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MODELLING THE IMMUNOPATHOGENESIS OF HIV-1 INFECTION AND THE EFFECT OF MULTIDRUG THERAPY: THE ROLE OF FUSION INHIBITORS IN HAART

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Abstract. There is currently tremendous effort being directed at developing potent, highly active antiretroviral therapies that can effectively control HIV-1 infection without the need for continuous, lifelong use of these drugs. In the ongoing search for powerful antiretroviral agents that can affect sustained control for HIV infection, mathematical models can help in assessing both the correlates of protective immunity and the clinical role of a given drug regimen as well as in understanding the efficacy of drug therapies administered at different stages of the disease. In this study, we develop a new mathematical model of the immuno-pathogenesis of HIV-1 infection, which we use to assess virological responses to both intracellular and extracellular antiretroviral drugs. We first develop a basic mathematical model of the immuno-pathogenesis of HIV-1 infection that incorporates three distinct stages in the infection cycle of HIV-1: entry of HIV-1 into the cytoplasm of CD4+ T cells, transcription of HIV-1 RNA to DNA within CD4+ T cells, and production of HIV-1 viral particles within CD4+ T cells. Then we extend the basic model to incorporate the effect of three major categories of anti-HIV-1 drugs: fusion/entry inhibitors (FIs), reverse transcriptase inhibitors (RTIs), and protease inhibitors (PIs). Model analysis establishes that the actual drug efficacy of FIs, γ and of PIs, κ is the same as their effective efficacies while the effective drug efficacy for the RTIs, r_ϵ, is dependent on the rate of transcription of the HIV-1 RNA to DNA, and the lifespan of infected CD4+ T cells where virions have only entered the cytoplasm and that this effective efficacy is less than the actual efficacy, ϵ. Our studies suggest that, of the three anti-HIV drug categories (FIs, RTIs, and PIs), any drug combination of two drugs that includes RTIs is the weakest in the control of HIV-1 infection.

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1. **Introduction.** HIV-1 belongs to the lentivirus subfamily of retroviruses. As with all retroviruses, the viral genes in infectious particles are carried as RNA, but upon infection of the host cell, reverse transcriptase catalyses the synthesis of double stranded DNA viral genome [14]. The HIV infection cycle can be categorised into six distinct states [2, 14]:

1. **Binding and Fusion:** HIV begins its infection cycle when it binds to a CD4 receptor and one of two coreceptors on the surface of a CD4+ T lymphocyte. The virus then fuses with the host cell. After fusion, the virus releases RNA, its genomic material, into the host cell.
2. **Reverse Transcription:** An HIV enzyme called reverse transcriptase converts the single-stranded HIV RNA to double-stranded DNA.
3. **Integration:** The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called integrase "hides" the HIV DNA within the host cell's own DNA (the integrated HIV DNA is called the provirus). The provirus may remain inactive for several years (this causes latent infection), producing few or no new copies of HIV.
4. **Transcription:** When the host cells receive a signal to become active, the provirus uses a host enzyme called RNA polymerase to create copies of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). The mRNA is used as a blueprint to make long chains of HIV proteins.
5. **Assembly:** An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.
6. **Budding:** The newly assembled virus pushes out ("buds") from the host cell. During budding, the new virus steals part of the cell's outer envelope. This protein, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co-receptors. The new copies of HIV can now move on to infect other cells.

HIV infection is primarily through direct infection of CD4+ T cells by the HIV through exploitation of the CCR5 and CXCR4 co-receptors expressed on their surfaces. Thus the major hallmarks of HIV infection include the destruction of helper CD4+ T lymphocytes and subsequent loss of immune competence [14, 32]. HIV infection impairs cell function by destroying cells required to build a robust immune response [32]. Depletion of the CD4+ T cells results in a weakened immune system. Then the infection progresses slowly to cause the AIDS condition where the immune system is prone to opportunistic infections. The rate of the infection progression depends on the robustness of human immune mechanisms that are mounted. CD4+ T cells depletion and the rate at which the virus mutates to strains that can escape the immune system [25] determine the extent of the immune compromisation HIV infection causes.

The evolution of HIV infection has been characterised in four main stages of disease progression. First is the initial inoculum, when the virus is introduced into the body. Second, is the initial transient, where the T cell and virus populations are in great flux [14, 16]. The viral load at this stage may vary significantly between individuals [3]. This is followed by the third stage, clinical latency. This is a period of time when there are extremely large numbers of virus and T cells undergoing

incredible dynamics, the overall result of which is an appearance of latency (disease steady state). Finally there is AIDS. This is characterised by the T cells dropping to very low numbers and the virus growing without bound, resulting in death [16]. This is also characterised by the development of opportunistic infections and other pathological conditions. Strong HIV-specific CD4+ T cell responses and strong HIV-specific CD8+ T cell responses during acute HIV-1 infection are associated with good control of early HIV-1 replication [26, 36, 37].

With the introduction of highly active antiretroviral therapy (HAART), a substantial reduction in HIV-associated morbidity and mortality can be achieved [29]. However the durability of suppression of HIV infection is often limited by a variety of factors including compliance, short- and long-term toxicity of anti-retroviral agents, unfavourable pharmacokinetics profiles, and alterations in the bio-availability and metabolism of anti-retroviral drugs [21, 29]. These factors contribute to persistent viral replication in patients receiving drug therapy, increasing the risk of viral resistance [21]. As a result, in clinical practice virological failure rates of up to 50% are common within the first two years of HAART and currently more than 50% of HIV-infected patients receiving anti-viral therapy have developed resistance to at least one of the compounds of their current regimen [29].

More than twenty approved HIV drugs are currently available, with most falling into one of two categories: reverse transcriptase inhibitors (RTIs) or protease inhibitors (PIs). These drugs work by interfering with some aspect of the viral life cycle. RTIs inhibit HIV RNA from being converted into DNA, thus blocking integration of the viral code into the target cell [1]. On the other hand, PIs function by preventing the assembly of key viral proteins after they have been produced by the infected host cell. Therefore PIs effectively reduce the number of infectious virus particles released by an infected cell. A third category of HIV drugs is a new family of antiretrovirals called fusion/entry inhibitors, presently represented only by one drug, enfuvirtide (T-20) [8, 33, 29]. Enfuvirtide is the first fusion inhibitor, but many other compounds are in the process of clinical development [8, 23, 24, 29]. FIs work by inhibiting viral entry into CD4+ T cells [8, 23, 24, 29]. The main steps in the viral entry process are, (i) attachment of the viral gp120 to the CD4+ cell receptor, (ii) binding of the gp120 to CCR5 or CXCR4 coreceptors, and (iii) fusion of the viral and cellular membranes [8, 23, 24]. Studies show that FIs the can work synergistically (FIs in combination with RTIs and PIs will produce better treatment results than when FIs and, RTIs and PIs are used separately) with other available drugs (RTIs and PIs) to suppress replication of HIV-1 strains in which multiple resistance mutation against currently available antiretroviral drugs, and have also been shown not to be cross-reactive [8, 23, 33].

Studies [29, 24, 21] demonstrate the efficacy of enfuvirtide (T-20), that is, the addition of T-20 to an optimised ground of antiretroviral on the basis of genotypic and phenotypic resistance testing significantly improves virological response (improves reduction of plasma viral load during anti-retroviral therapy), decreases virological failure, and increases CD4+ T cell count compared with the optimised background alone. HIV patients in these studies [21, 29, 24] were partitioned to receive either T-20 administration with the combination or the individualised antiretroviral treatment regimen alone (what they called "current standard of care" [SOC]). Then a two-arm study of TORO (T-20 versus Optimised Regimen Only) and SOC was conducted. In both arms, patients had an HIV median viral load of $5 \log_{10} copies/mL$. In the first arm TORO recipients achieved a reduction of $1.7 \log_{10} copies/mL$,

compared with $0.76 \log_{10} copies/mL$ reduction in SOC. In the second arm TORO achieved $1.43 \log_{10} copies/mL$ reduction, while $0.65 \log_{10} copies/mL$ reduction was achieved through SOC. These studies demonstrate the potency of FIs in combination with the current RTIs and PIs and show that addition of FIs to the current HIV treatment strategy has the potential to achieve better treatment results.

