NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Case 4: A 61-year-old man with HCV genotype 3 with cirrhosis

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Genotype 3 case

- 61-year-old man with HCV genotype 3
- Cirrhosis on biopsy in 2007
- FibroScan 17 kPa in 2013
- Partial responder to PEG-IFN and RBV (2006)
- cIFN + RBV 2010: HCV RNA 7,000 IU/mL at Week 12, discontinued
  - Very poor tolerability ("mental fog", visual changes, cough)
- Labs early 2014: **Albumin 3.0 gm/dL**
  AFP 15.2 ng/dL
  Platelets 72,000
  ALT 189 U/L, AST 171 U/L
  Alkaline phosphatase 98 U/L
  Total bilirubin 1.6 mg/dL
  Hemoglobin 13.8 gm/dL
- **MRI early 2014: small, nodular liver with spleen 16.6 cm; no HCC**
- **EGD moderate-sized varices, banded prophylactically**

How would you have managed this patient (early 2014)?

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

(1) No antiviral therapy

(2) PEG-IFN + RBV + sofosbuvir 12 weeks

(3) Sofosbuvir + RBV alone for 24 weeks

(4) Simeprevir + sofosbuvir 12 weeks

Course of recent therapy

- 1/15/14: Started sofosbuvir 400 mg and RBV 1200 mg
- 2/12/14 (week 4): TW4 HCV PCR 177 IU/mL, HgB 12.7
- 3/13/14 (week 8): TW 8 HCV PCR 18 IU/mL
- 3/27/2014 (week 10): HCV RNA not detected, PEG-IFN added to SOF + RBV
- 5/8/2014: TW16 HCV not detected
- 5/29/2014: TW 19 HCV RNA not detected, HgB 9.6
- 7/3/14: TW 24 HCV RNA not detected

What would you do now?

(1) Stop therapy and monitor HCV RNA

(2) Continue SOF + RBV for another 12-24 weeks

(3) Continue PEG-IFN + RBV + SOF for another 12 weeks

Post-therapy course

- Treatment was stopped after 24 weeks
- At follow-up week 4, HCV RNA 18,000 IU/mL (confirmed)

What would you do now? (Assuming unfettered access)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- No treatment, refer to transplant
- Retreat with SOF + RBV for 48 weeks
- Ledipasvir + SOF + RBV for 12 weeks
- Ledipasvir + SOF + RBV for 24 weeks
- Daclatasvir + SOF + RBV for 12 weeks
- Daclatasvir + SOF + RBV for 24 weeks
- ABT-450/r + ombitasvir + dasabuvir + RBV for 24 weeks

NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Considerations of Natural History of Genotype 3 HCV-Induced Liver Disease

HCV genotype 3 in the VA HCV Clinical Case Registry 2000-2009: Cirrhosis and HCC

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

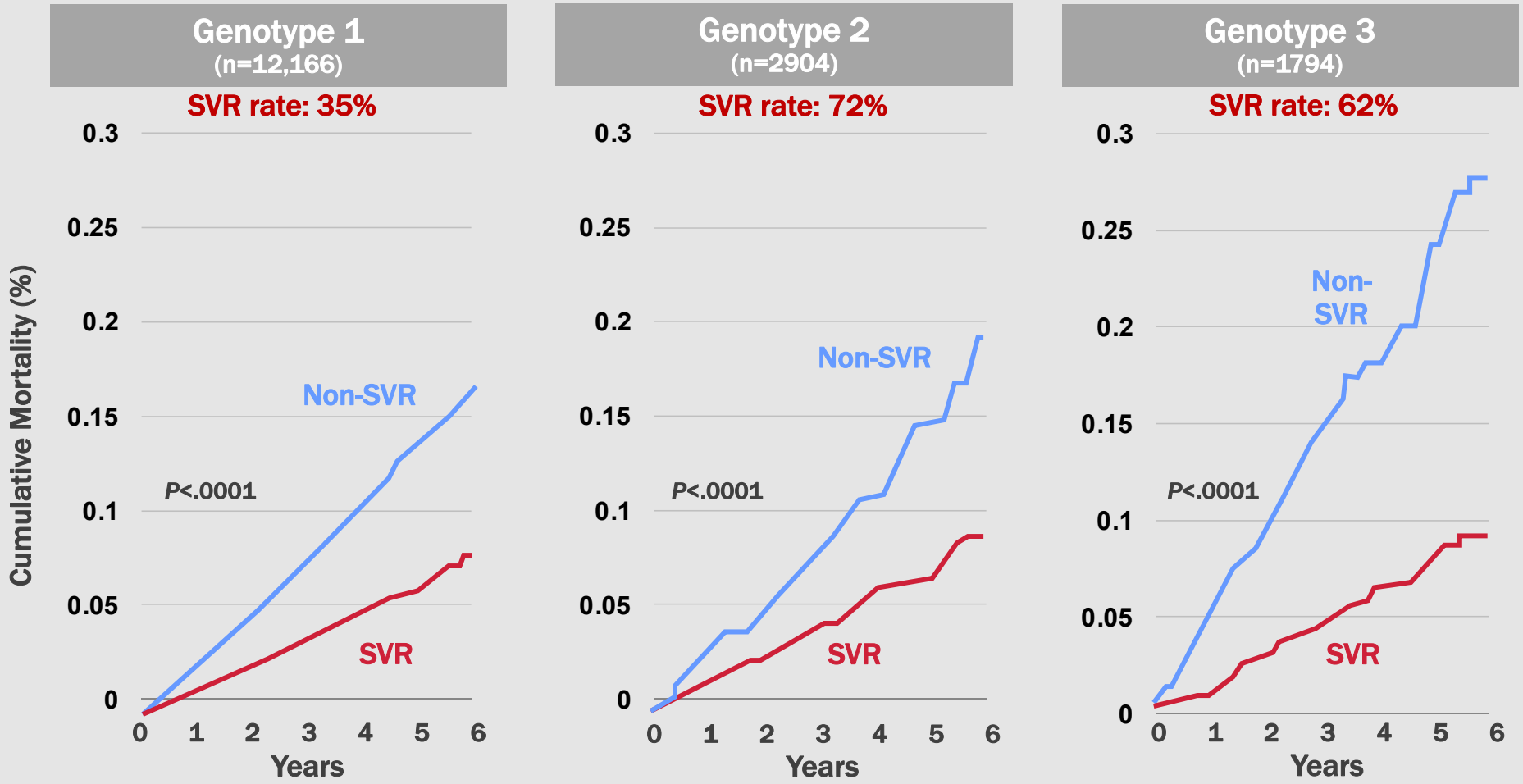
- 88,348 patients with genotype 1 (80%)
- 13,077 with genotype 2 (12%)
- 8,337 with genotype 3 (7.5%)
- Mean follow-up 5.4 years
- After adjustment for demographic, clinical, and antiviral treatment factors, comparison between genotypes 3 and 1:

	Hazard Ratio	Confidence Interval
Cirrhosis	1.31	1.22-1.39
HCC	1.80	1.61-2.03

Conclusion: Genotype 3 is associated with a significantly higher risk of cirrhosis and HCC vs genotype 1, independent of age, diabetes, BMI, or antiviral treatment

