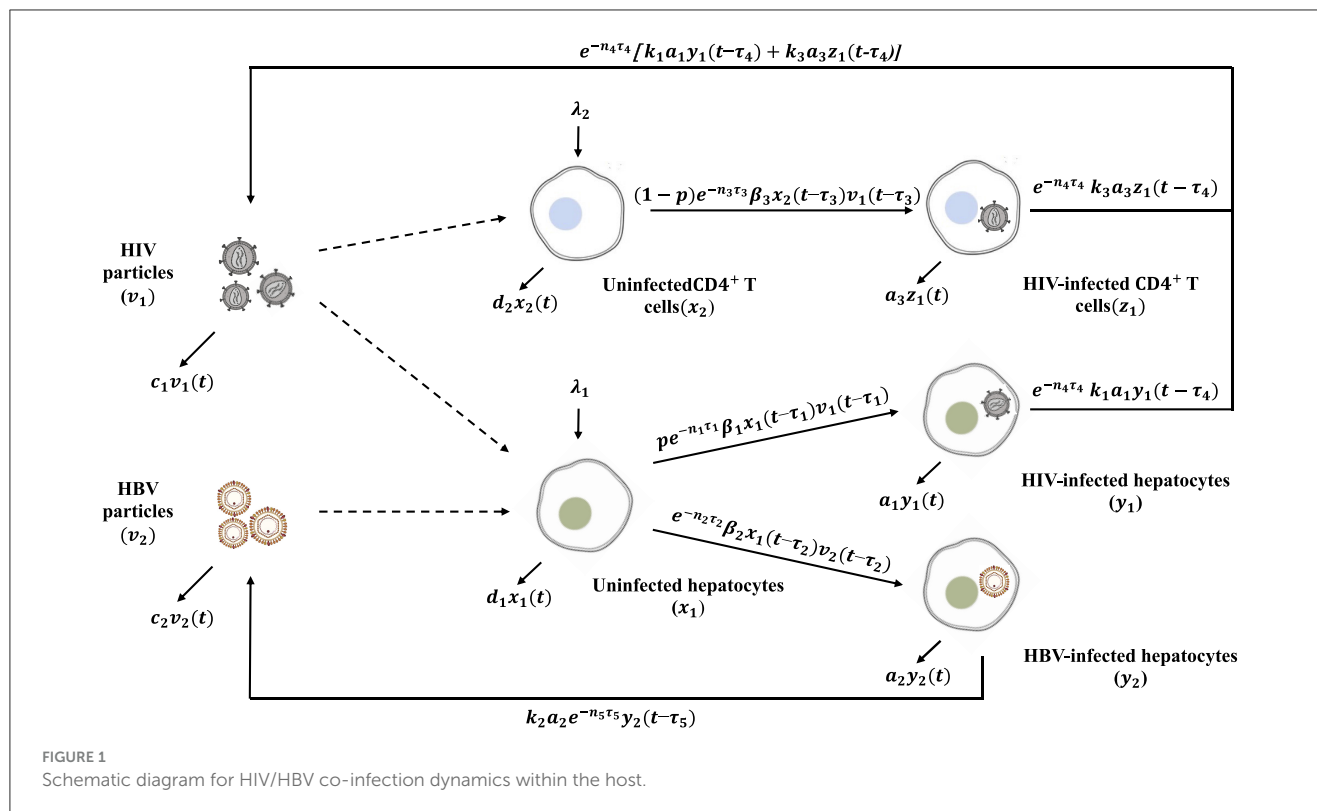
$$\begin{aligned}\dot{x}(t) &= \underbrace{\lambda}_{\text{production of uninfected hepatocytes}} - \underbrace{dx(t)}_{\text{death}} \\ &\quad - \underbrace{\beta_1 x(t) v_1(t)}_{\text{HIV-hepatocytes incidence}} - \underbrace{\beta_2 x(t) v_2(t)}_{\text{HBV-hepatocytes incidence}}, \\ \dot{y}_1(t) &= \underbrace{e^{-n_1 \tau_1} \beta_1 x(t - \tau_1) v_1(t - \tau_1)}_{\text{formation of HIV-infected hepatocytes}} - \underbrace{a_1 y_1(t)}_{\text{death}}, \\ \dot{y}_2(t) &= \underbrace{e^{-n_2 \tau_2} \beta_2 x(t - \tau_2) v_2(t - \tau_2)}_{\text{formation of HBV-infected hepatocytes}} - \underbrace{a_2 y_2(t)}_{\text{death}}, \\ \dot{v}_1(t) &= \underbrace{k_1 a_1 y_1(t)}_{\text{generation of HIV from HIV-infected hepatocytes}} \\ &\quad + \underbrace{m}_{\text{generation of HIV from infected other infected cells}} \\ &\quad - \underbrace{c_1 v_1(t)}_{\text{death}}, \\ \dot{v}_2(t) &= \underbrace{k_2 a_2 y_2(t)}_{\text{generation of HBV from HBV-infected hepatocytes}} \\ &\quad - \underbrace{c_2 v_2(t)}_{\text{death}}.\end{aligned}$$

At time t , the variables $x(t)$, $y_1(t)$, $y_2(t)$, $v_1(t)$, and $v_2(t)$ denotes the concentrations of uninfected hepatocytes, hepatocytes infected with HIV, hepatocytes infected with HBV, free HIV virions, and free HBV virions, respectively. τ_1 and τ_2 denote the respective time delays associated with the development of HIV-infected and HBV-infected hepatocytes. The factor $e^{-n_i \tau_i}$, $i = 1, 2$ represents the probability of survival of infected hepatocytes throughout the delay time $[t - \tau_i, t]$, and $n_i > 0$.

Notably, the model presented in [28] has certain limitations:

- (i) it overlooks the dynamic evolution of both uninfected and HIV-infected CD4⁺ T cell populations, opting instead to assume a fixed rate of HIV production from infected CD4⁺ T cells, thereby ignoring their temporal variation;
- (ii) it does not account for the maturation delay of newly produced virions;
- (iii) Global stability was established exclusively for the infection-free equilibrium.

Limitation (i) was partially resolved in the model proposed by [27], which incorporated the dynamics of CD4⁺ T lymphocyte populations. However, the mathematical analysis in that study was largely confined to establishing the boundedness and positivity of the solutions. In addition, only the infection-free equilibrium was identified and analyzed for local stability, while



a comprehensive investigation of other possible equilibria was not pursued.

This study builds upon and extends the models presented in [27, 28] by addressing key limitations. We explicitly model the dynamics of both uninfected and HIV-infected $CD4^+$ T lymphocytes, replace the assumption of a constant HIV production rate with a more realistic approach, and include a biologically relevant time delay to reflect delays in viral production and virion maturation. A rigorous mathematical analysis, including equilibrium identification and global stability examination, provides deeper insights into the system's long-term dynamics. These findings are supported by numerical simulations and sensitivity analyses that highlight the influence of critical parameters.

The main contributions of this study are:

- **Model enhancement:** Addressing limitations of previous models to better capture HIV-HBV co-infection dynamics.
- **Explicit immune cell dynamics:** Including both uninfected and infected $CD4^+$ T cells, with state-dependent HIV production.
- **Intracellular delay:** Introducing a time delay to represent the lag in viral production and the maturation process.
- **Mathematical analysis:** Identifying equilibria and establishing global stability for a comprehensive understanding.
- **Numerical simulations:** Illustrating biologically relevant scenarios that validate theoretical results.
- **Sensitivity analysis:** Exploring parameter impacts to inform potential control strategies.

2 Model formulation

In this section formulate our proposed model on based on the next Hypotheses:

- (H1): Seven populations are depicted in the model: Uninfected hepatocytes, $x_1(t)$, HIV-infected hepatocytes, $y_1(t)$, HBV-infected hepatocytes, $y_2(t)$, uninfected $CD4^+$ T cells, $x_2(t)$, HIV-infected $CD4^+$ T cells, $z_1(t)$, free HIV, $v_1(t)$, free HBV, $v_2(t)$, where t is the time. Compartments $(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$ die (or clear) at rates $(d_1x_1, a_1y_1, a_2y_2, d_2x_2, a_3z_1, c_1v_1, c_2v_2)$, respectively. The co-dynamics of HIV and HBV are illustrated in the schematic diagram shown in Figure 1.
- (H2): HBV targets uninfected hepatocytes of the liver [9], whereas HIV targets two cell types: uninfected hepatocytes [5, 6] and uninfected $CD4^+$ T cells [8]. When HIV enters the liver, it has a probability (p) of infecting a hepatocyte, and a probability of $1 - p$ of infecting a $CD4^+$ T cell [27].
- (H3): Uninfected hepatocytes are generated at rate λ_1 and are infected via two competing viruses, HIV and HBV, with rates $p\beta_1x_1v_1$ and $\beta_2x_1v_2$, respectively [27] (see Equation 1).
- (H4): HIV-infected and HBV-infected hepatocytes are generated at rates of $p\beta_1x_1v_1$ and $\beta_2x_1v_2$, respectively (see Equations 2, 3).
- (H5): Uninfected $CD4^+$ T cells are generated at rate λ_2 and can be infected by HIV at rate of $(1 - p)\beta_1x_1v_1$ [8, 27] (see Equation 4).
- (H6): HIV-infected $CD4^+$ T cells are formed at rate of $(1 - p)\beta_1x_1v_1$ [27] (see Equation 5).

(H7): HIV particles are produced from two sources, HIV-infected hepatocytes and HIV-infected CD4⁺ T cells at rates of $k_1 a_1 y_1$ and $k_3 a_3 z_1$, respectively [8, 27] (see Equation 6).

(H8): HBV-infected hepatocytes produce HBV particles at a rate $k_2 a_2 y_2$ [9, 27] (see Equation 7).

Based on Hypotheses (H1)-(H8), we formulate an HIV-HBV co-dynamics model with delays as follows:

$$\dot{x}_1(t) = \lambda_1 - d_1 x_1(t) - p \beta_1 x_1(t) v_1(t) - \beta_2 x_1(t) v_2(t), \quad (1)$$

$$\dot{y}_1(t) = p e^{-n_1 \tau_1} \beta_1 x_1(t - \tau_1) v_1(t - \tau_1) - a_1 y_1(t), \quad (2)$$

$$\dot{y}_2(t) = e^{-n_2 \tau_2} \beta_2 x_1(t - \tau_2) v_2(t - \tau_2) - a_2 y_2(t), \quad (3)$$

$$\dot{x}_2(t) = \lambda_2 - d_2 x_2(t) - (1 - p) \beta_3 x_2(t) v_1(t), \quad (4)$$

$$\dot{z}_1(t) = (1 - p) e^{-n_3 \tau_3} \beta_3 x_2(t - \tau_3) v_1(t - \tau_3) - a_3 z_1(t), \quad (5)$$

$$\dot{v}_1(t) = e^{-n_4 \tau_4} [k_1 a_1 y_1(t - \tau_4) + k_3 a_3 z_1(t - \tau_4)] - c_1 v_1(t), \quad (6)$$

$$\dot{v}_2(t) = k_2 a_2 e^{-n_5 \tau_5} y_2(t - \tau_5) - c_2 v_2(t). \quad (7)$$

The model incorporates five distinct time delays:

- The parameters τ_1 , τ_2 , and τ_3 correspond to the delays associated with the development of HIV-infected hepatocytes, HBV-infected hepatocytes and HIV-infected CD4⁺ T cells, respectively [28, 29]. The expression $e^{-n_i \tau_i}$ for $i = 1, 2, 3$, denotes the likelihood that hepatocytes or CD4⁺ T cells survive during the interval $[t - \tau_i, t]$, where $n_i > 0$.
- The delays τ_4 , and τ_5 represent the time required for newly released HIV and HBV to become mature, respectively. Similarly, the term $e^{-n_i \tau_i}$ for $i = 4, 5$ reflects the survival probability of viral particles throughout the corresponding maturation period $[t - \tau_i, t]$, assuming $n_i > 0$.

The initial conditions for model (Equations 1–7) are given as follows:

$$\begin{cases} (x_1, y_1, y_2, x_2, z_1, v_1, v_2)(\theta) = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6, \phi_7)(\theta) \\ \phi_i(\theta) \geq 0, i = 1, 2, \dots, 7, \quad \theta \in [-\tau^m, 0] \end{cases}$$

where $\tau^m = \max\{\tau_1, \tau_2, \dots, \tau_5\}$, $\phi_i \in C([-\tau^m, 0], \mathbb{R}_{\geq 0})$, and $C: [-\tau^m, 0] \rightarrow \mathbb{R}_{\geq 0}$ is the Banach space of continuous functions. The norm is defined as $\|\phi_i\| = \sup_{-\tau^m \leq \theta \leq 0} |\phi_i(\theta)|$ for $\phi_i \in C$, and $i = 1, 2, \dots, 7$. The standard theory of functional differential equations shows that, model (Equations 1–7) with initial conditions (Equation 2) has a unique solution [30, 31].

The model's variables and parameters are defined in Table 1.

3 Biological feasible domain

Let $F_i = e^{-n_i \tau_i}$ for $i = 1, 2, \dots, 5$, $\sigma_1 = \min\{d_1, a_1, a_2\}$ and $\sigma_2 = \min\{d_2, a_3\}$.

Lemma 1. The dynamics (Equations 1–7) with the initial states (Equation 2) admits nonnegative and ultimately bounded solutions.

Proof. Clearly, Equations 1, 4 of model (Equations 1–7) give $\dot{x}_i|_{x_i=0} = \lambda_i > 0$, which implies that $x_i(t) > 0$ for $i = 1, 2$ and all $t \geq 0$. Moreover, for $t \in [0, \tau^m]$ we have

TABLE 1 Variables and parameters description.

Variable	Description
x_1	Uninfected hepatocytes
y_1	HIV-infected hepatocytes
y_2	HBV-infected hepatocytes
x_2	Uninfected CD4 ⁺ T cells
z_1	HIV-infected CD4 ⁺ T cells
v_1	Free HIV
v_2	Free HBV
Parameter	Description
λ_1	Production rate of uninfected hepatocytes, x_1
λ_2	Production rate of uninfected CD4 ⁺ T cells, x_2
β_1	Rate at which HIV targets uninfected hepatocytes (v_1 and x_1)
β_2	Rate at which HBV targets uninfected hepatocytes (v_2 and x_1)
β_3	Rate at which HIV targets uninfected CD4 ⁺ T cells (v_1 and x_2)
d_1	Mortality rate of uninfected hepatocytes
d_2	Mortality rate of uninfected CD4 ⁺ T cells
a_1	Mortality rate of HIV-infected hepatocytes
a_2	Mortality rate of HBV-infected hepatocytes
a_3	Mortality rate of HIV-infected CD4 ⁺ T cells
c_1	Destruction rate of free HIV
c_2	Destruction rate of free HBV
p	Probability that HIV particles infect hepatocytes
$k_i, i = 1, 2, 3$	Average virion output from one infected cell
$\tau_i, i = 1, 2, 3, 4, 5$	Time delay parameters
$n_i, i = 1, 2, 3, 4, 5$	Average lifetime of a compartment i during a delay period

$$y_1(t) = e^{-a_1 t} \phi_2(0) + p \beta_1 F_1 \int_0^t e^{-a_1(t-\theta)} x_1(\theta - \tau_1) v_1(\theta - \tau_1) d\theta,$$

$$y_2(t) = e^{-a_2 t} \phi_3(0) + \beta_2 F_2 \int_0^t e^{-a_2(t-\theta)} x_1(\theta - \tau_2) v_2(\theta - \tau_2) d\theta,$$

$$z_1(t) = e^{-a_3 t} \phi_5(0) + (1 - p) \beta_3 F_3 \int_0^t e^{-a_3(t-\theta)} x_2(\theta - \tau_3) v_1(\theta - \tau_3) d\theta,$$

$$v_1(t) = e^{-c_1 t} \phi_6(0) + F_4 \int_0^t e^{-c_1(t-\theta)} [k_1 a_1 y_1(\theta - \tau_4) + k_3 a_3 y_3(\theta - \tau_4)] d\theta,$$

$$v_2(t) = e^{-c_2 t} \phi_7(0) + k_2 a_2 F_5 \int_0^t e^{-c_2(t-\theta)} y_2(\theta - \tau_5) d\theta,$$

which gives $(x_1, y_1, y_2, x_2, z_1, v_1, v_2)(t) \geq 0$. Hence, by recursive argumentation, we obtain that $(x_1, y_1, y_2, x_2, z_1, v_1, v_2)(t) \geq 0$ for any $t \geq 0$.

Next we prove the ultimately boundedness of the model's solution $(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$. From Equation 1, we have $\limsup_{t \rightarrow \infty} x_1(t) \leq \Gamma_1$, where $\Gamma_1 = \frac{\lambda_1}{d_1}$. Concerning, $y_1(t)$ and $y_2(t)$, we define

$$\psi_1(t) = x_1(t) + \frac{1}{F_1} y_1(t + \tau_1) + \frac{1}{F_2} y_2(t + \tau_2).$$

Then, we get

$$\begin{aligned}\dot{\psi}_1(t) &= \dot{x}_1(t) + \frac{1}{F_1}y_1(t + \tau_1) + \frac{1}{F_2}y_2(t + \tau_2) \\ &= \lambda_1 - d_1x_1(t) - p\beta_1x_1(t)v_1(t) - \beta_2x_1(t)v_2(t) \\ &\quad + p\beta_1x_1(t)v_1(t) - \frac{1}{F_1}a_1y_1(t + \tau_1) + \beta_2x_1(t)v_2(t) - \frac{1}{F_2}a_2y_2(t + \tau_2) \\ &= \lambda_1 - d_1x_1(t) - \frac{1}{F_1}a_1y_1(t + \tau_1) - \frac{1}{F_2}a_2y_2(t + \tau_2) \\ &\leq \lambda_1 - \sigma_1\psi_1(t).\end{aligned}$$

Thus $\limsup_{t \rightarrow \infty} \psi_1(t) \leq \Gamma_2$, and hence $\limsup_{t \rightarrow \infty} y_1(t) \leq \Gamma_2$ and $\limsup_{t \rightarrow \infty} y_2(t) \leq \Gamma_2$, where $\Gamma_2 = \frac{\lambda_1}{\sigma_1}$. From Equation 4, we have $\limsup_{t \rightarrow \infty} x_2(t) \leq \Gamma_3$, where $\Gamma_3 = \frac{\lambda_2}{d_2}$. Define

$$\psi_2(t) = x_2(t) + \frac{1}{F_3}z_1(t + \tau_3).$$

Then, we get

$$\begin{aligned}\dot{\psi}_2(t) &= \dot{x}_2(t) + \frac{1}{F_3}\dot{z}_1(t + \tau_3) \\ &= \lambda_2 - d_2x_2(t) - (1-p)\beta_3x_2(t)v_1(t) + (1-p)\beta_3x_2(t)v_1(t) \\ &\quad - \frac{a_3}{F_3}z_1(t + \tau_3) \\ &= \lambda_2 - d_2x_2(t) - \frac{a_3}{F_3}z_1(t + \tau_3) \\ &\leq \lambda_2 - \sigma_2\psi_2(t).\end{aligned}$$

This gives $\limsup_{t \rightarrow \infty} \psi_2(t) \leq \Gamma_4$, and hence $\limsup_{t \rightarrow \infty} z_1(t) \leq \Gamma_4$ where $\Gamma_4 = \frac{\lambda_2}{\sigma_2}$.

