Competition between zidovudine-sensitive and zidovudine-resistant strains of HIV

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Objective: To investigate competitive interactions between zidovudine-sensitive and resistant strains of HIV within the context of host–parasite population dynamic interactions between CD4+ cells and HIV.

Design: A mathematical model of the population dynamics of CD4+ cells, sensitive HIV and resistant HIV is developed.

Methods: The model is analysed numerically and analytically and model predictions are compared with previously published data on population dynamics of HIV and CD4+ cells in patients receiving zidovudine. A threshold result describing the critical dose of zidovudine above which resistant HIV will out-compete sensitive HIV is derived, as are expressions describing the critical effective doses for the eradication of sensitive and resistant strains. Numerical simulations of the dynamics of the shift from the pre-treatment, equilibrium to the treatment equilibrium are presented and an analytic expression approximating the time taken until virus growth restarts is derived.

Results: It is shown that competition between strains of virus is the important factor determining which type of virus will eventually start to grow during the course of zidovudine treatment, but host–parasite interactions are the important determinant of when viral resurgence occurs.

Conclusions: Although resistant strains are observed after prolonged treatment with zidovudine, this model suggests that it is the growing supply of uninfected CD4+ cells which causes the eventual upsurge in viral burden.

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Keywords: Zidovudine, mathematical model, population dynamics, drug resistance.

Introduction

Zidovudine is the only drug currently in widespread use for the antiretroviral treatment of HIV-infected individuals [1,2]. It is assumed that it acts by blocking reverse transcription [3], thus preventing the infection of new cells. Zidovudine works very well in the short-term, with patients experiencing a rise in CD4+ cell count and a fall in the amount of circulating virus, as well as improvements in immune responses and weight gain [2,4]. The success of the drug in preventing short-term mortality led to the early termination of the placebo-controlled clinical trial on ethical grounds [2]. However, these improvements are short-lived, and after about 6 months of treatment CD4+ cell counts begin to fall again, whilst viral titres begin to rise [5–11].

The question of why the benefits of zidovudine are short-lived is of great interest. The isolation of zidovudine-resistant strains of HIV from patients who have been on zidovudine therapy for more than 6 months provides part of the answer [12,13], and it has been suggested that it simply takes 6 months for such resistance to develop. An alternative hypothesis is that population dynamic interactions between CD4+ cells and HIV are responsible for the observed delay in the resurgence of virus. In an earlier paper [4] we showed that patterns of viral abundance observed during the first 6 months of treatment with zidovudine could be the result of non-linearities in the interactions between HIV and CD4+ cells. In that study we assumed that all strains of HIV were equally sensitive to zidovudine.

Our aim here is to present a model of interactions between CD4+ cells and two types of HIV, zidovudine-sensitive and zidovudine-resistant. This model allows us to investigate two quite different types of interaction. On the one hand, competition between different strains of HIV, and how the balance of that com-

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petition is altered by treatment with zidovudine can be studied; on the other host–parasite interactions between CD4+ cells and HIV. The model mimics observed behaviour in that it shows a period of very low viral burden with increasing CD4+ cell count, followed by a resurgence of virus and downturn in CD4+ count. We are able to show that competition between strains is the important factor determining what type of virus recurs (drug-sensitive or drug-resistant), whilst host–parasite population dynamic interactions are the important determinant of when that recurrence takes place. We are also able to explain the observed dichotomy in time to emergence of resistant strains between patients with AIDS-related complex (ARC) and those with AIDS, as well as that between patients on high and low doses of zidovudine.

We begin with a review of the relevant data in this field. There follows a presentation of the model and a discussion of its parameters. Results are divided into two parts, dealing first with competition between virus strains and then with host–parasite interactions between CD4+ cells and HIV. We end with a discussion of the relevance of our results.

Data review

We review two types of data: (1) time-series showing population dynamics of CD4+ cells and HIV in the months after initiation of zidovudine treatment; and (2) studies of differences in outcome between AIDS and ARC patients and between patients on high and low doses of zidovudine. Figure 1 reviews the available population dynamics data. These data are highly variable, consistent with the observed variability between individuals in many aspects of HIV infection. Despite great variability it is possible to detect overall patterns in the data. CD4+ cell counts rise and then fall, whilst p24 antigen first falls and then rises.

