Electronic appendix

1. Main simplifying assumptions

We made three main simplifying assumptions. First, we have not explicitly modeled the dynamics of neutralizing antibodies and CD8 T cells; we assumed that the HIV-specific immune response is related to the number of HIV-specific CD4 cells (Callaway et al. 1999; Kalams et al. 1999). Experimental work has shown that these cells are required for an effective response (Lu et al. 2004), as they are involved in the priming of the CTL response (Livingstone & Kuhn 1999; Ridge et al. 1998; Schoenberger et al. 1998), in the generation of a memory CD8 response (Borrow et al. 1996; Borrow et al. 1998; Ostrowski et al. 2000), and the antibody response (Oxenius et al. 1998). This assumption simplifies the model, but we do not expect the results to be affected qualitatively if we would include the dynamics of CD8 T cells and neutralizing antibodies. Furthermore, the avidities of the epitopes triggering the CD4 and the associated CD8 response are unrelated. Essentially, we assumed that the CD8 response avidities average out over the whole set of CD4 cell of a given avidity.

Second, we only took the lytic component of the CTL response into account, but we expect the results to be qualitatively similar if a non-lytic component was included (Korthals Altes et al. 2003).

Third, T helper clone size is, at large densities, controlled through intra-specific competition, reflected in the density-dependent death term $-\varepsilon H_i^2$ (Fraser et al. 2002). This sets an upper limit to clone size and prevents competitive exclusion between clones.

Otherwise, the helper cell clone with the highest avidity would outcompete all other clones. Experimental evidence indicates that different T cell clones do coexist during chronic infection with HIV (Betts et al. 2001; Betts et al. 2000; Frahm et al. 2004) and LCMV (Homann et al. 2001). In models, this can only be effected through intraspecific (within-clone) competition. Additionally, when the dominant response is removed in a primary immune response, the sub-dominant response does not expand to the levels reached by the dominant response, suggesting that cell numbers are regulated within a clone (van der Most et al. 1996; Vijh et al. 1999). Epitope down-modulation on the antigen-presenting cell has been proposed as a possible explanation for the fact that competition is much stronger within than between T helper cell clones (Scherer & Bonhoeffer 2005).

2. Relationship between viral setpoint and immune response avidity

We focus on the model presented in the methods, but with a single immune response clone.

Ignoring the small terms in the immune-controlled steady state (k=1.5, to have the same level of control by the immune response in the single clone situation as in the situation with multiple clones), we can simplify the model equations to:

$$\begin{cases} \dfrac{dT}{dt} = \sigma - \delta_T T \\ \dfrac{dH}{dt} = \dfrac{\alpha IH}{\gamma / q + I} - \varepsilon H^2 \\ \dfrac{dI}{dt} = \beta IT - kqIH \end{cases} \qquad (1)$$

in which the immune controlled-steady state is:

$$\bar{T} = \frac{\sigma}{\delta_T}, \bar{H} = \frac{(\alpha/\varepsilon)\bar{I}}{\gamma/q + \bar{I}}, \text{ and } \bar{I} = \frac{\beta\sigma\varepsilon\gamma}{q(kq\alpha\delta_T - \beta\sigma\varepsilon)}$$

With our parameter values this corresponds to the function $\bar{I} = \frac{0.8}{q(3q - 0.8)}$ (2)

As can be seen in Fig. A1, this simplification (equation (2)) does not hold for small *q*, as the impact of infection on the target cells T becomes more pronounced, and the dynamics of the T helper and infected cells more complex. Under these conditions, the infection term in the equation for target cells T cannot be ommitted. The death terms in the helper cells and infected cells also become significant, as well as the competition and infection terms in the helper T cell population.

In conclusion, we find a fitting analytical form for the relation between infected cells at steady state and the avidity of the response for the high-avidity range, but we cannot find this for all ranges of avidity.

3. Calculation of threshold avidity for expansion of an HIV-specific CD4 clone

A T helper clone will expand from the naïve state (in which $\sigma_H - \varepsilon H^2 - \delta_H H = 0$, because it is not stimulated by antigen) for a given level of infected cells $\bar{I}$, if and only if:

$$\frac{\alpha\bar{I}H}{\gamma/q + \bar{I}} - \beta\bar{I}H > 0$$

This condition can be further simplified to $\frac{\alpha}{\gamma/q+\bar{I}} > \beta \Leftrightarrow \gamma/q < \frac{\alpha-\beta\bar{I}}{\beta}$

So the functional avidity threshold q_T is defined as: $q_T = \frac{\gamma\beta}{\alpha-\beta\bar{I}}$

4. Robustness

We looked at several alternative models to test the robustness of our results. We looked at the scenario in which killing of infected cells by CTL is not avidity-dependent. In that case, the results are qualitatively similar, with one interesting exception. With the original model, we found a positive correlation between viral setpoint and the total number of CD4 T helper cells at setpoint (Supporting information, Fig. A4.1), whereas if killing of infected cells is not avidity-dependent, we find a negative correlation (Fig. A4.2, and (Muller et al. 2001)). However, in our model at least, the nature of this correlation and the underlying assumptions do not affect any other aspect of disease progression.

