


REVIEW

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Modelling intracellular delay and therapy interruptions within Ghanaian HIV population

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Abstract

This paper seeks to unveil the niche of delay differential equation in harmonizing low HIV viral haul and thereby articulating the adopted model, to delve into structured treatment interruptions. Therefore, an ordinary differential equation is schemed to consist of three components such as untainted CD4+ T-cells, tainted CD4+ T-cells (HIV) and CTL. A discrete time delay is ushered to the formulated model in order to account for vital components, such as intracellular delay and HIV latency which were missing in previous works but have been advocated for future research. It was divested that when the reproductive number was less than unity, the disease free equilibrium of the model was asymptotically stable. Hence the adopted model with or without the delay component articulates less production of virions as per the decline rate. Therefore CD4+ T-cells in the blood remains constant at δ_1/δ_3 , hence declining the virions level in the blood. As per the adopted model, the best STI practice is intimated for compliance.

Keywords: Cytotoxic Lymphocytes; Structured treatment interruption; Disease free Equilibrium: Human immunodeficiency virus; Basic reproductive number

1 Introduction

Comparatively, HIV like most viruses is very minute, unadorned organism which cannot reproduce unaided. It remains the most deadly disease [1] which has ever hit the planet since the last three decades. However, as the fight for survival between the virus and the human immune system persist [1–7], CD4+ T-lymphocytes and macrophage remediate the cellular defence mechanism of the body. The immune system [1, 7–14], congregates to filter diverse information from invading pathogens and perceives them through the T cell receptors (TCRs) (Fig. 1).

1.1 Modelling of intracellular delay

Delay differential equations (DDEs) have been valuable for innumerable years in control theory and recently interrelated to biological and mathematical models. Most biological frames [10] have time delay embedded in them, yet few scientist collaborate them due to the intricacies they stimulate. The principal intricacies in studying DDEs lie in their solitary transcendental character.

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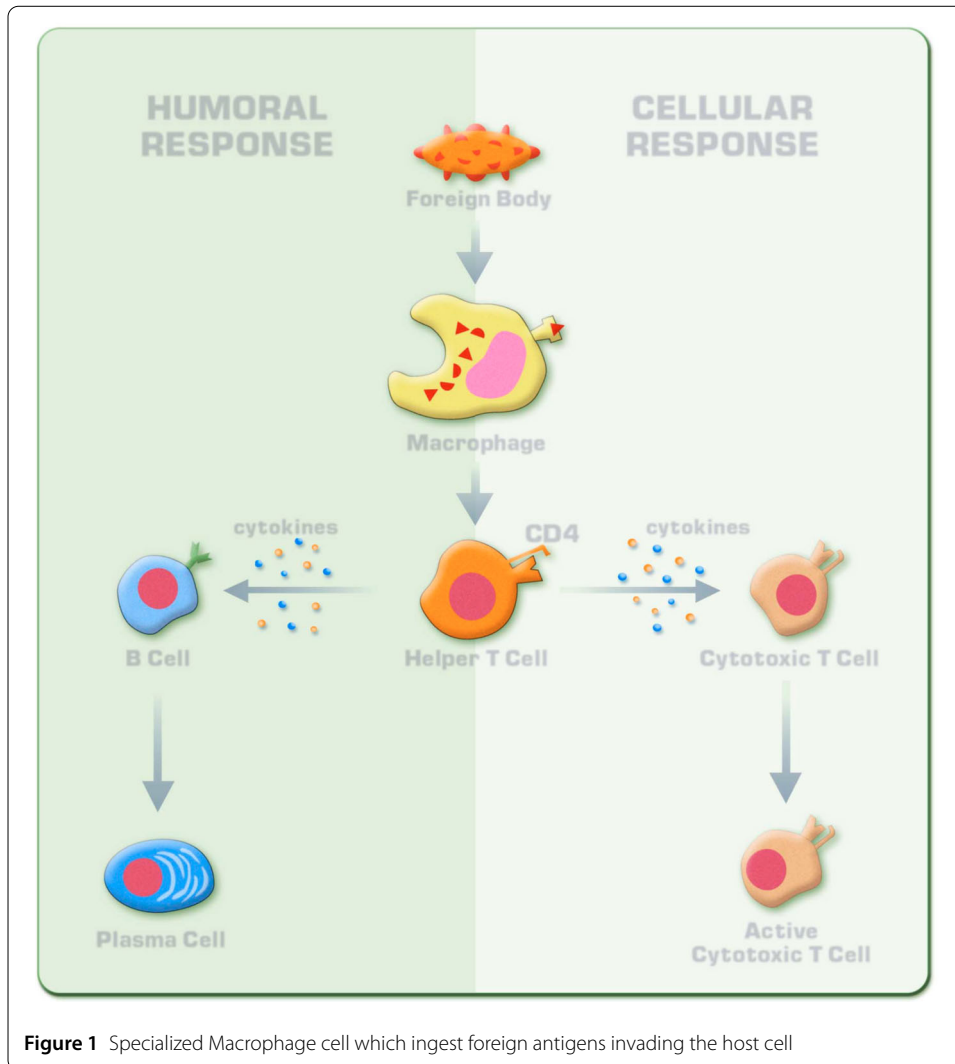


Figure 1 Specialized Macrophage cell which ingest foreign antigens invading the host cell

In this paper, we first formulate a system of ordinary differential equations expounded as follows

$$\begin{aligned}
 \frac{dx}{dt} &= a_1(1 - xy - x), \\
 \frac{dy}{dt} &= a_2(a_3xy - y) - a_4yz, \\
 \frac{dz}{dt} &= a_5(y - z),
 \end{aligned}
 \tag{1.1}$$

where CD4+ T-cell is symbolized as (x) , tainted cells as (y) and CTL as (z) .

Next, we define a translation operator T_τ where $\tau \geq 0$, and $T_\tau(T) = s(t - \tau)$. Therefore by nominal convenience $x_1 := T_\tau x$, $y_1 := T_\tau y$, and $z_1 := T_\tau z$, hence we express the system

of equations with delay as follows

$$\begin{cases} \frac{dx}{dt} = a_1(1 - xy - x), \\ \frac{dy}{dt} = a_2(a_3x_1y_1 - y) - a_4yz, \\ \frac{dz}{dt} = a_3(y - z). \end{cases} \tag{1.2}$$

The term $a_2a_3x_1y_1$, represents the rate equation and reflects a boundless time lag between the infection of CD4+ T-cell and the staging of new virions. Next we consider the well posedness and existence of equilibrium points.

2 Well posedness and existence of equilibrium points

We define equation (1.2) in terms of F, G and H as shown below;

$$\begin{aligned} \frac{dx}{dt} &= F(x, y, z, x_1, y_1, z_1), \\ \frac{dy}{dt} &= G(x, y, z, x_1, y_1, z_1), \\ \frac{dz}{dt} &= H(x, y, z, x_1, y_1, z_1). \end{aligned} \tag{2.1}$$

Equating (1.2) and (2.1), yields

$$\begin{aligned} F(x, y, z, x_1, y_1, z_1) &:= a_1(1 - xy - x), \\ G(x, y, z, x_1, y_1, z_1) &:= a_2(a_3, x_1, y_1 - y) - a_4yz, \\ H(x, y, z, x_1, y_1, z_1) &:= a_5(y - z). \end{aligned} \tag{2.2}$$

Further, we define a steady state for equation (2.2) in terms of $(\bar{x}, \bar{y}, \bar{z})$ and procure the equations below:

$$\begin{aligned} F(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0, \\ G(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0, \\ H(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0. \end{aligned} \tag{2.3}$$

Proposition 2.1 *If a_2a_3 and $z_1 := T_\tau z$, then the steady state solution of equation (2.1) is in unison with the steady state solution of equation (2.3).*

Proof Consider an immutable function $S(t)$ and its derivative $\frac{ds}{dt}$, assuming that the derivative of the function is $\frac{ds}{dt} = \frac{ds_1}{dt}$, then:

$$F(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0, \quad G(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0 \quad \text{and} \quad H(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0,$$

hence equations (2.1) and (2.3) have the same unvarying states.

