EFFECT OF IMMUNE RESPONSE DURING MULTIDRUG TREATMENT ON EMERGENCE OF HIV VIRAL STRAINS

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Abstract

This study describes HIV infection dynamics by considering a system of differential equations, which governs the interaction of uninfected CD4+ T-cells with free virus. The biological steps between the viral infection of CD4+ T-cells and production of HIV virions are incorporated into the system by considering the division of infected cells into two classes. A combined drug therapy is introduced into the system so as to reduce the viral load and thus increase the number of CD4+ T-cells. Emergence of the variants of drug resistant virus occurs due to the continuous viral replication in presence of drug therapy. This causes an incomplete viral suppression which enhances the risk of progression of disease towards AIDS. The system takes into account this fact by considering the two types of viral strains: wild-type and drug resistant strain. Further, the impact of immune response is considered on this twin-strain system under combined drug therapy. The stability of each of the three steady states emerging in this system are analysed. Conditions are obtained for the existence and stability of uninfected and infected steady states. Results from numerical simulations are exhibited to illustrate the evolution of both wild-type and mutant strains before and during therapy in the presence of immune response.
Keywords: CD4+ T-cells; HIV infection; drug resistant virus; mutation; efficacy; immune response

1 Introduction

Immune system of a body consists of T-cells, which are the key players in the defence of the body against pathogens. These cells provide immunity to extracellular pathogens by transmitting signals to antibodies. With CD4 receptors on their surfaces these T-cells (called, CD4+ T-cells) coordinate the immune system. HIV (human immunodeficiency virus) attacks those cells which are having CD4 receptors on their

surfaces. Therefore, the process of HIV infection starts with binding of its gp120 protein with these CD4+ T-cells. The HIV envelope and CD4+ T-cell membrane fuse together and allow the HIV virus to enter into CD4+ T-cell. Then, the virus transfuses the genetic material (viral RNA) into the host cell. After this transfusion, the viral RNA takes the help of reverse transcriptase enzyme to form DNA. With the help of integrase enzyme, HIV insert this viral DNA into DNA of CD4+ T-cell. Once integrated into the DNA of CD4+ T-cell, HIV begins to produce long chains of HIV proteins. Protease enzyme cuts these protein chains into smaller pieces and form the structure of a new HIV virus. Then, through budding process, newly formed copies of virus exit out of the host cell. These copies proceed further to infect a new cell and the process continues. Consequently, the human body detects the invasion of virus and reacts by stimulating CD4+ T-cells, which, in turn, stimulate the CTLs (i.e., CD8+ T-cells). These CTLs kill the infected CD4+ T-cells by proliferation and surrounding. One of the major problem with HIV is its potential for mutations, which increase the chances of escaping the attention of both antibodies and CD8+ T-cells. The virus infects faster than the replenishment of CTLs. Thus, this causes the depletion of CD4+ T-cells. Once the CD4+ T-cell count of an infected individual reaches below 200mm^{-3} cells, the stage is characterised as AIDS (acquired immune deficiency syndrome).

In the past, several mathematical models have been developed to describe the internal dynamics of HIV infection in an individual [1-7]. The models were designed by considering three compartments containing uninfected, infected CD4+ T-cells and virus population. In 1993, Perelson [1] developed a model by considering an additional class of infected CD4+ T-cells i.e., latently infected class, which proceeds to productively infected T-cells to produce the virus. Rong et al. [8] considered an age parameter in the model to identify the class of infected cells. Srivastava et al. [9] considered the division of infected cells into two classes: pre-RT class and post-RT class. Pre-RT class represents the cells that have been infected by the virus, but before the completion of reverse transcription. The post-RT class contains the infected cells that have finished the reverse transcription process and are capable of producing

new virus. Later studies [8-15] used these models to understand the mechanisms of HIV-1 infection and to devise drug therapy strategies to counter it.

Presently, there are four types of antiretroviral drugs used in the treatment of AIDS. These drugs are capable of interrupting the activities of the enzymes, which are essential to complete the different stages of the HIV replication cycle. For example, fusion inhibitors prevent the fusion of HIV envelope with host cell membrane. Integrase inhibitors block the activity of enzyme integrase that inserts the HIV DNA into the DNA of the host cell. Reverse transcriptase inhibitors (RTI) directly block the action of reverse transcriptase enzyme and mitigate the replication of HIV virus. Protease inhibitors block the activity of protease enzyme and thus preventing the immature HIV from becoming a mature virus. Thus, the new copies of HIV will not be able to infect the healthy cells. The simultaneous administration of two or more antiretrovial drugs are always preferred to control the extremely high replication rate of HIV.

The failure of drug therapy regimen occurs because of many host and viral factors, such as nonadherence to the treatment protocol, deleterious side effects, poor drug absorption. But, the presence or emergence of drug resistant viral strain is found to be a major factor. Many mathematical models have been proposed to study the dynamics of HIV with antiretroviral responses and the evolution of mutant strains [15-21]. An HIV infected patient can produce billions of viral particles everyday [7]. The process of reverse transcription by which RNA genome is reverse transcribed into proviral DNA is highly error prone. Thus, the chances of occurrence of mutations is quit high [22-23]. Due to mutations, single or combined, there is a reasonable chance of occurrence of drug resistant virus before the initiation of drug therapy [16]. They also suggested that under a wide range of conditions, treatment failure occurs due to the preexistence of drug resistant virus. Bonhoeffer et al. [17] analysed that if there is inherited drug resistant virus, then a very effective therapy would reduce the viral load at the initial stage. But, it would increase the resistant virus strains. Kirschner and webb [24] showed such an increase in drug resistant virus during monotherapy treatment of HIV infection. They made a comparison between the treatment outcomes, with drug therapy initiated at different T-cell levels. Mclean and Nowak [18]

determine that resistant virus would dominate the wild type virus during the course of multidrug therapy treatment. Riberio et al. [25] calculated the drug resistant virus before the initiation of therapy and suggested the preexistence of drug resistant virus in patients. Nowak et al. [13] compared the results of twin-strain model with clinical data available on drug resistance development in patients. Bonhoeffer and Nowak [26] suggested that it matters whether the drug resistant virus exists before the onset of therapy or produced by residual virus replication during therapy. Further, different drug regimens may be required in each case to get maximum clinical benefits.

It is noted that the reverse transcription is an important stage of the HIV replication life cycle and therefore the classification of infected cells is done in two subclasses: pre-RT and post-RT class. Using this classification, Srivastava et al [27] proposed a twin-strain model to study the effect of drugs (RTI and PI) on the evolution of drug resistant HIV mutants. In this present study, the pre-RT and post-RT classification is considered to modify the existing mathematical models of twin-strain virus. Further, it is noted that a healthy immune response of the host person creates an additional compartment in the model which can help in delaying the progression of HIV [28]. In the recent study, Kamboj and Sharma [29] discussed the importance of coupling between the immune response and multidrug therapy. Thus, in the present study, along with the full logistic term representing the proliferation of T-cells, the immune response of the body is incorporated into the model. Motive of this work is to analyse the effectiveness of drug therapy over the two strains of virus, i.e., drug sensitive as well as drug resistant virus. Further, the role of immune responses on drug resistant virus strain is explored. Ultimate expectation is any possibility of complete eradication of both types of strains in the presence of combined drug therapy with immune response. In this study, any variable representing cell population is considered as a continuous, differentiable variable and the exact value of population is approximated through the nearest integer value of the corresponding variable.

2 Model formulation

In the present model, a patient is considered under multidrug treatment with healthy cells $T(t)$ and infected cells $I(t)$, which are infected with free virus $V(t)$. The population of infected cells $I(t)$ is further divided into two categories: $T_1(t)$ for pre-RT class and $T_2(t)$ for post-RT class. The cells in pre-RT class (i.e., $T_1(t)$) will proceed to post-RT class to complete the HIV replication life cycle at a rate α. But, on the application of the RTI drug with efficacy $\eta \in (0, 1)$, all the cells in pre-RT class will not be able to complete reverse transcription process. Therefore, a fraction $(\eta\alpha T_1)$ of them will revert back to uninfected class and the remaining will proceed to post-RT class and turn into productively infected virus. The protease inhibitor (PI) drug with efficacy $\gamma \in (0, 1)$, prevents the post-RT cells to produce non-infectious virions with rate γN. Then, $(1 - \gamma)N$ measures the concentration of infectious virions, where N denotes the average number of viral particles produced by an infected cell. That means, the effect of PI restricts only to the infectious (V) virions, which constitutes a part of the newly produced virions. Since the replication rate of HIV virus is exponentially high therefore, the process of reverse transcription of viral RNA to proviral DNA is highly error prone. Consequently, the probability of occurrence of mutations is very high. For example, the average number of changes per genome is 0.3 per replication cycle, i.e., after reverse transcription about 22 percent of infected cells should carry proviral genomes with one mutation [30]. Hence, in presence of multidrug therapy, two strains of the virus, i.e., drug sensitive strain and drug resistant strain, are to be incorporated in the model. Now, the infected cells in pre-RT class are to be divided into two categories, i.e., $T_1 = T_1^s + T_1^r$; infected either by drug sensitive virus (T_1^s) or drug resistant virus (T_1^r). Similarly, T_2^s and T_2^r, the parts of T_2 cells, are infected by drug sensitive and drug resistant virus respectively. V_s and V_r be the population of infectious virus, which are drug sensitive and drug resistant respectively.

