# Virological mayhem

*Simon Wain-Hobson*

ONCE again we're back with HIV and AIDS, this time in the form of the data analyses by Wei *et al.*[1] and Ho *et al.*[2] that appear on pages 117 and 123 of this issue. The two groups have looked at the relationship between production of HIV-1 virions and turnover of CD4 T lymphocytes, the preferred target for HIV, in patients undergoing treatment with various drugs. The picture that emerges is of a titanic struggle between the virus and the immune system.

The background to this work lies in the rediscovery of HIV in lymphoid organs[3–5] and the realization that there is far more virus and infected cells around than hitherto thought[6–8]. Longitudinal studies have shown that the overall viral load, of both free virus and that within infected cells, increases slowly but inexorably, generally over a period of months to years.

Wei *et al.* and Ho *et al.* show that treatment of patients with a number of anti-HIV drugs results in a rapid reduction of free virus in the plasma within a few days. This reduction is accompanied by an increase in the number of circulating CD4 T cells. A dark side of treatment is the rapid appearance of drug-resistant mutants; a single base change is often sufficient to confer resistance. Whether the target is the viral polymerase or protease, resistant virus may be detectable within a week[9].

Similar data have been around for a year or two and are familiar to the specialist. So what's new? It is precisely the next step, so obvious in retrospect, that has now been made. Wei *et al.* and Ho *et al.* realized that such viral ups and downs provide us with the first glimpse of the dynamics of HIV production. By teaming up with mathematicians they were able to extract the pertinent information; the concordance of their data is remarkable.

Both groups treated mainly symptomatic patients with one of several different anti-HIV drugs. Extrapolating from the changes in the blood they could show that between $10^8$ and $10^9$ virions — the viral infectious units — were being cleared every day, equivalent to 30% of the total. As the levels of blood-borne viraemia show only gradual changes over many months, the daily rates of virus destruction and production must be comparable; that is, HIV production must be around $10^8$–$10^9$ per day. The values differed little between patients. Wei *et al.* were even able to show that the emergence rate of drug-resistant virus ($t_{1/2}$~2 days) was virtually identical to clearance rate at the start of therapy.

The concomitant recovery of CD4 cells following drug treatment was modelled by both groups, who assumed that the dynamics of blood lymphocytes (which represent some 2% of the total) reflected events throughout the body. Accordingly an average of $2\times10^9$ cells per day (range $0.1–7\times10^9$) must have been produced following drug treatment. Once again the rate of destruction of CD4 T cells could be inferred from the fact that changes in the absolute number of CD4 T cells is long (months to years) compared to the timescales involved here (days to weeks). The relatively small net losses of CD4 T cells, $20–200\times10^6$ per day, a figure derived from longitudinal studies of patients, represent the difference of two larger numbers. There is nothing surprising about rapid turnover in the immune system[10,11]. In the best studied system, the mouse, half of most B lymphocytes are renewed within ten days[10].

What is responsible for such efficient virus clearance and CD4 T-cell loss? As an intrinsic cytopathic effect of the virus is no longer credible[12,13], the immune system is the obvious answer. Antibodies specific for HIV, complement and macrophages could cope with the virus. Most of the infected CD4 T cells are to be found deep within the secondary lymphoid organs[3–5]. Yet infection results in the infiltration of HIV-specific cytotoxic T lymphocytes (CTL) or 'killer' cells[14,15]. The CTL are consummate brokers of viral infections and are highly efficient in clearing viruses[16]. So long as a few virus proteins are being produced, the infected cell is marked out as foreign and ripe for destruction, often before the cell has had time to make completed virions.

