Stability analysis of within-host SARS-CoV-2/HIV coinfection model

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The world has been suffering from the coronavirus disease 2019 (COVID-19) since late 2019. COVID-19 is caused by a virus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The human immunodeficiency virus (HIV) coinfection with SARS-CoV-2 has been reported in many patients around the world. This has raised the alarm for the importance of understanding the dynamics of coinfection and its impact on the lives of patients. As in other pandemics, mathematical modeling is one of the important tools that can help medical and experimental studies of COVID-19. In this paper, we develop a within-host SARS-CoV-2/HIV coinfection model. The model consists of six ordinary differential equations. It depicts the interactions between uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, uninfected CD4+ T cells, infected CD4+ T cells, and free HIV particles. We confirm that the solutions of the developed model are biologically acceptable by proving their nonnegativity and boundedness. We compute all possible steady states and derive their positivity conditions. We choose suitable Lyapunov functions to prove the global asymptotic stability of all steady states. We run some numerical simulations to enhance the global stability results. Based on our model, weak CD4+ T cell immune response or low CD4+ T cell counts in SARS-CoV-2/HIV coinfected patient increase the concentrations of infected epithelial cells and SARS-CoV-2 viral load. This causes the coinfected patient to suffer from severe SARS-CoV-2 infection. This result agrees with many studies which showed that HIV patients are at greater risk of suffering from severe COVID-19 when infected. More studies are needed to understand the nature of SARS-CoV-2/HIV coinfection and the role of different immune responses during infection.

KEYWORDS
coinfection, COVID-19, global stability, HIV, Lyapunov, SARS-CoV-2

MSC CLASSIFICATION
34D08, 34D23
INTRODUCTION

The world has been suffering from the coronavirus disease 2019 (COVID-19) since late 2019. It is one of the worst and most severe pandemics that we have lived through. COVID-19 is a fatal respiratory disease attributed to a virus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the epidemiological report published on June 1, 2021, by the World Health Organization (WHO), the total number of global COVID-19 deaths reached 3,530,837, and the overall number of confirmed cases exceeded 169 million. The largest number of new cases were recorded in India, Brazil, Argentina, the United States of America, and Colombia. There is a growing concern regarding SARS-CoV-2 coinfection with other viruses like the human immunodeficiency virus (HIV). Several cases of SARS-CoV-2/HIV coinfection have been reported globally. In 2019, around 38 million people were living with HIV, while 1,700,000 people were newly infected, and 690,000 died. This has raised the need to characterize the dynamics of SARS-CoV-2/HIV coinfection and its impact on the patients.

SARS-CoV-2 is an RNA virus belongs to the family Coronaviridae. It binds to the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell. ACE2 is expressed in the lungs, heart, pancreas, kidney, and other organs. Nevertheless, it is mainly expressed in the alveolar epithelial type 2 cells of the lungs, which makes them the main target for SARS-CoV-2. SARS-CoV-2 is primarily transmitted through respiratory droplets that contain viral particles. The U.S. Food and Drug Administration (FDA) has issued an emergency use authorization for many monoclonal antibody therapies for COVID-19. These therapies are used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older whose weights exceed 40 kg). Six COVID-19 vaccines have been approved so far by WHO for emergency use. These include Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, Johnson & Johnson-Janssen, Sinopharm, and Sinovac.

HIV is an RNA virus belongs to the lentivirus family. HIV binds to CD4 receptor, which is the main receptor targeted by HIV, of the host cell. CD4 is expressed in many immune cells such as the helper T cells or CD4+ T cells, macrophages, and dendritic cells. However, CD4+ T cells are the principal target of HIV. These cells are very important because they help many other immune cells such as CD8+ T cells and B cells to remove viral infections from the body. HIV infection causes a depletion in the number of CD4+ T cells, which impairs the immune system and reduces the ability of the body to fight other infections. HIV is primarily transmitted through sexual contact or blood. With persistent decline in CD4+ T cells, HIV can develop to the Acquired Immunodeficiency Syndrome (AIDS). Highly active antiretroviral therapy (HAART) is used to treat HIV. It suppresses viral replication, which can prevent the development to AIDS. Unfortunately, no HIV vaccine has been approved yet. The first reported case of SARS-CoV-2/HIV coinfection was for a man (61 years old), who had a confirmed SARS-CoV-2 infection in January 2020, from Wuhan, China. After that, many coinfection cases were reported in other countries. The most prevalent symptoms of SARS-CoV-2/HIV coinfection are cough, fever, or shortness of breath, which are identical to the symptoms recorded in SARS-CoV-2 patients without HIV. Recent studies have found that HIV patients are more likely to suffer from severe COVID-19 (with the need for the intensive care unit [ICU] or death) when infected. In particular, people living with HIV with low counts of CD4+ T cells or those not receiving antiretroviral therapy are at increased risk of COVID-19 severity. It was showed that low CD4+ T cell counts in HIV patients rise the risk of developing a severe SARS-CoV-2 infection by almost 5. Moreover, comorbidities such as hypertension, cancer, diabetes, neurological disease, respiratory disease, cardiovascular disease, and chronic kidney disease are additional risk factors for SARS-CoV-2/HIV coinfected patients. The current WHO recommendation involves the safety of COVID-19 vaccines (Pfizer-BioNTech, Oxford-AstraZeneca, Johnson & Johnson-Janssen) for people living with HIV.

Mathematical models have been used to support studies of viral infectious diseases. These models are mainly divided into two types. The first one is the epidemiological models that concentrate on the transmission dynamics of diseases between individuals and how to control diseases spread. The second one is the within-host models that investigate the interactions between viruses and human cells and how to control viral infections within the body. HIV within-host models have been widely studied and led to significant results. Some of these models were built using ordinary differential equations (ODEs) (see for example, previous studies), delay differential equations (DDEs) (see for example, other works), partial differential equations (PDEs) (see for example, other studies), and delay partial differential equations (DPDEs) (see for example, previous works). These models depict mainly the interactions between HIV particles, the targeted cells (CD4+ T cells), different types of infected cells, and immune cells.

On the other hand, within-host models of SARS-CoV-2 infection have been grabbed less attention, and a small number of works have been done so far. For example, Li et al developed a within-host ODE model to explore the interactions between uninfected epithelial cells, infected epithelial cells, and SARS-CoV-2. They utilized chest radiograph score data...
to get an estimation of the parameters of their model. Nath et al.\textsuperscript{36} mathematically analyzed the model of Li et al.\textsuperscript{36} by establishing the nonnegativity and boundedness of solutions and accomplishing stability analysis. Du and Yuan\textsuperscript{38} studied a similar model with adding the effect of antiviral treatments and making a comparison between SARS-CoV-2 and influenza viruses. Almocera et al.\textsuperscript{39} established a model that studies the interactions between SARS-CoV-2 and T cells with performing bifurcation and stability analyses. Elaiw and Al Agha\textsuperscript{40} developed a model that describes the occurrence of SARS-CoV-2 in cancer patients and the role of immune responses in this group of patients. Hattaf and Yousfi\textsuperscript{41} investigated a within-host model that depicts the interactions between host epithelial cells, SARS-CoV-2 virus, and cytotoxic T lymphocytes (CTLs) with virus-to-cell and cell-to-cell transmission modes.

Some coinfection models between SARS-CoV-2 and other viruses have been established. For example, Pinky and Dobrovolsky\textsuperscript{42} used a within-host model to depict the effect of coinfection between SARS-CoV-2 and influenza virus. Ahmed et al.\textsuperscript{43} developed a fractional epidemiological model to assess the pandemic situation in many countries affected by HIV and COVID-19 such as South Africa and Brazil. Pinky and Dobrovolsky\textsuperscript{44} formulated an epidemiological model to study the coinfection between SARS-CoV-2 and other viruses like influenza, respiratory syncytial virus (RSV), and rhinovirus.

However and to the best of our knowledge, no within-host SARS-CoV-2/HIV coinfection models with a mathematical analysis have been established yet. Coinfection models are needed to help understand the dynamics of SARS-CoV-2/HIV coinfection, to support the medical and experimental studies and to find more effective ways to treat HIV patients who get SARS-CoV-2 infection. In this paper, we develop a within-host model of SARS-CoV-2/HIV coinfection. The construction of this model follows similar principals to those used in constructing models of HIV and other viruses. For the developed model, we (i) prove that all model’s solutions are nonnegative as negative values are not accepted in biological models, (ii) confirm that all solutions have positive upper bounds, (iii) compute all model’s steady states which have only positive components, (iv) find the basic reproduction numbers and other threshold numbers, (v) choose appropriate Lyapunov functions and use them to prove the global stability of the different steady states, (vi) run some numerical simulations to enhance the global stability results, (vii) discuss the impact of low CD4\textsuperscript{+} T cell counts in SARS-CoV-2/HIV coinfected patients, and (viii) suggest some modeling ideas for future works.