To incorporate the response of the immune system, the CTLs/ immune cell population (E) present in the body is to be included in the model. Since, after reverse

transcription, CTLs attack only productively infected (post-RT) cells. It means, the other infected cells, which either revert back to uninfected class or in which reverse transcription has not been completed (i.e., pre-RT cells) do not have the ability to express HIV and cannot invite CTLs for immunity support. Therefore, the intensity of the immune response should depend on the concentration of post-RT cells (T_2^s and T_2^r). The mathematical model representing the above dynamics is written as follows:

$$\frac{dT}{dt} = s - \mu T + rT(1 - \frac{T}{T_{max}}) - kV_sT - kV_rT + (b_s + \eta^s\alpha_s)T_1^s + (b_r + \eta^r\alpha_r)T_1^r \quad (2.1)$$

$$\frac{dT_1^s}{dt} = kV_sT - (\mu_1 + \alpha_s + b_s)T_1^s, \quad (2.2)$$

$$\frac{dT_2^s}{dt} = (1-\mu_m)(1-\eta^s)\alpha_sT_1^s - \delta_sT_2^s - d_xET_2^s, \quad (2.3)$$

$$\frac{dV_s}{dt} = N\delta_s(1-\gamma^s)T_2^s - \mu_vV_s, \quad (2.4)$$

$$\frac{dT_1^r}{dt} = kTV_r - (\mu_1 + \alpha_r + b_r)T_1^r, \quad (2.5)$$

$$\frac{dT_2^r}{dt} = \mu_m(1-\eta^s)\alpha_sT_1^s + \alpha_r(1-\eta^r)T_1^r - \delta_rT_2^r - d_xET_2^r, \quad (2.6)$$

$$\frac{dV_r}{dt} = N\delta_r(1-\gamma^r)T_2^r - \mu_vV_r, \quad (2.7)$$

$$\frac{dE}{dt} = p(T_2^s + T_2^r) - d_EE, \quad (2.8)$$

with $T(0) = T_{00}$, $E(0) = E_0$, $T_1^s(0) = T_{10}$, $T_2^s(0) = T_{20}$, $V_s(0) = V_{10}$, $T_1^r(0) = T_{11}$, $T_2^r(0) = T_{21}$, $V_r(0) = V_{20}$.

In equation (2.1), s represents the rate at which new T-cells are created from sources within the body, such as thymus. The natural decay of these cells with time is given by μT. The logistic expression $rT(1-\frac{T}{T_{max}})$ represents the T-cells created by the proliferation of existing T-cells, in the presence of infection. Detailed discussion on the role of logistic term is found in [4, 31-32]. The parameter k represents the interaction-infection rate of T-cells with the virus, assumed to be same for both strains and μ_1 is the death rate of infected cells in pre-RT class. In equation (2.2) and (2.5) b_s and b_r are the reverting rates of infected T-cells to uninfected class due to the non-completion of reverse transcription for respective strains. In equation (2.3) and (2.6) δ_s and δ_r denotes the death rate of actively infected cells in post-RT class for respective strains.

In equation (2.4) and (2.7) μ_v denotes the clearance rate of virus which is assumed to be same for both strains. N in equation (2.4) and (2.7) represents the average number of viral particles produced by an infected cell, assumed to be same for both strains.

The parameters η^s (γ^s) and η^r (γ^r) in $[0, 1)$ represent the efficacy of drug RTI (PI) corresponding to drug sensitive and drug resistant virus strains, respectively. The parameter μ_m in equation (2.3) and (2.6) represents the rate at which cells infected by drug sensitive virus mutate and become drug resistant virus during the process of reverse transcription. The parameter d_x denotes the rate of clearance of infected cells (T_2^s and T_2^r) by CTLs. Therefore, term $d_x E T_2^r$ and $d_x E T_2^s$ in equation (2.3) and (2.6) represents the loss of infected cells (T_2^s and T_2^r) by CTLs. For simplicity, it is assumed that the immune cell population (E) are produced at the same constant proliferation rate p and the death rate d_E whether they are produced as a result of the presence of either kind of productively infected cells (T_2^s and T_2^r).

3 Analysis

The variables of the mathematical model (2.1-2.8) considered in the previous section represents the populations and for the model to be biologically realistic, it does not allow the cell populations to grow unbounded or get a negative value for all time. For the positivity of the solutions of the model, a non-negative orthant, $R_+^8 = \{x \in R^8 | x \geq 0\}$, is defined to contain, forever, any trajectory that starts in it. For this model, we have

$\frac{dT}{dt}|_{T=0} = s + (b_s + \eta^s \alpha_s) T_1^s + (b_r + \eta^r \alpha_r) T_1^r \geq 0, \quad \frac{dT_1^s}{dt}|_{T_1^s=0} = k V_s T \geq 0,$

$\frac{dT_2^s}{dt}|_{T_{2s}=0} = (1-\mu_m)(1-\eta^s)\alpha_s T_1^s \geq 0, \quad \frac{dV_s}{dt}|_{V_s=0} = N(1-\gamma^s)\delta_s T_2^s \geq 0,$

$\frac{dT_1^r}{dt}|_{T_1^r=0} = k V_r T \geq 0, \quad \frac{dT_2^r}{dt}|_{T_2^r=0} = \mu_m(1-\eta^s)\alpha_s T_1^s + \alpha_r(1-\eta^r) T_1^r \geq 0,$

$\frac{dV_r}{dt}|_{V_r=0} = N(1-\gamma^r)\delta_r T_2^r \geq 0, \quad \frac{dE}{dt}|_{E=0} = p(T_2^s + T_2^r) \geq 0.$

This shows that the vector field $(T, T_1^s, T_2^s, V_s, T_1^r, T_2^r, V_r, E)$, on each bounding hyperplane of R_+^8, is pointing to the inward direction of R_+^8. That means, all the solution trajectories initiating in R_+^8, will remain inside R_+^8 for all t. Hence, the positivity of

the solutions initiating in the interior of R^8_+ is guaranteed. Further on adding the equations (2.1), (2.2), (2.3), (2.5) and (2.6), we have,

$$\frac{d}{dt}(T+T_1^s+T_2^s+T_1^r+T_2^r) = s-\mu T+rT(1-\frac{T}{T_{max}})-\mu_1 T_1^s-\mu_1 T_1^r-\delta_s T_2^s-\delta_r T_2^r-d_x E(T_2^s+T_2^r),$$
$$\leq s+rT(1-\tfrac{T}{T_{max}})-\mu(T+T_1^s+T_2^s+T_1^r+T_2^r),$$

(since $\delta_s > \delta_r > \mu_1 > \mu$).

Let us denote $C = \max\left\{s+rT(1-\frac{T}{T_{max}})\right\}$, for $T \in (0, T_0]$, where $T_0 = \frac{(r-\mu)+\sqrt{(r-\mu)^2+4r_1 s}}{2r_1}$ with $r_1 = \frac{r}{T_{max}}$, obtained in next section from equation 2.1 so that $\lim_{t\to\infty}\sup(T+T_1^s+T_2^s+T_1^r+T_2^r) \leq \frac{C}{\mu}$. Therefore, without any loss of generality, it can be assumed that $\lim_{t\to\infty}\sup T(t) \leq \frac{C}{\mu}$, $\lim_{t\to\infty}\sup T_1^s(t) \leq \frac{C}{\mu}$ $\lim_{t\to\infty}\sup T_2^s(t) \leq \frac{C}{\mu}$, $\lim_{t\to\infty}\sup T_1^r(t) \leq \frac{C}{\mu}$, $\lim_{t\to\infty}\sup T_2^r(t) \leq \frac{C}{\mu}$. Now, this bound for T_2^s and T_2^r enables to find the bounds for $V_s(t)$ and $V_r(t)$ and $E(t)$ from the equations (2.8) and (2.9), respectively. So, finally, we have a bounded set $S = \{(T, T_1^s, T_2^s, V_s, T_1^r, T_2^r, V_r, E) \in R^8_+;$

$0 \leq T, T_1^s, T_2^s, T_1^r, T_2^r \leq \frac{C}{\mu}, 0 \leq V_s \leq \frac{N(1-\gamma^s)\delta_s C}{\mu_v \mu}, 0 \leq V_r \leq \frac{N(1-\gamma^r)\delta_r C}{\mu_v \mu}, 0 \leq E \leq \frac{2Cp}{d_E \mu}\}$.