Note that

$$\begin{aligned}\dot{v}_1(t) &= F_4[k_1a_1y_1(t - \tau_4) + k_3a_3z_1(t - \tau_4)] - c_1v_1(t) \\ &\leq F_4[k_1a_1\Gamma_2 + k_3a_3\Gamma_4] - c_1v_1(t) \\ &\leq k_1a_1\Gamma_2 + k_3a_3\Gamma_4 - c_1v_1(t).\end{aligned}$$

Consequently, $\limsup_{t \rightarrow \infty} v_1(t) \leq \Gamma_5$, where $\Gamma_5 = \frac{1}{c_1}[k_1a_1\Gamma_2 + k_3a_3\Gamma_4]$. Similarly, we have

$$\dot{v}_2(t) = F_5k_2a_2y_2(t - \tau_5) - c_2v_2(t) \leq F_5k_2a_2\Gamma_2 - c_2v_2(t) \leq k_2a_2\Gamma_2 - c_2v_2(t).$$

This yields $\limsup_{t \rightarrow \infty} v_2(t) \leq \Gamma_6$, where $\Gamma_6 = \frac{k_2a_2\Gamma_2}{c_2}$.

Based on Lemma 1, one can show

$$\Delta = \{(x_1, y_1, y_2, x_2, z_1, v_1, v_2) \in C_{\geq 0}^7 : \|x_1\| \leq \Gamma_1, \|y_1\| \leq \Gamma_2, \|y_2\| \leq \Gamma_2, \|x_2\| \leq \Gamma_3, \|z_1\| \leq \Gamma_4, \|v_1\| \leq \Gamma_5, \|v_2\| \leq \Gamma_6\},$$

is positively invariant w.r.t. system (Equation 1–7).

3.1 Equilibria and thresholds

This section analyzes the existence of equilibria for the proposed model. To compute the basic reproduction number, $\mathcal{R}_C$, associated with the HIV-HBV co-infection dynamics, we utilize the next-generation matrix approach as described by [32] (refer to the Appendix for details). The expression obtained for $\mathcal{R}_C$:

$$\mathcal{R}_C = \max\{\mathcal{R}_0, \mathcal{R}_1\},$$

where $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$, and

$$\begin{aligned}\mathcal{R}_{01} &= \frac{k_1p\beta_1\lambda_1F_1F_4}{c_1d_1}, \quad \mathcal{R}_{02} = \frac{k_3(1-p)\beta_3\lambda_2F_3F_4}{c_1d_2}, \text{ and} \\ \mathcal{R}_1 &= \frac{k_2\beta_2\lambda_1F_2F_5}{c_2d_1}.\end{aligned}$$

Here, $\mathcal{R}_0$ represents the basic reproduction number for an HIV infection in isolation, while $\mathcal{R}_1$ corresponds to that of HBV infection alone (see Appendix for derivation). Let us define $x_1^0 = \frac{\lambda_1}{d_1}$ and $x_2^0 = \frac{\lambda_2}{d_2}$ and let the following two indices be denoted by $\mathcal{R}_i > 0, i = 2, 3$ and given by

$$\mathcal{R}_2 = \frac{(1-p)k_2\beta_2k_3\beta_3\lambda_2F_2F_3F_5}{k_1p\beta_1c_2d_2F_1\left(\frac{\mathcal{R}_1}{\mathcal{R}_{01}} - 1\right)}, \text{ and } \mathcal{R}_3 = \frac{d_1(1-p)\beta_3}{p\beta_1d_2}\left(\frac{\mathcal{R}_1 - 1}{\mathcal{R}_2 - 1}\right).$$

Therefore, we obtain the following main result regarding the existence of the equilibria of the system (Equations 1–7).

Lemma 2.

- The system (Equation 1–7) admits an infection-free equilibrium denoted by $\mathcal{E}_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$.
- If $\mathcal{R}_0 > 1$, then the system admits an HIV-only infection equilibrium denoted by

$$\bar{\mathcal{E}} = (\bar{x}_1, \bar{y}_1, 0, \bar{x}_2, \bar{z}_1, \bar{v}_1, 0).$$

- When $\mathcal{R}_1 > 1$, the system admits an HBV-only infection equilibrium denoted by

$$\tilde{\mathcal{E}} = \left(\frac{x_1^0}{\mathcal{R}_1}, 0, \frac{c_2d_1}{a_2k_2\beta_2F_5}(\mathcal{R}_1 - 1), x_2^0, 0, 0, \frac{d_1}{\beta_2}(\mathcal{R}_1 - 1) \right).$$

- If $\mathcal{R}_1 > \mathcal{R}_{01}$, $\mathcal{R}_2 > 1$, and $\mathcal{R}_3 > 1$, the system possesses an HIV and HBV co-infection equilibrium denoted by

$$\mathcal{E}^* = (x_1^*, y_1^*, y_2^*, x_2^*, z_1^*, v_1^*, v_2^*).$$

Proof. The equilibrium points are normally given when the time-derivatives are all set to zero, so that here we have the following:

$$\begin{cases} 0 = \lambda_1 - d_1x_1 - p\beta_1x_1v_1 - \beta_2x_1v_2, \\ 0 = p\beta_1F_1x_1v_1 - a_1y_1, \\ 0 = \beta_2F_2x_1v_2 - a_2y_2, \\ 0 = \lambda_2 - d_2x_2 - (1-p)\beta_3x_2v_1, \\ 0 = (1-p)\beta_3F_3x_2v_1 - a_3z_1, \\ 0 = k_1a_1F_4y_1 + k_3a_3F_4z_1 - c_1v_1, \\ 0 = k_2a_2F_5y_2 - c_2v_2. \end{cases}$$

We have the following cases:

1. If $v_1 = v_2 = 0$, the model has infection-free equilibrium $\mathcal{E}_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$.
2. If $v_1 \neq 0$ and $v_2 = 0$, we obtain

$$y_2 = 0, x_1 = \frac{\lambda_1}{d_1 + p\beta_1 v_1}, x_2 = \frac{\lambda_2}{d_2 + (1-p)\beta_3 v_1},$$

$$y_1 = \frac{p\beta_1 \lambda_1 F_1 v_1}{a_1(d_1 + p\beta_1 v_1)}, z_1 = \frac{(1-p)\beta_3 \lambda_2 F_3 v_1}{a_3(d_2 + (1-p)\beta_3 v_1)},$$

and v_1 satisfies the following equation

$$\frac{k_1 p \beta_1 \lambda_1 F_1 F_4}{d_1 + p\beta_1 v_1} + \frac{k_3(1-p)\beta_3 \lambda_2 F_3 F_4}{d_2 + (1-p)\beta_3 v_1} - c_1 = 0.$$

Define a function f by

$$f(v_1) = \frac{k_1 p \beta_1 \lambda_1 F_1 F_4}{d_1 + p\beta_1 v_1} + \frac{k_3(1-p)\beta_3 \lambda_2 F_3 F_4}{d_2 + (1-p)\beta_3 v_1} - c_1,$$

Then we have

$$f(0) = \frac{k_1 p \beta_1 \lambda_1 F_1 F_4}{d_1} + \frac{k_3(1-p)\beta_3 \lambda_2 F_3 F_4}{d_2} - c_1$$

$$= c_1 \left(\frac{k_1 p \beta_1 \lambda_1 F_1 F_4}{c_1 d_1} + \frac{k_3(1-p)\beta_3 \lambda_2 F_3 F_4}{c_1 d_2} - 1 \right)$$

$$= c_1 (\mathcal{R}_{01} + \mathcal{R}_{02} - 1) = c_1 (\mathcal{R}_0 - 1).$$

Thus, $f(0) > 0$ when $\mathcal{R}_0 > 1$. In fact, $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ denote, respectively, the total number of newly HIV-infected hepatocytes and HIV-infected CD4⁺ T cells generated from a single HIV-infected hepatocyte and CD4⁺ T cell at the onset of HIV infection. The parameter $\mathcal{R}_0$ represents the basic reproductive number for a single HIV infection. We have $f(v_1) \rightarrow -c_1 < 0$ whenever $v_1 \rightarrow \infty$. Moreover,

$$f'(v_1) = - \left(\frac{k_1 p^2 \beta_1^2 \lambda_1 F_1 F_4}{(d_1 + p\beta_1 v_1)^2} + \frac{k_3(1-p)^2 \beta_3^2 \lambda_2 F_3 F_4}{(d_2 + (1-p)\beta_3 v_1)^2} \right) < 0.$$

Thus, f is strictly decreasing, and hence, if $\mathcal{R}_0 > 1$, there exists a unique $\bar{v}_1 \in (0, \infty)$ satisfying $f(\bar{v}_1) = 0$. Hence,

$$\bar{x}_1 = \frac{\lambda_1}{d_1 + p\beta_1 \bar{v}_1} > 0, \bar{y}_1 = \frac{p\beta_1 \lambda_1 \bar{v}_1 F_1}{a_1(d_1 + p\beta_1 \bar{v}_1)} > 0, \bar{x}_2 = \frac{\lambda_2}{d_2 + (1-p)\beta_3 \bar{v}_1} > 0, \text{ and } \bar{z}_1 = \frac{(1-p)\beta_3 \lambda_2 \bar{v}_1 F_3}{a_3(d_2 + (1-p)\beta_3 \bar{v}_1)} > 0,$$

where $\bar{v}_1$ satisfies the following quadratic equation:

$$-k_1 p \beta_1 \lambda_1 F_1 F_4 (d_2 + (1-p)\beta_3 \bar{v}_1) - k_3(1-p)\beta_3 \lambda_2 F_3 F_4 (d_1) + p\beta_1 \bar{v}_1 + c_1(d_1 + p\beta_1 \bar{v}_1)(d_2 + (1-p)\beta_3 \bar{v}_1) = 0,$$

which takes the form

$$a\bar{v}_1^2 + b\bar{v}_1 + c = 0, \quad (8)$$

where

$$a = c_1 p \beta_1 (1-p)\beta_3 > 0,$$

$$b = c_1(p\beta_1 d_2 + (1-p)\beta_3 d_1) - p\beta_1(1-p)\beta_3 F_4(k_1 \lambda_1 F_1 + k_3 \lambda_2 F_3),$$

$$c = c_1 d_1 d_2 - k_1 p \beta_1 \lambda_1 d_2 F_1 F_4 - k_3(1-p)\beta_3 \lambda_2 d_1 F_3 F_4$$

$$= c_1 d_1 d_2 \left(1 - \frac{k_1 p \beta_1 \lambda_1 F_1 F_4}{c_1 d_1} - \frac{k_3(1-p)\beta_3 \lambda_2 F_3 F_4}{c_1 d_2} \right)$$

$$= c_1 d_1 d_2 (1 - \mathcal{R}_0).$$

Clearly, $c < 0$ if $\mathcal{R}_0 > 1$. Equation 8 has a positive solution

$$\bar{v}_1 = \frac{-b + \sqrt{b^2 - 4ac}}{2a} > 0.$$

We obtain an HIV-only infection equilibrium

$$\bar{\mathcal{E}} = (\bar{x}_1, \bar{y}_1, 0, \bar{x}_2, \bar{z}_1, \bar{v}_1, 0).$$

This implies that $\bar{\mathcal{E}}$ exists when $\mathcal{R}_0 > 1$.

3. If $v_1 = 0$ and $v_2 \neq 0$, we obtain an HBV-only infection equilibrium

$$\tilde{\mathcal{E}} = (\tilde{x}_1, 0, \tilde{y}_2, \tilde{x}_2, 0, 0, \tilde{v}_2) = \left(\frac{x_1^0}{\mathcal{R}_1}, 0, \frac{c_2 d_1}{a_2 k_2 \beta_2 F_5} (\mathcal{R}_1 - 1), x_2^0, 0, 0, \frac{d_1}{\beta_2} (\mathcal{R}_1 - 1) \right).$$

Clearly, $\tilde{\mathcal{E}}$ exists when $\mathcal{R}_1 > 1$.

4. If $v_1 \neq 0$ and $v_2 \neq 0$, we obtain an HIV and HBV co-infection equilibrium

$$\mathcal{E}^* = (x_1^*, y_1^*, y_2^*, x_2^*, z_1^*, v_1^*, v_2^*)$$

where

$$x_1^* = \frac{x_1^0}{\mathcal{R}_1}, y_1^* = \frac{c_2 d_2 p \beta_1 F_1}{k_2 \beta_2 (1-p)\beta_3 a_1 F_2 F_5} (\mathcal{R}_2 - 1),$$

$$y_2^* = \frac{c_2 d_2 p \beta_1}{(1-p)\beta_2 \beta_3 a_2 k_2 F_5} (\mathcal{R}_2 - 1) (\mathcal{R}_3 - 1),$$

$$x_2^* = \frac{k_1 p \beta_1 c_2 F_1}{(1-p)k_2 \beta_2 k_3 \beta_3 F_2 F_3 F_5} \left(\frac{\mathcal{R}_1}{\mathcal{R}_{01}} - 1 \right),$$

$$z_1^* = \frac{k_1 p \beta_1 c_2 d_2 F_1}{a_3(1-p)k_2 \beta_2 k_3 \beta_3 F_2 F_5} \left(\frac{\mathcal{R}_1}{\mathcal{R}_{01}} - 1 \right) (\mathcal{R}_2 - 1),$$

$$v_1^* = \frac{d_2}{(1-p)\beta_3} (\mathcal{R}_2 - 1), v_2^* = \frac{p\beta_1 d_2}{\beta_2(1-p)\beta_3} (\mathcal{R}_2 - 1) (\mathcal{R}_3 - 1).$$

It is evident that $\mathcal{E}^*$ exists if $\mathcal{R}_1 > \mathcal{R}_{01}$, $\mathcal{R}_2 > 1$, and $\mathcal{R}_3 > 1$. This equilibrium represents the coexistence of HIV and HBV infections.

4 Global stability

The global asymptotic stability of all equilibrium points in the system (Equations 1–7) is investigated using Lyapunov's direct method in this section. The development of Lyapunov functions is based on the approach outlined in [33]. Let $\mathcal{F}$ represent the candidate Lyapunov function, and let Ω' denote the largest invariant subset of $\Omega = \left\{ (x_1, y_1, y_2, x_2, z_1, v_1, v_2) : \frac{d\mathcal{F}}{dt} = 0 \right\}$. Consider the function $\Phi(X) = X - \ln X - 1$. Let us denote by $(x_1, y_1, y_2, x_2, z_1, v_1, v_2) = (x_1, y_1, y_2, x_2, z_1, v_1, v_2)(t)$, and $(x_1^\tau, y_1^\tau, y_2^\tau, x_2^\tau, z_1^\tau, v_1^\tau, v_2^\tau) = (x_1, y_1, y_2, x_2, z_1, v_1, v_2)(t - \tau)$.

Theorem 1. The infection-free equilibrium $\mathcal{E}_0$ is globally asymptotically stable (GAS) when $\mathcal{R}_C \leq 1$.

