Treatment With Pegylated Interferon (Peg-INF) Plus Ribavirin (RBV) of HIV-infected Patients With Recurrent Hepatitis C Virus Infection After Liver Transplantation (LT): A Prospective Cohort Study

L. Castells, A. Rimola, **C. Manzardo*,** A. Valdivieso, J. Montero, R. Barcena, M. Abradelo, F. Xiol, V. Aguilera, M. Salcedo, M. Rodriguez, C. Bernal, F. Suarez, A. Antela, S. Olivares, S. del Campo, M. Laguno, J. Fernandez, G. de la Rosa, I. Perez, J. Gonzalez, J. Esteban-Mur, J. M. Miro
and the FIPSE OLT-HIV investigators

*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain
E-mail: jmmiro@ub.edu

Background

- Recurrent HCV infection after OLT is a major cause of graft loss and death in HCV/HIV-coinfected patients.
- Published information regarding the efficacy of anti-HCV therapy with Peg-INF and RBV in HCV/HIV-coinfected OLT recipients is limited to small case series.

Miro JM on behalf FIPSE. Am J Transpl, 2012; Terrault N. Liver Transpl, 2012.

Cause of Death in HCV-infected LT Recipients

Spanish prospective, multicenter, cohort study (FIPSE Study)

Preliminary results (2002-2006; end of follow-up: 2010)

Cause of death	HCV/HIV (n = 84)	HCV (n = 252)	p value
HCV recurrence	**18 (21%)**	**31 (12%)**	**0.049**
Infection	7 (8%)	15 (6%)	NS
Tumors	3 (4%)	4 (2%)	NS
Technical problems	0	6 (2%)	NS
Other	8 (10%)	19 (8%)	NS

Miro JM on behalf FIPSE. Am J Transpl; 2012; 12:1866-76

Objective

The aim of the present study was to evaluate the efficacy and safety of treatment with pegylated interferon (PegIFN) and ribavirin (RBV) for recurrent HCV infection after OLT in HIV/HCV-coinfected patients compared with a control group of HCV-monoinfected patients.

Patients and Methods

- Prospective, multicenter cohort study comprising 149 consecutive HIV/HCV-coinfected patients who underwent OLT between 2002 and 2009 in different centers in Spain and who were followed until July 2012.
- HIV-infected patients were matched with 447 HCV-monoinfected patients (1:3 ratio) who underwent OLT during the same period at the same sites. Other matched criteria were calendar year (±1 year), age (±12 years), gender, presence of HBV coinfection, and presence of hepatocellular carcinoma.
- The study population comprised HCV/HIV-coinfected patients who started post-OLT anti-HCV therapy with PegINF and RBV and who were matched with HCV-monoinfected controls treated against HCV in the same center.
- The study was approved by the Institutional Review Boards of all the participating sites. All patients signed the informed consent form.

OLT Inclusion Criteria

- Liver criteria: the same as for the non-HIV-infected population
- **HIV criteria**

  1) Clinical: no previous C events (CDC, 1993) except some opportunistic infections (TB, Can, PCP); and,

  2) Immunological: pre-OLT CD4 cell count >100 cells/mm^3 (>200 cells/mm^3 if previous opportunistic infections); and,

  3) Virological: RNA HIV-1 viral load <50 copies/mL on cART or, if detectable, post-SOT suppression predicted.
- Drug abuse: A) No heroin or cocaine abuse for >2 years; B) No alcohol abuse for >6 months.

* Miró JM et al. Enferm Infecc Microbiol Clin. 2005; 23:353-362.

HCV Recurrence: Diagnosis and Management

- During follow-up, livers were biopsied annually or bi-annually following the protocols of each center.
- Fibrosing cholestatic hepatitis and the fibrosis stage (METAVIR score) were defined according to standard histological criteria.
- Treatment of HCV recurrence was based on the same criteria as for HCV-monoinfected OLT recipients according to local protocols.
- **Treatment regimens:** Pegylated interferon (Peg-INF) α2a (Pegasys®; sc 180 µg/wk) or Peg-INF α2b (Peg-Intron®; sc 1.5 µg/kg/wk) plus ribavirin (RBV) (Rebetol® or Copegus®; 400-1000 mg/d) for 48 weeks.
- G-CSF or erythropoietin/darbepoetin were given when necessary.
- The biochemical response was defined as normalization of aminotransferase levels at the end of treatment regardless of the virological response.

