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RESEARCH ARTICLE

Analysis of CD4+ T cells in HIV-1 infection model combined with RTI and PI treatments

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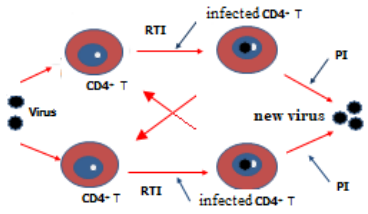
Graphical abstract



Abstract

HIV (Human Immunodeficiency Virus) is a retrovirus that attacks the immune system and subsequently leading to AIDS (Acquired Immunodeficiency Syndrome). CD4+ T cells are among the immune systems destroyed by HIV. The HIV transmission from cell to cell is an infection process of spreading HIV-1 infection. The study developed a mathematical model by considering the contact between HIV-1-infected CD4+ T cells and healthy CD4+ T cells, incorporating antiretroviral treatment. The stability of equilibriums for the model was studied. The local stability for disease-free equilibrium and the global stability for endemic equilibrium were studied. Numerical simulations were presented to examine the implication of antiretroviral therapy. Simulation results showed that reverse transcriptase inhibitor (RTI) therapy was more effective compared to protease inhibitor (PI) therapy in increasing the number of healthy CD4+ T cells.

Keywords: HIV-1 infection, CD4+T cells, stability, RTI, PI

INTRODUCTION

Human Immunodeficiency Virus (HIV) attacks the immune cells including CD4+ T cells. The decreasing number of CD4+ T cells causes the patient to develop Acquired Immunodeficiency Syndrome (AIDS). HIV-1 infection of CD4+ T cells through cell-to-cell is more efficient compared to HIV-1 infection through free virus. In the cell-to-cell transmission, HIV-1 infection of CD4+ T cells is transmitted through virological synapse (Hladik *et al*., 2007; Sattentau, 2010; Jolly, 2011).

HIV enters into hosts mediated by CD4+ T receptor and begins to infect the hosts. After being fused into the host, virus releases ribonucleic acid (RNA), and converts viral RNA into deoxyribonucleic acid (DNA) using reverse transcriptase enzyme. When HIV DNA enters the host's nucleus, it integrates with the host's DNA by using HIV integrase enzyme. The integration of HIV DNA and host's DNA is called provirus. After that, the provirus uses RNA polymerase to copy HIV genomic material and create long chain of HIV proteins. By using protease enzyme, new viral particles are assembled by cutting the HIV proteins, and then these particles move out from the host cells and mature to infect the immune system (Kirchhoff, 2013).

CD4+ T cells (stimulated or quiescent CD4+ T cells) have a primary role in spreading HIV-1 infection. Upon fusion in the body, the activated CD4+ T cells support the productive HIV-I infection. On the other hand, the quiescent CD4+ T cells in low level of deoxyribonucleotide triphosphates (dNTPs) limit reverse transcription process, thereby the virus fails to complete RNA reverse transcription, which then it is degraded in the cytoplasm of CD4+ T cells. The incomplete reverse transcription of viral RNA leads to abortive infection of CD4+ T cells. The abortive infection in CD4+ T cells is caused by inefficient reverse transcription in quiescent CD4+ T cells. Thus, the transmission of HIV-1 infection in quiescent CD4+ T cells becomes inefficient, and these cells turn to healthy cells (Klimas *et al*., 2008; Vatakis *et al.,* 2009; Swiggard *et al.,* 2004).

One of the strategies to prevent HIV-1 infection is through antiretroviral treatment involving the combination of RTIs and PIs treatments. Due to the potential role of reverse transcription of viral in supporting HIV-1 infection and viral replication of infected CD4+ T cells, the efforts have been conducted to prevent the kinetic process of DNA synthesis and new viral particles (Klimas *et al*., 2008). RTIs prevent the activity of reverse transcriptase enzyme, while PIs inhibit protease activity from producing the mature viral particles (Klimas *et al.,* 2008).

