The role of antigenic stimulation and cytotoxic T cell activity in regulating the long-term immunopathogenesis of HIV: mechanisms and clinical implications

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This paper develops a predictive mathematical model of cell infection, host immune response and viral replication that reproduces observed long-term trends in human immunodeficiency virus (HIV) pathogenesis. Cell activation induced by repeated exposure to many different antigens is proposed as the principal mechanism of providing target cells for HIV infection and, hence, of CD4⁺ T cell depletion, with regulation of the overall T cell pool size causing concomitant CD8 pool increases. The model correctly predicts the cross-patient variability in disease progression, the rate of which is found to depend on the efficacy of anti-HIV cytotoxic T lymphocyte responses, overall viral pathogenicity and random effects. The model also predicts a variety of responses to anti-viral therapy, including episodic residual viral replication and discordant responses and we find that such effects can be suppressed by increasing the potency of treatment.

Keywords: HIV pathogenesis; mathematical model; anti-viral treatment

1. INTRODUCTION

Much progress has been made in recent years in characterizing human immunodeficiency virus (HIV) replication within an infected patient (reviewed by Fauci *et al.* 1996; Haase 1999), its effect on T cell kinetics (Fleury *et al.* 1998; Pakker *et al.* 1998; Hellerstein *et al.* 1999), immunocompetence (reviewed in Powderly 1999) and the effect of anti-retroviral drug treatment in suppressing viral burden and slowing the progression to disease (Ho *et al.* 1995; Wei *et al.* 1995; Mocroft *et al.* 1998; Palella *et al.* 1998; Ledergerber *et al.* 1999). In some instances, the biological and population level processes underlying individual aspects of these dynamics are at least partly understood (reviewed by Finzi & Siliciano 1998). However, a comprehensive explanation of the long-term progression of HIV infection and the processes giving rise to acquired immune deficiency syndrome (AIDS) remains elusive, given the complexity and multifactorial nature of the interactions involved.

Here we derive an integrated population dynamic framework for characterizing the interactions between CD4⁺ and CD8⁺ T cells, HIV and other pathogens. This framework, which is schematically outlined in figure 1, extends existing work on HIV viral dynamics (for excellent reviews of past theoretical work see Perelson & Nelson (1999) and Nowak & May (2000)). Our model is based on a small number of simple biological assumptions and generates dynamics that are in good agreement with observed patterns. In particular, the model explains the following.

- (i) How the short time-scale (hours–days) processes of viral production, infection and clearance (Perelson

et al. 1996) and of T cell activation and division (Stevenson *et al.* 1990) interact with the longer time-scale (weeks) of the immunological process of antigen clearance to produce the very long time-scale (years) of HIV pathogenesis.

- (ii) The highly variable but stable progression of HIV disease as measured by declines in peripheral CD4⁺ T cell numbers and matching increases in CD8⁺ T cell numbers (Margolick *et al.* 1995).
- (iii) The observed correlation between set-point viral load and the duration of the asymptomatic period (Mellors *et al.* 1996; De Wolf *et al.* 1997).
- (iv) The variability in viral load both within and between patients.
- (v) The very low prevalence of infected cells throughout the course of infection (Chun *et al.* 1997).
- (vi) The relatively late onset of severe immunodeficiency that characterizes the development of AIDS (Powderly 1999).

The work also gives new insights into the interaction between anti-viral therapy and anti-HIV responses, which suggest that the degree of inhibition required for suppressing residual viral replication may be significantly larger than previously estimated (Ferguson *et al.* 1999).

Our analysis suggests that long-term HIV pathogenesis is the result of interactions between four key biological factors.

- (i) The effect of HIV in turning antigen-induced CD4⁺ T cell activation from a process that replenishes the quiescent cell pool into one that depletes it.
- (ii) Spatially localized invasion of non-HIV pathogens that leads to a steady rate of antigen-specific T cell activation.

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Figure 1. Outline of the basic compartmental model. The T cell population is subdivided as shown. However, this apparent simplicity captures in an effective manner the complexity of random antigenic exposure, resulting in multiple antigen-specific clonal cell expansions (Ferguson *et al.* 1999), which eventually drive the patient to AIDS.

