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

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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-1 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 cytotoxic 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 occurs, is 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), and free viruses (V). The model can be presented as follows:

\[
\frac{dT}{dt} = \lambda - \beta VT - \delta T + \left( \alpha - \mu + \rho \right) L,
\]

\[
\frac{dL}{dt} = \beta VT + \delta T - \mu L + \left( \mu + \alpha + \rho \right) L,
\]

\[
\frac{dT}{dt} = \left( 1 - \epsilon_{DT} \right) \alpha L - \mu T - V - \phi V,
\]

\[
\frac{dV}{dt} = N \delta \left( 1 - \epsilon_{IV} \right) T - \mu V - \phi V.
\]

The susceptible CD4⁺ T cells were recruited with the constant rate \( \lambda \) and undergo natural death at the constant rate \( \mu \). The infection rates of these cells by virus and infected CD4⁺ T cell were \( \beta_1 \) and \( \beta_2 \), respectively. These cells were increased due to RTI treatment and incomplete reverse transcription with the constant rates \( \alpha \) and \( \rho \), respectively. Parameters \( \alpha_{RTI} \) and \( \alpha_{PI} \) were the efficacy of RTI drug and PI drug, respectively, with \( 0 < \alpha_{RTI} < \alpha_{PI} \). 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 \( \alpha_{RTI}aL \) in pre-RT class returned to healthy CD4⁺ T cells, and other fraction of \( \alpha_{RTI}aL \) became the infected CD4⁺ T class with the change rate of pre-RT class into the infected CD4⁺ T class reduced to \( \alpha_{RTI}aL \) from \( \alpha \). Upon PI treatment, the new viral production by infected CD4⁺ T cells was reduced to \( \delta \alpha_{PI}L \) from \( \delta \alpha \). The population of free virus decreased due to natural death and clearance or degradation by immune system, with a constant rate \( \mu \), and \( \phi \), respectively. Next, the dynamics of equilibria and the viral cytotoxic 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:

\[
G = \begin{pmatrix}
\Theta_1 & \lambda \beta_1 \\
\Theta_2 & \mu_1(\phi + \mu_1)
\end{pmatrix},
\]

where

\[
\Theta_1 = \frac{\lambda \beta_1 (1 - \bar{U}_{\alpha}) \alpha}{\mu_1(\mu_1 + \alpha + \rho)} + \frac{\lambda \beta_1 (1 - \bar{U}_{\alpha}) \alpha N \delta (1 - \bar{U}_{\alpha})}{\mu_1(\mu_1 + \alpha + \rho)} \\
\Theta_2 = \frac{\lambda \beta_1}{\mu_1(\mu_1 + \alpha + \rho)} + \frac{\lambda \beta_1 N \delta (1 - \bar{U}_{\alpha})}{\mu_1(\mu_1 + \alpha + \rho)}.
\]

The basic reproduction ratio \( R_0 \) indicates the maximum eigenvalue of matrix \( G \). It can be written as the following equation:

\[
R_0 = \left( \frac{\lambda \beta_1}{\mu_1(\mu_1 + \alpha + \rho)} + \frac{\lambda \beta_1 N \delta (1 - \bar{U}_{\alpha})}{\mu_1(\mu_1 + \alpha + \rho)} \right) + \frac{\lambda \beta_2 (1 - \bar{U}_{\alpha}) \alpha}{\mu_1(\mu_1 + \alpha + \rho)},
\]

\[
R_{i,v} = \left( \frac{\lambda \beta_1 (1 - \bar{U}_{\alpha}) \alpha}{\mu_1(\mu_1 + \alpha + \rho)} + \frac{\lambda \beta_1 N \delta (1 - \bar{U}_{\alpha})}{\mu_1(\mu_1 + \alpha + \rho)} \right) + \frac{\lambda \beta_2 (1 - \bar{U}_{\alpha}) \alpha N \delta (1 - \bar{U}_{\alpha})}{\mu_1(\mu_1 + \alpha + \rho) + \phi + \mu_1},
\]

As in Chirove et al. (2014), Sutimin et al. (2017a, 2017b), sub-reproduction \( R_{i,v} \) interprets the cycle infection from an infected CD4⁺ T cell, then transmits the virus to healthy CD4⁺ T cells that become newly infected CD4⁺ T cells. Sub-reproduction ratio \( R_{i,v} \) 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 \( E^* = \left( \frac{\lambda}{\mu_1}, 0, 0, 0 \right) \). The local stability of \( E^* \) was given in the following theorem.