Several authors have put forward models in an attempt to explain the dynamics of viral production, the dynamics of the immune system, and the effect of antiretrovial therapy on HIV disease progression [35, 18, 16, 10]. A shortfall in the majority of these models is that they do not incorporate some effects of immune response, such as the proliferation of CD4+ T cells and CD8+ T cells after antigen stimulation. In the light given that CTLs play a significant role in the control of infection [36, 37], we developed models that include the effects of immune response based on CTL effects as well as drug therapy in a more elaborate manner on HIV disease [31, 13]. Nevertheless, none of these earlier studies have incorporated all three classes of antiretroviral drugs (FIs, RTIs and PIs). Previous models have only either incorporated the effect of RTIs or the effect of PIs [18, 16, 11] or the effect of a combination of RTIs and PIs [7, 31, 13]. Thus, to date mathematical models have only been used to assess the effect of intracellular anti-HIV drugs (RTIs and PIs). These models do not separate the process of HIV virion collision/fusion and entry into the cytoplasm of CD4+ T cells from transcription of HIV RNA into DNA which result in successful infection of CD4+ T cells. Here we, design a new mathematical model for HIV-1 infection dynamics, which represents in a more elaborate way the infection cycle of HIV-1 in which the aforementioned processes are distinct and different and do not occur at the same time. This approach enables models to incorporate the effects of multidrug treatment of HIV-1 infection in which FIs are also part of the treatment regimen. Therefore, the purpose of this study is to investigate the HIV-infection dynamics involved when the infection cycle of CD4+ T cells is staged into separate distinct phases and to show how the administration of HIV drugs in their three-fold modes of action (inhibition of fusion, inhibition of transcription and inhibition of production of new viral particles) affects the progression of the disease. The first stage of CD4+ T cell infection by HIV-1 are, first is collision/fusion of CD4+ T cells and HIV-1, which results in the successful entry of HIV virions into the cytoplasm of CD4+ T cells. At this stage transcription has not yet occurred; therefore, we define these cells as exposed CD4+ T cells, because they carry viral particles that have the potential to replicate. When successful reverse transcription occurs, then these exposed CD4+ T cells enter a second stage of infected CD4+ T cells where the viral RNA is converted to become DNA and can then later bud new HIV virions.

This paper is organised as follows: in Section 2 we present the new mathematical model that separates the process of collision/fusion and viral entry into CD4+ T cells from the process of transcription and its analysis. In Section 3 we present the HIV multi-drug therapy model that includes the administration of FIs, RTIs, and PIs. Numerical simulations of the models are presented in Section 4 and a discussion of results is done in Section 5.

2. **The basic model of HIV-1 immunopathogenesis.**

We develop a basic model of HIV-1 immunopathogenesis, which assumes interaction of four cell populations: (i) healthy CD4+ T cells (T_S) (we define these CD4+ T cells as susceptible);

(ii) infected CD4+ T cells where virions have only entered the cytoplasm but without transcription that has occurred (T_E), (which we define as exposed CD4+ T cells); (iii) infected CD4+ T cells which are a result of successful transcription (T_I) (these are defined as productively infected CD4+ T cells); (iv) HIV specific CTLs (C); and (v) the HIV pathogen (V). In this model we assume T cell and virus interactions in peripheral blood and do not consider the exchange of T cells and the virus between the blood and the lymph tissue compartments. However, a model that captures cell and virus dynamics between the two compartments may give more elaborate results. The interaction of T_S, T_E, T_I, C, and V is modelled by the following system of equations.

$$\frac{dT_S}{dt} = s_T + \frac{rT_SV}{V+A} - \frac{\beta_c V T_S}{1+a_0C} - \frac{kVT_S}{T_S+B} - \alpha_S T_S, \tag{1}$$

$$\frac{dT_E}{dt} = \frac{\beta_c V T_S}{1+a_0C} - \beta_v T_E - \alpha_E T_E, \tag{2}$$

$$\frac{dT_I}{dt} = \beta_v T_E - hT_IC - \alpha_I T_I, \tag{3}$$

$$\frac{dC}{dt} = s_C + pVT_SC - \alpha_C C, \tag{4}$$

$$\frac{dV}{dt} = \frac{N\alpha_I T_I}{1+a_1C} - \alpha_V V. \tag{5}$$

Equation (1) models the dynamics of health (susceptible) CD4+ T cells. In the first equation, s_T is the source of CD4+ T cells from the thymus [16]. The second term represents the proliferation of CD4+ T cells due to HIV at rate r, where A is the maximum proliferation stimulation of CD4+ T cells induced by the virus. The third term represents the collision, fusion, and entry of HIV virions into the cytoplasm of CD4+ T cells at rate β_c. The parameter β_c models three mechanisms; that is, (i) the rate at which virus and target collide, (ii) the fraction of cells which are activated and hence susceptible to infection, and (iii) the fraction of interactions between activated CD4+ T cells and virus which results in successful entry of virions into the cytoplasm of CD4+ T cells. The term $(1+a_0C)^{-1}$ models the inhibition of coreceptor binding/fusion of receptors that are expressed by CD4+ T cells that aid the entry of HIV virions by the activity of chemokines that are produced by HIV specific CTLs, where a_0 represents inhibition efficiency of CTLs. The process that results in transcription is modelled separately in equation (2) by β_v. The fourth term represents the loss of CD4+ T cells through apoptosis due to the bystander effect induced by HIV proteins [31] at rate k. The last term represents the natural death of susceptible CD4+ T cells at rate α_S.

Equation (2) describes the dynamics of CD4+ T cells that have been exposed to the virus (i.e., that have allowed viral entry into their cytoplasm). The first term on the right-hand side of equation (2) is from term 3 of equation (1) and is the source of CD4+ T cells where virions have just entered the cytoplasm but await transcription of HIV RNA to DNA to occur. This equation models the transition stage that the successful infection process of CD4+ T cells passes through before transcription occurs. Successful collisions result in the entry of viral particles in the CD4+ T cells. After entry of viral particles into the CD4+ T cells, the virus uses the CD4+ T cell machinery to replicate; then transcription of viral RNA to DNA occurs at rate β_v. Here β_v represents three processes in the HIV-1 infection cycle; that is, (i) reverse transcription, (ii) viral DNA and host DNA integration

and (iii) transcription that results in production of many copies of HIV virions. This equation describes the transition or the intermediate stage that the infection process passes through before the CD4+ T cells become productively infected. The last term represents the death of exposed CD4+ T cells at rate α_E during this transient stage.

Equation (3) models the dynamics of HIV infected CD4+ T cells that have moved from the exposed class after RNA to DNA transcription. The first term is the source of infected CD4+ T cells from term 2 of equation (2). The second term represents the killing of infected CD4+ T cells by the effects of HIV specific CTLs at rate h. The last term represents both the bursting and natural death of infected CD4+ T cells at rate α_I.

Equation (4) models the dynamics of HIV-specific CTLs. The term s_C models the production rate of specific CD8+ T cells from precursors. Naive specific CD8+ T cells differentiate into CTLs in response to HIV with help of CD4+ T cells at a rate p. The value p represents, (i) the fraction of helper CD4+ T cells that aid priming and proliferation of CTLs, (ii) rate of proliferation of CTLs, and (iii) differentiation of CD8+ precursors to CTLs. Garira et al. [13] and Wodarz and Nowak [36] used a similar term to model proliferation of HIV specific CTLs. With α_C we represent the natural death rate of HIV specific CTLs.

Equation (5) models the dynamics of the viral load. The first term represents the source of new virions from the bursting of infected CD4+ T cells. The burst size of infected CD4+ T cells is reduced by CTLs. CTLs release INF-γ, IL-6, and IL-10 cytokines that supress rate of virus production, hence reducing viral burst size [4, 30]. This reduction is modelled by the term $(1+a_1C)^{-1}$; here a_1 models the efficiency of cytokines produced by CTLs in inhibiting budding of new HIV virons. The last term represents the natural death of viral particles at rate α_V.