Further, by codifying a neighborhood close to the unvarying state solution, we let

$$x = \bar{x} + X, \quad y = \bar{y} + Y, \quad z = \bar{z} + Z, \quad x_1 = \bar{x} + X_1,$$

$$y_1 = \bar{y} + Y_1 \quad \text{and} \quad z_1 = \bar{z} + Z_1.$$

Next, we exploit the Taylor series about the point $(\bar{x}, \bar{y}, \bar{z})$ and withholding only the linear terms yields

$$\begin{aligned} \frac{dX}{dT} &= -a_1(\bar{y} + 1)X - a_1\bar{x}Y, \\ \frac{dY}{dt} &= a_2a_3\bar{y}X_1 + [a_2(a_3\bar{x}Y_1 - Y) - a_4\bar{z}Y] - a_4\bar{y}Z \quad \text{and} \\ \frac{dZ}{dt} &= a_5Y - a_5Z. \end{aligned} \tag{2.4}$$

Further, we linearized equation (2.4) as:

$$\begin{bmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \\ \frac{dZ}{dt} \end{bmatrix} = \begin{bmatrix} -a_1(\bar{y} + 1) & -a_1\bar{x} & 0 \\ a_2a_3\bar{y}e^{-\lambda t} & a_2(a_3\bar{x}e^{-\lambda t} - 1) - a_4\bar{z} & -a_4\bar{y} \\ 0 & a_5 & -a_5 \end{bmatrix} \begin{bmatrix} X \\ Y \\ Z \end{bmatrix}. \tag{2.5}$$

Next we let

$$B = \begin{bmatrix} -a_1(\bar{y} + 1) & -a_1\bar{x} & 0 \\ a_2a_3\bar{y}e^{-\lambda t} & a_2(a_3\bar{x}e^{-\lambda t} - 1) - a_4\bar{z} & -a_4\bar{y} \\ 0 & a_5 & -a_5 \end{bmatrix}.$$

Where B is the coefficient matrix of the linearized system and λ is the eigenvalue of matrix B . Hence the unvarying state of the delay system can be explored in terms of the eigenvalues of matrix B . □

3 Global stability of equilibrium E_0

In this section, we proceed by analyzing the universal stability of the disease-free equilibrium of the model. Hence we let (x_0, y_0, z_0) be an unvarying state solution of the following equations: $\frac{dx}{dt} = F(x, y, z, x_1, y_1, z_1)$, $\frac{dy}{dt} = G(x, y, z, x_1, y_1, z_1)$ and $\frac{dz}{dt} = H(x, y, z, x_1, y_1, z_1)$, then (x_0, y_0, z_0) is stable if $\epsilon > 0$ and $\delta > 0$ for (x, y, z) when

$$[x(t_0) - x_0]^2 + [y(t_0) - y_0]^2 + [z(t_0) - z_0]^2 < \delta^2. \tag{3.1}$$

Given that $t_0 \in [t_1 - \tau, t_1]$, then $[x(t) - x_0]^2 + [y(t) - y_0]^2 + [z(t) - z_0]^2 < \epsilon^2$ for all $t > t_1$.

On the other hand if (x_0, y_0, z_0) is stable and δ is chosen so that equation (3.1) is elucidated as $[x(t), y(t), z(t) \rightarrow (x_0, y_0, z_0)]$. Then as $t \rightarrow \infty$, (x_0, y_0, z_0) is globally asymptotically stable.

Proposition 3.1 *Suppose $a_1, a_2, a_3, a_5 > 0$:*

- (i) *Then if $a_3 < 1$, then the unvarying state of equation (1.2) of the system (2.1) is universally asymptotically stable for $\tau \geq 0$. Hence E_0 is stable.*
- (ii) *If $a_3 > 1$, then the unvarying state of equation (1.2) of the system (2.1) is globally unstable, hence E_0 is unstable.*

Proof Suppose the characteristic equation of matrix B is written as

$$U(\lambda) = \lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 + (d_1\lambda^2 + d_2\lambda + d_3)e^{-\tau\lambda} = 0. \tag{3.2}$$

Now if $\tau = 0$, then there is no delay in equation (3.2), hence Proposition 3.1 reduces to Proposition 2.1.

Conversely, when $\tau > 0$, and we surrogate the unvarying state of equations (1.2) and (2.2) and solve, we generate the characteristic equation

$$(\lambda + a_1)(\lambda + a_2 - a_2a_3e^{-\lambda\tau})(\lambda + a_5) = 0.$$

Next, by considering the unvarying state of equation (1.2), we ascertain that matrix B has three eigenvalues: $\lambda_1 = -a_1 < 0$, $\lambda_2 = -a_5 < 0$ and λ_3 in the form

$$\lambda_3 + a_2(a_3e^{-\tau\lambda_3} - 1) = 0.$$

Therefore, to find the location of λ_3 , we propose a function of the form

$$u(t) := t + a_2 - a_2a_3e^{-\lambda t}, \quad \text{where } t \in R.$$

By differentiating, we obtain $u'(t) = 1 + a_2a_3\tau e^{-\lambda t}$, which is always positive, hence the limit of the original equation is written as $\lim_{t \rightarrow \infty} u(t) = -\infty$ and $\lim_{t \rightarrow \infty} u(t) = \infty$. Therefore $u(t)$ has a distinctive zero revealed as $u(0) = a_2(1 - a_3)$. Hence we conclude that if $a_3 < 1$, $u(0) > 0$ and $\lambda_3 < 0$. Then the unvarying state of equation (2.5) is globally asymptotically stable for $\tau > 0$.

Conversely if $a_3 > 1$, then we conclude that the unvarying state of equation (1.2) is globally asymptotically unstable for $a_3 < 0$, $\lambda_3 > 0$ and $\tau > 0$. □

4 The endemic equilibrium

The endemic equilibrium E^* is obtained by filtering the real and imaginary parts from the equation below

$$\begin{aligned} & [b_3 + b_2\alpha + b_1\alpha^2 + \alpha^3 - b_1\omega^2 - 3\alpha\omega^2 + i(b_2\omega + 2b_1\alpha\omega + 3\alpha^2\omega - \omega^3) \\ & + e^{-\tau\alpha}[(d_2\omega + 2d_1\alpha\omega) \sin \omega\tau + (d_3 + d_2\alpha + d_1\alpha^2 - d_1\omega^2) \cos \omega\tau \\ & + ie^{-\tau\alpha}[(d_1\omega^2 - d_3 - d_2\alpha - d_1\alpha^2) \sin \omega\tau + (d_2\omega + 2d_1\omega) \cos \omega\tau] = 0, \end{aligned} \tag{4.1}$$

which yields

$$d_2\omega \sin \omega\tau + (d_3 - d_1\omega^2) \cos \omega\tau = b_1\omega^2 - b_3, \tag{4.2}$$

$$d_2\omega \cos \omega\tau - (d_3 - d_1\omega^2) \sin \omega\tau = \omega^3 - b_2\omega. \tag{4.3}$$

Summing the squares of equations (4.2) and (4.3)

$$u(\omega) := \omega^6 + (b_1^2 - 2b_2 - d_1^2)\omega^4 + (b_2^2 - 2b_1b_3 + 2d_1d_3 - d_2^2)\omega^2 + b_3^2 - d_3^2 = 0. \tag{4.4}$$

We further exploit equation (4.4) by surrogating the parameters below

$$m := \omega^2, \quad p := b_1^2 - 2b_2 - d_1^2, \quad q := b_2^2 - 2b_1b_3 + 2d_1d_3 - d_2^2 \quad \text{and} \quad r := b_3^2 - d_3^2.$$

Hence, the new equation reads

$$k(m) = m^3 + pm^2 + qm + r = 0. \tag{4.5}$$

Lemma 4.1 *Suppose $\tau > 0$ then equation (4.5) has no positive real root, hence all the roots have negative real parts.*

Proof Since equation (4.5) has no positive root, then ω is not the root of equation (4.4). Therefore for any real number ω , the value of $i\omega$ is also not the root of equation (4.4), hence $\lambda(\tau_c) = i\omega(\tau_c)$ is not the root of equation (4.4). This implies that only one positive real root exist for equation (4.5). Hence differentiating equation (4.5) yields

$$k'(m) = 3m^2 + 2pm + q. \tag{4.6}$$

Therefore the roots of equation (4.5) are

$$m_o = \frac{-p + \sqrt{p^2 - 3q}}{3} \quad \text{and} \quad \frac{-p - \sqrt{p^2 - 3q}}{3}. \quad \square$$

Lemma 4.2

- (i) *If $r < 0$ then it follows that $p^2 - 3q > 0$ has a positive root, provided $p < 0$.*
- (ii) *On the other hand if $r > 0$ then $p^2 - 3q < 0$, has no positive real roots.*

Proof (i). Suppose condition (i) holds and $r < 0$, then $k(0) = r < 0$, hence $\lim_{m \rightarrow \infty} k(m) = \infty$. Exploiting the intermediate value theorem, equation (4.6) yields t_o as a positive root and therefore $k(t_o) = 0$.

