Applied and Computational Mathematics
2021; 10(4): 91-99
http://www.sciencepublishinggroup.com/j/acm
doi: 10.11648/j.acm.20211004.12
ISSN: 2328-5605 (Print); ISSN: 2328-5613 (Online)

The Global Dynamics of HIV Latency Model Including Cell-to-Cell Viral Transmission

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To cite this article:
Wajahat Ali, Zhipeng Qiu. The Global Dynamics of HIV Latency Model Including Cell-to-Cell Viral Transmission. *Applied and Computational Mathematics*. Vol. 10, No. 4, 2021, pp. 91-99. doi: 10.11648/j.acm.20211004.12

Received: May 29, 2021; **Accepted**: June 21, 2021; **Published**: July 9, 2021

Abstract: HIV spreads by cell-to-cell transfer and the release of cell-free particles. A slightly more effective method of retroviral transmission is the direct cell-to-cell transfer of HIV, according to recent reports. Intracellular interaction between unhealthy and healthy cells, in combination with cytokine discharged by the cells included, may affect the susceptibility of a target resting CD4+T cell to HIV infection and the formation of latent infection. We suggest a class of HIV latency mathematical model, integrating both cell-free virus transmission and direct cell-to-cell diffusion to improve the understanding of the dynamics of the latent reservoirs. We incorporate four components in our model: the uninfected T cells, the latently infected T cells, the active-infected T cells and the HIV viruses. We examine the latency model by introducing the basic reproduction number. We first establish the non-negativity and boundedness of the solutions of the system, and then we investigate the global stability of the steady states. The diseased-free equilibrium is globally stable when the basic reproduction number is less than 1 and if the basic reproduction number is greater than 1, the diseased equilibrium exists and is globally stable. Numerical simulations are executed to interpret the theoretical outcomes and evaluate the relative contribution of latency fractions in the virus production and the HIV latent reservoir by providing estimates.

Keywords: HIV, Infected Latent Cells, Virus Intracellular Transmission, Global Stability

1. Introduction

The manner in which a pathogen evolves inside a host has significant implications for the effective establishment of an infection and its maintenance. Viruses have developed distinct mechanisms to attack the target cells so as for replication and infection dissemination.

In general, two main ways are identified for viral transmission, i.e. (i) virus cell-free (CF) transmission and (ii) virus cell-cell (CC) transmission [3]. Although CF viral particle diffusion allows distant cell infection whereas CC viral transmission relates to local diffusion, ignores complex operations of our body and is considered to have the ability to guard the viral particles from neutralization of antibodies, antiviral constraint aspects and few anti-retroviral remedies [4, 5]. Therefore, the CC transmission way is thought to be more responsible in spreading infection [6, 7].

In addition, virally induced bonds, or virological synapses are formed by cell contacts, among CD4+T cells, concentrating immense amount of particles at the place of intracellular contact [8–10]. The target cells receive a high MOI due to this process [2, 11]. It is still necessary to determine in detail the importance and input of every transmission modes to viral spread. However, a decent quantification of the transmission dynamics is required to address it.

Computational models formulated to observe the infection kinetics of HIV, containing both these transmission ways [1, 14–18, 31–41, 43, 46]. The relative contribution to the spread of HIV by the two transmission modes is studied by Komarova et al. [13] and Iwami et al. [12]. Lai [20, 21] derived models including both these ways of viral diffusion. H. Pourbashash et al. [17] analyzed a multi-strain model to show a competitive exclusion principle.

The highly suggestive obstacle for the HIV-1 infection wipeout is the presence of latent infected pools which subsist regardless of long-term viral multiplication restraint by HAART [22–24]. Most of infected latent cells are composed

of long living resting CD4+T cells and are managed by homeostatic proliferation [25–27]. These latent cells can produce virus infection by connecting with relevant antigens.

Motivated by the work of Alshorman et al. [28] and Lai et al. [20, 21], in this paper, we derive an HIV latency model which includes CF and CC. Firstly, we prove the non-negativity and boundedness of solutions of our model. Then, we perform the derivation of basic reproduction number $\mathcal{R}_0$ and equilibria. We investigate the global stability of two steady states. In the end, numerical simulations are performed to show the complexity of dynamics of model.

