

Eradication of HCV and Extrahepatic Comorbidities in HIV/HCV Coinfection

Juan Berenguer¹, Elena Rodríguez-Castellano², Ana Carrero¹, Miguel A Von Wichmann³, Marta Montero⁴, María J Galindo⁵, Josep Mallolas⁶, Manuel Crespo⁷, María J Téllez⁸, Carmen Quereda⁹, José Sanz¹⁰, Carlos Barros¹¹, Cristina Tural¹², Ignacio Santos¹³, Federico Pulido¹⁴, Josep M Guardiola¹⁵, Rafael Rubio¹⁴, María L Montes², Herminia Esteban¹⁶, Juan González-García²

¹Hospital General Universitario Gregorio Marañón (IiSGM), Madrid; ²Hospital Universitario La Paz (IdIPAZ), Madrid; ³Hospital Donostia, San Sebastián; ⁴Hospital Universitario La Fe, Valencia; ⁵Hospital Clínico Universitario, Valencia; ⁶Hospital Clinic, Barcelona; ⁷Complejo Hospitalario Universitario de Vigo, Vigo; ⁸Hospital Clínico San Carlos, Madrid; ⁹Hospital Universitario Ramón y Cajal, Madrid; ¹⁰Hospital Universitario Príncipe de Asturias, Alcalá de Henares; ¹¹Hospital Universitario de Móstoles, Móstoles; ¹²Hospital Universitari Germans Trias i Pujol, Badalona; ¹³Hospital Universitario de La Princesa, Madrid; ¹⁴Hospital Universitario 12 de Octubre (imas12), Madrid; ¹⁵Hospital de la Santa Creu i Sant Pau, Barcelona; ¹⁶Fundación SEIMC-GESIDA, Madrid.

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 mortality¹ as well as HIV progression and mortality not related to liver disease²
- Here, we studied the effect of SVR on non-liver-related (NLR) non-AIDS-related (NAR) events and mortality in HIV/HCV-coinfected patients after therapy with IF-RB