Conversely, if condition (ii) holds for which $r > 0$ and $p^2 - 3q < 0$, then m_o is real for which $m_o > 0$. Since $k(0) = r > 0$ and $k(m_o) < 0$, then by the intermediate value theorem, k has zero between the origin and m_o

(ii). conversely, if $q > \frac{1}{3}p^2$ then the zeros of m_o and m_1 of $K'(m)$ are not real. Henceforth $K'(m) = 0$ has no real root.

Consequently $q > \frac{1}{3}p^2 \geq 0$, has no real roots, given that K is an increasing function where $K(0) = r \geq 0$. We conclude that the model has a unique endemic equilibrium which is asymptotically stable if and only if $R_o > 1$, otherwise unstable. This unique endemic equilibrium occurs at $\tau \geq 0$. □

5 Existence of Hopf bifurcation

We introduce the Hopf bifurcation and therefore appraise the 3-dimensional system of differential equations as follows

$$\begin{aligned} \frac{dx}{dt} &= F(x, y, z, \tau), \\ \frac{dy}{dt} &= G(x, y, z, \tau), \\ \frac{dz}{dt} &= H(x, y, z, \tau). \end{aligned} \tag{5.1}$$

The following conditions holds if:

- (i) $F(\bar{x}, \bar{y}, \bar{z}, \tau) = G(\bar{x}, \bar{y}, \bar{z}, \tau) = H(\bar{x}, \bar{y}, \bar{z}, \tau) = 0$, then τ_c and $(\bar{x}, \bar{y}, \bar{z})$ remains as a steady state solution for equation (4.5).
- (ii) F, G and H are analytic in terms of (x, t, z) , then they are within the neighborhood of $(\bar{x}, \bar{y}, \bar{z}, \tau_c)$.
- (iii) the Jacobian matrix of equation (2.5) at $(\bar{x}, \bar{y}, \bar{z}, \tau)$ has a pair of complex conjugate eigenvalues, λ and $\bar{\lambda}$, then

$$\lambda(t) = \alpha(\tau) + i\omega(\tau), \quad \omega(\tau_c) = \omega_c > 0, \quad \alpha(\tau_c) = 0 \quad \text{and} \quad (5.2)$$

$$\frac{d\alpha(\tau)}{d\tau} I_\tau = \tau_C \neq 0.$$

- (iv) the remaining eigenvalues of the Jacobian matrix at $(\bar{x}, \bar{y}, \bar{z}, \tau_c)$ have strictly negative real part. Then the system (4.1) has a family of periodic solution: $\epsilon_H > 0$ and analytic function $\tau^H(\epsilon) = \sum_2^\infty T_i^H \epsilon^i$, where $0 < \epsilon < \epsilon_H$. Hence, $T^H(\epsilon)$ of $p_\epsilon(t)$ is analytic and of the form

$$T^H(\epsilon) = \frac{2\pi}{\omega_c} \left(1 + \sum_2^\infty T_i^H \epsilon^i \right) \quad (0 < \epsilon < \epsilon_H). \quad (5.3)$$

Next, we exploit the parameters of the analytic function to ensure the occurrence of Hopf bifurcation. Hence we denote the positive roots of equation (4.1) by m_j, j , where $j \in [0, 1, 2]$, depending on the number of positive roots in the equation. Therefore equation (4.1) has six positive roots such as $\omega_j, \lambda = i\omega$ and $\pm\sqrt{m_j}$ where $j = 0, 1, 2$. Consequently, substituting ω_j into equation (4.2) and (4.3) and solving for τ produces

$$\tau_j^{(n)} = \frac{1}{\omega_j} \arcsin \left[\frac{d_1 \omega_j^5 + (b_1 d_2 - d_3 - d_1 b_2) \omega_j^3 + (d_3 b_2 - b_3 d_2) \omega_j}{d_2^2 \omega_j^2 + (d_3 - d_1 \omega_j^2)^2} \right] + \frac{2\pi(n-1)}{\omega_j}. \quad (5.4)$$

Where $j = 0, 1, 2$ and $n = 1, 2, \dots$

Again, when we consider $\tau_c > 0$ to be a smaller value, where $\alpha(\tau_c) = 0$, then

$$\tau_c T_{jc}^{(nc)} = \min \{ \tau_j^{(\tau)} > 0, 0 \leq j \leq 2, n \geq 1 \}. \quad (5.5)$$

Where $\omega_c = \omega_{jc}$.

Theorem 5.1 Consider the time lag τ and the critical time lag τ_c and ω_c as defined in equation (4.5) and suppose $3\omega_c^6 + 2p\omega_c^4 + q\omega_c^2 \neq 0$ then the system of delay differential equation in terms of equation (2.1), portrays the Hopf bifurcation at the steady state in equation (1.2).

Proof We show that

$$\frac{d\alpha(\tau)}{d\tau} I_\tau = \tau_C \neq 0. \quad (5.6)$$

The existence of Equation (4.6) personifies the occurrence of Hopf bifurcation. Hence equating the real and imaginary parts of equations (4.2) and (4.3) to zero, we obtain the

following

$$\begin{aligned}
 & e^{-\tau\alpha} \left[(d_2 + 2d_1\alpha)\omega \sin \omega\tau + [(d_3 + d_2\alpha + d_1(\alpha^2 - \omega^2))] \cos \omega\tau \right] \\
 & = (b_1 + 3\alpha)\omega^2 - b_3 - b_2\alpha - b_1\alpha^2 - \alpha^3
 \end{aligned} \tag{5.7}$$

and

$$\begin{aligned}
 & e^{-\tau\alpha} \left[(d_1\omega^2 + d_3 - d_2\alpha - d_1\alpha^2) \sin \omega\tau + (d_2\omega + 2d_1\alpha\omega) \cos \omega\tau \right] \\
 & = \omega^3 - b_2\omega - 2b_1\alpha\omega - 3\alpha^2\omega.
 \end{aligned} \tag{5.8}$$

Further, we differentiate equations (5.7) and (5.8) with respect to τ and evaluate at $\tau = \tau_c$ where $\alpha\tau_c = 0$ and $\omega(\tau_c) = \omega_c$ and obtains the following

$$E_1 \frac{d\omega}{d\tau} \Big|_{\tau = \tau_c} - E_2 \frac{d\alpha}{d\tau} \Big|_{\tau = \tau_c} = E_3 \cos \omega_c \tau_c + E_4 \sin \omega_c \tau_c, \tag{5.9}$$

$$E_2 \frac{d\omega}{d\tau} \Big|_{\tau = \tau_c} - E_1 \frac{d\alpha}{d\tau} \Big|_{\tau = \tau_c} = E_3 \sin \omega_c \tau_c + E_4 \cos \omega_c \tau_c. \tag{5.10}$$

Where $E_1 := 2b_1\omega_c + (2d_1\omega_c - \tau_c d_2\omega_c) \cos \omega_c \tau_c + (\tau_c d_3 - d_2 - \tau_c d_1\omega_c^2) \sin \omega_c \tau_c$, $E_2 := b_2 - 3\omega_c^2 + (d_2 + \tau_c d_1\omega_c^2 - \tau_c d_3) \cos \omega_c \tau_c + (2d_1\omega_c - \tau_c d_2\omega_c) \sin \omega_c \tau_c$, $E_3 := d_2\omega_c^2$ and $E_4 := d_1\omega_c^3 - d_3\omega_c$.

Now by solving equations (5.9) and (5.10) together we have

$$\frac{d\alpha}{d\tau} \Big|_{\tau = \tau_c} = \frac{(E_1 E_4 - E_2 E_4) \sin \omega_c \tau_c - (E_1 E_4 + E_2 E_3) \cos \tau_c}{E_1^2 + E_2^2}. \tag{5.11}$$

Next we substitute equations (4.2) and (4.3) into equations (5.9) and (5.10) and yields

$$\cos \omega_c \tau_c = \frac{(b_1\omega_c^2 - b_3)(d_3 - d_1\omega_c^2 + d_2\omega_c(\omega_c^3 - b_2\omega_c))}{d_2^2 + (d_3 - d_1\omega_c^2)^2}, \tag{5.12}$$

$$\sin \omega_c \tau_c = \frac{d_2\omega_c(b_1\omega_c^2 - b_3) - (d_3 - d_1\omega_c^2)(\omega_c^3 - b_2\omega_c)}{d_2^2\omega_c^2 + (d_3 - d_1\omega_c^2)^2}. \tag{5.13}$$