Then, any solution trajectory, which initiates from an interior point of R^8_+, enters S and remains there forever.

4 Steady states

The model system (2.1)-(2.8) has three steady states:

(a) The infection free steady state $E_0 = (T_0, 0, 0, 0, 0, 0, 0, 0))$, where, for a new parameter $r_1 = \frac{r}{T_{max}}$, the equation (2.1) is solved to get $T_0 = \frac{(r-\mu)+\sqrt{(r-\mu)^2+4r_1 s}}{2r_1}$.

(b) The infected steady state $E_r = (\overline{T}, 0, 0, 0, \overline{T_1^r}, \overline{T_2^r}, \overline{V_r}, \overline{E})$, with only drug resistant viral strain, where $\overline{T} = \frac{(r-\mu+\beta_2)+\sqrt{(r-\mu+\beta_2)^2+4(\beta_1+r_1)s}}{2(\beta_1+r_1)}$, $\overline{T_1^r} = \frac{k\overline{T}\overline{V_r}}{\mu_1+\alpha_r+\beta_r}$,$\overline{T_2^r} = \frac{\mu_v \overline{V_r}}{N\delta_r(1-\gamma^r)}$, $\overline{V_r} = k_1\overline{T} - k_2, \overline{E} = \frac{p\mu_v\overline{V_r}}{d_E N\delta_r(1-\gamma^r}$, $k_1 = \frac{N^2\alpha_r{\delta_r}^2 d_e k(1-\eta^r)(1-\gamma^r)^2}{d_x p\mu_v^2(\mu_1+\alpha_r+\beta_r)}$, $k_2 = \frac{Nd_E\delta_r^2(1-\gamma^r)}{d_x p\mu_v}$, $\beta_1 = \frac{(1-\eta^r)\alpha_r+\mu_1)kk_1}{\mu_1+\alpha_r+\beta_r}$, $\beta_2 = \frac{k_2\beta_2}{k_1}$.

(c) The infected steady state with both drug sensitive and drug resistant strains present, is given by $E_m = (\tilde{T}, \tilde{T_1^s}, \tilde{T_2^s}, \tilde{V_s}, \tilde{T_1^r}, \tilde{T_2^r}, \tilde{V_r}, \tilde{E})$, where

$$\tilde{V_s} = k_7\tilde{T} - k_8 - k_9\tilde{V_r}, \quad \tilde{V_r} = \frac{\alpha_1\tilde{T^2} - \beta_3 T}{\gamma_1 T + \delta_1},$$

$$\tilde{T_1^s} = \frac{k\tilde{T}\tilde{V_s}}{\mu_1+\alpha_s+b_s}, \quad \tilde{T_2^s} = \frac{\mu_v\tilde{V_s}}{N\delta_s(1-\gamma^s)},$$

$$\tilde{T_1^r} = \frac{k\tilde{T}\tilde{V_r}}{\mu_1+\alpha_r+b_r}, \quad \tilde{T_2^r} = \frac{\mu_v\tilde{V_r}}{N\delta_r(1-\gamma^r)}, \quad \tilde{E} = \frac{p(\tilde{T_2^s}+\tilde{T_2^r})}{d_E},$$

$$k_7 = \frac{kd_eN^2\delta_s^2(1-\gamma^s)^2(1-\eta^s)(1-\mu_m)\alpha_s}{d_xp\mu_v^2(\mu_1+\alpha_s+b_s)}, \quad k_8 = \frac{d_eN\delta_s^2(1-\gamma^s)}{d_xp\mu_v}, \quad k_9 = \frac{\delta_s(1-\gamma^s)}{\delta_r(1-\gamma^r}),$$

$$\alpha_1 = k_7k_{10}, \quad \beta_3 = k_8k_{10}, \quad \gamma_1 = k_9k_{10}+k_7k_{14}-k_{11}, \quad \delta_1 = k_{12}-k_{14}k_8.$$

$\tilde{T}$ is obtained as the root of the cubic equation, given by

$$\alpha_3\tilde{T^3}+\alpha_4\tilde{T^2}+\alpha_5\tilde{T}+\alpha_6 = 0,$$

where

$$\alpha_3 = ((kk_9-k)+\frac{b_r+\eta^r\alpha_r}{\mu_1+\alpha_r+b_r}-\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s})\alpha_1+(\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s}kk_7-kk_7-r_1)\gamma_1,$$

$$\alpha_4 = \gamma_1(-\mu+kk_8-\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s}kk_8+r)+\delta_1(-kk_7+\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s}kk_7-r_1)+$$
$$\beta_1(k-kk_9+\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s}kk_9-\frac{b_r+\eta^r\alpha_r}{\mu_1+\alpha_r+b_r}kT),$$

$$\alpha_5 = s\gamma_1+(kk_8-\mu-\frac{b_s+\eta^s\alpha_s}{\mu_1+\alpha_s+b_s}kk_8+r)\delta_1, \quad \alpha_6 = s\delta_1.$$

Further, it is noted that $V_r = T_1^r = T_2^r = 0$ if $\mu_m = 0$. Thus, the steady state E_m reduces to steady state with sensitive virus only, (say, E_s).

5 Stability of steady states

The asymptotic stability of a steady state is decided by the eigenvalues of jacobian matrix. In the present problem, the system (2.1)-(2.8) is linearized around a steady state and the corresponding jacobian matrix **J** is obtained as follows:

$$\mathbf{J} = \begin{pmatrix}
-M & b_s+\eta^s\alpha_s & 0 & -kT & b_r+\eta^r\alpha_r & 0 & -kT & 0 \\
kV_s & -(\mu_1+\alpha_s+b_s) & 0 & kT & 0 & 0 & 0 & 0 \\
0 & (1-\eta^s)(1-\mu_m)\alpha_s & -(\delta_s+d_xE) & 0 & 0 & 0 & 0 & -d_xT_2^s \\
0 & 0 & N(1-\gamma^s)\delta_s & -\mu_v & 0 & 0 & 0 & 0 \\
kV_r & 0 & 0 & 0 & -(\mu_1+\alpha_r+b_r) & 0 & kT & 0 \\
0 & \mu_m(1-\eta^s)\alpha_s & 0 & 0 & \alpha_r(1-\eta^r) & -(\delta_r+d_xE) & 0 & -d_xT_2^r \\
0 & 0 & 0 & 0 & 0 & N(1-\gamma^r)\delta_r & -\mu_v & 0 \\
0 & 0 & p & 0 & 0 & p & 0 & -d_E
\end{pmatrix}$$

where $M = \mu - r + 2r_1T + kV_r + kV_s$ is a positive value.

5.1 Stability of uninfected steady state E_0

At steady state E_0, the corresponding jacobian matrix (say, $\mathbf{J_0}$) is obtained by substituting $T = T_0$ and $T_1^s = T_2^s = V_s = T_1^r = T_2^r = V_r = E = 0$ in the jacobian matrix $\mathbf{J}$. The characteristic equation $|\mathbf{J_0} - \lambda \mathbf{I}| = 0$ corresponding to the jacobian matrix $\mathbf{J_0}$ is given by

$$(\lambda + M_0)(\lambda + d_E)P_0(\lambda)Q_0(\lambda) = 0; \quad M_0 = \mu - r + 2r_1T_0 > 0, \tag{5.1}$$

where $P_0(\lambda) = \lambda^3 + A_0\lambda^2 + B_0\lambda + C_0$ and $Q_0(\lambda) = \lambda^3 + A_1\lambda^2 + B_1\lambda + C_1$.
The coefficients of these polynomials are expressed as follows:

$A_0 = \mu_1 + \alpha_s + b_s + \delta_s + \mu_v, \quad B_0 = (\mu_1 + \alpha_s + b_s)(\delta_s + \mu_v) + \delta_s\mu_v,$

$C_0 = k\alpha_s\delta_s(1-\eta^s)(1-\gamma^s)(1-\mu_m)(N_{01} - N)T_0; \quad N_{01} = \frac{(\mu_1+\alpha_s+b_s)\mu_v}{kT_0\alpha_s(1-\eta^s)(1-\gamma^s)(1-\mu_m)},$

$A_1 = \mu_1 + \alpha_r + b_r + \delta_r + \mu_v, \quad B_1 = (\mu_1 + \alpha_r + b_r)(\delta_r + \mu_v) + \delta_r\mu_v,$

$C_1 = k\alpha_r\delta_r(1-\eta^r)(1-\gamma^r)(N_{02} - N); \quad N_{02} = \frac{(\mu_1+\alpha_r+b_r)\mu_v}{kT_0\alpha_r(1-\eta^r)(1-\gamma^r)}.$

The characteristic equation (5.1) provides $\lambda = -M_0$ and $-d_E$ as two eigenvalues of the jacobian matrix J_0. The remaining six eigenvalues are obtained from the roots of $P_0(\lambda) = 0$ and $Q_0(\lambda) = 0$. The stability of uninfected steady state E_0 is ensured through the negative real parts of all the eight eigenvalues of $\mathbf{J_0}$. Obviously, the eigenvalues $-M_0$ and $-d_E$ meet this requirement. But, for other six eigenvalues, the roots of $P_0(\lambda) = 0$ and $Q_0(\lambda) = 0$ are to be checked.