2. The Model

We developed a following mathematical model.

$$\frac{dT(t)}{dt} = \lambda - d_T T - k_1 VT - k_2 TT^*,$$

$$\frac{dL(t)}{dt} = \alpha_1 k_1 VT + \alpha_2 k_2 TT^* - d_L L - bL,$$

$$\frac{dT^*(t)}{dt} = (1-\alpha_1)k_1 VT + (1-\alpha_2)k_2 TT^* - \delta T^* + bL,$$

$$\frac{dV(t)}{dt} = N\delta T^* - cV, \quad (1)$$

where the concentration of latent infected cells denoted by L. The concentration of uninfected cells, infected cells and free viruses is represented by T, T^* and V, respectively. The suspected cells become infected due to virus-to-cell and cell-associated infections at the rates $k_1 V T \; and \; k_2 TT^*$, respectively, where k_1 and k_2 denotes the incidence rates. The fractions $(1-\alpha_1, 1-\alpha_2 \; and \; \alpha_1, \alpha_2)$ represents the possibilities that upon infection, a suspected cell turns out to be either productively infected or latently infected, respectively. The death rate of latently infected cells and productively infected cells is denoted by d_L and δ. Parameter b represents the rate at which latently infected cells become productively infected cells. We did not add the proliferation of latently infected cells in this model but can do so as in [42].

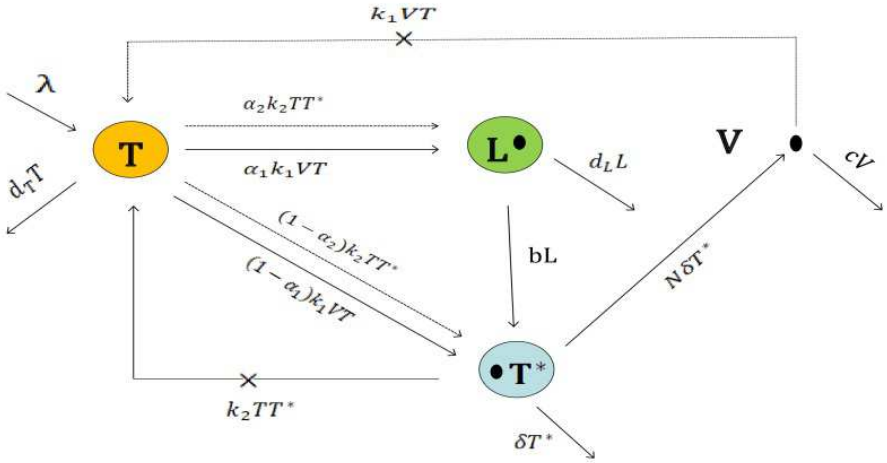

Figure 1. *Model (1) illustrative representation. Variables T, L, T^* and V represent infection-free CD4+ T cells, infected CD4+ T latent cells, productively unhealthy CD4+ T cells and CF, respectively.*

2.1. Non-negativity and Boundedness

Let us define

$$\Omega = \{(T, L, T^*, V) \in \mathbb{R}^4_{\geq 0} : 0 \leq T, L, T^* \leq M_1, 0 \leq V \leq M_2\}.$$

Lemma 2.1. The compact set Ω is positively invariant for system (1).

Table 1. *System framework.*

Parameter	Description	Rate	Units	Fountains
k_1	T-cells Infection proportion for CF	10^{-10}~10^{-8}	$d^{-1}ml$	[48]
k_2	T-cells Infection proportion for CC	10^{-8}~10^{-6}	$d^{-1}ml$	[17]
λ	T-cells origination proportion	10^4	$d^{-1}ml^{-1}$	[47]
d_T	T-cells mortality proportion	0.01	d^{-1}	[19]
b	T-cells (latent) stimulation proportion	0.01	d^{-1}	[42]
d_L	Infected T-cells (latent) mortality proportion	0.004	d^{-1}	[19]
δ	T-cells (infected) mortality proportion	1	d^{-1}	[36]
α_1	Latency proportion for CF	0.001	*No unit*	[49]
α_2	Latency proportion for CC	0.001	*No unit*	[49]
N	Viral explode proportion	100~2000	$d^{-1}cell^{-1}$	[42, 47]
c	Virions mortality proportion	23	d^{-1}	[36]

Proof.
We observe that

$$\dot{T}|_{(T=0)} = \lambda > 0,$$

$$\dot{L}|_{(L=0)} = (\alpha_1 k_1 V + \alpha_2 k_2 T^*)T \geq 0, \forall\, T, T^*, V \geq 0,$$

$$\dot{T^*}|_{(T^*=0)} = (1-\alpha_1)k_1 VT + bL, \forall\, T, L, V \geq 0,$$

$$\dot{T}|_{(V=0)} = N\delta T^*, \forall\, T^* \geq 0.$$

This confirms that $\big(T(t), L(t), T^*(t), V(t)\big) \in \mathbb{R}^4_{\geq 0}$ with $\big(T(0), L(0), T^*(0), V(0)\big) \in \mathbb{R}^4_{\geq 0}$. Let $G = T + L + T^* + \frac{1}{2N}V$. Then

