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A TWO-STRAIN HIV-1 MATHEMATICAL MODEL TO ASSESS THE EFFECTS OF CHEMOTHERAPY ON DISEASE PARAMETERS

Tinevimbo Shiri

Department of Applied Mathematics, National University of Science and Technology
P-O Box AC939 Ascot, Bulawayo, Zimbabwe

Winston Garira

Department of Applied Mathematics, National University of Science and Technology
P-O Box AC939 Ascot, Bulawayo, Zimbabwe

Senelani D. Musekwa

Department of Applied Mathematics, National University of Science and Technology
P-O Box AC939 Ascot, Bulawayo, Zimbabwe

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Abstract. Treatment of human immunodeficiency virus type 1 (HIV-1) infection during the symptomatic phase has significantly improved patient survival. We present a two-strain HIV mathematical model that captures the dynamics of the immune system and two HIV-1 variants under antiretroviral therapy. We explore the effects of chemotherapy on the dynamics of two viral strains and T lymphocytes with one mutant strain phenotypically resistant to drug effects. Model calculations show that there is a common pattern for CD4+ T cell count increase. There is a drastic increase of CD4+ T cells during the first few weeks of treatment, followed by a gradual increase, and these increases are strictly by clonal expansion of preexisting CD4+ T cells. Plasma HIV RNA dramatically decline to zero levels during the first week of drug administration. If drug efficacy is equal to or above a threshold efficacy, viral load remains at zero levels and if drug efficacy is less than the threshold efficacy, viral load gradually increases until it stabilizes. Viral rebound during treatment is entirely due to the recovery of CD4+ T cells. The results also reveal that there is a dynamic equilibrium between viral load and cytotoxic T lymphocyte (CTL) response in an infected individual during drug administration.

1. **Introduction.** A number of HIV-1 antiretroviral therapies have been developed that have potent and durable efficacy profiles, favorable resistance patterns, patient-friendly dosing schemes and minimal side effects. The use of these new HIV therapies have significantly contributed to decreased morbidity and mortality in HIV infected patients. Currently, these chemotherapies offer added dosing convenience and improved safety profiles. Clinical benefits of drug therapy for HIV infected individuals include maximum duration of suppressive antiviral activity and minimizing toxicity, ultimately leading to improved survival and quality of life.

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Triple or quadruple drug therapy combinations of reverse transcriptase inhibitors and protease inhibitors can reduce the virus load by orders of magnitude and can maintain plasma virus below detection limit for several months. Also, drug combinations have immunologic effects associated with increase in CD4+ T lymphocytes for a long period of time. However, deleterious side effects such as risk of cardiovascular, lactic acidosis and mitochondrial damage remain rife during prolonged drug administration [8]. Furthermore, it is not feasible that current drugs can eradicate HIV from infected individuals because of the presence of resistant mutants which when exposed to drugs are less affected or not affected at all. The resistant strains are as a result of mutations. These resistant strains can preexist in drug-naive patients or evolve after the initiation of therapy [1, 22].

New insights have been derived from mathematical models of antiviral drug treatment that have been developed to study the frequency of drug-resistant virus in untreated patients [17], the effect of treatment on reducing viral diversity [3, 16], long-term changes in viral load in treated patients to identify principal factors responsible for sustained suppression of virus load [2], the role of immune responses in the rise of drug-resistant mutants [22], conditions under which resistance dominates as a result of imperfect adherence [20], time evolution of intracellular concentrations of active forms of drugs [6], and the relationship between HIV and the immune system in the context of different antiviral treatment regimes [21]. Bonhoeffer and Nowak, [1] compared the likelihood of pre-existence of resistant strains with the likelihood of production of resistant virus during therapy using two strain basic models of viral dynamics. Bonhoeffer and Nowak showed that if resistant virus preexists before therapy, then a stronger therapy may lead to a greater initial reduction of virus load, but will cause a faster rise of resistant virus. The total benefit of treatment in this scenario is independent of the degree of inhibition of sensitive virus. One drawback of all the models developed is that they did not incorporate the effects of CTLs' lytic and nonlytic mechanisms on disease progression explicitly.

In the light of evidence that CTLs play a crucial role in controlling HIV-1 infection [10, 18, 13], here we design a model that incorporates explicitly the lytic and nonlytic effects of CTLs as well as drug effects on baseline HIV-1 disease parameters. CTLs can kill infected cells by direct contact (lytic response) or suppress HIV replication through the release of soluble antiviral factors (nonlytic response), including rantes, macrophage inflammatory protein-1α (MIP-1α), and macrophage inflammatory protein-1β (MIP-1β). In addition to CTL effects, we incorporate the feature of potential "bystander killing" of uninfected CD4+ T cells due to apoptotic receptors induced by viral particles. The primary goal of this paper is to establish virologic and immunologic effects of chemotherapy, that is, effects of drugs on HIV RNA viral load and on T lymphocyte (CD4+ T cells and CTLs) count of treatment-naive patients respectively, using a two strain viral immune dynamic model that assumes that one viral strain is resistant to therapy.

We will start by formulating a pretreatment model of two HIV-1 variants which describes the interaction of two viral strains and the immune system in section 2, and this builds on our earlier work [9]. We make an analysis of the pretreatment model in section 3 and investigate the effects of drugs using a mathematical model incorporating therapy in section 4. We use the fourth-order Runge-Kutta scheme to numerically simulate the effects of drugs in section 5. In section 6, we present some concluding remarks, and due to the arbitrariness of some parameter values

chosen in our numerical simulations, we also point out where the predictions agree and where they disagree with experimental evidence.

2. **The Pretreatment Model.** First, we present a basic model of HIV immune system dynamics that will form the basis for modifications that will incorporate the effects of chemotherapy on baseline HIV-1 disease parameters. The model builds on our earlier work [9], where a version of this model involving a single strain was studied in the context of optimal control. We modify the model [9] by incorporating mutation. Viral mutation can lead to epitope deletion, failure of antigen processing, loss of major histocompatibility complex class I (MHC I) binding, and impaired recognition by the T cell receptor (TCR) [18]. The viral heterogeneity is largely the result of the high error rate of the HIV reverse transcriptase enzyme, which produces the DNA copy of the viral RNA, together with the absence of any mechanism to correct such errors. The result is the production of HIV proviral DNA containing one or more mutations, and some of these mutations will lead to amino acid sequence changes in the viral envelope. It is these sequence differences which are responsible for the different biological properties of different isolates of HIV [13]. Most of these mutations affect the env gene, producing different envelope glycoproteins. A mutation able to reduce recognition of an epitope would give a viral variant a survival advantage, up to a time when the immune system discovers and reacts to the altered peptide [15]. In real situations, viruses have several different epitopes that can be recognized by immune responses. Some virus mutants may differ in one epitope but coincide in others. This means that the immune response may recognize a number of different virus strains, but fail to recognize others. We assume that viral strains are not recognized by the same immune responses; that is, immunity is not cross-reactive between the two strains. If the epitope fueling the dominant immune response mutates, the corresponding CTL clone (CTL population recognizing one epitope) may not recognize the mutant. Viral particles bearing this peptide then multiply almost unnoticed. Sometimes the immune system catches up with the renegade group and mounts a defense targeted against the new version of the epitope [15].

The pretreatment model simply monitors the temporal dynamics of seven populations, namely, uninfected CD4+ T cells, two groups of infected CD4+ T cells (one infected by wild-type strain virus and the other by a mutant strain virus), two viral strains (wild-type strain and the mutant strain), and two CTL clones (one group of CTLs recognizing wild-type strain viral infected CD4+ T cells and the other group of CTLs recognizing mutant strain viral infected CD4+ T cells). We assume that, during the course of normal wild-type strain viral replication, virus variants that are resistant to the present CTL response arise at a rate γ. We also assume that there is no back-mutation from the resistant strain to the wild-type strain. The two virus strains have different replication and cytopathic effects. The proposed model of evolutionary variants before initiation of therapy is schematically illustrated in figure 1.

