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A MODEL FOR TREATMENT STRATEGY IN THE CHEMOTHERAPY OF AIDS

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Mathematical models are developed for the chemotherapy of AIDS. The models are systems of differential equations describing the interaction of the HIV infected immune system with AZT chemotherapy. The models produce the three types of qualitative clinical behavior: an *uninfected steady state*, an *infected steady state* (latency) and a *progression to AIDS* state. The effect of treatment is to perturb the system from progression to AIDS back to latency. Simulation of treatment schedules is provided for the consideration of treatment regimes. The following issues of chemotherapy are addressed: (i) daily frequency of treatment, (ii) early versus late initiation of treatment and (iii) intermittent treatment with intervals of no treatment. The simulations suggest the following properties of AZT chemotherapy: (i) the daily period of treatment does not affect the outcome of the treatment, (ii) treatment should not begin until after the final decline of T cells begins (not until the T cell population falls below approximately 300 mm^{-3}) and then, it should be administered immediately and (iii) a possible strategy for treatment which may cope with side effects and/or resistance, is to treat intermittently with chemotherapy followed by interruptions in the treatment during which either a different drug or no treatment is administered. These properties are revealed in the simulations, as the model equations incorporate AZT chemotherapy as a weakly effective treatment process. We incorporate into the model the fact that AZT treatment does not eliminate HIV, but only restrains its progress. The mathematical model, although greatly simplified as a description of an extremely complex process, offers a means to pose hypotheses concerning treatment protocols, simulate alternative strategies and guide the qualitative understanding of AIDS chemotherapy.

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1. Introduction. Optimal treatment strategies for individuals infected with the human immunodeficiency virus (HIV) are a necessity for improving the effectiveness of chemotherapy for AIDS. AZT (Zidovudine) was approved for treatment of HIV infection in 1987. Three other drugs, DDC, DDI, and D4T, have since been approved. These drugs all work as inhibitors of reverse transcriptase. HIV is an RNA virus and when HIV infects a cell, its RNA is transcribed into DNA (a unique feature of a retrovirus). The role of these reverse transcriptase inhibitors is to interfere with the transcription of the RNA to DNA, thus, halting cellular infection and, hence, viral spread. Unfortunately, these drugs are not cures for the infection, but only serve as a maintenance program to temporarily prevent further progress of the virus. Despite this drawback, there is much clinical evidence to support the use of these chemotherapies in HIV infected individuals. Aside from the possibility of prolonging life in an HIV positive individual, it may make them less infectious to their sexual partners (Anderson *et al.*, 1992), as well as reduce rates of vertical transmission (Nozyce *et al.*, 1994). Controversy exists among clinicians, however, as to whom should be treated, when they should be treated and what treatment scheme should be used.

There is much available data on AZT treatment (McLeod and Hammer, 1992; Hirsch, 1990; Lundgren *et al.*, 1994). Many laboratories and clinics are keeping close accounts of patient treatment courses with respect to effectiveness and results. Of interest here is the fact that there are conflicting results as to whether treatment at the early stage of disease (defined as $CD4^+$ T cell counts between 200–500 mm^{-3} of blood) (Fischl *et al.*, 1990; Graham *et al.*, 1992; Lenderking *et al.*, 1994; Ruedy *et al.*, 1990; Volberding *et al.*, 1994) or later stage (below 200 mm^{-3}) (Hamilton *et al.*, 1992; Cox *et al.*, 1990) is better. The large scale Concorde study (Concorde Coordinating Committee, 1994) was devoted to this early versus late issue. The Concorde results seem to indicate that the early use of AZT in asymptomatic patients is not beneficial. Other questions regarding chemotherapy are whether the dosage should be large (defined as 600–1500 mg per day) or small (defined to be less than 600 mg per day) (Cooper *et al.*, 1991), what should be the duration of treatment and what periodicity of doses should be used (whether the drug should be administered every 4 hr, 8 hr, etc.) (McLeod and Hammer, 1992; Kaiser, 1993; Mulder *et al.*, 1994; Volberding *et al.*, 1990). The AZT manufacturer Burroughs-Wellcome is now re-evaluating its recommendations for dosing, which was initially 1200 mg per day (200 mg every 4 hr), and now recommends 600 mg per day (100 mg every 4 hr).

Further problems concerning AIDS chemotherapy involve the possibility of drug side effects, viral resistance and combined chemotherapy treatments using more than one drug. AIDS chemotherapy typically results in

harmful side effects such as nausea, diarrhea, anemia, neutropenia and cytotoxicity. These issues all effect the quality of life of the individual. These effects can sometimes be reduced through low dosage scheduling, and there are studies investigating the effectiveness of low dosages (Landonio *et al.*, 1993; Lenderking *et al.*, 1994). A serious problem with chemotherapy treatment of HIV infection is that it may lead (and usually has led) to drug resistance (McLeon and Nowak, 1992; Montaner *et al.*, 1993). This is due presumably to the ability of the virus to mutate and circumvent the normal transcription pathway which the chemotherapy interrupts. The maximal length of dosage, which has been successful until resistance was observed, is two years (McLeod and Hammer, 1992; Lagakos *et al.*, 1993; Volberding *et al.*, 1994), but it usually occurs sooner. Recent research suggests using "cocktails" (combined drugs) for treatment since there is a reduced chance of the virus mutating to be simultaneously resistant to all of the drugs present in the cocktail (Chow *et al.*, 1993; Meng *et al.*, 1992). Alternating schemes, where one drug is given for a period of time and then stopped, followed by another treatment with a different drug, may also aid in combating side effects (Volberding, 1994). Although here we do not directly model resistance effects, present work of these authors examines this more completely (Kirschner and Webb, 1995).

There have been several mathematical models to date examining the effects of AZT on the immune system once infected with HIV. For example, McLean and Nowak (1991) have presented a model dealing with the complication of the onset of AZT-resistant strains of HIV during treatment. Agur (1989) and Cojocaru and Agur (1993) have examined the effects of chemotherapy on normal uninfected cells through cell cycle-based drug protocols, with the aim of minimizing drug toxicity to these cells while maintaining treatment efficacy. Then, Cojocaru and Agur (1992) examined periodicity of AZT chemotherapy. Harnevo (1993) created a model to predict the onset of AIDS. In Perelson (1989) and Perelson *et al.* (1993) AZT treatment was studied with a model based on the number of virion produced per infected $CD4^+$ T cell. If the number of virion is forced below a bifurcation value through AZT treatment, then the immune system can recover to a state where an "uninfected state" is stable. Kirschner and Perelson (1995) dealt specifically with estimating an efficacious therapy regime to insure benefits to the patient. This "benefit" was based solely on an increase or retention of the $CD4^+$ T cell count. Results indicated that treatments which were only 50% effective over a two year period were most effective at bringing the T cells into stasis when the individual had approximately 500 T cells per cubic millimeter. This is considered "early treatment" in the above definitions (i.e. before AIDS).

The present study has two main goals. The first is to create a deterministic mathematical model for the chemotherapy of the HIV infected human immune system; the second is to use this model to simulate and compare dosing regimes in the chemotherapy treatment of AIDS.

