

HCV Relapse After Peg-Interferon Plus Ribavirin Therapy: Is 12-Week Assessment Upon Completion of Treatment Enough to Determine Sustained HCV Clearance?

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Background

- Recent recognition of late and very late HCV relapses in HIV-HCV coinfecting patients after completion of a course of peg-IFN+RBV therapy
- 12 weeks of follow-up was enough to confirm clearance of HCV in monoinfected patients treated with IFN monotherapy
 - Zeuzem S, et al. *J Hepatol.* 2003;39:106-11
- The use of RBV reduces the risk of relapse
 - Shiffman ML, et al. *Hepatology.* 2007;46:371-9

Background (cont)

- Hypothesis: HCV relapses in HIV-HCV coinfecting patients might occur more frequently and/or later than in HCV-monoinfecting patients
- Analysis of potential predictors of HCV relapse

Methods

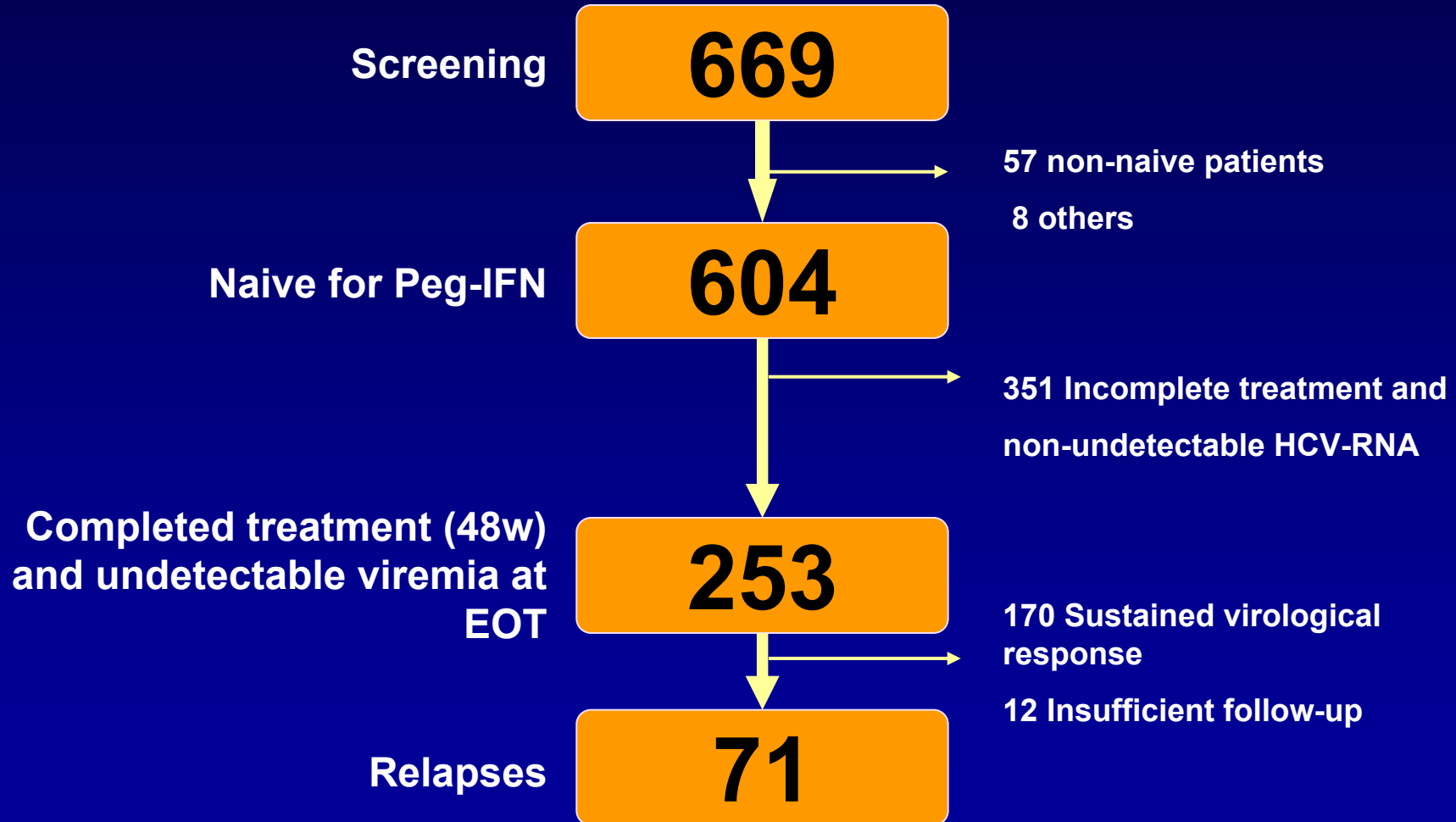
- Study design
 - Retrospective, observational exam of 2 cohorts of HCV-infected patients, differing in their HIV status
- Selection of patients
 - Screening
 - All HCV patients treated from January 2001 to January 2008 at University Hospital Carlos III, Madrid, Spain
 - Inclusion
 - Only naive patients treated with pegylated interferon and weight-based ribavirin for >48 weeks
 - Undetectable viremia at EOT
 - Exclusion
 - Insufficient post-EOT follow-up (<24 weeks)