Kanwal F, et al. *Hepatology*. 2014;60:98-105

SVR reduced risk of all-cause mortality in a retrospective VA study



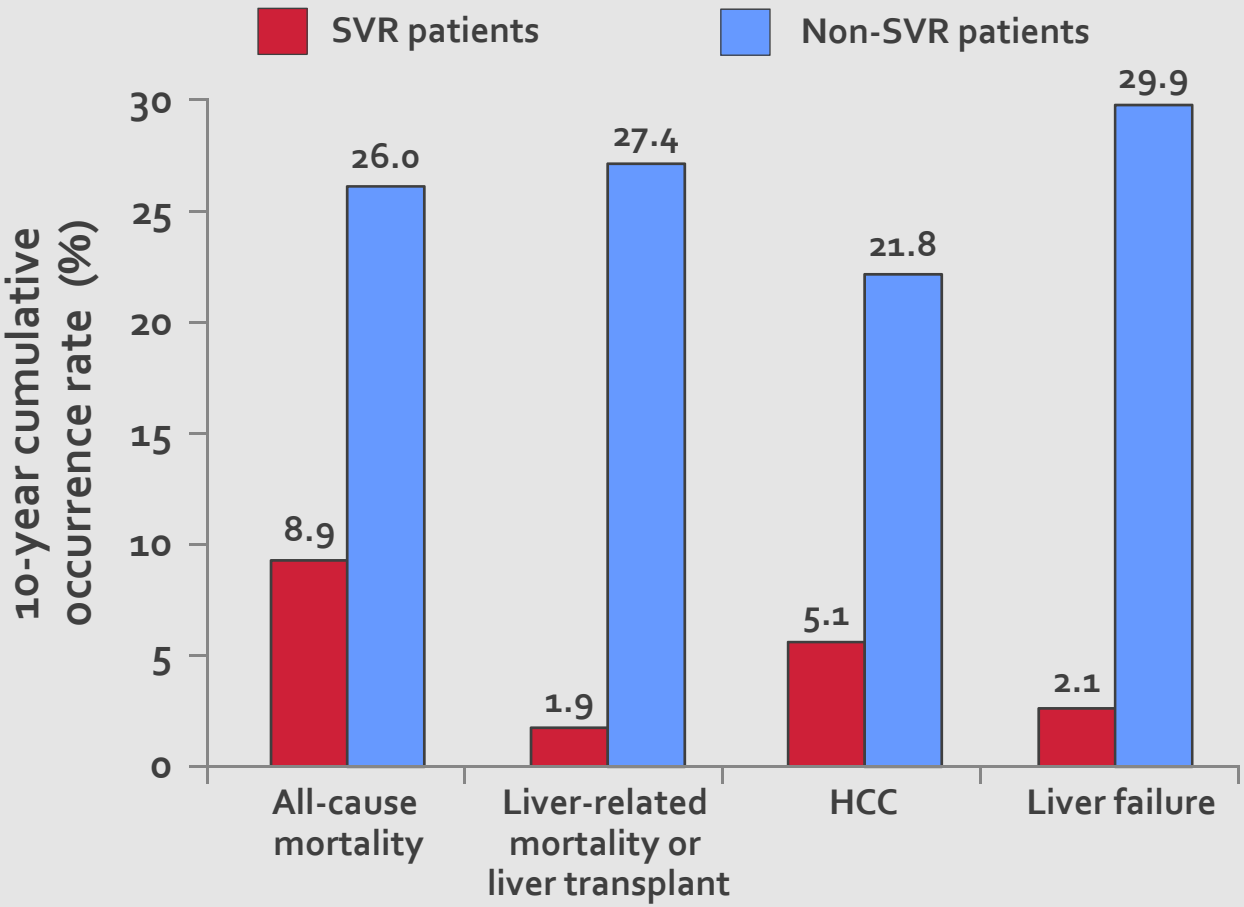
Retrospective analysis of veterans who received PEG-IFN + RBV at any VA medical facility (2001-2008). SVR=sustained virological response.

Backus LI, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516

SVR and all-cause mortality in CHC patients with advanced fibrosis

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

530 patients followed for a median of 8.4 years



- Baseline factors significantly associated with all-cause mortality:
  - Older age
  - **Genotype 3 (2-fold increase in mortality and HCC)**
  - Higher Ishak fibrosis score
  - Diabetes
  - Severe alcohol use

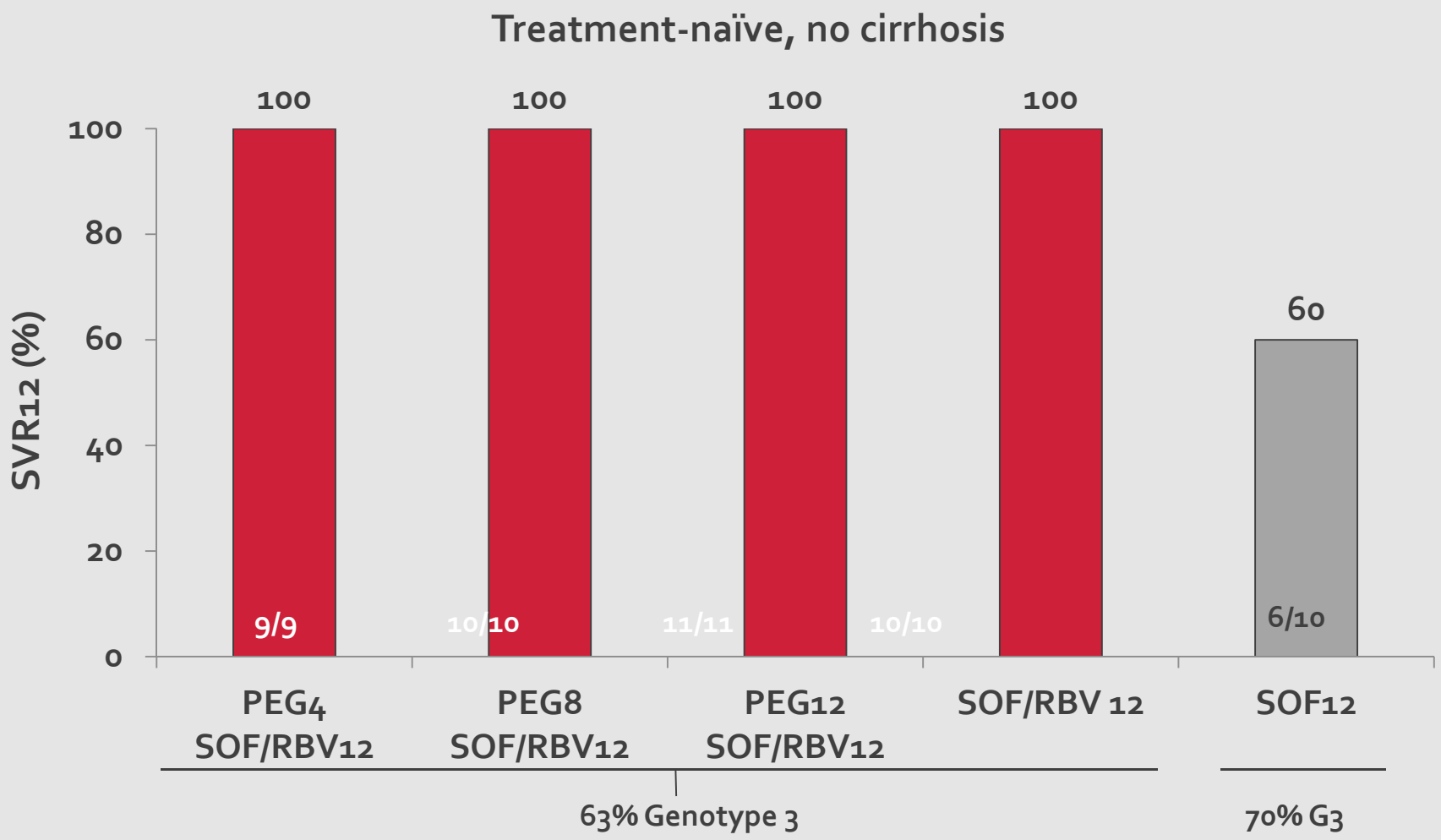
Van der Meer A, et al. *JAMA*. 2012;308:2584–2593

NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

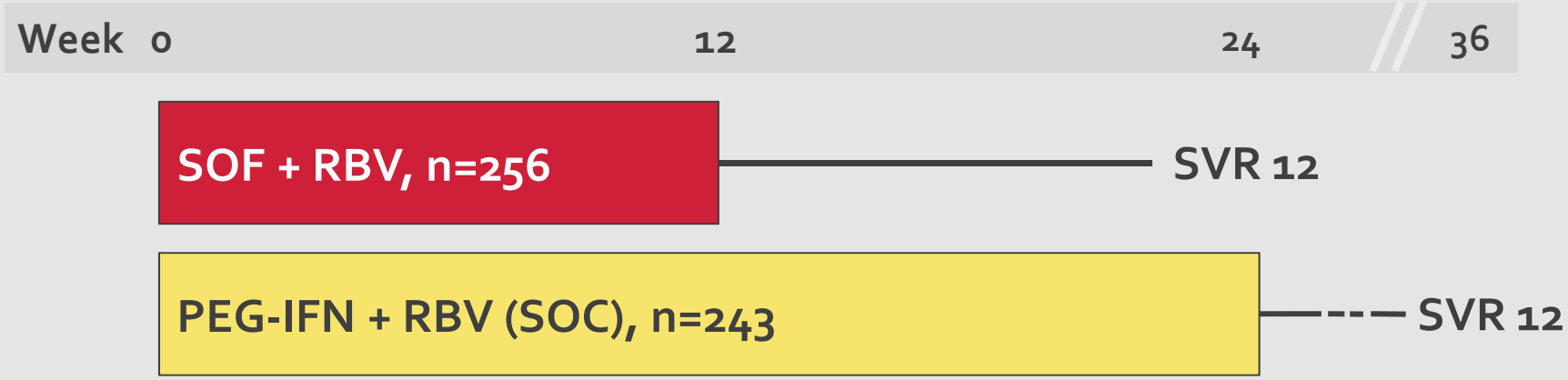
The Foundation for the Phase 3 Trials of Sofosbuvir + Ribavirin

ELECTRON: Sofosbuvir + RBV in HCV genotype 2 or 3 infection (n=50)



Gane EJ, et al. *N Engl J Med*. 2013;368:34-44

FISSION: Genotype 2, 3 treatment-naive

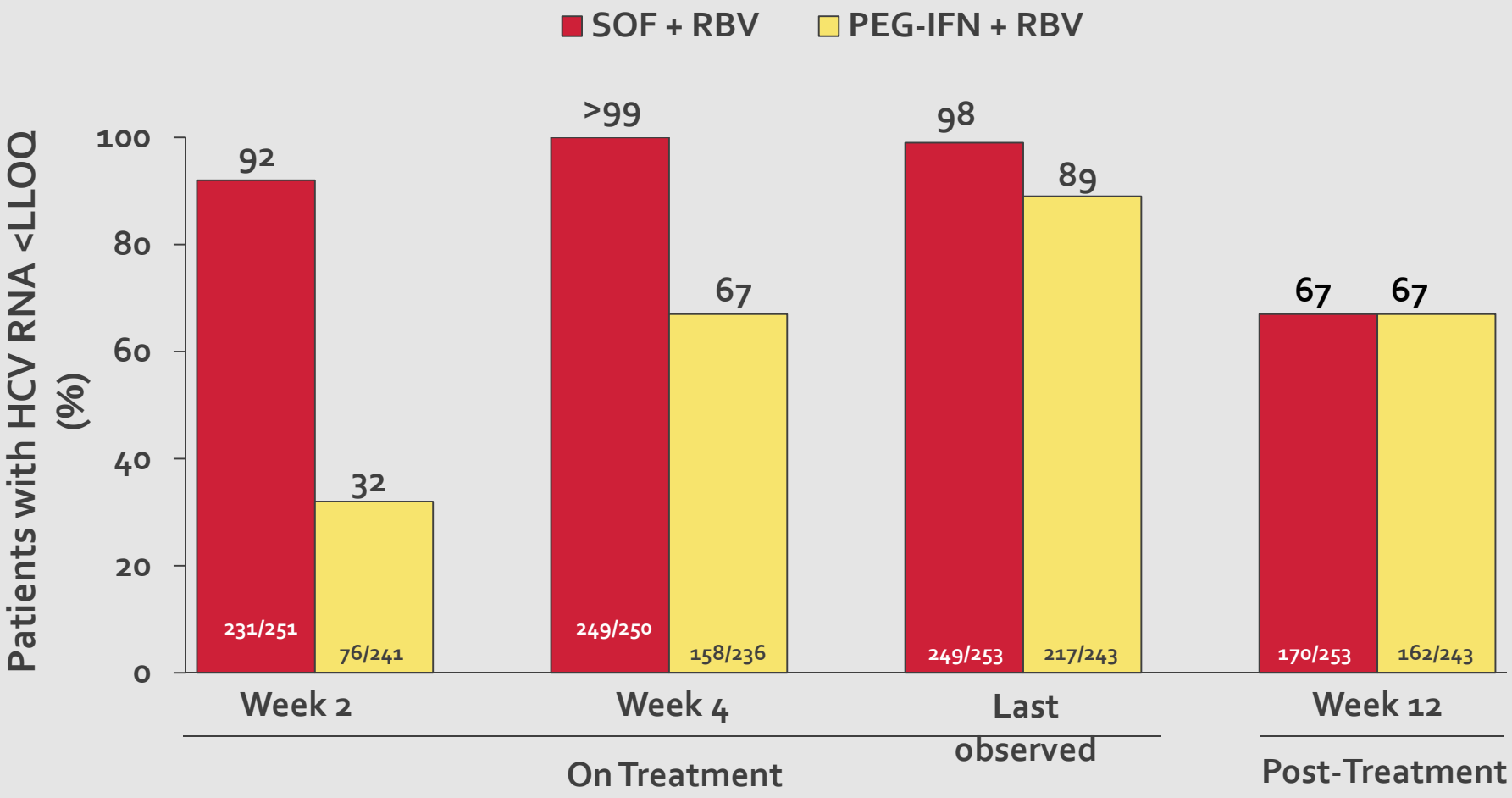


RBV dose 1000-1200 mg/day for SOF + RBV and 800 mg/day for PEG-IFN + RBV

- Targeted 3:1 enrollment of genotype 3:genotype 2 patients
- Expanded inclusion criteria
  - No upper limit to age or BMI
  - Opioid substitution permitted
  - Platelet count >75,000/mm^3 (cirrhotic)
- Randomization 1:1; stratified by genotype, HCV RNA, cirrhosis

