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Decrease of Ki-67 proliferation marker correlates with CD4+ cell count increase and predicts viral load suppression following 4 week AV-HALT treatment: clinical Proof-of-Concept of an immunological predictive marker.

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Background: Chronically excessive immune system activation plays a central role in HIV-AIDS pathogenesis. Although HAART an maximally suppress HIV viral load, T cell activation and proliferation markers do not return to non-HIV-infected values. An immunological biomarker predictive of viral suppression could be of value to clinicians selecting antiretroviral regimens. We tested whether pre-therapy Ki-67 proliferation marker values in naïve and Central Memory (CM) CD4+ T cells could predict HIV suppression by a newly-developed class of anti-HIV drugs known as AntiViral-HyperActivation Limiting Therapeutics (AV-HALTs) exhibiting dual activities: suppressing HIV replication and limiting excessive T cell proliferation.

Methods: Blood samples from 32 subjects receiving the AV-HALT VS411, a novel combination of an antiviral (low-dose, slow-release 2 ,3 -dideoxyinosine) and an antiproliferative drug (low-dose hydroxycarbamide), were analyzed in a multinational 4-week Phase IIa, dose-finding study using 10-color flow cytometry including T cell subsetting, activation and proliferation markers. Pearson correlation was employed for statistical analysis.

Results: At Day 28, the median decrease in HIV RNA was 1.47 log10 with only two of the 32 subjects reaching < 50 copies/mL; median CD4+ T cell increase was +108 cells/mm3. Significant correlations were found between the percentage of Ki-67+ naïve (CD45RA+CD27+) CD4+ T cells and CD4+ T cell counts at baseline and following treatment with r2=0.191 and r2=0.259, respectively (*P*< .05). A predictive correlation (r2= 0.262, *P*< .05) between the percentage of Ki-67+ CM (CD45RA-CD27+) CD4+ T cells at baseline and log10 HIV viral load changes observed after 28 days of AV-HALT therapy was also found.

Conclusion: Pre-treatment expression of the proliferation marker Ki-67 in Central Memory CD4+ T cells was predictive of viral load decline over 28 days of AV-HALT therapy. The study provides the clinical Proof-of-Concept that percentage of Ki-67+ Central Memory CD4+ T cells at baseline is predictive of HIV suppression following AV-HALT treatment.