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Modeling $CD4^+$ T cells and CTL response in HIV-1 infection with antiretroviral therapy

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Abstract

The majority of an immune system infected by HIV (Human Immunodeficiency Virus) is $CD4^+$ T cells. The HIV-1 transmission through cell to cell of $CD4^+$ T cells supports the productive infection. On the other hand, infected $CD4^+$ T cells stimulate cytotoxic T-lymphocytes cells to control HIV-1 infection. We develop and analyze a mathematical model incorporating the infection process through cell to cell contact of $CD4^+$ T cells, CTL compartment and the combination of RTI and PI treatments. By means of the alternative reproduction ratio, it is analyzed the stability criteria and the existence of endemic equilibrium. Numerical simulations are presented to study the implication of the combination of RTI and PI therapy. The results indicate that RTI drug shows more significant effect in reducing HIV-1 infection compared to PI drug.

Keywords: HIV-1, $CD4^+$ T cells, CTL cells, RTI, PI.

1. Introduction

HIV (Human Immunodeficiency Virus) attacks the host cells expressing $CD4^+$ molecule, the majority is $CD4^+$ T cells [1]. These cells play the main role in spreading HIV-1 infection within host cells. The transmission of HIV in the immune system can occur through the contact of infected host cells or free virus to healthy cells. Even viral transmission from infected host cells results the effective infection compared to viral transmission via a free virus. [2], [3], [4].

Infected $CD4^+$ T cells stimulate cytotoxic T-lymphocytes (CTL) cells. Cytotoxic ($CD8^+$) cells are effector cell that inhibits viral replication and eliminate by combating the infected cells. $CD8^+$ T cells have an important role in controlling HIV infection due to the elimination of infected cells forming viral replication [5, 9].

The process of viral reverse transcription that transcribes viral RNA to host DNA determines viral infection in target cells. Upon incomplete transcription within the host cell, $CD4^+$ T cells are able to degrade virus in the cytoplasm and return to healthy state. Otherwise, upon complete reverse transcription occurred in host cells, these cells become infectious and produce new viral particles to infect the target cells [6].

$CD4^+$ T cells have a critical role in HIV-1 infection. The stimulated $CD4^+$ T cells are able to create a productive infection. On the other hand, the resting cells are able to prevent the process of viral reverse transcription and lead to infection failure due to incomplete reverse transcription. The virus is degraded by resting cells [7], [9], [8].

Recently, the treatments of RTI (reverse transcript inhibitor) and PI (protease inhibitor) have been used to prevent HIV-1 infection for infected patients. RTI drugs function to block the mechanism of viral reverse transcription, while PI drugs block new viral reproduction from infected $CD4^+$ T cells. The therapy has been conducted in preventing viral DNA synthesis and new viral production [7].

Some studies have been established regarding HIV-1 infections in host cells. A model was proposed by Srivastava *et al.*. The model was established by considering on viral reverse transcription in the infection process of $CD4^+$ T cells [10]. Upon reverse transcription in $CD4^+$ T cells, these cells are classified into two sub populations, namely pre-RT and post-RT classes. They studied the effect of RTI treatment. Instead, they have not considered the infection by cell to cell contact cell as well as PI treatment.

A model was proposed by Chirove *et al.* [3] and Sutimin *et al.* [12], [13], to capture HIV-1 the infection of Langerhans and $CD4^+$ T cells in early HIV-1 infection. Chirove *et al.* used the behavior of alternative

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reproduction ratio to analyze the dynamics of the model. A model by considering the effect of RTI and PI drugs was proposed by Sutimin *et.al* to study the immune response of drugs in HIV-1 infection [12], [13].

Other studies, Tarfulea *et al.* established a model accommodating CTL cells and antiretroviral treatment in reducing HIV-1 infection [14], [15]. They investigated numerically the effect of CTL response and treatment of RTI and PI combination in controlling virus during early infection. The results show that the CTL response is more significant in increasing healthy CD4$^+$ T cells compared to therapy.

We develop the model's Srivastava by incorporating HIV transmission through cell to cell, the effect of PI drug and CTL compartment. analyze the model to determine the existence and stability of equilibria, as well as viral clearance effect of CD4$^+$ T cells. We investigate numerically the implication of RTI and PI treatment in various scenarios to find the effectiveness of drugs.

2. Model Formulation

We develop a model by considering HIV-1 transmission from the interaction between infected and healthy CD4$^+$ T cells, the effectiveness of RTI and PI drugs, and the compartment of CTL cells. The HIV-1 transmission in CD4$^+$ T cells can be presented in the following diagram.

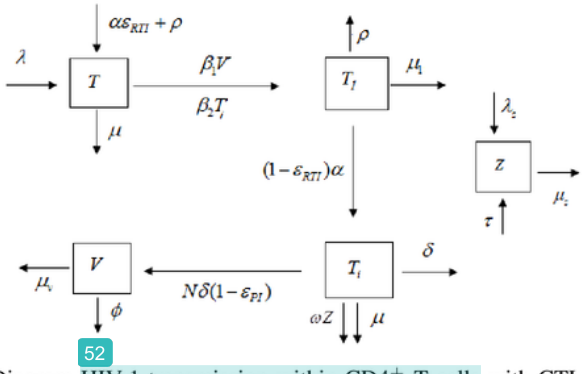

Fig. 1: Diagram HIV-1 transmission within CD4$^+$ T cells with CTL cells response.