The paper is arranged as follows. Section 2 explains the meanings of the different variables and parameters that form the model. Section 3 shows the basic properties of the model which include nonnegativity and boundedness of solutions. Furthermore, it presents all possible steady states of the developed model with the derivation of threshold numbers. Section 4 demonstrates the global stability of steady states. Section 5 presents some numerical simulations. In the last section, we summarize and discuss the results. Also, we suggest some potential future works.

2 | SARS-COV-2/HIV COINFECTION MODEL

This section describes the model intended to be studied in this paper. The proposed model takes the form

\begin{align}
\dot{X}(t) &= \rho - aX(t) - \eta X(t)V(t), \\
\dot{Y}(t) &= \eta X(t)V(t) - kY(t) - \mu Y(t)S(t), \\
\dot{V}(t) &= aY(t) - \delta V(t), \\
\dot{S}(t) &= \xi + uY(t)S(t) - \gamma S(t) - \theta S(t)H(t), \\
\dot{W}(t) &= \theta S(t)H(t) - \beta W(t), \\
\dot{H}(t) &= \lambda W(t) - \omega H(t),
\end{align}

where $X(t)$, $Y(t)$, $V(t)$, $S(t)$, $W(t)$, and $H(t)$ denote the concentrations of uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, uninfected CD4\textsuperscript{+} T cells, infected CD4\textsuperscript{+} T cells, and free HIV particles at time $t$. Epithelial cells are produced from a source at a constant rate $\rho$, die at rate $aX(t)$, and get infected by SARS-CoV-2 at rate $\eta X(t)V(t)$. Infected epithelial cells proliferate at rate $\eta X(t)V(t)$ and die at rate $kY(t)$. CD4\textsuperscript{+} T cells help CD8\textsuperscript{+} T cells or CTLs to kill infected epithelial cells at rate $\mu Y(t)S(t)$. Here, the target cells of HIV are responsible for the immune response against SARS-CoV-2. SARS-CoV-2 particles are produced from infected cells at rate $aY(t)$ and die at rate $\delta V(t)$. Uninfected CD4\textsuperscript{+} T cells are produced at a constant rate $\xi$, get stimulated by infected epithelial cells at rate $uY(t)S(t)$, die at rate $\gamma S(t)$, and get infected at rate $\theta S(t)H(t)$. Infected CD4\textsuperscript{+} T cells proliferate at rate $\theta S(t)H(t)$ and die at a natural death rate $\beta W(t)$. The meanings of the different parameters are summarized in Table 1. The formulation of the model is based on Nowak and Bangham’s model that was used widely to
TABLE 1 Values of parameters of model (1)

| Parameter | Description                                      | Value  | Reference       |
|-----------|--------------------------------------------------|--------|-----------------|
| \( \rho \) | Recruitment rate of uninfected epithelial cells | 0.02241| Nath et al.37    |
| \( \alpha \) | Death rate constant of uninfected epithelial cells | \( 10^{-3} \) | Nath et al.37 |
| \( \eta \) | Infection rate constant of epithelial cells     | Varied | –               |
| \( k \)  | Death rate constant of infected epithelial cells | 0.11   | Nath et al.37    |
| \( \mu \) | Indirect killing rate constant of infected epithelial cells | Varied | –               |
| \( a \)  | Production rate constant of SARS-CoV-2 by infected cells | 0.24   | Nath et al.37    |
| \( \delta \) | Death rate constant of free SARS-CoV-2 particles | Varied | –               |
| \( \xi \) | Recruitment rate of uninfected CD4+ T cells     | 10     | Perelson et al.21 |
| \( u \)  | Stimulation rate constant of CD4+ T cells       | 0.1    | Prakash et al.45 |
| \( \gamma \) | Death rate constant of uninfected CD4+ T cells | 0.01   | Callaway and Perelson46 |
| \( \theta \) | Infection rate constant of uninfected CD4+ T cells | Varied | –               |
| \( \beta \) | Death rate constant of infected CD4+ T cells    | 0.5    | Perelson and Nelson12   |
| \( \lambda \) | Production rate constant of HIV by infected cells | 5      | Adak and Bairagi47  |
| \( \omega \) | Death rate constant of free HIV particles      | 2      | Adak and Bairagi47 |

model HIV mono-infection. Their model was also used to model SARS-CoV-2 mono-infection. Here, we used the same principals to model SARS-CoV-2/HIV coinfection and connect the two infections together.

3 | BASIC PROPERTIES

This section proves the nonnegativity and boundedness of solutions of model (1). Additionally, it computes all possible steady states with the associated threshold numbers.

3.1 | Nonnegativity and boundedness

We define a compact set

\[
\Theta = \{ (X, Y, V, S, W, H) \in \mathbb{R}^6_+ : 0 \leq X(t), Y(t) \leq \Omega_1, 0 \leq V(t) \leq \Omega_2, 0 \leq S(t), W(t) \leq \Omega_3, 0 \leq H(t) \leq \Omega_4 \},
\]

where \( \Omega_j > 0, j = 1, 2, 3, 4 \).

**Proposition 1.** The set \( \Theta \) is positively invariant for model (1).

**Proof.** From model (1), we get

\[
\begin{align*}
\dot{X} \bigg|_{X=0} &= \rho > 0, \\
\dot{Y} \bigg|_{Y=0} &= \eta X(t)V(t) \geq 0 \text{ for all } V(t), X(t) \geq 0, \\
\dot{V} \bigg|_{V=0} &= \alpha Y(t) \geq 0 \text{ for all } Y(t) \geq 0, \\
\dot{S} \bigg|_{S=0} &= \xi > 0, \\
\dot{W} \bigg|_{W=0} &= \beta S(t)H(t) \geq 0 \text{ for all } H(t), S(t) \geq 0, \\
\dot{H} \bigg|_{H=0} &= \lambda W(t) \geq 0 \text{ for all } W(t) \geq 0.
\end{align*}
\]

Thus, \((X(t), Y(t), V(t), S(t), W(t), H(t)) \in \mathbb{R}^6_+\) for all \( t \geq 0 \) when \((X(0), Y(0), V(0), S(0), W(0), H(0)) \in \mathbb{R}^6_+\).

To show the boundedness of all state variables, we define

\[
\Psi(t) = X(t) + Y(t) + \frac{k}{2a}V(t) + \frac{\mu}{u}(S(t) + W(t)) + \frac{\mu \beta}{2u \lambda}H(t).
\]
Then, we obtain
\[
\dot{\Psi}(t) = \rho + \frac{\mu}{u} \xi - aX(t) - \frac{k}{2} Y(t) - \frac{k\delta}{2a} V(t) - \frac{\gamma \mu}{u} S(t) - \frac{\mu \beta}{2u} W(t) - \frac{\mu \beta \omega}{2u \lambda} H(t)
\]
\[
\leq \left( \rho + \frac{\mu}{u} \xi \right) - \Phi \left[ X(t) + Y(t) + \frac{k}{2a} V(t) + \frac{\mu}{u} (S(t) + W(t)) + \frac{\mu \beta}{2u \lambda} H(t) \right]
\]
\[
= \left( \rho + \frac{\mu}{u} \xi \right) - \Phi \Psi(t),
\]
where \( \Phi = \min \{ a, k/2, \delta, \gamma, \beta/2, \omega \} \). It follows that
\[
\Psi(t) \leq e^{-\Phi t} \left( \Psi(0) - \frac{\rho + \mu \xi}{\Phi} \right) + \frac{\rho + \mu \xi}{\Phi}. \]

Hence, \( 0 \leq \Psi(t) \leq \Omega_1 \) if \( \Psi(0) \leq \Omega_1 \) for \( t \geq 0 \), where \( \Omega_1 = \frac{\rho + \mu \xi}{\Phi} \). As \( X(t), Y(t), V(t), S(t), W(t), \) and \( H(t) \) are nonnegative, we get
\[
0 \leq X(t), Y(t) \leq \Omega_1, 0 \leq V(t) \leq \Omega_2, 0 \leq S(t), W(t) \leq \Omega_3, 0 \leq H(t) \leq \Omega_4
\]
if
\[
X(0) + Y(0) + \frac{k}{2a} V(0) + \frac{\mu}{u} (S(0) + W(0)) + \frac{\mu \beta}{2u \lambda} H(0) \leq \Omega_1,
\]
where \( \Omega_2 = \frac{2a}{k} \Omega_1, \Omega_3 = \frac{2}{\mu} \Omega_1, \) and \( \Omega_4 = \frac{2a \lambda}{\mu \beta} \Omega_1 \). This shows that the set \( \Theta \) is positively invariant. \( \square \)

3.2 Steady states

In this subsection, we find all possible steady states of model (1) and deduce four threshold parameters that cover the existence of these steady states.