Proof. Consider $\mathcal{F}_0(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$

$$\begin{aligned}\mathcal{F}_0 = & x_1^0 \Phi \left(\frac{x_1}{x_1^0} \right) + \frac{1}{F_1} y_1 + \frac{1}{F_2} y_2 + \frac{F_3}{F_1} \frac{k_3}{k_1} x_2^0 \Phi \left(\frac{x_2}{x_2^0} \right) + \frac{1}{F_1} \frac{k_3}{k_1} z_1 \\ & + \frac{1}{F_1 F_4 k_1} v_1 + \frac{1}{F_2 F_5 k_2} v_2 + p \beta_1 \int_{t-\tau_1}^t x_1(\theta) v_1(\theta) d\theta \\ & + \beta_2 \int_{t-\tau_2}^t x_1(\theta) v_2(\theta) d\theta \\ & + (1-p) \beta_3 \frac{k_3}{k_1} \frac{F_3}{F_1} \int_{t-\tau_3}^t x_2(\theta) v_1(\theta) d\theta \\ & + \frac{1}{F_1 k_1} \int_{t-\tau_4}^t (k_1 a_1 y_1(\theta) + k_3 a_3 z_1(\theta)) d\theta \\ & + \frac{1}{F_2} a_2 \int_{t-\tau_5}^t y_2(\theta) d\theta.\end{aligned}$$

Calculating $\frac{d\mathcal{F}_0}{dt}$ along the solution of system (Equations 1–7) as

$$\begin{aligned}\frac{d\mathcal{F}_0}{dt} = & \left(1 - \frac{x_1^0}{x_1} \right) \dot{x}_1 + \frac{1}{F_1} \dot{y}_1 + \frac{1}{F_2} \dot{y}_2 + \frac{F_3}{F_1} \frac{k_3}{k_1} \left(1 - \frac{x_2^0}{x_2} \right) \dot{x}_2 \\ & + \frac{1}{F_1} \frac{k_3}{k_1} \dot{z}_1 + \frac{1}{k_1 F_1 F_4} \dot{v}_1 + \frac{1}{k_2 F_2 F_5} \dot{v}_2 \\ & + p \beta_1 (x_1 v_1 - x_1^{\tau_1} v_1^{\tau_1}) + \beta_2 (x_1 v_2 - x_1^{\tau_2} v_2^{\tau_2}) \\ & + (1-p) \beta_3 \frac{k_3}{k_1} \frac{F_3}{F_1} (x_2 v_1 - x_2^{\tau_3} v_1^{\tau_3}) \\ & + \frac{1}{k_1 F_1} (k_1 a_1 y_1 + k_3 a_3 z_1 - k_1 a_1 y_1^{\tau_4} - k_3 a_3 z_1^{\tau_4}) \\ & + \frac{1}{F_2} a_2 (y_2 - y_2^{\tau_5}).\end{aligned}$$

From Equations 1–7 we obtain

$$\begin{aligned}\frac{d\mathcal{F}_0}{dt} = & \left(1 - \frac{x_1^0}{x_1} \right) (\lambda_1 - d_1 x_1 - p \beta_1 x_1 v_1 - \beta_2 x_1 v_2) + p \beta_1 x_1^{\tau_1} v_1^{\tau_1} \\ & - \frac{1}{F_1} a_1 y_1 + \beta_2 x_1^{\tau_2} v_2^{\tau_2} - \frac{1}{F_2} a_2 y_2 + \frac{F_3}{F_1} \frac{k_3}{k_1} \left(1 - \frac{x_2^0}{x_2} \right) \\ & (\lambda_2 - d_2 x_2 - (1-p) \beta_3 x_2 v_1) \\ & + \frac{1}{F_1} \frac{k_3}{k_1} ((1-p) F_3 \beta_3 x_2^{\tau_3} v_1^{\tau_3} - a_3 z_1) + \frac{1}{k_1 F_1 F_4} \\ & [F_4 (k_1 a_1 y_1^{\tau_4} + k_3 a_3 z_1^{\tau_4}) - c_1 v_1] \\ & + \frac{1}{k_2 F_2 F_5} (k_2 a_2 F_5 y_2^{\tau_5} - c_2 v_2) \\ & + p \beta_1 (x_1 v_1 - x_1^{\tau_1} v_1^{\tau_1}) + \beta_2 (x_1 v_2 - x_1^{\tau_2} v_2^{\tau_2}) \\ & + (1-p) \beta_3 \frac{k_3}{k_1} \frac{F_3}{F_1} (x_2 v_1 - x_2^{\tau_3} v_1^{\tau_3}) \\ & + \frac{1}{k_1 F_1} (k_1 a_1 y_1 + k_3 a_3 z_1 - k_1 a_1 y_1^{\tau_4} - k_3 a_3 z_1^{\tau_4}) \\ & + \frac{1}{F_2} a_2 (y_2 - y_2^{\tau_5}).\end{aligned}$$

Collecting terms as

$$\begin{aligned}\frac{d\mathcal{F}_0}{dt} = & \left(1 - \frac{x_1^0}{x_1} \right) (\lambda_1 - d_1 x_1) + p \beta_1 x_1^0 v_1 + \beta_2 x_1^0 v_2 \\ & + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{x_2^0}{x_2} \right) (\lambda_2 - d_2 x_2) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 x_2^0 v_1 \\ & - \frac{c_1}{k_1 F_1 F_4} v_1 - \frac{c_2}{k_2 F_2 F_5} v_2.\end{aligned}$$

Substituting $\lambda_1 = d_1 x_1^0$ and $\lambda_2 = d_2 x_2^0$, we obtain

$$\begin{aligned}\frac{d\mathcal{F}_0}{dt} = & -\frac{d_1}{x_1} (x_1 - x_1^0)^2 - \frac{F_3 k_3 d_2}{F_1 k_1 x_2} (x_2 - x_2^0)^2 \\ & + \frac{c_1}{F_1 F_4 k_1} \left(F_1 F_4 \frac{p \beta_1 k_1}{c_1} x_1^0 + F_3 F_4 \frac{(1-p) \beta_3 k_3}{c_1} x_2^0 - 1 \right) v_1 \\ & + \frac{c_2}{F_2 F_5 k_2} \left(F_2 F_5 \frac{\beta_2 k_2}{c_2} x_1^0 - 1 \right) v_2 \\ = & -\frac{d_1}{x_1} (x_1 - x_1^0)^2 - \frac{F_3 k_3 d_2}{F_1 k_1 x_2} (x_2 - x_2^0)^2 \\ & + \frac{c_1}{F_1 F_4 k_1} (\mathcal{R}_0 - 1) v_1 + \frac{c_2}{F_2 F_5 k_2} (\mathcal{R}_1 - 1) v_2.\end{aligned}$$

Therefore, for all $x_1, y_1, y_2, x_2, z_1, v_1, v_2 > 0$ we have $\frac{d\mathcal{F}_0}{dt} \leq 0$

when $\mathcal{R}_C \leq 1$. Moreover, $\frac{d\mathcal{F}_0}{dt} = 0$ when $x_1 = x_1^0$, $x_2 = x_2^0$, $(\mathcal{R}_0 - 1)v_1 = 0$, and $(\mathcal{R}_1 - 1)v_2 = 0$. According to [30], solutions of system (Equation 1–7) asymptotically approach the set Ω'_0 , which consists of elements satisfying $x_1(t) = x_1^0$, $x_2(t) = x_2^0$ and

$$(\mathcal{R}_0 - 1)v_1 = 0, \quad (9)$$

$$(\mathcal{R}_1 - 1)v_2 = 0. \quad (10)$$

Let us consider four cases:

- If $\mathcal{R}_C < 1$ then $\mathcal{R}_0 < 1$ and $\mathcal{R}_1 < 1$ and from Equations 9, 10, we obtain $v_1 = v_2 = 0$. Since Ω'_0 is invariant, we obtain $\dot{v}_1(t) = \dot{v}_2(t) = 0$. From Equations 6, 7, we have

$$0 = \dot{v}_1 = F_4 k_1 a_1 y_1^{\tau_4} + F_4 k_3 a_3 z_1^{\tau_4} \Rightarrow y_1(t) = z_1(t) = 0, \quad \forall t \geq 0, \quad (11)$$

and

$$0 = \dot{v}_2 = F_5 k_2 a_2 y_2^{\tau_5} \Rightarrow y_2(t) = 0, \quad \forall t \geq 0. \quad (12)$$

Hence, $\Omega'_0 = \{\mathcal{E}_0\}$.

- If $\mathcal{R}_0 = \mathcal{R}_1 = 1$, we have $x_1 = x_1^0$, $x_2 = x_2^0$ then $\dot{x}_1(t) = \dot{x}_2(t) = 0$. From Equations 1, 4, we have

$$\lambda_2 - d_2 x_2^0 - (1-p) \beta_3 x_2^0 v_1 = 0 \Rightarrow v_1(t) = 0, \quad \forall t \geq 0. \quad (13)$$

$$\lambda_1 - d_1 x_1^0 - p \beta_1 x_1^0 v_1 - \beta_2 x_1^0 v_2 = 0 \Rightarrow v_2(t) = 0, \quad \forall t \geq 0, \quad (14)$$

Equations 11, 12 imply $y_1(t) = z_1(t) = y_2(t) = 0, \forall t \geq 0$. Hence, $\Omega'_0 = \{\mathcal{E}_0\}$.

- If $\mathcal{R}_0 < 1$ and $\mathcal{R}_1 = 1$ then $v_1 = 0$ and thus Equation 14 gives $v_2(t) = 0, \forall t \geq 0$ and from Equations 11, 12, we obtain $y_1 = z_1 = y_2 = 0$. Hence, $\Omega'_0 = \{\mathcal{E}_0\}$.
- Similarly, if $\mathcal{R}_0 = 1$ and $\mathcal{R}_1 < 1$ then $v_2 = 0$ and thus Equation 13 provides $v_1(t) = 0, \forall t \geq 0$. From Equations 11, 12, we obtain $y_1 = z_1 = y_2 = 0$. Hence, $\Omega'_0 = \{\mathcal{E}_0\}$.

Lyapunov-LaSalle asymptotic stability theorem [34–36] reveals that $\mathcal{E}_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$ is GAS when $\mathcal{R}_C \leq 1$.

Theorem 2. If the HIV-only infection equilibrium $\bar{\mathcal{E}}$ exists ($\mathcal{R}_0 > 1$) then it is GAS under the condition $\mathcal{R}_1 \leq 1 + \frac{p \beta_1 v_1}{d_1}$.

Proof. Define a function $\bar{\mathcal{F}}(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$

$$\begin{aligned}\bar{\mathcal{F}} = & \bar{x}_1 \Phi\left(\frac{x_1}{\bar{x}_1}\right) + \frac{1}{F_1} \bar{y}_1 \Phi\left(\frac{y_1}{\bar{y}_1}\right) + \frac{1}{F_2} y_2 + \frac{F_3}{F_1} \frac{k_3}{k_1} \bar{x}_2 \Phi\left(\frac{x_2}{\bar{x}_2}\right) \\ & + \frac{1}{F_1} \frac{k_3}{k_1} \bar{z}_1 \Phi\left(\frac{z_1}{\bar{z}_1}\right) + \frac{1}{k_1 F_1 F_4} \bar{v}_1 \Phi\left(\frac{v_1}{\bar{v}_1}\right) + \frac{1}{k_2 F_2 F_5} v_2 + p \beta_1 \bar{x}_1 \bar{v}_1 \int_{t-\tau_1}^t \Phi\left(\frac{x_1(\theta) v_1(\theta)}{\bar{x}_1 \bar{v}_1}\right) d\theta \\ & + \beta_2 \int_{t-\tau_2}^t x_1(\theta) v_2(\theta) d\theta + (1-p) \beta_3 \frac{k_3}{k_1} \frac{F_3}{F_1} \bar{x}_2 \bar{v}_1 \int_{t-\tau_3}^t \Phi\left(\frac{x_2(\theta) v_1(\theta)}{\bar{x}_2 \bar{v}_1}\right) d\theta \\ & + \frac{1}{k_1 F_1} \int_{t-\tau_4}^t \left(k_1 a_1 \bar{y}_1 \Phi\left(\frac{y_1(\theta)}{\bar{y}_1}\right) + k_3 a_3 \bar{z}_1 \Phi\left(\frac{z_1(\theta)}{\bar{z}_1}\right) \right) d\theta + \frac{1}{F_2} a_2 \int_{t-\tau_5}^t y_2(\theta) d\theta.\end{aligned}$$

We calculate $\frac{d\bar{\mathcal{F}}}{dt}$ as follows:

$$\begin{aligned}\frac{d\bar{\mathcal{F}}}{dt} = & \left(1 - \frac{\bar{x}_1}{x_1}\right) (\lambda_1 - d_1 x_1 - p \beta_1 x_1 v_1 - \beta_2 x_1 v_2) + \frac{1}{F_1} \left(1 - \frac{\bar{y}_1}{y_1}\right) (p \beta_1 F_1 x_1^{\tau_1} v_1^{\tau_1} - a_1 y_1) \\ & + \frac{1}{F_2} (F_2 \beta_2 x_1^{\tau_2} v_2^{\tau_2} - a_2 y_2) + \frac{F_3}{F_1} \frac{k_3}{k_1} \left(1 - \frac{\bar{x}_2}{x_2}\right) (\lambda_2 - d_2 x_2 - (1-p) \beta_3 x_2 v_1) \\ & + \frac{1}{F_1} \frac{k_3}{k_1} \left(1 - \frac{\bar{z}_1}{z_1}\right) ((1-p) \beta_3 F_3 x_2^{\tau_3} v_1^{\tau_3} - a_3 z_1) + \frac{1}{k_1 F_1 F_4} \left(1 - \frac{\bar{v}_1}{v_1}\right) (F_4 k_1 a_1 y_1^{\tau_4} + F_4 k_3 a_3 z_1^{\tau_4} - c_1 v_1) \\ & + \frac{1}{k_2 F_2 F_5} (F_5 k_2 a_2 y_2^{\tau_5} - c_2 v_2) + p \beta_1 \bar{x}_1 \bar{v}_1 \left(\frac{x_1 v_1}{\bar{x}_1 \bar{v}_1} - \frac{x_1^{\tau_1} v_1^{\tau_1}}{\bar{x}_1 \bar{v}_1} + \ln\left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1}\right) \right) \\ & + \beta_2 (x_1 v_2 - x_1^{\tau_2} v_2^{\tau_2}) + (1-p) \beta_3 \frac{k_3}{k_1} \frac{F_3}{F_1} \bar{x}_2 \bar{v}_1 \left(\frac{x_2 v_1}{\bar{x}_2 \bar{v}_1} - \frac{x_2^{\tau_3} v_1^{\tau_3}}{\bar{x}_2 \bar{v}_1} + \ln\left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1}\right) \right) \\ & + \frac{1}{k_1 F_1} \left[k_1 a_1 \bar{y}_1 \left(\frac{y_1}{\bar{y}_1} - \frac{y_1^{\tau_4}}{\bar{y}_1} + \ln\left(\frac{y_1^{\tau_4}}{y_1}\right) \right) + k_3 a_3 \bar{z}_1 \left(\frac{z_1}{\bar{z}_1} - \frac{z_1^{\tau_4}}{\bar{z}_1} + \ln\left(\frac{z_1^{\tau_4}}{z_1}\right) \right) \right] + \frac{1}{F_2} a_2 (y_2 - y_2^{\tau_5}).\end{aligned}$$

Collecting terms, we get

$$\begin{aligned}\frac{d\bar{\mathcal{F}}}{dt} = & \left(1 - \frac{\bar{x}_1}{x_1}\right) (\lambda_1 - d_1 x_1) + p \beta_1 \bar{x}_1 v_1 + \beta_2 \bar{x}_1 v_2 - p \beta_1 \frac{\bar{y}_1}{y_1} x_1^{\tau_1} v_1^{\tau_1} + \frac{a_1}{F_1} \bar{y}_1 \\ & + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{\bar{x}_2}{x_2}\right) (\lambda_2 - d_2 x_2) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 v_1 - \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \frac{\bar{z}_1}{z_1} x_2^{\tau_3} v_1^{\tau_3} \\ & + \frac{a_3 k_3}{F_1 k_1} \bar{z}_1 - \frac{a_1}{F_1} \frac{\bar{v}_1}{v_1} y_1^{\tau_4} - \frac{a_3 k_3}{F_1 k_1} \frac{\bar{v}_1}{v_1} z_1^{\tau_4} + \frac{c_1}{k_1 F_1 F_4} \bar{v}_1 - \frac{c_1}{k_1 F_1 F_4} v_1 - \frac{c_2}{k_2 F_2 F_5} v_2 \\ & + p \beta_1 \bar{x}_1 \bar{v}_1 \ln\left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1}\right) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \ln\left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1}\right) + \frac{a_1}{F_1} \bar{y}_1 \ln\left(\frac{y_1^{\tau_4}}{y_1}\right) + \frac{k_3 a_3}{k_1 F_1} \bar{z}_1 \ln\left(\frac{z_1^{\tau_4}}{z_1}\right).\end{aligned}$$

By using the equilibrium conditions

$$\begin{aligned}\lambda_1 = & d_1 \bar{x}_1 + p \beta_1 \bar{x}_1 \bar{v}_1, \quad \lambda_2 = d_2 \bar{x}_2 + (1-p) \beta_3 \bar{x}_2 \bar{v}_1, \quad F_4 k_1 a_1 \bar{y}_1 + F_4 k_3 a_3 \bar{z}_1 = c_1 \bar{v}_1, \\ p F_1 \beta_1 \bar{x}_1 \bar{v}_1 = & a_1 \bar{y}_1, \quad (1-p) F_3 \beta_3 \bar{x}_2 \bar{v}_1 = a_3 \bar{z}_1,\end{aligned}$$

we obtain

$$\begin{aligned}\frac{d\bar{\mathcal{F}}}{dt} = & \left(1 - \frac{\bar{x}_1}{x_1}\right) (d_1 \bar{x}_1 - d_1 x_1) + p \beta_1 \bar{x}_1 \bar{v}_1 \left(1 - \frac{\bar{x}_1}{x_1}\right) + \beta_2 \bar{x}_1 v_2 - p \beta_1 \frac{\bar{y}_1}{y_1} x_1^{\tau_1} v_1^{\tau_1} + p \beta_1 \bar{x}_1 \bar{v}_1 \\ & + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{\bar{x}_2}{x_2}\right) (d_2 \bar{x}_2 - d_2 x_2) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \left(1 - \frac{\bar{x}_2}{x_2}\right) \\ & - \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \frac{\bar{z}_1}{z_1} x_2^{\tau_3} v_1^{\tau_3} + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 - p \beta_1 \bar{x}_1 \bar{v}_1 \frac{\bar{y}_1}{y_1} \frac{y_1^{\tau_4}}{\bar{y}_1} - \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \frac{\bar{z}_1}{z_1} \frac{z_1^{\tau_4}}{\bar{z}_1} \\ & + p \beta_1 \bar{x}_1 \bar{v}_1 + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 - \frac{c_2 v_2}{k_2 F_2 F_5} + p \beta_1 \bar{x}_1 \bar{v}_1 \ln\left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1}\right) \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \ln\left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1}\right) + p \beta_1 \bar{x}_1 \bar{v}_1 \ln\left(\frac{y_1^{\tau_4}}{y_1}\right) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \ln\left(\frac{z_1^{\tau_4}}{z_1}\right).\end{aligned}$$

Then

$$\begin{aligned} \frac{d\bar{\mathcal{F}}}{dt} = & -d_1 \frac{(\bar{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\bar{x}_2 - x_2)^2}{x_2} + \frac{1}{F_2 F_5} \left(F_2 F_5 \beta_2 \bar{x}_1 - \frac{c_2}{k_2} \right) v_2 \\ & + p \beta_1 \bar{x}_1 \bar{v}_1 \left(3 - \frac{\bar{x}_1}{x_1} - \frac{x_1^{\tau_1} v_1^{\tau_1} \bar{y}_1}{\bar{x}_1 \bar{v}_1 y_1} - \frac{y_1^{\tau_4} \bar{v}_1}{\bar{y}_1 v_1} + \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) \right) \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \left(3 - \frac{\bar{x}_2}{x_2} - \frac{x_2^{\tau_3} v_1^{\tau_3} \bar{z}_1}{\bar{x}_2 \bar{v}_1 z_1} - \frac{z_1^{\tau_4} \bar{v}_1}{\bar{z}_1 v_1} + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) + \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) \right). \end{aligned}$$

