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Research Article

Mathematical Analysis of the Role of HIV/HBV Latency in Hepatocytes

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The biggest challenge of treating HIV is rampant liver-related morbidity and mortality. This is, to some extent, attributed to hepatocytes acting as viral reservoirs to both HIV and HBV. Viral reservoirs harbour latent provirus, rendering it inaccessible by combinational antiretroviral therapy (cART) that is specific to actively proliferating virus. Latency reversal agents (LRA) such as *Shock and kill* or *lock and block*, aiming at activating the latently infected cells, have been developed. However, they are CD4+ cell-specific only. There is evidence that the low replication level of HIV in hepatocytes is mainly due to the latency of the provirus in these cells. LRA are developed to reduce the number of latently infected cells; however, the impact of the period viral latency in hepatocytes especially, during HIV/HBV coinfection, needs to be investigated. Viral coinfection coupled with lifelong treatment of HIV/HBV necessitates investigation for the optimal control strategy. We propose a coinfection mathematical model with delay and use optimal control theory to analyse the effect of viral latency in hepatocytes on the dynamics of HIV/HBV coinfection. Analytical results indicate that HBV cannot take a competitive exclusion against HIV; thus, the coinfection endemic equilibrium implies chronic HBV in HIV-infected patients. Numerical and analytical results indicate that both HIV and HBV viral loads are higher with longer viral latency period in hepatocytes, which indicates the need to upgrade LRA to other non-CD4+ cell viral reservoirs. Higher viral load caused by viral latency coupled with the effects of cART partly explains why liver-related complications are the leading cause of mortality in HIV-infected persons.

1. Introduction

1.1. Background. Since the introduction of highly active antiretroviral therapy (HAART) in 1980s, there has been progressive improvement in pharmacologically managing HIV to the extent that to date, the life expectancy of HIV-infected people is very close to that of coinfected ones. HIV ceased to be a deadly disease but rather a chronic one. Worldwide, there has been commendable use of combinational antiretroviral therapy (cART), and to date, one could expect that there is a cure to this epidemic that has been on the scene for decades. The current cART is pharmacologically designed to hinder viral progression in the viral replication cycle. This cycle starts with binding onto the host cell and ends with budding or viral replication [1]. One of the key bottlenecks, which has slowed the therapeutic management of the disease, is its ability to establish silent reservoirs within the patient. Viral latency is the ability of a provirus that has successfully integrated into a cell, to remain transcriptionally silent and dormant within a host cell for some time, but capable of producing viral copies upon stimulation [2, 3]. A cell that hosts a dormant virus is called a latently infected cell or a viral reservoir [4]. These reservoirs are predominantly CD4+ cells [1, 4], but research has indicated that there are so many other types of cells that harbour HIV infection [5]. When a cell is latently infected, then it cannot be cleared, neither therapeutically nor through immune killing by cytotoxic T lymphocytes. It is thus asserted that HIV would have a complete cure, if it were not for these viral reservoirs [2]. The challenges of the viral reservoirs stem from the fact that

the current cART responds only to active virally replicating host cells. Consequently, patients that are able to take their cART effectively are able to have undetectable viral load for some time, but due to latency, when the provirus rebound, the patient is again overwhelmed with an influx of viral copies. The problem of viral reservoirs has been addressed by numerous research. One major breakthrough was the introduction of a *shock and kill* strategy [5]. This strategy operates of the principle that a pharmacological agent, such as a cytokine or a small molecule, shocks the virus in the reservoir into transcription or activation [1]. A cell is reactivated the moment it is recognised as an antigen bearing cell that is eventually killed by cytotoxic T lymphocytes or therapeutically by cART. Since HIV reservoirs are predominantly memory CD+4 cells [1, 2], all latency reversal agents are CD4+ specific, implying that only CD4+ cells are activated. Recent studies have indicated that due to the nature of memory CD4+ cells which are the majority HIV viral reservoirs, some type of patients would require 70 years of therapy to completely eradicate all the virus [1]. Viral reservoirs are significantly complicating management of HIV, because the current indicator of the therapeutic effect of cART is the measure of viral copies per some capacity of blood. However, in many cases, patients display very low viral copies and sometimes undetectable during routine checks. Unfortunately, the clinical results are not a sole indicator of the therapeutic effect of cART, because low viral replication may be due to high levels of latency. Most reservoirs are created during acute stage of infection, and they are predominantly CD4+ resting cells in the memory subsets [4]. These cells remain in this state until they are stimulated either through antigen recognition or by any other stimuli. In addition to the *shock and kill* strategy, pharmacologists have developed the *block and lock* therapy [1]. This involves using latency-promoting agents that would target all viral reservoirs to create an irreversible state, such that a cell that is latently infected will never have a chance to rebound and produce viral genomes [1]. It has been stated that, if it was not for these viral reservoirs, HIV would be cured to date [1, 4]. A good example to justify this assertion is the "Berlin" patient, who recovered from HIV just because he had a bone marrow replacement, in which all resting CD4+ cells that were containing the latent provirus were removed [4]. A number of latency reversal agents such as histone deacetylase inhibitors, valproic acid, DNA methylation inhibitors, and protein kinase C agonists have been used [1, 4]. However, in addition to their undesired effects such as blocking the activity of HIV-specific cytotoxic T lymphocytes, there has been little success in cell activation and total clearance of provirus reservoirs [4].

Given that HIV latency in host cells still prevails and varies with respect to individual patients, the effect of the period of latency on the dynamics of the infection needs to be investigated. It is worth mentioning that in addition to CD4+ cells, HIV infects other body cells. There is still a debate on HIV infection in hepatocytes, despite evidence from research that HIV productively infects hepatocytes and other hepatoma cells in a CD4-independent way [6]. HIV has also a direct cytopathic effect on hepatocytes, primarily triggering apoptosis via the HIV gp120 protein-receptor signalling pathway [7]. These directly cytotoxic effects are enhanced in patients coinfected with HIV and viral hepatitis B (HBV), with each virus having significant effects on the others' replication [8]. There has been a lot of concern about high level of liver-related mortality in HIV-infected people, and coinfection with HBV has been mentioned out as one of the leading factors in addition to hepatotoxicity associated cART. The current cART meant to suppress viral replication is very ineffective in human hepatocytes [9], and this has been attributed to the fact that hepatocytes harbour both viruses. This study, therefore, uses mathematical models to investigate the impact of the latency period on the dynamics of HIV and HBV coinfection in the liver.

1.2. Mathematical Modelling. Mathematical models of ordinary or partial differential equations have been used for decades to help understand the within-host dynamics of viral infections. Nowak et al. [10] introduced a basic within-host viral infection model with three variables, namely, target healthy cells, infectious cells, and viral population. This model has been widely adopted and improved to model various aspects and dynamics of viral infections, with and without treatment [11, 12]. However, this basic model failed to capture some vital aspect of immunopathogenesis. It assumed that upon infection, cells instantly begin producing virus. Biologically, there is a time delay between viral entry into a host cell and the time the cell begins to release viral copies (intracellular delay) [13, 14].

The first intracellular delay model was introduced by Herz et al. [13], to characterize the time between the initial viral entry into a target cell and subsequent viral production. Their study reveals that combining the intracellular delay with less than 100% effective drug therapy results in increased infected cell death as compared to the case of perfect drug therapy. They further report that including a delay changes the estimated value of the viral clearance rate but does not change the productively infected T cell loss rate.

Since Herz et al. [13] studied a number of viral dynamics models, some have included one type of delay to cater for time between viral entry and actual production of virus [15, 16], while others have included more than one delay to cater for the time between viral infection and the actual time when cytotoxic T lymphocytes reach out to kill the infectious cells [14, 16, 17]. Pharmacological delay in the viral treatment has also been studied using mathematical models with medication [18, 19]. Intracellular delay of HIV infection dynamics in CD4+ cells [20–22], as well as HBV in hepatocytes [23, 24], has been studied. While some researchers used the basic model of Nowak et al. [10] and incorporated a delay similar to that of Herz et al. [13], others included latency and two delays, on the assumption that once a virus gains access to a host cell, the cell either becomes productive or remains latent until activation [25, 26].

Both discrete time delay [22, 27] and continuous delay described by gamma distribution [15, 28] have been studied. There are some studies on HIV dynamics in macrophages [26, 29, 30], but majority of within-host mathematical

models on HIV consider viral infection in CD4+ cells. To date, only our previous work in [30–33] considers the mathematical approach of HIV dynamics in hepatocytes. In this study, we look at the dynamics of HIV/HBV coinfection in human hepatocytes incorporating intracellular delay and antiretroviral therapy.

