Ribavirin: Farewell to an unsung hero?

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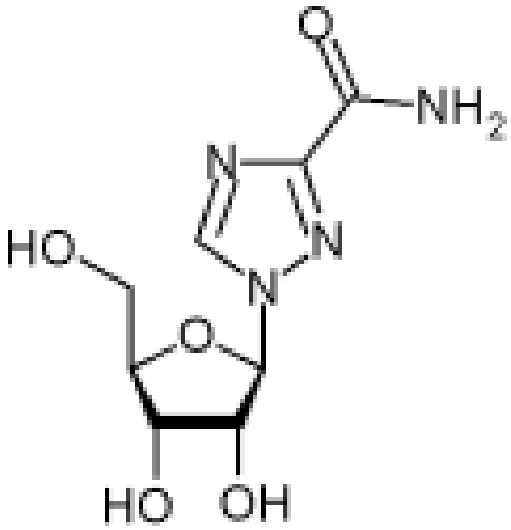
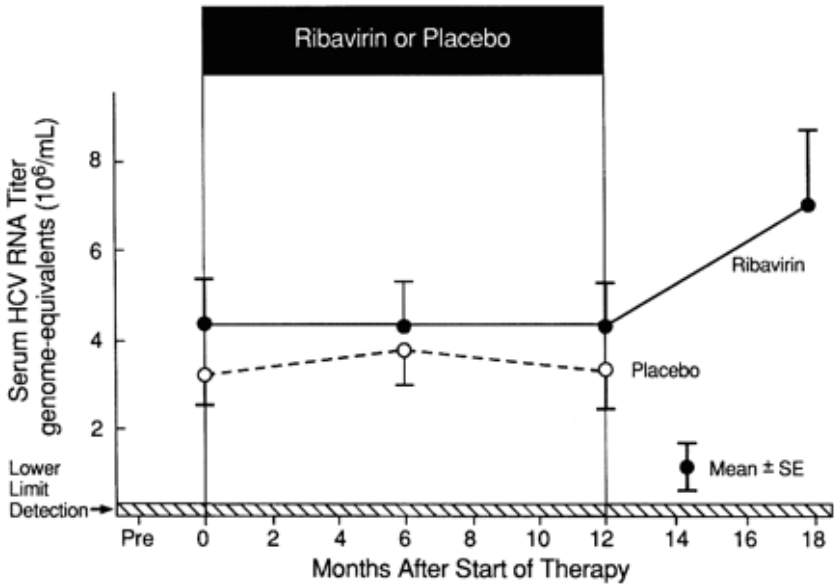
1-(β-D-Ribofuranosyl)-1H-1,2,4-triazole-3-carboxamide: A Purine nucleoside analogue

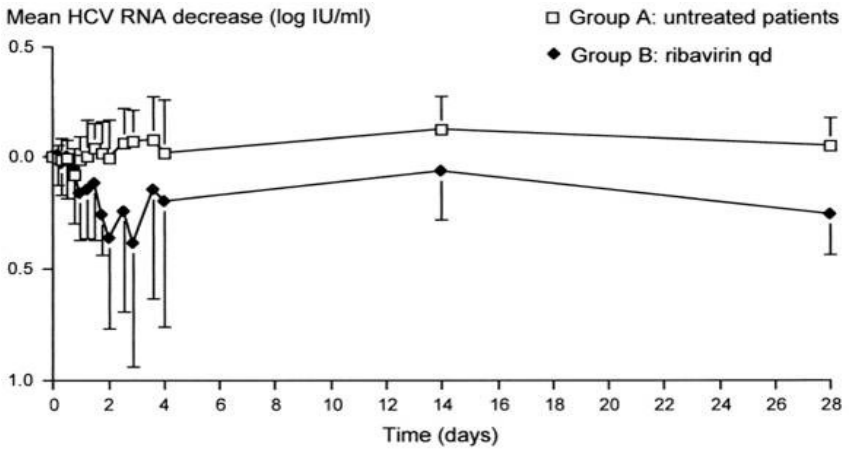
- 1970: Synthesis
  - Witkowski JT, Robins RK, Sidwell RW, Simon LN. J Med Chem 1972; 15:1150–1154
- 1972: Antiviral properties recognized
  - Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Broad-spectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. Science 1972; 177:705–706
- 1980: Aerosolized RBV approved for RSV
- Mid 1980s: Fails for HIV
- Early 1990s: Fails for HBV and HCV
- 1994 – 1998: Succeeds with IFN
- 2004: RBV dose response established for genotype 1
- 2011 - current: Critical component of PegIFN/RBV + DAA “triple therapy”
- 2013: Sofosbuvir + Ribavirin – the first approved “all oral” regimen



RBV alone has minimal suppression on HCV RNA levels and does not select for resistant HCV variants