Using the following equalities:

$$\begin{aligned} \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) &= \ln \left(\frac{\bar{x}_1}{x_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1} \bar{y}_1}{\bar{x}_1 \bar{v}_1 y_1} \right) + \ln \left(\frac{y_1^{\tau_4} \bar{v}_1}{\bar{y}_1 v_1} \right), \\ \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) + \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) &= \ln \left(\frac{\bar{x}_2}{x_2} \right) + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3} \bar{z}_1}{\bar{x}_2 \bar{v}_1 z_1} \right) + \ln \left(\frac{z_1^{\tau_4} \bar{v}_1}{\bar{z}_1 v_1} \right), \end{aligned}$$

we obtain

$$\begin{aligned} \frac{d\bar{\mathcal{F}}}{dt} = & -d_1 \frac{(\bar{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\bar{x}_2 - x_2)^2}{x_2} + \frac{1}{F_2 F_5} \left(F_2 F_5 \beta_2 \bar{x}_1 - \frac{c_2}{k_2} \right) v_2 \\ & - p \beta_1 \bar{x}_1 \bar{v}_1 \left[\Phi \left(\frac{\bar{x}_1}{x_1} \right) + \Phi \left(\frac{x_1^{\tau_1} v_1^{\tau_1} \bar{y}_1}{\bar{x}_1 \bar{v}_1 y_1} \right) + \Phi \left(\frac{y_1^{\tau_4} \bar{v}_1}{\bar{y}_1 v_1} \right) \right] \\ & - \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \left[\Phi \left(\frac{\bar{x}_2}{x_2} \right) + \Phi \left(\frac{x_2^{\tau_3} v_1^{\tau_3} \bar{z}_1}{\bar{x}_2 \bar{v}_1 z_1} \right) + \Phi \left(\frac{z_1^{\tau_4} \bar{v}_1}{\bar{z}_1 v_1} \right) \right]. \end{aligned}$$

We have

$$F_2 F_5 \beta_2 \bar{x}_1 - \frac{c_2}{k_2} = \frac{F_2 F_5 \beta_2 \lambda_1}{d_1 + p \beta_1 \bar{v}_1} - \frac{c_2}{k_2} = \frac{F_2 F_5 \beta_2 k_2 \lambda_1 - c_2 d_1 - c_2 p \beta_1 \bar{v}_1}{k_2 (d_1 + p \beta_1 \bar{v}_1)} = \frac{c_2 d_1 (\mathcal{R}_1 - 1)}{k_2 (d_1 + p \beta_1 \bar{v}_1)} - \frac{c_2 p \beta_1 \bar{v}_1}{k_2 (d_1 + p \beta_1 \bar{v}_1)}.$$

Therefore,

$$\begin{aligned} \frac{d\bar{\mathcal{F}}}{dt} = & -d_1 \frac{(\bar{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\bar{x}_2 - x_2)^2}{x_2} + \frac{c_2 d_1}{F_2 F_5 k_2 (d_1 + p \beta_1 \bar{v}_1)} \left(\mathcal{R}_1 - 1 - \frac{p \beta_1 \bar{v}_1}{d_1} \right) v_2 \\ & - p \beta_1 \bar{x}_1 \bar{v}_1 \left[\Phi \left(\frac{\bar{x}_1}{x_1} \right) + \Phi \left(\frac{x_1^{\tau_1} v_1^{\tau_1} \bar{y}_1}{\bar{x}_1 \bar{v}_1 y_1} \right) + \Phi \left(\frac{y_1^{\tau_4} \bar{v}_1}{\bar{y}_1 v_1} \right) \right] \\ & - \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 \bar{x}_2 \bar{v}_1 \left[\Phi \left(\frac{\bar{x}_2}{x_2} \right) + \Phi \left(\frac{x_2^{\tau_3} v_1^{\tau_3} \bar{z}_1}{\bar{x}_2 \bar{v}_1 z_1} \right) + \Phi \left(\frac{z_1^{\tau_4} \bar{v}_1}{\bar{z}_1 v_1} \right) \right]. \end{aligned}$$

It follows that $\frac{d\bar{\mathcal{F}}}{dt} \leq 0$ when $\mathcal{R}_1 \leq 1 + \frac{p \beta_1 \bar{v}_1}{d_1}$. Moreover, $\frac{d\bar{\mathcal{F}}}{dt} = 0$ if $(x_1, y_1, x_2, z_1, v_1) = (\bar{x}_1, \bar{y}_1, \bar{x}_2, \bar{z}_1, \bar{v}_1)$ and

$$\left(\mathcal{R}_1 - 1 - \frac{p \beta_1 \bar{v}_1}{d_1} \right) v_2 = 0.$$

We have two cases:

- $\mathcal{R}_1 < 1 + \frac{p \beta_1 \bar{v}_1}{d_1}$. Then $v_2 = 0$, and hence $\dot{v}_2 = 0$ and from Equation 7 we have $0 = \dot{v}_2 = F_5 k_2 a_2 y_2^{\tau_5} = 0$ and thus $y_2(t) = 0, \forall t \geq 0$. Hence, $\bar{\Omega}' = \{\bar{\mathcal{E}}\}$.
- $\mathcal{R}_1 = 1 + \frac{p \beta_1 \bar{v}_1}{d_1}$. From Equation 1 we have $0 = \dot{x}_1 = \lambda_1 - d_1 \bar{x}_1 - p \beta_1 \bar{x}_1 \bar{v}_1 - \beta_2 \bar{x}_1 v_2$, hence $v_2(t) = 0$, and from Equation 7 we obtain $y_2(t) = 0$ for any t . Hence, $\bar{\Omega}' = \{\bar{\mathcal{E}}\}$.

Lyapunov-LaSalle asymptotic stability theorem indicates that $\bar{\mathcal{E}}$ is GAS when $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 \leq 1$.

Theorem 3. If the HBV-only infection equilibrium $\bar{\mathcal{E}}$ exists (if $\mathcal{R}_1 > 1$) then it is GAS under the condition $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} \leq 1$.

Proof. Consider $\tilde{\mathcal{F}}(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$

$$\begin{aligned} \tilde{\mathcal{F}} = & \tilde{x}_1 \Phi \left(\frac{x_1}{\tilde{x}_1} \right) + \frac{1}{F_1} y_1 + \frac{1}{F_2} \tilde{y}_2 \Phi \left(\frac{y_2}{\tilde{y}_2} \right) + \frac{F_3}{F_1} \frac{k_3}{k_1} \tilde{x}_2 \Phi \left(\frac{x_2}{\tilde{x}_2} \right) + \frac{1}{F_1} \frac{k_3}{k_1} z_1 + \frac{1}{k_1 F_1 F_4} v_1 + \frac{1}{k_2 F_2 F_5} \tilde{v}_2 \Phi \left(\frac{v_2}{\tilde{v}_2} \right) \\ & + p \beta_1 \int_{t-\tau_1}^t x_1(\theta) v_1(\theta) d\theta + \beta_2 \tilde{x}_1 \tilde{v}_2 \int_{t-\tau_2}^t \Phi \left(\frac{x_1(\theta) v_2(\theta)}{\tilde{x}_1 \tilde{v}_2} \right) d\theta + \frac{F_3}{F_1} \frac{k_3}{k_1} (1-p) \beta_3 \int_{t-\tau_3}^t x_2(\theta) v_1(\theta) d\theta \\ & + \frac{1}{k_1 F_1} \int_{t-\tau_4}^t (k_1 a_1 y_1(\theta) + k_3 a_3 z_1(\theta)) d\theta + \frac{1}{F_2} a_2 \tilde{y}_2 \int_{t-\tau_5}^t \Phi \left(\frac{y_2(\theta)}{\tilde{y}_2} \right) d\theta. \end{aligned}$$

We calculate $\frac{d\tilde{\mathcal{F}}}{dt}$ as:

$$\begin{aligned}\frac{d\tilde{\mathcal{F}}}{dt} = & \left(1 - \frac{\tilde{x}_1}{x_1}\right) (\lambda_1 - d_1 x_1 - p\beta_1 x_1 v_1 - \beta_2 x_1 v_2) + \frac{1}{F_1} (pF_1 \beta_1 x_1^{\tau_1} v_1^{\tau_1} - a_1 y_1) \\ & + \frac{1}{F_2} \left(1 - \frac{\tilde{y}_2}{y_2}\right) (F_2 \beta_2 x_1^{\tau_2} v_2^{\tau_2} - a_2 y_2) + \frac{F_3}{F_1} \frac{k_3}{k_1} \left(1 - \frac{\tilde{x}_2}{x_2}\right) (\lambda_2 - d_2 x_2 - (1-p)\beta_3 x_2 v_1) \\ & + \frac{1}{F_1} \frac{k_3}{k_1} ((1-p)F_3 \beta_3 x_2^{\tau_3} v_1^{\tau_3} - a_3 z_1) + \frac{1}{k_1 F_1 F_4} [F_4 (k_1 a_1 y_1^{\tau_4} + k_3 a_3 z_1^{\tau_4}) - c_1 v_1] \\ & + \frac{1}{k_2 F_2 F_5} \left(1 - \frac{\tilde{v}_2}{v_2}\right) (k_2 a_2 F_5 y_2^{\tau_5} - c_2 v_2) + p\beta_1 (x_1 v_1 - x_1^{\tau_1} v_1^{\tau_1}) \\ & + \beta_2 \tilde{x}_1 \tilde{v}_2 \left(\frac{x_1 v_2}{\tilde{x}_1 \tilde{v}_2} - \frac{x_1^{\tau_2} v_2^{\tau_2}}{\tilde{x}_1 \tilde{v}_2} + \ln\left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2}\right)\right) + \frac{F_3}{F_1} \frac{k_3}{k_1} (1-p)\beta_3 (x_2 v_1 - x_2^{\tau_3} v_1^{\tau_3}) \\ & + \frac{1}{k_1 F_1} [k_1 a_1 (y_1 - y_1^{\tau_4}) + k_3 a_3 (z_1 - z_1^{\tau_4})] + \frac{1}{F_2} a_2 \tilde{y}_2 \left(\frac{y_2}{\tilde{y}_2} - \frac{y_2^{\tau_5}}{\tilde{y}_2} + \ln\left(\frac{y_2^{\tau_5}}{y_2}\right)\right).\end{aligned}$$

Collecting terms as:

$$\begin{aligned}\frac{d\tilde{\mathcal{F}}}{dt} = & \left(1 - \frac{\tilde{x}_1}{x_1}\right) (\lambda_1 - d_1 x_1) + p\beta_1 \tilde{x}_1 v_1 + \beta_2 \tilde{x}_1 v_2 - \beta_2 x_1^{\tau_2} v_2^{\tau_2} \frac{\tilde{y}_2}{y_2} + \frac{a_2}{F_2} \tilde{y}_2 + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{\tilde{x}_2}{x_2}\right) (\lambda_2 - d_2 x_2) \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 \tilde{x}_2 v_1 - \frac{c_1}{k_1 F_1 F_4} v_1 - \frac{c_2}{k_2 F_2 F_5} v_2 - \frac{a_2}{F_2} y_2^{\tau_5} \frac{\tilde{v}_2}{v_2} + \frac{c_2}{k_2 F_2 F_5} \tilde{v}_2 + \beta_2 \tilde{x}_1 \tilde{v}_2 \ln\left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2}\right) \\ & + \frac{a_2}{F_2} \tilde{y}_2 \ln\left(\frac{y_2^{\tau_5}}{y_2}\right).\end{aligned}$$

By using the conditions of $\tilde{\mathcal{E}}$,

$$\lambda_1 = d_1 \tilde{x}_1 + \beta_2 \tilde{x}_1 \tilde{v}_2, \quad F_2 \beta_2 \tilde{x}_1 \tilde{v}_2 = a_2 \tilde{y}_2, \quad \lambda_2 = d_2 \tilde{x}_2, \quad F_5 k_2 a_2 \tilde{y}_2 = F_2 F_5 k_2 \beta_2 \tilde{x}_1 \tilde{v}_2 = c_2 \tilde{v}_2,$$

we obtain

$$\begin{aligned}\frac{d\tilde{\mathcal{F}}}{dt} = & -d_1 \frac{(\tilde{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\tilde{x}_2 - x_2)^2}{x_2} + \frac{1}{F_1 F_4} \left(F_1 F_4 p\beta_1 \tilde{x}_1 + F_3 F_4 \frac{k_3}{k_1} (1-p)\beta_3 \tilde{x}_2 - \frac{c_1}{k_1}\right) v_1 \\ & + \beta_2 \tilde{x}_1 \tilde{v}_2 \left(3 - \frac{\tilde{x}_1}{x_1} - \frac{y_2^{\tau_5} \tilde{v}_2}{\tilde{y}_2 v_2} - \frac{x_1^{\tau_2} v_2^{\tau_2} \tilde{y}_2}{\tilde{x}_1 \tilde{v}_2 y_2} + \ln\left(\frac{y_2^{\tau_5}}{y_2}\right) + \ln\left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2}\right)\right).\end{aligned}$$

Applying the following equality:

$$\ln\left(\frac{y_2^{\tau_5}}{y_2}\right) + \ln\left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2}\right) = \ln\left(\frac{\tilde{x}_1}{x_1}\right) + \ln\left(\frac{y_2^{\tau_5} \tilde{v}_2}{\tilde{y}_2 v_2}\right) + \ln\left(\frac{x_1^{\tau_2} v_2^{\tau_2} \tilde{y}_2}{\tilde{x}_1 \tilde{v}_2 y_2}\right),$$

we obtain

$$\begin{aligned}\frac{d\tilde{\mathcal{F}}}{dt} = & -d_1 \frac{(\tilde{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\tilde{x}_2 - x_2)^2}{x_2} + \frac{1}{F_1 F_4} \left(F_1 F_4 p\beta_1 \tilde{x}_1 + F_3 F_4 \frac{k_3}{k_1} (1-p)\beta_3 \tilde{x}_2 - \frac{c_1}{k_1}\right) v_1 \\ & - \beta_2 \tilde{x}_1 \tilde{v}_2 \left(\Phi\left(\frac{\tilde{x}_1}{x_1}\right) + \Phi\left(\frac{y_2^{\tau_5} \tilde{v}_2}{\tilde{y}_2 v_2}\right) + \Phi\left(\frac{x_1^{\tau_2} v_2^{\tau_2} \tilde{y}_2}{\tilde{x}_1 \tilde{v}_2 y_2}\right)\right).\end{aligned}$$

Furthermore, we have

$$\begin{aligned}F_1 F_4 p\beta_1 \tilde{x}_1 + F_3 F_4 \frac{k_3}{k_1} (1-p)\beta_3 \tilde{x}_2 - \frac{c_1}{k_1} &= \frac{F_1 F_4 p\beta_1 c_2}{F_2 F_5 k_2 \beta_2} + F_3 F_4 \frac{k_3 (1-p)\beta_3}{k_1} \frac{\lambda_2}{d_2} - \frac{c_1}{k_1} \\ &= \frac{c_1}{k_1} \left(\frac{F_1 F_4 k_1 p\beta_1 c_2}{F_2 F_5 c_1 k_2 \beta_2} + \frac{F_3 F_4 k_3 (1-p)\beta_3 \lambda_2}{c_1 d_2} - 1\right) \\ &= \frac{c_1}{k_1} \left(\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} - 1\right).\end{aligned}$$

Then, we obtain the following:

$$\begin{aligned} \frac{d\tilde{\mathcal{F}}}{dt} = & -d_1 \frac{(\tilde{x}_1 - x_1)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(\tilde{x}_2 - x_2)^2}{x_2} + \frac{c_1}{k_1 F_1 F_4} \left(\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} - 1 \right) v_1 \\ & - \beta_2 \tilde{x}_1 \tilde{v}_2 \left(\Phi \left(\frac{\tilde{x}_1}{x_1} \right) + \Phi \left(\frac{y_2^{\tau_5} \tilde{v}_2}{y_2 v_2} \right) + \Phi \left(\frac{x_1^{\tau_2} v_2^{\tau_2} \tilde{y}_2}{\tilde{x}_1 \tilde{v}_2 y_2} \right) \right). \end{aligned}$$

If $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} \leq 1$, then we obtain $\frac{d\tilde{\mathcal{F}}}{dt} \leq 0$, where $\frac{d\tilde{\mathcal{F}}}{dt} = 0$ occurs at $(x_1, x_2, y_2, v_2) = (\tilde{x}_1, \tilde{x}_2, \tilde{y}_2, \tilde{v}_2)$, and

$$\left(\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} - 1 \right) v_1 = 0. \quad (15)$$

We have two cases:

- $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} = 1$, From Equation 4 we have

$$0 = \dot{x}_2 = \lambda_2 - d_2 \tilde{x}_2 - (1-p)\beta_3 \tilde{x}_2 v_1 = -(1-p)\beta_3 \tilde{x}_2 v_1 \implies v_1(t) = 0, \forall t \geq 0,$$

and from Equation 6 we have then

$$0 = \dot{v}_1 = F_4 k_1 a_1 y_1^{\tau_4} + F_4 k_3 a_3 z_1^{\tau_4} \implies y_1(t) = z_1(t) = 0, \forall t \geq 0. \quad (16)$$

Hence, $\tilde{\Omega}' = \{\tilde{\mathcal{E}}\}$.

- $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} < 1$, then $v_1 = 0$ and from Equation 16 we obtain $y_1 = z_1 = 0$. Hence, $\tilde{\Omega}' = \{\tilde{\mathcal{E}}\}$.

Lyapunov-LaSalle asymptotic stability theorem indicates that $\tilde{\mathcal{E}}$ is GAS when $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} \leq 1$.

Theorem 4. If the HIV and HBV co-infection equilibrium $\mathcal{E}^*$ exists (if $\mathcal{R}_1 > \mathcal{R}_{01}$, $\mathcal{R}_2 > 1$ and $\mathcal{R}_3 > 1$) then it is GAS.