- (iii) Homeostatic regulation of the overall T cell pool size that is blind to CD4 and CD8 surface markers, leading to gradual competitive exclusion of CD4 + T cells by CD8 + T cells under the fitness disadvantage caused by HIV infection.
- (iv) Anti-HIV cytotoxic T lymphocyte (CTL) responses that regulate but do not clear HIV.

Our view that patients' development of AIDS is not a result of sudden catastrophic changes but rather a steady progression to disease is supported by study of patient cohorts (Mellors *et al.* 1996; de Wolf *et al.* 1997; Lepri *et al.* 1997; Lyles *et al.* 1999).

2. T CELL DYNAMICS

Key to the model framework is that antigen-driven T cell activation is the principal driving process determining the natural history of HIV infection. Regular exposure to environmental, commensal and HIV antigens ensures a steady rate of CD4 + T cell activation, thereby providing target cells for HIV infection (Stevenson *et al.* 1990; Zack *et al.* 1990). The effect of T cell activation in enhancing viral replication is well established (Orendi *et al.* 1998) and its role in accelerating disease progression has been explored experimentally (Staprans *et al.* 1995; Ostrowski *et al.* 1998; Hazenberg *et al.* 2000a,b; Moriuchi *et al.* 2000). A positive correlation has been demonstrated in several patient cohorts (Bofill *et al.* 1996; Phillips *et al.* 1996; Liu *et al.* 1997; Fahey *et al.* 1998; Giorgi *et al.* 1999). The interaction between antigenic stimulation and viral dynamics has been explored extensively in earlier mathematical studies (Cooper 1986; McLean & Nowak 1992; Essunger & Perelson 1994; Mittler *et al.* 1996; Grossman *et al.* 1998; Wodarz *et al.* 1998).

In a healthy person, activation following antigenic exposure leads to an increase in the number of T cells specific to that antigen and, concomitantly, to the generation of T cell memory (Burnet 1959; Ahmed & Gray 1996). However, by infecting activated cells and

decreasing their survival the process of antigen clearance may be turned from a source of new cells to a drain (or sink) on the resting CD4 + T cell pool by HIV. Thus, our model predicts that the time-scale of HIV disease progression is set by the rate and duration of antigenic exposure, the resulting number of cells activated and their survival probabilities. The depletion of the quiescent CD4 cell pool is then a result of hundreds of antigenic exposures over many years.

Our model of T cell dynamics links two separate operational time-scales: the slow time-scale of resting T cells and the rapid time-scale of turnover of activated and HIV infected cells, thereby allowing the dynamics of both long-term pathogenesis and post-treatment viral decay to be described. Mathematically, the model is expressed as a system of coupled nonlinear ordinary differential equations defining the dynamics of sub-populations of T cells:

$$\frac{dx_4}{dt} = \lambda_4 - a_4 + 2p_a\mu_a x_{4a} + \mu x_4 - \Theta x_4(x_4 + x_8), \quad (1)$$

$$\frac{dx_8}{dt} = \lambda_8 - a_8 + 2p_a\mu_a x_{8a} + \mu x_8 - \Theta x_8(x_4 + x_8), \quad (2)$$

$$\frac{dx_{4a}}{dt} = a_4 - \mu_a x_{4a} - \beta v x_{4a}, \quad (3)$$

and

$$\frac{dx_{8a}}{dt} = a_8 - \mu_a x_{8a}, \quad (4)$$

where x_4 and x_8 are the numbers of uninfected resting CD4 + and CD8 + T cells, respectively, x_{4a} and x_{8a} are the numbers of activated T cells and v is the HIV viral load. These numbers are normalized so that, in HIV-uninfected patients, on average $x_4 + x_8 = 1$. The parameters of the model are defined in table 1. We assume that successful HIV replication occurs predominantly in

