T cell turnover and thymic function in HIV-1 infection
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2 Introduction
For years, HIV-1 was assumed to behave like any other chronic virus infection with periods of active virus replication alternated by prolonged times of true viral latency. In 1995, it was shown for the first time that HIV-1 infection is in fact characterized by continuously high-level virus production (1:2). In these studies, inhibition of virus assembly by protease-inhibitor containing antiretroviral regimens, or HAART (highly active anti-retroviral therapy), allowed calculation of plasma HIV-1 RNA decay rates and thereby pre-treatment virus production levels. Based on these data, it was estimated that per day at least $10^7 - 10^8$ virions are produced and destroyed (1:2), and later this number was adjusted to a production rate of $10^{10}$ virions per day (3). In analogy, CD4+ T cell production and destruction levels were analyzed. In the first few weeks after introduction of HAART, it was observed that CD4+ T cell levels in the blood rose to different extends in individual patients (1:2). CD4+ T cell numbers declined only slowly during untreated HIV-1 infection, compatible with a quasi steady-state situation pre-treatment. It was therefore assumed that the rise in peripheral blood CD4+ T cell numbers during HAART reflected high T cell production rates before HAART that were no longer balanced by virus-related T cell destruction. By analyzing CD4+ T cell recovery rates of individual patients it was estimated that during untreated HIV-1 infection, about $10^7$ CD4+ T cells are destroyed and replaced per day. It was believed that these were largely increased T cell production rates, driven by high virus -induced T cell death, which would in the end exhaust the immune system resulting in severe CD4+ T cell depletion and AIDS (2).

However, in subsequent studies it was shown that the early rapid increase in peripheral blood CD4+ T cell numbers consisted mainly of memory CD4+ T cells that had been trapped in lymphoid tissues during untreated HIV-1 infection and were released into the circulation upon reduction of plasma HIV-1 RNA levels and immune activation by HAART (4-7). In addition, HIV-1 infection was shown not to be associated with replicative exhaustion of the CD4+ T cell compartment. Telomere restriction fragment (TRF) analysis allows estimation of the replicative history of cells. Surprisingly, HIV-1 infection led to a decline in the median TRF length of CD8+ T cells, but not of CD4+ T cells (8). The absence of CD4+ T cell TRF shortening could not be attributed to enhanced telomerase activity (9), and mathematical modeling showed that constant TRF lengths allowed a maximal increase in CD4+ T cell turnover rates of 2 to 3 fold (10). Indeed, using Ki67 as a marker for cell proliferation, it was shown that untreated HIV-1 infection is associated with a modest increase in CD4+ T cell division rates (11:12).

In addition, T cell turnover was measured by in vivo labeling of dividing lymphocytes. Deuterium is a stable isotope that, when administered as deuterated glucose, builds into the DNA of dividing cells, including T cells (13). Using this label, it initially was suggested that untreated HIV-1 infection is associated with a reduced half life of CD4+ T cells. Following introduction of HAART, the production of CD4+ T cells increased which was associated with an increase in peripheral
blood CD4⁺ T cell numbers (13). In this cross-sectional study, CD4⁺ T cell half-lives did not improve during HAART, which was not completely understood. Finally, in vivo labeling of dividing lymphocytes with bromodeoxyuridine (BrdU) in simian immunodeficiency virus (SIV)-infected rhesus macaques showed that also in the animal model of HIV-1 infection, CD4⁺ T cell turnover was elevated several fold. Interestingly, increased label incorporation was also found in CD8⁺ T cells, as well as in natural killer (NK) cells and B lymphocytes (14:15). These lymphocyte subsets are not or only late depleted in HIV-1 infection, suggesting that it is not T cell loss that pushed T cell turnover rates to elevated levels. Taken together, HIV-1 and SIV infection were associated with increased lymphocyte turnover that was however not limited to the CD4⁺ T cell pool suggestive for a more complex mechanism than homeostatic proliferation. At the time experimental work on this thesis started (June 1998), the role of elevated T cell turnover rates in HIV-1 pathogenesis was to be re-evaluated.

References
