

A New Mathematical Model for Assessing Therapeutic Strategies for HIV Infection

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The requirements for the eradication of HIV in infected individuals are unknown. Intermittent administration of the immune activator interleukin-2 (IL-2) in combination with highly-active anti-retroviral therapy (HAART) has been suggested as an effective strategy to realize long-term control of HIV replication *in vivo*. However, potential latent virus reservoirs are considered to be a major impediment in achieving this goal. In this paper, a new mathematical model is designed and used to monitor the interactions between HIV, CD4 + T-cells, CD8 + T-cells, productively infected and latently infected CD4 + T-cells, and to evaluate therapeutic strategies during the first 3 years of HIV infection. The model shows that current anti-HIV therapies, including intermittent IL-2 and HAART, are insufficient in achieving eradication of HIV. However, it suggests that the HIV eradication may indeed be theoretically feasible if such therapy is administered continuously (without interruption) under some specified conditions. These conditions may realistically be achieved using an agent (such as a putative anti-HIV vaccine) that brings about a concomitant increase in the proliferation of HIV-specific CD4 + T- and CD8 + T-cells and the differentiation of CD8 + T-cells into anti-HIV cytotoxic T lymphocytes (CTLs).

Keywords: HIV; HAART; IL-2; CTL; Mathematical modeling

INTRODUCTION

“Hit early and hard” is a well-known strategy for the treatment of HIV infection often involving highly-active anti-retroviral therapy (HAART). Despite the success of HAART in decreasing plasma viremia to below detectable levels in many infected individuals (Chun and Fauci, 1999), the long-term control or eradication of HIV remains problematic. A key point associated with this problem is the persistence of latently-infected CD4 + T and other cells carrying replication-competent HIV. The replication-competent HIV can be isolated from individuals even after prolonged suppression of viremia as a result of receiving HAART (Chun *et al.*, 1997; Finzi *et al.*, 1997; Wong *et al.*, 1997). In such individuals, HIV reservoirs such as follicular dendritic cells (FDCs)-associated virus pool (Hlavacek *et al.*, 2000), macrophages (Orenstein *et al.*, 1997), brain cells, gut-associated lymphoid cells and cells from genital tract (Chun and Fauci, 1999) continue to persist. These viral reservoirs are

considered to be a major impediment in the eradication or long-term control of HIV (Chun *et al.*, 1997; Finzi *et al.*, 1997; Wong *et al.*, 1997; Cohen and Fauci, 1998; Cohen, 1998; Ho, 1998).

There is strong evidence that suggests that HIV-specific CD8 + T lymphocytes play a crucial role in control of HIV replication *in vivo*. These cells are the precursors for anti-HIV cytotoxic T lymphocytes (CTLs) that destroy HIV-producing cells and produce soluble factors that suppress HIV replication (Stranford *et al.*, 1999; Norris and Rosenberg, 2001). CD8 + T-cells from patients who are long-term non-progressors of HIV disease are known to exhibit much higher levels of these anti-HIV activities than those from patients with typical disease progression (Lifson *et al.*, 1991). The anti-HIV effects of CD8 + T-cells are further established by following *in vitro* experiments. Mitogenic stimulation of cultures of peripheral blood mononuclear cells (PBMC) from the long-term non-progressors produce very low levels of HIV as compared to PBMC cultures from typical disease

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progressors. Depletion of CD8 + T-cells from PBMC of the former causes a significant increase in HIV-1 replication in the cultures of remaining cells (Cao *et al.*, 1995). Further, the re-addition of autologous CD8 + T-cells back to PBMC causes a substantial inhibition of viral replication in a manner dependent on CD8 + T cell concentration (Walker *et al.*, 1986; 1991). Similar protective effects of CD8 + T-cells have been illustrated during simian immunodeficiency virus infection of macaques, which is used as a model for anti-HIV vaccine studies (Veazey *et al.*, 1998; Jin *et al.*, 1999; Schmitz *et al.*, 1999).

Intermittent administration of HAART and immune activators such as IL-2 has been proposed as a possible strategy for the control of viral replication (Ramratnam *et al.*, 2000). Interleukin-2 (IL-2) serves as a means of activating latently-infected CD4 + T-cells and, thereby, re-activating virus production from these cells; the anti-HIV CTLs may in turn detect and destroy such HIV-producing cells. In order to gain deeper insights into the effects of virus reservoirs, HIV-specific CD8 + T-cells, and a therapeutic strategy on HIV dynamics, we propose a deterministic mathematical model that considers interactions between HIV, CD4 + T-cells, CD8 + T-cells, and HIV-infected virus-producing and non-producing (latent) cells. In line with the “hit early and hard” treatment philosophy, the model is adapted and used to assess various therapeutic strategies during the first 3 years of infection.

