

# Immune response and virus population composition: HIV as a case study

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Based on the current understanding of the immune response, we present what we believe to be a new model of intrahost virus dynamics. The model takes into account the relationship between virus replication rate and the level of antigen displayed by infected cells, and shows how the cell-directed immune response controls both virus load and virus replication rate. In contrast to conventional wisdom, it shows that the predominant virus variant does not necessarily have the highest replication rate. A strong immune response produces a selective advantage for latent viruses, whereas a deteriorating immune response invites in viruses of higher replication rates. The model is analysed in light of the well-studied HIV/AIDS disease progression, and shows how a wide range of major, seemingly unrelated issues in the study of HIV may be accounted for in a simple and unified manner.

**Keywords:** HIV; AIDS; evolution of virulence; immune response; model; virus dynamics

## 1. INTRODUCTION

Viruses are highly complex invading machines, whose abilities and strategies have been forged by selection and competition over millions of years. The current understanding of intrahost virus dynamics is based largely on theoretical models (Nowak & May 1991, 1993; Nowak & Bangham 1996; Bonhoeffer *et al.* 1997a; Regoes *et al.* 1998; Kirschner 1999) in which competition between virus variants generally leads to the prevalence of the variant with the highest replication rate. However, this prediction contrasts with the observations seen in many disease progressions, such as those induced by HIV, herpes and Epstein–Barr viruses. In this modelling study, we revise conventional theory by taking into account the fact that the strength of the cell-directed immune response is directly correlated with virus replication rate (Vijh *et al.* 1998; Janeway 1999) and that, in effect, viruses that replicate prolifically are the most ‘visible’ to the immune system. By modifying a well-known intrahost virus competition model, we examine the implications of infected cell ‘visibility’. The emerging picture suggests subtle dynamics that have not, to our knowledge, previously been captured, whereby the prevalent virus variant is determined by a delicate interplay between its rate of replication, its visibility and the magnitude of the immune response.

The results of the general model were analysed taking into account HIV disease progression. HIV infection is of interest, here, because of the high variance in both severity and incubation time defining the course of the disease. Some patients infected with HIV rapidly progress to clinical symptoms (in less than five years), while others fail to show symptoms even 15 years after infection. The HIV initial virus load may vary significantly between different individuals and usually correlates with the incubation period (Lifson *et al.* 1997). Most evident in many HIV

patients is a transition from the slowly replicating non-syncytium inducing (NSI) to the rapidly replicating syncytium inducing (SI) variant (Cornelissen *et al.* 1995; Ercoli *et al.* 1997; Callaway *et al.* 1999) in the final stages of the disease. Therapy directed against the infection (highly active anti-retroviral therapy i.e. HAART) is only partially efficient, even in the absence of drug-resistant escape mutants, and causes major shifts in the viral quasi-species composition (Haase 1999). Also, AIDS is closely associated with opportunistic infections that ultimately cause the patient’s all too predictable death (Janeway 1999; Greenblatt *et al.* 2001). Current models have been able to explain particular aspects in the progression of the disease (Phillips 1996; Callaway *et al.* 1999; Wodarz *et al.* 2000), but not to create a coherent impression of the various aspects of the disease (but see Nowak and May 1994).

Cell-directed immune response carried out by T<sub>C</sub>-cells (cytotoxic T lymphocytes; CTL) is the major weapon deployed by the immune system in its struggle against HIV (Ogg *et al.* 1999). The nature of this response implies that infected cells that present only a small amount of antigen are less visible to the immune response than cells whose membrane is studded with many antigens (Germain & Stefanova 1999). Active T-cells probe bypassing cells with a low-affinity non-specific T-cell receptor (TCR), which binds major histocompatibility complex (MHC) molecules. The binding is considerably enhanced if the T<sub>C</sub>-cell CDR3 cell-line specific receptor binds its matching antigen, presented on the cell surface (Germain & Stefanova 1999). In turn, the number of matching antigens presented is a manifestation of the rate at which viral proteins and infective particles are produced (Del Val *et al.* 1991; Villanueva *et al.* 1994; Vijh *et al.* 1998; Montoya & Del Val 1999). Therefore, the probability that T<sub>C</sub>-cells recognize and destroy an infected cell is not constant; rather, an infected cell that produces only small amounts of antigenic proteins is more likely (as far as the immune system is concerned) to resemble a healthy cell than a highly productive, and thus highly ‘visible’, infected cell that the immune system easily recognizes. This key observation will be shown to have profound

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implications when modelling the viral quasi-species dynamics.