2. Model Formulation

We define five variables in the model: healthy hepatocytes T, HIV-infected hepatocytes I_h, HBV-infected hepatocytes I_b, HIV viral load V_h, and HBV viral load V_b. Healthy hepatocytes proliferate at a constant rate λ, are infected by HIV and HBV at rates β_1 and β_2, respectively, and are cleared naturally at rate d_1. In order to incorporate the intracellular phase of the virus life cycle, we assume that HIV production delays by τ_1, and for HBV, it is τ_2, behind the infection of a hepatocyte. This implies that recruitment of HIV and HBV virus-producing hepatocytes at time t is not given by the density $T(t)I_h(t)$ and $T(t)I_b(t)$ of newly infected cells. They are rather given by the density of cells that were infected at time $t-\tau_i$, $i=1,2$, that is, $T(t-\tau_1)V_h(t-\tau_1)$ and $T(t-\tau_2)V_b(t-\tau_2)$, given that they are still alive at time t [13].

The probability that a healthy hepatocyte will survive HIV and HBV latency and produce virions after activation is $e^{-d_1\tau_1}$ and $e^{-d_1\tau_2}$, respectively. HIV- and HBV-infected hepatocytes are cleared at rates d_2 and d_3, whereas the number of HIV and HBV virions produced by one infectious hepatocytes are n_1 and n_2. Due to low HIV infection in hepatocytes [34], we suppose that some of the infectious HIV copies that come from other cells such as CD4+ cells are moving freely in the liver. HIV viral copies are produced from other cells and macrophages at a constant rate m. HIV and HBV viral copies are cleared from the liver at rates c_1 and c_2, respectively. The system of equations describing HIV/HBV dynamics in hepatocytes given the above considerations can be stated as

$$\begin{aligned}
\frac{dT(t)}{dt} &= \lambda - (d_1 - \beta_1 V_h(t) - \beta_2 V_b(t))T(t),\\
\frac{dI_h(t)}{dt} &= e^{-d_1\tau_1}\beta_1 T(t-\tau_1)V_h(t-\tau_1) - d_2 I_h(t),\\
\frac{dI_b(t)}{dt} &= e^{-d_1\tau_2}\beta_2 T(t-\tau_2)V_b(t-\tau_2) - d_3 I_b(t),\\
\frac{dV_h(t)}{dt} &= n_1 d_2 I_h(t) + m - c_1 V_h(t)\\
\frac{dV_b(t)}{dt} &= n_2 d_3 I_b(t) - c_2 V_b(t).
\end{aligned} \tag{1}$$

2.1. Nonnegativity and Boundedness of Solutions. For initial conditions, let $\mathrm{X} = C([-\tau, 0]; \mathbb{R}^5)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to $\mathbb{R}^5$ supplied by the sup-norm $\|Q\| = \sup\{Q(s)\}$, where $Q(s) = \{Q_1(s), Q_2(s), Q_3(s), Q_4(s), Q_5(s)\}$ for $-\tau \le s \le 0$ and $\tau = \max\{\tau_1, \tau_2\}$.

Then, the initial function of the system (1) is given by $T(s) = \mathrm{Q}_1(s)$, $I_h(s) = \mathrm{Q}_2(s)$, $I_b(s) = \mathrm{Q}_3(s)$, $V_h(s) = \mathrm{Q}_4(s)$, and $V_b(s) = \mathrm{Q}_5(s)$, where

$$(Q_1(s), Q_2(s), Q_3(s), Q_4(s), Q_5(s)) \in X \tag{2}$$

and $Q_1(s)$, $Q_2(s)$, $Q_3(s)$, $Q_4(s)$, and $Q_5(s)$ are all nonnegative. Thus

$$\begin{aligned}
T(s) &> 0,\\
I_h(s) &> 0,\\
I_b(s) &> 0,\\
V_h(s) &> 0,\\
V_b(s) &> 0,\\
\forall s &\in [-\tau, 0].
\end{aligned} \tag{3}$$

Theorem 1. *For any nonnegative initial values $T(s)$, $I_h(s)$, $I_b(s)$, $V_h(s)$, and $V_b(s)$, in (3), all solutions to (1) are nonnegative for all $t \ge 0$.*

Proof. By the fundamental theory of functional differential equations [14], we suppose that there is a unique local solution $T(t)$, $I_h(t)$, $I_b(t)$, $V_h(t)$, and $V_b(t)$, for the given initial conditions in (3), to system (1) in $[0, T_f]$, where T_f is a finite number. Using the constant of variation formula, we get the following solutions to system (1):

$$\begin{aligned}
T(t) &= T(0)e^{-\int_0^t (d_1+\beta_1 V_h(\nu)+\beta_2 V_b(\nu))d\nu} + \int_0^t \left(\lambda e^{-\int_0^t (d_1+\beta_1 V_h(\nu)+\beta_2 V_b(\nu))d\nu}\right) d\xi,\\
I_h(t) &= I_h(0)e^{-d_2 t} + \int_0^t \left(e^{-d_1\tau_1}\beta_1 T(\xi-\tau_1)V_h(\xi-\tau_1)e^{-d_2(t-\xi)}\right) d\xi,\\
I_b(t) &= I_b(0)e^{-d_3 t} + \int_0^t \left(e^{-d_1\tau_2}\beta_2 T(\xi-\tau_2)V_b(\xi-\tau_2)e^{-d_3(t-\xi)}\right) d\xi,\\
V_h(t) &= V_h(0)e^{-c_1 t} + \int_0^t (n_1 d_2 I_h(\xi) + m)e^{-c_1(t-\xi)} d\xi,\\
V_b(t) &= V_b(0)e^{-c_2 t} + \int_0^t (n_2 d_3 I_b(\xi))e^{-c_2(t-\xi)} d\xi.
\end{aligned} \tag{4}$$

System (4) shows that the solutions of (1) are positive for all $t \ge 0$. □

Lemma 2. *The closed set $\Omega = \{T(t), I_h(t), I_b(t), V_h(t), V_b(t) \in \mathbb{R}^5 :\}$: $T(t) \ge 0, I_h(t) \ge 0, I_b(t) \ge 0, V_h(t) \ge 0, V_b(t) \ge 0$ is bounded with respect to (1).*

Proof. We show that the solutions are bounded on interval $t \in [0, \tau]$, for $\tau = \max\{\tau_1, \tau_2\}$.

We assume a functional

$$\begin{aligned}
F(t) = &\left(n_1 d_2 e^{-d_1\tau} + n_2 d_3 e^{-d_1\tau}\right) T(t) + n_1 d_2 I_h(t+\tau)\\
&+ n_2 d_3 I_b(t+\tau) + \frac{d_2}{2} V_h(t+\tau) + \frac{d_3}{2} V_b(t+\tau).
\end{aligned} \tag{5}$$

Differentiating Equation (5) and incorporation system (1) result in

$$\begin{aligned}\frac{dF(t)}{dt} &= e^{-d_1\tau}(n_1d_2+n_2d_3)(\lambda - d_1T(t) - \beta_1T(t)V_h(t)\\ &\quad - \beta_2V_b(t)T(t)) + n_1d_2\left(e^{-d_1\tau}\beta_1T(t)V_h(t) - d_2I_h(t)\right)\\ &\quad + n_2d_3\left(e^{-d_1\tau}\beta_2T(t)V_b(t) - d_3I_b(t)\right)\\ &\quad + \frac{d_2}{2}(n_1d_2I_h(t+\tau) + m - c_1V_h(t+\tau))\\ &\quad + \frac{d_3}{2}(n_2d_3I_b(t+\tau) - c_2V_b(t+\tau))\\ \frac{dF(t)}{dt} &= (n_1d_2+n_2d_3)\lambda e^{-d_1\tau} + \frac{d_2m}{2} - (n_1d_2+n_2n_3)e^{-d_1\tau}\beta_2T(t)V_b(t)\\ &\quad - \left\{d_1n_1d_2e^{-d_1\tau}T(t) + d_1n_2d_3e^{-d_1\tau}T(t)\right.\\ &\quad + \frac{n_1d_2^2}{2}I_h(t+\tau) + \frac{n_2d_3^2}{2}I_b(t+\tau) + \frac{d_2c_1}{2}V_h(t+\tau)\\ &\quad \left. + \frac{d_3c_2}{2}V_b(t+\tau)\right\}.\end{aligned} \tag{6}$$

It is indicated that

$$\frac{dF(t)}{dt} \le (n_1d_2+n_2d_3)\lambda e^{-d_1\tau} + \frac{d_2m}{2} - \theta F(t), \tag{7}$$

where

$$\theta = \min\left\{d_1, \frac{d_2}{2}, \frac{d_3}{2}, c_1, c_2\right\}. \tag{8}$$

Therefore

$$F(t) = F(0)e^{-\theta t} + \left(\frac{2(n_1d_2+n_2d_3)\lambda e^{-d_1\tau} + d_2m}{2\theta}\right)\left(1 - e^{-\theta t}\right). \tag{9}$$

