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HIV tropism and CD4⁺ T-cell depletion

To the editor—We fully support the conclusions reached by Grossman *et al.*[1] concerning the critical role of immune activation in HIV-1 pathogenesis. We also concur with the concerns they have expressed about incomplete and potentially flawed interpretations of the labeling experiments used to determine the rates of T-cell turnover in HIV-1 infection[2].

There is no doubt that HIV-1 can destroy CD4⁺ T-cells both *in vitro* and *in vivo*, but this cannot be the sole explanation for HIV-1 disease progression. As shown by studies of the natural hosts for simian immunodeficiency virus infection, such as sooty mangabey monkeys and African green monkeys, chronic high levels of virus replication can be tolerated without development of immunodeficiency disease[3,4]. As such, high-level replication of CD4⁺ T cell–tropic lentiviruses *per se* need not be lethal to the host. Rather, it is the interplay between the virus and the immune system that converts what might otherwise be a benign infection to a lethal one[1,3,5].

An important additional point of discussion is the phenotype of the HIV-1 strains that are present in infected humans[6]. Viruses that use the CCR5 coreceptor for entry (R5 strains) predominate in the early stages of infection in virtually all HIV-1 infected individuals. However, phenotypic variants using the CXCR4 coreceptor (X4 strains) are eventually detectable in about 50% of infected individuals and are associated with a more rapid rate of CD4⁺ T-cell loss[7]. In patients who have only R5 HIV-1 variants, immune activation is already chronic and strong, but increases significantly after X4 variants emerge[8].

Perhaps as important is the observation that R5 and X4 strains infect different CD4⁺ T-cell subpopulations. R5 viruses preferentially replicate in activated, memory/effector T cells while X4 viruses are also capable of infecting intrathymic T progenitor cells and naive T cells in the peripheral lymphoid system[9,10]. Indeed, circulating naive CD4⁺ T cells are infected at high frequency in patients with X4 virus and such infection is associated with a drop in their numbers[10,11]. Consequently, the emergence of X4 viruses in an infected person will both exacerbate ongoing chronic immune activation and facilitate the destruction of the very cells that are involved in maintenance of the naive and memory CD4⁺ T-cell pools. As a result, the regenerative capacity of the immune system will collapse[12].

In conclusion, we suggest that a complete and balanced understanding of HIV-1 pathogenesis is required for the design of novel immune-based therapies to supplement the present therapies that directly target the viral life cycle. The antiviral immune responses of HIV-1-infected adults and children can clearly be beneficial to the host, especially in the short-term, but the sustained overstimulation of the immune system during chronic infection may have a cumulative, detrimental effect. The direct damage that is inflicted on the immune system by HIV-1 replication and the indirect consequences of generalized immune activation together result in both accelerated CD4⁺ T-cell destruction, and an impaired ability of the immune system to regenerate and to repair the damage that it has incurred. If the virology and immunology research communities work together to understand this interplay more completely, more effective long-term treatments for HIV-1 infection might be designed.

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To the editor—I would like to comment on the article by Grossman *et al.*[1], since my name has been on papers on both sides of this debate. A key point raised by these authors is the notion of biphasic