According to Routh-Hurwitz criterion [33], all the roots of $P_0(\lambda) = 0$ and $Q_0(\lambda) = 0$ will have negative real parts if and only if A_0, B_0, C_0, A_1, B_1, C_1 are all positive and $A_0B_0 > C_0$, $A_1B_1 > C_1$. It is noted that A_0, B_0, $A_0B_0 - C_0$, A_1, B_1, $A_1B_1 - C_1$ are all positive, and therefore, the onus of deciding the asymptotic stability of E_0 stays with the value of C_0 and C_1 only. The coefficients C_0 and C_1 are positive if $N_{01} > N$ and $N_{02} > N$ respectively. That means, the asymptotically stability of the uninfected state E_0 is ensured with $N < N_{01}$ or $N < N_{02}$. On the other hand, for $N > N_{01}$ or $N > N_{02}$, C_0 and C_1 become negative, which implies a sign change in the coefficients of the cubic equations $P_0(\lambda) = 0$ and $Q_0(\lambda) = 0$. Then, according to the Descartes'

rule of signs, one positive root of the equation implies a positive eigenvalue for $\mathbf{J_0}$. That means, the uninfected state E_0 cannot be stable for $N > N_{01}$ and $N > N_{02}$. Also for $N = N_{01}$ or $N = N_{02}$, the cubic equation $P_0(\lambda) = 0$ or $Q_0(\lambda) = 0$ yields a zero eigenvalue and the reduced quadratic equation will have roots with negative real parts. Thus, according to Routh-Hurwitz conditions, the state E_0 becomes neutrally stable, when $N = N_{01}$ or $N = N_{02}$, .

Proposition 1. The uninfected steady state E_0 is locally asymptotically stable if N_{01} and N_{02} are greater than N.

5.2 Stability of steady state (E_r) infected with only drug resistant viral strain

The jacobian matrix $\mathbf{J_r}$ evaluated at steady state E_r is obtained from the Jacobian matrix $\mathbf{J}$, by substituting $T = \overline{T}$, $T_1^s = T_2^s = V_s = 0$, $T_1^r = \overline{T}_1^r$, $T_2^r = \overline{T}_2^r$, $V_r = \overline{V}_r$ and $E = \overline{E}$. The corresponding characteristic equation $|\mathbf{J_r} - \lambda\mathbf{I}| = 0$ is expressed as

$$P_1(\lambda)Q_1(\lambda) = 0, \tag{5.2}$$

where $P_1(\lambda) = \lambda^5 + A_3\lambda^4 + B_3\lambda^3 + C_3\lambda^2 + D_3\lambda + E_3$ and $Q_1(\lambda) = \lambda^3 + A_4\lambda^2 + B_4\lambda + C_4$. The coefficients of these polynomials are expressed as follows:

$$A_3 = k_4 + k_5 + k_6 + M_1; \quad M_1 = \mu - r + 2r_1\overline{T}_r + k\overline{V_r} > 0,$$

$$B_3 = \mu_v d_E + (k_4 + k_5)k_6 + k_4k_5 + pd_x\overline{T}_2^r + (k_4 + k_5 + k_6)M_1 - (b_r + \eta^r\alpha_r)k\overline{V}_r,$$

$$C_3 = (k_4 + k_5)\mu_v d_E + k_4k_5k_6 + d_xp(\mu_v + k_4)\overline{T}_2^r - k\alpha_r\delta_r(1-\eta^r)(1-\gamma^r)N\overline{T} + (\mu_v d_E + (k_4 + k_5)k_6 + k_4k_5 + pd_x\overline{T}_2^r)M_1 - k(b_r + \eta^r\alpha_r)(k_5 + k_6)\overline{V}_r,$$

$$D_3 = \mu_v d_E k_4k_5 + d_xpk_4\mu_v\overline{T}_2^r - k\alpha_r\delta_r(1-\eta^r)(1-\gamma^r)(d_E + M_1N\overline{T} + (k_4 + k_5)\mu_v d_E M_1 + k_4k_5k_6M_2 + pd_x(\mu_v + k_4)M_1\overline{T}_2^r - k(b_r + \eta^r\alpha_r)(\mu_v d_E + k_5(\mu_v + d_E\overline{V}_r)) + \alpha_r\delta_r k^2(1-\eta^r)(1-\gamma^r)N\overline{T}\overline{V}_r - kp(b_r + \eta^r\alpha_r)d_x\overline{V}_r\overline{T}_2^r$$

$$E_3 = k_4k_5\mu_v d_E M_1 + k_4\mu_v d_x pM_1\overline{T}_2^r - k(1-\eta^r)(1-\gamma^r)\alpha_r\delta_r d_E N M_1\overline{T} - k(b_r + \eta^r\alpha_r)k_5\mu_v d_E\overline{V}_r - kp\mu_v(b_r + \eta^r\alpha_r)d_x\overline{V}_r\overline{T}_2^r + k^2\alpha_r\delta_r(1-\eta^r)(1-\gamma^r)d_EN\overline{T}\overline{V}_r,$$

$$A_4 = u_1 + \alpha_s + b_s + \mu_v + \delta_s + d_x\overline{E},$$

$$B_4 = \mu_v(\mu_1 + \alpha_s + b_s) + (\delta_s + d_x\overline{E})(\mu_1 + \alpha_s + b_s + \mu_v),$$

$C_4 = (\delta_s + d_x\overline{E})(\mu_1 + \alpha_s + b_s)\mu_v - kN(1-\mu_m)\alpha_s\delta_s(1-\eta^s)(1-\gamma^s)$,
where $k_4 = \mu_1 + \alpha_r + b_r$, $k_5 = \delta_r + d_x\overline{E}$, $k_6 = \mu_v + d_E$.
The eigenvalues of J_r will have negative real parts if the roots of $P_1(\lambda) = 0$ and $Q_1(\lambda) = 0$ have negative real parts. In this case, the infected steady state E_r, if exists, becomes asymptotically stable. According to Routh-Hurwitz criterion, the equation $P_1(\lambda) = 0$ will have roots with negative real parts if $A_3 > 0$, $B_3 > 0$, $C_3 > 0$, $D_3 > 0$, $E_3 > 0$, $A_3B_3C_3 > C_3^2 + A_3^2D_3$ and $(A_3D_3 - E_3)(A_3B_3C_3 - C_3^2 - A_3^2D_3) > E_3(A_3B_3 - C_3)^2 + A_3E_3^2$. In an analogous manner, $Q_1(\lambda) = 0$ will have roots with negative real parts if $A_4 > 0$, $B_4 > 0$, $C_4 > 0$ and $A_4B_4 - C_4 > 0$.

Proposition 2. The steady state E_r infected with only drug resistant viral strain, if exists, will be asymptotically stable if the following conditions are satisfied
i)$A_3 > 0$, $B_3 > 0$, $C_3 > 0$, $D_3 > 0$, $E_3 > 0$, $A_3B_3C_3 > C_3^2 + A_3^2D_3$ and $(A_3D_3 - E_3)(A_3B_3C_3 - C_3^2 - A_3^2D_3) > E_3(A_3B_3 - C_3)^2 + A_3E_3^2$
ii) $A_4 > 0$, $B_4 > 0$, $C_4 > 0$ and $A_4B_4 - C_4 > 0$.

