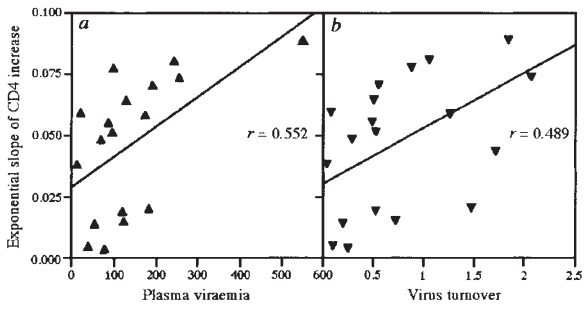

Correlation between baseline plasma viraemia (*a*) or virus turnover (*b*) and exponential slope of CD4 T-cell increase. Data are from Table 1, ref. 1.

exponential slope of "CD4 lymphocyte turnover" (0.004–0.088) shown in Table 1 of ref. 1 is inconsistent with replacement of CD4 T cells solely by rapid cell division, as the exponential slope should be relatively constant (reflecting mainly the relatively minor variations in cell-cycle time). Examination of lymph nodes from both HIV-infected progressors[4] and non-progressors[5] provides evidence for B-cell proliferation in germinal centres, but little evidence for a pool of proliferating CD4 T cells. In conclusion, a large part of the increase in CD4 T cells seen after acute antiviral therapy is probably due to reduced trapping in lymphoid tissue and a short-term reappearance of cells in the peripheral circulation.

Donald E. Mosier
Department of Immunology-IMM7,
The Scripps Research Institute,
La Jolla, California 92037, USA

1. Ho, D. D. *et al. Nature* **373**, 123–126 (1995).
2. Wei, X. *et al. Nature* **373**, 117–122 (1995).
3. Mackall, C *et al. Nature* **332**, 143–149 (1995),
4. Embretson, J. *et al. Nature* **362**, 359–362 (1993).
5. Pantaleo, G. *et al. New Engl. J. Med.* **332**, 209–216 (1995).

SIR — Wei *et al.*[1] and Ho *et al.*[2] report that administering inhibitors of viral replication to HIV-infected patients causes a considerable, transient increase in $CD4^+$ cell counts in the blood. From this, the authors conclude that the production of $CD4^+$ cells during HIV infection is very rapid and sufficient to replace about 5% of the $CD4^+$ cell pool each day. Wei *et al.* then speculate that it may be possible to achieve ". . . successful immunological reconstitution even in late-stage disease if effective control of viral replication can be sustained." Not surprisingly, this idea has elicited wide interest.

But the data on $CD4^+$ cell dynamics[1,2] are based solely on counting numbers of $CD4^+$ cells in blood: in neither study did the authors provide direct evidence on the rate of production (division) of $CD4^+$ cells. The tacit assumption in both studies is that finding an increase in $CD4^+$ cells in the blood is indicative of an increased production of these cells. In making this assumption, however, the authors ignore the possibility that their data simply reflect an alteration in lymphocyte migration.

Like $CD8^+$ cells and B cells, most $CD4^+$ cells are long-lived cells which recirculate continuously between blood and lymph via the lymphoid tissues[3–6]. But it is well known that lymphocyte migration is labile and can be radically altered by exposure to various infectious agents or to stress[4]: rapid alterations in lymphocyte migration can apply to resting cells and be associated with little or no change in the rate of lymphocyte turnover. Because viral infections often impede lymphocyte migration through the lymphoid tissues (the phenomenon of "trapping")[3,4], the transient increase in $CD4^+$ cell counts in the blood of HIV patients given antiviral agents could be a reflection of enhanced lymphocyte recirculation (decreased trapping) due to the reduction in the viral load. If so, most of the $CD4^+$ cells would be expected to display a resting rather than an activated phenotype. This is easily tested.

