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Anti-CD4 therapy for AIDS suggested by mathematical models

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SUMMARY

HIV-1 infection typically involves a long clinical latency stage during which CD4 counts decline slowly. For the later part of the clinical latency stage it was found recently that this is a highly dynamic phase characterized by rapid turnover rates. Clinical latency can therefore be considered as a quasi-equilibrium state in which CD4 and HIV-1 turnover are in almost perfect balance. Here we consider this quasi-equilibrium to be the stable steady state of a simple host-parasite model in which the parasite (HIV-1) level is determined by the availability of infectable hosts (activated CD4+ T cells). Such models adequately account for the clinical data on the evolution of drug resistant mutants appearing after the administration of anti-HIV drugs. The model suggests a novel therapeutic approach for AIDS: reducing the CD4 count slightly will strongly reduce the HIV load. Combining this anti-CD4 treatment with conventional anti-HIV therapy would prevent the outgrowth of drug resistant mutants.

1. INTRODUCTION

Recent clinical data on the decrease of the HIV-1 plasma level, and the increase of the CD4 T cell count, following the treatment with anti-viral drugs have been analysed mathematically to suggest that clinical HIV-1 latency involves high turnover rates of both the virus and the CD4+ T cells (Ho et al. 1995; Wei et al. 1995; Nowak & Perelson 1995a; Perelson et al. 1996). Given that the HIV-1 clinical latency stage typically lasts for several years (Fauci 1993; Levy 1993; Weiss 1993), these findings raise the question how virus levels are kept under control for so long (Coffin 1995a). One answer to this question is the ‘immunological view’ stating that the HIV-1 infection is controlled by the immune system. There is good empirical evidence for both a humoral (Fauci 1993; Levy 1993; Weiss 1993) and a cellular (Phillips et al. 1991; Nowak et al. 1995b; Klein et al. 1995; Nowak & Bangham 1996; Levy et al. 1996) immune response.

An alternative answer is the ‘ecological view’ stating that the HIV-1 infection is limited by the availability of target cells (McLean et al. 1991; McLean & Nowak 1992; Frost & McLean 1994; McLean & Frost 1995; Perelson et al. 1993; Essunger & Perelson 1994; Coffin 1995b; Phillips 1996). According to this view the immune response may be important, but is assumed to remain fairly constant over the time course of the clinical experiments discussed here. The data supporting the ecological view involve perturbations of the clinical latency equilibrium by therapeutic intervention. Increasing the activation and the numbers of CD4+ T cells by IL2 treatment increases both the viral RNA load and the CD4 cell count (Kovacs et al. 1995). Immunization of HIV-1 infected individuals with influenza vaccine has a side effect of increasing CD4+ T cell activation and transiently increases the plasma HIV-1 RNA levels significantly (O’brien et al. 1995; Stappans et al. 1995). Conversely, suppressing CD4+ T cell activation by cyclosporin (Andrieu et al. 1988; Fauci 1993; Schwartz et al. 1993; Weber & Galpin 1995) or prednisolone (Andrieu et al. 1995; Corey 1995) can be beneficial by increasing CD4 T cell counts, and, in one instance (Weber & Galpin 1995), decreasing the viral load. Note however, that cyclosporin also has direct anti-viral effects (Billich et al. 1995; Steinkasserer et al. 1995).

The ecological and immunological views are not mutually exclusive. First, during disease progression the infection could evolve from immunological to ecological control. This is supported by the IL2 treatments where the adverse effects on the viral load are most pronounced in late stage patients (Kovacs et al. 1995). Second, even if the control of the virus at the clinical latency equilibrium is dominated by the immune response (Nowak & Bangham 1996), perturbation of this equilibrium by therapeutic interventions can give rise to transients during which the fast expansion of target cells dominates over a more slowly changing immune response. Thus, whenever the immune response adapts sufficiently slow to changes in the virus load, the virus is transiently limited by the available target cells.