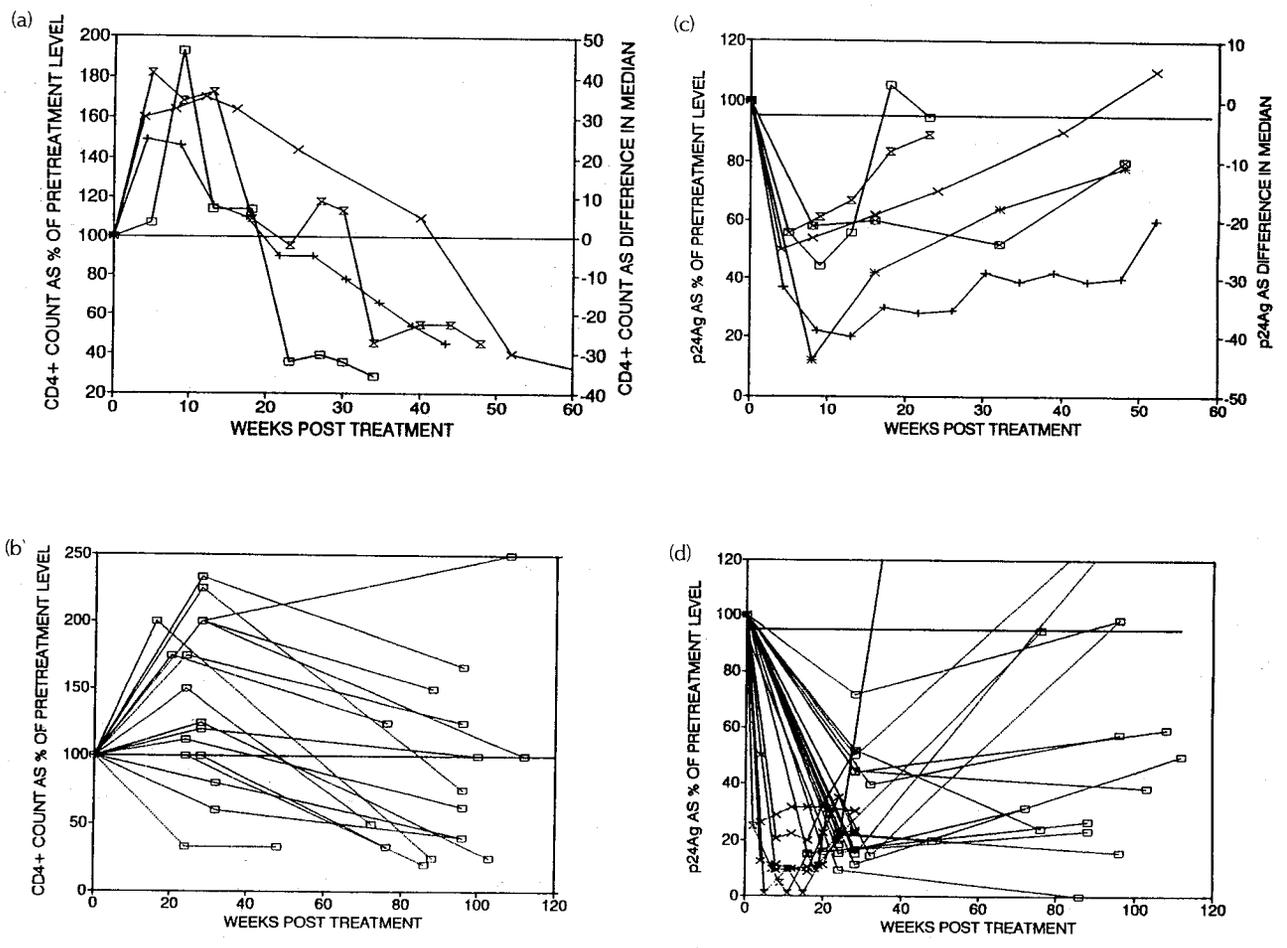

Fig. 1. Review of time-series data on CD4+ counts (a and b) and HIV p24 antigenaemia (c and d) during the first months of zidovudine therapy. Despite great variability it is possible to detect overall patterns in the data. CD4+ counts rise then fall, whilst p24 antigen falls and then rises. (a) and (c) are data averaged across individuals whilst (b) and (d) show data from individuals. Data types and sources are as follows: (a) Data are percentage change in mean CD4+ count (⧖, □and +) or change in median CD4+ count (× and *). Data are from: ⧖ and □, [9]; +, [5]; ×, [11]. (b) Data are from [10]. (c) Data are percentage change in mean p24 antigen level (⧖, □, and +) or change in median CD4+ count (×). Data are from: ⧖ and □, [9]; +, [5]; ×, [11]; ■ and *, [6]. (d) Data are from: ⧖, [17]; □, [10] and ×, [7].

Data on the genetic make-up of the recurring virus are currently rather sparse. Boucher *et al.* [10] found that, after 2 years of treatment, 16 out of 17 compliant patients had a viral burden that was mostly mutant at residue 215 of reverse transcriptase (a mutation that confers reduced sensitivity to zidovudine). However, at 6 months the mutation was detected in virus from only seven of the 17 individuals. Another study of mutations at the same site in the genome [15] investigated prevalence of mutant strains within the same individual. The study showed that, after 19 months of treatment, about 75% of strains had the resistance-bearing mutation at residue 215, whereas no clone had had it prior to treatment.

In Figure 2 the rate of emergence of resistant virus in patients on high and low doses of zidovudine, and in AIDS patients versus ARC patients are compared. This demonstrates that the proportion of viral isolates of the resistant type grows faster in AIDS patients and in patients on higher doses of zidovudine [10].