Upon HIV-1 fusion within CD4$^+$ T cells, these cells are classified into two classes, namely pre-RT class and post-RT (actively infected) class. The population of pre-RT class, in which the process of RT is not efficient, denoted by T_1. The population of post-RT class, in which the process of RT is complete, denoted by T_i. The population of susceptible CD4$^+$ T cells is denoted by T, the population of CTL cells, denoted by Z, and the population of free virus is denoted by V. The model is given as follows.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \beta_1 VT - \beta_2 TT_i - \mu T + (\epsilon_{RTI}\alpha + \rho)\, T_1,\\
\frac{dT_1}{dt} &= \beta_1 TV + \beta_2 TT_i - (\mu_1 + \alpha + \rho)\, T_1,\\
\frac{dT_i}{dt} &= (1-\epsilon_{RTI})\,\alpha T_1 - (\mu+\delta)\, T_i - \omega T_i Z, \qquad (1)\\
\frac{dZ}{dt} &= \lambda_z + \tau T_i - \mu_z Z,\\
\frac{dV}{dt} &= N\delta\,(1-\epsilon_{PI})\, T_i - \mu_v V - \phi V.
\end{aligned}$$

The population of CD4$^+$ T cells are produced by thymus with constant rate λ, and die naturally at a rate μ. Infection by a free virus and infected CD4$^+$ T cells are at constant rates β_1 and β_2, respectively. Upon RTI treatment and the process of inefficient reverse transcription, pre-RT class return to healthy CD4$^+$ T cells with the constant rates $\epsilon_{RTI}\alpha+\rho$. The incomplete reverse transcription leads to inflammation of pre-RT

CD4$^+$ T cells, assumed that this population dies at a constant rate μ_1, due to the inflammation. Due to RTI treatment, a part of $\epsilon_{RTI} T_1$ of pre-RT population back to susceptible, while other part, $(1-\epsilon_{RTI})\,\alpha T_1$ become infectious, and pre-RT class move to post-RT class at a rate $(1-\epsilon_{RTI})\,\alpha$. Infected CD4$^+$ T cells are killed by CTL cells with the constant rate ω.

The recruitment of CTL cells is assumed at constant λ_z. Due to the immune response of infected CD4$^+$ T cells, the proliferation of the CTL cells increase at a constant rate τ, and these cells die at the rate μ_z. Due to PI treatment, new viral produced by infected CD4$^+$ T cells reduce becoming $N\delta\,(1-\epsilon_{PI})$. The viral death rate and viral clearances level are μ_v and ϕ, respectively. The efficacy values of RTI and PI drugs are denoted by ϵ_{RTI} and ϵ_{PI}, respectively with $0 \le \epsilon_{RTI}, \epsilon_{PI} \le 1$.

3. Model Analysis

We analyze the existence of the endemic equilibrium point and the stability of equilibria for the model.

3.1. Alternative reproduction ratio

The alternative reproduction ratio is derived from the next generation matrix. The next generation matrix [16] of the Model 1 is given by

$$G = \begin{bmatrix} 0 & \frac{\beta_2\lambda\mu_z}{\mu(\delta\,\mu_z+\lambda_z\omega+\mu\mu_z)} & \frac{\beta_1\lambda}{\mu(\phi+\mu_v)} \\ \frac{(1-\epsilon_{RTI})\alpha}{\mu_1+\alpha+\rho} & 0 & 0 \\ 0 & \frac{N\delta\,(1-\epsilon_{PI})\mu_z}{\delta\,\mu_z+\lambda_z\omega+\mu\mu_z} & 0 \end{bmatrix}. \tag{2}$$

The characteristic polynomial corresponding to matrix G can be expressed as

$$P(X) = X^3 - B_1 X - B_0, \tag{3}$$

where

$$\begin{aligned} B_1 &= \frac{\alpha\,\beta_2\,(1-\epsilon_{RTI})\,\lambda\mu_z}{(\delta\,\mu_z+\lambda_z\omega+\mu\mu_z)\,\mu\,(\mu_1+\alpha+\rho)}, \\ B_0 &= \frac{\mu_z\lambda\,(1-\epsilon_{RTI})\,(1-\epsilon_{PI})\,\beta_1\delta\,\alpha\,N}{(\mu_1+\alpha+\rho)\,\mu\,(\phi+\mu_v)\,(\delta\,\mu_z+\lambda_z\omega+\mu\mu_z)}. \end{aligned}$$

The basic reproduction number $\Re_0$ cannot be formulated explicitly. Instead, we can determine alternative reproduction ratio, denoted $\Re_1$ which is equivalent to $\Re_0$. The alternative reproduction ratio is defined by $\Re_1^2 = B_0 + B_1$ (see [11]) that can be expressed as $\Re_0 = \Re_{T_i\mapsto T_i} + \Re_{T_i\mapsto V\mapsto T_i}$, where

$$\begin{aligned} \Re_{T_i\mapsto T_i} &= \frac{\beta_2\alpha\,(1-\epsilon_{RTI})\,\lambda\mu_z}{(\delta\,\mu_z+\lambda_z\omega+\mu\mu_z)\,\mu\,(\mu_1+\alpha+\rho)}, \\ \Re_{T_i\mapsto V\mapsto T_i} &= \frac{\mu_z\lambda\,(1-\epsilon_{RTI})\,(1-\epsilon_{PI})\,\beta_1\delta\,\alpha\,N}{(\mu_1+\alpha+\rho)\,\mu\,(\phi+\mu_v)\,(\delta\,\mu_z+\lambda_z\omega+\mu\mu_z)}. \end{aligned}$$

As in [11], [12], [13], sub-ratio $\Re_{T_i\mapsto T_i}$ indicates the infection path from an infected CD4$^+$ T cell to healthy CD4$^+$ T cells. Sub-ratio $\Re_{T_i\mapsto V\mapsto T_i}$ indicates the infection path from infected CD4$^+$ T cell then reproduces new virus particles infecting healthy CD4$^+$ T cells. The relation of basic reproduction ratio ($\Re_0$) and $\Re_1$ was given the following Theorem 3.1.

