MODELING WITHIN-HOST VIRAL DYNAMICS: THE ROLE OF CTL IMMUNE RESPONSES IN THE EVOLUTION OF DRUG RESISTANCE

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Abstract. To study the emergence and evolution of drug resistance during treatment of HIV infection, we study a mathematical model with two strains, one drug-sensitive and the other drug-resistant, by incorporating cytotoxic T lymphocyte (CTL) immune response. The reproductive numbers for each strain with and without the CTL immune response are obtained and shown to determine the stability of the steady states. By sensitivity analysis, we evaluate how the changes of parameters influence the reproductive numbers. The model shows that CTL immune response can suppress the development of drug resistance. There is a dynamic relationship between antiretroviral drug administration, the prevalence of drug resistance, the total level of viral production, and the strength of immune responses. We further investigate the scenario under which the drug-resistant strain can outcompete the wild-type strain. If drug efficacy is at an intermediate level, the drug-resistant virus is likely to arise. The slower the immune response wanes, the slower the drug-resistant strain grows. The results suggest that immunotherapy that aims to enhance immune responses, combined with antiretroviral drug treatment, may result in a functional control of HIV infection.

1. Introduction. As of 2018, acquired immunodeficiency syndrome (AIDS) was estimated to have killed more than 32 million people. Approximately 37.9 million people were living with AIDS [60]. Human immunodeficiency virus (HIV) is the causative agent of this deadly infection. It impairs the immune system by invading cells with CD4 molecules, mainly including T4 lymphocytes, mononuclear cells, macrophages and dendritic cells [30]. If left treated, the immune system will eventually fail to play its life-sustaining role [59]. There is considerable interest in studying
HIV dynamics before and during treatment and many mathematical models have been developed and analyzed [31, 19, 29].

The basic viral dynamic model includes three variables: uninfected CD4+ T cells, productively infected CD4+ T cells, and free virus [6, 34, 35]. This basic model can capture the essence of HIV infection. It helps to estimate rate constants of the initial viral expansion and decline, and the lifespan of infected cells. However, it only includes a single strain, i.e. the wild-type strain that does not contain any mutation. As HIV is a retrovirus, the reproduction can generate errors with a certain probability in each reverse transcription process. Some mutations occur at the target of antiretroviral drugs, which can reduce the susceptibility of HIV infection and replication to drugs [10]. Some studies suggested that drug-resistant variation might be an important reason of treatment failure [41, 40]. Therefore, in order to better control HIV infection, it is necessary to understand the mechanisms underlying the emergence and development of mutant strains.

Reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) are two commonly used antiretroviral drugs for the treatment of HIV infection. RTI blocks the reverse transcription from viral RNA to DNA, thus preventing target cells from being infected by free virus, while PI prevents infected cells from producing new infectious virus particles [15, 64]. The efficacy of the two drugs is often significantly compromised due to the occurrence of drug-resistant strains [10, 21]. Therefore, it is important to study the evolution of drug resistance under antiretroviral therapy (ART) for controlling the progress of HIV infection. Rong et al. [42] constructed a five-dimensional ordinary differential equation (ODE) to investigate the emergence and development of drug-resistant strains in the setting of ART. Wang et al. [57] considered a two-strain model that includes a general form of target cell density, drug resistance and intracellular delay. They showed that the rapid turnover of mutant virus mainly depends on the density of target cells. Biological insights into the evolution of drug-resistant strains have also been obtained from other mathematical models [6, 36, 44, 46, 65]. However, these studies do not include the immune response explicitly in the model. Both innate and adaptive immune responses may play a significant role in the controlling of viral replication [30].

During HIV infection, the cytotoxic T lymphocytes (CTLs) are a major component of the immune response against viral infection [7, 20, 22, 47, 54]. They can recognize and kill infected cells, and reduce the viral load by limiting viral replication in vivo. Therefore, the dynamics of HIV infection with CTL immune response have attracted much attention [9, 31, 53, 63, 68, 18]. Neither immune responses nor antiretroviral therapy can eradicate the virus [12, 14, 13]. There is a growing interest in considering both ART and immunotherapy in the treatment of HIV infection. Wang et al. [58] proposed two HIV models that combine CTL immune response with ART, and found that CTL immune response might be rebuilt through optimal antiretroviral treatment. Some other models have also been used to investigate the dynamics of the immune system and virus population under ART [3, 11, 16, 26, 62]. These models focus on how to rationally design treatment regimens to reconstruct CTL immune response when antigen stimuli are weak. In this paper, we aim to study the role of CTL immune response in the emergence and development of drug-resistant strains in the presence of treatment.

The structure of this paper is as follows. In Section 2, we formulate a model that describes the interaction between target cells, two viral strains, and the immune responses without ART. We analyze the model in Section 2.1 and 2.2, and perform
sensitivity analysis in Section 2.3. In Section 3, we study the model that includes ART. We conduct numerical investigation of the effects of ART and CTL immune responses on virus dynamics. In the last section, we present a brief discussion and conclusion.

2. The model before treatment. In this section, we develop a two-strain model of HIV infection with immune responses, which will be modified to include antiretroviral treatment in the next section. The model is built on a previous drug resistance model by including the CTL immune response [42].

Viruses have various epitopes that can be recognized by immune responses. They may differ in one epitope but coincide in other epitopes [33, 32]. We assume that the immunity is cross-reactive between the wild-type and mutant strains, i.e., wild-type virus and mutant virus can be both recognized by the immune response [30]. We also assume that cells infected by the wild-type virus become drug-resistant at a rate \( \mu \) (\( 0 < \mu < 1 \)) during the reverse transcription process from viral RNA to DNA. We ignore the backward mutation from the drug-resistant to drug sensitive virus [6]. Based on these assumptions, the model can be described by

\[
\begin{aligned}
\frac{dT(t)}{dt} &= \lambda - dT - \beta_s V_s T - \beta_r V_r T, \\
\frac{dT_s(t)}{dt} &= (1 - \mu)\beta_s V_s T - \delta T_s - kT_s Z, \\
\frac{dV_s(t)}{dt} &= p_s T_s - d_1 V_s, \\
\frac{dT_r(t)}{dt} &= \beta_r V_r T + \mu \beta_s V_s T - \delta T_r - kT_r Z, \\
\frac{dV_r(t)}{dt} &= p_r T_r - d_1 V_r, \\
\frac{dZ(t)}{dt} &= c(T_r + T_s)Z - bZ.
\end{aligned}
\]  

(1)

In equation (1), \( T(t), T_s(t) \) and \( T_r(t) \) denote uninfected CD4+ T cells, infected cells with drug-sensitive virus, and infected cells with drug-resistant virus at time \( t \), respectively. \( V_s(t) \) and \( V_r(t) \) are the drug-sensitive virus and drug-resistant virus at time \( t \), respectively. \( Z(t) \) denotes the cross-reactive immune response at time \( t \). \( \lambda \) is the production rate of uninfected CD4+ T cells and \( d \) is the death rate. \( \beta_s \) and \( \beta_r \) represent the infection rates of CD4+ T cells by wild-type and drug-resistant virus, respectively. \( \mu \) is the rate at which virus mutates during the reverse transcription process. Both types of infected cells are assumed to die at rate \( \delta \) and are further removed by the CTL immune response at rate \( k \). Wild-type and drug-resistant viruses are produced with the viral production rates \( p_s \) and \( p_r \), respectively. We assume that the wild-type and resistant viruses have the same clearance rate \( d_1 \). The parameter \( c \) is the generation rate of CTL proliferation in response to antigenic stimulation, and \( b \) is the death rate of CTLs [56]. The schematic diagram of the model (1) is given in Fig. 1. The detailed description and values of the parameters are listed in Table 1.