Theorem 1 If \( R_0 < 1 \), the uninfected equilibrium point \( E^* \) is locally asymptotically stable.

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

\[
J = \begin{pmatrix}
\mu_1 - \alpha \epsilon_{IV} + \rho & -\lambda \beta_1 & \lambda \beta_2 \\
0 & -\mu_1 - \alpha - \rho & \lambda \beta_1 \\
0 & (1 - \epsilon_{IV})\alpha & -\mu_1 - \delta - \phi \\
0 & 0 & N \delta(1 - \epsilon_{IV}) - \mu_1 - \phi
\end{pmatrix}
\]

One of the eigenvalues of \( \lambda(E^*) \) is \( \lambda = -\mu_1 \), while other solutions can be presented in the following equation:

\[
\lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 = a_0,
\]

where

\[
a_2 = \alpha + \delta + \phi + \rho + \mu_1 + \mu_1 + \mu_1,
\]

\[
a_3 = (1 - R_0)(\mu_1 + \alpha + \rho)(\mu_1 + \delta) + \frac{N \lambda \alpha \delta (1 - \bar{U}_{\alpha})(1 - \bar{U}_{\alpha}) \beta}{\mu_1(\phi + \mu_1)}
\]

\[
+ \left( \phi + \mu_1 \right)(\alpha + \delta + \mu_1 + \mu_1 + \mu_1),
\]

\[
a_3 = (1 - R_0)(\phi + \mu_1)(\mu_1 + \alpha + \rho).
\]

It was clear that \( a_1, a_2 > 0 \) if \( R_0 < 1 \). Next, the equation \( a_1a_2 - a_4 \) was calculated using algebraic calculation to obtain

\[
a_1a_2 - a_4 = \Psi((\mu_1 + \alpha + \rho)(\mu_1 + \alpha + \rho)(1 - R_0) + (\phi + \mu_1)a_1) + \frac{N \lambda \alpha \delta (1 - \bar{U}_{\alpha})(1 - \bar{U}_{\alpha}) \beta a_2}{\mu_1(\phi + \mu_1)}
\]

where \( \Psi = \alpha + \delta + \mu_1 + \mu_1 + \rho, (1 - \bar{U}_{\alpha}) > 0, \) and \( (1 - \bar{U}_{\alpha}) > 0 \). It was shown that \( a_1a_2 - a_4 > 0 \) if \( R_0 < 1 \). The Routh-Hurwitz
conditions were fulfilled if $\mathbb{R}_0 < 1$. So, if $\mathbb{R}_s < 1$, $E^*$ 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 $E^* = \left(T^*, L^*, T^*_v, V^*_v\right)$ was obtained, where

$$
T^* = \frac{\lambda}{\mu \mathbb{R}_s}, \quad \lambda = \left(1 - \frac{1}{\mathbb{R}_s}\right),
$$

$$
T^*_{v} = \frac{\alpha \lambda \left(1 - \frac{1}{\mathbb{R}_s}\right)}{\left(\mu_{v} + \delta\right)\left(1 - \frac{1}{\mathbb{R}_s}\right)}, \quad \text{and}
$$

$$
V^* = \frac{\alpha \delta \lambda \left(1 - \frac{1}{\mathbb{R}_s}\right)}{\left(\mu_{v} + \delta\right)\left(1 - \frac{1}{\mathbb{R}_s}\right)},
$$