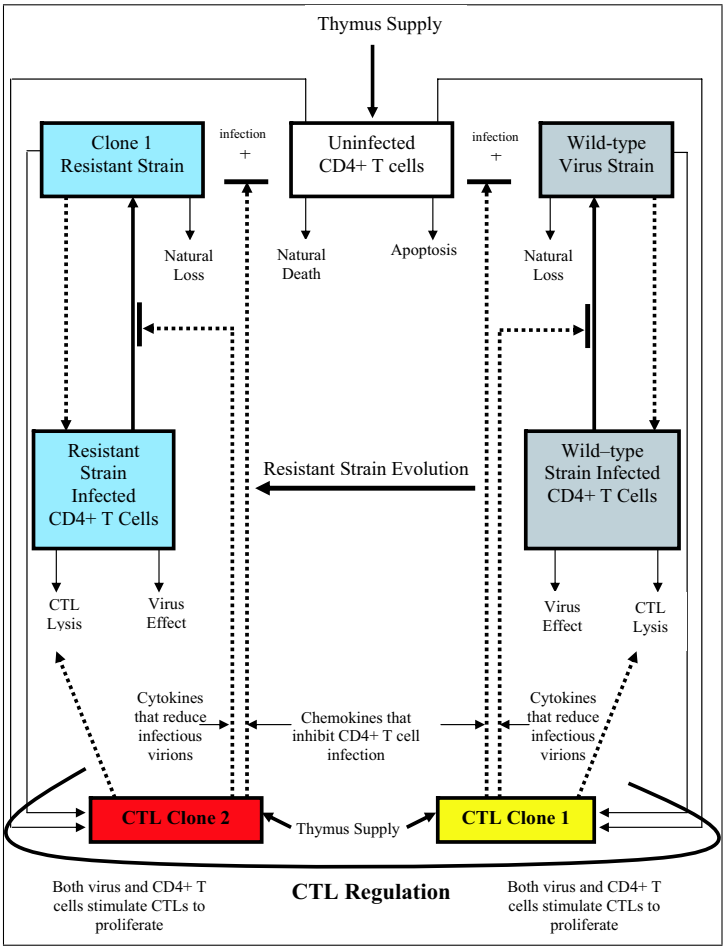

FIGURE 1. Schematic representation of the mathematical model of two evolutionary HIV-1 variants. Uninfected CD4+ T cells are produced at a rate s, and they are infected by wild-type strain viral particles. The uninfected CD4+ T cells are lost by natural death and also by "bystander killing." The body mounts an immune response to fight the virus, and specific CTL clones fight the virus with soluble factors such as chemokines and also kill infected cells. The initial CTL response against the wild-type virus, CTL clone 1, is specific to the wild-type strain. Due to virus mutation, new HIV-1 variants emerge and also infect CD4+ T cells. The body mounts another defense mechanism targeted against the new version of the viral strain, CTL clone 2. Infected CD4+ T cells are lost by virus cytopathogenecity and CTL lytic effects. The two viral strains have different cytopathic effects.

The mathematical model of two evolutionary variants is given by the nonlinear initial-value problem, where the rates of change of each variable with respect to time are:

$$\begin{aligned}
\frac{dT(t)}{dt} &= s + T(t)\left\{\sum_{i=1}^{2}\frac{r_i V_i(t)}{B_i^V + V_i(t)} - \sum_{i=1}^{2}\frac{k_i V_i(t)}{B_i^T + T(t)} - \sum_{i=1}^{2}\beta_i e^{-a_i C_i(t)} V_i(t)\right\} \\
&\quad - \mu_T T(t) \qquad (1)\\
\frac{dT_1^*(t)}{dt} &= e^{-a_1 C_1(t)}\beta_1 T(t) V_1(t)(1-\gamma) - \big(\alpha_1 + h_1 C_1(t)\big)T_1^*(t) \qquad (2)\\
\frac{dT_2^*(t)}{dt} &= e^{-a_2 C_2(t)}\beta_2 T(t) V_2(t) + \gamma e^{-a_1 C_1(t)}\beta_1 T(t) V_1(t) - \alpha_2 T_2^*(t) \\
&\quad - h_2 C_2(t) T_2^*(t) \qquad (3)\\
\frac{dV_i(t)}{dt} &= N_i \alpha_i T_i^*(t) e^{-b_i C_i(t)} - \mu_i V_i(t) \qquad (4)\\
\frac{dC_i(t)}{dt} &= s_i + p_i T(t) C_i(t) V_i(t) - \delta_i C_i(t), \qquad (5)
\end{aligned}$$

where $i = 1, 2$ and $T(t)$ is the population density of CD4+ T cells; $T_1^*(t)$ is the density of wild-type virus infected CD4+ T cells; $T_2^*(t)$ is the density of resistant virus infected CD4+ T cells; $V_1(t)$ is the wild type viral population; $V_2(t)$ is the CTL clone 1-resistant virus population; $C_1(t)$ is the density of CTLs specific to the wild type virus; and $C_2(t)$ is the population of CTLs specific to the newly evolved strain.

Equation (1) describes the dynamics of uninfected CD4+ T cells. The first term on the right-hand side, s, represents the source of new CD4+ T cells from the thymus [11]. This is followed by a proliferation term for CD4+ T cells in the presence of two virus strains: r_i is the proliferation rate induced by strain i. The parameter B_i^V is a parameter that determines the amount of strain i needed to generate half maximal stimulation, that is, saturation constant of the proliferative process [11]. This parameter is also referred to as "antigenicity" parameter: highly antigenic strains will have a low B_i^V value [4]. The third term represents the destruction of CD4+ T cells by the influence of toxic viral proteins. The parameter k_i represents the rate at which strain i induces apoptosis receptors. A feature of potential "bystander killing" of uninfected CD4+ T cells is a monotonic decreasing function as disease progresses; that is, there is an increase of apoptosis at low CD4+ T cell count because viral load would be high. At high CD4+ T cells, viral load is low; therefore, apoptosis decreases. The-second-from last term describes the infection of CD4+ T cells by the two viral strains. The two viral strains have different infectivity rates; that is, β_1 is the rate at which the wild-type strain virus infects CD4+ T cells; and β_2 is the rate at which the CTL clone 1-resistant strain infects CD4+ T cells. The presence of specific CTLs that release chemokines, such as β-chemokines that block the entry of certain virions into target cells [12], prevents infection of new cells by a factor $e^{-a_i C_i}$ for the specific CTL clone i. The parameters a_i represent the efficiency of CTL clone i infection of the CD4+ T cells infection by HIV strain i [9]. The term $-\mu_T T(t)$ is the natural death term for uninfected CD4+ T cells, and on average the life span is $1/\mu_T$.

Equation (2) describes the rate of change of CD4+ T cells infected by the wild-type strain virus. The first term on the right-hand side is a gain term for CD4+ T cells infected by the wild-type strain virus. A fraction of the virus's wild-type

strain mutates to resistant mutant viral particles during the transcription process at a rate γ. The wild-type strain infected CD4+ T cells die due to this strain's cytopathic effect, (that is the term $\alpha_1 T_1^*(t)$), and these cells are also killed through perforin-granzyme and Fas-Fas Ligand pathways by CTLs specific to the wild-type strain at a rate h_1.

The third equation describes the rate of change of CD4+ T cells infected by the resistant strain of the virus. Similar to the second equation, the first term on the right-hand side describes the gain for resistant-strain infected CD4+ T cells. The second term is a gain term of resistant strain virus infected CD4+ T cells through mutation of the wild-type strain during transcription process. The third term $\alpha_2 T_2^*(t)$ is a loss term due to the cytopathic effect of the resistant strain, and $h_2 T_2^*(t) C_2(t)$ is loss term due to the lytic effect of resistant-strain-specific CTLs prior to the assembly and release of infectious virions.

The fourth equation describes the rate of change of the two viral strain populations, where the first term on the right-hand side explains the source of strain i viral particles. The product $N_i \alpha_i$ is the average rate of strain i virus production per productively strain i-infected cell. CTLs specific to strain i release cytokines, principally interferon-γ (INF-γ), interleukin-6 (IL-6), and interleukin-10 (IL-10) [13], that can suppress the rate of virus production; therefore, they reduce viral burst by a factor of $e^{-b_i C_i}$, where b_i is the rate at which strain i specific CTL suppress viral production [9]. The last term on the right hand side represent the loss of strain i through natural death with an average life-span of $1/\mu_i$.

Equation (5) represents the dynamics of strain i-specific CTLs. The first term on the right-hand side, s_i, models the production rate of specific CD8+ T cells from precursors. Epitopes differ in their ability to induce CTL responses where the immunogenecity of an epitope is the rate at which it induces CTL proliferation. Naive specific CD8+ T cells differentiate into CTLs specific to the antigen in response to HIV antigen with the help of CD4+ T cells at a rate p_i, modelled by the second term. The last term, $\delta_i C_i(t)$ represents the loss of CTLs by natural death. A summary of variables and parameters used in our model appears in table 1.