Disceglie AM et al 1995

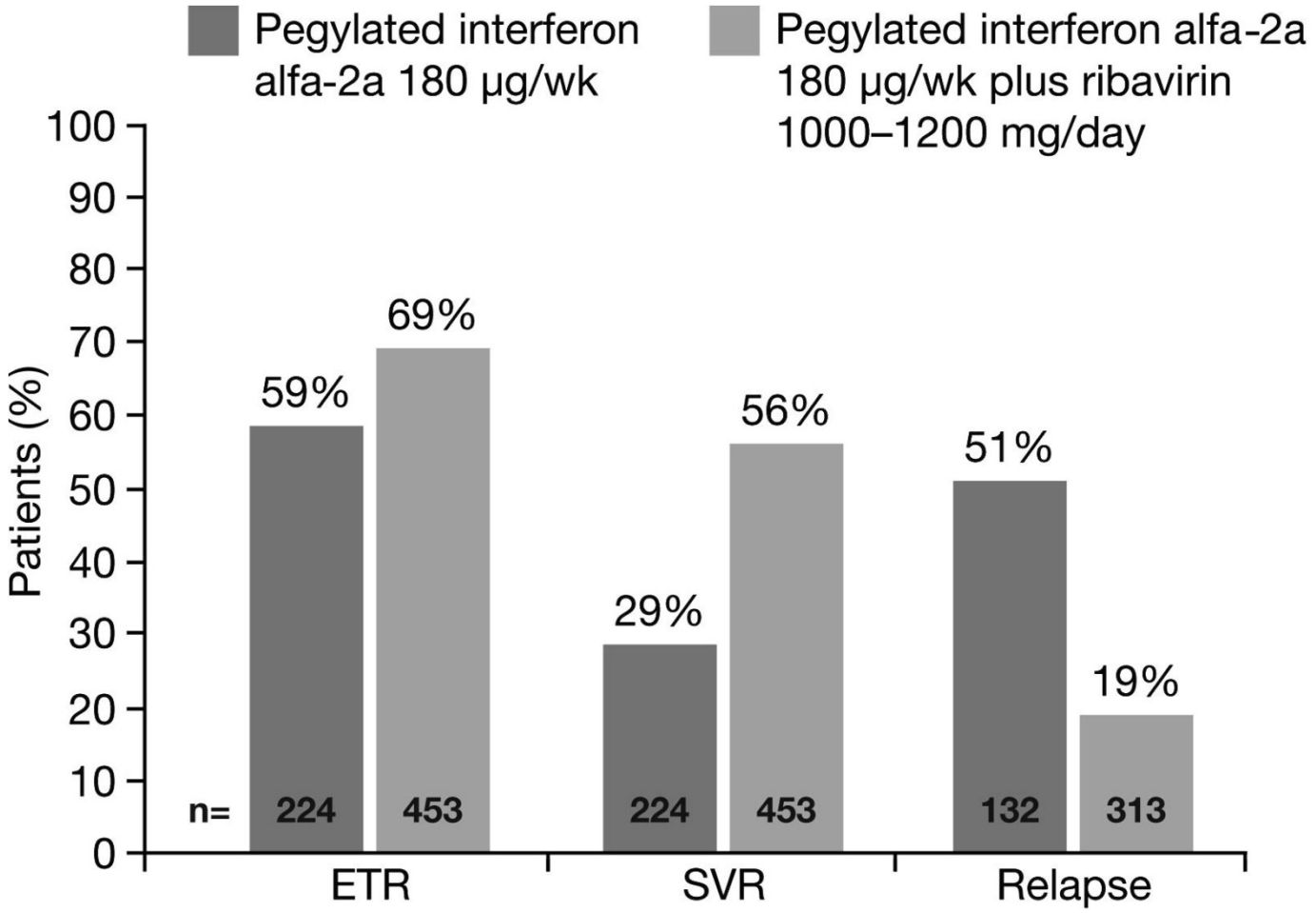


Pawlotsky J-M. Gastroenterology 2004:126:703

Consistent effect of RBV on HCV RNA response with IFN

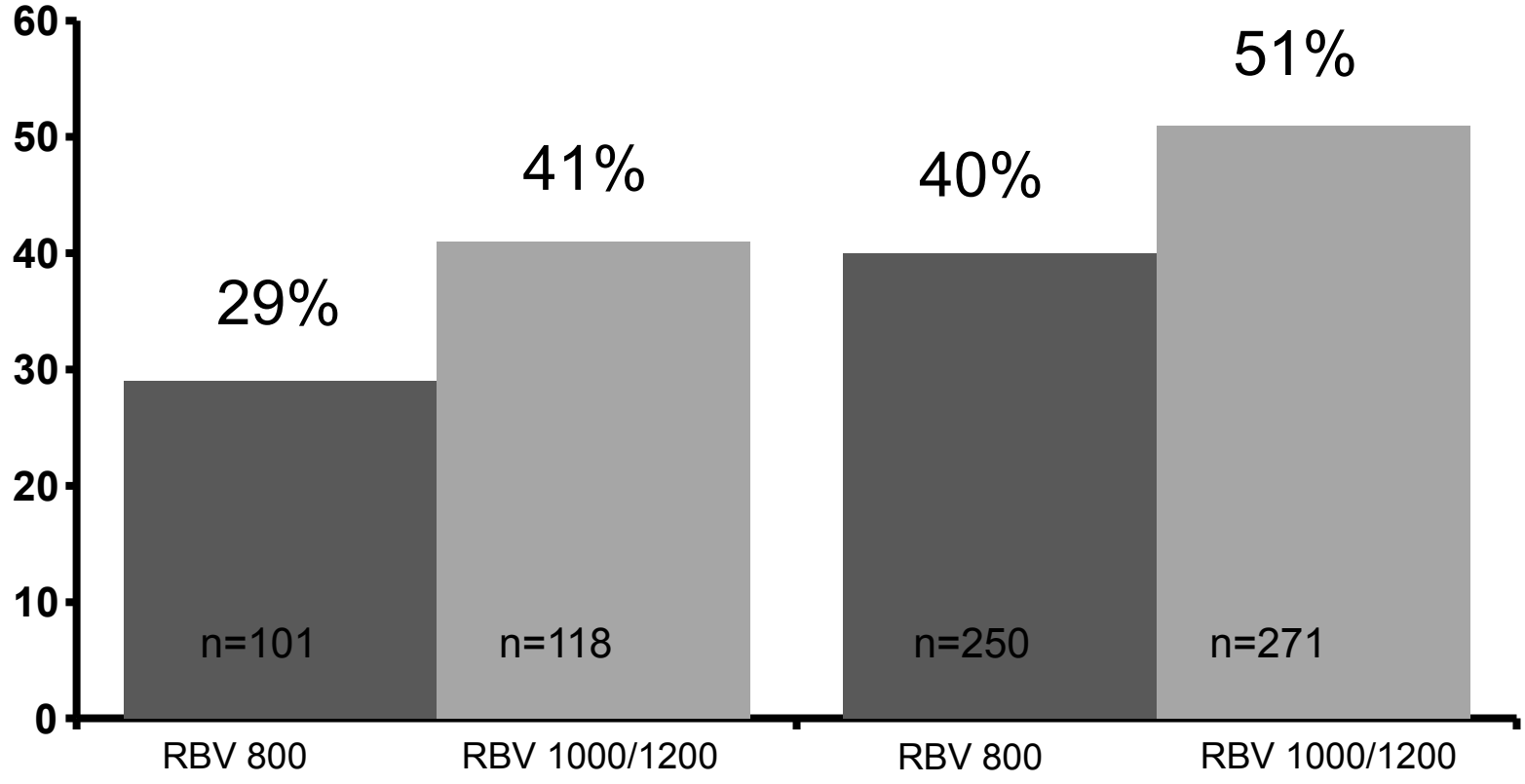
Study	Population	Regimen	Magnitude of RBV effect
McHutchison 1998	All	IFN alfa-2b	+ 25%
Poynard 1998	All	IFN alfa-2b	+ 24%
Fried 2002	All	PegIFN alfa-2a	+ 27%
Hadziyannis 2004	Geno 1	PegIFN alfa-2a 1000/1200 versus 800 mg/d	+ 11.9% with higher dose
R1626	Geno 1	PegIFN alfa-2a + R1626 1500 mg	+ 48% (week 4)
PROVE 2	Geno 1	PegIFN alfa-2a + TVR	+ 26% (12 weeks of therapy)
PROVE 3	Geno 1 Treatment experienced	PegINF alfa-2a + TVR	+ 31% (24 weeks of therapy