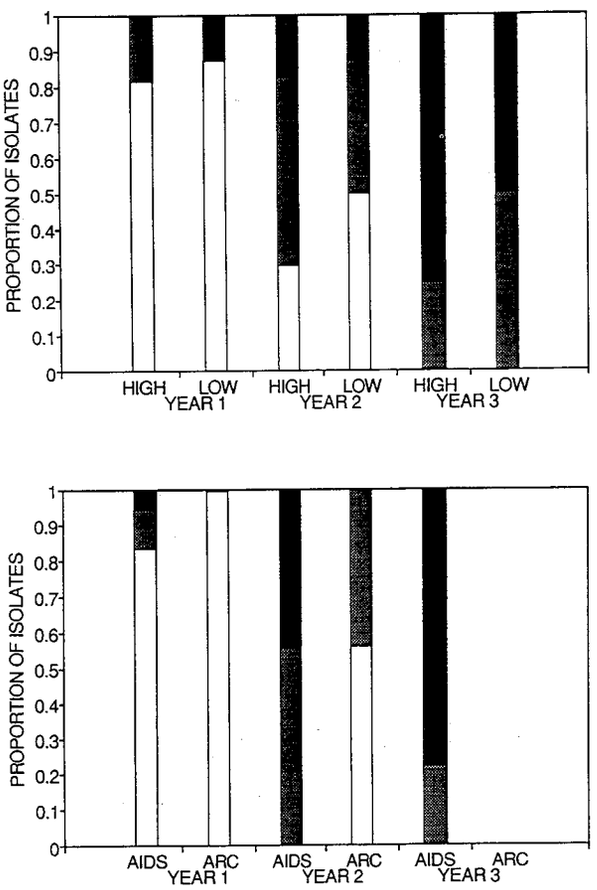

Fig. 2. Dichotomies in the rate of detection of zidovudine-resistant strains of HIV. (a), zidovudine-resistant strains of HIV may evolve more rapidly in patients on high doses than in patients on low doses; (b), zidovudine-resistant strains of HIV may evolve more rapidly in AIDS patients than in AIDS-related complex patients. □, sensitive; ▣, mixed; ■, resistant. Data are from [18].

Model

The model counts three populations: uninfected CD4+ cells (X), CD4+ cells infected with virus sensitive to zidovudine (L_S) and CD4+ cells infected with virus partly resistant to zidovudine (L_R). Uninfected CD4+ cells migrate from the thymus at constant rate Λ and have per capita death rate μ. The non-linearities in the model lie in the infection rate, where it is assumed that new infections arise at a rate proportional to the product of the number of uninfected cells and the number of infected cells. These assumptions give an equation for uninfected cell dynamics as follows:

$$\frac{dX}{dt} = \Lambda - \mu X - X(\beta_S L_S + \beta_R L_R)$$

Where β_S and β_R are the infectivity parameters of sensitive and resistant virus.

In the absence of zidovudine, sensitive strains are assumed to have a fitness advantage over resistant, thus $\beta_S > \beta_R$. This assumption is supported by the observation that untreated patients always have mostly sensitive strains, whilst resistant strains appear in large quantities only after some time of treatment. We assume that there are errors in replication, so that a proportion Q of infections are faithful (producing progeny of the parent type) whilst the remainder result in mutation to the opposite type. Many mutations will be lethal, but the size of the infectivity parameters, β_S and β_R, take this into account. With infected cells removed (because they are killed by the virus or by immune responses) at per capita rate α equations for infected cells are:

$$\frac{dL_S}{dt} = Q\beta_S L_S X + (1-Q)\beta_R L_R X - \alpha L_S$$

$$\frac{dL_R}{dt} = (1-Q)\beta_S L_S X + Q\beta_R L_R X - \alpha L_R$$

We model treatment with zidovudine by reducing the infectivity parameters, β_S and β_R, reflecting the assumption that zidovudine acts by blocking new infections. For a dose of zidovudine that blocks 80% of new infections by sensitive virus, we reduce β_S to 20% of its present value. This was done by introducing a parameter z, which represents the effective dose of zidovudine. The value taken by z ranges from 0 (representing no treatment) to 1 (representing complete blocking of all reverse transcription in sensitive strains). z is therefore the probability that a new infection with a sensitive strain will be blocked. The relationship between z, the effective dose, and the actual dose administered is presumably a saturation function, rising linearly at

very low doses and levelling off at high doses. To include treatment we multiply β_S by $(1\text{-}z)$, and, assuming that resistant virus is less affected by zidovudine than sensitive, we multiply β_R by $(1\text{-}pz)$ where p is the relative efficacy of zidovudine at blocking new infections with resistant virus. pz is therefore the probability that a new infection with resistant strain will be blocked. A dose of zidovudine that blocks 90% of new infections with sensitive virus and 30% of new infections with resistant virus is modelled by setting $z = 0.9$ and $p =$ one-third.

A schematic diagram of this model is presented in Fig. 3 and a summary of parameters, parameter value and interpretations in Table 1.

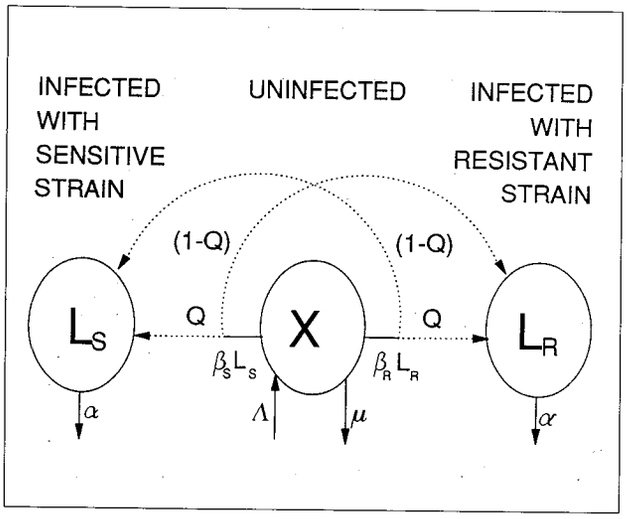

Fig. 3. Schematic representation of the model. Uninfected CD4+ cells (X) immigrate from the bone marrow at rate Λ and if they remain uninfected have average lifespan $1/\mu$. They become infected at per capita rate proportional to the amount of sensitive virus (L_S) and resistant virus (L_R) present, with constants of proportionality β_S and β_R, respectively. A fraction of Q of infections give rise to progeny of the parent type whilst the remainder mutate to the opposite type. Infected cells have average lifespan $1/\alpha$.