MODEL DEVELOPMENT

The model monitors the temporal dynamics of five populations namely: uninfected CD4 + T-cells (X , cells/ μ l), productively-infected CD4 + T-cells (T_i , cells/ μ l), CD8 + T-cells (Y , cells/ μ l), latently-infected CD4 + T-cells (L , cells/ μ l) and plasma viral load (V , copies/ μ l). The model is given by the non-linear initial-value problem (IVP) below:

$$\frac{dX}{dt} = r_1 - d_1X - \alpha VX + \beta_1 XV \quad (1)$$

$$\frac{dT_i}{dt} = \alpha VX - d_2T_i - \theta pYT_i + aL \quad (2)$$

$$\frac{dY}{dt} = r_2 - d_3Y + \beta_2 YVX \quad (3)$$

$$\frac{dL}{dt} = \gamma T_i - d_4L - aL \quad (4)$$

$$\frac{dV}{dt} = NT_i + r_3 - d_5V \quad (5)$$

Equation (1) defines the dynamics of the uninfected CD4 + T-cells population, wherein r_1 represents their production rate from thymus, d_1 is their natural death rate, α is a loss coefficient due to HIV infection, and β_1 is a proliferation coefficient accounting for their proliferation in response to HIV antigens. A recent study by McCune *et al.* (2000) suggested that for a long-term kinetic model, the source of new T-cells does not remain constant. However, since our model considers the dynamics of HIV during the first 3 years of infection only, we have chosen a constant source r_1 . The model accounts for the increase in HIV-specific CD4 + T cell populations by incorporating the proliferation term βXV . Kirschner and Webb (1996, 1998) used a time-dependent source term for CD4 + T-cells.

Equation (2) models the CD4 + T-cells that are productively-infected by HIV. Here, d_2 represents their natural death rate, $0 < \theta < 1$ models the efficiency of CTL action against HIV-infected cells. It should be mentioned that θ is assumed less than unity to account for the failure of CTL killing due, primarily, to naturally occurring escape mutants and possible probabilistic lack of access to infected cells. Wodarz and Nowak (1999) assigned the value unity to this constant (denoted by p in their paper). The parameter p in Eq. (2) is associated with the proportion of CD8 + T-cells that differentiate into HIV-specific CTLs. This parameter will be enhanced by an anti-HIV vaccine because of vaccine-induced increase in HIV-specific CD8 + T-cells as well as increased “help” due to vaccine-induced rise in HIV-specific CD4 + T cell numbers. The last term of Eq. (2) comes from the re-activation, at a rate a , of latently-infected CD4 + T-cells to produce HIV.

In Eq. (3), r_2 and d_3 represent the production and death rates of CD8 + T-cells, respectively. The last term defines the proliferation of CD8 + T-cells in response to HIV antigen with the help of CD4 + T-cells at a rate β_2 . This is due to the fact that the growth of CD8 + CTL precursor T-cells depend not only on the stimulation of virus, but also on the CD4 + T cell help (Altfeld and Rosenberg, 2000). Wodarz and Nowak (1999) used a similar triple mass action term to model the proliferation of HIV-specific CTL precursors.

Equation (4) models the rate of change of latently-infected CD4 + T-cells that constitute a significant part of HIV reservoir. The constant γ represents the proportion of HIV-infected CD4 + T-cells that undergo latency, d_4 represents the natural death of these cells. The last term of Eq. (4) accounts for the immuno-stimulatory effects (either by environmental antigens or cytokines) that cause the re-activation of latently-infected cells at a rate a .

In Eq. (5), N represents the number of HIV virions produced *per* infected cell (T_i), r_3 represents a constant influx of HIV from non-CD4 + T cell sources (such as monocytes, macrophages, FDCs, etc.). Kirschner and Webb (1996) first introduced a time-dependent viral input term from the lymph node (which includes many of the cells modeled by r_3). It should be mentioned however that the viral input from non-CD4 + T cell sources is not likely to be greatly altered or to