Proof. Define $\mathcal{F}^*(x_1, y_1, y_2, x_2, z_1, v_1, v_2)$ be defined as:

$$\begin{aligned} \mathcal{F}^* = & x_1^* \Phi \left(\frac{x_1}{x_1^*} \right) + \frac{1}{F_1} y_1^* \Phi \left(\frac{y_1}{y_1^*} \right) + \frac{1}{F_2} y_2^* \Phi \left(\frac{y_2}{y_2^*} \right) + \frac{F_3 k_3}{F_1 k_1} x_2^* \Phi \left(\frac{x_2}{x_2^*} \right) \\ & + \frac{1}{F_1 k_1} z_1^* \Phi \left(\frac{z_1}{z_1^*} \right) + \frac{1}{k_1 F_1 F_4} v_1^* \Phi \left(\frac{v_1}{v_1^*} \right) + \frac{1}{k_2 F_2 F_5} v_2^* \Phi \left(\frac{v_2}{v_2^*} \right) \\ & + p \beta_1 x_1^* v_1^* \int_{t-\tau_1}^t \Phi \left(\frac{x_1(\theta) v_1(\theta)}{x_1^* v_1^*} \right) d\theta + \beta_2 x_1^* v_2^* \int_{t-\tau_2}^t \Phi \left(\frac{x_1(\theta) v_2(\theta)}{x_1^* v_2^*} \right) d\theta \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 x_2^* v_1^* \int_{t-\tau_3}^t \Phi \left(\frac{x_2(\theta) v_1(\theta)}{x_2^* v_1^*} \right) d\theta \\ & + \frac{1}{k_1 F_1} \int_{t-\tau_4}^t \left(k_1 a_1 y_1^* \Phi \left(\frac{y_1(\theta)}{y_1^*} \right) + k_3 a_3 z_1^* \Phi \left(\frac{z_1(\theta)}{z_1^*} \right) \right) d\theta + \frac{1}{F_2} a_2 y_2^* \int_{t-\tau_5}^t \Phi \left(\frac{y_2(\theta)}{y_2^*} \right) d\theta. \end{aligned}$$

Calculating $\frac{d\mathcal{F}^*}{dt}$ as:

$$\begin{aligned} \frac{d\mathcal{F}^*}{dt} = & \left(1 - \frac{x_1^*}{x_1} \right) (\lambda_1 - d_1 x_1 - p \beta_1 x_1 v_1 - \beta_2 x_1 v_2) + \frac{1}{F_1} \left(1 - \frac{y_1^*}{y_1} \right) (p F_1 \beta_1 x_1^{\tau_1} v_1^{\tau_1} - a_1 y_1) \\ & + \frac{1}{F_2} \left(1 - \frac{y_2^*}{y_2} \right) (F_2 \beta_2 x_1^{\tau_2} v_2^{\tau_2} - a_2 y_2) + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{x_2^*}{x_2} \right) (\lambda_2 - d_2 x_2 - (1-p) \beta_3 x_2 v_1) \\ & + \frac{1}{F_1 k_1} \left(1 - \frac{z_1^*}{z_1} \right) ((1-p) F_3 \beta_3 x_2^{\tau_3} v_1^{\tau_3} - a_3 z_1) + \frac{1}{k_1 F_1 F_4} \left(1 - \frac{v_1^*}{v_1} \right) [F_4 (k_1 a_1 y_1^{\tau_4} + k_3 a_3 z_1^{\tau_4}) - c_1 v_1] \\ & + \frac{1}{k_2 F_2 F_5} \left(1 - \frac{v_2^*}{v_2} \right) (k_2 a_2 F_5 y_2^{\tau_5} - c_2 v_2) + p \beta_1 x_1^* v_1^* \left(\frac{x_1 v_1}{x_1^* v_1^*} - \frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1^* v_1^*} + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) \right) \\ & + \beta_2 x_1^* v_2^* \left(\frac{x_1 v_2}{x_1^* v_2^*} - \frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1^* v_2^*} + \ln \left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2} \right) \right) + \frac{F_3 k_3}{F_1 k_1} (1-p) \beta_3 x_2^* v_1^* \left(\frac{x_2 v_1}{x_2^* v_1^*} - \frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2^* v_1^*} + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) \right) \\ & + \frac{1}{k_1 F_1} \left[k_1 a_1 y_1^* \left(\frac{y_1}{y_1^*} - \frac{y_1^{\tau_4}}{y_1^*} + \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) \right) + k_3 a_3 z_1^* \left(\frac{z_1}{z_1^*} - \frac{z_1^{\tau_4}}{z_1^*} + \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) \right) \right] \\ & + \frac{1}{F_2} a_2 y_2^* \left(\frac{y_2}{y_2^*} - \frac{y_2^{\tau_5}}{y_2^*} + \ln \left(\frac{y_2^{\tau_5}}{y_2} \right) \right). \end{aligned}$$

Collecting terms we obtain the following:

$$\begin{aligned} \frac{d\mathcal{F}^*}{dt} = & \left(1 - \frac{x_1^*}{x_1}\right) (\lambda_1 - d_1 x_1) + p\beta_1 x_1^* v_1 + \beta_2 x_1^* v_2 + \frac{a_1}{F_1} y_1^* + \frac{a_2}{F_2} y_2^* + \frac{F_3 k_3}{F_1 k_1} \left(1 - \frac{x_2^*}{x_2}\right) (\lambda_2 - d_2 x_2) \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 x_2^* v_1 + \frac{a_3 k_3}{F_1 k_1} z_1^* - \frac{c_1}{k_1 F_1 F_4} v_1 + \frac{c_1}{k_1 F_1 F_4} v_1^* - \frac{c_2}{k_2 F_2 F_5} v_2 \\ & + \frac{c_2}{k_2 F_2 F_5} v_2^* - p\beta_1 \frac{x_1^{\tau_1} v_1^{\tau_1} y_1^*}{y_1} + p\beta_1 x_1^* v_1^* \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) - \beta_2 \frac{x_1^{\tau_2} v_2^{\tau_2} y_2^*}{y_2} + \beta_2 x_1^* v_2^* \ln \left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2} \right) \\ & - \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 \frac{x_2^{\tau_3} v_1^{\tau_3} z_1^*}{z_1} + \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 x_2^* v_1^* \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) \\ & - \frac{a_1}{F_1} \frac{y_1^{\tau_4} v_1^*}{v_1} + \frac{a_1}{F_1} y_1^* \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) - \frac{a_3 k_3}{F_1 k_1} \frac{z_1^{\tau_4} v_1^*}{v_1} + \frac{a_3 k_3}{F_1 k_1} z_1^* \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) - \frac{a_2}{F_2} \frac{y_2^{\tau_5} v_2^*}{v_2} + \frac{a_2}{F_2} y_2^* \ln \left(\frac{y_2^{\tau_5}}{y_2} \right). \end{aligned}$$

By using the equilibrium conditions

$$\begin{aligned} \lambda_1 = d_1 x_1^* + p\beta_1 x_1^* v_1^* + \beta_2 x_1^* v_2^*, \quad F_1 p\beta_1 x_1^* v_1^* = a_1 y_1^*, \quad F_2 \beta_2 x_1^* v_2^* = a_2 y_2^*, \quad \lambda_2 = d_2 x_2^* + (1-p)\beta_3 x_2^* v_1^*, \\ F_3 (1-p)\beta_3 x_2^* v_1^* = a_3 z_1^*, \quad c_1 v_1^* = F_4 k_1 a_1 y_1^* + F_4 k_3 a_3 z_1^*, \quad c_2 v_2^* = F_5 k_2 a_2 y_2^*, \end{aligned}$$

we obtain

$$\begin{aligned} \frac{d\mathcal{F}^*}{dt} = & -d_1 \frac{(x_1 - x_1^*)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(x_2 - x_2^*)^2}{x_2} \\ & + p\beta_1 x_1^* v_1^* \left(3 - \frac{x_1^*}{x_1} - \frac{y_1^{\tau_4} v_1^*}{y_1^* v_1} - \frac{x_1^{\tau_1} v_1^{\tau_1} y_1^*}{x_1^* v_1^* y_1} + \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) \right) \\ & + \beta_2 x_1^* v_2^* \left(3 - \frac{x_1^*}{x_1} - \frac{y_2^{\tau_5} v_2^*}{y_2^* v_2} - \frac{x_1^{\tau_2} v_2^{\tau_2} y_2^*}{x_1^* v_2^* y_2} + \ln \left(\frac{y_2^{\tau_5}}{y_2} \right) + \ln \left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2} \right) \right) \\ & + \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 x_2^* v_1^* \left(3 - \frac{x_2^*}{x_2} - \frac{z_1^{\tau_4} v_1^*}{z_1^* v_1} - \frac{x_2^{\tau_3} v_1^{\tau_3} z_1^*}{x_2^* v_1^* z_1} + \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) \right). \end{aligned}$$

Applying the following equalities:

$$\begin{aligned} \ln \left(\frac{y_1^{\tau_4}}{y_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1}}{x_1 v_1} \right) &= \ln \left(\frac{x_1^*}{x_1} \right) + \ln \left(\frac{y_1^{\tau_4} v_1^*}{y_1^* v_1} \right) + \ln \left(\frac{x_1^{\tau_1} v_1^{\tau_1} y_1^*}{x_1^* v_1^* y_1} \right), \\ \ln \left(\frac{y_2^{\tau_5}}{y_2} \right) + \ln \left(\frac{x_1^{\tau_2} v_2^{\tau_2}}{x_1 v_2} \right) &= \ln \left(\frac{x_1^*}{x_1} \right) + \ln \left(\frac{y_2^{\tau_5} v_2^*}{y_2^* v_2} \right) + \ln \left(\frac{x_1^{\tau_2} v_2^{\tau_2} y_2^*}{x_1^* v_2^* y_2} \right), \\ \ln \left(\frac{z_1^{\tau_4}}{z_1} \right) + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3}}{x_2 v_1} \right) &= \ln \left(\frac{x_2^*}{x_2} \right) + \ln \left(\frac{z_1^{\tau_4} v_1^*}{z_1^* v_1} \right) + \ln \left(\frac{x_2^{\tau_3} v_1^{\tau_3} z_1^*}{x_2^* v_1^* z_1} \right), \end{aligned}$$

we obtain

$$\begin{aligned} \frac{d\mathcal{F}^*}{dt} = & -d_1 \frac{(x_1 - x_1^*)^2}{x_1} - \frac{d_2 F_3 k_3}{F_1 k_1} \frac{(x_2 - x_2^*)^2}{x_2} \\ & - p\beta_1 x_1^* v_1^* \left(\Phi \left(\frac{x_1^*}{x_1} \right) + \Phi \left(\frac{y_1^{\tau_4} v_1^*}{y_1^* v_1} \right) + \Phi \left(\frac{x_1^{\tau_1} v_1^{\tau_1} y_1^*}{x_1^* v_1^* y_1} \right) \right) \\ & - \beta_2 x_1^* v_2^* \left(\Phi \left(\frac{x_1^*}{x_1} \right) + \Phi \left(\frac{y_2^{\tau_5} v_2^*}{y_2^* v_2} \right) + \Phi \left(\frac{x_1^{\tau_2} v_2^{\tau_2} y_2^*}{x_1^* v_2^* y_2} \right) \right) \\ & - \frac{F_3 k_3}{F_1 k_1} (1-p)\beta_3 x_2^* v_1^* \left(\Phi \left(\frac{x_2^*}{x_2} \right) + \Phi \left(\frac{z_1^{\tau_4} v_1^*}{z_1^* v_1} \right) + \Phi \left(\frac{x_2^{\tau_3} v_1^{\tau_3} z_1^*}{x_2^* v_1^* z_1} \right) \right). \end{aligned}$$

Therefore, we obtain $\frac{d\mathcal{F}^*}{dt} \leq 0$ for all $x_1, y_1, y_2, x_2, z_1, v_1, v_2 > 0$. Moreover, $\frac{d\mathcal{F}^*}{dt} = 0$ when $(x_1, x_2, y_1, y_2, z_1, v_1, v_2) = (x_1^*, x_2^*, y_1^*, y_2^*, z_1^*, v_1^*, v_2^*)$. Therefore, $\Omega^{*'} = \{\mathcal{E}^*\}$. Applying **Lyapunov-LaSalle asymptotic stability theorem** we obtain that $\mathcal{E}^*$ is GAS.

TABLE 2 Derivation of conditions for existence and global stability of the four equilibria.

Equilibrium	Existence conditions	Global stability conditions
$\mathcal{E}_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$	None	$\max(\mathcal{R}_0, \mathcal{R}_1) \leq 1$
$\tilde{\mathcal{E}} = (\tilde{x}_1, \tilde{y}_1, 0, \tilde{x}_2, \tilde{z}_1, \tilde{v}_1, 0)$	$\mathcal{R}_0 > 1$	$\mathcal{R}_1 \leq 1 + \frac{\rho\beta_1\tilde{v}_1}{d_1}$ and $\mathcal{R}_0 > 1$
$\tilde{\tilde{\mathcal{E}}} = (\tilde{\tilde{x}}_1, 0, \tilde{\tilde{y}}_2, \tilde{\tilde{x}}_2, 0, 0, \tilde{\tilde{v}}_2)$	$\mathcal{R}_1 > 1$	$\frac{\mathcal{R}_1}{\mathcal{R}_{01}} + \mathcal{R}_{02} \leq 1$
$\mathcal{E}^* = (x_1^*, y_1^*, y_2^*, x_2^*, z_1^*, v_1^*, v_2^*)$	$\mathcal{R}_1 > \mathcal{R}_{01},$ $\mathcal{R}_2 > 1,$ $\mathcal{R}_3 > 1$	$\mathcal{R}_1 > \mathcal{R}_{01}, \mathcal{R}_2 > 1,$ $\mathcal{R}_3 > 1$

Table 2 provides a concise overview of the conditions for existence and global stability of the four equilibria.

Remark 1. An important and promising direction for future investigation involves incorporating memory effects into our model by employing fractional differential equations (FDEs) [37, 38]. Unlike classical differential equations, FDEs are particularly effective in modeling systems where the current state depends not only on present conditions but also on the history of the system—an attribute often observed in complex biological processes, including viral infections and immune responses. The intrinsic non-locality and memory-retaining nature of FDEs make them especially suitable for capturing the nuanced dynamics of HIV-HBV co-infection. In recent studies, there has been growing interest in using the Lyapunov stability theory to establish the global behavior of fractional-order systems, as highlighted in the works of [39, 40]. The Lyapunov functions introduced in this section are not only essential for the integer-order formulation of our model but also form a foundational framework that can be extended to analyze the global stability of its fractional counterpart. Such an extension would offer deeper insights into the long-term progression and control of co-infection under memory-influenced dynamics.

5 Numerical simulations

5.1 Stability of equilibria

We conduct numerical simulations for the system defined by Equations 1–7, using parameter values listed in Table 3. Some of the parameter values, as presented in Table 3, were sourced from existing literature. The rest were estimated based on plausible assumptions intended purely for illustrative and computational exploration. This was necessitated by the lack of precise clinical data, especially concerning individuals co-infected with HIV and HBV. Challenges such as ethical considerations, logistical hurdles, and small patient cohorts contribute to this data gap, making accurate parameter estimation difficult. Nevertheless, the chosen values offer a meaningful foundation for analyzing the model's qualitative dynamics and serve as a stepping stone for future research as more empirical data become available.

The system of delay differential equations is solved using the MATLAB solver dde23. To validate the theoretical findings discussed in earlier sections, we vary selected parameters that have a

TABLE 3 Model parameters.

Parameter	Value	Source
λ_1	10 cells mm ⁻³ day ⁻¹	[49–51]
λ_2	10 cells mm ⁻³ day ⁻¹	[44, 52]
d_1	0.01 day ⁻¹	[17, 53]
d_2	0.01 day ⁻¹	[44, 52]
a_2	0.0693 day ⁻¹	[54, 55]
p	0.3	[27]
$\tau_i, i = 1, 2, \dots, 5$	0.1 day	Assumed
$n_i, i = 1, 2, \dots, 5$	1 day ⁻¹	Assumed
c_1	2.4 day ⁻¹	[11, 56, 57]
c_2	0.67 day ⁻¹	[9, 58, 59]
k_2	12.5541 viruses cells ⁻¹	[60]
k_3	6 viruses cells ⁻¹	[61]
a_1	0.5 day ⁻¹	Assumed
k_1	6 viruses cells ⁻¹	Assumed
a_3	0.5 day ⁻¹	[62, 63]
$\beta_i, i = 1, 2, 3$	(Varied) virus ⁻¹ mm ³ day ⁻¹	Assumed

notable impact on the threshold values and, in turn, on the system's stability behavior.

To validate the results of our global stability analysis, we demonstrate that the trajectories of the system, regardless of their starting points within the biologically feasible domain, consistently evolve toward the equilibrium point that satisfies the established stability criteria. This behavior confirms that the equilibrium state dictates the system's long-term dynamics for all permissible initial conditions. Drawing methodological inspiration from the study of [41], we proceed by examining the system's response to the following representative set of initial values:

$$\begin{aligned}x_1(\theta) &= 700 + 10 \sin \theta - 40k, \quad y_1(\theta) = 0.05 + 0.01 \sin \theta + 0.01k, \\y_2(\theta) &= 20 + 2 \sin \theta + 8k, \\x_2(\theta) &= 700 + 10 \sin \theta - 40k, \quad z_1(\theta) = 1 + 0.1 \sin \theta + 0.3k, \quad v_1(\theta) \\&= 1 + 0.2 \sin \theta + 1.2k, \\v_2(\theta) &= 50 + 3 \sin \theta + 6k, \quad k = 1, 2, \dots, 12, \quad \theta \in [-0.1, 0].\end{aligned}$$

To investigate the dynamical behavior of the system under varying infection pressures, we select different values for the transmission rates β_1 , β_2 , and β_3 . These values are chosen to illustrate distinct virological scenarios, ranging from disease eradication to full co-infection. The remaining parameters are fixed as presented in Table 3. Additionally, we set $\tau_i = 0.1$ for $i = 1, 2, \dots, 5$. We analyze four representative cases:

Case 1: Complete clearance of both infections

When the infection rates are set to $\beta_1 = 0.0001$, $\beta_2 = 0.00002$ and $\beta_3 = 0.00003$, the calculated basic reproduction numbers are $\mathcal{R}_0 = 0.10439 < 1$ and $\mathcal{R}_1 = 0.30682 < 1$. Under these conditions, the

