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MATHEMATICAL ANALYSIS OF A MODEL WITH HIV-1 MUTATION IN THE MIDST OF A CELLULAR IMMUNE RESPONSE

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Obias Chimbola Mulenga[1,2]

[1] *Department of Mathematics and Statistical Sciences, Botswana International University of Science and Technology, Palapye, Botswana*
[2]Department of Mathematics and Statistics, Mulungushi University, Kabwe, Zambia.
E - mail addresses: obiasmc@yahoo.co.uk

Abstract: Many people living with HIV-1/AIDS (PLWH) today can live longer due to potent highly active antiretroviral therapy (HAART). However, another concern has arisen as the HIV virus mutates into drug resistant variants. It is therefore imperative that research be directed to finding out the conditions under which the sensitive variant survives in the presence of mutations. In this study an in-host deterministic model is developed to find out the different states that can exist and the conditions in which the different equilibria can be globally asymptotically stable (GAS). The current model steady states have been established and we have proved their global stability via the construction of suitable Lyapunov functions and invocation of the LaSalle's invariance principle. It is further observed that if $\mathcal{R}_{rc} > 1$, then $x_1^{(3)} > x_1^{(1)}, x_3^{(3)} < x_3^{(1)}, x_5^{(3)} < x_5^{(1)}$ and $x_8^{(3)} < x_8^{(1)}$.

Keywords: Stability, HIV, Lyapunov function, Immunity

1. Introduction

Over the past decade, the world has recorded an impressive progress with regards to the unprecedented increase in the number of people accessing antiretroviral therapy (ART), which in a way has improved the lives of tens of millions of people living with HIV/AIDS (PLWH). As at December, 2019, approximately 25.4 million people out of the 38 million people living with HIV were receiving ART globally [10]. However, this heightened use of HIV medicines has been observed with the emergence of HIV drug resistance,the levels of which have steadily continued to increase [10]. HIV drug resistance is as a result of changes in the HIV genetic make up that affects the current HIV-1 drugs to block the replication of the virus.

All current antiretroviral drugs, with no exception of the newer ones, are at risk of becoming inactive because of the emergence of drug-resitance virus strains. If left unattended, HIV drug resistance has a potential of jeopardizing the efficacy of ARTs, which will ultimately lead to increased numbers of HIV infections and HIV associated morbidity and mortality. The magnitude of this problem is worse especially in Sub Saharan Africa where many patients are unable to remain committed to taking their drugs at the prescribed times. This may be to difficulties faced in accessing health facilities, excessive alcohol consumption etc. In other words, non adherence to the drug treatment protocols. A good number of mathematical modellers, working on in-host HIV-1 modeling, have endeavoured to address the problem of drug resistance as witnessed in many patients on HAART. For a good review the reader is directed to see [4, 11, 12, 15, 14, 13]. The model developed in [14] incorporates all the necessary populations to decipher the implication of drug resistance with regards to HIV infection. However, one important aspect was overlooked, the immunity reaction to the infection. When a pathogen is introduced into the body, firstly, an innate immune response is elicited. This

arm of immunity is non-specific and within a short time the pathogen is eliminated from the body. However, for HIV infection, this innate immunity is inadequate to clear the infection. So, a more robust form of immunity, the adaptive, is activated through the help of the innate immunity. This form of immunity is pathogen specific. As the host does not have so many of the cells specific to a particular pathogen, in this case, HIV-1, the few $CD8^+$ T cells that are available are made to undergo proliferation so that the right number of cytotoxic T cells is achieved to fight off the infection. It is therefore, necessary that the class of immune cells be included in a model that describes the viral infections. The model equilibria were obtained. However, the conditions under which these steady states are globally asymptotically stable are missing.

In this article, we develop a mathematical model that incorporates two strains of HIV-1 virus, the wild type (drug sensitive) and mutated or drug resistant strain. We assume that the susceptible $CD4^+$ T cells can be infected by both types of virus with infectivity rates β_r and β_s for mutated virus and wild type virus, respectively.

The current work mimics the model that was developed in [14]. Unlike the model developed in [14], we incorporate a class of activated $CD8^+$ T cells which lyse the infected cells. The production of these cells is dependent on the antigenic stimulation from both actively infected T cells.

Our main objective is to determine the different equilibria for the model, decipher the conditions of existence and the employ the Lyapunov function techniques, with the aid of the invariance principle, to prove the global stability of all the steady states. Our article is organised as follows: In section one, we formulate the model that incorporates eight populations- the uninfected $CD4^+$ T cells,x_1, latently infected $CD4^+$ T cells as a result of the wild-type HIV-1 virus infecting the target $CD4^+$ T cells,x_2, latently infected $CD4^+$ T cells as a result of the mutated HIV-1 virus infecting the target $CD4^+$ T cell,x_3, actively infected $CD4^+$ T cells, (x_4, x_5), due to activation of latently infected $CD4^+$ T cells, $CD8^+$ T cells, x_6, wild-type HIV-1 virions, x_7 and mutated HIV-1 vrions, x_8. In section two, we prove the positivity and boundedness of solutions. This is important to ensure that none of the model solutions goes negative or grows unboundedly as we are modeling the populations of cells and virions. We have also found the five model equilibria and the basic reproduction number. In section three, we prove the global stability of all the model equilibria by constructing suitable Lyapunov functions. Lastly, we conduct some numerical simulations.

1.1. Model description

$$\dot{x}_1 = \Pi_1 - \beta_s x_1 x_7 - \beta_r x_1 x_8 - \mu_1 x_1, \tag{1}$$

Eqn. (1) represents the dynamics of target CD4 T cells, x_1. The first term is the constant source from the bone marrow and the thymus. The second term is the infection of these cells by a wide type (drug sensitive) strain of HIV-1, at a constant rate, β_s, and the the third term is the infection of CD4 T cells by a mutated variant of HIV-1 at a constant rate, β_r. The fourth term is death of these cells at a constant rate, μ_1.

$$\dot{x}_2 = (1-\rho)\beta_s x_1 x_7 - \alpha_2 x_2 - \mu_2 x_2, \tag{2}$$

Eqn. (2) represents the dynamics of latently infected CD4 T cells infected by a sensitive strain of which a fraction, ρ, of the total infections mutate due to errors the reverse transcriptase commits as viral RNA gets transcribed into DNA. The first term represents the infections that remain faithful to the sensitive strain. The second term depicts the progression to productive infection of these cells at a constant rate, α_2. The last term is the natural death of these cells at a constant rate, μ_2.

$$\dot{x}_3 = \rho\beta_s x_1 x_7 + \beta_r x_1 x_8 - \alpha_3 x_3 - \mu_3 x_3, \tag{3}$$

Eqn. (3) represents the latently infected CD4 T cells that arise as a result of mutated virus infecting the susceptible cells at a constant rate, β_r, and the those infection arising from mutation. The third term is progression of there cells to productive infection at a constant rate, α_3, and the last term is the death of there cells at a constant rate, μ_3. In this paper, we shall assume that $\mu_2 = \mu_3$ and $\alpha_2 = \alpha_3$.

$$\dot{x}_4 = \alpha_2 x_2 - \gamma_6 x_4 x_6 - \mu_4 x_4, \tag{4}$$

Eqn. (4) represents a class of productively infected CD4 cells. The first term is gain from Eqn. (2). The second term depicts the lysing of these cells by the cytotoxic T lymphocytes. The last term is the death of these cells at a constant rate, μ_4.

$$\dot{x}_5 = \alpha_3 x_3 - \gamma_6 x_5 x_6 - \mu_5 x_5, \tag{5}$$

Eqn. (5) represents a class of productively infected CD4 cells. The first term is gain from Eqn. (3). The second term depicts the lysing of these cells by the cytotoxic T lymphocytes. The last term is the death of these cells at a constant rate, μ_5.

$$\dot{x}_6 = r_6(x_4 + x_5)x_6 - \mu_6 x_6, \tag{6}$$

Eqn. (5) represents the dynamics with of the cross- reactive immune response at any time t. The parameter r_6 is the proliferation rate of the cytotoxic T lymphocytes (CTLs) as a response to the antigenic stimulation and the last term depicts the death rate of these cells at a constant rate, μ_6.

$$\dot{x}_7 = N_7 \mu_4 x_4 - \mu_7 x_7, \tag{7}$$

Eqn. (7) represents the dynamics of a wild type virus, x_7. The first term depicts the production of these cells from the bursting productively infected CD4 T cells infected by a sensitive variant of HIV-1. The last term is the clearance of these viruses at a constant rate, μ_7.

$$\dot{x}_8 = N_8 \mu_5 x_5 - \mu_8 x_8. \tag{8}$$

Eqn. (7) represents the dynamics of a mutated type virus, x_8. The first term depicts the production of these cells from the bursting productively infected CD4 T cells infected by a mutated variant of HIV-1. The last term is the clearance of these viruses at a constant rate, μ_8.