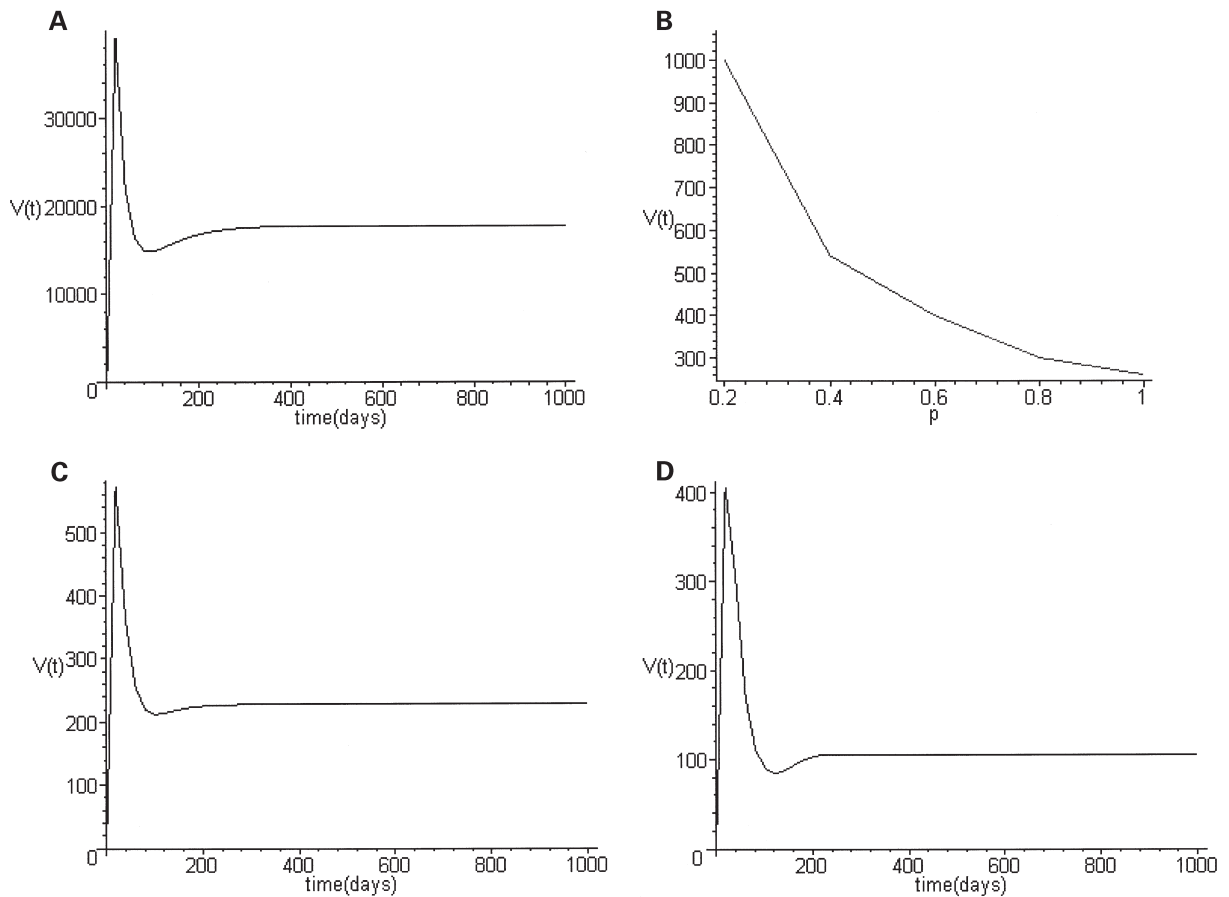


FIGURE 1 (A) Kinetics of HIV with $p = 0.01$ using Eqs. (1)–(5). (B) Kinetics of HIV with various values of p using Eqs. (1)–(5). (C) Kinetics of HIV with $p = \theta = 1$ using Eqs. (1)–(5). (D) Kinetics of HIV with $p = \theta = 1$, $r_3 = 0$ using Eqs. (1)–(5)

greatly contribute to plasma virus load during transition from early to the late stages of HIV disease. We, therefore, have chosen to use a constant viral input term.

SIMULATION RESULTS (IN THE ABSENCE OF ANY THERAPY)

The solution of the model equations above is obtained using Maple software version 6. For simulation purposes, the following initial and parameter values will be used: $X^0 = 1000(\text{cells}/\mu\text{l})$, $T_i^0 = 100(\text{cells}/\mu\text{l})$, $L^0 = 10(\text{cells}/\mu\text{l})$, $Y^0 = 500(\text{cells}/\mu\text{l})$, $V^0 = 0.001(\text{copies}/\mu\text{l})$, $r_1 = 10$, $r_2 = 20$, $d_1 = d_2 = d_3 = d_4 = 0.03$, $r_3 = 5$, $d_5 = 0.05$, $\alpha = 2.5 \times 10^{-4}$, $\beta_1 = \beta_2 = 4 \times 10^{-7}$, $\theta = 0.8$, $0 < p < 1$, $N = 1000$, $\gamma = 0.5$, $a = 0.01$ (see Kirschner and Webb 1996, 1997; Stilianakis *et al.*, 1997; Mittler *et al.*, 1998; Wein *et al.*, 1998; Arnaout *et al.*, 1999; Perelson and Nelson, 1999; Culshaw and Ruan, 2000). It should be mentioned that although β_1 may be theoretically different from β_2 , we are not aware of a published evidence for differences in the rate of clonal expansion of CD4 + and CD8 + T-cells in HIV-infected patients. Therefore, for simulation convenience, we have chosen to use $\beta = \beta_1 = \beta_2$.