3. **Analysis of the basic model.** The equilibrium states of the basic model are obtained by setting the right-hand side of equations (1-5) to zero. The disease-free equilibrium state of equations (1-5) is given by

$$\widetilde{E} \quad = \quad (\widetilde{T}_S, \widetilde{T}_E, \widetilde{T}_I, \widetilde{C}, \widetilde{V}) = (\frac{s_T}{\alpha_S}, 0, 0, \frac{s_C}{\alpha_C}, 0), \tag{6}$$

and an HIV-infected state is given by

$$\hat{E} \quad = \quad (\hat{T}_S, \hat{T}_E, \hat{T}_I, \hat{C}, \hat{V}), \tag{7}$$

where $\hat{T}_S$, $\hat{T}_E$, $\hat{T}_I$, $\hat{C}$, and $\hat{V}$ are given by expressions (8-12). The endemic equilibrium value of health CD4+ T cells is given by

$$\hat{T}_S = \frac{(s_T+Bu_0-k\hat{V})+\sqrt{(s_T+Bu_0-k\hat{V})^2-4u_0s_TB}}{2u_0}, \tag{8}$$

$$where\ u_0 = \frac{r\hat{V}}{\hat{V}+A} - \frac{\beta_c\hat{V}}{1+a_0\hat{C}} - \alpha_S.$$

Expression (8) shows that CD4+ T cells proliferate due to the presence of the HIV pathogen, yet are also depleted by the virus. The population density of exposed CD4+ T cells waiting for transcription to occur is given by

$$\hat{T}_E = \Big(\frac{\beta_c\hat{V}\hat{T}_S}{(1+a_0\hat{C})(\beta_v+\alpha_E)}\Big). \tag{9}$$

This expression shows that $\hat{T}_E$ will increase as collision rate β_c increases; $\hat{T}_E$ will decrease as the CTL response increases and as the transcription rate increases. Increase in transcription rate implies that more cells move from the transition stage

into the infected stage, hence less CD4+ T cells in the transition stage. Also increasing CTL effects that inhibit viral entry into CD4+ T cells, β_c, reduce $\hat{T}_E$.

The infected CD4+ T cell endemic equilibrium is given by

$$\hat{T}_I = \Big(\frac{\beta_v \hat{T}_E}{(h\hat{C}+\alpha_I)}\Big). \tag{10}$$

This shows that increasing the population of infected T cell depends on the rate of transcription and lytic killing by CTLs and decrease in $\hat{T}_E$ population reduce their population.

The equilibrium value of HIV-specific CTLs is given by

$$\hat{C} = \Big(\frac{s_C}{\alpha_C - p\hat{T}_S\hat{V}}\Big). \tag{11}$$

This expression shows that there is an inverse relationship between $\hat{V}$ and $\hat{T}_S$, that is, for $\hat{C}$ to be positive, $\alpha_C > p\hat{T}_S\hat{V}$, $(\hat{V} < \big(\frac{\alpha_C}{p\hat{T}_S}\big), \Rightarrow \hat{V} \propto \frac{1}{\hat{T}_S})$. The viral steady state is given by

$$\hat{V} = \Big(\frac{N\alpha_I \hat{T}_I}{\alpha_V(1+a_1\hat{C})}\Big). \tag{12}$$

This shows that viral load increases as the burst sizes and burst rate of $\hat{T}_I$ increase and is reduced by HIV specific CTL response.

We calculate the reproduction number of the basic model given by equations (1-5) in order to determine the stability of $\widetilde{E}$ and $\widehat{E}$, using the next generation method [9]. We define the reproduction number as the number of newly infected CD4+ T cells arising from one HIV infected CD4+ T cell. We define heterogeneity using groups defined by fixed characteristics. Our model can be written in the form:

$$\begin{aligned}
\frac{dX}{dt} &= f(\mathbf{X},\mathbf{Y},\mathbf{Z}),\\
\frac{dY}{dt} &= g(\mathbf{X},\mathbf{Y},\mathbf{Z}),\\
\frac{dZ}{dt} &= h(\mathbf{X},\mathbf{Y},\mathbf{Z}),
\end{aligned} \tag{13}$$

where $\mathbf{X} \in \Re^2$, $\mathbf{Y} \in \Re$, $\mathbf{Z} \in \Re^2$, and $h(\mathbf{X},0,0) = 0$. Assuming that the equation $g(\mathbf{X}^*,\mathbf{Y},\mathbf{X}) = 0$ implicitly determines a function $Y = \widetilde{g}(\mathbf{X}^*,\mathbf{Y})$. We let $\mathbf{A} = \mathbf{D}_Z h(\mathbf{X}^*, \widetilde{g}(\mathbf{X}^*,0),0)$ and further assume that $\mathbf{A}$ can be written in the form $\mathbf{A} = \mathbf{M} - \mathbf{D}$, with $\mathbf{M} \geq 0$ (that is $m_{ij} \geq 0$) and $\mathbf{D} > 0$, a diagonal matrix. The reproduction ratio is then evaluated from the matrix $\mathbf{MD^{-1}}$.

The cell population subgroups are divided as follows, (a) $\mathbf{X}$: are cells that are uninfected by the virus, (b) $\mathbf{Z}$: cells that are virus infected (infected CD4+ T cells), and (c) $\mathbf{Y}$: the HIV pathogen. Therefore, we set $\mathbf{X} = (T_S, C)$,$\mathbf{Y} = V$, $\mathbf{Z} = (T_E, T_I)$, and $\mathbf{X}^* = (\frac{s_T}{\alpha_S}, 0, \frac{s_C}{\alpha_C}, 0)$. Let $\mathbf{U}_0 = (\mathbf{X}^*, 0, 0)$ denote the virus free equilibrium, that is $f(\mathbf{X}^*,0,0) = g(\mathbf{X}^*,0,0) = h(\mathbf{X}^*,0,0) = 0$ and $Y = \widetilde{g}(\mathbf{X}^*,\mathbf{Z})$, where

$$\widetilde{g}(\mathbf{X}^*,\mathbf{Z}) = \frac{N\alpha_I \widetilde{T}_I}{\alpha_V(1+a_1\widetilde{C})}.$$

We compute $A = D_Z(X^*, \widetilde{g}(X^*,0),0)$ and get

$$\mathbf{M} = \begin{pmatrix} 0 & \frac{\beta_c \widetilde{T}_S N\alpha_I}{\alpha_V(1+a_0\widetilde{C})(1+a_1\widetilde{C})} \\ \beta_v & 0 \end{pmatrix},$$

and

$$\mathbf{D^{-1}} = \begin{pmatrix} \frac{1}{(\beta_v+\alpha_E)} & 0 \\ 0 & \frac{1}{(h\widetilde{C}+\alpha_I)} \end{pmatrix}.$$

The preproduction ratio is given by the next generation spectral radius $\rho(MD^{-1})$ to be

$$R_0 = \sqrt{\frac{\beta_v\beta_c N\alpha_I\widetilde{T}_S}{\alpha_V(h\widetilde{C}+\alpha_I)(1+a_0\widetilde{C})(1+a_1\widetilde{C})(\beta_v+\alpha_E)}}. \tag{14}$$

TABLE 1. Table of parameters used in the model. Est means estimated.