To compute the steady states of the model, we solve the following system of algebraic equations
\[
\begin{align*}
0 &= \rho - aX - \eta XV, \\
0 &= \eta XV - kY - \mu YS, \\
0 &= aY - \delta V, \\
0 &= \xi + uYS - \gamma S - \theta SH, \\
0 &= \theta SH - \beta W, \\
0 &= \lambda W - \omega H.
\end{align*}
\]

Accordingly, we find that model (1) has four steady states:

1. The uninfected steady state \( \Delta_0 = (X_0, 0, 0, S_0, 0, 0) \), where \( X_0 = \rho/a \) and \( S_0 = \xi/\gamma \).
2. The single HIV-infection steady state \( \Delta_H = (X_1, 0, 0, S_1, W_1, H_1) \), where
\[
X_1 = X_0, \quad S_1 = \frac{S_0}{R_1}, \quad W_1 = \frac{\gamma \omega}{\theta \lambda} (R_1 - 1), \quad H_1 = \frac{\gamma}{\theta} (R_1 - 1),
\]
where \( R_1 = \frac{\xi \theta \lambda}{\beta \gamma \omega} \). Here, \( R_1 \) is the basic reproduction number for HIV infection. It determines the establishment of HIV infection in the body. We see that \( W_1 > 0 \) and \( H_1 > 0 \) if \( R_1 > 1 \). Therefore, \( \Delta_H \) exists when \( R_1 > 1 \).
3. The single SARS-CoV-2–infection steady state \( \Delta_V = (X_2, Y_2, V_2, S_2, 0, 0) \), where
\[
Y_2 = \frac{\delta V_2}{a}, \quad S_2 = \frac{\xi}{\gamma - aY_2}, \quad X_2 = \frac{Y_2 k + S_2 Y_2 \mu}{\eta V_2}, \quad (2)
\]
and $V_2$ satisfies the following equation:

$$\frac{u\delta^2 k V_2^2 + (u\alpha \delta k - a\gamma \delta k - a\delta \mu \xi - a\omega \eta) V_2 - a\alpha \gamma \delta k - a\alpha \delta \mu \xi + a^2 \gamma \eta \rho}{a\eta (a\gamma - u\delta V_2)} = 0. \quad (3)$$

Now, we show that there exists a positive root for Equation (3). We define a function $G(V)$ as

$$G(V) = \frac{u\delta^2 k V^2 + (u\alpha \delta k - a\gamma \delta k - a\delta \mu \xi - a\omega \eta) V - a\alpha \gamma \delta k - a\alpha \delta \mu \xi + a^2 \gamma \eta \rho}{a\eta (a\gamma - u\delta V)}.$$

We have

$$G(0) = \frac{-a\alpha \gamma \delta k - a\alpha \delta \mu \xi + a^2 \gamma \eta \rho}{a^2 \gamma \eta} = \frac{a\alpha \gamma \delta k + a\alpha \delta \mu \xi}{a\gamma \eta} (R_2 - 1),$$

where $R_2 = a\alpha \gamma \rho / a\delta (\gamma k + \mu \xi)$. This implies that $G(0) > 0$ when $R_2 > 1$. Moreover, we find that

$$\lim_{V \to \frac{\mu}{\gamma k}} G(V) = -\infty.$$

It follows that there exists $0 < V_2 < a\gamma / u\delta$ such that $G(V_2) = 0$. From Equation (2), we get $Y_2 > 0$, $S_2 > 0$ and $X_2 > 0$. As a result, we deduce that $\Delta_V$ exists when $R_2 > 1$. Note that $R_2$ can be rewritten as

$$R_2 = \frac{a\gamma \rho}{a\delta \left(1 + \frac{\mu}{\gamma k}\right)} = \frac{R_b}{1 + \frac{\mu}{\gamma k}},$$

where $R_b = a\alpha \gamma \rho / a\alpha \delta \mu \xi$ is the basic reproduction number for SARS-CoV-2 infection in the absence of immune response. It determines the establishment of SARS-CoV-2 infection in the body.

4. The SARS-CoV-2/HIV coinfection steady state $\Delta_{VH} = (X_3, Y_3, V_3, S_3, W_3, H_3)$, where

$$X_3 = \frac{\delta (\theta k \lambda + \beta \mu \omega)}{a\eta \lambda}, \quad Y_3 = \frac{a\delta}{a\eta} \left(\frac{a\theta \lambda \rho}{a\delta (\theta k \lambda + \beta \mu \omega)} - 1\right), \quad V_3 = \frac{a}{\eta} \left(\frac{a\theta \lambda \rho}{a\delta (\theta k \lambda + \beta \mu \omega)} - 1\right),$$

$$S_3 = \frac{b\omega}{\theta \lambda}, \quad W_3 = \frac{\omega(u\alpha \delta + a\gamma \eta)}{a\theta \lambda} \left(\left(\frac{\lambda \xi}{b\omega} + \frac{u\lambda \rho}{\theta k \lambda + \beta \mu \omega}\right) \frac{a\theta}{u\alpha \delta + a\gamma \eta} - 1\right),$$

$$H_3 = \frac{u\alpha \delta + a\gamma \eta}{a\theta \lambda} \left(\left(\frac{\lambda \xi}{b\omega} + \frac{u\lambda \rho}{\theta k \lambda + \beta \mu \omega}\right) \frac{a\theta}{u\alpha \delta + a\gamma \eta} - 1\right).$$

It follows that $W_3 > 0$ and $H_3 > 0$ only when $(\lambda \xi / b\omega + u\lambda \rho / (\theta k \lambda + \beta \mu \omega)) a\theta \lambda / (u\alpha \delta + a\gamma \eta) > 1$. On the other hand, $Y_3 > 0$ and $V_3 > 0$ only when $a\theta \lambda \rho / a\delta (\theta k \lambda + \beta \mu \omega) > 1$.

Thus, we can rewrite the components of $\Delta_{VH}$ as

$$X_3 = \frac{X_0}{R_4}, \quad Y_3 = \frac{a\delta}{a\eta} (R_4 - 1), \quad V_3 = \frac{a}{\eta} (R_4 - 1),$$

$$S_3 = \frac{b\omega}{\theta \lambda}, \quad W_3 = \frac{\omega(u\alpha \delta + a\gamma \eta)}{a\theta \lambda} (R_3 - 1), \quad H_3 = \frac{u\alpha \delta + a\gamma \eta}{a\theta} (R_3 - 1),$$

where

$$R_3 = \left(\frac{\lambda \xi}{b\omega} + \frac{u\lambda \rho}{\theta k \lambda + \beta \mu \omega}\right) \frac{a\theta}{u\alpha \delta + a\gamma \eta},$$

$$R_4 = \frac{a\theta \lambda \rho}{a\delta (\theta k \lambda + \beta \mu \omega)}.$$
Therefore, $\Delta_{VH}$ exists when $R_3 > 1$ and $R_4 > 1$. Here, $R_3$ and $R_4$ are threshold numbers that determine the occurrence of SARS-CoV-2/HIV coinfection. Note that we can rewrite $R_3$ as

$$R_3 = \frac{\xi \theta \lambda \alpha \gamma}{\beta \gamma \omega (u \alpha \delta + a \gamma \eta)} + \frac{a \eta \theta \lambda \mu \alpha \delta}{a \delta (\theta k \lambda + \beta \mu \omega) (u \alpha \delta + a \gamma \eta)} = R_1 \frac{\alpha \gamma \eta}{u \alpha \delta + a \gamma \eta} + R_1 \frac{u \alpha \delta}{u \alpha \delta + a \gamma \eta} < R_1 + R_4,$$

which implies that $R_3 < R_1$ and $R_3 < R_4$.

All steady states of model (1) and their existence conditions are summarized in Table 2. For simplicity, we will use the following contractions in the next sections:

$$X(t) \equiv X, \ Y(t) \equiv Y, \ V(t) \equiv V, \ S(t) \equiv S, \ W(t) \equiv W, \ H(t) \equiv H.$$

## 4 | GLOBAL PROPERTIES

In this section, we show the global asymptotic stability of all steady states by constructing Lyapunov functions following the method presented in other works.\(^48^{–50}\) We define $F(\nu) = \nu - 1 - \ln \nu$. We will use the arithmetic-geometric mean inequality

$$\frac{1}{n} \sum_{i=1}^{n} \chi_i \geq \sqrt[n]{\frac{1}{n} \prod_{i=1}^{n} \chi_i}, \ \chi_i \geq 0, \ i = 1, 2, \ldots$$

which yields

$$\frac{S_j}{S} + \frac{SW_j H}{S WH_j} + \frac{WH_j}{W_H} \geq 3, \ j = 1, 3, \quad (4)$$

$$\frac{X_j}{X} + \frac{XY_j V}{X_V Y_j} + \frac{Y V_j}{Y V} \geq 3, \ j = 2, 3. \quad (5)$$

**Theorem 1.** If $R_1 \leq 1$ and $R_2 \leq 1$, then the steady state $\Delta_0$ is globally asymptotically stable (G.A.S).