$$\dot{G} = \lambda - d_T T - k_1 VT - k_2 TT^* + \alpha_1 k_1 VT + \alpha_2 k_2 TT^* - d_L L - bL$$

$$+(1-\alpha_1)k_1 VT + (1-\alpha_2)k_2 TT^* - \delta T^* + bL + \frac{1}{2N}(N\delta T^* - cV)$$

$$= \lambda - d_T T - d_L L - \delta T^* - \frac{cV}{2N}$$

$$\leq \lambda - \sigma\left(T + L + T^* - \frac{1}{2N}V\right) = \lambda - \sigma G,$$

where $\sigma = \min\{d_T, d_L, \delta, c\}$. Hence $0 \leq G(t) \leq M_1$ for all $t \geq 0$ if $G(0) \leq M_1$, where $M_1 = \frac{\lambda}{\sigma}$. Consequently, $0 \leq T, L, T^* \leq M_1$ *and* $0 \leq V \leq M_2\ \forall\, t \geq 0$ if $T(0) + L(0) + T^*(0) + \frac{1}{2N}V(0) \leq M_1$, where $M_2 = \frac{2N\lambda}{\sigma}$. This establishes the boundedness of $T(t), L(t), T^*(t)$ *and* $V(t)$.

2.2. Reproduction Numbers and Equilibria

The equilibria of model (1) should satisfy the following equalities.

$$\lambda - d_T T - k_1 VT - k_2 TT^* = 0,$$

$$\alpha_1 k_1 VT + \alpha_2 k_2 TT^* - d_L L - bL = 0,$$

$$(1-\alpha_1)k_1 VT + (1-\alpha_2)k_2 TT^* - \delta T^* + bL = 0,$$

$$N\delta T^* - cV = 0.$$

Straightforward calculation shows that our system (1) has two following steady states.

i. the healthy equilibrium: $E_0 = (T_0, 0, 0, 0)$, where $T_0 = \frac{\lambda}{d_T}$.
ii. the chronic equilibrium: $\bar{E} = (\bar{T}, \bar{L}, \bar{T}^*, \bar{V})$.

Inspired by the method in Diekmann *et al.* [29] and van den Driessche and Watmough [30], let us introduce the basic reproduction number for our system (1).

$$\mathcal{R}_0 = \frac{Nk_1\lambda}{cd_T}\left(\frac{b\alpha_1}{b+d_L} + (1-\alpha_1)\right) + \frac{k_2\lambda}{\delta d_T}\left(\frac{b\alpha_2}{b+d_L} + (1-\alpha_2)\right),$$

where $\frac{Nk_1\lambda}{cd_T}$ and $\frac{k_2\lambda}{\delta d_T}$ are the basic reproduction numbers through virus-to-cell infection and cell-associated infection, respectively. We also observe that $\mathcal{R}_0$ determined here is similar to that attained from the threshold condition ensuring the existence of the endemic steady state.

When $\mathcal{R}_0 > 1$ then

$$\bar{T} = \frac{\lambda}{d_T \mathcal{R}_0},$$

$$\bar{L} = \frac{\lambda(N\delta\alpha_1 k_1 + c\alpha_2 k_2)(\mathcal{R}_0 - 1)}{\mathcal{R}_0(b+d_L)(N\delta k_1 + ck_2)},$$

$$\bar{T}^* = \frac{cd_T(\mathcal{R}_0 - 1)}{(N\delta k_1 + ck_2)},$$

$$\bar{V} = \frac{N\delta d_T(\mathcal{R}_0 - 1)}{(N\delta k_1 + ck_2)},$$

Theorem 2.2. We have $\mathcal{R}_0$ from our system (1), then

i. System (1) has just non-disease equilibrium E_0 if $\mathcal{R}_0 < 1$:
ii. System (1) has two equilibria E_0 and $\bar{E}$ if $\mathcal{R}_0 > 1$:

Its proof can be evaluated by simple arithmetic and we skipped it here.

3. Global Stability Analysis of System with $\alpha_1 = \alpha_2$

We formulate Lyapunov functionals to examine the global kinetics of system's (1) steady states in this section. We assume $\alpha_1 = \alpha_2$ while the case of $\alpha_1 \neq \alpha_2$ remains to be further studied.

Theorem 3.1. If $\mathcal{R}_0 < 1$, then the healthy equilibrium E_0 is globally asymptotically stable, while $\alpha_1 = \alpha_2$.