Thus, $F(t)$ is bounded and so are the functions $T(t)$, $I_h(t)$, $I_b(t)$, $V_h(t)$ and $V_b(t)$. □

2.2. Steady States of the System. For steady states, it is assumed that there is no delay dependence, that is

$$\begin{aligned}&\lim_{t\to\infty}T(t-\tau) \longrightarrow \lim_{t\to\infty}T(t), \lim_{t\to\infty}V_h(t-\tau) \longrightarrow \lim_{t\to\infty}V_h(t),\\ &\lim_{t\to\infty}V_b(t-\tau) \longrightarrow \lim_{t\to\infty}V_b(t).\end{aligned} \tag{10}$$

2.2.1. Local Stability and Disease-Free Equilibrium. System (1) has a disease-free steady state defined as $D_f = (\lambda/d_1, 0, 0, 0, 0)$. The local stability of D_f is governed by the basic reproduction number R_0, which is the number of secondary viral infections resulting from one virally infected cell in a wholly susceptible cell population. R_0 is established using the next generation operator method as in [35]. It can be shown that the spectral radius of the next generation matrix, which defines the R_0, is given by

$$R_0 = \max\{R_h, R_b\}, \tag{11}$$

where

$$\begin{aligned}R_h &= \frac{n_1\beta_1\lambda e^{-d_1\tau_1}}{c_1d_1},\\ R_b &= \frac{n_2\beta_2\lambda e^{-d_1\tau_2}}{c_2d_1}.\end{aligned} \tag{12}$$

R_h and R_b are the numbers of secondary infections resulting from one HIV and HBV infectious hepatocyte, respectively. Each HIV and HBV productive hepatocyte infects $\beta_1\lambda/d_1$ and $\beta_2\lambda/d_1$ target hepatocytes for a viral lifespan of n_1/c_1 and n_2/c_2. This is conditioned on that when a cell is infected by HIV and HBV, it will survive for the time period of τ_1 and τ_2, with a probability $e^{-d_1\tau_1}$ and $e^{-d_1\tau_2}$.

From Theorem 3 of Van den Driessche and Watmough [35], we deduce the following theorem.

Theorem 3. *The disease-free equilibrium D_f is locally asymptotically stable when $R_0 < 1$, and unstable otherwise.*

In order to establish other conditions that determine the stability of D_f, we use the Jacobian matrix of system (1).

$$J_{D_f} = \begin{bmatrix} -d_1 & 0 & 0 & \frac{-\beta_1\lambda}{d_1} & \frac{-\beta_2\lambda}{d_1}\\ 0 & -d_2 & 0 & \frac{-\beta_1\lambda e^{-d_1\tau_1}}{d_1} & 0\\ 0 & 0 & -d_3 & 0 & \frac{-\beta_2\lambda e^{-d_1\tau_1}}{d_1}\\ 0 & n_1d_2 & 0 & -c_1 & 0\\ 0 & 0 & n_2d_3 & 0 & -c_2 \end{bmatrix}, \tag{13}$$

from which it is seen that $\text{trace}(J_{D_f}) < 0$ and

$$\det\left(J_{D_f}\right) = -d_2\left(c_2d_3 - \frac{n_2d_3\beta_2\lambda e^{-d_1\tau_1}}{d_1}\right)\left(d_2c_1 - \frac{\beta_1\lambda_1n_1d_2e^{-d_1\tau_1}}{d_1}\right). \tag{14}$$

We establish that $\det(J_{D_f}) < 0$ only if

$$\begin{aligned}\frac{n_2\beta_2\lambda e^{-d_1\tau}}{d_1c_2} &< 1,\\ \frac{n_1\beta_1\lambda e^{-d_1\tau}}{d_1c_1} &< 1.\end{aligned} \tag{15}$$

We thus deduce the following theorem.

Theorem 4. *The disease-free equilibrium D_f is locally asymptotically stable when $R_0 < 1$ given that $R_h < 1$ and $R_b < 1$.*

Figure 1 shows higher level of R_b and compared to R_h, which is an indication that HBV is more aggressive in hepatocytes than HIV is. Both reproduction numbers grow with respective increasing infection rates and are inversely proportional to delay in viral production.

To further ascertain the influence of one virus on the other, we express R_h in terms of R_b to have

$$R_b = \frac{R_h c_1 n_2 \beta_2 e^{d_1(\tau_1-\tau_2)}}{c_2 n_1}. \tag{16}$$

For strictly positive parameters, $\partial R_b/\partial R_h > 0$ and $\partial R_h/\partial R_b > 0$, implying that the presence of HIV in the liver influences the increase of HBV and vice versa [36, 37].

2.2.2. Global Stability of Disease-Free Equilibrium. The global stability is of system (1) is derived using a theorem by Castillo-Chavez [38] as shown in Appendix A.

Theorem 5. Castillo-Chavez et al. [38]. *We write system (1) in the form*

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z), \\ \frac{dZ}{dt} &= G(X, Z), G(X, 0) = 0. \end{aligned} \tag{17}$$

where $X = (T)'$ *and* $Z = (I_h, I_b, V_h, V_b)'$. *We derive* $M = D_Z G(X^*, 0)$ *called the Metzler matrix, whose off-diagonal elements are nonnegative, as*

$$M = \begin{bmatrix} -d_2 & 0 & \dfrac{\beta_1 \lambda e^{-d_1\tau_1}}{d_1} & 0 \\ 0 & -d_3 & 0 & \dfrac{\beta_2 \lambda e^{-d_1\tau_2}}{d_1} \\ n_1 d_2 & 0 & -c_1 & 0 \\ 0 & n_2 d_3 & 0 & -c_2 \end{bmatrix}, \tag{18}$$

$$\widehat{G}(X, Z) = MZ - G(X, Z) = \begin{bmatrix} 0 \\ 0 \\ m \\ 0 \end{bmatrix}.$$

Since $\widehat{G} \geq 0$ *for all* (X, Z) *in the region where the model makes biological meaning, then* D_f *is globally asymptotically stable.*

2.3. Existence of Boundary and Interior Equilibria with Possible Competitive Exclusion. System (1) is expected to have three nontrivial equilibria as follows:

(i) HIV-only boundary equilibrium $E_H(T^*, I_h^*, 0, V_h^*, 0)$

(ii) HBV-only boundary equilibrium $E_B(T^+, 0, I_b^+, 0, V_b^+)$

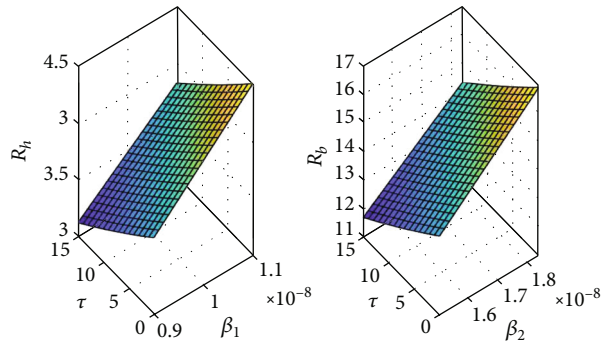

FIGURE 1: HIV and HBV basic reproduction numbers with varying infection rates (β_1, β_2) and latency period τ.

(iii) The coinfection equilibrium $E_{HB}(T^{**}, I_h^{**}, I_b^{**}, V_h^{**}, V_b^{**})$.

Solving system (1) by equating the left-hand side to zero results in two equilibria, that is, HIV-only and coinfection equilibria, indicating that $E_B(T^+, 0, I_b^+, 0, V_b^+)$, do not exist. The absence of HBV-only endemic equilibrium is an indication that, given the proliferation of HIV from other cells other than hepatocytes, it is not likely that HBV will take competitive exclusion over HIV in the liver. The HIV-only endemic equilibrium $E_H(T^*, I_h^*, 0, V_h^*, 0)$ is given by

$$\begin{aligned} T^* &= \frac{A + e^{d_1\tau_1}(B + C) - \sqrt{\left((A + e^{d_1\tau_1}(B + C))^2 - 4D\right)}}{2d_1 n_1 \beta_1}, \\ I_h^* &= \frac{e^{-d_1\tau_1}\left(A - e^{d_1\tau_1}(B + C) + \sqrt{\left((A + e^{d_1\tau_1}(B + C))^2 - 4D\right)}\right)}{2d_2 n_1 \beta_1}, \\ V_h^* &= \frac{e^{-d_1\tau_1}\left(A + e^{d_1\tau_1}(-B + C) + \sqrt{\left((A + e^{d_1\tau_1}(B + C))^2 - 4D\right)}\right)}{2c_1 \beta_1}, \end{aligned} \tag{19}$$

where $A = \lambda n_1 \beta_1$, $B = c_1 d_1$, $C = m\beta_1$, and $D = e^{d_1\tau_1}\lambda c_1 d_1 n_1 \beta_1$. It is analytically cumbersome to deduce the conditions under which this steady state exists.