Name	Value	Definition	Units	Reference
r	0.01000	CD4+ proliferation rate	day^{-1}	[31, 16, 19]
β_c	0.00250	Collision/fusion rate	day^{-1}	Est
s_T	20.0000	CD4+T supply rate	$mm^{-3}day^{-1}$	[12, 16, 34]
A	400.000	CD4+ Sat Limit due to HIV	CD4+ T mm^{-3}	[31]
a_0	0.0100	Infection inhibition factor	Scalar	Est
β_v	0.00045	HIV CD4+ T infection rate	$mm^{-3}day^{-1}$	[31, 16, 19]
B	350.000	Apoptosis Sat Limit	CD4+ T $mm^{-3}day^{-1}$	[31]
α_S	0.02000	CD4+ T death rate	day^{-1}	[22, 31]
h	0.00250	Lysis of T_I	$mm^{-3}day^{-1}$	Est
s_C	10.0	CTL supply rate	$mm^{-3}day^{-1}$	[31, 13]
k	0.00001	Apoptosis	$mm^{-3}day^{-1}$	Est
α_V	1.50000	HIV death rate	day^{-1}	[31, 16, 19]
α_E	0.02000	T_E death rate	day^{-1}	Est.
α_I	0.02500	T_I death rate	day^{-1}	[12, 31]
p	0.00001	CTL proliferation	day^{-1}	[31, 13]
α_c	1.50000	HIV CTL death rate	day^{-1}	[31, 13]
a_1	0.01500	Virion production reduction factor	Scalar	Est
N	1000.00	T_I virus burst size	$VT_I{}^{-1}$	[31, 16, 19]

If $R_0 < 1$, then $\widetilde{E}$ is asympototically stable and is unstable if $R_0 > 1$ (infection then gives an HIV infected endemic state, $\hat{E}$). Therefore, to control HIV infection the reproduction ration R_0 should be reduced to a value less than one. Expression (14) shows that this can be achieved by reducing β_c, β_v, N and α_I. While increasing CTL activity that include lytic killing, hindrance of viral entry into CD4+ T cells and hindrance of the assembling of HIV virions from infected CD4+ T cells. The value of R_0 shows the quantity $\frac{\beta_v}{\beta_v+\alpha_E}$ is the effective transcription rate whose overall effect is to increase R_0 for increasing β_v values.

Figure 1 shows the qualitative behaviour of the state variables $T_S(t)$, $T_E(t)$, $T_I(t)$, $V(t)$, and $C(t)$ for the model system (1-5) during the first 2000 days of infection. The parameter values used in the numerical simulations of the basic model are shown in Table 1.

Programming language in C^{++} based on the Runge Kutta method of order four was used to simulate the results in Figure 1. The initial values of the five interacting populations of model system (1-5) are $T_S(0) = 1000\ cells\ mm^{-3}$, $T_E(0) = 0.0\ cells\ mm^{-3}$, $T_I(0) = 0.0\ cells\ mm^{-3}$, $V(0) = 10\ copies\ mm^{-3}$, and $C(0) = 10\ cells\ mm^{-3}$. The numerical results shown in Figure 1 for the model system (1-5) approach an immune controlled infected steady state in agreement with the analytic results for $R_0 = 4.104184841 > 1$.

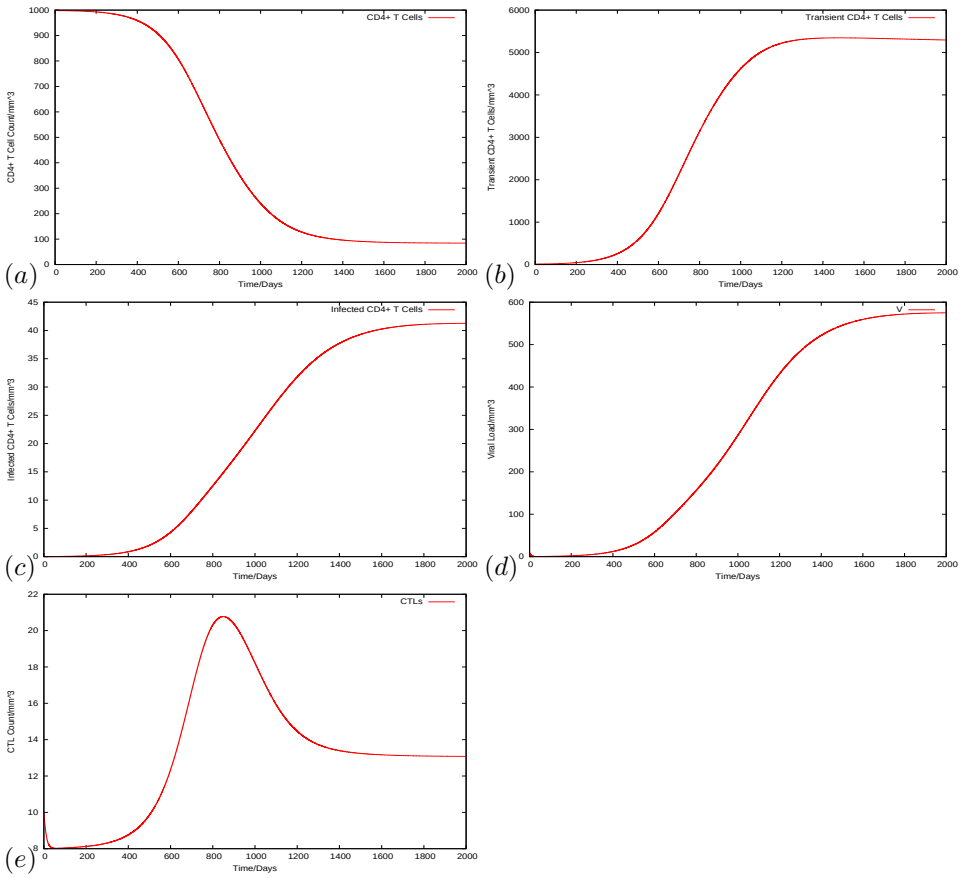

FIGURE 1. Graphs of numerical solutions showing propagation of T cells and the HIV pathogen during the first 2000 days of HIV infection: (a) susceptible CD4+ T cells, (b) exposed CD4+ T cells, (c) productively infected CD4+ T cells, (d) viral load, and (e) HIV-specific CTLs.

4. **Therapy model.** In this section we extend the basic model of the immunopathogenesis of HIV-1 infection by incorporating three categories of antiretroviral drugs;

namely, fusion/entry inhibitors (FIs), reverse transcriptase inhibitors (RTIs), and protease inhibitors (PIs). Administration of these three categories of anti-HIV-1 drugs results in the modification of the model parameters β_c, β_v, and N. Assuming that fusion inhibitors (FIs) are administered, the rate of entry of virions into the cytoplasm of CD4+ T cells parameter β_c is modified to become $\beta_c(1-\gamma)$, where γ is the efficacy of FIs and $0 < \gamma < 1$. The efficacy of FIs is the probability with which FIs prevent entry of virions into the cytoplasm of CD4+ T cells. Assuming that reverse transcriptase inhibitors (RTIs) are administered, then the rate of transcription of the HIV-1 RNA to DNA parameter β_v, is modified to become $\beta_v(1-\epsilon)$, where ϵ is the efficacy of RTIs and $0 < \epsilon < 1$. The efficacy of RTIs is the probability with which RTIs abort reverse transcription of HIV-1 RNA to DNA and hence prevent successful infection of CD4+ T cells. If we also assume that protease inhibitors (PIs) are administered, then the burst size parameter N is modified to become $(1-\epsilon)N$, where ϵ is the efficacy of PIs and $0 < \epsilon < 1$. The efficacy of PIs is the probability with which they render newly produced virions non-infectious. Thus the use of PIs will result in the production of non-infectious virus. Hence the model for the multidrug therapy, which includes FIs, RTIs plus PIs and assumes six interacting populations, the components being: the uninfected CD4+ T cells ($T_S, cells/mm^3$), infected CD4+ T cells where the virions have only entered the cytoplasm of the CD4+ T cells ($T_E, cells/mm^3$), infected CD4+ T cell where transcription of the HIV-1 RNA to DNA has occurred ($T_I, cells/mm^3$), infectious plasma viral load ($V, copies/mm^3$), non-infectious plasma viral load ($V^*, copies/mm^3$), and HIV-1 specific CTLs ($C, cells/mm^3$) is

$$\frac{dT_S}{dt} = s_T + \frac{rT_SV}{V+A} - \frac{\beta_c(1-\gamma)VT_S}{1+a_0C} - \frac{kT_SV}{T_S+B} - \alpha_S T_S, \tag{15}$$

$$\frac{dT_E}{dt} = \frac{(1-\gamma)\beta_c VT_S}{1+a_0C} - (1-\epsilon)\beta_v T_E - \alpha_E T_E, \tag{16}$$

$$\frac{dT_I}{dt} = (1-\epsilon)\beta_v T_E - hT_I - \alpha_I T_I, \tag{17}$$

$$\frac{dC}{dt} = s_C + pVTC - \alpha_C C, \tag{18}$$

$$\frac{dV}{dt} = \frac{(1-\kappa)N\alpha_I T_I}{1+a_1C} - \alpha_V V, \tag{19}$$

$$\frac{dV^*}{dt} = \frac{\kappa N\alpha_I T_I}{1+a_1C} - \alpha_V V^*. \tag{20}$$

