VI CONGRESO DE LA SVFH

Simposium Hepatitis C

Valencia 25 de Abril de 2015

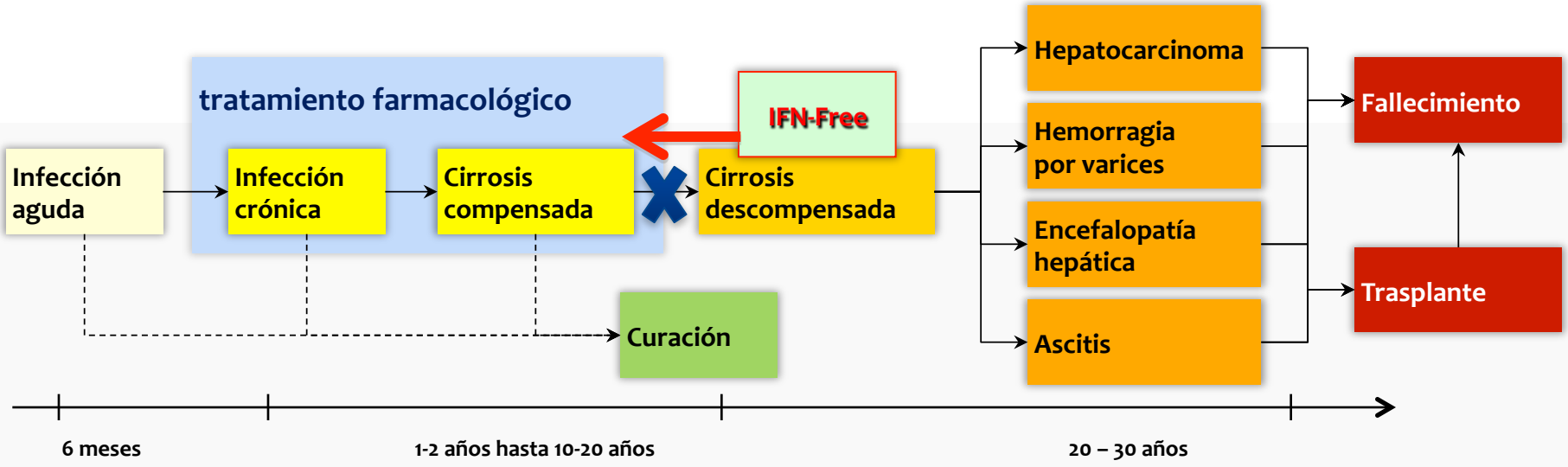
Respuestas para un nuevo abordaje de la hepatitis C

Antonio Palau Canós

Médico Adjunto Servicio de Aparato Digestivo
Hospital General Universitario de Castellón

¿Porqué es necesario tratar la Hepatitis C?

- **Es una enfermedad curable** cuya evolución natural conduce a **cirrosis**, estado a partir del cual se desarrollan el resto de complicaciones, con un importante **impacto económico** y en la **vida del paciente**



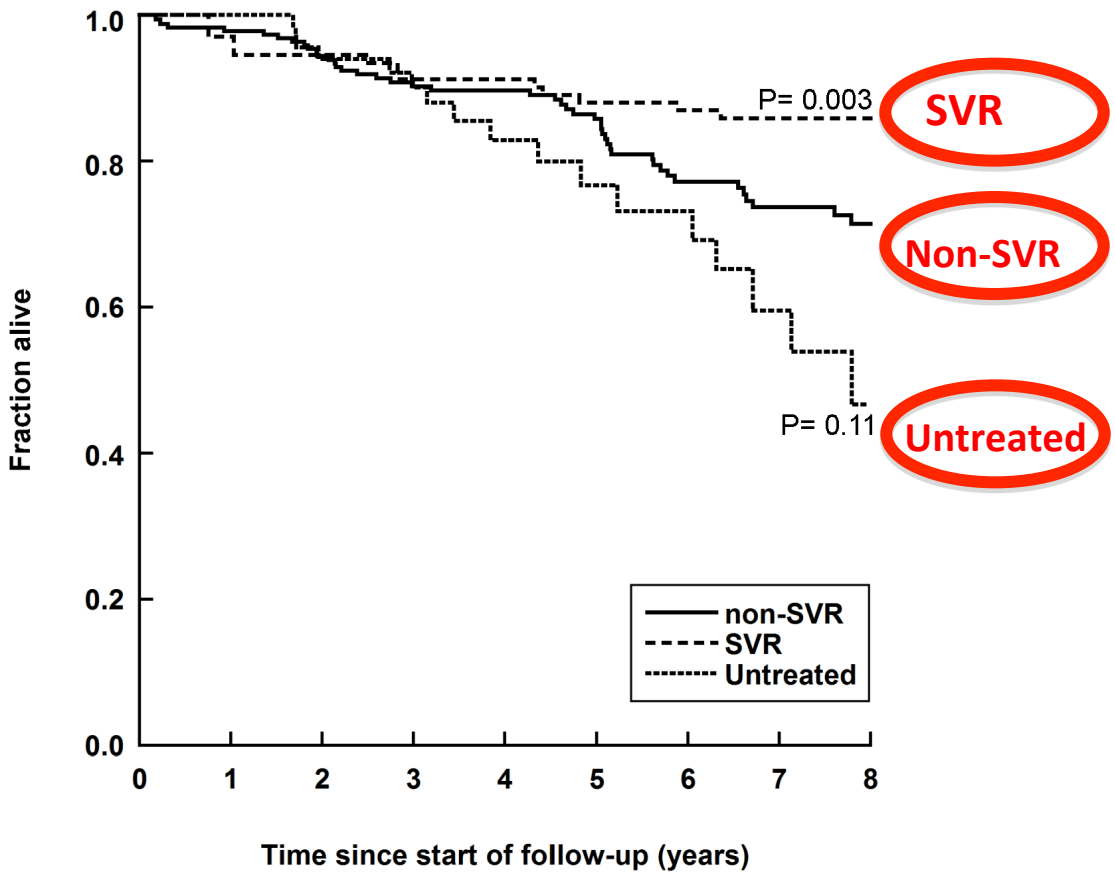
"El objetivo del tratamiento es erradicar la infección por el VHC con el fin de prevenir las complicaciones de la enfermedad hepática relacionada con el VHC, cirrosis, hepatocarcinoma, y la muerte." [1]

Disminuir las indicaciones de THO

[1] *EASL Clinical Practice Guidelines: Management of HCV infection; Modelo adpatado de Enf Emerg 2003;5(2):90-96 M. Buti y M. Casado, Hoofnagle 1997, Thein 2008, Seef 1997*

Mayor supervivencia global en los pacientes con RVS

Evaluación prospectiva de 351 pacientes cirróticos durante una media de 5.3 años



No at risk for non-SVR:	*127*	*176*	*135*	*85*	*44*
SVR:	*24*	*67*	*82*	*77*	*61*
Untreated:	*200*	*58*	*26*	*13*	*3*

Aleman S et al, Clin Infec Dis 2013: 57(2):230-6

Ciclo vital VHC y dianas de los AAD

- IFN
- Ribavirina

Entry inhibitors

Occludine

HCV

CLDN1

LDL-R

SR-B1

CD81

fusion
uncoating

translation
polyprotein procession

HCV proteins

RNA replication

assembly
release

α-glucosidase inhibitors

NS5B inhibitors
Cyclophilin B inhibitors

NS3/4A inhibitors

- Boceprevir
- Telaprevir
- Simeprevir
- ABT 450/r
- Grazoprevir

NS5A inhibitors

- Daclatasvir
- Ledipasvir
- Ombitasvir
- Elbasvir

- Sofosbuvir
- Dasabuvir
- MK-3682

HCV [illegible] and targets for directly acting antiviral (DAA) agents

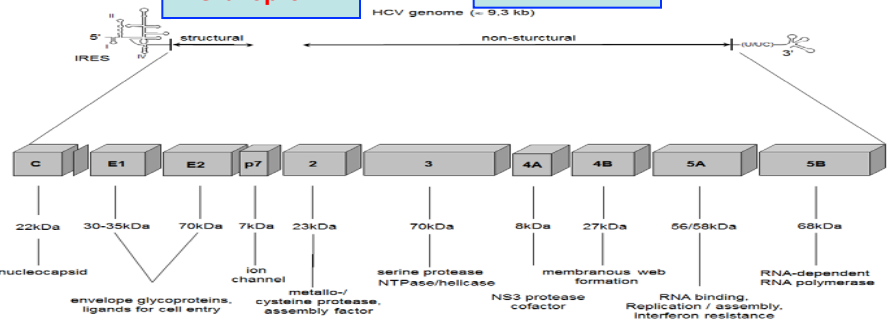


Figure 2. Genomic organisation of HCV

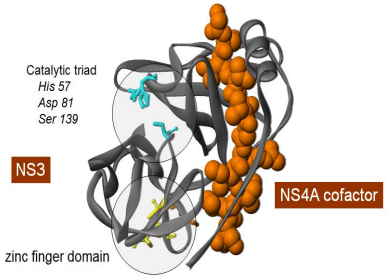


Figure 3. Molecular structure of the HCV NS3/4A protease

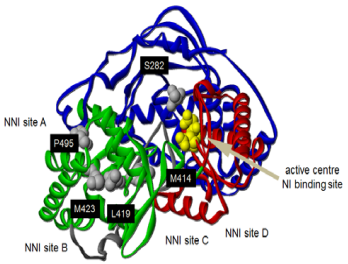


Figure 6. Structure of the HCV NS5B RNA polymerase and binding sites

Evaluación clínica del paciente con hepatitis C

A) Clasificarlo según ttos previos:

- **Naïve**
- **Fallo de respuesta a terapias previas (Biterapia clásica ó IPs de 1ª generación:**
  - **Recidivantes**
  - **No respondedores**

B) Caracterización virológica de la infección:

- **Genotipo y subtipo**
- **Carga viral**
- **Descartar otras posibles coinfecciones → VHB y HIV**

C) Evaluación de los polimorfirmos de:

- **IL-28 B**
- **Q80K si genotipo 1a**

ESTRATEGIA TERAPÉUTICA PARA LA HEPATITIS CRÓNICA CAUSADA POR EL VIRUS DE LA HEPATITIS C EN EL SISTEMA NACIONAL DE SALUD

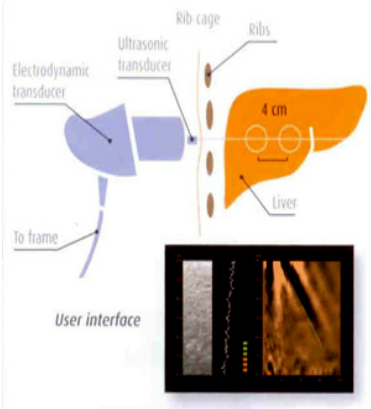
http://aeeh.es/wp-content/uploads/2015/04/a77478e2a1147600cb9979b5992281cb.pdf

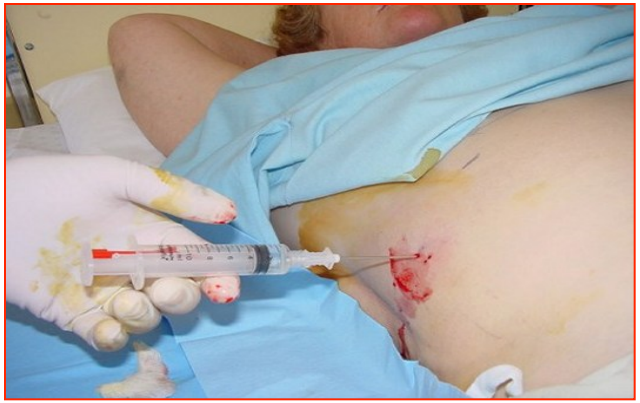
Evaluación clínica del paciente con hepatitis C

D) Evaluación de la Fibrosis Hepática

- La Fibrosis tiene un desarrollo dinámico, no lineal y es variable interpaciente
- Biopsia hepática, Fibroscan+/- parámetros biológicos
- Diagnóstico clínico de Cirrosis hepática
  - → Compensada o Descompensada (CTP/MELD)