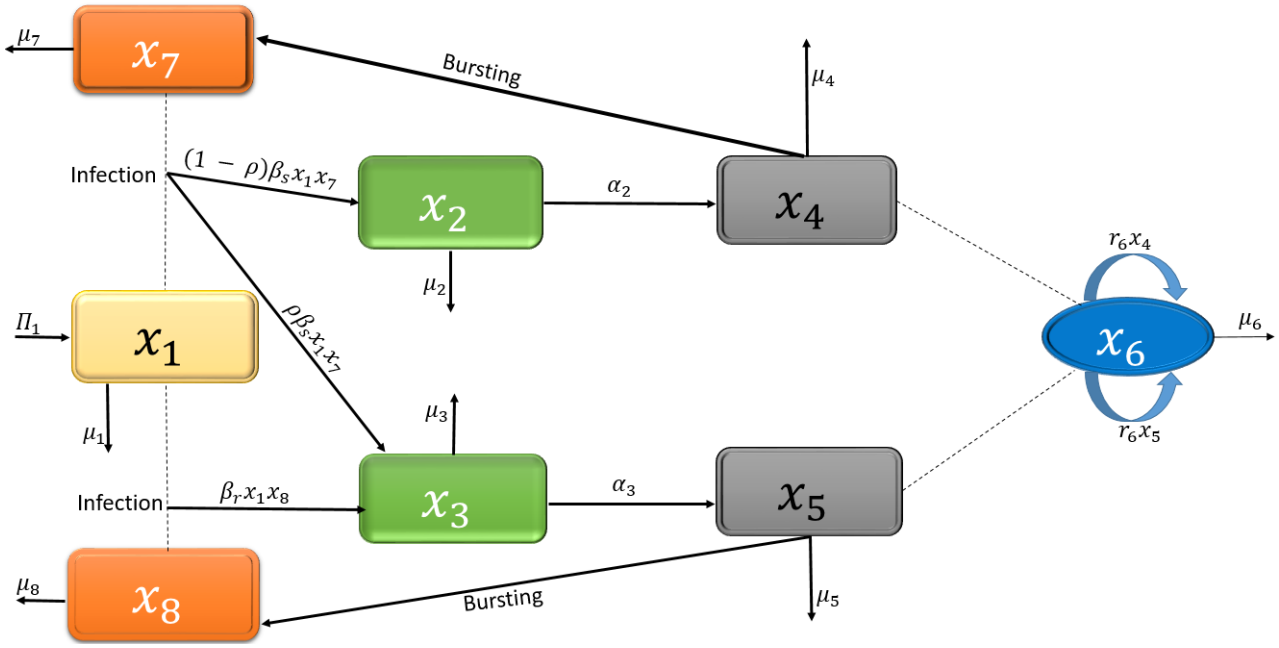


Figure 1: Schematic diagram for the model with mutation.

2. Model Analysis

2.1. Positivity and boundedness of Solutions

We assume that the initial values of the variables of the model (1) – (8) are nonnegative. Then, we show that the solutions, $x_i(t),\ t>0$, are also nonnegative.

Theorem 1. *Let*

$$\Omega = \Big\{\big(x_1(t), x_2(t), ..., x_8(t)\big) \in \mathbb{R}^8_+ : x_i(0) = x_{0_i} \geq 0,\ i = 1, 2, ..., 8\Big\}, \textit{ then the solutions } x_i(t) \textit{ are nonnegative and there exists } M > 0 \textit{ such that } |x_j| \leq M \textit{ for all } j = 1, 2, ..., 8 \textit{ and } t \geq 0. \tag{9}$$

Proof. We first consider the uninfected $CD4^+$ T cell equation

$$\begin{aligned} \dot{x}_1 &= \Pi_1 - \beta_s x_1 x_7 - \beta_s x_1 x_8 - \mu_1 x_1 \\ &\geq -\Big(\beta_s x_7 + \beta_r x_8 + \mu_1\Big) x_1, \end{aligned} \tag{10}$$

Note that for $i = 7, 8$,

$$\dot{x}_i \geq -\mu_i x_i \Rightarrow x_i(t) \geq x_i(0) exp\Big(-\mu_i t\Big) \geq 0. \tag{11}$$

We therefore obtain from Eqn. (10), after integration from 0 to t,

$$x_1(t) \geq x_1(0) exp\Big(-\big(\mu_1 + \beta_s x_7(\eta) + \beta_r x_8(\eta)\big)t\Big) \geq 0. \tag{12}$$

Analogously, we can show that $x_i(t), i = 2, 3, ..., 6$ are nonnegative.

To establish boundedness, it suffices to show that there exists $M > 0$ such that for all $t \geq 0$ and $j = 1, 2, ..., 8, x_j(t) \leq M$.

Variable	Initial Value	Reference
$x_1(0)$	10^6 cell ml^{-1}	[3]
$x_2(0)$	0 cell ml^{-1}	
$x_3(0)$	0 cell ml^{-1}	
$x_4(0)$	0 cell ml^{-1}	
$x_5(0)$	0 cell ml^{-1}	
$x_6(0)$	5×10^5 cell ml^{-1}	[1]
$x_7(0)$	10^{-6} cell ml^{-1}	[2]
$x_8(0)$	0 cell ml^{-1}	
Parameter	**Value**	**Reference**
α_2	0.01	[9]
α_3	0.01	[9]
β_s	2.4×10^{-8} ml virion^{-1} day^{-1}	[1]
β_r	2.0×10^{-8} ml virion^{-1} day^{-1}	[4]
Π_1	10^4 cell ml^{-1} day^{-1}	[1]
μ_1	0.01 day^{-1}	[1]
μ_2, μ_3	4×10^{-3} day^{-1}	[9]
μ_4	$[0.1, 0.9]$ day^{-1}	[4]
μ_5	$[0.1, 0.9]$ day^{-1}	[4]
μ_6	0.03[0.01,1] day^{-1}	[1, 6, 8]
μ_7, μ_8	23 day^{-1}	[9]
N_7	3000 virions cell^{-1}	[9]
N_8	2000 virions cell^{-1}	[9]
ρ	3×10^{-5} ml cell^{-1} day^{-1}	[9]
γ_6	2×10^{-7} ml cell^{-1} day^{-1}	[1]
r_6	$0.0003[0, 0.001]$ ml cell^{-1} day^{-1}	[7, 8]

Table 1: Parameters values of the model.

To this end, we define a function

$$y_T(t) = \sum_{i=1}^{5} x_i + \frac{\gamma_6}{r_6} x_6, \tag{13}$$

Then,

$$\begin{cases} \dot{y}_T(t) \leq \Pi_1 - \hat{\mu} y_T(t), \text{ where } \hat{\mu} = \min_{i=1,2,\ldots,6} \mu_i \;\Rightarrow\; y_T(t) \leq max\{y_T(0), \frac{\Pi_1}{\hat{\mu}}\} = M_1 \text{ for all } t \geq 0, \\ x_6(t) \leq \frac{r_6}{\gamma_6} M_1 = M_2, \\ x_i(t) \leq \max_{i=7,8}\{x_i(0), \frac{N_i \mu_{i-3} M_1}{\mu_i}\} = M_{i-4}, \; i = 7, 8. \end{cases} \tag{14}$$

Choosing $M = max_{k=1,2,3,4}\{M_k\} \;\Rightarrow\; x_j(t) \leq M$ for all $t \geq 0$. □

2.2. Basic Reproduction number, $\mathcal{R}_0$, and the Equilibria.

The system of equations (1)−(8) is equipped with four equilibria. We begin by stating the infection free equilibrium, denoted by E_0, which represents a state of no pathogen present. That is the heathy state of the host.

In this section, we employ the next generation matrix technique in determining the parameter that

Variable	Definitions
x_1	Density of uninfected CD4$^+$ T cells
x_2	Density of CD4$^+$ T cells latently infected by wild-type virus
x_3	Density of CD4$^+$ T cells latently infected by mutated virus
x_4	Density of CD4$^+$ T cells actively infected by wild-type virus
x_5	Density of CD4$^+$ T cells actively infected by mutated virus
x_6	Density of HIV-1 specific activated CD8$^+$ T cells
x_7	Concentration of wild-type HIV-1
x_8	Concentration of mutated HIV-1
Parameter	**Definitions**
α_2	Activation rate for latently infected wild-type T cells
α_3	Activation rate for latently infected mutated T cells
β_s	Infection rate of T cells by wild-type HIV-1
β_r	Infection rate of T cells by mutated HIV-1
Π_1	Source of immunocompetent CD4$^+$ T cells from the thymus
μ_1	Death rate of CD4$^+$ T cells
μ_2, μ_3	Death rate of latently infected T cells
μ_4	Death rate of actively infected T cells with wild-type virus
μ_5	Death rate of actively infected T cells with wild-type virus
μ_6	Death rate of HIV-1 specific activated CD8$^+$ T cells
μ_7, μ_8	Clearance rate of free virus
N_7	Burst size of wild-type virus
N_8	Burst size of wild-type virus
ρ	Mutation rate from wild-type to mutated variant
γ_6	Killing rate of infected cells by CTL
r_6	Generation rate of CTL

Table 2: State variables and parameters of the model with definitions.

governs the spread of the infection with a host. Here, we have

$$E_0 = \Big(\frac{\Pi_1}{\mu_1}, 0, 0, 0, 0, 0, 0, 0\Big), \tag{15}$$

Let F represent the matrix of appearance of new infection and V, the matrix of transfer of infections from one compartment to another. These matrix are each evaluated at E_0 and thus, we have

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{(1-\rho)\beta_s\Pi_1}{\mu_1} & 0 \\ 0 & 0 & 0 & 0 & \frac{\rho\beta_s\Pi_1}{\mu_1} & \frac{\beta_r\Pi_1}{\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \qquad V^{-1} = \begin{pmatrix} \frac{1}{\varphi_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\varphi_2} & 0 & 0 & 0 & 0 \\ \frac{\alpha_2}{\mu_4\varphi_1} & 0 & \frac{1}{\mu_4} & 0 & 0 & 0 \\ 0 & \frac{\alpha_3}{\mu_5\varphi_2} & 0 & \frac{1}{\mu_5} & 0 & 0 \\ \frac{N_7\alpha_2}{\mu_7\varphi_1} & 0 & \frac{N_7}{\mu_7} & 0 & \frac{1}{\mu_7} & 0 \\ 0 & \frac{N_8\alpha_3}{\mu_8\varphi_2} & 0 & \frac{N_8}{\mu_8} & 0 & \frac{1}{\mu_8} \end{pmatrix} \tag{16}$$

$$\varphi_l = \mu_{l+1} + \alpha_{l+1}, \quad l = 1, 2. \tag{17}$$

$$FV^{-1} = \begin{pmatrix} \frac{N_7\Pi_1\alpha_2\beta_s(1-\rho)}{\mu_1\mu_7\varphi_1} & 0 & \frac{N_7\Pi_1\Pi_1\beta_s(1-\rho)}{\mu_1\mu_7} & 0 & \frac{\Pi_1\beta_s(1-\rho)}{\mu_1\mu_7} & 0 \\ \frac{N_7\Pi_1\alpha_2\beta_s\rho}{\mu_1\mu_7\varphi_1} & \frac{N_8\Pi_1\alpha_3\beta_r}{\mu_1\mu_8\varphi_2} & \frac{N_7\Pi_1\beta_s\rho}{\mu_1\mu_7} & \frac{N_8\Pi_1\beta_r}{\mu_1\mu_8} & \frac{\Pi_1\beta_s\rho}{\mu_1\mu_7} & \frac{\Pi_1\beta_r}{\mu_1\mu_8} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{18}$$