The recent clinical trials with anti-viral drugs like protease inhibitors (Ho et al. 1995; Wei et al. 1995; Nowak et al. 1995a; Perelson et al. 1996) and reverse-transcriptase (RT) inhibitors (Schuurman et al. 1993; Wei et al. 1995; De Jong et al. 1996) tend to be unsuccessful because the virus evolves drug-resistant mutants (Larder et al. 1989, 1991). These evolutionary data have adequately been described by mathematical models confirming to the ecological view (McLean et
Figure 1. Anti-viral treatment for math-AIDS and for a representative example (i.e. Case number 11) from a group of 20 asymptomatic or mildly symptomatic AIDS patients treated with the RT-inhibitor lamivudine (Schuurman et al. 1995). The initial CD4 T cell count and viral RNA load of Case number 11 were 215 cells per µl and 3.6 x 10⁴ copies per µl, respectively. Assuming this to be an equilibrium we obtain the same initial condition in our model by setting ϵ = 1136 and γ = 2.2 x 10⁻⁴ T cells per scaled virus particle per day. We mimic the lamivudine treatment by administering an RT-inhibitor at day zero, i.e. we set the effective drug concentration D = 10. Thus the RT fitness of the wild-type decreases 11-fold (see equation (1a)), whereas that of the drug-resistant mutant decreases marginally (i.e. by 2 %, see equation (1b)). Setting D to higher values hardly changes the math-AIDS results. Figure 1a, b depict a timeplot of the CD4 T cell count per µl. The data (a) and the model (b) are in close agreement. Figure 1c, d depict the total viral RNA load per ml (solid line with circles), and the RNA loads of the wild type (dashed line with diamonds) and the drug-resistant mutant (dash-dotted line with squares). We assume that the drug-resistant mutant is present at low concentration, i.e. T_r(0) = 0.1 cell per ml, before the onset of treatment (Najera et al. 1995). The model and the data agree closely on the slope with which the total RNA load decreases. In the model and in the data we find that the drug-resistant mutant has completely replaced the wild type after about 2 weeks. In the data we find a rebound of the wild type after about 3 weeks. For the current parameter values, such a rebound is absent from the model. Decreasing the effective drug concentration and/or the RT fitness ε of the mutant we can obtain similar wild-type rebounds in the model (McLean et al. 1991; McLean & Frost 1995; De Jong et al. 1996; Stilianakis et al. 1996). Within the ecological view, the wild type rebound is explained by the recovery of the CD4 count. This provides more ‘food’ for the virus and thus compensates for the anti-viral treatment. We conclude that our simple host–parasite model provides a reasonable fit for both our own clinical data (i.e. Case number 11), and for a compilation of several independent clinical data sets (Coffin 1995a). Parameters: σ = 10, d_w = 0.01, d_r = 0.5, γ = 0.99, τ = 750 and α = 0.01. The proportional relation between infected cells and virus stems from a quasi steady state assumption, i.e. from dv/T_i/dt = N_T_i d_r/T_r where N is the number of particles produced per T cell and d_r is the inverse lifetime of the particles. Hence γ = c/T_i, where c = N d_r/d_t. Note that the HIV-1 RNA load is 2(V_u + V_r).

Figure 2. Lamivudine treatment in a second representative example (i.e. Case number 20 (Schuurman et al. 1995)) and in our model. The initial CD4 T cell count and viral RNA load of this case were 190 cells per µl and 2.66 x 10⁵ copies per ml, respectively. We obtain the same initial condition in our model by setting ϵ = 8046 and γ = 3.6 x 10⁻⁶ T cells per scaled virus particle per day. Case number 20 is more typical for the lamivudine data because the total CD4 increase is rather limited (i.e. about 30 %). Additionally, the data show that before the onset of treatment 2% of viral quasi species is drug-resistant. We therefore increase the mutant’s initial density by setting T_r(0) = 0.1. Thus we obtain an initial viral load of the mutant that is similar to that of the data (cf. panel c). All other parameters of the model are kept the same as those in figure 1. The time plots of the CD4 T cell count per µl in the data (a) and the model (b) agree reasonably. The total CD4 increase in the model is indeed much smaller than that in figure 1 (note difference in scale of the vertical axis). Thus the mild increase of the CD4 counts in the lamivudine data (as compared with the protease data (Ho et al. 1995; Wei et al. 1995)) can partly be explained by the higher initial frequencies of the drug-resistant mutants (lamivudine-resistant mutants require only one point mutation (Schuurman et al. 1995)). The time plots of the viral RNA load per ml of the data (c) and the model (d) are in qualitative agreement. The total decrease in the viral load in the data is however ten-fold larger than that in the model. Given the simplicity of our model we however consider this fit between model and data to be reasonable.

