Clinical Consequences of Achieving End-of-Treatment Response but Not Sustained Virologic Response to Interferon Plus Ribavirin in HIV/HCV-Coinfected Patients

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Background and Aims

- We showed that, in HIV/HCV coinfected patients, a sustained virologic response (SVR) after therapy with interferon plus ribavirin (IF-RB) reduces liver-related complications and mortality[1] as well as HIV progression and mortality not related to liver disease[2]
- Here, we assess the impact of end-of-treatment response (ETR), but not SVR, on the following:
  - Mortality and liver-related events.
  - HIV progression and mortality not related to liver disease.

[1]Berenguer, J. et al. Hepatology 2009;50:407-413
[2]Berenguer J, et al. 17th CROI, 2010. (Oral Presentation #167).

Study Design

Setting	20 clinical centers in Spain
Patients	HIV/HCV+ patients who started IF-RB between Jan 2000 and Jul 2007
Data retrieval	Data were entered into a common database at each institution by means of an ad hoc online application
Follow-up (every 6 mo)	▪ Survival ▪ Liver decompensation ▪ HIV-related diseases ▪ ART and lab results (CD4+ cells, HIV-VL, HCV-RNA) ▪ Liver biopsies, if any ▪ In cirrhotic patients: alpha-fetoprotein (AFP) and ultrasound scan
Study duration	From the date IF-RB was stopped to death or last FU visit Administrative censoring date: 31 April, 2009

Definitions

Sustained Virologic Response (SVR)

- The SVR was defined as an undetectable serum HCV-RNA level 24 weeks after discontinuation of therapy.

End-of-Treatment Response (ETR)

- Defined as an undetectable serum HCV-RNA level at the end of programmed therapy (48 wk), with subsequent relapse

No Response (NR)

- Patients not fulfilling ETR or SVR criteria were classified as NR

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 forms were requested. All the information was reviewed by a "mortality committee", which classified deaths in accordance with the opinion of the attending clinician

Patient Characteristics

Characteristic	Patients (N=1428)
Male sex – n (%)	1047 (74)
Age – yr, median (IQR)	42 (38-45)
Prior injection drug use – n (%)	1142 (81)
CDC category C – n (%)	310 (22)
CD4 cells nadir-n/mm^3 – median (IQR)	216 (116-333)
CD4 cells baseline-n/mm^3 –median (IQR)	528 (384-719)
HIV RNA 50 copies/mL baseline – n (%)	848 (62)
HCV genotype 1-4 – n (%)	858 (60)
HCV RNA ≥ 500,000 IU/mL	931 (65)
Advanced fibrosis (F>3 or APRI >2)	429 (30)
Alcohol intake >50 g/d – n (%)	69 (5)
HAART during HCV treatment – n (%)	1205 (84)

Treatment Regimens and Response

Treatment Regimen	n (%)
Non-peg IF + RB	194 (14)
Peg IF 2b + RB	549 (38)
Peg IF 2a + RB	685 (48)

Treatment Response	n (%)
SVR	520 (36)
ETR	211 (15)
NR	697 (49)

Factors independently associated with SVR			
Variable	**OR**	**95% CI**	***P***
Type of IF			
Non-peg IF	Ref	-	
Peg IF 2b	1.72	1.05 - 2.82	.031
Peg IF 2a	2.13	1.30 - 3.50	.003
CDC category A/B	1.71	1.13 - 2.60	.012
Nadir CD4+cell count	1.00	1.00 - 1.00	.125
HCV genotype 2-3	4.70	3.39 - 6.52	.000
HCV-RNA < 500 k IU/mL	1.95	1.40 - 2.69	.000
METAVIR F0-F2	2.25	1.61 - 3.13	.000
Alcoholintake < 50 g/d	2.46	1.03 - 5.88	.043

Frequency of Events During FU Stratified According to Response to IF-RB

	NR (n=697)	ETR (n=211)	SVR (n=520)
Follow-up – mo, median (IQR)	49.1 (31.5 - 66.2)	46.8 (28.5 - 64.3)	46.6 (29.4 - 64.7)*
Lost to follow-up – n (%)	119 (17.1)	22 (10.4)	50 (9.6)*
Deaths – n (%)	59 (8.5)	4 (1.9)*	6 (1.2)*
Liver-related (LR) – n (%)	35 (5)	1 (0.5)*	2 (0.4)*
AIDS-related – n (%)	3 (0.4)	0 (0)	0 (0)
Other causes – n (%)	21 (3)	3 (1.4)	4 (0.8)*
AIDS-related other causes – n (%)	24 (3.4)	3 (1.4)	4 (0.8)*
New CDC category C	21 (3.1)	9 (4.3)	3 (0.6)*†
New CDC category C/Non-LR deaths	41 (6)	11 (5.2)	7 (1.4)*†
Liver decompensation – n (%)	75 (11)	9 (4.3)*	2 (0.4)*†
Hepatocellular carcinoma – n (%)	15 (2.2)	1 (0.5)	0 (0)
Liver transplantation – n (%)	14 (2.1)	2 (1)	0 (0)