3. **Analysis of the Pretreatment Model.** We analyze system of equations (1)-(2) by determining its steady states. A steady state of a system is a point in phase space for which the system will not change in time. The dynamical system,(equations (1)-(5)) has an uninfected steady state given by:

$$\Big(\bar{T}_u, \bar{T}^*_{1,u}, \bar{T}^*_{2,u}, \bar{V}_{1,u}, \bar{V}_{2,u}, \bar{C}_{1,u}, \bar{C}_{2,u}\Big) = \Big(\frac{s}{\mu_T}, 0, 0, 0, 0, \frac{s_1}{\delta_1}, \frac{s_2}{\delta_2}\Big), \tag{6}$$

which corresponds to a situation when an individual has an abortive infection. If infection persists after the initial inoculum the system converges to an infected steady state given by

$$\bar{E} = \Big(\bar{T}_p, \bar{T}^*_{1,p}, \bar{T}^*_{2,p}, \bar{V}_{1,p}, \bar{V}_{2,p}, \bar{C}_{1,p}, \bar{C}_{2,p}\Big), \tag{7}$$

where $\bar{T}_p$, $\bar{T}^*_{1,p}$, $\bar{T}^*_{2,p}$, $\bar{V}_{2,p}$, $\bar{C}_{1,p}$ and $\bar{C}_{2,p}$ are given by expressions (8), (9), (10), (12), (13), and (14), respectively. The uninfected CD4+ T cells has a steady-state value

$$\bar{T}_p = \frac{\mu_1(\alpha_1 + h_1 \bar{C}_{1,p}) e^{(a_1+b_1)\bar{C}_{1,p}}}{(1-\gamma)\alpha_1 \beta_1 N_1}. \tag{8}$$

The equilibrium density of healthy CD4+ T cells during the chronic phase of HIV-1 infection depends on the kinetic parameters of the wild-type strain viral population

TABLE 1. Description of the units of variables and parameters used in the model of two evolutionary viral strains

Symbol	**Description**	**Units**
Variables		
T	Uninfected CD4+ T cells	cells mm^{-3}
T_1^*	Wild-type strain infected CD4+ T cells	cells mm^{-3}
T_2^*	Mutant strain infected CD4+ T cells	cells mm^{-3}
V_1	Wild-type strain infectious virus	copies mm^{-3}
V_2	Mutant strain infectious virus	copies mm^{-3}
C_1	CTLs specific to wild-type strain virus	cells mm^{-3}
C_2	CTLs specific to mutant strain virus	cells mm^{-3}
Parameters		
s	Supply rate of CD4+ T cells	cells mm^{-3} day^{-1}
μ_T	Death rate of CD4+ T cells	day^{-1}
r_1,r_2	Proliferation rates of CD4 cells	day^{-1}
k_1, k_2	Apoptosis rates	$\frac{\text{cells } mm^{-3}}{\text{copies } mm^3 \text{ day}^1}$
β_1, β_2	Rates CD4+ T cells are infected by virus	copies mm^3 day^{-1}
a_1, a_2	Rates CTLs reduce infectivity	cells mm^3
γ	Virus mutation rate	$\frac{\text{mutations}}{\text{nucleotide}}$
α_1, α_2	Virus cytopathic rates	day^{-1}
h_1, h_2	Rates CTLs lyse infected cells	cells mm^3 day^{-1}
N_1, N_2	Virus burst sizes	$\frac{\text{cells}^{-1}\ mm^3}{\text{copies } mm^3}$
μ_1, μ_2	Virus clearance rates	day^{-1}
s_1, s_2	CTL supply rates	cells mm^{-3} day^{-1}
p_1, p_2	CTL proliferation rates	$\frac{\text{cells } mm^3}{\text{copies } mm^3 day^1}$
δ_1, δ_2	Natural CTL death rates	day^{-1}
B_1^T, B_2^T	Stimulation constants	cells mm^{-3}
B_1^V, B_2^V	Stimulation constants	copies mm^{-3}

and CTL clone 1 effects; that is, the density is dependent on the viral production rate of the nonmutating wild-type strain virions, $(1-\gamma)\alpha_1 N_1$, wild-type virus infectivity, β_1, wild-type virus clearance rate, μ_1, CTL clone 1's lytic and nonlytic effects and the average clearance rate of wild-type virus infected cells, $(\alpha_1 + h_1\bar{C}_1)$. The equilibrium population of wild-type infected cells is

$$\bar{T}_{1,p}^* = \frac{\mu_1 \bar{V}_{1,p} e^{b_1 \bar{C}_{1,p}}}{N_1 \alpha_1}, \tag{9}$$

and the density of mutant strain population is

$$\bar{T}^*_{2,p} = \frac{\mu_2 \bar{V}_{2,p} e^{b_2 \bar{C}_{2,p}}}{N_2 \alpha_2}, \tag{10}$$

such that the total number of infected cells at equilibrium is given by

$$\bar{T}^*_{1,p} + \bar{T}^*_{2,p} = \frac{\mu_1 \bar{V}_{1,p} e^{b_1 \bar{C}_{1,p}}}{N_1 \alpha_1} + \frac{\mu_2 \bar{V}_{2,p} e^{b_2 \bar{C}_{2,p}}}{N_2 \alpha_2}. \tag{11}$$

The equilibrium number of infected cells depends on the two virus strains' average clearance rates, viral production rates, and the effects of specific CTL clones in reducing burst sizes. The abundance of the mutant strain viral population during the chronic phase is

$$\bar{V}_{p,2} = \frac{\gamma \beta_1 \alpha_2 N_2 \bar{T}_p e^{-(a_1 \bar{C}_{1,p} + b_2 \bar{C}_{2,p})}}{\mu_2(\alpha_2 + h_2 \bar{C}_{2,p}) - \beta_2 \alpha_2 N_2 \bar{T}_p e^{-(a_2 + b_2)\bar{C}_{2,p}}} \bar{V}_{1,p}. \tag{12}$$

Expression (12) means that during the chronic phase of HIV-1 infection, the density of the mutant strain virus population is dependent on the mutating equilibrium wild-type strain virus population, $\gamma \bar{V}_{1,p}$, CTL effector mechanisms of both clones, infectivity of two virus strains, the equilibrium density of health CD4+ T cells, and the average clearance rate of mutant strain infected CD4+ T cells. During the chronic phase, the equilibrium density of CTL clone 1 is given by

$$\bar{C}_{1,p} = \frac{s_1}{\delta_1 - p_1 \bar{T}_p \bar{V}_{1,p}}, \tag{13}$$

and the density of CTL clone 2 is given by

$$\bar{C}_{2,p} = \frac{s_2}{\delta_2 - p_2 \bar{T}_p \bar{V}_{2,p}}. \tag{14}$$

Equations (13) and (14) largely depend on the densities of healthy CD4+ T cells and virus population. The expression for $\bar{V}_{1,p}$ is too long to be written down, but we indicate that it can be obtained by solving equation (1) for $\frac{dT(t)}{dt} = 0$ after substituting the expressions (8), (12), (13), and (14). The equilibrium value of the wild-type viral population expression involves apoptosis and proliferation rates, the production rate of CD4+ T cells, and the effectiveness of CTLs in suppressing HIV replication. The endemic infected state given by equation (7) and also shown by figure 2 corresponds to the prolonged asymptomatic phase (chronic phase) in HIV-1 infected patients, and in most cases this will ultimately lead to a situation when the viral population overwhelms the immune system leading to acquired immune deficiency syndrome (AIDS). The AIDS stage is associated with a weakened immune system which has difficulty in fighting off opportunistic infections. The infected steady state gives the HIV-1 parameters that will be perturbed by drug effects. Current recommendations suggest that treatment is to be offered to symptomatic patients or those with a CD4+ T cell count below 200 cells mm^{-3}.

To calculate the reproductive ratios for the two viral variants, we adopt the method of [5] where the reproductive ratio is defined as the spectral radius of the "next generation operator approach." We define heterogeneity using groups defined

by fixed characteristics; that is, our model can be written in the form:

$$\begin{aligned} \frac{dX}{dt} &= f(\mathbf{X},\mathbf{Y},\mathbf{Z}),\\ \frac{dY}{dt} &= g(\mathbf{X},\mathbf{Y},\mathbf{Z}),\\ \frac{dZ}{dt} &= h(\mathbf{X},\mathbf{Y},\mathbf{Z}), \end{aligned} \tag{15}$$

where $\mathbf{X}\in\mathbb{R}^3$, $\mathbf{Y}\in\mathbb{R}^2$, $\mathbf{Z}\in\mathbb{R}^2$, and $h(\mathbf{X},0,0)=0$. Assuming that the equation $g(\mathbf{X}^*,\mathbf{Y},\mathbf{Z})=0$ implicitly determines a function $Y=\tilde{g}(\mathbf{X}^*,\mathbf{Y})$. We also let that $\mathbf{A}=\mathbf{D}_Z h(\mathbf{X}^*,\tilde{g}(\mathbf{X}^*,0),0)$ and further assume that $\mathbf{A}$ can be written in the form $\mathbf{A}=\mathbf{M}\mathbf{D}^{-1}$, with $\mathbf{M}\geq 0$ (that is, $m_{ij}\geq 0$) and $\mathbf{D}>0$, a diagonal matrix. The two reproductive ratios are obtained by evaluating the eigenvalues of the matrix $\mathbf{M}\mathbf{D}^{-1}$. The population is divided into the following subgroups: uninfected CD4+ T cells susceptible to infection (T); infected CD4+ T cells with strain i ($i=1$ represents the wild-type strain and $i=2$ the resistant strain) of HIV (T_i^*); HIV strain i (V_i); and CTL clones C_i ($i=1$ represents CTL clone specific to strain 1 and $i=2$ the clone specific to strain 2). We set $\mathbf{X}=(T,C_1,C_2)$, $\mathbf{Y}=(V_1,V_2)$ and $\mathbf{Z}=(T_1^*,T_2^*)$. The components of $\mathbf{X}$ denote the number of uninfected CD4+ T cells susceptible to infection and the two classes of CTLs that are not infected by the virus where $\mathbf{X}^*=(\frac{s}{\mu_T},\frac{s_1}{\delta_1},\frac{s_2}{\delta_2})$. The components of $\mathbf{Y}$ represent the number of two infectious viral strains, and the components of $\mathbf{Z}$ denote the number of infected CD4+ T cells by different strains. Let $\mathbf{U}_0=(\frac{s}{\mu_T},0,0,0,0,\frac{s_1}{\delta_1},\frac{s_2}{\delta_2})$ denote the virus-free equilibrium and $\tilde{g}(\mathbf{X}^*,\mathbf{Z})=(\tilde{g_1}(\mathbf{X}^*,\mathbf{Z}),\tilde{g_2}(\mathbf{X}^*,\mathbf{Z}))$ with

$$\tilde{g_1}=\frac{N_1\alpha_1 T_1^* e^{-b_1\bar{C}_{1,u}}}{\mu_1} \qquad \text{and} \qquad \tilde{g_2}=\frac{N_2\alpha_2 T_2^* e^{-b_2\bar{C}_{2,u}}}{\mu_2}.$$