In view of the fact that HIV-specific CD8 + CTLs play a critical role in controlling HIV replication, the model is

used to monitor the dynamics of HIV with increasing values of p (the proportion of CD8 + T-cells that differentiate into CTLs) using the aforementioned parameter and initial values (Fig. 1). Figure 1A shows that when $p = 0.01$ (i.e., 1% of HIV-specific CD8 + T-cells differentiate into CTLs), the virus reaches a peak of about 40,000 copies at about 17 days and a steady-state of about 18,000 copies at Day 400 or soon thereafter. Figure 1B summarizes the effects of increasing values of p on the steady-state viral load. While confirming the importance of HIV-specific CD8 + CTLs in suppressing HIV, these data show that even at very high values of p (e.g. $p = 1$), low levels of HIV continue to persist. In fact, even in the presence of theoretical maximum anti-HIV CTL action (i.e., $\theta = 1$ and $p = 1$), the virus could not be eliminated, although both the peak and steady-state values of HIV are reduced dramatically in comparison to the data shown in Fig. 1A (see Fig. 1C). The same observation was made in the theoretical absence of non-CD4 + T cell HIV reservoir (Fig. 1D). Thus, even the best anti-HIV CTL response would be unable to eliminate HIV regardless of the presence or absence of the non-CD4 + T cell viral reservoir. This elucidates the need for therapeutic measures (such as antiretroviral therapy and/or anti-HIV therapeutic vaccine) to help towards viral elimination.

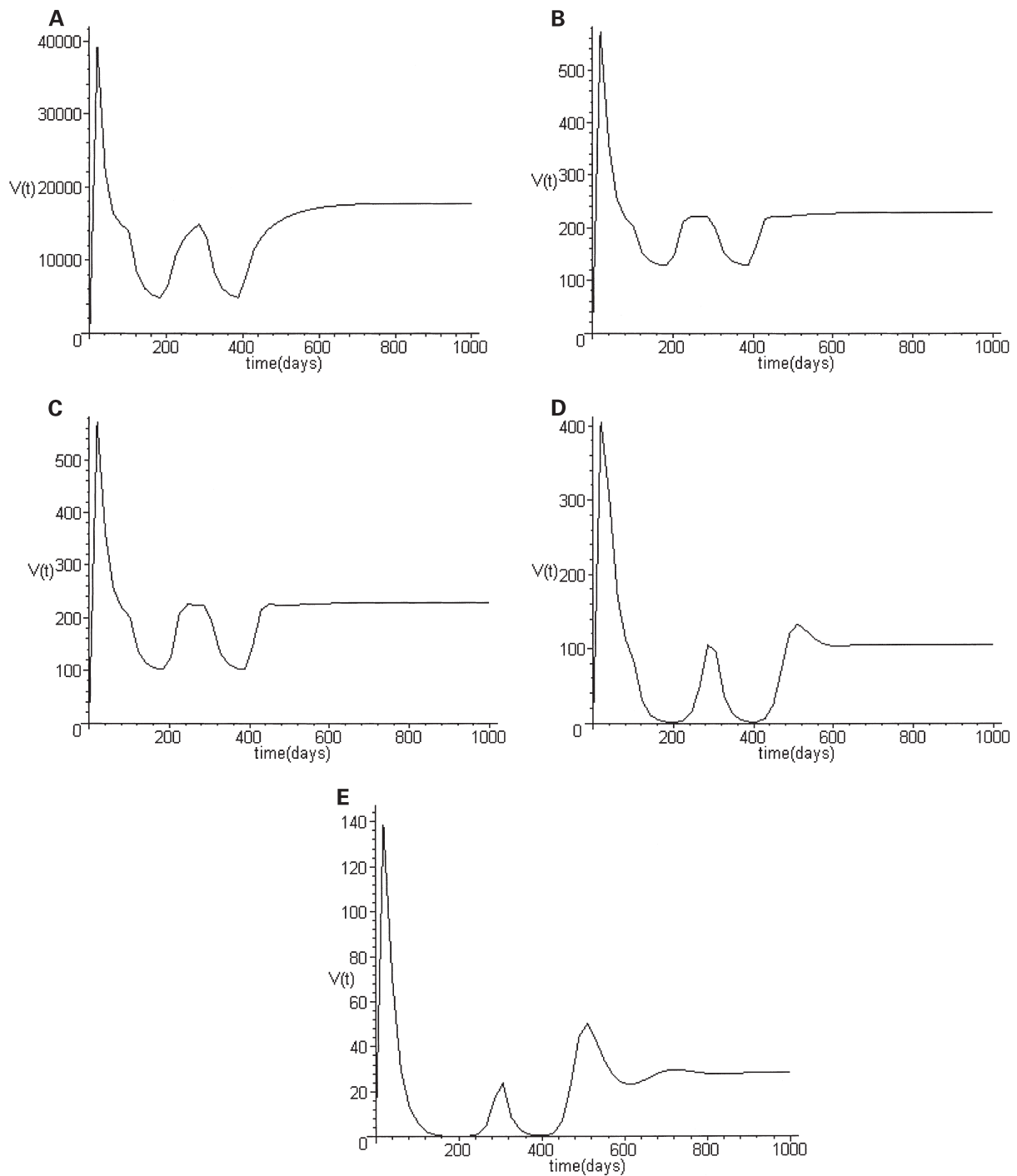


FIGURE 2 (A) Kinetics of HIV with $p = 0.01$, 80% effective intermittent HAART and IL-2 using Eqs. (6)–(10). (B) Kinetics of HIV with $p = \theta = 1$, 80% effective intermittent HAART and IL-2 using Eqs. (6)–(10). (C) Kinetics of HIV with $p = \theta = 1$, 100% effective intermittent HAART and IL-2 using Eqs. (6)–(10). (D) Kinetics of HIV with $p = \theta = 1$, 100% effective intermittent HAART and IL-2, $r_3 = 0$ using Eqs. (6)–(10). (E) Kinetics of HIV with $p = \theta = 1$, 100% effective intermittent HAART and IL-2 with $r_3 = 0$ and 20-fold increase in the proliferation of CD4 + and CD8 + T-cells using Eqs. (6)–(10).