2. Methods

Model 1. To model the interaction of the immune system with HIV we consider the group of white blood cells (lymphocytes) which have the protein marker CD4; these cells are referred to as $CD4^+$ T cells. It is precisely these cells which become infected with HIV. The HIV also has a protein, GP120, that has a high affinity for the CD4 protein on the T cell. Binding takes place, and the contents of the virus are then inserted into the host cell. The $CD4^+$ T cell is now infected. After a short time period (less than 24 hr) (Dimitrov *et al.*, 1993), the viral RNA has been converted to viral DNA (using viral reverse transcriptase), and then the viral DNA is incorporated into the host genome. The models consider both the non-infected (T) and infected (T^i) $CD4^+$ T cells. Since an immune response is included in the model (i.e., T cells killing virus via killing infected T cells) the class of $CD8^+$ T cells must also be included in the T population.[1] These cells cannot become infected with the virus, but do destroy infected T cells, and hence virus, during the cellular immune response. In essence, we are including the T cells which are HIV-specific in their immune response. Finally, the population of virus that is free living in the blood (V) is included. We assume the dynamics of these three populations, in the single compartment of the blood periphery, are

$$\frac{dT(t)}{dt} = s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C + V(t)} - k_V T(t)V(t), \tag{1}$$

$$\frac{dT^i(t)}{dt} = k_V T(t)V(t) - \mu_{T^i} T^i(t) - r\frac{T^i(t)V(t)}{C + V(t)}, \tag{2}$$

$$\frac{dV(t)}{dt} = Nr\frac{T^i(t)V(t)}{C + V(t)} - k_T T(t)V(t) + \frac{g_V V(t)}{b + V(t)}. \tag{3}$$

Initial conditions are $T(0) = T_0$, $T^i(0) = 0$ and $V(0) = V_0$. (We assume the initial innoculum is free virus and not infected cells; however, the model is robust in either case.) The model is explained as follows. The first term of

[1] Another model was considered where the T cells were compartmentalized into two groups, $T4$ and $T8$, representing the two types of lymphocytes. This did not change the overall qualitative results of the model, so the model is developed with only one T cell compartment incorporating both types of T cells.

equation (1) represents the source of new T cells from the thymus (see Table 1 for the form of $s(t)$). Since it has been shown that virus can infect thymocytes, we choose a function describing the decreasing source as a function of viral load, assuming that the uninfected T cell populations are reduced by half. Further work on the role of the thymus in HIV infection is presented in Kirschner *et al.* (1995). This is followed by a natural death term, because cells have a finite life span, the average of which is $1/\mu_T$. The next term represents the stimulation of T cells to proliferate in the presence of virus; r is the maximal proliferation rate and C is the half-saturation constant of the proliferation process. The idea is as follows. It is clear that both $CD8^+$ and $CD4^+$ T cells specific to HIV will be directly stimulated; however, we also know that T cells, once activated, stimulate other $CD8^+$ and $CD4^+$ T cells (which may or may not be specific to HIV). We believe this term encompasses these desired effects. The last term represents the infection of $CD4^+$ T cells by virus. This term is a mass action type-term with a constant rate k_V. We assume the law of mass action applies here based on the large numbers of cells and virion involved.

Table Variables and parameters

Notation	Definition	Values
	Dependent Variables	
T	Uninfected $CD4^+$ T cell population	2000 mm^{-3}
T'	Infected $CD4^+$ T cell population	0.0
V	Infectious HIV population	1.0×10^{-3} mm
	Parameters and Constants	
$s(t)$	Source of new $CD4^+$ T cells from thymus	$\left(5 + \frac{5}{1+V(t)}\right)$
μT	Death rate of uninfected $CD4^+$ T cell popullation	0.02 day^{-1}
$\mu T'$	Death rate of infected $CD4^+$ T cell population	0.24 day^{-1}
k_V	Rate $CD4^+$ T cells becomes infected by free virus	2.4×10^{-5} mm^3 day^-
k_T	Rate $CD8^+$ T cells kill virus	7.4×10^{-4} mm^3 day^-
r	Maximal proliferation of the $CD4^+$ T cell population	0.01 day^{-1}
N	Number of free virus produced by bursting infected cells	1000
C	Half-saturation constant of the proliferation process	100 mm^{-3}
b	Half-saturation constant of the external viral source	10 mm^{-3}
g_V	Growth rate of external viral source other than T cells	5 day − 1
a_{max}	Maximum age (life span) of infected $CD4^+$ T cells	12 day
a_1	$[0, a_1]$ is max interval during which reverse transcriptase occurs	0.25 day^{-1}
$\gamma(t, a)$	Periodic, of period p, treatment function	Varies
p	Period of dosage in treatment function	$0 \le p \le 1$ day
c	Total daily drug dosage in chemotherapy	Varies
k	Decay rate of AZT based on half-life of 1 hr	16.66 day^{-1}

Equation (2) describes changes in the infected population of $CD4^+$ T cells. The first term, a gain term for T^i, carries from the loss term in equation (1). Then, infected cells are lost either by having finite life span or by being stimulated to proliferate. They are destroyed during the proliferation process by bursting due to the large viral load (Haseltine and Wong-Staal, 1988).

In equation (3), both the first and third terms are the source for the virus population. Virion are released by the burst of the infected $CD4^+$ T cells (from equation (2)), described by the first term, in which an average of N particles are released per infected cell. The third term represents growth of virus from other infected cells (such as macrophages and infected thymocytes). The growth rate of the process is g_V and the half-saturation constant is b. This term also accounts for natural viral death.[2] The second term is a loss term by the specific immune response (i.e. $CD8^+$ T cells killing virus). This also is a mass action type term, with a rate k_T.

The model (1)–(3) describes the interaction of the immune system with HIV. Models including macrophages (Kirschner and Perelson, 1995) and the role of the infected thymus (Kirschner *et al.*, 1995) have recently been studied. All of these models exhibit the qualitative behavior of the decline of T cells over time together with the growth of virus.

The mathematical analysis of the steady states of Model 1 is presented in the Appendix.

Model 2. In order to allow a mechanistic description of chemotherapy, we incorporate age structure into the infected $CD4^+$ T cells of Model 1. The age structured model, which is mechanistically based on a time scale commensurate with a drug administration schedule of several doses per day, is better suited to the comparison of different number of doses per day. Let a denote the age of cellular infection (i.e. time elapsed since the cell became infected with HIV) and let $T^i(t, a)$ be the density of infected T cells with age of infection a at time t. The total infected T cell population at time t is $\int_0^{a_{\max}} T^i(t, a)\, da$, where $a_{\max}$ is the maximum age of infected T

[2] The external growth term for virus $g_V V/(b+V)$, accounts for both external growth as well as natural death of virus. During the course of the infection, before the viral explosion and T cell crash, the viral load is relatively small. Hence, this term is linearly approximated to be $g_V V$ and can easily incorporate a linear loss term such as $\mu_V V$. At the time of AIDS, when the viral load is high (in this model the focus is on the rapid/high virus), the viral population changes as much as eight orders of magnitude, which cannot be modeled by a linear term; hence, the non-linear term serves as a better approximate of the system. If, however, the $-\mu_V V$ term is included, then a fourth steady state arises, which is not a valid steady state (negative values). Finally, the virus that die naturally do not directly affect the dynamics of the model, since they do not have a chance to infect T cells.

cells. The system (1)–(3) is modified as follows:

$$\frac{dT(t)}{dt} = s(t) - \mu T(t) + rT(t)\frac{V(t)}{C+V(t)} - k_V T(t)V(t),$$

$$T^i(t,0) = k_V T(t)V(t),$$

$$\frac{\partial T^i(t,a)}{\partial t} + \frac{\partial T^i(t,a)}{\partial a} = -\mu_{T^i} T^i(t,a) - rT^i(t,a)\frac{V(t)}{C+V(t)},$$

$$\frac{dV(t)}{dt} = Nr\frac{V(t)}{C+V(t)}\int_0^{a_{\max}} T^i(t,a)\,da - k_T T(t)V(t) + \frac{g_V V(t)}{b+V(t)},$$

with initial conditions $T(0) = T_0$, $V(0) = V_0$ and $T^i(0,a) = 0$, $0 \le a \le a_{\max}$.