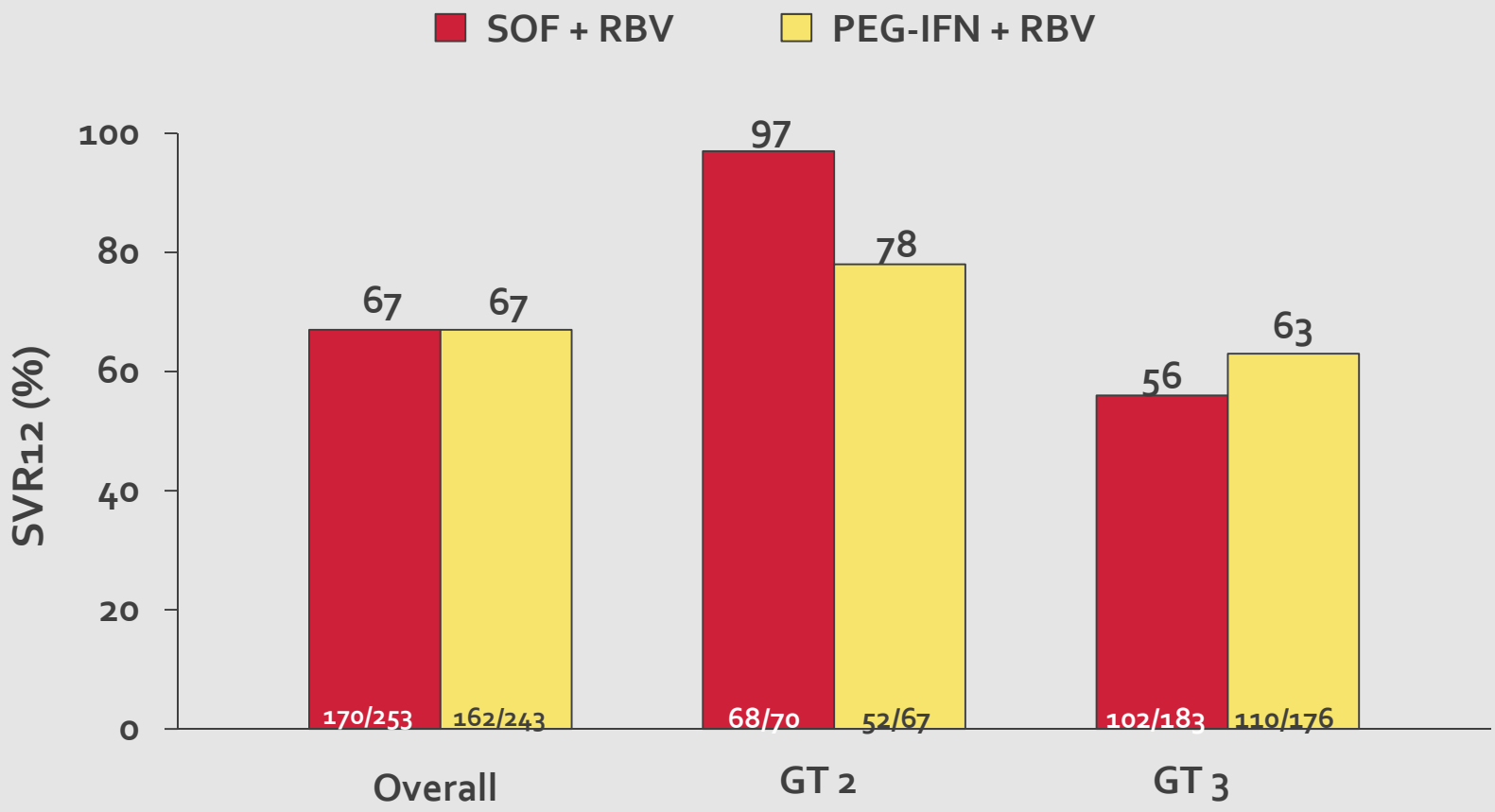
Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1887

FISSION: Virologic response



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

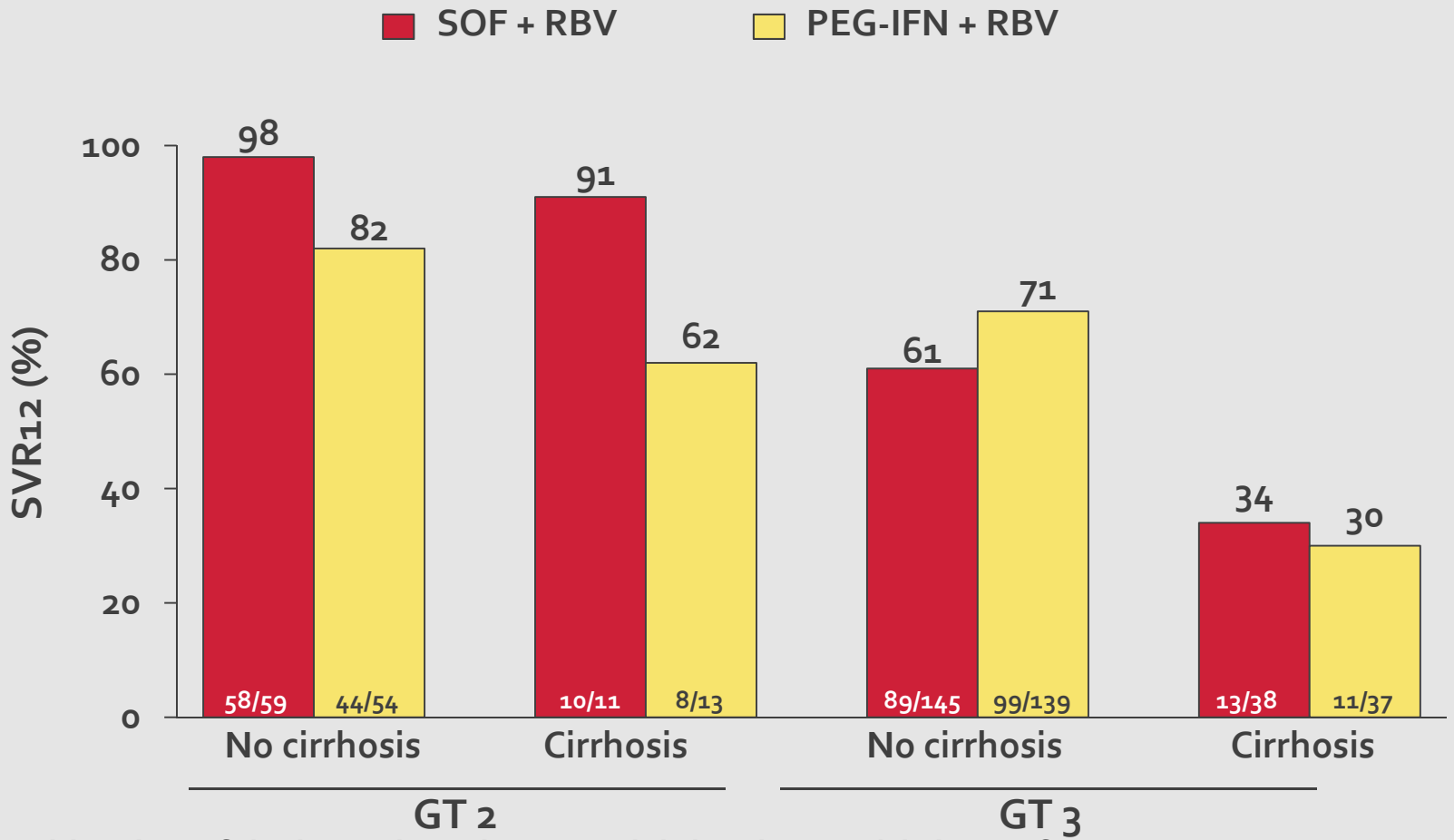
FISSION: SVR12 rates by HCV genotype



The combination of daclatasvir and asuneprivir has been withdrawn from FDA consideration, but the triple therapy regimen noted above is in trials.