From Eqn. (18), we see that the basic reproduction number, $\mathcal{R}_0$, is given by

$$\mathcal{R}_0 = \max\{\mathcal{R}_s, \mathcal{R}_r\},. \tag{19}$$

where

$$\mathcal{R}_s = \frac{N_7\Pi_1\alpha_2\beta_s(1-\rho)}{\mu_1\mu_7\varphi_1}, \qquad \mathcal{R}_r = \frac{N_8\Pi_1\alpha_3\beta_r}{\mu_1\mu_8\varphi_2},. \tag{20}$$

To determine all the equilibria of the model, (1) – (8), we set each right side of the equations, (1) – (8), to zero and solve the resulting nonlinear system simultaneously from which we get:

2.2.1. The infection equilibrium point with only the drug resistant strain and no CTL immune response present, E_1

The steady state, E_1, describes a state where only the drug resistant strain of HIV-1 is present and a dysfunctional cellular immune response.
Let $x_i^{(1)}$ denote the i^{th} coordinate of E_1 for $i = 1, 2, ..., 8$ where

$$\begin{cases} x_1^{(1)} = \frac{\Pi_1}{\mu_1\mathcal{R}_r}, \quad x_2^{(1)} = 0, \quad x_3^{(1)} = \frac{\Pi_1}{\varphi_2}\left(1 - \frac{1}{\mathcal{R}_1}\right), \\ x_4^{(1)} = 0, \quad x_5^{(1)} = \frac{\alpha_3\Pi_1}{\mu_5\varphi_2}\left(1 - \frac{1}{\mathcal{R}_r}\right), \quad x_6^{(1)} = 0, \quad x_7^{(1)} = 0, \quad x_8^{(1)} = \frac{\mu_1}{\beta_r}\left(\mathcal{R}_r - 1\right). \end{cases} \tag{21}$$

2.2.2. The Infection equilibrium point with both strains of virus but no CTL immune response, E_2

The steady state, E_2, describes a state where both strains of HIV-1 virus exist but no cellular-mediated immune response.
Let $x_i^{(2)}$ denote the i^{th} coordinate of E_2 for $i = 1, 2, ..., 8$ where

$$\begin{cases} x_1^{(2)} = \frac{\Pi_1}{\mu_1+\beta_s x_7^{(2)}+\beta_r x_8^{(2)}}, \quad x_2^{(2)} = \frac{(1-\rho)\beta_s\Pi_1 x_7^{(2)}}{\varphi_1\left(\mu_1+\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}, \quad x_3^{(2)} = \frac{\Pi_1\left(\rho\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}{\varphi_2\left(\mu_1+\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}, \\ x_4^{(2)} = \frac{\alpha_2\Pi_1(1-\rho)\beta_s x_7^{(2)}}{\varphi_1\mu_4\left(\mu_1+\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}, \quad x_5^{(2)} = \frac{\alpha_3\Pi_1\left(\rho\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}{\varphi_2\mu_5\left(\mu_1+\beta_s x_7^{(2)}+\beta_r x_8^{(2)}\right)}, \quad x_6^{(2)} = 0, \\ x_7^{(2)} = \frac{\mu_1}{\beta_s}\left(\mathcal{R}_s - 1\right)\left(1 - \frac{\mathcal{R}_r}{\mathcal{R}_s}\right), \quad x_8^{(2)} = \frac{\mu_1}{\beta_r}\mathcal{R}_r\left(1 - \frac{1}{\mathcal{R}_s}\right). \end{cases} \tag{22}$$

2.2.3. The infection equilibrium point with only drug resistant strain and CTL immune response present, E_3

The steady state, E_3, describes a state where only the mutated variant of HIV-1 virus exist and the CTL immune response is available.
Let $x_i^{(3)}$ denote the i^{th} coordinate of E_3 for $i = 1, 2, ..., 8$ where

$$\begin{cases} x_1^{(3)} = \frac{\Pi_1}{\mu_1+\beta_r x_8^{(3)}}, \quad x_2^{(3)} = 0, \quad x_3^{(3)} = \frac{\Pi_1\beta_r x_8^{(3)}}{\varphi_2\left(\mu_1+\beta_r x_8^{(3)}\right)}, \quad x_4^{(3)} = 0, \\ x_5^{(3)} = \frac{\alpha_3\Pi_1\beta_r x_8^{(3)}}{\varphi_2\left(\mu_5+\gamma_6 x_6^{(3)}\right)\left(\mu_1+\beta_r x_8^{(3)}\right)}, \quad x_6^{(3)} = \frac{\mu_5}{\gamma_6}\left(\mathcal{R}_{rc} - 1\right), \\ x_7^{(3)} = 0, \quad x_8^{(3)} = \frac{N_8\mu_5\mu_6}{r_6\mu_8}, \quad \mathcal{R}_{rc} = \frac{\mathcal{R}_r}{1+\frac{\beta_r}{\mu_1}x_8^{(3)}} < \mathcal{R}_r. \end{cases} \tag{23}$$

The quantity $\frac{\mathcal{R}_r}{1+\frac{\beta_r}{\mu_1}x_8^{(3)}}$ measures the level at which the CTL immune response is activated.

2.2.4. The positive equilibrium, E_4

The steady state, E_4, describes a state where all the coordinates of E_4 are strictly positive. Let $x_i^{(4)}$ denote the i^{th} coordinate of E_4 for $i = 1, 2, ..., 8$ where

$$\begin{cases} x_1^{(4)} = \frac{\Pi_1}{\mu_1+\beta_s x_7^{(4)}+\beta_r x_8^{(4)}}, \quad x_2^{(4)} = \frac{\left(1-\rho\right)\beta_s \Pi_1 x_7^{(4)}}{\varphi_1\left(\mu_1+\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}, \\ x_3^{(4)} = \frac{\Pi_1\left(\rho\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}{\varphi_2\left(\mu_1+\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}, \quad x_4^{(4)} = \frac{\Pi_1\alpha_2\left(1-\rho\right)\beta_s x_7^{(4)}}{\varphi_1\mu_4\mathcal{R}_{sc}\left(\mu_1+\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}, \\ x_5^{(4)} = \frac{\alpha_3\Pi_1\left(\rho\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}{\varphi_2\left(\mu_5+\mu_4\left(\mathcal{R}_{sc}-1\right)\right)\left(\mu_1+\beta_s x_7^{(4)}+\beta_r x_8^{(4)}\right)}, \quad x_6^{(4)} = \frac{\mu_4}{\gamma_6}\left(\mathcal{R}_{sc}-1\right) > 0, \\ \quad \text{where} \quad \mathcal{R}_{sc} = \frac{\mathcal{R}_s}{1+\frac{\beta_s x_7^{(4)}+\beta_r x_8^{(4)}}{\mu_1}} \\ x_7^{(4)} = \frac{-C_1-\sqrt{C_1^2-4C_0C_2}}{2C_2}, \quad x_8^{(4)} = \frac{-B_1+\sqrt{B_1^2-4B_0B_2}}{2B_2} > 0. \end{cases} \tag{24}$$

where $x_7^{(4)}$ and $x_8^{(4)}$ are, respectively, positive zeros of the functions, $G_1(x_7)$ and $G_2(x_8)$ defined in the appendix.

Mathematical analysis of some of the above model equilibria reveals some interesting results that may be obscured in the numerical simulations

Observation 1. *(a) If $\mathcal{R}_s = \mathcal{R}_r = 1$, then the equilibrium point, E_2, reduces to E_0.*

(b) If $\mathcal{R}_s = \mathcal{R}_r \neq 1$, then the equilibrium point,E_2, reduces to E_1.

Observation 2. *(a) If $\mathcal{R}_{rc} = 1$, then the equilibrium point, E_3, reduces to E_1.*

(b) If $\mathcal{R}_{rc} > 1$, then $x_1^{(3)} > x_1^{(1)}, x_3^{(3)} < x_3^{(1)}, x_5^{(3)} < x_5^{(1)}, x_8^{(3)} < x_8^{(1)}$.

3. Global Stability.

In this subsection, we establish the global asymptotic stability of all the equilibria of system (1) – (8) by employing the method of Lyapunov function and applying LaSalle's invariance principle. Consider the function $G(x) = x - 1 - \ln x$. Then, $G(x) \geq 0$ for $x > 0$ and $G(x) = 0$ if and only if $x = 1$.

Theorem 2. *Consider the system (1) – (8). The infection free equilibrium is globally asymptotically stable if $\mathcal{R}_s < \left(1-\rho\right)$ and $\mathcal{R}_r < 1$.*

Proof. Consider the following Lyapunov function, L_0, defined by

$$\begin{aligned} V_0 &= x_1^0 G\left(\frac{x_1}{x_1^0}\right) + \sum_{i=1}^{7}\eta_i x_{i+1}, \\ &\text{where } \eta_1 = \eta_2 = 1, \eta_3 = \frac{\varphi_1}{\alpha_2}, \eta_4 = \frac{\varphi_2}{\alpha_3}, \eta_5 = \frac{\gamma_6\varphi_1}{\alpha_2 r_6}, \eta_6 = \frac{\varphi_1}{\alpha_2 N_7}, \eta_7 = \frac{\varphi_2}{\alpha_3 N_8}, . \end{aligned} \tag{25}$$

Differentiating Eqn.(25) along the solutions of system (1) – (8) with respect to time, t, yields

$$\dot{V}_0 = \mu_1 x_1^0\left(2 - \frac{x_1^0}{x_1} - \frac{x_1}{x_1^0}\right) + \beta_s x_1^0 x_7 - \eta_6\mu_7 x_7 + \beta_r x_1^0 x_8 - \eta_7\mu_8 x_8.$$

$$= \mu_1 x_1^0\Big(2 - \frac{x_1^0}{x_1} - \frac{x_1}{x_1^0}\Big) + \frac{\mu_7\varphi_1}{\alpha_2 N_7}\Big(\frac{1}{(1-\rho)}\mathcal{R}_s - 1\Big)x_7 + \frac{\varphi_2\mu_8}{\alpha_3 N_8}\Big(\mathcal{R}_r - 1\Big)x_8, . \quad (26)$$

Hence, if $\mathcal{R}_s < (1-\rho)$ and $\mathcal{R}_r < 1$, then $\dot{V}_0 \leq 0$ for all $x_1, x_7, x_8 > 0$. It follows from LaSalle's invariance principle the E_0 is globally asymptotically stable (GAS). □

From straightforward algebraic manipulations, we have the following theorem.