Assessing the endemicity of either infection under the circumstance that HIV viral copies that infect hepatocytes are only proliferated in hepatic cells, it is assumed that $m = 0$. In this case, we have both HIV-only (E_h) and HBV-only (E_b) endemic equilibria.

For the case of HIV-only, the endemic equilibrium, the point under the assumption that $m = 0$, is given by

$$E_h(T^-, I_h^-, 0, V_h^-, 0) = \left(\frac{\lambda}{d_1 R_h}, \frac{(R_h - 1)d_1 c_1}{\beta_1 n_1 d_2}, 0, \frac{(R_h - 1)d_1}{\beta_1}\right). \tag{20}$$

We can then derive the following result.

Lemma 6. *If HIV that infects liver cells proliferates only in hepatic cells, then HIV-only endemic equilibrium will exist when $R_h > 1$.*

2.3.1. Local Stability of E_h. Assuming that E_h exists when $(V_b, I_b) \longrightarrow (0,0)$ as $t \longrightarrow \infty$, the Jacobian matrix of system (1) is derived as

$$J_{E_h} = \begin{bmatrix} -d_1 & 0 & 0 & \beta_1 T^- & -\beta_2 T^- \\ 0 & -d_2 & 0 & \beta_1 e^{-d_1\tau_1} T^- & 0 \\ 0 & 0 & -d_3 & 0 & \beta_2 e^{-d_1\tau_2} T^- \\ 0 & n_1 d_2 & 0 & -c_1 & 0 \\ 0 & 0 & n_2 d_3 & 0 & -c_2 \end{bmatrix}. \tag{21}$$

The determinant of J_{E_h} is given by

$$\begin{aligned} |J_{E_h}| &= n_1 d_2 \left(e^{-d_1\tau_1} T^- \beta_1 - d_2\right)(V_h^- \beta_1 + d_1)\left(d_3 c_2 - n_2 d_3 \beta_2 e^{-d_1\tau_2} T^-\right) \\ &= \frac{n_1 d_2}{d_1 R_h}(V_h^- \beta_1 + d_1)\left(\lambda \beta_1 e^{-d_1\tau_1} - d_1 d_2 R_h\right)\left(d_3 c_2 - n_2 d_3 \beta_2 e^{-d_1\tau_2} T^-\right) \\ &= d_2 (V_h^- \beta_1 + d_1)(c_1 - d_2 n_1)\left(d_3 c_2 - n_2 d_3 \beta_2 e^{-d_1\tau_2} T^-\right) \\ &= \frac{d_2 d_3 c_2}{R_h}(V_h^- \beta_1 + d_1)(c_1 - d_2 n_1)(R_h - R_b). \end{aligned} \tag{22}$$

Given that $\text{trace}(J_{E_h}) < 0$, we deduce the following.

Result 1. HIV-only endemic equilibrium is locally asymptotically stable only if (i) $c_1/n_1 > d_2$ and $R_b > R_h$ or (ii) $c_1/n_1 < d_2$ and $R_h > R_b$.

Considering the HBV-only endemic equilibrium when $m = 0$, E_b exists when $(V_h, I_h) \longrightarrow (0,0)$ as $t \longrightarrow \infty$ and is given by

$$E_b\left(T', 0, {I_b}', 0, {V_b}'\right) = \left(\frac{\lambda}{d_1 R_b}, 0, \frac{(R_b - 1)d_1 c_2}{\beta_2 n_2 d_3}, 0, \frac{(R_b - 1)d_1}{\beta_2}\right). \tag{23}$$

Thus, E_b exists when $R_b > 1$. Using the same method as above, the conditions for local stability of of E_b can be established.

2.3.2. Existence of the Interior Equilibrium E_{HB} when $m \neq 0$. Coinfection endemic equilibrium $E_{HB}(T^{**}, I_h^{**}, I_b^{**}, V_h^{**}, V_b^{**})$ is defined as

$$T^{**} = \frac{e^{d_1\tau_2} c_2}{n_2 \beta_2}, \tag{24}$$

$$I_h^{**} = \frac{m R_h}{n_1 d_2 (R_b - R_h)}, \tag{25}$$

$$I_b^{**} = \frac{c_1 c_2 d_1 (R_h - R_b)(R_b - 1) + c_2 m \beta_1 R_b}{d_3 n_2 \beta_2 c_1 (R_h - R_b)}, \tag{26}$$

$$V_h^{**} = \frac{m R_b}{c_1 (R_b - R_h)}, \tag{27}$$

$$V_b^{**} = \frac{c_1 d_1 (R_b - 1) + m\beta_1}{c_1 \beta_2} + \frac{m c_2 \beta_1 R_h}{\beta_2 c_1 (R_h - R_b)}. \tag{28}$$

It is not likely that both virus exist in same magnitude over the infection period. As $t \longrightarrow \infty$, either HIV or HBV will dominate the liver. HIV dominates when $R_h > R_b$. In this case, if $R_b > 1$, then I_b and V_b will exist (Equations (26) and (28)), but I_h and V_h will not lie within a biologically feasible solution set, as seen in Equations (25) and (27). Thus, the coinfection endemic equilibrium E_{HB} will not exist when the liver is dominated by HIV. On the other hand, when hepatitis dominates the liver at endemicity of the coinfection, that is, $R_b > R_h$ together with $R_b > 1$ (of course, HBV can only become endemic when $R_b > 1$), then only I_h and V_h will surely exist with respect to Equations (25) and (27). We investigate the parametric conditions that allow for the feasibility of I_b and V_b.

Using Equation (26), if $R_b > R_h$, then $I_b > 0$ only if

$$c_2 m \beta_1 R_b + c_1 c_2 d_1 (R_h - R_b)(R_b - 1) < 0. \tag{29}$$

Using Equation (28), if $R_b > R_h$, then $V_b > 0$ only if

$$(R_h - R_b)(c_1 d_1 (R_b - 1) + m\beta_1) + m c_2 \beta_1 R_h < 0. \tag{30}$$

Rearranging (29) gives

$$(R_b - R_h) > \frac{c_2 m \beta_1 R_b}{c_1 c_2 d_1 (R_b - 1)}, \tag{31}$$

and rearranging (30) gives

$$(R_b - R_h) > \frac{m c_2 \beta_1 R_b}{c_1 d_1 (R_b - 1) + m\beta_1}. \tag{32}$$

Thus, for a biologically feasible solution, we have

$$(R_b - R_h) > \min\left\{\frac{c_2 m \beta_1 R_b}{c_1 c_2 d_1 (R_b - 1)}, \frac{m c_2 \beta_1 R_b}{c_1 d_1 (R_b - 1) + m\beta_1}\right\}. \tag{33}$$

We therefore deduce the following result.

Result 2. Whenever $R_b > 1$, the coinfection endemic equilibrium state E_{HB} exists anywhere in the biologically feasible region

Table 1: Parameters values used in simulations.

Par	Description	Value	Ref
λ	Rate of creation of hepatocytes from within the body	1.2×10^4	[25]
β_1	Rate of transmission of HIV in hepatocytes	1.0×10^{-8}	[32]
d_1	Natural death rate of uninfected hepatocytes	0.0039	[39]
β_2	Rate of transmission of HBV in hepatocytes	1.67×10^{-8}	[19, 40]
d_2	Death rate of HIV-infected hepatocytes	0.05	[31]
d_3	Death rate of HBV-infected hepatocytes	0.0693	[39]
n_1	Burst size of HIV-infected hepatocytes	200	Estimate
n_2	Burst size of HBV-infected hepatocytes	200	[19]
m	Number of viral copies from CD4+ cells	50000	Estimate
c_1	Rate of clearance of HIV	1.5	[10]
c_2	Rate of clearance of HBV	0.67	[19]
τ	Intracellular delay	5	[19]

defined by $(R_b - R_h) > \min\{(c_2 m\beta_1 R_b/c_1 c_2 d_1(R_b - 1)), (mc_2 \beta_1 R_b/c_1 d_1(R_b - 1) + m\beta_1)\}$.

2.4. Numerical Results of the Model. In this section, we present the numerical results of system (1), with parameter values as indicated in Table 1. Due to lack of previous studies on the dynamics of HIV in hepatocytes, we assume that HIV and HBV have the same period of latency in hepatocytes. This indicates the probability that an HIV or HBV producing hepatocyte surviving through the time period $\tau_1 = \tau_2$ is theoretically equal. Biologically, according to Alshorman et al. [25], the initial value of healthy cells $(T(0))$, proliferation rate λ, and clearance rate d_1 are related by $\lambda = d_1 T(0)$; thus, initial values are as follows:

$$\begin{aligned} T(0) &= 3.0769 \times 10^6, I_h(0) \\ &= 10, I_b(0) \\ &= 10, V_h(0) \\ &= 100, V_b(0) \\ &= 100. \end{aligned} \tag{34}$$

Numerical results of system (1) are shown in Figure 2. Variables approach an infected steady state, because parameter values as shown in Table 1 satisfy the condition in Result 2. Comparing the dynamics with and without delay, Figure 3 shows that the peak times of both virus as well as the decay time of healthy hepatocytes are longer with delay than without. We summarise the peak values and times as presented in Table 2.

