

Perspectives

Resistance, Remission, and Qualitative Differences in HIV Chemotherapy

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Appendix

For the model without treatment, it is assumed that only drug-sensitive virus, uninfected CD4+ T cells, and CD4+ T cells infected by drug-sensitive virus are present. The equations for the model without treatment are as follows (24):

$$(A.1): dT(t)/dt = S(t) - \mu_T T(t) + p_1(t) T(t) V_s(t) - k_s V_s(t) T(t)$$

$$(A.2): dT_s(t)/dt = k_s V_s(t) T(t) - \mu_{Ti} T_s(t) - p_2(t) T_s(t) V_s(t)$$

$$(A.3): dV_s(t)/dt = p_3(t) T_s(t) V_s(t) - k_v T(t) V_s(t) + G_s(t)$$

In (A.1) $S(t)$ represents the external input of uninfected CD4+ T cells from the thymus, bone marrow, or other sources. It is assumed that there is a deterioration of this source as the viral level increases during the course of HIV infection. The form of this source is $S(t) = S_1 - S_2 V_s(t)/(B_s + V_s(t))$, where B_s is a saturation constant (the various saturation constants in the model are designed to adjust the rate parameters to large changes in the population levels during disease progression or treatment). In (A.1) μ_T is the death rate of uninfected CD4+ T cells whose average lifespan is $1/\mu_T$ (25). In (A.1) the term $p_1(t) T(t) V_s(t)$ represents CD4+ T-cell proliferation in the plasma due to an immune response that incorporates both direct and indirect effects of antigen stimulation ($p_1(t) = p_1/(C + V_s(t))$, where C is a saturation constant). This term accounts for the above normal turnover of CD4+ T cells (other forms for this production have been used, including a logistic approach [26]). The form assumed here idealizes the growth mechanisms of CD4+ T cells, since subpopulations of antigen specific CD4+ T cells are not modeled. In (A.1) k_s is the infection rate of CD4+ T cells by virus (it is assumed that the rate of infection is governed by the mass action term $k_s V_s(t) T(t)$). In the absence of virus the CD4+ T-cell population converges to a steady state of S_1/μ_T .

In (A.2) there is a gain term $k_s V_s(t) T(t)$ of CD4+ T cells infected by drug-sensitive virus, a loss term $\mu_{Ti} T_s(t)$ due to the death of these cells independent of the virus population, and a loss term $p_2(t) T_s(t) V_s(t)$ dependent on the virus population due to bursting or other causes (where $p_2(t) = p_2/(C_i + V_s(t))$ and C_i is a saturation constant). The dependence of the loss term $p_2(t) T_s(t) V_s(t)$ on $V_s(t)$ allows for an increased rate of bursting of infected cells as the immune system collapses and fewer of these cells are removed by CD8+ T cells.

In (A.3) the virus population is increased by the term $p_3(t) T_s(t) V_s(t)$, where $p_3(t) = p_3/(C_i + V_s(t))$. This term corresponds to the internal production of virus in the blood. The dependence of this term on $T_s(t)$ allows for a decreased rate of viral production in the plasma when the infected CD4+ T-cell population in the plasma collapses. Since most of the plasma virus is contributed by the external lymph source, the plasma virus population still increases steeply at the end stage of the disease. In (A.3) the virus population is decreased by the loss term $k_v T(t) V_s(t)$, which represents viral clearance. In (A.3) there is a source of virus from the external lymphoid compartment, which is represented by the term $G_s(t) = G_s V_s(t)/(B + V_s(t))$ (B is a saturation constant). This term accounts for most of the virus present in the blood (8).

The lifespans of infected CD4+ T cells and virus can be computed from the terms in (A.2) and (A.3) during the asymptomatic period of infection (when the rates of population increase are almost balanced by the rates of population decrease). The loss terms in (A.2) yield an average infected CD4+ T-cell lifespan of $1/(\mu_{Ti} + p_2 V_s(t)/(C_i + V_s(t)))$, which decreases from $= 1/\mu_{Ti}$ to $1/(\mu_{Ti} + p_2)$ as $V_s(t)$ increases. The loss term in (A.3) yields an average virus lifespan of $1/(k_v T(t))$, which increases from $1/(k_v T(0))$ as $T(t)$ decreases.