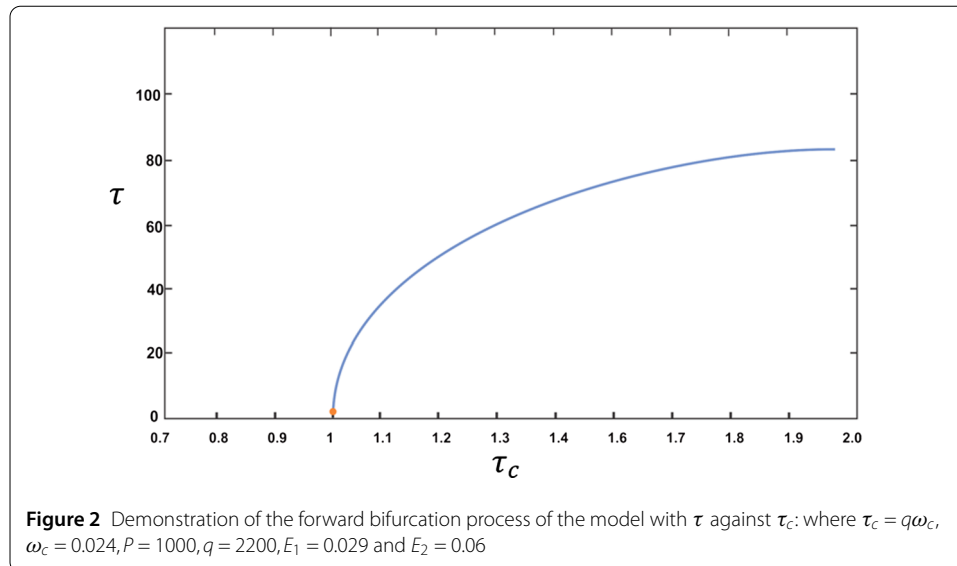
Finally, we incorporate equations (5.12) and (5.13) into equation (5.11) and obtains

$$\frac{d\alpha}{d\tau} \Big|_{\tau = \tau_c} = \frac{3w_c^6 + 2p\omega_c^4 + q\omega_c^2}{E_1^2 + E_2^2} \neq 0. \tag{5.14}$$

Consequently we conclude based on equations (5.12), (5.13) and (5.14), the existence of Hopf bifurcation when, τ passes through the critical value τ_c . □

5.1 Proof for the existence of Hopf bifurcation

In this section we prove the existence of Hopf Bifurcation by assuming that $a_1, a_2, a_5 > 0$ and $a_3 > 1$, for τ_c and ω_c as defined in equation (4.6). Therefore by Lemma 4.2(i) if $p \geq 0, q \geq 0$, then we conclude that the system of delay differential equations proposed in equation (2.1) for the whole delay process has Hopf bifurcation. Consequently, the Hopf bifurcation occurs at $p \geq 0, q \geq 0$, when $3w_c^6 + 2p\omega_c^4 + q\omega_c^2 \neq 0$. This is further supported



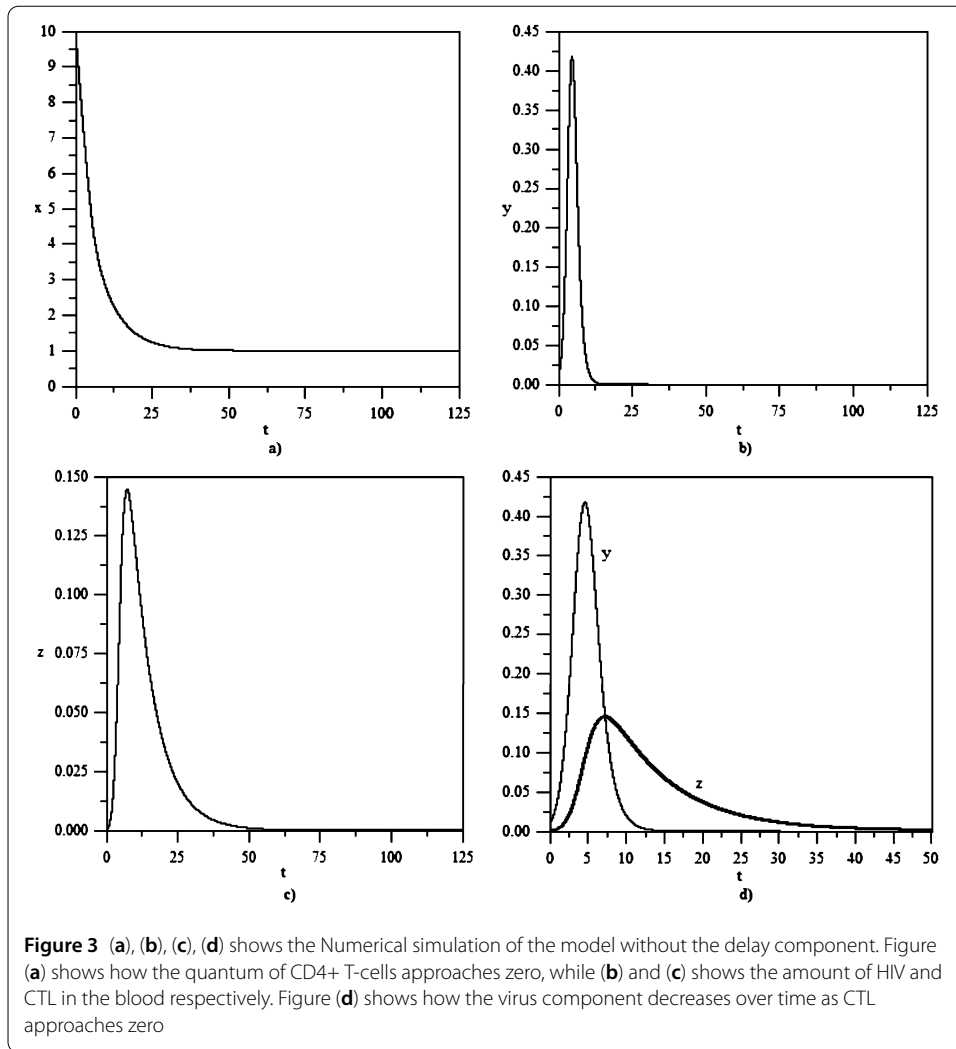
by Lemma 4.1 and Theorem 5.1. The forward bifurcation analysis is portrayed by Fig. 2, where $\tau = q\omega_c$, $\omega_c = 0.024$, $P = 1000$, $q = 2200$, $E_1 = 0.029$ and $E_2 = 0.06$. The conditions for the existence of Hopf bifurcation have been extrapolated by the above analysis. Hence, Fig. 2 portrays the conditions for the model to have a forward bifurcation under a single endemic equilibrium.

6 Numerical simulation

The numerical simulations are engaging around the convergence of orbits of the global stability and the existence of Hopf bifurcation for the system (5.14). The results are enjoined to flaunt the effects of intracellular delay on the qualitative behavior of the three variables: CD4+ T-cell, symbolized (x), cells tainted with HIV, symbolized (y) and CTL, symbolized (z) [7, 14].

Firstly, the model was analyzed without the delay component embedded (ODE), under the following conditions: affirmation of the qualitative conduct of the three variables such as CD4+ T-cell (x), HIV (y), and CTL (z). The affirmation of the three variables was done alongside with controlling the fundamental reproductive rate of the virus. Therefore when equation (1.1) was solved numerically as per the 6th order Runge–Kutta strategy with $a_1 = 0.224$, $a_2 = 0.941$, $a_3 = 0.369$, $a_4 = 4.651$, $a_5 = 1.311$. It was ascertained that the quantum of CD4+ T-cells were consistent over time, whilst CTL and the virus level in the blood approaches zero (Fig. 3). In relation to Proposition 3.1(i) and equation (1.1), when $a_3 < 1$, a steady state was attained at $(1, 0, 0)$. Therefore the conceptive pace of the infection happens to be under control and hence the decline rate of viral production is higher than the production rate. The virus at this stage cannot spread and hence eliminated from the blood as the quantum of CD4+ Tcells remains constant at δ_1/δ_3 (Fig. 3).

