Baseline Plasma and T-cell Immune Profiles Linked to Liver Stiffness Regression After HCV Cure

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BACKGROUND / OBJECTIVE

Liver fibrosis regression after hepatitis C virus (HCV) cure is variable, particularly in patients with advanced cirrhosis. Although direct-acting antivirals (DAAs) achieve a sustained virological response (SVR) in over 95% of cases, the long-term risk of decompensation and hepatocellular carcinoma remains, suggesting the persistence of an "*immunological scar*". Immunological drivers of fibrosis regression remain poorly understood, and the impact of HIV coinfection is especially unclear.



This study aimed to **identify baseline plasma and T-cell immune biomarkers associated with liver stiffness regression following DAA therapy** in people with HIV (PWH) and without HIV (PWoH) and advanced cirrhosis

METHODS

- **Design:** Prospective multicenter study
- Participants with HCV-related advanced cirrhosis (54 PWH and 23 PWoH) who achieved SVR after DAA therapy
- **Liver stiffness measurement (LSM)** was assessed by transient elastography at baseline and 48 weeks post-treatment. Advance cirrhosis was defined as LSM ≥25 kPa.
- **Plasma biomarkers:** multiplex immunoassay
- **Multiparametric flow cytometry**: Detailed CD4⁺ and CD8⁺ T-cell immunophenotyping
- Associations between baseline biomarkers and longitudinal changes in LSM were evaluated using generalized linear mixed models (GLMMs), adjusting p-values

Immune drivers of liver stiffness regression after HCV cure differed by HIV status, with inflammation predominating in people without HIV and memory T-cell dysfunction in people with HIV. A preserved CD127⁺ CD8⁺ T-cell phenotype consistently predicted improved hepatic recovery across groups

RESULTS

Table 1. Baseline characteristics of people with advanced HCV-related cirrhosis, stratified by HIV status

	PWoH (n=23)	PWH (n=54)	p
Gender (male)	11 (47.8)	44 (81.5)	**0.003**
Age (years)	63.5 (52.9-70.3)	51.7 (48.7-53.8)	**<0.001**
Smoker			**0.042**
Never	9 (39.1)	7 (13)	
Previously (≥ 6 months)	6 (26.1)	12 (22.2)	
Nowadays	8 (34.8)	34 (63)	
Alcohol intake			**0.029**
Never	17 (73.9)	23 (42.6)	
Previously (≥ 6 months)	6 (26.1)	26 (48.1)	
Nowadays	0 (0)	5 (9.3)	
Intravenous drug use			**<0.001**
Never	20 (87)	12 (22.2)	
Previously (≥ 6 months)	3 (13)	42 (77.8)	
BMI (kg/m²) (n=70)	27.1 (24.8-32.5)	24.1 (21.8-26.4)	**0.002**
BMI ≥ 25 kg/m²	14 (73.7)	19 (37.3)	**0.004**
Treatments			
Previous HCV therapy (IFNα+rib)	18 (78.3)	25 (46.3)	**0.010**
Statins	22 (95.7)	45 (83.3)	0.141
Antiretroviral therapy			
NRTI+NNRTI-based	-	7 (13.2)	-
NRTI+II-based	-	27 (50.9)	-
NRTI+PI-based	-	7 (13.2)	-
PI+II+others-based	-	4 (7.5)	-
Others	-	8 (15.1)	-
HIV markers			
Prior AIDS	-	19 (35.2)	-
Nadir CD4⁺ T-cells (cells/mm³)	-	99 (70-207)	-
Nadir CD4⁺ <200 cells/mm³	-	39 (73.6)	-
CD4⁺ T-cells (cells/mm³)	-	439 (234-719)	-
CD4⁺ <500 cells/mm³	-	32 (59.3)	-
HCV-related data			
HCV genotype			0.508
1	18 (78.3)	34 (63)	
3	3 (13)	8 (14.8)	
4	2 (8.7)	11 (20.4)	
Log_{10} HCV-RNA (IU/mL)	6.1 (5.6-6.4)	6.2 (5.7-6.7)	0.330
HCV-RNA ≥850,000 IU/mL	9 (39.1)	18 (33.3)	0.626
Liver disease			
LSM (kPa)	29.9 (27-48.8)	29.3 (24.5-38.5)	0.273
<25 kPa	5 (21.7)	14 (25.9)	0.405
25-40 kPa	10 (43.5)	29 (53.7)	
≥40 kPa	8 (34.8)	11 (20.4)	

Statistics: Values expressed as absolute number (percentage) and median (interquartile range). P-values, raw p-values; q-values, p-values corrected for multiple testing using the false discovery rate (Benjamini and Hochberg) procedure. The statistically significant differences are shown in bold. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; BMI, body mass index; IFNα, interferon-alpha; rib, ribavirine; NRTI, nucleoside analogue HIV reverse transcriptase inhibitor; NNRTI, non-nucleoside analogue HIV reverse transcriptase inhibitor; PI, protease inhibitor; II, integrase inhibitor; AIDS, acquired immune deficiency syndrome; HCV-RNA, HCV plasma viral load; LSM, liver stiffness measurement; PWH, people with HIV; PWoH, people without HIV; p, raw p-values.

Table 2. Changes in crude LSM values from baseline to 48 weeks post-treatment.