¹Berenguer, J. et al. Hepatology 2009; 50: 407

²Berenguer J, et al. Clinical Infectious Diseases 2012; 55: 728

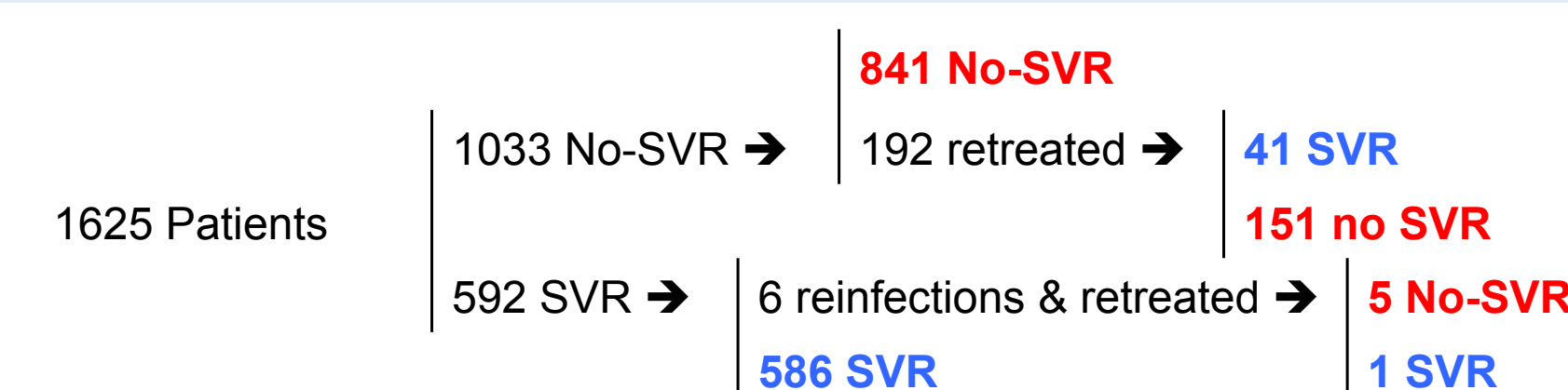
Design and definitions

Design (GeSIDA 3603)	<ul style="list-style-type: none"> Cohort of HIV/HCV-coinfected patients treated with IF-RB during 2000-2008 in 19 centers (prospective since 2003) Database was modified (June 2014) to include NLR-NAR events
Events	<ul style="list-style-type: none"> Mortality (overall and cause-specific) Events (liver-related, AIDS-related, NLR-NAR)
NLR-NAR Events*	<ul style="list-style-type: none"> Cardiovascular events (coronary, cerebrovascular, etc.) Renal (chronic renal failure, dialysis, transplantation) Bone (fractures and avascular bone necrosis) Diabetes mellitus Cancer (NLR-NAR) Sepsis requiring hospitalization (NAR)
Duration	<ul style="list-style-type: none"> From the date IF-RB was stopped to death or last follow-up visit Administrative censoring date: 31 May, 2014
Monitoring	<ul style="list-style-type: none"> All centers were monitored before the final analysis
Analysis	<ul style="list-style-type: none"> As some patients experienced reinfections and some underwent retreatment, we performed several analyses. Primary analysis, patients with SVR after retreatment (after failure or relapse) were included in the SVR group. Sensitivity analyses (x3): i) excluding follow-up in retreated patients at the date of initiation of retreatment, ii) excluding retreated patients, and iii) considering response status as time-dependent

*Defined according to the Cohort of the Spanish AIDS Research Network (AIDS 2013; 27:181).

Treatment response

- Initial treatment response was categorized as
 - SVR in 592 (36%) patients
 - 6 had a HCV reinfection during follow-up
 - No response in 1033 (64%) patients.
- A total of 198 patients were retreated during follow-up
 - 192 patients who failed the first anti-HCV therapy course
 - 6 patients with reinfections
 - 42 retreated patients achieved SVR (including 1 of 6 reinfected)
- Primary analysis
 - 628 responders (586 + 41 + 1)
 - 997 non-responders (841 + 151 + 5)



Patient characteristics

Characteristic	No SVR (n=997)	SVR (n=628)	Total (n=1625)
Male sex, No. (%)	753 (75.5)	466 (74.2)	1219 (75)
Age, y, median (IQR) (baseline)	40 (37 - 43)	40 (37 - 43)	40 (37 - 43)
Follow-up months, median (IQR)	65 (42 - 85)	65 (43 - 86)	65 (43 - 85)
Prior injection drug use, No. (%)	802 (80.4)	510 (81.2)	1312 (80.7)
CDC disease category C, No. (%) ^a	245 (24.6)	125 (19.9) *	370 (22.8)
CD4 ⁺ nadir, cells/mm ³ , median (IQR)	200 (100 - 313)	212 (113 - 333)	204 (106 - 322)
cART during anti-HCV treatment, No. (%)	848 (85.1)	518 (82.5)	1366 (84.1)
CD4 ⁺ baseline, cells/mm ³ , median (IQR)	515 (374 - 718)	536 (404 - 729)	527 (391 - 724)
Undetectable HIV RNA baseline, No. (%)	667 (66.9)	460 (73.2) *	1127 (69.4)
HCV genotype, No. (%) ^b			
1	581 (58.3)	224 (35.7) *	805 (49.5)
2	13 (1.3)	24 (3.8) *	37 (2.3)
3	214 (21.5)	332 (52.9) *	546 (33.6)
4	170 (17.1)	40 (6.4) *	210 (12.9)
Unknown	10 (1)	5 (0.8)	15 (0.9)
HCV-RNA ≥ 500 000 IU/mL, No. (%)	644 (64.6)	340 (54.1) *	984 (60.6)
FIB-4 score, No. (%)			
< 3.25	671 (67.3)	486 (77.4) *	1157 (71.2)
≥ 3.25	207 (20.8)	71 (11.3) *	278 (17.1)
Unknown	119 (11.9)	71 (11.3)	190 (11.7)
Current alcohol intake > 50 g/d, No. (%)	58 (5.8)	19 (3) *	77 (4.7)

*P<.05 with the No SVR group.