5.3 Stability of steady state (E_m) infected with both viral strains

The jacobian matrix $\mathbf{J_m}$ for the infected steady state E_m is obtained by substituting $T = \tilde{T}$, $T_1^s = \tilde{T}_1^s$, $T_2^s = \tilde{T}_2^s$, $V_s = \tilde{V}_s$, $T_1^r = \tilde{T}_1^r$, $T_2^r = \tilde{T}_2^r$, $V_r = \tilde{V}_r$, $E = \tilde{E}$ in the jacobian matrix $\mathbf{J}$. It is noted that the corresponding characteristic equation

$$|\mathbf{J_m} - \lambda\mathbf{I}| = 0, \tag{5.3}$$

is an eighth degree equation. This matrix $\mathbf{J_m}$ could not be divided into blocks so as to get a smaller degree characteristic equations, as in the previous cases. Thus, it is difficult to find the nature of roots for this eighth degree equation analytically. Hence, the nature of roots of equation (5.3) is checked numerically, whenever required.

Proposition 3. The infected steady state E_m, if exists, will be asymptotically stable

if determinantal (5.3) will have all the roots with negative real parts.

6 Numerical example

The system (5.1)-(5.8) of nonlinear ordinary differential equations is solved numerically using MATLAB for the following values of various parameters [1,27,34].

$N = 1000,\ T_{max} = 1500\text{mm}^{-3},\ (s,\ k) = (10,\ 0.000024)\text{mm}^{-3}\text{day}^{-1}$;

$(b_s,\ b_r,\ \alpha_s,\ \alpha_r,\ \delta_s,\ \delta_r) = (0.1,\ ,0.06,\ 7,\ 2,\ 0.26,\ 0.16)\text{day}^{-1}$ and

$(r,\ \mu_1,\ \mu_v,\ p,\ d_x,\ d_E, \mu_m) = (0.3,\ 0.015,\ 2.4,\ 1.02,\ 0.01,\ 0.1,\ 0.03)\text{day}^{-1}$.

Initial conditions are chosen as

$T(0) = 300\text{mm}^{-3}$, $T_1^s(0) = T_2^s(0) = V_s(0) = T_1^r(0) = T_2^r(0) = V_r(0) = 10\text{mm}^{-3}$, and $E(0) = 1\text{mm}^{-3}$. Numerical example is solved for different combinations of efficacies $(\eta^s,\ \gamma^s,\ \eta^r,\ \gamma^r)$ in drug therapy. The drug efficacies for drug sensitive and drug resistant strains are related as $\eta^r = \epsilon\eta^s$, $\gamma^r = \epsilon\gamma^s$, where $\epsilon \in (0, 1)$ represents the resistance level of HIV mutants.

Case 1. Without drug therapy (i.e., $\eta^s = \gamma^s = \eta^r = \gamma^r = 0$)

For the values of various parameters mentioned above, all the roots of the equation (5.3) have negative real parts. This satisfies the conditions in proposition 3, and hence implies the existence of the steady state E_m, given by $(T, T_1^s, T_2^s, V_s, T_1^r, T_2^r, V_r,\ E) = (553.75, 2.01, 9.918, 1074.4, 0.42, 1.01, 66.89, 111.39)\text{mm}^{-3}$. Both the virus strains i.e., wild-type (V_s) and mutant (V_r) coexist but the mutant strain V_r is very low due to low mutation rate $\mu_m = 0.03$. Therefore, the wild type virus V_s dominates over the mutant virus, before the initiation of therapy. Thus, it may be noted that the mutant virus V_r was existing before the initiation of antiretroviral therapy on a chronically infected HIV patient. For $\mu_m = 0$, the steady state E_m reduces to another steady state E_s given by $(T, T_1^s, T_2^s, V_s, T_1^r, T_2^r, V_r,\ E) = (536.11, 2.14, 10.89, 1180.4, 0, 0, 0, 111.13)\text{mm}^{-3}$. The presence of mutant virus is observed, as the mutations starts from wild-type to the mutant strain (i.e., $\mu_m \neq 0$). The variations of T-cell population, wild type virus V_s, mutant virus V_r and the total viral load $V = V_s + V_r$ are shown in figure 1, for

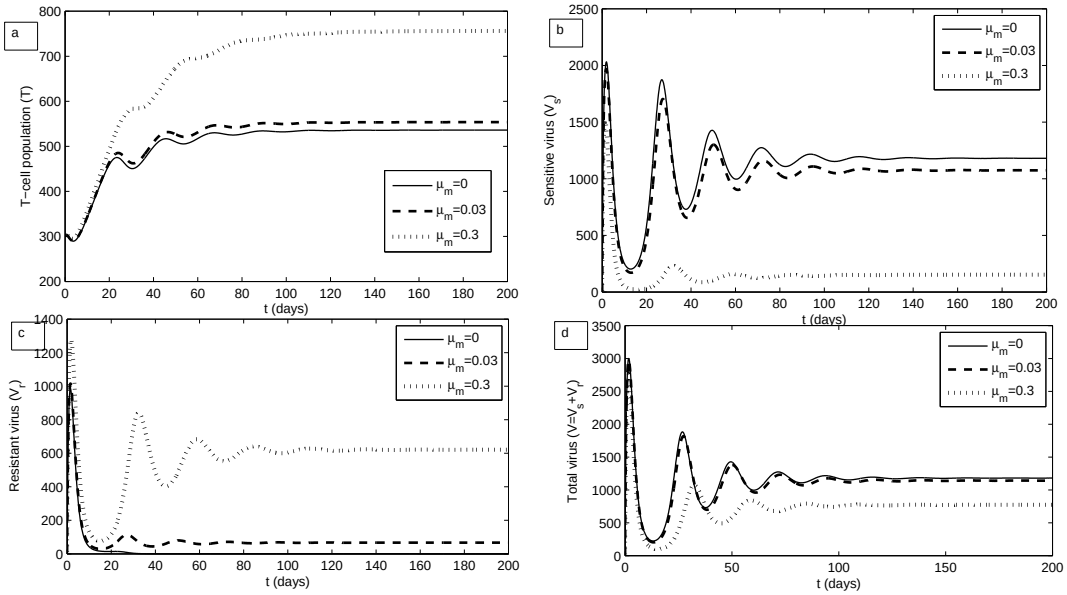

Figure 1: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time

different values of μ_m. In this figure, with increase in μ_m, the wild type virus V_s decreases and mutant virus V_r increases but the total virus V decreases. Consequently, the decrease in total virus V results in an increase of the T-cell population (T).

Case 2. RTI drug therapy only

It is calculated that the conditions given in proposition 2 are satistied for $\epsilon = .5$ and the efficacies (η^s, γ^s)=$(0.6, 0)$, $(0.7, 0)$, $(0.8, 0)$, $(0.9, 0)$. Therefore, the steady state E_r exists for the above values of efficacies. In each case, the resistant virus dominates the sensitive virus. The sensitive viral load (V_s) decreases and vanishes in about 50 days, as shown in figure 2b. The resistant viral load (V_r) also decreases with increase in efficacy η^s and, for $\eta^s = 0.9, \eta^r = 0.45$, it reaches the steady state of 500mm^{-3} in about 150 days, as shown in figure 2c. For $\mu = 0.03$, the V_r obtained in this case is higher than that obtained in absence of drug therapy. That means, drug therapy is increasing the drug resistant strains. The total viral load (V) decreases with the increase of η^s, as shown in figure 2d. Consequently, the T-cell population increases with the increase of η^s as shown in figure 2a. It is noted that the system could never attains the uninfected steady state E_0 for any $\eta^s \in (0, 1)$. Therefore, despite the

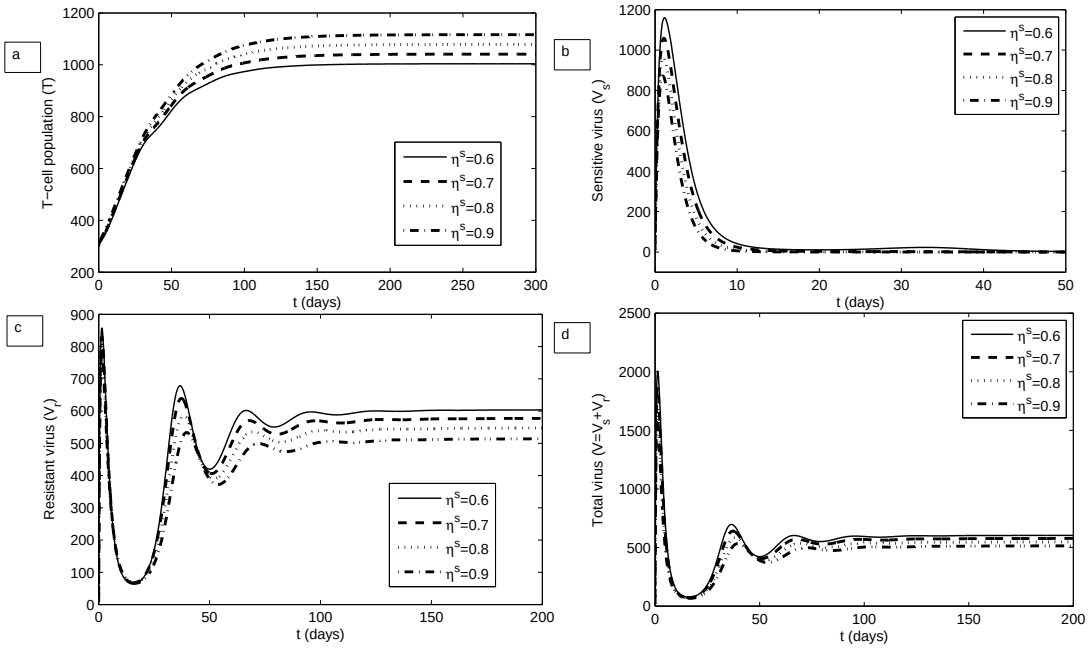

Figure 2: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time for $\gamma^s = 0$

vanishing of sensitive virus, there will never be complete eradication of total virus, because of the presence of drug resistant virus.

