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IMPACT OF HCV CLEARANCE ON ON NK CELLS AND HIV TRANSCRIPTION IN COINFECTED SUBJECTS

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BACKGROUND

Hepatitis C is a frequent coinfection among PLWH. HCV replication and its subsequent clearance with direct acting antivirals (DAA) can potentially modify how HIV persists on antiretroviral therapy (ART). Since Natural killer (NK) cells are key effectors against both viruses and may be involved in shaping HIV reservoir, we studied NK cell phenotype before and after HCV treatment with DAAs and its association with HIV persistence.

MAIN FINDINGS:

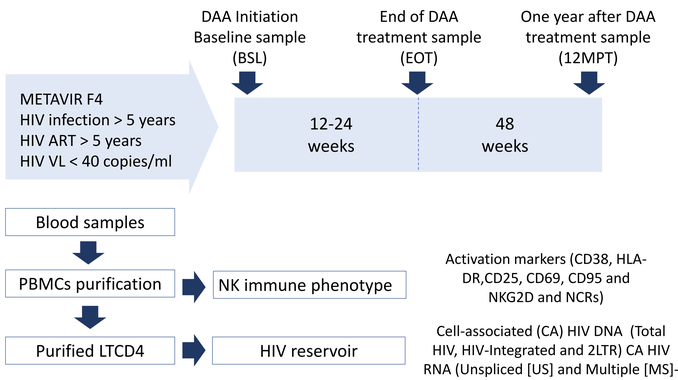
- **Globally, HCV clearance with DAA was associated with a down-modulation of several activation markers in NK cells.**
- **Cell-associated US-HIV RNA was significantly increased after one year of HCV eradication with DAA.**
- **Higher levels of NK cell activation correlated with higher US-HIV RNA after HCV clearance.**

CONCLUSIONS

Downregulation of NK cell activation was observed immediately after HCV clearance although some markers rebounded one year later, in concomitance with increased transcriptional activity of HIV reservoir. This may be reflecting the priming of NK cells by the residual HIV transcription and might point out a role for NK cells in shaping HIV persistence.

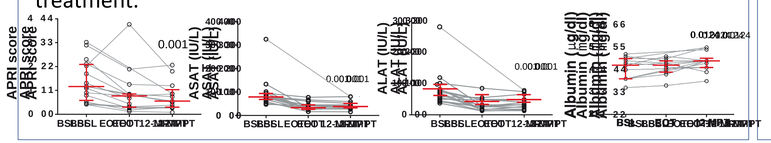
METHODS

HIV/HCV-coinfected individuals on suppressive ART (n=19) received sofosbuvir/daclatasvir alone or with ribavirin (n=7). Blood samples were obtained before HCV treatment (BSL), at end-of-treatment (EOT) and at 12 months after EOT (12MPT):



CLINICAL PARAMETERS

Out of the enrolled subjects, 73% were male (mean age=49±5.9 years old). Median (IQR) time from HIV, HCV diagnosis and ART treatment were 19 (12-21), 13 (11-22), 10.5 (4-16.5) years, respectively. At enrollment, median LTCD4 count was 291 (231-776) cells/µl; LTCD8 count 849 (498-1263) and % NK 8,9 (5,6-16,2). CD4+ and CD8+ T cell count, CD4/CD8 ratio and frequency of NK cells were not modify by DAA therapy. Conversely, liver inflammation diminished after treatment.



RESULTS

NK CELL IMMUNE PHENOTYPE

At EOT, surface expression of HLA-DR, CD38, NKG2D, and CD95, decreased compared to BSL (p=0.0002, p=0.006, p=0.0005, p=0.001 and p=0.001, respectively). CD95+, HLA-DR+, and HLA-DR+/CD38+ NK cells rebounded at 12MPT compared to EOT.

Higher percentages of non-activated NK cells were observed at EOT (HLA-DR-/CD38- and CD25-/CD69-/CD95-) and at 12MPT (HLA-DR-/CD38-).