Theorem 3. *(1) The infection free equilibrium point, E_0, exists always.*

(2) The infection equilibrium point with only the drug resistant strain and no CTL immune response, E_1, exists if $\mathcal{R}_r > 1$.

(3) The CTL immune absent equilibrium point, E_2, exists if $\mathcal{R}_s > \max\{1, \mathcal{R}_r\}$.

(4) The infection equilibrium point with drug resistant strain and CTL immune response equilibrium, E_3, exists if $\mathcal{R}_{rc} > 1$.

(5) The positive equilibrium point, E_4, exists if $\mathcal{R}_{sc} > 1$.

Theorem 4. *If $\max\{1, \frac{\mathcal{R}_s}{1-\rho}\} < \mathcal{R}_r \leq \frac{r_6\alpha_3\Pi_1}{r_6\alpha_3\Pi_1 - \mu_5\mu_6\varphi_2}$, then E_1 of model (1) – (8) is globally asymptotically stable.*

Proof. Define a Lyapunov function V_1 as follows:

$$\begin{aligned} V_1(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8) &= x_1^{(1)} G\Big(\frac{x_1}{x_1^{(1)}}\Big) + x_2 + x_3^{(1)} G\Big(\frac{x_3}{x_3^{(1)}}\Big) + \frac{\mu_2+\alpha_2}{\alpha_2}x_4 + \frac{(\mu_3+\alpha_3)}{\alpha_3}x_5^{(1)} G\Big(\frac{x_5}{x_5^{(1)}}\Big) \\ &\quad + \frac{\gamma(\mu_2+\alpha_2)}{\alpha_2 r_6}x_6 + \frac{\mu_2+\alpha_2}{\alpha_2 N_7}x_7 + \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}x_8^{(1)} G\Big(\frac{x_8}{x_8^{(1)}}\Big). \end{aligned}$$

We have $V_1(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8) > 0$ for all $x_i > 0,\ i = 1, 2, ..., 8$ and $V_1(x_1^{(1)}, 0, x_3^{(1)}, 0, x_5^{(1)}, 0, 0, x_8^{(1)}) = 0$. Find the derivative of V_1 along the trajectories of (1) – (8), we get

$$\begin{aligned} \dot{V}_1 &= \Big(1 - \frac{x_1^{(1)}}{x_1}\Big)\Big(\Pi_1 - \beta_s x_1 x_7 - \beta_r x_1 x_8 - \mu_1 x_1\Big) + (1-\rho)\beta_s x_1 x_7 - \alpha_2 x_2 - \mu_2 x_2 + \Big(1 - \frac{x_3^{(1)}}{x_3}\Big) \times \\ &\quad \Big(\rho\beta_s x_1 x_7 + \beta_r x_1 x_8 - \alpha_3 x_3 - \mu_3 x_3\Big) + \frac{(\mu_2+\alpha_2)}{\alpha_2}\Big(\alpha_2 x_2 - \gamma_6 x_4 x_6 - \mu_4 x_4\Big) \\ &\quad + \frac{(\mu_3+\alpha_3)}{\alpha_3}\Big(1 - \frac{x_5^{(1)}}{x_5}\Big)\Big(\alpha_3 x_3 - \gamma_6 x_5 x_6 - \mu_5 x_5\Big) + \frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\Big(r_6 x_4 x_6 + r_6 x_5 x_6 - \mu_6 x_6\Big) \\ &\quad + \frac{(\mu_2+\alpha_2)}{\alpha_2 N_7}\Big(N_7\mu_4 x_4 - \mu_7 x_7\Big) + \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}\Big(1 - \frac{x_8^{(1)}}{x_8}\Big)\Big(N_8\mu_5 x_5 - \mu_8 x_8\Big). \end{aligned} \quad (27)$$

Applying $\Pi_1 = \beta_r x_1^{(1)} x_8^{(1)} + \mu_1 x_1^{(1)}$ and collecting terms in Eqn. (27) we get

$$\begin{aligned} \dot{V}_1 &= \mu_1 x_1^{(1)}\Big(2 - \frac{x_1^{(1)}}{x_1} - \frac{x_1}{x_1^{(1)}}\Big) + \beta_r x_1^{(1)} x_8^{(1)} - \beta_r x_1^{(1)} x_8^{(1)}\frac{x_1^{(1)}}{x_1} + \beta_s x_1^{(1)} x_7 \\ &\quad + \beta_r x_1^{(1)} x_8 - \rho\beta_s x_1 x_7\frac{x_3^{(1)}}{x_3} - \beta_r x_1 x_8\frac{x_3^{(1)}}{x_3} + (\alpha_2+\mu_2)x_3^{(1)} - \frac{(\mu_3+\alpha_3)}{\alpha_3}\alpha_2 x_3\frac{x_5^{(1)}}{x_5} \\ &\quad + \frac{(\mu_3+\alpha_3)}{\alpha_3}\gamma_6 x_5^{(1)} x_6 + \frac{(\mu_3+\alpha_3)}{\alpha_3}\mu_5 x_5^{(1)} - \frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\mu_6 x_6 \\ &\quad - \frac{(\mu_2+\alpha_2)}{\alpha_2 N_7}\mu_7 x_7 - \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}\mu_8 x_8 - \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}N_8\mu_5 x_5\frac{x_8^{(1)}}{x_8} + \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}\mu_8 x_8^{(1)}. \end{aligned} \quad (28)$$

Using the equilibrium conditions for E_1 in Eqn. (28) and simplifying yields

$$\begin{aligned}\dot{V}_1 &= \mu_1 x_1^{(1)}\Big(2-\frac{x_1^{(1)}}{x_1}-\frac{x_1}{x_1^{(1)}}\Big)+\beta_r x_1^{(1)}x_8^{(1)}\Big(4-\frac{x_1^{(1)}}{x_1}-\frac{x_1}{x_1^{(1)}}\frac{x_8}{x_8^{(1)}}\frac{x_3^{(1)}}{x_3}-\frac{x_3}{x_3^{(1)}}\frac{x_5^{(1)}}{x_5}-\frac{x_5}{x_5^{(1)}}\frac{x_8^{(1)}}{x_8}\Big)\\ &+\frac{\mu_7(\mu_2+\alpha_2)}{\alpha_2 N_7}\Big(\frac{\mathcal{R}_s}{(1-\rho)\mathcal{R}_r}-1\Big)x_7-\rho\beta_s x_1^{(1)}\frac{x_1}{x_1^{(1)}}\frac{x_3^{(1)}}{x_3}x_7\\ &+\frac{\gamma_6\mu_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\Big(\frac{r_6}{\mu_6}x_5^{(1)}-1\Big)x_6\le 0 \text{ for all } x_1,x_3,x_5,x_6,x_7,x_8>0. \qquad (29)\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean and the invocation of the LaSalle's invariance principle, the result is established. □

Theorem 5. *If* $\mathcal{R}_s>\max\{1,\mathcal{R}_r\}, x_4^{(2)}+x_5^{(2)}<\frac{\mu_6}{r_6}$, *and* $\frac{x_7}{x_7^{(2)}}<1$, *then* E_2 *of model* (1) − (8) *is globally asymptotically stable.*

Proof. Consider the Lyapunov function, V_2, defined as follows:

$$\begin{aligned}V_2(x_1,x_2,x_3,x_4,x_5,x_6,x_7,x_8) &= x_1^{(2)}G\Big(\frac{x_1}{x_1^{(2)}}\Big)+x_2^{(2)}G\Big(\frac{x_2}{x_2^{(2)}}\Big)+x_3^{(2)}G\Big(\frac{x_3}{x_3^{(2)}}\Big)+\frac{\mu_2+\alpha_2}{\alpha_2}x_4^{(2)}G\Big(\frac{x_4}{x_4^{(2)}}\Big)\\ &+\frac{(\mu_3+\alpha_3)}{\alpha_3}x_5^{(2)}G\Big(\frac{x_5}{x_5^{(2)}}\Big)+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}x_6+\frac{\mu_2+\alpha_2}{\alpha_2 N_7}x_7^{(2)}G\Big(\frac{x_7}{x_7^{(2)}}\Big)\\ &+\frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}x_8^{(2)}G\Big(\frac{x_8}{x_8^{(2)}}\Big).\end{aligned}$$

We have $V_2(x_1,x_2,x_3,x_4,x_5,x_6,x_7,x_8)>0$ for all $x_i>0,\ i=1,2,...,8$ and $V_2(x_1^{(2)},x_2^{(2)},x_3^{(2)},x_4^{(2)},x_5^{(2)},0,x_7^{(2)},x_8^{(2)})=0$.