Equations (4)–(7) are derived under the same biological assumptions as described for equations (1)–(3). Equation (6) describes the change in $T^i(t,a)$ in time t and cellular infection age a. The boundary condition (5) arises from the input of infected T cells with infection age 0. When the infected cells die (from bursting) in (6), the integral of $T^i(t,a)$ over all possible ages of infection arises as the source of the virus (7).

The mathematical analysis of the steady states of Model 2 is presented in the Appendix.

Chemotherapy of Model 1. To include AZT chemotherapy in Model 1, it is necessary to mimic the effects of the drug, which serves to reduce viral infectivity. The parameter k_V in Model 1 is multiplied by a function which is "off" outside the treatment period and "on" during the treatment period. When the treatment is "on," viral infectivity is reduced, which mimics the effect of treatment for a given time frame. The scalar function which achieves this is

$$\mathbf{z}(t) = \begin{cases} 1 & \text{outside the treatment period,} \\ P(t) & \text{percent effectiveness during AZT treatment,} \end{cases}$$

where $P(t)$ is a periodic treatment function, $0 < P(t) < 1$. This would affect

Model 1 in equations (1) and (2) as follows:

$$\frac{dT(t)}{dt} = s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C+V(t)} - z(t)\cdot k_V T(t)V(t),$$

$$\frac{dT^i(t)}{dt} = z(t)\cdot k_V T(t)V(t) - \mu_{T^i} T^i(t) - r\frac{T^i(t)V(t)}{C+V(t)},$$

$$\frac{dV(t)}{dt} = Nr\frac{T^i(t)V(t)}{C+V(t)} - k_T T(t)V(t) + \frac{g_V V(t)}{c+V(t)},$$

where the initial conditions are still $T(0) = T_0$, $T^i(0) = 0$ and $V(0) = V_0$. It has recently been shown (McKallip *et al.*, 1995) that since AZT affects transcription of RNA to DNA, it also inhibits normal thymocyte differentiation. We do not model this effect here, but consider it in the resistance models (Kirschner and Webb, 1995). Drugs such as AZT reduce viral activity in a dose dependent manner. The efficacy of the chemotherapy may differ from patient to patient; therefore, $P(t)$ represents the varying effectiveness of the drug in halting viral activity in a given patient. $P(t)$ is not directly correlated to the actual oral dose of the drug in this simplistic approach.

Chemotherapy of Model 2. In Model 2 age structure is used to model the mechanism by which AZT serves to interrupt the T cell infection process. Only T^i cells with age less than a_1 are affected by the drug (where a_1 is the maximum age at which reverse transcription takes place). T^i cells with age less than a_1 revert back to the uninfected class during the "on" phase of the treatment.[3] In this model, treatment corresponds to a loss term $-\gamma(t,a;p)T^i(t,a)$ added to equation (6), where the treatment function $\gamma(t,a;p)$ is periodic in time t with period p and depends on the age of cellular infection a. The equations are

$$\frac{dT}{dt} = s(t) - \mu T(t) + rT(t)\frac{V(t)}{C+V(t)} - k_V T(t)V(t) + \int_0^{a_1} \gamma(t,a;p)T^i(t,a)\,da,$$

[3] In these models it is assumed that only one virus infects a T cell at any given time. This is feasible, since infected T cells tend to shed their CD4. In reality, this number may be larger, but it is assumed that one virus is successful, unless AZT treatment is present, and then only cells which are in the first $[0, a_1]$ age class are affected by treatment.

$$T^i(t,0) = k_V T(t) V(t),$$

$$\frac{\partial T^i}{\partial t} + \frac{\partial T^i}{\partial a} = -\mu_{T^i}(t,a) - rT^i(t,a)\frac{V(t)}{C+V(t)} - \gamma(\mathbf{t},\mathbf{a};\mathbf{p})\mathbf{T}^i(\mathbf{t},\mathbf{a}),$$

$$\frac{dV}{dt} = Nr\frac{V(t)}{C+V(t)}\int_{a_1}^{a_{\max}} T^i(t,a)\,da - k_T T(t)V(t) + \frac{g_V V(t)}{b+V(t)},$$

with initial conditions $T(0) = T_0$, $V(0) = V_0$ and $T^i(0,a) = T_0^i(a)$.

Although we do not directly model the pharmacokinetics of AZT chemotherapy, we do take into account some key aspects of the treatment. For example, since AZT has a half-life of 1 hr, we assume that $\gamma(t,a;p)$ is an exponential decaying function in t during each period, with decay rate $k = 16.66$, were time units are in days. Assume that the chemotherapy only has effect during the first a_1 hours after cellular infection (for AZT $a_1 = 6$ hr (Dimitrov *et al.*, 1993)) and that the period p has range $0 < p \le 1$ (= day). The intensity of chemotherapy has value c at the beginning of each period. This value has no *direct* correlation with actual oral dosages, but serves to determine an appropriate range for that parameter. The *average value* of the treatment for any period is

$$\frac{1}{p}\int_0^p ce^{-kt}\,dt = \frac{c(1-e^{-kp})}{kp}$$

Therefore, to remove the period dependence from the average value of treatment, scale c by $(1-e^{-kp})/p$. This correlates to the desired total daily dose being divided by the number of doses given per day. The treatment function $\gamma(t,a;p)$ is then

$$\begin{cases} \dfrac{cp}{(1-e^{-kp})}e^{-kt}, & \text{if } 0 \le a \le a_1 \text{ and } 0 \le t \le p, \\ \dfrac{cp}{(1-e^{-kp})}e^{-k(t-p)}, & \text{if } 0 \le a \le a_1 \text{ and } p \le t \le 2p, \\ \vdots & \\ 0, & \text{if } a > a_1. \end{cases}$$

3. Results

Parameter values. A complete list of parameters and their estimated values is given in Table 1. The majority of the values have been taken from data, and a complete discussion of their values can be found in Perelson

et al. (1993). There are not good data available for the maximal age of $CD4^+$ T cells, whether infected or uninfected. Here, the maximal age of infected T cells is taken to be 12 days. (In Fig. 2C, the distribution for the infected class is given.) By about day 12 it is clear that most of the cells are included in the distribution, and the remainder, in the tail, do not account for a significant amount. The maximal interval during which reverse transcription occurs (i.e. $[0, a_1]$) is approximately 6 hr after binding of HIV to T cell takes place (Dimitrov *et al.*, 1993). This is an important parameter, as the infected T cells during this stage are susceptible to treatment. If this time frame were longer, more cells would be susceptible to chemotherapy; if it were shorter, less cells would be affected. The parameters associated with the treatment come from experimental data using AZT. There is a relation between the standard 500–1500 mg dosages and the parameter d in the dosing regime. Also, the periods of treatment come directly from the Burroughs-Wellcome Co. insert for AZT, as well as the value of the half-life.

Results without chemotherapy. To begin numerical studies of these models, first examine them in the absence of treatment. Using a solver for ordinary differential equations from Mathematica (Wolfram, 1988) equations (1)–(3) were solved together with the parameter values from Table 1. Three different numerical solutions are given in Fig. 1. Most likely, during the course of the infection, the patient first moves into the infected steady state for a period of time (usually referred to as the latent stage; Fig. 1A). Then, some mechanism of the infection changes after a period of time, and the patient then progresses to AIDS (Fig. 1B). The mechanism in this model which causes the switch is the external growth of virus, namely, the parameter g_V. In the infected steady state, g_V has a value of 5, and if this value is increased (for example, due to mutations or increased efficiency in viral production), the system moves to AIDS. Figure 1C represents the complete course of HIV infection which is also attainable with this model.

