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Modeling of HIV-1 Infection Incorporating Cell-to-Cell Transmission and Viral Clearance of CD4$^+$T cells

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Abstract. CD4$^+$ T cells are as immune system destroyed by HIV (Human Immunodeficiency Virus) and play pivotal role in the spread of viral transmission. The viral transmission in host cells occurred through cell-cell contact and cell-free virus. We develop a mathematical model by incorporating the viral infection through cell-cell, viral degradation, and the effect of antiretroviral treatments. The basic reproduction ratio is predicted by alternative reproduction ratio to investigate the uninfected and infected equilibrium points for the model. Simulation results are conducted to explore the implication of the combination of RTI and PI therapy in various scenarios and the effect of viral clearance. When the host cells is still enough able in responding HIV-1, the viral count can be eliminated up to undetected virus in the body.

INTRODUCTION

The majority of immune cells destroyed by HIV (Human Immunodeficiency Virus) is CD4$^+$ T cells. These cells play the role in transmitting HIV-1 [1] through cell-cell transmission [2]. Upon the virus in body, the activated CD4$^+$T cells experience the fast infection leading to the productive infections, but the quiescent cells experience the ineffective infection leading to fail infections ultimately the viral is degraded in cytoplasm [3].

The treatment of RTI (reverse transcript inhibitor) and PI (protease inhibitor) treatments has been used to reduce the progression of HIV-1 infection. RTI drugs for blocking the mechanism of viral reverse transcription, while PI drugs for inhibiting new viral reproduction in infected cells. The therapy has been conducted in preventing viral DNA synthesis and new viral production [4].

Some studies have explored for modeling the spread of HIV-1 infection within immune cells. A mathematical model was established and analyzed by Srivastava *et al.* [5], in which the infection mechanism based on viral reverse transcription process. After infection, CD4$^+$T cells were classified becoming latent class and infected class. They took into account the effect of RTI treatment. Instead, they have not incorporated the viral transmission through the cell-cell interaction and the factor of PI treatment. In the previous studies, Chirove *et al.* [6] and Sutimin *et al.* [7, 8] proposed and analyze mathematical models involving Langerhans to explore the implication of RTI and PI treatments. They modeled the concentrations of RTI and PI drugs as periodic function. Instead, this studies have not considered the reverse transcription mechanism of the viral infection in CD4$^+$ T cells.

We are motivated to develop a model by incorporating viral transmission through cell-cell transmissions [2], and viral degradation within CD4$^+$ T cells [4, 3]. We analyze the dynamic of the model. Simulation results are presented to explore the implication of antiretroviral therapy, and outcome of viral clearance with respect to the dynamic of CD4$^+$T cells and virions.

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MODEL FORMULATION

The population of CD4$^+$T cells is classified into two classes, latent infection class (T_1) and actively infected class (T_i). The healthy CD4$^+$T cells (T), and free virus population (V). The model equation is formulated as,

$$\begin{aligned}
\frac{dT}{dt} &= \Lambda - \beta_1 VT - \beta_2 TT_i - \mu T + (\epsilon_{RTI}\alpha + \omega)\, T_1, \\
\frac{dT_1}{dt} &= \beta_1 TV + \beta_2 TT_i - (\mu_1 + \alpha + \omega)\, T_1, \\
\frac{dT_i}{dt} &= (1 - \epsilon_{RTI})\, \alpha T_1 - (\mu + \delta)\, T_i \\
\frac{dV}{dt} &= N\delta\,(1 - \epsilon_{PI})\, T_i - \mu_v V - \phi VT
\end{aligned} \tag{1}$$

The recruitment rate of CD4$^+$T cells is Λ, die naturally with the rate μ. These cells are infected by free virus and the infectious cells at rates β_1 and β_2, respectively. The part of CD4$^+$ T cells in latent class return to healthy at rate $\epsilon_{RTI}\alpha + \omega$, while other part become infectious with rate $(1 - \epsilon_{RTI})\,\alpha$. The latent class die out by inflammation at a rate μ_1. The infected CD4$^+$ T cells die out due to viral lysis at rate δ. Upon PI treatment, the number of new viral replication from infected CD4$^+$T cells reduces becoming $N\delta\,(1 - \epsilon_{PI})$. The population of free virus die naturally and viral clearance in CD4$^+$T cells with rates μ_v and ϕ, respectively. The efficacies value of RTI and PI drugs are ϵ_{RTI}, ϵ_{PI}, respectively with $0 \le \epsilon_{RTI}, \epsilon_{PI} \le 1$.

