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CXCR4-TROPIC HUMAN IMMUNODEFICIENCY VIRUS CAN ESTABLISH LATENT INFECTION IN NAÏVE CD4+ RESTING T CELLS

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Introduction: Current antiretroviral therapies can reduce viral replication and minimize plasma viral loads to levels below the limits of detection for most assays. Nevertheless, therapy discontinuation invariably leads to viral production from protected, yet un-identified, reservoir pools. Determining the source of this virus reservoir in patients on HAART is of great importance to eradicating infection and finding a cure. Resting CD4+ T cells are capable of harboring latent HIV infection. Work in our laboratory has shown that, *in vitro*, HIV directly integrates into resting CD4+ T cells providing a model for latency. More recently we showed that CXCR4(X4)-tropic HIV integrates directly into naïve CD4+ T cells when CD4+ T cells, directly isolated from blood, are infected. This result led us to ask if naïve cells contribute significantly to HIV reservoirs.

Methods: To answer this question, we sorted blood into naïve and memory cell subsets before inoculating with pNL4-3 and pNL-AD8 HIV clones. We incubated the cells for 48-120 hours and measured viral binding, viral fusion, total HIV DNA, integrated HIV DNA, and p24 production.

Results: We again found that only X4-tropic and not R5-tropic viruses integrated directly into naïve cells, while both viruses integrated directly into memory cells. Here we demonstrate for the first time that resting naïve cells express low levels of HIV Gag but do not produce infectious virions unless stimulated to enter the cell cycle and thus are latently infected in our *in vitro* model – similar to memory CD4+ T cells.

Conclusions: The contribution of the naïve cell subset to viral reservoirs has been underestimated heretofore, but here we provide evidence that suggests this long-lived, quiescent CD4+ T cell subset may play an important role in the maintenance of latency in some patients.