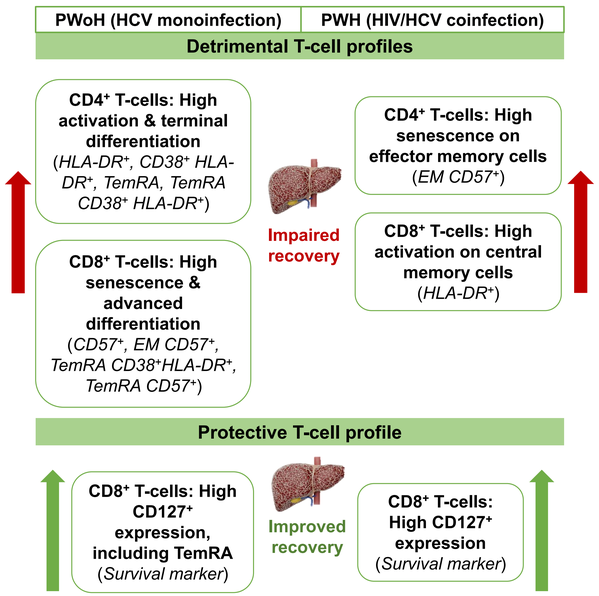
Groups	Baseline	48 weeks post-cure	Absolute Change	p-value [1]
PWoH (n=23)	29.9 (27.0; 61.9)	18.4 (14.1; 44.3)	-11.5 (-35.1; -5.8)	**0.010**
PWH (n=54)	29.3 (24.5; 36.3)	20.9 (15.3; 28.4)	-8.4 (-13.9; -2.3)	**<0.001**
p-value [2]	0.485	0.638	0.415	

Data are presented as median (IQR). [1]Within-group p-values (Baseline vs 48 Weeks) calculated using the Wilcoxon signed-rank test. [2]Between-group p-values (PWoH vs PWH) calculated using the Mann-Whitney U test. Statistically significant p-values (p<0.05) shown in bold. Abbreviations: IQR, interquartile range; LSM, liver stiffness measurement; PWH, people with HIV; PWoH, people without HIV.

Table 3. Baseline plasma cytokines associated with liver stiffness regression after HCV treatment.

	PWoH			PWH		
Cytokines	**AMR (95%CI)**	**p-value**	**q-value**	**AMR (95%CI)**	**p-value**	**q-value**
IFNγ	1.26 (1.03; 1.54)	**0.023**	**0.038**	1.01 (0.9; 1.13)	0.881	0.897
IL12p70	1.22 (0.92; 1.61)	0.164	0.205	0.95 (0.81; 1.12)	0.558	0.797
IL2	1.37 (1.07; 1.75)	**0.011**	**0.028**	0.96 (0.87; 1.07)	0.482	0.797
IL10	1.19 (0.87; 1.63)	0.267	0.297	0.86 (0.73; 1.02)	0.085	0.797
IL4	1.3 (1.08; 1.56)	**0.005**	**0.017**	0.99 (0.88; 1.1)	0.822	0.897
IL17A	1.89 (1.27; 2.82)	**0.002**	**0.010**	1.01 (0.89; 1.14)	0.897	0.897
IL1β	1.1 (1.02; 1.19)	**0.015**	**0.030**	0.9 (0.75; 1.07)	0.217	0.797
IL18	0.94 (0.76; 1.16)	0.570	0.570	0.96 (0.86; 1.08)	0.533	0.797
IL6	1.23 (1.01; 1.5)	**0.038**	0.054	0.95 (0.85; 1.05)	0.318	0.797
TNFα	1.38 (1.18; 1.61)	**<0.001**	**<0.001**	0.93 (0.79; 1.1)	0.382	0.797

AMR (95%CI) and p-values, derived from GLMMs (gamma family, log link). The AMR represents the multiplicative factor on the ratio of post-treatment to pre-treatment LSM for each one-unit increase in the log-transformed baseline marker. An AMR >1 indicates an association with impaired liver stiffness regression (higher residual stiffness) post-HCV treatment. In comparison, an AMR <1 indicates an association with improved liver stiffness regression (lower residual stiffness) post-HCV treatment. Q-values are p-values adjusted for multiple comparisons using the False Discovery Rate procedure (Benjamini and Hochberg). Values in bold highlight statistically significant associations after correction for multiple comparisons (q-value<0.20) or significant unadjusted p-values (p-value<0.05). Abbreviations: PWoH, people without HIV; PWH, people with HIV; AMR, Arithmetic Mean Ratio (AMR).



Distinct immunological signatures of LSM regression were identified according to HIV status. In **PWoH, impaired regression was associated with elevated baseline levels of systemic proinflammatory cytokines**, including IFN-γ, IL-2, IL-4, IL-17A, IL-1β, and TNF-α, together with **higher frequencies of terminally differentiated (TemRA) CD4⁺ T-cells and senescent (CD57⁺) CD8⁺ T-cells** across multiple subsets.

Higher proportions of protective CD127⁺ TemRA CD8⁺ T-cells were associated with **improved regression**. In contrast, **plasma inflammation was not predictive in PWH**. Instead, **impaired regression** was linked to higher **frequencies of dysfunctional Effector Memory** (EM) **CD4⁺ T-cells**, particularly **CD57⁺ subset**, and **activated Central Memory** (CM) **CD8⁺ T-cells**. A **protective** trend was observed **for CD127** expression **on CD8⁺ T-cells**

CONCLUSIONS

Determinants of liver recovery after HCV cure **differ by HIV status**. In **PWoH, systemic inflammation and T-cell exhaustion** shape regression, whereas in **PWH**, the **baseline functional state of T-cell memory pools** is the primary driver. Importantly, a protective CD127⁺ survival phenotype across CD8⁺ T-cell populations emerged as a marker of improved recovery. Findings support the role of immune monitoring as a prognostic tool and highlight CD127⁺ T-cell preservation as potential therapeutic target to enhance hepatic outcomes after viral cure

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