Find the derivative of V_2 along the trajectories of (1) − (8), we get

$$\begin{aligned}\dot{V}_2 &= \Big(1-\frac{x_1^{(2)}}{x_1}\Big)\Big(\Pi_1-\beta_r x_1x_7-\beta_r x_1x_8-\mu_1x_1\Big)+\Big(1-\frac{x_2^{(2)}}{x_2}\Big)\Big((1-\rho)\beta_s x_1x_7-(\alpha_2+\mu_2)x_2\Big)\\ &+\Big(1-\frac{x_3^{(2)}}{x_3}\Big)\Big(\rho\beta_s x_1x_7+\beta_r x_1x_8-(\alpha_3+\mu_3)x_3\Big)+\frac{(\mu_2+\alpha_2)}{\alpha_2}\Big(1-\frac{x_4^{(2)}}{x_4}\Big)\Big(\alpha_2x_2-\gamma_6x_4x_6-\mu_4x_4\Big)\\ &+\frac{(\mu_3+\alpha_3)}{\alpha_3}\Big(1-\frac{x_5^{(2)}}{x_5}\Big)\Big(\alpha_3x_3-\gamma_6x_5x_6-\mu_5x_5\Big)+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\Big(r_6x_4x_6+r_6x_5x_6-\mu_6x_6\Big)\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\Big(1-\frac{x_7^{(2)}}{x_7}\Big)\Big(N_7\mu_4x_4-\mu_7x_7\Big)+\frac{(\mu_3+\alpha_3)}{\alpha_3N_8}\Big(1-\frac{x_8^{(2)}}{x_8}\Big)\Big(N_8\mu_5x_5-\mu_8x_8\Big). \qquad (30)\end{aligned}$$

Applying $\Pi_1=\beta_s x_1^{(2)}x_7^{(2)}+\beta_r x_1^{(2)}x_8^{(2)}+\mu_1x_1^{(2)}$ in Eqn.(30) and collecting terms we get

$$\begin{aligned}\dot{V}_2 &= \mu_1x_1^{(2)}\Big(2-\frac{x_1^{(2)}}{x_1}-\frac{x_1}{x_1^{(2)}}\Big)+\beta_s x_1^{(2)}x_7^{(2)}+\beta_r x_1^{(2)}x_8^{(2)}\\ &-\beta_s x_1^{(2)}x_7^{(2)}\frac{x_1^{(2)}}{x_1}-\beta_r x_1^{(2)}x_8^{(2)}\frac{x_1^{(2)}}{x_1}+\beta_s x_1^{(2)}x_7+\beta_r x_1^{(2)}x_8-(1-\rho)\beta_s x_1x_7\frac{x_2^{(2)}}{x_2}\\ &+(\alpha_2+\mu_2)x_2^{(2)}-\rho\beta_s x_1x_7\frac{x_3^{(2)}}{x_3}-\beta_r x_1x_8\frac{x_3^{(2)}}{x_3}+(\alpha_2+\mu_2)x_3^{(2)}-(\mu_2+\alpha_2)x_2\frac{x_4^{(2)}}{x_4}\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_4^{(2)}x_6+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_4x_4^{(2)}-(\mu_2+\alpha_2)x_3\frac{x_5^{(2)}}{x_5}\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_5^{(2)}x_6+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5^{(2)}-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\mu_6x_6\end{aligned}$$

$$-\frac{(\mu_2+\alpha_2)}{\alpha_2 N_7}\mu_7 x_7 - \frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_4 x_4 \frac{x_7^{(2)}}{x_7} + \frac{(\mu_2+\alpha_2)}{\alpha_2 N_7}\mu_7 x_7^{(2)}$$
$$-\frac{(\mu_2+\alpha_2)}{\alpha_2 N_8}\mu_8 x_8 - \frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5 x_5 \frac{x_8^{(2)}}{x_8} + \frac{(\mu_2+\alpha_2)}{\alpha_2 N_8}\mu_8 x_8^{(2)}. \tag{31}$$

At E_2, the system (1) – (8) satisfies

$$(1-\rho)\beta_s x_1^{(2)} x_7^{(2)} = (\alpha_2+\mu_2)x_2^{(2)};\ \ \rho\beta_s x_1^{(2)} x_7^{(2)} + \beta_r x_1^{(2)} x_8^{(2)} = (\alpha_2+\mu_2)x_3^{(2)};\ \ \alpha_2 x_2^{(2)} = \mu_4 x_4^{(2)};\ \ \alpha_2 x_3^{(2)} = \mu_5 x_5^{(2)};$$
$$N_7\mu_4 x_4^{(2)} = \mu_7 x_7^{(2)};\ \ N_8\mu_5 x_5^{(2)} = \mu_8 x_8^{(2)}.$$

Applying these conditions yields

$$\begin{aligned}
\dot{V}_2 &= \mu_1 x_1^{(2)}\Big(2 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\Big) + (1-\rho)\beta_s x_1^{(2)} x_7^{(2)}\Big(4 - \frac{x_1^{(2)}}{x_1} - \frac{x_2}{x_2^{(2)}}\frac{x_4^{(2)}}{x_4} \\
&\quad - \frac{x_4}{x_4^{(2)}}\frac{x_7^{(2)}}{x_7} - \frac{x_1}{x_1^{(2)}}\frac{x_2^{(2)}}{x_2}\frac{x_7}{x_7^{(2)}}\Big) + \rho\beta_s x_1^{(2)} x_7^{(2)}\Big(4 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\frac{x_3^{(2)}}{x_3}\frac{x_7}{x_7^{(2)}} \\
&\quad - \frac{x_3}{x_3^{(2)}}\frac{x_5^{(2)}}{x_5} - \frac{x_8}{x_8^{(2)}} - \frac{x_5}{x_5^{(2)}}\frac{x_8^{(2)}}{x_8} + \frac{x_7}{x_7^{(2)}}\Big) \\
&\quad + \beta_r x_1^{(2)} x_8^{(2)}\Big(4 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\frac{x_3^{(2)}}{x_3}\frac{x_8}{x_8^{(2)}} - \frac{x_3}{x_3^{(2)}}\frac{x_5^{(2)}}{x_5} - \frac{x_5}{x_5^{(2)}}\frac{x_8^{(2)}}{x_8}\Big) \\
&\quad + \frac{\mu_6\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\Big(\frac{r_6}{\mu_6}(x_4^{(2)} + x_5^{(2)}) - 1\Big)x_6 \\
&\le \mu_1 x_1^{(2)}\Big(2 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\Big) + (1-\rho)\beta_s x_1^{(2)} x_7^{(2)}\Big(4 - \frac{x_1^{(2)}}{x_1} - \frac{x_2}{x_2^{(2)}}\frac{x_4^{(2)}}{x_4} \\
&\quad - \frac{x_4}{x_4^{(2)}}\frac{x_7^{(2)}}{x_7} - \frac{x_1}{x_1^{(2)}}\frac{x_2^{(2)}}{x_2}\frac{x_7}{x_7^{(2)}}\Big) + \rho\beta_s x_1^{(2)} x_7^{(2)}\Big(5 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\frac{x_3^{(2)}}{x_3} \\
&\quad - \frac{x_3}{x_3^{(2)}}\frac{x_5^{(2)}}{x_5} - \frac{x_8}{x_8^{(2)}} - \frac{x_5}{x_5^{(2)}}\frac{x_8^{(2)}}{x_8}\Big) \\
&\quad + \beta_r x_1^{(2)} x_8^{(2)}\Big(4 - \frac{x_1^{(2)}}{x_1} - \frac{x_1}{x_1^{(2)}}\frac{x_3^{(2)}}{x_3}\frac{x_8}{x_8^{(2)}} - \frac{x_3}{x_3^{(2)}}\frac{x_5^{(2)}}{x_5} - \frac{x_5}{x_5^{(2)}}\frac{x_8^{(2)}}{x_8}\Big) \\
&\quad + \frac{\mu_6\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}\Big(\frac{r_6}{\mu_6}(x_4^{(2)} + x_5^{(2)}) - 1\Big)x_6 \le 0 \text{ for all } x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8 > 0.
\end{aligned} \tag{32}$$

Since the arithmetic mean is greater than or equal to the geometric mean and following the invocation of the LaSalle's invariance principle, the result is established. □

Theorem 6. *If* $\mathcal{R}_{rc} > 1$, $\frac{x_8}{x_8^{(3)}} < 1$, *and* $\frac{x_1}{x_1^{(3)}}\frac{x_3^{(3)}}{x_3} > \frac{1}{\rho}$, *then* E_3 *of model* (1) – (8) *is globally asymptotically stable.*

Proof. Consider the Lyapunov function, V_3, defined as follows:

$$\begin{aligned}
V_3(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8) &= x_1^{(3)} G\Big(\frac{x_1}{x_1^{(3)}}\Big) + x_2 + x_3^{(3)} G\Big(\frac{x_3}{x_3^{(3)}}\Big) + \frac{\mu_2+\alpha_2}{\alpha_2}x_4 + \frac{(\mu_3+\alpha_3)}{\alpha_3}x_5^{(3)} G\Big(\frac{x_5}{x_5^{(3)}}\Big) \\
&\quad + \frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}x_6^{(3)} G\Big(\frac{x_6}{x_6^{(3)}}\Big) + \frac{\mu_2+\alpha_2}{\alpha_2 N_7}x_7 + \frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}x_8^{(3)} G\Big(\frac{x_8}{x_8^{(3)}}\Big).
\end{aligned}$$

We have $V_3(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8) > 0$ for all $x_i > 0,\ i = 1, 2, ..., 8$ and $V_3(x_1^{(3)}, 0, x_3^{(3)}, 0, x_5^{(3)}, x_6^{(3)}, 0, x_8^{(3)}) = 0$.

