Population dynamics of HIV within an individual after treatment with zidovudine

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A new mechanism is proposed for the apparent breakthrough of HIV that occurs approximately 6 months after the commencement of therapy with zidovudine (AZT). Using a simple mathematical model of the interacting population dynamics of HIV and its major host cell in the circulation (the CD4+ lymphocyte), predicted patterns of HIV plasma viraemia in the weeks following treatment with zidovudine are generated. These are in close agreement with observed patterns despite the fact that the model contains no mechanisms for the development of drug-resistant strains of virus. It is suggested that the patterns of viral abundance observed during the first 6 months after treatment may be the result of non-linearities in the interactions between HIV and CD4+ cells, and that it is only after the first post-treatment burst of viral production that drug resistance plays an important role.

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Introduction

Treatment of AIDS patients with 3′-azido-2′, 3′-dideoxythymidine (zidovudine, AZT) leads to significant short-term reduction in disease progression and in the amount of HIV in plasma. However, 6–12 months after the initiation of therapy the levels of plasma HIV rise again [1–3]. Two mechanisms have been proposed for this apparent breakthrough of HIV: the development of drug resistance, and the existence of 'zidovudine-proof' sanctuaries [4,5]. We propose a third mechanism that should be taken into account in any discussion of the long-term effect of zidovudine, namely, that the observed patterns of viral abundance simply reflect the natural dynamics of a parasite (HIV) after chemotherapeutic protection of its host (CD4+ cells). We present a simple mathematical model of the population dynamics of CD4+ cells (the main reservoir of HIV in the circulation [6]) and HIV, which we use to investigate the likely impact of zidovudine therapy upon patients with AIDS-related complex (ARC) and AIDS [7]. We are able to show that observed patterns of CD4+ cell counts and viral abundance can be explained without recourse to any mechanism of drug resistance or viral sanctuary. We do not wish to suggest that zidovudine-resistant strains of HIV play no role in the long-term outcome of treatment with zidovudine. Rather, our aim is to show that by considering host–parasite population dynamics subsequent to zidovudine therapy, a number of apparently contradictory experimental results can be explained.

Model

Our method has been to develop a simple mathematical model with which to investigate the post-treatment dynamics of HIV within an individual. Data on temporal patterns of HIV dynamics are available on two time scales. On the time scale of years, progression of disease manifests as a slow decline in the number of CD4+ cells over many years [8]. This is accompanied by a rise in titres of infectious HIV in plasma and peripheral blood mononuclear cells [9]. Data on post-treatment dynamics are available over time scales of months and show that, following the initiation of zidovudine therapy, the load of cell-free virus drops rapidly, but after a few months, levels of virus start to rise again [1,3,9].

We are interested in the course of events over time scales of about 6 months, so we use an equilibrium model in which, in the absence of drug treatment, population sizes

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are constant. In so doing we avoid making assumptions about the cause of disease progression, although, as discussed below, disease progression could be included in the model in a number of different ways.

Our model consists of four ordinary differential equations describing the dynamics of uninfected CD4+ cells (R), latently infected cells (L; i.e. cells that are infected but are not producing any free virus), actively infected cells (E; which are producing virus), and cell-free virus (V). Uninfected cells arise at a rate that decreases with a growing burden of free virus and either live out their natural lifespan, which is of length $1/\mu$, or are infected at per capita rate βV.

$$\frac{dR}{dt} = \frac{\Gamma}{(1 + \kappa V)} - \mu R - \beta RV \qquad (1)$$

On infection, cells either develop a latent infection or immediately enter a phase of active production of virus. Latently infected cells have the same mean lifespan $1/\mu$ as uninfected cells, but can be transformed into actively infected cells at rate α. This would presumably be by the effect of immune activation, a phenomenon that has been extensively studied in other models [10,11].

$$\frac{dL}{dt} = p\beta RV - (\mu + \alpha)L \qquad (2)$$

Actively infected cells arise either as new infections or from the activation of latently infected cells. They have a lifespan of $1/\delta$ which is shorter than that of uninfected cells.

$$\frac{dE}{dt} = (1 - p)\beta RV + \alpha L - \delta E \qquad (3)$$

Actively infected cells are the source of free virus in the circulation which is cleared at per virion rate $1/\sigma$.

$$\frac{dV}{dt} = \pi E - \sigma V \qquad (4)$$

Figure 1 gives a schematic representation of the model; Table 1 summarizes the biological interpretations of the model's parameters, the values used in the numerical simulations, and the interpretations of those numerical values. Currently available data only allow us to assign rough ranges to the parameter values in the model. However, we do have estimates of the sizes of the four model populations in uninfected individuals and at various stages of disease progression [6,9]. These 'fixed points' reduce the number of degrees of freedom available when assigning values to the model's parameters.