2.1. Reproduction numbers and equilibria. System (1) always has the disease-free equilibrium \( E^0 = (\frac{\lambda}{d}, 0, 0, 0, 0, 0) \). Using the next-generation method [51], we define the matrices of the new infection terms and the transfer terms, i.e. \( F \) and \( V \):

\[
F = \begin{pmatrix}
0 & (1 - \mu)\beta_s \lambda d & 0 & 0 & 0 \\
0 & \mu \beta_s \lambda d & 0 & \beta_r \lambda d & 0 \\
0 & 0 & \beta_r \lambda d & 0 & 0 \\
0 & 0 & 0 & \beta_r \lambda d & 0 \\
0 & 0 & 0 & 0 & \beta_r \lambda d \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}, \quad V = \begin{pmatrix}
\delta & 0 & 0 & 0 & 0 \\
0 & -p_s & d_1 & 0 & 0 \\
0 & 0 & \delta & 0 & 0 \\
0 & 0 & 0 & -p_r & d_1 \\
0 & 0 & 0 & 0 & -p_r \end{pmatrix}.
\]
Figure 1. The schematic diagram of HIV transmission with wild-type and resistant virus

Table 1. Parameter descriptions and sources for their values

| Parameter | Value | Ranges     | Description                                                                 | Reference |
|-----------|-------|------------|------------------------------------------------------------------------------|-----------|
| $\lambda$ | $10^4$ | $100 \sim 200000$ | Production rate of uninfected cells                                           | [42]      |
| $d$       | 0.01   | $0.001 \sim 0.8$ | Death rate of uninfected cells                                                | [34]      |
| $\beta_s$ | $2.4 \times 10^{-8}$ | $10^{-6} \sim 2.4 \times 10^{-8}$ | Infection rate of uninfected cells by wild-type virus                        | [34]      |
| $\beta_r$ | $2.0 \times 10^{-8}$ | $10^{-6} \sim 2.0 \times 10^{-6}$ | Infection rate of uninfected cells by drug-resistant virus                    | [42]      |
| $\delta$  | 0.3    | $0.1 \sim 0.9$ | Death rate of infected cells                                                   | [42]      |
| $k_c$     | 0.002  | -           | Clearance rate of infected cells by CTL killing                               | [48, 1]   |
| $p_s$     | 900    | $90 \sim 1000$ | Generation rate of wild-type virus                                            | [8, 17]   |
| $p_r$     | 600    | $60 \sim 1000$ | Generation rate of drug-resistant virus                                       | [8, 17]   |
| $d_1$     | 23     | $10 \sim 50$  | Clearance rate of wild-type and resistant virus                               | [39]      |
| $c$       | 0.003  | $0.0 \sim 0.001$ | Generation rate of CTL                                                        | [55, 61]  |
| $b$       | 0.01   | $0.01 \sim 1$  | Death rate of CTL                                                            | [48, 61]  |
| $\epsilon_{RTI}$ | Varied | $0 \sim 1$ | Efficacy of RTI                                                              | see text  |
| $\epsilon_{PI}$ | Varied | $0 \sim 1$ | Efficacy of PI                                                               | see text  |
| $\sigma_{RTI}$ | Varied | $0 \sim 1$ | Resistance ratio of RTI                                                       | see text  |
| $\sigma_{PI}$ | Varied | $0 \sim 1$ | Resistance ratio of PI                                                       | see text  |

Therefore, the basic reproduction number can be calculated by the spectral radius of operator $\mathbf{FV}^{-1}$:

$$R_0 = \rho(\mathbf{FV}^{-1}) = \max \{ R_s, R_r \} ,$$

where

$$R_s = \frac{(1 - \mu) \beta_s p_s \lambda}{dd_1 \delta}, \quad R_r = \frac{\beta_r p_r \lambda}{dd_1 \delta} .$$

We call $R_s$ the basic reproductive number of wild-type strain and $R_r$ the basic reproductive number of drug-resistant strain. We also define the CTL immune response reproduction numbers $R_{cs}$ and $R_{cr}$ [2, 49, 19]

$$R_{cs} = \frac{c(1 - \mu) \beta_s p_s - \delta dd_s}{\delta b(1 - \mu) \beta_s p_s} = \frac{c\lambda (R_s - 1)}{b\delta R_s} , \quad R_{cr} = \frac{c\lambda (R_r - 1)}{b\delta R_r} .$$

Note that only when $R_s > 1, R_{cs} > 1, R_r > 1, R_{cr}$ exists. We introduce the CTL immune response reproduction numbers not only to distinguish from the basic reproduction number but also to classify the model dynamics. We will show that the stability of steady states is determined by $R_s, R_r, R_{cs}$ and $R_{cr}$. 
Straightforward computation shows that system (1) has three potential boundary equilibria and one positive equilibrium:

(i) The CTL immune-free equilibrium

\[ E^f = (T^f, T'_f, V'^f, T'^f, V'^f, 0) \]

\[ = \left( \frac{d_1 s}{1 - \mu}, \frac{\lambda (1 - \mu) (R_s - 1)(R_r - R_s)}{R_c \delta (1 - \mu) R_r - R_s}, \frac{\mu \lambda (1 - R_s)}{\delta (1 - \mu) R_r - R_s}, \frac{p_c}{d_1}, \frac{p_r}{d_1}, 0 \right); \]

(ii) The infected equilibrium with only drug-resistant strain

\[ E^r = (T^r, 0, 0, T'_r, V'_r, 0) = \left( \frac{d_1 s}{\beta_r p_r}, 0, 0, \frac{\lambda}{\delta} (1 - \frac{1}{R_r}), \frac{p_r}{d_1} T'_r, 0 \right); \]

(iii) The infected equilibrium with drug-resistant strain and CTL immune response

\[ E^{rc} = (T^{rc}, 0, 0, T'_r, V'_r, 0) = \left( \frac{\lambda^2 c}{(\lambda c + R_r \delta b) d}, 0, 0, \frac{b c}{d_1} T^{rc}, \frac{b R_s \delta^2 (R_{cr} - 1)}{c \lambda (k c + k b \delta R_s)} \right); \]

(iv) The positive equilibrium

\[ E^* = (T^*, T'_*, V'_*, T'^*, V'^*, Z^*) \]

\[ = \left( \frac{\lambda^2 c}{(\lambda c + R_r \delta b) d}, \frac{b}{\beta_r p_r}, \frac{b R_s (1 - \frac{1}{(1 - \mu) R_s})}{c R_r (1 - \frac{R_s}{(1 - \mu) R_s})}, \frac{p_c}{d_1}, \frac{p_r}{d_1} T'_r, \frac{b R_s \delta^2 (R_{cr} - 1)}{c \lambda (k c + k b \delta R_s)} \right). \]

Based on straightforward algebraic calculation, we have the following theorem.

**Theorem 2.1.** (1) The disease-free equilibrium \( E^0 \) always exists.

(2) The infected equilibrium with only drug-resistant strain \( E^r \) exists if and only if \( R_r > 1 \); The infected equilibrium with drug-resistant strain and CTL immune response \( E^{rc} \) exists if and only if \( R_r > 1 \) and \( R_{cr} > 1 \).

(3) The CTL immune-free equilibrium \( E^f \) exists if and only if \( R_s > 1 \) and \( \frac{R_s}{R_r} > 1 \); The positive equilibrium \( E^* \) exists if and only if \( R_s > 1 \), \( R_{cr} > 1 \) and \( \frac{R_s}{R_r} > 1 \).