Recently, some researchers have developed mathematical models to explain the spread of HIV-1 infection in the immune system. A mathematical model was proposed and analysed (Srivastava *et al*., 2009). They studied the HIV-1 infection of CD4+ T cells by dividing these cells into two sub-classes. The first class involves CD4+ T cells that fail to complete reverse transcription called pre-RT class while the second class is the cells that complete reverse transcription and become the active infection, called post-RT class. Srivastava *et al*. (2009) established the model by incorporating RTI efficacy. However, they did not consider HIV-1 transmission through cell-to-cell and the effect of PI efficacy.

Other mathematical model was also established and analysed (Chirove *et al.,* 2014, Sutimin *et al*., 2017a, 2017b) to explore the implication of infected Langerhans and CD4+ T cells during early HIV-1 infection. In the model, HIV-1 transmission was established by considering the direct contact from the infected host cell to healthy hosts.

In this study, the model from Srivastava *et al*. (2009) was modified to capture HIV-1 infection in CD4+ T cells by incorporating cell-to-cell viral transmission in CD4+ T cells, the effect of PI efficacy and viral degradation by immune system. The existence equilibriums, stability equilibrium, and cytopathic effect of virus. The numerical simulations were analysed, and the dynamics of CD4+ T cells in different treatment scenarios were presented.

MODEL FORMULATION

The previous model from Srivastava *et al*. (2009) was modified as follows by introducing HIV-1 transmission from infected cell to healthy CD4$^+$ T cell and incorporating PI treatment. Upon cell-to-cell transmission, CD4$^+$ T cells may become the stimulated or quiescent CD4$^+$ T cells (Zack *et al.,* 1990). Upon infection, CD4$^+$ T cells can be divided into two classes; the first class is CD4$^+$ T cells in early viral reverse transcription, called pre-RT class and the second class is CD4$^+$ T cells, in which the viral reverse transcription is occurred, called post-RT class (actively infected class). This model consists of four nonlinear differential equations describing the population of susceptible CD4$^+$ T cells (T), pre-RT (L), post-RT (T_i), and free viruses (V). The model can be presented as follows:

$$\frac{dT}{dt} = \lambda - \beta_1 VT - \beta_2 TT_i - \mu_t T + (\varepsilon_{RTI}\alpha + \rho)L, \quad (1)$$

$$\frac{dL}{dt} = \beta_1 VT + \beta_2 TT_i - (\mu_1 + \alpha + \rho)L, \quad (2)$$

$$\frac{dT_i}{dt} = (1-\varepsilon_{RTI})\alpha L - (\mu_t + \delta)T_i, \quad (3)$$

$$\frac{dL}{dt} = N\delta(1-\varepsilon_{PI})T_i - \mu_v V - \phi V. \quad (4)$$

The susceptible CD4$^+$ T cells were recruited with the constant rate λ and undergone natural death at the constant rate μ_t. The infection rates of these cells by virus and infected CD4$^+$ T cell were β_1 and β_2, respectively. These cells were increased due to RTI treatment and incomplete reverse transcription with the constant rates $\varepsilon_{RTI}\alpha$ and ρ, respectively. Parameters ε_{RTI} and ε_{PI} were the efficacy of RTI drug and PI drug, respectively, with $0 \le \varepsilon_{RTI}, \varepsilon_{PI} \le 1$. The population of pre-RT class diminished with a constant rate due to the inflammation of CD4$^+$ T cells in pre-RT class.

Upon RTI treatment, a fraction of $\varepsilon_{RTI}\alpha L$ in pre-RT class returned to healthy CD4$^+$T cells, and other fraction of $(1-\varepsilon_{RTI})\alpha L$ became the infected CD4$^+$T class with the change rate of pre-RT class into the infected CD4$^+$T class reduced to $(1-\varepsilon_{RTI})\alpha$ from α. Upon PI treatment, the new viral production by infected CD4$^+$T cells was reduced to $N\delta(1-\varepsilon_{PI})$ from $N\delta$. The population of free virus decreased due to natural death and clearance or degradation by immune system with a constant rate μ_v and ϕ, respectively. Next, the dynamics of equilibriums and the viral cytopathic effect are addressed.