The equations for the model with treatment are as follows:

$$(A.4): dT(t)/dt = S_0(t) - \mu_T T(t) + p_1(t) T(t) V(t) - (\eta_1(t) k_s V_s(t) + k_r V_r(t)) T(t)$$

$$(A.5): dT_s(t)/dt = \eta_1(t) k_s V_s(t) T(t) - \mu_{Ti} T_s(t) - p_2(t) T_s(t) V(t)$$

$$(A.6): dT_r(t)/dt = k_r V_r(t) T(t) \mu_{Ti} T_r(t) - p_2(t) T_r(t) V(t)$$

$$(A.7): dV_s(t)/dt = (1-q)p_3(t) T_s(t) V(t) - k_v T(t) V_s(t) + \eta_2(t) G_s V_s(t)/(B + V(t))$$

$$(A.8): dV_r(t)/dt = p_3(t) T_r(t) V(t) + q p_3(t) T_s(t) V(t) - k_v T(t) V_r(t) + G_r(V(t)) V_r(t)/(B + V(t))$$

In the model, treatment inhibits (with a delay) new infections of CD4+ T cells and inhibits (with a delay) the influx of virus from the external source. In equations (A.4) - (A.8) $V(t) = V_s(t) + V_r(t)$ is the total virus population at time t , and its inclusion in the rate coefficients results in competition between the sensitive and resistant viral strains. In these equations, treatment is modeled by the decreasing functions $\eta_1(t) = \exp(-c_1 t)$ (which inhibits the rate at which uninfected CD4+ T cells become infected) and $\eta_2(t) = \text{maximum}\{\exp(-c_2 t), c_3\}$ (which inhibits the influx of virus from the external lymphoid compartment). The parameters c_1 , c_2 , and c_3 control the speed and strength of the drug-induced inhibitions. The form of the treatment function $\eta_1(t)$ produces an eventual complete inhibition of infection of CD4+ T cells in the plasma but does not do so immediately upon treatment (1-3). The form of the treatment function $\eta_2(t)$ produces a delayed and incomplete suppression of viral influx from the external lymphoid system (18). Treatment does not affect the drug-resistant virus or the CD4+ T cells infected by drug-resistant virus.

When treatment begins, it is assumed that the source term of CD4+ T cells in equation (A.4) has the value $S_0(t) = \text{minimum}\{ S_0, S_1 - S_2 V(t)/(B_s + V(t)) \}$, where S_0 is the value of the source of CD4+ T cells when treatment is started (S_0 is obtained from the source function $S(t)$ in the model without treatment). This assumption means that the source of CD4+ T cells does not increase once treatment begins but may decrease if the virus population later increases because of the development of resistance or the cessation of treatment.

In the model, it is assumed that there is no significant level of background resistant virus present to substantially affect the dynamics before treatment begins. After treatment begins, drug-resistant virus does become significant and is introduced into the virus population as a proportion q of the drug-sensitive virus population (19). It is not assumed that drug administration induces resistant mutations, but only that it gives selective advantage to them. The value of q corresponds to the capacity of resistant variants to mutate (larger q corresponds to monotherapy and smaller q to combined therapy). It is assumed that the external input of drug-resistant virus from the lymphoid compartment is controlled by the threshold function $G_r(V)$, where $G_r(V) = 0$ if V is less than the threshold value V_0 and $G_r(V) = G_s$ if V is greater than V_0 . This assumption means that the capacity of the resistant virus to become established requires that the total virus population level remain above the threshold V_0 .

The lack of correlation of the slopes in Figure 2b to starting CD4+ T-cell counts in Figure 2a can be explained in terms of equation (A.7). When treatment starts at time t_0 , $G_s/(B+V(t_0)) \approx k_v T(t_0)$ (since the virus population is changing very slowly before treatment starts and the major source of virus present is due to the external source). After treatment starts, $dV_s(t)/dt \approx r(t)V_s(t)$, where $r(t) = c_2(t) G_s/(B+V(t)) - k_v T(t)$. If $c_2(t) \approx 1$ (which corresponds to slow clearance of the external compartment), then $r(t) \approx 0$ and $r(t)$ does not have a strong dependence on $T(t_0)$ (as in Figure 2b). If $c_2(t) \approx 0$ (which corresponds to rapid clearance of the external lymphoid compartment), then $r(t) \approx -k_v T(t)$ and thus shows a strong dependence on $T(t_0)$ (as in Figure 4b). A similar argument using equation (A.4) shows that when $c_1(t) \approx 0$ (as in Figures 2a and 4a), then the exponential rates of increase in CD4+ T-cell counts are inversely correlated to treatment CD4+ T-cell starting values.