Figure 2. A simulation of a patient with 'modal' parameters: (a–c) the natural history of infection and (d) primary infection. The parameters for this simulation are defined in table 1. The parameter values were chosen consistent with direct estimates (Ho *et al.* 1995; Wei *et al.* 1995; Perelson *et al.* 1996) and in order to generate patterns consistent with data gathered from peripheral blood samples from infected patients. In this scenario, anti-viral therapy must block > 99.5% of all replication in order to achieve viral suppression. The average basic reproductive numbers are $\langle R_0 \rangle = 200$ and $\langle R^{ctl}_0 \rangle = 8$ (the angled brackets denote the average over time). The average lifetime of a productively infected cell after primary infection is $1/(\alpha^{ctl}) \approx 1.9$ h, but as the CTL effect rapidly fades after the initiation of anti-viral therapy it rapidly extends to $1/\alpha = 2$ days, similar to published estimates (Ho *et al.* 1995; Wei *et al.* 1995; Perelson *et al.* 1996). For the same reason, our choice of $R_0 = 200$ is not inconsistent with previous estimates (Nowak *et al.* 1997; Little *et al.* 1999), which calculated only the lower bounds of the basic reproductive number. (c) The evolution of T helper competence in the course of infection. During primary infection I_H is very small, resulting in transient symptomatic disease. Competence then recovers to an order of magnitude below normal, with a second slower but persistent drop observed when CD4 counts reach a very low level, corresponding to symptomatic AIDS. However, we do not capture all the features of late-stage AIDS here, such as the sometimes observed increase in viral load and fall in total CD3 + T cell numbers (Margolick *et al.* 1995), which could be caused by changes in the trafficking patterns between lymphatic tissues and peripheral blood.

activated CD4+ T cells following the evidence in Stevenson *et al.* (1990) and Zack *et al.* (1990).

The T cell dynamics defined by equations (1)–(4) describe the effect of four basic processes: (i) recruitment of new T cells from the thymus (at rates λ_4 and λ_8), (ii) cell activation by antigens, cell cycling and subsequent division or activation-induced cell death (activation at rates a_4 and a_8 , cycling at rate μ_a with a probability of successful division of p_a), (iii) homeostatic division and death (at rates μ and $\Theta = \lambda_4 + \lambda_8 + \mu + 2a_0(2p_a + 1)$ chosen so that on average $x_4 + x_8 = 1$ at steady state), and (iv) infection of activated CD4+ T cells by HIV (at rate βv). The fixed probability of activation-induced cell death in the absence of HIV infection ($= 1 - p_a$) is the average over a complete T cell response to a specific antigenic stimulus: this probability is low in the early part of an immune response during clonal expansion and increases

during clonal contraction (Ahmed & Gray 1996). That antigenic stimulus results in a substantial net increase in cells while levels of activation-induced cell death are high (Ahmed & Gray 1996) indicates that p_a is slightly greater than 0.5.

Intuitive insight into the effect of HIV on T cell dynamics can be obtained by integrating out the rapid time-scales of viral turnover and cell activation (i.e. by averaging over short-term fluctuations in viral load and activated T cell numbers). This is done by taking $dx_{4a}/dt = dx_{8a}/dt = dv/dt = 0$ in equations (1)–(4). While there is evidence of significant changes in homeostasis occurring during HIV infection, in particular increases in T cell turnover (Hellerstein *et al.* 1999), we find that in our model these changes (e.g. increasing μ) do not qualitatively modify the model predictions. We can thus derive the simple approximate equation for CD4+ T cell dynamics as

Table 1. Parameters of the model.