Response to Anti-HCV Treatment and Statistical Analysis

- **Virological Definitions**
  - Early virological response (EVR): ↓ ≥2 log of HCV RNA viral load (VL) at 12 weeks.
  - End-of-treatment response (ETR): negative HCV RNA VL at 48 weeks.
  - Sustained virological response (SVR): negative HCV RNA VL 24 weeks after the end of treatment.

- **Statistical analysis**
  - Outcomes after starting antiviral therapy were analyzed by intention-to-treat.
  - Patient survival was calculated with the date of the initiation of anti-HCV therapy as the start date. Survival time from the start date was estimated using the Kaplan-Meier product-limit method.
  - Univariate and multivariate analyses of predictors of SVR were performed.

Results

HIV/HCV+
n=149

No HCV treatment
n=65 (44%)

HCV treatment
N=84 (56%)*

HCV treatment
- Only INF n=3
- Classic INF+RBV=1
- Ongoing n=2

N=78
Finished 48-week therapy n=34 (44%)
Premature discontinuation n=44 (56%)**
- **Toxicity, n=17 (22%)*****
- Lack of efficacy, n=20 (26%)
- Death, n=5 (6%)
- Other, n=2 (2%)

HCV+
n=447

No HCV treatment
n=240 (54%)

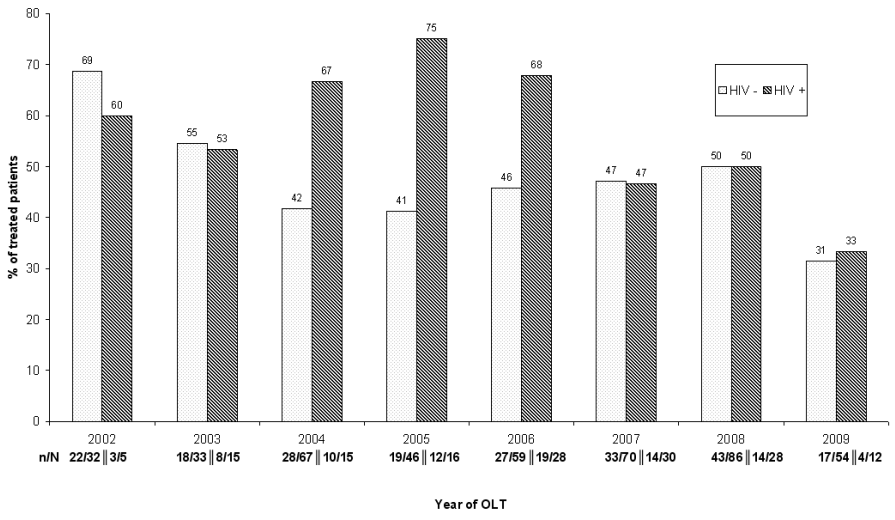
HCV treatment
N=207 (46%)*

HCV treatment
- Ongoing n=31

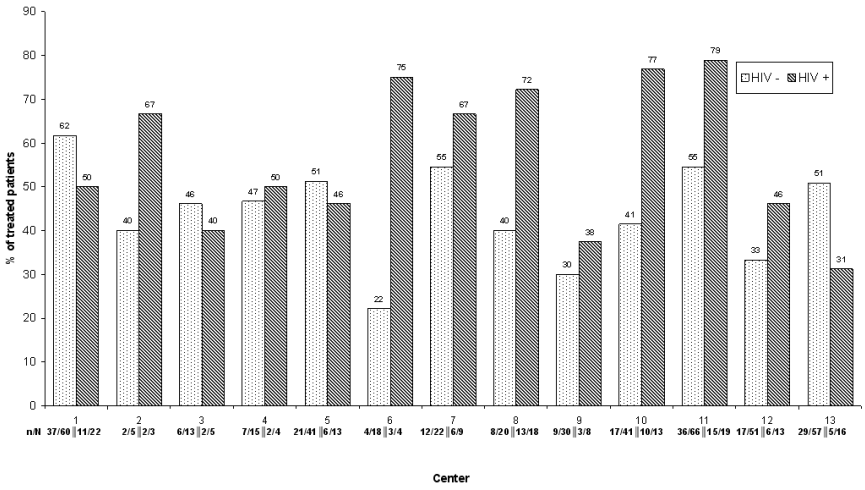
N=176
Finished 48-week therapy n=107 (61%)
Premature discontinuation n=69 (39%)**
- **Toxicity, n=19 (11%)*****
- Lack of efficacy, n=37 (21%)
- Death, n=4 (2%)
- Other, n=2 (1%)
- Unknown, n=7 (4%)

