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Changes in immune cell subsets in HCV and HCV/HIV patients upon virally-effective DAA

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BACKGROUND

Direct-Acting Antivirals (DAAs) eradicate HCV and reduce **liver fibrosis** by containing **inflammation**. Virologic response correlates with the restoration of NK and CD8, however, little is known on the **effects of DAAs on γδ, Th17 and Treg which all play a role in liver fibrogenesis**. Further, while **B-cell activation** has been linked to extrahepatic manifestations of HCV, literature is lacking on the role of these cells in liver damage.

METHODS

We enrolled **97 virally-infected (VI) subjects**
(15 HIV cART-suppressed; 35 HCV naive to HCV therapy; 47 HIV/HCV cART-suppressed and naive to HCV therapy) and 10 age-matched healthy controls (HC). All HCV-infected individuals underwent DAA therapy.

At baseline (T0) and 12 weeks after End of Treatment (SVR12) we measured: (i) γδ frequency (CD3+Pan γδ+), activation (CD69/CD38), (ii) Th17-like (CD4+CD161+CCR6+); (iii) Treg (CD4+CD25+CD127-); (iv) B cell frequency (CD19+), activation (CD86/CD38); v) γ-globulin levels.vi) Fibrosis stage was determined by transient elastography (Fibroscan) Statistical analysis as appropriate

Modulation of T-cell and B-cell compartment in HCV and HIV/HCV co-infected subjects upon virally-effective DAA, is linked to the hepatic stiffness, suggesting that DAA-mediated lightening of the pro-inflammatory liver insult may limit organ damage

RESULTS

- At T0, VI presented lower Th17 and higher Treg versus HC (Fig1A). DAA led to a further contraction of Th17 and no changes in Treg frequency (Fig.1B).
- While total γδ were comparable in VI and HC both prior to and following treatment (Fig.1B), activated γδ subset decreased upon DAA (Fig.1C). Compared to HC, VI also featured higher B-cell frequencies and activation which both decreased during DAA (Fig1C).
- Accordingly, γ-globulin concentrations also diminished in HCV mono and co-infection following DAA and correlated with B-cell activation (Fig1D).
- In VI, a low vδ2/Th17 ratio, known to predict liver damage, increased from baseline to SVR12, yet remained lower than HC (HIV/HCV vs HC: p=.04; HCV vs HC: p=.03) and negatively correlated with liver stiffness (Fig.1E) and serum ALT and AST (Fig.1F) Further, also γ-globulin levels were positively linked to liver fibrosis indexes following DAAs (r=0.6, p<.0001).

Fig1 A-B

	HC (n=10)	HIV (n=15)	HCV (n=35)	HIV/HCV (n=47)	[a]p
*Treg**					
CD4+CD25+CD127- , % (IQR)	0.89 (2.32-14.4)	2.47 (0.50-5.43)	2.96 (0.93-8.21)	3.85 (0.71-11.6)	**0.039**
*Th17**					
CD4+CD161+CCR6+, % (IQR)	3.92 (0.92-5.92)	1.68 (0.70-2.55)	1.75 (0-4.72)	1.98 (0-1.98)	**0.029**
*γδ**					
CD3+pan γδ+, % (IQR)	3.47 (1.17-14.68)	2.77 (0.52-1.70)	2.22 (0.65-2.81)	2.84 (0.29-1.74)	0.084
B cells*					
CD19+, % (IQR)	8.47 (1.17-14.68)	11.77 (0.52-1.70)	19.2 (0.65-2.81)	16.4 (0.29-1.74)	**0.044**

HCV	T0	SVR12	[b]p
*Treg**			
CD4+CD25+CD127- % (IQR)	2,88 (1.73-7.85)	2.61 (1.20-4.14)	0.421
*Th17**			
CD4+CD161+CCR6+, % (IQR)	2.01 (0.89-4.54)	1.71 (0.47-2.97)	**0.051**
*γδ**			
CD3+pan γδ+, % (IQR)	2.22 (0.65-2.81)	2.34 (0.76-3.21)	0.211
HIV/HCV	**T0**	**SVR12**	**[b]p**
*Treg**			
CD4+CD25+CD127- % (IQR)	3,85 (0.71-11.6)	2.99 (0.57-8.93)	0.523
*Th17**			
CD4+CD161+CCR6+, % (IQR)	1.98 (0.64-6.98)	1.6 (0.57-3.89)	**0.047**
*γδ**			
CD3+pan γδ+, % (IQR)	2.84 (0.29-1.74)	2.99(0.86-3.01)	0.213