2.2. **Stability results.** We study the local stability of equilibria \( E^0, E^r, E^{rc}, E^f \) and \( E^* \). Let \( \bar{E} = (\bar{T}, \bar{T}_s, \bar{V}, \bar{T}_r, \bar{V}_r, \bar{Z}) \) represent any equilibrium of system (1). We obtain the corresponding characteristic equation

\[
\begin{vmatrix}
-d - \beta_r \bar{V}_r - \mu \beta_s \bar{V}_s - \xi & 0 & -\beta_r \bar{V}_r & 0 & -\beta_r \bar{V}_r & 0 \\
0 & -\delta - k \bar{Z} - \xi & 0 & -\beta_r \bar{V}_r & 0 & -k \bar{T}_r \\
0 & 0 & -\delta - k \bar{Z} - \xi & 0 & 0 & -k \bar{T}_r \\
0 & 0 & 0 & -\delta - k \bar{Z} - \xi & 0 & -k \bar{T}_r \\
0 & 0 & 0 & 0 & -d_1 - \xi & 0 \\
\end{vmatrix} = 0,
\]

where \( \xi \) denotes the eigenvalue.

Using the Routh-Hurwitz criterion [4], we can prove the local stability of \( E^0, E^r, E^{rc}, E^f \) under some conditions involving the reproduction numbers. The proof of the theorem involves tedious algebraic computation and is given in Appendix.

**Theorem 2.2.** (1) The disease-free equilibrium \( E^0 \) is locally asymptotically stable (L.A.S) if \( R_0 < 1 \) and unstable if \( R_0 > 1 \).

(2) If \( R_r > R_s, R_r > 1 \) and \( R_{cr} < 1 \), then the infected equilibrium with only drug-resistant strain \( E^r \) is L.A.S.

(3) If \( R_r > R_s, R_r > 1 \) and \( R_{cr} > 1 \), then the infected equilibrium with drug-resistant strain and CTL immune response \( E^{rc} \) is L.A.S.
(4) If $R_s > R_r$, $R_s > 1$ and $R_{cs} < 1$, then the CTL immune-free equilibrium $E^f$ is L.A.S.

Although we do not have an analytic result for $E^\star$, numerical studies suggest that $E^\star$ is L.A.S whenever it exists, i.e. when $R_s > R_r$, $R_s > 1$ and $R_{cs} > 1$.

The stability results of the system (1) are summarized in Table 2.

### Table 2. Summary of the stability results of system (1)

| Conditions | System (1) |
|------------|------------|
| $R_0 < 1$  | $E^0$ is L.A.S |
| $R_0 > 1$, $R_s < R_r$ | $R_{cr} < 1$, $E^\star$ is L.A.S |
| $R_s > R_r$, $R_{cs} < 1$ | $E^t$ is L.A.S |
| $R_s > R_r$, $R_{cs} > 1$ | $E^f$ is L.A.S |

![Figure 2.](image)

**Figure 2.** The dynamics of infection before converging to steady states. (a) – (d) represent uninfected cells, wild-type virus, resistant virus, and CTL cells, respectively. The blue solid line is the case in which CTL cells are present. The parameters are from Table 1 and $b = 0.1$. We have $R_s = 3.13 > R_r = 1.74 > 1$, $R_{cs} = 68.1 > 1$. Solution trajectories of the system converge to the positive equilibrium $E^\star = (415257, 14994.3, 586870, 1.01219, 26.4110, 44.9845)$. The red dotted line refers to the case in which CTL cells are absent. The parameter $c$ is 0. This yields $R_s = 3.13 > R_r = 1.74 > 1$, $R_{cs} = 0 < 1$. Solution trajectories of the system converge to the CTL immune-free equilibrium $E^f = (318355, 23056.2, 902393, 1.55640, 40.6104, 0)$.  

![Table 2. Summary of the stability results of system (1)](image)
In view of the mutation-associated fitness loss [42], we expect that the wild-type virus dominates the virus population without antiretroviral therapy. This is observed in the predicted dynamics by Fig. 2. The blue solid line in Fig. 2 presents the infection dynamics in the presence of CTLs, while the red dotted line presents that without CTLs. In both cases, wild-type virus outcompetes the mutant virus. We also observe that in the absence of CTLs, the solution converges to the CTL immune-free equilibrium $E^f$, while in the presence of CTLs, the solution converges to the positive equilibrium $E^\ast$. In Fig. 2(c), the blue solid line reaches a lower peak and converges to the steady state that is also lower than the red dotted line. This suggests that the CTL immune response can limit the production of drug-resistant virus. Note that CTLs do not disappear but remain at a certain level. Thus, CTLs cells persist when the infection becomes chronic (Fig. 2(d)). The parameter values used in numerical simulation in this paper are shown in Table 1.

Figure 3. Sensitivity analysis for four reproduction numbers. (a) The PRCC of $R_s$ for seven parameters, (b) the PRCC of $R_r$ for six parameters, (c) the PRCC of $R_{cs}$ for nine parameters, and (d) the PRCC of $R_{cr}$ for eight parameters.

2.3. Sensitivity analysis. According to the above analysis, we know that the reproductive numbers play an important role in predicting the dynamics of HIV infection. In this section, we perform sensitivity analysis to determine the parameters that affect the four reproductive numbers [25, 5, 67]. The analysis is based on the Latin hypercube sampling (LHS) scheme and partial rank correlation coefficient (PRCC) method. The results of sensitivity analysis were plotted in Fig. 3.

Using LHS, 100 samples are taken from the uniform distribution in the parameter ranges. The PRCC between reproduction numbers and each parameter is calculated. PRCC falls between -1 and 1. The absolute value of PRCC close to 1 indicates that the parameter has a strong impact on the model output. More precisely, there exists a strong correlation between the input parameter and the output variable when $|PRCC| > 0.4$, the correlation is moderate when $0.2 < |PRCC| < 0.4$, and the correlation is weak when $|PRCC| < 0.2$ [19]. The sign of the PRCC represents positive or negative correlation between the input and output variables [66]. It
follows from Fig. 3(a) that the parameters that have a significant impact on $R_s$ are $\beta_s, \lambda, p_s, d, d_1$ and $\delta$, among which $\beta_s, \lambda, p_s$ are positively correlated with $R_s$, while $d, d_1, \delta$ are negatively correlated. Fig. 3(c) shows that the influence of $\lambda, \delta$ on $R_{cs}$ is similar to that on $R_s$. The parameters $c$ and $b$ can also greatly change $R_{cs}$. Comparing with the above, the influence of $\lambda, \delta, c$ and $b$ on $R_{cr}$ is similar (Fig. 3(d)). Fig. 3(b) shows that $R_r$ is highly correlated to the parameters $\beta_r, \lambda, p_r, d, d_1$ and $\delta$. The four reproduction numbers are all sensitive to the production rate of uninfected cells.

3. Model with antiretroviral therapy. In this section, we modified model (1) by including combination antiretroviral therapy (cART). A combination of reverse transcriptase inhibitors (RTI) and protease inhibitors (PI) is usually used in the treatment of HIV infection. We let $\varepsilon_{RTI}$ and $\varepsilon_{PI}$ be the effectiveness of RTI and PI for the wild-type strain, respectively. $\varepsilon_{RTI}$ and $\varepsilon_{PI}$ are between 0 and 1. Comparing with the wild-type strain, drug-resistant strain is less sensitive to the two drugs. We define the resistance ratios, $\sigma_{RTI}$ and $\sigma_{PI}$, which are between 0 and 1. Thus, $\varepsilon_{RTI}\sigma_{RTI}$ and $\varepsilon_{PI}\sigma_{PI}$ are the drug efficacy of RTI and PI for the drug-resistant strain, respectively. Note that $\varepsilon_i = 0$ (i=RTI or PI) means that the inhibitors are completely ineffective, while $\varepsilon_i = 1$ means that the inhibitors are 100% effective against the wild-type strain.