Theorem 3.1. *The reproduction ratio, $\Re_0$ and alternative reproduction ratio, $\Re_1$ for system 1 hold the equivalent properties as follows.*

i. $\Re_0 = 1$ *if only if* $\Re_1 = 1$.
ii. $\Re_0 < 1$ *if only if* $\Re_1 < 1$, *and* $\Re_0 > 1$ *if only if* $\Re_1 > 1$.

Proof: First, we show that Eq. (3) has only one positive real root with the largest modulus. Let x_1, x_2 and x_3 be the roots of polynomial in Eq. (3), then it holds

$$\begin{aligned} x_1 + x_2 + x_3 &= 0, && (4)\\ x_1x_2 + x_1x_3 + x_2x_3 &= -B_1 < 0, && (5)\\ x_1x_2x_3 &= B_0 > 0. && (6) \end{aligned}$$

From Eq. (4) and Eq. (6), the polynomial equation has only real positive one root and two negative real roots or two complex roots with negative real parts. Next, we show that one positive real root has the largest modulus.

Case 1: For one positive root and negative real roots. Without loss of the generality, let $x_1 > 0$ and $x_2, x_3 < 0$. From Eq. (4), we have $x_1 = -x_2 - x_3 > 0$. Thus $|x_1| > |x_2|$ and $|x_1| > |x_3|$.

Case 2: For one positive root and two complex roots. Let $x_1 > 0$, $x_2 = ai + b$, and $x_3 = ai - b$. From Eq. (5), it can be written as $x_1(x_2 + x_3) + a^2 + b^2 = -B_1$, thus

$$2ax_1 + a^2 + b^2 = -B_1 < 0 \quad (7)$$

On the other hand, from Eq. (4), we have $x_1 + 2a = 0$ or $a = -\frac{x_1}{2}$. Thus, the Equation (7) can be written as

$$-x_1^2 + a^2 + b^2 = -B_1 < 0 \quad (8)$$

From the Equation (8), we have $x_1^2 > a^2 + b^2$. It is shown that the polynomial in Eq. (3) has exactly one positive real root that has the largest modulus. Next, we prove $i.$ as follows. When $\Re_0 = 1$, then it holds $P(1) = 0$. It means $1 - B_1 - B_0 = 0$. Thus $B_1 + B_0 = 1 = \Re_1$. Conversely, if $\Re_1 = 1$, then $1 = B_1 + B_0$ or $1 - B_1 - B_0 = 0$. It means $P(1) = 0$, thus $\Re_0 = 1$. The proof $ii.$ is as follows. Let $\Re_0 < 1$, then it holds

$$P(\Re_0) \equiv \Re_0^3 - B_1\Re_0 - B_0 = 0 \quad (9)$$

The Equation (9) can be written as

$$\begin{aligned} \Re_0\left(\Re_0^2 - B_1\right) &= B_0, && (10)\\ &= \Re_1^2 - B_1, \text{since } \Re_1^2 = B_1 + B_0. && (11) \end{aligned}$$

Since $\Re_0 > 1$, we have $\Re_1^2 - B_1 = \Re_0\left(\Re_0^2 - B_1\right) > \Re_0^2 - B_1$. It means that $\Re_1^2 > \Re_0^2 > 1$, thus $\Re_1 > 1$. By contrapositive, if $\Re_1 > 1$ then $\Re_0 > 1$, it means if $\Re_0 \leq 1$ then $\Re_1 \leq 1$. The proof, if $\Re_0 = 1$ then $\Re_0 = 0$, is given in (i). Now, let $\Re_0 < 1$, from Eq. (9), we have $\Re_1^2 - B_1 = \Re_0\left(\Re_0^2 - B_1\right) < \Re_0^2 - B_1$. It is obtained $\Re_1^2 < \Re_0^2 < 1$, thus $\Re_1 < 1$. The second statement of (ii) is proven similarly. It completes the proof. ■

3.2. Stability analysis of uninfected steady state

Uninfected equilibrium point is $E^0 = \left(T^0, T_1^0, T_i^0, Z^0, V^0\right) = \left(\frac{\lambda}{\mu}, 0, 0, \frac{\lambda_z}{\mu_z}, 0\right)$. The local stability of E^0 is given in the following theorem.

Theorem 3.2. *The uninfected equilibrium point E^0 is locally asymptotically stable, if $\Re_1 < 1$.*

Proof: The Jacobian matrix of the model 1 at E^0 can be written by

$$J\left(E^0\right) = \begin{bmatrix} -\mu & \alpha\epsilon_{RTI} + \rho & -\frac{\beta_2\lambda}{\mu} & 0 & -\frac{\lambda\beta_1}{\mu} \\ 0 & -\mu_1 - \alpha - \rho & \frac{\beta_2\lambda}{\mu} & 0 & \frac{\lambda\beta_1}{\mu} \\ 0 & (1-\epsilon_{RTI})\alpha & -\frac{\lambda_z\omega}{\mu_z} - \delta - \mu & 0 & 0 \\ 0 & 0 & \tau & -\mu_z & 0 \\ 0 & 0 & N\delta(1-\epsilon_{PI}) & 0 & -\phi - \mu_v \end{bmatrix}. \quad (12)$$

The eigenvalues of $J\left(E^0\right)$ are $-\mu, -\mu_z$, and others are solutions of the cube equation

