ideal Darwinian system” has been the central hypothesis of our previous papers on the subject.

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REFERENCES AND NOTES
2. F. Medema and M. R. Klein, ibid., p. 505.
13. In patient P4, there is increased variation in an HLA-B7 restricted epitope (although it has not been formally demonstrated that the patient’s CTL indeed recognize this epitope). In patients P3, P4, and P5 there is a faster rate of accumulation of non synonymous substitutions than in patients P1, P2, and P6, which leads Wolinsky et al. to conclude that the increase in genetic diversity correlates with positive selection for change.

Response: The “diversity threshold theory” posits that the capability of the immune response is exceeded when antigenic diversity increases beyond a threshold (1, 2). This central tenet is controversial. The high mutation rates inherent to the replicative processes and the short genome doubling time are major factors involved in rapid virus evolution (3). Furthermore, it is the high replicative capacity of the virus rather than the generation of diversity per se that destroys the host. Thus, within a particular host, diversity is driven by the collective sum of all the selective forces acting on the HIV-1 quasispecies virus population, rather than a specific immune parameter by or in itself (4).

The theory predicts two possible outcomes. First, infected individuals with diversity higher than their individual specific threshold lose immune control and rapidly progress to AIDS, while those below their individual specific threshold remain clinically stable. Second, an increase in antigenic diversity over time in the same individual gives rise to loss of immune control and faster progression to AIDS once the individual’s specific threshold is crossed.

The fact that the magnitude of the diversity threshold could be different in different infected individuals is a result of the inherent plasticity of the mathematical model used to derive the antigenic diversity threshold theory (1, 2). As a consequence, the model becomes virtually untestable. The actual model could encompass many different possible parameters that can trigger the trajectory to AIDS, all of which are sensitive to initial conditions (3) and better expressed as a nondimensional threshold condition (6). Thus, stochastic simulations of the infection process only partially characterize the model dynamics (3).

The results of our study (7) do not support a model that relates increasing antigenic diversity to pathogenic progres-

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Fig. 1. Lack of correlation between progression to AIDS and HIV-1 diversity. Rate of CD4 T cell decline (heavy solid line, read against y-axis at left innermost) and the HIV-1 proviral-associated RNA burden (light line with triangles, read against y-axis at right) in the six different patients [see Wolinsky et al. (7) for more details] correlates neither with the subjects’ viral diversity, measured by Shannon entropy measurements (large circles, read against y-axis at left outermost) of the proviral gp120 sequences, nor with the median Hamming distance (filled hatch, read against y-axis at left outermost) between the sequences in each time point. Shannon entropy and median Hamming distance were calculated according to methods described in the report by Wolinsky et al. and are given as percentage of the maximum entropy (1.69 = 100%; P4 at 48 months) and median Hamming distance (9.91 = 100%; P4 at 48 months) among these patients. Dotted vertical lines represent the time of clinical AIDS diagnosis. Dashed vertical lines represent the time of death of the study subject. An increase in the viral burden or in the rate of CD4 T cell depletion during progression to disease of each subject is not necessarily correlated with an increase in viral diversity for that study subject. Rather, for several subjects, an increase in HIV-1 diversity occurs when the viral burden decreases and CD4 T cell count increases.
sion. Although Nowak et al. attribute the limited diversity observed for those people who had a more rapid rate of CD4 T cell loss after primary infection to the transgression of their individual specific threshold, such a threshold is nonexistent or negligible. A diversity threshold of "one strain" (1, 2, 8) cannot be considered a threshold because a lower value of diversity is not possible. Furthermore, a stochastic simulation of these "weak immune responders" models a viral burden that continues to escalate exponentially. This is not biologically plausible.

The model would also predict that, at least in some individuals, the apparent diversity of viral forms in a quasispecies virus population expands before a precipitous decline in the CD4 T cell count (1, 2). We find that within infected individuals with slower rates of CD4 T cell loss, higher viral diversity did not correlate with an increase in the viral burden or CD4 T cell decline (Fig. 1). The results, while limited by a small sample size, are nevertheless not consistent with the outcome Nowak et al. predict (1, 2, 7).

We used a measure of protein diversity as a surrogate for antigenic diversity and tracked substitutions in well-characterized CTL epitopes (7). The relevant caveats concerning these analyses were considered and explained at length in the text and notes of our report (7). However, using the analytical measures and parameters put forth by Nowak et al., which are more appropriately a measure of genetic distance than protein diversity, we are still unable to support the premise that breaching a specific antigenic diversity threshold is a likely precipitating event to the progression to disease (7, 8).

Nowak et al. submit that a valid empirical test of the diversity threshold theory is to assess antigenic oscillations and shifting immunodominance in defined human leukocyte antigen (HLA) class I-restricted epitopes (9, 10). We found the genetic characterization of unambiguously defined HLA class I-restricted CTL epitopes in Env and a significant response against Env in two patients (P4 and P5) rather than one, as stated by Nowak et al. Nowak et al. further contend that, because of other potentially confounding selective forces, Gag and Pol are more appropriate regions for analysis than is Env. Their reasoning and their interpretation of our results are difficult to rectify with the current state of knowledge about the biology of the cell-mediated immune response (11).

Nowak et al. concur with our final conclusion that "HIV-1 quasispecies dynamics are compatible with an ideal Darwinian system." We agree with Nowak et al.'s assertion that viral evolution is driven by selective forces. We suggest that the problem is with their interpretation of the model, specifically the statement that an "antigenic diversity threshold" has an important role in viral pathogenesis.

When judged by empiricism in the context of reasonable definitions that distinguish between antigenic and genetic diversity and the potential for applicability to other biological systems (3), the "diversity threshold theory" lacks relevance and sufficient experimental support. Specifically: (i) the theory does not explain the limited diversity observed for those people who have a rapid rate of CD4 T cell loss after primary infection, and (ii) existence of an "antigenic diversity threshold" for those people with a lower rate of CD4 T cell loss has yet to be demonstrated experimentally.

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Response: HIV-1 Evolution and Disease Progression
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