(Values marked with an asterisk are expressed as a fraction of the total resting T cell pool at steady state.)

symbol	description	value in simulation	comments
λ_4 and λ_8	daily rate of thymic production of new CD4 + and CD8 + T cells*	$\lambda_4 + \lambda_8 = 10^{-4}$ and $\lambda_4 = 5\lambda_8$	chosen so that the pre-infection CD4/CD8 ratio = 2
a_0	average rate of T cell activation per antigenic exposure*	10^{-4}day^{-1}	chosen to match the observed rate of disease progression (Babiker <i>et al.</i> 2000)
μ	daily rate of non-antigen-driven homeostatic T cell division*	0.01	chosen to match directly observed turnover rates (Hellerstein <i>et al.</i> 1999)
x_S	relative T cell pool size below which T cell activation fails due to exhaustion of repertoire*	0.05	value at which T helper competence starts to decline
μ_a	activated T cell division rate	1 day^{-1}	—
p_a	average probability of an activated T cell successfully dividing in an HIV-negative control	0.55	—
β	average per virion infection rate of an activated CD4 + T cell	754 day^{-1}	chosen so that the average $R_0 = 200$ at viral set point, the rate of activated cell infection is $\beta v = 7.02\text{day}^{-1}$
α	death rate of productively infected cell (in the absence of CTL)	0.5 day^{-1}	matches inferred estimates (Ho <i>et al.</i> 1995; Wei <i>et al.</i> 1995)
α_L	rate of reactivation of latent infected cells	0.01 day^{-1}	the same as μ
f_L	proportion of successful infections that result in latency	10^{-5}	—
p	maximum proliferation rate of anti-HIV CTLs	0.5 day^{-1}	—
d	death rate of anti-HIV CTLs	0.05 day^{-1}	—
z_0	pre-infection frequency of anti-HIV CTLs*	10^{-6}	—
y_T	threshold value of infected cells for the logistic proliferative response of CTLs to HIV*	$10^{-3.5}$	—
b/c	ratio of viral production rate in productively infected cells and viral lifetime	265	chosen to match the modal viral set-point of $10^{4.12}$ (Mellors <i>et al.</i> 1996).
σ	maximum rate of CTL killing of HIV-infected cells	10^4day^{-1}	—
N_{PB}	typical pre-infection T cell count	1500 mm^{-3}	the peripheral blood (PB) CD4 count is $N_{PB}(x_4 + x_{4a} + y + y_L)$ the PB CD8 count is $N_{PB}(x_8 + x_{8a} + z)$
θ_4 and θ_8	average clearance rate in antigenic exposure model	0.02 day^{-1}	—
e_4 and e_8	average exposure rate in antigenic exposure model	0.1day^{-1}	the average number of concurrent antigenic exposures = 5

$$\frac{dx_4}{dt} \approx \lambda_4 + a_4 \left(\frac{2p_a}{1 + \frac{\beta v}{\mu_a}} - 1 \right). \quad (5)$$

In the absence of HIV ($v=0$) both cell recruitment and cell activation (at respective rates of λ_4 and a_4) act as sources of new CD4 cells. The effect of HIV is then to reduce the average probability of active CD4 cell division from p_a to $p_a/(1 + \beta v/\mu_a)$. Hence, when the viral load v is above the threshold value $\mu_a(2p_a + 1)/\beta$ HIV changes antigenic exposure from a source of new CD4 cells to a continuous drain on the CD4 + T cell pool. The logistic dependence of dx_4/dt on v in equation (5) explains the

surprising nonlinearity of the observed dependence on the viral load of patient survival time (i.e. that variations in set-point viral load over a 1000-fold range result in only fivefold variations in survival time).

3. ANTIGENIC EXPOSURE AND T CELL ACTIVATION

The variable a_4 denotes the rate of CD4 activation by all antigens (HIV and non-HIV) and describes the overall effect of multiple clonal T cell responses to many different antigens over time. What then determines the value of a_4 and, thus, controls the overall rate of progression? In order to explain the steadiness of the decline in

CD4, we hypothesize that bursts of activation occur predominantly in localized sites, for example in lymph nodes and in lymphoid patches around the digestive or respiratory tracts. We show in electronic Appendix A that, in the case of localized antigen presentation, the availability of antigen presenting sites is expected to limit the rate of T cell activation, which then occurs at an approximately constant rate. This leads to the following approximation for the rate of CD4 + (subscript $i=4$) and CD8 + (subscript $i=8$) T cell activation:

$$a_i = a_0 k_i \frac{x_i}{x_i + x_s}. \quad (6)$$

Here, x_s is the T cell density above which the binding process between T cells and antigen presenting sites saturates, a_0 is the average level of T cell activation per antigenic exposure and k_i is the number of concurrent antigenic exposures. We incorporate the continuous process of exposure to and clearance of antigens as a simple random process. The dynamics are governed by stochastic equations for the time evolution of the probabilities of k_4 major histocompatibility complex–class II (MHC-II)-restricted and k_8 MHC-I-restricted concurrent antigenic exposures, i.e.