Examining the partial differential equation model numerically was more difficult. A program was written based on the method of characteristics and the Runge–Kutta method, which solves Model 2 using the parameter values from Table 1. As the equations differ only in the age of infection terms, the results of Model 2 are expected to be similar to that of Model 1. This is true and the two models differ slightly in local behavior, but globally have the same qualitative features. Figure 2 gives the numerical solutions of Model 2. Figure 2A represents the infected steady state and Fig. 2B

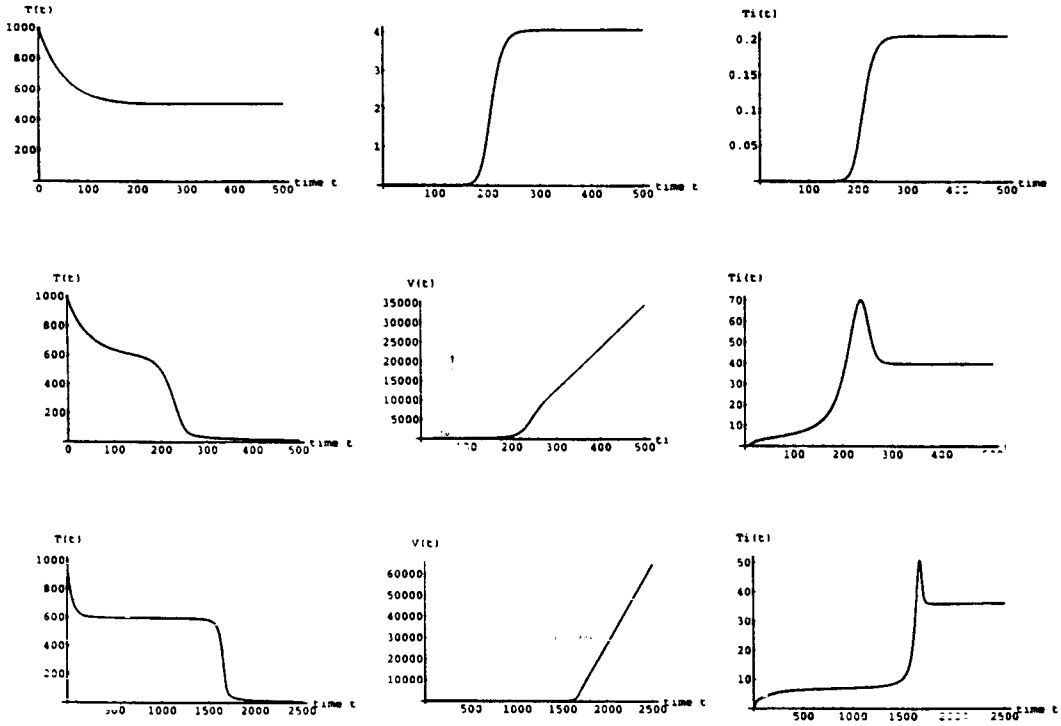

Figure 1. The numerical solutions to Model 1, equations (1)–(3). Parameter values used to generate these figures can be found in Table 1. (A) The *infected steady state* with $g_V = 5$. If the external source is increased, i.e. $g_V = 20$. then it pushes the system into the (B) the *Progression to AIDS*. (C) HIV infection. This occurs when the external growth is variable and changes from $g_V = 5$ to $g_V = 20$ over time. (Notice the steep crash at day 1500 occurs over a period of a year.)

represents AIDS. Since the infected T cell class is now age dependent. the distribution over age and time, given an initial condition of zero, is also given (Fig. 2C).

Chemotherapy results. The simulations of chemotherapy explore many issues. First, chemotherapy results of Model 1 are compared with Model 2. Second, within each of the models different periods of treatment are compared: early versus late treatment and large versus small doses.

For chemotherapy simulations in Model 1, as described in Methods, consider both continuous treatment (early vs late) and periodic treatment incremented twice a day and six times a day (where $P(t) = 0.5$ for the first half of each treatment period and $P(t) = 0$ for the second half of each

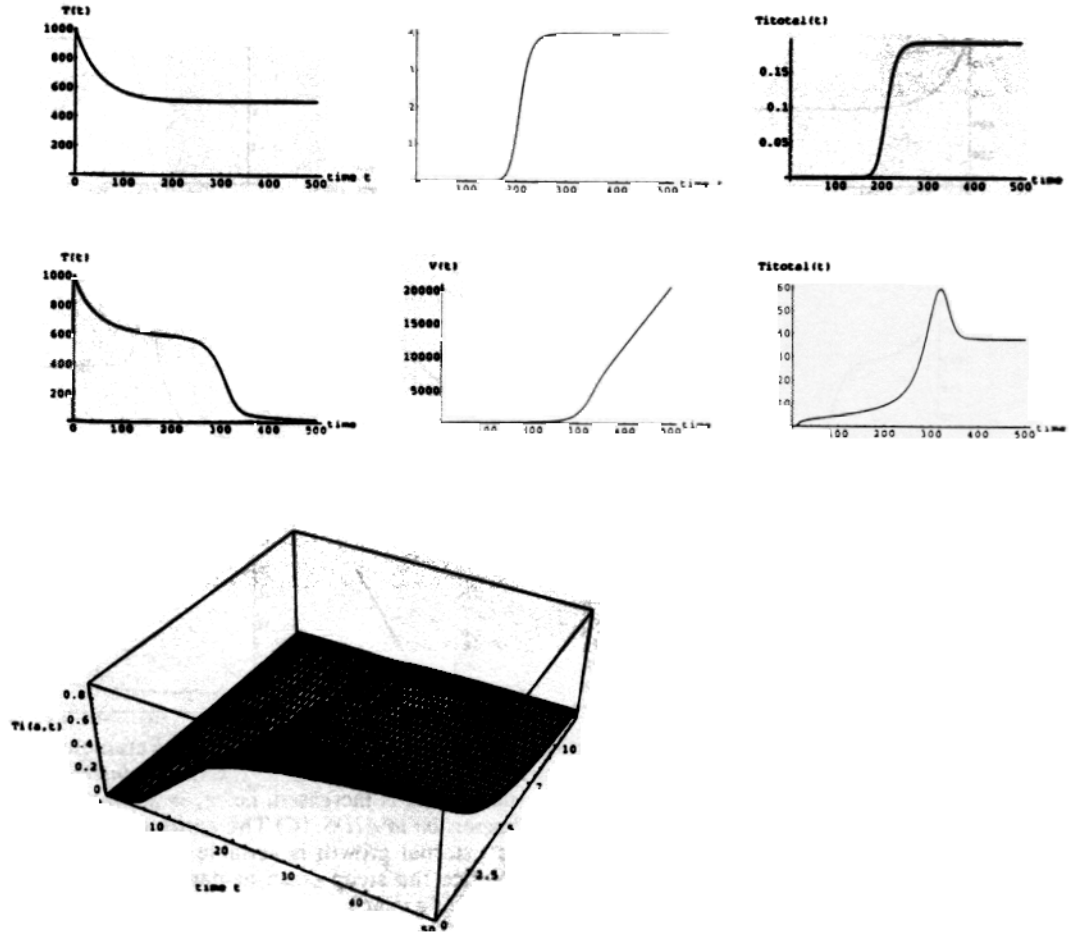

Figure 2. The numerical solutions to Model 2, equations (4)–(7). Parameter values used to generate these figures can be found in Table 1. (A) The *infected steady state*. If the external source is increased, i.e. $g_V = 20$, then it pushes the system into (B) the *progression to AIDS*. (C) The distribution of infected T cells, $T^i(t, a)$.

treatment period). The results are given in Fig. 3. Considered in each of these cases are early treatment (beginning treatment after 100 days into the decline) and late treatment (beginning treatment after 200 days into the decline). Clearly, later treatment is better. The time frame during which the patient has a high T cell count is extended by over 100 days. In all cases, a minimal amount of treatment was all that was necessary to perturb the system from AIDS into the infected steady state.