MODEL ANALYSIS

The next generation matrix (Diekmann *et al*., 2000) of the model (1)-(4) can be given in the following equation:

$$G = \begin{pmatrix} \Theta_1 & \Theta_2 & \dfrac{\lambda\beta_1}{\mu_t(\phi+\mu_v)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad (5)$$

where

$$\Theta_1 = \frac{\lambda\beta_2(1-\varepsilon_{RTI})\alpha}{\mu_t(\mu_1+\alpha+\rho)(\mu_t+\delta)} + \frac{\lambda\beta_1(1-\varepsilon_{RTI})\alpha N\delta(1-\varepsilon_{PI})}{\mu_t(\mu_1+\alpha+\rho)(\mu_t+\delta)(\phi+\mu_v)}$$

$$\Theta_2 = \frac{\lambda\beta_2}{\mu_t(\mu_t+\delta)} + \frac{\lambda\beta_1 N\delta(1-\varepsilon_{PI})}{\mu_t(\mu_t+\delta)(\phi+\mu_v)}.$$

The basic reproduction ratio $\Re_0$ indicates the maximum eigenvalue of matrix G. It can be written in the following equation:

The $\Re_0$ can be written in the sum of sub-reproduction ratio, $\Re_{T_i T_i}$, $\Re_{T_i V T_i}$, where

$$\Re_{T_i T_i} = \frac{\lambda\beta_2(1-\varepsilon_{RTI})\alpha}{\mu_t(\mu_1+\alpha+\rho)(\mu_t+\delta)},$$

$$\Re_{T_i V T_i} = \frac{\lambda\beta_1(1-\varepsilon_{RTI})\alpha N\delta(1-\varepsilon_{PI})}{\mu_t(\mu_1+\alpha+\rho)(\mu_t+\delta)(\phi+\mu_v)}.$$

As in Chirove *et al.* (2014), Sutimin *et al*. (2017a, 2017b), sub-reproduction $\Re_{T_i T_i}$ interprets the cycle infection from an infected CD4$^+$ T cell, then transmits the virus to health CD4$^+$T cells that become newly infected CD4$^+$ T cells. Sub-reproduction ratio $\Re_{T_i V T_i}$ is the new infection generated from infected CD4$^+$ T cell to produce new virions that infect susceptible CD4$^+$ T cells.

Stability analysis of uninfected steady state

Uninfected equilibrium point was $E^0 = \left(\dfrac{\lambda}{\mu_t}, 0, 0, 0\right)$. The local stability of E^0 was given in the following theorem.

Theorem 1 If $\Re_0 < 1$, the uninfected equilibrium point E^0 is locally asymptotically stable.

Proof The Jacobian matrix of the model (1)-(4) at E^0 can be presented in the following equation:

$$J = \begin{pmatrix} \mu_t & \alpha\varepsilon_{RTI} + \rho & -\dfrac{\lambda\beta_2}{\mu_t} & -\dfrac{\lambda\beta_1}{\mu_t} \\ 0 & -\mu_1 - \alpha - \rho & \dfrac{\lambda\beta_2}{\mu_t} & \dfrac{\lambda\beta_1}{\mu_t} \\ 0 & (1-\varepsilon_{RTI})\alpha & -\mu_t - \delta & 0 \\ 0 & 0 & N\delta(1-\varepsilon_{PI}) & -\mu_v - \phi \end{pmatrix} \quad (6)$$

One of the eigenvalues of $J(E^0)$ is $\lambda_1 = -\mu_t$, while other solutions can be presented in the following equation:

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0, \quad (7)$$

where

$$a_2 = \alpha + \delta + \phi + \rho + \mu_1 + \mu_t + \mu_v,$$

$$a_1 = (1-\Re_0)(\mu_1+\alpha+\rho)(\mu_t+\delta) + \frac{N\lambda\alpha\delta(1-\varepsilon_{PI})(1-\varepsilon_{RTI})\beta_1}{\mu_t(\phi+\mu_v)} + (\phi+\mu_v)(\alpha+\delta+\mu_1+\mu_t+\rho),$$