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

FISSION: SVR12 rates by HCV genotype and cirrhosis status



The combination of daclatasvir and asuneprivir has been withdrawn from FDA consideration, but the triple therapy regimen noted above is in trials.

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

FISSION: Multivariate logistic regression

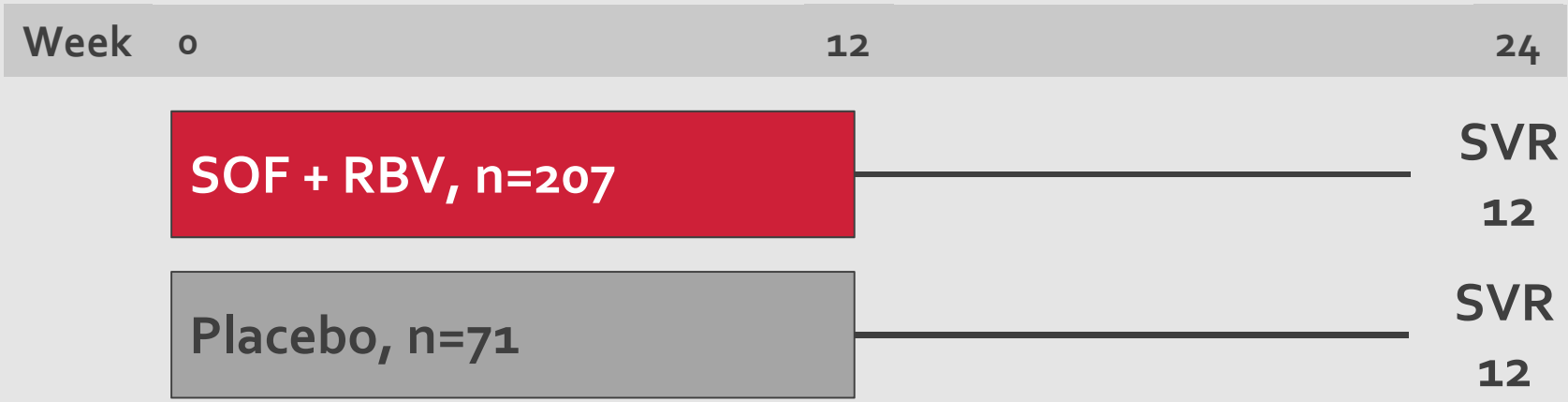
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Factors associated with SVR12 with SOF+RBV

Variable	Odds Ratio	*P* value
Genotype 2 vs 3	42.5	<0.0001
Cirrhosis: no vs yes	2.9	0.005
Baseline HCV RNA < vs ≥ 6 log	2.3	0.009
RBV exposure, mg/kg/day	1.3	0.002

Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1888

POSITRON: Genotype 2, 3 IFN-ineligible, intolerant, or unwilling

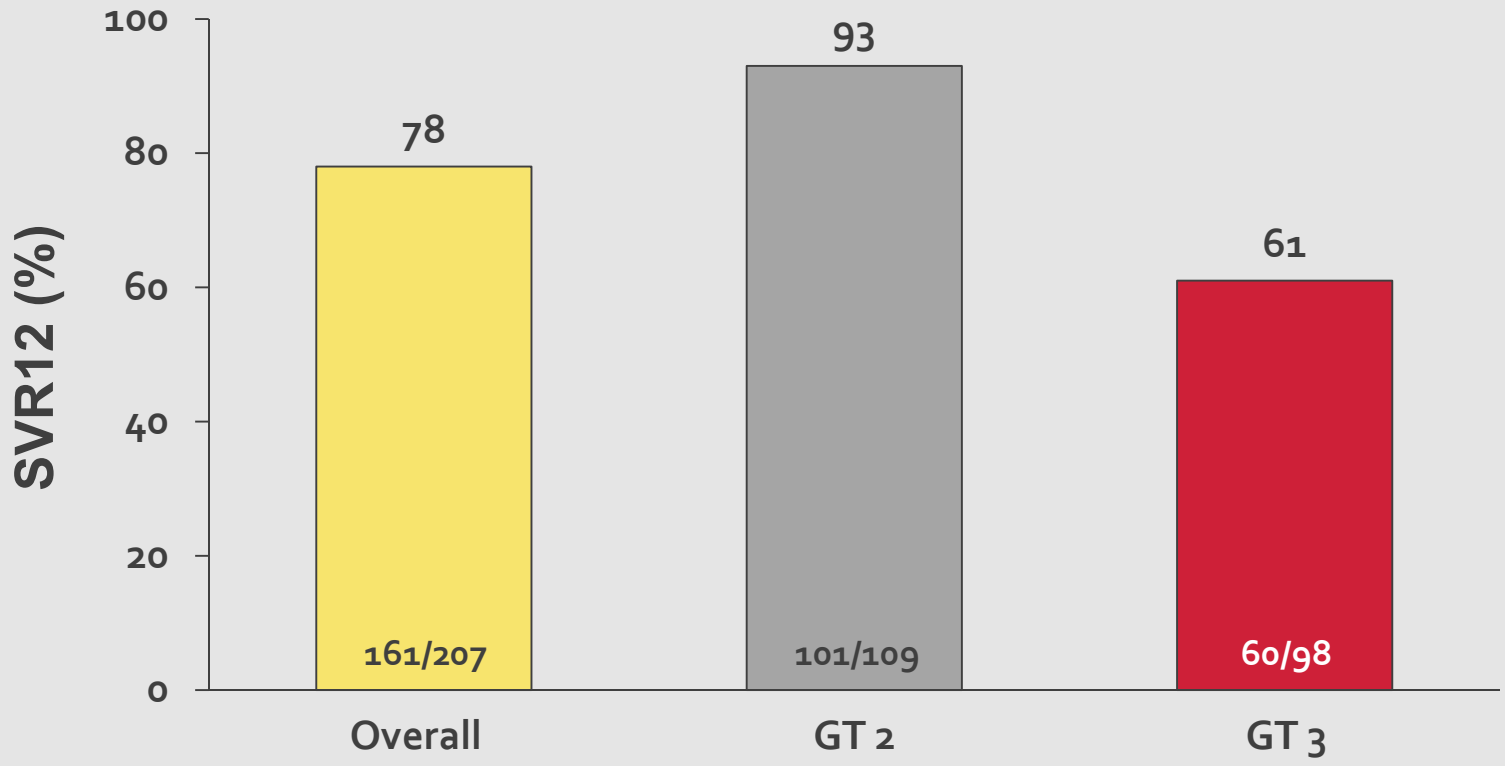


SOF dose: 400 mg once daily; RBV dose: 1000-1200 mg/day.