F0 o F1	F2	F3	F4	
Hepatitis Crónica			*Cirrosis compensda*	*Cirrosis descompensada*





TRATAMIENTO DEL PACIENTE:

-Comorbilidades

-Medicación concomitante

-¿Con qué lo trato??

www.hep-druginteractions.org

Recientes alertas FDA y EMA sobre bradiarritmias graves en pacientes con AMIODARONA y las combinaciones:

- SOFOS+SIMEPREVIR
- SOFOS/LEDIPASVIR
- SOFOS + DACLATASVIR

ESTRATEGIA TERAPÉUTICA PARA LA HEPATITIS CRÓNICA CAUSADA POR EL VIRUS DE LA HEPATITIS C EN EL SISTEMA NACIONAL DE SALUD

http://aeeh.es/wp-content/uploads/2015/04/a77478e2a1147600cb9979b5992281cb.pdf

¿Con qué lo trato? → > 23 esquemas de tratamiento posibles

1ª opción de tratamiento en hepatitis C

GENOTIPO	*NAÏVE* NO CIRROSIS	*NAÏVE* CIRROSIS	PRETRATADOS NO CIRROSIS	PRETRATADOS CIRROSIS
1a	SOF/LDV 12s (8s[1]) 3D AbbVie+RBV 12s SMV+SOF±RBV 12s	SOF/LDV+RBV 12s 3D AbbVie+RBV 12s SMV+SOF±RBV 12s	SOF/LDV±RBV 12s[2,3] 3D AbbVie+RBV 12s SMV+SOF±RBV 12s[4]	SOF/LDV+RBV 12s[2] 3D AbbVie+RBV 24s SMV+SOF±RBV 12s[4]
1b	SOF/LDV 12s (8s[1]) 3D AbbVie 12 s SMV+SOF±RBV 12s	SOF/LDV+RBV 12s 3D AbbVie+RBV 12s SMV+SOF±RBV 12s	SOF/LDV±RBV 12s[2,3] 3D AbbVie 12s SMV+SOF±RBV 12s[4]	SOF/LDV+RBV 12s[2] 3D AbbVie+RBV 12s SMV+SOF±RBV 12s[4]
2	SOF+RBV 12s	SOF+RBV 16s	**Recaedores** SOF+RBV 12s **No respondedores** SOF+IFN+RBV 12s SOF+RBV 16-24s	**Recaedores** SOF+RBV 16s **No respondedores** SOF+IFN+RBV 12s SOF+RBV 16-24s
3	SOF+IFN+RBV 12s SOF+RBV 24s SOF+DCV 12s SOF/LDV+RBV 12s	SOF+IFN+RBV 12s SOF+RBV 24s SOF/LDV+RBV 12s	SOF+IFN+RBV 12s SOF+DCV 12s SOF/LDV+RBV 12s	SOF+IFN+RBV 12s SOF+DCV+RBV 12s SOF+DCV 24s SOF/LDV+RBV 12s
4	SOF/LDV 12s PTVr/OBV+RBV 12s SOF+RBV 24s	SOF/LDV 12s PTVr/OBV+RBV 24s SOF+RBV 24s	**Recaedores** SOF/LDV 12s PTVr/OBV+RBV 12s SOF+RBV 24s **No respondedores** SOF/LDV 12s PTVr/OBV+RBV 12s	**Recaedores** SOF/LDV 12s PTVr/OBV+RBV 24s SOF+RBV 24s **No respondedores** SOF/LDV 12s
5, 6	SOF+IFN+RBV 12s	SOF+IFN+RBV 12s	SOF+IFN+RBV 12s	SOF+IFN+RBV 12s

[1] Factores predictores de respuesta favorables (RNA VHC <6x10[6] UI/ml, 6,78 log). [2] Incluyendo fracasos a BOC/TVR.
[3] Con RBV en fracasos a SOF. [4] Poco estudiada en fracasos a BOC/TVR. 3D AbbVie: PTVr/OBV+DSV

ESTRATEGIA TERAPÉUTICA PARA LA HEPATITIS CRÓNICA CAUSADA POR EL VIRUS DE LA HEPATITIS C EN EL SISTEMA NACIONAL DE SALUD

http://aeeh.es/wp-content/uploads/2015/04/a77478e2a1147600cb9979b5992281cb.pdf

2ª-3ª opción de tratamiento en hepatitis C

GENOTIPO	*NAÏVE* NO CIRROSIS	*NAÏVE* CIRROSIS	PRETRATADOS NO CIRROSIS	PRETRATADOS CIRROSIS
1a	SOF+DCV±RBV 12s SOF+IFN+RBV 12s SMV+IFN+RBV 24s[1]	SOF+DCV±RBV 12s SOF+IFN+RBV 12s SMV+IFN+RBV 24s[1]	SOF+DCV±RBV 24s[2] SOF+IFN+RBV 12s SMV+IFN+RBV 24s[3]	SOF+DCV±RBV 24s[2] SOF+IFN+RBV 12s SMV+IFN+RBV 24s[3]
1b	SOF+DCV±RBV 12s SOF+IFN+RBV 12s SMV+IFN+RBV 24s[1]	SOF+DCV±RBV 12s SOF+IFN+RBV 12s SMV+IFN+RBV 24s[1]	SOF+DCV±RBV 24s[2] SOF+IFN+RBV 12s	SOF+DCV±RBV 24s[2] SOF+IFN+RBV 12s
4	SMV+SOF 12s SOF+IFN+RBV 12s SOF+DCV 12s SMV+IFN+RBV 24s DCV+IFN+RBV 24s	SMV+SOF 12s SOF+IFN+RBV 12s SOF+DCV 24s SMV+IFN+RBV 24s DCV+IFN+RBV 24s	**Recaedores** SMV+SOF 12s SOF+IFN+RBV 12s SOF+DCV 12s SMV+IFN+RBV 24s DCV+IFN+RBV 24 **No respondedores** SOF+RBV 24s SOF+DCV 12s SMV+SOF 12s	**Recaedores** SMV+SOF 12s SOF+IFN+RBV 12s SOF+DCV 24s SMV+IFN+RBV 24s DCV+IFN+RBV 24s **No respondedores** SOF+RBV 24s SOF+DCV 24s SMV+SOF 12s

[1] Suspender tratamiento si RNA VHC es detectable en semana 4.
[2] Incluyendo fracasos a BOC/TVR.
[3] Solo en recaedores.

Y… ¿con qué me dejan tratarlo?:

- **Cambio radical en los últimos dos meses → DGF/SAISE→ Descentralización**
- **Se permite el uso de terapias IFN-FREE para F2, F3, F4 y excepciones**
- **Los esquemas con IFN quedan para pacientes con F0 o F1**

ESTRATEGIA TERAPÉUTICA PARA LA HEPATITIS CRÓNICA CAUSADA POR EL VIRUS DE LA HEPATITIS C EN EL SISTEMA NACIONAL DE SALUD

http://aeeh.es/wp-content/uploads/2015/04/a77478e2a1147600cb9979b5992281cb.pdf

Características del tratamiento ideal para VHC

SVR > 90%

Seguridad

Coste

Importancia Muy Alta

Versatilidad

Duración de tratamiento

Posibilidad de Rescate si FV

Importancia Alta

Pocas interacciones medicamentosas

Comodidad Posológica/nº de comprimidos

Valor Añadido

Genotipo 1

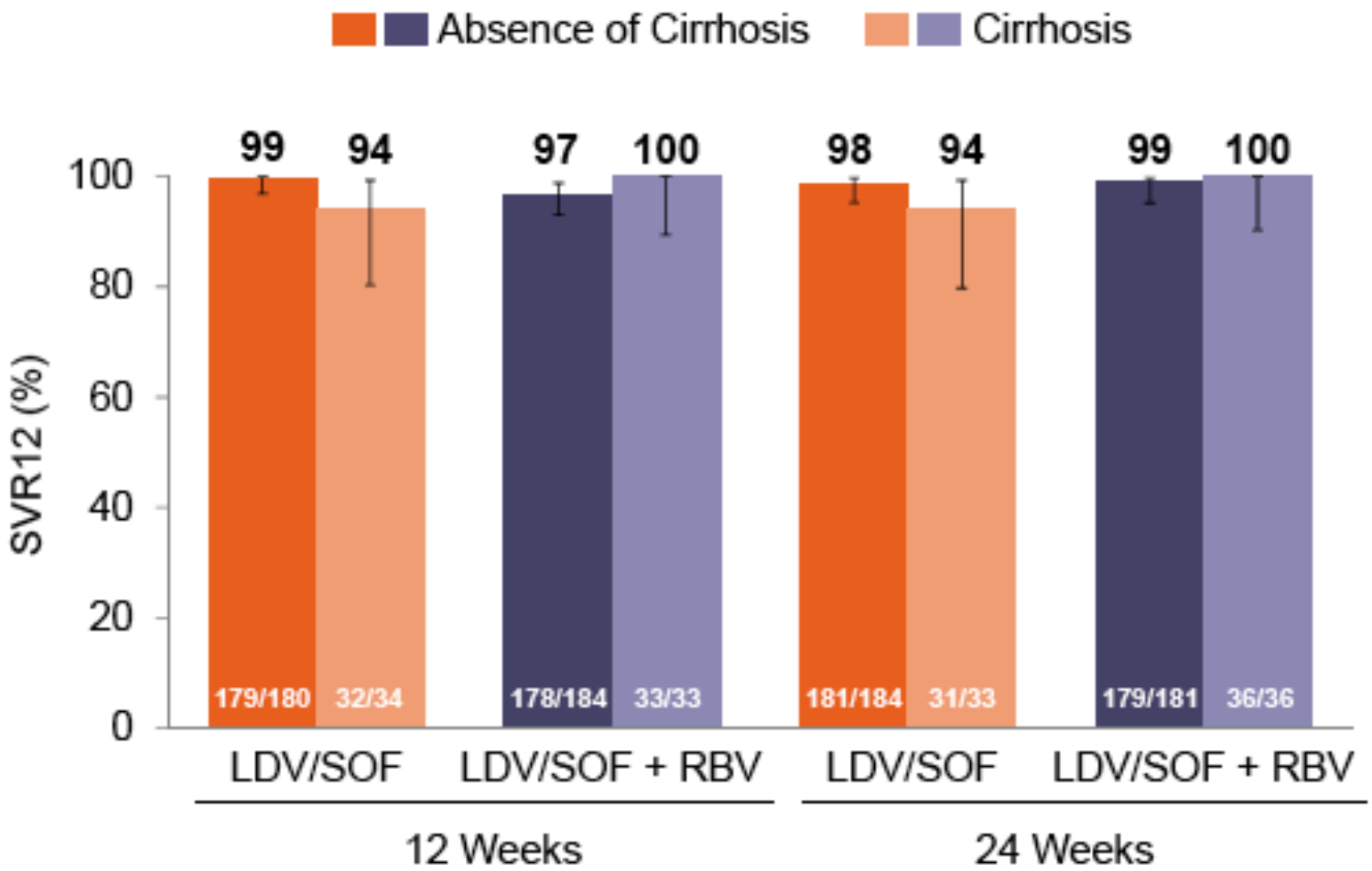
- IFN:
  - PegIFN+Riba +Sofosbuvir
  - PegIFN+Riba+Simeprevir
- IFN Free:
  - Sofosbuvir/Ledipasvir
  - Combo 3D
  - Sofosbuvir + Simeprevir
  - Sofosbuvir + Daclatasvir