Proof. Initially, we claim that $T(t) \leq T_0$ for any $t \geq 0$. Otherwise there exists $t_1 > 0$ such that $T(t_1) > T_0$ and $\frac{dT}{dt}(t_1) > 0$.

$$\frac{dT}{dt}(t_1) = \lambda - d_T T(t_1) - k_1 V(t_1) T(t_1) - k_2 T(t_1) T^*(t_1) \leq 0, \quad (2)$$

which contradicts with $\frac{dT}{dt}(t_1) > 0$. Now, we construct the Lyapunov function

$$X(t) = bL + (d_L + b)T^* + \frac{k_1(b + d_L(1-\alpha_1))T_0 V}{c}. \quad (3)$$

Now compute the derivation of $X(t)$ along the system's (1) solution, then

$$\begin{aligned}
\frac{dX}{dt} &= b(\alpha_1 k_1 VT + \alpha_2 k_2 TT^* - d_L L - bL) + (d_L + b)((1-\alpha_1)k_1 VT \\
&\quad + (1-\alpha_2)k_2 TT^* - \delta T^* + bL) + \frac{k_1(b + d_L(1-\alpha_1))T_0}{c}(N\delta T^* - cV) \\
&= \big(b + d_L(1-\alpha_1)\big)(k_1 VT + k_2 TT^*) - (b + d_L)\delta T^* \\
&\quad + \frac{k_1(b + d_L(1-\alpha_1))T_0}{c}(N\delta T^* - cV) \\
&= \big(b + d_L(1-\alpha_1)\big)(k_1 VT + k_2 TT^*)(T - T_0) + (d_L + b)\delta T^*(\mathcal{R}_0 - 1). \quad (4)
\end{aligned}$$

Hence, $\frac{dX}{dt} \leq 0$ when $\mathcal{R}_0 < 1$. Moreover $\frac{dX}{dt} = 0$ iff $T = T_0; L = 0; T^* = 0$ and $V = 0$. Largest consistent set within $(T;\ L;\ T^*;\ V): \frac{dX}{dt} = 0$ be the singleton set E_0. By using LaSalle's invariance principle, we attain that the infection-free equilibrium E_0 is globally asymptotically stable [44].

Theorem 3.2. If $\mathcal{R}_0 > 1$, then the acute-infection equilibrium $\bar{E}$ is globally asymptotically stable, while $\alpha_1 = \alpha_2$.

Proof. Let us formulate Lyapunov functional

$$\begin{aligned}
Y(t) &= \big(b + d_L(1-\alpha_1)\big)\left[T(t) - \bar{T} - \bar{T} ln \frac{T}{\bar{T}}\right] + b\left[L(t) - \bar{L} - \bar{L} ln \frac{L}{\bar{L}}\right] \\
&\quad + (b + d_L)\left[T^*(t) - \bar{T}^* - \bar{T}^* ln \frac{T^*}{\bar{T}^*}\right] + \frac{k_1(b + d_L(1-\alpha_1))\bar{T}}{c}\left[V(t) - \bar{V} - \bar{V} ln \frac{V}{\bar{V}}\right]. \quad (5)
\end{aligned}$$

Then the derivative of Y along system's (1) solution is

$$\begin{aligned}
\frac{dY}{dt} &= \big(b + d_L(1-\alpha_1)\big)\left(1 - \frac{\bar{T}}{T}\right)(\lambda - d_T T - k_1 VT - k_2 TT^*) + b\left(1 - \frac{\bar{L}}{L}\right)(\alpha_1 k_1 VT + \alpha_2 k_2 TT^* \\
&\quad - d_L L - bL) + (b + d_L)\left(1 - \frac{\bar{T}^*}{T^*}\right)((1-\alpha_1)k_1 VT + (1-\alpha_2)k_2 TT^* - \delta T^* + bL) + \frac{k_1(b + d_L(1-\alpha_1))\bar{T}}{c}(N\delta T^* - cV)\left(1 - \frac{\bar{V}}{V}\right) \\
&= \big(b + d_L(1-\alpha_1)\big)\left(1 - \frac{\bar{T}}{T}\right)(\lambda - d_T T - \lambda + d_T T) - k_1\big(b + d_L(1-a_1)\big)VT \\
&\quad - k_2\big(b + d_L(1-a_1)\big)TT^* + k_1\big(b + d_L(1-a_1)\big)\bar{V}\bar{T} + k_2\big(b + d_L(1-a_1)\big)\bar{T}\bar{T}^* \\
&\quad - k_1\big(b + d_L(1-a_1)\big)\frac{\bar{V}\bar{T}^2}{T} - k_2\big(b + d_L(1-a_1)\big)\frac{\bar{T}^2\bar{T}^*}{T} + k_1\big(b + d_L(1-a_1)\big)V\bar{T} \\
&\quad + k_2(b + d_L(1-a_1))\bar{T}T^* + k_1\alpha_1 bVT + k_2\alpha_1 bTT^* - b(b + d_L)L + b(b + d_L)\bar{L} \\
&\quad - k_1\alpha_1 b\frac{VT\bar{L}}{L} - k_2\alpha_1 b\frac{TT^*\bar{L}}{L} + k_1(b + d_L)(1-a_1)VT + k_2(b + d_L)(1-a_1)TT^* \\
&\quad + b(b + d_L)L - \delta(b + d_L)T^* + \delta(b + d_L)\bar{T}^* - k_1(b + d_L)(1-a_1)\frac{VT\bar{T}^*}{T^*} - k_2(b + d_L) \\
&\quad (1-a_1)T\bar{T}^* - b(b + d_L)\frac{L\bar{T}^*}{T^*} + \frac{k_1 N\delta\big(b + d_L(1-a_1)\big)T^*\bar{T}}{c} - k_1\big(b + d_L(1-a_1)\big)V\bar{T}
\end{aligned}$$

