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Liver fibrosis hinders T-cell homeostasis restoration after HCV eradication with DAAs

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I. Background

- A significant impact of HCV coinfection on several immune parameters of HIV pathogenesis has been recently shown.
- However, to what extent these alterations are diminished or even abolished after HCV eradication with direct acting antivirals (DAAs) has not been clarified.
- Herein, we have analyzed the effect of HCV on several immune parameters of HIV pathogenesis and its evolution after HCV eradication with DAAs in HIV patients coinfected with HCV.

II. Methods

- Fifty cART-suppressed chronic HIV-infected patients maintaining undetectable plasma viremia (pVL<50 copies/mL) were included: 25 HIV-monoinfected and 25 HCV/HIV co-infected patients naive for anti-VHC therapy at the time of inclusion. Twenty healthy controls (HC) were also included (**Table 1**).
- In HCV/HIV group, peripheral blood mononuclear cells (PBMCs) prior to the start of DAAs treatment and at 12 weeks after its completion (when sustained virological response -SVR- is assessed) were collected. In the HIV-monoinfected group a single sample of PBMCs was collected from each patient.
- Maturation (CD45RA and CD27), activation (CD38 and HLADR), apoptosis (CD28 and CD95), senescence (CD28 and CD57) and exhaustion (PD1 and Tim3) of CD4 and CD8 T cells were assessed by flow cytometry.
- Inter and intra-group comparisons were performed using non-parametric tests.

Table 1. Characteristics of patients included in the study

Characteristic	Study Group		p-value[1]
	HIV-monoinfected patients	HCV/HIV-coinfected patients	
n	25	25	NA
Age (years)	48[40-53]	44[39-48]	0,213
Male (%)	96	100	0,312
CD4 nadir (cells/μL)	290[210-405]	336[185-465]	0,570
Time since HIV diagnosis (years)	9[6-12]	8[3-13]	0,526
Time on cART (years)	6[4-9]	4[2-8]	0,175
HIV transmission risk			
Sexual transmission (%)	96	96	1,000
Parenteral transmission (%)	4	4	
Liver fibrosis			
stage F0-F1 (%)	NA	60	NA
stage ≥F2 (%)		40	

Data are given as median [IQR], except sex, HIV transmission risk, HCV genotype, DAAs regimens and liver fibrosis, expressed as %; p-value[1]: p-values for the different comparisons (Mann-Whitney U test or χ^2 test); NA: not apply.

III. Results

- The whole population of HIV-infected patients showed increased exhaustion and senescence of CD4 and CD8 T cells, and increased activation of CD8 T cells, compared to healthy controls (**Figure 1**).

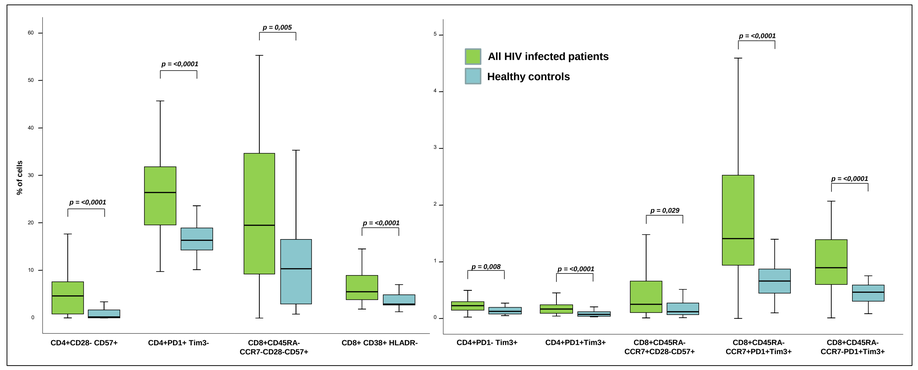

Figure 1. Box-plots graphs showing levels of exhaustion, activation and senesce in different CD4 and CD8 T cells subsets, in the whole HIV-infected population and in healthy controls. p-values for the inter-group comparison (Mann-Whitney U test) are shown.

- Compared to HIV-monoinfected group, HCV/HCV coinfected patients before DAAs therapy presented higher exhaustion of effector CD4 (p=0.001) and CD8 (p=0.006) T cells; and higher activation of total (p=0.026), effector memory (p=0.006) and effector (p<0.0001) CD8 T cells (**Figure 2**).
- After HCV eradication with DAAs, differences between HCV/HIV coinfected and HIV-monoinfected patients diminished, except activation(p=0.002) and exhaustion (p=0.053) of effector CD8 T cells, that remained increased in HCV/HIV group (**Figure 2**).