Results

The behaviour of this model is best understood by separately considering the two issues of competition between the strains of virus and host–parasite interactions between infected and uninfected cells. This division neatly coincides with separate consideration of the long-term, equilibrium behaviour of the model and its shorter-term, dynamic behaviour.

Competition between virus strains is best considered in terms of reproductive fitness, which can be characterized by a single parameter, the basic reproductive rate. For sensitive strains, this is defined as the number of new cells infected with sensitive virus that would arise as a direct result of introducing one cell infected with sensitive virus into an uninfected person if that person already had an immune response to HIV. (Thus, density dependent effects would be absent, but the death rate of infected cells, α, would be the same as in a person with a fully developed anti-HIV immune response.) Prior to infection, there are Λ/μ uninfected cells, and a cell infected with sensitive virus will infect β_S of them per unit time. A fraction Q of those infections will give rise to new cells infected with sensitive virus. Finally, an infected cell is cleared after time $1/\alpha$. Putting these together yields:

$$R_{0S} = \frac{\Lambda\beta_S Q}{\mu\alpha}$$

In the same way the basic reproductive rate for resistant virus is:

$$R_{0R} = \frac{\Lambda\beta_R Q}{\mu\alpha}$$

In the absence of any treatment we assumed that the fitness advantage lies with sensitive strains, so $R_{0S} > R_{0R}$, sensitive virus out-competes resistant and the resistant strains are only maintained by mutation. However, zidovudine has more effect on sensitive strains than it does on resistant strains, so treatment acts to shift the balance of competition in favour of resistant strains. This biological assumption appears in the model through the way in which the basic reproductive rates are altered by treatment. Under an effective dose of zidovudine z the basic reproductive rate for sensitive strain becomes $(1\text{-}z)R_{0S}$ and the basic reproductive rate for resistant strain becomes $(1\text{-}pz)R_{0R}$. Thus, although $R_{0S} > R_{0R}$ in the absence of treatment, there is an effective dose above which resistant strains gain the selective advantage and the roles are reversed; resistant strains out-compete sensitive, and sensitive strains are only maintained by mutation. We designate the level of treatment at which this cross-over occurs z^*. Clearly z^* satisfies the following:

$$(1\text{-}z^*)R_{0S} = (1\text{-}pz^*)R_{0R}$$

The crossover from dominance of sensitive strains at effective doses below z^* to dominance of resistant strains above z^* is very sharp. The sharpness of the transition depends on the value of Q, that is, the proportion of viral offspring that are faithful copies of the parent. This is illustrated in Fig. 4, and a description of how the equilibrium population levels are calculated is given in the legend.

A simple relationship between the size of the basic reproductive rate for sensitive strains and the CD4+ count in an untreated individual provides a useful method for estimating the size of R_{0S}. It is trivial to

Table 1.

Parameter	Biological meaning	Value	Interpretation of value
Λ	Immigration rate of CD4+ cells from the bone marrow	2×10^8	The total CD4+ count of an uninfected individual is 5×10^9, i.e., 1000 cells/μl
μ	Death rate of uninfected CD4+ cells	0.04	Uninfected cells live for about 6 m
β_S	Infectivity parameter for sensitive strains	7.2×10^{-8}	Given other parameter values this choice of β_S represents the the assumption that AIDS patients have a CD4+ count of 100 cells/μl
β_R	Infectivity parameter for resistant strains	2.4×10^{-8}	In the absence of zidovudine, resistant strains have one-third of the reproductive potential of sensitive strains
Q	Probability that a new infection is of the same type as the infecting strain	0.9995	The probability of mutating in either direction between sensitive and resistant strains is 1 in 2000
α	Death rate of an infected cell	71.92 (ARC) 35.96 (AIDS)	In ARC patients an infected cell survives for about 2.5 h on average, and in AIDS patients an infected cell survives twice as long
z	Effective dose; i.e., proportion of new infections with sensitive strain that are blocked by a given dose of zidovudine	0–1	An effective dose of 0 represents no blocking of new infections and an effective dose of 1 represents complete blocking of all new infections
p	Effect of zidovudine on resistant strains relative to its effect on sensitive strains	0.33	Zidovudine blocks one-third as many new infections with resitant strains as it does with sensitive strains

ARC, AIDS-related complex; m, months; Λ, rate per week; μ and α, rates per cell per week; β_S and β_R, rates per cell per cell per week; Q, z and p, probabilities.

show that in an uninfected individual the size of the CD4+ cell population (let us call it X_0) is given by $X_0 = \Lambda/\mu$, whilst in an infected but untreated individual the equilibrium size of the uninfected cell population (let us call it X^*) is given by $X^* \simeq \alpha/\beta_S$. From inspection it is easily seen that

$$R_{0S} = \frac{X_0}{X^*}$$

The significance of this relationship is that it allows us to estimate the magnitude of R_{0S} at different stages of disease. An individual with a CD4+ count of 100 cells/μl has about one-tenth as many CD4+ cells as an uninfected individual, so R_{0S} is approximately equal to 10 at that stage of disease. This result is analogous to the result in theoretical epidemiology that the basic reproductive rate for an infectious disease is equal to the reciprocal of the proportion of the population that are susceptible to that infection [16].