$$+k_1(b+d_L(1-a_1))\bar{V}\bar{T}-\frac{k_1N\delta(b+d_L(1-a_1)\bar{V}T^*\bar{T}}{cV}$$

$$=-\big(b+d_L(1-\alpha_1)\big)d_T(T-\bar{T})^2+k_1(b+d_L)(1-a_1)\bar{V}\bar{T}+k_2(b+d_L)(1-a_1)\bar{T}\bar{T}^*+$$

$$k_1\alpha_1b\bar{V}\bar{T}+k_2\alpha_1b\bar{T}\bar{T}^*-k_1(b+d_L)(1-a_1)\frac{\bar{V}\bar{T}^2}{T}-k_1\alpha_1b\frac{\bar{V}\bar{T}^2}{T}-k_2(b+d_L)$$

$$(1-a_1)\frac{\bar{T}^2\bar{T}^*}{T}-k_2\alpha_1b\frac{\bar{T}^2\bar{T}^*}{T}-k_1(b+d_L)(1-a_1)VT-k_1\alpha_1bVT-k_2(b+d_L)$$

$$(1-a_1)T-k_2\alpha_1bTT^*+k_1(b+d_LV\bar{T}+k_2\big(b+d_L(1-\alpha_1)\big)\bar{T}T^*+k_1\alpha_1bVT$$

$$+k_2\alpha_1bTT^*-b(b+d_L)L-k_1\alpha_1b\frac{VT\bar{L}}{L}-k_2\alpha_1b\frac{TT^*\bar{L}}{L}+k_1\alpha_1b\bar{V}\bar{T}+k_2\alpha_1b\bar{T}\bar{T}^*$$

$$+k_1(b+d_L)(1-a_1)VT+k_2(b+d_L)(1-a_1)TT^*+b(b+d_L)L-\delta(b+d_L)T^*$$

$$-k_1(b+d_L)(1-a_1)\frac{VT\bar{T}^*}{T^*}-k_2(b+d_L)(1-a_1)T\bar{T}^*+k_1(b+d_L)(1-a_1)\bar{V}\bar{T}$$

$$-k_1\alpha_1b\frac{\bar{V}\bar{T}L\bar{T}^*}{T^*\bar{L}}-k_2\alpha_1b\frac{\bar{T}L\bar{T}^{*2}}{T^*\bar{L}}+k_1\alpha_1b\bar{V}\bar{T}+k_2\alpha_1b\bar{T}\bar{T}^*+k_2(b+d_L)(1-a_1)\bar{T}\bar{T}^*$$

$$+\delta(b+d_L)T^*-k_1\big(b+d_L(1-\alpha_1)\big)\frac{\bar{V}^2\bar{T}T^*}{\bar{T}^*V}+k_1(b+d_L)(1-a_1)\bar{V}\bar{T}+k_1b\alpha_1\bar{V}\bar{T}-k_1\big(b+d_L(1-\alpha_1)\big)\bar{T}T^*,$$

where we used

$$\frac{k_1N\delta\big(b+d_L(1-\alpha_1)\big)T^*\bar{T}}{c}=\delta(b+d_L)-k_2\big(b+d_L)(1-\alpha_1)\big)\bar{T}T^*, \tag{6}$$