$$\frac{dp_{k_i}}{dt} = \theta_i(k_i + 1)p_{k_i+1} - (e_i + \theta_i k_i)p_{k_i} + e_i p_{k_i-1}, \quad (7)$$

where e_i and θ_i are the exposure and clearance rates, respectively. This stochastic system is simulated by generating Poisson-distributed events for fixed time-steps and is coupled to the deterministic model by numerically integrating the deterministic equations over the same time-step.

Figure 2 shows the combined effect of antigenic stimulation and HIV infection in producing the key features of untreated chronic HIV infection: a steady but variable decline in CD4 + T cells (Phillips *et al.* 1991), with a corresponding rise in CD8 + cells (Margolick *et al.* 1993), along with a very low prevalence of infected cells (Chun *et al.* 1997).

4. CD4 CELL DESTRUCTION, HIV VIRAL LOAD AND IMMUNOCOMPETENCE

The relationship between disease progression and immunocompetence can also be described in this framework. Though the interaction between CD4 + T cell help and the efficacy of other immune responses has been demonstrated to be important (Battegay *et al.* 1994; Matloubian *et al.* 1994; Rosenberg *et al.* 2000), the quantitative nature of this interaction has yet to be fully understood. Given the complexity and incomplete understanding of the interaction, we define a surrogate measure of the competence of the T helper response in the HIV-infected host as the number of activated CD4 T cells available for each antigenic exposure relative to the same quantity pre-HIV infection, namely $I_H = a_4/k_4 a_0$. At the quasi-steady state, this can be approximated by

$$I_H = \frac{x_4}{x_4 + x_s} \frac{1}{1 + \beta v / \mu_a}. \quad (8)$$

This expression states that T helper competence decreases logarithmically with both decreasing CD4 cell count and increasing HIV viral load and is plotted for a typical model outcome in figure 2c. Since T help is not necessary for the short-term clearance of acute infections (Battegay *et al.* 1994; Matloubian *et al.* 1994; Rosenberg *et al.* 2000) (although it does determine persistence) this expression is not fed back into the model, but rather is taken as a measure of the severity of each antigenic exposure.

5. HIV VIRAL DYNAMICS AND CTL CONTROL OF HIV

Anti-HIV CTL responses play a central role within our conceptual framework of HIV pathogenesis: although many other arms of the immune system may contribute to controlling HIV (see for example Parren *et al.* 1999; Rosenberg *et al.* 2000), there is increasingly strong evidence suggesting that the CTL response is key (reviewed by McMichael *et al.* 2000). While it has been shown that some features of primary infection could be explained solely by the natural epidemic dynamics of HIV expansion and subsequent exhaustion of target cells (Phillips 1996), our framework agrees with recent studies (Stafford *et al.* 2000) indicating that the natural history of primary infection (as described by Kaufmann *et al.* 1998b) is better explained by the establishment of CTL control of HIV, as shown in figure 2d. This figure also exhibits the establishment of the clinically important long-lived infected cell pool within days of infection (figure 2d), in agreement with recent data (Zhang *et al.* 1999).