RBV increases EOT response and reduces viral relapse



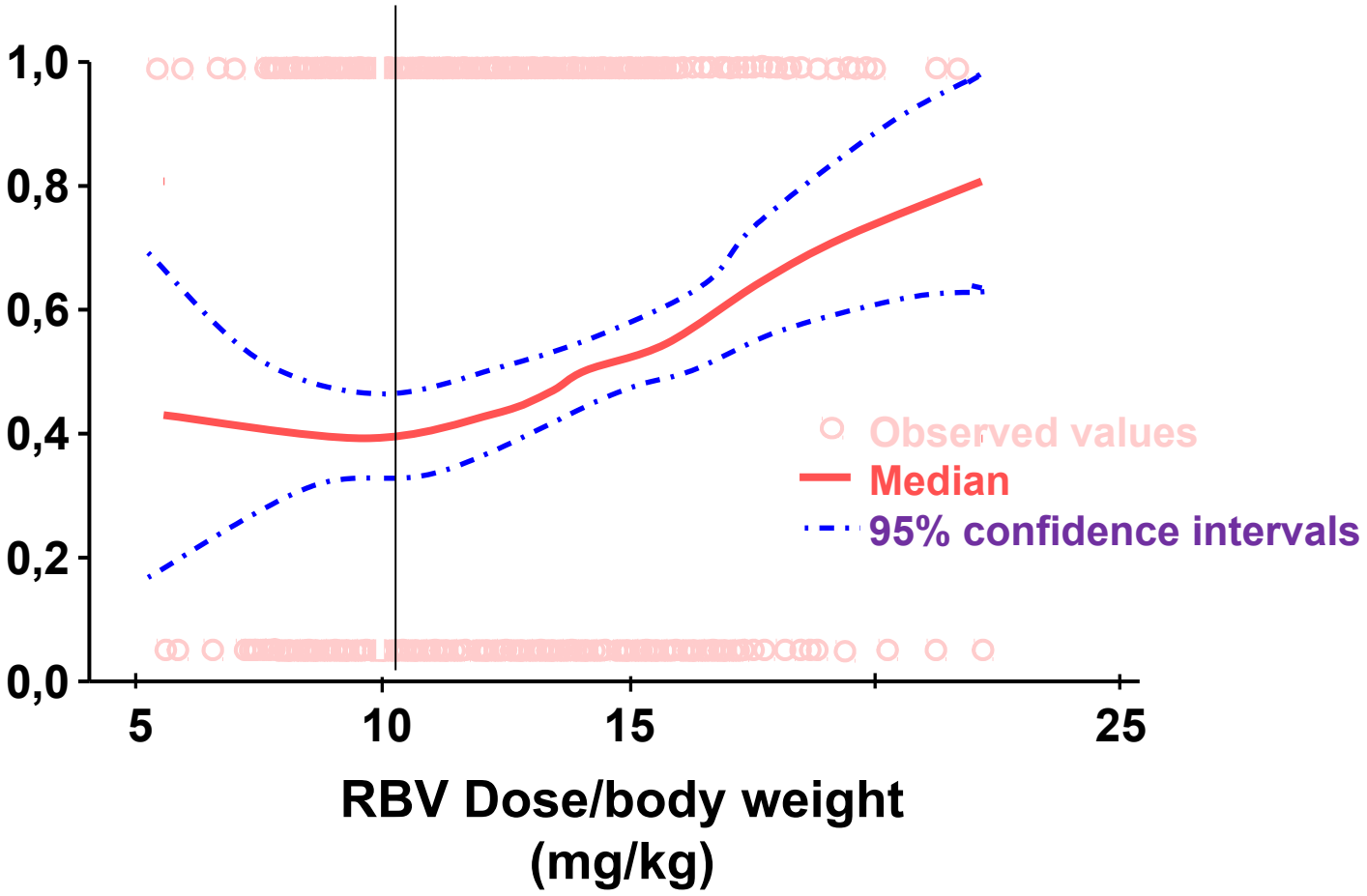
Fried et al. NEJM 2002

RBV dose and genotype 1



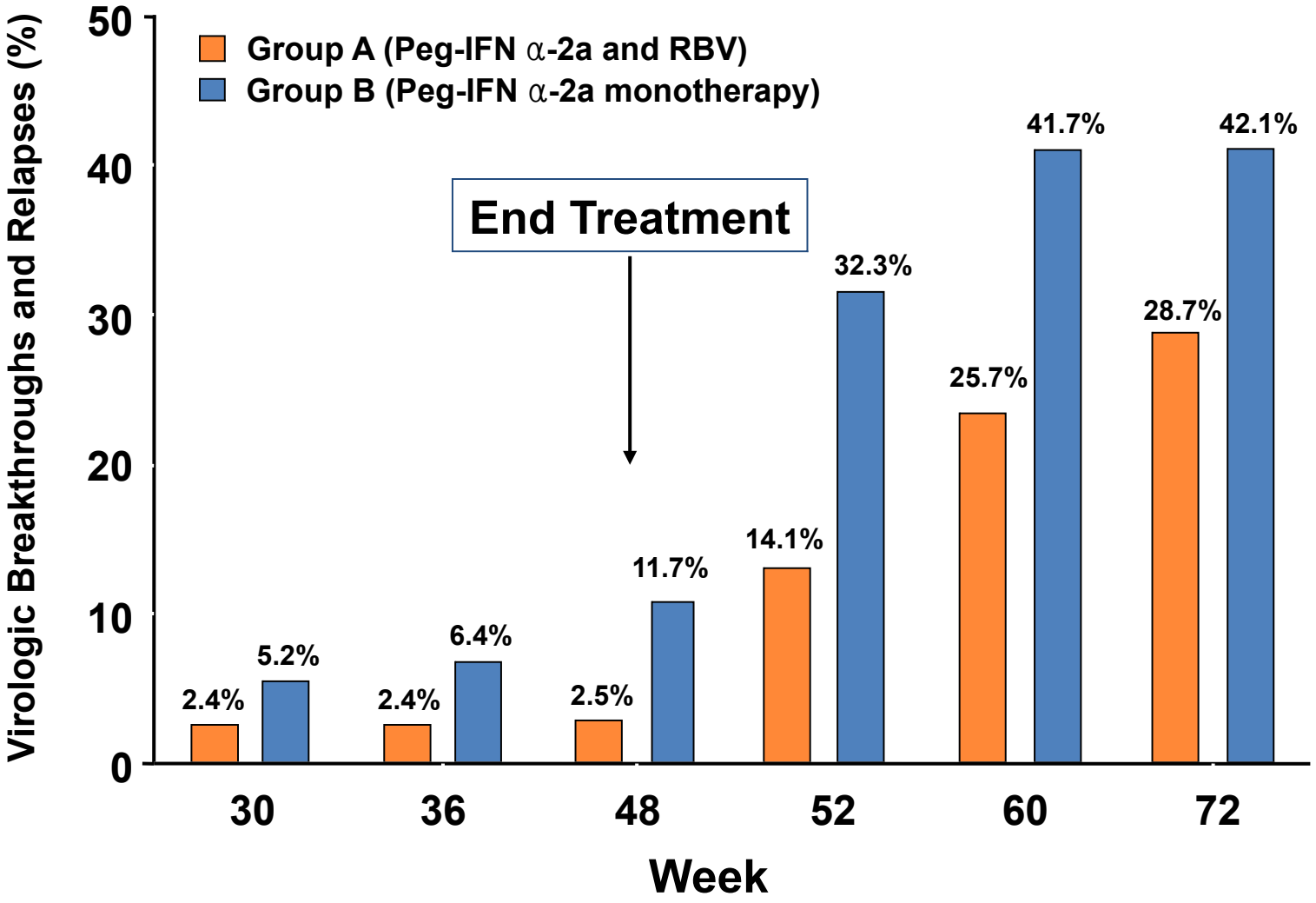
Hadziyannis et al. Ann Intern Med 2004