$$a_0 = (1-\Re_0)(\phi+\mu_v)(\mu_t+\delta)(\mu_1+\alpha+\rho).$$

It was clear that $a_2, a_1 > 0$ if $\Re_0 < 1$. Next, the equation $a_2 a_1 - a_0$ was calculated using algebraic calculation to obtain

$$a_2 a_1 - a_0 = \Psi\left((\mu_t+\delta)(\mu_1+\alpha+\rho)(1-\Re_0) + (\phi+\mu_v)a_2\right) + \frac{N\lambda\alpha\delta(1-\varepsilon_{PI})(1-\varepsilon_{RTI})a_2\beta_1}{\mu_t(\phi+\mu_v)}$$

where $\Psi = \alpha + \delta + \mu_1 + \mu_t + \rho$, $(1-\varepsilon_{RTI}) > 0$, and $(1-\varepsilon_{PI}) > 0$. It was shown that $a_2 a_1 - a_0 > 0$ if $\Re_0 < 1$. The Routh-Hurwitz

conditions were fulfilled if $\Re_0 < 1$. So, if $\Re_0 < 1$, E^0 indicates locally asymptotically stable.

Stability of endemic equilibrium

The global stability of endemic equilibrium was shown by constructing a Lyapunov function. From the calculation, the endemic equilibrium point $E^* = \left(T^*, L^*, T_i^*, V^*\right)$ was obtained, where

$$T^* = \frac{\lambda}{\mu_t \Re_0}, L^* = \frac{\lambda}{\left(1-\acute{U}_{RTI}\right)\alpha + \mu_1}\left(1-\frac{1}{\Re_0}\right),$$

$$T_i^* = \frac{\alpha\lambda\left(1-\acute{U}_{RTI}\right)}{\left(\mu_t+\delta\right)\left(\left(1-\acute{U}_{RTI}\right)\alpha+\mu_1\right)}\left(1-\frac{1}{\Re_0}\right), \text{ and}$$

$$V^* = \frac{N\alpha\delta\lambda\left(1-\acute{U}_{RTI}\right)\left(1-\acute{U}_{PI}\right)}{\left(\phi+\mu_v\right)\left(\mu_t+\delta\right)\left(\left(1-\acute{U}_{RTI}\right)\alpha+\mu_1\right)}\left(1-\frac{1}{\Re_0}\right).$$

It can be seen that $\Re_0 > 1$ guarantees the existence of the endemic state. It was also easy to see that $\Omega = \left\{\left(T, L, T_i, V\right) \in R_+^4 : T, L, T_i, V \le M\right\}$,

$M = \max\left\{\frac{\lambda}{\mu_t}, \frac{\delta N\lambda\left(1-\acute{U}_{PI}\right)}{\mu_t\left(\mu_v+\phi\right)}\right\}$ is a positively invariant set with $T(0), L(0), T_i(0), V(0) > 0$. The global stability of endemic equilibrium was established, which is given in the next theorem by constructing a Lyapunov function.

Theorem 2: If $\Re_0 > 1$, the endemic equilibrium point E^* of the system (1)-(4) is globally asymptotically stable.

Proof: We give a Lyapunov function

$$F\left(T, L, T_i, V\right) = T - T^* - T^* \ln\left(\frac{T}{T^*}\right) + a_1\left(L - L^* - L^* \ln\left(\frac{L}{L^*}\right)\right) + a_2\left(T_i - T_i^* - T_i^* \ln\left(\frac{Ti}{T_i^*}\right)\right) + a_3\left(V - V^* - V^* \ln\left(\frac{V}{V^*}\right)\right) \quad (8)$$

where $a_1, a_2, a_3 > 0$ is determined. It can be seen that $F \in C^1$, $F(E^*)=0$, and $F(E) > 0$ for $E \ne E^*$. The derivative of F to t along solutions of the model (1)-(4) was obtained as follows:

$$\begin{aligned}\frac{dF}{dt} &= \frac{T-T^*}{T}\frac{dT}{dt} + a_1\frac{L-L^*}{T}\frac{dL}{dt} + a_2\frac{V-V^*}{T}\frac{dT_i}{dt} + +a_3\frac{V-V^*}{T}\frac{dV}{dt} \\ &= C - \mu_t T - \left(a_1\left(\mu_1+\alpha+\rho\right) - \left(\acute{U}_{RTI}\alpha+\rho\right) - a_2\left(1-\acute{U}_{RTI}\right)\alpha\right)L \\ &\quad -\left(a_2\left(\mu_t+\delta\right) - \beta_2 T^* - a_3 N\delta\left(1-\acute{U}_{PI}\right)\right)T_i - \beta_1\left(1-a_1\right)VT \\ &\quad -\left(a_3\left(\mu_v+\phi\right) - \beta_1 T^*\right)V - \beta_2\left(1-a_1\right)TT_i - \lambda T^*\frac{1}{T} \\ &\quad -a_1\beta_1 L^*\frac{VT}{L} - \left(\acute{U}_{RTI}\alpha+\rho\right)T^*\frac{VT}{L} - a_1\beta_2 L^*\frac{TT_i}{L} \\ &\quad -a_2\left(1-\acute{U}_{RTI}\right)\alpha T_i^*\frac{L}{T_i} - a_3 N\delta\left(1-\acute{U}_{PI}\right)V^*\frac{T_i}{V}\end{aligned} \quad (9)$$

where

$$C = \lambda + \mu_t T^* + a_1\left(\mu_1+\alpha+\rho\right)L^* + a_2\left(\mu_t+\delta\right)T_i^* + a_3\left(\mu_v+\phi\right)V^*.$$

For the simplicity, new notations, $x = \frac{T}{T^*}, y = \frac{L}{L^*}, w = \frac{T_i}{T_i^*}, z = \frac{V}{V^*}$ was considered. The equation (9) can be written as

$$\begin{aligned}\frac{dF}{dt} &= C - \mu_t T^* x - \left(a_2\left(\mu_t+\delta\right) - \beta_2 T^* - a_3 N\delta\left(1-\acute{U}_{PI}\right)\right)T_i^* w \\ &\quad -\left(a_1\left(\mu_1+\alpha+\rho\right) - \left(\acute{U}_{RTI}\alpha+\rho\right) - a_2\left(1-\acute{U}_{RTI}\right)\alpha\right)L^* y \\ &\quad -\left(a_3\left(\mu_v+\phi\right) - \beta_1 T^*\right)V^* z - \beta_1\left(1-a_1\right)V^*T^* xz \\ &\quad -\beta_2\left(1-a_1\right)T^*T_i^* xw - \lambda\frac{1}{x} - \left(\acute{U}_{RTI}\alpha+\rho\right)L^*\frac{y}{x} \\ &\quad -a_1\beta_1 V^*T^*\frac{xz}{y} \\ &\quad -a_1\beta_2 T^*T_i^*\frac{xw}{y} - a_2\left(1-\acute{U}_{RTI}\right)\alpha L^*\frac{y}{w} - a_3 N\delta\left(1-\acute{U}_{PI}\right)T_i^*\frac{w}{z}\end{aligned} \quad (10)$$

Set $D = \left\{x, y, w, z, xz, xw, \frac{1}{x}, \frac{y}{x}, \frac{xz}{y}, \frac{xw}{y}, \frac{y}{w}, \frac{w}{z}\right\}$ was considered related to terms in (10). The mean of arithmetic and geometric for sub sets $\left\{x, \frac{1}{x}\right\}$, $\left\{\frac{1}{x}, \frac{xw}{y}, \frac{y}{w}\right\}$, and $\left\{\frac{1}{x}, \frac{xz}{y}, \frac{y}{w}, \frac{w}{z}\right\}$ were used, so the equation (10) can be written as follows:

$$\begin{aligned}\frac{dF}{dt} &= b_1\left(2 - x - \frac{1}{x}\right) + b_2\left(3 - \frac{1}{x} - \frac{y}{w} - \frac{xw}{y}\right) - \left(\acute{U}_{RTI}\alpha+\rho\right)L^*\frac{y}{x} \\ &\quad +b_3\left(4 - \frac{1}{x} - \frac{y}{w} - \frac{w}{z} - \frac{xz}{y}\right).\end{aligned} \quad (11)$$