With the same initial values for infectious classes and viral copies, despite the influx of HIV from cells other than hepatocytes, HBV peak values are a hundred-fold higher than HIV. Additionally, HBV peaks later than HIV, which also seems to support another study [3] that indicates that the presence of HIV changes the natural history of HBV, with the progression of liver-related diseases 17 times more in the coinfected than in HBV monoinfected individuals. With varying delay period, Figure 4 shows that the longer it takes for HIV and HBV to replicate in hepatocytes, the more the HIV and the less the HBV virus multiplies.

3. Optimal Control Problem

The optimal control method has been studied widely in a number of settings including analysis of control strategies in infectious diseases. In within-host viral dynamics particularly, controls are antiretroviral drugs used to suppress the progression of a pathogen. In some studies, controls are instantaneous [41, 42], while in others, a pharmacodynamics delay is incorporated [18, 43]. HIV and HBV combinational antiretroviral therapy (cART) consists of infusion, integrase, reverse transcriptase, and protease inhibitors, all aiming at blocking viral replication *in vivo* [16]. In HIV/HBV-coinfected persons, cART is supposed to suppress replication rate of both virus in all body cells. It has been reported that, generally, cART is not as effective in hepatocytes as compared in CD4+ cells, possibly because of high level of HIV latency in this type of cells [3].

Different classes of antiretroviral drugs serve different purposes and act at different stages of viral progression. Most of the drugs are enzyme inhibitors, and they incapacitate different enzymes that aid viral multiplication within a host cell. In order to monitor effectiveness of cART in HIV- or HIV/HBV-coinfected patients, frequent viral load testing, regulated by WHO [44], is carried out.

Time-dependent resultant efficacy $\phi(t)$, for $0 \le \phi(t) \le 1$, is considered. It is assumed that in the case of two enzyme inhibitors, whose efficacies are $\phi_1(t)$ and $\phi_2(t)$, we have $\phi(t) = \phi_1(t) + \phi_2(t) - \phi_1(t)\phi_2(t)$. Thus, $1 - \phi(t) = (1 - \phi_1(t))(1 - \phi_2(t))$, which indicates that the two drugs act independently with additive efficacy. The same argument can be used even

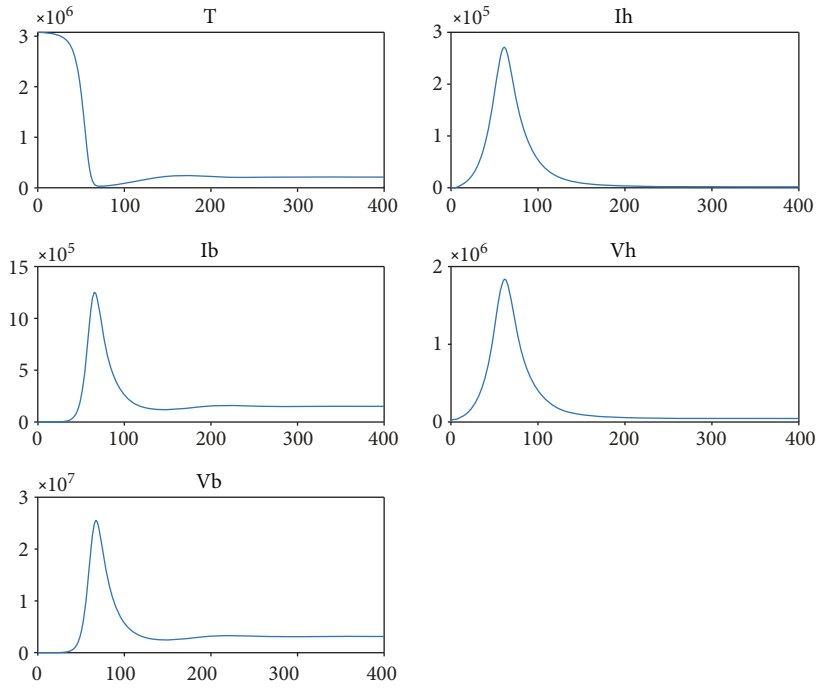

Figure 2: Dynamics of delayed system (1) with the delay parameter as $\tau_1 = \tau_2 = 5$ days. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

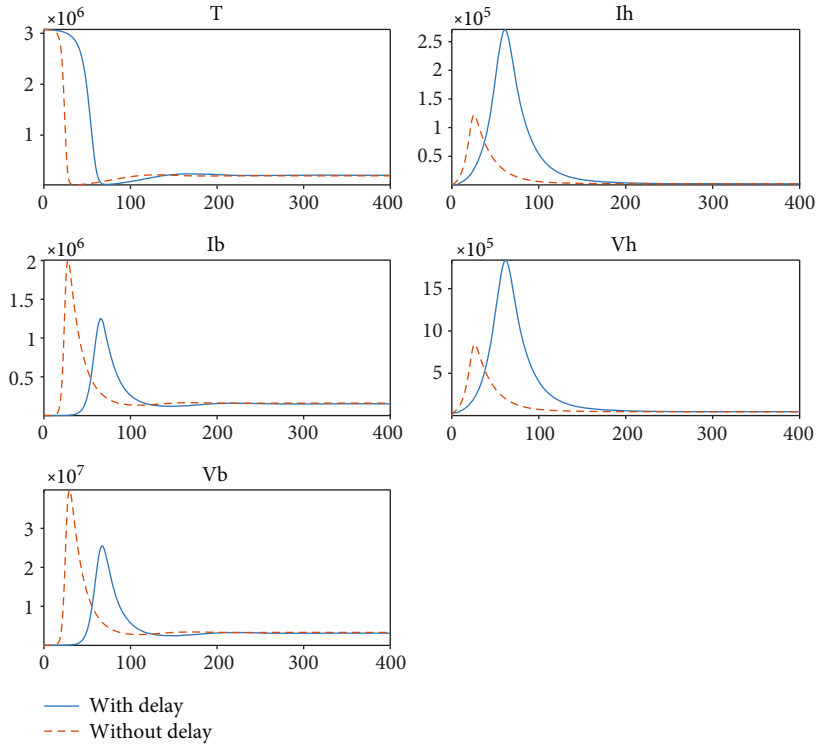

Figure 3: Comparing the dynamics of system (1) with and without delay. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

Table 2: Peak values and time for HIV and HBV, with and without delay.

	HIV peak time	HBV peak time	HIV peak value	HBV peak value
With delay	87	100	512,600	12,940,000
Without delay	49	54	275,400	15,950,000

when three types of enzyme inhibitors are used. Considering an instantaneous control efficacy, the optimal control problem is given as

$$\begin{aligned}
\frac{dT(t)}{dt} &= \lambda - d_1 T(t) - \beta_1 T(t) V_h(t) - \beta_2 T(t) V_b(t),\\
\frac{dI_h(t)}{dt} &= e^{-d_1\tau_1}\beta_1 T(t-\tau_1) V_h(t-\tau_1) - d_2 I_h(t),\\
\frac{dI_b(t)}{dt} &= e^{-d_1\tau_2}\beta_2 T(t-\tau_2) V_b(t-\tau_2) - d_3 I_b(t),\\
\frac{dV_h(t)}{dt} &= (1-\phi(t)) n_1 d_2 I_h(t) + (1-\phi(t)) m - c_1 V_h(t),\\
\frac{dV_b(t)}{dt} &= (1-\phi(t)) n_2 d_3 I_b(t) - c_2 V_b(t).
\end{aligned} \tag{35}$$

It is worth noting that Equation (35) is similar to Equation (1), with all parameters taking the same descriptions as indicated in Section 2. However, the resultant efficacy $\phi(t)$ is expected to reduce the number of viral copies in a coinfected person. Thus, the number of HIV $(n_1 d_2 I_h(t) + m)$ and HBV $(n_2 d_3 I_b(t))$ copies generated are reduced to $(1-\phi(t)) n_1 d_2 I_h(t) + (1-\phi(t)) m$ and $(1-\phi(t)) n_2 d_3 I_b(t)$, respectively. This indicated that the higher the value of $\phi(t)$, the fewer the viral copies, and when the cART is 100% efficacious ($\phi(t) = 1$), then no viral copies will be produced.