Case 3. PI drug therapy only

Analogous to the case 2, the conditions given in proposition 2 are satisfied for the pairs of efficacies, given by (η^s, γ^s)=$(0, 0.6), (0, 0.7), (0, 0.8), (0, 0.9)$. Therefore, the steady state E_r exists for the above pairs of efficacies. In this case, again the resistant virus dominates the sensitive virus. For $\mu = 0.03$, the resistant strains obtained in this case is higher than that obtained in absence of drug therapy, but less than that obtained with RTI. The sensitive strains decrease and vanish in about 15 days, as shown in figure 3b. The resistant virus also decreases with increase in efficacy γ^s and, for $\gamma^s = 0.9, \gamma^r = 0.45$, it reaches the steady state of 300mm^{-3} in about 150 days, as shown in figure 3c. The T-cell population increases but viral load decreases with the increase of efficacy γ^r, as shown in figures 3a and 3d, respectively. The total viral load obtained in this case is lower than that obtained for RTI in figure 2d.

It is noted from figures 2 and 3 that PI drug is more effective than RTI, as the resistant virus and the total virus obtained in this case is weak as compared to case

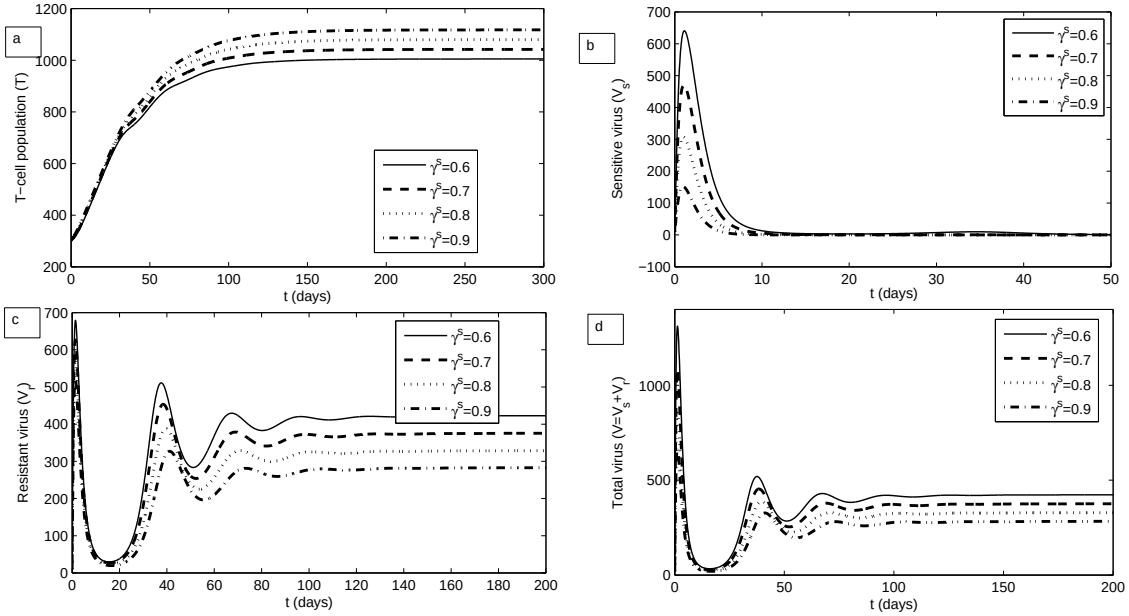

Figure 3: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time for $\eta^s = 0$

of RTI drug. Analogous to the case 2, there will never be complete eradication of resistant virus, in this case also. It is further noted that the drug PI works more

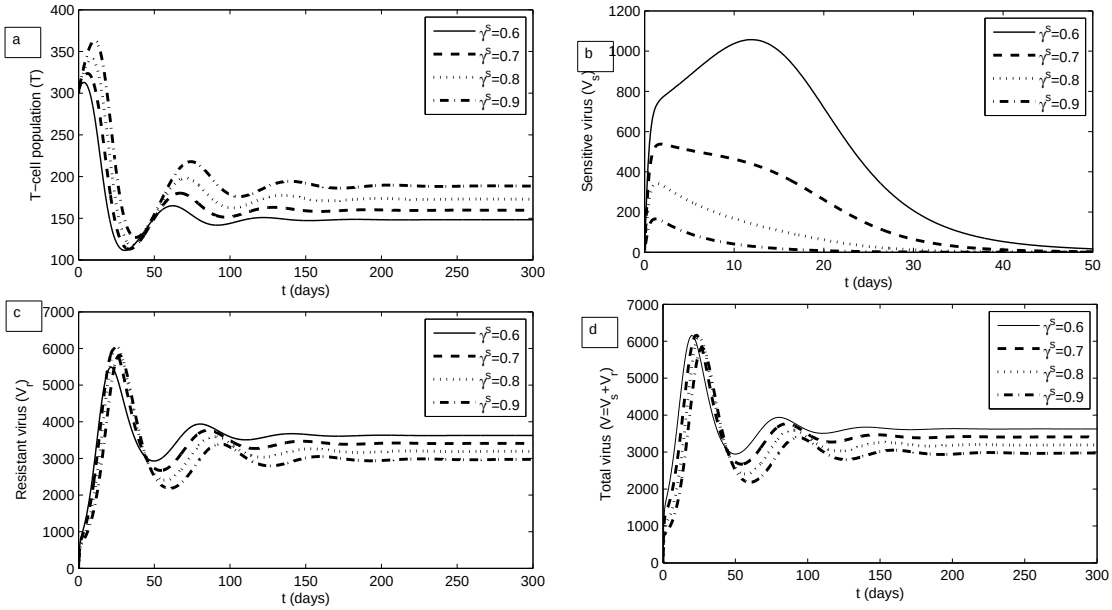

Figure 4: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time for $\eta^s = 0$ without immune system

efficiently, when immune cell contribution is taken into consideration. For $\gamma^s = 0.9$,

it is observed from figure 4 that, in the presence of immune response, the resistant virus attains its steady value 300mm^{-3} in about 150 days. Whereas, in absence of immune response, the corresponding steady value 3000mm^{-3} is obtained in 250 days. Also, in presence of immune response, the sensitive virus vanishes in about 10 days, which is 40 days earlier than the time taken in the absence.