Find the derivative of V_3 along the trajectories of (1) – (8), we get

$$\begin{aligned}\dot{V}_3 &= \Big(1-\frac{x_1^{(3)}}{x_1}\Big)\Big(\Pi_1-\beta_r x_1x_7-\beta_r x_1x_8-\mu_1x_1\Big)+(1-\rho)\beta_s x_1x_7-(\alpha_2+\mu_2)x_2\\
&+\Big(1-\frac{x_3^{(3)}}{x_3}\Big)\Big(\rho\beta_s x_1x_7+\beta_r x_1x_8-(\alpha_3+\mu_3)x_3\Big)+\frac{(\mu_2+\alpha_2)}{\alpha_2}\Big(\alpha_2x_2-\gamma_6x_4x_6-\mu_4x_4\Big)\\
&+\frac{(\mu_3+\alpha_3)}{\alpha_3}\Big(1-\frac{x_5^{(3)}}{x_5}\Big)\Big(\alpha_3x_3-\gamma_6x_5x_6-\mu_5x_5\Big)+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\Big(1-\frac{x_6^{(3)}}{x_6}\Big)\Big(r_6x_4x_6+r_6x_5x_6-\mu_6x_6\Big)\\
&+\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\Big(N_7\mu_4x_4-\mu_7x_7\Big)+\frac{(\mu_3+\alpha_3)}{\alpha_3N_8}\Big(1-\frac{x_8^{(3)}}{x_8}\Big)\Big(N_8\mu_5x_5-\mu_8x_8\Big). \qquad (33)\end{aligned}$$

Applying $\Pi_1=\beta_r x_1^{(3)}x_8^{(3)}+\mu_1x_1^{(3)}$ in Eqn.(33) and collecting terms we get

$$\begin{aligned}\dot{V}_3 &= \mu_1x_1^{(3)}\Big(2-\frac{x_1^{(3)}}{x_1}-\frac{x_1}{x_1^{(3)}}\Big)+\beta_r x_1^{(3)}x_8^{(3)}-\beta_r x_1^{(3)}x_8^{(3)}\frac{x_1^{(3)}}{x_1}\\
&+\beta_s x_1^{(3)}x_7+\beta_r x_1^{(3)}x_8-\rho\beta_s x_1x_7\frac{x_3^{(3)}}{x_3}-\beta_r x_1x_8\frac{x_3^{(3)}}{x_3}+(\alpha_2+\mu_2)x_3^{(3)}-(\mu_2+\alpha_2)x_3\frac{x_5^{(3)}}{x_5}\\
&+\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_5^{(3)}x_6+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5^{(3)}-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\mu_6x_6\\
&-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2}x_4x_6^{(3)}-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2}x_5x_6^{(3)}+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\mu_6x_6^{(3)}\\
&-\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\mu_7x_7-\frac{(\mu_2+\alpha_2)}{\alpha_2N_8}\mu_8x_8-\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5\frac{x_8^{(3)}}{x_8}\\
&+\frac{(\mu_2+\alpha_2)}{\alpha_2N_8}\mu_8x_8^{(3)}. \qquad (34)\end{aligned}$$

At E_3, the system (1) – (8) satisfies

$$\beta_r x_1^{(3)}x_8^{(3)} = (\alpha_2+\mu_2)x_3^{(3)};\ \ \alpha_2x_3^{(3)}=\gamma_6x_5^{(3)}x_6^{(3)}+\mu_5x_5^{(3)};\ \ r_6x_5^{(3)}x_6^{(3)}=\mu_6x_6^{(3)};\ \ N_8\mu_5x_5^{(3)}=\mu_8x_8^{(3)} \qquad (35)$$

Applying these conditions yields

$$\begin{aligned}\dot{V}_3 &= \mu_1x_1^{(3)}\Big(2-\frac{x_1^{(3)}}{x_1}-\frac{x_1}{x_1^{(3)}}\Big)+\beta_r x_1^{(3)}x_8^{(3)}\Big(4-\frac{x_1^{(3)}}{x_1}-\frac{x_1}{x_1^{(3)}}\frac{x_3^{(3)}}{x_3}\frac{x_8}{x_8^{(3)}}-\frac{x_3}{x_3^{(3)}}\frac{x_5^{(3)}}{x_5}-\frac{x_5}{x_5^{(3)}}\frac{x_8^{(3)}}{x_8}\Big)\\
&-\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_5^{(3)}x_6^{(3)}\Big(1+\frac{x_5}{x_5^{(3)}}\Big)\Big(1-\frac{x_8}{x_8^{(3)}}\Big)\\
&+\beta_s x_1^{(3)}\Big(1-\rho\frac{x_1}{x_1^{(3)}}\frac{x_3^{(3)}}{x_3}\Big)x_7-\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_2x_7-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2}x_4x_6^{(3)}\le 0 \text{ for all } x_1,x_3,x_4,x_5,x_8>0. \qquad (36)\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean and following the invocation of the LaSalle's invariance principle, the result is established. □

Theorem 7. *If* $\mathcal{R}_{sc}>1, \frac{x_5}{x_5^{(4)}}+\frac{x_7}{x_7^{(4)}}<1, \frac{x_1}{x_1^{(4)}}\frac{x_3^{(4)}}{x_3}<1$ *and* $1<\frac{x_7^{(4)}}{x_7}<\frac{x_8^{(4)}}{x_8}<2$, *then* E_4 *of model* (1) – (8) *is globally asymptotically stable.*

Proof. Consider the Lyapunov function, V_4, defined as follows:

$$\begin{aligned} V_4(x_1,x_2,x_3,x_4,x_5,x_6,x_7,x_8) &= x_1^{(4)}G\Big(\frac{x_1}{x_1^{(4)}}\Big)+x_2^{(4)}G\Big(\frac{x_2}{x_2^{(4)}}\Big)+x_3^{(4)}G\Big(\frac{x_3}{x_3^{(4)}}\Big)+\frac{\mu_2+\alpha_2}{\alpha_2}x_4^{(4)}G\Big(\frac{x_4}{x_4^{(4)}}\Big)\\ &+\frac{(\mu_3+\alpha_3)}{\alpha_3}x_5^{(4)}G\Big(\frac{x_5}{x_5^{(4)}}\Big)+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2 r_6}x_6^{(4)}G\Big(\frac{x_6}{x_6^{(4)}}\Big)\\ &+\frac{\mu_2+\alpha_2}{\alpha_2 N_7}x_7^{(4)}G\Big(\frac{x_7}{x_7^{(4)}}\Big)+\frac{(\mu_3+\alpha_3)}{\alpha_3 N_8}x_8^{(4)}G\Big(\frac{x_8}{x_8^{(4)}}\Big). \end{aligned}$$

We have $V_4(x_1,x_2,x_3,x_4,x_5,x_6,x_7,x_8)>0$ for all $x_i>0,\ i=1,2,...,8$ and $V_4(x_1^{(4)},x_2^{(4)},x_3^{(4)},x_4^{(4)},x_5^{(4)},x_6^{(4)},x_7^{(4)},x_8^{(4)})=0$.

Finding the derivative of V_4 along the trajectories of (1) – (8), we get

$$\begin{aligned} \dot{V}_4 &= \Big(1-\frac{x_1^{(4)}}{x_1}\Big)\Big(\Pi_1-\beta_r x_1x_7-\beta_r x_1x_8-\mu_1x_1\Big)+\Big(1-\frac{x_2^{(4)}}{x_2}\Big)\Big((1-\rho)\beta_s x_1x_7-(\alpha_2+\mu_2)x_2\Big)\\ &+\Big(1-\frac{x_3^{(4)}}{x_3}\Big)\Big(\rho\beta_s x_1x_7+\beta_r x_1x_8-(\alpha_3+\mu_3)x_3\Big)+\frac{(\mu_2+\alpha_2)}{\alpha_2}\Big(1-\frac{x_4^{(4)}}{x_4}\Big)\Big(\alpha_2x_2-\gamma_6x_4x_6-\mu_4x_4\Big)\\ &+\frac{(\mu_3+\alpha_3)}{\alpha_3}\Big(1-\frac{x_5^{(4)}}{x_5}\Big)\Big(\alpha_3x_3-\gamma_6x_5x_6-\mu_5x_5\Big)+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\Big(1-\frac{x_6^{(4)}}{x_6}\Big)\Big(r_6x_4x_6+r_6x_5x_6-\mu_6x_6\Big)\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\Big(1-\frac{x_7^{(4)}}{x_7}\Big)\Big(N_7\mu_4x_4-\mu_7x_7\Big)+\frac{(\mu_3+\alpha_3)}{\alpha_3N_8}\Big(1-\frac{x_8^{(4)}}{x_8}\Big)\Big(N_8\mu_5x_5-\mu_8x_8\Big). \end{aligned} \tag{37}$$

Applying $\Pi_1=\beta_s x_1^{(4)}x_7^{(4)}+\beta_r x_1^{(4)}x_8^{(4)}+\mu_1x_1^{(4)}$ in Eqn.(37) and collecting terms we get

$$\begin{aligned} \dot{V}_4 &= \mu_1x_1^{(4)}\Big(2-\frac{x_1^{(4)}}{x_1}-\frac{x_1}{x_1^{(4)}}\Big)+\beta_s x_1^{(4)}x_7^{(4)}+\beta_r x_1^{(4)}x_8^{(4)}\\ &-\beta_s x_1^{(4)}x_7^{(4)}\frac{x_1^{(4)}}{x_1}-\beta_r x_1^{(4)}x_8^{(4)}\frac{x_1^{(4)}}{x_1}+\beta_s x_1^{(4)}x_7^{(4)}\frac{x_7}{x_7^{(4)}}+\beta_r x_1^{(4)}x_8^{(4)}\frac{x_8}{x_8^{(4)}}\\ &-(1-\rho)\beta_s x_1^{(4)}x_7^{(4)}\frac{x_1}{x_1^{(4)}}\frac{x_2^{(4)}}{x_2}\frac{x_7}{x_7^{(4)}}+(\alpha_2+\mu_2)x_2^{(4)}-\rho\beta_s x_1^{(4)}x_7^{(4)}\frac{x_1}{x_1^{(4)}}\frac{x_3^{(4)}}{x_3}\frac{x_7}{x_7^{(4)}}\\ &-\beta_r x_1^{(4)}x_8^{(4)}\frac{x_1}{x_1^{(4)}}\frac{x_3^{(4)}}{x_3}\frac{x_8}{x_8^{(4)}}+(\alpha_2+\mu_2)x_3^{(4)}-(\mu_2+\alpha_2)x_2^{(4)}\frac{x_2}{x_2^{(4)}}\frac{x_4^{(4)}}{x_4}\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_4^{(4)}x_6^{(4)}\frac{x_6}{x_6^{(4)}}+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_4x_4^{(4)}-(\mu_2+\alpha_2)x_3^{(4)}\frac{x_3}{x_3^{(4)}}\frac{x_5^{(4)}}{x_5}\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6x_5^{(4)}x_6^{(4)}\frac{x_6}{x_6^{(4)}}+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5^{(4)}-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\mu_6x_6^{(4)}\frac{x_6}{x_6^{(4)}}\\ &-\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2}x_4^{(4)}x_6^{(4)}\frac{x_4}{x_4^{(4)}}-\frac{-\gamma_6(\mu_2+\alpha_2)}{\alpha_2}x_5^{(4)}x_6^{(4)}\frac{x_5}{x_5^{(4)}}\\ &+\frac{\gamma_6(\mu_2+\alpha_2)}{\alpha_2r_6}\mu_6x_6^{(4)}-\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\mu_7x_7^{(4)}\frac{x_7}{x_7^{(4)}}\\ &-\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_4x_4^{(4)}\frac{x_4}{x_4^{(4)}}\frac{x_7^{(4)}}{x_7}+\frac{(\mu_2+\alpha_2)}{\alpha_2N_7}\mu_7x_7^{(4)}\\ &+\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5^{(4)}\frac{x_5}{x_5^{(4)}}-\frac{(\mu_2+\alpha_2)}{\alpha_2N_8}\mu_8x_8^{(4)}\frac{x_8}{x_8^{(4)}}\\ &-\frac{(\mu_2+\alpha_2)}{\alpha_2}\mu_5x_5^{(4)}\frac{x_5}{x_5^{(4)}}\frac{x_8^{(4)}}{x_8}+\frac{(\mu_2+\alpha_2)}{\alpha_2N_8}\mu_8x_8^{(4)}. \end{aligned} \tag{38}$$