## 2. THE MODEL

The concepts introduced above are incorporated into a simple model commonly used to describe virus dynamics (Nowak & May 1993; Nowak & Bangham 1996; Altes & Jansen 2000). We investigate new ground by considering a term that accounts for infected-cell visibility—the probability that an infected cell is recognized and lysed by the immune response CTL. In the model (equations (2.1)), healthy target cells ( $x$ ) encounter virus particles ( $v_i$ ), to produce infected cells ( $y_i$ ), which in turn produce the corresponding virus particles ( $v_i$ ) at a rate  $k_i$ . The subscript  $i$  ( $i = 1, 2, \dots, n$ ) denotes each of the  $n$  variants of the viruses and their associated infected cells. The reproduction rate,  $k_i$ , of nascent viruses is the sole feature that differentiates virus variants.

In our model, all virus particles, of all variants, decay at a uniform rate ( $e$ ). Infected cells die both due to some constant death rate  $d_1$  (greater than healthy cells death rate and equal for all variants) and by the action of an immune response of strength controlled by parameter,  $d_2$ . Note that, in this model,  $d_2$  represents the maximal upper limit at which immune cells can destroy infected cells. We chose a single immune response for two main reasons. First, it is well known that a single immune response can be specific against many virus variants (Buseyne & Riviere 2001). Moreover, a virus with a lower replication rate probably elicits a smaller immune response (considering visibility) than a variant of a high replication rate. Therefore, the single immune response is a ‘worst-case scenario’ for the viruses with a lower replication rate, and this is precisely the case we wish to examine. Second, this simple model allows us to communicate more clearly an underlying principle that we believe governs the composition of intrahost virus population. The results for a model with a dynamic immune response are essentially the same (G. Almgoy and L. Stone, unpublished data).

The probability that a  $T_C$ -cell effectively recognizes infected cells is given by  $f(k)$ , a monotonically increasing function of the virus replication rate,  $k$ . Thus, the greater the number of virus particles that are produced from an infected cell, the more conspicuous the infected cell appears to the immune system cells. (Viral evasive mechanisms do not alter this basic fact.) We are thus led to a simple set of ordinary differential equations, given here in rescaled form (see electronic Appendix A, available on The Royal Society’s Publications Web site):

$$\begin{aligned} \frac{dx}{dt} &= 1 - x - x \sum_{i=1}^n v_i, \\ \frac{dy_i}{dt} &= x v_i - y_i F(k_i), \\ \frac{dv_i}{dt} &= k_i y_i - e v_i + \epsilon_i \quad i = 1 \dots n; \quad n \geq 2, \end{aligned} \quad (2.1)$$

where

$$F(k_i) = d_1 + d_2 f(k_i) \quad 0 \leq f(k_i) \leq 1.$$

Finally,

$$\epsilon_i \equiv \mu \sum_{\substack{j=1 \\ j \neq i}}^n y_j$$

is a mutation term introduced to account for the creation of virus variant  $i$  from all other variants (see also § 3).

We are interested in the vector of cell and virus density:

$$\mathbf{X} = (x, y_1, \dots, y_n, v_1, \dots, v_n). \quad (2.2)$$

With  $\mu = 0$ , there are  $n + 1$  possible equilibrium solutions to equation (2.2), one trivial solution:

$$x^* = 1, \quad y_i^* = 0, \quad v_i^* = 0 \quad \text{for } i = 1, 2, \dots, n, \quad (2.3)$$

and  $n$  non-trivial solutions of the form:

$$\mathbf{X}^{(i)} = (x^*; 0, \dots, 0, y_i^*, 0, \dots, 0; 0 \dots, 0, v_i^*, 0, \dots, 0)$$

for  $i = 1, 2, \dots, n$

with:

$$\begin{aligned} x^* &= \frac{eF(k_i)}{k_i}, \\ y_i^* &= \left( \frac{1}{F(k_i)} - \frac{e}{k_i} \right), \\ v_i^* &= \left( \frac{k_i}{eF(k_i)} - 1 \right). \end{aligned} \quad (2.4)$$

Here, as elsewhere below, the asterisk notation denotes equilibrium; thus  $x^*$  refers to the value of variable  $x$  when at equilibrium.