Underlying our model of HIV and T cell dynamics is the ‘basic model of viral dynamics’, which was recently reviewed in Nowak & May (2000). There has also been considerable work extending this model in order to consider many of the issues we discuss here. Our model synthesizes some of these developments, presents novel insights into the processes involved and provides a predictive framework that is both consistent with the rapid time-scale of viral replication and the slow time-scale of HIV immunopathogenesis. First of all, as in Cooper (1986), McLean & Nowak (1992), Essunger & Perelson (1994), Mittler *et al.* (1996), Grossman *et al.* (1998) and Wodarz *et al.* (1998), we distinguish between resting and activated CD4 + T cells, with successful infection occurring predominantly in activated cells (Stevenson *et al.* 1990; Zack *et al.* 1990). Second, we pay close attention to the proliferative dynamics of anti-HIV CTL. We incorporate an effective model of the CTL cell cycle, which was developed in Ferguson *et al.* (1999), which results in a bounded proliferation rate that is proportional to a logistic ‘activity’ function $\varepsilon = y/(y + y_T)$, where y is the number of productively infected cells. We have found that the clearance of infected cells is best matched by hypothesizing that anti-HIV CTLs, though long-lived (> 10 days) (Ogg *et al.* 1999), are only effectively cytotoxic during the activated phase of their replication cycle. The clearance of infected cells is thus taken to be proportional to ε . The dynamics of viral replication are thus determined by the following set of equations:

$$\frac{dy}{dt} = (1 - f_L)\beta v x_{4a} + a_L y_L - (\alpha + \sigma \varepsilon z)y, \quad (9)$$

Figure 3. Generated simulations of the progression of infection in 100 patients. The pre-infection CD4 fraction f_4 (as calculated from λ_4 and λ_8) was chosen from a logistic transform of a normal deviate to have a mean of 0.66 and a standard deviation (s.d.) of 0.05, while y_T and σ were log-normally distributed (normal distributions with means of 3.5 and 2 and s.d.s of 0.75 and 0.5, respectively), with all other parameters from table 1. (a) The serial CD4 counts for the 100 patients. (b) The predicted nonlinear correlation between viral load and the time from infection to AIDS (defined here as $CD4 < 200$). (c) The inverse nonlinear correlation between the frequency of anti-HIV CTLs and viral load. (d) Simulation of the effect of ageing on the rate of disease progression: Kaplan-Meier curves for the development of AIDS where a decreasing rate of thymic output λ is used as a surrogate marker for ageing and is varied as shown: the results were found to agree with Babiker *et al* (2000).

$$\frac{dy_L}{dt} = f_L \beta v x_{4a} - a_L y_L, \quad (10)$$

and

$$\frac{dz}{dt} = d(z_0 - z) + p \epsilon z, \quad (11)$$

where y_L is the number of long-lived latent infected CD4⁺ T cells capable of viral production upon activation and z is the number of anti-HIV CTLs. Since free virus is known to be short-lived, the virus load v is assumed to be in equilibrium with y , i.e. we take $v = by/c$, where b is the production rate of virus by productively infected cells and c is the free virus clearance rate. The parameters are described in table 1. Overall, the complete model is defined by equations (1)–(4) and (6)–(11).

6. THE BASIC REPRODUCTION NUMBER OF HIV

The most fundamental quantity of any model of pathogen dynamics is the basic reproductive number R_0

(Anderson & May 1991; Nowak & May 2000), which quantifies replicative capacity. Here, it is defined as the number of new virions produced by a single HIV virion in its lifetime in a pool of completely uninfected cells. In the absence of a CTL response its value is given by $R_0 = a_4 b \beta / \mu_a c \alpha$. R_0 increases with k (the burst size of an infected cell), a_4 (the rate of CD4⁺ T cell activation) and β (the infectivity of the virus) and decreases with μ_a , c and α , which are the rates of CD4⁺ T cell division, viral clearance and infected cell death, respectively. Since a_4 is a dynamic variable of the model and depends on antigenic exposure, unlike the basic model of viral dynamics (Nowak & May 2000; though see Wodarz *et al.* 1998), here the basic reproductive number R_0 changes over time.

