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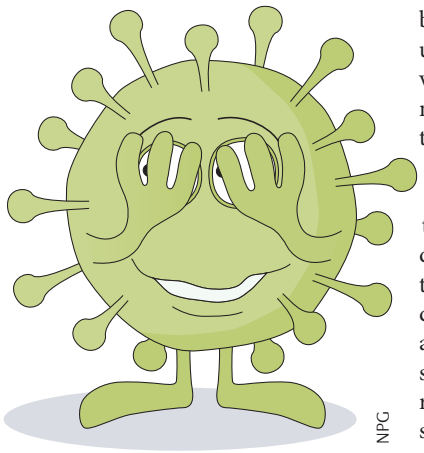
VIRAL INFECTION

Playing hide and seek with HIV

Antiretroviral therapy (ART) can suppress HIV replication, lowering RNA levels to below the detection limit in the blood. However, virus replication rebounds once therapy is stopped as HIV establishes a reservoir of latently infected cells, which harbour integrated viral DNA but do not necessarily produce HIV RNA. Whether there is ongoing viral replication despite successful ART has been debated intensely, as ongoing replication would have implications for the eradication of the latent reservoir and for the development of resistance to antiretroviral drugs. Lorenzo-Redondo *et al.* now find that HIV continues to replicate even when HIV RNA in the blood is undetectable, thereby replenishing the latent reservoir in lymphoid tissues.



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To track continuing viral evolution, which can only happen if viral replication occurs, the authors deep-sequenced HIV DNA in cells from three different patients, who were tested repeatedly while they underwent ART. In contrast to previous studies, the authors studied cells not only from the blood but also from inguinal lymph nodes to sample the reservoir in lymphoid tissues. All three patients had high levels of viral RNA in the blood when they started ART; in two of the patients ART suppressed HIV RNA to undetectable levels in the first few weeks of treatment, whereas one patient only reached complete suppression after 6 months of treatment. However, all three patients had evidence of ongoing viral evolution in the HIV DNA sequences from both the blood and lymph nodes. Phylogenetic trees constructed on the basis of haplotypes of HIV Gag and Pol regions showed continuous divergence during the 6 months of treatment, with mutation rates that were similar to previously estimated mutation rates in infected untreated hosts. Two of the patients harboured some haplotypes that remained unchanged for several months, which is most likely to reflect the proliferation and survival of HIV DNA-containing cells but not active viral replication. The majority of haplotype lineages diverged and there was a clear pattern of compartmentalized evolution — HIV evolved and diversified in lymph nodes, from where it migrated to the blood. This is consistent with a model of continuing replication in lymphoid tissues and the release of infected cells into the blood.

> “there was a clear pattern of compartmentalized evolution — HIV evolved and diversified in lymph nodes”

Interestingly, the authors did not detect the emergence of drug-resistant lineages, which might be expected in patients who are undergoing ART and have ongoing viral replication and continuously mutating viral lineages. To explain this phenomenon, the authors developed a mathematical model of virus evolution and spread between two compartments with distinct drug concentrations. In this model, the scenario that best fits the patient data assumes little penetration of antiretroviral drugs into sanctuary sites, which enables viruses to replicate but does not enable the selection of drug-resistant but less fit viruses. Partially resistant strains, for which the fitness cost of resistance is smaller, would still be suppressed by the high drug concentrations in the main compartment, and competition from non-resistant strains in the sanctuary site would make the evolution of fully resistant strains unlikely.

The patient and modelling data support the notion that continuous HIV replication in lymphoid tissues, in which drug penetration is low, and trafficking of infected cells to other body sites, replenishes the viral reservoir without selecting for drug resistance. This highlights the challenge of delivering effective therapies to cells throughout lymphoid tissues, which would be needed to eradicate the viral reservoir.

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ORIGINAL ARTICLE Lorenzo-Redondo, R. *et al.* Persistent HIV-1 replication maintains the tissue reservoir during therapy. *Nature* http://dx.doi.org/10.1038/nature16933 (2016)

FURTHER READING Laskey, S. B. & Siliciano, R. F. A mechanistic theory to explain the efficacy of antiretroviral therapy. *Nat. Rev. Microbiol.* **12**, 772–780 (2014)