There is a number of different mathematical models of the progression from HIV infection to AIDS. Some are based on the idea that disease progression is driven by the indirect effect of other infections which cause activation and subsequent killing of CD4+ cells [10,11]. Another theory is that the long incubation period is caused by long-term latency in infected cells [12], and a third is that disease progression is driven by increasing diversity of HIV [13]. In our model, progression to disease could be included as any one of such processes. Increased activation of latently infected cells through an increasing burden of opportunistic infections could be modelled as a mechanism that acts to increase α. The evolution of more virulent strains could be represented by decreasing p or increasing β or δ. A failing immune response to free virus could be modelled as a mechanism acting to decrease σ. By abdicating the responsibility of modelling disease progression, we gain a more generic result. The results that follow will hold true for any model where circulating CD4+ cells are the major source of circulating cell free virus.

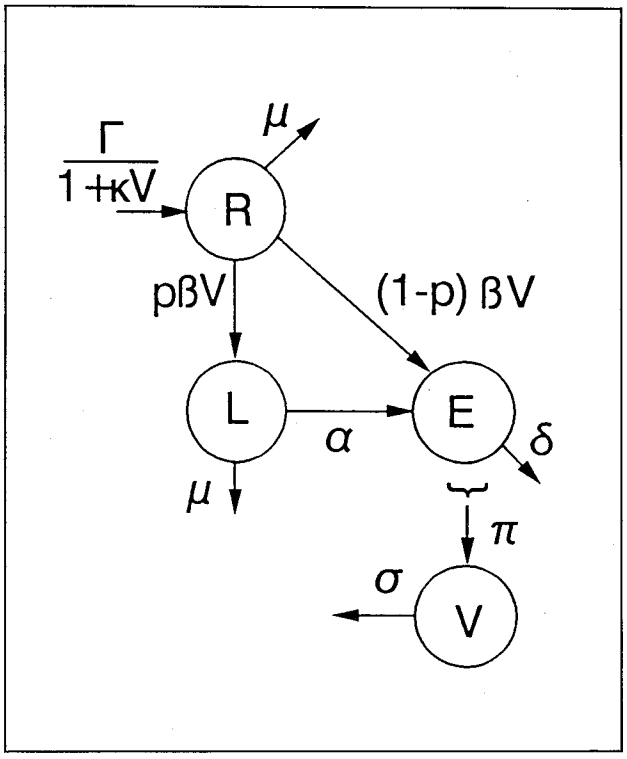

Fig. 1. Schematic representation of the model. Uninfected CD4+ cells (R) arise at a rate $[\Gamma/(1 + \kappa V)]$ that falls with growing viral burden (V) [16]. These cells have natural lifespan $1/\mu$, and are infected by free virus (V) at per capita rate βV. Upon infection, a proportion p enter the latently infected state (L), where they remain subject to the same death rate, μ, as their uninfected equivalents. From the latent state they are stimulated to productive infection (E) at per capita rate α. The remaining proportion $(1 - p)$ of newly infected CD4+ cells enter productive infection (E) directly. Productively infected cells live for time $1/\delta$ during which they produce π virions (V) per unit time. Free virus (V) has an average lifetime $1/\sigma$ in the circulation before being destroyed.

Results and interpretation

Numerical simulation of these equations (using a fourth-order Runge-Kutta algorithm and a step length of 100

Table 1. Biological interpretation and numerical values of model parameters.

Symbol	Biological interpretation	Value in simulations (per week)	Interpretation of numerical value
μ	Background death rate of uninfected CD4+ cells	0.04	Average lifespan of a CD4+ cell in the absence of HIV is 25 weeks
Γ	Immigration rate of CD4+ cells	2×10^8	Population of CD4+ cells in circulation of an uninfected individual approximately 1×10^9/l
δ	Death rate of actively infected CD4+ cells	16	A CD4+ cell which is expressing virus lives, on average, for approximately half a day
π	Rate of production of virions by an actively infected cell	300	An actively infected cell produces 300 virions per week
p	Proportion of newly infected CD4+ cells which become latently infected	Range 0.9–0.1	Initially almost all infected cells enter a latent infection, but as disease progresses more and more cells are activated at the time they are infected and immediately have a productive infection
α	Stimulation rate of latently infected cells	Range 0.0001–0.2	Initially a CD4+ cell has a 1 in 25 chance of being activated and producing virus during its natural lifespan, chronic activation in AIDS raises this likelihood to 50 to 1
$\varkappa$	Rate of destruction of precursors to CD4+ cells in the bone marrow	4.31×10^{-6}	An AIDS patient with approximately 8×10^5 virions will have the rate of influx of healthy CD4+ cells reduced by a factor of 4
β	Infectivity of cell-free HIV	2.05×10^{-9}	The relative sizes of δ, $\varkappa$ and β determine the proportion of CD4+ depletion, that is from the killing of circulating cells or from the diminution of the rate of influx of new cells; here an intermediate set of values is used, representing the assumption that both modes of depletion are important
σ	Removal rate of cell-free HIV from circulation	3.75	A virion will spend an average of approximately 2 days in the circulation before being removed