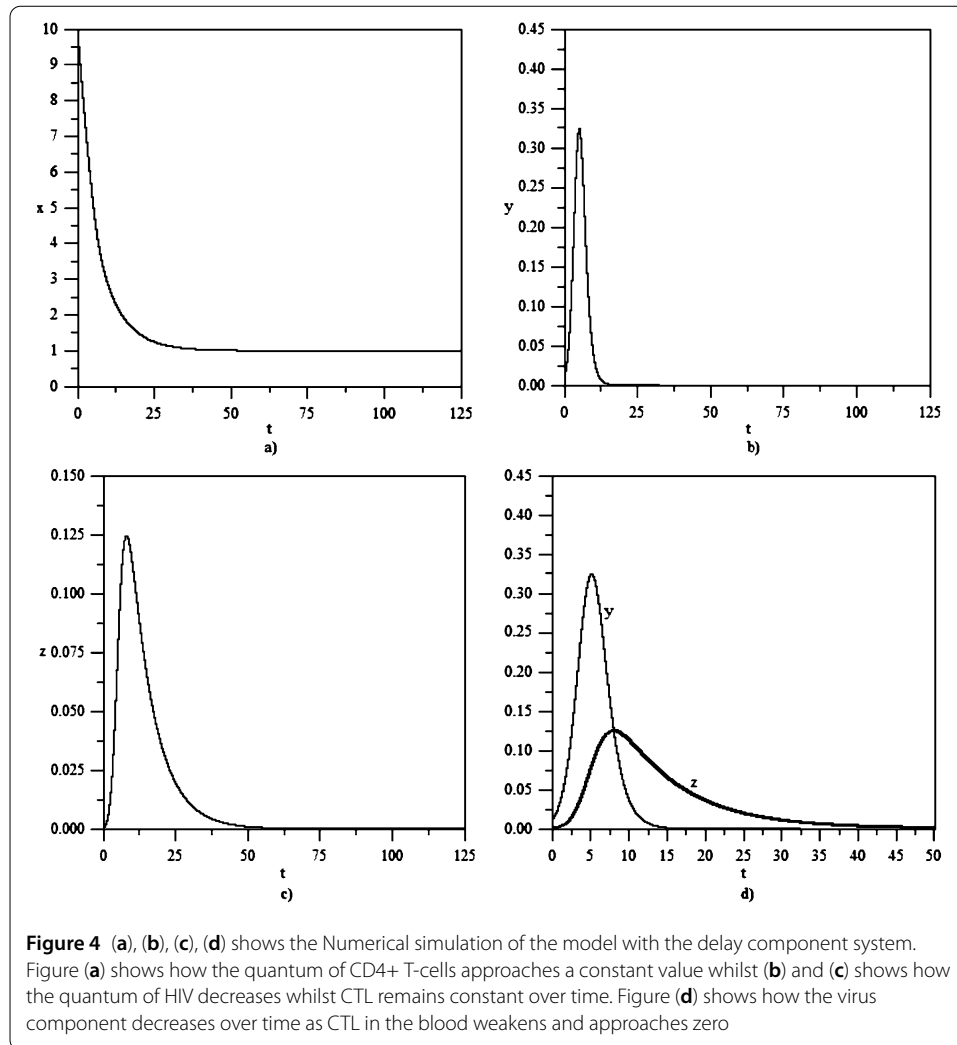
On the contrary, the model was further analyzed with the delay component (DDE), under the following conditions: affirmation of the qualitative conduct of the three variables such as CD4+ T-cell (x), HIV (y), and CTL (z). The affirmation of the three variables was done alongside with controlling the fundamental reproductive rate of the virus. Next equation (1.2) was solved numerically using the 6th order Runge–Kutta technique where



$a_1 = 0.224, a_2 = 0.941, a_3 = 0.369, a_4 = 4.651, \tau = 0.191$. It was ascertained that the quantum of CD4+ T-cells were consistent over time, whilst CTL and the virus level in the blood approaches zero (Fig. 4). In relation to Proposition 3.1(i) and equation (1.2), when $a_3 < 1$, a steady state was attained at $(1, 0, 0)$. Therefore the conceptive pace of the infection happens to be under control and hence the decline rate of viral production is higher than the production rate. The virus at this stage cannot spread, hence eliminated from the blood as the quantum of CD4+ T-cells remains constant at δ_1/δ_3 (Fig. 4).

The model with delay was more advantageous over the non-delay model, because it was more stable at the trajectory. It supports viral peak postponement and virological suppression better than the non-delay (Figs. 3 and 4).

Another dimension to the analysis was the removal of the delay component under the following conditions: affirmation of the qualitative conduct of the three variables such as CD4+ T-cell (x), HIV (y), and CTL (z). This time the fundamental reproductive rate of the virus was uncontrolled. Now when equation (1.1) was solved numerically as per the 6th order Runge–Kutta strategy with now $a_1 = 0.1038, a_2 = 3.22, a_3 = 2.64, a_4 = 7.41, a_5 = 4.17$. The density of HIV and CTL approaches the vanishing point to confirm the connection between the virus and the immune response, as depicted in Fig. 5. This implies that the

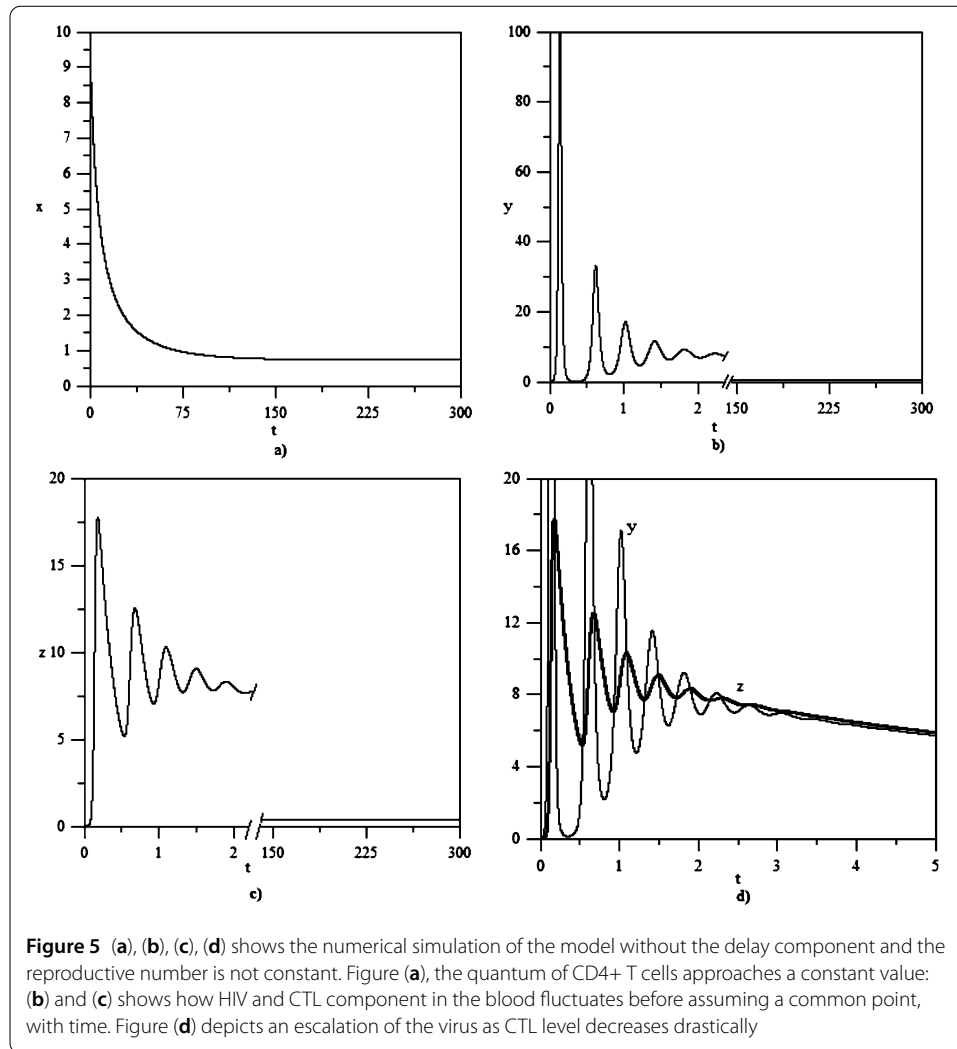


essential conceptive pace of the infection is not under control and hence the decline rate of viral production is lower than the production rate. Infection rate surges and more virions are produced in the blood (Fig. 5).

Contrary to the above, the model was analyzed further with the delay component (DDE), under the following conditions: affirmation of the qualitative conduct of the three variables such as CD4+ T-cell (x), HIV (y), and CTL (z). The fundamental reproductive rate of the virus was uncontrolled and equation (1.2) was solved numerically using the 6th order Runge–Kutta technique where $a_1 = 0.1038, a_2 = 3.22, a_3 = 2.64, a_4 = 7.41, \tau = 0.19$. It was observed that the essential conceptive pace of the infection was not under control and hence the decline rate of viral production was lower than the production rate (Fig. 6). Therefore the elongation of the infection [2, 3, 13] on an individual leads to the inception of AIDS.

