HIV Status Drives Distinct Immune Pathways of Persistent Portal Hypertension After HCV Cure

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BACKGROUND / OBJECTIVE

Persistent **portal hypertension** after **hepatitis C virus (HCV) cure** remains a major determinant of prognosis in **advanced cirrhosis**, yet its immunological drivers are poorly defined, particularly in **people with HIV (PWH)**. The **hepatic venous pressure gradient (HVPG)** is the gold standard for assessing portal hypertension and a strong predictor of outcomes.

Despite high rates of **sustained virological response with direct-acting antivirals (DAAs)**, a substantial proportion of patients show **incomplete HVPG regression**.
Understanding the baseline immune features that condition post-cure recovery is essential for risk stratification and the development of targeted therapies.

This study aimed to identify the baseline immunological determinants of HVPG regression after DAA therapy in people with advanced HCV-related cirrhosis

METHODS

- **Design:** Prospective multicenter study
- Individuals with **advanced HCV-related cirrhosis** (18 people **without HIV [PWoH]** and 23 **PWH**) who achieved HCV cure with DAAs
- All participants had **baseline HVPG** measurements and a **follow-up evaluation 48 weeks post-therapy**
- **Plasma biomarkers:** multiplex immunoassay
- **Multiparametric flow cytometry**: Detailed CD4⁺ and CD8⁺ T-cell immunophenotyping
- Associations between baseline immune markers and longitudinal HVPG changes. Using generalized **linear mixed-effects models**, with q-values controlling for multiple testing

After HCV cure in advanced cirrhosis, persistent portal hypertension is driven by systemic inflammation and broad CD4⁺ activation in people without HIV, but by endothelial dysfunction and exhausted CD4⁺ memory phenotypes in people with HIV

RESULTS

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

	PWoH (n=18)	PWH (n=23)	p
Gender (male)	8 (44.4%)	19 (82.6%)	**0.011**
Age (years)	62.8 (52.9-66.3)	52.1 (48.7-53.2)	**<0.001**
Smoker			0.101
Never	7 (38.9%)	3 (13.0%)	
Previously (≥ 6 months)	4 (22.2%)	4 (17.4%)	
Nowadays	7 (38.9%)	16 (69.6%)	
Alcohol intake			0.347
Never	13 (72.2%)	13 (56.5%)	
Previously (≥ 6 months)	5 (27.8%)	8 (34.8%)	
Nowadays	0 (0.0%)	2 (8.7%)	
Intravenous drug use			**<0.001**
Never	16 (88.9%)	7 (30.4%)	
Previously (≥ 6 months)	2 (11.1%)	16 (69.6%)	
BMI (kg/m²) (n=36)	27 (25.6-31.2)	24.5 (22.9-27.3)	0.064
BMI ≥ 25 kg/m²	11 (78.6%)	9 (40.9%)	0.067
Treatments			
Previous HCV therapy (IFNα+rib)	15 (83.3)	9 (39.1)	**0.004**
Statins	17 (94.4)	18 (78.3)	0.146
Antiretroviral therapy			
-NRTI+NNRTI-based	-	2 (8.7%)	-
-NRTI+II-based	-	12 (52.2%)	-
-NRTI+PI-based	-	4 (17.4%)	-
-PI+II+others-based	-	3 (13%)	-
-Others	-	2 (8.7%)	-
HIV markers			
Prior AIDS	-	8 (34.8%)	-
Nadir CD4⁺ T-cells (cells/mm³)	-	99 (54-207)	-
Nadir CD4⁺ <200 cells/mm³	-	17 (73.9%)	-
CD4⁺ T-cells (cells/mm³)	-	490 (234-721)	-
CD4⁺ <500 cells/mm³	-	13 (56.5%)	-
HCV markers			
HCV genotype (n=40)			0.224
1	15 (83.3%)	13 (56.5%)	
3	2 (11.1%)	3 (13.0%)	
4	1 (5.6%)	6 (26.1%)	
Log_{10} HCV-RNA (IU/mL)	6 (5.6-6.3)	6.2 (5.5-6.7)	0.462
HCV-RNA ≥850,000 IU/mL	8 (44.4%)	10 (43.5%)	0.951
Liver disease			
LSM (kPa)	32.1 (21.3-61.5)	35.3 (22.3-41.6)	0.486
<25 kPa	5 (27.8%)	6 (26.1%)	0.359
25-40 kPa	5 (27.8%)	11 (47.8%)	
≥40 kPa	8 (44.4%)	6 (26.1%)	
Child-Pugh Score (n=38)	5 (6-7)	5 (5-5)	**0.016**
Child-Pugh ≥7	5 (33.3%)	3 (13%)	0.134
Decompensated cirrhosis	11 (61.1%)	8 (34.8%)	0.093
HVPG (mmHg)	17 (14.5-18.5)	15 (11-17.5)	0.188
<16 mmHg	8 (44.4%)	13 (56.5%)	0.459
16-20 mmHg	6 (33.3%)	8 (34.8%)	
>=20 mmHg	4 (22.2%)	2 (8.7%)	