Therefore

$$\mathbf{M}=\begin{pmatrix} \frac{\beta_1\alpha_1 N_1(1-\gamma)\bar{T}_u e^{-(a_1+b_1)\bar{C}_{1,u}}}{\mu_1} & 0\\ \\ \frac{\gamma\beta_1\alpha_1 N_1\bar{T}_u e^{-(a_1+b_1)\bar{C}_{1,u}}}{\mu_1} & \frac{\beta_2\alpha_2 N_2\bar{T}_u e^{-(a_2+b_2)\bar{C}_{2,u}}}{\mu_2} \end{pmatrix}$$

and

$$\mathbf{D}=\begin{pmatrix} -(\alpha_1+h_1\bar{C}_{1,u}) & 0\\ \\ 0 & -(\alpha_2+h_2\bar{C}_{2,u}) \end{pmatrix}.$$

The two eigenvalues λ_1 and λ_2 of $\mathbf{M}\mathbf{D}^{-1}$ are

$$\lambda_1=\frac{(1-\gamma)\beta_1\alpha_1 N_1 s e^{-(a_1+b_1)\bar{C}_{1,u}}}{\mu_1\mu_T(\alpha_1+h_1\bar{C}_{1,u})} \qquad \text{and} \qquad \lambda_2=\frac{\beta_2\alpha_2 N_2 s e^{-(a_2+b_2)\bar{C}_{2,u}}}{\mu_2\mu_T(\alpha_2+h_2\bar{C}_{2,u})},$$

where

$$\bar{C}_{1,u}=\frac{s_1}{\delta_1} \qquad \text{and} \qquad \bar{C}_{2,u}=\frac{s_2}{\delta_2}.$$

It follows that the wild-type strain's reproductive ratio is

$$R_{01}=\frac{(1-\gamma)\beta_1\alpha_1 N_1 s e^{-(a_1+b_1)\bar{C}_{1,u}}}{\mu_1\mu_T(\alpha_1+h_1\bar{C}_{1,u})} \tag{16}$$

and that the resistant strain's reproductive ratio is

$$R_{02} = \frac{\beta_2 \alpha_2 N_2 s e^{-(a_2+b_2)\bar{C}_{2,u}}}{\mu_2 \mu_T (\alpha_2 + h_2 \bar{C}_{2,u})}. \tag{17}$$

The basic reproductive ratio for the system is the maximum of these two reproductive ratios [7]. If both R_{01} and R_{02} are less than one, then the viral population cannot grow within an individual and so the immune system can resolve the infection; that is, infection becomes abortive. If, on the other hand, the two reproductive ratios are greater than one or if any one of the reproductive ratios is greater than one, then the viral population can grow and can establish an infection. Persistence of an infection depends entirely on the the two strains' virulence and the potency of the immune response in controlling viral population as shown by the two reproductive ratios. By substituting for $\frac{s}{\mu_T}$ from equation (16), we can rewrite equation (17) as

$$R_{02} = \frac{R_{01}}{(1-\gamma)} \left(\frac{\beta_2 e^{-a_2 \bar{C}_{2,u}}}{\beta_1 e^{-a_1 \bar{C}_{1,u}}} \right) \left(\frac{N_2 e^{-b_2 \bar{C}_{2,u}} \alpha_2}{N_1 e^{-b_1 \bar{C}_{1,u}} \alpha_1} \right) \left(\frac{\mu_1}{\mu_2} \right) \left(\frac{\alpha_1 + h_1 \bar{C}_{1,u}}{\alpha_2 + h_2 \bar{C}_{2,u}} \right). \tag{18}$$

The reproductive ratio of the mutant strain virus is governed by the following proportions:

1. mutation rate of the wild-type strain
2. proportion of mutant strain infectivity to the wild-type strain infectivity $\left(\frac{\beta_2 e^{-a_2 \bar{C}_{2,u}}}{\beta_1 e^{-a_1 \bar{C}_{1,u}}} \right)$
3. rates of viral production of the mutant strain to the wild-type strain $\left(\frac{N_2 e^{-b_2 \bar{C}_{2,u}} \alpha_2}{N_1 e^{-b_1 \bar{C}_{1,u}} \alpha_1} \right)$
4. virion clearance rate of wild-type to the mutant strain $\left(\frac{\mu_1}{\mu_2} \right)$
5. the equilibrium average life-span of mutant strain to the equilibrium average life-span of wild-type strain infected cells $\left(\frac{\alpha_1 + h_1 \bar{C}_{1,u}}{\alpha_2 + h_2 \bar{C}_{2,u}} \right)$

We assume that CTL activity is polyclonal; that is, CTL activity is against multiple HIV gene products because CTLs can show cross-reactivity for serologically distinct strains of virus through recognition of peptide epitopes in conserved proteins shared between virus strains (e.g, matrix proteins and nucleoproteins) [13]. We also consider the extreme cases that the two strains have the same infectivity rates and average life-spans. This essentially means that the two viral strains have different replication rates and cytopathic effects. These assumptions are not necessary but allows us to gain clear mathematical analytical insights. Using these assumptions, equation (18) becomes

$$R_{02} = \frac{R_{01}}{1-\gamma} \Big(\frac{N_2 \alpha_2}{N_1 \alpha_1} \Big) \Big(\frac{\alpha_1 + h \bar{C}_u}{\alpha_2 + h \bar{C}_u} \Big), \tag{19}$$

where $\bar{C}_u$ is the number of CTLs before infection and h the rate at which each CTL lyse infected cells. We have $R_{02} < R_{01}$ if

$$\frac{1}{1-\gamma} \Big(\frac{N_2 \alpha_2}{N_1 \alpha_1} \Big) \Big(\frac{\alpha_1 + h \bar{C}_u}{\alpha_2 + h \bar{C}_u} \Big) < 1, \quad \text{which implies} \quad N_2 < (1-\gamma) N_1 \Big(\frac{\alpha_1}{\alpha_2} \Big) \Big(\frac{\alpha_2 + h \bar{C}_u}{\alpha_1 + h \bar{C}_u} \Big).$$

On the other hand, we have $R_{02} > R_{01}$ if

$$\frac{1}{1-\gamma} \Big(\frac{N_2 \alpha_2}{N_1 \alpha_1} \Big) \Big(\frac{\alpha_1 + h \bar{C}_u}{\alpha_2 + h \bar{C}_u} \Big) < 1, \quad \text{which implies} \quad N_2 > (1-\gamma) N_1 \Big(\frac{\alpha_1}{\alpha_2} \Big) \Big(\frac{\alpha_2 + h \bar{C}_u}{\alpha_1 + h \bar{C}_u} \Big).$$

If the production of mutant-strain viral particles per infected cell is greater than the production of wild-type strain viral particles per non-mutating wild-type strain infected cell, then $R_{02} > R_{01}$; otherwise $R_{02} < R_{01}$. The model results show that even if $R_{01} < 1$, R_{02} can still be greater than one depending on the mutant strain viral particles' virulence. Figure 2 shows the qualitative behavior of the seven populations of system (1)-(5) during the first 200 days of infection. The parameter values used to numerically solve the infection model are in table 2:

TABLE 2. Parameter values used in numerical simulations

Parameter	Value
s	20
s_1	10
s_2	10
β_1	2×10^{-5}
β_2	5×10^{-5}
B_T^1	350
B_T^2	250
B_V^1	400
B_V^2	300
h_1	2×10^{-3}
h_2	2×10^{-3}
μ_T	0.02
δ_1	1.4
δ_2	1.4
μ_1	0.95
μ_2	0.85
k_1	2×10^{-3}
k_2	2.5×10^{-3}
r_1	0.01
r_2	0.02
α_1	0.25
α_2	0.3
p_1	1×10^{-5}
p_2	1×10^{-5}
N_1	1000
N_2	1500
a_1	0.002
a_2	0.002
b_1	0.05
b_2	0.05
γ	3×10^{-5}

Without loss of generality, we assume that CTL effects are similar ($a_2 = a_1$, $b_2 = b_1$, and $h_2 = h_1$). The initial values for the populations are $T(0)$=1000 cells mm^{-3}, $T_1^*(0)$=0 cells mm^{-3}, $T_2^*(0)$=0 cells mm^{-3}, $V_1^I(0)$=0.001 copies mm^{-3}, $V_2(0)$=0 copies mm^{-3}, $C_1(0)$=10 cells mm^{-3}, and $C_2(0)$=10 cells mm^{-3}. Most of these

parameter values have been used in [9] and other references quoted therein. The graphs of the solution curves to system (1)-(5) approach an infected steady state in agreement with analytic results, where $R_{01} = 14$ and $R_{02} = 58$.