The expression for the dynamics of the T helper cells is a rather complex mathematical expression. We here review the robustness of our results for changes in the formulation of these dynamics. The constant source of naïve T helper cells allows for a background level of helper cells in the absence of infection, but is not an element necessary for the results. We modeled competition within T cell populations of the same specificity through density-dependent death. In fact, this is mathematically similar to having a logistic growth term ($r*(K-H_i)*H_i$). To guarantee coexistence of clones of different specificities, competition should occur within clones rather (or more) than between

clones. An alternative way of describing competition is by limiting growth —as opposed to increasing death— as helper cell densities increase. The growth term would then be formulated as follows: $\alpha q_i I/(\gamma+q_i(I+H_i))$. This is less preferable, because biologically not as transparent as the expression we used ($\alpha q_i I/(\gamma+q_i I)$, in which γ/q_i corresponded to the number of infected cells eliciting a half maximal CD4 response. Preliminary results with this alternative growth expression suggest similar results would be obtained.

We looked at the effect of considering a different distribution for the CD4 helper clone avidities within a repertoire, on the relationship between setpoint and immune response characteristics. Assuming a uniform rather than an exponential distribution of avidities, we observed that all avidity measures of the repertoire as detailed in the paper, correlated (negatively) equally well with setpoint. As in our main work, the number of clones at setpoint were a much poorer correlate of setpoint (results not shown).

We have chosen not to include a cross-reactive response such as neutralising antibodies or a cross-reactive CTL response. It was included in the antigenic diversity threshold model, and the threshold only existed if the cross-reactive immune response was unable to control the infection by itself (Nowak et al. 1991). Here, the same result applies: the pattern of disease progression is similar when we include a cross-reactive response, as long as this is insufficient to control infection on its own (simulations not shown).

Finally, we simulated the course of infection, assuming escape mutations have a fitness cost. Essentially, this means that viral fitness progressively decreases, delaying the onset

of AIDS. In our simulation, the loss of fitness associated with each mutation, as expressed in a decrease of the infectivity term (β), has to be small. Otherwise, the virus cannot accumulate “enough” escape mutations to cause AIDS, because infectivity simply becomes too low to sustain infection.

Literature appendix

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Figures legends (electronic appendix)

Fig. A1:

Infected cells at steady state as a function of avidity of the T helper response, in a single clone model. Parameter values are as in Fig. 2, except for the killing rate of infected cells k, which is 5 times as high as in the multiclonal setting (k=1.5). We have done so in order to achieve roughly the same level of virus control by the immune response in the single clone situation as in the polyclonal situation. For high avidity q, the steady state number of infected cells is close to the value obtained with the simplification derived in section 2 of the appendix (equation (2)).

Fig. A2:

Simulated viral setpoint plotted against average avidity of the repertoire, with all clones responding (black symbols; identical to Fig. 2a) or with only the five best clones allowed to respond (open symbols). A patient with a repertoire of high average avidity, with only the five best clones responding, controls the virus to almost the same setpoint level as with the full repertoire. A patient with poor-avidity repertoire, however, has a viral setpoint controlled by the five best clones about a factor two higher than with the full repertoire. The outlier is due to the inclusion of a high-amplitude oscillation in the total number of infected cells between day 150 and 250. Correlation coefficient also given for the dataset without outlier. Parameters as in Fig. 2.

Fig. A3:

Simulated time to AIDS plotted against average avidity of the repertoire, with all clones responding (black symbols) or only the five best clones responding (open symbols). For clarity, we averaged time to AIDS across patients with the same repertoire. Parameters as in Fig. 3.

Fig. A4:

Parameter values as in Fig. 2.

1. Average infected cells between day 150-250 *p.i.* correlates positively with total helper cell numbers averaged over this period, when lysis of infected cells is dependent on avidity of the response.

2. Average infected cells between day 150-250 *p.i.* correlates negatively with total helper cell numbers averaged over this period, when lysis of infected cells is independent of avidity of the response.