Sofosbuvir/Ledipasvir

Perfil de seguridad y posología excelente

SVR12: Absence of Cirrhosis vs Cirrhosis

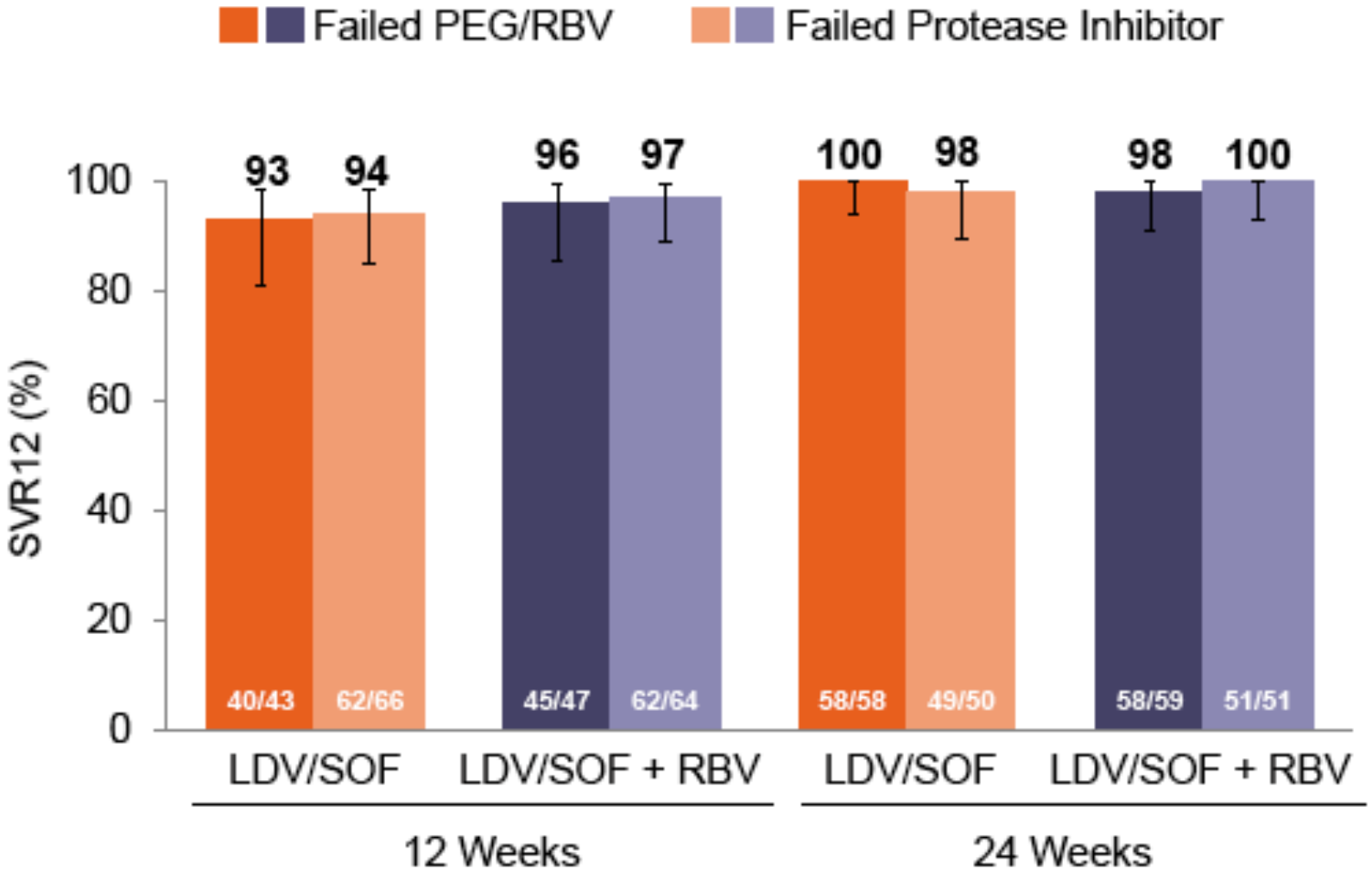
GT 1 Treatment-Naïve (ION-1)



- **12 sem son tan efectivas como 24 s**
- **La Ribavirina no es necesaria**
- **Thus, sofosbuvir/ledipasvir for 12w became an approved treatment by the FDA for patients with genotype 1 HCV**

SVR12: PEG/RBV vs PI + PEG/RBV Failures

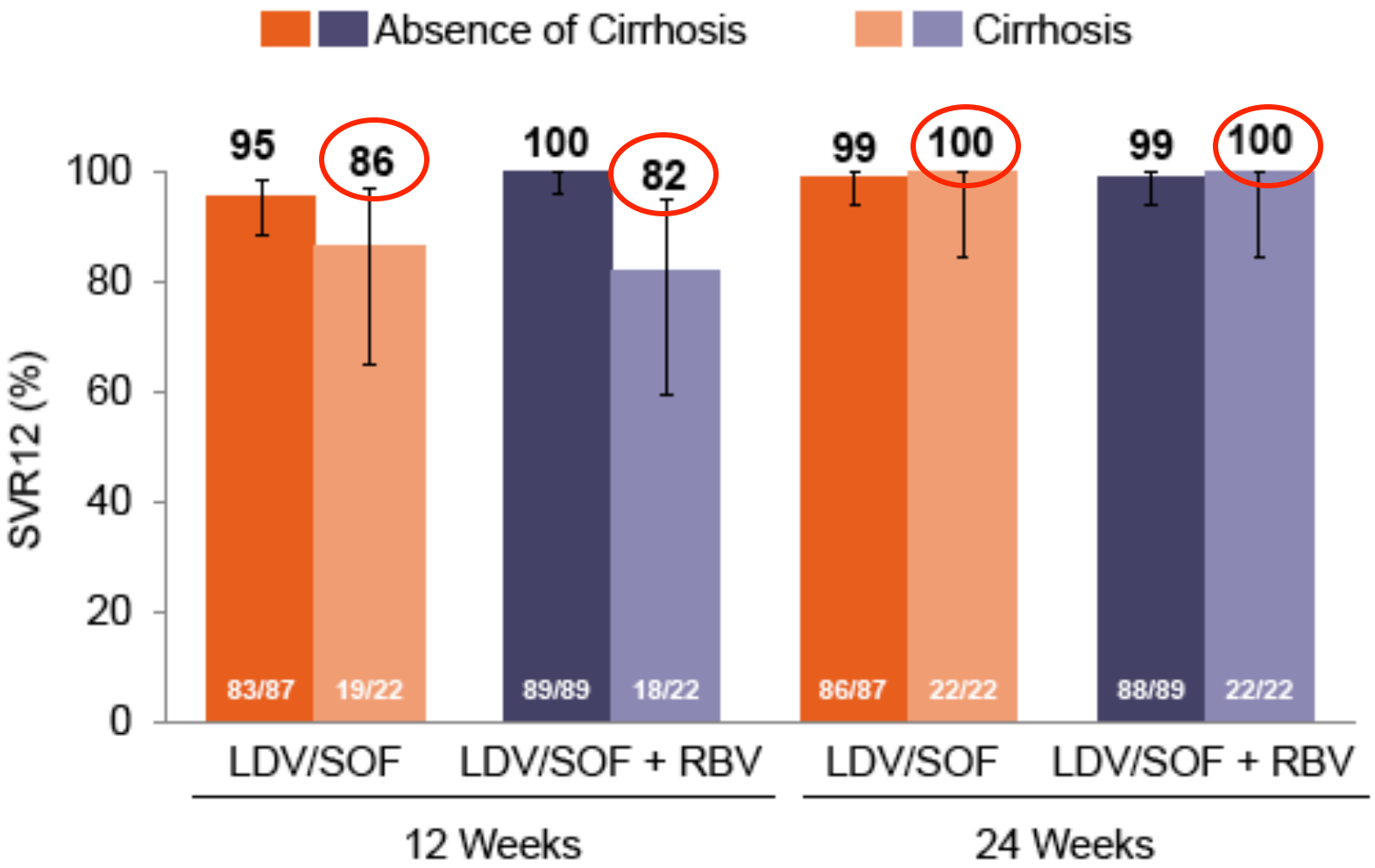
GT 1 Treatment-Experienced (ION-2)



- **Casi un 60% de fracasos a triple terapia con IPs de 1ª generación**

SVR12: Absence of Cirrhosis vs Cirrhosis

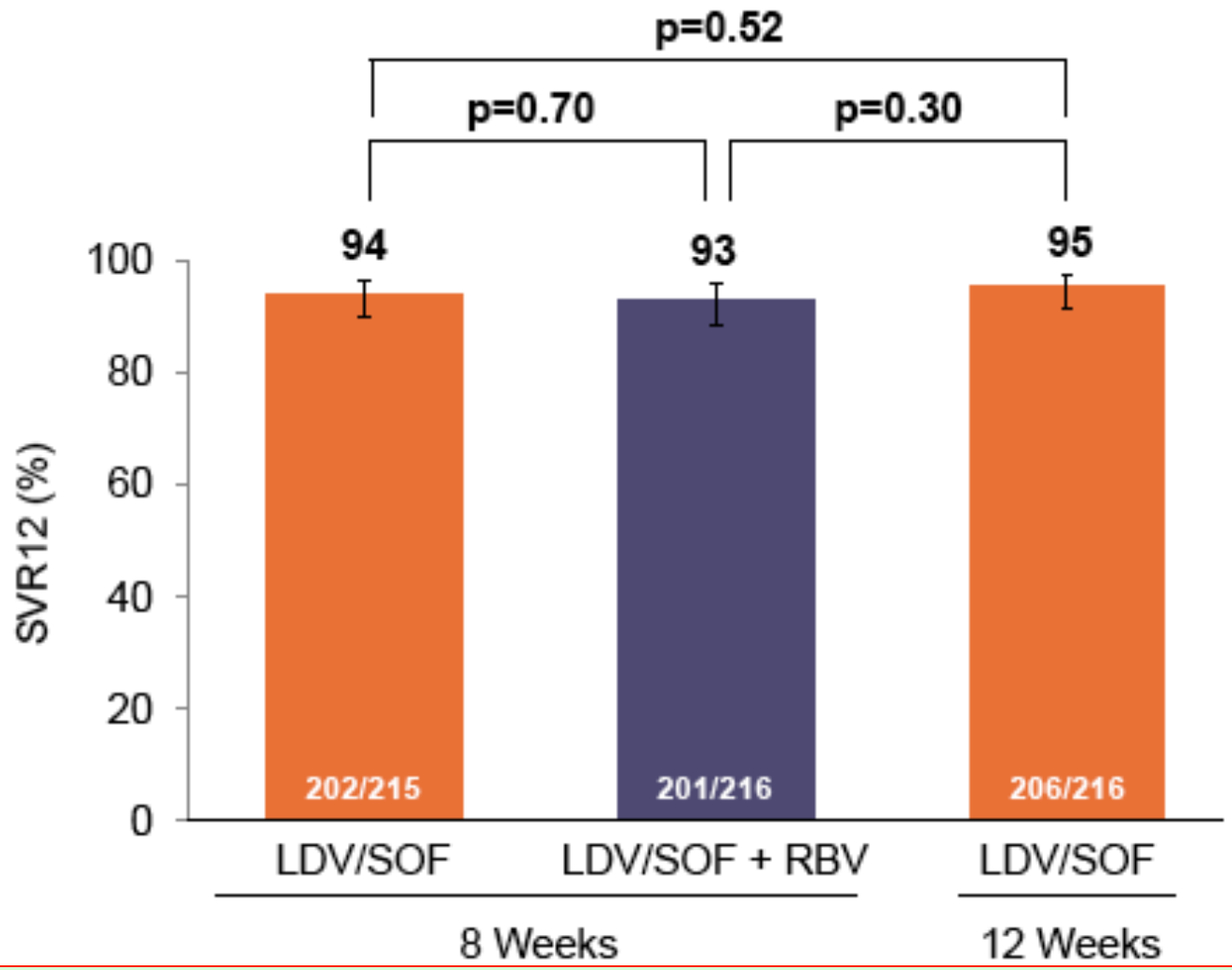
GT 1 Treatment-Experienced (ION-2)



- **12 sem son tan efectivas como 24 s en ausencia de Cirrosis**
- **La Ribavirina no es necesaria sin CH, pero en CH → Prolongar a 24 sem el tto o añadirla si se opta por acortar a 12 semanas**

Results: Non-Inferiority Comparison

GT 1 Treatment-Naïve (ION-3) SIN CIRROSIS



- **Estudio de no inferioridad→ No diferencias 8-12 sem independientemente del uso de Ribavirina**
- **Opción contemplada en las Guías→ En pacientes sin CH**