P-values, raw p-values; q-values, p-values corrected for multiple testing using the false discovery rate (Benjamini and Hochberg) procedure. Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFNα, interferon-alpha; NRTI, nucleoside analogue HIV reverse transcriptase inhibitor; NNRTI, non-nucleoside analogue HIV reverse transcriptase inhibitor; PI, protease inhibitor; II, integrase inhibitor; HCV-RNA, HCV plasma viral load; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; PWH, people with HIV; PWoH, people without HIV; rib, ribavirin.

Distinct immunological signatures of impaired HVPG regression emerged by HIV status

In **PWoH**, incomplete HVPG regression was associated with a proinflammatory cytokine profile [TNF-α, IL-17A and IL-10] and broad CD4⁺ T-cell activation [HLA-DR⁺, CD38⁺HLA-DR⁺], particularly within central memory (CM, CD45RA⁻CD28⁺) and effector memory (EM, CD45RA⁻CD28⁻) T cell subsets

In **PWH**, impaired regression was driven by endothelial dysfunction [sVCAM-1] and a more restricted CD4⁺ T-cell activation pattern confined to EM [HLA-DR⁺] and TemRA [CD38⁺HLA-DR⁺] subsets

CD8⁺ T-cell phenotypes were not significantly associated with HVPG dynamics. Larger baseline CM CD4⁺ T-cell pool was protective only in PWoH

Table 2. Association between baseline plasma biomarkers and HVPG regression after 48 weeks of completing HCV treatment.

	PWoH			PWH		
Plasma biomarkers	**AMR (95%CI)**	**p-value**	**q-value**	**AMR (95%CI)**	**p-value**	**q-value**
Th1/Th2/Th17 cytokines						
IFNγ	1.08 (1.00; 1.17)	**0.050**	0.150	1.03 (0.72; 1.47)	0.865	0.865
IL12p70	1.12 (0.93; 1.35)	0.246	0.428	1.17 (0.87; 1.57)	0.293	0.600
IL2	1.12 (0.91; 1.38)	0.285	0.428	1.12 (0.61; 2.04)	0.723	0.838
IL10	1.20 (1.05; 1.38)	**0.007**	**0.028**	0.89 (0.77; 1.03)	0.121	0.600
IL4	1.10 (0.91; 1.34)	0.325	0.433	1.15 (0.86; 1.52)	0.345	0.600
IL17A	1.28 (1.10; 1.50)	**0.002**	**0.012**	1.27 (0.77; 2.12)	0.350	0.600
Inflammatory cytokines						
IL1β	1.03 (0.99; 1.06)	0.136	0.326	1.07 (0.68; 1.67)	0.768	0.838
IL18	1.00 (0.94; 1.07)	0.911	0.911	0.92 (0.78; 1.08)	0.307	0.600
IL6	1.06 (0.95; 1.18)	0.274	0.428	0.96 (0.88; 1.03)	0.256	0.600
TNFα	1.13 (1.05; 1.21)	**0.001**	**0.012**	1.08 (0.72; 1.62)	0.710	0.838
Endothelial dysfunction						
sVCAM1	1.07 (0.55; 2.09)	0.840	0.911	1.58 (1.12; 2.22)	**0.008**	**0.096**
sICAM1	1.02 (0.90; 1.16)	0.741	0.889	1.06 (0.92; 1.23)	0.412	0.618

Arithmetic Mean Ratio (AMR) with 95% Confidence Intervals and p-values, derived from a generalized linear mixed-effects model (gamma family, log link). AMR represents the multiplicative change in the ratio of post- to pre-treatment HVPG for each one-unit increase in the log-transformed baseline marker. An AMR > 1 indicates an association with impaired regression (higher residual HVPG), while an AMR < 1 indicates an association with improved regression (lower residual HVPG). 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<0.10) or significant unadjusted p-values (p-value<0.05).

Table 3. Association between baseline CD4⁺ T-cell subsets (percentage) and HVPG regression (mmHg) 48 weeks after completing HCV treatment.