Dose response relationship with PegIFN α-2a and RBV: Genotype 1



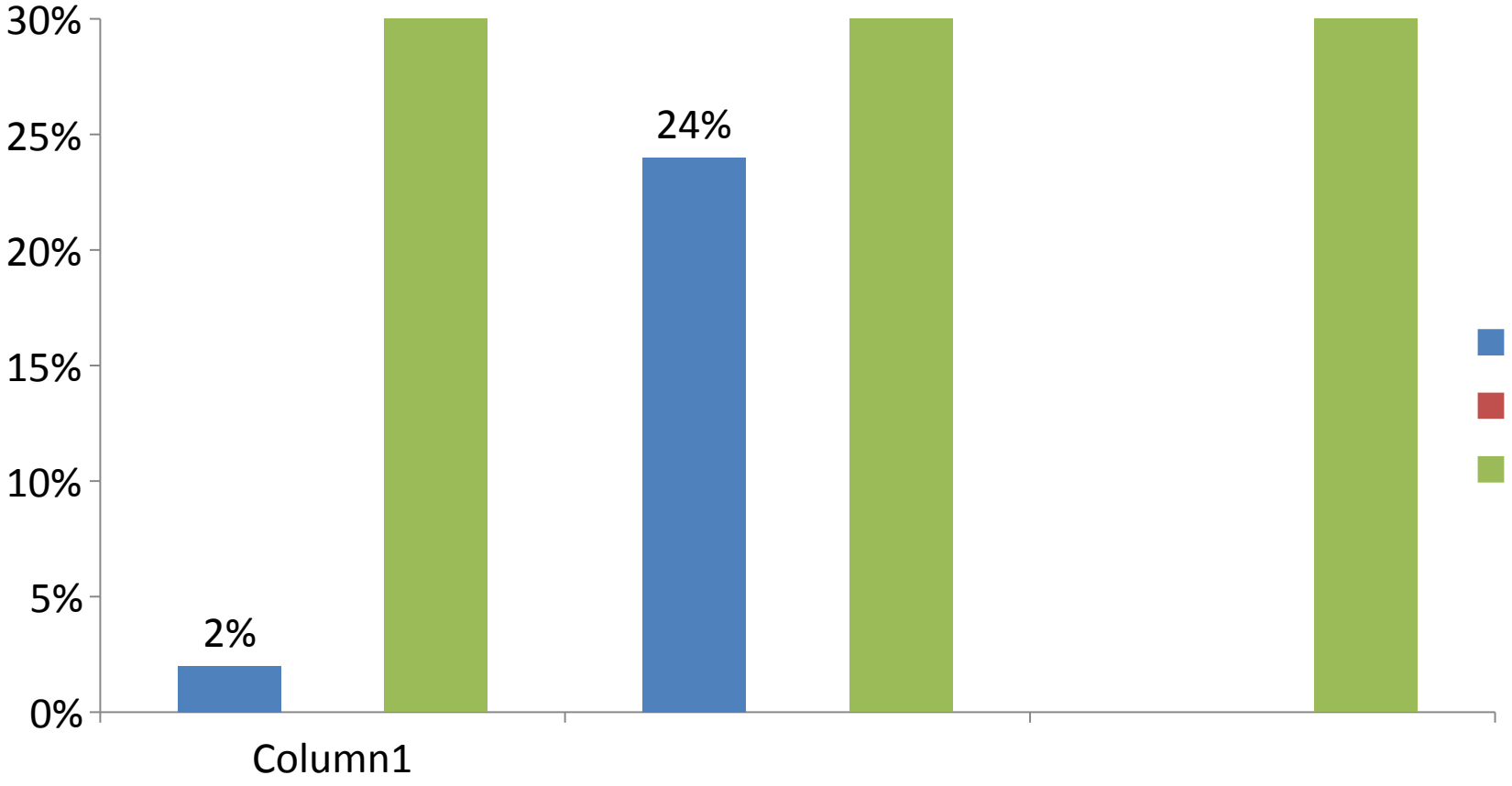
Snoeck E et al. *Br J Clin Pharmacol*. 2006:62:699-709.

Effect of Discontinuing RBV in Patients Responding to Therapy: Virologic Breakthroughs and Relapses

