Long-term Clinical Outcome in HIV/HCV-Coinfected Patients with Advanced Liver Fibrosis With and Without Sustained Virological Response Following Interferon Plus Ribavirin

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Background & Aims

- We have shown that sustained virological response (SVR) following IFN-RBV in HIV/HCV+ patients reduced liver-related morbidity and mortality *
- In this study we evaluated the long-term clinical outcome of SVR following IFN-RBV in the subgroup of coinfected patients with biopsy confirmed advanced liver fibrosis (METAVIR F3-F4) in the GESIDA 3603/5607 Study Cohort.

*Berenguer J, et al. Hepatology 2009; 50 (2): 407-13.

Patient Characteristics

Characteristic	Patients (N = 448)
Male sex – nº (%)	343 (76.9)
Age - yr, median (IQR)	41.9 (38.1; 44.2)
Weight - kg, median (IQR)	68 (60; 77)
Prior injection-drug use – nº (%)	387 (87.2)
CDC disease category C – nº (%)	124 (27.8)
CD4 + cells baseline – nº/mm3	352 (251; 501)
HIV-RNA < 50 copies/ml. baseline – nº(%)	294 (68.5)
Duration of HCV infection, median (IQR)	19 (13; 22)
HCV genotype 1-4 - nº (%)	311 (71.3)
HCV-RNA ≥ 500,000 IU/mL – nº (%)	250 (66.7)
METAVIR fibrosis score – nº (%)	
- F3	312 (69.6)
- F4	136 (30.4)
HBsAg positive	22 (5.0)
Current intake of > EtOH daily – nº (%)	28 (6.8)
Methadone use– nº (%)	56 (13.7)

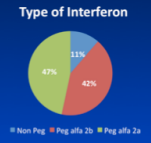
Rate of events during FU in 448 HIV/HCV+ patients with F3-F4 with/without SVR after IFN + RBV

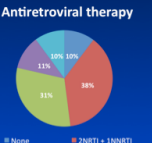
	Rate/100 person-years (95% CI)		
Event	Non-SVR (n=333)	SVR (n=115)	P
Follow-up -mo, median (IQR)	62.6 (44.3; 82.9)	58.8 (41.3; 79)	.163
Loss to follow-up	4.52 (3.52 - 5.53)	2.5 (1.19 - 3.81)	.038
Liver decompensation	3.52 (2.61 - 4.44)	0.18 (0 - 0.53)	<.001
Hepatocellular carcinoma	0.76 (0.35 - 1.18)	0 (0 - 0)	.036
Liver transplantation	0.88 (0.44 - 1.33)	0.18 (0 - 0.52)	.076
New AIDS-defining conditions	0.94 (0.48 - 1.4)	0.54 (0- 1.15)	.391
Deaths overall	2.43 (1.69 - 3.16)	0 (0 - 0)	<.001
Liver-related	1.62 (1.02 - 2.22)	0 (0 - 0)	.003
AIDS-related	0.17 (0 - 0.37)	0 (0 - 0)	.317
Non–liver-related non–AIDS-related	0.64 (0.26 - 1.01)	0 (0 - 0)	.053

Study Design
GESIDA 3603/5607 Study Cohort

Setting	19 clinical centers in Spain
Patients	HIV/HCV+ patients who started IFN-RBV between Jan 2000 and Dec 2008
Data Retrieval	Data were entered into a common database at each institution by means of an ad hoc online application
Follow-Up (every 6mo)	Clinical (survival, decompensation, HIV-related diseases, ART) and labs (CD4+, HIV viral load, HCV RNA). Liver biopsies, if any. In cirrhotics α-fetoprotein (AFP) and US scan
Length of the study	From the date SVR or non-SVR was confirmed to death or the last follow-up visit.
Monitoring	All sites were monitored to verify that the information in the database was consistent with the patient's medical history.