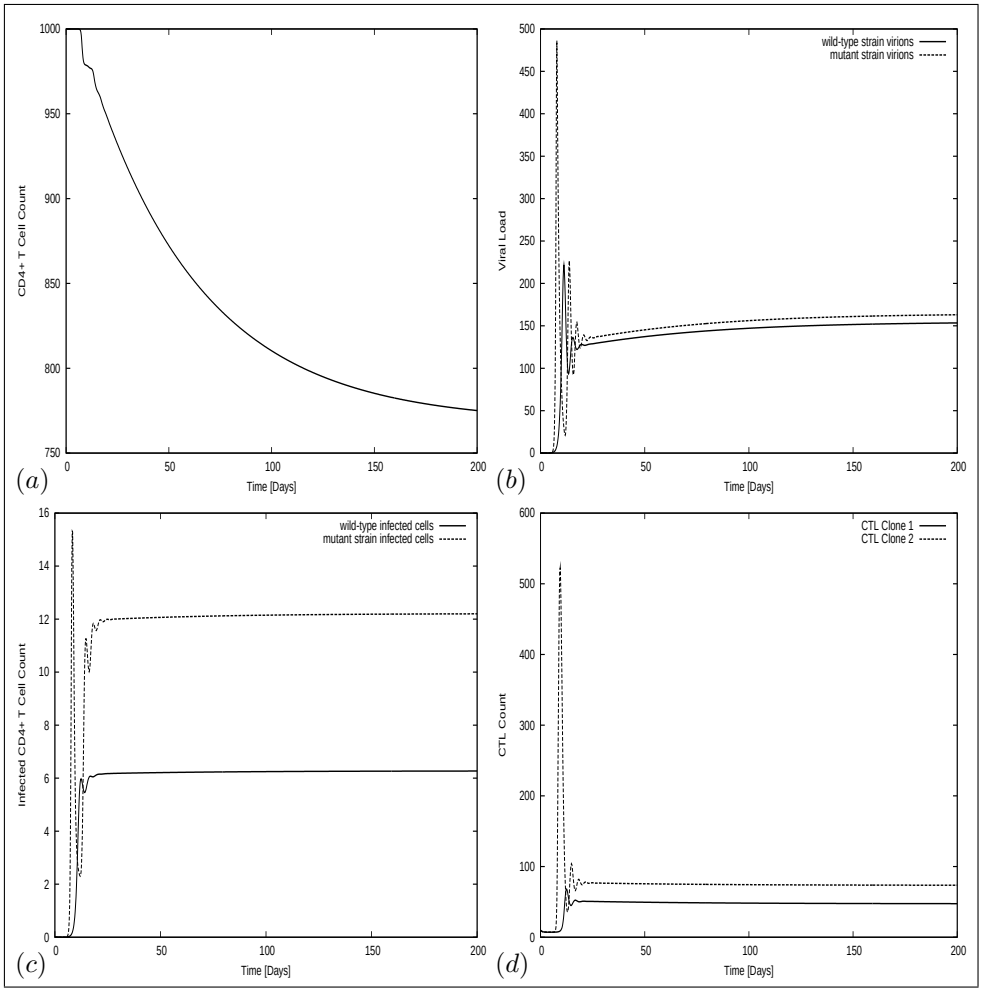

FIGURE 2. Graph of the numerical solution to the system (1)-(5), showing propagation of CD4+ T cells, viral strains, and CTL-specific cells during the first 200 days of infection: (a) CD4+ T cell kinetics during the first 200 days of infection, (b) viral strains kinetics during the first 200 days of infection, (c) infected CD4+ T cells kinetics that evolve during 200 days of infection, and (d) abundance of CTLs specific to each strain.

4. **Effects of Chemotherapy.** If the immune system fails to control the virus we approach a severe stage associated with a clinical spectrum of symptoms; that is,

the AIDS stage. It is at this stage when therapy is started in an attempt to augment CTL responses in infected individuals. To study the effects of chemotherapy we extend the model given by equations (1)-(5) by incorporating the effects of drug efficacy. We incorporate in our model, two commonly used categories of antiretroviral drugs, namely, reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), and assume that the drugs act only on the wild-type strain virus and the mutant strain viral particles are not susceptible to the drug's antiviral effects. Assuming that reverse transcriptase inhibitors are administered, then the infectivity of the wild-type strain is modified to $(1-\epsilon_{RTI})\beta_1$, where ϵ_{RTI} is the efficacy of RTIs and $0 < \epsilon_{RTI} < 1$. If we also assume that PIs are administered, then the burst size parameter of the wild-type infectious viral particles becomes $(1-\epsilon_{PI})N_1$, where ϵ_{PI} is the efficacy of PIs and $0 < \epsilon_{PI} < 1$. Protease inhibitors render some of the wild-type viral particles noninfectious with efficacy, ϵ_{PI}. We assume that there are no pharmacological and intracellular delays; that is, upon drug administration the drug starts to work. Hence the model for chemotherapy (RTIs plus PIs) assumes eight interacting species, the components being: healthy CD4+ T cells (T), wild-type virus-infected CD4+ T cells (T_1^*), mutant strain virus-infected CD4+ T cells (T_2^*), infectious wild-type strain viral particles (V_1^I), noninfectious wild-type viral particles (V_1^{NI}), infectious mutant strain plasma viral load (V_2), CTLs specific to the wild-type virus particles (C_1), and mutant strain virus-specific CTLs (C_2). Thus, the model becomes

$$\begin{aligned}
\frac{dT(t)}{dt} &= s + T(t)\left(\frac{r_1 V_1^I(t)}{B_1^V + V_1^I(t)} + \frac{r_2 V_2(t)}{B_2^V + V_2(t)}\right) - \mu_T T(t) \\
&\quad -T(t)\left(\frac{k_1 V_1^I(t)}{B_1^T + T(t)} + \frac{k_2 V_2(t)}{B_2^T + T(t)}\right) - \beta_2 e^{-a_2 C_2(t)} T(t) V_2(t) \\
&\quad -(1-\epsilon_{RTI})\beta_1 e^{-a_1 C_1(t)} T(t) V_1^I(t) \qquad (20) \\
\frac{dT_1^*(t)}{dt} &= (1-\gamma)(1-\epsilon_{RTI})\beta_1 e^{-a_1 C_1(t)} T(t) V_1^I(t) - (\alpha_1 + h_1 C_1(t)) T_1^*(t) \qquad (21) \\
\frac{dT_2^*(t)}{dt} &= \beta_2 e^{-a_2 C_2(t)} T(t) V_2(t) + \gamma(1-\epsilon_{RTI})\beta_1 e^{-a_1 C_1(t)} T(t) V_1^I(t) - \alpha_2 T_2^*(t) \\
&\quad -h_2 C_2(t) T_2^*(t) \qquad (22) \\
\frac{dV_1^I(t)}{dt} &= (1-\epsilon_{PI}) N_1 \alpha_1 T_1^*(t) e^{-b_1 C_1(t)} - \mu_1 V_1^I(t) \qquad (23) \\
\frac{dV_1^{NI}(t)}{dt} &= \epsilon_{PI} N_1 \alpha_1 T_1^*(t) e^{-b_1 C_1(t)} - \mu_1 V_1^{NI}(t) \qquad (24) \\
\frac{dV_2(t)}{dt} &= N_2 \alpha_2 T_2^*(t) e^{-b_2 C_2(t)} - \mu_2 V_2(t) \qquad (25) \\
\frac{dC_1(t)}{dt} &= s_1 + p_1 T(t) C_1(t) V_1^I(t) - \delta_1 C_1(t) \qquad (26) \\
\frac{dC_2(t)}{dt} &= s_2 + p_2 T(t) C_2(t) V_2(t) - \delta_2 C_2(t). \qquad (27)
\end{aligned}$$

Equations (20), (21), and (22) are simple modifications of equations (1), (2), and (3) respectively where the wild-type strain's infectivity rate parameter has been modified to incorporate the effects of RTIs. Similarly, equations (23) and (24) are an extension of equation (4), for $i = 1$, incorporating the effects of PIs. Because PIs render newly produced wild-type strain virions non-infectious, we now have

two wild-type strain virus subpopulations: V_1^I- is infectious wild-type strain virus whose dynamics is described by equation (23), and V_1^{NI}- is the wild-type virions rendered non-infectious by PI whose dynamics is described by equation (24). We also assume that the two wild-type strain subpopulations have the same clearance rate from the system. Equations (25) and (26) are the same as equations (4) and (5), for $i = 2$, respectively. Also, CTL clone 1 cells are stimulated to proliferate by the infectious wild-type strain viral particles.