Combo 3D

VIEKIRAX

EXVIERA

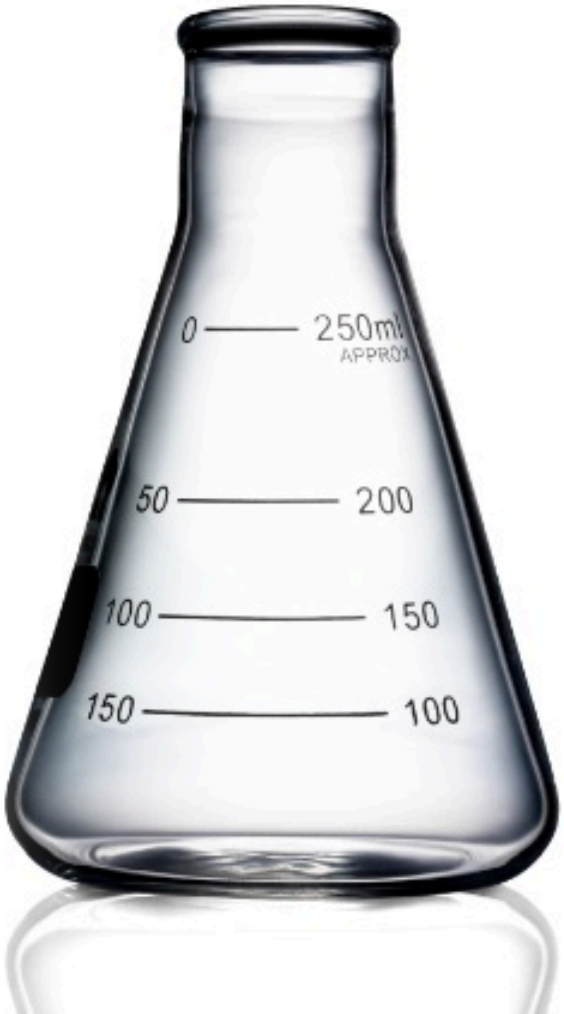
- Perfil de seguridad muy favorable siendo las RAM más frecuentes Nausesas, prurito, cefalea
- Anemia en función del uso o no de Riba

abbvie

Estudios en GT1

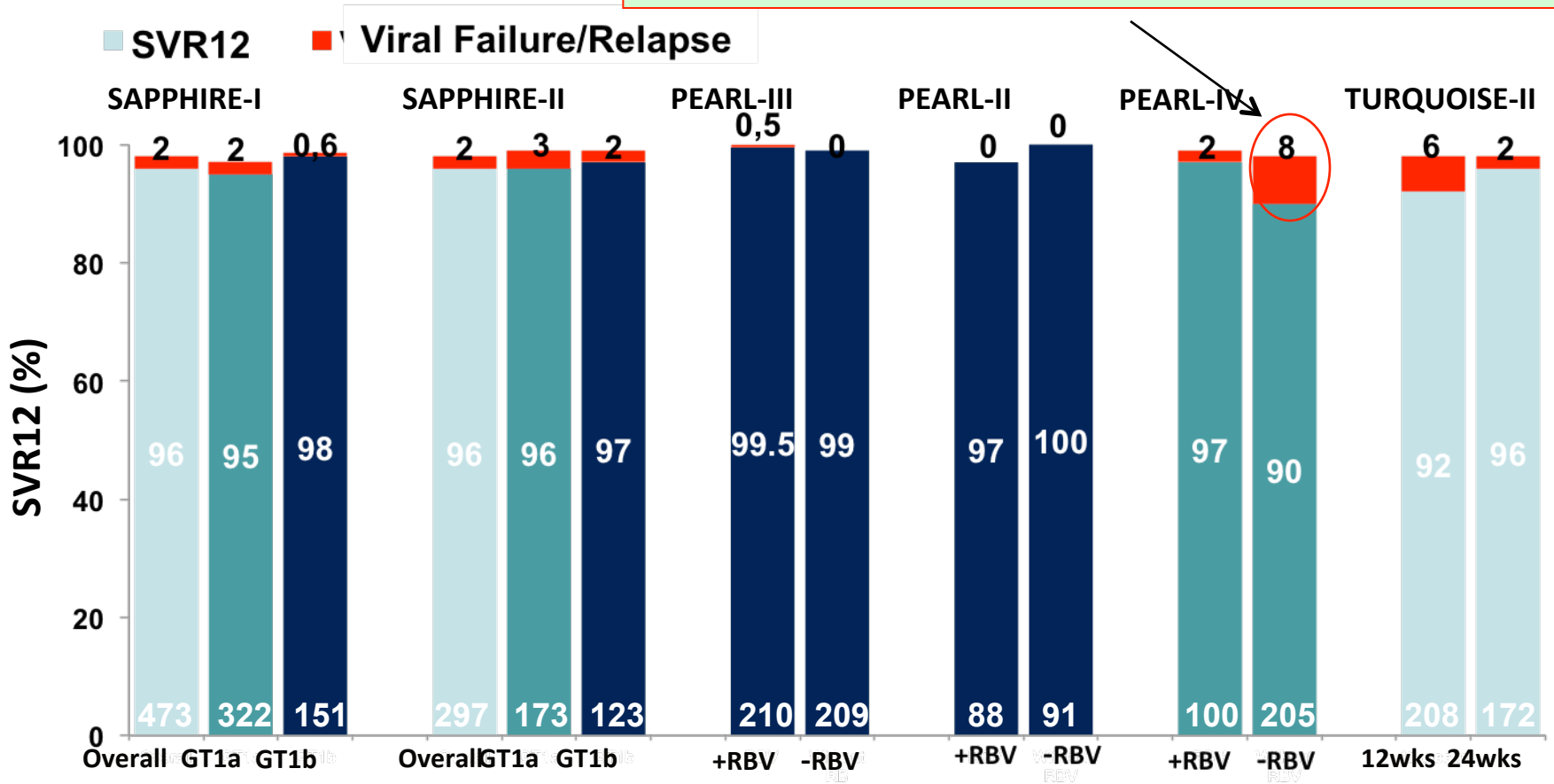
- **GT 1: Fase 3**
  - SAPPHIRE I→ Naïve
  - SAPPHIRE II→ Tratados PR
  - PEARL-II→Tratados PR y Genotipo 1b
  - PEARL-III→ Naïve genotipo 1b
  - PEARL-IV→ Naïve genotipo 1a
  - TURQUOISE II→ **Cirrosis compensada**
    Naïve y pretratados

- **Brazos con 12 y a 24 sem**
- **No evidencias en CH descompensada**
- **No evidencias en fallo a IPs**



Estudios Fase 3: Resultados

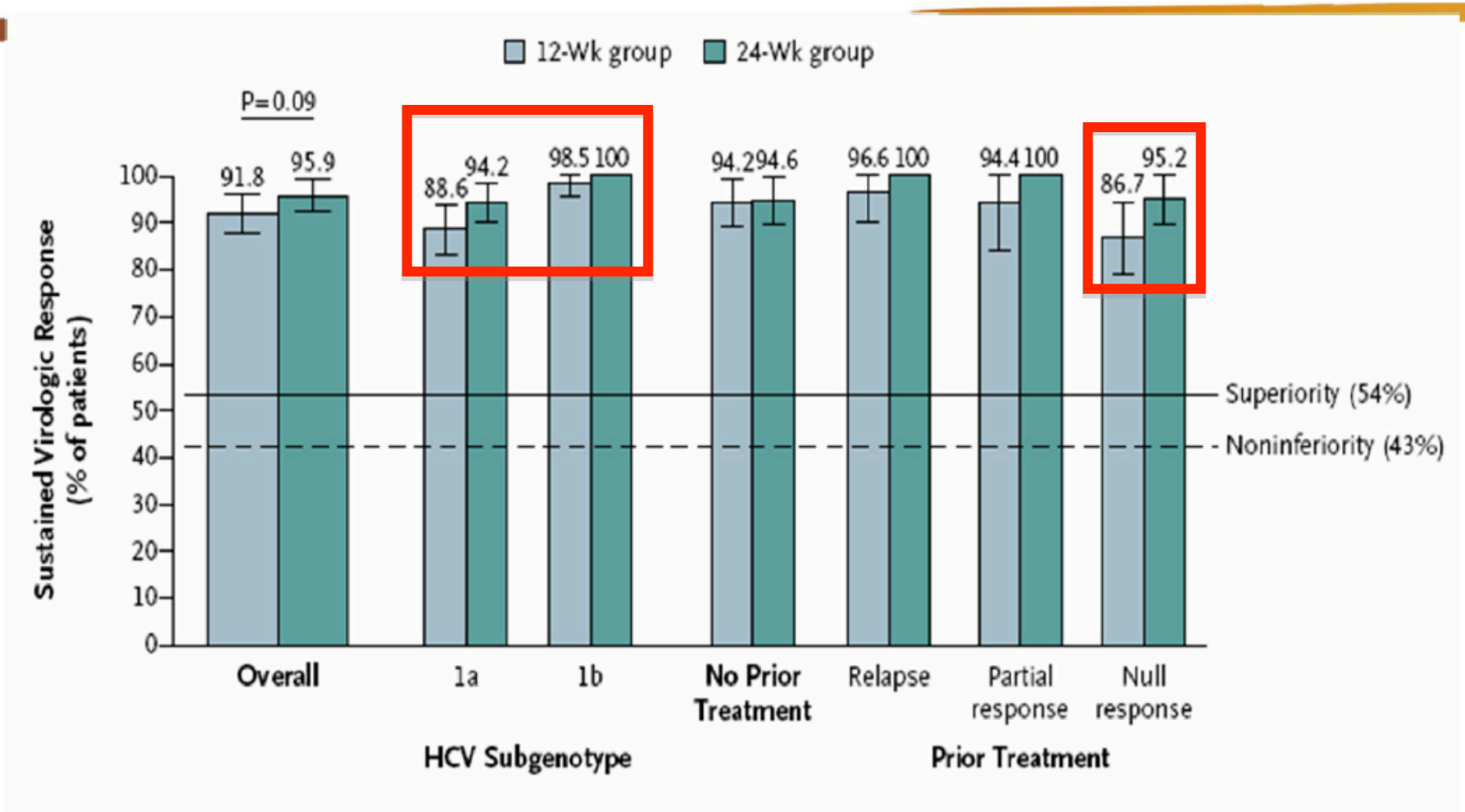
Se recomienda añadir RBV en 1a



Compensated Cirrhosis	✗	✗	✗	✗	✗	✓ ✓
Treatment	Naive	Experienced	Naive	Experienced	Naive	Naïve/experienced
Subtype	GT1a/b	GT1a/b	GT1b	GT1b	GT1a	GT1a/b

1.Feld J, *et al. NEJM* 2014; 2. Zeuzem S, *et al. NEJM;* 2014; 3. Andreone, *et al.* Gastro 2014; 4.Ferenci P, *et al. NEJM* 2014; 5.Ferenci P, *et al. NEJM* 2014; 6. Poordad F, *et al. NEJM* 2014.