steps per week) yields the solutions depicted in Figs 2 and 3.

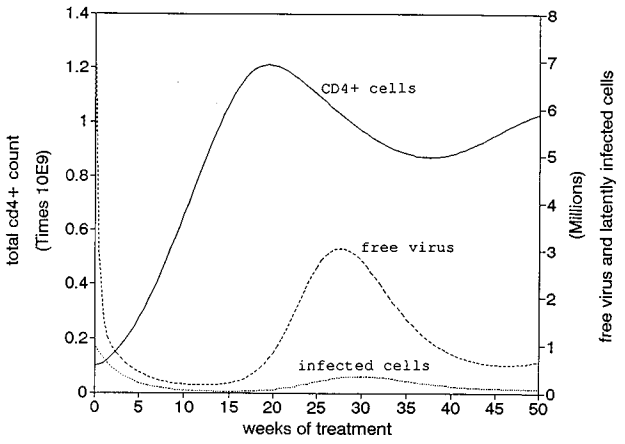

Fig. 2. Post-treatment dynamics of uninfected cells, latently infected cells, and cell-free virus. Introduction of zidovudine therapy is modelled by reducing the infectivity parameter β by amount $(1 - z)$, where z measures the efficacy of zidovudine at blocking new infections. Here, the impact of zidovudine at 90% efficacy is simulated over the course of 50 weeks post-treatment. ——, CD4+ count; - - - -, cell-free virus; ·····, latently-infected cells. There is no change in parameter values over the 50 weeks; the downturn in CD4+ count and upsurge in free virus at 15 weeks are simply manifestations of the natural dynamics of this system. Parameter values as in Table 1, with $\alpha = 0.288$ and $p = 0.2$.

We wish to draw attention to a number of features of Fig. 2. Levels of plasma viraemia fall very rapidly after the commencement of zidovudine therapy, whilst the number of latently infected cells falls much more slowly. This is in agreement with published observations [9]. More importantly, after a period of improvement, with rising CD4+ counts and falling viral titres, there is spontaneous reversal at time 15–20 weeks. CD4+ counts fall and levels of free virus start to rise again. This is a natural consequence of the interacting dynamics of HIV and CD4+ cells. Expressed verbally, the pattern is generated in the following way. Zidovudine is introduced into an environment where there are relatively few CD4+ cells. The combined effects of low CD4+ count and blocking of new infections by zidovudine cause the precipitous drop in the amount of free virus (and the somewhat slower drop in the number of latently infected cells). With virus at very low levels, CD4+ counts increase rapidly until they reach a level great enough to stimulate the production of large amounts of cell-free virus. This causes the burst of viral production at about 25 weeks. There then follows a period of damped oscillations until HIV and CD4+ cells settle to their new, post-treatment equilibrium. There is no need to invoke the emergence of zidovudine-resistant viral strains to derive the shape of curves in Fig. 2, nor do we need to use arguments about the progression of disease; in Fig. 2, all parameters are fixed throughout the simulation.

Figure 3 shows comparisons between numerical simulations and data. In both parts of this figure, we assume that zidovudine is administered against a background of unchanging CD4+ counts. The different values of parameters α and p in Fig. 3a and 3b were chosen so that the pretreatment population sizes of the four model compart-