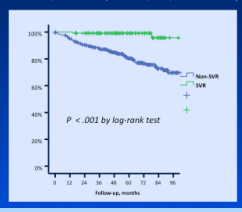
Treatment Details





Kaplan-Meier Estimator of Liver-related Events*
in 448 HIV/HCV+ patients with F3-F4 stratified according to response to IFN-RBV

* Liver-related death, liver decompensation, HCC, and liver transplantation



Sustained Virological Response Definition
GESIDA 3603/5607 Study Cohort

- SVR was defined as an undetectable serum HCV-RNA level 24 weeks after discontinuation of therapy
- Patients not fulfilling SVR criteria, including those who relapsed after achieving End of Treatment Response, were classified as non-SVR.

SVR & Independent Factors Associated With an SVR
by Multiple Logistic-Regression Analysis

SVR = 115 (25.7%)

Variable*	OR	95% CI	P
Type of Interferon			
Non-Peg α2a/α2b	Ref.	-	-
Peg α2a/α2b	2.88	(1.10; 7.52)	.031
CDC category A/B	1.31	(.978; 2.862)	.389
Nadir CD4 + cells	1.00	(1.0; 1.0)	.785
HCV genotype 2-3	4.11	(2.39; 7.05)	<.001
HCV-RNA < 500K IU/mL	1.92	(1.13; 3.27)	.015
No intake of < 50 g et-OH	1.25	(.43; 3.61)	.678

*The final model included variables associated with SVR by univariate logistic-regression analysis

Multivariate Analysis of Factors Associated with Liver-related Events* by Cox Regression Analysis

	Adjusted HR	95% CI	P
Non-SVR vs. SVR	12.60	(3.08; 51.49)	<.001
Age	1.02	(0.98; 1.07)	.343
Male sex	1.61	(0.86; 3.01)	.137
History of IDU	0.66	(0.36; 1.19)	.167
CDC Category C vs. A/B	0.82	(0.48; 1.41)	.474
Nadir CD4+ cells	1.00	(1; 1)	.712

* Liver-related death, liver decompensation, HCC, and liver transplantation

Endpoints

Liver-related complications
Liver decompensation
- Ascites, porto-systemic encephalopathy, upper GI bleeding

Hepatocellular carcinoma (HCC)
- Histologically or clinically confirmed (high AFP values and imaging)

Liver transplantation

HIV progression
New AIDS-defining conditions (ADC); 1993 CDC Clinical Classification

Mortality*
Liver-related death
- When the train of events that ended in death was caused by liver decompensation or HCC

AIDS-related death
- When death was directly related to one ADC

Other causes
- Non–liver-related and non–AIDS-related

* Death reports, autopsy reports (if available), and protocolized formularies were requested. All the information was reviewed by a "mortality committee", which classified deaths in accordance with the opinion of the attending clinician

Frequency of events during FU in 448 HIV/HCV+ patients with F3-F4 with/without SVR after IFN + RBV

	Frequency of events N (%)		
Event	Non-SVR (n=333)	SVR (n=115)	P
Follow-up -mo, median (IQR)	62.6 (44.3; 82.9)	58.8 (41.3; 79)	.163
Loss to follow-up	78 (23.4)	14 (12.2)	.010
Liver decompensation	57 (17.1)	1 (0.9)	<.001
Hepatocellular carcinoma	13 (3.9)	0 (0)	.031
Liver transplantation	15 (4.5)	1 (0.9)	.070
New AIDS-defining conditions	16 (4.8)	3 (2.6)	.311
Deaths overall	42 (12.6)	0 (0)	<.001
Liver-related	28 (8.4)	0 (0)	.001
AIDS-related	3 (0.9)	0 (0)	.307
Non–liver-related non–AIDS-related	11 (3.3)	0 (0)	.048

Conclusions

- Our results suggest that SVR after IFN-RBV in HIV/HCV+ patients with F3-F4 reduces the risk of long-term clinical outcomes such as liver-related death, liver decompensation, and hepatocarcinoma.

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