al. 1991; McLean & Nowak 1992; Frost & McLean 1994; McLean & Frost 1995; De Jong et al. 1996; Stilianakis et al. 1996). All of these models are conventional host–parasite models for the infection of CD4+ host T cells by the HIV-1 parasite. Recent work (McLean & Frost 1995; De Jong et al. 1996; Stilianakis et al. 1996) demonstrates that the complex evolutionary timecourse of the various drug-resistant mutants appearing after treatment with zidovudine can be accounted for by such host–parasite models. Like the recent mathematical analysis supporting the notion of a highly dynamic clinical latency phase (Ho et al. 1995; Wei et al. 1995; Nowak et al. 1995a; Perelson et al. 1996), these host–parasite models assume clinical latency to be a quasi-equilibrium that is perturbed by one of the anti-HIV drugs. Figures 1 and 2 illustrate the close correspondence between an example of such
a host–parasite model and the response of the HIV-1 quasi species to lamivudine treatment (Schuurman et al. 1995). In these host–parasite models HIV-1 production is limited by the availability of target cells, i.e. activated CD4+ T cells, and by the rapid clearance rates which are possibly caused by the immune response. For simplicity we here use the conventional CD4 T cell count as a measure for the target cell density. A natural consequence of our assumption that the target cells are a limiting factor is that, for each particular quasi-equilibrium in the clinical latency phase, the CD4 T cell count represents exactly the critical number of target cells the virus, at that particular time point, requires for its survival (i.e. requires for having a reproduction ratio $R$ larger than one). Thus, one can treat this mathematical form of AIDS (math-AIDS) by deliberately reducing the target cell density, here the CD4 count. This threshold target cell density is determined by the parameters defining the current clinical latency state. Hence the threshold will decrease by disease progression. Thus, clinical examples of patients with normal viral loads, but extremely low CD4 counts (Ho et al. 1995; Schuurman et al. 1995), need not contradict the ecological view. Even with so few peripheral CD4+ T cells the lymphoid tissue could still have high numbers of activated CD4+ T cells and virus (Emberton et al. 1993; Pantaleo et al. 1993), the virus quasi species of such cases could have evolved high infection and/or production rates (Tersmette et al. 1989), and is likely to have evolved tropisms for other types of target cells (Levy 1993; Weiss 1993).

2. MODEL

In response to an anti-HIV therapy the virus quasi species typically evolves several drug-resistant mutants (Larder et al. 1989, 1991; Wei et al. 1995; Coffin 1995b; Schuurman et al. 1995; De Jong et al. 1996). In our data on the resistance to the RT-inhibitor lamivudine we find two drug-resistant mutants that are caused by a mutation in codon 184 of the HIV-1 RT gene, which replaces the wild type methionine residue (ATG) with either an isoleucine (ATA) or a valine (GTA) (Schuurman et al. 1995). As the drug-resistance of both mutants is 500–1000 fold greater than that of the wild type, and as both mutants appear within a 2–3 week period, we will combine them into one population called the drug-resistant mutant strain $V_e$. The drug-sensitive wild type is denoted by $V_w$. Each of the two strains has a specific RT fitness, i.e. $f_w$ and $f_e$, which combines the infection rate in the absence of the drug with the resistance in the presence of the drug. In the absence of the drug we scale the RT fitness of the wild type to be one, and we call the RT fitness of the mutant $e$. Because the RT fitness of mutants in the absence of the drug is usually just a few percent less than that of the wild type (Coffin 1995b; C. A. B. Boucher unpublished data) we conservatively set this RT fitness to $e = 0.99$. For the RT fitness in the presence of the drug we employ the conventional notion of the inhibitory concentration, i.e. the IC$_{50}$, which is the drug concentration at which the effect of the drug is half-maximal. Scaling the IC$_{50}$ of the wild type to one we obtain

$$f_w = \frac{1}{1 + D'} \quad \text{and} \quad f_e = \frac{e}{1 + D/f_e}$$

where $D$ is the effective lamivudine concentration, and $r = 750$ is the IC$_{50}$ of the mutant (Schuurman et al. 1995).