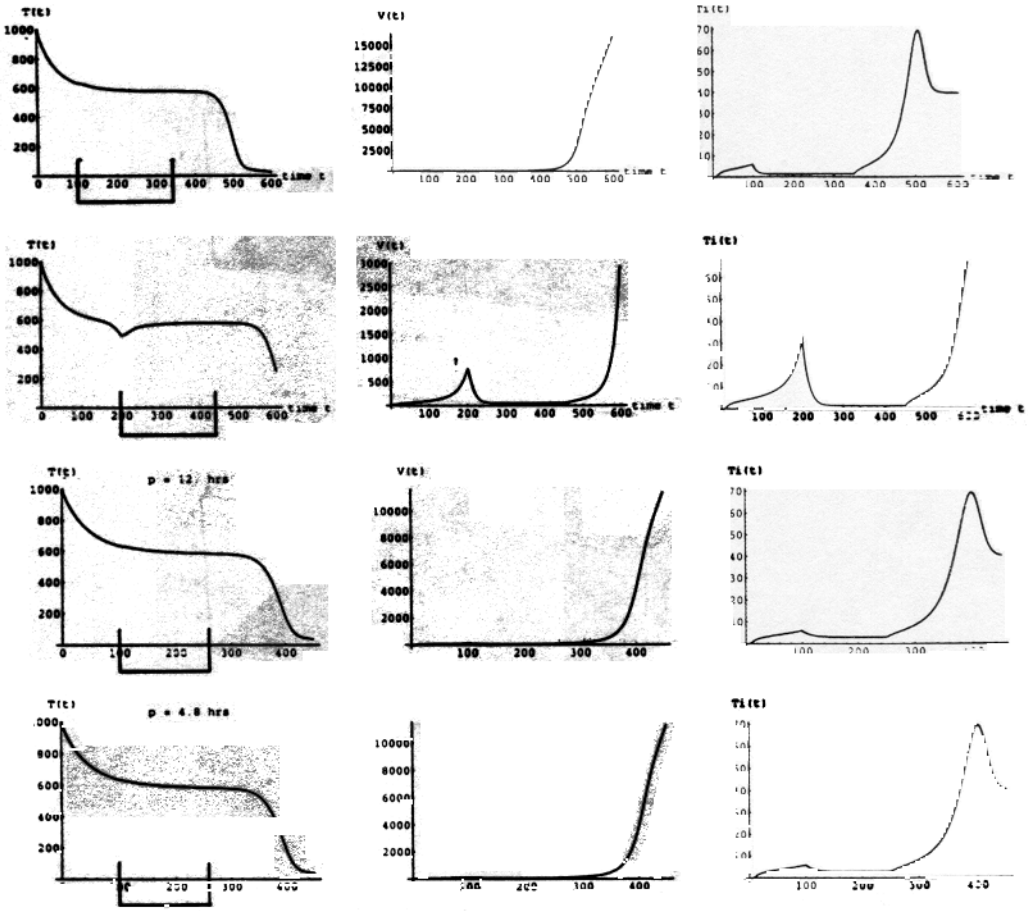

Figure 3. The numerical solutions to Model 1 including the chemotherapy. All treatment was carried out during the progression to AIDS with $g_V = 20$ (cross-reference with Fig. 1B). Hash marks indicate treatment initiation and cessation. (A) Early continuous treatment (beginning at 100 days and lasting 250 days). (B) Late continuous treatment (beginning at 200 days and lasting 250 days). (C) Periodic treatment every 12 hr. (D) Periodic treatment every 4 hr, each beginning at 100 days and lasting 150 days. In each of the panels, the vertical axes are different. This corresponds to the average dosing being independent of the period. The age dependence is present since the drug only works up to age a_1.

For chemotherapy simulations in Model 2, as described in Methods, we also considered the different periods of treatment as mentioned above for Model 1. Figure 4 gives examples of different treatment function $\gamma(t, a; p)$. Figure 4A represents a treatment which is administered every 4 hr, Fig. 4B every 8 hr and Fig. 4C every 12 hr. Figures 5 and 6 gives the solutions of

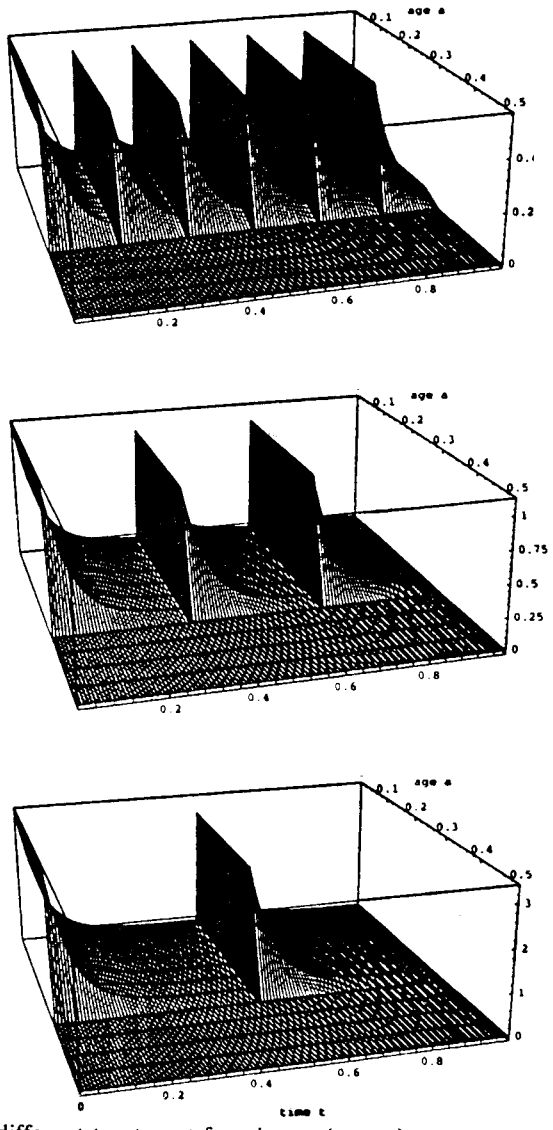

Figure 4. The different treatment functions $\gamma(t, a; p)$ used in the simulations of Figs. 5 and 6. (A) Treatment every 4 hr (which is the present recommended schedule). (B) Treatment every 8 hr. (C) Treatment every 12 hr.

Model 2 with different periods of treatment (i.e. daily periodic treatment scheduling). Figure 5 represents early periodic treatments (beginning at 100 days and lasting 150 days). Here, the first point is that the period of treatment administration (that is, every 4.8, 12 or 24 hr) does not reveal a significant difference in the overall dynamics. Second, when compared with