It can be seen that $\mathbb{R}_s > 1$ guarantees the existence of the endemic state. It was also easy to see that

$$
\Omega = \left\{\left(T,L,T_v,V\right) \in \mathbb{R}^4 : T,L,T_v,V \leq M\right\},
$$

$$
M = \max \left\{\frac{\lambda}{\mu}, \frac{\delta N \lambda}{\mu_{v} (\mu_{v} + \phi)}\right\}
$$

is a positively invariant set with $T(0), L(0), T(0), V(0) > 0$. The global stability of endemic equilibrium was established, which is given in the next theorem by constructing a Lyapunov function.

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

**Proof:** We give a Lyapunov function

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

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

$$
\frac{dF}{dt} = \frac{dT}{dt} - \frac{dL}{dt} + a_1 \left(\frac{dL}{dt} - \frac{L}{L^*} \frac{dL}{dt}\right) + a_2 \left(\frac{dT}{dt} - \frac{T}{T^*} \frac{dT}{dt}\right) + a_3 \left(\frac{dV}{dt} - \frac{V}{V^*} \frac{dV}{dt}\right)
$$

$$
= C - \mu T - \left(a_1 \left(\mu_{v} + \alpha + \rho\right) - a_2 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) L
$$

$$
- \left(a_3 \left(\mu_{v} + \delta\right) - a_4 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) T
$$

$$
- \left(a_2 \left(\mu_{v} + \phi\right) - a_3 \left(\mu_{v} + \delta\right) - a_4 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) T_v
$$

$$
- \lambda T^* \frac{T}{T^*} + \left(\frac{a_1 \mu_{v} L}{L^*} + a_2 \mu_{v} T^* \frac{T}{T^*} - a_3 \mu_{v} T_v \frac{T_v}{T^*_v}\right)
$$

$$
- \left(\frac{a_1 \mu_{v} L}{L^*} + a_2 \mu_{v} T^* \frac{T}{T^*} - a_3 \mu_{v} T_v \frac{T_v}{T^*_v}\right) + \left(\frac{a_1 \mu_{v} L}{L^*} + a_2 \mu_{v} T^* \frac{T}{T^*} - a_3 \mu_{v} T_v \frac{T_v}{T^*_v}\right)
$$

$$
= \lambda + \mu T^* + a_1 \left(\mu_{v} + \alpha + \rho\right) L + a_2 \left(\mu_{v} + \delta\right) T + a_3 \left(\mu_{v} + \phi\right) T_v
$$

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

$$
\frac{dF}{dt} = C - \mu T^* x - \left(a_1 \left(\mu_{v} + \alpha + \rho\right) - a_2 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) \frac{T}{T^*}
$$

$$
- \left(a_3 \left(\mu_{v} + \delta\right) - a_4 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) \frac{T_v}{T^*_v}
$$

$$
- \left(a_2 \left(\mu_{v} + \phi\right) - a_3 \left(\mu_{v} + \delta\right) - a_4 \left(1 - \frac{1}{\mathbb{R}_s}\right)\right) \frac{T_v}{T^*_v}
$$

$$
- \lambda \frac{T}{T^*} + \frac{a_1 \mu_{v} L}{L^*} \frac{T}{T^*} + \frac{a_2 \mu_{v} T^* \frac{T}{T^*}}{T^*} - \frac{a_3 \mu_{v} T_v \frac{T_v}{T^*_v}}{T_v}
$$

$$
- \left(\frac{a_1 \mu_{v} L}{L^*} + a_2 \mu_{v} T^* \frac{T}{T^*} - a_3 \mu_{v} T_v \frac{T_v}{T^*_v}\right) + \left(\frac{a_1 \mu_{v} L}{L^*} + a_2 \mu_{v} T^* \frac{T}{T^*} - a_3 \mu_{v} T_v \frac{T_v}{T^*_v}\right)
$$

$$
= \lambda + \mu T^* + a_1 \left(\mu_{v} + \alpha + \rho\right) L + a_2 \left(\mu_{v} + \delta\right) T + a_3 \left(\mu_{v} + \phi\right) T_v
$$