The constants $b_1, b_2, b_3, a_1, a_2, a_3$ can be determined and the relationship can be made:

$\lambda + \left(\acute{U}\alpha+\rho\right)L^* = \beta_1 T^*V^* + \beta_2 T^*T_i^* + \mu_t T^*$,

$\beta_1 T^*V^* + \beta_2 T^*T_i^* = \left(\mu_1+\alpha+\rho\right)L^*$, $\left(\mu_t+\delta\right)T_i^* = \left(1-\acute{U}_{RTI}\right)\alpha L^*$, and

$\left(\mu_v+\phi\right)V^* = N\delta\left(1-\acute{U}_{PI}\right)T_i^*$.

Equating coefficients in the same terms of equation (10) and (11), we get

$2b_1 + 3b_2 + 4b_3 = C, 1 - a_1 = 0, b_1 = \mu_t T^*, b_1 + b_2 + b_3 = \lambda,$

$b_2 + b_3 = a_2\left(1-\acute{U}_{RTI}\right)\alpha L^*$, $a_3 N\delta\left(1-\acute{U}_{PI}\right) = a_2\left(\mu_t+\delta\right) - \beta_2 T^*$,

$a_2\left(1-\acute{U}_{RTI}\right)\alpha = a_1\left(\mu_1+\alpha+\rho\right) - \left(\acute{U}_{RTI}\alpha+\rho\right)$, $b_2 = a_1\beta_1 T^*T_i^*$,

$$b_3 = a_3 N\delta\left(1-\acute{U}_{PI}\right) = a_1\beta_1 T^*V^*, a_3 = a_2\frac{\left(\mu_t+\delta\right)}{N\delta\left(1-\acute{U}_{PI}\right)} = \frac{\beta_1 T^*}{N\delta\left(1-\acute{U}_{PI}\right)}.$$

Thus, we can choose

$$a_1 = 1, a_2 = \frac{\mu_1 + \left(1-\acute{U}_{RTI}\right)}{\left(1-\acute{U}_{RTI}\right)\alpha},$$

$$a_3 = \frac{\left(\mu_t+\delta\right)\left(\left(1-\acute{U}_{RTI}\right)\alpha+\mu_1\right)}{N\delta\alpha\left(1-\acute{U}_{R}TI\right)\left(1-\acute{U}_{PI}\right)} - \frac{\beta_1 T^*}{N\delta\left(1-\acute{U}_{PI}\right)} = \frac{\beta_1 T^*}{\mu_v+\phi}$$

Using the inequality of arithmetic and geometric mean, the equation (11) can be written as follows:

$$\begin{aligned}\frac{dF}{dt} &= \mu_t T^*\left(2 - x - \frac{1}{x}\right) + \beta_2 T^*V^*\left(3 - \frac{1}{x} - \frac{y}{w} - \frac{xw}{y}\right) + \\ &\quad \beta_1 T^*V^*\left(4 - \frac{1}{x} - \frac{y}{w} - \frac{w}{z} - \frac{xz}{y}\right) - \left(\acute{U}_{RTI}\alpha+\rho\right)L^*\frac{y}{x} < 0.\end{aligned} \quad (12)$$

It can be seen that $\frac{dF}{dt}=0$ for $T=T^*, L=L^*, T_i=T_i^*, V=V^*$, the maximal invariance set of $\left\{(T,L,T_i,V) \mid \frac{dF}{dt}=0\right\}$ was the singleton E^*. Thus, E^* indicates globally asymptotically stable. The proof was then completed.

Next, $\Re_0$ was analysed due to viral lysis to reveal the endemicity of HIV infection. Derivative $\Re_0$ with respect to δ was resulted from,

$$\frac{\partial \Re_0}{\partial \delta}=\frac{\lambda\alpha\left(1-\acute{U}_{RTI}\right)\beta_1\left(1-\acute{U}_{PI}\right)\left(N-N_c\right)}{\left(\mu_1+\alpha+\rho\right)\left(\mu_t+\delta\right)^2\left(\mu_v+\phi\right)} \tag{13}$$

where,

$$N_c=\frac{\beta_2\left(\mu_v+\phi\right)}{\beta_1\left(1-\acute{U}_{PI}\right)\mu_t} \tag{14}$$

The number N_c is the critical number of virion replications generated from infected CD4$^+$ T cells. A theorem of the relationship of N and N_c in the endemicity level was provided.