Methods (cont)

- Variables examined
 - HIV coinfection
 - Demographics, liver function, HCV characteristics, treatment modalities and outcome
- Definition of HCV relapse
 - Real-time PCR assay (COBAS Taqman, Roche)
Limit: 10 IU/mL
 - Three categories
 - Early relapse — EOT– W12
 - Late relapse — W12 – W24
 - Very late relapse — >W24
- Definition of EOT
 - Estimation from last visit to the pharmacy and number of doses administered at that moment

Results

Study Population



Baseline Characteristics

	HCV	HIV/HCV	<i>P</i>
No.	243	361	
Demographics			
Sex (% male)	142 (58.4)	266 (73.7)	<0.001
Age (yrs)	46.3 ± 0.61	41.4 ± 0.30	<0.001
Liver function			
Pretreatment ALT ratio (>3)	17 (8.9)	44 (13.2)	0.094
AST/ALT	0.76 ± 0.2	0.83 ± 0.01	0.024
FIB-4	1.78 ± 0.09	2.09 ± 0.08	0.023
APRI	0.92 ± 0.007	1.27 ± 0.06	0.010
Stiffness (METAVIR)*,†			
0-1	48 (43.6)	62 (31.2)	
2	31 (28.2)	42 (21.1)	
3	11 (10)	39 (19.6)	
4	20 (18.2)	56 (28.1)	0.009

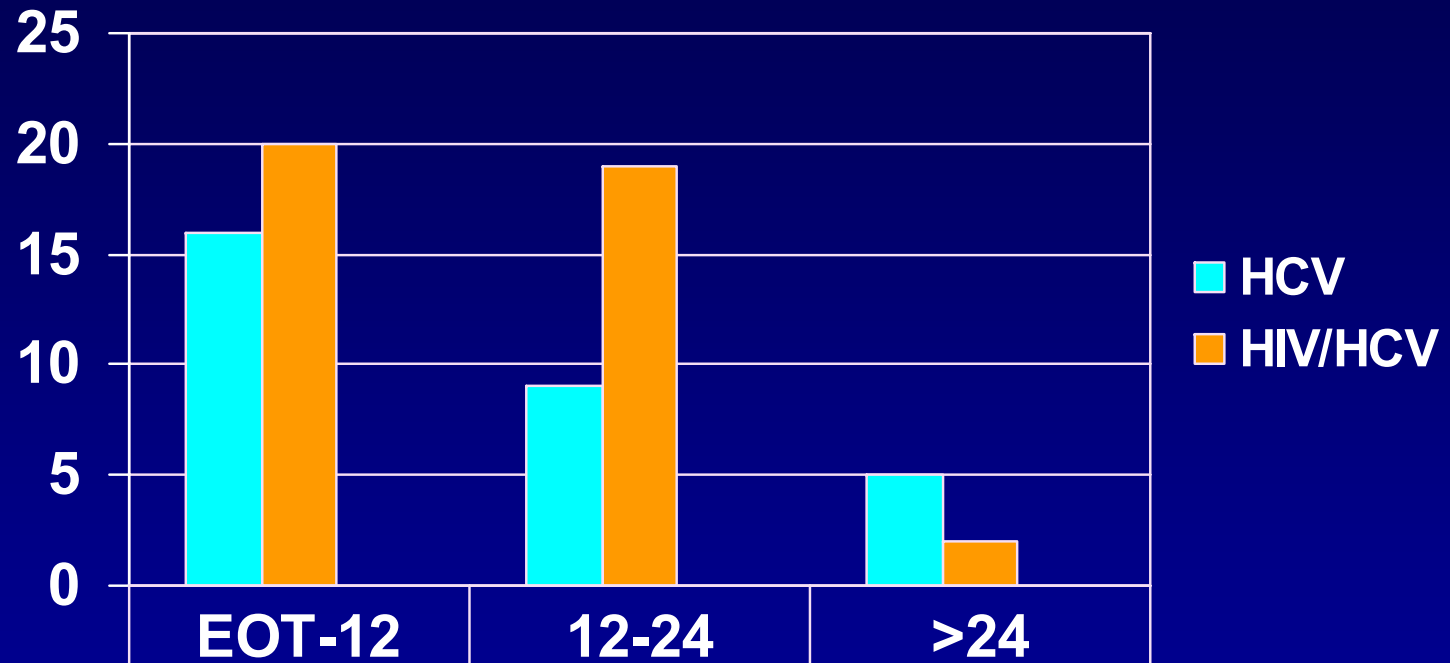
*Stiffness was available for 51% of patients.

