

ORAL PRESENTATION

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Epigenetic drug Gar1041 in combination with antiretroviral therapy transiently reduces the proviral DNA reservoir in SIVmac251-infected macaques

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Background

It was recently hypothesized that the lentiviral reservoir in central memory (T_{CM}) and transitional memory (T_{TM}) CD4+ cells could be restricted by new therapies targeting pathways downstream of homeostatic proliferation or pathways associated with "stem cell-ness", such as those developed for the treatment of leukemias. Gar1041 is one such epigenetic drug adopted in the experimental treatment of certain types of leukemia.

Methods

SIVmac251-infected primates with viral loads stably suppressed by ART (tenofovir/emtricitabine/raltegravir) were administered for two months: Gar1041 twice daily (a starting dose of 1.5g in the first week followed by 2g in the remaining period). ART was continued during Gar1041 treatment. Proviral DNA was quantitated using a Taqman real-time PCR.

Results

The proviral DNA content of PBMCs, which had shown no significant changes during 54 days of treatment with ART alone ($p > 0.05$), fell below the level of detection (2 copies/ 10^6 cells) in all study subjects within one month of Gar1041 treatment ($p < 0.05$; Bonferroni's test following significant [$p = 0.0003$] repeated measures ANOVA). No significant changes were noticed in a control group treated with ART alone ($p = 0.49$). The decrease in proviral

DNA was associated with a significant ($p = 0.0156$) decrease in the proportions of the T_{CM} CD4+ cell subpopulation in peripheral blood. However, both proviral DNA and the proportions of T_{CM} CD4+ rebound after two months of therapy.

Conclusions

The present study furnishes proof of concept that pharmacological strategies may impact on the proviral DNA reservoir. However, the renewal of the phenotype T_{CM} compartment, associated with the reconstitution of proviral DNA in peripheral blood from an as yet unidentified reservoir, will require integration with other experimental approaches.

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