In analogy to epidemic models, we define the reproductive ratio:

$$R_0^i = \frac{k_i}{eF(k_i)}. \quad (2.5)$$

The trivial equilibrium is locally stable if and only if all  $R_0^i$  are less than unity (see electronic Appendix B). However, if there are such variants for which  $R_0^i > 1$ , then the unique, locally stable equilibrium is determined by the variant with the greatest  $R_0$ , i.e., the one for which

$$R_0^j = \max_i \{R_0^i\}, \quad (2.6)$$

implying that variant  $j$  has the best ratio of new infectious particles production,  $k_j$ , to the immune system destruction rate of free viruses and infected cells,  $eF(k_j)$ .  $R_0$  is thus a measure of fitness; only the viral variant with the greatest value of  $R_0$  is able to survive, although coexistence is possible in the presence of mutations (see § 3), or a dynamic, variant-directed immune response (G. Almgoy and L. Stone, work in progress).

## 3. ANALYSIS

We first revisit the standard model for intrahost virus dynamics (Nowak & May 1993; Nowak *et al.* 1996; Phillips 1996; Wodarz *et al.* 1999) where visibility is not accounted for in any way, i.e.  $f(k) \equiv 1$ . For this model, we can write  $R_0$  as:

$$R_0^i = \frac{k_i}{e(d_1 + d_2)}.$$

Hence, if  $k_1 > k_2$  then  $R_0^1 > R_0^2$ , and the strain with the largest  $k$  always takes over. This last result is in sharp contrast to observations; actual HIV infections are commonly dominated by the less productive (low- $k$ ) NSI variants

until the final stages of the disease, whereas the highly prolific (high- $k$ ) SI variants appear only when the immune system is severely impaired (Ercoli *et al.* 1997). To avoid this difficulty, Callaway *et al.* (1999) postulate that a transition from the NSI to the prolific SI phenotype is due to the higher antigenicity in the V3 region of the SI variants. This is possibly a valid assumption, but we present a different solution that has the added advantage of explaining the more general principles driving the virus dynamics over the disease progression.

We therefore examined a more biologically realistic immune response that incorporates the effects of visibility, i.e. where  $f(k)$  is a monotonically increasing function of virus replication rate,  $k$ . We suppose that the probability,  $P$ , that an immune system cell binds an antigen present on the outer surface of an infected cell is of the simplest possible form, namely  $P = \alpha k$ , where  $\alpha$  is a constant. We note, however, that the results that follow are robust to the particular type of functional form and are equally valid if, for example, antigen presentation by an infected cell is a process with a saturation point (Montoya & Del Val 1999; Price *et al.* 1999) such as  $P = k/(k + s)$  (see § 4 and electronic Appendix C). As there is a need for more than one binding interaction (Germain & Stefanova 1999), the probability that  $n$  such events should occur must be considered, and it would be reasonable to approximate:

$$f(k) = P^n.$$

Note that in the remainder of the paper we have chosen to work with  $n = 2$ , although qualitatively similar results are found for  $n > 2$  (see electronic Appendix C).