We write two differential equations for the infected T cells actively producing either $V_w$ or $V_e$, i.e.

$$\frac{dT_w}{dt} = \gamma T_s f_w V_w - d_i T_w$$  \hspace{1cm} (2)

$$\frac{dT_e}{dt} = \gamma T_s f_e V_e - d_i T_e$$  \hspace{1cm} (3)

where the $T_s$ variable denotes the infectable CD4+ T cells, $\gamma$ is an infection rate, and $d_i$ is the turnover rate of productively infected CD4 cells. This turnover rate has recently been estimated to be close to $d_i = 0.5$ per day (Ho et al. 1995; Wei et al. 1995; Nowak et al. 1995a; Perelson et al. 1996). As the viral particles have a six-fold higher turnover rate than the CD4 cells (Perelson et al. 1996) it is reasonable to assume that the number of virus particles is proportional to the corresponding number of infected cells, i.e. we assume $V_w = \epsilon T_w$ and $V_e = \epsilon T_e$ (see legend to figure 1).

The reproduction ratio is classically defined as the number of target cells that become productively infected over the entire lifespan of a productively infected cell. From equation (2) we derive that, before treatment (i.e. when $f_w = 1$), the reproduction ratio of the wild type virus is $R = \gamma T_s / d_i$. Similarly, we derive from (2) that its equilibrium is at $T_w = d_i / (\gamma r)$. Thus we see (i) that the virus determines the equilibrium CD4 count, and (ii) that at equilibrium $R = 1$, i.e. every virus particle is on average replaced by exactly one other particle. We can therefore ’starve’ the HIV-1 infection by reducing the target cells to a level below that of the clinical latency equilibrium of $T_w = d_i / (\gamma r)$. This is the main result of this paper.

We now proceed by adding an equation for the uninfected T cells to illustrate that these models are in agreement with data, and to explore an immunosuppressive anti-CD4 treatment. The T cell repertoire is maintained by self-renewal and by a source of virgin T cells from the thymus. Most previous models for studying drug-resistance rely on the thymus for maintaining the T cell repertoire (McLean et al. 1991; McLean & Nowak 1992; Frost & McLean 1994; McLean & Frost 1995). The process of T cell self-renewal on the other hand can be modelled by simple logistic growth or by distinguishing resting and cycling T cells (Perelson et al. 1993; Essunger & Perelson 1994; Stilianakis et al. 1996). For the results presented here it makes no difference what model we choose. Thus we opt for mathematical convenience and write that the T cell repertoire is maintained by the thymus, i.e.

$$\frac{dT_s}{dt} = \sigma - d_T T_s - \gamma T_s (f_w V_w + f_e V_e),$$  \hspace{1cm} (4)

where $\sigma$ is the source of newborn cells from the thymus,

\( d_r \) is the death rate of uninfected CD4 cells, and the \( \gamma \) term describes the infection of \( T_c \) cells by either wild type or by resistant virus. As the model combines resting and cycling \( T \) cells the lifetime of the \( T \) cells is set to an intermediate length of 100 d (cf. McLean & Mitchie 1995), i.e. we set \( d_r = 0.01 \) per day. Thus we obtain a normal CD4 count of a 1000 cells per \( \mu l \) when we set \( \sigma = 10 \) cells per \( \mu l \) per day (which is in full agreement with recent estimates (Ho et al. 1995; Wei et al. 1995)).