which we get by combining the following identities

$$\delta\bar{T}^*+d_L\bar{L}=k_1\bar{V}\bar{T}-k_2\bar{T}\bar{T}^*,$$

$$\bar{L}=\frac{\alpha_1\delta\bar{T}^*}{b+d_L(1-\alpha_1)},$$

$$\bar{T}^*=\frac{k_1\big(b+d_L(1-\alpha_1)\big)\bar{V}\bar{T}}{\delta(b+d_L)-k_2\big(b+d_L(1-\alpha_1)\big)\bar{T}},$$

$$N\delta\bar{T}^*=c\bar{V}. \tag{7}$$

Thus equation becomes

$$\frac{dY}{dt}=-\big(b+d_L(1-\alpha_1)\big)d_T(T-\bar{T})^2+k_1\big(b+d_L)(1-\alpha_1)\big)\bar{V}\bar{T}\left(3-\frac{\bar{T}}{T}-\frac{TV\bar{T}^*}{\bar{V}\bar{T}T^*}-\frac{\bar{V}T^*}{V\bar{T}^*}\right)$$

$$+k_1b\alpha_1\frac{\bar{V}}{\bar{T}}\left(4-\frac{\bar{T}}{T}-\frac{TV\bar{L}}{\bar{V}\bar{T}L}-\frac{L\bar{T}^*}{\bar{L}T^*}-\frac{\bar{V}T^*}{V\bar{T}^*}\right)+k_2\big(b+d_L)(1-\alpha_1)\big)\bar{T}^*\bar{T}\left(2-\frac{\bar{T}}{T}-\frac{T}{\bar{T}}\right)+k_2b\alpha_1\bar{T}^*\bar{T}(3-\frac{\bar{T}}{T}-\frac{TT^*\bar{L}}{\bar{T}^*\bar{T}L}-\frac{L\bar{T}^*}{\bar{L}T^*}). \tag{8}$$

The arithmetic-geometric mean inequality $(\frac{1}{n}\sum_{i=1}^{n}y_i\geq\sqrt[n]{\prod_{i=1}^{n}y_i})$ implies $\frac{dY}{dt}\Big|_{(3)}\leq 0$ with equality if and only if $T=\bar{T},L=\bar{L},T^*=\bar{T}^*,V=\bar{V}$. Thus, the largest consistent set in $\left\{(T,L,T^*,V)\in\mathbb{R}^4_+:\frac{dY}{dt}\Big|_{(3)}\leq 0\right\}$ be the singleton set $\{\bar{E}\}$. It evolves from LaSalle invariance principle that the equilibrium $\bar{E}$ is globally asymptotically stable if $\mathcal{R}_0>1$. This completes the proof of the theorem.

4. Numerical Simulations

Some mathematical simulations have been executed in this section to explain the stability outcomes and analyze the relative contributions of both viral transmission ways for viral load and latent infected cell reservoir. We considered the proportion of latency fractions is 0.001 ($\alpha_1=\alpha_2$) while values of all other parameters are given in Table 1. We computed the basic reproductivity $\mathcal{R}_0=0.2<1$ for healthy equilibrium by utilizing our parameters. So it evolves from our outcomes in

Theorem (3.1) that $E_0 = (10^6, 0, 0, 0)$ is globally asymptotically stable. The basic reproductivity for the infected equilibrium is $\mathcal{R}_0 = 2.20 > 1$ by doing simple arithmetic. Hence, the infected equilibrium $\overline{E} = (4.5 \times 10^5, 3.90 \times 10^3, 388.73, 3380.28)$ is globally asymptotically stable by Theorem (3.2). The outcomes of E_0 and $\overline{E}$ are numerically exhibited in Figure 2 and Figure 3, respectively.