Recall that, in the absence of mutations, there is no coexistence and the virus strain with the highest fitness survives (equation (2.6)). Setting  $dR_0/dk = 0$ , one can find the value  $k$  for which the fitness  $R_0$  of the virus is a local maximum. Thus, with  $P = k/k_{\max}$  as the binding probability ( $k_{\max}$  being the maximum possible number of antigens presented and assumed to be greater than maximal virus replication rate), we have:

$$R_0^i = \frac{k_i}{e(d_1 + d_2(k_i/k_{\max})^2)} \quad (3.1)$$

and the optimal replication rate is thus found to be:

$$k_{\text{opt}} = k_{\max} \sqrt{\frac{d_1}{d_2}}. \quad (3.2)$$

Upon substituting  $k_{\text{opt}}$ , the maximal  $R_0$  is thus:

$$R_0^{\text{opt}} = \frac{k_{\max}}{2e} \sqrt{\frac{1}{d_2 d_1}}. \quad (3.3)$$

In the limiting case, where virus replication rates are distributed continuously, the single viral variant that survives will have a replication rate  $k_{\text{opt}}$  and fitness  $R_0^{\text{opt}}$ , as given by equations (3.2) and (3.3). The graphical representation of this result is given in figure 1, which demonstrates the inverse relationship between immune response magnitude ( $d_2$ ) and the optimal replication rate ( $R_0^{\text{opt}}$ ).

If virus replication rates are discrete rather than continuously distributed, the dominant variant will be the one that has a maximal  $R_0$ , as given by equation (2.6), and must, necessarily, be the virus strain whose fitness is closest to  $R_0^{\text{opt}}$ . In all cases, it is clear from equation (3.2) that

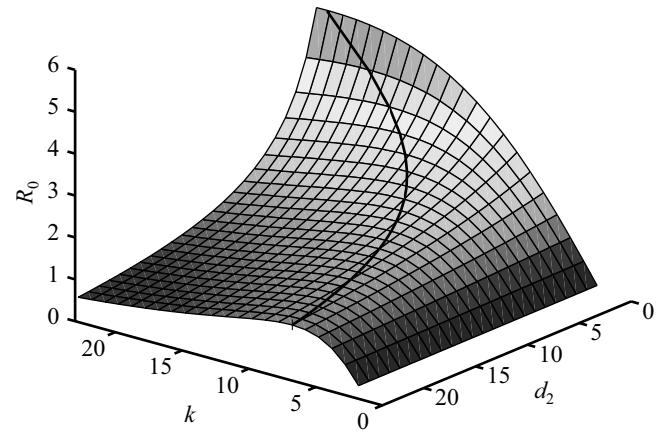


Figure 1. The reproductive ratio ( $R_0$ ) plotted as a function of the immune response strength ( $d_2$ ) and the virus replication rate ( $k$ ). The optimal reproductive ratio  $R_0^{\text{opt}}$  (thick black line) gives the optimal replication rate  $k_{\text{opt}}$  for any given immune response  $d_2$ . As  $d_2$  decreases, the optimal replication rate ( $k_{\text{opt}}$ ) increases according to the inverse relationship predicted by equation (3.2). Note that, for a still-intact immune system with large  $d_2$ , the optimal replication rate  $k_{\text{opt}}$  changes relatively slowly with  $d_2$ , as is characteristic of the latent stage for viral diseases such as AIDS.

the replication rate of the surviving virus is at some intermediate level that is inversely proportional to the immune response magnitude ( $d_2$ ). This key result is in conflict with the common assumption, which states that the virus with the greatest replication rate outcompetes all other viruses.

Equation (3.2) provides a clear statement regarding the manner in which the virus composition shifts when the immune system ( $d_2$ ) weakens or is boosted. A weakening of the immune system will increase  $k_{\text{opt}}$  and thus has the potential to stabilize an equilibrium solution that has a higher replication rate,  $k$ . Although the model is simplistic in that only a single virus strain survives, we have found that the same qualitative results emerge in systems in which there is a coexistence of viral strains. Coexistence can be studied either by including the possibility of mutations or adding the visibility function into more complicated model structures (e.g. a dynamic immune response directed at different epitopes; Nowak *et al.* (1996)). For these more complicated models, the optimal viral variant becomes the most prevalent of the coexisting viruses rather than the sole surviving one, and  $k_{\text{opt}}$  similarly varies inversely with  $d_2$  (G. Almy and L. Stone, unpublished data).