Treatment strategy $\phi(t)$ that minimises the number of HIV and HBV viral load in the liver and consequently maximises healthy hepatocytes for the entire treatment duration T_f is investigated. The strategy $\phi(t)$ should minimise the viral load, as well as the cost of treatment and the corresponding side effects of the medication that result in reduced density of the pathogen. The objective function is defined as

$$J(\phi(t)) = \int_0^{T_f} V_h(t) + V_b(t) + A\frac{\phi^2(t)}{2}\, dt. \tag{36}$$

Parameter A is established by combining the benefits and costs of the treatment such that it equalises the size of the term $\phi(t)$ and reflects the severity of the side effects of the drugs. The cost function is quadratic because it should be nonlinear at the optimal controls $\phi^*(t)$. However, there is no linear relationship between the effect of the therapy on hepatocytes and viral load [45, 46]. We seek an optimal control strategy $\phi^*(t)$ such that

$$J(\phi^*) = \min\{J(\phi(t)) : \phi(t) \in U\}, \tag{37}$$

where U is the control set defined by

$$U = \left\{\phi : \phi \text{ is Lebesgue measurable}, \forall 0 \le \phi(t) \le 1,\ t \in \left[0, T_f\right]\right\}. \tag{38}$$

3.1. Existence of an Optimal Control. The existence of an optimal control $\phi^*(t)$ can be proved by the results of Fleming and Rishe in [47].

Theorem 7. *Consider the control problem with system (35). There exists an optimal control $\phi^* \in U$ such that*

$$J(\phi^*) = \min\{J(\phi(t)) : \phi(t) \in U\}. \tag{39}$$

Proof. To use an existence result in Fleming and Rishe in [47], we must check the following properties.

(1) The set of controls and corresponding state variables is nonempty

(2) The control set U is convex and closed

(3) The right-hand side of the state system is bounded by a linear function in the state and control variables

(4) The integrand of the objective functional is convex on U

(5) There exist constants $c_1, c_2 > 0$ and $\beta > 1$ such that the integrand $L(V_h, V_b, \phi)$ of the objective functional satisfies

$$L(V_h, V_b, \phi) \ge c_2 + c_1\left(|\phi|^2\right)^{\beta/2}. \tag{40}$$

□

The control $\phi(t)$ from (38) and state variables $T(t)$, $I_h(t), I_b(t), V_h(t)$, and $V_b(t)$ from (4) are nonnegative and nonempty which satisfy condition (1). The control set is convex and closed by definition in (38). Since the state system (35) is linear in $\phi(t)$, the right-hand side satisfies condition (3). Using the boundedness of solution as indicated in Section 2.1, the integrand in the objective function (36) is convex on U (because its quadratic in $\phi(t)$); thus, condition (4) is satisfied. Finally, we can easily see that there exists a constant $\beta > 1$ and positive numbers c_1 and c_2 satisfying Equation (40).

3.2. Characterization of the Optimal Control. In order to derive the necessary condition for the optimal control, Pontryagin's maximum principle with delay given by Gollmann et al. [18] is used. First, we define the Lagrangian for the optimal control problem (35) as

$$L(V_h, V_b, \phi) = V_h(t) + V_b(t) + A\frac{\phi^2(t)}{2}. \tag{41}$$

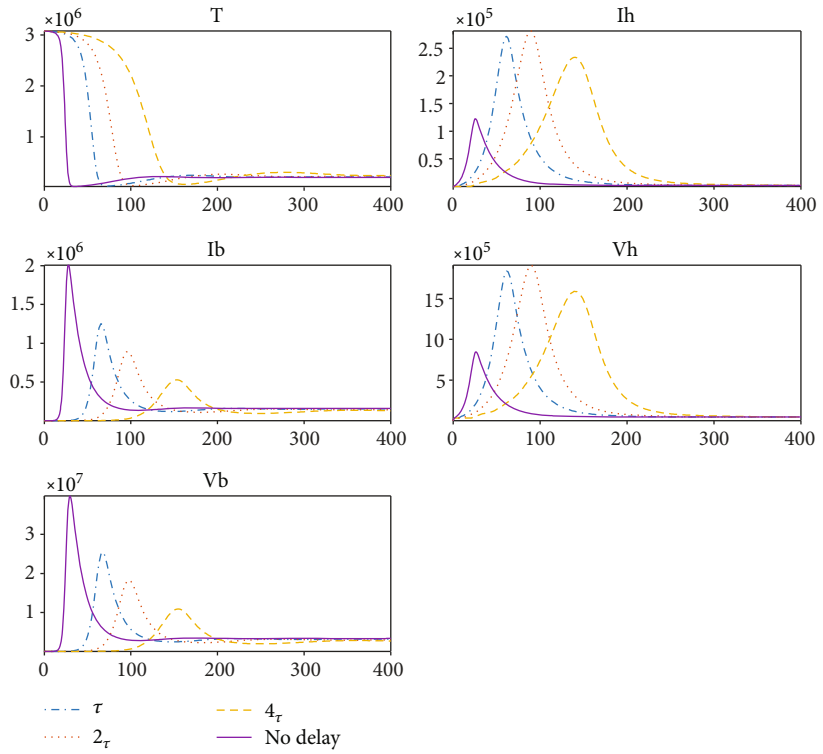

Figure 4: Dynamics of delayed system (1) with varying delay (τ) values. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

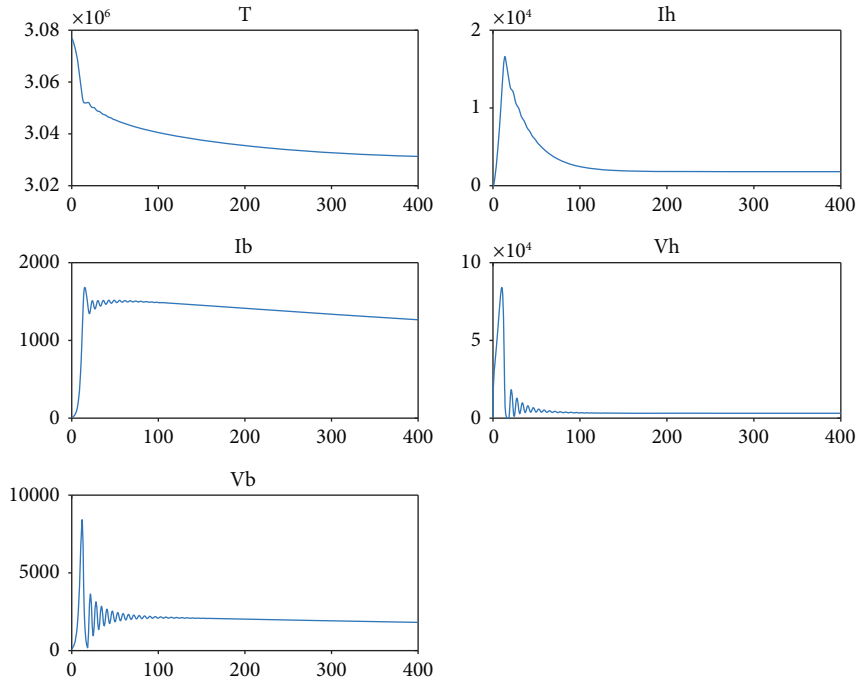

Figure 5: Delayed HIV/HBV model with optimal control. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

The principle converts the system (35), the objective function (36), and the optimal control (39) into a problem of minimising the Hamiltonian given by

$$H(T, I_h, I_b, V_h, V_b, \phi, \lambda_i, t) = L(V_h, V_b, \phi) + \sum_{i=1}^{5} f_i \lambda_i, \quad (42)$$

where λ_i for $i = 1, \cdots, 5$ are the adjoint functions and f_i are the right hand side of the system of state variables in (35). Using the principle in [18], we arrive at the following theorem.

