IAS 2011

6th IAS CONFERENCE ON HIV PATHOGENESIS, TREATMENT AND PREVENTION

17-20 JULY 2011 - ROME, ITALY

ISTITUTO SUPERIORE DI SANITÀ

International AIDS Society
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Abstract A-361-0131-02595

Ki-67 proliferation marker significantly decreases despite incomplete virus suppression in both naïve and central memory CD4+ T cell subsets following 4-week AV-HALT treatment: a novel strategy to reduce viral reservoirs and immune system hyperactivation.

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Background: HIV-infected Ki-67+ Central Memory (CM) CD4+ T cells play a fundamental role as a viral reservoir. Although HAART can maximally suppress HIV viral load, it does not return T cell subsets to non-HIV-infected values. We examined whether viral reservoirs and immune system hyperactivation are affected by a newly-developed class of anti-HIV drugs called 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, double blinded, placebo controlled study, using 10-color flow cytometry including T cell subsetting, activation and proliferation markers. Two-tailed paired t-test and non-parametric Wilcoxon test were employed for statistical analysis.

Results: The median decrease in HIV RNA at Day 28 was 1.47 log10 with only two subjects reaching < 50 copies/mL; median CD4+ T cell increase was +108 cells/mm3. The median percentage of naïve (CD45RA+CD27+) CD4+ T cells increased from 37.60% to 39.46% whereas CM (CD45RA-CD27+) CD4+ T cells decreased from 40.07% to 37.30% ($P < .05$). The median percentage of Ki-67+ cells decreased in both naïve and CM CD4+ T cells from 0.79% to 0.57% ($P < .05$) and from 3.88% to 3.27% ($P < .05$).

Conclusion: A significant decrease in the percentage of CM CD4+ T cells and in the percentage of Ki-67-expressing cells in both CD4+ naïve and CM T cell subsets was achieved after 28 days of AV-HALT therapy despite incomplete HIV suppression. These results suggest that both viral reservoirs and immune system hyperactivation driving disease progression can be specifically and effectively targeted and reduced by AV- HALTs.