7 Structured treatment interruption

The quest for legit structured treatment interruptions has necessitated the essence of intracellular delay in STI models. Currently, the adopted STI used by many HIV individuals does not incorporate days-off for drug assimilation by the body. Arguably therapy inter-

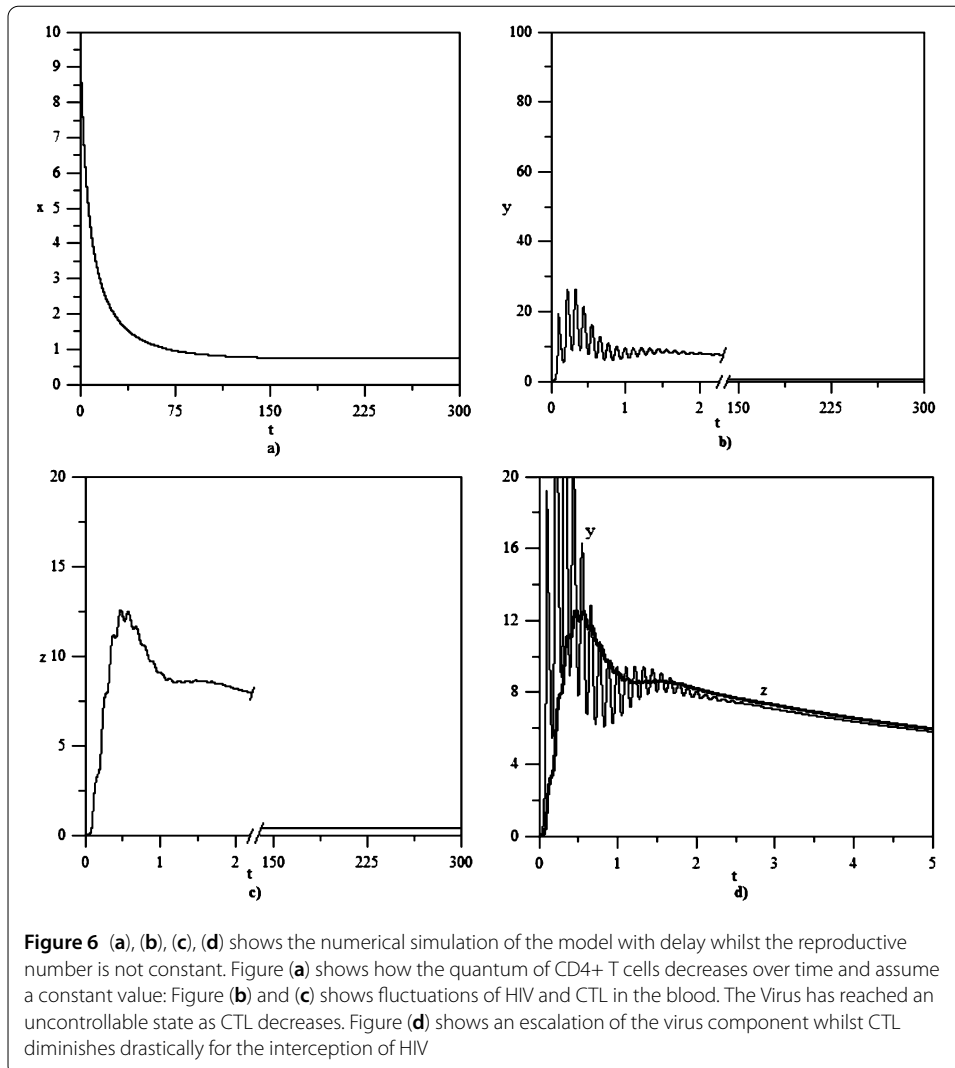


ruptions should align across days and weeks, in order to allow for drug assimilation. Find below some of the STI systems embedded to validate the model.

7.1 Two-weeks-on two-weeks-off strategy (14/14)

The scenario above relates to 14 days on treatment and 14 days off regime therapy, designed for HIV patients. However, adherence to the regime yields an auto viral control compared to the primitive STI system [11], which aligns with lengthy periods of therapy. In reference to Fig. 7, this strategy yields a momentous average viral load of 586 virions/ml and 3371 virions/m at peak level. On the contrary, a continuous therapy without any interruption increases the viral haul to 633 virions/ml on the average. This implies that the shorter the period for a particular therapy, the lower the peak viral haul. Therefore the lower the peak viral haul, the less the augmentation of viral strains, responsible for drug resistance mutations (Fig. 7).

Further, the graphs also deal with non-delay and therefore an average viral haul of 8446 virions/ml was produced (Fig. 7(b)). The amount of virions produced by the non-delay therapy was higher and therefore signals the essence of delay. Hence, with reference

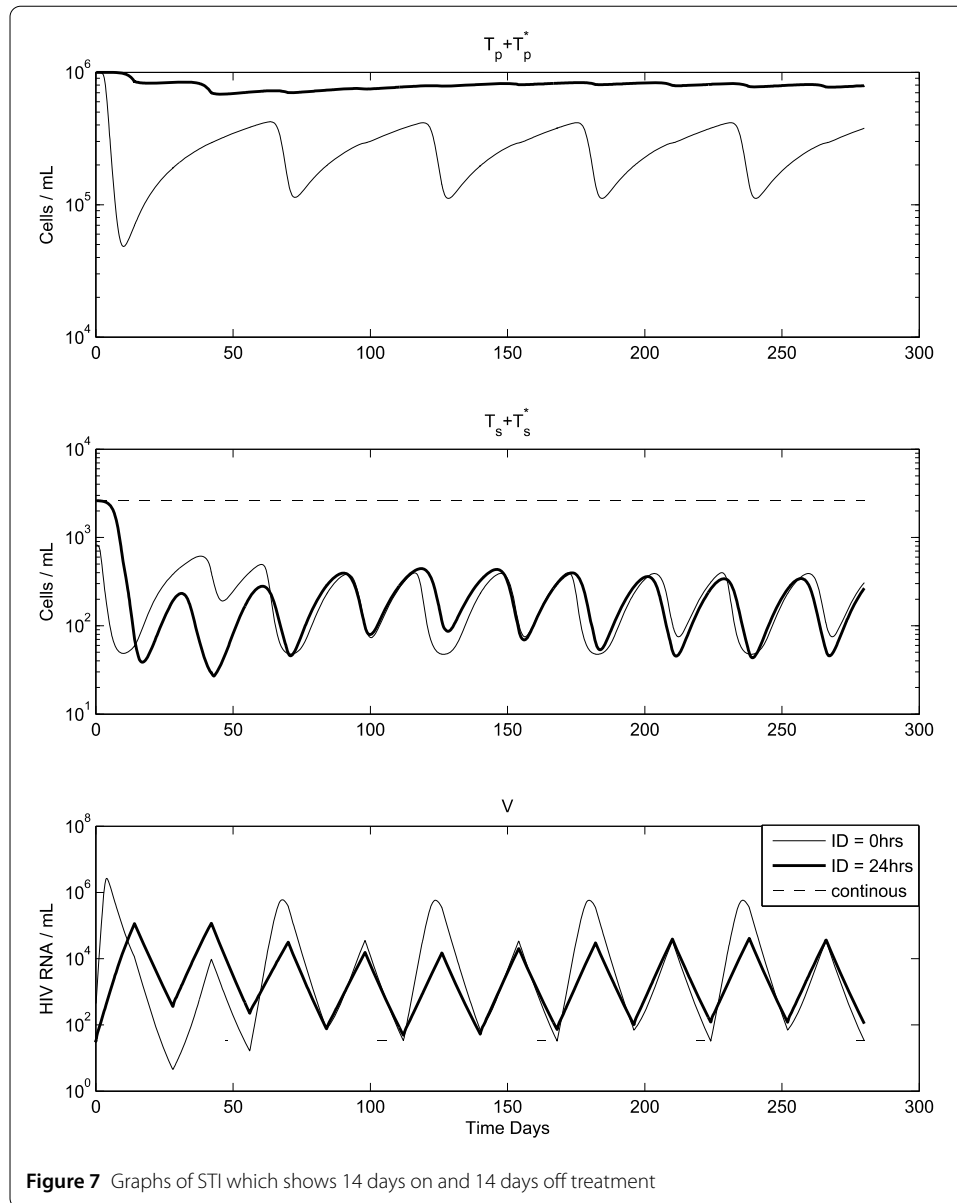


to the ongoing discussion, a short cycle therapy is recommended on the basis of controlling viral rebound.

7.2 Five-days-on two-days-off strategy (5/2)

The five days on and two days off STI strategy allows treatment from Monday to Friday, with Saturday and Sunday as weekends off treatment. This strategy, also inferred as weekend off strategy is vital in subduing long term viral replication [1, 11]. It enhances a decrease in drug residual level, since its squatty intermission period allows for the assimilation of DRM. Hence in curbing down monotherapy situations, the usage of particular drugs should be disengaged for suitable metabolism rate.