Theorem 3 There exists a critical number N_c, considering:

i. $\Re_0$ decreases with respect to δ, when $N<N_c$.

ii. $\Re_0$ increase with respect to δ, when $N>N_c$, and

iii. $\Re_0$ remains constant with respect to δ, when $N=N_c$.

Proof For $N<N_c$, it was seen that $\frac{\partial \Re_0}{\partial \delta}<0$, thus $\Re_0$ decreases while δ increases. Conversely, if $N>N_c$, it leads to $\frac{\partial \Re_0}{\partial \delta}>0$. It is shown that the increase of δ leads to the decrease in $\Re_0$. For $N=N_c$, it shows that $\frac{\partial \Re_0}{\partial \delta}=0$. It means that $\Re_0$ remains constant for the change of δ. The proof was then completed.

NUMERICAL SIMULATIONS

The parameter values for simulation were taken from literatures presented in Table 1.

Table 1 The values of parameter and units.

Parameters	Values	Units	Refences
λ	10,20	cells/day^{-1}	(Perelson *et al.*,1993)
β_1	(0.00002,0.005)	virions^{-1}day^{-1}	(Kirschner, 1996, Stafford *et al.,* 2000)
β_2	0.002 (0.00001,0.01)	cells^{-1}day^{-1}	(Bonhoeffer *et al.,* 1997) (Chirove *et al.,* 2014)
μ_t	0.01, 0.1	day^{-1}	(Stafford *et al., 2000,* Culshaw *et al.*,2000)
μ_1	0.015	day^{-1}	(Srivastava *et* al., 2009)
μ_v	2.4	day^{-1}	(Perelson *et al.*,1993)
δ	0.24	day^{-1}	(Perelson *et al.*,1993)
N	(100,1000)	virions/day^{-1}	(Adams *et al.*, 2005)
ϕ	(2, 9)	day^{-1}	(Perelson *et al,* 1993)

The dynamic of CD4$^+$ T cells and virus populations were simulated to examine the effects of combined RTIs and PIs treatments in different scenarios with initial conditions $T(0)=1000\frac{cells}{mm^3}$, $L(0)=0\frac{cells}{mm^3}, T_i(0)=0\frac{virions}{mm^3}$, and $V(0)=0.001\frac{virions}{mm^3}$ (Perelson *et al.,* 1993). Afterwards, the clearance effect of virus to the dynamic of CD4$^+$ T cells and free virus populations were investigated.

Figure 1 shows the impact of combination of RTI and PI treatments to the evolution of CD4$^+$ T cells and free virus populations in different scenarios of treatments. The overall efficacy of drugs was defined, when RTI and PI drugs were taken simultaneously (Tarfulea *et al.*, 201), as $\acute{U}=1-\left(1-\acute{U}_{RTI}\right)\left(1-\acute{U}_{PI}\right)$. In the simulations, we took $\acute{U}=0.99$ with different values of $\acute{U}_{RTI}$ and $\acute{U}_{PI}$. Scenarios of treatments were considered as follows.

Scenario 1: both RTI and PI drugs were taken with efficacies $\acute{U}_{RTI}=0.91, \acute{U}_{PI}=0.89$, respectively.

Scenario 2: $\acute{U}_{RTI}=0.9, \acute{U}_{PI}=0.9$ were considered.

Scenario 3: $\acute{U}_{RTI}=0.89, \acute{U}_{PI}=0.91$ were considered, and

Scenario 4: $\acute{U}_{RTI}=0.88, \acute{U}_{PI}=0.915$ were used.