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 = 0, \quad (13)$$

where

$$\begin{aligned}
A_2 &= \alpha+\delta+\phi+\rho+\mu_1+\mu+\mu_v+\frac{\lambda_z\omega}{\mu_z},\\
A_1 &= \frac{1}{\mu_z}\left(1-\Re_I^2\right)(\mu_1+\alpha+\rho)(\delta\mu_z+\lambda_z\omega+\mu\mu_z)\\
&\quad+\frac{\lambda(1-\epsilon_{RTI})\alpha N\delta(1-\epsilon_{PI})\beta_1}{\mu(\phi+\mu_v)}+\frac{(\phi+\mu_v)\omega\lambda_z}{\mu_z}\\
&\quad+(\phi+\mu_v)(\alpha+\delta+\rho+\mu_1+\mu),\\
A_0 &= \frac{1}{\mu_z}\left(1-\Re_I^2\right)(\mu_1+\alpha+\rho)(\delta\mu_z+\lambda_z\omega+\mu\mu_z)(\phi+\mu_v).
\end{aligned}$$

It is seen that $A_2, A_1 > 0$ if $\Re_1 < 1$. Next, we calculate $A_2A_1 - A_0$. Manipulating calculation, it is obtained

$$\begin{aligned}
A_2A_1-A_0 &= \frac{(\delta\mu_z+\lambda_z\omega+\mu\mu_z)(\mu_1+\alpha+\rho)\Psi_1(1-\Re_0)}{{\mu_z}^2}\\
&\quad+\frac{N\alpha\delta(1-\epsilon_{PI})(1-\epsilon_{RTI})\lambda\Psi_2\beta_1}{\mu_z\mu(\phi+\mu_v)}+\frac{(\phi+\mu_v)\Psi_1\Psi_2}{{\mu_z}^2},
\end{aligned}\tag{14}$$

where

$$\begin{aligned}
\Psi_1 &= (\alpha+\delta+\rho+\mu_1+\mu)\mu_z+\lambda_z\omega,\\
\Psi_2 &= (\alpha+\delta+\phi+\rho+\mu_1+\mu+\mu_v)\mu_z+\lambda_z\omega.
\end{aligned}$$

The Routh-Hurwitz criterion is fulfilled when $\Re_1 < 1$. It shows that E^0 locally asymptotically stable. ■

3.3. The existence and uniqueness of endemic equilibrium

The endemic equilibrium point of the model is $E^* = (T^*, T_1^*, T_i^*, Z^*, V^*)$, where

$$\begin{aligned}
T^* &= \frac{\omega\tau(\phi+\mu_v)(\mu_1+\alpha+\rho)T_i^*}{\alpha(1-\epsilon_{RTI})\mu_z(N\delta\beta_1(1-\epsilon_{PI})+\beta_2\phi+\beta_2\mu_v)}+\\
&\quad\frac{(\phi+\mu_v)(\delta\mu_z+\lambda_z\omega+\mu\mu_z)(\mu_1+\alpha+\rho)}{\alpha(1-\epsilon_{RTI})\mu_z(N\delta\beta_1(1-\epsilon_{PI})+\beta_2\phi+\beta_2\mu_v)},\\
T_1^* &= \frac{T_i^*(T_i^*\omega\tau+\delta\mu_z+\lambda_z\omega+\mu\mu_z)}{\alpha(1-\epsilon_{RTI})\mu_z},\\
Z^* &= \frac{\tau T_i^*+\lambda_z}{\mu_z},\\
V^* &= \frac{NT_i^*\delta(1-\epsilon_{PI})}{\phi+\mu_v}.
\end{aligned}$$

The value of T_i^* is the positive root of a quadratic equation

$$b_2T_i^2+b_1T_i+b_0=0,\tag{15}$$

where

$$\begin{aligned}
b_2 &= \omega\tau((1-\epsilon_{RTI})\alpha+\mu_1)(N\delta\beta_1(1-\epsilon_{PI})+\beta_2\phi+\beta_2\mu_v)>0,\\
b_1 &= N\delta(1-\epsilon_{PI})(\delta\mu_z+\lambda_z\omega+\mu\mu_z)((1-\epsilon_{RTI})\alpha+\mu_1)\beta_1\\
&\quad+(\phi+\mu_v)(\delta\mu_z+\lambda_z\omega+\mu\mu_z)((1-\epsilon_{RTI})\alpha+\mu_1)\beta_2\\
&\quad+\omega\tau\mu(\phi+\mu_v)(\mu_1+\alpha+\rho),\\
b_0 &= \mu(\mu_1+\alpha+\rho)(\delta\mu_z+\lambda_z\omega+\mu\mu_z)(\phi+\mu_v)\left(1-\Re_I^2\right).
\end{aligned}$$

Due to $b_2 > 0$, Eq. (15) has exactly one positive root if only if $b_0 < 0$, it is fulfilled when $\Re_1 > 1$.

We investigate the parameter $\Re_1$ due to the effect of viral lysis corresponding to the critical number of viral production for the endemicity of HIV-1 infection. Differentiating $\Re_1^2$ with respect to δ is obtained as follows,

$$\frac{\partial \Re_1^2}{\partial \delta} = \frac{(1-\epsilon_{RTI})\,\alpha\,\lambda\mu_z\beta_1\,(1-\epsilon_{PI})\,(\lambda_z\omega+\mu\,\mu_z)\,(N-N_c)}{\mu\,(\mu_1+\alpha+\rho)\,(\delta\,\mu_z+\lambda_z\omega+\mu\,\mu_z)^2\,(\phi+\mu_v)}, \tag{16}$$

where

$$N_c = \frac{\beta_2\mu_z\,(\phi+\mu_v)}{\beta_1\,(1-\epsilon_{PI})\,(\lambda_z\omega+\mu\,\mu_z)}. \tag{17}$$

The quantity N_c is defined as the critical viral production of infected CD4$^+$ T cells. From this result, the relationship between N and N_c is given in the following theorem.