**P*=0.042; ** P=0.016; ***P=0.034

Anti-HCV Treatment by Year



Anti-HCV Treatment by Site



Patient and Donor Characteristics (I)

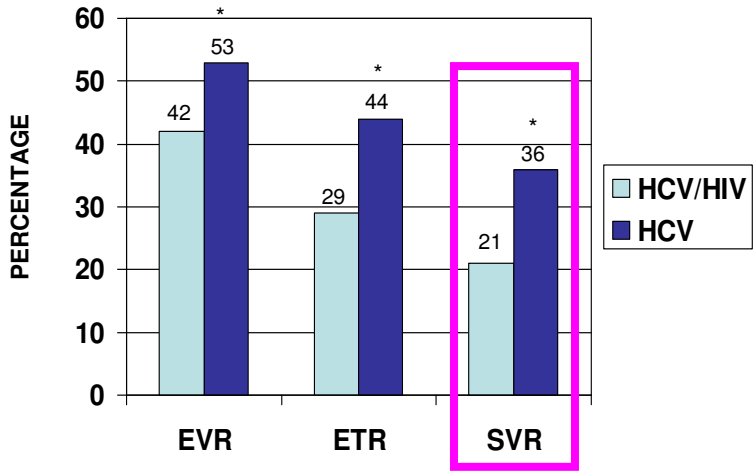
	HCV/HIV coinfection	HCV monoinfection	*p* value
No. of cases	**78**	**176**	
Baseline variables			
Age (y)	**43 (39-46)**	**47 (43-53)**	**<.0001**
Male gender, n (%)	59 (76%)	135 (77%)	0.873
Pre-OLT anti-HCV treatment, n (%)	30 (38%)	48 (27%)	0.140
Hepatocellular carcinoma, n (%)	14 (18%)	28 (16%)	0.739
MELD score at listing	15 (12-18)	15 (12-19)	0.699
CD4 cell count	**315 (209-435)**	**NA**	-
Plasma HIV RNA VL<50 copies/mL	**68 (87%)**	**NA**	-
Donor characteristics			
Age (y)	53 (43-66)	50 (36-64)	0.147
Cause of donor brain death, n (%)			0.066
Vascular	45 (58%)	112 (64%)	
Cranial trauma	19 (24%)	53 (30%)	
Other	12(15%)	11 (6%)	

Patient Characteristics (II)

Pre-HCV treatment variables	HCV/HIV Coinfection N=78	HCV Monoinfection N=176	*p* value
Months from OLT to anti-HCV treatment	10 (5-18)	15 (7-21)	0.02389
HCV genotype, n (%) 1 2 3 4 Other/non-typable	 42 (54%) 0 (-) 17 (22%) 14 (18%) 5 (6.5%)	 147 (84%) 2 (1%) 13 (7%) 6 (3.5%) 8 (5%)	<.0001
Plasma HCV RNA viral load (log_{10})	6.65 (6.11-7.23)	6.64 (6.08-7.10)	0.576
AST, IU/mL	127 (82-203)	156 (87-252)	0.1985
ALT, IU/mL	116 (78-191)	175 (96-297)	0.0075
Liver biopsy, n *(%)*	61 (78%)	147 (83%)	
Histologically severe HCV reinfection - Fibrosing cholestatic hepatitis - Acute hepatitis with bridging necrosis - Chronic hepatitis (F3-F4 stage)	18 (30%) 8 (13%) 3 (5%) 7 (12%)	24 (16%) 4 (3%) 2 (1%) 18 (12%)	0.0375
Type of pegylated-Interferon - Alpha 2A - Alpha 2B - Not specified	 25 (32%) 52 (67%) 1 (1%)	 49 (28%) 117 (66%) 10 (6%)	0.2807