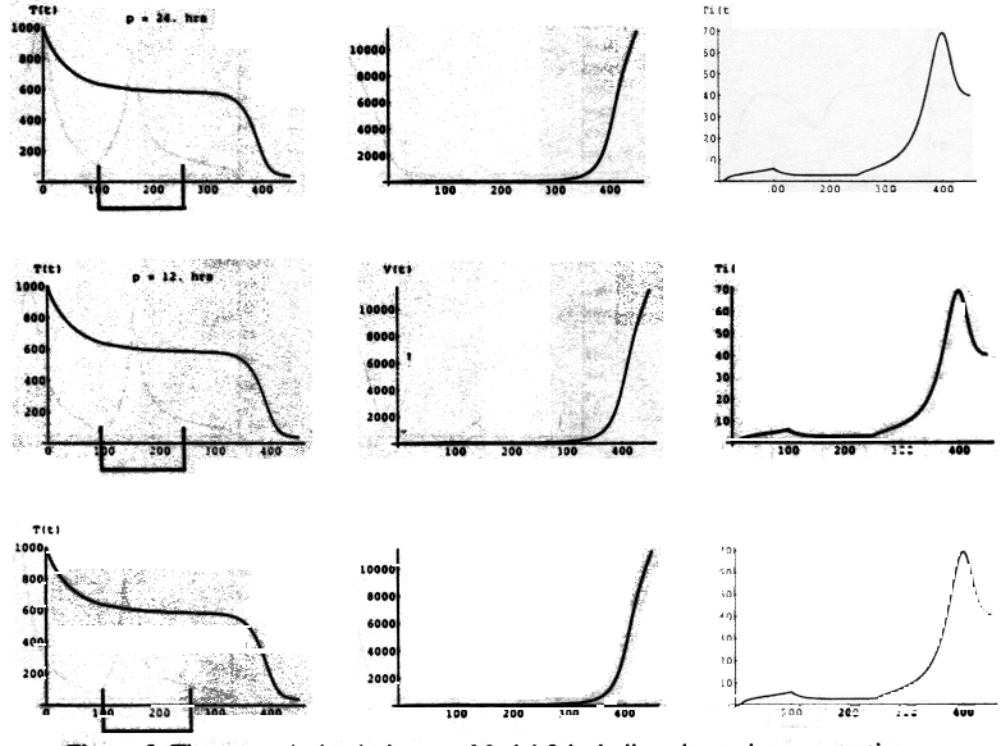

Figure 5. The numerical solutions to Model 2 including chemotherapy starting at an early stage of the disease progression (100 days) administered for 150 days. All treatment was carried out during the progression to AIDS, i.e. $g_V = 20$ (cross-reference with Fig. 2B). Hash marks indicate treatment initiation and cessation. (A) Treatment once a day (cross-reference with Fig. 4). (B) Treatment every 12 hr (cross-reference with Fig. 4C). (C) Treatment every 4 hr (cross-reference with Fig. 4A).

Fig. 6, which shows the same treatments, only administered after the progression to AIDS (beginning at 300 days and lasting 100 days), the length of time with a extended high T cell count is over 100 days longer. These simulations suggests that there is no benefit for early treatment. This agrees with the findings of the Concorde study (Concorde Coordinating Committee, 1994), which found no advantage to early treatment.

Different dosage sizes c are compared in Fig. 7. Figure 7A represents an extremely small dose size, Fig. 7B is a moderate dose and Fig. 7C is a very large dose. First noted is that the small dose has a very low effect, but the medium and large doses have the same effect. This seems to indicate that there is a certain minimum dose, below which there is almost no effect and above which the extra drug amount serves no positive role. Again, in all

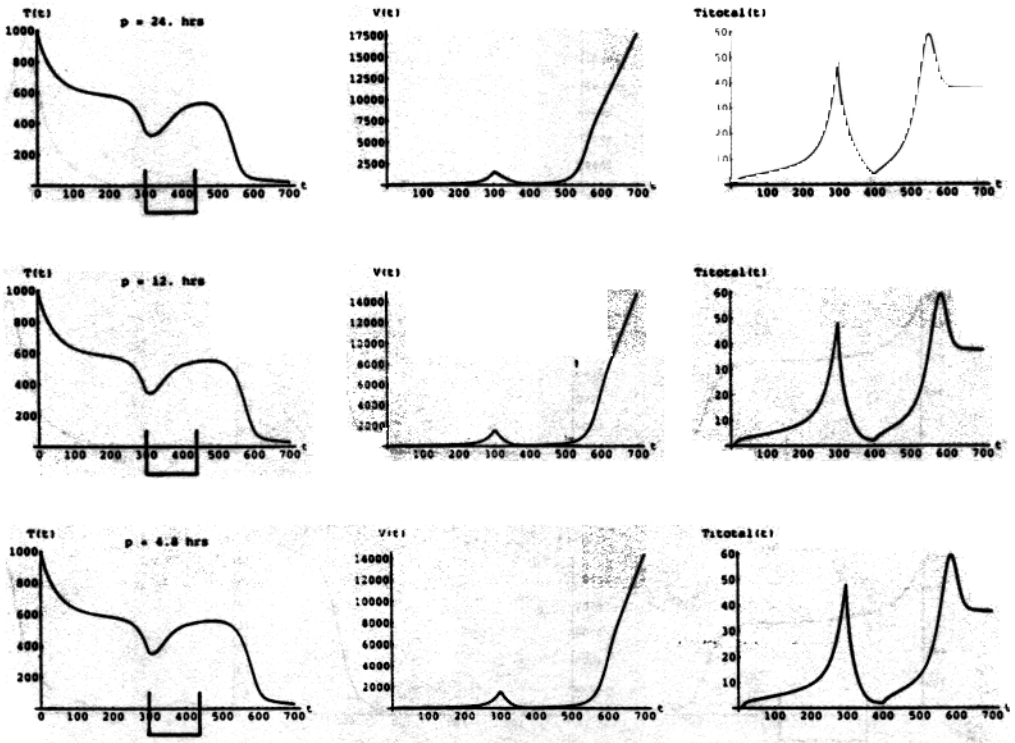

Figure 6. The numerical solutions to Model 2 including chemotherapy starting at a late stage of the disease progression (300 days) administered for 150 days. All treatment was carried out during the progression to AIDS, i.e. $g_V = 20$ (cross-reference with Fig. 2B). Hash marks indicate treatment initiation and cessation. (A) Treatment once a day (cross-reference with Fig. 4). (B) Treatment every 12 hr (cross-reference with Fig. 4C). (C) Treatment every 4 hr (cross-reference with Fig. 4A).

cases, a minimal amount of treatment was all that was necessary to perturb the system from AIDS into the infected steady state.

Intermittent chemotherapy schemes. Because of the harmful and sometimes unmanageable side effects of chemotherapy, as well as resistance problems, alternative methods of dosing are necessary. To date, the main focus in dealing with side effects has been lowering the administered doses. However, even this is not sufficient in increasing the quality of life (Lenderking *et al.*, 1994). The issue of resistance has been addressed by multi-drug chemotherapies. Here, two alternative methods are suggested, which may aid in dealing with these issues.