Combinacion 3D + RIBA en Cirroticos : Estudio Turquoise



En GT1a, en pacientes null response, se ve una diferencia entre 12 y 24 semanas, que no es significativa, pero podría indicar que este tipo de pacientes se puede beneficiar de un tratamiento más prolongado de 24 semanas→ GUÍAS

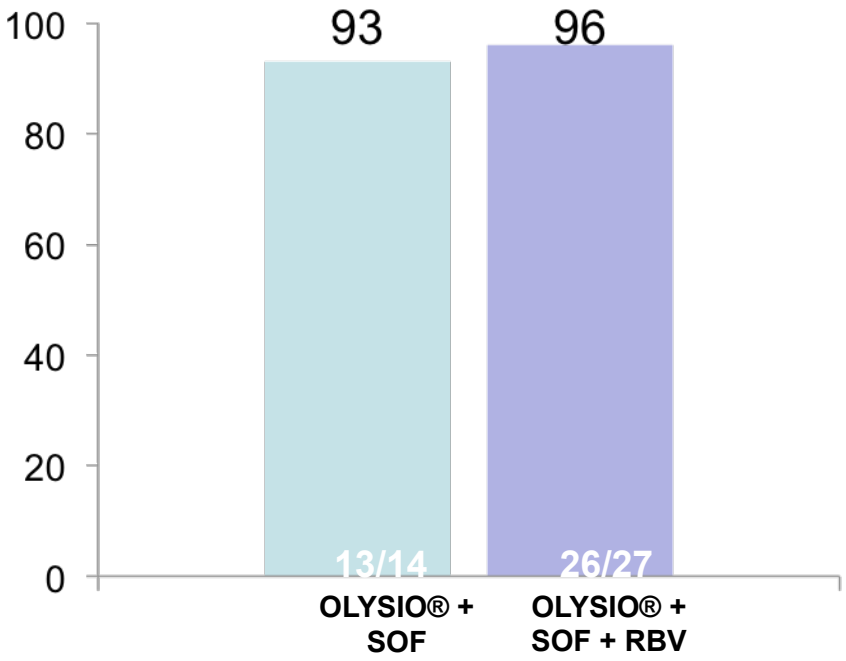
Poordad F, et al. N Engl J Med 2014. DOI:10.1056/NEJMoa1402869

Sofosbuvir + Simeprevir

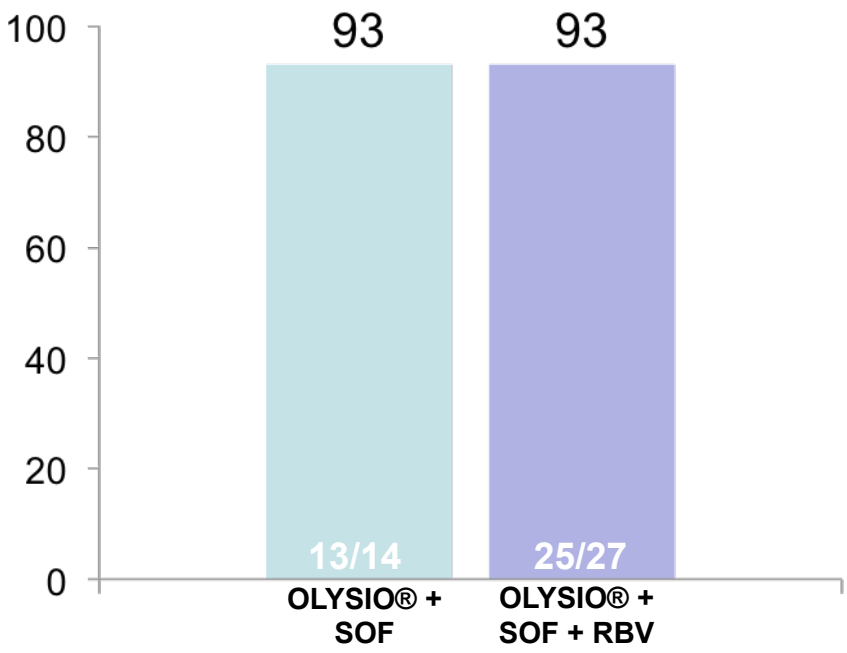
COSMOS → Simeprevir + Sofosbuvir:

Alta eficacia que no se ve alterada por:
- **El tipo de respuesta al tratamiento previo**
- **12 semanas de tratamiento**
- **Uso o no de ribavirina**

Cohorte 1: RVS en pacientes nulos F0-F2*



Cohorte 2: RVS en pacientes naive y nulos F3-F4*



***12-week treatment**
SVR12 Intent-To-Treat (ITT) analysis

1. Lawitz E et al. Lancet. 2014 Jul 26. pii: S0140-6736(14)61036-9..
2. Ficha Técnica de OLYSIO® http://www.ema.europa.eu.

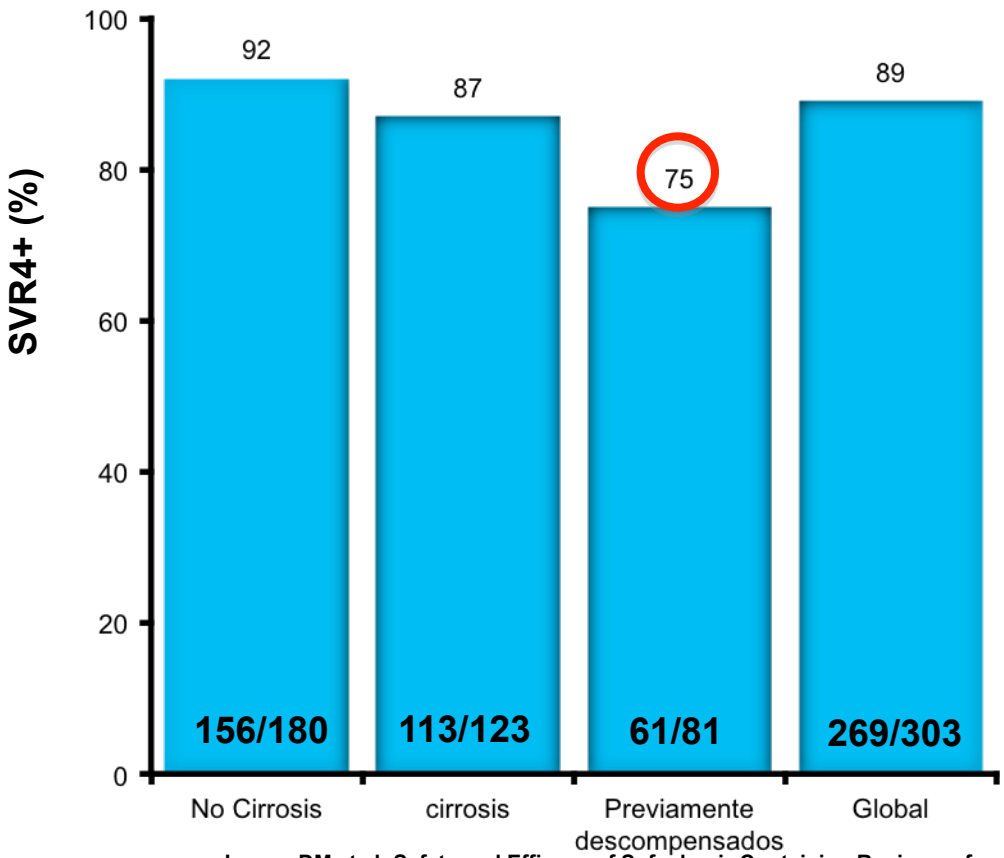
SIM/SOF ± RBV - características basales SVR4 evaluable en 303 pacientes

HCV-TARGET

	SMV + SOF (N=784)	SMV + SOF + RBV (N=228)
Male	478 (65,3%)	147 (65,3%)
Mean, age	59,5 (20-83)	58,8 (29-80)
Age 65+	190 (24,6%)	40 (17,8%)
Race/ethnicity		
Caucasian	584 (74,5%)	177 (77,6)%
Black	96 (12,5%)	33 (14,7)%
Treatment status		
Naïve	318 (40,6%)	82 (36%)
Experienced	485 (59,3%)	144 (63,2%)
DAA failure	**76 (24,8%)**	**45 (31,3%)**
Cirrhosis	**440 (56,1%)**	**137 (60,1%)**
HX descompensation	**167 (44,8%)**	**60 (50,8%)**
MELD > 10	**122 (32,7%)**	**34 (28,8%)**
LIVER CANCER	**88 (11,2%)**	**32 (14%)**
LIVER TRANSPLANT	**111 (14,2%)**	**32 (14%)**
HIV	**8 (1%)**	**7 (3,1%)**

*Total starting therapy. RVS4 disponible para 303/369 pacientes
78% (253/323) pacientes no cirroticos G1, naïve, tenían un ARN – VHC < 6 millones de UI/MI)

Perfil de seguridad → Muy favorable



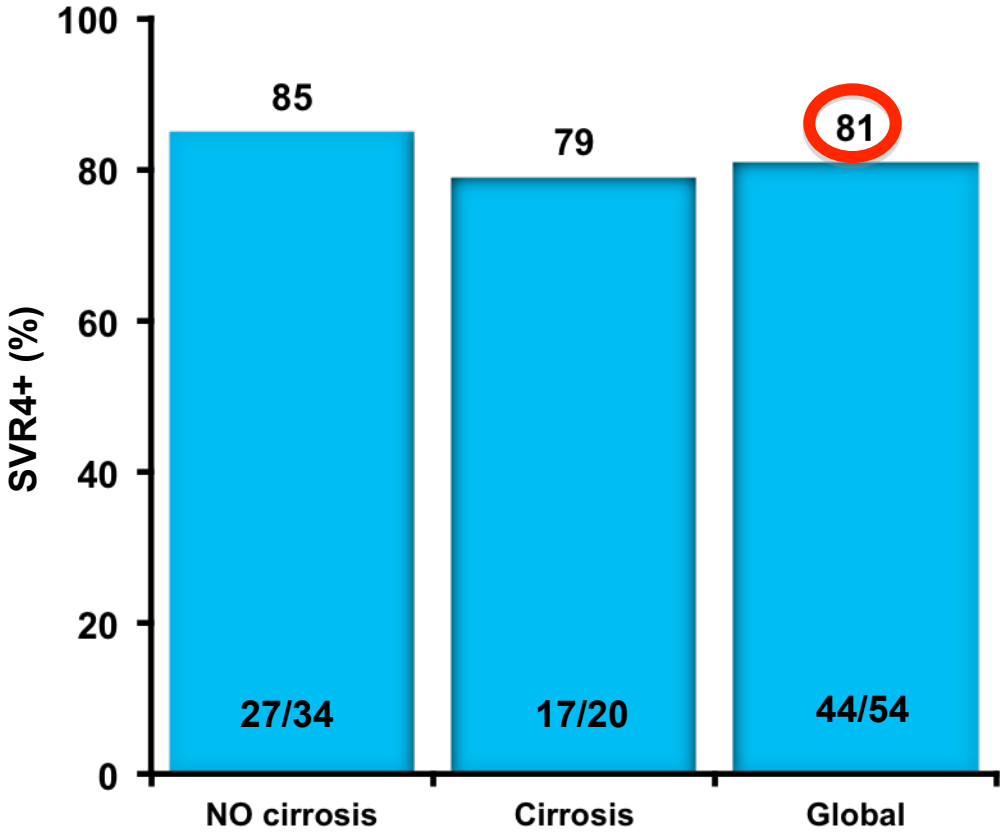
Jensen DM et al; Safety and Efficacy of Sofosbuvir-Containing Regimens for Hepatitis C: Real-World Experience in a Diverse, Longitudinal Observational Cohort
Boston Nov 2014