To reiterate, we take issue with the view that the data of refs 1 and 2 demonstrate that $CD4^+$ cells have a high rate of self renewal. In our opinion the transient elevation of $CD4^+$ cells seen in the blood could be an epiphenomenon: the reduction in the viral load induced by the antiviral agents reduces trapping of $CD4^+$ cells and thereby facilitates recirculation of these cells.

Jonathan Sprent
David Tough
Department of Immunology,
Scripps Research Institute,
La Jolla, California 92037, USA

1. Wei, X. *et al. Nature* **373**, 117–122 (1994)
2. Ho, D.D. *et al. Nature* **373**, 123–126 (1994).
3. Ford, W.L. *Prog. Allergy* **19**, 1–59 (1975).
4. Sprent, J. *The Lymphocyte: Structure and Function* (ed. Marchalonis, J. J.) 43–112 (Dekker, New York, 1977).
5. Sprent, J. *Curr. Opin. Immun.* **55**, 433–438 (1993).
6. Sprent, J. & Tough, D. *J. exp. Med.* **179**, 1127–1135 (1994).

SIR — Ho *et al.*[1] and Wei *et al.*[2] report that levels of cell-free virus in the plasma of HIV-1-infected patients fell approximately 100-fold within 2–4 weeks of the start of antiviral therapy, and was accompanied by a rise (approximately 200 cells per μl) of $CD4^+$ lymphocytes. The authors assumed that the rise in $CD4^+$ cell number observed equalled the number of cells that were not infected and killed by HIV-1 as a consequence of the effective therapy, and calculated that HIV-1 infected and killed approximately 4×10^7 $CD4^+$ peripheral blood lymphocytes each day. They also proposed that the measured rise in circulating $CD4^+$ cells reflected an increase in the total number of $CD4^+$ lymphocytes in all body compartments of an infected individual. Because only 2% of lymphocytes are present in the peripheral blood, the authors multiplied the $CD4^+$ cell increase by 50 and calculated that an HIV-1 AIDS patient can replace approximately 2×10^9 cells each day. We believe that these analyses grossly overestimate the number of the $CD4^+$ cells killed by the virus and the regenerative capacity of the immune system in AIDS patients.

We have monitored wild-type and mutant HIV-1 infection kinetics in a variety of tissue culture systems and have derived infection rate constants that allow two critical parameters of the virus life cycle to be calculated: (1) the number of infectious virus particles (n) produced during a single cycle of replication; and (2) the time (t_i) required to complete one cycle of infection[3]. During a single cycle, each infected cell generated approximately 10^5 physical particles and 10–100 infectious particles, depending on the particular isolate used.

The t_i calculated for several independent tissue-culture infections (3–4 days) is strikingly similar to the reported half-life (1.5–2 days) of cell-free virus particles (measured by RNA PCR) or HIV-1-producing cells in individuals responding to potent antiviral agents[1,2]. We have also determined the *in vivo* infection rate constants and n values from published reports of individuals undergoing a primary HIV-1 infection or AIDS patients receiving potent antiviral drugs[2,4–6]. The rate constant for the exponential increase of drug-resistant viral RNA in the plasma of AIDS patients was reported to be 0.27 (ref. 2). We calculated a very similar rate constant (approximately 0.3) for patients undergoing a primary HIV-1 infection[4–6]. Assuming that the length of a single cycle *in vivo* is also 3 days, the value of n under these conditions would be 2.5 ($n = \exp(kt_i) = \exp(0.3 \times 3)$). Thus 2–3 infectious HIV-1 particles, on average, are released from each cell in the two types of *in vivo* infections.

An independent quantitative study, using an end-point dilution approach, reported that one infectious particle corresponded to about 6×10^4 physical particles in HIV-1-infected individuals[7]. Thus, in both tissue culture and *in vivo* infections, an infected cell produces approximately 10^5 physical particles and far fewer infectious virions.

The two recent *Nature* reports[1,2] estimated the number of newly infected/replaced $CD4^+$ cells in the peripheral blood of AIDS patients to be 4×10^7 per day. As noted above, this number of infected cells should gen-