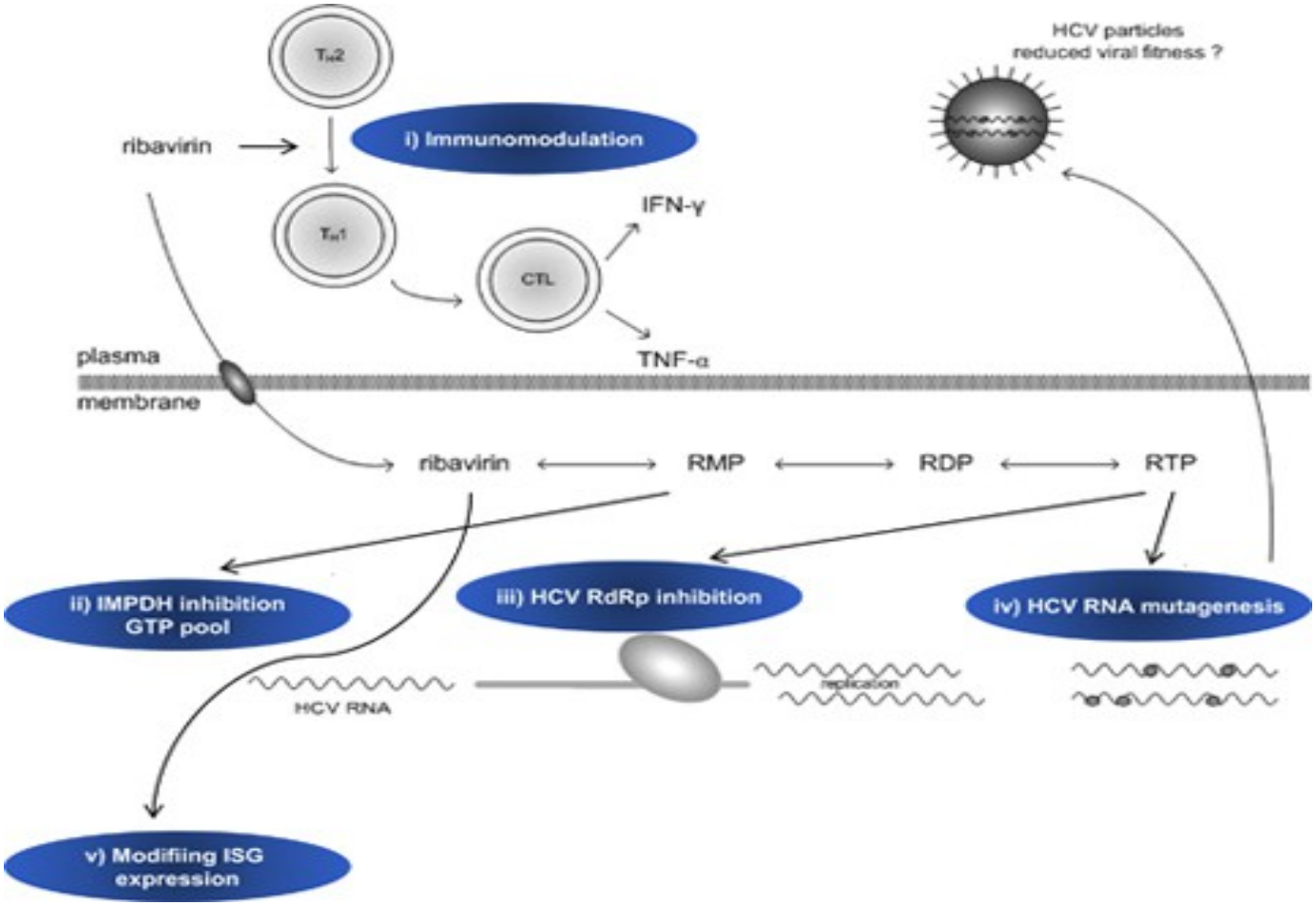


Bronowicki JP et al. *Gastroenterology*. 2006;131:1040-1048.

PROVE-2: RBV significantly reduces selection of Telaprevir resistant HCV variants



Proposed RBV mechanism of action

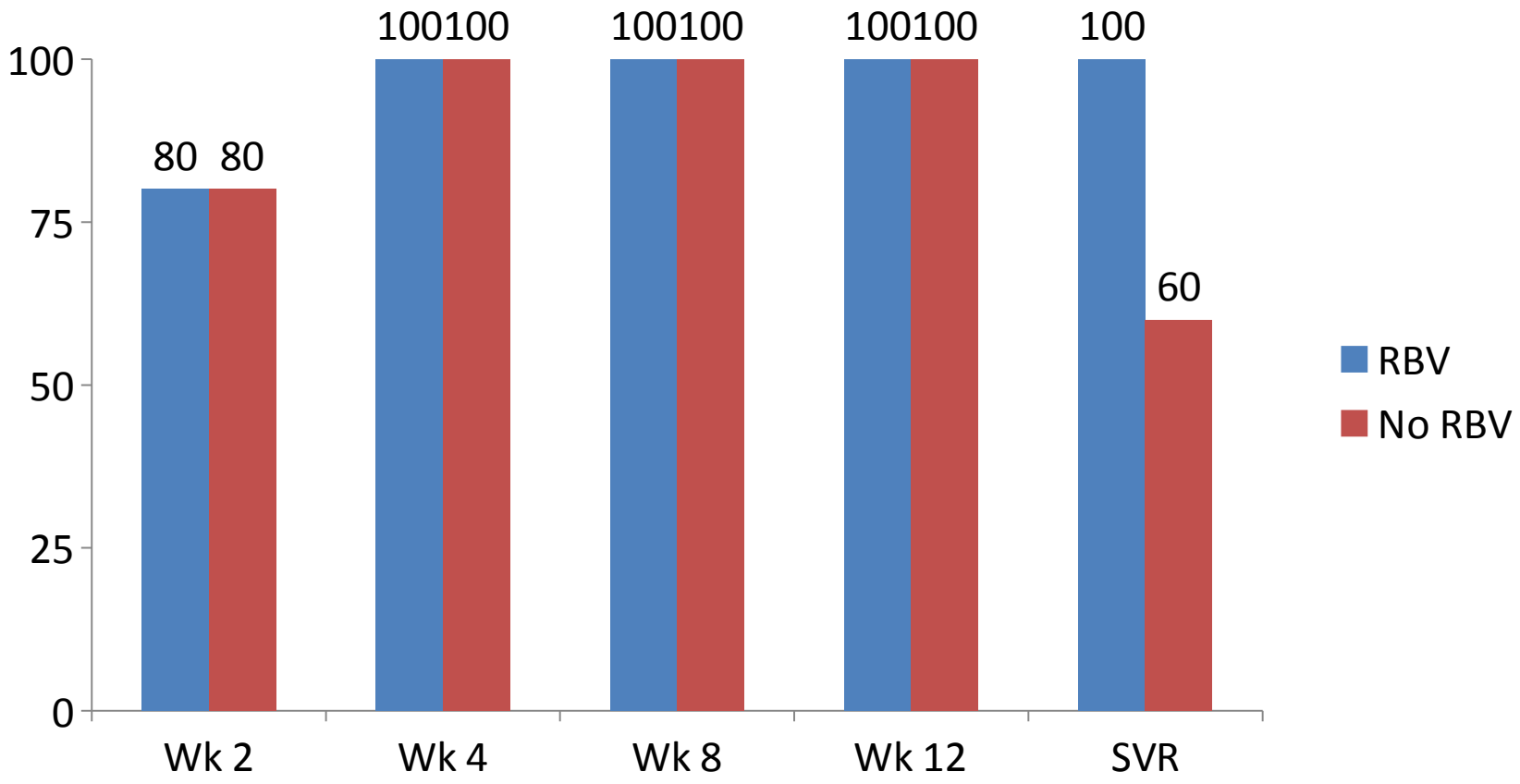


Hofmann, Herrmann, Sarrazin, Zeuzem et al. Liver International 2008

"If the lack of effect of RBV could be shown for combinations of effective small molecule HCV inhibitors, we can stop arguing about RBV's mode of action and simply remove it from future therapies"