At E_4, the system (1) – (8) satisfies

$$(1-\rho)\beta_s x_1^{(4)} x_7^{(4)} = (\alpha_2+\mu_2)x_2^{(4)};\quad \rho\beta_s x_1^{(4)} x_7^{(4)} + \beta_r x_1^{(4)} x_8^{(4)} = (\alpha_3+\mu_3)x_3^{(4)};\quad \alpha_2 x_2^{(4)} = \gamma_6 x_4^{(4)} x_6^{(4)} + \mu_4 x_4^{(4)};$$
$$\alpha_3 x_3^{(4)} = \gamma_6 x_5^{(4)} x_6^{(4)} + \mu_5 x_5^{(4)};\quad r_6 x_4^{(4)} x_6^{(4)} + r_6 x_5^{(4)} x_6^{(4)} = \mu_6 x_6^{(4)};\quad N_7\mu_4 x_4^{(4)} = \mu_7 x_7^{(4)};\quad N_8\mu_5 x_5^{(4)} = \mu_8 x_8^{(4)}.$$

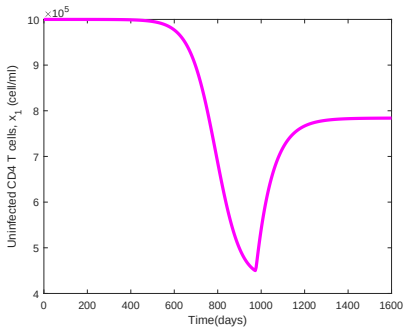
Applying these conditions yields

$$\begin{aligned}
\dot{V}_4 \leq\ & \mu_1 x_1^{(4)}\Big(2 - \frac{x_1^{(4)}}{x_1} - \frac{x_1}{x_1^{(4)}}\Big) + (\mu_2+\alpha_2)x_2^{(4)}\Big(4 - \frac{x_1^{(4)}}{x_1} - \frac{x_1}{x_1^{(4)}}\frac{x_2^{(4)}}{x_2}\frac{x_7}{x_7^{(4)}} \\
& - \frac{x_2}{x_2^{(4)}}\frac{x_4^{(4)}}{x_4} - \frac{x_4}{x_4^{(4)}}\frac{x_7^{(4)}}{x_7}\Big) + (\alpha_2+\mu_2)x_3^{(4)}\Big(5 - \frac{x_1^{(4)}}{x_1} - \frac{x_1}{x_1^{(4)}}\frac{x_3^{(4)}}{x_3} \\
& - \frac{x_3}{x_3^{(4)}}\frac{x_5^{(4)}}{x_5} - \frac{x_8}{x_8^{(4)}} - \frac{x_5}{x_5^{(4)}}\frac{x_8^{(4)}}{x_8}\Big) - \frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6 x_4^{(4)} x_6^{(4)}\Big(1 + \frac{x_4}{x_4^{(4)}}\Big)\Big(1 - \frac{x_7}{x_7^{(4)}}\Big) \\
& - \frac{(\mu_2+\alpha_2)}{\alpha_2}\gamma_6 x_5^{(4)} x_6^{(4)}\left(\frac{x_5}{x_5^{(4)}}\Big(2 - \frac{x_8^{(4)}}{x_8}\Big) + \Big(1 - \frac{x_8}{x_8^{(4)}}\Big)\right) \\
& - \beta_r x_1^{(4)} x_8^{(4)}\Big(\frac{x_7}{x_7^{(4)}} - \frac{x_8}{x_8^{(4)}}\Big)\Big(1 - \frac{x_1}{x_1^{(4)}}\frac{x_3^{(4)}}{x_3}\Big) \leq 0 \text{ for all } x_1, x_2, x_3, x_4, x_5, x_7, x_8 > 0. \qquad (39)
\end{aligned}$$

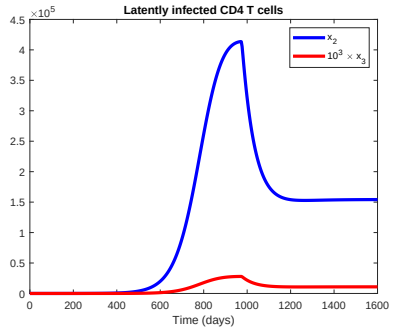
Since the arithmetic mean is greater than or equal to the geometric mean and following the invocation of the LaSalle's invariance principle, the result is established. □

4. Numerical Simulations

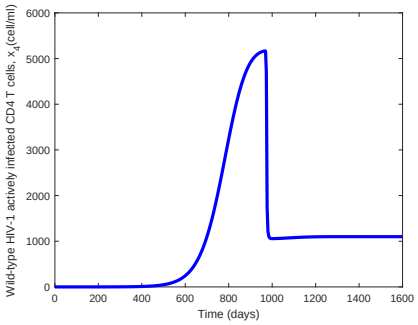
In this section, we make use of the parameter values listed in Table 1 to simulate the model. For these values, the basic reproduction number, $\mathcal{R}_0 = 2.2360$.



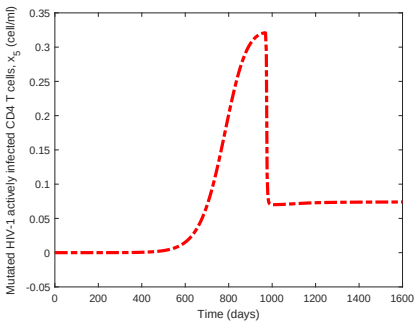
(a) Uninfected CD4 T cells, (x_1)



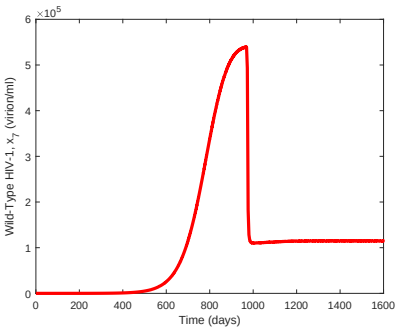
(b) Latently infected CD4 T cells,(x_2, x_3)



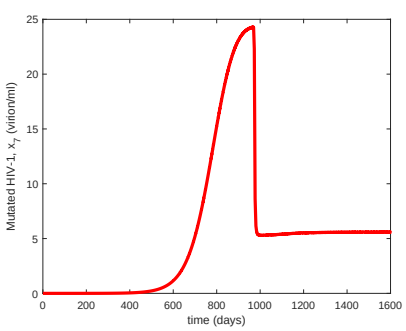
(c) Wild-type HIV-1 actively infected CD4 T cells,(x_4)



(d) Mutated HIV-1 actively infected CD4 T cells,x_5



(e) Wild-type HIV-1 virions,(x_7)



(f) Mutated HIV-1 virions,(x_8)

Figure 2: Dynamics of different populations in the first 1600 days.

Figure 2(a) depicts the dynamics of the uninfected CD4 T cells in the presence of HIV-1 infection. The initial population level of these cells is 10^6 cells/ml. The target population level gradually declines to the lowest level of about 4.5×10^5 cells/ml by the 965^{th} day before increasing to the steady state values of about 7.8×10^5 cells/ml. Figure 2(b) simulates the populations of latently infected CD4 T cells. It is important to observe that the levels of infected cells arising from the infection by mutated virus are much lower than the ones from the wild-type strain of virus. This is observation is also true for the two virus strains themselves (Figures 2(e), 2(f)). This is consistent with what has been reported elsewhere in the literature.

5. Discussion and conclusion

The current administration of HAART to HIV patients has yielded positive results. Many of these people can now live healthy lives and contribute to the growth of their economies. However, HAART treatment has no capacity to eradicate the HIV virus in these individuals despite reducing the viral loads, in most cases, to below detection levels. It is therefore important that, once one commences the HAART treatment, they remain on it for life and adhere to the treatment protocols as advised lest one risks the drugs to become resistant to HIV.