MODEL ANALYSIS

Alternative reproduction ratio, $\Re_1$ that has equivalent properties with basic reproduction ratio $\Re_0$ near unity was constructed in [6, 7, 8, 9]. Using this ratio $\Re_1$, it is addressed the existence and stability of equilibriums for the system (1). The alternative reproduction ratio can be expressed by,

$$\Re_1^2 = \Re_{T_i \mapsto T_i} + \Re_{T_i \mapsto V \mapsto T_i}, \tag{2}$$

where $\Re_{T_i \mapsto T_i} = \frac{\Lambda\beta_2(1-\epsilon_{RTI})\alpha}{\mu(\mu_1+\alpha+\omega)(\mu+\delta)}$, $\Re_{T_i \mapsto V \mapsto T_i} = \frac{\Lambda\beta_1\alpha N\delta(1-\epsilon_{RTI})(1-\epsilon_{PI})}{\mu(\mu_1+\alpha+\omega)(\mu+\delta)(\phi+\mu_v)}$. Sub ratio $\Re_{T_i \mapsto T_i}$ is the infection generated by an infectious cell, then infects the healthy CD4$^+$ T cells causing infectious. Sub ratio $\Re_{T_i \mapsto V \mapsto T_i}$ represents the viral infection affected from infected CD4$^+$ T cell, then producing new viral particles that infects healthy CD4$^+$ T cells becoming infectious.

Stability of Uninfected Equilibrium

The local stability of uninfected equilibrium $E^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$ is given in the next theorem.

Theorem*:* The uninfected equilibrium point E^0 is locally asymptotically stable for $\Re_1 < 1$ and unstable for $\Re_1 > 1$.

Proof*:* The Jacobian matrix of the equation (1) at E^0 that is presented by $J\left(E^0\right)$ has eigenvalue $\lambda_1 = -\mu$, and others fulfill the cube equation,

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 = 0, \tag{3}$$

where, $A_2 = \mu + \alpha + \delta + \rho + \mu_1 + \mu_v + \frac{\Lambda\phi}{\mu}$, $A_0 = \frac{\left(1-\Re_1^2\right)(\Lambda\phi+\mu\mu_v)(\mu+\delta)(\mu_1+\alpha+\rho)}{\mu}$, and $A_1 = \left(1 - \Re_1^2\right)(\mu_1 + \alpha + \rho)\,(\mu + \delta) + \frac{\alpha\Lambda(1-\epsilon_{RTI})N\delta(1-\epsilon_{PI})\beta_1}{\Lambda\phi+\mu\mu_v} + \frac{(\Lambda\phi+\mu\mu_v)(\alpha+\delta+\rho+\mu_1+\mu)}{\mu}$. We see that $A_2, A_1 > 0$ if $\Re_1 < 1$. Consider that $A_2A_1 - A_0 = (\mu_1 + \alpha + \rho)\,(\mu + \delta)\,\Phi\left(1 - \Re_1^2\right) + \frac{\left(\Lambda^2\phi^2+2\Lambda\phi\mu\mu_v+\mu^2\mu_v{}^2\right)\Phi\Psi}{\mu^2(\Lambda\phi+\mu\mu_v)} + \frac{N\alpha\delta\Lambda\beta_1(1-\epsilon_{PI})(1-\epsilon_{RTI})\mu\Psi}{\mu^2(\Lambda\phi+\mu\mu_v)}$, where $\Psi = \alpha\mu + \delta\mu + \lambda\phi + \rho\mu + \mu_1\mu + \mu^2 + \mu\mu_v$, $\Phi = \alpha + \delta + \rho + \mu_1 + \mu$. Routh-Hurwitz criterion is satisfied, when $\Re_1 < 1$. Thus, E^0 is locally asymptotically stable, when $\Re_1 < 1$.