The constants $b_1, b_2, b_3, b_4, a_1, a_2, a_3$ can be determined and the relationship can be made:

$$
\lambda + (\mu_{v} + \alpha + \rho) L = \beta_{T} T^* V^* + \beta_{T} T^*_v V^*_v + \mu T^*,
$$

$$
\beta_{T} V^* + \beta_{T} T^*_v V^*_v = (\mu_{v} + \alpha + \rho) L, (\mu_{v} + \delta) T = (1 - \frac{1}{\mathbb{R}_s}) \mu L', \text{ and}
$$

$$
(\mu_{v} + \phi) T^*_v = N \delta (1 - \frac{1}{\mathbb{R}_s}) T
$$

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

$$
b_1 + b_2 = C + a_1 - b_4 = 0, b_1 = \mu T^*, b_2 + b_3 = \lambda,
$$

$$
b_2 + b_3 = a_1 \left(1 - \frac{1}{\mathbb{R}_s}\right) \mu L', a_1 N \delta (1 - \frac{1}{\mathbb{R}_s}) = a_2 \left(\mu_{v} + \alpha + \rho\right) - \mu T^*,
$$

$$
a_1 \left(1 - \frac{1}{\mathbb{R}_s}\right) a_2 \left(\mu_{v} + \alpha + \rho\right) - (1 - \frac{1}{\mathbb{R}_s}) \mu L', b_2 = a_3 \mu T^*_v,
$$

$$
a_2 = a_1 N \delta (1 - \frac{1}{\mathbb{R}_s}) = a_1 \left(\mu_{v} + \alpha + \rho\right) - a_3 \left(\mu_{v} + \delta\right) T, b_3 = a_3 \mu T^*_v,
$$

$$
a_1 = 1, a_2 = \frac{\mu_{v} + \alpha + \rho}{\left(1 - \frac{1}{\mathbb{R}_s}\right) \mu L'},
$$

$$
a_3 = \frac{\mu_{v} + \delta}{\left(1 - \frac{1}{\mathbb{R}_s}\right) \mu L'}
$$

where $C = \lambda + \mu T^* + a_1 \left(\mu_{v} + \alpha + \rho\right) L + a_2 \left(\mu_{v} + \delta\right) T + a_3 \left(\mu_{v} + \phi\right) T_v$. Using the inequality of arithmetic and geometric mean, the equation (11) can be written as follows:

$$
\frac{dF}{dt} = \mu T^* \left(2 - \frac{1}{x} + b_1 \beta_{T} V^* \left(\frac{3}{x} \frac{1}{y} \frac{1}{w} \frac{1}{z}\right) + \beta_{T} T^* V^* \left(\frac{4}{x} \frac{1}{y} \frac{1}{w} \frac{1}{z}\right) - (\mu_{v} + \alpha + \rho) L \frac{y}{x} < 0\right).
$$
It can be seen that \( \frac{df}{dt} = 0 \) for \( T = T^*, L = L^*, T = T^*, V = V^* \), the maximal invariance set of \( \{(T, L, T, V) | \frac{df}{dt} = 0 \} \) was the singleton \( E^* \). Thus, \( E^* \) indicates globally asymptotically stable. The proof was then completed.

Next, \( R_i \) was analysed due to viral lysis to reveal the endemicity of HIV infection. Derivative \( R_i \) with respect to \( \delta \) was resulted from,

\[
\frac{dR_i}{d\delta} = \lambda \alpha \left( 1 - U_{ii} \right) \beta \left( 1 - U_{ii} \right) \left( N - N_i \right)
\]

where,

\[
N_i = \frac{\beta \left( \mu + \delta \right)}{\beta \left( 1 - U_{ii} \right) \mu_i}
\]

The number \( N_i \) is the critical number of virion replications generated from infected CD4+ T cells. A theorem of the relationship of \( N \) and \( N_i \) in the endemicity level was provided.