- Perelson and Layden, Gastroenterology May 2007

ELECTRON: Sofosbuvir with or without RBV for genotype 2 or 3



Gane E et al. N Engl J Med 2013; 368:34-44

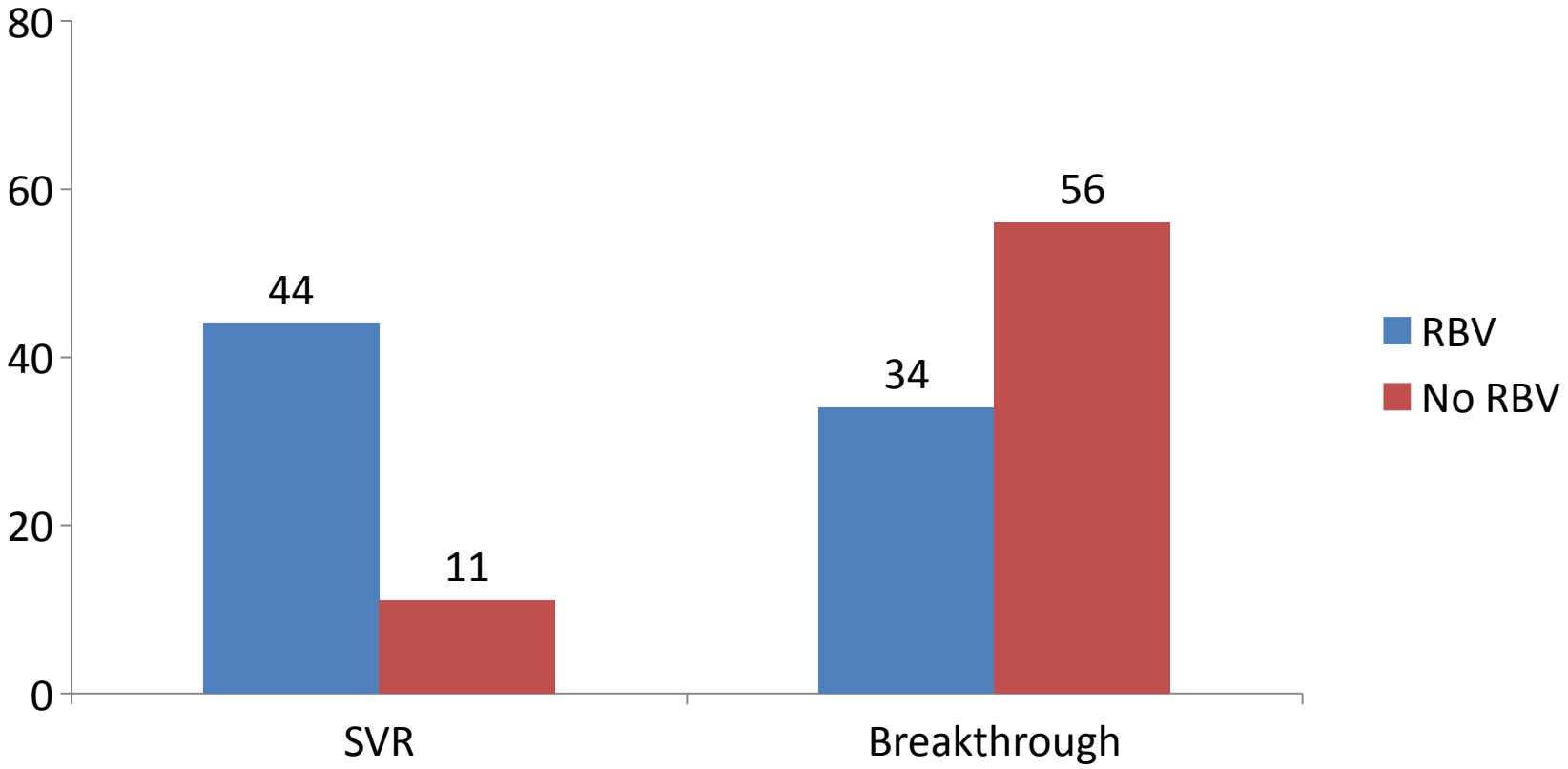
Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection: RBV exposure is associated with SVR

Table S8. Multivariate Logistic Regression in Assessing Factors Associated With SVR12 in SOF + RBV Patients in FISSION: Full Analysis Set

Variable	Odds Ratio	95% Confidence Limit	2-Sided *P* value
HCV genotype: 2 vs 3	42.486	(9.539, 189.239)	<0.0001
Cirrhosis: no vs yes	2.935	(1.377, 6.257)	0.005
Baseline HCV RNA: < vs ≥6 $\log_{10}$ IU/mL	2.325	(1.237, 4.368)	0.009
RBV exposure, mg/kg/d	1.258	(1.088, 1.455)	0.002

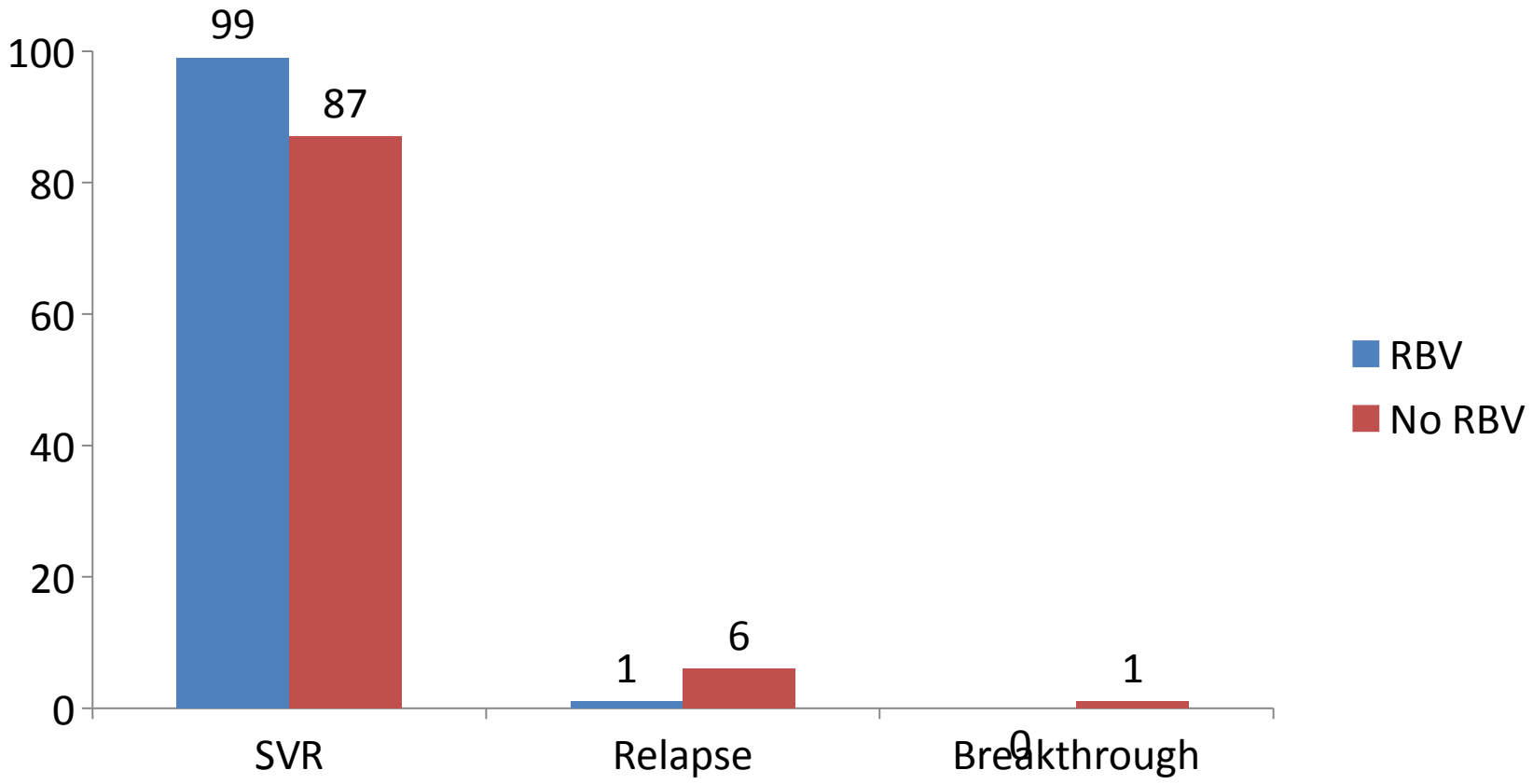
Lawitz et al. N Engl J Med 2013; 368:1878-1887

