Hepatitis C therapy with Interferon-alfa and Ribavirin reduces CD4 T cell-associated HIV-1 DNA in HIV-1/HCV co-infected patients

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Background

■IFN-alfa, as a type I interferon with potent antiviral activities, can cure hepatitis C infection in a significant proportion of patients in combination with Ribavirin.

■IFN-alfa also exerts active antiviral activities against HIV-1 in vitro and in vivo.

■A recent clinical trial has shown a reduction of integrated HIV-1 DNA in a group of HIV-1 infected patients who spontaneously controlled plasma viremia after receiving treatment with IFN-alfa monotherapy.

■Effects of IFN-alfa against HIV-1 latent infected cells in HIV-1/HCV co-infected patients receiving suppressive antiretroviral combination therapy remain less defined.

■Here, we analyzed changes of the HIV-1 CD4 T cell reservoir in a cohort of HAART-treated HIV/HCV co-infected patients with undergoing HCV treatment with IFN-alfa and Ribavirin.

Methods

Participants

■HIV/HCV co-infected patients: on suppressive HAART and HCV treatment with IFN-alfa (180ug/week of pegylated IFN-alfa 2a) and Ribavirin (600mg BID for >75kg body weight, 500mg BID for <75kg body weight) at the Virgen del Rocio Hospital, Sevilla, Spain. (n=12)

Isolation of CD4 T cells

■CD4 T cells were isolated from PBMCs magnetically labeled with CD4 MicroBeads® (Miltenyi Biotec) using autoMACS Pro Separator.

HIV reservoir quantification

■Cell-associated HIV-1 DNA was analyzed using established qPCR protocols. (Buzon MJ, Nat Med 2010)

HIV-1 reactivation assays

■Cells were incubated with IFN-alfa (1000Units/ml), RBV (1ug/ml) or panobinostat (0.1uM). Cell-associated HIV-1 RNA and cell-associated HIV-1 DNA were analyzed after 48hours or 5 days respectively.

Results

■**Changes in HIV-1 DNA in isolated CD4 T cells were analyzed in time intervals** preceding IFN-alfa/RBV treatment (51 weeks, range: 26-71), during the time of IFN-alfa/RBV exposure (36.5 weeks, range: 9-82 weeks), and during a time period after completion of HCV treatment (35.5 weeks, range: 21-84 weeks) (Figure A).

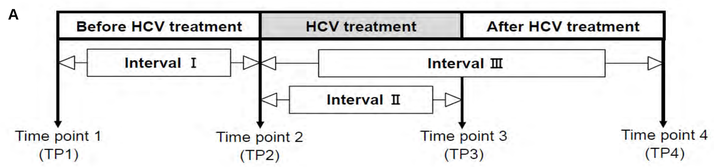

Figure A, Time intervals during which changes in HIV-1 DNA were evaluated in HIV-1/HCV co-infected patients.

■**A significant, approximately 2-fold decrease of cell-associated HIV-1 DNA in CD4 T cells during IFN-alfa/RBV therapy (Figure B).** The decrease persisted after IFN-alfa/RBV therapy ceased, but no further reduction of viral CD4 T cell-associated DNA was noticed when IFN-alfa/RBV treatment was stopped (Figure C-D).

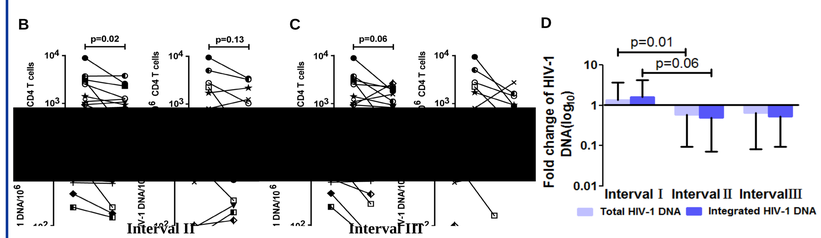

Figure B-D, Changes in total (left panel) and integrated (right panel) HIV-1 DNA in CD4 T cells from HIV-1/HCV co-infected study patients during indicated time intervals.

■**A trend for an inverse relation between the reduction of HIV-1 DNA in CD4 T cells and corresponding declines of absolute CD4 during treatment with IFN-alfa/RBV**, indicating that more pronounced decrease of HIV-1 DNA occurred in patients who did not develop substantial treatment-associated lymphopenia. (Figure E)

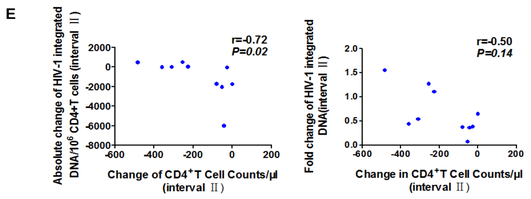

Figure E, Inverse association between CD4 T cell changes during HCV therapy and corresponding absolute and relative changes in CD4 T cell-associated integrated HIV-1 DNA.

■**IFN-alfa or IFN-alfa/RBV did not reactivate HIV-1 gene expression**, nor affect HIV-1 DNA levels during in vitro exposure of CD4 T cells from HAART-treated patients to IFN-alfa. (Figure F) As an indicative internal control, the interferon-stimulated gene IRF-7 was upregulated by exogenous IFN-alfa induction. **(**Figure G)

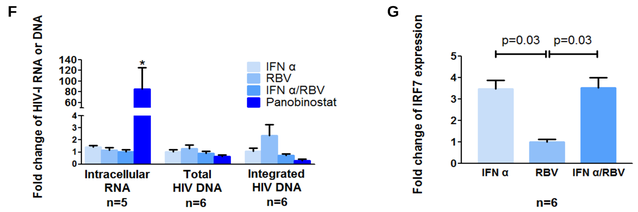

Figure F, Analysis of HIV-1 RNA and total or integrated HIV-1 DNA in primary CD4 T cells from HAART-treated patients after in vitro exposure to IFN-alfa, IFN-alfa/RBV or panobinostat; Figure G, IRF-7 mRNA expression in CD4 T cells ex-vivo exposure of CD4 T cells to IFN-alfa, or IFN-alfa/RBV.

Conclusions

■Pharmaceutical administration of IFN-alfa/RBV for HCV therapy can cause a moderate, but significant decrease of total and integrated HIV-1 DNA in CD4 T cells from HIV-1/HCV co-infected patients. However, the reduction is likely not due to direct effects of IFN-alfa on HIV-1 gene transcription or viral reactivation from latency.

■Further investigation of the mechanisms underlying the reduction in HIV-1 DNA during IFN-alfa/RBV therapy may be helpful for designing improved clinical strategies to target HIV-1 reservoirs that persist despite HAART.

Acknowledgements

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