The modified model including antiretroviral drugs can be described by the following ODE system:

$$
\begin{align*}
\frac{dT(t)}{dt} &= \lambda - dT - (1 - \varepsilon_{RTI})\beta_s V_i sT - (1 - \varepsilon_{RTI}\sigma_{RTI})\beta_r V_i rT, \\
\frac{dV_i s(t)}{dt} &= (1 - \varepsilon_{RTI}) (1 - \mu) \beta_s V_i sT - \delta T s - kT s Z, \\
\frac{dV_i r(t)}{dt} &= (1 - \varepsilon_{PI}) p r T s - d_1 V_i r, \\
\frac{dV_i N t(t)}{dt} &= \varepsilon_{PI} p r T s - d_1 V_i N t, \\
\frac{dV_i N I(t)}{dt} &= (1 - \varepsilon_{RTI}\sigma_{RTI}) \beta_r V_i rT + \mu(1 - \varepsilon_{RTI}) \beta_s V_i sT - \delta T r - kT r Z, \\
\frac{dV_i N I(t)}{dt} &= (1 - \varepsilon_{PI}\sigma_{PI}) p r T r - d_1 V_i r, \\
\frac{dV_i N N I(t)}{dt} &= \varepsilon_{PI}\sigma_{PI} p r T r - d_1 V_i N N I, \\
\frac{dZ(t)}{dt} &= c(T r + T s) Z - b Z,
\end{align*}
$$

(3)

$V_i N I(t)$ and $V_i N N I(t)$ are non-infectious virus particles generated due to the effect of PIs. The total viruses of drug-sensitive and drug-resistant are $V_s = V_i s + V_i N I$ and $V_r = V_i r + V_i N N I$, respectively. Using the same method as [45] (details can be found in the Appendix), we can reduce the dimension and write the model as

$$
\begin{align*}
\frac{dT(t)}{dt} &= \lambda - dT - (1 - \eta_s)\beta_s V_s T - (1 - \eta_r)\beta_r V_r T, \\
\frac{dV_s(t)}{dt} &= (1 - \eta_s) (1 - \mu) \beta_s V_s T - \delta T s - kT s Z, \\
\frac{dV_r(t)}{dt} &= (1 - \eta_r) \beta_r V_r T + \mu(1 - \eta_s) \beta_s V_s T - \delta T r - kT r Z, \\
\frac{dV_r(t)}{dt} &= \eta_r T r - d_1 V_r, \\
\frac{dZ(t)}{dt} &= c(T r + T s) Z - b Z,
\end{align*}
$$

(4)

where $\eta_s = 1 - (1 - \varepsilon_{RTI})(1 - \varepsilon_{RTI})$ and $\eta_r = 1 - (1 - \varepsilon_{RTI}\sigma_{RTI})(1 - \varepsilon_{PI}\sigma_{PI})$ are the overall drug efficacy of wild-type and resistant virus, respectively. Antiretroviral therapy reduces the infection rates $\beta_s$ and $\beta_r$ to $(1 - \eta_s)\beta_s$ and $(1 - \eta_r)\beta_r$, respectively. Therefore, the steady states and reproduction numbers of the pretreatment model can be obtained accordingly. We change the notation from $A$ to $A'$, for
example, under treatment the steady state $E^f$ becomes $E'^f$ and the reproduction number $R_s$ becomes $R'_s$. It is clear that the incorporation of therapy does not affect our analysis of the equilibria of the model.

![Figure 4](image-url)

**Figure 4.** Predicted dynamics of system (4) under treatment. (a) – (d) represent uninfected cells, wild-type virus, resistant virus, and CTL cells, respectively. The blue solid line represents the case in which CTL cells are present. The parameters given in Table 1 are used and $b = 0.1$. This yields $R'_s = 1.57 > R'_r = 1.54 > 1$ and $R'_{cs} = 36.30 > 1$. Thus, solutions trajectories of the system converge to the interior equilibrium $E'^* = (733912, 7673.78, 243257, 13.8008, 346.384, 23.0628)$. The red dotted line refers to the case in which CTL cells are absent. Parameters from Table 1 are used and $b = 0.1, c = 0$. In this case, $R'_s = 1.57 > R'_r = 1.54 > 1$ and $R'_{cs} = 0 < 1$. Solutions trajectories of the system converge to the CTL immune-free equilibrium $E'^f = (635966, 12174.6, 476875, 21.8671, 571.018, 0)$.

During drug treatment, drug-resistant virus increases (compare Fig. 2(c) and Fig. 4(c)). This is because the therapy inhibits the replication of wild-type virus, which leads to an increase in target cells and thus the growth of drug-resistant virus. Thus, drug-resistant virus increases due to the increased availability of target cells [30]. Because the total viral load decreases in the presence of drugs, the CTL immune response eventually converges to a lower level (compare Fig. 2(d) and Fig. 4(d)). Although the CTL immune response is not strong under a low level of antigen stimulation, it can further reduce the viral load under treatment by comparing the steady states in Fig. 2 and Fig. 4, namely, $\frac{\nu_f' + \nu_{fr}'}{\nu_f' + \nu_{fr}'} > \frac{\nu_f' + \nu_{fr}'}{\nu_f' + \nu_{fr}'}$. This prediction is consistent with that found in [62, 58]. From Fig. 4(b) and (c), we also notice that the wild-type virus dominates the virus population with parameter values used in the simulation.
To obtain the condition under which the drug-resistant stain invades and outcompetes the wild-type strain, we perform the numerical simulation in Fig. 5. As stated in document [23], the overall drug efficacy may be as low as 68% for some combination therapies, meaning that $\eta_s$ is almost impossible to equal 1. Without losing generality, we assume that the maximum value of $\eta_s$ is 0.9. The dark surface shows the reproductive number of wild-type strain and the light surface is the resistant strain (Fig. 5(a)). Figure 5(b) is the projection of Fig. 5(a) on the $\beta_s - \eta_s$ plane and Fig. 5(c) is part of Fig. 5(b). For the drug-resistant strain to dominate the virus population, the reproduction number of the resistant strain needs to be greater than that of the sensitive strain. In Fig. 5(a), we observe that $R'_s$ is greater than or equal to $R'_r$ when $\eta_s$ is less than 0.51. In other words, the resistant strain may be able to invade and outcompete the wild-type strain when the drug efficacy $\eta_s$ is above the numerical threshold 0.51. This result also indicates that the resistant strain may not be an issue during treatment if the drugs are less effective. For a small infection rate $\beta_s$, $R'_r$ and $R'_s$ both become less than 1 as the overall drug efficacy of combination therapy $\eta_s$ increases to above a threshold value. This means that both strains of virus will be eradicated for a high efficacy (Fig. 5(b)).

![Figure 5](image_url)

**Figure 5.** Invasion of drug-resistant virus. (a) Effects of the infection rate $\beta_s$ and overall drug efficacy $\eta_s$ on $R'_s$ and $R'_r$. (b) The projection of (a) on the $\beta_s - \eta_s$ plane. (c) Part of (b) when $\eta_s$ is from 0.4 to 0.6. The vertical line in magenta represents $\eta_s = 0.51$. In the simulation, we assume that $\eta_r = 0.23\eta_s$, $\beta_r = 0.83\beta_s$. The other parameters are given in Table 1.

