HCV viremia affects immune phenotypes in Elite controllers of HIV infection- A Women's Interagency HIV Study

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Introduction

- HCV and HIV both independently lead to immune dysregulation[1,2].
- Chronic immune activation is a hallmark of HIV disease[3].
- HCV-positive viremic women with HIV co-infection who have high levels of T cell activation may have increased risk of AIDS[4].
- A recent study conducted on chronically HCV co-infected natural controllers suggested that though natural suppressors of HIV infection clear HCV at a faster rate compared to HCV mono-infected and HIV/HCV co-infected patients (non controllers), there remains an immune suppressive effect of chronic HCV infection as observed by significantly lower CD4 % and CD4 counts in the natural controllers compared to controls[5].

Thus in this study we investigated the effect of HCV viremia on the immune mechanisms associated with natural control in HIV/HCV co-infected subjects.

Materials and methods

We investigated the effect of HCV viremia on immune phenotypes in HIV and HCV Co-infected women in the Women Interagency HIV Study (WIHS). We evaluated immune response patterns in the following groups of women all of whom were HCV Ab positive matched by age and then race:

- Elite controllers defined as ARV-naïve, CD4 > 500, VL < 50 copies RNA/mL,for at least 3 visits (1.5 years: n=20),
- HIV controlled on cART (individuals who are currently on ARVs CD4 > 350, VL < 50, for at least 1.5y (HIVc n=20)
- HIV uncontrolled on cART (individuals who are currently on ARVs but with detectable HIV RNA for at least 3 visits (1.5 years: HIVuc n=22)
- HIV uninfected women (n=18)

Within groups, we compared HCV RNA positive (HCVRNA+) and negative (HCVRNA-) women

Liver fibrosis: serum markers (APRI and FIB-4 values) were used to evaluate the extent of liver fibrosis.

$$\text{APRI} = \frac{(\text{AST/upper limit of normal AST}) \times 100}{\text{Platelet Count } (10^9/\text{L})}$$

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST}}{\text{Platelet Count } (10^9/\text{L}) \times \text{ALT}^{1/2}}$$

Immune Markers: We evaluated T cell activation (CD38+, HLADR+), and apoptosis markers (Caspase-3+) as well as frequency of regulatory T cells (CD4+CD25+ FoxP3+) in reposited PBMC specimens. Intracellular Cytokine responses [interferon (IFN)-g, IL-2, IL-17] were evaluated in CD4 and CD8 T cells following 6h of PMA+Ionomycin stimulation using 10 color flow cytometry.

Results:

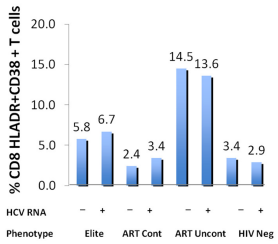
Demographics, HIV and HCV status of Study Participants

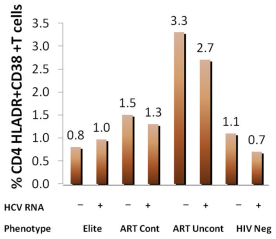
Group	HCV RNA	HIV RNA	CD4	HCV RNA	Age	Race
		copies/mL Median (min, max)	cells/mm³ Mean (SD)	copies/mL Mean (SD)	Years Mean (SD)	AA
Elite	Negative	ud	897 (255)	NA	46.9 (7.7)	4/9
	Positive	ud	918 (429)	888210 (688730)	47.56 (6.4)	7/10
ART controlled	Negative	ud	991 (338)	ud	51.2 (7.0)	6/10
	Positive	ud	722 (226)	4347210 (5534360)	51.0 (4.1)	7/10
ART uncontrolled	Negative	6000 (150, 130,000)	297 (171)	ud	48.8 (7.8)	5/10
	Positive	1000 (80, 12000)	294 (169)	2155545 (1563552)	48.6 (5.9)	6/11
HIV negative	Negative	na	1123 (336)	ud	51.3 (4.8)	4/8
	Positive	na	910 (254)	1107233 (1159649)	45.5 (7.5)	5/10

Lower APRI and FIB-4 in Elite/HCV RNA- vs. Elite/HCV RNA+

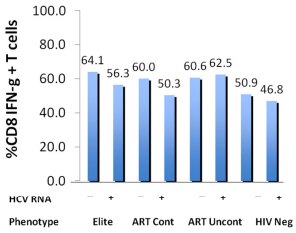
Group	Elite		ART controlled		ART uncontrolled		HIV Negative	
HCV RNA	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve
APRI Mean (SD)	0.17 (0.05)	0.41 (0.32)	0.26 (0.19)	0.46 (0.25)	0.37 (0.17)	0.80 (0.54)	0.17 (0.07)	1.47 (1.08)
FIB-4 Mean (SD)	0.89 (0.26)	1.37 (0.72)	1.19 (0.54)	1.42 (0.51)	1.43 (0.66)	2.25 (1.51)	0.91 (0.32)	4.05 (3.45)

Higher CD8 T cells activation in ELITES compared to ART controlled and HIV negatives with trend towards higher activation in Elite/HCVRNA+ vs. Elite/HCVRNA-

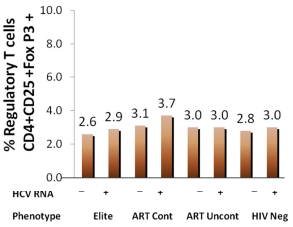




HCV viremia in Elites was associated with decrease in Interferon-γ in CD8 T cells compared to Elites/HCVRNA-



HCV viremia did not alter frequency of Regulatory T Cells between groups



Summary

1. PBMC from Elites/HCVRNA- compared to HIV-/ HCVRNA- had
   - Higher % of total CD8+ (mean 42±15.6 vs 30.2±7.2; p=0.037) [data not shown]
   - Trend towards higher activated CD8+ HLADR+ CD38+ median 5.8 [17.3, 0.3 max, min] vs. 3.4 [8.06,3.4] p=0.10)
2. Elites/HCVRNA- significantly lower CD8 T cell activation compared to HIV uncontrolled/HCV RNA- median 5.8 [17.3, 0.3 max, min] vs. median 14.5 (31.2, 6.6 max, min) (p=0.001).
3. The presence of HCV viremia in Elites led to
   - Decreased CD8+IFN-γ+
   - Increased CD8+HLADR+CD38+
   - No change in T-regs
   - Increased liver fibrosis

Conclusions

HCV viremia in Elite controllers is associated elevated levels of immune activation compared to HIVRNA-HCVRNA- women though less immune activation than HIVuc. HCV viremia in elite controllers was associated with decreased CD8 T cell IFN-g responsiveness, an effect that may be important to the regulation of viral infections in these patients.

Literature cited

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