SIM/SOF ± RBV – En fracaso previo a IP`s

SVR4 evaluable en 54 pacientes

HCV-TARGET

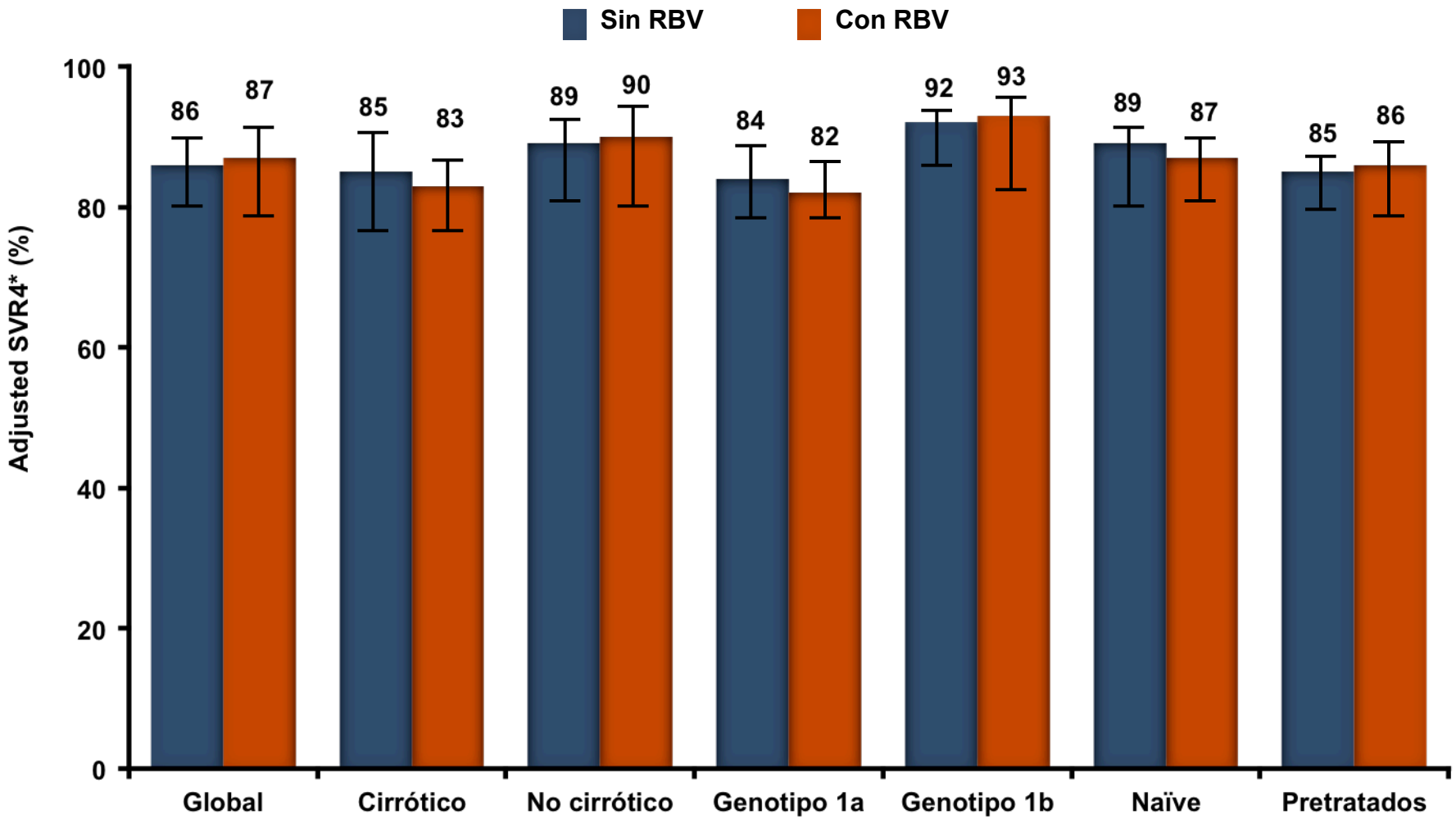
	SMV + SOF (N=784)	SMV + SOF + RBV (N=228)
Male	478 (65,3%)	147 (65,3%)
Mean, age	59,5 (20-83)	58,8 (29-80)
Age 65+	190 (24,6%)	40 (17,8%)
Race/ethnicity		
Caucasian	584 (74,5%)	177 (77,6)%
Black	96 (12,5%)	33 (14,7)%
Treatment status		
Naïve	318 (40,6%)	82 (36%)
Experienced	485 (59,3%)	144 (63,2%)
DAA failure	**76 (24,8%)**	**45 (31,3%)**
Cirrhosis	**440 (56,1%)**	**137 (60,1%)**
HX descompensation	**167 (44,8%)**	**60 (50,8%)**
MELD > 10	**122 (32,7%)**	**34 (28,8%)**
LIVER CANCER	**88 (11,2%)**	**32 (14%)**
LIVER TRANSPLANT	**111 (14,2%)**	**32 (14%)**
HIV	**8 (1%)**	**7 (3,1%)**



RVS4 disponible en 54/69 pacientes
Cohorte de pacientes con inicio de tto en o antes del 15/4/14

Jensen DM et al; Safety and Efficacy of Sofosbuvir-Containing Regimens for Hepatitis C: Real-World Experience in a Diverse, Longitudinal Observational Cohort
Boston Nov 2014

SIM/SOF ± RBV: PAPEL DE LA RIBAVIRINA



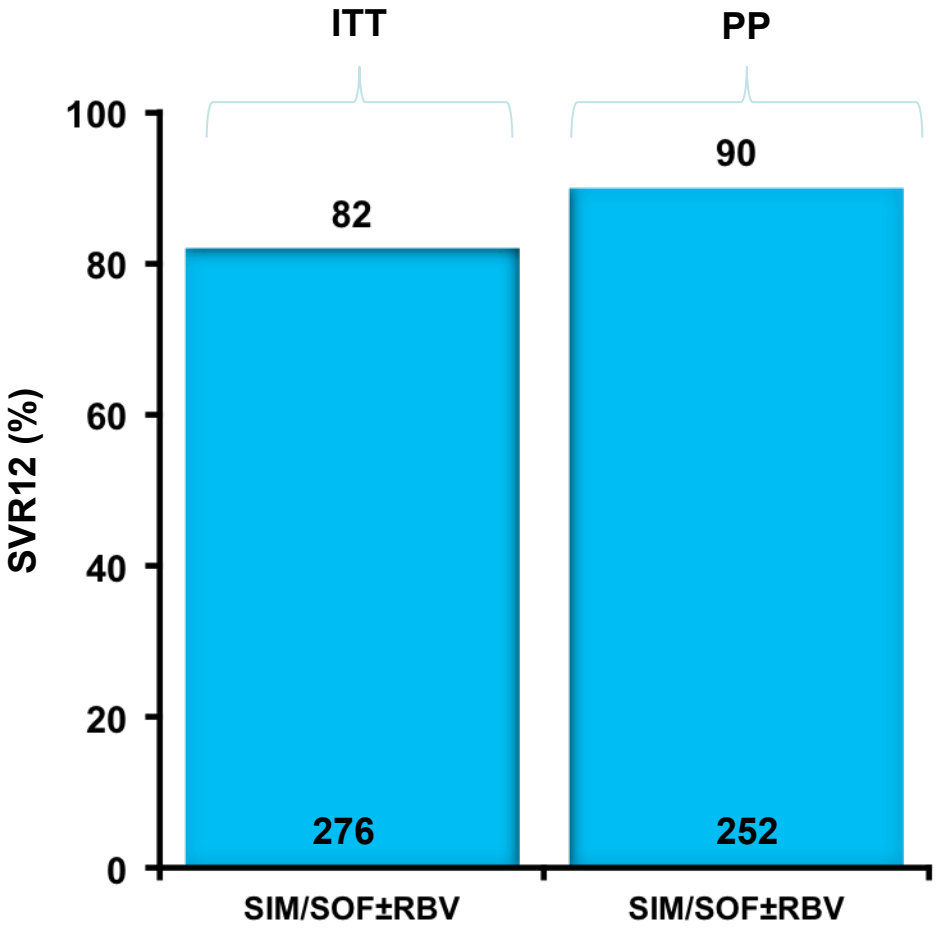
- **La RBV parece no influir en la RVS**
- **Pero son datos de RVS 4s**

Jensen D, et al. AASLD 2014. Oral presentation 45

Trio Health

Cohorte TRIO perfil de seguridad y RVS 12

Excelente perfil de seguridad Tasas de discontinuación por EA`s muy bajas, inferiores en el grupo SIM/ SOF vs SOF/PR



* SVRs for cell with n<=5 not shown

Dieterich et al; Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network, AASLD Boston 2014

Daclatasvir

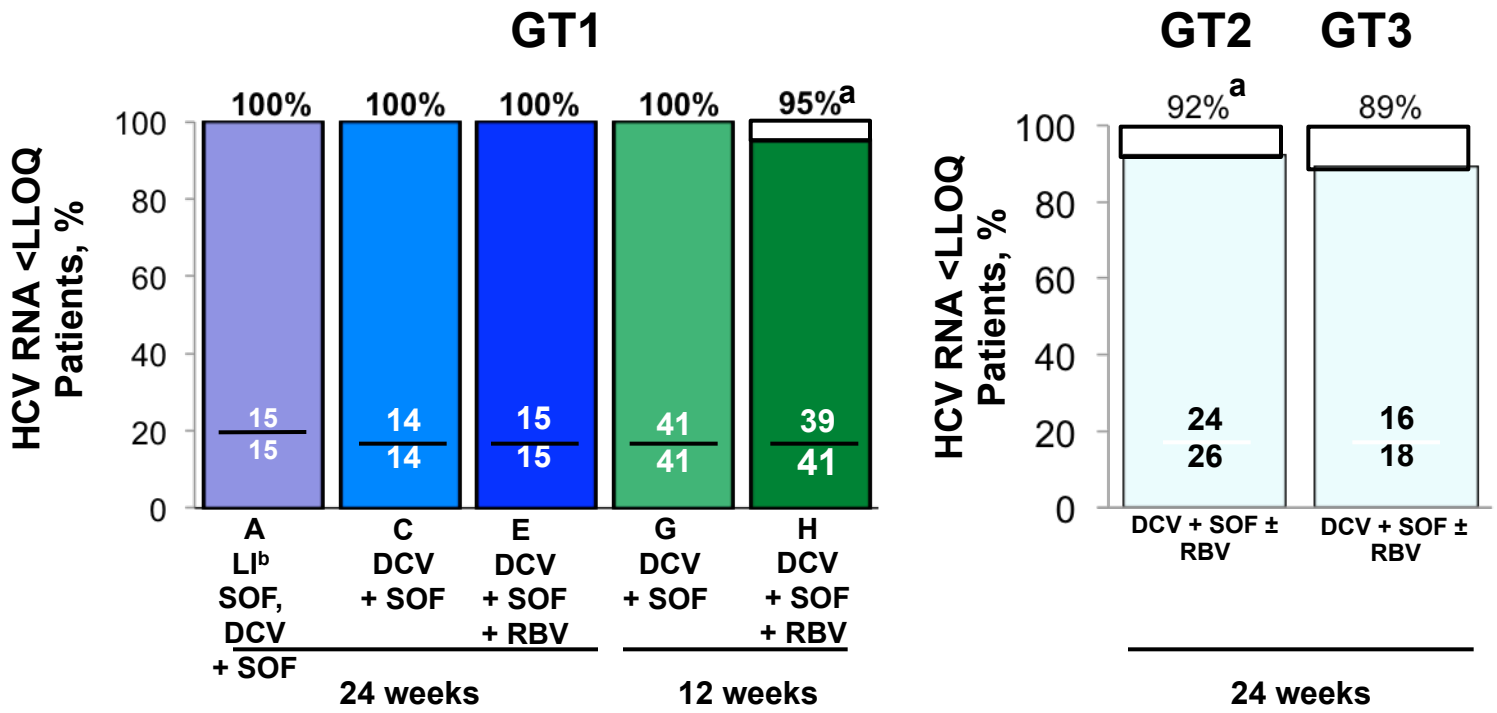
Estudio pivotal 040

Evaluar daclatasvir (DCV) + sofosbuvir (SOF) ± ribavirina (RBV) en:

- Pacientes naive
- Genotipos 1, 2 y 3
- Pacientes con G1 que han fracasado a un tratamiento basado en telaprevir (TVR) o boceprevir (BOC)
- Se exploran 12 y 24 semanas

Sulkowski et al. N Engl J Med 2014;370:211–21.

AI444-040 – Pacientes naïve
RVS_{12} (mITT)

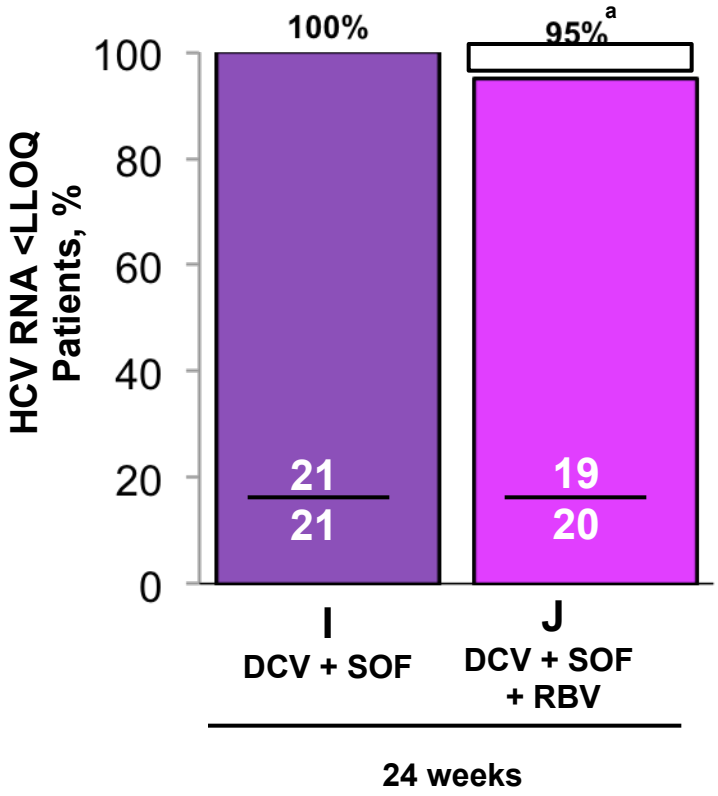


- SVR_{12} rates were 98% in GT1a and 100% in GT1b
- SVR_{24} rates ranged from 93–100% in GT1, and 88–100% in GT2/3[c]

LI, lead in; LLOQ = lower limit of quantitation (25 IU/mL), mITT, modified intent to treat
[a]One patient had missing data at post treatment week 12 but achieved SVR24, and one who was lost to follow-up after achieving SVR4
[b]LI (lead in) with SOF was not included in subsequent trials
[c]93% and 88% were the percentage for the lead in arm.