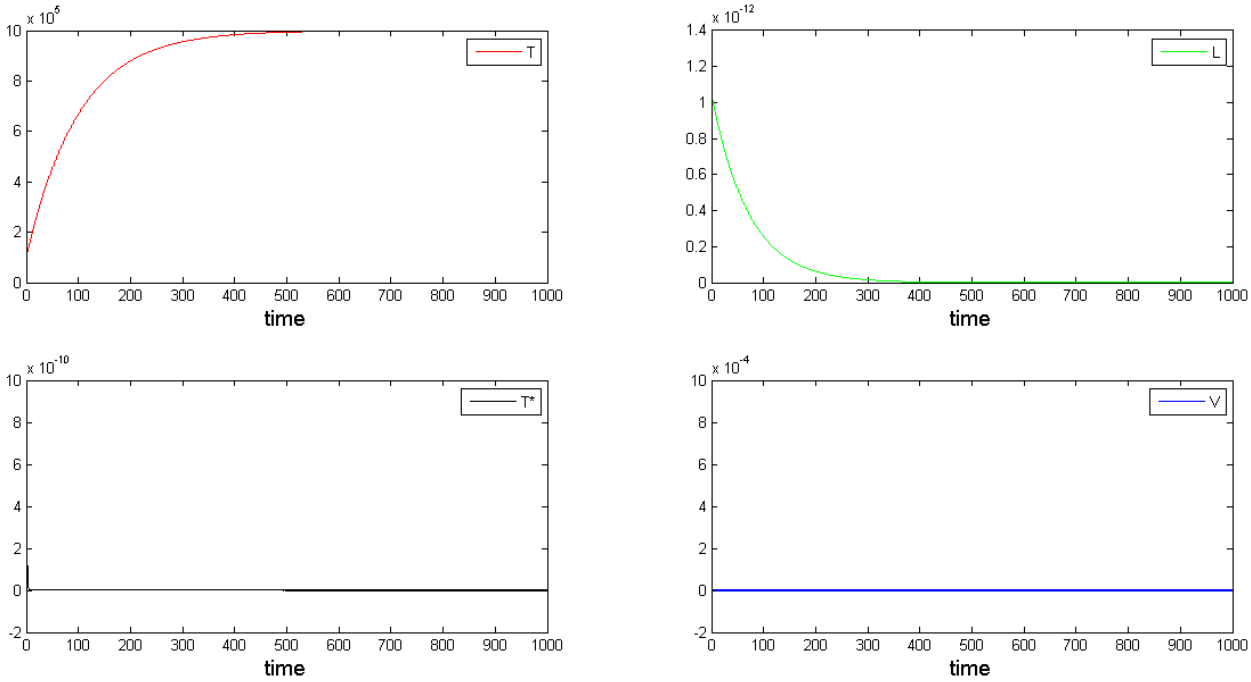

Figure 2. *Kinetics anticipated by system (1) for $\mathcal{R}_0 < 1$. We have $\delta = 1$; $b = 0.01$; $d_L = 0.004$; $N = 100$; $\lambda = 10^4$; $k_1 = 2.4 \times 10^{-10}$; $c = 23$; $k_2 = 10^{-8}$. IC are $T(0) = 10^5, L(0) = 0, T^*(0) = 0$ and $V(0) = 10^{-3}$.*

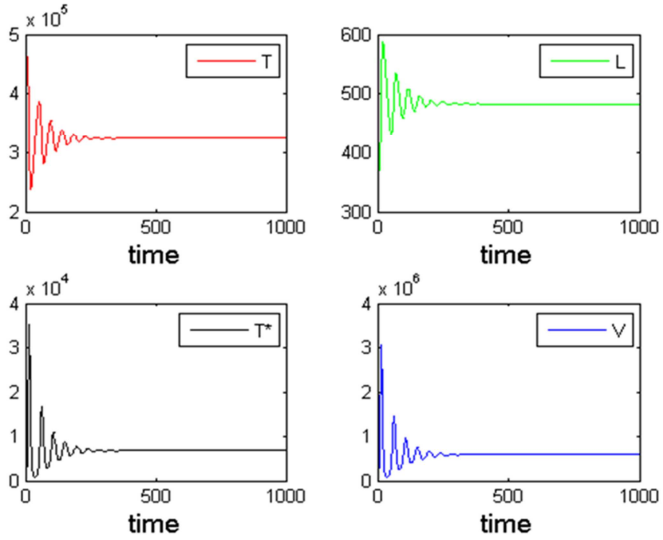

Figure 3. *Kinetics anticipated by system (1) for $\mathcal{R}_0 > 1$. We have $\delta = 1$; $b = 0.01$; $d_L = 0.004$; $N = 2000$; $\lambda = 10^4$; $k_1 = 2.4 \times 10^{-8}$; $c = 23$; $k_2 = 10^{-6}$. IC are $T(0) = 4.4 \times 10^5, L(0) = 3.88 \times 10^2, T^*(0) = 380$ and $V(0) = 3379$.*

5. Relative Contribution (RC)

The significant proposition is the influence of CF and CC on the viral load and the latent containers. We utilized the subsequent fractions RC_L and RC_V to appraise it.