Frequency and rate of events

	Frequency, No. (%)		Rate/100 person-years (95% CI)			
	No SVR N=992	SVR N=633	P ¹	No SVR	SVR	P ²
Lost to follow-up	162 (16.2)	74 (11.8)	.013	3.19 (2.72 - 3.72)	2.33 (1.83 - 2.92)	.021
Overall mortality	145 (14.5)	30 (4.8)	<.001	2.75 (2.32 - 3.23)	0.93 (0.63 - 1.33)	<.001
Liver-related	83 (8.3)	6 (1.0)	<.001	1.57 (1.25 - 1.95)	0.19 (0.07 - 0.41)	<.001
Non-liver-related	62 (6.2)	24 (3.8)	.036	1.17 (0.90 - 1.50)	0.75 (0.48 - 1.11)	.009
AIDS-related	8 (0.8)	2 (0.3)	.224	0.15 (0.07 - 0.30)	0.06 (0.01 - 0.22)	.045
NLR-NAR	54 (5.4)	22 (3.5)	.075	1.02 (0.77 - 1.33)	0.68 (0.43 - 1.03)	.039
CDC category C disease	43 (4.3)	9 (1.4)	.001	0.81 (0.59 - 1.10)	0.28 (0.13 - 0.53)	.001
Liver decompensation	123 (12.3)	7 (1.1)	<.001	2.44 (2.03 - 2.91)	0.22 (0.09 - 0.45)	<.001
Hepatocellular carcinoma	29 (2.9)	3 (0.5)	.001	0.55 (0.37 - 0.79)	0.09 (0.02 - 0.27)	<.001
Liver transplantation, No. (%)	16 (1.6)	1 (0.2)	.005	0.30 (0.17 - 0.49)	0.03 (0 - 0.17)	.002
NLR-NAR events						
Diabetes mellitus	76 (7.6)	23 (3.7)	.001	1.48 (1.16 - 1.85)	0.72 (0.46 - 1.08)	.004
NLR-NAR cancer	67 (6.7)	33 (5.3)	.231	1.28 (0.99 - 1.63)	1.04 (0.72 - 1.46)	.382
Cardiovascular events	52 (5.2)	39 (6.2)	.396	0.99 (0.74 - 1.30)	1.24 (0.88 - 1.69)	.502
Sepsis requiring hospitalization	62 (6.2)	19 (3.0)	.004	1.19 (0.91 - 1.52)	0.59 (0.36 - 0.93)	.017
Bone events	33 (3.3)	24 (3.8)	.585	0.63 (0.44 - 0.89)	0.75 (0.48 - 1.12)	.422
Renal events	28 (2.8)	6 (1.0)	.011	0.53 (0.35 - 0.77)	0.19 (0.07 - 0.41)	.006

P¹: Pearson chi-square test; P²: Gray's test for cumulative incidence

Hazard ratio of events during FU Responders vs Non-responders

	Univariate analysis ^a		Multivariate analysis ^{b,d}	
	HR (95% CI)	P	HR (95% CI)	P
Overall deaths	0.35 (0.24 - 0.52)	<.001	0.37 (0.25 - 0.56)	<.001
	sHR (95% CI)		sHR (95% CI)	
Cause-specific deaths				
Liver-related deaths	0.12 (0.05 - 0.28)	<.001	0.13 (0.06 - 0.30)	<.001
Non-liver-related deaths	0.69 (0.43 - 1.1)	.119	0.73 (0.45 - 1.21)	.225
AIDS-related deaths	0.45 (0.09 - 2.22)	.325	0.36 (0.09 - 1.41)	.143
NLR-NAR deaths	0.73 (0.44 - 1.19)	.204	0.80 (0.47 - 1.36)	.406
New AIDS-defining events	0.34 (0.16 - 0.72)	.004	0.37 (0.17 - 0.80)	.011
Liver-related events				
Liver decompensation	0.09 (0.04 - 0.2)	<.001	0.10 (0.05 - 0.22)	<.001
Hepatocarcinoma	0.12 (0.03 - 0.5)	.004	0.13 (0.03 - 0.50)	.003
Liver transplantation	0.10 (0.01 - 0.77)	.027	0.12 (0.02 - 0.79)	.027
NLR-NAR events				
Diabetes mellitus	0.53 (0.33 - 0.84)	.007	0.56 (0.34 - 0.90)	.018
Cancer	0.91 (0.6 - 1.38)	.650	0.90 (0.57 - 1.43)	.665
Cardiovascular event	1.41 (0.93 - 2.13)	.105	1.56 (1 - 2.43)	.052
Sepsis requiring hospitalization	0.55 (0.33 - 0.92)	.024	0.90 (0.57 - 1.43)	.665
Bone event	1.39 (0.82 - 2.35)	.225	1.27 (0.69 - 2.33)	.442
Renal event	0.39 (0.16 - 0.95)	.038	0.38 (0.15 - 0.98)	.046