		PWoH			PWH		
T-cell Subset	**Marker**	**AMR (95% CI)**	**p-value**	**q-value**	**AMR (95% CI)**	**p-value**	**q-value**
	Base Population	-	-		-	-	
Total CD4⁺	CD38⁺	1.12 (0.98; 1.28)	0.094	0.187	1.12 (0.76; 1.65)	0.576	0.883
	HLA-DR⁺	1.41 (1.20; 1.67)	**<0.001**	**<0.001**	1.19 (1.02; 1.39)	**0.031**	0.155
	CD38⁺ HLA-DR⁺	1.30 (1.11; 1.52)	**0.001**	**0.007**	1.08 (0.92; 1.28)	0.344	0.860
	CD57⁺	1.03 (0.93; 1.15)	0.510	0.678	0.92 (0.74; 1.14)	0.435	0.883
Naïve	Naïve	1.23 (0.97; 1.56)	0.095	0.187	0.94 (0.70; 1.25)	0.662	0.883
Central Memory (CM) (CD4⁺CD45RA⁻CD28⁺)	CM	0.75 (0.58; 0.97)	**0.026**	**0.074**	1.15 (0.76; 1.73)	0.507	0.883
	CD38⁺	1.14 (0.97; 1.32)	0.103	0.187	0.97 (0.78; 1.20)	0.771	0.903
	HLA-DR⁺	1.25 (1.08; 1.45)	**0.003**	**0.015**	1.07 (0.89; 1.28)	0.455	0.883
	CD38⁺ HLA-DR⁺	1.22 (1.09; 1.38)	**0.001**	**0.007**	0.93 (0.70; 1.25)	0.647	0.883
	CD57⁺	1.16 (1.02; 1.33)	**0.026**	**0.074**	0.82 (0.61; 1.10)	0.189	0.540
Effector Memory (EM) (CD4⁺CD45RA⁻CD28⁻)	EM	1.08 (1.02; 1.14)	**0.005**	**0.020**	0.98 (0.88; 1.09)	0.719	0.899
	CD38⁺	1.03 (0.94; 1.12)	0.578	0.680	0.96 (0.83; 1.10)	0.538	0.883
	HLA-DR⁺	1.01 (0.92; 1.12)	0.837	0.863	1.08 (1.03; 1.14)	**0.003**	**0.030**
	CD38⁺ HLA-DR⁺	0.95 (0.86; 1.04)	0.230	0.354	1.06 (0.99; 1.12)	0.088	0.330
	CD57⁺	1.02 (0.84; 1.23)	0.863	0.863	1.00 (0.87; 1.15)	0.986	0.986
TemRA (CD4⁺CD45RA⁺CD28⁻)	TemRA	1.04 (0.91; 1.19)	0.542	0.678	1.01 (0.92; 1.11)	0.813	0.903
	CD38⁺	1.11 (0.99; 1.25)	0.081	0.187	0.98 (0.76; 1.28)	0.905	0.953
	HLA-DR⁺	1.09 (0.97; 1.23)	0.166	0.277	1.10 (0.98; 1.24)	0.099	0.330
	CD38⁺ HLA-DR⁺	1.03 (0.91; 1.16)	0.667	0.741	1.12 (1.04; 1.20)	**0.002**	**0.030**
	CD57⁺	0.98 (0.92; 1.04)	0.463	0.661	1.08 (1.01; 1.15)	**0.023**	0.153

Data are presented as Arithmetic Mean Ratio (AMR) with 95% Confidence Intervals derived from a generalized linear mixed-effects model (gamma family, log link). The AMR represents the multiplicative change in the ratio of post- to pre-treatment HVPG for each one-unit increase in the log-transformed baseline marker. An AMR > 1 indicates an association with impaired regression (higher residual HVPG), while an AMR < 1 indicates an association with improved regression (lower residual HVPG). Only markers with a statistically significant association ($p < 0.05$) in at least one stratum are shown. 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<0.10) or significant unadjusted p-values (p-value<0.05).

CONCLUSIONS HIV coinfection reshapes the immunological determinants of post-cure portal hypertension recovery. In PWoH, systemic inflammation and widespread CD4⁺ activation dominate, whereas in PWH, endothelial injury and a more exhausted memory T-cell phenotype are key. The absence of the protective CM CD4+ compartment in PWH underscores profound immune exhaustion in this population. These findings highlight the need for stratified approaches to manage residual portal hypertension after HCV cure

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