Drugs perturb the equilibrium densities of wild-type virus, uninfected CD4+ T cells, and the wild-type infected CD4+ T cells. The uninfected steady state of the system of equations (20) to (27) is given by

$$\Big(\bar{T}_p, \bar{T}^*_{1,p}, \bar{T}^*_{2,p}, \bar{C}_{1,p}, \bar{C}_{2,p}, \bar{V}_{2,p}, \bar{V}^{NI}_{1,p}, \bar{V}^I_{1,p}\Big) = \Big(\frac{s}{\mu_T}, 0, 0, \frac{s_1}{\delta_1}, \frac{s_2}{\delta_2}, 0, 0, 0\Big), \tag{28}$$

which resembles a situation when chemotherapy eradicates disease. The endemic infected steady state is given by:

$$\bar{E} = \Big(\bar{T}_s, \bar{T}^*_{1,s}, \bar{T}^*_{2,s}, \bar{C}_{1,s}, \bar{C}_{2,s}, \bar{V}_{2,s}, \bar{V}^{NI}_{1,s}, \bar{V}^I_{1,s}\Big), \tag{29}$$

where $\bar{T}_s$, $\bar{T}^*_{1,s}$, $\bar{T}^*_{2,s}$, $\bar{C}_{1,s}$, $\bar{C}_{2,s}$, $\bar{V}_{2,s}$ and $\bar{V}^{NI}_{1,s}$ are given by expressions (30), (31), (32), (35), (36), (33), and (34), respectively. The equilibrium abundance of healthy CD4+ T cells is given by

$$\bar{T}_s = \frac{\mu_1(\alpha_1 + h_1\bar{C}_{1,s})e^{(a_1+b_1)\bar{C}_{1,s}}}{(1-\epsilon_{RTI})(1-\epsilon_{PI})(1-\gamma)\alpha_1\beta_1 N_1}. \tag{30}$$

The effects of chemotherapy on CD4+ T cells are to decrease the rate at which they are infected by the wild-type strain virus population and also to reduce the number of infectious wild-type strain virions produced. In reducing the infectious wild-type strain viral population, the equilibrium value of CTL clone 1 is also reduced. The equilibrium state value of the wild-type strain infected cells is given by

$$\bar{T}^*_{1,s} = \frac{\mu_1\bar{V}^I_{1,s}e^{b_1\bar{C}_{1,s}}}{(1-\epsilon_{PI})N_1\alpha_1}, \tag{31}$$

where the drugs reduce the burst size of infectious wild-type strain-infected cells by a factor $(1 - \epsilon_{PI})$. This results in a reduction of wild-type-strain infected cells. The mutant strain infected CD4+ T cells has a steady-state value

$$\bar{T}^*_{2,s} = \frac{\mu_2\bar{V}_{2,s}e^{b_2\bar{C}_{2,s}}}{N_2\alpha_2}, \tag{32}$$

which is also reduced by drug effects, since drugs lower the equilibrium value of the mutant strain viral particles. Mutant strain virus population at equilibrium is given by

$$\bar{V}_{2,s} = \frac{(1-\epsilon_{RTI})\beta_1\alpha_2 N_2\gamma\bar{T}_s e^{-(a_1\bar{C}_{1,s}+b_2\bar{C}_{2,s})}}{\mu_2(\alpha_2 + h_2\bar{C}_{2,s}) - \beta_2\alpha_2 N_2\bar{T}_s e^{-(a_2+b_2)\bar{C}_{2,s}}}\bar{V}^I_{1,s}. \tag{33}$$

Drugs have an indirect effect on the mutant strain viral load as they directly affect the kinetic parameters of the wild-type strain viral particles. Mutant strain viral particles are linearly related to the wild-type strain viral population. Drugs decrease the density of non-mutating infectious wild-type virus. The noninfectious wild-type strain viral population at equilibrium is given by

$$\bar{V}^{NI}_{1,s} = \frac{\epsilon_{PI}\bar{V}^I_{1,s}}{1-\epsilon_{PI}}, \tag{34}$$

which entirely depends on the efficacy of the protease inhibitor. HIV-1 specific CTL clone 1 cells have an equilibrium density given by

$$\bar{C}_{1,s} = \frac{s_1}{\delta_1 - p_1 \bar{T}_s \bar{V}_{1,s}^I}, \tag{35}$$

and the CTL clone 2 density is

$$\bar{C}_{2,s} = \frac{s_2}{\delta_2 - p_2 \bar{T}_s \bar{V}_{2,s}}. \tag{36}$$

The drugs affect the equilibrium abundance of viral load by reducing the pretreatment quantities implies that at equilibrium CTL quantities are also reduced. If drugs are potent enough to reduce viral load to zero levels, then infection can be resolved. The explicit expression for $\bar{V}_{1,s}^I$ is too long to be written down, but we remark that its value can be determined by solving equation (18) for $\frac{dT(t)}{dt} = 0$ using expressions (30), (33), (34), (35), and (36). The equilibrium value of the wild-type strain virus population expression involves apoptosis and proliferation rates, production rate of CD4+ T cells, and the effectiveness of CTLs in suppressing HIV replication. The uninfected CD4+ T cell steady state can be written in the form:

$$\bar{T}_s = \frac{1}{(1-\epsilon_{RTI})(1-\epsilon_{PI})} \Big(\frac{\alpha_1 + h_1 \bar{C}_{1,s}}{\alpha_1 + h_1 \bar{C}_{1,p}} \Big) \Big(e^{-(a_1+b_1)(\bar{C}_{1,p} - \bar{C}_{1,s})} \Big) \bar{T}_p. \tag{37}$$

Now the equilibrium density of the uninfected cells depends on drug efficacy and CTL control. We let $(\epsilon_{RTI} + \epsilon_{PI} - \epsilon_{PI}\epsilon_{RTI}) = \eta$, be the total drug efficacy. Of interest is the minimum drug efficacy necessary to retain the immune CD4+ T cells to preinfection levels; that is, η_c is the value of η at which $\bar{T}_s = \frac{s}{\mu_T}$. The critical efficacy value given by the model is

$$\eta_c = 1 - \Big(\frac{\alpha_1 + h_1 \bar{C}_{1,s}}{\alpha_1 + h_1 \bar{C}_{1,p}} \Big) \Big(\frac{e^{-(a_1+b_1)\bar{C}_{1,p}}}{e^{-(a_1+b_1)\bar{C}_{2,s}}} \Big) \frac{\bar{T}_p}{\bar{T}_u}. \tag{38}$$

The critical drug regimen efficacy to clear the wild-type viral population is determined by three proportions, namely,

1. the proportion of the equilibrium life-span of wild-type strain infected cells before therapy administration to the equilibrium life-span of wild-type strain infected cells during therapy uptake $\Big(\frac{\alpha_1 + h_1 \bar{C}_{1,s}}{\alpha_1 + h_1 \bar{C}_{1,p}} \Big)$,
2. the proportion of equilibrium CTL effectiveness in inhibiting infection of CD4+ T cells and reducing infectious wild-type viral particles to the equilibrium CTL effects during therapy, $\Big(\frac{e^{-(a_1+b_1)\bar{C}_{1,p}}}{e^{-(a_1+b_1)\bar{C}_{2,s}}} \Big)$,
3. the proportion of equilibrium abundance of CD4+ T cells before therapy to the equilibrium abundance of CD4+ T cells prior to infection $\frac{\bar{T}_p}{\bar{T}_u}$.

Drug efficacy needed to control disease is increased by:

1. a decrease in effectiveness of CTLs in reducing number of infectious wild-type strain viral particles,
2. a decrease in inhibitory effects of CTLs in reducing viral infectivity,
3. an increase in the life-span of infected CD4+ T cells during therapy.

Infectious virions before therapy are in large numbers compared to infectious virions after therapy, because some viral particles will be rendered noninfectious. This implies that the equilibrium abundance of CTLs specific to the wild-type strain under therapy is low because of low infectious wild-type strain virions, which in turn implies high CD4+ T cell levels. This shows that there is a dynamic equilibrium

between viral load and CTLs in infected individuals during drug administration. Low titers of wild-type strain viral population imply few viral particles mutating, which leads to low mutant strain viral particles, implying better clinical benefits.