CTL cytolytic activity increases the death rate of infected cells and results in the following new expression for the reproductive number after maturation of the CTL response:

$$R_0^{ct} = \min \left(R_0, 1 + R_0 y_T \frac{\alpha}{a_4 p - d} \right). \quad (12)$$

Figure 4. (a–c) Three simulated patients with ‘modal’ parameters (from table 1) treated by anti-retroviral therapy 3 years after infection by HIV. Average post-therapy R_0 values are shown (denoted as $\langle R_0 \rangle$) corresponding to increases in the potency of the anti-viral regimen from top to bottom (note that when $R_0 < 1$ then $R^{ctl}_0 = R_0$). (a) The patient illustrates a discordant response (increasing CD4 and stable viral load). (b) In this patient the virus decays, but antigenic exposure intermittently raises the R_0 value, thereby resulting in episodic viral replication. (c) In this patient the potency of the therapy is sufficient for largely suppressing viral replication. (d) The final patient instead receives a hypothetical therapeutic vaccine (e.g. synthetic or auto-vaccination by structured treatment interruption), which boosts the CTL affinity for HIV 40-fold (thus reducing y_T 40-fold). Provided the virus does not mutate and escape this CTL response, this treatment results in lasting increases in CD4 counts.

Here d is the death rate of CTLs, p is their maximum proliferation rate and y_T is the threshold density of infected cells that is required to trigger CTL proliferation, a quantity that is inversely proportional to CTLs’ affinity for HIV. That the above expression for R^{ctl}_0 takes the form of the lower of two values reflects the existence of two distinct dynamical regimes in the model, the first with no lasting CTL response and the second with a stable effective CTL response: the criterion determining which regime is entered is which of the two expressions defining R^{ctl}_0 is smallest. The death rate of infected cells in the presence of a CTL response is increased from α to $\alpha^{ctl} = \alpha R_0 / R^{ctl}_0$.

This analysis provides further support for the hypothesis that the inability of the CTL response to clear HIV depends critically on the duration of the cytolytic effect immediately following activation by recognition of a viral antigen (Wodarz *et al.* 2000b). If this is short, as we

suggest above, then CTL lysis of infected cells will rapidly cease as the density of viral antigens drops, thus preventing complete clearance of the virus, but rather maintaining a dynamic equilibrium where viral replication is controlled. Unlike models which do allow clearance of HIV (where the duration of the cytolytic effect is longer), this model reproduces the inverse correlation of anti-HIV CTLs with viral load between patients (Ogg *et al.* 1998; Dalod *et al.* 1999; Kalams *et al.* 1999a) (see figure 3c), i.e. the positive correlation within a patient (Dalod *et al.* 1998, 1999; Kalams *et al.* 1999b; Ogg *et al.* 1999; Pitcher *et al.* 1999) through time (analysis not shown). The model also captures the relative stability of the viral load throughout HIV infection (Mellors *et al.* 1996; De Wolf *et al.* 1997; Lyles *et al.* 1999): most models allowing clearance predict large predator–prey type oscillations in the viral load if clearance fails (Nowak *et al.* 1995; Nowak & May 2000).

7. VARIABILITY BETWEEN HIV PATIENTS

The correlation between HIV viral load and patient survival in untreated infection is well established (Jurriaans *et al.* 1994; Mellors *et al.* 1996; de Wolf *et al.* 1997). However, since viral loads vary up to 1000-fold between patients and incubation periods by little more than fivefold, this correlation is necessarily nonlinear. This key feature of HIV pathogenesis is generated naturally by our model as a consequence of the saturation of infection within the limited pool of activated CD4⁺ T cells (i.e. the logistic dependence on viral load in equation (5)).

The predicted pattern of variation between patients is illustrated in figure 3. CD4 expression in thymic emigrants and anti-HIV CTL affinity are assumed to be log-normally distributed across patients, generating a log-normally distributed viral set-point, which was matched to observations from cohort data (Mellors *et al.* 1996). The resulting incubation period distribution predicted by the model agrees with known data (Babiker *et al.* 2000), with a median time to AIDS of 8 years (interquartile range 6–13 years). The nonlinear correlation between the set-point viral load and incubation period is demonstrated in figure 3*b*. This correlation is predicted to be weak as a result of environmental stochasticity in the pattern of patient antigenic exposure. A further prediction of the model is demonstrated in figure 3*d*. By using thymic output as a surrogate marker for age at infection (Douek *et al.* 1998), we predict an inverse correlation between HIV incubation period and age, as has been observed (Babiker *et al.* 2000).

