

# HAART Is Associated With a Lower Level Of Hepatic Necroinflammatory Activity In HIV-HCV Coinfected Patients With CD4 > 350 at the time of liver biopsy.

Poster H 2319

J.F. Pascual Pareja, A. Caminoa, J. Larrauri, J. González-García, J. Díez, M. Montes, M. Mora, J. Bernardino, J. Arribas.  
Hosp. La Paz, Madrid, Spain. Contact: jfpascualpareja@yahoo.es

## Background

•After the introduction of HAART the importance of liver-related mortality in HIV-HCV coinfecting patients has increased.

•Sustained virological response to anti-HCV treatment can prevent fibrosis progression, decrease end-stage liver disease and increase survival. Unfortunately, only a minority of patients can be appropriately selected for treatment and the overall rates of sustained virological response are relatively low in HIV-HCV coinfecting patients.

•Several cohorts have suggested that immune recovery after HAART can attenuate liver fibrosis and necroinflammatory activity. However, it is not known if an earlier initiation of HAART with CD4 cell counts above the current recommended threshold in antiretroviral naïve patients could be beneficial in HIV-HCV coinfecting patients.

•Although maintaining a higher count of CD4 cells could slow down liver fibrosis progression, it is also possible that drug-induced steatosis, the immune reconstitution syndrome and drug-related hepatotoxicity secondary to HAART might be detrimental for fibrosis progression.

## Objective

To try to evaluate the impact of HAART in the liver damage of HIV-HCV coinfecting patients with relatively preserved immune status we have performed a detailed study of liver histology of patients who had liver biopsies performed when CD4 cell counts were higher than 350 cells/μL.

## Materials & Methods I

### •Patients:

- Inclusion criteria were: 1) HCV infection diagnosed by a positive serum HCV RNA PCR; 2) CD4 cell count above 350 cells/μL at the time of liver biopsy.

- Exclusion criteria: positive hepatitis B surface antigen, prior anti-HCV therapy, unknown date of HCV infection (defined as the date of first transfusion or the first year of injecting drug use), obvious noncompliance with antiretroviral therapy, nonassessable liver biopsy sample and impossibility to collect the clinical or analytical variables.

### •Liver histology:

- A single pathologist (A.C.) blinded to all clinical results evaluated all slides.
- Necroinflammatory activity (NA) and fibrosis was scored by the Scheuer System.
- Steatosis was scored according to the % hepatocytes affected.

## Materials & Methods II

### •Statistical analysis:

- We performed multivariate regression analysis to assess the association of use of HAART at the moment of biopsy and high liver necroinflammatory activity (Scheuer' score ≥ 3).

- We included in the model the following possible confounding independent variables: sex, age, alcohol abuse (daily consumption of any amount of alcohol.), HCV genotype (1 or 4 vs. other genotypes), serum HCV RNA levels at liver biopsy (< or > 800,000 IU/mL), Nadir CD4 (cells μ/L), CD4 cell counts at the time of liver biopsy (cells μ/L), low HIV viral load (< 400 copies/mL), ALT levels (IU/L), advanced fibrosis (Scheuer' score ≥ 3) and presence of any grade of steatosis.

## Results

### Characteristics of study population (119 HIV/HCV co-infected patients)

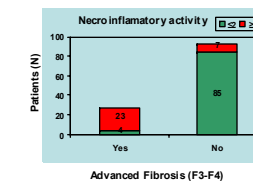
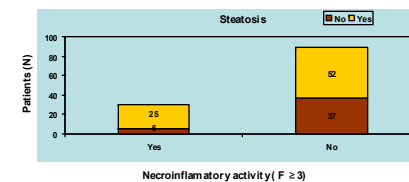
	Median (IQR)	N (%)
<b>Male sex</b>		93 (78.2)
<b>Caucasian race</b>		119 (100)
<b>Age (yr)</b>	38 (35-41)	
<b>Weight (Kg)</b>	68 (59-76.5)	
<b>Duration of HCV infection (yrs)</b>	20 (15-22)	
<b>AIDS diagnosis</b>		60 (47.6)
<b>Current alcohol abuse</b>		29 (24.4)
<b>ALT (U/L)</b>	87 (54-131)	
<b>HCV viral load &gt;800000 cp/mL</b>		58 (48.7)
<b>HCV Genotype 1 or 4</b>		85 (71.4)
<b>CD4 cells/μL (Nadir)</b>	210 (113-336)	
<b>CD4 cells/μL (at liver biopsy)</b>	549 (456-675)	
<b>HIV RNA &lt;400 cp/mL (at liver biopsy)</b>		71 (59.7)
<b>Current HAART*</b>		93 (78.2%)
<b>Duration of HAART in days</b>	1444 (1152-1913)	

\*Of the 26 patients not receiving HAART at the time of biopsy, 19 were antiretroviral naïve and seven had interrupted HAART for a median of 106.3 (27.1 – 122.1) weeks before the liver biopsy.