- Expanded inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper limit to age or BMI
  - No lower limit to platelets or neutrophils
- Stratified by presence or absence of cirrhosis

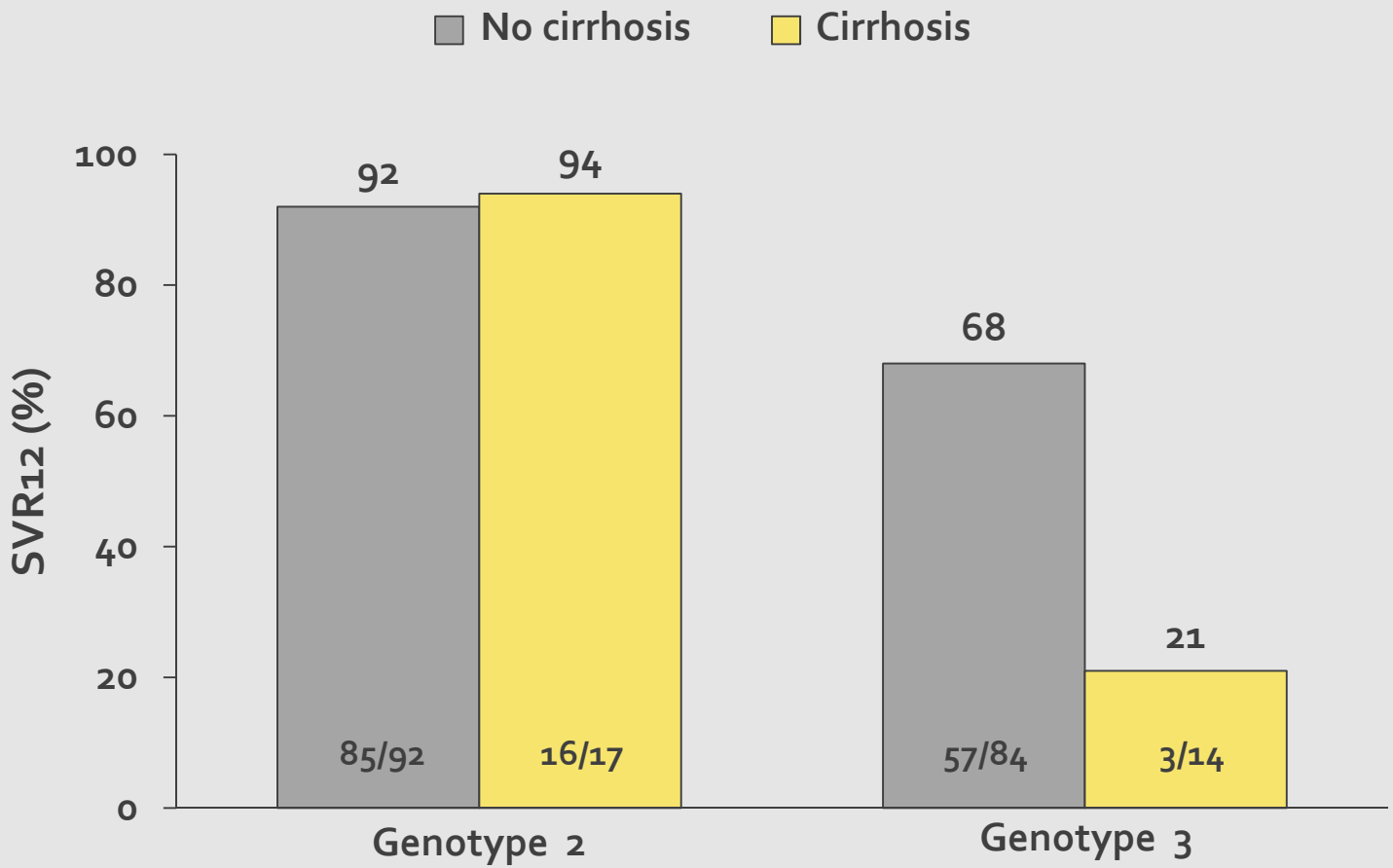
Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

POSITRON: SVR12 by HCV genotype



Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

POSITRON: SVR12 by cirrhosis status



Jacobson IM, et al. *N Engl J Med*. *2013;*368:1867-1877

Safety: Placebo vs SOF+RBV (POSITRON)

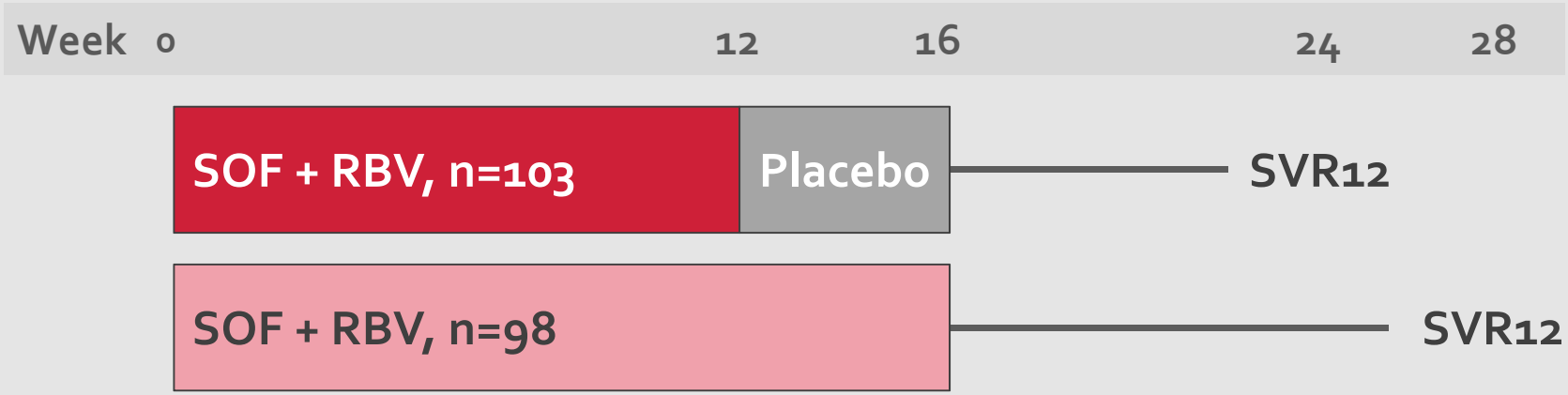
Patients	Placebo (N=71) %	SOF+RBV (N=207) %
Any adverse event	77	89
Grade ≥3 AE	1	8
Serious AE	3	5
Treatment D/C due to AE	4	2
Fatigue	24	44
Insomnia	4	19
Anemia	0	13
Hemoglobin < 10 gm/dL	0	7
Hemoglobin < 8.5 gm/dL	0	<1