INTERMITTENT DRUG THERAPY

Since the administration of IL-2 during intermittent HAART has been used to reactivate latent CD4 + T cell viral reservoirs (see, for instance, Chun *et al.*, 1999; Finzi *et al.*, 1999; Ramratnam *et al.*, 2000), this study focuses on investigating the effects of intermittent IL-2 plus HAART

on the dynamics of HIV. To achieve this, we employ the Heaviside function:

$$H(t - \tau) = \begin{cases} 0, & t < \tau \\ 1, & t \geq \tau \end{cases}$$

Let $p(t)$ represent the intermittent application of HAART given by

$$p(t) = H(t - 100) - H(t - 200) \\ + H(t - 300) - H(t - 400)$$

and let $q(t)$ represent the corresponding application of IL-2 given by

$$q(t) = H(t - 100) - H(t - 200) \\ + H(t - 300) - H(t - 400).$$

Thus, $p(t)$ and $q(t)$ imply that both HAART and IL-2 therapy are implemented during the two periods of time: from Day 100 to Day 200 and from Day 300 to Day 400. We chose the duration of therapy to be 100 days because it is now known that short-term therapy (3 months) increases both the rates of production of CD4 + and CD8 + T-cells (about 1.8-fold) and their losses (about 1.5-fold), whereas long-term therapy (> 12 months), the production rates recover to the level (baseline) prior to therapy (McCune *et al.*, 2000). A number of theoretical studies have been conducted on the impact of intermittent HAART on controlling viral replication (see, for instance, Wodarz and Nowak, 1999; Zhang *et al.*, 1999; Bonhoeffer *et al.*, 1997, 2000; Wodarz *et al.* 2000a,b). To our knowledge, none has incorporated the aforementioned increases in the rates of production or losses of CD4 + and CD8 + T-cells.

An elegant study by Chun *et al.*, 1999 indicates that the size of the pool of resting CD4 + T-cells containing replication-competent HIV in the blood of patients receiving HAART plus intermittent IL-2 was significantly lower than that of patients receiving HAART alone. Here, we assume that IL-2 therapy is 80% effective and that HAART can also reduce virus replication by 80%. Thus, the dynamic equations for the above therapeutic strategies (based on experimental observations and the assumptions outline above) can be summarized as:

$$\frac{dX}{dt} = r_1[1 + 0.8p(t)] - d_1X[1 + 0.5p(t)] - \alpha VX + \beta XV \quad (6)$$

$$\frac{dT_i}{dt} = \alpha VX - d_2T_i - \theta pYT_i + [a + 0.8q(t)]L \quad (7)$$

$$\frac{dY}{dt} = r_2[1 + 0.8p(t)] - d_3Y[1 + 0.5p(t)] + \beta YVX \quad (8)$$

$$\frac{dL}{dt} = \gamma T_i - d_4L - [a + 0.8q(t)]L \quad (9)$$

$$\frac{dV}{dt} = NT_i[1 - 0.8p(t)] + r_3[1 - 0.8p(t)] - d_5V \quad (10)$$

Using the parameter and initial values given in “Simulation results”, this model (consisting of Eqs. (6)–(10)) was simulated as follows. Figure 2A depicts the dynamic behavior of the model when $p = 0.01$ and HAART and IL-2 therapy are implemented at Day 100. As in Fig. 1A, the virus peaks prior to initiation of therapy. After the introduction of HAART plus IL-2 therapy on Day 100, the viral load decreases rapidly until the suspension of the therapies on Day 200. Once the therapies were discontinued, the viral load reverts back to a new peak that is lower than the initial peak. The re-introduction of HAART and IL-2 on Day 300 once again suppresses HIV to the level seen on Day 200. Upon the final withdrawal of the therapy on Day 400, the virus attains a steady-state value which is exactly the same as that observed in Fig. 1A without therapy.