3. RESULTS

We first compare the behaviour of our model with our data on the response of the plasma HIV-1 RNA load and the CD4 T cell count to treatment with lamivudine (Schuurman et al. 1995). This study involved 20 asymptomatic or mildly symptomatic HIV-1 infected men with an average CD4 T cell count of about 200 cells per \( \mu l \) and HIV-1 RNA loads ranging between \( 4 \times 10^3 \) to \( 9 \times 10^3 \) RNA copies per \( \mu l \). Following treatment with lamivudine, HIV-1 RNA loads dropped to about 95% below baseline in about a week. Thus, the typical exponential slope of the RNA decline is comparable to that reported recently (Ho et al. 1995; Wei et al. 1995; Nowak et al. 1995a; Perelson et al. 1996), i.e. \( \ln(0.05)/7 \approx 0.4 \) per day. An unexpected finding in the lamivudine data is that the CD4 cell counts decrease in about one third of the patients. Thus the average CD4 increases is about one cell per day only (Schuurman et al. 1995), which is small compared with the slope of eight CD4 cells per \( \mu l \) per day reported recently (Ho et al. 1995; Wei et al. 1995).

For a generic comparison of our model with the several clinical data sets we therefore pick two cases from our lamivudine study with significant increases in the CD4 cell counts (Schuurman et al. 1995). The parameters \( e \) and \( \gamma \) are set such that the equilibrium of the model corresponds to the initial CD4 count and the initial viral load of each patient. Lamivudine treatment is simulated by setting \( D = 10 \) (see equation 1). In figures 1 and 2 we plot the CD4 counts, the total RNA load, and the RNA load of the wild type and the drug-resistant mutant as they are obtained from the data and from the model. The model behaviour and the lamivudine data correspond closely. Additionally, the model behaviour is in close correspondence with the earlier clinical data on both protease inhibitors and RT-inhibitors (Ho et al. 1995; Wei et al. 1995; Coffin 1995b). As the virus quasi species contains, or rapidly evolves, mutants with both a high drug-resistance and with a RT fitness comparable to that of the wild type, drug therapies like this tend to be unsuccessful.

By considering the pre-treatment situation more closely we now develop our immuno-suppressive therapy for math-AIDS. Because the mutant strain is typically small in the pre-treatment situation we can ignore equation (3). Thus, the model simplifies into a simple epidemic of one parasite \( T_c \) infecting a host population \( T_r \) with a reproduction ratio of \( R = r_T / d_r \). In epidemiology it is well known that a parasite requires a critical density of infectable hosts for its survival (Kermack & McKendrick 1927), i.e. in our case the virus will only survive when \( R \geq 1 \). At the clinical latency equilibrium \( R = 1 \) because the CD4 level, i.e. \( T_c = d_r / (r_T) \) (see equation 2), is exactly at the threshold.

Thus, bringing the target cell level below that of the clinical latency quasi-equilibrium should eradicate the virus in our model. This means that a therapeutic approach for math-AIDS is the administration of an immuno-suppressive drug reducing CD4+ T cell activation or the CD4 T cell counts (e.g. cyclosporin, or an anti-CD4 antibody (Wofsy & Carteron 1990)). In our simple model we implement the latter by adding to equation (4) a term increasing the removal of CD4+ T cells, i.e.

\[
\frac{dT_c}{dt} = -d_r T_c - \gamma T_c (f_0 V_0 + f_i V_i) - \alpha T_c - \sigma T_c, \tag{5}
\]

where \( \sigma \) is the rate at which CD4 T cells are removed by the drug. Similar results would be obtained if we were to reduce the source of target cells \( \sigma \) as a model for blocking CD4 T cell activation (not shown). In the absence of the virus the equilibrium of equation (5) is at \( T_c = \sigma / (d_r + \alpha) \). Hence we find the critical anti-CD4 treatment at which \( R = 1 \) by setting this non-infected equilibrium equal to the clinical latency equilibrium, i.e. by setting \( \sigma / (d_r + \alpha) = d_r / (r_T) \).