**Proof.** Construct a Lyapunov function $\theta_0(X, Y, V, S, W, H)$ as

$$\theta_0 = X_0 F\left(\frac{X}{X_0}\right) + Y + \frac{\eta X_0}{\delta} V + \frac{\mu}{u} S_0 F\left(\frac{S}{S_0}\right) + \frac{\mu}{u} W + \frac{\mu \beta}{\lambda} H.$$ 

Clearly, $\theta_0(X, Y, S, W, H) > 0$ for all $X, Y, S, W, H > 0$, and $\theta_0(X_0, 0, S_0, 0, 0) = 0$. Calculating $d\theta_0/dt$ along the solutions of system (1) gives
\[
\frac{d\theta_0}{dt} = \left(1 - \frac{X_0}{X}\right) \dot{X} + \dot{Y} + \frac{\eta X_0}{\delta} \dot{V} + \frac{u}{\delta} \left(1 - \frac{S_0}{S}\right) \dot{S} + \frac{\mu}{\delta} \dot{W} + \frac{\mu \beta}{u \lambda} \dot{H}
\]
\[
= \left(1 - \frac{X_0}{X}\right) \left(\rho - aX - \eta XV + (\eta XV - kY - \mu YS) + \frac{\eta X_0}{\delta} (aY - \delta V)\right)
\]
\[
+ \frac{\mu}{u} \left(1 - \frac{S_0}{S}\right) (\xi + uYS - \gamma S - \theta SH) + \frac{\mu}{u} (\theta SH - \beta W) + \frac{\mu \beta}{u \lambda} (\lambda W - \omega H).\]

Using \(\rho = aX_0\) and \(\xi = \gamma S_0\), we obtain
\[
\frac{d\theta_0}{dt} = -\frac{\alpha}{X} (X - X_0)^2 + \eta VX_0 - kY - \mu YS + \frac{\eta X_0}{\delta} aY - \eta X_0 V
\]
\[
- \frac{\mu}{u} \frac{\gamma}{S} (S - S_0)^2 + \mu YS - \mu YS_0 + \frac{\mu}{u} \theta S_0 H - \frac{\mu \beta}{u \lambda} \omega H
\]
\[
= -\frac{\alpha}{X} (X - X_0)^2 - \frac{\mu \gamma}{u S} (S - S_0)^2 + \frac{\eta X_0}{\delta} \left(a - k\right) - \frac{\mu}{u} \frac{\gamma}{S} - \frac{\beta}{\omega} H
\]
\[
= -\frac{\alpha}{X} (X - X_0)^2 - \frac{\mu \gamma}{u S} (S - S_0)^2 + \frac{\gamma k + \mu \xi}{\gamma} \left(S - S_0\right) + \frac{\mu}{u} \frac{\gamma}{S} \left(S_0\right) - \frac{\beta}{\omega} H
\]
\[
= -\frac{\alpha}{X} (X - X_0)^2 - \frac{\mu \gamma}{u S} (S - S_0)^2 + \frac{\gamma k + \mu \xi}{\gamma} \left(S_0 - S\right) + \frac{\mu}{u} \frac{\gamma}{S} \left(S_0\right) - \frac{\beta}{\omega} H
\]

Since \(R_1 \leq 1\) and \(R_2 \leq 1\), we get \(d\theta_0/dt \leq 0\) for all \(X, Y, V, S, W, H > 0\). Also, \(d\theta_0/dt = 0\) when \(X = X_0, S = S_0\), and \(Y = H = 0\). Define \(T_0 = \{(X, Y, V, S, W, H) : d\theta_0/dt = 0\}\) and let \(T'_0\) be the largest invariant subset of \(T_0\). The solutions of model (1) converge to \(T'_0\). The set \(T'_0\) includes elements with \(X = X_0, S = S_0, Y = H = 0\), and hence \(\dot{Y} = \dot{H} = 0\). The second and last equations of model (1) yield
\[
0 = \dot{Y} = \eta VX_0,
\]
\[
0 = \dot{H} = \lambda W.
\]

Thus, \(V = W = 0\) for all \(t\). Therefore, \(T'_0 = \{\Delta_0\}\), and by applying Lyapunov–LaSalle asymptotic stability theorem,\(^{51-53}\) we get that \(\Delta_0\) is G.A.S.

**Theorem 2.** If \(R_1 > 1\) and \(R_4 \leq 1\), then the steady state \(\Delta_H\) is G.A.S.

**Proof.** Define a Lyapunov function \(\theta_1(X, Y, V, S, W, H)\) as
\[
\theta_1 = X_1 F \left(\frac{X}{X_1}\right) + Y + \frac{\eta X_1}{\delta} V + \frac{u}{\delta} S_1 F \left(\frac{S}{S_1}\right) + \frac{u}{\delta} W_1 F \left(\frac{W}{W_1}\right) + \frac{\mu}{\delta} \frac{\beta}{u \lambda} H_1 F \left(\frac{H}{H_1}\right).
\]

Differentiating \(\theta_1\), we obtain
\[
\frac{d\theta_1}{dt} = \left(1 - \frac{X_1}{X}\right) \dot{X} + \dot{Y} + \frac{\eta X_1}{\delta} \dot{V} + \frac{u}{\delta} \left(1 - \frac{S_1}{S}\right) \dot{S} + \frac{\mu}{\delta} \left(1 - \frac{W_1}{W}\right) \dot{W} + \frac{\mu \beta}{u \lambda} \left(1 - \frac{H_1}{H}\right) \dot{H}
\]
\[
= \left(1 - \frac{X_1}{X}\right) \left(\rho - aX - \eta XV + (\eta XV - kY - \mu YS) + \frac{\eta X_1}{\delta} (aY - \delta V)\right)
\]
\[
+ \frac{\mu}{u} \left(1 - \frac{S_1}{S}\right) (\xi + uYS - \gamma S - \theta SH) + \frac{\mu}{u} \left(1 - \frac{W_1}{W}\right) (\theta SH - \beta W) + \frac{\mu \beta}{u \lambda} \left(1 - \frac{H_1}{H}\right) (\lambda W - \omega H)
\]
\[
= \left(1 - \frac{X_1}{X}\right) \left(\rho - aX + \eta VX_1 - kY + \frac{\eta X_1}{\delta} aY - \eta VX_1 + \frac{u}{\delta} \left(1 - \frac{S_1}{S}\right) (\xi - \gamma S)
\]
\[
- \mu YS_1 + \frac{\mu}{u} \theta S_1 H - \frac{\mu}{u} \theta SH W_1 W + \frac{\mu}{u} \beta W_1 - \frac{\mu}{u} \beta W_1 H = \frac{\mu \beta}{u \lambda} H + \frac{\mu \beta}{u \lambda} H_1.
\]
By using the steady state conditions for $\Delta H$, we get
\[
\begin{align*}
\rho &= aX_1, \\
\xi &= \gamma S_1 + \theta H_1 S_1, \\
\theta H_1 S_1 &= \beta W_1, \\
\lambda W_1 &= \omega H_1.
\end{align*}
\]

Then, we obtain
\[
\frac{d\theta_1}{dt} = -\frac{a}{X} (X - X_1)^2 - kY + \frac{\eta X_1}{\delta} aY - \frac{\mu \gamma}{u} S (S - S_1)^2 + \frac{\mu}{u} \theta H_1 S_1 - \frac{\mu}{u} \theta H_1 S_1 \frac{S_1}{S} \\
&\quad - \mu Y S_1 + \frac{\mu}{u} \theta H S_1 - \frac{\mu}{u} \theta H S \frac{W_1}{W} + \frac{\mu}{u} \beta \frac{W_1}{H} H - \frac{\mu}{u} \beta \frac{W_1}{H} H + \frac{\mu}{u} \beta \frac{W_1}{H} H \\
&= -\frac{a}{X} (X - X_1)^2 - \frac{\mu \gamma}{u} (S - S_1)^2 + \left(\frac{\eta X_1}{\delta} a - k - \mu S_1\right) Y + \frac{\mu}{u} \theta H_1 S_1 \left(3 - \frac{S_1}{S} - \frac{SW_1 H}{S_1 WH_1} - \frac{WH_1}{W_1 H}\right) \\
&\quad + \frac{\mu}{u} \theta H_1 S_1 \left(3 - \frac{S_1}{S} - \frac{SW_1 H}{S_1 WH_1} - \frac{WH_1}{W_1 H}\right) \\
&= -\frac{a}{X} (X - X_1)^2 - \frac{\mu \gamma}{u} (S - S_1)^2 + \frac{\theta k + \beta \mu \omega}{\theta \lambda} \left(R_4 - 1\right) Y + \frac{\mu}{u} \theta H_1 S_1 \left(3 - \frac{S_1}{S} - \frac{SW_1 H}{S_1 WH_1} - \frac{WH_1}{W_1 H}\right).
\]

Since $R_4 \leq 1$ and by using the inequality in (4) for $j = 1$, we find that $d\theta_1 / dt \leq 0$ for all $X, Y, V, S, W, H > 0$. Moreover, $d\theta_1 / dt = 0$ when $X = X_1, S = S_1, W = W_1, H = H_1$, and $Y = 0$. The solutions of model (1) converge to $T'$, the largest invariant subset of $T_1 = \{(X, Y, V, S, W, H) : d\theta_1 / dt = 0\}$. The set $T'$ includes $Y = 0$, and then $\dot{Y} = 0$. The second equation of system (1) implies
\[
0 = \dot{Y} = \eta VX_1,
\]
which yields $V = 0$ for all $t$. Hence, $T' = \{\Delta H\}$, and $\Delta H$ is G.A.S using Lyapunov–LaSalle asymptotic stability theorem.\(\square\)