Equations (15-19) describe the dynamics of T cells with the virus during administration of FIs, RTIs, and PIs. These equations are described basically in the same way as in the basic model of HIV-1 infection. The difference is that the parameters β_v, β_c, and N are modified as a result of drug administration and that there is now presence of the non-infectious virus. Equation (20) describes the dynamics of the non-infectious virus due to the administration of PIs.

4.1. **Treatment model analysis.** The equilibrium states of the therapy model are obtained by setting the right-hand side of equations (15-20) to zero. The disease-free equilibrium state of equations (15-20) is given by

$$\widetilde{E} = (\widetilde{T}_S, \widetilde{T}_E, \widetilde{T}_I, \widetilde{C}, \widetilde{V}, \widetilde{V}^*) = (\frac{s_T}{\alpha_S}, 0, 0, \frac{s_C}{\alpha_C}, 0, 0), \tag{21}$$

and an HIV-infected state is given by

$$\bar{E} \quad = \quad (\bar{T}_S, \bar{T}_E, \bar{T}_I, \bar{C}, \bar{V}, \bar{V}^*), \tag{22}$$

where $\bar{T}_S$, $\bar{T}_E$, $\bar{T}_I$, $\bar{C}$, $\bar{V}$, and $\bar{V}^*$ are given by expressions (23-28). The endemic equilibrium value of health CD4+ T cells is given by

$$\bar{T}_S = \frac{(s_T + Bu_0 - k\bar{V}) + \sqrt{(s_T + Bu_0 - k\bar{V})^2 - 4u_0 s_T B}}{2u_0}, \tag{23}$$
$$where\ u_0 = \frac{r\bar{V}}{\bar{V}+A} - \frac{(1-\gamma)\beta_c \bar{V}}{1+a_0\bar{C}} - \alpha_S.$$

This shows that CD4+ T cells proliferate because of the presence of the HIV pathogen, yet are also depleted by the virus. The term $(1-\gamma)$ further reduces the value of β_c as γ increases. The population density of CD4+ T cells that have been entered by HIV virions but without transcription that has occurred is given by

$$\bar{T}_E = \left(\frac{(1-\gamma)\beta_c \bar{V} \bar{T}_S}{(1+a_0\bar{C})((1-\epsilon)\beta_v + \alpha_E)} \right). \tag{24}$$

This expression shows that FIs and RTIs have an antagonistic effect of the equilibrium value of T_E. The endemic equilibrium value of infected CD4+ T cells is given by

$$\bar{T}_I = \left(\frac{(1-\epsilon)\beta_v \bar{T}_E}{(h\bar{C} + \alpha_I)} \right). \tag{25}$$

Infected CD4+ T cells can be reduced by increasing the efficacy of RTIs (ϵ); that is by reducing the transcription rate. The equilibrium value of HIV specific CTLs is given by

$$\bar{C} = \left(\frac{s_C}{\alpha_C - p\bar{T}_S \bar{V}} \right). \tag{26}$$

This expression shows that there is an inverse relationship between V and T_S, that is, for $\bar{C}$ to be positive, $\alpha_C > p\bar{T}_S\bar{V}$, $(\bar{V} < \left(\frac{\alpha_C}{p\bar{T}_S}\right), \Rightarrow \bar{V} \propto \frac{1}{\bar{T}_S})$. The viral steady state is given by

$$\bar{V} = \left(\frac{(1-\kappa) N \alpha_I \bar{T}_I}{\alpha_V (1 + a_1 \bar{C})} \right). \tag{27}$$

This shows that viral load increases as the burst sizes and burst rate of T_I increase and is reduced as efficacy of PIs (κ) and HIV specific CTL response increase. At equilibrium the level of non-infectious virus is given by

$$\bar{V}^* = \left(\frac{\kappa N \alpha_I \bar{T}_I}{\alpha_V (1 + a_1 \bar{C})} \right). \tag{28}$$

Generally the non-infectious virus increase as the efficacy of PIs increase.

In order to determine the conditions for stability of the disease-free state as given by expression (21) and the endemic state given by expression (22) we need calculate the reproduction number. We calculate the reproduction number using the approach we used in Section 3. We define the reproduction number as the number of newly infected CD4+ T cells arising from one HIV-infected CD4+ T cell when there is administration of HIV drugs. Using the same method we define heterogeneity using groups defined by fixed characteristics; our model can be written in the form (13). Where $\mathbf{X_A} \in \Re^2$, $\mathbf{Y_A} \in \Re$, $\mathbf{Z_A} \in \Re^2$, and $h_A(\mathbf{X_A}, 0, 0) = 0$. We follow the same procedure as we did in computing the reproduction ratio for the basic model. Assuming that the equation $g_A(\mathbf{X_A^*}, \mathbf{Y_A}, \mathbf{X_A}) = 0$ implicitly determines a function $Y_A = \widetilde{g}_A(\mathbf{X_A^*}, \mathbf{Y_A})$. We let $\mathbf{A_A} = \mathbf{D}_{Z_A} h_A(\mathbf{X_A^*}, \widetilde{g}_A(\mathbf{X_A^*}, 0), 0)$ and further assume that $\mathbf{A_A}$ can be written in the form $\mathbf{A_A} = \mathbf{M_A} - \mathbf{D_A}$, with $\mathbf{M_A} \geq 0$ (that is,

$m_{ij} \geq 0$) and $\mathbf{D_A} > 0$, a diagonal matrix. The reproduction ratio is then evaluated from the matrix $\mathbf{M_A D_A^{-1}}$.

The cell population subgroups are divided as follows; (a) $\mathbf{X_A}$ are cells that are uninfected by the virus; (b) $\mathbf{Z_A}$ cells that are virus infected (infected CD4+ T cells); and (c) $\mathbf{Y_A}$ is the HIV pathogen. Therefore, we set $\mathbf{X_A} = (T_S, C)$,$\mathbf{Y_A} = V$, $\mathbf{Z_A} = (T_E, T_I)$, and $\mathbf{X_A^*} = (\frac{s_T}{\alpha_S}, 0, \frac{s_C}{\alpha_C}, 0)$. Let $\mathbf{U}_{0A} = (\mathbf{X_A}^*, 0, 0)$ denote the virus free equilibrium; that is $f_A(\mathbf{X_A}^*, 0, 0) = g_A(\mathbf{X_A}^*, 0, 0) = h_A(\mathbf{X_A}^*, 0, 0) = 0$ and $Y_A = \widetilde{g}_A(\mathbf{X_A}^*, \mathbf{Z_A})$, where

$$\widetilde{g}_A(\mathbf{X_A}^*, \mathbf{Z_A}) = \frac{(1-\kappa)N\alpha_I \widetilde{T}_I}{\alpha_V(1 + a_0\widetilde{C})}.$$