Note: *data are presented as median (Interquartile range), statistical analyses: t test or Anova as appropriate. *data are presented as absolute numbers (%), statistical analyses: Fisher's or Chi-squared test as appropriate. [a] p values among 4 groups; [b] p values among HIV and HCV/HIV groups; p values among HCV and HCV/HIV groups.;

Fig1 D

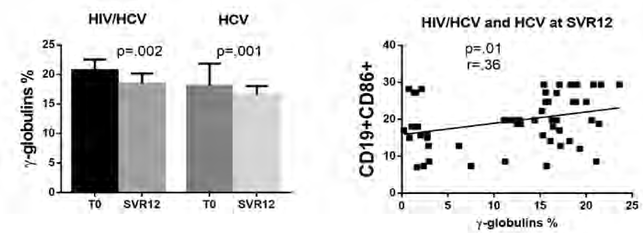
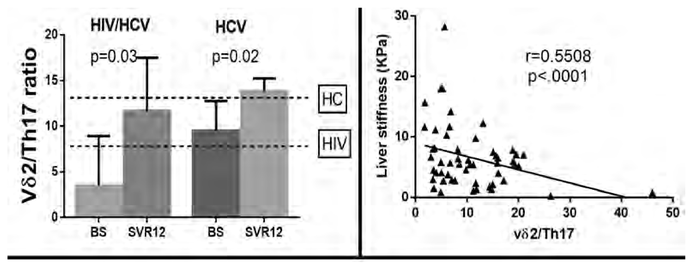


Fig1 E-F



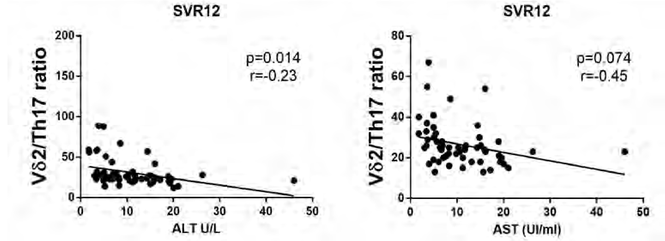
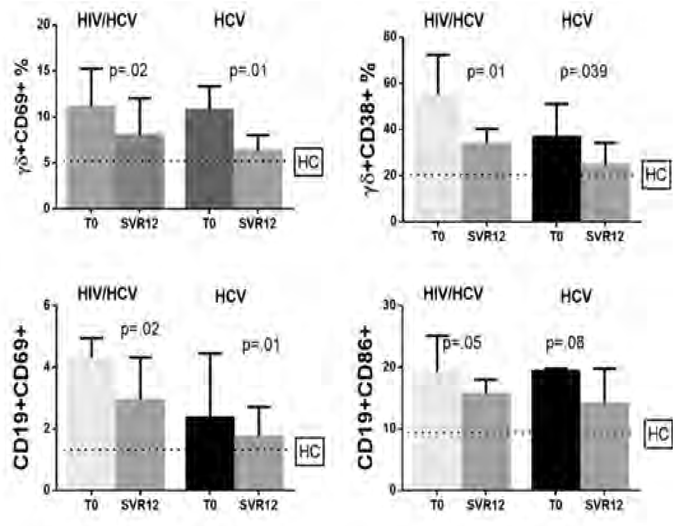


Fig1 C



CONCLUSIONS

Effective DAA in both HCV- mono and HIV/HCV co-infected subjects resulted in decreased B- and γδ cell activation, with recovery of vδ2/Th17 ratio. These changes are linked to the reduction of hepatic necrosis and stiffness, suggesting that DAA-mediated lightening of the pro-inflammatory liver insult may limit organ damage

ADDITIONAL KEY INFORMATION

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