Simulating the case when $p = \theta = 1$ (representing a 100% efficiency level of anti-HIV CTL action), the model suggests a much larger decline in both the peak (570 copies) and the steady-state (230 copies) values (Fig. 2B). The combined effect of the theoretical maximum anti-HIV CTL action ($\theta = 1$ and $p = 1$) coupled with 100% efficacies of HAART and IL-2 therapy was also simulated. It is evident from the result shown in Fig. 2C that despite the presence of a theoretically-perfect anti-HIV CTL response and HAART plus IL-2 therapy, the virus continues to persist (at approximately 200 copies). In fact, even in the absence of non-CD4 + T cell HIV reservoir ($r_3 = 0$), this combination of perfect anti-HIV CTL and HAART and IL-2 therapy could not eradicate HIV (see Fig. 2D). This may be because, while intermittent HAART plus IL-2 therapy could activate and eliminate latently-infected cells, the virions produced following such activation (prior to death) are expected to infect new CD4 + T cell targets and thereby continuing the cycle of infection and death of additional cells. In summary, these simulations demonstrate that the above strategy, using intermittent HAART and IL-2, is inadequate to achieve HIV eradication. This is consistent with the clinical and experimental findings reviewed by Norris and Rosenberg (2001).

Clearly, the use of yet another anti-HIV mechanism such as an anti-HIV therapeutic vaccine either alone or in combination with the above therapies, is necessary if HIV eradication is to be realized. We modeled this possibility by implementing a putative anti-HIV vaccine that is known to enhance the proliferation of both HIV-specific CD8 + and CD4 + T-cells (i.e., to increase the parameter β) and is expected to enhance the differentiation of HIV-specific CD8 + T-cells into anti-HIV CTLs (i.e., to increase the parameter p) due to increase in the available “help” from vaccine-induced rise in CD4 + T-cells. For simplicity, we assume that this anti-HIV vaccine can also remove viral input from non-CD4 + T cell sources (i.e. $r_3 = 0$). This added function of the vaccine could be theoretically achieved by employing a new class of antiretroviral drugs that target non-CD4 + T cell HIV reservoirs. By simulating the model with a 20-fold increase in β using