We compute $A_A = D_{Z_A}(X_A^*, \widetilde{g}_A(X_A^*, 0), 0)$ and get

$$\mathbf{M} = \begin{pmatrix} 0 & \frac{(1-\gamma)(1-\kappa)\beta_c \widetilde{T}_S N\alpha_I}{\alpha_V(1+a_0\widetilde{C})(1+a_1\widetilde{C})} \\ (1-\epsilon)\beta_v & 0 \end{pmatrix},$$

and

$$\mathbf{D^{-1}} = \begin{pmatrix} \frac{1}{((1-\epsilon)\beta_v + \alpha_E)} & 0 \\ 0 & \frac{1}{(h\widetilde{C}+\alpha_I)} \end{pmatrix}.$$

The reproduction ratio is given by the next-generation spectral radius $\rho(M_A D_A^{-1})$ to be

$$R_T = \sqrt{\frac{\beta_c\beta_v N(1-\gamma)(1-\kappa)(1-\epsilon)\alpha_I \widetilde{T}_S}{\alpha_V(h\widetilde{C}+\alpha_I)(1+a_0\widetilde{C})(1+a_1\widetilde{C})((1-\epsilon)\beta_v + \alpha_E)}}. \tag{29}$$

$$R_T = R_0\sqrt{(1-\gamma)(1-\kappa)(1-r_e)}. \tag{30}$$

where $r_\epsilon = \frac{\epsilon\alpha_E}{\beta_v(1-\epsilon)+\alpha_E}$ is the effective efficacy of RTIs.

The reason for RTIs to have an effective efficacy that is less than the actual efficacy might lie in the fact that CD4+ T cells have high levels of deoxynucleoside triphosphates (dNTPs), which impairs their catalytic activities. RTIs have been noticed to be more effective in HIV-infected macrophages than in CD4+ T cells, because CD4+ T cells have dNTPs levels that are six- to twenty-fold greater than those found in macrophages [5, 6, 27]. Apart from the issues of bioavailability and phamacokinetics that affect all the three drugs, this might the reason behind reduced efficiency of RTIs. This result is derived mathematically; therefore, biological investigations may be needed for validation. Moreover, increasing ϵ increases r_ϵ, and reducing β_v increases r_ϵ. Since $R_T = R_0\sqrt{(1-\gamma)(1-\kappa)(1-r_\epsilon)}$, it follows that increasing r_ϵ will decrease HIV infection progression during HIV therapy, or increasing R_0 will mean more work to be done by therapy to eradicate it.

In Section 2, we observed from expression (14) that reducing R_0 to a value less that one may help to control HIV infection; that is, if $R_T < 1$, then therapy may control or suppress infection to levels below detection, or else it fails. Expression (29) shows that administration of FIs, RTIs, and PIs aid in reducing the disease reproduction number as the drug efficacies γ, ϵ and κ increase or approach one.

5. **Numerical simulations.** In this section we present numerical simulations of the treatment model. The C^{++} programming language was used to simulate the results to investigate the best treatment strategy that can be employed to combat HIV infection using the Runge-kutta fourth order scheme. The parameter values used are given in Table 1, and the calculated reproduction numbers of monotherapy and combined drug therapies are given in Table 5.

We carry out simulations to determined the best drug combination that can be administered in treating HIV and to determine the performance of each treatment strategies. In this experiment three different levels (Table 3) of drug efficacies were tested.

TABLE 2. Monotherapy and combined therapy reproduction numbers calculated with the assumption that $\gamma = \epsilon = \kappa = 0.95$.

Parameter	Definition	Calculated
r_ϵ	Effective efficacy of RTIs	0.948932451
R_0	Pre-treatment reproduction number	4.104184841
$R_\gamma = R_0\sqrt{(1-\gamma)}$	FIs monotherapy reproduction number	0.917723629
$R_\epsilon = R_0\sqrt{(1-r_\epsilon)}$	RTIs monotherapy reproduction number	0.927469035
$R_\kappa = R_0\sqrt{(1-\kappa)}$	PIs monotherapy reproduction number	0.0.917723629
$R_{\gamma\kappa} = R_0\sqrt{(1-\gamma)(1-\kappa)}$	FIs and PIs therapy reproduction number	0.205209242
$R_{\gamma\epsilon} = R_0\sqrt{(1-\gamma)(1-r_\epsilon)}$	FIs and RTIs therapy reproduction number	0.207388381
$R_{\kappa\epsilon} = R_0\sqrt{(1-\kappa)(1-r_\epsilon)}$	PIs and RTIs therapy reproduction number	0.207388381
$R_T = R_0\sqrt{(1-\gamma)(1-\kappa)(1-r_\epsilon)}$	FIs, RTIs and PIs therapy reproduction number	0.046373451

TABLE 3. Key for treatment strategy efficacy values used to simulate HIV treatment simulations. For each treatment strategy drug efficacy values were set at the same value.

Key	Efficacy parameter	Value used
L-efficacy	$\gamma = \epsilon = \kappa$	0.35
M-efficacy	$\gamma = \epsilon = \kappa$	0.65
H-efficacy	$\gamma = \epsilon = \kappa$	0.95

In Figure 2, we show the effects of three-drug HIV treatment strategies with different efficacy values. These simulations demonstrate that using different drug efficacy values results in different levels of infection suppression. In the use of L-efficacies CD4+ T cells are boosted but infected, and the viral load are left still in considerably high levels. The M-efficacy strategy produces better results than the L-efficacy strategy. Yet again is not strong enough to completely remove the infection, eventhough it has the potential to reduce the viral load and infected CD4+ T cells to a better degree than the L-efficacy strategy. Compared with the

other strategies here, using the H-efficacy strategy produces the best result. This treatment strategy achieves the best recovery of CD4+ T cells, and clearance of infected CD4+ T cells and the viral load is achieved faster.

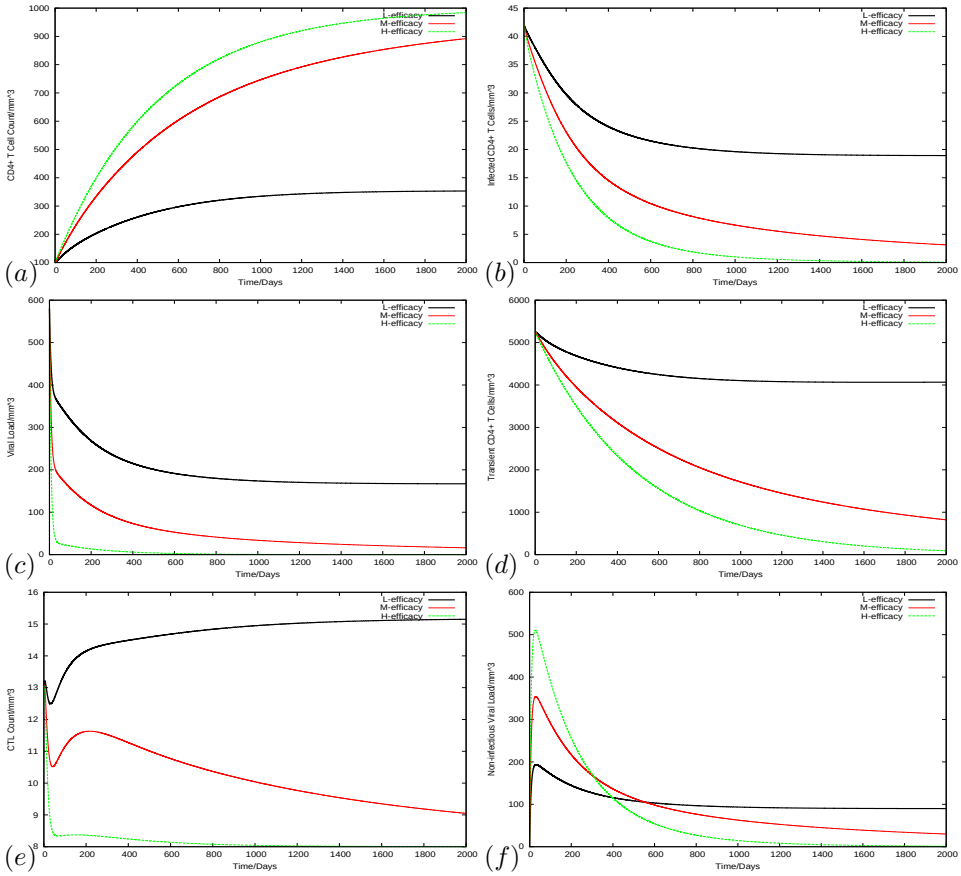

FIGURE 2. Graphs of numerical solutions showing propagation T cells and the HIV pathogen during HAART: (a) susceptible CD4+ T cells, (b) infected CD4+ T cells, (c) viral load, (d) exposed CD4+ T cells, (e) HIV-specific CTLs and (f) non-infectious HIV virions. Initial conditions: $T_S = 100.0$, $T_E = 5250.0$, $T_I = 42.0$, $V = 580.0$, $C = 13.0$, $V^* = 0.0$.