**Theorem 3.** If $R_2 > 1$ and $R_3 \leq 1$, then the steady state $\Delta V$ is G.A.S.

**Proof.** Define a Lyapunov function $\theta_2(X, Y, V, S, W, H)$ as
\[
\theta_2 = X_2 F \left(\frac{X}{X_2}\right) + Y_2 F \left(\frac{Y}{Y_2}\right) + \frac{\eta X_2}{\delta} V_2 F \left(\frac{V}{V_2}\right) + \frac{\mu}{u} S_2 F \left(\frac{S}{S_2}\right) + \frac{\mu}{u} W + \frac{\mu}{u} \beta H.
\]

Differentiating $\theta_2$, we obtain
\[
\frac{d\theta_2}{dt} = \left(1 - \frac{X_2}{X}\right) \dot{X} + \left(1 - \frac{Y_2}{Y}\right) \dot{Y} + \frac{\eta X_2}{\delta} \left(1 - \frac{V_2}{V}\right) \dot{V} + \frac{\mu}{u} \left(1 - \frac{S_2}{S}\right) \dot{S} + \frac{\mu}{u} \dot{W} + \frac{\mu}{u} \beta \dot{H}
\]
\[
= \left(1 - \frac{X_2}{X}\right) \left(\rho - aX - \eta XV\right) + \left(1 - \frac{Y_2}{Y}\right) \left(\eta XV - kY - \mu YS\right) + \frac{\eta X_2}{\delta} \left(1 - \frac{V_2}{V}\right) \left(aY - \delta V\right) \\
&\quad + \frac{\mu}{u} \left(1 - \frac{S_2}{S}\right) \left(\xi + uYS - \gamma S - \theta SH\right) + \frac{\mu}{u} \left(\theta SH - \beta W\right) + \frac{\mu}{u} \beta \left(\lambda W - \omega H\right) \\
&= \left(1 - \frac{X_2}{X}\right) \left(\rho - aX\right) - \eta XV \frac{Y_2}{Y} - kY + \eta XV \frac{Y_2}{Y} - kY + \mu Y_2 S + \frac{\eta X_2}{\delta} aY - \frac{\eta X_2}{\delta} aY \frac{V_2}{V} \\
&\quad + \eta V_2 X_2 + \frac{\mu}{u} \left(1 - \frac{S_2}{S}\right) \left(\xi - \gamma S\right) - \mu Y S_2 + \frac{\mu}{u} \theta H S_2 - \frac{\mu}{u} \beta \omega H.
\]
Theorem 4.

If $R_3 > 1$ and $1 < R_3 \leq 1 + \lambda \xi \eta / \beta \omega (ua\delta + a\gamma \eta)$, then the steady state $\Delta_{V^H}$ is G.A.S.

Proof. Define a Lyapunov function $\theta_3(X, Y, V, S, W, H)$ as

$$
\theta_3 = X_3F \left( \frac{X}{X_3} \right) + Y_3F \left( \frac{Y}{Y_3} \right) + \eta X_3 \delta V_3F \left( \frac{V}{V_3} \right) + \mu u S_3F \left( \frac{S}{S_3} \right) + \mu W_3F \left( \frac{W}{W_3} \right) + \frac{\mu \beta}{u \lambda} H_3F \left( \frac{H}{H_3} \right).
$$
Differentiating $\theta_3$, we obtain

$$\frac{d\theta_3}{dt} = \left(1 - \frac{X_3}{X}\right) \dot{X} + \left(1 - \frac{Y_3}{Y}\right) \dot{Y} + \frac{\eta X_3}{\delta} \left(1 - \frac{V_3}{V}\right) \dot{V} + \frac{\mu}{u} \left(1 - \frac{S_3}{S}\right) \dot{S} + \frac{\mu}{u} \left(1 - \frac{W_3}{W}\right) \dot{W} + \frac{\mu}{u} \left(1 - \frac{H_3}{H}\right) \dot{H}$$

$$= \left(1 - \frac{X_3}{X}\right) \left(\rho - aX - \eta VX\right) + \left(1 - \frac{Y_3}{Y}\right) \left(\eta VX - kY - \mu YS\right) + \frac{\eta X_3}{\delta} \left(1 - \frac{V_3}{V}\right) (aY - \delta V)$$

$$+ \frac{\mu}{u} \left(1 - \frac{S_3}{S}\right) \left(\xi + uYS - \gamma S - \theta SH\right) + \frac{\mu}{u} \left(1 - \frac{W_3}{W}\right) \left(\theta SH - \beta W\right) + \frac{\mu}{u} \left(1 - \frac{H_3}{H}\right) (\lambda W - \omega H)$$

$$= \left(1 - \frac{X_3}{X}\right) \left(\rho - aX\right) - \eta VX_3 \left(\frac{Y_3}{Y}\right) - kY + kY + \mu YS + \frac{\eta X_3}{\delta} - aY - \frac{\eta X_3}{\delta} - aY \frac{V_3}{V} + \eta V_3 X_3$$

$$+ \frac{\mu}{u} \left(1 - \frac{S_3}{S}\right) \left(\xi - \gamma S\right) + \frac{\mu}{u} \theta HS_3 - \mu YS_3 - \frac{\mu}{u} \theta SH \frac{W_3}{W} + \frac{\mu}{u} \beta W_3 - \frac{\mu}{u} \beta W \frac{H_3}{H} + \frac{\mu}{u} \beta \omega \frac{H_3}{H} + \frac{\mu}{u} \beta \omega H_3.$$  

By using the steady state conditions for $\Delta_{VH}$,

$$\begin{cases}
\rho = aX_3 + \eta V_3 X_3,
\eta V_3 X_2 = kY + \mu Y_3 S_3,
\alpha Y_3 = \delta V_3,
\xi = \gamma S_3 + \theta H_3 S_3 - uY_3 S_3,
\theta H_3 S_3 = \beta W_3,
\lambda W_3 = \omega H_3,
\end{cases}$$

we obtain

$$\frac{d\theta_3}{dt} = -\frac{a}{X} (X - X_3)^2 - \frac{\mu}{u} \left(\frac{Y}{S} (S - S_3)^2 + 3\eta V_3 X_3 - \eta V_3 X_3 \frac{X_3}{X} - \eta V_3 X_3 \frac{X_3}{X} \frac{XY_3 V}{X_3 Y_3 V} - \eta V_3 X_3 \frac{XY_3 V}{X_3 Y_3 V} + 3 \frac{\mu}{u} \theta H_3 S_3 \right.$$ 

$$- \frac{\mu}{u} \theta H_3 S_3 \frac{S_3}{S} - \frac{\mu}{u} \theta H_3 S_3 \frac{S_3}{S} - \frac{\mu}{u} \theta H_3 S_3 \frac{S_3}{S} - \frac{\mu}{u} \theta H_3 S_3 \frac{S_3}{S} - \frac{2\mu Y_3 S_3 + \mu Y_3 S_3 S_3 + \mu Y_3 S_3 S_3 + \mu Y_3 S_3}{S_3}$$

$$= -\frac{a}{X} (X - X_3)^2 - \frac{\mu}{u} \left(\frac{Y}{S} (S - S_3)^2 + \eta V_3 X_3 \left(3 - \frac{X_3}{X} \frac{XY_3 V}{X_3 Y_3 V} - \frac{Y_3}{Y_3 V}\right)\right.$$ 

$$- \frac{\mu}{u} \theta H_3 S_3 \left(2 - \frac{S_3}{S} - \frac{S_3}{S} + \frac{\mu}{u} \theta H_3 S_3 \left(3 - \frac{S_3}{S} - \frac{S_3}{S} - \frac{SW_3 H_3}{SW_3 H_3} - \frac{WH_3}{H_3}\right)\right.$$ 

$$= -\frac{a}{X} (X - X_3)^2 + \frac{\mu}{u} \left(\frac{u a \delta + \alpha \eta}{S} (S - S_3)^2 \frac{\mu}{u} \theta H_3 S_3 \left(3 - \frac{S_3}{S} - \frac{S_3}{S} - \frac{SW_3 H_3}{SW_3 H_3} - \frac{WH_3}{H_3}\right)\right.$$ 

$$+ \eta V_3 X_3 \left(3 - \frac{X_3}{X} - \frac{XY_3 V}{X_3 Y_3 V} - \frac{Y_3}{Y_3 V}\right) + \frac{\mu}{u} \theta H_3 S_3 \left(3 - \frac{S_3}{S} - \frac{S_3}{S} - \frac{SW_3 H_3}{SW_3 H_3} - \frac{WH_3}{H_3}\right).$$