Theorem 3.3. *The critical number N_c determines the endemicity level of HIV-1 infection as follows*

i. *The level of $\Re_1$ decreases with respect to δ, when $N < N_c$.*
ii. *The level of $\Re_1$ increase with respect to δ, when $N > N_c$, and*
iii. *The level of $\Re_1$ remains constant with respect to δ, when $N = N_c$.*

Proof: When $N < N_c$, it implies that $\frac{\partial \Re_1^2}{\partial \delta} < 0$, so $\Re_1$ decreases with respect to δ. But when $N > N_c$, it implies $\frac{\partial \Re_1^2}{\partial \delta} > 0$, it means that $\Re_1$ increases with respect to δ. For $N = N_c$, implies $\frac{\partial \Re_1^2}{\partial \delta} = 0$. It shows that $\Re_1$ remains constant with respect to δ. ■

3.4. The stability of endemic equilibrium

We use Lyapunov function to analyze global stability of endemic equilibrium. The global stability is given in the following Theorem.

Theorem 3.4. *The endemic equilibrium point E^0 is globally asymptotically stable, if $\Re_1 > 1$.*

Proof: We construct a Lyapunov function as follows,

$$\begin{aligned} L(T,L,T_i,V) &= T-T^*-T^*\ln\left(\frac{T}{T^*}\right)+c_1\left(T_1-T_1^*-L^*\ln\left(\frac{T_1}{T_1^*}\right)\right)+ \\ &\quad c_2\left(T_i-T_i^*-T_i^*\ln\left(\frac{Ti}{T_i^*}\right)\right)+c_3\left(Z-Z^*-Z^*\ln\left(\frac{Z}{Z^*}\right)\right) \\ &\quad +c_4\left(V-V^*-V^*\ln\left(\frac{V}{V^*}\right)\right), \end{aligned} \tag{18}$$

where c_1, c_2, c_3 and c_4 are positive constants that must be determined. It is shown $F \in C^1$, $F(E^*) = 0$. Differentiating F due to t in along solutions, we obtain

$$\begin{aligned} \frac{dL}{dt} &= \frac{T-T^*}{T}\frac{dT}{dt}+a_1\frac{T_1-T_1^*}{T_1}\frac{dT_1}{dt}+c_2\frac{T_i-T_i^*}{T_i}\frac{dT_i}{dt}+c_3\frac{Z-Z^*}{Z}\frac{dZ}{dt} \\ &\quad +c_4\frac{V-V^*}{V}\frac{dV}{dt} \\ &= K-\mu T+[A_0-c_1A_1+c_2\,(1-\epsilon_{RTI})\,\alpha]\,T_1+[c_2\omega T_i^*-c_3\mu_z]\,Z \\ &\quad +[\beta_2T^*-c_2A_2+c_3\tau+a_4\,(1-\epsilon_{PI}N\delta)]\,T_i+[\beta_1T^*-c_4A_3]\,V \\ &\quad +[c_1\beta_1-\beta_1]\,VT+[c_1\beta_2-\beta_2]\,TT_i-c_2\omega T_iZ-\lambda\frac{T^*}{T}-A_0T^*\frac{T_1}{T} \\ &\quad -c_1\beta_1L^*\frac{TV}{T_1}-c_1\beta_2L^*\frac{TT_i}{T_1}-c_2\,(1-\epsilon_{RTI})\,\alpha T_i^*\frac{T_1}{T_i}-c_3\lambda_z\frac{Z^*}{Z} \\ &\quad -c_3\tau Z^*\frac{T_i}{Z}-c_4\,(1-\epsilon_{PI})\,N\delta V^*\frac{T_i}{V}, \end{aligned} \tag{19}$$

where $K = \lambda+\mu T^*+c_1A_1T_1^*+c_2A_2T_i^*+c_3\mu_z Z^*+c_4A_3V^*+c_3\lambda_z$, with $A_0 = \epsilon_{RTI}\alpha+\rho$, $A_1 = \mu_1+\alpha+\rho$, $A_2 = \mu+\delta$ and $A_3 = \mu_v+\phi$. We let the new notations, $x = \frac{T}{T^*}, y = \frac{L}{L^*}, w = \frac{T_i}{T_i^*}, z = \frac{Z}{Z^*}$ and $u = \frac{V}{V^*}$. The Equation (19) becomes

$$\begin{aligned}\frac{dL}{dt} &= K-\mu T^*x+\left[A_0-c_1A_1+c_2\left(1-\epsilon_{RTI}\right)\alpha\right]T_1^*y+\left[c_2\omega T_i^*-c_3\mu_z\right]Z^*z\\ &\left[\beta_2T^*-c_2A_2+c_3\tau+a_4\left(1-\epsilon_{PI}N\delta\right)\right]T_i^*w+\left[\beta_1T^*-c_4A_3\right]V^*u\\ &+\left[c_1\beta_1-\beta_1\right]V^*T^*xu+\left[c_1\beta_2-\beta_2\right]T^*T_i^*xw-c_2\omega T_i^*Z^*zw-\lambda\frac{1}{x}-A_0T_1^*\frac{y}{x}\\ &-c_1\beta_1T^*V^*\frac{xu}{y}-c_1\beta_2T^*T_i^*\frac{xw}{y}-c_2\left(1-\epsilon_{RTI}\right)\alpha T_1^*\frac{y}{w}-c_3\lambda_z\frac{1}{z}\\ &-c_3\tau T_i^*\frac{w}{z}-c_4\left(1-\epsilon_{PI}\right)N\delta T_i^*\frac{w}{z}. \end{aligned} \tag{20}$$