Sulkowski et al. N Engl J Med 2014;370:211–21.

AI444-040 – Fracasos a IP's RVS_{12} (mITT)

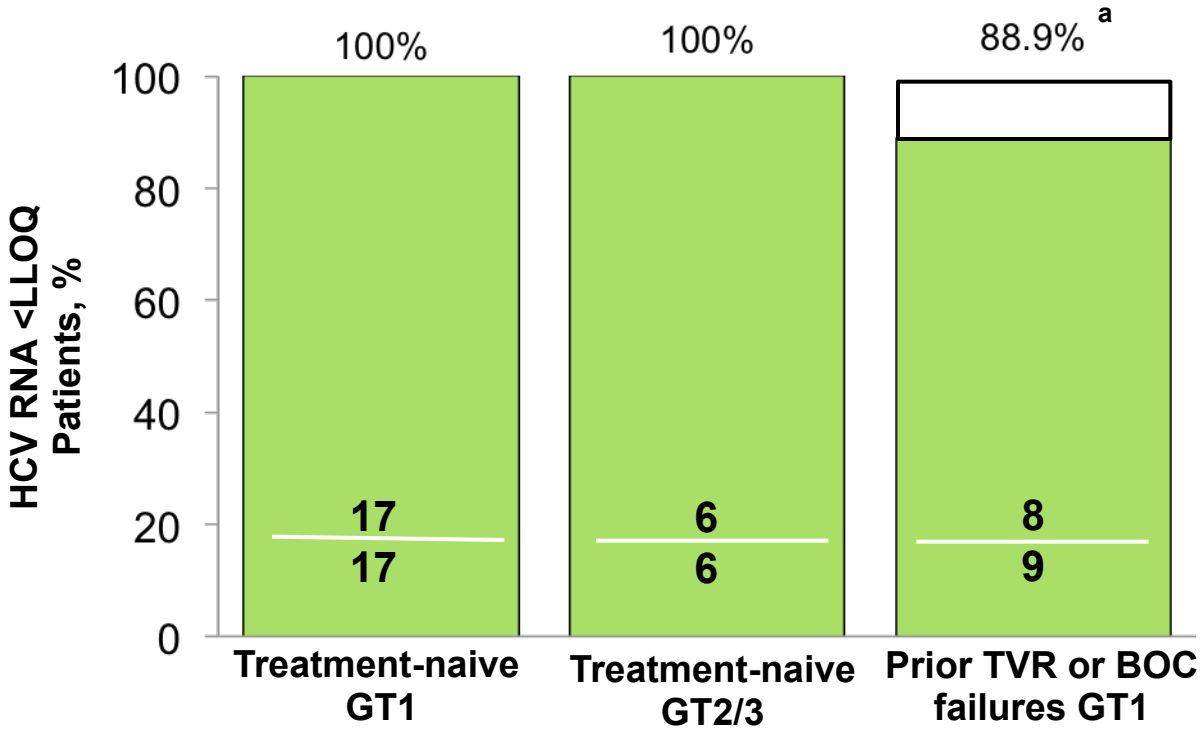


- 33 of 41 patients had previously received TVR regimens and 8 had received BOC
- End of treatment (EOT) responses were 100%, with or without RBV

[a]One patient with missing data at post treatment week 12, who achieved SVR_{24}

Sulkowski et al. N Engl J Med 2014;370:211–21.

AI444-040 – Pacientes con fibrosis F3 – F4 o F4* RVS12 (mITT)



- Ningún paciente con fibrosis F4* tuvo un fracaso virológico

[a]One patient with F4 fibrosis* had missing HCV RNA results at follow-up week 12 who achieved SVR_{24}.
***The Metavir score was derived from FibroTest score and classified according to the manufacturer's instructions (www.biopredictive.com); patients with a score of F4 were required to have no evidence of cirrhosis on the basis of a liver biopsy.**

BMS. Data on file. DACL002; Sulkowski et al. N Engl J Med 2014;370:211–21.

Efectos adversos muy favorables incluso con RBV

	Treatment-naive patients					Prior TVR or BOC failures	
Treatment duration	24 Weeks			12 Weeks		24 Weeks	
Patients with event, n (%)	A and B SOF 7-D lead-In SOF +DCV (n = 31)	C and D DCV +SOF (n = 28)		G DCV +SOF (n = 41)	H DCV +SOF +RBV (n = 41)	I DCV +SOF (n = 21)	
Any AE	25 (81)	26 (93)	26 (90)	38 (93)	38 (93)	16 (76)	20 (100)
AE occurring in ≥25% in any group[a]							
Fatigue	9 (29)	14 (50)	9 (31)	16 (39)	15 (37)	6 (29)	9 (45)
Headache	5 (16)	8 (29)	11 (38)	14 (34)	9 (22)	7 (33)	7 (35)
Nausea	5 (16)	9 (32)	9 (31)	8 (20)	8 (20)	0	2 (10)
Grade 3 or 4 AE	0	2 (7)[b]	2 (7)	1 (2)	0	0	1 (5)
Discontinuation due to AE	0	1 (4)	1 (3)	0	0	0	0
SAE[c]	2 (6)	4 (14)	2 (7)	1 (2)	0	0	1 (5)

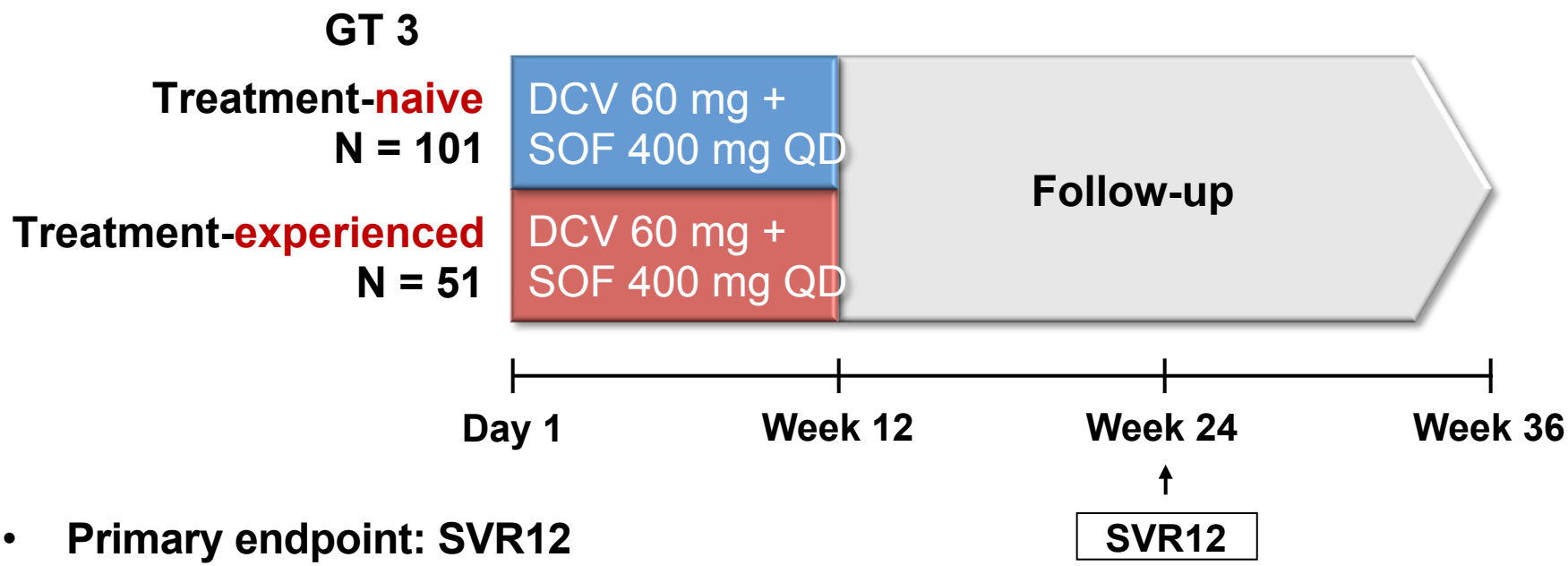
[a]All events listed were mild or moderate in intensity. [b]2 patients had a total of 4 events. [c] 5 events of overdose (extra study medication doses), classified as SAEs, are not included in the table; no clinically significant effects were reported from any of the overdoses

Sulkowski et al. N Engl J Med 2014;370:211–21.

Genotipo 3

- **IFN:**
  - **PegIFN+Riba +Sofosbuvir**
    - **12 sem (Lonestar-2→ RVS 83%)**
    - **Relapsers a Sofos+Riba → RVS 91%**
- **IFN Free:**
  - **Sofosbuvir + Ribavirina → RVS subóptima en CH**
    - **Fission → RVS Subóptima 56%**
    - **Positron→ RVS 61%**
    - **Fusion→ RVS 12s--< 30% a 16s→ 62%**
    - **Valence→ 24 sem→ Peor resultado en CH pretratados**
  - **Sofosbuvir + Daclatasvir**

ALLY-3: Study Design

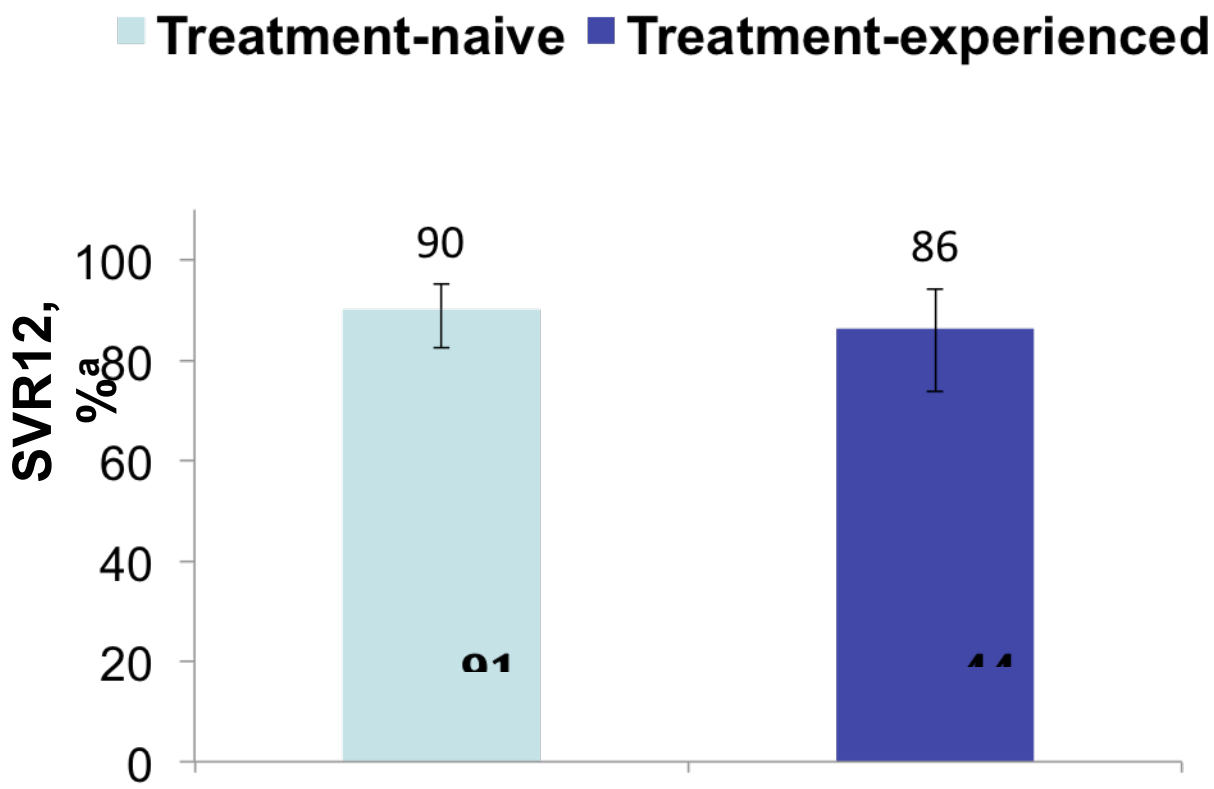


- **Primary endpoint: SVR12**
  - **HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12[a]**
- **Eligible patients**
  - **Age ≥ 18 years with chronic GT 3 infection and HCV RNA ≥ 10,000 IU/mL**
  - **Treatment-naive or -experienced (prior treatment failures), including patients with cirrhosis**
  - **Those who received prior treatment with NS5A inhibitors were excluded**

[a] Assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).