AEs (>10%) SOF+RBV>PBO

AE profile of SOF reflects the AE profiles of the drugs with which it is given

Jacobson IM, et al. *NEJM.* 2013;368;1867-77

FUSION: Genotype 2, 3 with prior treatment failure

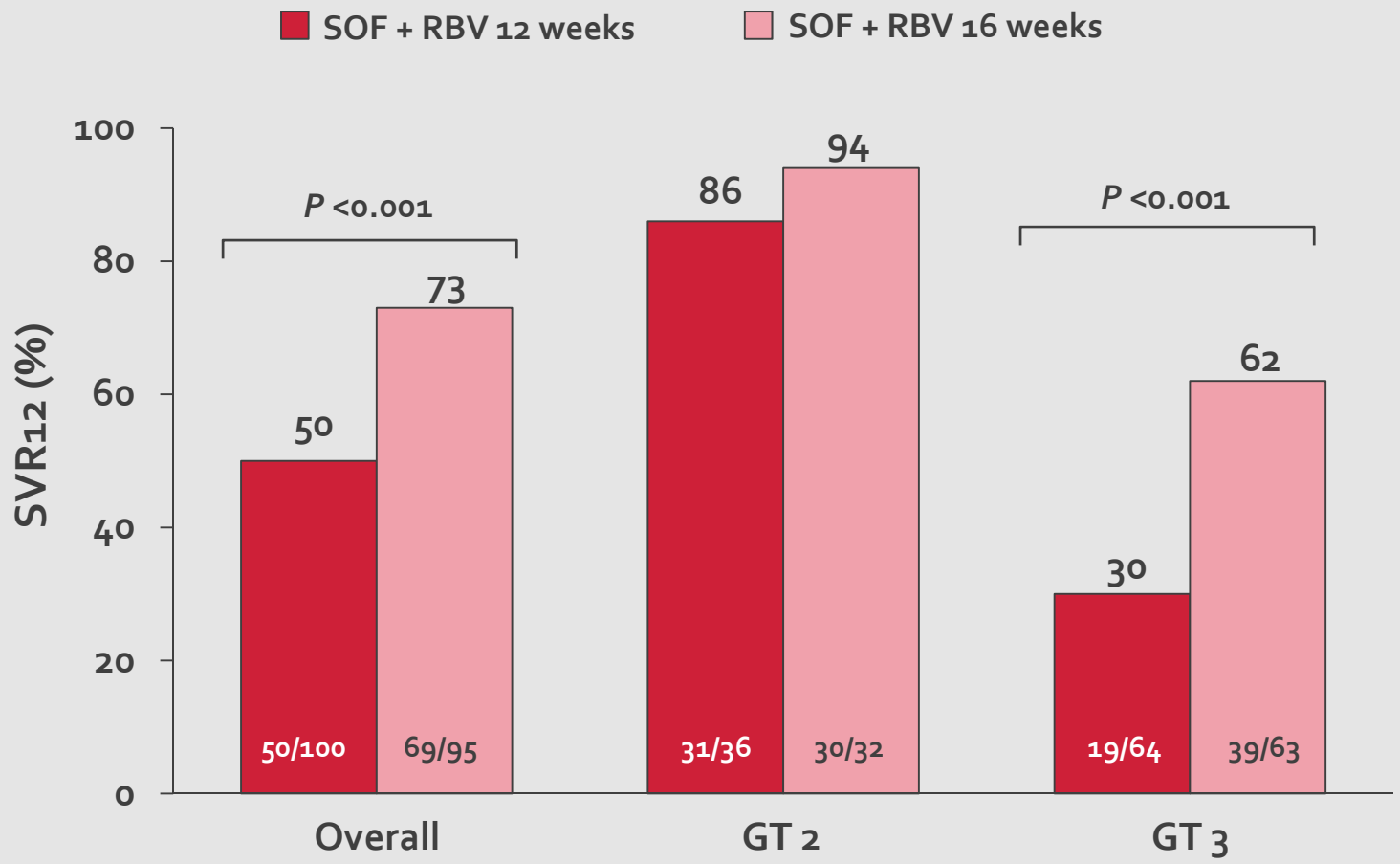


SOF dose 400 mg once daily; RBV dose 1000-1200 mg/day.

- Expanded inclusion criteria
  - Targeted 30% enrollment of patients with cirrhosis
  - No upper limit to age or BMI
  - Platelet count ≥50,000/mm^3, no neutrophil minimum
- Randomized (1:1), double-blind, placebo-controlled
- Stratified by cirrhosis and genotype

Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

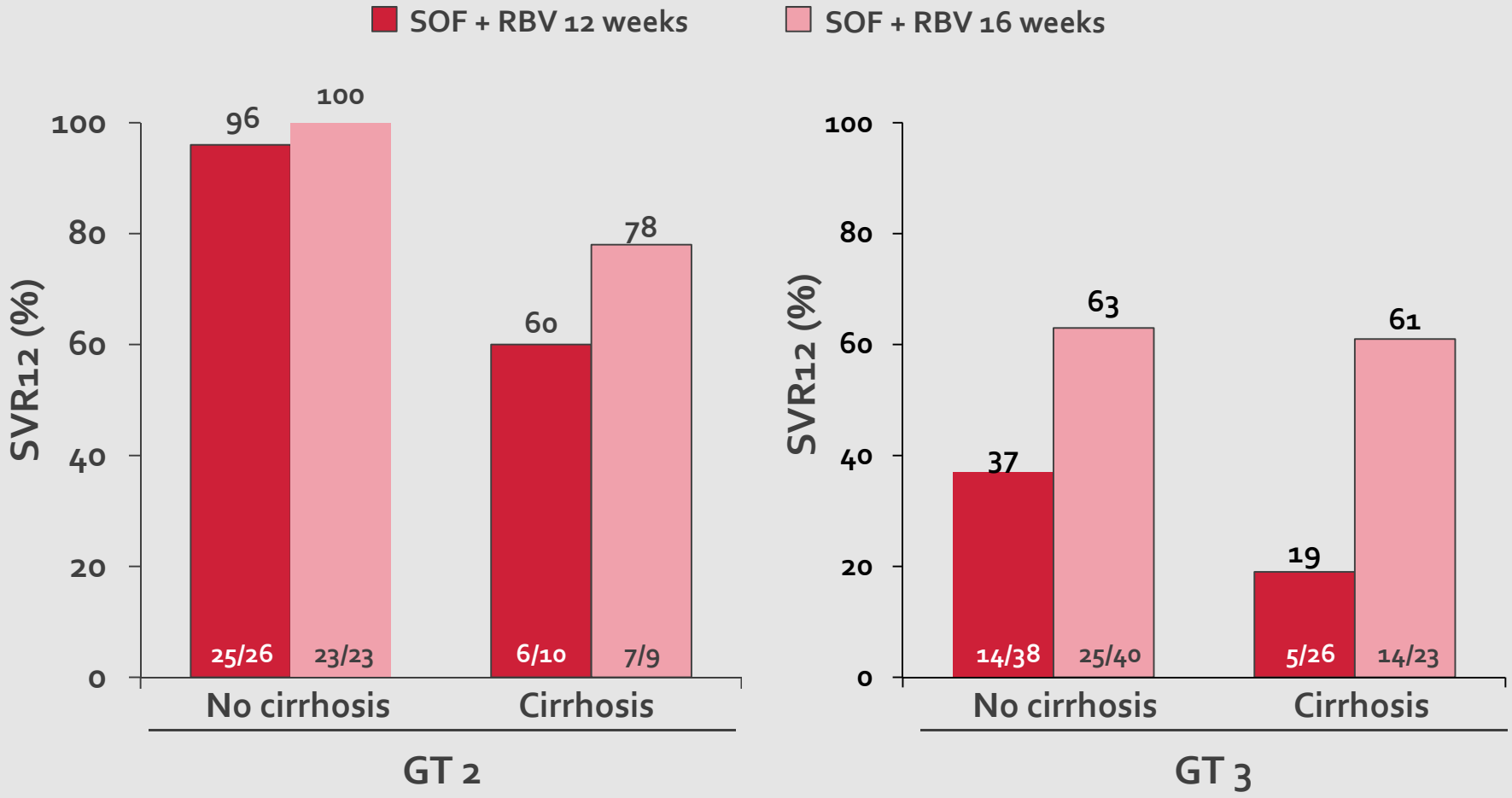
FUSION: SVR12 by HCV genotype



Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

FUSION results: SVR12 by HCV genotype and cirrhosis status

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

Error bars represent 95% confidence intervals.