We construct a variable set, $D = \left\{x, y, z, w, u, xw, xu, zw, \frac{1}{x}, \frac{1}{z}, \frac{y}{x}, \frac{w}{z}, \frac{w}{u}, \frac{xz}{y}, \frac{xu}{y}, \frac{xw}{y}\right\}$ related to terms in Eq. (20). There are three sub sets of D, in which the product of elements is unity, namely $\left\{x, \frac{1}{x}\right\}$, $\left\{\frac{1}{x}, \frac{y}{w}, \frac{xw}{y}\right\}$ and $\left\{\frac{1}{x}, \frac{y}{w}, \frac{w}{u}, , \frac{xu}{y}\right\}$. Equating coefficients of y, w, u, z, xu, xw to zero in Eq. (20). The Equation (20) can be constructed as follows,

$$\begin{aligned}\frac{dL}{dt} &= b_1\left(2-x-\frac{1}{x}\right)+b_2\left(2-z-\frac{1}{z}\right)+b_3\left(3-\frac{1}{x}-\frac{y}{w}-\frac{xw}{y}\right)+\\ &b_4\left(4-\frac{1}{x}-\frac{y}{w}-\frac{w}{u}-\frac{xu}{y}\right)-c_2\omega T_i^*Z^*zw-A_0L^*\frac{y}{x}-c_3\tau T_i^*\frac{w}{z}. \end{aligned} \tag{21}$$

The constants $b_1, b_2, b_3, a_1, a_2, a_3$ can be obtained with considering the relation

$$\begin{aligned}\lambda+\left(\epsilon_{RTI}\alpha+\rho\right)T_1^* &= \beta_1T^*V^*+\beta_2T^*T_i^*+\mu T^*,\\ \beta_1T^*V^*+\beta_2T^*T_i^* &= \left(\mu_1+\alpha+\rho\right)L^*,\\ \left(\mu+\delta\right)T_i^*+\omega T_i^*Z^* &= \left(1-\epsilon_{RTI}\right)\alpha L^*,\\ \mu_zZ^* &= \lambda_z+\tau T_i^*,\\ \left(\mu_v+\phi\right)V^* &= N\delta\left(1-\epsilon_{PI}\right)T_i^*. \end{aligned}$$

Equating coefficients in the similar terms of Equation (20) and (21), we get,
$2b_1+2b_2+3b_3+4b_4 = K,\ c_1-1 = 0,\ b_1 = \mu T^*,\ b_2 = c_3\mu_z-c_2\omega T_i^* = c_3\lambda_z,$
$b_1+b_2+b_3 = \lambda,\ b_3+b_4 = c_2\left(1-\epsilon_{RTI}\right)\alpha T_1^*,\ b_3 = c_1\beta_2T^*T_i^*$
$b_3+b_4 = c_2\left(1-\epsilon_{RTI}\right)\alpha T_1^*, b_4 = c_4\left(1-\epsilon_{PI}\right)N\delta T_i^* = c_1\beta_1V^*T^*$. We can choose $c_1 = 1,\ c_2 = \frac{A_1T_1^*}{\left(1-\epsilon_{RTI}\right)\alpha T_1^*},\ c_3 = \frac{\omega A_1T_1^*T_i^*}{\left(1-\epsilon_{PI}\right)\left(\mu_z-\lambda_z\right)}$ and $c_4 = \frac{\beta_1V^*T^*}{\left(1-\epsilon_{PI}\right)N\delta T_i^*}$. Considering the inequality of arithmetic and geometric mean, the Equation 21 can be written by

$$\begin{aligned}\frac{dL}{dt} &= \mu T^*\left(2-x-\frac{1}{x}\right)+\frac{\omega\lambda_zA_1T_1^*T_i^*}{\left(1-\epsilon_{PI}\right)\left(\mu_z-\lambda_z\right)}\left(2-z-\frac{1}{z}\right)+\\ &\beta_2T^*V^*\left(3-\frac{1}{x}-\frac{y}{w}-\frac{xw}{y}\right)+\beta_1T^*V^*\left(4-\frac{1}{x}-\frac{y}{w}-\frac{w}{u}-\frac{xu}{y}\right)\\ &-A_0T_1^*\frac{y}{x}-\frac{\omega A_1T_1^*T_i^*Z^*}{\left(1-\epsilon_{RTI}\right)\alpha T_1^*}zw-\frac{\omega\tau A_1T_1^*T_i^*}{\left(1-\epsilon_{RTI}\right)\alpha T^*\left(\mu_z-\lambda_z\right)}\frac{w}{z}\leq 0. \end{aligned}$$

40

It can be seen that $\frac{dL}{dt} = 0$ when $T = T^*, T_1 = T_1^*, T_i = T_i^*, Z = Z^*$ and $V = V^*$ thus the maximal invariance set of $\left\{(T, T_1, T_i, Z, V)\,|\,\frac{dL}{dt} = 0\right\}$ is the singleton E^*. Thus E^* indicates globally asymptotically stable. The proof is completed. ■

4. NUMERICAL SIMULATIONS

In the section, we present the simulation results regarding to evolutions of CD4$^+$ T cells, CTL cells, and viral free populations to investigate the impact of combining RTI and PI treatments. The parameter values used in the simulations are determined from literature as given in Table I.

TABLE I: The values of parameter and units

Parameters	Values	Units	References
λ	10, 20	cells day^{-1}	[18], [22]
λ_z	0.0001	cells day^{-1}	[21]
τ	0.1	day^{-1}	[23]
α	0.4	day^{-1}	[10]
β_1	(0.00002, 0.005)	virions^{-1} day^{-1}	[19], [20]
ρ	0.05	day^{-1}	[10]
ω	0.01	day^{-1}	[21]
β_2	(0.00001, 0.01)	cells^{-1} day^{-1}	[11]
μ	0.01, 0.02	day^{-1}	[18], [22]
μ_1	0.015	day^{-1}	[10]
μ_z	0.1, 0.2	day^{-1}	[14], [24]
μ_v	2.4	day^{-1}	[18]
δ	0.24	day^{-1}	[18]
N	(100, 1000)	virions day^{-1}	[21]
ϕ	(2, 9)	day^{-1}	[18]

We simulate the evolution of CD4$^+$ T cells, CTL cells, and virus populations to investigate numerically the effect of RTIs and PIs treatments. The initial conditions are taken $T(0) = 850\ \frac{cells}{mm^3}$, $T_1(0) = 40\ \frac{cells}{mm^3}$, $T_i(0) = 41\ \frac{cells}{mm^3}$, and $V(0) = 3.76\ \frac{virions}{mm^3}$ [26]. Next, we shall investigate the clearance effect of the virus to the dynamic of CD4$^+$ T cells and free virus population.