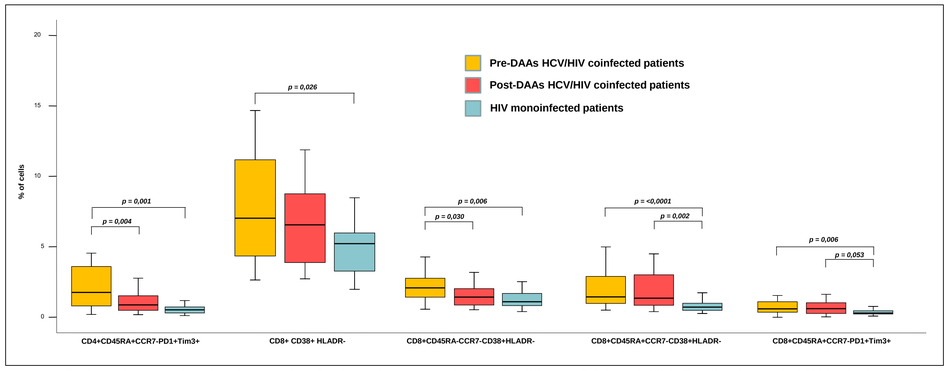

Figure 2. Box-plots graphs showing levels of exhaustion and activation in different CD4 and CD8 T cell subsets in HCV/HIV (pre and post-DAAs treatment), and in HIV-monoinfected patients. p-values for the comparison (Mann-Whitney U test and Wilcoxon signed-rank test) are shown.

- Before DAAs therapy, HCV/HIV patients with liver fibrosis (stage ≥F2) showed increased senescence and activation in several CD8 T cell subsets compared to HCV/HIV patients without liver fibrosis (stage F0/F1). In fact, significant increases in senescence and activation with respect to HIV-monoinfected patients were only observed in HCV/HIV coinfected patients with liver fibrosis (**Figure 3**).

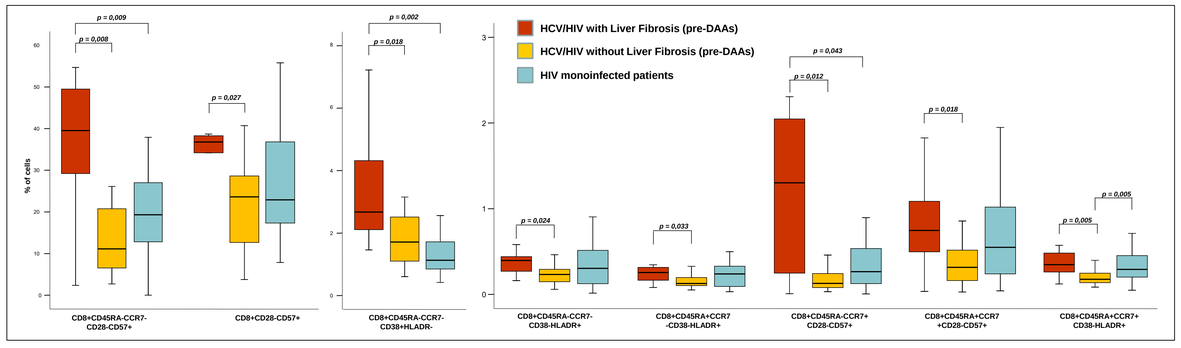

Figure 3. Box-plots graphs showing the levels of senescence and activation in different CD8 T cell subsets according to presence or absence of liver fibrosis in HCV/HIV coinfected compared to HIV monoinfected patients. p-values for the different comparisons (Mann-Whitney U test) are shown.

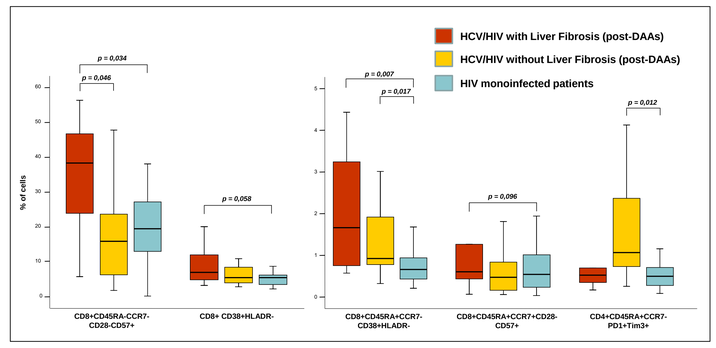

Figure 4. Box-plots showing the levels of senescence and activation in different CD8-T cell subsets according to presence or absence of liver fibrosis in HCV/HIV patients, and HIV monoinfected subjects. P-values for the different comparisons (Mann-Whitney U test) are shown.

- Finally, we found that the effect of HCV eradication on immune parameters restoration was, in general, less pronounced in HCV/HIV patients with liver fibrosis compared to those without liver fibrosis. Thus, after HCV eradication HCV/HIV patients with liver fibrosis presented increased levels of senescence and activation of CD8 T cells compared to HIV monoinfected patients and to HCV/HIV coinfected patients without liver fibrosis. In contrast, exhaustion of effector CD4 T cells was increased in HCV/HIV coinfected patients without liver fibrosis with respect to HIV monoinfected patients (**Figure 4**).

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V. Conclusions

- Our data demonstrate that the presence of HCV coinfection and liver fibrosis significantly impact on several immune markers of HIV pathogenesis.
- Eradication of HCV with DAAs ameliorates but does not normalize these alterations, what is partially hindered by the presence of liver fibrosis.
- These data prompts HCV treatment in HCV/HIV coinfected patients at the earliest stages of liver damage to enhance restoration of T-cell homeostasis.