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Cell-associated HIV-1 unspliced to multiply spliced RNA ratio at 12 weeks ART correlates with markers of immune activation and apoptosis and predicts the CD4+ T-cell count at 96 weeks ART

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Background: Incomplete restoration of CD4+ T-cell count during virologically successful antiretroviral therapy (ART) is a major predictor of morbidity and mortality. For better understanding of HIV-1 pathogenesis and improved design of curative strategies, it is important to determine whether the degree of HIV-1 persistence, measured at baseline or early on ART, can predict subsequent immunological response to the long-term therapy and whether viral persistence is associated with host biomarkers of immune dysfunction.

Methods: Total and episomal (2-LTR circles) HIV-1 DNA, unspliced and multiply spliced (total and tat/rev) cell-associated HIV-1 RNA, as well as markers of CD4+ and CD8+ T-cell activation, proliferation, senescence, apoptosis, exhaustion, thymic migration, and CD4+ and CD8+ T-cell subsets (naïve, central memory, effector memory, transitional memory), were longitudinally measured in a cohort of 28 HIV-infected patients at 0, 12, 24, 48, and 96 weeks of virologically suppressive ART.

Results: No baseline HIV-1 marker was predictive of CD4+ T-cell count at 96 weeks of ART. However, at 12 weeks of ART, cell-associated HIV-1 unspliced to multiply spliced-total (US/MS) RNA ratio strongly negatively correlated with both absolute CD4+ T-cell count at 96 weeks of ART (rho=-0,56, P=0,004) and with relative increase in CD4+ T-cell count between baseline and 96 weeks of ART (rho=-0,55, P=0,004). US/MS RNA ratio at 12 weeks ART was not associated with baseline CD4+ T-cell count. Moreover, US/MS RNA ratio at 12 weeks ART strongly positively correlated with markers of CD4+ T-cell activation (CD4+/CD38+/HLA-DR+: rho=0,63, P=0,001) and apoptosis (CD4+/Annexin-V+/FAS+: rho=0,59, P=0,002).

Conclusions: We observed that US/MS RNA ratio at 12 weeks ART positively correlated with immune activation and apoptosis and predicted lower CD4+ T-cell count at 96 weeks ART. Because HIV life cycle involves a temporal shift from the production of multiply spliced to the production of unspliced RNA species, higher US/MS RNA ratio in a patient might reflect the higher frequency of HIV-infected cells in the later stages of viral life cycle, which is characterized by expression of viral proteins and presentation of antigens. Such cells could exert pressure on the host immune system, causing persistent immune activation and apoptosis and contributing to poor immunological response to ART.