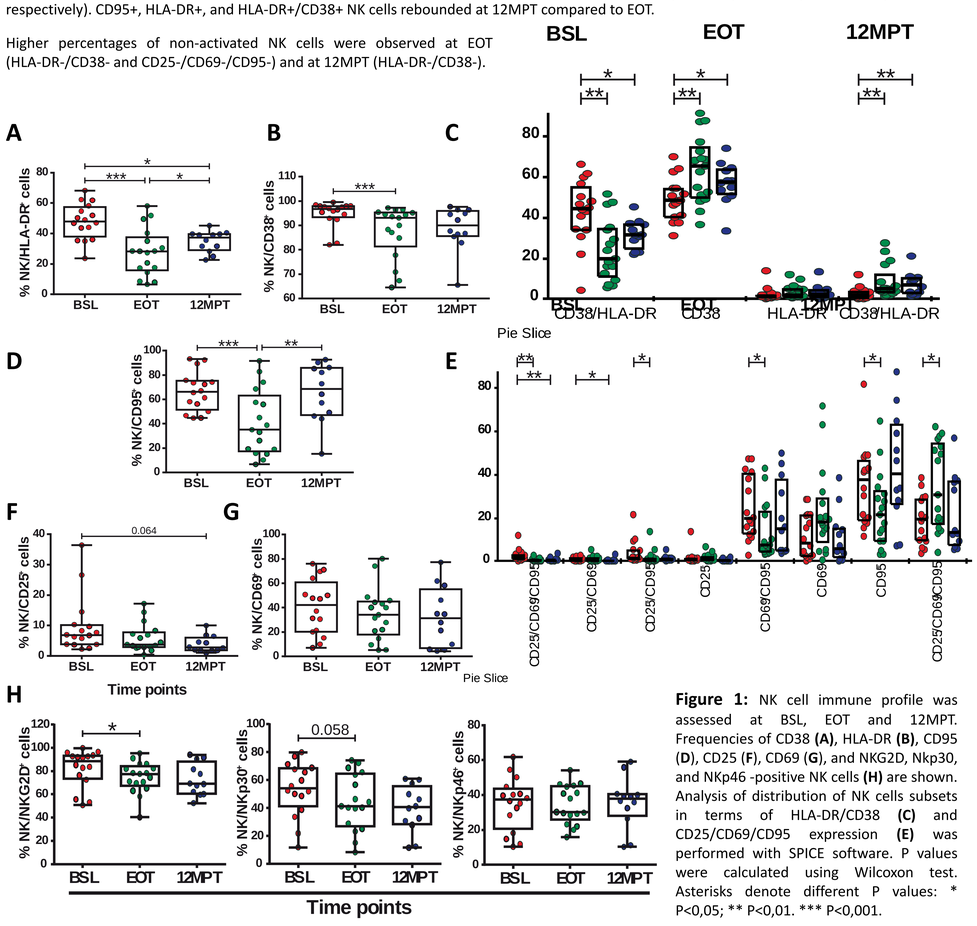
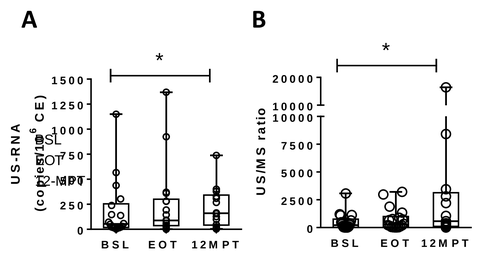


Figure 1: NK cell immune profile was assessed at BSL, EOT and 12MPT. Frequencies of CD38 **(A)**, HLA-DR **(B)**, CD95 **(D)**, CD25 **(F)**, CD69 **(G)**, and NKG2D, Nkp30, and NKp46 -positive NK cells **(H)** are shown. Analysis of distribution of NK cells subsets in terms of HLA-DR/CD38 **(C)** and CD25/CD69/CD95 expression **(E)** was performed with SPICE software. P values were calculated using Wilcoxon test. Asterisks denote different P values: * P<0,05; ** P<0,01. *** P<0,001.

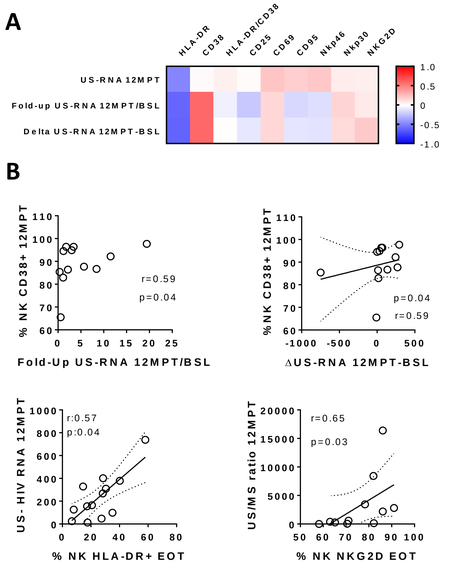
HIV RESERVOIR DYNAMICS DURING DAA THERAPY



There were no statistically significant differences in CA-HIV DNA and MS- RNA for the three time points evaluated. Conversely, CA-US HIV RNA and US/MS ratio were significantly higher in CD4+ T-cells collected at 12-MPT compared to BSL.

Figure 2: Cell associated (CA)-RNA (US and MS-RNA) were measured at BSL, EOT and 12MPT on HIV/HCV-coinfected subjects. US-RNA **(A)** and US/MS **(B)** ratio are shown. * P<0,05.

NK CELL IMMUNE ACTIVATION AND HIV PERSISTANCE



Spearman's correlations showed that higher levels of EOT and 12MPT NK cell activation correlated with higher 12MPT US-RNA. Particularly, EOT-expression of HLA-DR correlated with 12MPT US-RNA (r=0.57, p=0.04). Also, 12MPT CD38 expression correlated with fold change in US-RNA levels between12MPT and BSL (r=0.5919, p=0.0462).

Figure 3: Heat map representation of Spearman rank correlation coefficients computed for the expression of NK cell immune markers at 12MPT versus HIV unspliced (US)-RNA at 12MPT, US-RNA fold up between 12MPT and BSL time points and differences between US-RNA at 12MPT minus levels at BSL. Colors denote both the correlation direction and strength of association (**A**).
Statistical significant associations at 12MPT and EOT are further shown below. Spermans's r and p values are listed.