Since $1 < R_3 \leq 1 + \lambda \xi + \eta (\mu \alpha \delta + \alpha \eta)$ and using inequalities (4) and (5), we get $d\theta_3/dt \leq 0$ for all $X, Y, V, S, W, H > 0$. Moreover, $d\theta_3/dt = 0$ when $X = X_3, S = S_3, Y = Y_3, V = V_3, W = W_3$, and $H = H_3$. The solutions of model (1) converge to $T_3'$ which is the largest invariant subset of $T_3 = \{(X, Y, V, S, W, H) : d\theta_3/dt = 0\}$. Hence, $T_3' = \{\Delta_{VH}\}$, and $\Delta_{VH}$ is G.A.S using Lyapunov–LaSalle asymptotic stability theorem. \(\square\)

The global stability conditions of all steady states are summarized in Table 3.

| Steady state | Global stability conditions |
|-------------|-----------------------------|
| $\Delta_3$ = (X, 0, 0, S, 0, 0) | $R_3 \leq 1$ and $R_2 \leq 1$ | | CASE 3. Global stability conditions of the steady states of model (1) |
This section presents some numerical simulations to assist the results gained in the previous sections. In addition, it shows the impact of low number of CD4$^+$ T cells on SARS-CoV-2/HIV coinfection. To achieve this goal, we consider three sets of initial conditions as follows:

**Initial 1:** $X(0) = 5$, $Y(0) = 0.0001$, $V(0) = 0.0002$, $S(0) = 100$, $W(0) = 5$, $H(0) = 10$.

**Initial 2:** $X(0) = 10$, $Y(0) = 0.001$, $V(0) = 0.002$, $S(0) = 200$, $W(0) = 10$, $H(0) = 15$.

**Initial 3:** $X(0) = 15$, $Y(0) = 0.002$, $V(0) = 0.003$, $S(0) = 300$, $W(0) = 15$, $H(0) = 20$.

**FIGURE 1** The numerical simulations of model (1) for $\eta = 0.9$, $\mu = 1$, $\delta = 5.36$, and $\theta = 0.0001$ with three different sets of initial conditions. The uninfected steady state $\Delta_0 = (22.41, 0, 0, 1000, 0, 0)$ is G.A.S. [Colour figure can be viewed at wileyonlinelibrary.com]
The selection of these values is optional. Furthermore, it is divided into three sets to ensure that the global stability of the steady states is not affected by the choice of initial conditions. We use the MATLAB solver ode45 to solve system (1). According to the global stability of the steady states $\Delta_0$, $\Delta_H$, $\Delta_V$, and $\Delta_{VH}$ in Theorems 1–4, we split the simulations into four cases. In these cases, we vary the values of $\eta$, $\mu$, $\delta$, and $\theta$ of model (1). The values of all other parameters are fixed and listed in Table 1. The four cases are given as follows:

(i) We take $\eta = 0.9$, $\mu = 1$, $\delta = 5.36$, and $\theta = 0.0001$. The thresholds in this case are given by $R_1 = 0.5 < 1$ and $R_2 = 9.03 \times 10^{-4} < 1$. In harmony with Theorem 1, the steady state $\Delta_0 = (22.41, 0, 0, 1000, 0, 0)$ is G.A.S (see Figure 1). This is an optimal case when the person does not suffer from neither SARS-CoV-2 infection nor HIV infection.

FIGURE 2 The numerical simulations of model (1) for $\eta = 0.55$, $\mu = 1$, $\delta = 5.36$, and $\theta = 0.0016$ with three different sets of initial conditions. The single HIV-infection steady state $\Delta_H = (22.41, 0, 0, 125, 17.5, 43.75)$ is G.A.S [Colour figure can be viewed at wileyonlinelibrary.com]
(ii) We choose $\eta = 0.55$, $\mu = 1$, $\delta = 5.36$, and $\theta = 0.0016$. This provides us with $R_1 = 8 > 1$ and $R_4 = 0.0044 < 1$. According to Theorem 2, the steady state $\Delta_H = (22.41, 0, 0, 125, 17.5, 43.75)$ is G.A.S (see Figure 2). This point represents the case when a person has HIV infection with low CD4$^+$ T cell counts, while SARS-CoV-2 infection is not detected.

(iii) We select $\eta = 2.9$, $\mu = 0.02$, $\delta = 0.03$, and $\theta = 0.0001$. This gives $R_2 = 25.8534 > 1$ and $R_3 = 0.5054 < 1$. In this case, the solutions globally converge to the steady state $\Delta_V = (0.876, 0.0011, 0.0085, 1010.71, 0, 0)$. This result agrees with Theorem 3 and is displayed in Figure 3. This case represents a person with SARS-CoV-2 infection, but he does not have HIV disease.

**FIGURE 3** The numerical simulations of model (1) for $\eta = 2.9$, $\mu = 0.02$, $\delta = 0.03$, and $\theta = 0.0001$ with three different sets of initial conditions. The single SARS-CoV-2-infection steady state $\Delta_V = (0.876, 0.0011, 0.0085, 1010.71, 0, 0)$ is G.A.S [Colour figure can be viewed at wileyonlinelibrary.com]
(iv) We consider $\eta = 2.9, \mu = 0.02, \delta = 0.1$, and $\theta = 0.0016$. This implies that $R_3 = 8.0743 > 1$, $R_3 < 1 + \frac{\lambda \kappa}{\beta_0 \mu \delta + \alpha \gamma} = 8.9885$, and $R_4 = 59.76 > 1$. In harmony with Theorem 4, the steady state $\Delta_{VH} = (0.375, 0.0084, 0.02, 125, 17.71, 44.28)$ is G.A.S (see Figure 4). In this case, SARS-CoV-2/HIV coinfection occurs, where an HIV patient gets infected with COVID-19. CD4$^+$ T cells, which are the main target of HIV, are recruited to clear SARS-CoV-2 infection from the body. However, if the patient has low CD4$^+$ T cell counts, the clearance of SARS-CoV-2 may not be achieved. This can lead to severe infection and death.

For further confirmation of the asymptotic stability of $\Delta_{VH}$, we calculate the Jacobian matrix of model (1) at the steady state $\Delta = (X, Y, V, S, W, H)$ as

![Graphs of model simulations for different initial conditions](image-url)

**FIGURE 4** The numerical simulations of model (1) for $\eta = 2.9, \mu = 0.02, \delta = 0.1$, and $\theta = 0.0016$ with three different sets of initial conditions. The SARS-CoV-2/HIV coinfection steady state $\Delta_{VH} = (0.375, 0.0084, 0.02, 125, 17.71, 44.28)$ is G.A.S [Colour figure can be viewed at wileyonlinelibrary.com]
The effect of killing rate of CD4$^+$ T cells

To see the effect of changing the value of $\mu$ on the stability of system (1), we pick up the same values considered in case (iv) ($\eta = 2.9$, $\delta = 0.1$, and $\theta = 0.0016$) with increasing the value of $\mu$ from $\mu = 0.02$ to $\mu = 1.5$. This gives $R_1 = 8 > 1$ and $R_4 = 0.8314 < 1$, so the steady state $\Delta_H = (22.41, 0, 0.125, 17.5, 43.75)$ is G.A.S. Mathematically, increasing the value of $\mu$ inverts the value of $R_4$ from $R_4 = 59.76 > 1$ to $R_4 = 0.8314 < 1$, which means that a bifurcation occurs at $R_4 = 1$. As a result, the steady state $\Delta_{V_H}$ loses its stability, and $\Delta_0$ becomes G.A.S. Biologically, increasing the value of $\mu$ corresponds the situation when SARS-CoV-2 is cleared from the body of HIV-infected patient.

Furthermore, to observe the impact of increasing or decreasing the value of $\mu$ on the concentrations of infected epithelial cells and SARS-CoV-2, we consider case (iv) with different values of $\mu$ (see Figure 5). We see that reducing the killing rate constant $\mu$ of CD4$^+$ T cells increases the concentrations of infected epithelial cells and SARS-CoV-2 particles, while increasing the killing rate does the opposite effect.

**TABLE 4** Local stability of the steady state $\Delta_{V_H}$

| Case | The steady states | $\text{Re}(\mathcal{L}_j)$, $j = 1, 2, \ldots, 6$ | Stability |
|------|------------------|---------------------------------|-----------|
| (iv) | $\Delta_0 = (22.41, 0, 0, 1000, 0, 0)$ | $(-20.8613, -4.1762, 1.6762, 0.6513, -0.01, -0.001)$ | Unstable |
|      | $\Delta_H = (22.41, 0, 125, 17.5, 43.75)$ | $(-5.49896, 2.78896, -2.5115, -0.0343, -0.0343, -0.0001)$ | Unstable |
|      | $\Delta_Y = (2.9172, 0.001, 0.0023, 1009.69, 0, 0)$ | $(-20.4038, -4.1894, 1.6894, -0.0039, -0.0039, -0.0099)$ | Unstable |
|      | $\Delta_{V_H} = (0.375, 0.0084, 0.02, 125, 17.7144, 28)$ | $(-2.7113, -2.5117, -0.0347, -0.0347, -0.0287, -0.0287)$ | Stable |

**FIGURE 5** The effect of decreasing $\mu$ on the concentrations of infected epithelial cells $Y(t)$ and SARS-CoV-2 particles $V(t)$. The parameters considered here are $\eta = 2.9$, $\delta = 0.1$, and $\theta = 0.0016$ with initial conditions $(X(0), Y(0), V(0), S(0), W(0), H(0)) = (5, 0.0001, 0.0002, 100, 5, 10)$ [Colour figure can be viewed at wileyonlinelibrary.com]
The above results indicate that high killing rate of CD4+ T cells is required to clear SARS-CoV-2 from the body of HIV patient. On the other hand, low killing rate or low CD4+ T cell counts allows SARS-CoV-2 to replicate and infect more healthy epithelial cells. As a result, SARS-CoV-2/HIV coinfected patient may suffer from severe SARS-CoV-2 infection and die.