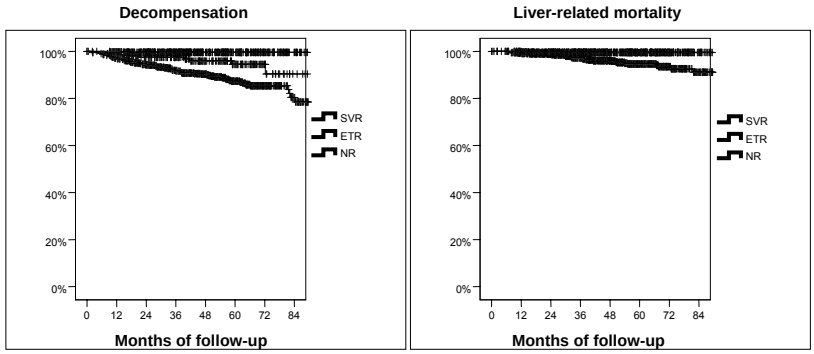
* Statistically significant differences (*P*<.05) with the NR group.
† Statistically significant differences (*P*<.05) with the ETR

Rate of events during FU stratified according to response to IF-RB

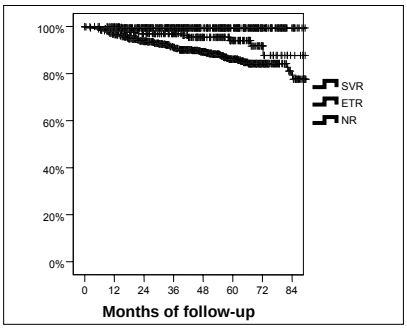
	Rate/100 person-years (95% CI)		
Event	**NR (n=697)**	**ETR (n=211)**	**SVR (n=520)**
Lost to follow-up	4.19 (3.44 - 4.95)	2.73 (1.59 - 3.87)	2.61 (1.89 - 3.34) *
Deaths – n (%)	2.06 (1.54 - 2.59)	0.49 (0.01 - 0.97) *	0.31 (0.06 - 0.56) *
Liver-related (LR)	1.22 (0.82 - 1.63)	0.12 (0 - 0.36) *	0.10 (0 - 0.25) *
AIDS-related	0.10 (0 - 0.22)	0 (0 - 0)	0 (0 - 0)
Other causes	0.73 (0.42 - 1.05)	0.37 (0 - 0.78)	0.21 (0 - 0.41) *
AIDS-related/other causes	0.84 (0.5 - 1.17)	0.37 (0 - 0.78)	0.21 (0 - 0.41) *
New CDC category C	0.74 (0.42 - 1.06)	1.11 (0.39 - 1.84)	0.15 (0 - 0.33) *†
New CDC cat C/Non-LR deaths	1.45 (1.01 - 1.89)	1.36 (0.56 - 2.16)	0.36 (0.09 - 0.63) *†
Liver decompensation	2.73 (2.11 - 3.35)	1.12 (0.39 - 1.85) *	0.10 (0 - 0.25) *†
Hepatocellular carcinoma	0.53 (0.26 - 0.79)	0.12 (0 - 0.36)	0 (0 - 0) *
Liver transplantation	0.49 (0.23 - 0.75)	0.24 (0 - 0.58)	0 (0 - 0) *†

* Statistically significant differences (P<.05) with the group NR.
†Statistically significant differences (P<.05) with the group

Decompensation and LR-mortality in 1428 HIV/HCV+ Patients According to Response to IF-RB



Liver-related Events* in 1428 HIV/HCV+ Patients According to Response to IF-RB



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

Multivariate Analysis of Factors Associated With Liver-related Events*

Cox Regression Analysis

Outcome	Adjusted HR≠	95% CI	*P*
NR	1.00	-	-
ETR	0.40	0.17 - 0.9	.032
SVR	0.08	0.03 - 0.3	<.001

≠ Age, sex, HCV genotype, HCV-RNA, CDC clinical category, nadir CD4+ cell count, HIV transmission category, liver fibrosis

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

Conclusions

- In HIV/HCV-coinfected patients treated with IF-RB, best outcomes were achieved with an SVR.
- However, ETR was associated with less liver-related mortality and decompensation than NR.
- SVR, but not ETR, was associated with less HIV progression and mortality not related to liver disease.

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Abstract

Background: We showed that a sustained viral response (SVR) after therapy with interferon-ribavirin (IF-RB) reduces liver-related (LR) complications and mortality in HIV/HCV-coinfected patients. Here, we assess the impact of end-of-treatment response (ETR) but not SVR on mortality and LR events.

Methods: We analyzed the GESIDA 3603 Cohort (HIV/HCV-coinfected patients treated with IF-RB in 19 centers in Spain). Response to IF-RB was categorized as SVR, ETR (without SVR), and no response (NR). The study started when IF-RB was stopped and ended at death or the last follow-up visit.

Results: The table shows the frequency of events stratified according to response to treatment in 1428 patients.

	NR (697)	**ETR (211)**	**SVR (520)**
Follow-up mo, median (IQR)	49.1 (31.5-66.2)	46.8 (28.5-64.3)	46.6 (29.4-64.7) * †
Liver-related death, n (%)	35 (5.0)	1 (0.5) *	2 (0.4) *
Liver decompensation, n (%)	75 (11.0)	9 (4.3) *	2 (0.4) * †
* *P*<.05 with respect to NR. †*P*<.05 with respect to ETR			

We performed a Cox regression analysis adjusted for age, sex, risk group, CDC category, nadir CD4+, HCV genotype, HCV RNA, and fibrosis stage. When we took NR as the reference, the adjusted HR (95% CI) of LR events (LR death, decompensation, hepatocarcinoma, and transplantation) was 0.40 (0.17-0.9; *P*=0.032) for ETR and 0.08 (0.03-0.3; *P*<0.001) for SVR.

Conclusions: Best outcomes were achieved with an SVR. However, ETR was associated with less LR mortality and decompensation than NR.