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NAÏVE CD4+ T CELL HOMEOSTASIS DURING HIV INFECTION

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OBJECTIVES: To determine the effect of HIV infection and HAART treatment on naïve CD4+ T-cell homeostasis.

METHODS: PBMC from seronegative and seropositive individuals were phenotyped and sorted into two naïve CD4+ T-cell subsets defined by CD45RA and CD31. Genomic DNA was extracted from the sorted cells and used to measure telomere length by Real-Time PCR.

RESULTS: We and others have recently shown that naïve CD4+ T-cells maintain homeostasis by low level proliferation while still retaining a naïve phenotype. In general, the so-called “undifferentiated” naïve cells undergoing minimal proliferation express CD45RA, and CD31, while their “differentiated” naïve cell progeny lose CD31 expression. Here we present our results from a cross-sectional study, which demonstrate that HAART-naïve HIV+ participants within 1-3 years of infection have significantly fewer undifferentiated (CD45RA+/CD31+) and differentiated (CD45RA+/CD31-) naïve CD4+ T-cells than seronegative controls ($p=0.002$). Real-Time PCR analysis on naïve CD4+ T-cells from the same HIV+ participants revealed telomere lengths that were similar to those from seronegative individuals 30 years older. In a longitudinal study, immunophenotyping of cells from HIV+ participants who were on HAART for two years showed reconstitution of the CD4+/CD45RA+/CD31+ subset ($p=0.20$), suggestive of new thymic output. However, the more differentiated naïve (CD4+/CD45RA+/CD31-) subset failed to reconstitute to levels observed in seronegative controls ($p=0.001$).

CONCLUSIONS: Reduced numbers of naïve CD4+ T-cells and shortened telomeres suggest that HIV infection mimics aging in the naïve CD4+ T-cell compartment. Our results also indicate that HAART may not be able to fully reverse this effect. As aging is known to detrimentally affect T-cell function and to increase susceptibility to infectious disease, our data provide a possible mechanism by which adaptive immune responses to HIV and to opportunistic infections are hampered. These results have important implications both for HIV+ individuals on HAART and for the increasing population of older HIV+ individuals.



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Immune Activation in HIV Pathogenesis

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