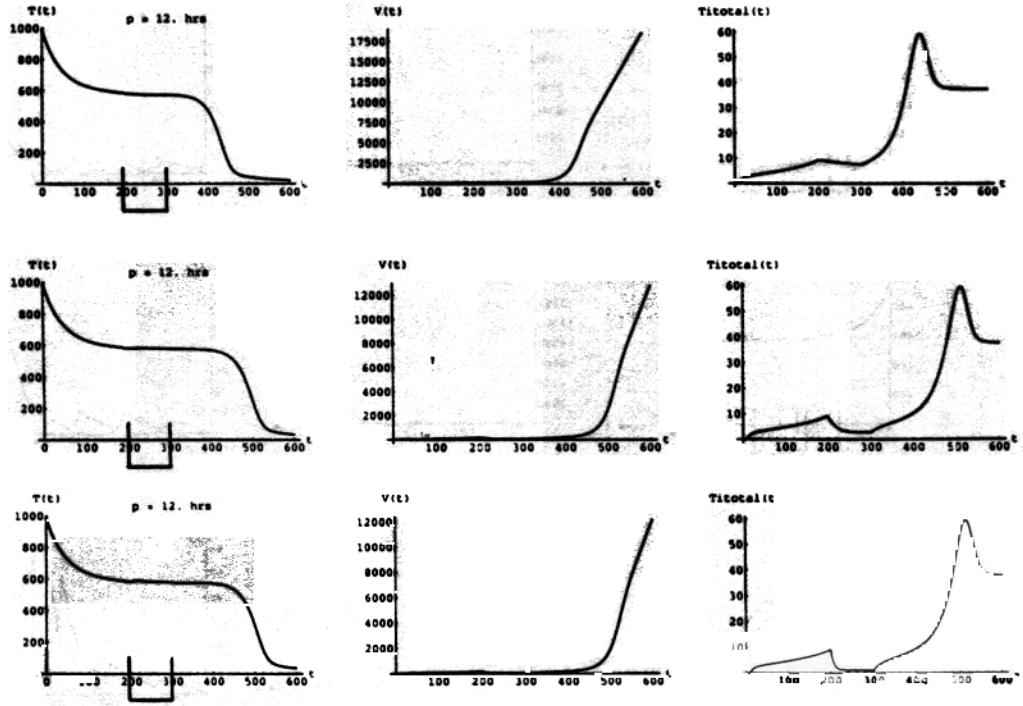

Figure 7. The numerical solutions to Model 2 for chemotherapy comparing dosage size c. Chemotherapy starts at after 200 days into the disease progression and is administered for 100 days. All treatment was carried out during the progression to AIDS, i.e. $g_V = 20$ (cross-reference with Fig. 2B). Hash marks indicate treatment initiation and cessation. (A) A small dose ($c = 1.0$). (B) A medium dose ($c = 10.0$). (C) A large dose ($c = 40.0$). All other results (Fig. 5 and 6) were carried out with a value of $c = 20.0$.

First, the models suggest that there is a delay period after treatment is halted before the T cell decline reappears (cf. Figs. 3–7: the delay appears to be approximately 50 days long). This would suggest that alternating successful periods of treatment with no treatment (for the length of the specific delay) would be a method in which one could extend the treatment periods longer and reduce toxicity through less frequent administration. Conventional practice opposes interrupted treatment because of resistant strains. The present strategy in combating resistance, however, is to administer several drugs at once, thus minimizing the possibility of mutant strains developing simultaneously to all the drugs. In particular, for strongly effective drugs (i.e. drugs which eliminate the infectious agent) this strategy minimizes drug resistance. AZT treatment, however, is weakly effective (i.e. it does not eliminate the infectious agent); therefore, this traditional view

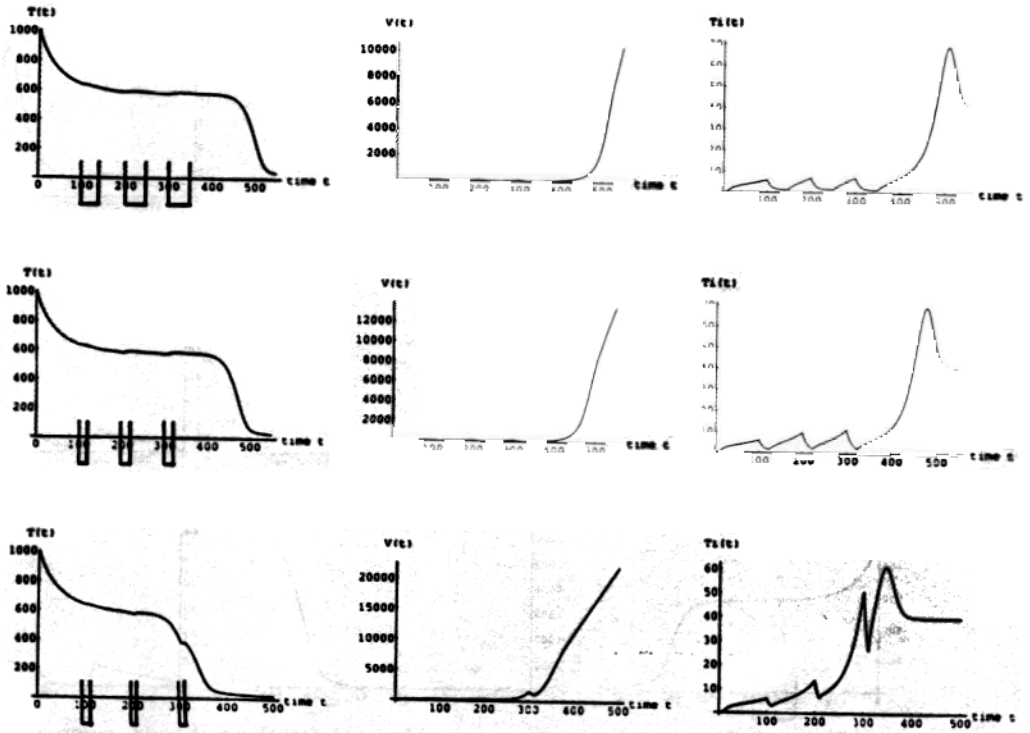

Figure 8. The numerical solutions to Model 1 for the intermittent chemotherapy scheme. Chemotherapy starts at an early stage of the disease progression (after 100 days). All treatment was carried out during the progression to AIDS, i.e. $f_V = 20$ (cross-reference with Fig. 2B). Hash marks indicate treatment initiation and cessation. Different on–off schemes of intermittent treatment were tested: (A) The effects of intermittent treatment where the treatment is on for 50 days, then off for 50 days (repeated three times): (B) An intermittent therapy of on for 25 days, off for 75 days (repeated three times): (C) therapy on for 10 days, and off for 90 days (repeated three times).

may not apply. This hypothesis was tested, however, with Model 1 (for simplicity), the results of which are given in Fig. 8. Continuous treatment was used during the treatment "on" periods, since there is no qualitative difference between continuous versus periodic treatment in Model 1 (cf. Fig. 3). Here different period lengths of "on–off" treatments are tested, two of which are successful in retaining the T cell counts. Figure 8A represents continuous treatment alternating on and off in 50 days intervals. Figure 8B is continuous treatment on for 25 days and off for 75 days. Finally, Fig. 8C represents treatment on for 10 days continuously and off for 90 days. Of the three different intermittent treatment strategies, the

first is most effective in maintaining the T cell count the longest. The third strategy is the least effective of the three treatments.

If it is not feasible to take the patient off chemotherapy for even short periods of time, then the models suggest that intermittent therapy with another drug may be just as effective. Volberding (1994) recently suggested this as a possible approach and this model supports that claim as well.

4. Discussion. The goals of this study were to first create a mathematical model which described the interaction of the immune system with HIV, and then to use the model to explore chemotherapy treatments. The following issues of treatment scheduling were investigated: frequent versus infrequent dosing periods, early versus late treatment and high versus low doses. Using both the non-mechanistic (Model 1) and mechanistic (Model 2) approaches, similar results and conclusions were obtained for both. Model 1, although non-mechanistic in the way chemotherapy is modeled. does agree with the overall results of Model 2. Model 2, however, is closer to the biology in that it relates to the time scale which is a key component in the administration of drugs. By allowing for an age variable, the biological effects are modeled more realistically, particularly in the comparison of number of AZT doses per day. In particular, the life cycle of the virus occurs on an hourly basis, which explicitly accounts for administering treatment during the appropriate time during which reverse transcription takes place.

The first, and main conclusion from this study is that the periodicity of treatment during a given day does not reveal a significant difference in the overall effect, quantitatively or qualitatively. This means that whether one receives a 500 mg does once a day or 100 mg doses five times a day. the overall result is the same. This is because the treatment serves only to perturb the system from AIDS into the infected steady state. There are obvious advantages to less frequent dosing. First, administration of the drug is more manageable for the patient (the recommended dosing of AZT every 4 hr is a severe hardship on AIDS patients). Second, less frequent doses, rather than just smaller ones, could possibly lower toxicity and side effects to the patient. Finally, since the choice of the treatment period is not significant, in agreement with the results of Agur (1989) and Cojocaru and Agur (1993), which recommended a dosing scheme that is synchronous with the cell cycle of normal lymphocytes, the sparing of host cells may be profound.

