HIV results in the frame

The following is a selection of the correspondence received about two papers published on 12 January on the dynamics of HIV infection *in vivo*.

Results confirmed

SIR — Elegant studies using early, frequently sampled patients on nevirapine and protease inhibitors (ABT-538 and L-735.524) have now made it possible to calculate the rapid turnover of HIV-1 virions in infected patients[1,2]: the rate of plasma retroviral decay revealed a half-time of about 2 days for free virus particles or virus-producing cells, indicating that about 30% of the plasma virus population in infected patients is replaced every day. These observations have important implications for our understanding of HIV pathogenesis, and here, using a similar analysis in our previously analysed cohort of 11 AZT-treated patients[3–5], we confirm the earlier findings[1,2].

Our patients were homosexual men with CDC group IV disease, who had had no prior AZT therapy[5]. Serum HIV-1 RNA only from enveloped virions was measured with an assay previously described[6]. After starting treatment, serum samples were taken every 2–3 days.

Virus levels declined rapidly and reached a nadir (or inflexion point) after 6–14 days of therapy. AZT prevents the infection of new cells, but not the production of virus from cells already infected. Thus we expect serum virus to decline according to $v(t) = v(0)[ue^{-at} - ae^{-ut}]/u - a)$[1]. Here $v(t)$ denotes plasma virus at day t after treatment has started; $v(0)$ is the initial viral load; a and u describe the decay of the virus-producing cells and free serum virus, respectively. We do not have enough data points to fit this function, but we approximate the compound decay by a simple exponential decline. It is important to note that data on serum HIV-1 RNA do not allow us to determine which of the two decay processes is rate-determining. Hence the estimated half-time, being a function of the survival of virus particles in the serum and the decay of virus-producing cells, can represent only the upper limit of viral half-time, assuming immediate and absolute inhibition of viral synthesis, which would seem implausible.

The table shows the analysis of our patients. For each patient the initial viral load (in copies per ml), the minimum virus load (and the day when it was reached), the rate of decline, the daily turnover, the half-life time and the data points used for the fit of the exponential decay curve are shown. The average rate of virus decline is 0.46 ± 0.31 (days), the daily turnover is 35 ± 17%, and the half-life time is 1.9 ± 1.1 days. (For these averages we leave out patient 1, who never achieved a 50% decline in serum viral load and whose viral half-life time is about 9 standard deviations higher than the mean value.) This is in excellent agreement with earlier observations and the results obtained by Wei *et al.*[1] and Ho *et al.*[2]. These data confirm the high level of virus production and rapid turnover of HIV particles in infected patients.

DYNAMICS OF HIV INFECTION

Patient	Initial virus load	Minimum virus load	Rate of decline	Daily turnover	Half-life time	Data points used for fit
1	2,300	1,480 (7)	0.06	0.06	11.0	2
2	30,000	3,000 (8)	0.27	0.24	2.6	3
3	18,000	80 (7)	1.10	0.67	0.6	3
4	320	40 (7)	0.30	0.26	2.3	2
5	420	80 (6)	0.35	0.30	2.0	3
6	1,680	140 (14)	0.34	0.29	2.0	3
7	2,380	640 (6)	0.17	0.16	4.0	3
8	8,480	140 (8)	0.35	0.30	1.0	4
9	11,760	140 (8)	0.63	0.46	1.1	4
10	25,600	440 (8)	0.88	0.58	0.8	3
11	1,280	220 (7)	0.25	0.22	2.8	2
Mean ± 1 s.d. (with patient 1)			0.43 ± 0.31	0.32 ± 0.18	2.7 ± 2.9	
Mean ± 1 s.d. (without patient 1)			0.46 ± 0.31	0.34 ± 0.17	1.9 ± 1.1	

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$CD4^+$ cell turnover

SIR — The provocative papers by Ho *et al.*[1] and Wei *et al.*[2] both conclude that antiviral therapy of HIV infection results in a rapid turnover of CD4 T cells, leading to the net production of about 2×10^9 CD4 T cells each day. Three explanations could account for the rapid increase in CD4 T cells in the first weeks after initiation of therapy: (1) new production from thymic progenitors; (2) proliferation of peripheral CD4 T cells; or (3) mobilization of CD4 T cells from infected lymphoid tissue. New production of CD4 T cells in the thymus of adults with chronic HIV infection seems highly unlikely[3], so the competing hypotheses are cell proliferation versus cell mobilization.

Both papers conclude that there is a high rate of CD4 T-cell proliferation which, in the absence of antiviral treatment, is balanced by an equally high rate of HIV-induced CD4 T-cell death — the mobilization of CD4 T cells is not considered. The data shown in Fig. 2*b* of ref. 1 are informative for deciding between proliferation versus mobilization of CD4 T cells. The rate of CD4 T-cell expansion might be expected to be independent of or positively correlated with pre-therapy CD4 T-cell counts, because patients with the lowest starting CD4 T-cell count should have fewer proliferating T cells as well as destruction of lymph-node architecture[4,5]. However, the patients with the lowest starting CD4 T-cell count actually show the highest rate of CD4 T-cell recovery (Fig. 2*b* of ref. 1).

An alternative possibility is that a higher viral load is correlated with more trapping of CD4 T cells in lymphoid tissues, and that effective antiviral therapy liberates these cells into the peripheral circulation. Were this explanation to be true, then replotting Fig. 2*b* of ref. 1 as the exponential slope of CD4 increase versus the baseline plasma viraemia should show as significant correlation as the original figure. The recalculated figure is shown here (*a*). The correlation coefficient is +0.55, which is statistically identical to the original figure plotting the slope of CD4 T-cell change versus starting CD4 number ($r = -0.57$). If the rate of virus turnover is plotted against the slope of CD4 T-cell increase (*b* in the figure), a positive correlation is also seen, so both a high starting virus load and a large drop in virus load following therapy predict more rapid CD4 T-cell recovery, and their effects cannot be distinguished from a low initial CD4 T-cell count. It is thus equally likely that the starting viral load and the magnitude of the antiviral effect determine the ability of CD4 T cells to reappear in the peripheral circulation, which is consistent with the mobilization hypothesis.

In addition, the 22-fold variation in the