Theorem 8. *Given an optimal control $\phi^* \in U$ and solutions T^*, I_h^*, I_b^*, V_h^*, and V_b^* of the corresponding state system (35), there exist adjoint functions $\lambda_1, \cdots, \lambda_5$ which satisfy*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (d_1 + \beta_1 V_h^*(t) + \beta_2 V_b^*(t))\lambda_1(t) - \chi_{[0,T_f-\tau_1]} \\
&\quad \cdot \left(e^{-d_1\tau_1}\beta_1 V_h^*(t)\lambda_1(t+\tau_1)\right) \\
&\quad - \chi_{[0,T_f-\tau_2]}(\beta_2 V_b^*(t)\lambda_3(t+\tau_2)), \\
\frac{d\lambda_2}{dt} &= d_2\lambda_2(t) - (1-\phi^*(t))n_1 d_2 \lambda_4(t), \\
\frac{d\lambda_3}{dt} &= d_3\lambda_3(t) - (1-\phi^*(t))n_2 d_2 \lambda_5(t), \\
\frac{d\lambda_4}{dt} &= 1 + c_1\lambda_4(t) + \lambda_1(t)\beta_1 T^*(t) - \chi_{[0,T_f-\tau_1]} \\
&\quad \cdot \left(e^{-d_1\tau_1}\beta_1 T^*(t)\lambda_2(t+\tau_1), \right. \\
\frac{d\lambda_5}{dt} &= 1 + c_2\lambda_5(t) + \lambda_1(t)\beta_2 T^*(t) - \chi_{[0,T_f-\tau_2]} \\
&\quad \cdot \left(e^{-d_1\tau_2}\beta_2 T^*(t)\lambda_3(t+\tau_2). \right.
\end{aligned} \quad (43)$$

with transversality conditions $\lambda_i(T_f) = 0$, for $i = 1, \cdots, 5$, and the corresponding optimal control given by

$$\phi^*(t) = \min\left(1, \max\left(0, \frac{(n_1 d_2 I_h^*(t) + m)\lambda_4(t) + n_2 d_3 I_b^*(t)\lambda_5}{A}\right)\right), \quad (44)$$

and $\chi_{[0,T_f-\tau_i]}$ is the characteristic function on interval $[0, T_f - \tau_i]$ defined by

$$\chi_{[a,b]}(t)\begin{cases} 1, & \text{if } t \in [a,b], \\ 0, & \text{otherwise}. \end{cases} \quad (45)$$

Proof. Using Pontryagin's maximum principle with delay in state [18], we can obtain the adjoint equations and transversality conditions as

$$\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= -\frac{\partial H}{\partial T} - \chi_{[0,T_f-\tau_i]}\frac{\partial H(t+\tau_i)}{\partial T(t-\tau_i)}, \lambda_1(T_f) = 0, \\
\frac{d\lambda_2(t)}{dt} &= -\frac{\partial H}{\partial I_h}, \lambda_2(T_f) = 0, \\
\frac{d\lambda_3(t)}{dt} &= -\frac{\partial H}{\partial I_b}, \lambda_3(T_f) = 0, \\
\frac{d\lambda_4(t)}{dt} &= -\frac{\partial H}{\partial V_h} - \chi_{[0,T_f-\tau_1]}\frac{\partial H(t+\tau_1)}{\partial V_h(t-\tau_1)}, \lambda_4(T_f) = 0, \\
\frac{d\lambda_5(t)}{dt} &= -\frac{\partial H}{\partial V_b} - \chi_{[0,T_f-\tau_2]}\frac{\partial H(t+\tau_2)}{\partial V_b(t-\tau_2)}, \lambda_5(T_f) = 0.
\end{aligned} \quad (46)$$

For $i = 1, 2$, the optimal control ϕ^* can be solved using the optimality condition

$$\frac{\partial H}{\partial \phi} = 0, \quad (47)$$

and by the bounds of $\phi(t)$ defined in (38), it is easy to show that Equation (44) holds. □

Combining the state variables in Equation (35), the system of adjoint variables (44), and the optimal control (44), the optimality system is derived as

$$\begin{aligned}
\frac{dT^*(t)}{dt} &= \lambda - d_1 T^*(t) - \beta_1 T^*(t) V_h^*(t) - \beta_2 T^*(t) V_b^*(t), \\
\frac{dI_h^*(t)}{dt} &= e^{-d_1\tau_1}\beta_1 T^*(t-\tau_1) V_h^*(t-\tau_1) - d_2 I_h^*(t), \\
\frac{dI_b^*(t)}{dt} &= e^{-d_1\tau_2}\beta_2 T^*(t-\tau_2) V_b^*(t-\tau_2) - d_3 I_b^*(t), \\
\frac{dV_h^*(t)}{dt} &= (1-\phi^*(t))n_1 d_2 I_h^*(t) + (1-\phi(t))m^* - c_1 V_h^*(t), \\
\frac{dV_b^*(t)}{dt} &= (1-\phi^*(t))n_2 d_3 I_b^*(t) - c_2 V_b^*(t), \\
\frac{d\lambda_1(t)}{dt} &= (d_1 + \beta_1 V_h^*(t) + \beta_2 V_b^*(t))\lambda_1(t) - \chi_{[0,T_f-\tau_1]} \\
&\quad \cdot \left(e^{-d_1\tau_1}\beta_1 V_h^*(t)\lambda_1(t+\tau_1)\right) \\
&\quad - \chi_{[0,T_f-\tau_2]}(\beta_2 V_b^*(t)\lambda_3(t+\tau_2)), \\
\frac{d\lambda_2(t)}{dt} &= d_2\lambda_2(t) - (1-\phi^*(t))n_1 d_2\lambda_4(t), \\
\frac{d\lambda_3(t)}{dt} &= d_3\lambda_3(t) - (1-\phi^*(t))n_2 d_2\lambda_5(t), \\
\frac{d\lambda_4(t)}{dt} &= 1 + c_1\lambda_4(t) + \lambda_1(t)\beta_1 T^*(t) - \chi_{[0,T_f-\tau_1]} \\
&\quad \cdot \left(e^{-d_1\tau_1}\beta_1 T^*(t)\lambda_2(t+\tau_1), \right. \\
\frac{d\lambda_5(t)}{dt} &= 1 + c_2\lambda_5(t) + \lambda_1(t)\beta_2 T^*(t) - \chi_{[0,T_f-\tau_2]} \\
&\quad \cdot \left(e^{-d_1\tau_2}\beta_2 T^*(t)\lambda_3(t+\tau_2), \right.
\end{aligned} \quad (48)$$

where $\phi^*(t)$ is given by Equation (44).

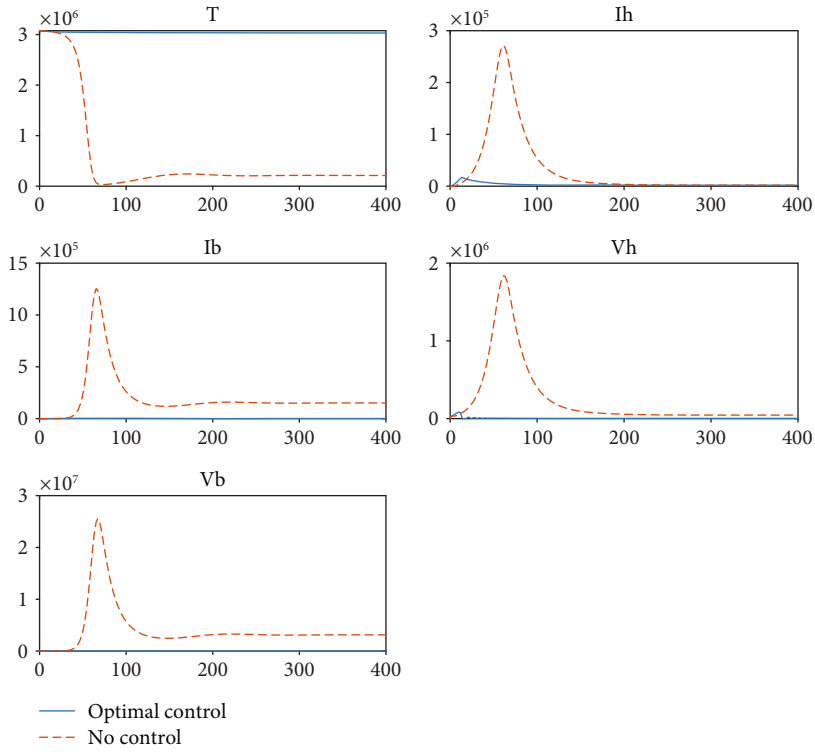

Figure 6: Dynamics of delayed HIV/HBV model with and without control. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

3.3. Numerical Results of the Optimal Control System. Numerical results of the optimality system (48) are obtained by finite difference approximation method [40], between $t = 0$ and $T_f = 400$ days. Parameter values are as shown in Table 1, and the initial values are as shown in (34). Figures 5 and 6 show that medication is able to control either infection. This is in support to the objective of the control strategy, which is aimed at minimising the viral load. However, the reduction in viral load seems not to imply significant growth in healthy hepatocytes as also shown in Figure 5. Nonetheless, it is the opposite when compared to Figure 6.

With initial viral copies of both infections set as 10, numerical results indicate that at the end of control period, there are 3141 copies of HIV and 1918 copies of HBV. Comparing with 45820 and 3.094×10^6 copies of HIV and HBV, respectively, without control, is a clear indication that therapy is more effective in reducing HBV load. The control profile in Figure 7 shows the treatment administration schedule over the period of 300 days. The control should be applied at maximum effectiveness during the first two weeks because of the high viral load in the patient. There is periodicity in control application for the next 4 months before a steady upper bound, but the control does not go below 80%. This indicates that considering all the assumptions taken in this study, if efficacy is maintained beyond 80%, it is possible to reduce the HIV/HBV load in coinfected patients and the systemic cost.

