Abstract: Although combined antiretroviral therapy (ART) generally suppresses HIV replication to undetectable plasma levels for prolonged periods, it fails to eradicate the virus. HIV can persist within a small pool of long-lived resting memory CD4+ T cells infected with integrated latent virus. This latent reservoir appears to involve several memory CD4+ T-cell subsets at distinct differentiation stages with different phenotypic and functional properties, forming distinct ‘sub-reservoirs’. Here we show the existence of a dynamic process that progressively reduces the size of the latent reservoir around a core of less differentiated memory CD4+ T-cell subsets (for example, central memory CD4+ T cells and the recently identified stem cell-like memory CD4+ T cells). Our results also stress the importance of early initiation of effective ART to limit the size of the TCM sub-reservoir, which appears directly related to cumulative virus exposure.

Methods: We conducted a cross-sectional study on 45 strictly selected patients. Inclusion criteria were: plasma virus load undetectable (≤20 copies per mL) for ≥24 to 189 months without any viral blip and a CD4+ T cell count higher than 500 /mm³ of blood. Highly purified memory CD4+ T-cell subsets were sorted: stem cell memory CD4+ T cells (TSCM), central memory CD4+ T cells (TCM), effector memory CD4+ T cells (TECM), and an additional subset with an intermediate phenotype (TINT). Integrated HIV DNA was quantified in these cells by two-step ALU/qPCR. To take possible inter-patient variability into account and to validate this cross-sectional analysis, the results were analysed with the Monte Carlo (MC) algorithm.

During HIV infection the relative size of the TSCM subset within memory CD4+ T cells remains stable

Figure 1: (a) Shows the gating strategy used to sort the memory cell subsets. (b) The absolute number of cells in each memory subset (TSCM, TCM, TDM, and TFM) was determined in HIV-infected patients with undetectable plasma viral load on ART (UNO, n=38), as well as in age- and sex-matched viiremic patients (VIR, n=18) and HIV-coinfected healthy donors (HD, n=20). (c) Shows the percentage of each memory subset within the compartment formed by the four memory subsets analysed.

PD-1 is less strongly expressed on TCM

Figure 4: Surface PD-1 expression on blood memory CD4+ T-cell subsets was analysed in 15 patients with undetectable plasma virus on ART (a) and in 15 viiremic patients (b). Data are expressed as the difference in PD-1 mean fluorescence intensity (MFI) relative to naïve CD4+ T cells. Representative PD-1 staining is shown. (P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

Conclusion: We provide results that suggest a progressive reduction of the size of the blood latent reservoir around a core of less-differentiated memory subsets (TSCM and TDM) CD4+ T cells. This process appears to be driven by the differences in initial sizes and decay rates between latently infected memory subsets. Our results also suggest an extreme stability of the TCM sub-reservoir, the size of which is directly related to cumulative virus plasma exposure before the onset of ART, stressing the importance of early initiation of effective ART. The presence of these intrinsic dynamics within the latent reservoir may have implications for the design of optimal HIV therapeutic purging strategies.