The size of the basic reproductive rates provides information about the effective dose at which strains can be eradicated. If the basic reproductive rate for either strain is <1, that strain would be eradicated in the absence of the other, and is only maintained by mutation. If both reproductive rates are <1, HIV is eradicated and the infection is cured. So there are a further two treatment levels that are of interest: the two critical treatment levels for eradication of sensitive and resistant virus. These are signified by z_{CS} and z_{CR}, respectively, and satisfy the following:

$$z_{CS} = 1 - \frac{1}{R_{0S}}$$

$$z_{CR} = \frac{1}{p}\left[1 - \frac{1}{R_{0R}}\right]$$

These two quantities are direct equivalents of the critical vaccination proportion for the eradication of an infectious disease [16]. There are two possibilities for the relative sizes of the three special treatment levels. Either $z^* < z_{CS} < z_{CR}$ or $z_{CR} < z_{CS} < z^*$. Which of these pertains depends on the degree of resistance to zidovudine achieved by the resistant strains. This degree of resistance is measured by parameter p, the effect of a given dose of zidovudine upon resistant strains, relative to the effect of the same dose upon sensitive strains. It is easily shown that there is a critical value of p:

$$p_c = \frac{R_{0S}(R_{0R} - 1)}{R_{0R}(R_{0S} - 1)}$$

For values of p below this threshold $z^* < z_{CS} < z_{CR}$ and above it $z_{CR} < z_{CS} < z^*$. This has the intuitively sensible interpretation that if the resistant strains are 'very resistant' (p small) then they will achieve a competitive advantage over sensitive strains before either is eradicated, whilst if resistant strains are 'not very resistant' (p close to 1) it should be possible to eradicate both strains at levels of treatment below those at which resistant virus is favoured. These notions are illustrated in Figs 5a and c, whilst Figs 5b and d show the predicted equilibrium virus population sizes for given basic reproductive rates and effective drug doses.

These considerations of the sizes of R_{0S} and R_{0R} and the effective dose z help us to understand how drug treatment can shift the balance of competition between the two strains of virus and so determine which strains are dominant in the treatment equilibrium. In order to understand the dynamics of the shift from the pre-treatment to the treatment equilibrium we must consider host–parasite interactions between CD4+ cells and HIV. We use two methods to study popula-