†Correlation with METAVIR was: 0/1= <7.1 kPa; 2 = 7.1-9.4; 3 = 9.4-12.5; 4 ≥12.5.

Baseline Characteristics (cont)

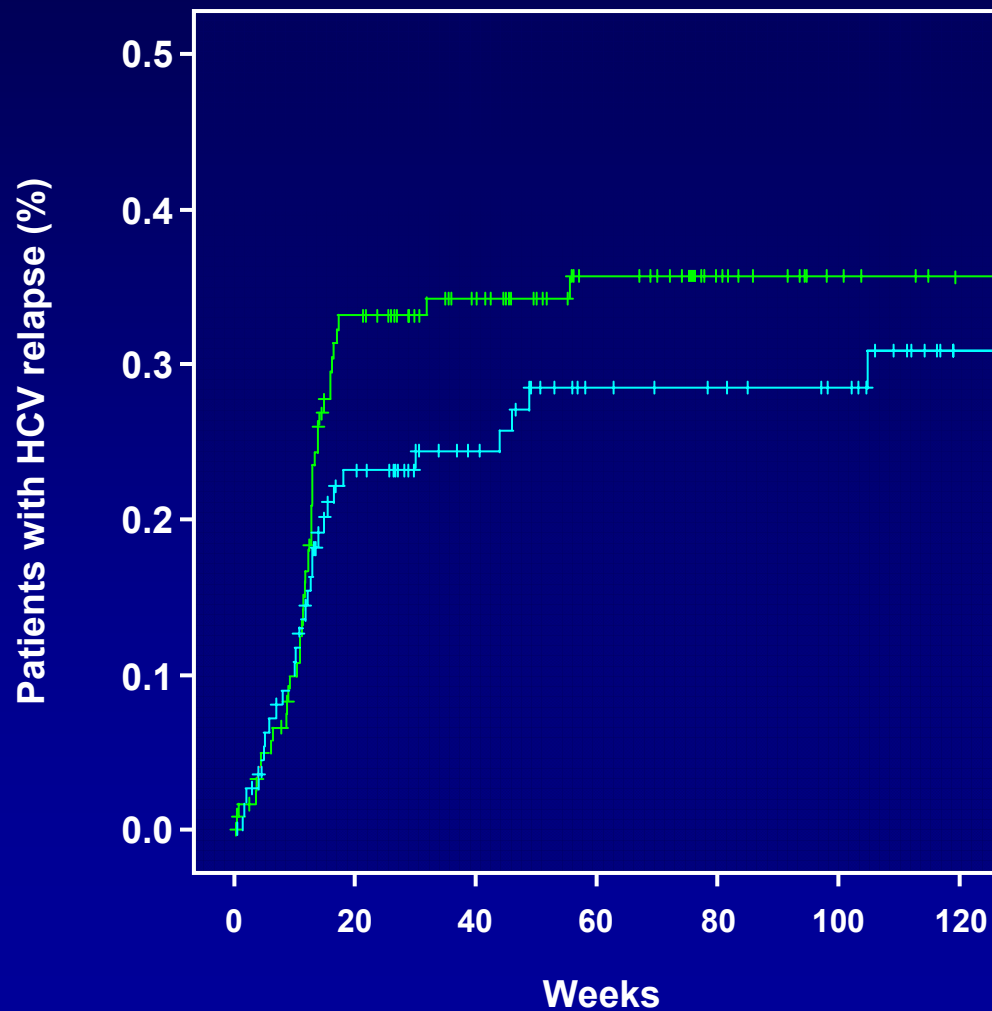
	HCV	HIV/HCV	<i>P</i>
HCV infection			
HCV-RNA >850,000 copies/mL*	133 (61.0)	214 (66.3)	0.124
HCV genotype			
1-4	160 (79.6)	247 (70.2)	0.016
2-3	40 (16.4)	105 (29.0)	<0.001
Antiviral therapy			
Alfa-2a IFN (%)	210 (86.4)	230 (63.7)	<0.001
IFN adjustment			
Reduction	6 (2.5)	21 (5.8)	
Maintenance	237 (97.5)	339 (93.9)	
Increment	0 (0)	1 (0.3)	0.105
RBV dosage (daily calculated)	1140.7 ± 388.7	1238.0 ± 663.5	0.041
Outcome			
Undetectable HCV-RNA at EOT (ITT)	119 (48.9)	134 (37.1)	0.004
Relapse	30 (25.2)	41 (30.6)	0.600

