erate $10^{12}-10^{13}$ physical virus particles (4×10^7 cells $\times10^5$ virions released per cell). However, the plasma virus load measured by both groups was only 10^8–10^9 particles, each with a half-life of about 1–2 days[2]. This amount of virus would be produced by only 10^3–10^4 not 4×10^7 $CD4^+$ cells per day. Alternatively, if the number of physical particles produced each day was actually 10^{12}–10^{13}, then each released virion would have a half-life of approximately 10 s, which is unrealistic. Unfortunately, neither group directly measured the number of productively infected cells in their analyses of virus and $CD4^+$ lymphocyte turnover during antiviral therapy. The number of newly infected cells per day was estimated from increases in $CD4^+$ cell number, assuming, as noted above, a quasi-steady-state relationship between $CD4^+$ lymphocyte replacement and killing.

Although the measured rise in circulating $CD4^+$ cells is substantial, this increase may not be representative of total $CD4^+$ cell turnover. Lymphocyte trafficking, homing and recirculation is a complex, multifactorial process and changes in the $CD4^+$ cell number in the peripheral blood may not reflect simple quasi-steady-state alterations. Because lymphocytes in the peripheral blood comprise such a small fraction (1/50) of the total lymphocytes in the body, major changes can occur, for example, as a consequence of the rapid redistribution of cells from different compartments that attends normal diurnal variation[8]. Further, most lymphocytes do not circulate in either the blood or lymphatics but reside in spatially heterogeneous environments[9]. Thus the 50-fold multiplication step to calculate the total number of $CD4^+$ cells killed by HIV-1 and replaced each day, which assumes rapid and complete exchange of lymphocytes between the peripheral blood and the rest of the body, is not warranted for such a large, heterogeneous non-equilibrated system unless the numbers and dynamic properties of cells residing in diverse major compartments are directly measured.

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Antiviral therapy

SIR — Ho *et al.*[1] state that "patients with lower initial CD4 cell counts had more prominent rises" (in CD4 count during treatment). This conclusion was substantiated with an analysis showing a correlation coefficient of -0.57 ($P<0.01$) for the association between initial CD4 count and slope of log CD4 count increase after therapy. This finding suggests there may be a greater propensity for CD4 lymphocyte regeneration at lower CD4 counts compared with higher counts. This could explain the paradox of why the CD4 count decline is on average more rapid early in HIV infection, when the CD4 count is high and cellular and cell-free virus are low, rather than later in the infection when CD4 counts are lower and virus levels are substantially higher[2].

However, although indeed the number of new cells appearing in the blood per existing cell is greater at lower CD4 counts, the absolute number of new cells appearing in the blood at any given time may not necessarily be greater, for which the slope of unlogged CD4 count increase after therapy must be measured. When this is done the correlation coefficient for the association between initial CD4 count and slope of CD4 count increase is 0.08 ($P = 0.75$; Spearman rank correlation coefficient), suggesting that on average no more new cells appear in the blood in a given time after starting therapy in individuals with lower CD4 counts than in those with higher counts. When looked at in this light, the results[1] do not appear to explain the paradox. The suggestion[3,4] that the immune system is likely to play a major role in cell destruction — rather than the process being mainly due to direct cell killing by virus — is more consistent with the data as it offers a possible explanation for why the rate of CD4 count decline gradually decreases as more severe immunodeficiency develops.

Ho *et al.* also suggest[1] that analyses of the marked CD4 count rises seen after therapy "demonstrate convincingly that the CD4 lymphocyte depletion seen in AIDS is primarily a consequence of the destruction of these cells induced by HIV-1, not a lack of production". Although this may be correct, it is not clear how the latter possibility has been excluded: if HIV-1 inhibited CD4 cell production, a rise in cell numbers might be expected when HIV-1 levels are drastically reduced by therapy. It is also not clear that the newly increased CD4 count in the blood is indeed due to newly produced cells. As the viral load decreases acutely, the redistribution of CD4 cells from tissues to blood, perhaps with an accompanied decrease in CD8 count[5], is possible.

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Other approaches

SIR — Some[1,2] have inferred from two recent papers[3,4] that $CD4^+$ T-cell infection determines parameters of HIV disease, and that immunostimulatory therapies are doomed to fail[3]. But alternative interpretations remain.

The new work[3,4] reports that the turnover of $CD4^+$ lymphocytes in AIDS patients is about 8 cells per μl blood per day. Does this turnover reflect an accelerated rate of $CD4^+$ T-cell production that strains the long-term proliferative capacity of the immune system? A definitive answer awaits accurate estimates of the turnover and half-life of both proliferating and peripheral $CD4^+$ T cells in healthy individuals, normative data for which the immunological community strangely lacks a robust appraisal. However, taking 75 days (range of 50–100 days, as adopted in ref. 4) as a best current estimate of peripheral blood mononuclear cell half-life in the circulation, and 1,100 $CD4^+$ cells per μl peripheral blood as an accepted average[5], we can calculate that $0.5\times1{,}100/75$, or about 7, $CD4^+$ T cells per μl are normally replaced in the circulation each day. This turnover number is surprisingly close to that calculated in AIDS patients, suggesting that the infection-specific rate of $CD4^+$ T-cell production is close to normal and unlikely to exhaust proliferating populations, even after years of disease. If so, immunostimulatory strategies should not yet be discounted as viable therapeutic approaches against AIDS.

A most remarkable observation by both groups[3,4] is that, in each patient, post-treatment titres of resistant (mutant) viral strains rapidly rise very nearly to pretreatment levels. Why are the antiviral responses of the immune system, despite its activation against HIV-1, unable to maintain viral replication at lower levels once the infection has been reduced by chemotherapy? Although viral replication immediately after the emergence of resistant strains outstrips the antiviral defences of the immune system, the rate of increase of virus production eventually slows, establishing an equilibrium between production and clearance of the virus.

One simple hypothesis would account for this phenomenon. If $CD4^+$ T-cell