Faldaprevir and Deleobuvir for HCV Genotype 1a Infection: Role of RBV



Zeuzem S et al. N Engl J Med 2013; 369:630-639

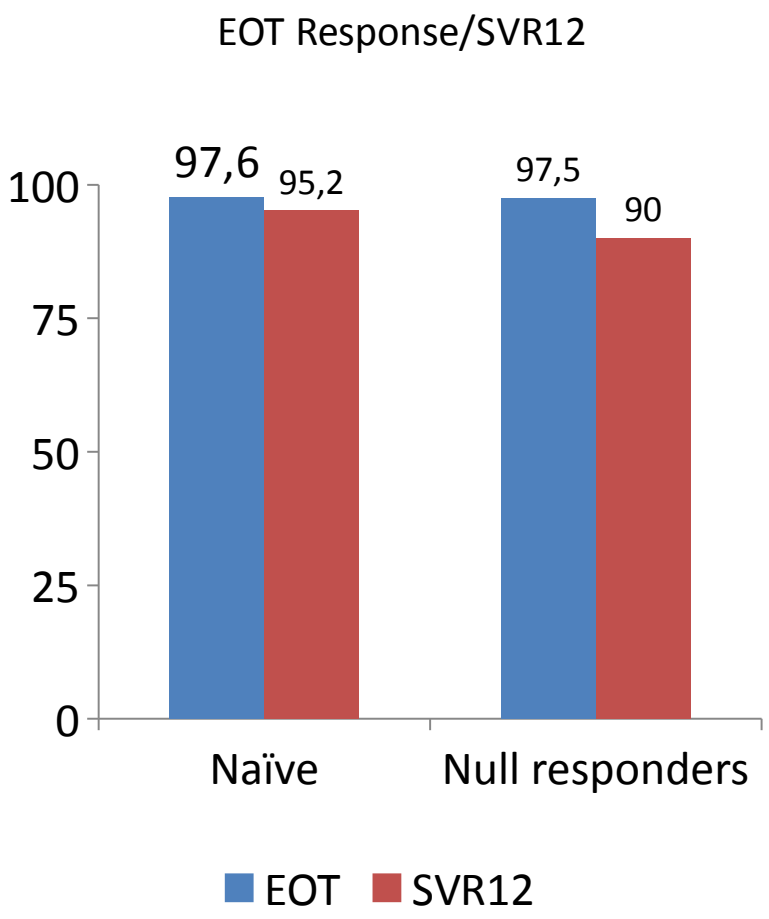
ABT450/r + ABT267 + ABT333 with or without RBV for 12 weeks



AVIATOR Study in press

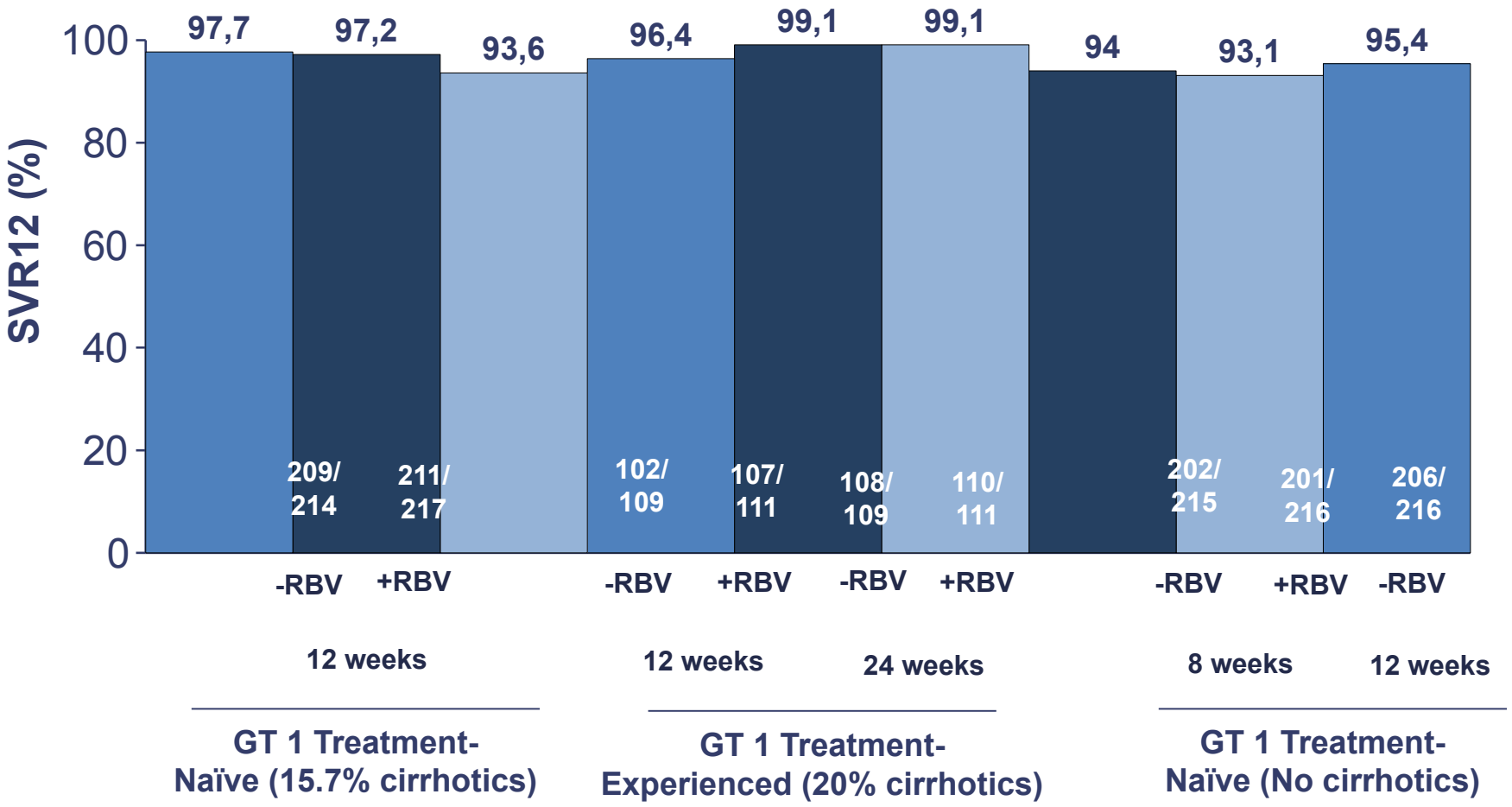
ABT-450/r + ABT-267 in genotype 1b-infected, treatment-naïve and null responders patients: PEARL-I