The finding that more cells turn over than free virus would at first sight seem counter-intuitive, particularly as CD4 T-cell loss is a consequence of viral infection. This shows that total virus is underestimated by the two new studies, the virus in the periphery probably representing the excess production. But it is exactly what would be expected if CTL were stopping the vast majority of infected cells from producing progeny, leaving only a very small proportion able to produce virus. Indeed the tempo of virus sequence divergence requires such a result[13]. Note that CTL succeed by killing the virus-infected cell, so that the price to pay for viral clearance is a small part of the host. This is not a problem in an acute viral infection which is over in days, leaving ample time to recover the lost cells.

That billions of virions and infected cells can be destroyed every day vividly illustrates the very hostile environment created by the immune system — the meanest of streets are nothing by comparison. HIV counters by massive force of numbers. So long as a few progeny survive to continue replication and transmission then, from the point of view of the virus, that is a success story despite the billions destroyed. That the surface is, for many years, relatively calm is a tribute to the heroic efforts of the immune system. With so much virus and so many infected cells around, the AIDS-without-HIV hypotheses can definitely be sidelined.

Are there any practical implications of these new findings? Given that the virus is replicating 24 hours a day and from day one, antiviral treatment is called for at all stages of disease. Any means to reduce viral spread will ultimately be beneficial. Yet an asymptomatic patient can harbour at least $10^6$ genetically distinct variants of HIV, and for an AIDS patient the figure is more than $10^8$, among which one may find drug-resistant mutations even in the absence of therapy[17]. Against this background, monotherapy cannot succeed. Only combinations of drugs have the potential to outgun the virus. The recovery of the CD4 count, even in symptomatic infection, implies that immune reconstitution may be possible as long as replication of the virus can be held in check.

The new analyses are most welcome because they clarify the picture considerably. They show that HIV is behaving more and more like a virus, without frills or special effects. It is unique and subtle, but a virus nonetheless.

Finally, at a time when there is discussion as how best to channel resources for AIDS research[18], it is worth noting that the main elements of our current picture of AIDS have come from old HIV hands rather than from insights into other viral or microbial lifestyles. True, there has been much poor AIDS research, many trivial theories and — yes — an appreciation of the immunopathology[16] was long overdue. But the analyses of Wei *et al.* and Ho *et al.* show that there is a strong signal in AIDS research despite all the noise. Things are finally getting interesting. □

*Simon Wain-Hobson is at the Institut Pasteur, 28 rue du Dr Roux, 75724 Paris Cedex 15, France.*

1. Wei, X. *et al. Nature* **373**, 117–122 (1995).
2. Ho, D. D. *et al. Nature* **373**, 123–126 (1995).
3. Racz, P. *et al. Progr. Allergy* **37**, 81–181 (1986).
4. Pantaleo, G. *et al. Nature* **362**, 355–358 (1993).
5. Embretson, J. *et al. Nature* **362**, 359–362 (1993).
6. Piatak, M. *et al. Science* **259**, 1749–1754 (1993).
7. Simmonds, P. *et al. J. Virol.* **64**, 864–872 (1990).
8. Connor, R. I., Mohri, H., Cao, Y. & Ho, D. D. *J. Virol.* **67**, 1772–1777 (1993).
9. Richman, D. D. *et al. J. Virol.* **68**, 1660–1666 (1994).
10. Freitas, A. A. & Rocha, B. B. *Immun. Today* **14**, 25 (1993).
11. Michie, C. A., McLean, A., Alcock, C. & Beverley, P. C. L. *Nature* **360**, 264–265 (1992).
12. Phillips, A. N. *et al. Nature* **367**, 124 (1994).
13. Wain-Hobson, S. *Nature* **366**, 22 (1993).
14. Tenner-Racz, K. *et al. Am. J. Path.* **142**, 1750 (1993).
15. Cheynier, R. *et al. Cell* **78**, 373–387 (1994).
16. Zinkernagel, R. M. & Hengartner, H. *Immun. Today* **15**, 262–268 (1994).
17. Najera, I. *et al. J. Virol.* **69**, 23–31 (1995).
18. Fields, B. *Nature* **369**, 95–96 (1994).