Solving for \( \alpha \), we obtain \( \alpha = \sigma e d_r / (d_r - d_r + d_r) \) for the critical anti-CD4 treatment beyond which the virus is eradicated. One can easily check from our model that this rate \( \alpha \) corresponds to the equilibrium rate at which a target cell is expected to be infected by virus. Thus, by suppressing as many T cells as the virus is infecting, the critical anti-CD4 treatment yields a CD4+ T count that is identical to that of the clinical latency equilibrium. Because the virus is infecting large numbers of T cells per day (Ho et al. 1995; Perelson et al. 1996), the anti-CD4 treatment has to be strong. The surprising mathematical result is however that, despite the strong treatment, the CD4 T cell count of the math-AIDS patient need only by reduced marginally.

This is illustrated in figure 3 where we introduce the anti-CD4 therapy into the clinical latency state of the math-AIDS case depicted in figure 1. The effects of a minimal anti-CD4 treatment is studied by setting \( \alpha = 0.041 \) in figure 3a. We observe that HIV RNA levels decline steadily, that CD4 levels decline about 25% until day 15, and then recover to about 10% below baseline. The CD4 recovery is caused by the reduction of the virus load. The crucial new phenomenon is that the virus never rebounds (as long as the anti-CD4 therapy is continued). Slowly increasing the dosage of the anti-CD4 therapy until one observes a rapid drop of the HIV-1 RNA load, allows one to determine in vivo the critical anti-CD4 treatment. In figure 3b we linearly increase the anti-CD4 treatment from \( \alpha = 0 \) at day zero to \( \alpha = 0.041 \) at day 41, from then on the treatment remains at \( \alpha = 0.041 \).

Our immuno-suppressive therapy should have a highly synergistic effect on any of the conventional anti-viral drugs. In Figure 3c we do a combination of the anti-CD4 and the anti-HIV treatment in the math-AIDS patient depicted in figure 1. Importantly, the drug-resistant mutants do not appear (cf. figure 1), and

the CD4 levels never decrease more than 10%. Thus, by careful tuning the anti-CD4 therapy one can prevent the outgrowth of the drug-resistant mutants while keeping the CD4 count at reasonable levels.

4. CAVEATS

Decreasing activated CD4+ T cells is here proven to be an efficient therapy for math-AIDS, but the strong suppressive treatment that we require could of course be dangerous in AIDS patients. Here we spell out a number of caveats. First, AIDS patients typically suffer from various opportunistic infections, which become problematic, and eventually lethal, when CD4 levels drop further by ongoing HIV infection. Suppressing the CD4+ T cells any further may therefore have counter-productive effects. This would suggest testing the anti-CD4 therapy early in clinical latency so that the CD4 T cell counts can be kept above the clinical level below which the opportunistic infections become problematic (see however the discussion below). Second, reducing the target cell density only marginally (or slowly, figure 3b) may invite the virus to evolve mutants which survive on lower target cell densities, i.e. it may invite the virus to increase the number of virus particles per productively infected T cell (c), and/or the infection rate (γ). Thus the anti-CD4 therapy needs to be strong and might be dangerous. This suggests that employing the synergy between anti-HIV with anti-CD4 therapy could indeed be more successful because the mutants selected by an anti-HIV therapy tend to have somewhat lower infection rates (Coffin 1995k; C. A. B. Boucher, unpublished data). Third, we expect the virus to evolve novel tropisms. However, if one could develop an anti-CD4 approach reducing not only CD4+ T cells, but also all other CD4+ cell types, the virus would have to evolve an entirely new route of cellular infection.

5. DISCUSSION

Our hypothesis is extremely controversial. Most previous therapies were aimed at increasing the CD4 count. Here we propose to prevent the CD4 count from increasing, or even to lower it. It seems likely however that the increase of the CD4 levels following an anti-HIV therapy reflects an increase in the availability of target cells and increases the spread of the (pre-existing) drug-resistant mutants (see the data in figure 1, and McLean & Frost (1995) and De Jong et al. (1996)). As the drug-resistant mutants make the anti-HIV therapy quite unsuccessful, the possibility that the appearance of drug-resistant variants can be prevented by an anti-CD4 treatment is not only extremely controversial but also extremely intriguing.