The models described in this paper have evolved from earlier models by the authors (24,26-28). A major goal of the present work is to align the model simulations with an expanding base of data for HIV dynamics. The construction of the present models is based in part on theoretical assumptions about the rate changes of the interacting populations and in part on simulation of their known dynamic properties. Another major goal of the present work is to derive insight into the qualitative distinctions between monotherapy resistance and combined-therapy remission. In the model (A.4)-(A.8), this distinction resides in the mutation parameter q , which corresponds to the capacity of resistant virus to arise as a proportion of sensitive virus when the total virus population is above the threshold value V_0 . When q is large (monotherapy), the total virus population does not fall below V_0 , and resistant virus becomes established. When q is small (combined therapy) and the total virus population is brought below V_0 sufficiently fast in the first days and weeks of treatment, the resistant virus population cannot grow.

The models of this paper differ from earlier models (1-3). The models here describe disease progression, whereas others (1-3) describe short intervals of treatment from presumed dynamic

steady states. The models here describe dynamics in the plasma, whereas others (1,3) describe dynamics in the total body. The models of this paper distinguish between the behavior of virus in the plasma and in the lymph system. In the models here, the virus increases steeply in the plasma but saturates in the lymph system. The assumption of a large saturating external source of virus to the plasma is required in this model for the simulation of data.

The models of this paper also assume that the viral clearance rate depends on the CD4+ T-cell level, whereas other models (1-3) assume that this rate is constant. This last assumption is required in our models to obtain the dynamics of disease progression. This assumption is reasonable in understanding how the virus population can increase steeply in the plasma as the CD4+ T-cell population in the plasma collapses. If the viral clearance rate in the plasma is independent of CD4+ T-cell levels, the steep increase of plasma virus (as much as 100-fold) at disease end would have to result from increased production. But the CD4+ T-cell population in the plasma collapses to near 0 so that this population cannot account for the high viral increase. In the models here, this steep increase of plasma virus results from the collapse of the immune response (which means that the plasma viral clearance rate should depend on CD4+ T-cell levels) and from a continuing influx of virus from the saturated external lymph source.

We provide a list of parameter values for the models with and without treatment (Table).

Table. Parameter values for the models

Parameters and Constants	Values
μ_T = mortality rate of uninfected CD4+ T cells	0.005/day
μ_{Ti} = mortality rate of infected CD4 + T cells	0.25/day
k_s = rate CD4+ T cells are infected by sensitive virus	0.0005 mm ³ /day
k_r = rate CD4+ T cells are infected by resistant virus	0.0005 mm ³ /day
k_v = rate of virus loss due to the immune response	0.0062 mm ³ /day
p_1 = production rate of uninfected CD4+ T cells	0.025/day
p_2 = production rate of infected CD4+ T cells	0.25/day
p_3 = production rate of virus in the blood	0.8/day
G_s = external lymphoid sensitive virus source constant	41.2/mm ³ day
G_r = external lymphoid resistant virus source constant	specified in text
V_0 = threshold value for remission	specified in figure legends
q = proportion of drug-resistant virus produced from wild type virus	specified in figure legends
C = half saturation constant of uninfected CD4+ T cells	47.0/mm ³
C_i = half saturation constant of infected CD4+ T cells	47.0/mm ³
B = half saturation constant of external virus input	2.0/mm ³
B_s = half saturation constant of CD4+ T-cell source	13.8/mm ³
S_1 = source of CD4+ T cells in absence of the disease	4.0/mm ³ day
S_2 = reduction constant of CD4+ T-cell source	2.8/mm ³ day
c_1 = treatment parameter for suppression of the rate of CD4+ T-cell	specified in figure legends

infection by virus

c_2 = treatment parameter for suppression of the rate of virus contributed by the external lymphoid compartment	specified in figure legends
c_3 = treatment parameter for maximal suppression of virus contributed by the external lymphoid compartment	specified in figure legends
η_1 = treatment function for inhibition of the rate at which virus infects uninfected CD4+ T cells	specified in text
η_2 = treatment function for inhibition of the rate of virus influx from the external lymphoid system virus	specified in text

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