$$RC_L = \frac{\alpha_1 k_1 TV}{\alpha_2 k_2 TT^*}, \tag{9}$$

and

$$RC_V = \frac{(1-\alpha_1) k_1 TV}{(1-\alpha_2) k_2 TT^*}, \tag{10}$$

As we know that the proportionality relation between viral load and productively-diseased cells (quasi steady state assumption),

$$V = \frac{N\delta T^*}{c},$$

then RC_L and RC_V becomes

$$RC_V \approx \frac{(1-\alpha_1)k_1 N\delta}{(1-\alpha_2)k_2 c}, \quad (11)$$

and

$$RC_V \approx \frac{\alpha_1 k_1 N\delta}{\alpha_2 k_2 c}, \quad (12)$$

Recall that

$$\mathcal{R}_0 = \frac{Nk_1\lambda}{cd_T}\left(\frac{b\alpha_1}{b+d_L} + (1-\alpha_1)\right) + \frac{k_2\lambda}{\delta d_T}\left(\frac{b\alpha_2}{b+d_L} + (1-\alpha_2)\right),$$

where first and second term represents the basic reproduction number from CF infection and CC infection, respectively. As the fractions α_1 and α_2 are very small, we had

$$\frac{\text{basic reproduction number from CF infection}}{\text{basic reproduction number from CC infection}} \approx \frac{k_1 N\delta}{k_2 c}. \quad (13)$$

Therefore, we acquired the following estimates

$$RC_V \approx \frac{(1-\alpha_1)}{(1-\alpha_2)} \cdot \frac{\text{basic reproduction number from CF infection}}{\text{basic reproduction number from CC infection}}, \quad (14)$$

and

$$RC_L \approx \frac{\alpha_1}{\alpha_2} \cdot \frac{\text{basic reproduction number from CF infection}}{\text{basic reproduction number from CC infection}}. \quad (15)$$

Estimates in equation (14) and (15) agree with the plotted RC after a very short time. The effect of α_1 and α_2 is highly dependent on RC_V and RC_L from the estimates (14) and (15).

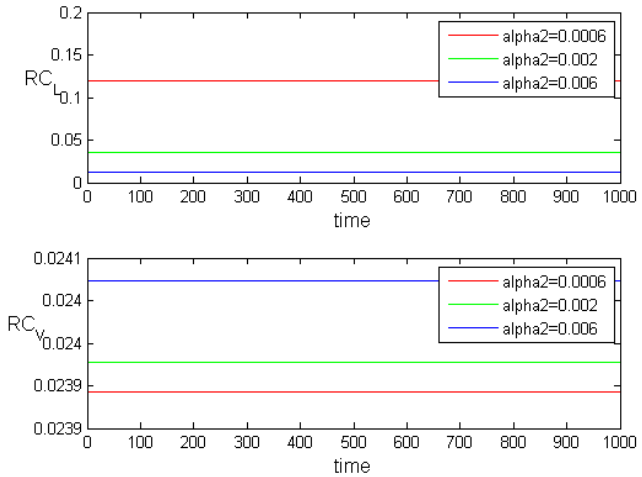

Figure 4. *Relative contribution to viral load and infected (latent) cells from CF and CC. Latency fraction* α_1 *are* (0.0006; 0.002; 0.006) *and* $\alpha_2 = 0.003$*(fixed): We have* $\delta = 1$*;* $b = 0.01$*;* $d_L = 0.004$*;* $N = 2000$*;* $\lambda = 10^4$*;* $k_1 = 2.4 \times 10^{-8}$*;* $c = 23$*;* $k_2 = 10^{-6}$*. IC are* $T(0) = 10^5, L(0) = 0, T^*(0) = 0$ *and* $V(0) = 10^{-3}$*.*

6. Conclusion

HIV studies have determined that virus can infect cells by way of CC and CF [3, 19]. Many HIV mathematical systems have examined virus kinetics with only CF infection. Here, we have globally analyzed an HIV (latency) model containing two types of viral transmission strategies (CF and CC). We have established positivity and boundedness of our system (1) and also obtained the basic reproduction number, $\mathcal{R}_0$. We have proved that healthy steady state is globally asymptotically stable if $\mathcal{R}_0$ is smaller than 1 and if $\mathcal{R}_0$ is larger than 1, then an unhealthy steady state occurs that is globally asymptotically stable.

We have exhibited the RC of viral transmission strategies (CF and CC) in HIV infection with the assistance of arithmetical and graphical mediums. We have obtained their RC estimates (theoretically) for viral load and latent containers. From which, we considered that viral load and latent containers highly depend on these latency fractions. However, because of uncertain parameter values, RC remains unknown until further investigated.

Future Work

Currently available HAART therapy is effective in repressing HIV replication beneath the detection limit of conventional clinical examines, but it does not entirely eradicate HIV. Clinical studies show that there is a rapid viral bounce back after the suspension of HAART, which demonstrates the presence of latent reservoirs. To eliminate these viral reservoirs, a shock and kill therapeutic technique has recently been suggested [50]. We may improve our knowledge of the dynamics of the latent reservoir by incorporating the shock and kill approach in our model.

Competing Interests

The authors declare that there is no conflict of interest.

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