Using the method of [5], the reproductive ratio of the wild-type strain is given by

$$R'_{01} = \frac{(1-\gamma)(1-\epsilon_{RTI})(1-\epsilon_{PI})\beta_1\alpha_1 N_1 s e^{-(a_1+b_1)\bar{C}_{1,u}}}{\mu_1\mu_T(\alpha_1+h_1\bar{C}_{1,u})}, \tag{39}$$

where $\bar{C}_{1,u} = \frac{s_1}{\delta_1}$, $\bar{C}_{2,u} = \frac{s_2}{\delta_2}$ and the reproductive ratio of the mutant strain remains as in equation (17). The consequences of drug administration are that $R'_{01} < R_{01}$. If we rewrite equation (39) in terms of R_{01} we get the following expression:

$$R'_{01} = (1-\epsilon_{RTI})(1-\epsilon_{PI})R_{01}, \tag{40}$$

for $R_{01} > 1$, since therapy is administered only to symptomatic patients. For a potent combination regimen, we have $R'_{01} < 1$, which gives the following result:

$$\eta > 1 - \frac{1}{R_{01}}, \tag{41}$$

for $\eta = \epsilon_{RTI} + \epsilon_{PI} - \epsilon_{RTI}\epsilon_{PI}$. This gives the critical total drug regimen efficacy to eradicate infection as

$$\eta_c = 1 - \frac{1}{R_{01}}. \tag{42}$$

Equations (38) and (42) give us the following result:

$$R_{01} = \frac{(1-\gamma)\beta_1\alpha_1 N_1 e^{-(a_1+b_2)\bar{C}_{1,s}}\bar{T}_u}{\mu_1(\alpha_1+h_1\bar{C}_{1,s})}, \tag{43}$$

if and only if $\bar{C}_{1,s} = \bar{C}_{1,u}$; that is, complete wild-type viral population eradication by chemotherapy is achieved if the antiviral CTL clone 1 response is returned to pre-infection levels.

5. **Numerical Simulations.** In this section we use numerical simulations to investigate the effects of drugs on HIV-1 disease parameters. A fourth-order Runge-Kutta scheme is used to simulate the results. Because of the deleterious side effects of drugs and drug resistance, we consider short term administration of drugs where we assumed that no side effects occur during the first 200 days. The initial conditions for all the numerical simulations are $T(0)$=200 cells mm^{-3}, $T_1^*(0)$=600 cells mm^{-3}, $T_2^*(0)$=500 cells mm^{-3}, $V_1^I(0)$=3,000 copies mm^{-3}, $V_2(0)$=2,500 copies mm^{-3}, $C_1(0)$=400 cells mm^{-3}, $C_2(0)$=400 cells mm^{-3} and $V_1^{NI}(0)$=0 copies mm^{-3}. The parameter values used to generate the computer simulations of changes over time in HIV abundance, CD4+ T cell count, and CTL count in an individual patient, as described by system of equations (15)-(22) are as in figure 2. In figure 3 the drug efficacies are given by $\epsilon_{RTI} = 0.45$ and $\epsilon_{PI} = 0.5$, with a total efficacy of 0.725. Using the above parameter values and these drug efficacy values, we depict a less effective drug regimen, because minimum efficacy to eradicate wild-type strain viral particles is 0.93, since the reproductive ratio of the wild-type strain is 14. Also the virus reproductive ratio of the mutant strain virus population is 58 which means that any drug intended to eradicate this strain should have at least an efficacy of 0.98. Since the drugs do not act on the mutant strain, this population continues to exist. Suppression of the wild-type strain viral population is not complete, therefore, disease progresses. The total viral load is lowered to zero levels during the first

week of therapy, but thereafter it rebounds. After rebound, the mutant strain viral levels remain high until therapy is stopped. Over the 200-day course of therapy administration, CD4+ T cells drastically increase during the first week, thereafter they gradually increase. CTL counts initially increase to high levels during the first week of therapy and then drastically drop and stabilize at low levels.

In figures 4 and 5, we show the evolution of the virus when combined drug efficacy is increased to the minimum efficacy (0.927) and slightly above the minimum efficacy (0.932), respectively, and other parameters remain as in figure 2. Serum levels of HIV RNA decay exponentially, and the CD4+ T cell count increases. The potency of the drugs has enhanced the increase in CD4+ T cells and also managed to eradicate the wild-type strain virus population. Of interest is the density of mutant strain viral particles, which remain in large numbers, solely because drugs have no effect on this population.

In all these numerical simulations the slopes for exponential decay are very similar in figures 3, 4, and 5 which we attribute to the death of infected CD4+ T cells. The fact that the drug has no effect on the mutant strain virus population is the reason disease progresses, as shown by figure 3. The rebound of viral load is entirely due to the recovery of CD4+ T cells; that is, more prey will be available to the predator [19]. The most common pattern of CD4+ T cell kinetics, is an initial dramatic increase in CD4+ T cell count in the first few weeks of drug therapy, followed by a more gradual increase. Increase in CD4+ T cells is strictly by clonal expansion of pre-existing naive CD4+ T cells, since the model does not capture CD4+ T cells "retrafficking" effect–a phenomenon in which once viral load is suppressed by drugs, CD4+ T cells regain their ability to travel from lymphocytes into the blood stream. Our numerical results (figure 3, 4, and 5) show that during the first week of therapy viral load decays exponentially to zero levels. If drug efficacy is potent enough to eradicate infection, viral loads remain at zero levels, and if drugs are less potent, the viral load will gradually increase until it stabilizes.

Similarly, we can also consider a case when $R_{02} < R_{01}$, all greater than 1. If drugs act only on the wild-type viral strain and if drug efficacy is potent enough to clear the wild-type viral population, disease still progresses. On the other hand, if the drugs act on both viral strain populations, the critical efficacy to eradicate the entire viral population is given by the reproductive ratio of the system; that is, it is given by the virus population with the largest reproductive ratio. These results show that the existence of drug resistant strains makes HIV-1 disease eradication impossible.

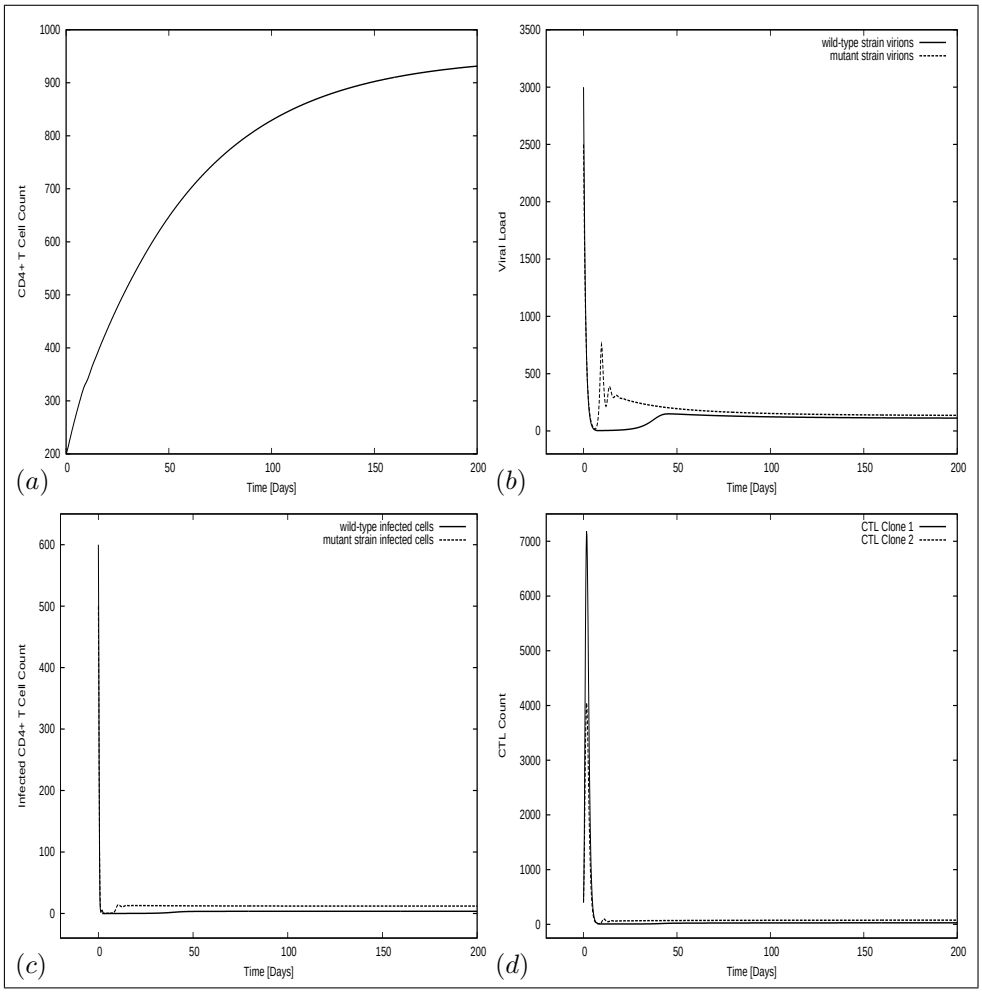

FIGURE 3. Graph of the numerical solution to the system, showing propagation of CD4+ T cells, viral strains, and CTL-specific cells during the first 200 days of combined therapy administration: (a) CD4+ T cell kinetics during the first 200 days of therapy, (b) viral strains kinetics during the first 200 days of therapy, (c) infected CD4+ T cells kinetics that evolve during 200 days of therapy uptake, and (d) abundance of CTLs specific to each strain. Drug efficacy is given by $\epsilon_{RTI} = 0.45$ and $\epsilon_{PI} = 0.5$.