From Fig. 5, we know that under certain conditions the resistant strain can invade the wild-type strain during treatment. Figure 6 depicts the dynamics of system (4) when $\eta_s$ is greater than 0.51 or less than 0.51. In Fig. 6(a) and (b), $\eta_s = 0.6876$ and $R'_s = 0.9778 < 1 < R'_r = 1.455$, $R'_{cr} = 312.7 > 1$. Thus, the solutions of the system
Figure 6. Predicted dynamics of system (4) when drug resistance invades during treatment. Figure (a) – (b) shows the wild-type virus and the resistant virus, respectively. \( \eta_s = 0.6876, \eta_r = 0.1635, R'_s = 0.9778 < 1 < R'_r = 1.455, R_{cr} = 312.7 > 1. \) The solutions of the system converge to the infected equilibrium with drug-resistant strain and CTL immune response \( E^{cr} = (928780, 0, 0, 1756.85, 45817.3, 52.7080). \) Figure (c) – (d) is similar to (a) – (b) except \( \eta_s = 0.4330, \eta_r = 0.0957. \) In this case, \( R'_s = 1.573 < R'_r = 1.775, R'_{cs} = 436.6 > 1. \) Both strains of virus persist and the solutions of the system converge to the interior equilibrium \( E'^* = (872574, 2744.46, 86963.0, 0.722593, 18.1288, 82.2710). \) The parameters are from Table 1.

The solutions of the system converge to the infected equilibrium with drug-resistant strain and CTL immune response \( E^{cr} = (928780, 0, 0, 1756.85, 45817.3, 52.7080). \) In Fig. 6(c) and (d), \( \eta_s = 0.4330 \) and \( R'_r = 1.573 < R'_s = 1.775, R'_{cs} = 436.6 > 1. \) The solutions of the system converge to the interior equilibrium \( E'^* = (872574, 2744.46, 86963.0, 0.722593, 18.1288, 82.2710). \) These simulations agree with the analytical stability and invasion results. Based on these results, we will study the role of CTL immune response in the evolution of drug-resistant virus in the presence of treatment (in the case that the drug-resistant strain has prevailed over the wild-type strain).

Figure 7 shows how the immune cell proliferation affects the dynamics of drug-resistant virus. Wild-type virus dominates the population before treatment and it simulates the CTL immune response [27]. Drug administration leads to the decline of the wild-type strain and the emergence of drug-resistant strain. In Fig. 7, we chose \( \eta_s = 0.5328 \) such that drug-resistant strain dominates the population. We found that the CTL immune response has a significant effect on the change of virus (especially drug-resistant virus). In the absence of CTLs (i.e. \( c = 0 \)), the wild-type virus experiences a substantial increase to the peak level, followed by a decline to extinction, while drug-resistant virus increases to a stable steady state (see Fig. 7(b,c)). Including CTLs significantly reduces the drug-resistant viral load (Fig. 7(c)). The results show that the CTL immune response can limit the development
Figure 7. Dynamics of system (4) with different values of $c$ (the proliferation rate of CTLs). Green dashed-dot line is for $c = 0$, black solid line is for $c = 0.00003$, blue dashed line is for $c = 0.0002$, and red dot line is for $c = 0.001$. We chose $\eta_s = 0.5328$, $\eta_r = 0.1221$ and the other parameters can be found in Table 1.

Figure 8. Drug resistance dynamics under different drug efficacies. (a) The immune clearance rate is $b = 0.1$ and (b) $b = 0.01$. Green curve is for $\eta_s = 0.52, \eta_r = 0.12$, red curve is for $\eta_s = 0.69, \eta_r = 0.16$, and blue curve is for $\eta_s = 0.96, \eta_r = 0.29$. $c$ is fixed at 0.001 and other parameters are given in Table 1.

of the drug-resistant strain even when the resistant virus outcompetes the wild-type strain and dominates the virus population.

Figure 8 shows how the immune decay and drug efficacy affect the drug resistance dynamics. We studied the dynamics of the resistant virus using different values of $b$ (the death rate of CTLs) and drug efficacies. In Fig. 8(a), we chose $b = 0.1$ and in Fig. 8(b), we chose a smaller value $b = 0.01$. The values of the other parameters are the same as those in Fig. 7. It is clear that the slower the immune response wanes, the slower the resistant strain arises (compare (a) with (b)). Furthermore, the decay of CTL immune responses plays an important role in the dynamics of drug-resistant virus when treatment is not very effective. Interestingly, comparing
\( \eta_s = 0.52 \) (green line) and \( \eta_s = 0.96 \) (blue line), the drug-resistant virus increases to the maximum viral load when \( \eta_s = 0.69 \) (red line). This implies that drug efficacy in the intermediate range is more likely to lead to the growth of drug-resistant virus. In fact, there is a dynamic relationship between drug efficacy and the growth of drug-resistant virus. When the drug efficacy is small, drug selection pressure is low. Wild-type virus outcompetes drug-resistant virus. The resistant virus remains at a very low level compared with the wild-type virus although two strains coexist (see Fig. 6(c,d)); when the drug efficacy is very high, wild-type virus will be completely suppressed. Drug resistant virus is suppressed, too, because we assume that drug resistant virus is still partially sensitive to the treatment.

4. Discussion and conclusion. In HIV-infected patients, ART can suppress the viral load to below the detection limit but cannot achieve viral eradication. Ongoing viral replication, particularly in patients receiving suboptimal treatment, may lead to the accumulation of drug-resistant virus and treatment failure. Mathematical models have been developed to study the prevalence of mutant variants before therapy and their competition with the wild-type virus in the presence of drug pressure [42, 43, 52, 37, 38, 50, 29]. Many models ignored the effect of CTL immune responses, which play an important role in controlling viral replication. In a recent study, Ngina et al. [29] used a ten-dimensional model to evaluate the optimal treatment strategy that minimizes the levels of drug resistant and wild type viruses. The paper also includes CD8+ T-cells in the model and found that protease inhibitor might be a very effective drug in controlling HIV infection.

In this paper, we analyze a two-strain viral dynamic model that includes the effect of CTL responses. We start with a model that describes the interaction between the two strains (mutant and wild-type) and the immune system before treatment. Before therapy, the mutant strain exists due to mutations during RNA reverse transcription. Including CTL effect in the model leads to lower levels of both wild-type and mutant virus, and a higher level of uninfected CD4+ T cell (Fig. 2). Mathematical analysis of the model shows that there are five possible steady states: infection-free equilibrium \( E^0 \), CTL immune-free equilibrium \( E^f \), infected equilibrium with only drug-resistant strain \( E^r \), infected equilibrium with drug-resistant strain and CTL immune response \( E^{rc} \) and the positive equilibrium \( E^{\ast} \) (in which all the variables are positive). The basic reproductive number \( R_0 = \max \{R_s, R_r\} \) and the CTL immune response reproduction numbers for two strains \( (R_{cs}, R_{cr}) \) are obtained. We show that the local stability of equilibria are determined by the relative magnitudes of the reproduction numbers \( R_0, R_{cs} \) and \( R_{cr} \) (Table 2). In view of the important role of the reproduction numbers \( R_0, R_{cs} \) and \( R_{cr} \) on the dynamics, we also perform the sensitivity analysis of these reproduction numbers on a few key parameters through Monte-Carlo simulation (Fig. 3).

HIV morbidity and mortality have been significantly reduced because of the administration of highly active antiretroviral therapy since the mid-1990s [28]. Drug resistance can emerge, persist, and pose a challenge for future treatment, particularly in patients with suboptimal treatment [10]. We include drug therapy in the two-strain model with CTL response. The inclusion of treatment doesn’t bring difficulty in the analysis of the model because drug efficacy is assumed to be constant. Numerical investigations show that that the combination of CTL response and drug treatment can further control HIV infection and replication (see Fig. 2 and Fig. 4). We have obtained the invasion conditions under which the drug-resistant strain can
outcompete the wild-type strain in the presence of drug pressure (Fig. 5). There is a balance between drug use, the prevalence of drug resistance, and the overall viral load. Immune response was also shown to play an important role in the control of drug resistance (Fig. 7 and Fig. 8). Immunotherapy that aims to enhance the immune response, combined with antiretroviral therapy, may result in a functional control of HIV infection.

Appendix. (i) Stability of the infection-free equilibrium.