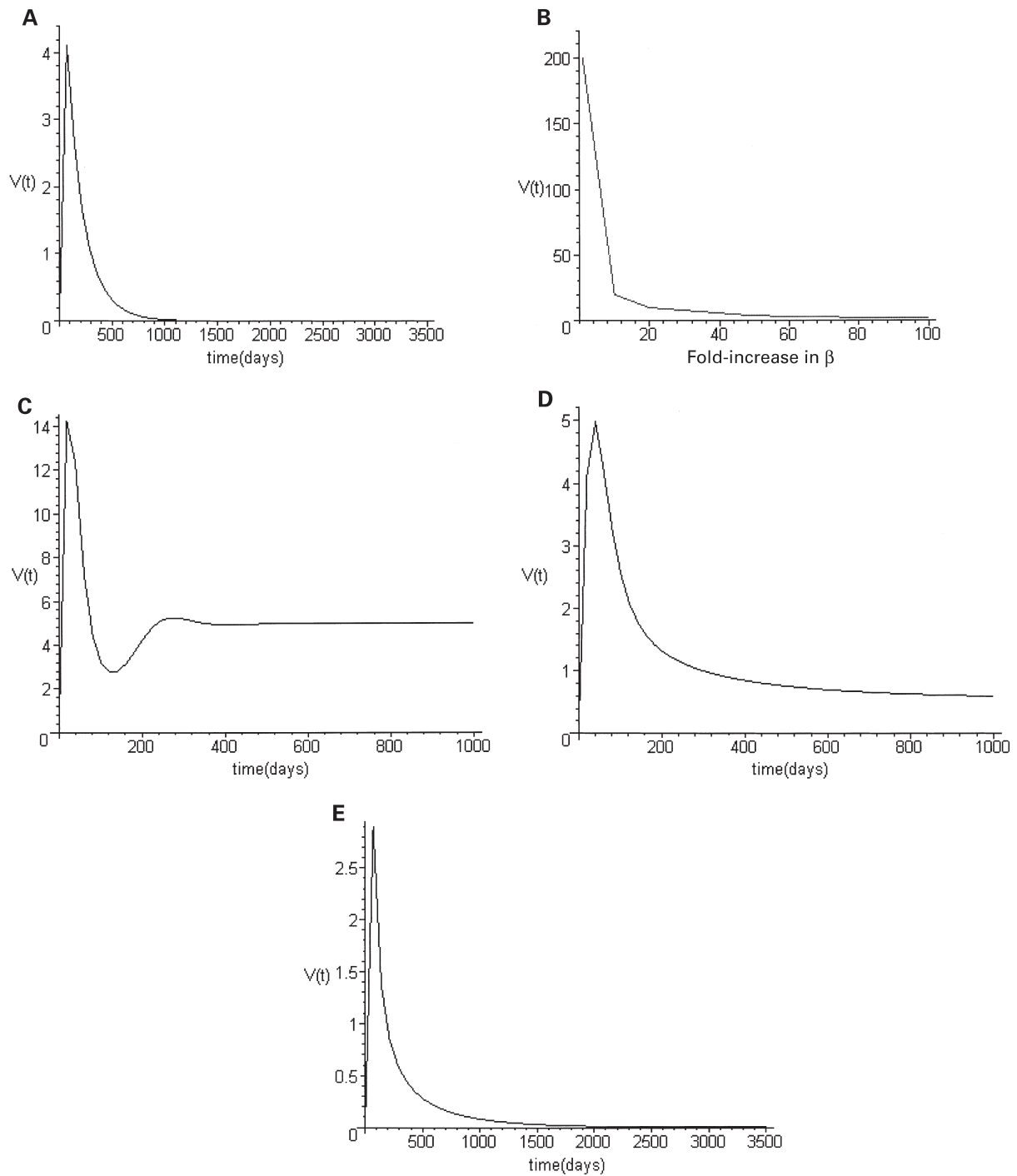


FIGURE 3 (A) Kinetics of HIV with $p = \theta = 0.8$, $r_3 = 0$ with 80% effective continuous HAART and IL-2 using Eqs. (6)–(10). (B) Kinetics of HIV with various fold-increases in the proliferation of CD4 + T and CD8 + T-cells, $p = 0.2$, $\theta = 0.8$, $r = 0$ with continuous 80% effective HAART and IL-2 therapy using Eqs. (6)–(10). (C) Kinetics of HIV with 20-fold increase in the proliferation of CD4 + T and CD8 + T-cells, $p = 0.4$, $\theta = 0.8$, $r_3 = 0$ with continuous 80% effective HAART and IL-2 therapy using Eqs. (6)–(10). (D) Kinetics of HIV with 20-fold increase in the proliferation of CD4 + T and CD8 + T-cells, $p = 0.6$, $\theta = 0.8$, $r_3 = 0$ with continuous 80% effective HAART and IL-2 therapy using Eqs. (6)–(10) with $p(t) = q(t) = 1$. (E) Kinetics of HIV with 20-fold increase in the proliferation of CD4 + T and CD8 + T-cells, $p = 0.65$, $\theta = 0.8$, $r_3 = 0$ with continuous 80% effective HAART and IL-2 therapy using Eqs. (6)–(10) with $p(t) = \theta(t) = 1$.

maximum anti-HIV CTL response ($p = \theta = 1$) and 100% effective intermittent HAART and IL-2 therapy with $r_3 = 0$, we observed that although there is a significant drop in the steady-state viral level, the virus could not be eradicated (Fig. 2E).

CONTINUOUS THERAPY

In contrast to intermittent therapy, however, when HAART and IL-2 therapy were implemented early in infection and maintained continuously, without any

interruption, (i.e. $p(t) = q(t) = 1$), we observed that the virus could be eradicated, even in the absence of the aforementioned putative anti-HIV vaccine, within a little over 3 years of therapy provided $p = \theta \geq 0.8$, $r_3 = 0$ and HAART and IL-2 are 80% effective (see Fig. 3A). It should be mentioned, however, that due to severe immunodeficiency during the course of HIV infection, the requirement of $p = q \geq 0.8$ may not be attainable; although the use of an anti-HIV vaccine may help to realize this goal.

Consequently, we simulated the model in the presence of putative anti-HIV vaccine capable of increasing both β and p . Figure 3B shows the effect of fold-increase in β on the viral load using the parameter values in “Simulation results (in the absence of any therapy)” (note that, in this case p is fixed at 0.2, and θ at 0.8 allowing 20% CTL failure due to virus escape mutations). It is clear from Fig. 3B that not even a 100-fold increase in β is sufficient to eradicate HIV. In fact, we found that even a 1000-fold increase in β failed to achieve the desired eradication despite a prolonged remission.

We therefore examined the effect of increasing values of p with β fixed at a moderate 20-fold increase to determine (if possible) the critical value of p , ranging from 0.2 to 1, necessary for HIV eradication. Figures 3C and D show that although a rise in the value of p to 0.4 or 0.6 significantly decreases the steady-state viral load, it failed to eradicate HIV. However, when p was increased to 0.65, the virus was eradicated and did not re-appear even when the observation was extended beyond 9 years (Fig. 3E). Thus, in addition to enhancing β and p , the use of an anti-HIV vaccine relaxes the requirement for HIV eradication in terms of p (requiring $p = 0.65$ instead of $p = 0.8$ in the case without vaccine). These results imply that a putative anti-HIV vaccine, which is capable of increasing the proliferation of HIV-specific CD4 + T and CD8 + T-cells by 20-fold (i.e. $\beta = 20 \times 4 \times 10^{-7}$) and the differentiation of CD8 + anti-HIV CTLs to $p \geq 0.65$, can eradicate HIV provided it is used in conjunction with a continuous 80% effective HAART and IL-2 therapy and another drug that can eliminate the non-CD4 + T cell HIV reservoirs ($r_3 = 0$). By augmenting β and p and relaxing the requirement in terms of p , the use of anti-HIV vaccine makes HIV eradication a more realistic possibility.

DISCUSSION

Ever since the emergence of HIV disease in early 1980s, an understanding of the conditions necessary for the eradication of HIV in infected individuals has been a highly-sought objective of HIV research. However, despite major advances in the understanding of HIV pathogenesis, little is known about the requirements for HIV eradication.