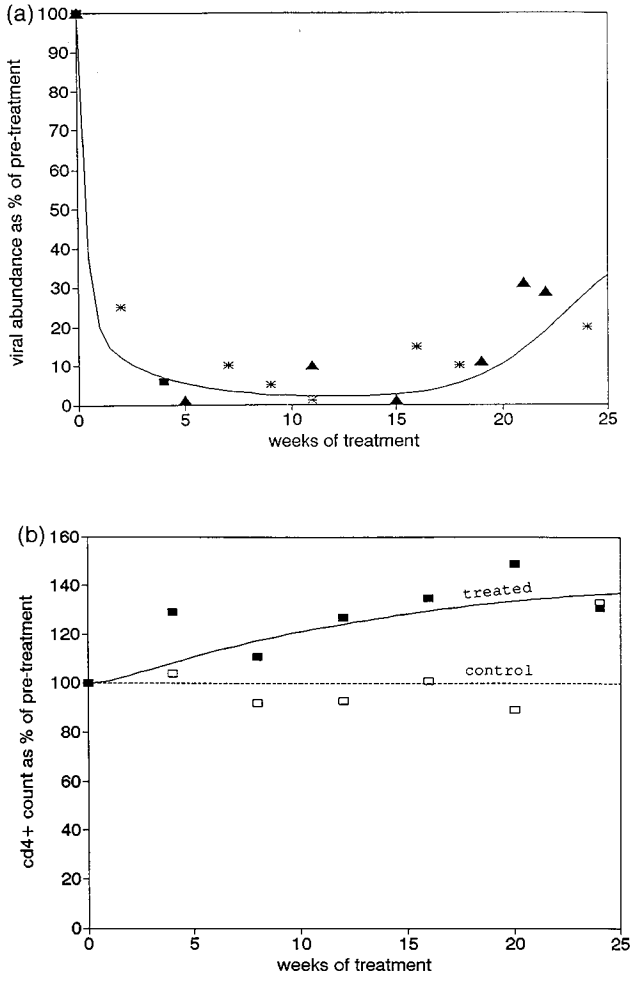

Fig. 3. Model projections compared with data. Throughout, lines are model projections and points are data. (a) Free virus as a percentage of pretreatment level; ■, end-point dilution assay (the two points are from means across seven patients [9]); ★ and ▲, p24 antigen levels (data are from two individuals [1]); -, model projections using the same parameter values as in Fig. 2 (these parameter values yield starting population levels representative of an AIDS patient, and the data are from AIDS patients). (b) CD4+ counts with (—— and ■) and without (- - - - and □) zidovudine in AIDS-related complex (ARC). These data are from patients with ARC in a placebo-controlled trial [17] and represent means across 9–61 patients. Parameter values are as in Table 1, with $\alpha = 0.001$, $p = 0.925$ and $z = 0.3$; these yield a pretreatment CD4+ count of 0.2×10^9/l, a level consistent with those of approximately 200×10^6/l at the start of the study.

ments were representative of those in AIDS and ARC patients, respectively. Although we have been able to place some constraints on the estimated values of the model's parameters, there are still broad possible ranges for each parameter. The numerical results shown are based on a small subset of parameter values from within these ranges. We could have chosen equally plausible parameter values where the resurgence of virus did not occur for several years, or, indeed, where the effect of zidovudine was great enough to eliminate HIV infection. We will present a detailed discussion of the model's sensitivity to parameter variation and the criteria for disease elimination elsewhere (McLean *et al.*, manuscript in preparation). However, the essential point that we wish to make is independent of these difficult considerations about parameter values. In any host–parasite system there is a general propensity for a perturbation (such as zidovudine treatment) to produce an oscillatory rather than a smooth approach to the new steady state.

Discussion

Using this simple model of host–parasite population dynamics, we are able to generate patterns of viral abundance and CD4+ cell counts very similar to those which have been observed in people with ARC and AIDS treated with zidovudine. Because of non-linearities in the interactions between HIV and CD4+ cells, the shift from pretreatment to post-treatment equilibria can be oscillatory. This result is not specific to zidovudine, and the model is appropriate to other antiviral drugs such as 2′, 3′-dideoxyinosine (ddI) [14]. We propose that the observed 'breakthrough of HIV' is the first of these oscillations, and that it is *after* the post-treatment burst of viral production that zidovudine-resistant strains become significant. This would help to explain why isolates from patients treated for less than 6 months do not show any differences in sensitivity to zidovudine [5] whilst re-emergence of virus is already apparent at 6 months [1]. It could also shed light on the *in vitro* result that breakthrough virus in zidovudine-treated culture does not appear to be resistant to zidovudine [15]. If the post-treatment re-emergence of virus is driven by simple dynamics, it would be easier to understand why the appearance of resistant strains does not appear to be associated with deterioration in clinical status [5]. Indeed, we suggest that zidovudine-resistant mutants do not cause the post-treatment resurgence but that their emergence may be driven by this burst of viral production under the selective pressure of drug treatment. This possibility generates interesting questions about the interplay of cell and virus population dynamics and the evolution of resistant viral strains that we are currently investigating.

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