Nelson DR et al. Hepatology 2015; 61: 1127-1135

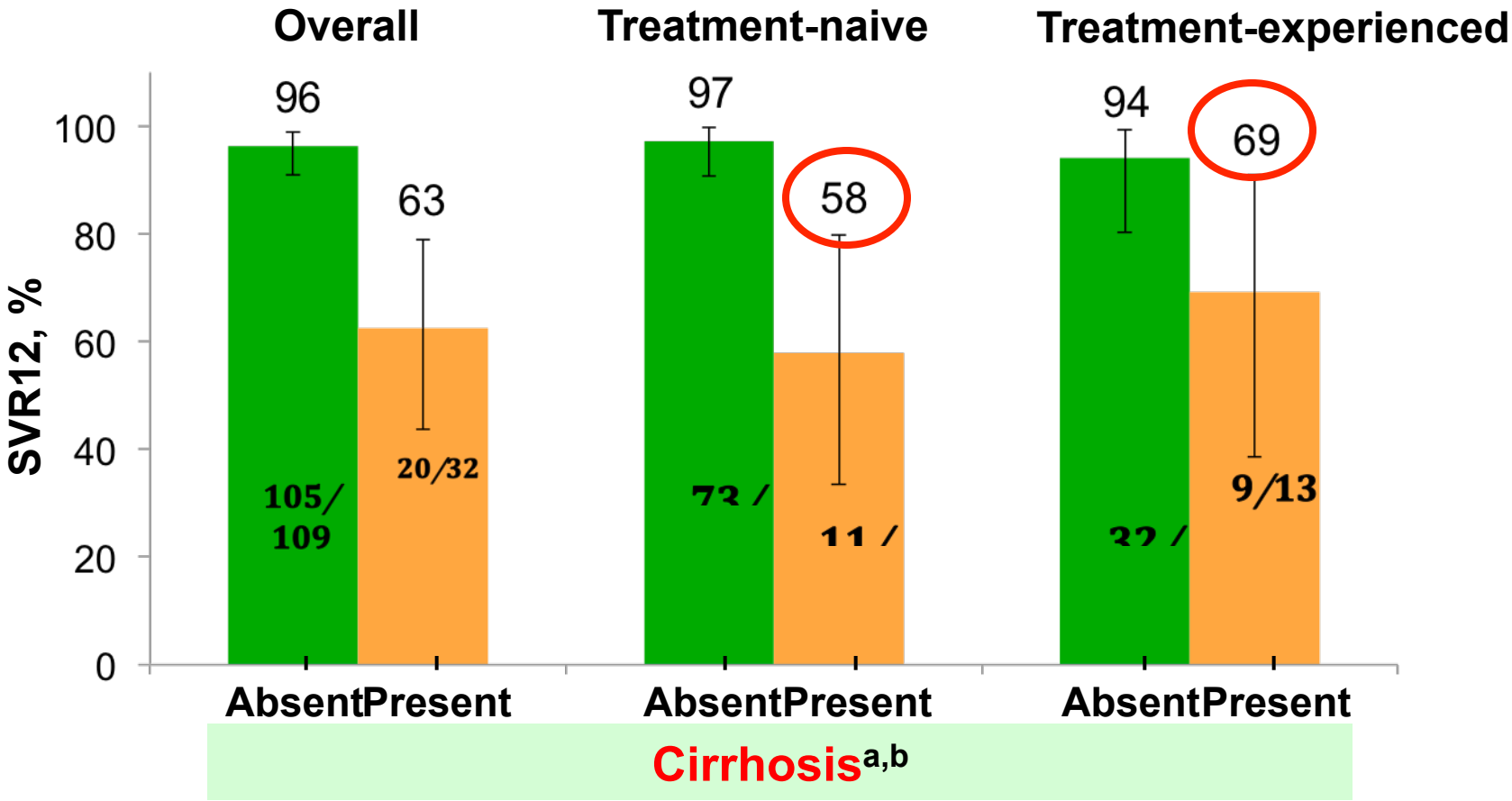
SVR12: Primary Endpoint



[a] HCV RNA < LLOQ (25 IU/mL); error bars reflect 95% confidence intervals.

Nelson DR et al. Hepatology 2015; 61: 1127-1135

SVR12 in Patients With Cirrhosis n= 141



- **Among patients with cirrhosis, 34% (11/32) had baseline platelet counts < 100,000/mm^3**

[a] Cirrhosis status determined in 141 patients by liver biopsy (METAVIR F4), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and APRI (aspartate aminotransferase to platelet ratio index) > 2.

[b] Cirrhosis status for 11 patients was inconclusive (FibroTest score > 0.48 to < 0.75 or APRI > 1 to ≤ 2).

Nelson DR et al. Hepatology 2015; 61: 1127-1135

Perfil de seguridad muy favorable

Eficacia y Seguridad en Cirrosis descompensada

- Evidencia disponible excasa en
  - Sofosbuvir + Daclatasvir
  - Harvoni
  - Simeprevir contraindicado
  - Combo 3D sin evidencia

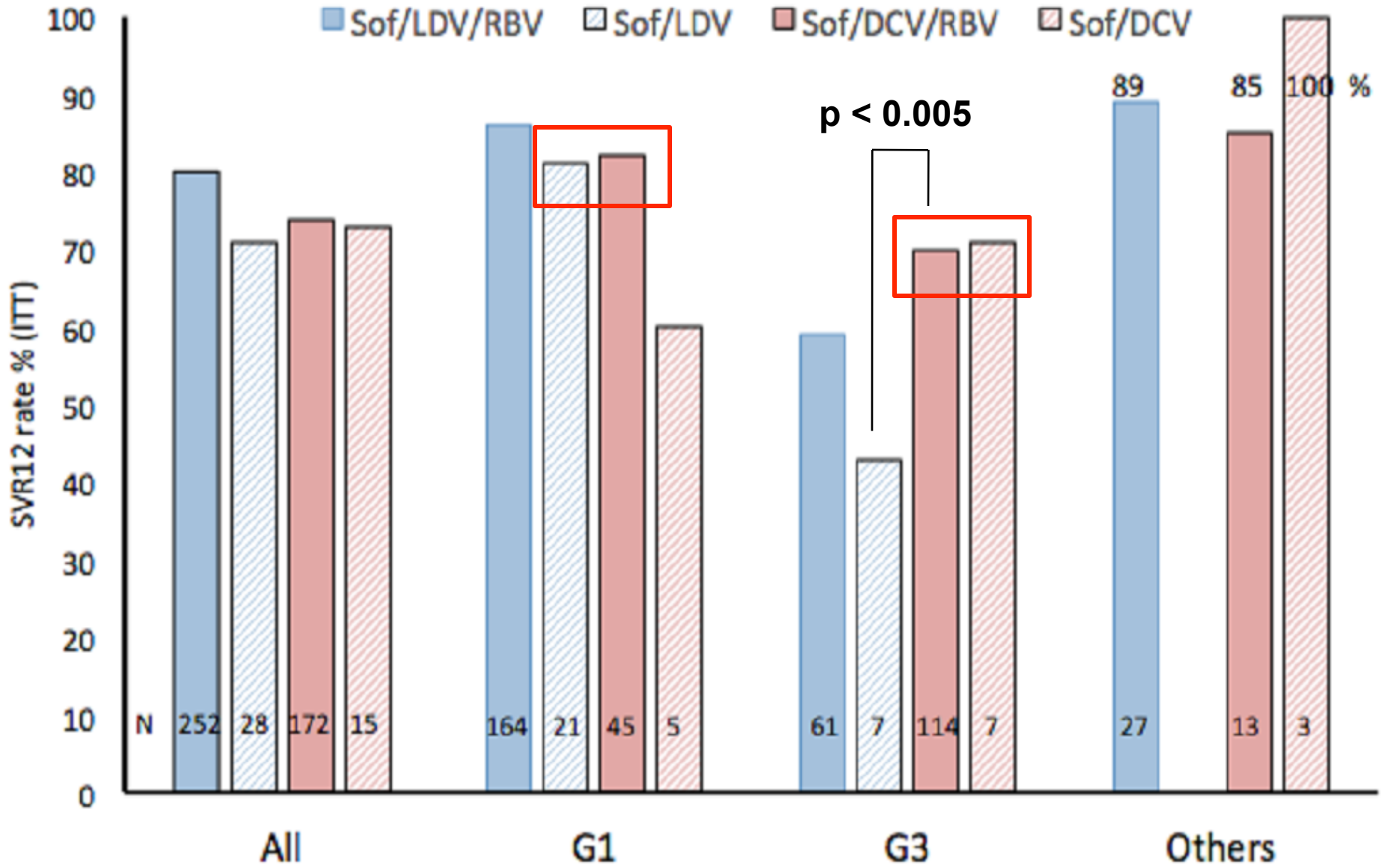
Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV Genotypes 1 and 3

- **Práctica clínica real**
- **Cohorte UK EAP (n = 467, G1= 235 G3= 189. CTP B y C**
- **Un 40% logra una mejoría del estadío funcional hepático**

GR Foster, J. McLauchlan, W. Irving, M. Cheung, B. Hudson, S. Verma, K. Agarwal, HCV Research UK EAP Group

EASL VIENA 2015

SVR12 by Genotype and Regime



SVR12 defined as HCV RNA at 12 weeks post-treatment < 30 IU/ml

EASL VIENA 2015

Serious Adverse Events

(by follow up week 4)

	Number of events (% of total SAEs)	Number of patients (% of total population)
Total SAEs	175	119 (25.5%)
Likely related to liver disease and/ or HCV therapy	138 (78.9%)	100 (21.4%)
Likely unrelated to liver disease and/or HCV therapy	37 (21.1%)	37 (7.9%)
Ascites	55 (31.4%)	38 (8.1%)
Hepatic encephalopathy	28 (16%)	23 (4.9%)
Variceal bleed	6 (3.4%)	6 (1.3%)
Infection	26 (14.9%)	23 (4.9%)
Liver transplantation		16 (3.4%)
New HCC		7 (1.5%)
Discontinuation of DAAs		42 (9%)
Deaths		14 (3.0%)

Guía EASL Abril 2015.- No CH (Naïve y pretratados)

Table 5. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Guía EASL Abril 2015.- CH compensada y pretratados

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Conclusiones

- Los ensayos de registros y algunos estudios en práctica clínica real demuestran tasas de RVS cercanas al 90% en la mayoría de esquemas sin IFN en genotipo 1
- Los esquemas disponibles para genotipo 3 en el paciente cirrótico no logra un perfil de respuesta adecuado
- Los pacientes con cirrosis descompensada podrán beneficiarse de estos esquemas, si bien son esperables más efectos secundarios potencialmente graves
- En el paciente con Cirrosis establecida, curar la infección no equivale a curar la enfermedad