The second conclusion from this study relates to the question of early versus late treatment. In both Model 1 and Model 2 the numerical results reveal two periods of decline. The first is due to the initial transient stage of

the infection (resulting from the immune response which is present early in the infection (Redfield and Burke, 1988); the second is due to the eventual, large viral load (Ho *et al.*, 1995) (directly or indirectly) pushing the T cells to zero. This study indicates that chemotherapy treatment should begin only after the second decline takes place, namely, when the final crash of T cells begins to occur. Treatment at that time pushes the system back to just before the crash, and the T cells no longer decline, but remain in stasis until treatment is halted.

The third result compares the size of dosage. In examining different doses (Fig. 7), there is no clear benefit from a large dose of chemotherapy. The uninfected T cell population behaves identically and there is only a small difference in the overall total infected T cell population during treatment. If smaller doses are preferred (based on toxicity), this model suggests that a small dose is just as effective.

At present, dosing schemes for these chemotherapies are based primarily on the pharmacokinetics of the drugs. In particular, the half-life plays a key role. Since this model of chemotherapy accounts for this, the results could be significant in the consideration of treatment scheduling.

It should be noted here that in the dynamics of this and other diseases, such as cancer, disease progression states are not states of stabilization, but states where there is a rapid physical collapse of the system. In these models, the infected steady state (latency period) is a state of stabilization; however, the progression to AIDS (collapse of the $CD4^+$ T cell population) is not, since the viral population grows without bound. The fact that AZT chemotherapy serves to perturb the collapsing system back into a stable state is the central thesis of this paper.

Finally, these results suggest that the possibility of using multi-drug type treatment to combat resistance may be better facilitated by an intermittent treatment strategy. If one drug is administered for a length of time and then followed by either a different drug treatment for a long period or no treatment for a shorter period or in synchrony with another drug, it could extend the total length of time treatment is admissible and, hence, extend the time to the onset of AIDS. These schemes may also aid in reducing toxicity and side effects, although we do not directly model these phenomena. A major reason for the chemotheraputic failure of AZT is drug resistance. The models we have presented here do not incorporate resistance phenomena. In a second study the authors develop models which directly address resistance questions (Kirschner and Webb, 1995).

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APPENDIX

Analysis of Model 1. We begin the analysis of Model 1, equations (1)–(3), by examining steady state solutions. For simplification of analysis, we assume that the T cell source from equation 1, $0.5s + 0.5s/(1 + V(t))$, is approximated by a constant s:

$$s = \mu_T \bar{T} - r\frac{\bar{T}\bar{V}}{C+\bar{V}} = k_V \bar{T}\bar{V},$$

$$k_V \bar{T}\bar{V} = \mu_{T^i}\bar{T}^i + r\frac{\bar{T}^i\bar{V}}{C+\bar{V}},$$

$$Nr\frac{\bar{T}^i\bar{V}}{C+\bar{V}} = k_T\bar{T}\bar{V} - \frac{g_V\bar{V}}{b+\bar{V}}. \tag{A3}$$

Solving equation (A2) for population $\bar{T}^i$ and substituting into (A3) yields two equations in two unknowns:

$$s = \mu_T\bar{T} - r\frac{\bar{T}\bar{V}}{C+\bar{V}} + k_V\bar{T}\bar{V},$$

$$\frac{Nr\bar{V}^2k_V\bar{T}}{\mu_{T^i}(C+\bar{V})+r\bar{V}} = k_T\bar{T}\bar{V} - \frac{g_V\bar{V}}{b+\bar{V}} \tag{A5}$$

Solving both equations (A4) and (A5) for population $\bar{T}$, gives

$$\bar{T} = \frac{s}{\mu_T - r\bar{V}/(C+\bar{V}) + k_V\bar{V}} \tag{A6a}$$

$$= \frac{g_V/(b+\bar{V})}{k_T - Nr\bar{V}k_V/(\mu_{T^i}(C+\bar{V})+r\bar{V})}$$

Equation (A5) has another solution of $\bar{V} = 0$ (which implies $\bar{T} = s/\mu_T$). Now setting (A6a) = (A6b),

$$s(b+\bar{V})\left[k_T - \frac{Nr\bar{V}k_V}{\mu_{T^i}(C+\bar{V})+r\bar{V}}\right] = g_V\left[\mu_T - r\frac{\bar{V}}{C+\bar{V}} + k_V\bar{V}\right]$$

This last equation is cubic in $\bar{V}$, with the coefficients given as expressions of the parameters. With the parameter values given in Table 1, there are three roots: one positive and two imaginary. Hence, the different steady states for the system are as follows: *uninfected steady state* (where the virus population and infected cells are $\bar{V} = 0$ and $\bar{T} = s/\mu_T$) and *infected steady state* (both virus and T cells exist at some positive level). This corresponds to the extended latent period of the disease. Another limiting behavior for the system is

progression to AIDS (the T cell population goes to 0, T^i goes to a positive constant and V grows linearly without bound, which is consistent with the Center for Disease Control's definition for AIDS related complexes (ARC) and (AIDS). A linearized stability analysis of the uninfected steady state reveals a threshold condition for local stability. More precisely, if $R_0 = gV/k_T b < 1$, the system recovers from infection; if $R_0 > 1$, the uninfected state becomes unstable and the infected steady states assumes stability.

Analysis of Model 2. To being the analysis of Model 2, equations (4)–(7), assume (without loss of generality):

(i) that the T cell source from equation (1), $0.5s + 0.5s/(1 + V(t))$, is approximated by a constant s,

(ii) that $a_{\max} = \infty$ and define $T^i(t) = \int_0^\infty T^i(t, a)\,da$. (This is valid since the tail of the distribution with age class larger than 12 days is negligible (cf. Fig. 2C).)

Now, integrate (6) with respect to age (from 0 to ∞) to obtain

$$\frac{dT^i(t)}{dt} + T^i(t)\left(\mu_{T^i} + \frac{r\bar{V}(t)}{C + V(t)}\right) = k_V V(t) T(t),$$

which is the same as equation (2). Solving for steady states in (4)–(7) yields

$$s = \mu\bar{T} + r\bar{T}\frac{\bar{V}}{C + \bar{V}} + k_V \bar{T}\bar{V}, \tag{A7}$$

$$\bar{T}^i(0) = k_V \bar{T}\bar{V}, \tag{A8}$$

$$\frac{d\bar{T}^i}{da} = -\bar{T}^i(a)\left(\frac{r\bar{V}}{C + \bar{V}} + \mu_{T^i}\right), \tag{A9}$$

$$Nr\frac{\bar{V}}{C + \bar{V}}\int_0^{a_{\max}} \bar{T}^i(a)\,da = k_T \bar{T}\bar{V} - \frac{g_V \bar{V}}{b + \bar{V}}. \tag{A10}$$

If (A8) and (A9) are considered as an initial value problem, the solution is

$$\bar{T}^i(a) = \exp\left(-\left(\mu_{T^i} + \frac{r\bar{V}}{C + \bar{V}}\right)a\right) k_V \bar{V}\bar{T}.$$

Let $\bar{T}^i = \int_0^{a_{\max}} \bar{T}^i(a)\,da$,

$$\bar{T}^i = \int_0^{a_{\max}} \exp\left(-\left(\mu_{T^i} + \frac{r\bar{V}}{C + \bar{V}}\right)a\right) K_V \bar{V}\bar{T}\,da = \frac{k_V \bar{V}\bar{T}}{\mu_{T^i} - r\bar{V}/(C + \bar{V})},$$

which is the same as equation (A2). Thus, the steady state problem for Model 2 is the same as the steady state problem for Model 1, namely, once the values for $\bar{T}$ and $\bar{V}$ are known (they are the same as calculated for Model 1), the value of $\bar{T}^i(a)$ can be found.

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