From equation (2), we obtain the characteristic equation at $E^0$

$$(\xi + d)(\xi + b)\left(\xi^2 + (\delta + d_1)\xi + \delta d_1 - (1 - \mu)p_s \beta_s \frac{\lambda}{d}\right)\left(\xi^2 + (\delta + d_1)\xi + \delta d_1 - p_r \beta_r \frac{\lambda}{d}\right) = 0,$$

(5)

where $\xi$ is the eigenvalue. Equation (5) has two negative eigenvalues $-d$ and $-b$. The remaining four eigenvalues have negative real part if $R_0 < 1$ (i.e. $R_s < 1$ and $R_r < 1$).

(ii) Stability of the infected equilibrium with only drug-resistant strain.

The characteristic polynomial at the steady state $E^r$ is given by

$$(-d - \frac{\lambda \beta_r p_r (1 - \frac{1}{R_r})}{d_1 \delta} - \xi) \left(\xi^2 + (d_1 + \delta)\xi + \delta d_1 - (1 - \mu)\beta_s p_s \frac{\delta d_1}{\beta_r p_r}\right) \times 
\left(\frac{c\lambda (1 - \frac{1}{R_r})}{\delta} - b - \xi\right)\left(\xi^2 + (d R_r + d_1 + \delta)\xi^2 + (d_1 + \delta) d R_r \xi + \delta d_1 d(R_r - 1)\right) = 0.$$  

(6)

Equation (6) has solutions $\xi_1 = -d - \frac{\lambda \beta_r p_r (1 - \frac{1}{R_r})}{d_1 \delta}$ and $\xi_2 = \frac{c\lambda (1 - \frac{1}{R_r})}{\delta} - b$. It is clear that $\xi_1 < 0$ when $R_r > 1$, and $\xi_2 < 0$ when $R_{cr} < 1$.

Let

$$Q(\xi) = \xi^2 + (d_1 + \delta)\xi + \delta d_1 - (1 - \mu)\beta_s p_s \frac{\delta d_1}{\beta_r p_r}.$$  

(7)

We know that all the roots of $Q(\xi) = 0$ have negative real part when $R_s < R_r$.

The remaining eigenvalues are determined by the following equation

$$\xi^3 + a_1 \xi^2 + a_2 \xi + a_3 = 0,$$

(8)

where

$$a_1 = d R_r + d_1 + \delta > 0, \quad a_2 = (d_1 + \delta) d R_r > 0, \quad a_3 = \delta d_1 d(R_r - 1).$$

We have $a_3 > 0$ when $R_r > 1$. Moreover, we can verify that

$$H_1 = a_1 > 0, \quad H_2 = a_1 a_2 - a_3 > 0.$$  

(9)

By Routh-Hurwitz criterion, all the roots of equation (8) have negative real part. Therefore, $E^r$ is locally asymptotically stable (L.A.S) when $R_r > R_s, R_r > 1, R_{cr} < 1$.

(iii) Stability of the infected equilibrium with drug-resistant strain and CTL immune response.
When eigenvalues are determined by the following equation where

\[
(\xi^2 + \left(\frac{(R_r - 1)c\lambda - \delta bR_r}{c\lambda + bR_r}\delta + \delta + d_1\right)\xi + d_1(\delta + \frac{(R_r - 1)c\lambda - \delta bR_r}{c\lambda + bR_r}\delta) - (1 - \mu)\times p_s\beta_s \frac{\lambda^2 c}{(\lambda c + R_r\delta b)d}) \times \left(\xi^4 + a_1\xi^3 + a_2\xi^2 + a_3\xi + a_4\right) = 0,
\]

where

\[
a_1 = d + \delta + d_1 + \beta_r \frac{bp_r}{cd_1} + \frac{(R_r - 1)c\lambda - \delta bR_r}{c\lambda + bR_r}\delta, \\
a_2 = \frac{1}{c\lambda + R_r\delta b} \left(\left(c\lambda\delta + bd_1\delta\right)\left(d + \frac{bp_r\beta_r}{cd_1}\right) - b^2\delta^2\right)R_r + cd_1\lambda(d + \frac{bp_r\beta_r}{cd_1}) + \beta c\lambda(\delta b(R_r - 1)), \\
a_3 = \frac{1}{c\lambda + R_r\delta b} \left(b\delta(d_1 + d + \frac{bp_r\beta_r}{cd_1})(c\lambda(R_r - 1) - bR_r\delta) + \frac{p_r^2\beta_r^2\lambda^2b}{d_1}\right), \\
a_4 = \frac{1}{c\lambda + R_r\delta b} \left(d_1\delta(c\lambda(R_r - 1) - bR_r\delta)(d + \frac{bp_r\beta_r}{cd_1})\right).
\]

Let

\[
F(\xi) = \xi^2 + \left(\frac{(R_r - 1)c\lambda - \delta bR_r}{c\lambda + bR_r}\delta + \delta + d_1\right)\xi + d_1(\delta + \frac{(R_r - 1)c\lambda - \delta bR_r}{c\lambda + bR_r}\delta) - (1 - \mu)p_s\beta_s \frac{\lambda^2 c}{(\lambda c + R_r\delta b)d}.
\]

When \(R_r > R_s\), all the roots of \(F(\xi) = 0\) have negative real part. The remaining eigenvalues are determined by the following equation

\[
\xi^4 + a_1\xi^3 + a_2\xi^2 + a_3\xi + a_4 = 0,
\]

where \(a_1 > 0\) and \(a_4 > 0\). When \(R_r > 1, R_{cr} > 1\), the inequalities \(a_2 > 0, a_3 > 0\) are also valid. Moreover, we can verify that

\[
H_1 = a_1 > 0, \quad H_2 = a_1a_2 - a_3 > 0, \quad H_3 = a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0, \quad H_4 = a_4H_3 > 0.
\]

Again by Routh-Hurwitz criterion, we know that all the roots of the polynomial equation (12) have negative real parts. Thus, the equilibrium \(E^{rc}\) is L.A.S when \(R_r > R_s, R_r > 1, R_{cr} > 1\).

(iv) Stability of the CTL immune-free equilibrium.

We have the following characteristic equation at \(E^f\)

\[
\left(\frac{c\lambda(R_s - 1)}{R_s\delta} - b - \xi\right)(\xi^5 + a_1\xi^4 + a_2\xi^3 + a_3\xi^2 + a_4\xi + a_5) = 0,
\]

(14)
where
\[ a_1 = 2d_1 + \delta + R_s d + \delta, \quad a_2 = (d_1 + R_s d + \delta)(d_1 + \delta) + (R_s d d_1 + \delta d_1(1 - \frac{R_r}{R_s}) + R_s d \delta), \]
\[ a_3 = (R_s - 1)d d_1 \delta + (R_s d d_1 + R_s d \delta + \delta d_1(1 - \frac{R_r}{R_s}))(d_1 + \delta) + R_s d d_1 \delta - \lambda \beta \rho, \]
\[ a_4 = (R_s - 1)d d_1 \delta(d_1 + \delta)(R_s d d_1 \delta - \lambda \beta \rho)(d_1 + \delta), \]
\[ a_5 = (1 - (1 - \mu)R_r) \frac{\delta^2 dd_1(R_s - 1)(R_r - R_s)}{(1 - \mu)R_r - R_s}. \]

We have \( \xi_1 = \frac{c \lambda (R_r - 1)}{R_r \delta} - b < 0 \) when \( R_{cr} < 1 \). The remaining eigenvalues are determined by the equation
\[ \xi^5 + a_1 \xi^4 + a_2 \xi^3 + a_3 \xi^2 + a_4 \xi + a_5 = 0, \quad (15) \]
where \( a_1 > 0 \). When \( R_s > R_r, R_s > 1 \), we further have \( a_2 > 0, a_3 > 0, a_4 > 0, a_5 > 0 \). We can also verify that
\[ H_1 = a_1 > 0, \quad H_2 = a_1 a_2 - a_3 > 0, \quad H_3 = a_1 a_2 a_3 + a_1 a_5 - a_3^2 - a_1^2 a_4 > 0, \]
\[ H_4 = a_3 H_3 + a_1 a_4 a_5 - a_2 a_3 H_2 - a_5^2 > 0, \quad H_5 = a_5 H_4 > 0. \quad (16) \]

By Routh-Hurwitz criterion, all the roots of the polynomial equation (15) have negative real part. Thus, the equilibrium \( E^I \) is L.A.S when \( R_s > R_r, R_s > 1, R_{cr} < 1 \).