Administration of monotherapy shows different effects of each drug on different stages of the HIV-infection process. As far as the recovery of CD4+ T cell count is concerned, results in Figure 3 show that administration of FIs monotherapy produces the best results over the other monotherapy treatments. FIs are followed by PIs in boosting CD4+ T cells count, while the RTIs monotherapy treatment achieves the best results in reducing the levels of infected CD4+ T cells and is followed by FIs. The highest reduction in the viral load is achieved by the administration of PIs, and the administration of FIs achieves the least reduction of the viral load. The calculated values (Table 5) of the drug monotherapy reproduction ratios

suggest that RTIs monotherapy is the least effective since $R_\epsilon > (R_\gamma, R_\kappa)$. These results show that each HIV drug is best in one specific area; therefore, to address all aspects of the HIV-infection process requires administration of combined treatment strategies. Also, studies [29, 24, 8] have shown that monotherapy treatment strategies are more susceptible to development of drug-resistant strains.

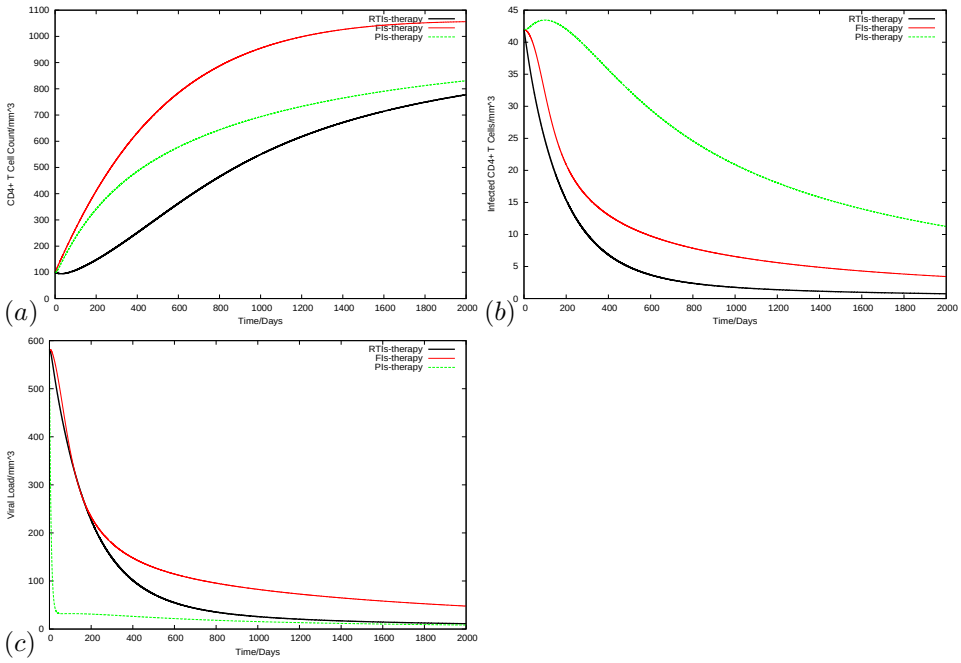

FIGURE 3. Graphs to show the efficay of monotherapy as possible HIV treatment strategies: (a) susceptible CD4+ T cell count, (b) productively infected CD4+ T cell count and (c) viral load. Initial conditions: $T_S = 100.0$, $T_E = 5250.0$, $T_I = 42.0$, $V = 580.0$, $C = 13.0$, $V^* = 0.0$.

To investigate the potency of all possible drug combination (that is, FIs and PIs, FIs and RTIs, RTIs, and PIs), we used equal efficacy values for the drugs in the two-drug combinations, and then compared their performances. FIs/PIs combination is compared with the FIs/RTIs and with the RTIs and PIs combinations; then these three two-drug combinations are further compared with the three-drug combination that comprise of FIs, RTIs and PIs.

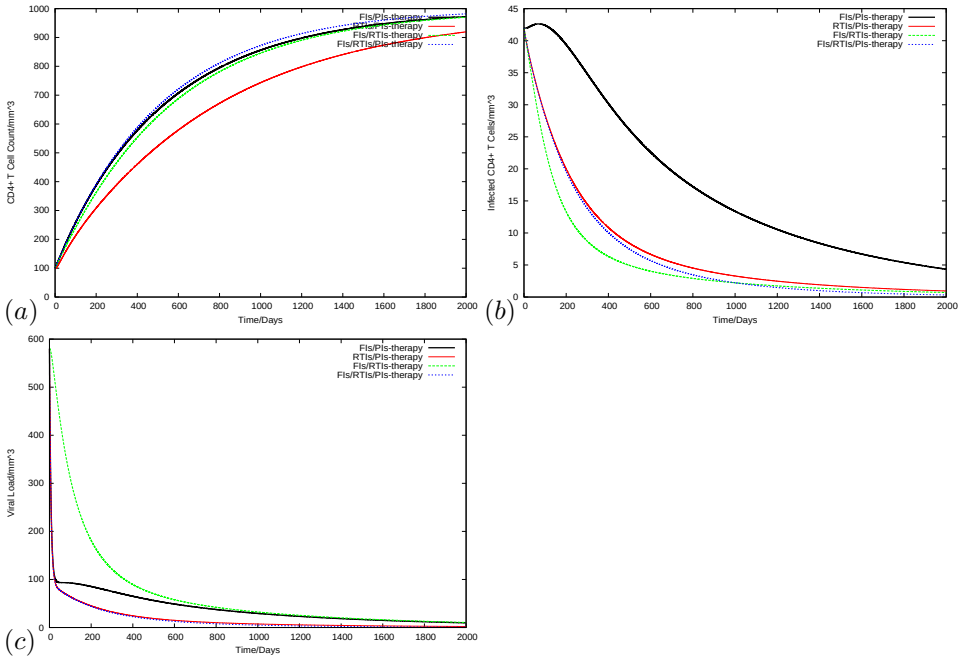

FIGURE 4. Graphs to identify the best combination of two or three drugs that produces the most desired results: (a) susceptible CD4+ T cell count, (b) productively infected CD4+ T cell count and (c) viral load. Initial conditions: $T_S = 100.0$, $T_E = 5250.0$, $T_I = 42.0$, $V = 580.0$, $C = 13.0$, $V^* = 0.0$.