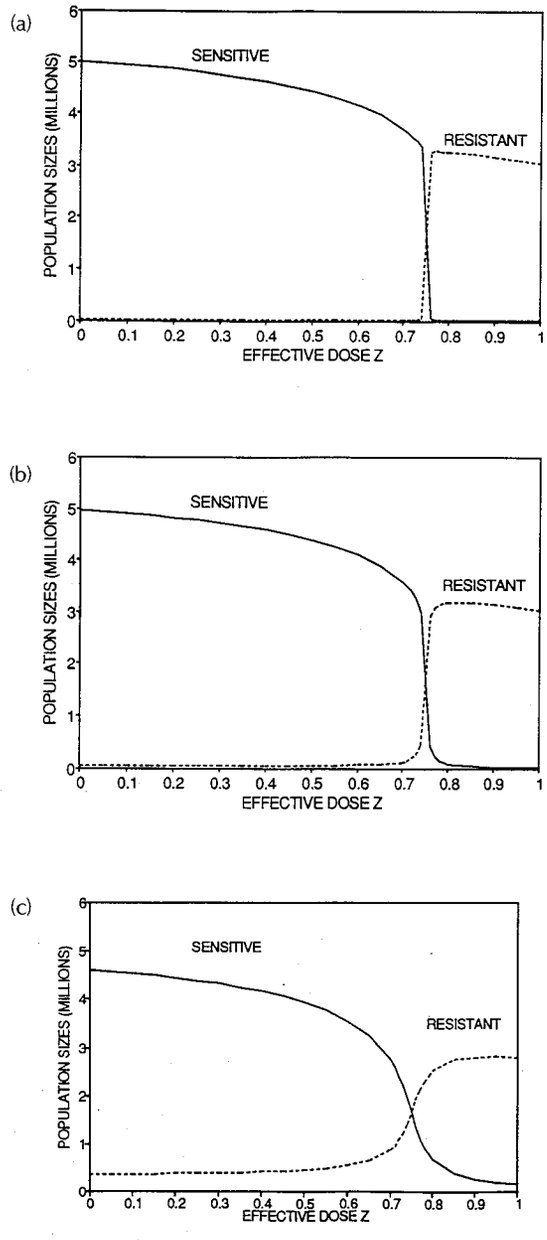

Fig. 4. Equilibrium population sizes of sensitive and resistant virus strains at different effective doses of zidovudine. Parameter values are as given in Table 1, with $\alpha = 35.96$. Sensitive strains predominate at low doses of zidovudine and resistant strains at high doses of zidovudine, and the crossover at z^* is sharp. (With this set of parameters $z^* \simeq 0.75$.) The degree of sharpness of the crossover is determined by the magnitude of the mutation rate (1-Q). The larger the mutation rate, the smoother the crossover population sizes for three different values of Q are shown: (a) $Q = 0.9995$, 1 in 2000 progeny are mutants; (b) $Q = 0.995$, 1 in 200 progeny are mutants; (c) $Q = 0.95$, 1 in 20 progeny are mutants. Equilibrium population sizes are found by finding λ, the largest eigenvalue of the matrix

$$\Phi = \begin{bmatrix} Q\beta_S & (1-Q)\beta_R \\ (1-Q)\beta_S & Q\beta_R \end{bmatrix}$$

and setting the equilibrium size of the uninfected CD4+ cell population equal $X^* = \lambda/\alpha$. Equilibrium infected cell populations L_S^* and L_R^* are set to be the elements of the eigenvector corresponding to the eigenvalue λ, scaled so that $dX/dt = 0$ is satisfied.

tion dynamic interactions between uninfected and infected cells. Numerical simulations of changing population size give us a detailed view of the course of events during the shift from the pre-treatment to the treatment equilibrium for a particular set of parameter values. For a broader view of the overall pattern we develop an expression that approximates the time that will pass before virus growth restarts after treatment has been introduced.

Figure 6 shows two simulations of the shift from the pre-treatment to the treatment equilibrium. In both simulations the pattern is the same. After treatment starts, the viral burden falls rapidly and stays low for some time, during which the CD4+ count slowly recovers. After an interval, there is a burst of viral production and the CD4+ count falls. With increasing effective dose z the time taken to resurgence of virus lengthens, and we move from a domain where resurgent virus is zidovudine-sensitive (Fig. 6a) to a domain where resurgent virus is zidovudine-resistant (Fig. 6b). The pattern is the same, however, whether it is sensitive or resistant virus that is resurgent. This is because that pattern is a natural consequence of the interacting dynamics of infected and uninfected cells and is therefore independent of which type of virus has the fitness advantage. The viral burden falls to very low levels immediately after treatment. This is because the combination of a relatively low CD4+ count and the blocking of new infections by zidovudine make it very difficult for new infections to be established. For a time, therefore, the rate of clearance of infected cells outstrips the rate of production of new ones. It is not until the CD4+ count grows large enough to tip this balance back in favour of producing new infections that the viral burden starts to rise again.

The very sharp transition in population behaviour shown by this model is only a crude caricature of observed events (models which acknowledge more of the complexity of HIV's life cycle mimic the data more closely [6]). However, the simplicity of the model's behaviour allows us to make a useful approximation to the time that will pass before the viral burden achieves its pre-treatment level under a given effective dose, z.

The approximation follows a method described elsewhere [17] and, in brief, is as follows: we wish to find an approximation for t such that either $L_S(t) = L_S(0)$ (if $z < z^*$ and it is sensitive strain that resurges) or $L_R(t) = L_S(0)$ (if $z > z^*$ and it is resistant strain that resurges). Using $dX/dt \simeq \Lambda - \mu X$ as an approximation for the dynamics of uninfected cells yields $X(t) \simeq \Lambda/\mu + e^{-\mu t}(X(0) - \Lambda/\mu)$. Approximating $e^{-\mu t}$ by $1 - \mu t + \mu^2 t^2/2$ we can make the further approximation:

$$\int_0^t X(s)\, ds \simeq X(0)t + t^2\,(\Lambda - \mu X(0))/2.$$

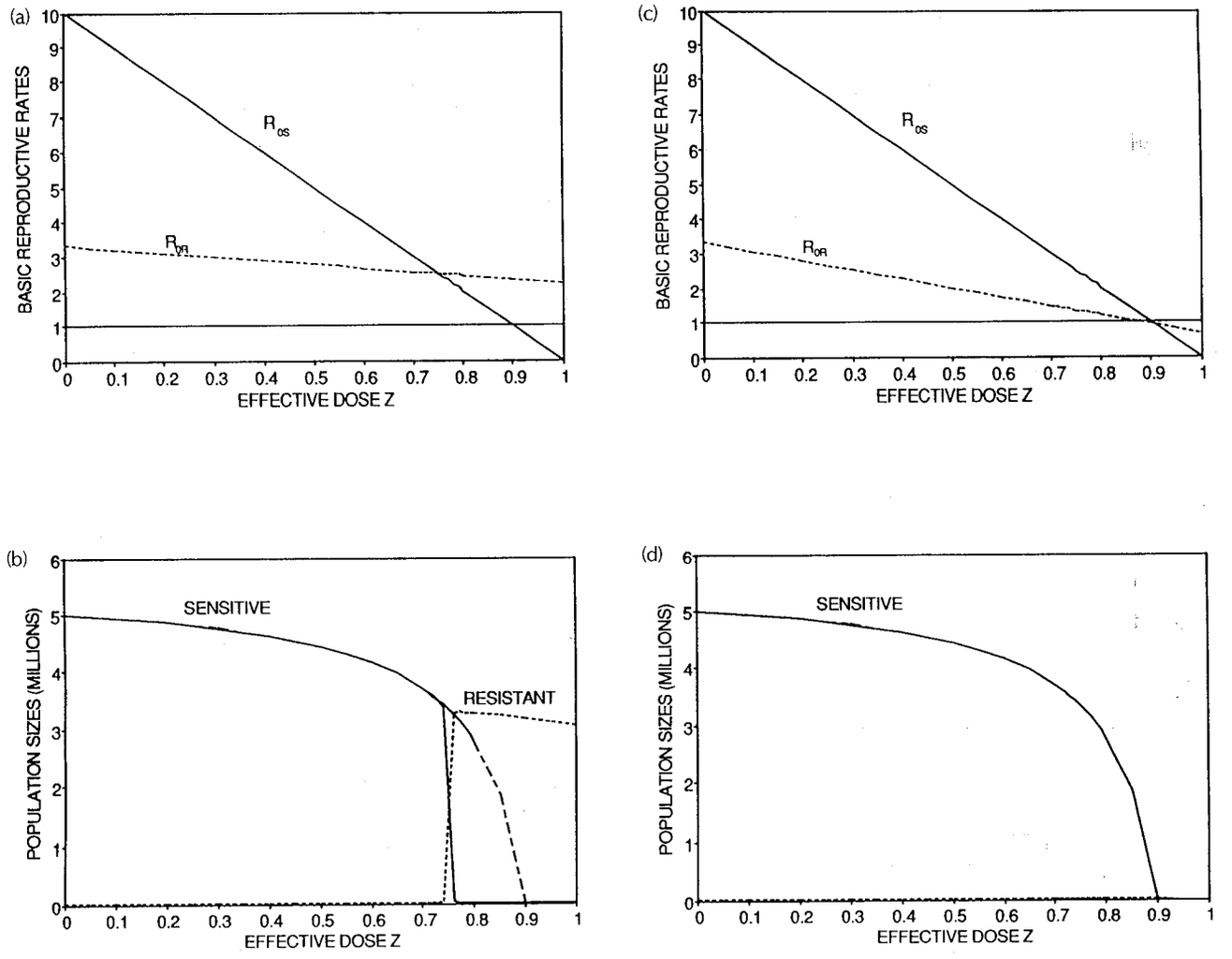

Fig. 5. Basic reproductive rates (a) and (c) and equilibrium virus populations (b) and (d) at different doses of zidovudine. Parameter values are as in Table 1 with $\alpha = 35.96$, yielding $p_c \simeq 0.78$. In (a) and (b), $p = 0.3333$ so $p < p_c$ and $z^* < z_{CS} < z_{CR}$; resistant strains out-compete sensitive strains before either is eradicated. In (c) and (d), $p = 0.9$ so $p > p_c$ and therefore $z_{CR} < z_{CS} < z^*$; both strains are eradicated at a dose below that at which resistant strains would have out-competed sensitive strains. (b), ——, population size of sensitive strains that would occur if resistant strains were not present, showing how virus would have been eradicated at effective dose z_{CS} if mutations conferring resistance had not occurred.

If $z < z^*$ then it is sensitive virus that will resurge, and virus dynamics are therefore dominated by sensitive virus. With resistant virus at very low levels, sensitive virus dynamics can be described by

$dL_s/dt \simeq Q(1\text{-}z)\beta_S L_S X\text{-}\alpha L_S$, with solution

$\mathrm{Ln}[L_S(t)/L_S(0)] \simeq Q(1\text{-}z)\,\beta_s \int_0^t X(s)ds - \alpha t$. When

$L_S(t) = L_S(0)$, $In[L_S(t)/L_S(0)] = 0$.

We can therefore find t such that $L_S(t) = L_S(0)$ by setting the expression for $\mathrm{ln}[L_S(t)/L_S(0)]$ equal to zero and, using the approximation for $\int_0^t X(s)ds$, solve for t.

We obtain $t = 0$ or $[t \simeq 2z/\mu(R_{0S} \simeq 1)(1-z)]$.

If $z > z^*$

then it is resistant virus that will resurge, and we apply the same treatment to:

$dL_R/dt \simeq Q(1\text{-}pz)\beta_R L_R X\text{-}\alpha L_R$ to obtain:

$$[t \simeq 2[R_{0S}\text{-}R_{0R}(1\text{-}pz)]/[\mu(R_{0S}-1)R_{0R}(1\text{-}pz)].$$

In Fig. 7 the time taken until virus growth restarts is plotted against effective dose, z, for two different sets of parameter values, representing ARC and AIDS patients. If the effective dose is higher, the time until viral growth restarts is longer, and for a given effective dose it takes longer for virus growth to restart in ARC patients than in AIDS patients.