We have not modelled evolution in the HIV genome, which will contribute to the progression to AIDS. However, the link between the time-scales of mutation as a function of viral load and long-term pathogenesis has not been clarified in purely evolutionary models (Nowak *et al.* 1991, 1995). Those models also do not predict several key features of long-term pathogenesis, such as the nonlinear correlation structure illustrated in figure 3*b*. We therefore do not believe that viral evolution is the primary process explaining pathogenesis, although its potentially important secondary role is the topic of ongoing research.

8. CLINICAL IMPLICATIONS

As seen in figure 4, the model accurately captures the dynamics of rapid viral turnover in the activated CD4 cell pool as well as a long-lived infected cell pool and, thus, describes the biphasic decay of virus following the initiation of anti-retroviral therapy (Perelson *et al.* 1996). Our analysis makes several novel predictions about HIV treatment. First, the model predicts that there is a level of drug efficacy which does not reduce viral replication below the self-sustaining threshold ($R_0 < 1$) and, thus, is unable to reduce the viral load substantially, but is sufficient to lower virus-induced killing of proliferating CD4 cells enough to give a sustained recovery of CD4 cell numbers. This explains 'discordant' responses to therapy (Kaufmann *et al.* 1998*a*), as illustrated in figure 4*a* and furthermore suggests that 'discordance' would be eliminated by increasing the potency of treatment.

Second, the basic reproductive number R_0 is not constant, but rather varies randomly with antigenic exposure around a mean value. Thus, when therapy reduces R_0 on average slightly below unity, fluctuations in antigenic exposure can result in periods of sustained viral replication with $R_0 > 1$, even in patients known to have good adherence to treatment regimens, as illustrated in figure 4*b*. We predict that these episodic 'bursts' of residual viral replication (Ramratnam *et al.* 2000) can be suppressed by increasing the potency of therapy, as illustrated in figure 4*c*. As a corollary, immune stimulation therapy aiming to flush the long-lived infected cell reservoir with activating cells will also increase R_0 , possibly above unity even under very potent anti-viral drug regimens, an issue that is explored in Fraser *et al.* (2000).

Third, when treatment is sufficiently potent to reduce viral replication below the self-sustaining threshold, CTL cytolytic activity will rapidly cease (declining much faster than the observed decline in anti-HIV CTL numbers), thereby increasing the infected cell lifetime. Hence, first phase rates of decline (Ho *et al.* 1995; Wei *et al.* 1995) are predicted to overestimate the lifetime of infected cells in untreated infection significantly and, thus, underestimate the steady state rate of turnover of infected cells. Our analysis does not support the hypothesis that the whole of the first phase of viral decay can be assigned to CTL killing, as in Arnaout *et al.* (2000). Initial decays following drug treatment may be slower in primary infection than later in infection, as recently observed in Putter *et al.* (2000), although this will only affect the start of the first phase of viral decay.

Fourth, the CTL model that best matches observed dynamical trends is one that is unable to clear HIV (an equilibrium between CTLs and virus is always reached), but acts to reduce the basic reproductive number R_0^{ctl} towards unity. CTL action can reduce the viral load sufficiently to halt the progression to disease: the effect of a treatment strategy that boosts the efficacy of the CTL response is illustrated in figure 4*d*. Such a therapeutic vaccination could be achieved by immunization or by structured treatment interruption, which may act to boost CTL efficacy indirectly via increased T helper function (Wodarz & Nowak 1999; Bonhoeffer *et al.* 2000; Rosenberg *et al.* 2000; Wodarz *et al.* 2000*a*). However, viral escape from CTL suppression by mutation could again increase the rate of progression. Hence, improvements in the number and activity of the dominant CTL responses may only have a transient effect. A lasting effect is difficult to generate unless the functional CTL response is broad in specificity (Harrer *et al.* 1996; Rosenberg *et al.* 2000).

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