The main controversy remains our assumption that the virus can be target-cell-limited. Not denying that

the immune response may dominate in the control of the virus in the clinical latency equilibrium, we would argue that several clinical data sets do support the notion that the virus becomes target-cell-limited when the clinical latency equilibrium is perturbed by therapeutic intervention. Perturbations of the clinical latency equilibrium with anti-viral drugs inhibiting HIV-1 RT or HIV-1 protease (Ho et al. 1995; Wei et al. 1995; Nowak et al. 1995a; Perelson et al. 1996), with the immuno-stimulatory drug IL2 (Kovacs et al. 1995), with influenza vaccination (Staprans et al. 1995), and with immuno-suppressive drugs like cyclosporin or prednisolone (Andrieu et al. 1988, 1995; Fauci 1993; Schwarz et al. 1993; Weber & Galpin 1995; Corey 1995), are all reported to affect target cell numbers (as measured by the CD4 cell count). The fact that immuno-stimulation by either influenza vaccination (Staprans et al. 1995; O’Brien et al. 1995) or IL2 treatment tends to increase the viral load (Kovacs et al. 1995), and that immuno-suppression can have beneficial effects (Andrieu et al. 1988, 1995; Fauci 1993; Schwarz et al. 1993; Weber & Galpin 1995; Corey 1995), is most readily explained by target-cell limitation, i.e. by the ecological view.

The issue is complicated however because the ecological and immunological views are not mutually exclusive, e.g. during disease progression the infection could evolve from immunological to ecological control. If this is so, anti-CD4 treatment will be detrimental during the early stages and beneficial during the late stages of disease. Furthermore, in models where the specific immune response changes rather slowly (e.g. because of immune memory effects) the more rapid ecological effects dominate transiently such that anti-CD4 treatment is transiently beneficial (manuscript in preparation).

The fact that in some of the data on the immuno-suppressive therapies the CD4 count increases but the viral load hardly responds (Andrieu et al. 1988, 1995; Corey 1995), is in agreement with a more detailed model of ours in which HIV-1 only infects activated T cells (De Jong et al. 1996; Stilianakis et al. 1996). The same model also allows us to model disease progression as the hyperactivation of the immune system (Fauci 1993). Thus, modelling progression by increasing the T cell activation rate, our ecological model accounts for the conventional increase in the viral load accompanied by a degree of the CD4 levels (De Jong et al. 1996; Stilianakis et al. 1996).

The main problem to expect with an anti-CD4 therapy is that the virus will not really be eradicated. HIV-1 can persist in long-lived cells (e.g. wild-type HIV-1 DNA remains present for months after anti-HIV therapy (Wei et al. 1995; C. A. B. Boucher, unpublished data). Thus one expects the virus to reappear from such ‘reservoirs’ as soon as the anti-CD4 treatment is interrupted. Clinical data (Weber & Galpin 1995) from an AIDS patient treated with cyclosporin are in agreement with this. Over a 30-week-period the patient’s CD4 counts fell from 960 to 530, and the viral load dropped 84%. When the cyclosporin treatment was interrupted, viral load and CD4 counts rose back to baseline. Similar data have hitherto been interpreted in the light of chronic hyperactivation (Ascher & Sheppard 1988; Fauci 1993) or auto-immune effects (Habeshaw et al. 1992; Weiss 1993; Andrieu et al. 1995) involved in HIV-1 infection.

Given the results presented here we prefer to interpret these data as support for the ecological view, and as its natural consequence, as support for an anti-CD4 therapy. Moreover, an anti-CD4 therapy killing CD4+ cells should be much more effective than cyclosporin because killing CD4+ cells should also affect virus hiding in the resting T cell (Bukrinsky et al. 1991; Zack et al. 1991) and macrophage reservoirs (Weiss 1993). Finally, we stress again that our hypothesis depends strongly on the ecological view that we have adopted here, and that anti-CD4 treatment should be detrimental if this view turns out to be wrong. As a critical test distinguishing the ecological from the immunological view one should begin to design experiments measuring the effects of anti-CD4 treatments in animal models.

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