HIV slowly destroys the cell-directed immune response (directly or indirectly) and, as a result, a transition from slow (NSI) to rapidly (SI) replicating variants ( $k_{\text{NSI}} < k_{\text{SI}}$ ) is apparent as the immune system declines (Ercoli *et al.* 1997; Ostrowski *et al.* 1998; Kirschner 1999). This is reflected in the model, as follows. Once established, the immune response  $d_2$  is initially large, and the virus fitnesses are such that  $R_0^{\text{NSI}} > R_0^{\text{SI}}$ . Hence, the population is dominated by the NSI phenotype. As the immune response  $d_2$  decreases, the fitness of both subpopulations  $R_0^{\text{NSI}}$  and  $R_0^{\text{SI}}$  increases at different rates, with the SI variant benefiting more from the weakening of the immune system. As such, when  $d_2$  drops below a certain critical

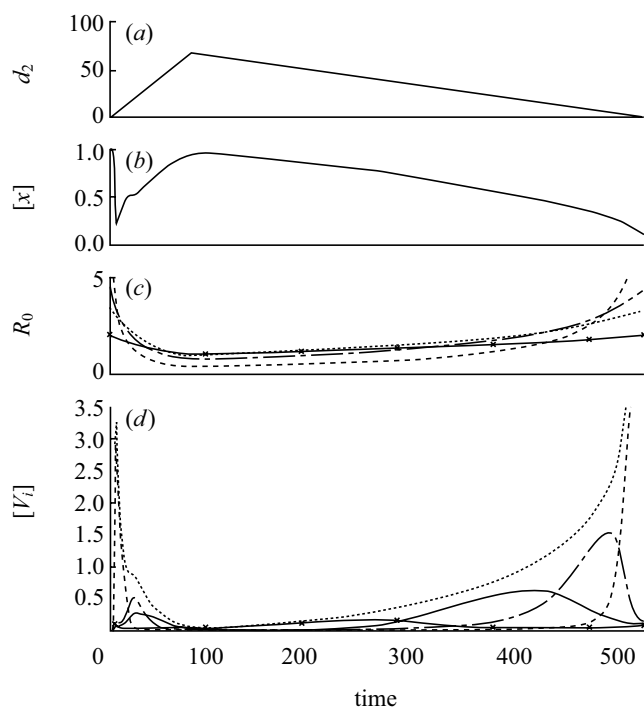


Figure 2. (a) HIV-directed immune response ( $d_2$ ) begins at a very low level and builds up during the first few weeks of the infection ( $t = 0.80$ ). In order to portray the initial dynamics, the times chosen for immune response build up are unrealistically long compared with incubation time. (b) Target-cell population rapidly decreases during the initial infection ( $t = 0-20$ ). As the cell-directed immune response builds, there is a gradual increase in target cells that peaks ( $t \sim 100$ ). A decrease in target cells follows, culminating in a steep decline ( $t \sim 500$ ). (c) The reproductive ratio  $R_0$  of the virus variants as the immune response  $d_2$  is changed according to the immune response magnitude in (a). The SI variant ( $k = 20$ , dashed line) initially has the highest reproductive ratio. As the immune response deteriorates, the NSI variants gain dominance ( $k = 9$ , dotted line;  $k = 7$ , crosses;  $k = 4$ , dashed and dotted). The dashed line indicates the minimal reproductive ratio ( $R_0 = 1$ ) below which all viral variants are unable to survive. (d) An initial peak of viraemia (total virus load, dotted line) is characterized by the dominance of the most highly replicating variant (dashed line). An increase in total virus load and the dominant virus replication rate (phenotype switching) follows the decline in the immune response magnitude,  $d_2$ , as seen at the final stages of the disease ( $t = 480-530$ ).

level  $d_c$ , the virus population switches from an NSI to an SI phenotype at  $R_0^{\text{NSI}} = R_0^{\text{SI}}$ . A simple calculation based on equation (3.1) shows:

$$d_c = \frac{d_1 k_{\text{max}}^2}{k_{\text{SI}} k_{\text{NSI}}} \quad (3.4)$$

Similarly, a switch from SI to NSI can be expected when the immune response,  $d_2$  is raised to the point where it exceeds the critical level,  $d_c$  (figure 2).