Stability of infected equilibrium

The infected equilibrium of the model is $E^* = \left(T^*, T_1^*, T_i^*, V^*\right)$, where

$$\begin{aligned} T^* &= \frac{N\alpha\delta\,\Lambda\,(1-\epsilon_{PI})(1-\epsilon_{RTI}) - \mu_v(\mu+\delta)(\alpha\,(1-\epsilon_{RTI})+\mu_1)V^*}{\phi\,(\mu+\delta)(\alpha\,(1-\epsilon_{RTI})+\mu_1)V + N\alpha\delta\,(1-\epsilon_{PI})(1-\epsilon_{RTI})\mu} \\ T_1^* &= \frac{V^*(\phi\Lambda+\mu\mu_v)(\mu+\delta)}{\phi\,(\mu+\delta)(\alpha\,(1-\epsilon_{RTI})+\mu_1)V + N\alpha\delta\,(1-\epsilon_{PI})(1-\epsilon_{RTI})\mu}, \\ T_i^* &= \frac{V^*\alpha\,(1-\epsilon_{RTI})(\phi\Lambda+\mu\mu_v)}{\phi\,(\mu+\delta)(\alpha\,(1-\epsilon_{RTI})+\mu_1)V^* + N\alpha\delta\,(1-\epsilon_{PI})(1-\epsilon_{RTI})\mu}, \end{aligned} \tag{4}$$

The positive value V^* is the root of polynomial

$$a_2V^2 + a_1V + a_0 = 0, \tag{5}$$

where

$$\begin{aligned} a_2 &= -\phi\beta_1\mu_v(\mu+\delta)^2(\alpha\,(1-\epsilon_{RTI})+\mu_1)^2 < 0, \\ a_1 &= (\alpha\,(1-\epsilon_{RTI})+\mu_1)(\delta+\mu)^2\phi\,(\Lambda\phi+\mu\mu_v)(\mu_1+\alpha+\rho)\left(\Re_I^2-1\right) \\ &\quad -\frac{1}{\mu}(\alpha\,(1-\epsilon_{RTI})+\mu_1)(\delta+\mu_t)\alpha\,(1-\epsilon_{RTI})(\Lambda\phi+\mu\mu_v)^2\beta_2 - \\ &\quad (\alpha\,(1-\epsilon_{RTI})+\mu_1)(\delta+\mu)\alpha\,(1-\epsilon_{RTI})N\delta\beta_1(1-\epsilon_{PI})\mu\mu_v, \\ a_0 &= \mu\,(\Lambda\phi+\mu\mu_v)(\delta+\mu)(\mu_1+\alpha+\rho)\left(\Re_I^2-1\right). \end{aligned}$$

The quadratic equation (5) has exactly one positive root V^* when $\frac{a_0}{a_2} < 0$. Since $a_2 < 0$, then it holds if $a_0 > 0$. Thus the existence and uniqueness for infected equilibrium E^* is $\Re_1 > 1$. It is enough easy to see that set $\Omega = \left\{(T,T_1,T_i,V) \in \mathbb{R}_+^4 | T,T_1,T_i,V \le M\right\}$, with $M = \max\left\{\frac{\Lambda}{\mu}, \frac{N\delta\Lambda(1-\epsilon_{PI})}{\mu\mu_v}\right\}$ is positively invariant with $T(0), T_1(0), T_i(0), V(0) > 0$. Next, we analyze the global stability of endemic equilibrium.

Theorem*:* The infected equilibrium, E^*, is globally asymptotically stable for $\Re_1 > 1$ and unstable for $\Re_1 < 1$.

Proof*:* It is definded a Lyapunov function as,

$L(T,T_1,T_i,V) = \left(S - S^* - S^* ln\frac{S}{S^*}\right) + a_1\left(T_1 - T_1^* - T_1^* ln\frac{T_1}{T_1^*}\right) + a_2\left(T_i - T_i^* - T_i^* ln\frac{T_i}{T_i^*}\right) + a_3\left(V - V^* - V^* ln\frac{V}{V*}\right)$,