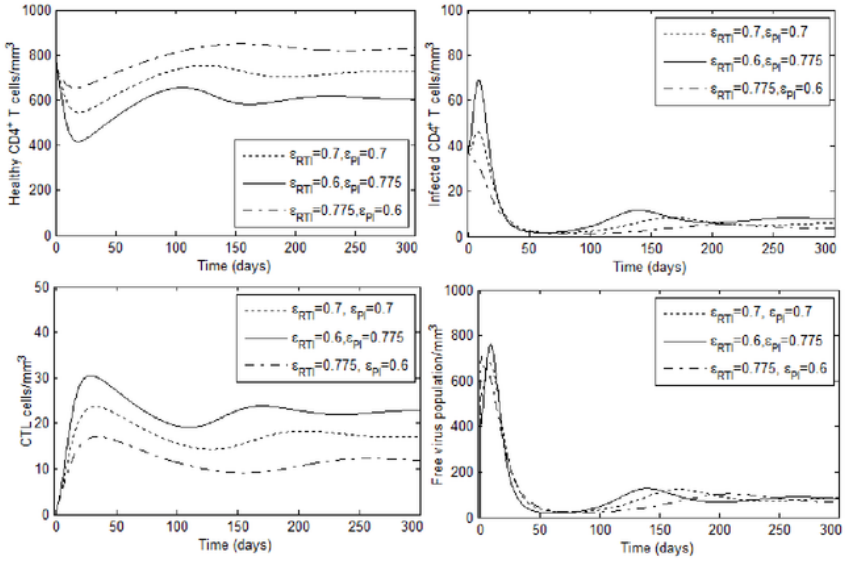

Fig. 2: The evolution of CD4$^+$ T cells, CTL cells and free viral populations in different scenarios of RTI and PI treatments with $\lambda = 10, \lambda_z = 0.0001, \beta_1 = 0.000024, \beta_2 = 0.0022, \alpha = 0.4, \rho = 0.05, \omega = 0.01, \delta = 0.26, \mu = 0.01, \mu_1 = 0.015, \mu_v = 2.4, N = 900, \phi = 3, \tau = 0.1, \mu_z = 0.1$.

In the simulation, we investigate the impact of RTI and PI treatments related to the dynamics of $CD4^+$ T cells, CTL cells, and free virus in various scenarios. We consider the certain value of the overall drug efficacy for RTI and PI drugs when these drugs are administered simultaneously. Then using the value to compare therapy in the different combination of RTI and PI drugs. The value of the overall drug efficacy was defined [25] as $\epsilon = 1 - (1 - \epsilon_{RTI})(1 - \epsilon_{PI})$. We take $\epsilon = 0.91$ with different values of ϵ_{RTI} and ϵ_{PI}. We consider the scenario of treatments as follows. Scenario 1: when RTI and PI drugs are administered with the efficacy values $\epsilon_{RTI} = 0.7, \epsilon_{PI} = 0.7$, respectively. Scenario 2: when efficacy values of RTI and PI drugs are considered $\epsilon_{RTI} = 0.6, \epsilon_{PI} = 0.775$, respectively. And scenario 3: when drug efficacies of RTI and PI are taken $\epsilon_{RTI} = 0.755, \epsilon_{PI} = 0.6$, respectively.

In Figure 2, we can see that by considering the drug efficacy values, it shows that RTI drug contributes more effectively to the number of healthy $CD4^+$ T cells compare to PI drug, otherwise, it reduces to the number of CTL cells and free viral populations. Furthermore, the contribution of RTI drug is higher compared to PI drug in increasing $CD4^+$ T cells, and it is related to the decreasing of infected $CD4^+$ T cells, CTL cells, and free viral populations. In the combination treatments of RTI and PI drugs, increasing RTI drug efficacy is more effective in reducing HIV-1 infection compare to PI drug.

5. Conclusion

The mechanism of HIV-1 infection in $CD4^+$ T cells through reverse transcription process and cell to cells contact determine the spread of HIV-1 infection. We modified a modeling from Srivastava's model [10] that considers the incomplete and complete reverse transcription. In the paper, we develop a model by incorporating the factor of cell to cells contact between $CD4^+$ T cells in transmitting the virus and CTL compartment. We also study the impact of the combination of RTI and PI treatments in reducing HIV infection during early infection.

By using the alternative reproduction ratio composed two cycles of infections, we analyze the local stability of uninfected equilibrium and the existence of the endemic equilibrium. The global stability of endemic equilibrium is analyzed by establishing Lyapunov function. When the ratio exceeds unity, the virus died out finally. Conversely, when the ratio larger than one, HIV disease still persist in the body.

In the combination of RTI and PI treatments, it shows that RTI drug provides more significant effect in reducing HIV infection compared to PI drug. Thus, we suggest that RTI drug may be more effective in reducing the progression of HIV-1 infection compared to PI drug, in the absence of drugs resistance.