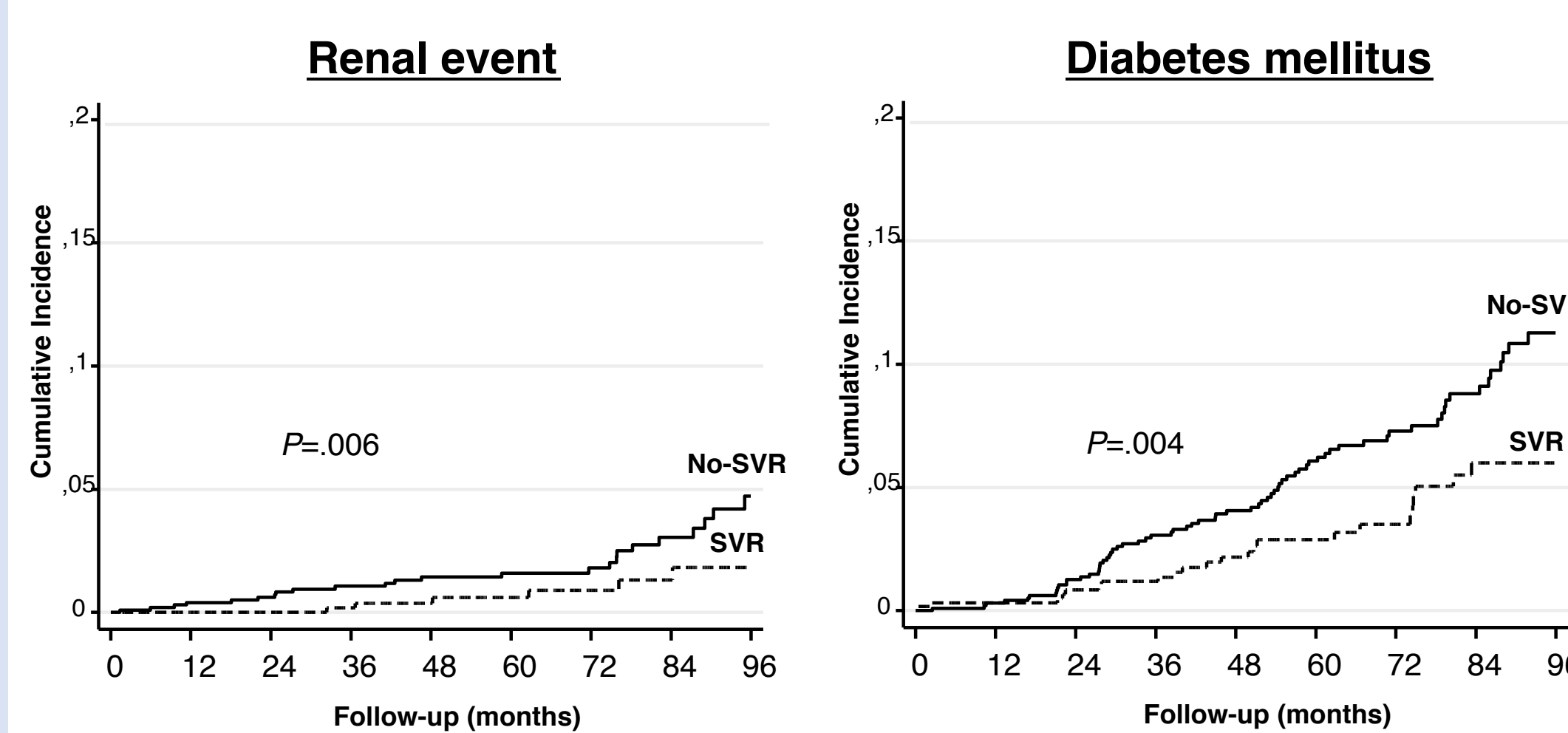
^aCox regression for comparison of the HR of overall death. Fine and Gray regression for comparison of the sHR of events, in the presence of competing risks.
^bAdjusted for age, sex, prior AIDS-defining conditions (yes vs. no), HIV-transmission category (injection drug users vs. non-injection drug users), nadir CD4⁺ cell count, cART (yes vs. no), undetectable HIV-RNA at baseline (yes vs. no), FIB-4 ≥3.25 (yes vs. no), genotype (3 vs. other genotypes). **Abbreviations:** HR, hazard ratio; CI, confidence interval; sHR, subhazard ratio.