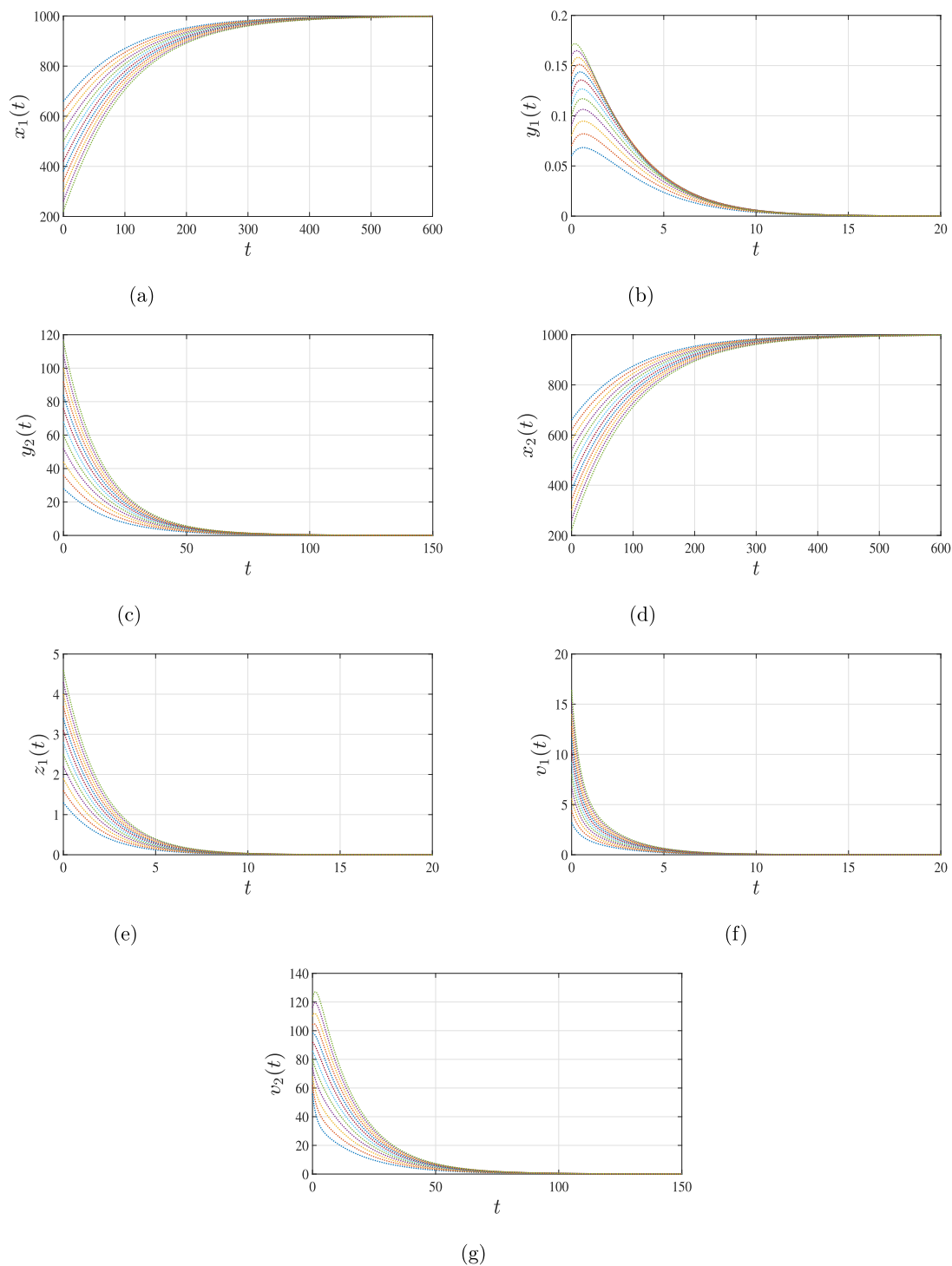


FIGURE 2

Simulation results for Case 1 demonstrating the global asymptotic stability of the infection-free equilibrium point $\mathcal{E}_0 = (1,000, 0, 0, 1,000, 0, 0, 0)$. When the basic reproduction number satisfies $\mathcal{R}_C \leq 1$, all trajectories of system [Equations 1–7](#) converge to $\mathcal{E}_0$ over time, regardless of the initial conditions. This indicates that the infection cannot persist below this threshold. **(a)** Uninfected hepatocytes. **(b)** HIV-infected hepatocytes. **(c)** HBV-infected hepatocytes. **(d)** Uninfected CD4^+ T cells. **(e)** HIV-infected CD4^+ T cells. **(f)** HIV. **(g)** HBV.

system stabilizes at the infection-free equilibrium point $\mathcal{E}_0 = (1000, 0, 0, 1000, 0, 0, 0)$, which is GAS. As illustrated in [Figure 2](#), all trajectories converge to $\mathcal{E}_0$, indicating that both HIV and HBV are eradicated and the uninfected hepatocytes

and CD4^+ T cells return to their normal physiological levels. This outcome confirms the theoretical results stated in Theorem 1.

Case 2: HIV persistence with HBV elimination

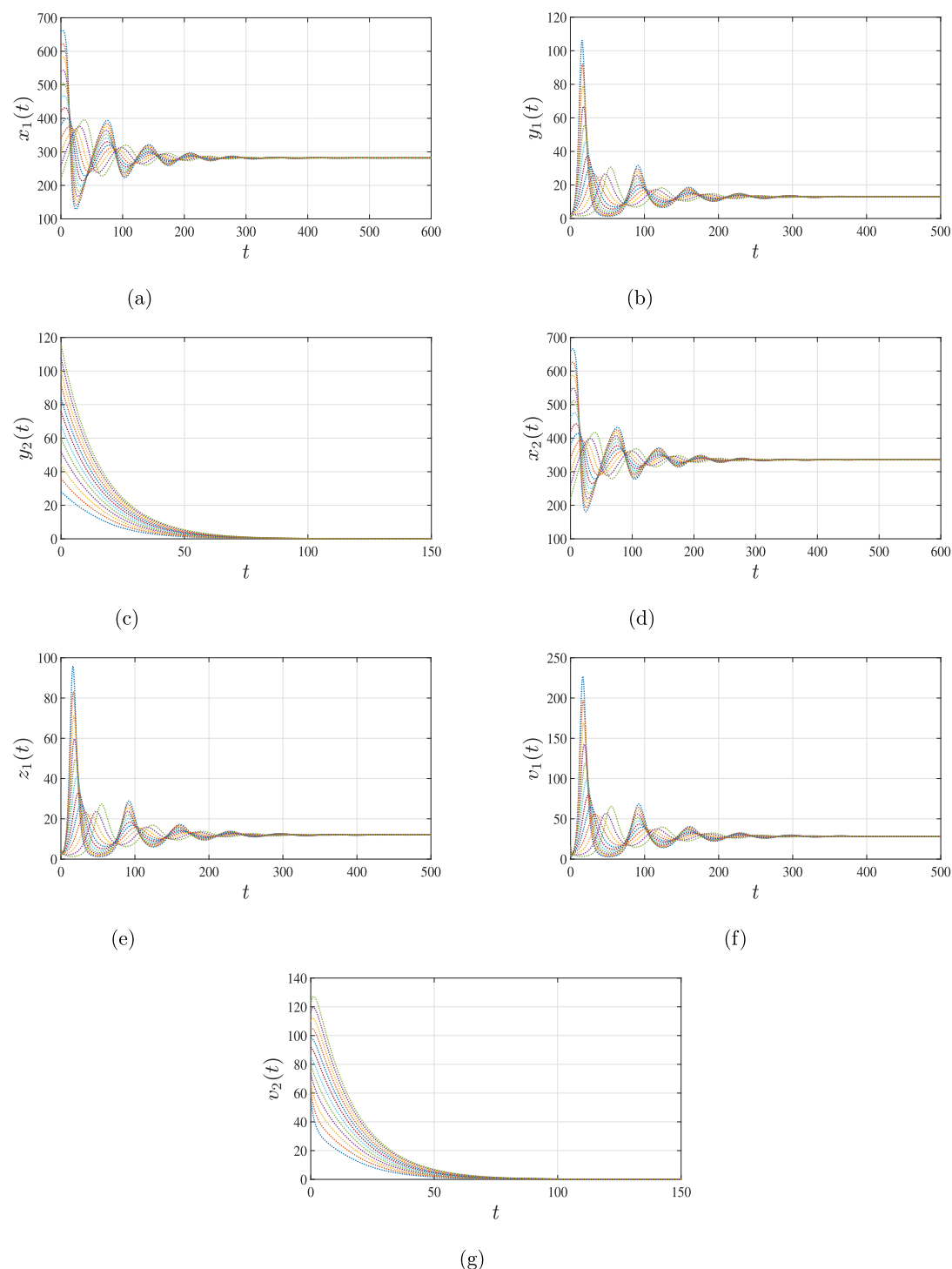


FIGURE 3

Simulation results for case 2 illustrating the persistence of HIV single-infection. When $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 \leq 1 + \frac{\rho\beta_1\bar{v}_1}{d_1}$ the solutions of system Equations 1–7, starting from different initial conditions, converge to the equilibrium point $\bar{\mathcal{E}} = (203.17, 14.42, 0, 884.38, 2.0923, 18.676, 0)$. This indicates that HIV persists in the body, while HBV is cleared over time. (a) Uninfected hepatocytes. (b) HIV-infected hepatocytes. (c) HBV-infected hepatocytes. (d) Uninfected CD4⁺ T cells. (e) HIV-infected CD4⁺ T cells. (f) HIV. (g) HBV.

For the parameter set $\beta_1 = 0.003$, $\beta_2 = 0.00002$ and $\beta_3 = 0.001$, we obtain $\mathcal{R}_0 = 3.2749 > 1$ and $\mathcal{R}_1 = 0.30682 < 3.5470 = 1 + \frac{\rho\beta_1\bar{v}_1}{d_1}$. In this scenario, only the HIV infection remains

active while HBV is cleared. The solution of the system converges to the equilibrium point $\bar{\mathcal{E}} = (281.931, 12.995, 0, 335.461, 12.026, 28.3, 0)$, where HBV-related compartments approach zero. Figure 3 supports this outcome,

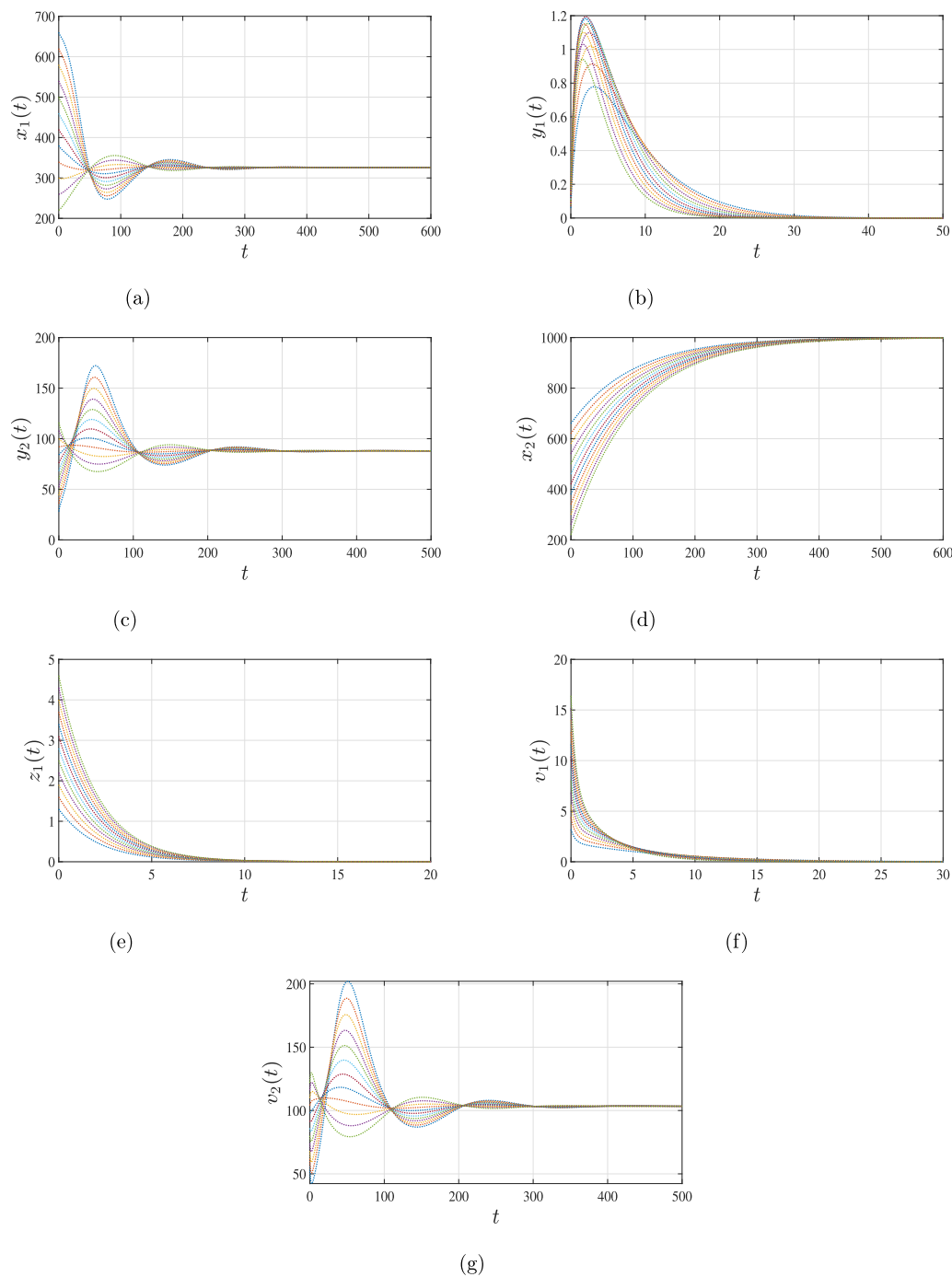


FIGURE 4

Simulation results for Case 3 illustrating the persistence of HBV single-infection. When $\mathcal{R}_1 > 1$ and $\frac{\mathcal{R}_{01}}{\mathcal{R}_1} + \mathcal{R}_{02} \leq 1$, the solutions of system

Equations 1–7, starting from different initial conditions, converge to the equilibrium point $\tilde{\mathcal{E}} = (325.93, 0, 88.013, 1000, 0, 0, 103.41)$. This indicates that HBV persists in the body, while HIV is cleared over time. (a) Uninfected hepatocytes. (b) HIV-infected hepatocytes. (c) HBV-infected hepatocytes. (d) Uninfected CD4⁺ T cells. (e) HIV-infected CD4⁺ T cells. (f) HIV. (g) HBV.

which aligns with the theoretical conclusions presented in Theorem 2.

Case 3: HBV persistence with HIV clearance

Choosing $\beta_1 = 0.0017$, $\beta_2 = 0.0002$, and $\beta_3 = 0.00001$ leads to $\mathcal{R}_0 = 1.0582 > 1$, $\mathcal{R}_1 = 3.0682 > 1$ and

$\mathcal{R}_{02} + \frac{\mathcal{R}_{01}}{\mathcal{R}_1} = 0.35455 < 1$. The system evolves toward the equilibrium $\tilde{\mathcal{E}} = (325.93, 0, 88.013, 1000, 0, 0, 103.41)$, indicating persistence of HBV infection and clearance of HIV. The simulation results depicted in Figure 4 validate the analytical findings of Theorem 3.

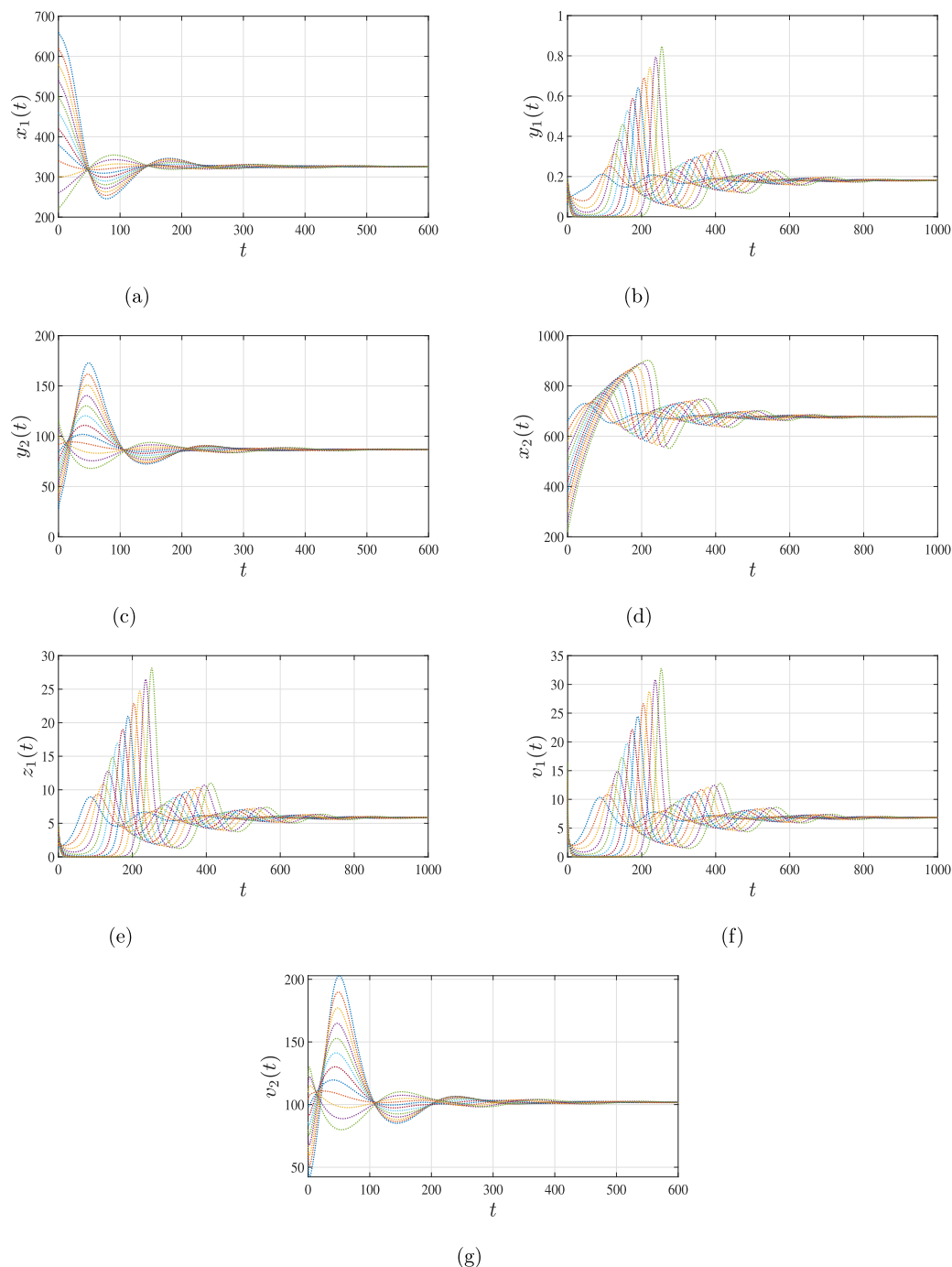


FIGURE 5

Simulation results for Case 4 illustrating the persistence of both HIV and HBV co-infection. When $\mathcal{R}_1 > \mathcal{R}_{01}$, $\mathcal{R}_2 > 1$, and $\mathcal{R}_3 > 1$, the solutions of system Equations 1–7, starting from three distinct initial conditions, converge to the endemic equilibrium point

$\mathcal{E}^* = (325.93, 0.18091, 86.707, 676.99, 5.8454, 6.816, 101.88)$. This indicates that both HIV and HBV persist in the body under this scenario. (a) Uninfected hepatocytes. (b) HIV-infected hepatocytes. (c) HBV-infected hepatocytes. (d) Uninfected CD4⁺ T cells. (e) HIV-infected CD4⁺ T cells. (f) HIV. (g) HBV.