(v) Simplify model (3) to model (4).

![Figure 9](image_url)

Figure 9. (a) The difference between non-infectious and infectious wild-type virus concentrations. (b) The difference between non-infectious and infectious drug-resistant virus concentrations. Shortly after initiation of potent antiretroviral therapy, the difference between non-infectious and infectious viral levels (logarithm with base 10) approaches a constant. The parameters can be found in Table 1.

From Fig. 9, we notice that the differences between infectious virus and non-infectious virus, both wild-type and drug-resistant virus, i.e., \(| \log_{10} V_{NI} - \log_{10} V^I_s | \) and \(| \log_{10} V_{NI} - \log_{10} V^I_s | \), approach a constant after a short time under protease inhibitor therapy. This result is consistent with that found in [45]. Therefore, we can simplify the model in the same way as in reference [45]. To be more precise, let
\[ \eta_h = 1 - (1 - \varepsilon_{RTI})(1 - \varepsilon_{PT}), \quad V^I_s = \alpha V^N_s, \quad V_s = V^I_s + V^N_s. \]
Hence
\[ V_s' = \frac{\alpha}{1+\alpha} V_s, \]  
and
\[ \frac{dV_s}{dt} = 1 + \frac{\alpha}{1-\varepsilon_{PI}} (p_s T_s - d_s V_s). \]  
On the other hand,
\[ \frac{dV_s}{dt} = \frac{dV_s^N}{dt} + \frac{dV_s^f}{dt} = p_s T_s - d_s V_s. \]
Comparing (18) and (19), we get
\[ (1-\varepsilon_{PI}) = \frac{\alpha}{1+\alpha}. \]
Hence
\[ (1-\varepsilon_{RTI}) V_s' = (1-\eta_s) V_s. \]
Let
\[ \eta_r = 1 - (1-\varepsilon_{RTI}) (1-\varepsilon_{PI}) \]
In the same way, we can get
\[ (1-\varepsilon_{RTI}) V_r' = (1-\eta_r) V_r. \]
Therefore, we can simplify model (3) to model (4).

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REFERENCES

[1] B. M. Adams, H. T. Banks, M. Davidian, H.-D. Kwon, H. T. Tran, S. N. Wynne and E. S. Rosenberg, HIV dynamics: Modeling, data analysis, and optimal treatment protocols, J. Comput. Appl. Math., 184 (2005), 10–49.

[2] K. Allali, J. Danane and Y. Kuang, Global analysis for an HIV infection model with CTL immune response and infected cells in eclipse phase, Appl. Sci., 7 (2017), 861.

[3] R. A. Arnaout, N. Martin A and D. Wodarz, HIV–1 dynamics revisited: Biphasic decay by Cytotoxic T Lymphocyte killing?, Proc. R. Soc. Lond. B, 267 (2000), 1347–1354.

[4] N. P. Bhatia and G. P. Szegö, Stability Theory of Dynamical Systems, Springer Science & Business Media, 2002.

[5] S. M. Blower, D. Hartel, H. Dowlatabadi, R. M. Anderson and R. M. May, Drugs, sex and HIV: A mathematical model for New York City, Proc. R. Soc. Lond. B, 331 (1991), 171–187.

[6] S. Bonhoeffer, R. M. May, G. M. Shaw and M. A. Nowak, Virus dynamics and drug therapy, P. Natl. A. Sci., 94 (1997), 6971–6976.

[7] J. Cao, J. McNevin, S. Holte, L. Fink, L. Corey and M. J. McElrath, Comprehensive analysis of human immunodeficiency virus type 1 (HIV-1)-specific gamma interferon-secreting CD8+ T cells in primary HIV-1 infection, J. Virol., 77 (2003), 6867–6878.

[8] H. Y. Chen, M. Di Mascio, A. S. Perelson, D. D. Ho and L. Zhang, Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques, P. Natl. A. Sci., 104 (2007), 19079–19084.

[9] M. Chiue, B. Bivort, D. Bortz and P. Nelson, Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models, Math. Biosci., 200 (2006), 1–27.

[10] F. Clavel and A. J. Hance, HIV drug resistance, New. Engl. J. Med., 350 (2004), 1023–1035.

[11] R. V. Culshaw, S. Ruan and R. J. Spiteri, Optimal HIV treatment by maximising immune response, J. Math. Biol., 48 (2004), 545–562.

[12] M. P. Davenport, R. M. Ribeiro and A. S. Perelson, Kinetics of virus-specific CD8+ T cells and the control of human immunodeficiency virus infection, J. Virol., 78 (2004), 10096–10103.
[13] M. P. Davenport, R. M. Ribeiro, L. Zhang, D. P. Wilson and A. S. Perelson, Understanding the mechanisms and limitations of immune control of HIV, *Immunol. Rev.*, 216 (2007), 164–175.

[14] M. P. Davenport, et al., High-potency human immunodeficiency virus vaccination leads to delayed and reduced CD8+ T-cell expansion but improved virus control, *J. Virol.*, 79 (2005), 10059–10062.

[15] S. G. Deeks, M. Smith, M. Holodniy and J. O. Kahn, HIV-1 protease inhibitors: A review for clinicians, *Jama*, 277 (1997), 145–153.

[16] P. Dubey, U. S. Dubey and B. Dubey, Modeling the role of acquired immune response and antiretroviral therapy in the dynamics of HIV infection, *Math. Comput. Simulat.*, 144 (2018), 120–137.

[17] M. A. Gilchrist, D. Coombs and A. S. Perelson, Optimizing within-host viral fitness: Infected cell lifespan and virion production rate, *J. Theor. Biol.*, 229 (2004), 281–288.

[18] T. Guo and Z. Qiu, The effects of CTL immune response on HIV infection model with potent therapy, latently infected cells and cell-to-cell viral transmission, *Bull. Malays. Math. Sci. Soc.*, 43 (2020), 581–607.

[19] T. Guo, Z. Qiu and L. Rong, Analysis of an hiv model with immune responses and cell-to-cell transmission, *Bull. Math. Biol.*, 59 (1997), 763–785.

[20] R. Koup, J. T. Safrit, Y. Cao, C. A. Andrews, G. McLeod, W. Borkowsky, C. Farthing and D. D. Ho, Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome, *J. Virol.*, 68 (1994), 4650–4655.

[21] M. Louie, et al., Determining the relative efficacy of highly active antiretroviral therapy, *J. Infect. Dis.*, 187 (2003), 896–900.

[22] D. E. Kirschner and G. Webb, Understanding drug resistance for monotherapy treatment of HIV infection, *Bull. Math. Biol.*, 59 (1997), 763–785.

[23] S. H. Michaels, R. Clark and P. Kissinger, Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection, *New. Engl. J. Med.*, 339 (1998), 405–406.

[24] P. Ngina, R. W. Mbogo and L. S. Luboobi, HIV drug resistance: Insights from mathematical modelling, *Appl. Math. Model.*, 75 (2019), 141–161.