In addition, the five days on and two days off regime, supports a decline of the maximum viral haul. It is worth to note that escalations in viral haul have been a headache for most scientists. The peak viral haul is crucial and personifies a larger viral pool which begets mutations. Based on the 5/2 strategy a cost saving of 29% is marginalized, compared to the continual therapy. In addition, the 5/2 strategy produces low viral haul due to limited viral rebound. Furthermore, the strategy is useful to places where therapy is not consistent and



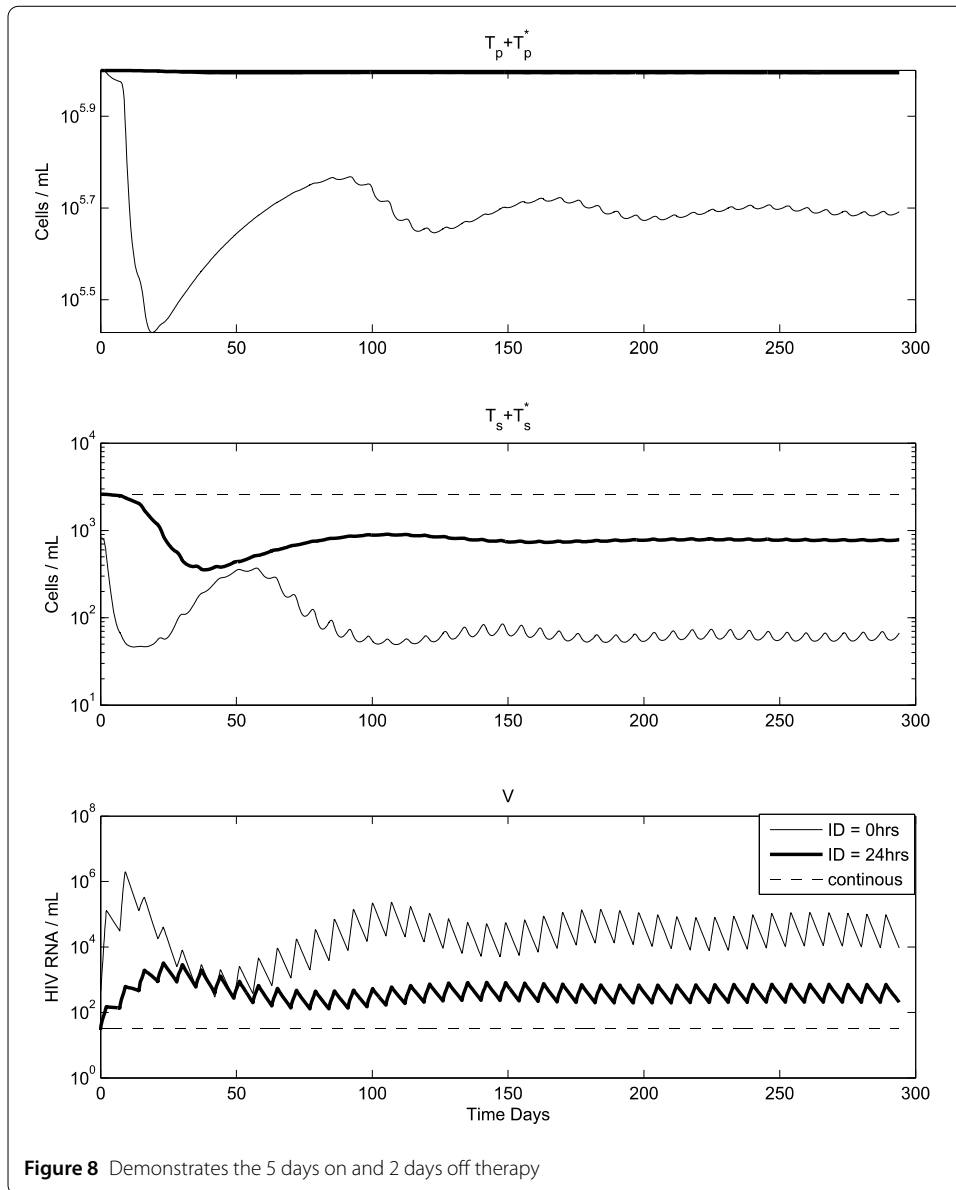
hence reliable to stop therapy for two days, than to abort the whole process due to limited drug availability. In accordance with the above discussions, the 5/2 strategy appears to be reasonably successful in producing positive results [1, 11], as depicted by Fig. 8.

From Fig. 8, the 5 days on and two days off therapy induces a mean viral haul of 331 virions/ml with zero delay and 412 virions/ml within 24 hours.

7.3 Impact of varying the on and off period

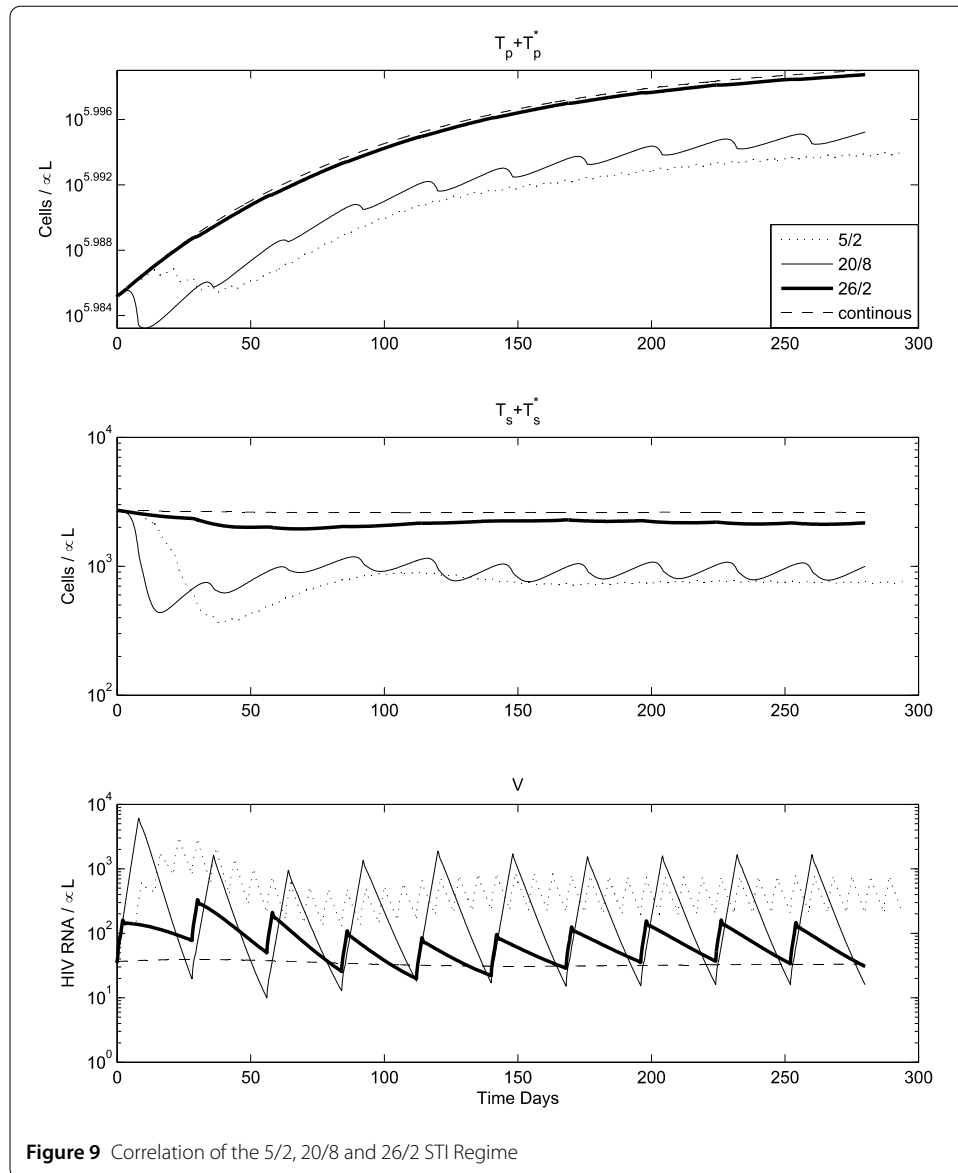
The idea of varying treatment on and off has conceived imperative due to less access to ARV, cost concerns and ceaseless treatment. However off-treatment should not be prolonged due to high viral rebound and viral mutation to drugs.