where $a_1, a_2, a_3 > 0$. Differentiating L with respect to time t results in

$$\begin{aligned} \frac{dL}{dt} &= K + (a_3\phi V^* - \mu)T + (\beta_1a_1 - \beta_1)VT + (a_1\beta_2 - \beta_2)TT_i + (A_1 - a_1A_2 + a_2(1-\epsilon_{RTI})\alpha)T_1 \\ &\quad + (\beta_2T^* - a_2A_3 + a_3N\delta(1-\epsilon_{PI}))T_i + (\beta_1T^* - a_3\mu_v)V - \Lambda\frac{T^*}{T} - A_1T^*\frac{T_1}{T} - a_1\beta_1T_1^*\frac{VT}{T_1} - a_1\beta_2T_1^*\frac{TT_i}{T_1} \\ &\quad -a_2(1-\epsilon_{RTI})\alpha T_i^*\frac{T_1}{T_i} - a_2N\delta(1-\epsilon_{PI}V^*)\frac{T_i}{V} - a_3\phi VT. \end{aligned} \tag{6}$$

where $K = \Lambda + \mu T^* + a_1A_2T_1^* + a_2A_3T_i^* + a_3\mu_vV^*$, $A_1 = \epsilon_{RTI}\alpha + \omega$, $A_2 = \mu_1 + \alpha + \omega$ and $A_3 = \mu + \delta$. Let $x = \frac{T}{T^*}, y = \frac{T_1}{T_1^*}, z = \frac{T_i}{T_i^*}$ and $w = \frac{V}{V^*}$. The equation (6) becomes

$$\frac{dL}{dt} = b_1\left(2 - x - \frac{1}{x}\right) + b_2\left(3 - \frac{1}{x} - \frac{y}{z} - \frac{xz}{y}\right) + b_3\left(4 - \frac{1}{x} - \frac{y}{z} - \frac{z}{u} - \frac{xu}{y}\right) - a_3\phi V^*T^*xu, \tag{7}$$

The coefficients b_i are related to a_i, $i = 1,...,3$. Equating the coefficients in the same terms, it can be chosen $a_1 = 1$, $a_2 = \frac{\beta_1V^*T^*}{N\delta(1-\epsilon_{PI})T_i^*} = \frac{\mu+\alpha(1-\epsilon_{RTI})}{\alpha(1-\epsilon_{RTI})}$, and $a_3 = \frac{\beta_1T^*}{\mu_v} = \frac{(\mu+\delta)\beta_1VT - N\delta\beta_2(1-\epsilon_{PI})T}{N^2\delta^2(1-\epsilon_{PI})^2}$. It holds that $\left(2 - x - \frac{1}{x}\right) \le 0$, for $x > 0$, $\left(3 - \frac{1}{x} - \frac{y}{z} - \frac{xz}{y}\right) \le 0$, for $x,y,z > 0$ and $\left(4 - \frac{1}{x} - \frac{y}{z} - \frac{z}{u} - \frac{xu}{y}\right) \le 0$, for $x,y,z,u > 0$, we can get $\frac{dL}{dt} \le 0$. We see that $\frac{dL}{dt} = 0$ when $T = T^*, T_1 = T_1^*, T_i = T_i^*, Z = Z^*$ and $V = V^*$, so the maximal invariance set of $\left\{(T,T_1,T_i,Z,V) | \frac{dL}{dt} = 0\right\}$ is the point set $\{E^*\}$. Using the principle of LaSalle Invariance [10], E^* is globally asymptotically stable.

SIMULATION RESULTS

Simulation results are presented to examine the impact of RTI and PI treatments and viral degradation. We take initial values $T(0) = 850\ \frac{cells}{mm^3}$, $T_1(0) = 40\ \frac{cells}{mm^3}$, $T_i(0) = 41\ \frac{cells}{mm^3}$, and $V(0) = 3.76\ \frac{virions}{mm^3}$ [11]. We consider the certain value