Time to HCV Relapse



HCV	16	9	5
HIV/HCV	20	19	2
P Value	0.737	0.094	0.190

Time to HCV Relapse



HCV relapse: N=71

Mono versus
coinfected

$P = 0.274$

- HCV infection
- HIV/HCV coinfection
- + HCV censored
- + HIV/HCV censored

Predictors HCV Relapse

	EOT – W12	W12 – W24	>24W
	36	28	7
Sex (male)	22 (61%)	16 (57.1)	5 (71.4)
HIV coinfection	20 (55.5%)	19 (67.8)	2 (40)
HCV genotypes*			
1-4	29 (85.3%)	27 (96.4)	6 (85.7)
2-3	4 (11.1%)	1 (3%)	0
Peg-IFN alfa2a	28 (77.8%)	25 (89.3)	4 (57.1)
ALT >3-fold ULN	4 (12.5%)	1 (4)	0 (0)
Stiffness (METAVIR)			
0-1	5 (33.3%)	7 (41.2)	1
2	4 (26.7%)	3 (17.6)	NA
3	2 (13.3%)	3 (17.6)	
4	4 (26.7%)	4 (23.5)	
HCV-RNA >850,000	19 (61.3%)	18 (75)	3 (75)

*Genotype not available for 3 patients.

Predictors HCV Relapse (cont)

Period	EOT - W12		W12 - W24		>24W	
	HCV	HIV-HCV	HCV	HIV-HCV	HCV	HCV-HCV
No.	16	20	9	19	5	2
Genotypes						
1-4	13	16	9	18	4	2
2-3		4		1		
6	1					
NA*	2				1	

- In HIV-HCV coinfecting patients, infection with genotypes 1-4 versus 2-3 was significantly associated with HCV relapse
 - RR: 4.22
 - CI 95% [1.4–11.9]
 - $P < 0.01$

*Genotype not available.

Characteristics of Very Late Relapses

Age	Sex	HIV coinfection	Genotype	Weeks treated	EOT	HCV viral load	Time to relapse	Peg-IFN dosage	Ribavirin dosage
39	F	No	NA	56	14-Oct-05	957,000	30.0	180	1333
55	M	No	1	60	01-Jul-05	306,000	48.8	180	1146
44	M	No	1	53	13-Feb-03	34,000	104.8	120	1416
44	M	No	1	54	08-Nov-02	5,660,000	44.0	120	1335
45	F	No	4	44	19-Mar-04	148,000	46.0	180	785
45	M	Yes	1	50	28-Mar-03	4,070,000	31.8	120	1210
42	M	Yes	1	52	08-Sep-06	117,000	55.5	180	1419

Conclusions

- In HCV mono and HCV-HIV coinfecting patients
 - Incidence of relapse does not differ significantly, although it tends to be more frequent in coinfecting than in mono-infected patients
 - Timing to relapse does not differ significantly comparing mono and coinfecting patients
 - 24 weeks of follow-up is still warranted to confirm SVR, and very late relapses may rarely occur in both mono and coinfecting patients
- In HIV-HCV coinfecting patients
 - Genotypes 1-4 are associated with a higher risk of HCV relapse than genotypes 2-3
- Other factors will be tested in a case-control study (relapsers vs SVR)