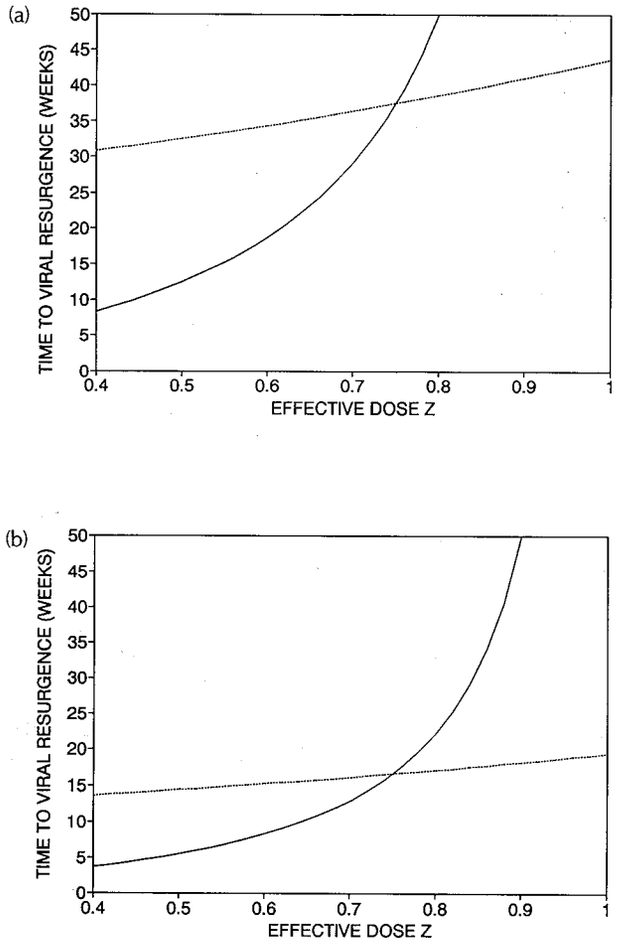

Fig. 6. Numerical simulations of population dynamics during the shift from the pre-treatment equilibrium to the treatment equilibrium. Parameter values are as in Table 1, with $\alpha = 35.96$, yielding $z^* \simeq 0.75$. In (a) $z = 0.7 < z^*$, so it is sensitive virus that resurges, whilst in (b) $z = 0.9 > z^*$ so it is resistant virus that resurges.

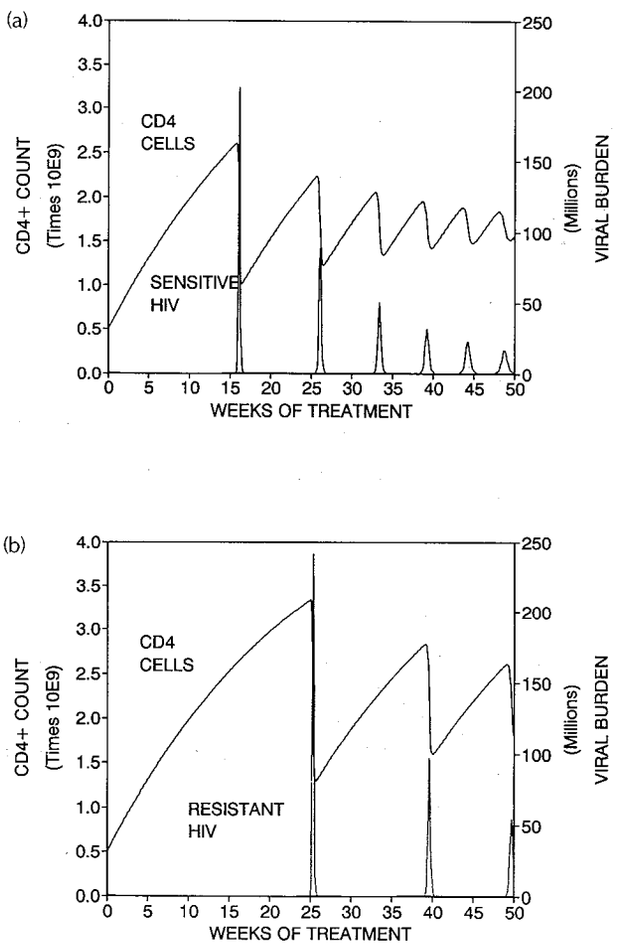

Fig. 7. Time taken before virus reachieves its pretreatment level. Parameter values are as in Table 1 with $\alpha = 71.92$ in (a) and $\alpha = 35.96$ in (b). Thus (a) is drawn with a set of parameter values representing patients with AIDS-related complex whilst (b) is drawn with a set of parameter values representing patients with AIDS. Time it would take for sensitive virus to resurge if only sensitive virus (——) or resistant virus (·····) were present. The actual time taken before virus growth restarts will be whichever of these is the smaller.

Conclusions

We have presented a hypothesis about why the benefits of zidovudine are short-lived, illustrated this hypothesis through a mathematical model, and characterized this model's behaviour. The important result that emerges is that although resistant strains are observed after prolonged treatment with zidovudine, it is the growing supply of uninfected CD4+ cells that causes the eventual upsurge in viral burden. An important corollary of this event is that efforts to slow the evolution of resistant strains (for example, by alternating high and low doses of zidovudine) are pointless. Once CD4+ counts become high enough, viral growth will restart. Although this is a somewhat gloomy conclusion, there is a useful insight to be gained. If one concedes that all that can be achieved with zidovudine is to 'buy time', then one should 'buy' all the time possible by giving large doses early on when the virus's basic reproductive rate is still low. This will certainly lead to the emergence of resistant strains, but the time taken until virus resurges will be longer than if a lower dose is given.

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