Case 4. Combined (RTI+PI) drug therapy

For the pairs of efficacies (η^s, γ^s)=$(0.5, 0.6), (0.6, 0.7), (0.7, 0.8), (0.8, 0.9)$, and $\epsilon = .5$, the conditions given in proposition 2 are satisfied. Therefore, the steady state E_r exists. For each of these pairs of efficacies, the sensitive virus vanishes in about 10 days, as shown in figure 5b. It is noted from figure 5c that, for (η^s, γ^s)=$(0.8, 0.9)$,

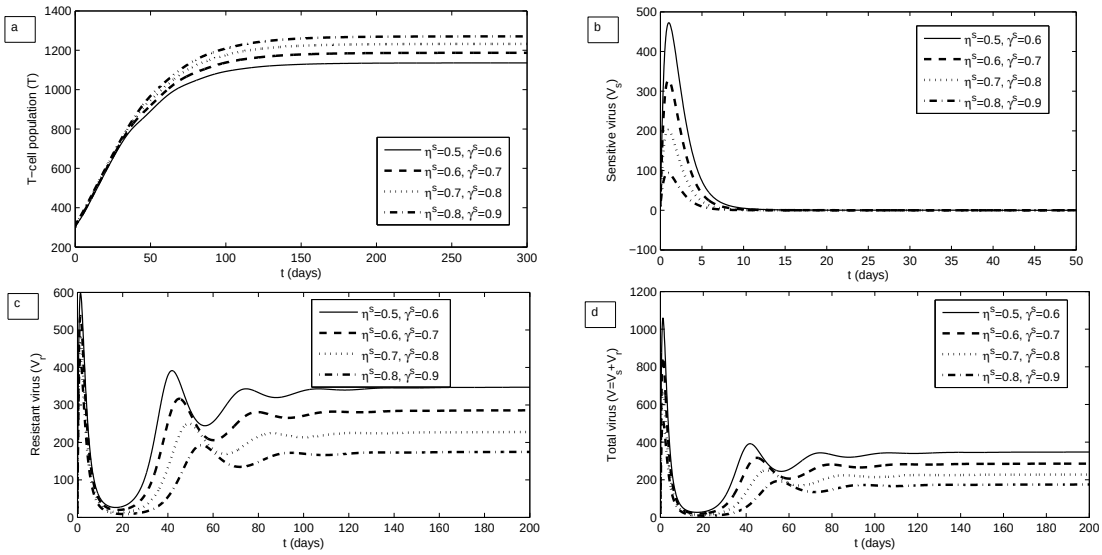

Figure 5: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time

the resistant virus dominates the sensitive virus and reached its steady state value 180mm^{-3} in about 150 days. The resistant virus decreases with increase in efficacy of drug. Consequently, the total virus V decreases and attains steady value 180mm^{-3} in 150 days, as shown in figures 5c and 5d, respectively. Therefore, the T-cell population increases with decrease in total virus as shown in figure 5a. This implies that the combined drug therapy may eradicate the sensitive virus but may not be able to eradicate the resistant virus. Therefore, due to the presence of resistant virus, the

combined drug therapy of a very high efficacy fails to eradicate the virus completely. The T-cell population obtained is higher and the total viral load obtained is very low in comparison to the cases of single drug therapy (PI and RTI). For combined drug

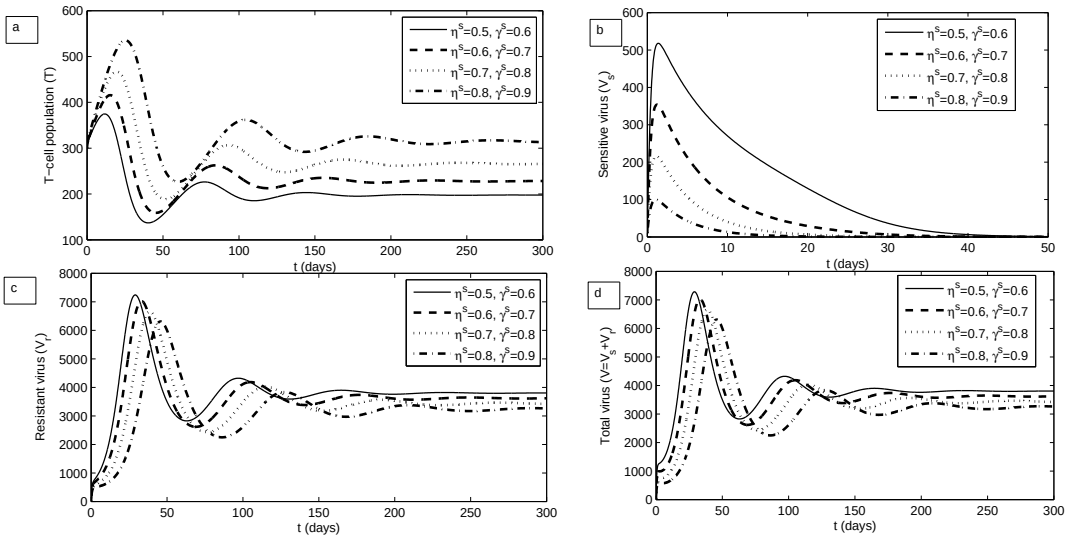

Figure 6: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time without immune system i.e., $d_x = p = d_E = 0$

therapy, in the absence of immune response of the individual, it is noted from figure 6 that the resistant virus again dominates the sensitive virus, which vanishes after 40 days. The resistant virus obtained in this case attains its steady value 3000mm^{-3} in about 300 days, for $(\eta^s, \gamma^s) = (0.8, 0.9)$, as shown in figure 6c. This value of resistant virus is higher than that obtained for active immune response. Therefore, it is observed from figures 6a and 6d that, the total viral load (V) obtained is high and T-cell population obtained is low for $(\eta^s = 0.8, \gamma^s = 0.9)$, as compared to the case of active immune response. This shows the importance of active immune response with combined drug therapy in eradicating the resistant strains.

The parameters involved in the model to describe the role of active immune system are proliferation rate of immune cells (p), interaction rate of immune cells with the infected cells (d_x) and the death rate of immune cell population (d_E). For the already chosen values of relevant parameters and $(\eta^s = 0.5, \gamma^s = 0.6)$, the variations of T-cell population, sensitive virus, resistant virus and total virus are shown in figure 7, for different values of p. From figure 7c, the decrease of resistant virus is observed, with

the increase in proliferation rate p, so as to attain its steady value 150mm^{-3} for p=2.5, in about 200 days. The sensitive virus vanishes in about 10 days as shown in figure 7b. Therefore, the total virus V decreases and consequently, the T-cell population increases with increase of p, as shown in figures 7d and 7a respectively.

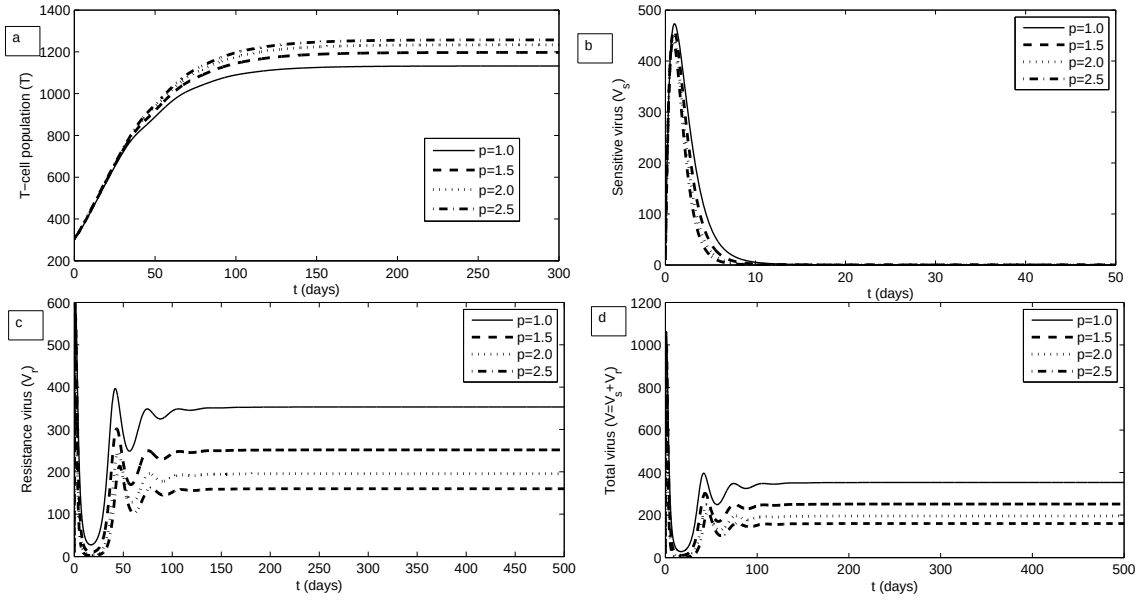

Figure 7: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time

The variations of T-cell population (T) and total virus (V) with infected cells are shown in figures 8a and 8d, respectively. The values of interaction rate of immune cells, i.e. d_x, are fixed at 0.005, 0.01, 0.05 and 0.1. It is noted that, the T-cell population (total virus) increases (decreases) with increase in d_x. The sensitive virus vanishes and resistant virus decreases with increase in d_x as shown in figures 8b and 8c, respectively. The variations of T-cell population, sensitive virus, resistant virus and the total virus is shown in figure 9, for different values of death rate of immune cell population (d_E). From figures 9c and 9d, with the increase in parameter d_E, the resistant virus V_r dominates the decreasing sensitive virus, which ultimately disappears in about 50 days. As a result, in figure 9d, the total virus V increases. Consequently, the T-cell population decreases with increase of d_E, as shown in figure 9a.