#### (a) Alternative visibility functions

There are many functions that are candidates for  $f(k)$ , the visibility function. However, in selecting which one we use, we have to rely on reasoning and/or biological intuition whenever experimental results do not give a more

precise direction. The most biologically reasonable alternative visibility function that we have tested is a general saturating function, raised to the  $n$ th power to account for the multiple interactions between TCR and MHC-peptide complexes needed for efficient target-cell killing. Thus:

$$f(k) = \left( \frac{k}{k+s} \right)^n,$$

where  $s$  is the saturation parameter and  $n$  the number of bindings. Saturation here means that there is a maximum number of MHC-peptide complexes that may be presented on the cell surface. Note that, when  $k$  is relatively large,  $f(k) \sim 1$ , indicating that after the saturation point, it is always advantageous for the virus to increase its replication rate. However, given the extremely versatile nature of the antigen presentation, it seems unlikely that such a situation will occur, as many of the antigens presented are self-antigens and the virus proteins have to outnumber these considerably in order to saturate the antigen presentation system. The results that we obtained using this function are qualitatively similar to the ones presented above and are also discussed in more detail in electronic Appendix C.

#### (b) Mutations and coexistence

In this model, we treat mutations as the product of some minor error in the replication cycle inside the infected cell. Briefly, an HIV particle infecting a target cell first requires a reverse transcription, followed by integration into the host genome (to create the provirus), transcription of the viral DNA (provirus) into the infective RNA and coding mRNA, and finally the packaging and budding of new infective particles to start a new infection cycle. For our modelling purposes it is sufficient to assume that mutations occur only on the reverse transcription stage; an infective particle of variant  $i$  enters a susceptible cell,  $x$ , producing many infective particles of variant  $i$  as well as viruses of other variants at some mutation rate,  $\mu$ . Conversely, virus particles of variant  $i$  are also produced from other variants. For simplicity, we assume that all mutations are equally probable. We arrive at the mutation term,  $\epsilon_i$ :

$$\epsilon_i \equiv \mu \sum_{j=1}^n y_{ij}$$

where  $y_i$  represents the concentration of cells infected with virus variant  $i$  (equation (2.2)).

The numerical simulations in figures 2 and 3 demonstrate that this model allows for stable coexistence and the conservation of variants with lower reproductive ratios than the dominant strain, although these variants are maintained at low concentrations.

## 4. RESULTS

The model accounts for many of the specific HIV-related phenomena in a comprehensive manner. It is assumed that, at the initial stages of infection, a specific cell-directed immune response is virtually non-existent and rapidly builds up, as reflected in the parameter  $d_2$  (figure 2a;  $t = 0-80$ ). It is also assumed that there are