Results in Figure 4 demonstrate that the three-drug combination therapy produce the best results in all stages of HIV infection. Figure 4(a) shows that administration of FIs/RTIs/PIs achieves the highest recovery of CD4+ T cells, followed by the administration of FIs and PIs. The least recovery of CD4+ T cells is seen when RTIs and PIs are administered. The highest reduction in the levels of infected CD4+ cells is achieved both by administration of FIs/RTIs/PIs and FIs/RTIs (combination of FIs and RTIs reduce infected CD4+ T cell levels faster than FIs, RTIs, and PIs in the first 800 days, but after this interval the latter attain the lowest level of infected CD4+ T cells) (Figure 4(b)). Least reduction in infected CD4+ T cells is achieved when FIs and PIs are administered (Figure 4(b)). Also, the highest reduction in the viral load is achieved through administration of FIs/RTIs/PIs and RTIs/PIs, and the least reduction in the viral load is achieved when FIs/RTIs are administered. The reproduction ratios (Table 5) of the combined therapies suggest that the combination of FIs and PIs will produce better treatment results than any combination therapy of two drugs that include RTIs. This follows from the observation that $(R_{\kappa\epsilon} = R_{\gamma\epsilon}) > R_{\gamma\kappa}$. The use of combined therapy improves on the efficacy values that each drug will require to eradicate the infection. The results show that the three-drug therapy has the lowest reproduction number. This shows that the three-drug therapy is better than the two-drug therapy combination. This demonstrate that the use of FIs to complement the antiretrovirals already on the market (RTIs and PIs) could change the face of HAART. This analysis also suggests that

the use of FIs and PIs as a combined-therapy strategy may produce better results than any combination of two drugs that include RTIs, that is a combination of FIs and RTIs and a combination of RTIs and PIs. This might be linked to the reduced performance of RTIs by dNTPs levels in CD4+ T cells, dNTPs levels are related to low performance of RTIs in CD4+ T cells than in HIV-infected macrophages [5, 6, 27]. Nevertheless, a therapy that includes all the drugs will produce the best results. These results are in line with the reproduction numbers shown in Table 5. The three-drug combination reduces the disease reproduction number the most, followed by the two-drug combination therapies, and the least reduction in the disease reproduction numbers is noticed in monotherapy drug usage. The addition of FIs to the existing HAART strategy of RTIs and PIs has the potential to reduce the reproduction number (=0.207388381) achieved by RTIs and PIs to a much lower reproduction number (=0.046373481) (Table 5). These results also show that the best results in each stage are achieved when a certain combination is administered.

We further investigate the performance of each drug in a three-drug combination therapy to distinguish the most potent drug. In this experiment, we fixed two drugs at a low efficacy value of 0.55 with the third drug as high as 0.95. Each drug is in turn raised to 0.95, while the others are fixed at 0.55; then their influence on the HIV progression pattern was evaluated.

TABLE 4. Key for treatment strategy efficacy values used to investigate the most potent drug in the 3 drug therapy combination. The drug with * is the drug with the highest efficacy of 0.95, while the rest are fixed at 0.55.

Combination therapy	Fixed efficacy values	Varying efficacy values
FIs/RTIs/PIs*	$\gamma = \epsilon = 0.55$	$\kappa = 0.95$
FIs*/RTIs/PIs	$\epsilon = \kappa = 0.55$	$\gamma = 0.95$
FIs/RTIs*/PIs	$\gamma = \kappa = 0.55$	$\epsilon = 0.95$

Figure 5 show the effects of fixing other drugs and increasing one drug. These results prove that FIs have the highest potency to boost CD4+ T cell count, while RTIs boost CD4+ T cells the least. Figure 5 (b) shows that RTIs have the highest potency to reduce infected CD4+ T cells followed by FIs. And Figure 5 (c) demonstrates that PIs reduce the viral load the most, while FIs have the least potency in reducing viral load.

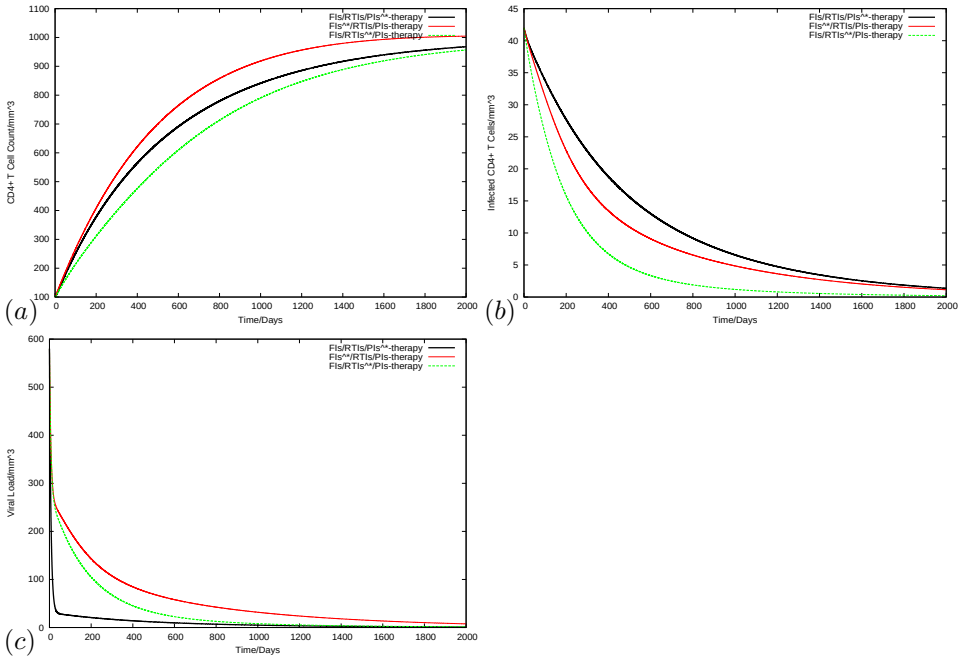

FIGURE 5. Graphs that show the most potent drug in the three-drug combination therapy. (a) susceptible CD4+ T cells count, (b) productively infected CD4+ T cell count and (c) viral load. Initial conditions: $T_S = 100.0$, $T_E = 5250.0$, $T_I = 42.0$, $V = 580.0$, $C = 13.0$, $V^* = 0.0$.

6. **Discussion.** In this paper we presented a new mathematical model for HIV in-vivo dynamics by separating the collision/fusion process of CD4+ T cells with the HIV virions from the HIV transcription process. This is accomplished by adding a transition stage of transiently infected CD4+ T cells that are a result of successful collision and fusion process but still waiting for HIV transcription to occur. This way of modelling makes it possible to incorporate FIs in mathematical models and study their significance if added to already existing HAART drugs.

Numerical and analytical analysis of the therapy model suggests that high-efficacy HIV drugs are required to effectively control the HIV infection. Monotherapy simulations demonstrate that HIV drugs are quite specific and distinct in their modes of action and are specific to specific stages of the HIV infection cycle. Combination therapies of two drugs indicate that each drug combination is best either at boosting CD4+ T cells (combination of FIs and PIs), or reducing levels of infected CD4+ T cells (combination of FIs and RTIs), or at reducing the viral load (combination of RTIs and PIs). Computation and comparison of reproduction numbers of the two-drug combined therapies suggest that the combination of FIs and PIs has collectively the highest performance over RTIs and PIs, and over the FIs and RTIs combinations. This suggests that FIs-and-PIs combination therapy can be a better treatment strategy than the current combination of RTIs and PIs, even though RTIs and PIs are best at reducing the viral load and FIs and RTIs are best at reducing the levels of infected CD4+ T cells (FIs and PIs are best in boosting

the CD4+ T cell count). However, the three-drug combination treatment strategy performs better at all stages of HIV infection processes than any of the two drug combination strategies. Our studies, however, fail to identify the most potent drug in the three-drug combination therapy, this might be a result of the fact that these drugs exhibit different modes of action and they work at different stages of the HIV infection process. The numerical simulations also demonstrate that FIs have the highest potency in boosting CD4+ T cells, while RTIs boost CD4+ T cells the least; RTIs have the highest potency in reducing levels of infected CD4+ T cells followed by FIs; PIs reduce the viral load the most; whereas FIs have the least potency in reducing the viral load.

Our studies demonstrate that the addition of FIs to the RTIs and PIs will be of beneficial, since the three drugs complement each other very well. FIs will add a dimension of fusion inhibition that was missing in the combination therapy of RTIs and PIs. This study shows that the fusion process is key to successful HIV infection process and HIV infection dynamics, and therefore reducing β_c with the help of FIs has high dividends. Generally, results from our study are in line with the results from the TORO studies [29, 24, 21], which demonstrated that addition of FIs to the current treatment strategy of RTIs and PIs significantly improves HIV treatment.

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