**Theorem 3** There exists a critical number \( N_i^* \), considering:

i. \( R_i \) decreases with respect to \( \delta \), when \( N < N_i \).

ii. \( R_i \) increase with respect to \( \delta \), when \( N > N_i \); and

iii. \( R_i \) remains constant with respect to \( \delta \), when \( N = N_i \).

**Proof** For \( N < N_i \), it was seen that \( \frac{dR_i}{d\delta} < 0 \), thus \( R_i \) decreases while \( \delta \) increases. Conversely, if \( N > N_i \), it leads to \( \frac{dR_i}{d\delta} > 0 \). It is shown that the increase of \( \delta \) leads to the decrease in \( R_i \). For \( N = N_i \), it shows that \( \frac{dR_i}{d\delta} = 0 \). It means that \( R_i \) remains constant for the change of \( \delta \). The proof was then completed.

**NUMERICAL SIMULATIONS**

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

| Parameters | Values | Units | Refences |
|------------|--------|-------|----------|
| \( \lambda \) | 10,20 | cells/day \(^{-1}\) | (Perelson et al., 1993) |
| \( \beta_i \) | (0.00002,0.005) | virions/day \(^{-1}\) | (Kirschner, 1996, Stafford et al., 2000) |
| \( \beta_i \) | (0.00001,0.01) | cells/day \(^{-1}\) | (Bonhoeffer et al., 1997) |
| \( \mu_i \) | 0.01, 0.1 | day \(^{-1}\) | (Chirose et al., 2014) |
| \( \mu_i \) | 0.015 | day \(^{-1}\) | (Stafford et al., 2000, Culshaw et al.2000) |
| \( \mu_i \) | 0.015 | day \(^{-1}\) | (Srivastava et al., 2009) |
| \( \mu_i \) | 2.4 | day \(^{-1}\) | (Perelson et al., 1993) |
| \( \delta \) | 0.24 | day \(^{-1}\) | (Perelson et al., 1993) |
| \( N \) | (100,1000) | viral/day \(^{-1}\) | (Adams et al., 2005) |
| \( \phi \) | (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 \( T(0) = 1000 \) cell/mm \(^2\), \( L(0) = 0 \) cell/mm \(^2\), \( T_r(0) = 0 \) virus/mm \(^2\), and \( V(0) = 0.00 \) virus/mm \(^2\) (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 drugs 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., 2011), as \( \pi = 1 - (1 - U_{ii}) (1 - U_{ij}) \). In the simulations, we took \( \pi = 0.99 \) with different values of \( U_{ij} \) and \( U_{ij} \). Scenarios of treatments were considered as follows.

Scenario 1: both RTI and PI drugs were taken with efficacies \( U_{ij} = 0.91, U_{ij} = 0.89 \), respectively.

Scenario 2: \( U_{ij} = 0.9, U_{ij} = 0.9 \) were considered.

Scenario 3: \( U_{ij} = 0.89, U_{ij} = 0.91 \) were considered, and

Scenario 4: \( U_{ij} = 0.88, U_{ij} = 0.915 \) were used.

![Fig. 1](image1.png) The evolution of CD4+ T cells and free virus populations in different treatment of RTI and PI drugs with \( \lambda = 10, \beta = 0.0005, \beta = 0.002, \alpha = 0.4, \rho = 0.05, \delta = 0.26, \mu = 0.01, \mu = 0.015, \mu = 2.4, N = 800, \phi = 3 \).

![Fig. 2](image2.png) The evolution of CD4+ T cells and free virus population for the variation in the clearance level \( \phi \) with \( \lambda = 10, \beta = 0.0005, \beta = 0.001, \alpha = 0.4, \rho = 0.05, \delta = 0.26, \mu = 0.01, \mu = 0.015, \mu = 2.4, N = 800 \).

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 populations.

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 state is achieved when the basic reproduction ratio exceeds unity.

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