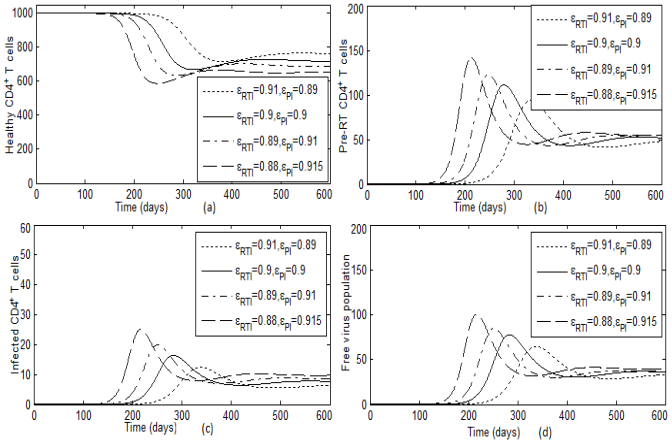


Fig. 1 The evolution of CD4$^+$ T cells and free virus populations in different treatment of RTI and PI drugs with $\lambda=10, \beta_1=0.0005, \beta_2=0.002, \alpha=0.4, \rho=0.05, \delta=0.26, \mu_t=0.01, \mu_1=0.015, \mu_v=2.4, N=800, \phi=3$.

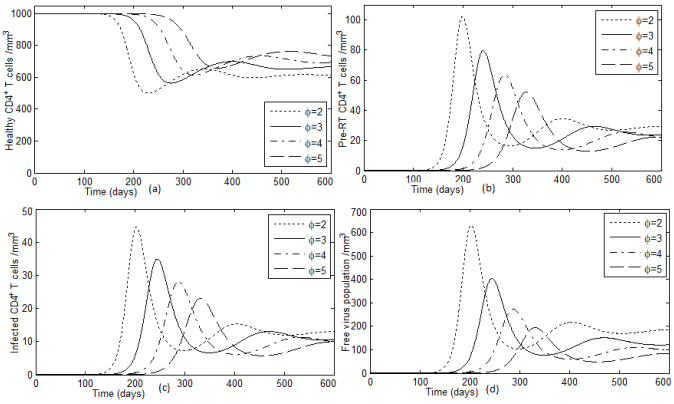


Fig. 2 The evolution of CD4$^+$ T cells and free virus population for the variation in the clearance level ϕ with λ=10, β_1=0.00005, $\beta_2=0.001, \alpha=0.4, \rho=0.05, \delta=0.26, \mu_t=0.01, \mu_1=0.015, \mu_v=2.4, N=800$.

In the combination of RTI and PI drugs as seen in Fig.1, the increase of efficacy of RTI drug was faster in increasing the healthy CD4$^+$ T cells compared to the efficacy of PI drug. The increase of

healthy $CD4^+$ T cells was correlated to the decrease of infected $CD4^+$ T cells and free virus populations.

From the combination of RTI and PI drugs in Fig. 1, we can see that the increase of efficacy of RTI drug was fast in increasing the healthy $CD4^+$ T cells compared to the efficacy of PI drug. The increase of healthy $CD4^+$ T cells was correlated to the decrease of infected $CD4^+$ T cells and free virus population.

In Figure 2, it can be seen that the increase of the virus clearance level by immune system resulted in the increase of the healthy $CD4^+$ T cells. The increase of $CD4^+$ T cells was correlated to the decrease of the infected CD4+T cells and free virus populations. The results indicate that when the immune system is able to respond fairly to the virus, it is able to block the HIV infection during early infection.

CONCLUSION

A mathematical model has been modified within the host of $CD4^+$ T cells proposed by Srivastava *et al*. We established and analysed the behaviour of the mathematical model of the HIV-1 infection in $CD4^+$ T cells during early infection by considering the implication of HIV transmission through cell-to-cell contact from the infected $CD4^+$ T cell to healthy $CD4^+$ T cell. The basic reproduction ratio derived from the next generation matrix for the model has been used to determine the local stability of uninfected equilibriums and the existence of endemic equilibrium. It can be expressed in the sum of two sub-reproduction ratios. If the ratio is less than unity, the uninfected equilibrium is indicated locally asymptotically stable, while global stability of the endemic state is achieved when the ratio exceeds unity.

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