This chapter contrasts the 5/2 system, the 20/8 system and the 26/2 system and suggest the way forward. The ceaseless treatment period was used as reference and therapy was tempered as per the three systems above (Fig. 9). It was observed that tempering with



therapy for a short period of time was essential due to the following reasons: accessibility to ARV, cost concerns and discontinuity of therapy due to ARV shortage. Therefore the shorter the time frames for off treatment, the better the results and the lesser the viral rebound [11–14].

In accordance with the ongoing analysis, it was ascertained that the 26/2 system (Table 1) stimulates a reliable outcome, however the system is not decisive due to its little cost sparing of about 7%. On the other side, the 20/8 system appears to have a lower viral haul than the 5/2 system. The respective average and peak viral hauls for the 20/8 system were 352 virions/ml and 751 virions/ml respectively. The 5/2 system also articulated 437 virions/ml and 756 virions/ml respectively. In view of the above outcome a trade-off is simulated to enhance the choice and adoption of a suitable treatment interruption (Fig. 9). Therefore the next section enhances the selection of the overall regime for compliance.



7.4 Overall STI regime comparison

The above examination has conceived essential in adjusting treatment on and off, thereby diminishing the pinnacle viral haul. Therefore, based on the above analysis the 18/3 and 24/4 systems have been recommended for compliance and adoption due to low viral haul production (Fig. 10). The 18/3 system produces an average and peak virions of 120 and 285 virions/ml respectively, whilst the 24/4 system produces 118 and 338 virions/ml respectively (Fig. 10).

8 Conclusion

The aim of the paper is to unveil the niche of delay differential equation in harmonizing low level HIV viral haul and thereby articulating the adopted model to delve into structured treatment interruptions.

Hence, the sturdiness of the model with delay (equation (1.2)) and without delay (equation (1.1)) was assessed. Numerical simulations were used to consolidate the results.

Table 1 Demonstration of treatment strategies, viral load level and corresponding cost

Strategy on/off days	Average Viral haul Virions/ml	Peak Viral haul	% Cost Saving Virions/ml
5/2	437	756	29
12/2	126	320	14
11/3	209	623	21
19/2	86	171	10
18/3	120	285	14
17/4	168	465	19
20/8	352	751	24
26/2	70	138	7
25/3	92	218	11
24/4	118	338	14
23/5	151	507	18
22/6	201	743	21
21/7	558	1086	25
30/5	114	408	14
36/6	121	495	14
42/7	117	610	14

The demands for the stability of Hopf bifurcation were authenticated in itemizing the initial conditions of the model (Fig. 2). The existence of Hopf bifurcation [3, 4] has been proved and hence occurs when, τ passes through the critical value τ_c .

The analysis of the results indicated that when the basic reproductive rate of the virus was under control and the delay component τ were embedded in the model to verify the qualitative behavior of the three variables, such CD4+ T cells (x), HIV cells (y) and CTL (z). It was concluded that when $a_3 < 1$, then by Proposition 3.1(i): a steady state exists at (1,0, 0). Therefore the pace of infection by the virus is under control and the decline rate of viral production is higher than the production rate at δ_1/δ_3

Conversely when $a_3 > 1$, then as per Proposition 3.1(ii): a non-existence steady state occurs. Therefore the pace of the contagion is higher than the decline rate at δ_1/δ_3 and AIDS intercepts. [2]

Adherence to the conditions imposed on Proposition 3.1(i) when $a_3 < 1$, intimates that the reproductive ratio of the virus is under control. This signifies a stable CD4+ T cells, hence adherence to therapy could delay AIDS interception. Further, by the conditions of Proposition 3.1(i) we have revealed an abortive attempt by the virus due to the consistent increase in CD4+ T cells (Fig. 4). Hence, CTL consequently eliminates the virus from the body. This is made possible when CD4+ T cells converges at δ_1/δ_3

Again sustenance of the imposed conditions on Proposition 3.1(i), is central to virological suppression and increased life expectancy under HIV [9, 11, 14]. Therefore it is imperative to ascertain the time frame, for the adaptive immune response of the body to emerge in regulating viral replication. This is supported when $a_3 < 1$.

Further, in compliance with the rigorous analysis imposed on treatment options, the study hereby recommends for a short period off medication. This certifies that treatment should be expelled for only few days to allow for drug assimilation [8]. Therefore in reference to the imposed interactions on STI systems, the study recommends for the 24 days on treatment and 4 days off treatment for compliance. 18 days on treatment and 3 days off treatment is also supported by the study. [8, 12]

Notwithstanding, due to increased imposition on treatment interruptions the study recommends for the application of controlled techniques to enhance the adopted model.

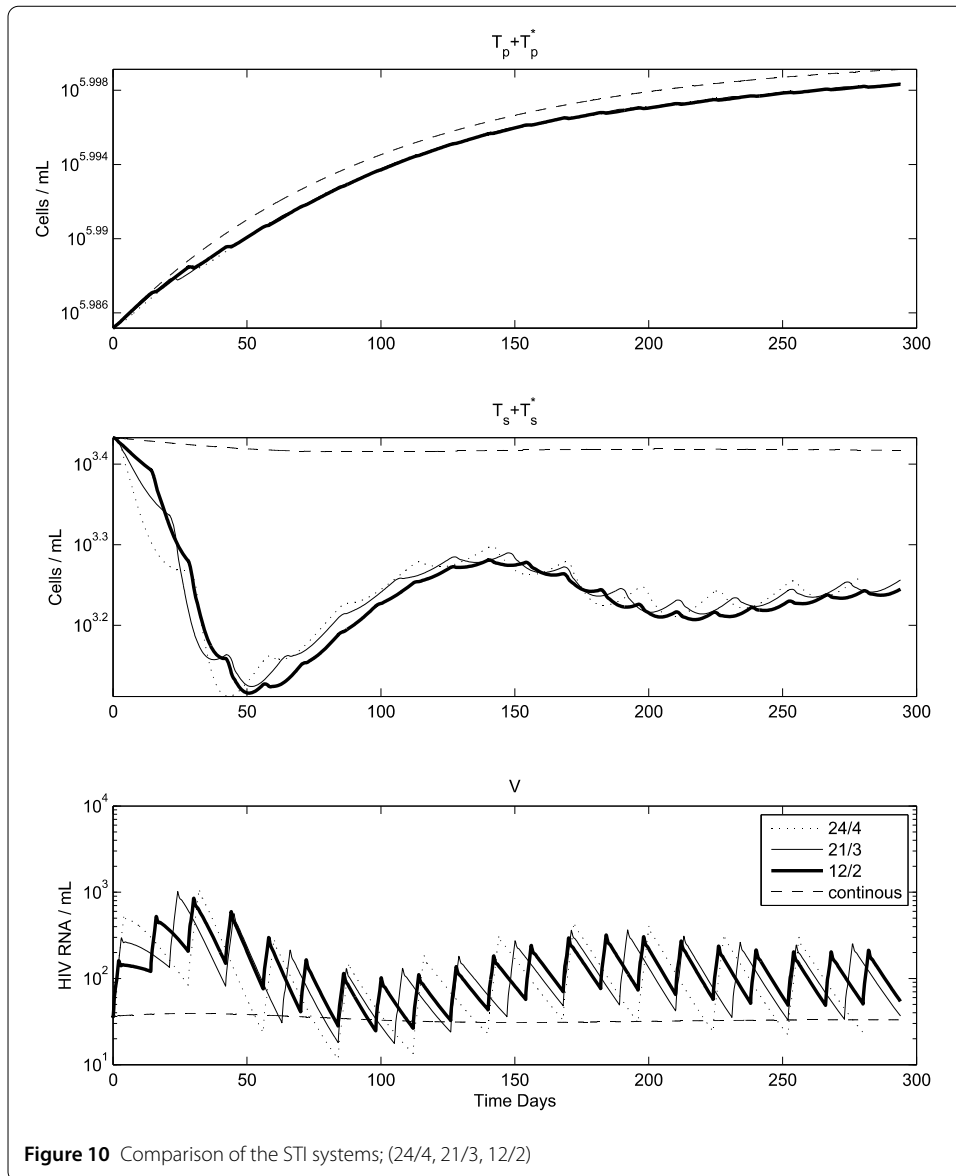


Figure 10 Comparison of the STI systems; (24/4, 21/3, 12/2)

Finally, the use of optimal control with distributed delay could also be exploited due to increase in target cells complexities [6].

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Availability of data and materials

Due to very strict ethical reasons, the analyzed data for the study is not publicly available.

Competing interests

The authors by declaration have no competing interest.

Authors' contributions

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