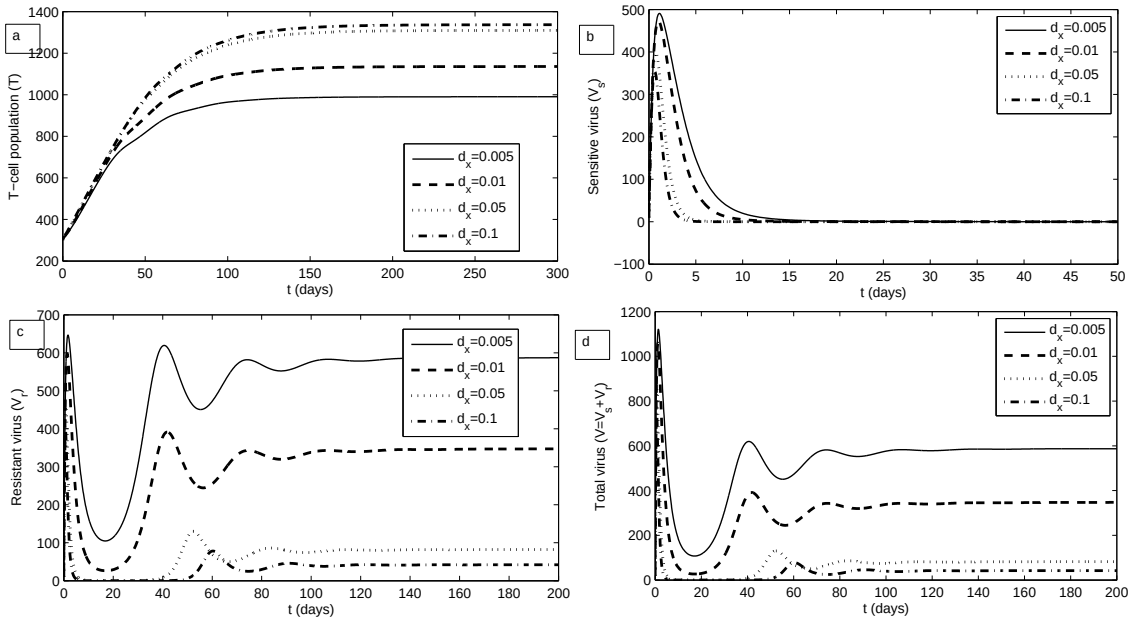

Figure 8: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time

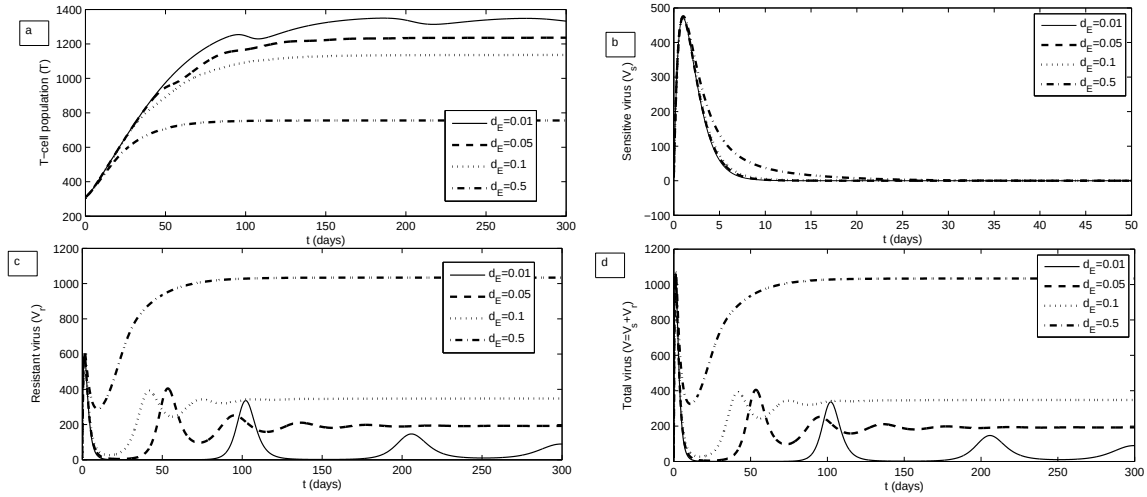

Figure 9: Variations of T-cell population (T), sensitive virus (V_s), resistant virus and total virus (V) with time

In the figure 10a, the population of resistant virus calculated for ($\eta^s = 0.5, \gamma^s = 0.6$) and $p = 2.5$ is 170mm^{-3}. Whereas, this population is found to be 180mm^{-3} when ($\eta^s = 0.8, \gamma^s = 0.9$) and $p = 1$. This shows that the with the support of a

strong immune system (i.e., higher proliferation rate), even a drug of lesser efficacy can reduce the resistant virus to a desired level, which otherwise needs the drug of very higher efficacy. The variation of resistant virus for $(\eta^s = 0.5, \gamma^s = 0.6, d_x = 0.1)$ and $(\eta^s = 0.8, \gamma^s = 0.9), d_x = 0.01$ are shown in figure 10b. It is noted that the resistant virus obtained in the former case is less as compared to the latter case. That means, the drug of lesser efficacy can work quite efficiently in the presence of a strong immune system, in comparison to weak immune system. The decrease in d_E implies a strong immune system, as shown in figure 10c. This is observed from the decrease in resistant virus population as $(\eta^s = 0.5, \gamma^s = 0.6, d_E = 0.05)$ are replaced with $(\eta^s = 0.8, \gamma^s = 0.9, d_E = 0.5)$.

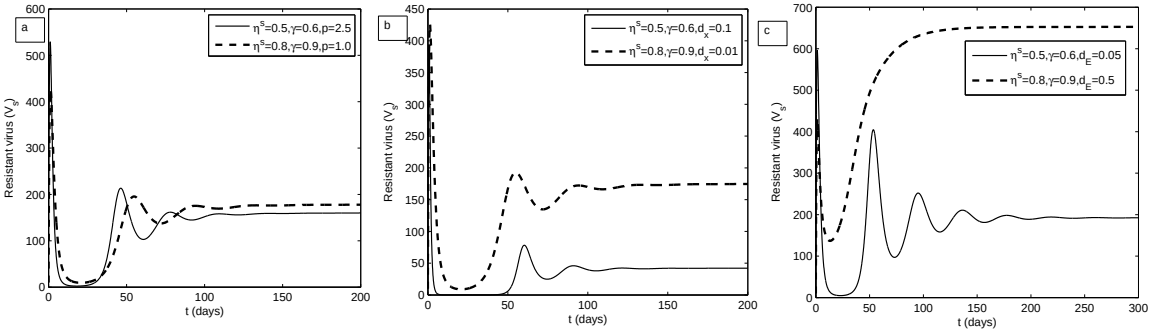

Figure 10: Variations of resistant virus (V_r) with time for parameters a) proliferation rate p b) interaction rate d_x c) death rate d_E

7 Conclusions

A mathematical model consisting of a system of nonlinear differential equations is considered to study the mechanism of emergence of resistant virus strain under a composite drug treatment along with an active immune response of human body. The present study analyses how a combined drug therapy in presence of immune response could become more effective drug therapy for both strains of the virus. It is shown that the drug resistant virus may exist before the initiation of therapy and increases in presence of therapy due to mutations. It is observed that the combined drug therapy of very high efficacy is able to reduce the viral load. It further in-

creases the T-cell population to a desired level, which should be essential to reduce the risk of disease progression. But, it does not eradicate the resistant virus completely. That means, the drug regimen fails to eradicate the virus completely, due to the presence/emergence of drug resistant virus. Further, it is noted that the drug resistant virus can be reduced by strengthening the immune response of the body, i.e., by increasing/decreasing the values of those parameters on which the effectiveness of immune system depends. For example, by increasing the proliferation rate and interaction rate of immune cells and decreasing the death rate of immune cells, the drug of lesser efficacy will be able to reduce the resistant virus upto a level that is maintained by drug of higher efficacy. This leads to an interpretation that the problems appeared due to the high dosages of drug therapy required to maintain the viral load to a low level may be resolved by alternative treatments that enhances a patient's natural immune response. It is possible that the drug of higher efficacy alone may not be able to eradicate the viral load completely because of presence of drug resistant virus. Whereas, the progression of disease towards AIDS may be prevented through low efficacy drugs but with the support of immune response. The considered model may be modified further with the introduction of time delay associated with immune response of the body. The concentration of any drug in the blood and in the cells varies continuously due to various factors. Whereas, in mathematical models, drug efficacies are generally assumed to be constant. Thus, to get a more realistic picture of HIV dynamics with resistant virus, the model used in the present study can be modified further to incorporate the time dependent efficacies of the drugs.

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