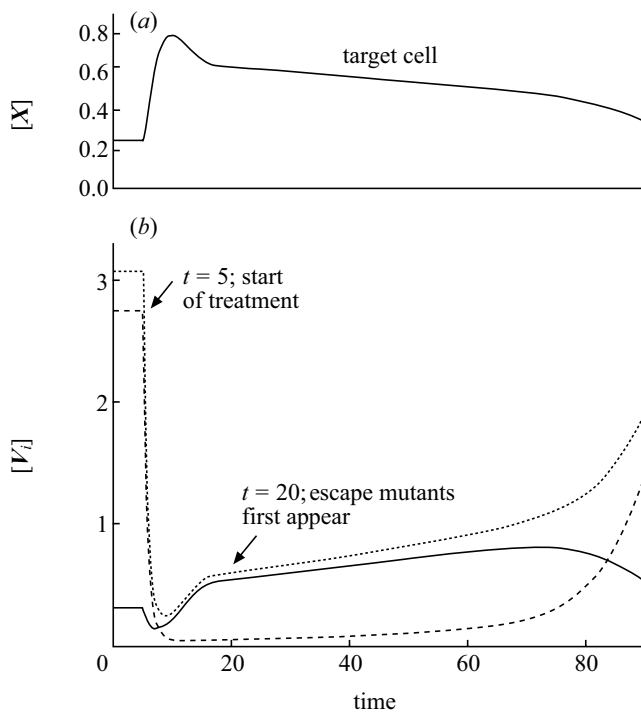


Figure 3. Effect of therapy on virus concentration. The effect of therapy is modelled as equivalent to an increase in immune response strength,  $d_2$ . Therapy is indicated by a stepwise increase in  $d_2$  ( $t = 5$ ) and is followed by (a) an increase in target cells and (b) a phenotype switch with virus load considerably reduced. Note the undershoot and the rebound of virus levels that arise independently of the appearance of escape mutants. Nevertheless, as escape mutants start to emerge ( $t = 20$ ), virus levels gradually return to pretreatment levels. Total virus load, dotted line; high- $k$ , dashed line; low- $k$ , solid line.

essentially two major viral classes with different average replication rates, high- $k$  (SI,  $k = 20$ ) and low- $k$  (NSI,  $k = 4, 7, 9$ ). As already discussed, when the initial immune response is lower than a critical level, the model predicts a viral population dominated by the SI phenotype. Indeed, as figure 2*d* shows, initially there is a burst in the total virus load (dotted line) composed largely of the SI variant.

A switch to an NSI-dominated latent phase of variable length soon follows the mounting of a specific immune response (figure 2*c,d*). However, the immune response magnitude declines (figure 2*a*;  $t = 80-530$ ) as HIV destroys the immune system by its very replication. As the immune system deteriorates, and since the NSI subpopulation itself is divided into variants of different replication rates (Haase 1999), consecutive switching events occur as viruses of greater replication rates within the NSI subpopulation gain a selective advantage. With each switch, total virus load increases and target cell population decreases further (figure 2*b,d*;  $t = 80-400$ ). At the final symptomatic stages of the disease ( $t = 400-530$ ) the immune response is sufficiently low for the SI high- $k$  variant to gain dominance. A marked decrease in target-cell population follows the ensuing steep increase in virus load (figure 2*b,d*;  $t = 400-530$ ).

Clinical studies have demonstrated that the period of time needed for the immune response to decrease sufficiently for the SI variants to gain a selective advantage

(i.e. the incubation period) is determined by the initial immune response and viral load (Lifson *et al.* 1997; Arnaut *et al.* 1999; Ogg *et al.* 1999). This is also an elementary prediction of the model. Since the replication rates of the dominant virus and the immune response are inversely proportional, it is to be expected that a virus variant of a somewhat higher replication rate (and a higher virus load) should follow a weak initial immune response. Because the production rate of new viruses determines the rate at which the immune system is destroyed, a higher initial replication rate characteristic of weak responders entails a faster destruction of the immune system and therefore a shorter incubation period. In this respect, it is interesting to note that HIV patients in San Francisco develop AIDS more slowly than patients in Africa (the 'transmission hypothesis' of Ewald (1994) and Freeman & Haron (2001)). From studying the model, it can be seen that this result is to be expected, as native Africans are less well nourished and more exposed to parasites than residents of the San Francisco area, and thus their immune response is also weaker than that of a person living in a western society. Consequently, the average replication rate of HIV resident in Africans is likely to be higher.

Response to therapy is another issue of wide concern; observations from HIV patients under treatment with HAART indicate that infected cells of lower replication rates gain dominance as therapy begins (Haase 1999), but the disease is only suppressed, not eradicated. The same analysis as used previously may account for these findings. A reasonable first approximation in modelling drug therapy is to equate the effect of HAART as an increase in the immune response,  $d_2$ . From this consideration, efficient drug therapy (modelled here by a strong immune response) is likely to remove virus-infected cells of high replication rates. However, the virus population as a whole is not eliminated but only greatly reduced, for as the highly prolific variants are rapidly removed the less productive but more drug-resilient variants take over. The result is illustrated in figure 3 ( $t = 5-20$ ) and bears a striking resemblance to clinical studies (Bonhoeffer *et al.* 1997). This peaceful intermission only lasts for a relatively short time-interval since drug-resistant escape mutants soon arise by mutation from the 'latent' reservoir, escaping the effects of the treatment and, in effect, reducing  $d_2$  gradually to its pre-treatment level. The reduced selective pressure makes higher replication rates, possible once more (figure 3;  $t = 20-90$ ).