5.2 | Sensitivity analysis

Sensitivity analysis allows us to measure a relative change in a variable when a parameter changes. We perform sensitivity analyses for $R_1$ and $R_2$ due to their pivotal role in determining the stability of the uninfected steady state $\Delta_0$. Following Chitnis et al., the normalized forward sensitivity index of a variable $v$ with respect to a parameter $p$ is defined as

$$\Gamma_p^v = \frac{\partial v}{\partial p} \cdot \frac{p}{v},$$

where $v$ is a differentiable function.

5.2.1 | Sensitivity analysis of $R_1$

The normalized forward sensitivity index of $R_1$ with respect to a parameter $p$ is given by

$$\Gamma_p^{R_1} = \frac{\partial R_1}{\partial p} \cdot \frac{p}{R_1}.$$ We compute the sensitivity indices of $R_1$ to each parameter that it includes using the parameter values given in Table 1. The results are presented in Table 5. It is easy to see that the sensitivity indices of $R_1$ do not depend on any parameter values. For example, the sensitivity index of $R_1$ with respect to $\xi$ is

$$\Gamma_{\xi}^{R_1} = \frac{\partial R_1}{\partial \xi} \cdot \frac{\xi}{R_1} = \frac{\theta \gamma \omega}{\beta \gamma \omega} \cdot \frac{\xi}{\xi \theta \lambda} = 1.$$ Thus, it is helpful to interpret the sign of the sensitivity indices of $R_1$. Based on the results in Table 5, the recruitment rate of uninfected CD4+ T cells, $\xi$, the infection rate of CD4+ T cells, $\theta$, and the production rate of HIV, $\lambda$, are the parameters that contribute to the growth of HIV in the body. On the other hand, the death rate of infected CD4+ T cells, $\beta$, and the death rate of HIV particles, $\omega$, are the parameters that have important role in fighting the growth of HIV in the body.

5.2.2 | Sensitivity analysis of $R_2$

The normalized forward sensitivity index of $R_2$ with respect to a parameter $p$ is given by

$$\Gamma_p^{R_2} = \frac{\partial R_2}{\partial p} \cdot \frac{p}{R_2}.$$ Similar to $R_1$, we compute the sensitivity indices of $R_2$ to each parameter that it includes using the values in Table 1. The results are shown in Table 6. We can see that the least sensitive parameter is the death rate of infected epithelial cells, $k$. In general, it can be observed from Table 6 that when one of the parameters with a positive sensitivity index ($a, \gamma, \eta, \rho$) is increased while the other parameters remain constant, this increases the value of $R_2$. This implies that these parameters contribute to the growth of SARS-CoV-2. On the other hand, the parameters with negative sensitivity indices contribute to the reduction in the load of SARS-CoV-2.

| Parameter | Sensitivity index |
|-----------|------------------|
| $\xi$     | 1                |
| $\theta$  | 1                |
| $\lambda$ | 1                |
| $\beta$   | -1               |
| $\gamma$  | -1               |
| $\omega$  | -1               |

**TABLE 5** Sensitivity indices of $R_1$
TABLE 6  Sensitivity indices of $R_2$

| Parameter | Sensitivity index |
|-----------|------------------|
| $a$       | 1                |
| $\eta$    | 1                |
| $\rho$    | 1                |
| $\alpha$  | $-1$             |
| $\delta$  | $-1$             |
| $\gamma$  | 0.99453          |
| $\mu$     | $-0.99453$       |
| $\xi$     | $-0.99453$       |
| $k$       | $-0.00546992$    |

6 | DISCUSSION

SARS-CoV-2 is a new virus that appeared in China in late 2019 and spread to most countries around the world. SARS-CoV-2/HIV coinfection has been recorded in many countries around the world. Many studies argued that SARS-CoV-2 infection is associated with a higher risk of death in HIV patients. This has shed light on the importance of studying the dynamics of SARS-CoV-2/HIV coinfection. Mathematical modeling has been believed to have an important role in understanding new infections. We developed a within-host SARS-CoV-2/HIV coinfection model of six ODEs. This model takes into consideration the interactions between uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, uninfected CD4$^+$ T cells, infected CD4$^+$ T cells, and free HIV particles. We find that the model has four steady states as the following:

(i) The uninfected steady state $\Delta_0$ always exists, and it is G.A.S if $R_1 \leq 1$ and $R_2 \leq 1$. This represents the case when a person is HIV-free and SARS-CoV-2-free.

(ii) The single HIV-infection steady state $\Delta_{H}$ exists if $R_1 > 1$, and it is G.A.S if $R_4 \leq 1$. This represents a person living with HIV but not infected with SARS-CoV-2.

(iii) The single SARS-CoV-2-infection steady state $\Delta_{V}$ exists if $R_3 > 1$, and it is G.A.S if $R_3 \leq 1$. This corresponds the case of a patient having SARS-CoV-2 infection, but he is HIV-free.

(iv) The SARS-CoV-2/HIV coinfection steady state $\Delta_{HV}$ exists and is G.A.S if $R_3 > 1, R_4 > 1, \text{ and } R_3 < 1 + \lambda \xi a \eta / \beta \omega (\omega a \delta + a \eta)$. This represents the case of coinfected patient.

We confirmed the compatibility of numerical simulations with theoretical results. We found that the killing rate $\mu$ of CD4$^+$ T cells affects the global stability of steady states. Increasing the value of $\mu$ causes the SARS-CoV-2/HIV coinfection steady state to lose its stability, while the single HIV infection becomes G.A.S. This represents the situation when the coinfected patient becomes SARS-CoV-2-free, which can be obtained under effective treatments. Additionally, based on our model, decreasing the value of $\mu$ increases the concentrations of infected epithelial cells and SARS-CoV-2 particles. This means that low CD4$^+$ T cell counts can increase the severity of SARS-CoV-2 infection in HIV patients with low immunity. These results agree with many studies which showed that HIV patients with low CD4$^+$ T cell counts or not receiving antiretroviral therapy are at increased risk of getting SARS-CoV-2 infection and death. However, some studies suggested that weak immunity and low CD4$^+$ T cell counts in HIV patients can protect them from developing severe COVID-19 when infected. Therefore, more studies are needed to fill this gap in SARS-CoV-2/HIV coinfection research and understand the full impact of coinfection on patients’ lives.