Case 4: Coexistence of HIV and HBV

Finally, for $\beta_1 = 0.00015$, $\beta_2 = 0.0002$ and $\beta_3 = 0.001$, the system exhibits a more complex dynamic with $\mathcal{R}_1 = 3.0682 > \mathcal{R}_{01} = 0.092107$, $\mathcal{R}_2 = 1.4771 > 1$, $\mathcal{R}_3 = 67.429 > 1$. In this case, both HIV and HBV persist, and the system converges to a co-infected equilibrium

$\mathcal{E}^* = (325.93, 0.18091, 86.707, 676.99, 5.8454, 6.816, 101.88)$, which is GAS. The long-term dynamics illustrated in Figure 5 confirm the results of Theorem 4, demonstrating stable co-infection of both viruses.

The outcomes of these four scenarios clearly illustrate the significant impact of infection rate parameters on the progression

TABLE 4 Sensitivity of $\mathcal{R}_0$.

Parameter l	λ_1	k_1	β_1	λ_2	k_3	β_3	p
$S_l^{\mathcal{R}_0}$	0.42149	0.42149	0.42149	0.57851	0.57851	0.57851	0.17355
Parameter l	d_1	d_2	c_1	τ_1	n_1	τ_3	n_3
$S_l^{\mathcal{R}_0}$	-0.42149	-0.57851	-1	-0.042149	-0.042149	-0.057851	-0.057851
Parameter l	τ_4	n_4					
$S_l^{\mathcal{R}_0}$	-0.1	-0.1					

and stability of the system. Varying these rates leads to distinct biological outcomes, including total clearance of both viruses, dominance of one infection, or stable coexistence of HIV and HBV. The close agreement between simulation results and analytical predictions reinforces the model's reliability in representing the intricate dynamics of HIV-HBV co-infection.

5.2 Sensitivity analysis

Sensitivity analysis aims to assess how variations in model parameters influence the system's output dynamics [42]. A common method involves calculating sensitivity indices, which quantify the proportional change in a model outcome resulting from a small change in a specific parameter. This technique is particularly useful for identifying parameters that most significantly affect the basic reproduction numbers $\mathcal{R}_i$, where $i = 0, 1$. Given that $\mathcal{R}_0$ and $\mathcal{R}_1$ are differentiable functions of key parameters, their sensitivity indices can be derived using partial derivatives [43]. In this study, we focus on computing the sensitivity indices for both $\mathcal{R}_0$ and $\mathcal{R}_1$, with the goal of understanding how different parameters contribute to the stability of the infection-free equilibrium $\mathcal{E}_0$. The normalized sensitivity index of $\mathcal{R}_i$ w.r.t. a given parameter η is given as follows [42]:

$$S_{\eta}^{\mathcal{R}_i} = \frac{\partial \mathcal{R}_i}{\partial \eta} \times \frac{\eta}{\mathcal{R}_i}, i = 0, 1.$$

5.2.1 Sensitivity analysis of $\mathcal{R}_0$

To investigate how variations in model parameters affect the basic reproduction number HIV-only infection $\mathcal{R}_0$, we compute normalized sensitivity indices. These indices reflect the proportional change in $\mathcal{R}_0$ resulting from a small perturbation in a given parameter. The general formula used for this computation is based on partial derivatives of $\mathcal{R}_0$ with respect to each parameter.

$$\begin{aligned} S_{\lambda_1}^{\mathcal{R}_0} &= S_{k_1}^{\mathcal{R}_0} = S_{\beta_1}^{\mathcal{R}_0} = -S_{d_1}^{\mathcal{R}_0} = \frac{\lambda_1 k_1 p \beta_1 F_1 F_4}{c_1 d_1 \mathcal{R}_0}, S_{\lambda_2}^{\mathcal{R}_0} = S_{k_3}^{\mathcal{R}_0} = S_{\beta_3}^{\mathcal{R}_0} \\ &= -S_{d_2}^{\mathcal{R}_0} = \frac{\lambda_2 k_3 (1-p) \beta_3 F_3 F_4}{c_1 d_2 \mathcal{R}_0}, \\ S_{c_1}^{\mathcal{R}_0} &= -1, S_p^{\mathcal{R}_0} = \frac{p(k_1 \beta_1 \lambda_1 d_2 F_1 F_4 - k_3 \beta_3 \lambda_2 d_1 F_3 F_4)}{p k_1 \beta_1 \lambda_1 d_2 F_1 F_4 + (1-p) k_3 \beta_3 \lambda_2 d_1 F_3 F_4}, S_{n_1}^{\mathcal{R}_0} \\ &= S_{\tau_1}^{\mathcal{R}_0} = -n_1 \tau_1 \frac{\lambda_1 k_1 p \beta_1 F_1 F_4}{c_1 d_1 \mathcal{R}_0} \\ S_{n_3}^{\mathcal{R}_0} &= S_{\tau_3}^{\mathcal{R}_0} = -n_3 \tau_3 \frac{\lambda_2 k_3 (1-p) \beta_3 F_3 F_4}{c_1 d_2 \mathcal{R}_0}, S_{n_4}^{\mathcal{R}_0} = S_{\tau_4}^{\mathcal{R}_0} = -n_4 \tau_4. \end{aligned}$$

TABLE 5 Sensitivity of $\mathcal{R}_1$.

Parameter l	k_2	β_2	λ_1	c_2	d_1	τ_2	n_2	τ_5	n_5
$S_l^{\mathcal{R}_1}$	1	1	1	-1	-1	-0.1	-0.1	-0.1	-0.1

Using parameter values $\beta_1 = 0.0017$, $\beta_2 = 0.0002$, $\beta_3 = 0.001$, and $\tau_i = 0.1$ for $i = 1, 2, \dots, 5$ along with the values listed in Table 3, we calculate the sensitivity indices of $\mathcal{R}_0$ as shown in Table 4.

From the computed indices, we observe that parameters λ_1 , k_1 , β_1 , λ_2 , k_3 , β_3 , and p positively influence $\mathcal{R}_0$; increases in any of these raise the value of $\mathcal{R}_0$. On the other hand, parameters such as d_1 , d_2 , c_1 , τ_1 , n_1 , τ_3 , n_3 , τ_4 , and n_4 have a negative effect on $\mathcal{R}_0$, meaning that increasing them leads to a reduction in viral transmission potential.

The impact of selected parameters can be summarized as follows:

- A 10% increase in λ_1 , k_1 , or β_1 leads to a 4.2149% increase in $\mathcal{R}_0$, while the same percentage increase in λ_2 , k_3 , or β_3 yields a 5.7851% rise in $\mathcal{R}_0$.
- Conversely, increasing d_1 or d_2 by 10% results in 4.2149% and 5.7851% reductions in $\mathcal{R}_0$, respectively.
- A 10% rise (or drop) in the parameter c_1 results in a corresponding 10% reduction (or increase) in the value of $\mathcal{R}_0$.
- Parameter p has a more modest yet significant influence; a 10% increase in p increases $\mathcal{R}_0$ by approximately 1.7355%.
- Time-delay-related parameters such as τ_1 or n_1 impact $\mathcal{R}_0$ by about 4.215%, while τ_3 , n_3 contribute about 5.785% each, and τ_4 , n_4 account for a 10% effect.

These results indicate that $\mathcal{R}_0$ is especially sensitive to λ_2 , k_3 , β_3 , p , d_2 and c_1 , in agreement with biological expectations, since HIV predominantly targets CD4⁺ T cells.

5.2.2 Sensitivity analysis of $\mathcal{R}_1$

We now turn our attention to the basic reproduction number of HBV-only infection $\mathcal{R}_1$. The corresponding sensitivity indices are derived as follows: $S_{k_2}^{\mathcal{R}_1} = S_{\beta_2}^{\mathcal{R}_1} = S_{\lambda_1}^{\mathcal{R}_1} = -S_{c_2}^{\mathcal{R}_1} = -S_{d_1}^{\mathcal{R}_1} = 1$, $S_{n_2}^{\mathcal{R}_1} = S_{\tau_2}^{\mathcal{R}_1} = -n_2 \tau_2$ and $S_{n_5}^{\mathcal{R}_1} = S_{\tau_5}^{\mathcal{R}_1} = -n_5 \tau_5$. Using the same parameter values as before, the calculated indices for $\mathcal{R}_1$ are summarized in Table 5.

The analysis reveals that $\mathcal{R}_1$ is positively affected by increases in k_2 , β_2 , and λ_1 , while it decreases with higher values of c_2 and d_1 . Specifically:

- A 10% increase in k_2 , β_2 , or λ_1 results in a 10% increase in $\mathcal{R}_1$.
- A 10% increase in c_2 or d_1 leads to a 10% decrease in $\mathcal{R}_1$.
- Likewise, increasing τ_2 or n_2 by 100% reduces $\mathcal{R}_1$ by 10%, and the same applies to τ_5 and n_5 .

The reproduction number $\mathcal{R}_1$ shows no sensitivity to the remaining parameters in system (Equation 1–7), indicating that the progression of HBV infection in this model is primarily governed by a smaller subset of variables.

5.3 Co-infection dynamics of HIV and HBV under antiviral therapies

To address the impact of antiviral therapies on the progression of HIV and HBV co-infection, we modify the original system of Equations 1–7 by incorporating two pharmacological interventions:

(i) an antiretroviral drug with efficacy parameter $\epsilon_1 \in [0, 1]$ targeting HIV [44], and

(ii) an anti-HBV agent with efficacy $\epsilon_2 \in [0, 1]$ aimed at suppressing hepatitis B viral replication [45].

The resulting treatment-augmented model is expressed as follows:

$$\dot{x}_1 = \lambda_1 - d_1 x_1 - (1 - \epsilon_1) p \beta_1 x_1 v_1 - (1 - \epsilon_2) \beta_2 x_1 v_2, \quad (17)$$

$$\dot{y}_1 = p F_1 \beta_1 (1 - \epsilon_1) x_1^{r_1} v_1^{r_1} - a_1 y_1, \quad (18)$$

$$\dot{y}_2 = (1 - \epsilon_2) F_2 \beta_2 x_1^{r_2} v_2^{r_2} - a_2 y_2, \quad (19)$$

$$\dot{x}_2 = \lambda_2 - d_2 x_2 - (1 - \epsilon_1)(1 - p) \beta_3 x_2 v_1, \quad (20)$$

$$\dot{z}_1 = (1 - \epsilon_1)(1 - p) F_3 \beta_3 x_2^{r_3} v_1^{r_3} - a_3 z_1, \quad (21)$$

$$\dot{v}_1 = F_4 [k_1 a_1 y_1^{r_4} + k_3 a_3 z_1^{r_4}] - c_1 v_1, \quad (22)$$

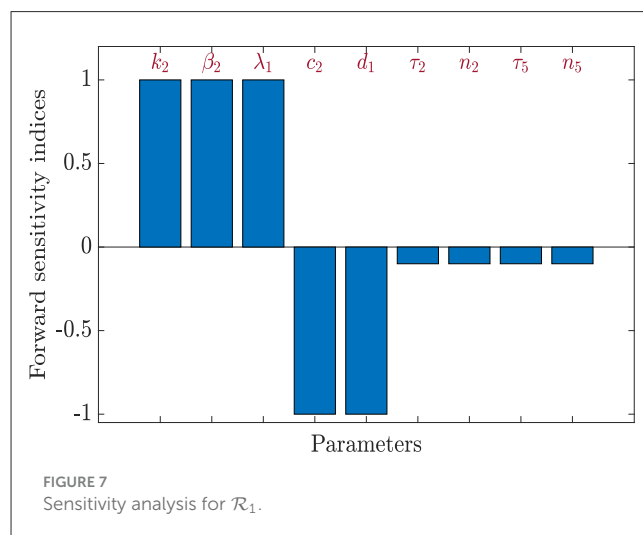
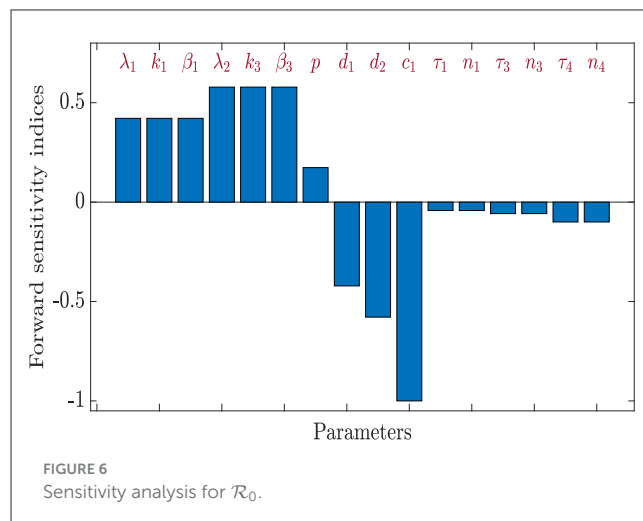
$$\dot{v}_2 = k_2 a_2 F_5 y_2^{r_5} - c_2 v_2. \quad (23)$$

The therapeutic impact can be understood by analyzing the basic reproduction numbers for HIV and HBV in the presence of treatment. Referring to the basic reproduction numbers $\mathcal{R}_0$ (for HIV) and $\mathcal{R}_1$ (for HBV) as previously defined in Section 3.1, the modified reproduction numbers under drug action are computed as follows:

$$\begin{aligned} \mathcal{R}_0^{\text{treated}}(\epsilon_1) &= \frac{k_1(1 - \epsilon_1)p\beta_1\lambda_1 F_1 F_4}{c_1 d_1} + \frac{k_3(1 - \epsilon_1)(1 - p)\beta_3\lambda_2 F_3 F_4}{c_1 d_2} \\ &= (1 - \epsilon_1)\mathcal{R}_0 \leq \mathcal{R}_0, \text{ and} \\ \mathcal{R}_1^{\text{treated}}(\epsilon_2) &= \frac{k_2(1 - \epsilon_2)\beta_2\lambda_1 F_2 F_5}{c_2 d_1} = (1 - \epsilon_2)\mathcal{R}_1 \leq \mathcal{R}_1. \end{aligned}$$

TABLE 6 Impact of drug efficacies ϵ_1 and ϵ_2 on $\mathcal{R}_0^{\text{with anti-HIV}}(\epsilon_1)$ and $\mathcal{R}_1^{\text{with anti-HBV}}(\epsilon_2)$.

Cases	ϵ_1	ϵ_2	$\mathcal{R}_0^{\text{with anti-HIV}}(\epsilon_1)$	$\mathcal{R}_1^{\text{with anti-HBV}}(\epsilon_2)$
Drug efficacy case 1 (DE-1)	0.1	0.4	1.3724	1.8409
Drug efficacy case 2 (DE-2)	0.2	0.5	1.2199	1.5341
Drug efficacy case 3 (DE-3)	0.3	0.6	1.0674	1.2273
Drug efficacy case 4 (DE-4)	0.34421	0.67407	1	1
Drug efficacy case 5 (DE-5)	0.4	0.85	0.91493	0.4602



To ensure long-term viral clearance, the aim is to suppress both reproduction numbers below unity:

$$\mathcal{R}_0^{\text{treated}}(\epsilon_1) \leq 1 \text{ and } \mathcal{R}_1^{\text{treated}}(\epsilon_2),$$

which would guarantee global asymptotic stability of the disease-free equilibrium $\mathcal{E}_0$.

Solving the above inequalities yields the minimum efficacies—also termed critical drug efficacies—required for viral eradication:

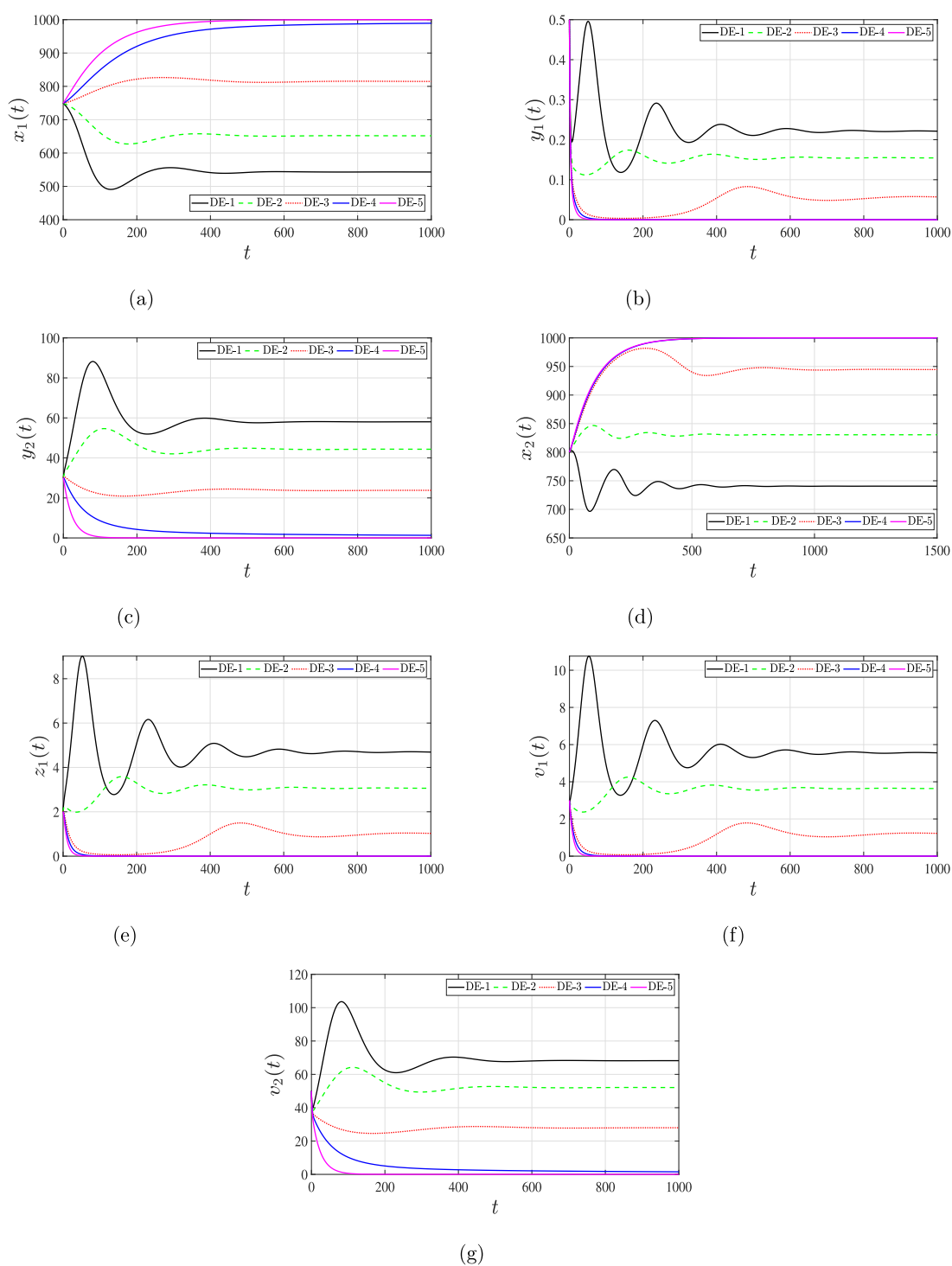


FIGURE 8

Solutions of system (Equations 16–22) for different antiviral effectiveness rates, ϵ_1 and ϵ_2 . (a) Uninfected hepatocytes. (b) HIV-infected hepatocytes. (c) HBV-infected hepatocytes. (d) Uninfected CD4⁺ T cells. (e) HIV-infected CD4⁺ T cells. (f) HIV. (g) HBV.