Non-AIDS-related events during follow-up

EVENT	No SVR (n=997)	SVR (n=628)	Total (N=1625)	EVENT	No SVR (n=997)	SVR (n=628)	Total (N=1625)
Diabetes mellitus ¹	76 (7.6)	22 (3.5)	98 (6.0)	Cardiovascular events	52 (5.2)	36 (5.7)	88 (5.4)
Cancer (NLR-NAR)	66 (6.6)	31 (4.9)	97 (6.0)	• Acute myocardial infarction	19 (1.9)	22 (3.5)	41 (2.5)
• Lung	7 (0.7)	5 (0.8)	12 (0.7)	• Angina	8 (0.8)	2 (0.3)	10 (0.6)
• Anus	6 (0.6)	2 (0.3)	8 (0.5)	• Cerebrovascular transient ischemic attack	2 (0.2)	3 (0.5)	5 (0.3)
• Head and neck	4 (0.4)	3 (0.5)	7 (0.4)	• Cerebrovascular reversible ischemic deficit	2 (0.2)	0 (0)	2 (0.1)
• Vagina/vulva	6 (0.6)	1 (0.2)	7 (0.4)	• Cerebrovascular established stroke	3 (0.3)	4 (0.6)	7 (0.4)
• Colorectal	6 (0.6)	0 (0)	6 (0.4)	• Asymptomatic cerebrovascular disease	0 (0)	1 (0.2)	1 (0.1)
• Breast	5 (0.5)	0 (0)	5 (0.3)	• Peripheral arterial disease	7 (0.7)	2 (0.3)	9 (0.6)
• Skin non-melanoma	5 (0.5)	0 (0)	5 (0.3)	• Congestive heart failure	4 (0.4)	1 (0.2)	5 (0.3)
• Hodgkin lymphoma	2 (0.2)	2 (0.3)	4 (0.2)	• Pulmonary hypertension	5 (0.5)	1 (0.2)	6 (0.4)
• Brain	3 (0.3)	0 (0)	3 (0.2)	• Mesenteric ischemia	1 (0.1)	0 (0)	1 (0.1)
• Sarcoma	1 (0.1)	2 (0.3)	3 (0.2)	• Aortic dissection	1 (0.1)	0 (0)	1 (0.1)
• Penis	2 (0.2)	1 (0.2)	3 (0.2)	NAR sepsis requiring hospitalization	62 (6.2)	18 (2.9)	80 (4.9)
• Esophagus	1 (0.1)	1 (0.2)	2 (0.1)	Bone-related events	33 (3.3)	23 (3.7)	56 (3.4)
• Stomach	2 (0.2)	0 (0)	2 (0.1)	• Large bone fracture	23 (2.3)	18 (2.9)	41 (2.5)
• Other hematologic	1 (0.1)	1 (0.2)	2 (0.1)	• Avascular necrosis of bone	5 (0.5)	5 (0.8)	10 (0.6)
• Prostate	1 (0.1)	1 (0.2)	2 (0.1)	• Vertebral fracture	5 (0.5)	0 (0)	5 (0.3)
• Other	14 (1.4)	12 (1.9)	26 (1.6)	Renal events	28 (2.8)	6 (1.0)	34 (2.1)
				• Chronic kidney disease ²	25 (2.5)	5 (0.8)	30 (1.8)
				• Initiation of dialysis	3 (0.3)	1 (0.2)	4 (0.2)

¹Fasting plasma glucose >126 mg/dL (7.0 mmol/L) on at least 2 separate consecutive occasions, no evidence of normal glucose levels in the range.
²Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for more than 3 months. eGFR can be calculated with CKD-EPI or MDRD formulas.

Cumulative incidence of renal events and diabetes mellitus



Differences were compared by the Gray's test

Conclusions

- Eradication of HCV in coinfecting patients was independently associated with a reduction in the hazard of overall death and LR death but not of NLR death.
- Eradication of HCV in coinfecting patients was also independently associated with a reduction in the hazard of renal events and diabetes mellitus.
- Eradication of HCV was not independently associated with a reduction in the hazard of cancer, bone events, and sepsis requiring hospitalization.
- A non-significant trend was found towards an increased hazard of cardiovascular events in responders in comparison with non-responders.
- All findings were confirmed by the 3 sensitivity analyses

Funding: Fundación para la Investigación y la Prevención del SIDA en España (FIPSE), Refs. 36443/03 and 36702/07; and by the RD12/0017/0004 and RD12/0017/0016 projects as part of the Plan Nacional R+D+I and cofinanced by ISCIII – Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER). Juan Berenguer is an investigator of the Programa de Intensificación de la Actividad Investigadora en el Sistema Nacional de Salud (I3SNS) (Refs. INT15/00079).