Virological Response (I)

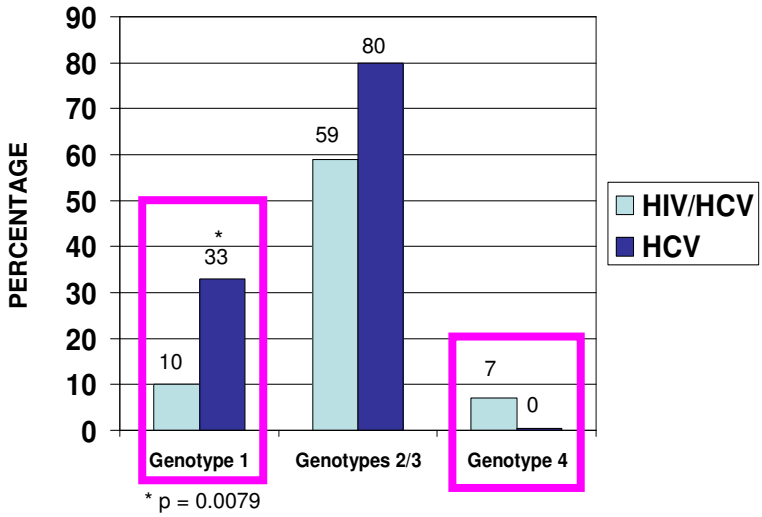
All genotypes



* p < 0.05

Virological Response (II)

SVR according to genotype



Anti-HCV Treatment: Other Results

	HCV/HIV coinfection	HCV monoinfection	*p* value
No. of cases	**78**	**176**	
Follow-up after starting anti-HCV therapy (years)	2.50 (1.3-4.1)	2.42 (1.1-3.7)	0.292
Biochemical response, n (%)	**21 (27%)**	**106 (60%)**	**<.001**
Treatment discontinuation due to severe toxicity, n (%)	**17 (22%)**	**19 (11%)**	**0.034**
Use of growth factors, n (%) - Erythropoietin/darbepoetin - Filgrastim	43 (55%) 21 (27%)	92 (56%) 40 (24%)	0.847 0.634
PegIFN maintenance therapy, n (%)	8 (10%)	19 (11%)	1.000
Retransplantation, n (%)	2 (3%)	17 (10%)	0.067
Mortality, n (%)	**31 (40%)**	**37 (21%)**	**0.003**

HIV evolution during anti-HCV Treatment

	0	6	12	18 mo
CD4*	315 209-435	180 95-288	226 138-398	310 214-458
HIV VL <50 copies/mL	87%	97%	97%	93%
OIs	CAN VZV		TB CMV	

* Median (IQR)