[25] P. D. Mason, M. I. Bowmer, C. M. Howley, M. Gallant, J. C. Myers and M. D. Grant, Antiretroviral drug resistance mutations sustain or enhance CTL recognition of common HIV-1 pol epitopes, *J. Immunol.*, 172 (2004), 7212–7219.

[26] A. R. McLean and M. A. Nowak, Competition between zidovudine-sensitive and zidovudine-resistant strains of HIV, *Aids*, 6 (1992), 71–79.

[27] S. H. Michaels, R. Clark and P. Kissinger, Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection, *New. Engl. J. Med.*, 339 (1998), 405–406.

[28] P. Ngina, R. W. Mbogo and L. S. Luboobi, HIV drug resistance: Insights from mathematical modelling, *Appl. Math. Model.*, 75 (2019), 141–161.

[29] M. Nowak and R. M. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology: Mathematical Principles of Immunology and Virology*, Oxford University Press, UK, 2000.

[30] M. A. Nowak and C. R. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, 272 (1996), 74–79.

[31] M. A. Nowak and R. M. May, *Mathematical biology of HIV infections: Antigenic variation and diversity threshold*, *Math. Biosci.*, 106 (1991), 1–21.

[32] M. A. Nowak and A. J. McMichael, How HIV defeats the immune system, *Sci. Am.*, 273 (1995), 58–65.

[33] A. S. Perelson, D. E. Kirschner and R. De Boer, Dynamics of HIV infection of CD4+ T cells, *Math. Biosci.*, 114 (1993), 81–125.

[34] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard and D. D. Ho, HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, *Science*, 271 (1996), 1582–1586.

[35] A. S. Perelson and R. M. Ribeiro, Modeling the within-host dynamics of HIV infection, *BMC Biol.*, 11 (2013), 96.
[37] Z. Qiu and Z. Feng, The dynamics of an epidemic model with targeted antiviral prophylaxis, *J. Biol. Dyn.*, 4 (2010), 506–526.

[38] S. M. Raimundo, H. M. Yang, E. Venturino and E. Massad, Modeling the emergence of HIV-1 drug resistance resulting from antiretroviral therapy: Insights from theoretical and numerical studies, *BioSystems*, 108 (2012), 1–13.

[39] B. Ramratnam, et al., Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis, *The Lancet*, 354 (1999), 1782–1785.

[40] R. M. Ribeiro and S. Bonhoeffer, Production of resistant HIV mutants during antiretroviral therapy, *P. Natl. A. Sci.*, 97 (2000), 7681–7686.

[41] R. M. Ribeiro, S. Bonhoeffer and M. A. Nowak, The frequency of resistant mutant virus before antiviral therapy, *Aids*, 12 (1998), 461–465.

[42] L. Rong, Z. Feng and A. S. Perelson, Emergence of HIV-1 drug resistance during antiretroviral treatment, *Bull. Math. Biol.*, 69 (2007), 2027–2060.

[43] L. Rong, Z. Feng and A. S. Perelson, Mathematical modeling of HIV-1 infection and drug therapy, *Math. Model. Bios.*, 87–131.

[44] L. Rong, M. A. Gilchrist, Z. Feng and A. S. Perelson, Modeling within-host HIV-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility, *J. Theor. Biol.*, 247 (2007), 804–818.

[45] L. Rong and A. S. Perelson, Asymmetric division of activated latently infected cells may explain the decay kinetics of the HIV-1 latent reservoir and intermittent viral blips, *Math. Biosci.*, 217 (2009), 77–87.

[46] B. Sebastian and A. N. Martin, Pre–existence and emergence of drug resistance in HIV–1 infection, *Proc. R. Soc. Lond. B*, 264 (1997), 631–637.

[47] A. K. Sewell, D. A. Price, A. Oxenius, A. D. Kelleher and R. E. Phillips, Cytotoxic T Lymphocyte responses to human immunodeficiency virus: Control and escape, *Stem Cells*, 18 (2000), 230–244.

[48] T. Shiri, W. Garira and S. D. Musekwa, A two-strain hiv-1 mathematical model to assess the effects of chemotherapy on disease parameters, *Math. Biosci. Eng.*, 2 (2005), 811.

[49] M. O. Souza and J. P. Zubelli, Global stability for a class of virus models with Cytotoxic T Lymphocyte immune response and antigenic variation, *Bull. Math. Biol.*, 73 (2011), 609–625.

[50] N. Tarfulea and P. Read, A mathematical model for the emergence of HIV drug resistance during periodic bang-bang type antiretroviral treatment, *Involve, J. Math.*, 8 (2015), 401–420.

[51] P. Van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, 180 (2002), 29–48.

[52] L. M. Wahl and M. A. Nowak, Adherence and drug resistance: Predictions for therapy outcome, *Proc. Biol. Sci.*, 267 (2000), 835–843.

[53] K. Wang, W. Wang and X. Liu, Global stability in a viral infection model with lytic and nonlytic immune responses, *Comput. Math. Appl.*, 51 (2006), 1593–1610.

[54] K. Wang, W. Wang, H. Pang and X. Liu, Complex dynamic behavior in a viral model with delayed immune response, *Physica D: Nonlinear Phenomena*, 226 (2007), 197–208.

[55] X. Wang, A. Elaiw and X. Song, Global properties of a delayed HIV infection model with CTL immune response, *Appl. Math. Comput.*, 218 (2012), 9405–9414.

[56] X. Wang, Y. Tao and X. Song, Global stability of a virus dynamics model with beddington-deangelis incidence rate and CTL immune response, *Nonlinear Dyn.*, 66 (2011), 825–830.

[57] Y. Wang, F. Brauer, J. Wu and J. M. Heffernan, A delay-dependent model with HIV drug resistance during therapy, *J. Math. Anal. Appl.*, 414 (2014), 514–531.

[58] Y. Wang, Y. Zhou, F. Brauer and J. M. Heffernan, Viral dynamics model with CTL immune response incorporating antiretroviral therapy, *J. Math. Biol.*, 67 (2013), 901–934.

[59] R. A. Weiss, How does HIV cause AIDS?, *Science*, 260 (1993), 1273–1279.

[60] WHO, HIV/AIDS: Key facts, http://www.who.int/news-room/fact-sheets/detail/hiv-aids, 2018.

[61] D. Wodarz and A. L. Lloyd, Immune responses and the emergence of drug–resistant virus strains in vivo, *Proc. R. Soc. Lond. B.*, 271 (2004), 1101–1109.

[62] D. Wodarz and M. A. Nowak, Specific therapy regimes could lead to long-term immunological control of HIV, *P. Natl. A. Sci.*, 96 (1999), 14464–14469.

[63] D. Wodarz and M. A. Nowak, Immune responses and viral phenotype: Do replication rate and cytopathogenicity influence virus load?, *Comput. Math. Method. M.*, 2 (2000), 113–127.
[64] D. Wodarz and M. A. Nowak, Mathematical models of HIV pathogenesis and treatment, *BioEssays*, 24 (2002), 1178–1187.

[65] J. Wu, P. Yan and C. Archibald, Modelling the evolution of drug resistance in the presence of antiviral drugs, *BMC Public Health*, 7 (2007), 300.

[66] J. Wu, R. Dhingra, M. Gambhir and J. V. Remais, Sensitivity analysis of infectious disease models: Methods, advances and their application, *J. R. Soc. Interface*, 10 (2013), 20121018.

[67] Y. Xiao, S. Tang, Y. Zhou, R. J. Smith, J. Wu and N. Wang, Predicting the HIV/AIDS epidemic and measuring the effect of mobility in mainland China, *J. Theor. Biol.*, 317 (2013), 271–285.

[68] H. Zhu and X. Zou, Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay, *Discrete Contin. Dyn. Syst. Ser. B*, 12 (2009), 511–524.

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