Mathematical models have been developed to study the prevalence of mutant strains prior to commencement of therapy and their competition with the drug sensitive virus in the presence of drug pressure [4, 11, 12, 15, 14, 13]. Many of the models ignored the important role that cellular mediated immunity plays in the fight of viral infections. It is also necessary to investigate the conditions under which several models'equilibria can be globally asymptotically stable.
In observation 1(a) we have found that the infection equilibrium point with both virus strains available, but no CTL immune response,E_2, can be reduced to the infection free equilibrium point, E_0, provided $\mathcal{R}_s = \mathcal{R}_r = 1$. It therefore follows that under this condition HIV can not establish itself in the host. However,in observation 1 (b), for $\mathcal{R}_s = \mathcal{R}_r \neq 1$, E_2 reduces to E_1. Note that under this condition the drug sensitive virus clears from the host and only the drug resistant strain of virus dominates. In this case there is no benefit that the patient can receive from HAART.
In observation 2 (a), when $\mathcal{R}_{rc} = 1$, the infection equilibrium point with only the mutated HIV virus and CTL mediated immunity, E_3, reduces to one E_1. In other words the cellular immunity response disappears. This could be due to the fact that the $CD8^+$ T cells become dysfunctional. In observation 2 (b), when $\mathcal{R}_{rc} > 1$, we have $x_1^{(3)} > x_1^{(1)}$. Therefore, when only the mutated virus is present, the cellular mediated immunity can make the uninfected CD4 T cell population to increase. This is consistent with what is expected from a competent immune response. Further it is observed that the levels of infected CD4 T cells and HIV virions are lower in the presence of the cellular-mediated immune response ($x_3^{(3)} < x_1^{(1)}, x_5^{(3)} < x_5^{(1)}, x_8^{(3)} < x_8^{(1)}$).

6. Appendix

The coordinates, $x_7^{(4)}$ and $x_8^{(4)}$, for the positive equilibrium point E_4 are, respectively, positive solutions to the equations

$$\begin{aligned} G_1(x_7) &= C_2x_7^2 + C_1x_7 + C_0 = 0, \\ G_2(x_8) &= B_2x_8^2 + B_1x_8 + B_0 = 0, \end{aligned}$$

where the coefficients are defined as follows.

$$\begin{cases} B_2 = \alpha_2\alpha_3\beta_r\mu_5\mu_7\mu_8 - \alpha_2\alpha_3\mu_4\mu_7\mu_8 - \alpha_2\beta_r\mu_3\mu_4\mu_7\mu_8 - \alpha_3\beta_r\mu_2\mu_4\mu_7\mu_8 + \alpha_2\beta_r\mu_3\mu_5\mu_7\mu_8 \\ \qquad + \alpha_3\beta_r\mu_2\mu_5\mu_7\mu_8 - \beta_r\mu_2\mu_3\mu_4\mu_7\mu_8 + \beta_r\mu_2\mu_3\mu_5\mu_7\mu_8 \\ \qquad = \beta_r\mu_7\mu_8\big(\mu_5 - \mu_4\big)\varphi_1\varphi_2 > 0, \text{if } \mu_5 > \mu_4 \\ B_1 = \alpha_2\alpha_3\mu_1\mu_5\mu_7\mu_8 - \alpha_2\alpha_3\mu_1\mu_4\mu_7\mu_8 - \alpha_2\mu_1\mu_3\mu_4\mu_7\mu_8 - \alpha_3\mu_1\mu_2\mu_4\mu_7\mu_8 + \alpha_2\mu_1\mu_3\mu_5\mu_7\mu_8 \\ \qquad + \alpha_3\mu_1\mu_2\mu_5\mu_7\mu_8 - \mu_1\mu_2\mu_3\mu_4\mu_7\mu_8 + \mu_1\mu_2\mu_3\mu_5\mu_7\mu_8 + N_7\Pi_1\alpha_2\beta_s\mu_3\mu_4\mu_8 - N_8\Pi_1\alpha_3\beta_r\mu_2\mu_5\mu_7 \\ \qquad - \alpha_2\alpha_3\beta_s\mu_4\mu_7\mu_8x_7 + \alpha_2\alpha_3\beta_s\mu_5\mu_7\mu_8x_7 - \alpha_2\beta_s\mu_3\mu_4\mu_7\mu_8x_7 - \alpha_3\beta_s\mu_2\mu_4\mu_7\mu_8x_7 + \alpha_2\beta_s\mu_3\mu_5\mu_7\mu_8x_7 \\ \qquad + \alpha_3\beta_s\mu_2\mu_5\mu_7\mu_8x_7 - \beta_s\mu_2\mu_3\mu_4\mu_7\mu_8x_7 + \beta_s\mu_2\mu_3\mu_5\mu_7\mu_8x_7 + N_7\Pi_1\alpha_2\alpha_3\beta_s\mu_4\mu_8 - N_8\Pi_1\alpha_2\alpha_3\beta_r\mu_5\mu_7 \\ \qquad - N_7\Pi_1\alpha_2\alpha_3\beta_s\mu_4\mu_8\rho - N_7\Pi_1\alpha_2\beta_s\mu_3\mu_4\mu_8\rho \\ \qquad = \varphi_1\varphi_2\mu_7\mu_8\big(\mu_5 - \mu_4\big)\big(\mu_1 + \beta_sx_7\big) + N_7\Pi_1\alpha_2\beta_s\mu_4\mu_8\big(1-\rho\big)\varphi_2 - N_8\Pi_1\alpha_3\beta_r\mu_7\mu_8\varphi_1 \\ B_0 = -N_8\Pi_1\alpha_3\beta_s\mu_5\mu_7\rho\varphi_1x_7 < 0, \text{ for all } x_7 > 0. \\ C_2 = \alpha_2\alpha_3\beta_s\mu_4\mu_7^2r_6 - \alpha_2\alpha_3\beta_s\mu_5\mu_7^2r_6 + \alpha_2\beta_s\mu_3\mu_4\mu_7^2r_6 + \alpha_3\beta_s\mu_2\mu_4\mu_7^2r_6 - \alpha_2\beta_s\mu_3\mu_5\mu_7^2r_6 \\ \qquad - \alpha_3\beta_s\mu_2\mu_5\mu_7^2r_6 + \beta_s\mu_2\mu_3\mu_4\mu_7^2r_6 - \beta_s\mu_2\mu_3\mu_5\mu_7^2r_6 \\ \qquad = \beta_s\mu_7^2r_6\varphi_1\varphi_2\big(\mu_4 - \mu_5\big) < 0, \text{ if } \mu_5 > \mu_4. \\ C_1 = \alpha_2\alpha_3\mu_1\mu_4\mu_7^2r_6 - \alpha_2\alpha_3\mu_1\mu_5\mu_7^2r_6 + \alpha_2\mu_1\mu_3\mu_4\mu_7^2r_6 + \alpha_3\mu_1\mu_2\mu_4\mu_7^2r_6 - \alpha_2\mu_1\mu_3\mu_5\mu_7^2r_6 \\ \qquad - \alpha_3\mu_1\mu_2\mu_5\mu_7^2r_6 + \mu_1\mu_2\mu_3\mu_4\mu_7^2r_6 - \mu_1\mu_2\mu_3\mu_5\mu_7^2r_6 - N_7\alpha_2\alpha_3\beta_s\mu_4^2\mu_6\mu_7 - N_7\alpha_2\beta_s\mu_3\mu_4^2\mu_6\mu_7 \\ \qquad - N_7\alpha_3\beta_s\mu_2\mu_4^2\mu_6\mu_7 - N_7\beta_s\mu_2\mu_3\mu_4^2\mu_6\mu_7 + \alpha_2\alpha_3\beta_r\mu_4\mu_7^2r_6x_8 - \alpha_2\alpha_3\beta_r\mu_5\mu_7^2r_6x_8 + \alpha_2\beta_r\mu_3\mu_4\mu_7^2r_6x_8 \\ \qquad + \alpha_3\beta_r\mu_2\mu_4\mu_7^2r_6x_8 - \alpha_2\beta_r\mu_3\mu_5\mu_7^2r_6x_8 - \alpha_3\beta_r\mu_2\mu_5\mu_7^2r_6x_8 + \beta_r\mu_2\mu_3\mu_4\mu_7^2r_6x_8 - \beta_r\mu_2\mu_3\mu_5\mu_7^2r_6x_8 \\ \qquad - N_7\Pi_1\alpha_2\alpha_3\beta_s\mu_4\mu_7r_6 - N_7\Pi_1\alpha_2\beta_s\mu_3\mu_4\mu_7r_6 + N_7\alpha_2\alpha_3\beta_s\mu_4\mu_5\mu_6\mu_7 + N_7\alpha_2\beta_s\mu_3\mu_4\mu_5\mu_6\mu_7 \\ \qquad + N_7\alpha_3\beta_s\mu_2\mu_4\mu_5\mu_6\mu_7 + N_7\beta_s\mu_2\mu_3\mu_4\mu_5\mu_6\mu_7 + N_7\Pi_1\alpha_2\beta_s\mu_3\mu_4\mu_7r_6\rho - N_7\Pi_1\alpha_3\beta_s\mu_2\mu_4\mu_7r_6\rho \\ C_0 = N_7^2\Pi_1\alpha_2\alpha_3\beta_s\mu_4^2\mu_6\big(1-\rho\big) + N_7^2\Pi_1\alpha_2\beta_s\mu_3\mu_4^2\mu_6\big(1-\rho\big) + N_7\alpha_2\mu_1\mu_3\mu_4\mu_6\mu_7\big(\mu_5 - \mu_4\big) \\ \qquad + N_7\alpha_3\mu_1\mu_2\mu_4\mu_6\mu_7\big(\mu_5 - \mu_4\big) + N_7\alpha_2\alpha_3\mu_1\mu_4\mu_6\mu_7\big(\mu_5 - \mu_4\big) + N_7\alpha_2\alpha_3\beta_r\mu_4\mu_6\mu_7x_8\big(\mu_5 - \mu_4\big) \\ \qquad - N_7\Pi_1\alpha_3\beta_r\mu_4\mu_7r_6x_8\varphi_1 + N_7\beta_r\mu_2\mu_4\mu_5\mu_6\mu_7x_8\varphi_2 + N_7\mu_1\mu_2\mu_3\mu_4\mu_6\big(\mu_5 - \mu_4\big) \\ \qquad - N_7\beta_r\mu_3\mu_4^2\mu_6\mu_7x_8\varphi_1 + N_7\beta_r\mu_4\mu_6\mu_7x_8\big(\alpha_2\mu_3\mu_5 - \alpha_3\mu_2\mu_4\big) \end{cases} \tag{40}$$

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