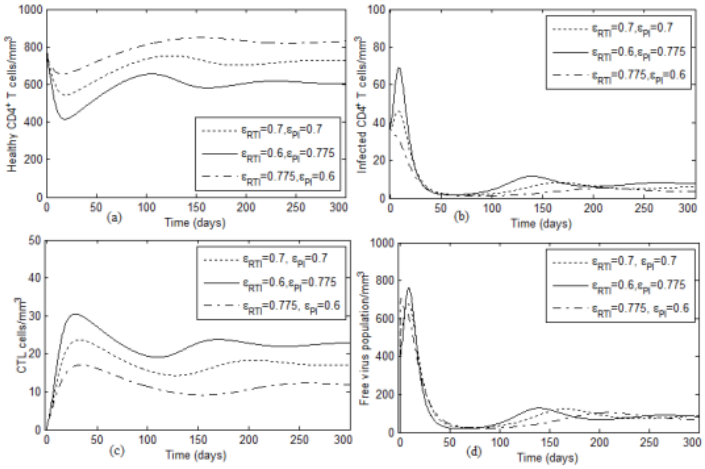

FIGURE 1. Dynamics of CD4$^+$T cells and virions in various scenarios of treatment with $\Lambda = 10, \beta_1 = 0.00095, \beta_2 = 0.00125, \alpha = 0.4, \omega = 0.05, \delta = 0.24, \mu = 0.01, \mu_1 = 0.015, \mu_v = 2.4, N = 1000, \phi = 3$

of the overall drug efficacy for RTI and PI drugs, when these drugs are administered simultaneously, then using this value to compare RTI and PI treatments in the different scenarios. The value of overall efficacy of RTI and PI in [12] is defined by $\epsilon = 1 - (1 - \epsilon_{RTI})(1 - \epsilon_{PI})$. We take $\epsilon = 0.91$ with different scenarios as follows. Scenario 1: when the efficacy values of RTI and PI drugs are $\epsilon_{RTI} = 0.7$, $\epsilon_{PI} = 0.7$, respectively. Scenario 2: when the efficacy values of RTI and PI drugs are taken $\epsilon_{RTI} = 0.6$, $\epsilon_{PI} = 0.775$, respectively. And scenario 3: when the efficacy values of RTI and PI drugs are considered $\epsilon_{RTI} = 0.755$, $\epsilon_{PI} = 0.6$, respectively. These simulations are given in Figure 1. Next, we simulate the effect of viral degradation by CD4$^+$ T cells that is given in Figure 2.

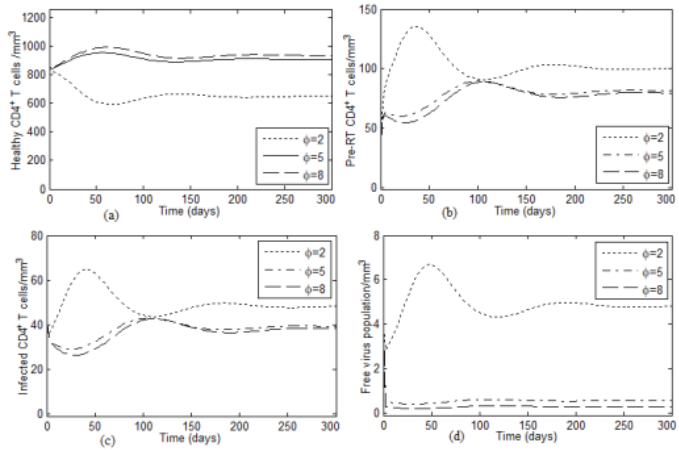

FIGURE 2. Dynamics of CD4$^+$T cells and virions for the variation level of the viral clearance, ϕ with $\Lambda = 20, \beta_1 = 0.0005, \beta_2 = 0.001, \alpha = 0.4, \omega = 0.05, \delta = 0.24, \mu = 0.01, \mu_1 = 0.015, \mu_v = 2.4, N = 900$

CONCLUSION

An mathematical model of HIV-1 infection of $CD4^+T$ cells was studied by introducing; cell-cell contact, viral clearance, and the effect of RTI and PI therapy. The basic reproduction ratio can be predicted by an alternative reproduction ratio that is formulated as the sum of two ratios explaining the cycle of infection paths. By using the alternative reproduction ratio, it is analyzed the local stability of uninfected equilibrium and the existence of the infected equilibrium. The global stability of the infected equilibrium is analyzed by establishing Lyapunov function. When the ratio exceeds unity, the virus is undetected in the body. Conversely, when the ratio larger than one, HIV disease still persist in the body for long term.

In the combination of RTI and PI treatments, it shows that RTI drug provide more significantly effect in reducing HIV-1 infection compared to PI drug. It concludes that RTI drug may be more effective in reducing the spread of infection compared to PI drug, in the absence of drugs resistance. The results show that beside using antiretroviral treatment, therapy or vaccine for reinforcing the immune system is needed to increase the level of viral degradation.

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