- ABT450/ritonavir/ABT267 x 12 weeks
  - No RBV or non-nucleoside polymerase inhibitor (ABT-333)
- Treatment naïve (n=42) and prior null responders (n=40); All < F4
- Non-SVR patients
  - Naïve: Lost to follow-up, n=2
  - Null responders: Failures, n=4
    - Viral breakthrough, n=1
    - Relapse, n=3
- No discontinuations due to AE
  - Drug interruption due to grade 3 ALT increase, n=1



Lawitz E et al. The Liver Meeting 2013; Abstract 75

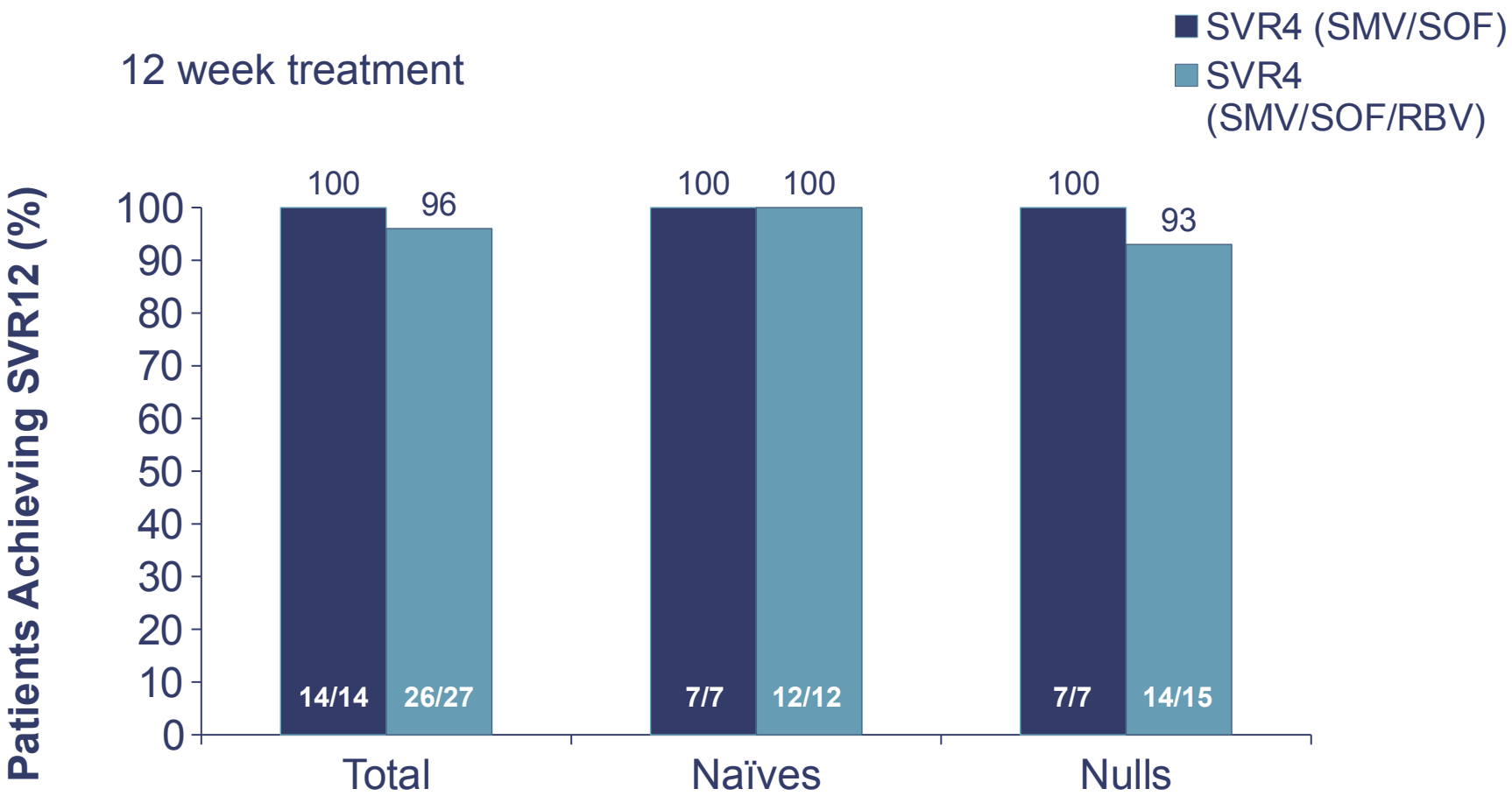
SOF/LDV FDC: SVR12 Results (ION-1, ION-2 and ION-3)



Gilead press release, December 18, 2013.

COSMOS: Simeprevir/Sofosbuvir for naive and prior null responders with METAVIR F3/4 (cohort 2)

Interim Analysis, SVR4



Jacobson IM, et al. Abstract #LB-3, AASLD 2013

Ribavirin in 2014 and beyond

Favor removal of RBV

- RBV is mutagenic and teratogenic
  - Use in third trimester to prevent mother to child transmission?
- Ribavirin is difficult to use in older patients and/or those with renal insufficiency
- No need to monitor CBC during therapy in RBV-free, IFN-free regimens

Favor inclusion of RBV

- May increase the SVR rate for some regimens and some HCV variants
- RBV cost is very low
- Anemia is mild in the absence of interferon alfa


Bring out yer Dead!
LotB:
I'm not dead yet!