Finally, opportunistic infections are known to emerge at the final stages of AIDS in many patients, ranging from retroviral viruses to fungal and bacterial infections (Fields *et al.* 1996; Telzak *et al.* 1998; Janeway 1999; Greenblatt *et al.* 2001). These viruses are rarely detected in the population and are therefore hardly ever transmitted horizontally (from one individual to another by physical contact). These two facts suggest that the virus already existed in a small fraction of the cells of these individuals even before they were infected with HIV. Why were the viruses not eradicated by the previously potent immune system, and by what mechanism can the virus sense the impairment of the immune response, if it is indeed latent? We suggest that the viruses cited are practically invisible to the immune response due to very low expression levels; however, some minimal replication level is maintained. Those

viral variants replicating at a more prolific rate are rapidly removed. However, such variants continue to periodically emerge from the almost latent reservoir, either by a mutation that increases the replication rate or by arbitrarily entering a cell type allowing more rapid replication. Once the immune system is sufficiently debilitated, these variants become the rule and an opportunistic infection ensues. We explain this opportunistic mechanism, for the first time, to the best of our knowledge, within the framework of the simple model proposed here.

## 5. CONCLUSIONS

We have demonstrated that high replication rates are not necessarily advantageous for viruses and are in fact disadvantageous against a potent immune response. Thus, our results suggest that the most fit viruses are those that are able to maintain themselves in a careful limbo between replication and latency, avoiding immune system recognition on the one hand and maintaining the virus population and infectivity on the other (a latent virus is generally non-infective due to low viraemia levels). A virus that is able to lower its replication rate when facing a potent immune response and thereby disassemble a healthy cell has a reduced chance of being detected by the immune response and an increased chance of survival. Thus, when immune pressure is increased, the virus population succeeds by decreasing its replication rate and, conversely, an emergence of viruses with high replication rates follows the deterioration of the immune response. Our results are especially important when applied to HIV infection, where the long-term efforts of the immune system, as well as drug treatment, fail to eradicate the virus completely, presumably because of the virus's mutational ability and/or a latent reservoir of viruses.

The results obtained also have implications for one of the underlying assumptions in the evolution of virulence; it cannot be assumed that intrahost competition in general selects for virulence, while the population interhost dynamics have an antagonistic, pacifying effect, ultimately giving rise to intermediate virulence levels (Nowak & May 1994; May & Nowak 1995). Our results show that intrahost dynamics in healthy individuals are sufficient to suppress viruses with high replication rates, in HIV as in other infections such as tuberculosis, herpes etc., where a correlation between immune response and virus activity level is evident (Fields 1996; Kirschner 1999). It can be argued that the latency and reactivation of the viruses are the mechanism of some intricate intracellular molecular switch. However, these molecular switches are the product of genes that have been rearranged and altered by mutation. Thus, even the existence of a proper molecular switch that determines the virus replication rate is itself resolved by the dynamics of the population as a whole. It should also be noted that viral evasive mechanisms make the virus harder to detect, leading to high virus replication rates despite a possibly potent immune response. However, even in this situation, there is still an optimal virus replication rate that decreases with the immune response increase. Moreover, other factors may influence the replication rate of virus variants. For example, we are currently studying the production of defective interfering particles (DIP) as a viral mechanism that could possibly alter con-

siderably viral fitness at the intra- as well as on the interhost level (G. Almgoy and L. Stone, unpublished data).

Because it is assumed that the cell-directed immune response (and not the humoral response) is the one relevant in the struggle against infection, it should be noted that the model, in its present form, mainly applies to viruses and not to other parasites in general. In consideration of this remark, other parasites should be studied according to the specific host immune mechanism (cell-directed, humoral, complement) applied by the host in order to remove that parasite. It cannot be assumed that the relationships found here for viruses such as HIV is valid for other parasites that are not eradicated mainly by the action of the cell-directed immune response.

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