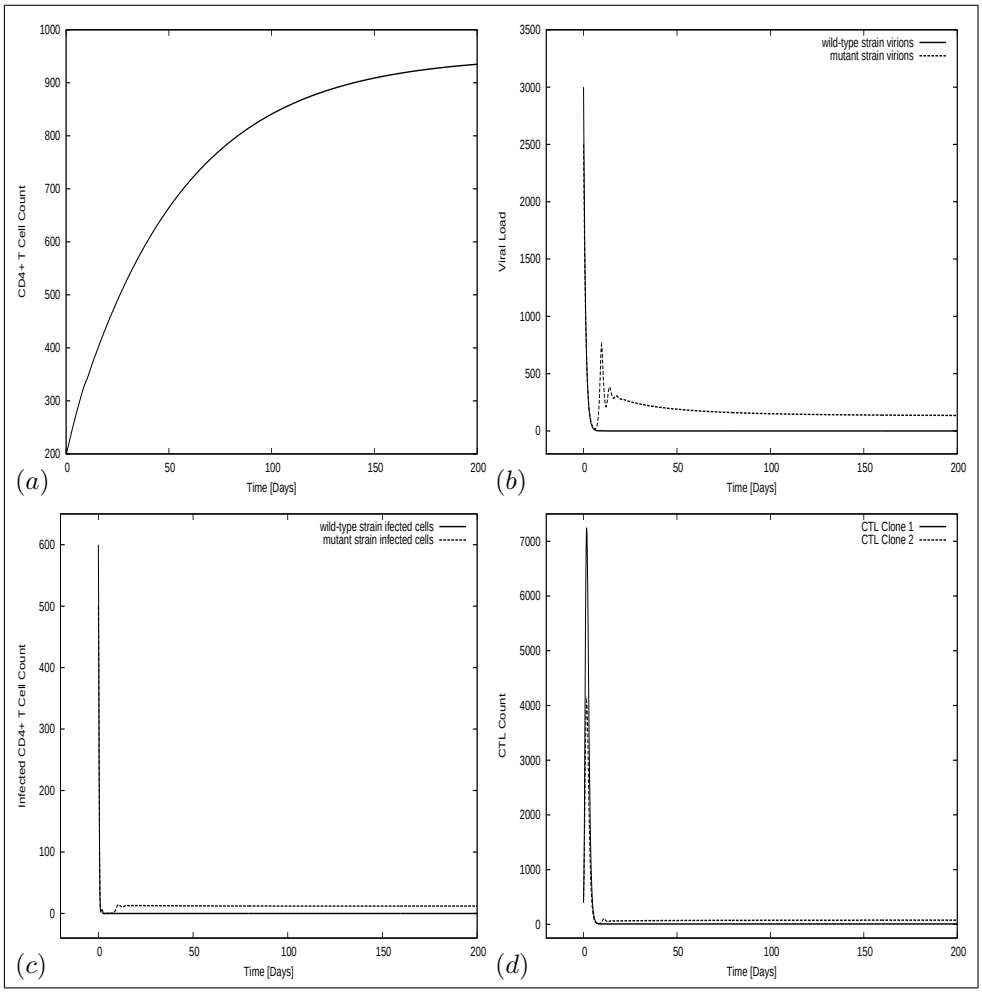

FIGURE 4. Graph of the numerical solution to the system, showing propagation of CD4+ T cells, viral strains and CTL specific cells during the first 200 days of combined therapy administration: (a) CD4+ T cell kinetics during the first 200 days of therapy, (b) viral strains kinetics during the first 200 days of therapy, (c) infected CD4+ T cells kinetics that evolve during 200 days of therapy uptake, and (d) abundance of CTLs specific to each strain. Drug efficacy is given by $\epsilon_{RTI} = 0.6$ and $\epsilon_{PI} = 0.807$.

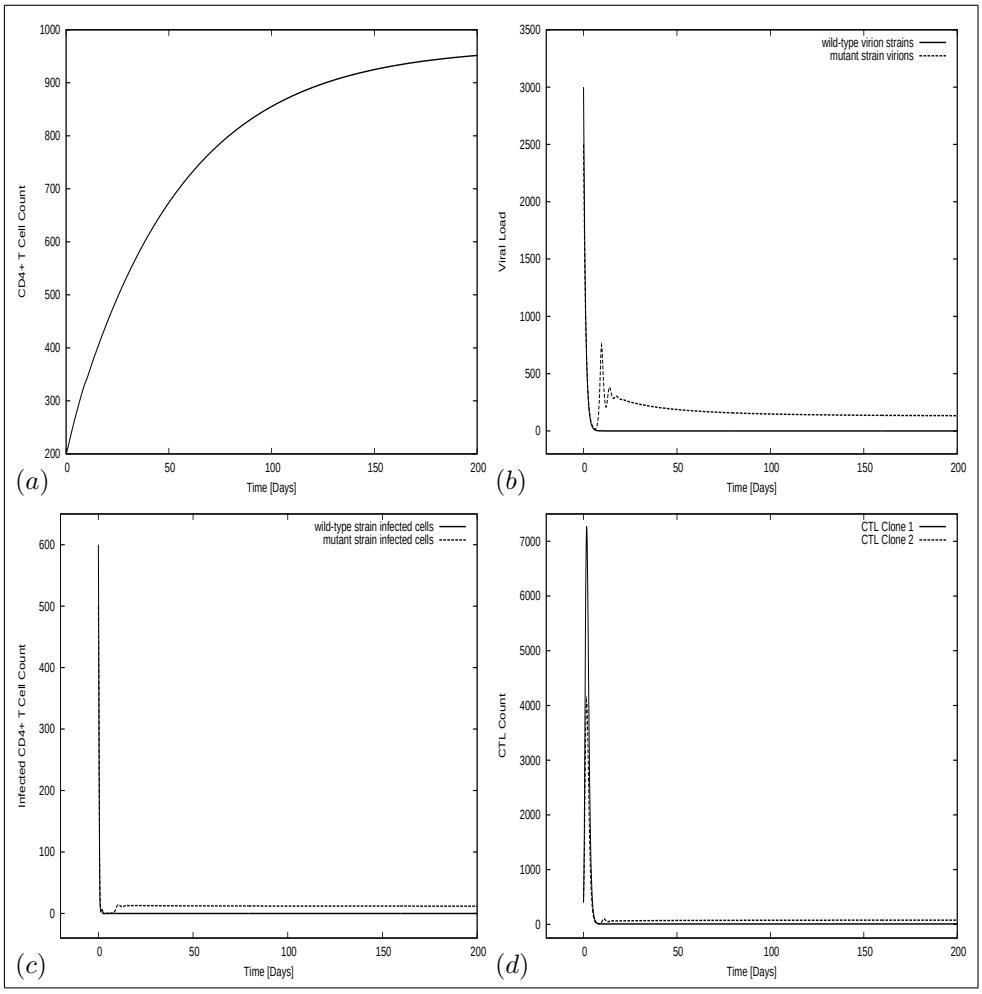

FIGURE 5. Graph of the numerical solution to the system, showing propagation of CD4+ T cells, viral strains and CTL specific cells during the first 200 days of combined therapy administration: (a) CD4+ T cell kinetics during the first 200 days of therapy, (b) viral strains kinetics during the first 200 days of therapy, (c) infected CD4+ T cells kinetics that evolve during 200 days of therapy uptake, and (d) abundance of CTLs specific to each strain. Drug efficacy is given by $\epsilon_{RTI} = 0.66$ and $\epsilon_{PI} = 0.8$.

6. **Discussion and Conclusion.** Antiretroviral drugs have gone a long way in conferring clinical benefits to symptomatic HIV-infected individuals; that is, increasing CD4+ T cell counts and suppressing HIV RNA viral load below detection levels, despite significant metabolic drug toxicities. Using a mathematical model, we considered the effect of drugs on HIV-1 disease parameters and deduced that

the model qualitatively accounts for the initial and the second phases of virus decay during antiretroviral administration [14]. The results show the following:

1. If the immune control and drugs are potent enough to maintain infected CD4+ T cells at low levels, there are clinical benefits.
2. There is a dynamic equilibrium between viral load and CTL response; that is, after commencement of antiretroviral therapy, the number of CTLs increases and with ongoing suppression of HIV, the number of CTLs decline. If the viral load increases again, the number of CTLs increase as well.
3. Drug resistance is the major factor that makes complete disease eradication by therapy impossible as shown by the numerical results.

There are significant differences between the model behavior and clinical findings. To start with, upon onset of therapy, there is no initial delay where viral loads remain at pretreatment levels. Thus, one could argue that to rectify the difference we should incorporate pharmacokinetic and intracellular time delays. This aspect will be considered elsewhere. Second, in our dynamical model, we considered only a single-point mutation which has no stochasticity: mutation is implemented as a constant process. Stochasticity of the mutation process is a source of variation, and depends on selective pressure exerted on the viral population by both drugs and CTLs. With respect to the parameter values used in simulations (especially viral kinetics), infectivity and apoptosis rate remain the most important unknowns. Although predicted trends qualitatively agree with observed clinical findings, the quantitative results depend on accurate parameter values. Estimating these values *in vitro* is extremely difficult.

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E-mail address: tshiri@nust.ac.zw
E-mail address: wgarira@nust.ac.zw
E-mail address: sdmusekwa@nust.ac.zw