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References

[1] F. Hladik, P. Sakchalathorn, L. Ballweber, G. Lentz, M. Fialkow, D. Eschenbach, M. J. McElrath. Initial Events in Establishing Vaginal Entry and Infection by Human Immunodeficiency Virus Type-1. *Immunity,* 26(2): 257–270, 2007.

[2] Q. J. Sattentau. Cell-to-Cell Spread of Retroviruses. *Viruses,* 2(6): 1306–1321, 2010.

[3] C. Jolly. Cell-to-cell transmission of retroviruses: Innate immunity and interferon-induced restriction factors. *Virology,* 411(2): 251–259, 2011.

[4] A. Del Portillo, J. Tripodi, V. Najfeld, D. Wodarz, D. N. Levy, B. K. Chen, Multiploid inheritance of HIV-1 during cell-to-cell infection. *J.Virol,* 85(14): 7169–7176, 2011.

[5] N. Gulzar and K. F. T. Copeland. CD8+ T-Cells: Function and Response to HIV Infection. *Current HIV Research,* 2:23–37,2004.

[6] F. Kirchhoff. HIV Life Cycle: Overview. *Encyclopedia of AIDS,* pp. 1–9, 2013.

[7] N. N. Klimas, A. O. Koneru and M. A. Fletcher. Overview of HIV. *Psychosomatic Medicine,* 70: 523–530, 2008.

[8] D. N. Vatakis, S. Kim, N. Kim, S. A. Chow, and J. A. Zack. Human Immunodeficiency Virus Integration Efficiency and Site Selection in Quiescent CD4+ T Cells. *J. Virology,* pp. 8925–8928, 2009.

[9] W. J. Swiggard, U. ODoherty, D. McGain, D. Jeyakumar and M. H. Malim. Long HIV type 1 reverse transcripts can accumulate stably within resting CD4+ T cells while short ones are degraded. *AIDS Res. Hum. Retrovir.,* 20: 285–295, 2004.

[10] P. K. Srivastava, M. Banerjee and P. Chandra. Modeling the Drug Therapy for HIV Infection. *J. Biol. Sys.,* 17(2): 213–223, 2009.

[11] F. Chirove, Sutimin, E. Soewono and N. Nuraini. Analysis of combined Langerhans and $CD4^+$ T cells HIV infection. *SIAM J. Appl. Math.,* 74(4): 1174–1193, 2014.

[12] Sutimin, F. Chirove, E. Soewono, N. Nuraini and L. B. Suromo. Ultra A model incorporating combined RTIs and PIs therapy during early HIV-1 infection. *Math. Bio.,* 285: 102–111, 2017.

[13] Sutimin, N. Nuraini, F. Chirove and L. B. Suromo. Modelling Multiple Dosing with Drug Holiday in Antiretroviral Treatment on HIV-1 Infection. *J. Math. Fund. Sci.,* 49(1): 1–17, 2017.

[14] N. Tarfulea, A. Blink, E. Nelson, Jr. D. Turpin. A CTL-Inclusive Mathematical Model for Antiretroviral Treatment of HIV Infection. *Int. J. Biomath.,* 4(1): 1–22, 2011.

[15] N. E. Tarfulea. A Mathematical Model for CTL Effect on a Latently Infected Cell Inclusive HIV Dynamics and Treatment. *AIP Conf. Proc. 1895, 070005*, 4(1): 1–10, 2017.

[16] O. Diekmann and J. A. P. Heesterbeek. *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*. John Wiley & Sons, Chichester, UK. 2000.

[17] M. Sugaya, K. Lor, R. A. Koup, D. C. Douek, A. Blauvelt. HIV-Infected *Langerhans* Cells Preferentially Transmit Virus to Proliferating Autologous CD4$^+$ Memory T Cells Located within *Langerhans* Cell-T Cell Clusters. *The J Immunol.,* 172(4): 2219–2224, 2004.

[18] A. S. Perelson, D. E. Kirschner and R. D. Boer. Dynamics of HIV infection of CD4$^+$T cells. *Math. Bio.,* 114(1): 81–125, 1993.

[19] D. Kirschner. Using mathematics to understand HIV immune dynamics. *Notices Amer. Math. Soc.,* 43: 191–202, 1996.

[20] Z. Wang and X. Liu. A chronic viral infection model with immune impairment. *J. Theoret. Biol.,* 249: 532–542, 2007.

[21] B. M. Adams, H. T. Banks, M. Davidian, H. D. Kwon, H. T. Tran, S. N. Wynne and E. S. Rosenberg. HIV dynamics: Modeling, data analysis, and optimal treatment protocols. *J.Comput. Appl. Math.,* 184: 10–49, 2005.

[22] R. Culshaw and S. Ruan. A delay-differential equation model of HIV infection of CD4$^+$ T-cells,. *J. Math. Biosci.,* 165: 27–39, 2000.

[23] D. Wodarz, R. M. May and M. A. Nowak. The role of antigen-independent persistence of memory cytotoxic T lymphocytes. *Int. Immunol.,* 12: 467–477, 2000.

[24] S. Bonhoeffer, J. M. Coffin and M. A. Nowak. Human Immunodeficiency Virus drug therapy and virus load. *J. Virol.,* 71: 3275–3278, 1997.

[25] L. Rong, Z. Feng and A. S. Perelson. Emergence of HIV-1 drug resistance during antiretroviral treatment. *Bull. Math. Biol.,* 69: 2027–2060, 2007.

[26] P. S. Rivadeneira, C. H. Moog, G. B. Stan, C. Brunet, F. Raffi, V. Ferr, V. Costanza, M. J. Mhawej, F. Biafore, D. A. Ouattara, D. Ernst, R. Fonteneau and X. Xia. Mathematical Modeling of HIV Dynamics after Antiretroviral Therapy Initiation: A Review. *Biores Open Access.,* 3(5): 233–241, 2014.

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