Comparing with the existing models, the model studied and analyzed in this research is the first model that takes into account the effect of SARS-CoV-2/HIV coinfection. The data on SARS-CoV-2/HIV coinfection are still very limited. As data become available, the model can be fitted with real data to find a better approximation of model's parameters. Consequently, the model can be used to support experimental and medical studies in (i) determining the value of parameters required to clear SARS-CoV-2 infection from HIV-infected patients, (ii) testing the effect of low CD4$^+$ T cell counts on the severity of COVID-19 in HIV patients, (iii) checking the importance of model (1) on the coinfection between HIV and SARS-CoV-2, and (iv) understanding the dynamics of coinfection, which can have an important role in developing new treatments for this group of patients. The principal limitation of this paper is that we did not utilize real data to estimate the parameters’ values in model (1). We took the values from well-studied HIV models or SARS-CoV-2 models. This is because the scarcity of data on SARS-CoV-2/HIV coinfection as we mentioned before. Accordingly, the results can be verified when more data are available.
Model (1) can be improved by (i) adding an equation that simulates the role of CTL immunity during SARS-CoV-2/HIV coinfection, (ii) considering the impact of time delays associated with some biological processes in the model, (iii) taking into consideration the impact of spatial distributions of cells, SARS-CoV-2 and HIV, which will convert the ODEs to PDEs, (iv) adding the effect of HAART of HIV on virus reproduction, and (v) using the new generalized fractional derivative presented in Hattaf55 instead of the classical derivative in (1) to explore the memory effect on the dynamics of model (1).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Coronavirus disease (COVID-19), weekly epidemiological update (1 June 2021), World Health Organization (WHO). Available online: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20210601_weekly_epi_update_42.pdf?sfvrsn=5b0bb9c7c_5&download=true; 2021.
2. Kanwugu ON, Adadi P. HIV/SARS-CoV-2 coinfection: a global perspective. J Med Virol. 2020;93(2):726-732.
3. Global HIV programme, HIV data and statistics, World Health Organization (WHO). Available online: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics; 2021.
4. Bakouny Z, Hawley JE, Choueiri TK, Peters S, Rini BI, Warner JL, Painter CA. COVID-19 and cancer: current challenges and perspectives. Cancer Cell. 2020;38:629-646.
5. Gatechompol S, Avihingsanon A, Putcharoen O, Ruxrungtham K, Kuritzkes DR. COVID-19 and HIV infection co-pandemics and their impact: a review of the literature. AIDS Res Ther. 2021;18(28). doi:10.1186/s12981-021-00335-1
6. Al Agha A, Alshehaiween S, Elaiw A, Alshaikh M. Global analysis of delayed SARS-CoV-2/cancer model with immune response. Mathematics. 2021;9(11):1-27.
7. Evans N, Martinez E, Petrosillo N, Nichols J. COVID-19 and human immunodeficiency virus: pathogen pincer attack. HIV/AIDS - Res Palliat Care. 2021;13:361-375.
8. The U.S. Food and Drug Administration, COVID-19 treatments. Available online: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19; 2021.
9. COVID-19 vaccines, World Health Organization (WHO). Available online: https://extranet.who.int/pqweb/sites/default/files/documents/Status; 2021.
10. Elaiw AM, Al Agha AD. Stability of a general HIV-1 reaction-diffusion model with multiple delays and immune response. Phys A: Stat Mech Appl. 2019;536:1-20.
11. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021;184(4):861-880.
12. Perelson AS, Nelson PW. Mathematical analysis of HIV-1 dynamics in vivo. SIAM Rev. 1999;41(1):3-44.
13. Peng X, Ouyang J, Isnard S, Lin J, Fombuena B, Zhu B, Routy JP. Sharing CD4+ T cell loss: when COVID-19 and HIV collide on immune system. Front Immunol. 2020;11:1-11.
14. Ssentongo P, Heilbrunn ES, Ssentongo AE, Advani S, Chinchilli VM, Nunez JJ, Du P. Epidemiology and outcomes of COVID-19 in HIV-infected individuals: a systematic review and meta-analysis. Sci Rep. 2021;11(1):1-12.
15. Ambrosioni J, Blanco J, Reyes-Urueña JM, et al. Overview of SARS-CoV-2 infection in adults living with HIV. Lancet HIV. 2021;8(5):E294-E305.
16. Sharov KS. HIV/SARS-CoV-2 co-infection: T cell profile, cytokine dynamics and role of exhausted lymphocytes. Int J Infect Dis. 2021;102:163-169.
17. Coronavirus disease (COVID-19): COVID-19 vaccines and people living with HIV, World Health Organization (WHO). Available online: https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-covid-19-vaccines-and-people-living-with-hiv; 2021.
18. Currie C, Fowler J, Kotiadis K, Monks T. How simulation modelling can help reduce the impact of COVID-19. J Simul. 2020;14(2):83-97.
19. Nowak MA, Bangham CRM. Population dynamics of immune responses to persistent viruses. Science. 1996;272:74-79.
20. Elaiw AM. Global properties of a class of HIV models. *Nonlinear Anal Real World Appl.* 2010;11(4):2253-2263.
21. Perelson A, Kirschner D, De Boer R. Dynamics of HIV infection of CD4+ T cells. *Math Biosci.* 1993;114(1):81-125.
22. Perelson A, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature.* 1997;387:188-191.
23. Culshaw R, Ruan S, Spiteri R. Optimal HIV treatment by maximising immune response. *J Math Biol.* 2004;48(5):545-562.
24. Pawelek K, Liu S, Pyalevani F, Rong L. A model of HIV-1 infection with two time delays: mathematical analysis and comparison with patient data. *Math Biosci.* 2012;235(1):98-109.
25. Shu H, Wang L, Wathamough J. Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and CTL immune responses. *SIAM J Appl Math.* 2013;73(3):1280-1302.
26. Li Y, Xu R, Mao S. Global dynamics of a delayed HIV-1 infection model with CTL immune response. *Discret Dyn Nat Soc.* 2011;1:1-13.
27. Xu R. Global stability of an HIV-1 infection model with saturation infection and intracellular delay. *J Math Anal Appl.* 2011;375:75-81.
28. Hattaf K, Yousfi N. Modeling the adaptive immunity and both modes of transmission in HIV Infection. *Compuation.* 2018;6(37):1-18.
29. Al Agha AD, Elaiw AM. Stability of a general reaction-diffusion HIV-1 dynamics model with humoral immunity. *Eur Phys J Plus.* 2019;134(8):1-18.
30. Ren X, Tian Y, Liu L, Liu X. A reaction-diffusion within-host HIV model with cell-to-cell transmission. *J Math Biol.* 2018;76:1831-1872.
31. Lai X, Zou X. A reaction diffusion system modeling virus dynamics and CTL response with chemotaxis. *Discrete Contin Dyn Syst.* 2016;21(8):2567-2585.
32. Zhuang K. Dynamics of a diffusive viral model with Beddington-DeAngelis incidence rate and CTL immune response. *J Nonlinear Sci Appl.* 2017;10(11):5753-5762.
33. Polyanin AD, Sorokin VG, Vyazmin AV. Reaction-diffusion models with delay: some properties, equations, problems, and solutions. *Theor Found Chem Eng.* 2018;52(3):334-348.
34. Kang C, Miao H, Chen X, Xu J, Huang D. Global stability of a diffusive and delayed virus dynamics model with Crowley-Martin incidence function and CTL immune response. *Adv Differ Equ.* 2017;2017(324):1-16.
35. Miao H, Teng Z, Abdurahman X, Li Z. Global stability of a diffusive and delayed virus infection model with general incidence function and adaptive immune response. *Comput Appl Math.* 2018;37(3):3780-3805.
36. Li C, Xu J, Liu Z, Zhou Y. The within-host viral kinetics of SARS-CoV-2. *Math Biosci Eng.* 2020;17(4):2853-2861.
37. Nath BJ, Dehingia K, Mishra VN, Chu Y, Sarmah HK. Mathematical analysis of a within-host model of SARS-CoV-2. *Adv Differ Equ.* 2021;2021(1):1-11.
38. Du SQ, Yuan W. Mathematical modeling of interaction between innate and adaptive immune responses in COVID-19 and implications for viral pathogenesis. *J Med Virol.* 2020;92(9):1615-1628.
39. Almocera AS, Quiroz G, Hernandez-Vargas EA. Stability analysis in COVID-19 within-host model with immune response. *Commun Nonlinear Sci Numer Simul.* 2020;95:105584.
40. Elaiw AM, Al Agha AD. Global dynamics of SARS-CoV-2/cancer model with immune responses. *Appl Math Comput.* 2021;408:1-19.
41. Hattaf K, Yousfi N. Dynamics of SARS-CoV-2 infection model with two modes of transmission and immune response. *Math Biosci Eng.* 2020;17(5):5326-5340.
42. Pinky L, Dobrovolny HM. SARS-CoV-2 coincfections: could influenza and the common cold be beneficial? *J Med Virol.* 2020;1-8.
43. Ahmed I, Doungmo Goufo EF, Yusuf A, et al. An epidemic prediction from analysis of a combined HIV-COVID-19 co-infection model via ABC-fractional operator. *Alex Eng J.* 2021;60(3):2979-2995.
44. Pinky L, Dobrovolny HM. Epidemiological consequences of viral interference: a mathematical modeling study of two interacting viruses. *Front Microbiol.* 2022;13:1-12.
45. Prakash M, Rakkiyappan R, Manivannan A, Cao J. Dynamical analysis of antigen-driven T-cell infection model with multiple delays. *Appl Math Comput.* 2019;354:266-281.
46. Callaway DS, Perelson AS. HIV-1 infection and low steady state viral loads. *Bull Math Biol.* 2002;64:29-64.
47. Adak D, Bairagi N. Analysis and computation of multi-pathways and multi-delays HIV-1 infection model. *Appl Math Model.* 2018;54:517-536.
48. Korobeinikov A. Global properties of basic virus dynamics models. *Bull Math Biol.* 2004;66(4):879-883.
49. Roy P, Roy A, Khailov E, Al Basir F, Grigorieva E. A model of the optimal immunotherapy of psoriasis by introducing IL-10 and IL-22 inhibitor. *J Biol Syst.* 2020;28(3):609-639.
50. Cao X, Roy A, Al Basir F, Roy F. Global dynamics of HIV infection with two disease transmission routes - a mathematical model. *Commun Math Biol Neurosci.* 2020;2020(8):1-16.
51. Barbashin EA. *Introduction to the Theory of Stability.* Wolters-Noordhoff; 1970.
52. La Salle JP. The stability of Dynamical Systems. Society for Industrial and Applied Mathematics; 1976.
53. Lyapunov AM. The general problem of the stability of motion. *Int J Control.* 1992;55(3):531-534.
54. Chitnis N, Hyman JM, Cushing JM. Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. *Bull Math Biol.* 2008;70(5):1272-1296.
55. Hattaf K. A new generalized definition of fractional derivative with non-singular kernel. *Computation.* 2020;8(49):1-9.

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