## Results

### Characteristics of liver biopsy

		N (%)
Grade of fibrosis (Scheuer System)	0	3 (2.5)
	1	62 (52.1)
	2	27 (22.7)
	3	23 (19.3)
	4	4 (3.4)
Grade of Necroinflammatory activity (Scheuer System)	0	2 (1.7)
	1	19 (15.1)
	2	69 (58)
	3	26 (21.8)
	4	4 (3.4)
Grade of Steatosis (% hepatocytes affected)	None	42 (35.3)
	<10%	12 (10.1)
	10-30%	43 (36.1)
	31-60%	15 (12.6)
	>60%	7 (5.9)



### Factors associated with Necroinflammatory activity ≥ 3

Characteristic	NA ≥ 3 (n=30)	NA < 3 (n=89)	Univariate analysis p value	Multivariate analysis OR (95%CI) p value
Age (yr)	37 (34-40)	38 (35-41)	NS	
Male Sex	24 (80)	69 (77.5)	NS	
Alcohol Abuse*	12 (40)	17 (19.1)	0.021	NS
ALT (U/L)	137 (56-203)	92 (51-113)	0.022	1.01 (1-1.02) 0.052
Current HAART	20 (66.7)	73 (82)	0.078	0.16 (0.03-0.78) 0.024
Duration of HAART in days	1504 (1268-1972)	1421 (1127-1908)	NS	
Nadir CD4 (cells/μL)	152 (81-331)	218 (117-345)	NS	
CD4 (cells/μL) at liver biopsy	593 (447-645)	615 (464-684)	NS	
HIV RNA <400 copies/mL	16 (53.3)	55 (61.8)	NS	
HCV RNA >800,000 copies/mL	17 (56.7)	41 (46.1)	NS	
HCV Genotype 1 or 4	21 (70)	64 (71.9)	NS	
Fibrosis score ≥ 3	23 (76.7)	4 (4.5)	<0.001	131.9 (24.8-700.8) <0.001
Any grade of Steatosis	25 (83.3)	52 (58.4)	0.014	NS

## Discussion

•In our study we have found that use of HAART appear to significantly decrease liver necroinflammatory activity in HIV/HCV coinfecting patients with CD4 T cell count >350 cells/μL.

• HAART might be beneficial through the inhibition of HIV replication in the liver. Two recent studies have suggested that HIV can directly cause liver damage (1, 2). In addition, Lin and colleagues have shown that exposure to the gp120 protein promoted HCV replication (3).

•Surprisingly, in our study suppression of HIV replication below 400 copies/mL was not associated with a lower level of necroinflammatory activity. Since we have evaluated only one viral load at the time of liver biopsy this result should be taken with caution.

•Another possible beneficial mechanism of HAART upon liver histology could be by decreasing the level of proinflammatory cytokines in HIV/HCV coinfecting patients (4).

•Steatosis was not associated with liver necroinflammatory activity in the multivariate model probably because steatosis was also highly associated with advanced fibrosis.

## Conclusions

•Use of HAART was associated with lower levels of Necroinflammatory Activity.

•Necroinflammatory Activity was strongly associated with higher fibrosis scores.

•These results suggest that HAART might decrease hepatitis C activity in HIV/HCV coinfecting patients with > 350 CD4.

## References

1. Tuyama AC, Hong F, Schecter AD. HIV entry and replication in stellate cells promotes cellular activation and fibrogenesis: Implications for hepatic fibrosis in HIV/HCV co-infection. 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). Boston, 2-6 Noviembre. Abstract LB3.
2. Bruno R, Galastri S, Marra F. Gp120 induces directional migration of Human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). Boston, 2-6 Noviembre. Abstract 125.
3. W Lin, EM Weinberg, AW Tai, and others. HIV Increases HCV Replication in a TGF-beta1-Dependent Manner. Gastroenterology. 2008; 134(3): 803-811.
4. Kuntzen T, Tural C, Li B, Feldmann G, Kupfer B, Nischalke HD, et al. Intrahepatic mRNA expression in hepatitis C virus and HIV/hepatitis C virus co-infection: infiltrating cells, cytokines, and influence of HAART. AIDS. 2008; 22: 203-10.