After the establishment of the etiology of HIV disease and the structure and replication cycle of HIV in mid

1980s, a direct relationship between HIV replication and the progression to AIDS was recognized (Mellors *et al.*, 1996). The suppression of HIV replication or viremia therefore became the main target of anti-HIV therapies, which was successfully achieved by the implementation of HAART following the discovery of protease inhibitors in mid 1990s (see Ho, 1998). However, it was soon recognized that while HAART is highly effective in suppressing HIV replication, it fails to eradicate the virus largely due to the persistence of latent viral reservoirs and ongoing low levels of HIV replication in compartments that are inaccessible by HAART (see Pomerantz, 2001). Subsequent attempts to eliminate HIV by combining HAART with IL-2 therapy, that reactivates HIV replication in latently-infected CD4 + T-cells and thereby exposing them to CTL action, were also proven unsuccessful even though these treatments led to marked decrease in virus load (Chun *et al.*, 1997; 1998; 1999). The assessment of relative merits and demerits of the above therapeutic strategies can be facilitated through the use of suitable mathematical models such as the one described in this paper.

We have developed a new five-dimensional deterministic model for HIV pathogenesis to assess therapeutic strategies for HIV infection and to determine conditions necessary for eradicating the virus. Our study focuses on the dynamics of HIV, first in the absence of any therapy, then during the intermittent HAART and IL-2 therapy (with and without an anti-HIV “vaccine-like” agent that selectively augments the proliferation of HIV-specific T-cells as well as the differentiation of HIV-specific CD8 + T-cells into anti-HIV CTLs), and finally during the continuous HAART and IL-2 therapy in the presence of such an agent.

Numerous simulations of this model confirm the important role HIV-specific CTLs play in suppressing viremia (Fig. 1). Further, the model reveals that even the maximum possible and perfect anti-HIV CTL activity (where $p = \theta = 1$) would fail to eliminate HIV even in the absence of the non-CD4 + T cell HIV reservoirs (Fig. 1). The model suggests that the implementation of 80% effective HAART plus IL-2 therapy, when administered intermittently, can only induce remission and not viral eradication (Fig. 2). In Fig. 2A, a significant level of HIV reappeared after the first interruption of therapy on Day 200. This is apparently indicative of IL-2-induced reactivation of HIV production from latently-infected CD4 + T-cells. The model reveals that even under conditions of 100% effective intermittent HAART plus IL-2 therapy and theoretically-perfect anti-HIV CTL action ($p = \theta = 1$), low levels of virus still persist (Fig. 2C and D). These findings confirm that anti-HIV CTL action, even in the presence of 100% effective intermittent HAART and IL-2 therapy, is insufficient to eradicate HIV. We, consequently, explored conditions that could lead to the eradication of HIV.

Inherent in this model is the proliferation parameter β and a CTL differentiation parameter p . Since anti-HIV

vaccines are expected to specifically augment the proliferation of HIV-specific CD4 + T and CD8 + T-cells and, in turn, the differentiation of HIV-specific CD8 + CTLs, the parameters β and p will jointly enable the assessment of the efficacy of such vaccine. The model therefore provides a basis for exploring the effects of combining anti-HIV therapies (HAART and IL-2) with a putative therapeutic vaccine. By using 100% effective intermittent HAART and IL-2 therapy together with a putative anti-HIV vaccine that increases the proliferation of HIV-specific CD4 + T and CD8 + T-cells by 20-fold and leads to a theoretically perfect anti-HIV CTL activity ($p = \theta = 1$), the virus persists despite prolonged suppression even in the absence of r_3 (Fig. 2E).

In contrast, however, we found that if anti-HIV therapy is administered continuously, HIV eradication is feasible in the absence of virus reservoir provided $p = \theta \geq 0.8$ (Fig. 3A); a goal attainable by the use of an anti-HIV vaccine. Such a vaccine also relaxes the requirement in terms of p (reducing from 0.8 to 0.65) (Fig. 3E), making HIV eradication more feasible.

CONCLUSIONS

Based on the parameter values used in our simulations, the eradication of HIV in an infected individual is theoretically feasible. To realistically achieve such eradication, attention should be focused on the development of:

- i) a potent vaccine that stimulates an increase in both the proliferation of HIV-specific CD4 + T and CD8 + T-cells and the differentiation of HIV-specific CD8 + T-cells into anti-HIV CTLs, and
- ii) a new class of anti-HIV drugs that target and eliminate non-CD4 + T cell HIV reservoirs.

There have been major advancements in the development of simple and safe anti-HIV vaccines. For instance, Letvin *et al.* (1997) reported that immunization with an HIV envelope-encoding DNA sequence offers protection against HIV challenge. A number of recent studies have further shown the effectiveness of vaccination using DNA encoding specific regions of HIV (Kent *et al.*, 1998; Cafaro *et al.*, 1999; Robinson *et al.*, 1999). These vaccines are expected to increase the proliferation of HIV-specific CD4 + T and CD8 + T-cells *in vivo*.

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