- $\epsilon_1^{\text{cr}} = 1 - \frac{1}{\mathcal{R}_0}$ ensuring $\mathcal{R}_0^{\text{treated}}(\epsilon_1) \leq 1$ for all $\epsilon_1 \geq \epsilon_1^{\text{cr}}$
- $\epsilon_2^{\text{cr}} = 1 - \frac{1}{\mathcal{R}_1}$ ensuring $\mathcal{R}_1^{\text{treated}}(\epsilon_2) \leq 1$ for all $\epsilon_2 \geq \epsilon_2^{\text{cr}}$

Using model parameters including $\beta_1 = 0.00015$, $\beta_2 = 0.0002$, $\beta_3 = 0.001$, $\tau_i = 0.1$ for $i = 1, 2, \dots, 5$, along with values from Table 3, we compute the following thresholds:

- $\epsilon_1^{cr} \simeq 0.34421$
- $\epsilon_2^{cr} \simeq 0.6741$

The results provided in Figures 6, 7 can be interpreted as follows.

(i) If $\epsilon_1 \geq 0.34421 \leq 1$ and $\epsilon_2 \geq 0.67407$, both HIV and HBV infections are effectively controlled, and the system stabilizes at the disease-free state $\mathcal{E}_0$ (GAS).

(ii) If $\epsilon_1 < 0.34421$ and/or $\epsilon_2 < 0.67407$, then at least one reproduction number exceeds 1, causing the infection-free equilibrium to lose stability. In such cases, a chronic infection equilibrium may emerge and become globally attractive.

To further analyze therapeutic outcomes, we simulate the model system (Equations 17–23) under varying drug efficacies, employing the following set of initial functions for $\theta \in [-0.1, 0]$:

$$\begin{aligned}x_1(\theta) &= 750 + 10 \sin \theta, \quad y_1(\theta) = 0.5 + 0.1 \sin \theta, \quad y_2(\theta) = 30 + 3 \sin \theta, \\x_2(\theta) &= 800 + 10 \sin \theta, \quad z_1(\theta) = 2 + 0.1 \sin \theta, \quad v_1(\theta) = 3 + 0.1 \sin \theta, \\v_2(\theta) &= 50 + 3 \sin \theta.\end{aligned}$$

We examine a range of ϵ_1 and ϵ_2 values as detailed in Table 6.

Simulation outcomes, summarized in Table 6 and illustrated in Figure 8, reveal that increasing antiviral efficacies leads to a marked decline in both $\mathcal{R}_0^{\text{treated}}$ and $\mathcal{R}_1^{\text{treated}}$. This pharmacodynamic effect contributes to the restoration of healthy hepatocyte and CD4⁺ T cell populations, while infected compartments (e.g., y_1, y_2, z_1) and viral loads (v_1, v_2) decrease accordingly.

These findings highlight the critical role of treatment efficacy in shifting the system dynamics toward recovery, emphasizing the need for optimal dosing strategies to achieve viral suppression and potential eradication. The analysis demonstrates that when antiviral drug efficacies exceed specific threshold values, the basic reproduction numbers fall below one, leading the system toward a globally stable, infection-free equilibrium. This underscores the importance of well-calibrated therapeutic interventions in effectively controlling and potentially eliminating HIV and HBV co-infections.

The set of equations defined by Equations 17–23 can be viewed through the framework of a nonlinear control system, in which the parameters ϵ_1 and ϵ_2 represent controllable inputs corresponding to the efficacies of anti-HIV and anti-HBV therapies, respectively. By treating these drug efficacies as control variables, we can employ tools from optimal control theory to determine treatment strategies that minimize viral loads and optimize patient outcomes [46–48]. This approach enables the systematic design of therapeutic protocols for individuals co-infected with HIV and HBV, ensuring both effectiveness and efficiency in long-term disease management.

5.3.1 Influence of time delays on the dynamics of HIV-HBV co-infection

Among the various time delay parameters influencing the system dynamics, it has been observed that the basic reproduction number $\mathcal{R}_0$ is most sensitive to variations in the delay parameter τ_4 (maturation delay of newly released HIV), while $\mathcal{R}_1$ is similarly influenced by the delay τ_5 (maturation delay of newly released

TABLE 7 Effect of time delays τ_4 and τ_5 on $\mathcal{R}_0(\tau_4)$ and $\mathcal{R}_1(\tau_5)$.

Scenarios	τ_4	τ_5	$\mathcal{R}_0(\tau_4)$	$\mathcal{R}_1(\tau_5)$
Time delay scenario 1 (TD-1)	0.3	0.8	1.366	1.6671
Time delay scenario 2 (TD-2)	0.5	1	1.236	1.3649
Time delay scenario 3 (TD-3)	0.5	1.2	1.1184	1.1175
Time delay scenario 4 (TD-4)	0.61192	1.3111	1	1
Time delay scenario 5 (TD-5)	0.7	1.5	0.91569	0.8279
Time delay scenario 6 (TD-6)	0.8	1.8	0.82855	0.6133

HBV). Given this sensitivity, our analysis will focus on assessing how delays τ_4 and τ_5 affect the co-dynamics of HIV and HBV.

Using the transmission rate parameters $\beta_1 = 0.00015$, $\beta_2 = 0.0002$ and $\beta_3 = 0.001$, along with other parameter values specified in Table 3, we fix $\tau_1 = \tau_2 = \tau_3 = 0.01$ and vary τ_4 and τ_5 to explore their impact on the stability of the disease-free equilibrium point $\mathcal{E}_0$. Since the expressions for $\mathcal{R}_0$ and $\mathcal{R}_1$ explicitly incorporate τ_4 and τ_5 , respectively, any modification in these delays will directly affect the stability characteristics of $\mathcal{E}_0$. Notably, increasing either τ_4 or τ_5 tends to reduce the corresponding reproduction number, thus potentially promoting system stability.

The initial conditions for the delay differential system (Equation 1–7) are defined over the interval $\theta \in [-4, 0]$ as:

$$\begin{aligned}x_1(\theta) &= 850 + 10 \sin \theta, \quad y_1(\theta) = 0.5 + 0.1 \sin \theta, \quad y_2(\theta) = 25 + 3 \sin \theta, \\x_2(\theta) &= 800 + 10 \sin \theta, \quad z_1(\theta) = 25 + 2 \sin \theta, \quad v_1(\theta) = 15 + 0.5 \sin \theta, \\v_2(\theta) &= 15 + 0.6 \sin \theta.\end{aligned}$$

To determine the threshold values of τ_4 and τ_5 that ensure global asymptotic stability of the infection-free state, we express the reproduction numbers as functions of these delays:

$$\begin{aligned}\mathcal{R}_0(\tau_4) &= e^{-n_4 \tau_4} \left(\frac{k_1 p \beta_1 \lambda_1 e^{-n_1 \tau_1}}{c_1 d_1} + \frac{k_3 (1-p) \beta_3 \lambda_2 e^{-n_3 \tau_3}}{c_1 d_2} \right), \\ \mathcal{R}_1(\tau_5) &= e^{-n_5 \tau_5} \frac{k_2 \beta_2 \lambda_1 e^{-n_2 \tau_2}}{c_2 d_1}.\end{aligned}$$

To guarantee that $\mathcal{R}_0(\tau_4) \leq 1$ and $\mathcal{R}_1(\tau_5) \leq 1$, we compute the critical values τ_4^{cr} and τ_5^{cr} as:

$$\begin{aligned}\tau_4^{cr} &= \max \left\{ 0, \frac{1}{n_4} \ln \left(\frac{k_1 p \beta_1 \lambda_1 e^{-n_1 \tau_1}}{c_1 d_1} + \frac{k_3 (1-p) \beta_3 \lambda_2 e^{-n_3 \tau_3}}{c_1 d_2} \right) \right\}, \\ \tau_5^{cr} &= \max \left\{ 0, \frac{1}{n_5} \ln \left(\frac{k_2 \beta_2 \lambda_1 e^{-n_2 \tau_2}}{c_2 d_1} \right) \right\}.\end{aligned}$$

Substituting the parameter values from Table 3, we obtain the numerical approximations: $\tau_4^{cr} \simeq 0.61192$ and $\tau_5^{cr} \simeq 1.3111$. Therefore:

- If $\tau_4^{cr} \geq 0.61192$ and $\tau_5^{cr} \geq 1.3111$, then both $\mathcal{R}_0(\tau_4) \leq 1$ and $\mathcal{R}_1(\tau_5) \leq 1$, ensuring that the infection-free equilibrium $\mathcal{E}_0$ is GAS.

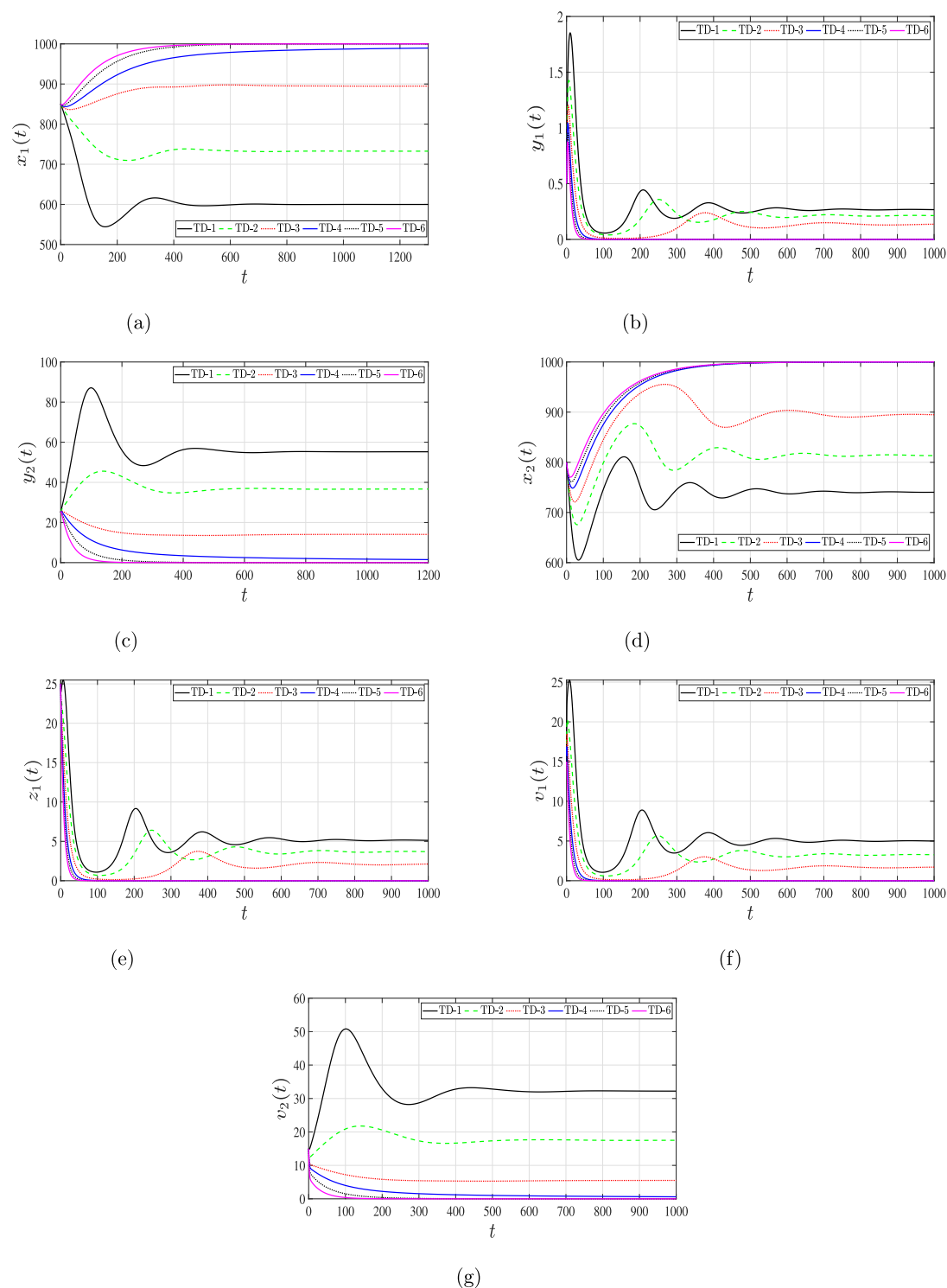


FIGURE 9

Solutions of system (Equation 1–7) for different time delays, τ_4 and τ_5 . (a) Uninfected hepatocytes. (b) HIV-infected hepatocytes. (c) HBV-infected hepatocytes. (d) Uninfected CD4⁺ T cells. (e) HIV-infected CD4⁺ T cells. (f) HIV. (g) HBV.

- Conversely, if $\tau_4^{cr} < 0.61192$ or $\tau_5^{cr} < 1.3111$, the corresponding reproduction number(s) exceed 1, destabilizing $\mathcal{E}_0$ and possibly rendering another equilibrium globally attractive.

As observed in Table 7, increasing the delays τ_4 and τ_5 leads to a reduction in the reproductive numbers $\mathcal{R}_0(\tau_4)$ and $\mathcal{R}_1(\tau_5)$. Figure 9 presents the simulation outcomes for the full system, demonstrating the profound influence of time delays on the system

dynamics. Increasing the delay durations τ_4 and τ_5 enhances the populations of uninfected hepatocytes and $CD4^+$ T cells, while simultaneously decreasing the concentrations of infected cells and viral loads. This dynamic underscores the biological relevance of incorporating intracellular delays in modeling, as they exhibit effects analogous to therapeutic interventions.

In summary, incorporating biologically realistic time delays into the model not only changes the system's qualitative behavior but also offers insights into the development of novel therapies aimed at extending these delays. Such treatments could help slow down virus-cell interactions and prolong the maturation period of viruses released from infected cells. This, in turn, could significantly contribute to controlling the progression of viral activity within the host and enhancing the elimination of viruses from the body.

6 Conclusions

This study develops a mathematical model describing the within-host co-infection dynamics of HIV and HBV. In this framework, HBV primarily infects hepatocytes, while HIV targets both $CD4^+$ T lymphocytes and hepatocytes. The system is represented by seven nonlinear delay differential equations (DDEs), which account for the interactions among uninfected hepatocytes, hepatocytes infected with either HIV or HBV, uninfected $CD4^+$ T lymphocytes, HIV-infected $CD4^+$ T lymphocytes, and free viral particles of both HIV and HBV. Two distinct delays are incorporated into the model: one representing the latency in cell infection and the other reflecting the maturation period of newly produced virions. The model ensures that all solutions are biologically feasible, remaining non-negative and bounded over time. Four equilibrium states are identified, and corresponding threshold quantities $\mathcal{R}_i$ (for $i = 0, 1, 2, 3$) are derived to characterize their behavior. Conditions guaranteeing the global asymptotic stability of each equilibrium point are established using Lyapunov function techniques along with LaSalle's invariance principle. We performed numerical simulations and sensitivity analysis to validate the theoretical findings and to determine the most effective parameters on the basic reproduction numbers for HIV-only ($\mathcal{R}_0$) and HBV-only ($\mathcal{R}_1$) infections. We also studied the effects of two types of antiviral treatments: one for HIV and the other for HBV. We calculated the minimum treatment efficacy needed for clearing the virus from the body. Furthermore, we studied the effect of time delays on the dynamics of viral co-infection and found that these delays reduce the basic reproduction numbers. This highlights the role and importance of considering time delays in modeling viral co-infection, as neglecting these delays leads to an overestimation of the drug's efficacy required to clear the virus. It is also noted that longer delays show effects similar to antiviral therapy, which gives some insight into the idea that finding a treatment that extends the time delay period indicates a potential therapeutic benefit. These insights underscore the importance of incorporating time delays into treatment models and may contribute to the development of more effective strategies for managing coinfection.

The proposed model is capable of capturing a range of clinically observed scenarios such as

- Individuals who successfully avoid infection.
- Cases involving HIV infection alone.
- Cases involving HBV infection alone.
- Chronic co-infection with both HIV and HBV.

This framework also highlights the significant role of antiviral treatments in restoring immune competence and preserving liver function. Mathematical modeling of HIV-HBV co-infection at the within-host level has enhanced our understanding of how these viruses interact and influence disease progression. It also supports the optimization of therapeutic approaches tailored to individual patient needs.

The findings of this study contribute meaningfully to the clinical management of HIV-HBV co-infections. By identifying thresholds for treatment effectiveness and outlining conditions that lead to viral clearance or persistence, this study aids in refining treatment strategies, guiding personalized care and improving patient outcomes. Additionally, these insights can support broader public health efforts aimed at mitigating the long-term burden of co-infections.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AE: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. AA: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. AH: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fams.2025.1633039/full#supplementary-material>

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