Predictors of SVR in HCV-infected OLT recipients

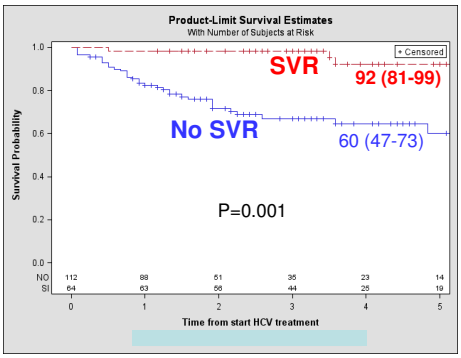
	Hazard ratio (95% CI)	*p* value
HIV-infection, No *vs.* Yes	2.22 (1.18-4.17)	0.0133
Recipient age, <40 *vs.* ≥40 years	0.57 (0.27-1.21)	0.1434
Recipient gender, Male *vs.* Female	0.67 (0.36-1.23)	0.1935
Pre-LT anti-HCV treatment, No *vs.* Yes	1.144(0.64-2.05)	0.6519
Donor age, <60 *vs.* ≥60 years	3.91 (1.97-7.74)	0.0001
Donor cause of death, Cranial trauma *vs.* Other	1.32 (0.74-2.35)	0.5267
Interval between OLT and anti-HCV treatment**, Short *vs.* Long	1.17 (0.68-2.00)	0.5676
Pre-treatment plasma HCV RNA viral load, Low *vs.* High	2.52 (1.42-4.47)	0.0016
HCV genotype, 2/3 *vs.* 1/4	6.31 (2.81-14.18)	0.0001
Histologically severe HCV recurrence, No *vs.* Yes	1.51 (0.75-3.02)	0.2484
Type of immunosuppression, CsA *vs.* No-CsA	0.73 (0.37-1.43)	0.3258
Early virological response (EVR), Yes [60%] *vs.* No [0%]	NA	<0.001

Predictors of SVR in HCV/HIV-coinfected OLT recipients

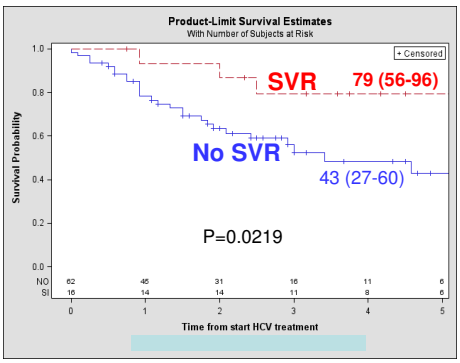
	Hazard ratio (95% CI)	*p* value
Recipient age, <40 *vs.* ≥40 years	0.32 (0.07-1.56)	0.1605
Recipient gender, Male *vs.* Female	0.64 (0.19-2.16)	0.4733
Pre-LT anti-HCV treatment, No *vs.* Yes	2.17 (0.63-7.48)	0.2213
Donor age, <60 *vs.* ≥60 years	**3.85 (0.80-18.5)**	**0.0925**
Donor cause of death, Cranial trauma *vs.* Other	2.17 (0.66-7.09)	0.1998
Interval between OLT and anti-HCV treatment**, Short *vs.* Long	1.67 (0.55-5.05)	0.3662
Pre-treatment plasma HCV RNA viral load, Low *vs.* High	2.55 (0.68-9.56)	0.1666
HCV genotype, 2/3 vs. 1/4	**14.57 (3.84-55)**	**<0.001**
Histologically severe HCV recurrence, No *vs.* Yes	1.74 (0.42-7.28)	0.4468
Type of immunosuppression, CsA *vs.* No-CsA	0.65 (0.19-2.26)	0.500
Early virological response, Yes [48%] *vs.* No [0%]	**NA**	**<0.001**
AIDS criteria, Yes *vs.* No	2.07 (0.34-12.5)	0.4265
CD4 nadir, ≥100 *vs.* < 100 cells/mm^3	1.15 (0.30-4.49)	0.8364

Survival After Anti-HCV Therapy

HCV-monoinfected patients



HCV/HIV-coinfected patients



Limitations

Lack of data on

- Polymorphisms in *IL28B*
- Rapid virological response (RVR)
- 80-80-80 data in control group
- Details of toxicity/adverse effects
- Rejection episodes in control group

Conclusions

In comparison with HCV-monoinfected LT recipients, anti-HCV treatment with Peg-INF plus RBV in HCV/HIV-coinfected LT recipients showed the following:

- Lower efficacy, especially in genotypes 1 (and 4)
- More toxicity
- Satisfactory survival at 5 years in responders (79% *vs.* 92% in HIV negative recipients)

→ There is an urgent need for more effective therapies, especially for GT1 and GT4.

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Organizaciones No Gubernamentales

STUDY LEADERS

JM Miro, A. Moreno, A. Rimola

STUDY COORDINATORS

B. Moyano, C. Manzardo

STATISTICIAN

Iñaki Perez

INTERNATIONAL OLT EXPERTS

M. Roland, P. Stock, D. Samuel, P. Grossi