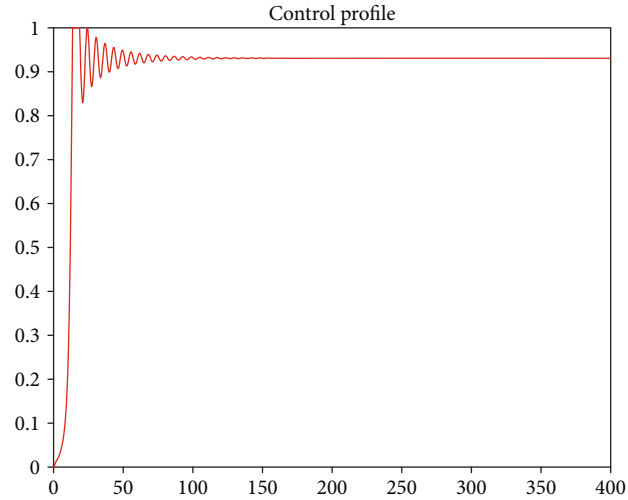

Figure 7: Control profile of delayed HIV/HBV model. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

Figure 8 shows that there is an increase in both HIV and HBV copies with increase in delay period. We have seen that without the control presented in Section 2.4, the delay only increases HIV copies and not HBV. This suggests that the longer the virus hides in a host cell, the less effective the therapy and consequently the more viral load in the patient

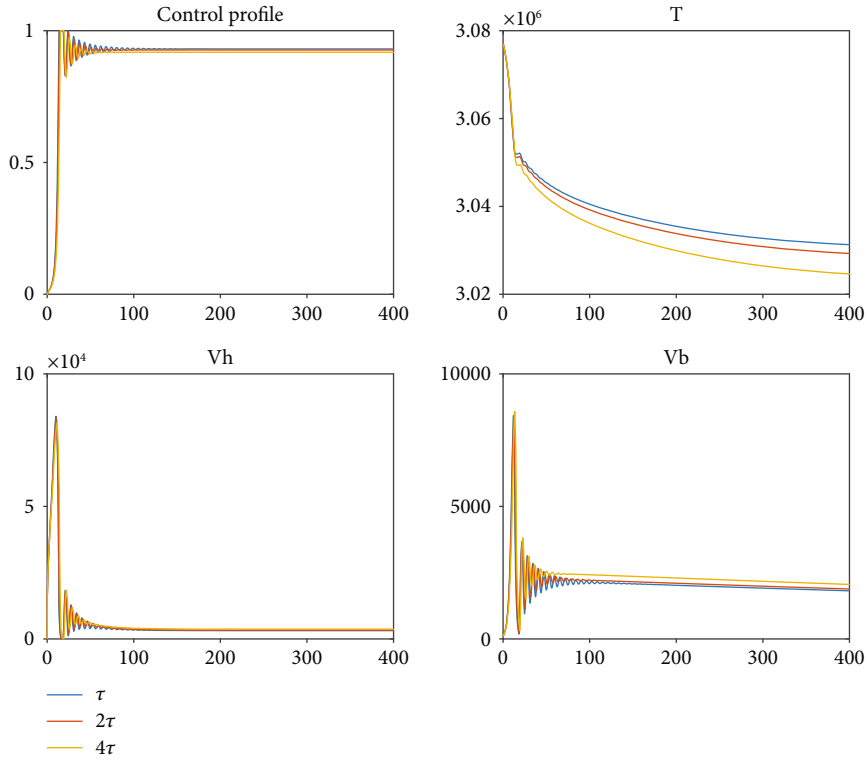

FIGURE 8: Healthy hepatocytes, control profiles, HIV copies, and HBV copies with varying intracellular delay periods. Parameter values are as shown in Table 1. Horizontal axes represent time in days.

is. We can also observe from unlike in Figure 6, where HBV is tens of thousands more than HIV, that when control is applied, HBV load becomes less than HIV load, which is an indication that therapy is more effective in controlling HBV.

4. Discussion and Conclusion

This study proposed a mathematical model representing coinfection of HBV and HIV in human hepatocytes. The model included a time delay to represent the time between viral entry into a host cell and the actual time when the cell is able to replicate viral copies. When the virus gain entry into a host cell, the integrated provirus may remain latent for a number of years without replication. The cell hosting a provirus is regarded as a viral reservoir. The reservoir is not able to attract cytotoxic killing from the virus-specific lymphocyte, neither can it be cleared using cART. The effect of latency period on the dynamics of HIV/HBV infection was investigated. Analytically, model solutions were found to be positive and bounded. The disease-free equilibrium D_f was computed and the basic reproduction number R_0 deduced. It was established that D_f is locally asymptotically stable, when $R_0 < 1$ and unstable when $R_0 > 1$. Results indicate that HBV cannot gain competitive exclusiveness over HIV given the influx of HIV from other cells; thus, there is no HBV-only endemic equilibrium point. Coinfection endemic exists with some parametric conditions indicated in Result 2. Failure to have a possible HBV-only endemic equilibrium, but rather an HIV-only and coinfection endemic equilibria, is an indication that HBV becomes chronic in HIV-infected patients [3].

Assuming equal intracellular delay for both HIV and HBV of 5 days, numerical results show that there is higher HIV load with viral latency than without. However, the effect of latency period on the number of viral copies is not seen at the start of the infection. This is an indication that the influx of HIV viremia is the one that has an impact on the HBV viral load that consequently shoot up. This could signify that hepatocytes acting as HIV reservoirs have a greater impact on HIV dynamics, which consequently influences HBV. It has been previously reported that HIV alters the dynamics of HBV in a manner that is not yet known [3].

With parameter values used in simulations, it was found that $R_0 = R_b$, where R_b is the number of secondary infections resulting from one HBV infectious hepatocyte. This is evidenced by higher HBV viral load as compared to HIV in numerical simulations and is in line with study by Parvez [3], who reports that HIV coinfection significantly alters the natural history of hepatitis B and therefore complicates the disease management. They further assert that, in HIV-coinfected individuals, liver-related mortality is over 17 times higher than those with HBV monoinfection. Even though the use of cART has changed the overall outcome of HIV in infected patients, from a fatal to a chronic one, pharmacologists are still trying to find an absolute cure to

the disease. Their efforts have been hindered by viral reservoirs that harbour the provirus for a long time making cART inefficient, since it targets only actively replicating virus. Given both challenges of viral latency and lifelong treatment, optimal therapy that minimises active viral load and cost of treatment, combined with side effects, needed to be investigated. By using Pontryagin's maximum principle of delayed models, the optimal control problem was characterized and the expression of the optimal control was computed. Using the finite difference approximation method, simulation results show that the resultant control strategy is effective in reducing the active viral load of either infection. The optimal efficacy that minimises the viral load for the entire control period of 400 days is over 80%. It is important to note that as latency reversal agents are manufactured, there is also a need to ensure that the current cART is highly efficacious in eliminating all actively replicating virus.

Numerical results from the optimal control model with varying delay periods indicate that the longer the delay is, the more HIV and HBV viral load builds up. An increase in HIV and HBV copies with increase in latency period, in the presence of cART, is an indication that viral latency hinders drug management and control [3, 9]. Generally, latent reversal agents should not only be CD4+ cell-specific since there is evidence that CD4+ cells are not the only viral reservoirs. For the liver specifically and in HIV/HBV-coinfected patients, HIV latency does not only lead to higher HIV load and hinder drug management, but it also implicates higher HBV viral load in the liver.

Appendices

A. Castillo-Chavez Theorem [38]

$$\begin{cases} \dfrac{dX}{dt} = F(X, Z) \\ \dfrac{dZ}{dt} = G(X, Z), G(X, 0) = 0. \end{cases} \tag{A.1}$$

where the components of the column-vector $X \in \mathbb{R}^m$ denotes the number of uninfected individuals and the components of vector $Z \in \mathbb{R}^n$ denotes the number of infected individuals. Let $U_0 = (X^*, 0)$ denote the disease-free equilibrium of this system. The fixed point $U_0 = (X^*, 0)$ is a globally asymptotically stable equilibrium for this system provided that $R_0 < 1$ (locally asymptotically stable) and the following two conditions satisfied:

Theorem 9. *For a system*

(H1): For $dX/dT = F(X, 0)$, X^* is globally asymptotically stable

(H1): $G(X, Z) = MZ - \cup G(X, Z) \geq 0$ for $(X, Z) \in \Omega$ where $M = D_Z G(X^*, 0)$ is a Metzler matrix (the off-diagonal elements of M are nonnegative), and Ω is the region where the model makes biological meaning.

Data Availability

The data supporting this coinfection model is from previously published research articles as cited in Table 1.

Conflicts of Interest

The authors declare that there are no conflicts of interest concerning the publication of this paper.

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