MILESTONE 13

A tap and drain: sinking CD4$^+$ T cells

The hallmark of HIV-1 infection is a progressive reduction in CD4$^+$ T cells, which leads to a general decline in immune function and is the primary factor responsible for the clinical course of disease. Although the discovery of CD4 as a receptor for HIV-1 in the 1980s (MILESTONE 3) could help explain the susceptibility of CD4$^+$ T cells to infection, the mechanisms responsible for their decline remained elusive. In 1995, two seminal studies by the groups of George Shaw and David Ho published in *Nature* provided important insights on the dynamics and pathophysiology of HIV-1 infection, including pivotal observations concerning CD4$^+$ T cell decline.

The advent of new quantitative assays for measuring HIV-1 RNA concentrations (viral load) and experimental drugs that could potently inhibit HIV-1 replication enabled both groups to perform experiments in which the rates of CD4$^+$ T cell and viral turnover could be extrapolated from measurements of changes in plasma viral load and CD4$^+$ T cell counts following antiviral therapy. In both studies, abrupt inhibition of viral replication led to a substantial rise in CD4$^+$ T cell numbers and revealed a scenario in which continuous and highly productive viral replication drove rapid turnover of CD4$^+$ T cells.

The initial stage of HIV-1 infection is followed by an asymptomatic period that can last for years before disease progresses and results in the development of AIDS. Given that this asymptomatic period is accompanied by relatively stable levels of CD4$^+$ T cells and viral load, loss of these cells was initially thought to involve a gradual process of destruction. However, these new findings challenged this view, supporting a model of accelerated CD4$^+$ T cell destruction, which Ho and colleagues likened to a 'tap-and-drain' scenario.

> the idea of drug resistance and immune escape fueled the search for effective antiviral strategies

In this analogy, the destruction of CD4$^+$ T cells (the drain) is counterbalanced by homeostatic production of T cells (the tap) during the asymptomatic period; however, once production of T cells becomes exhausted, this balance is disrupted, resulting in eventual loss of CD4$^+$ T cells (emptying of the sink) and AIDS. Although the mechanisms underlying this imbalance were an area of debate and later evidence pointed to the existence of other (potentially non-mutually exclusive) models of CD4$^+$ T cell depletion (MILESTONE 10), the findings nonetheless had important clinical implications.

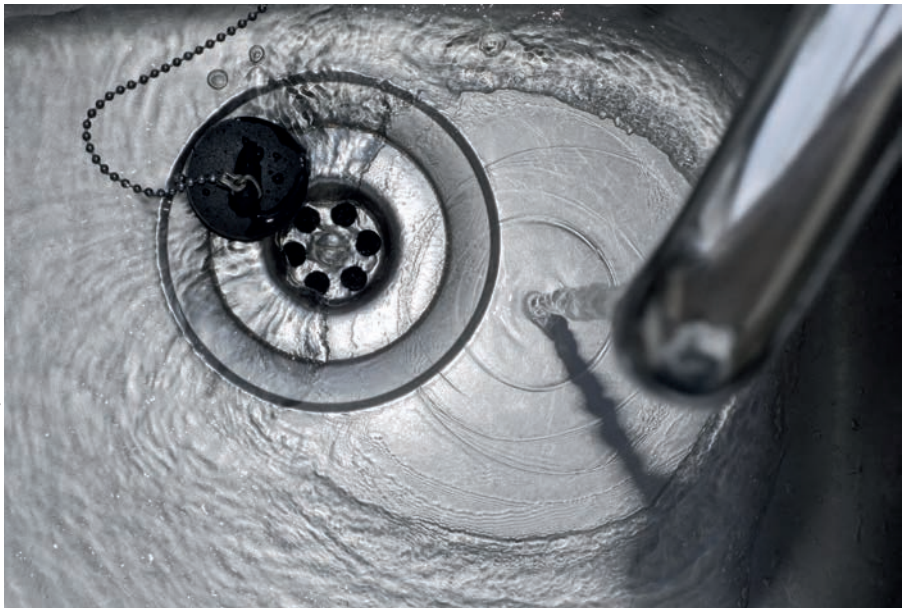
In both studies, evolving resistance to the antiviral drug led to a rise in viral load and a concurrent decrease in CD4$^+$ T cell numbers to pretreatment levels. The previously unrecognized regenerative capacity of CD4$^+$ T cells in HIV-1 infection along with the idea of drug resistance and immune escape fueled the search for effective antiviral strategies.

The findings also raised questions about the utility of CD4$^+$ T cell count as a predictor of long-term survival (at the time, it was the main surrogate marker of disease progression). Just one year later, John Mellors and colleagues linked viral load and HIV prognosis in a paper published in *Science*. By measuring plasma HIV-1 RNA concentrations in a cohort of 180 HIV-seropositive men who were followed for >10 years, they reported that plasma viral load (irrespective of duration of infection) was a better predictor of patient outcome (that is, progression to AIDS or death) than number of CD4$^+$ T cells.

Thomas Quinn and colleagues later revealed that viral load was also a risk factor for viral transmission. Of the factors they measured (including various behavioral and biological risk factors) in a study of 415 couples who were followed for up to 30 months, viral load was the best predictor. Indeed, measurements of viral load are now routinely used for the clinical assessment and monitoring of patients infected with HIV-1, alongside CD4$^+$ T cell count.

These findings spurred the development of antiviral therapies and therapeutic strategies (such as combination therapies) to reduce viral load in individuals infected with HIV-1, with the aim of improving long-term patient outcomes and potentially preventing viral transmission (MILESTONE 14, 20, 21).

Jessica McHugh,
Nature Reviews Rheumatology



Credit: incamerastock/Alamy Stock Photo

ORIGINAL ARTICLES Wei, X. et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* **373**, 117–122 (1995) | Ho, D. D. et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* **373**, 123–126 (1995) | Mellors, J. W. et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* **273**, 1167–1170 (1996) | Quinn, T. C. et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N. Engl. J. Med.* **342**, 921–929 (2000)
FURTHER READING Rowland-Jones, S. L. AIDS pathogenesis: what have two decades of HIV research taught us? *Nat. Rev. Immunol.* **3**, 343–348 (2003) | Simon, V. & Ho, D. D. HIV-1 dynamics in vivo: implications for therapy. *Nat. Rev. Microbiol.* **1**, 181–190 (2003) | Douek, D. C., Picker, L. J. & Koup, R. A. T cell dynamics in HIV-1 infection. *Annu. Rev. Immunol.* **21**, 265 –304 (2003)