FUSION: Multivariate logistic regression

Factors associated with SVR12 in FUSION

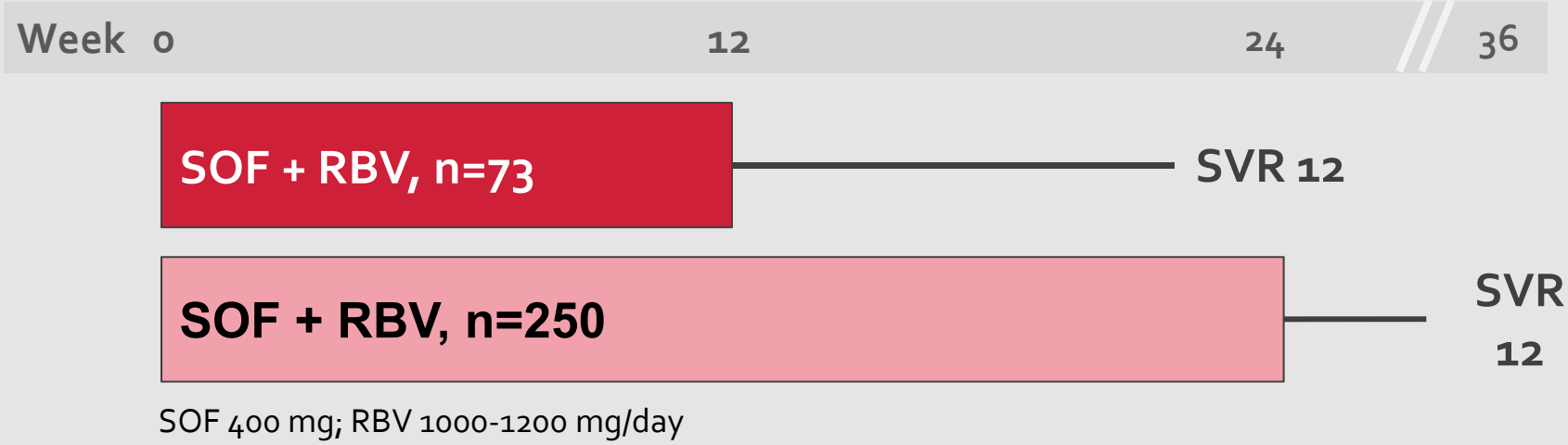
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

12 Weeks		
Variable	**Odds Ratio**	***P* value**
Genotype 2 vs 3	21.4	<0.0001
Baseline weight-based RBV dose	1.5	0.012
Cirrhosis: no vs yes	3.1	0.046

16 Weeks		
Variable	**Odds Ratio**	***P* value**
Genotype 2 vs 3	10.5	0.003
Sex: Female vs male	3.98	0.027

Jacobson IM, et al. *N Engl J Med. 2013;*368:1867-1877

VALENCE: Genotype 2, 3
Treatment-naïve and treatment-experienced



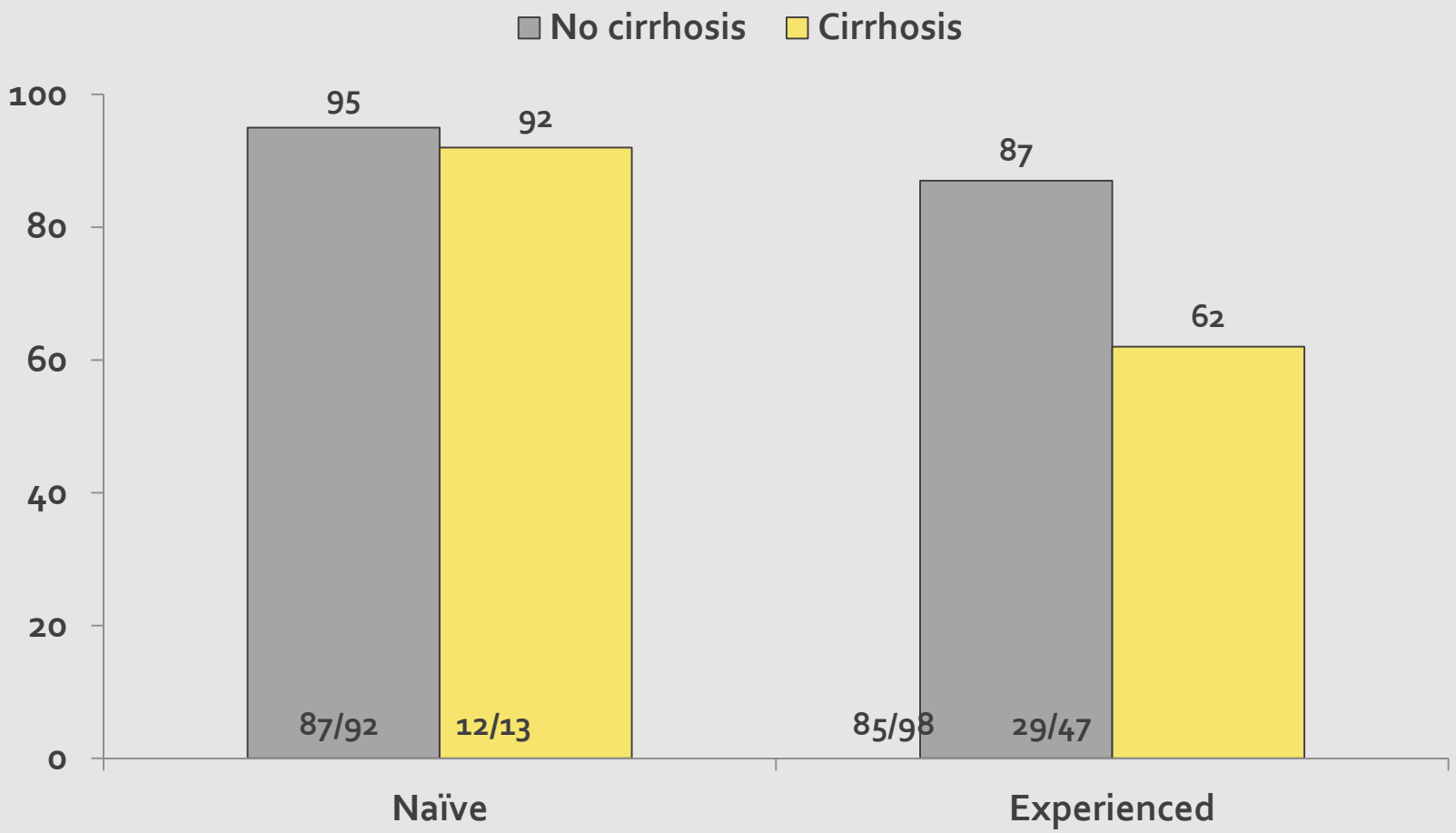
SOF 400 mg; RBV 1000-1200 mg/day

- Amended from initial protocol with 12 weeks of therapy for G3 naïve

Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001

Sofosbuvir + ribavirin for genotype 3

VALENCE: 24 weeks, n= 250



Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001

VALENCE: Multivariate logistic regression

Factors associated with SVR12 (genotype 3)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Variable	Odds Ratio	*P* value
Age < 50 vs ≥ 50	2.8	0.016
Sex: Female vs male	3.2	0.0183
Cirrhosis: no vs yes	2.9	0.005
Baseline HCV RNA < vs ≥ 6 log	2.3	0.009

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

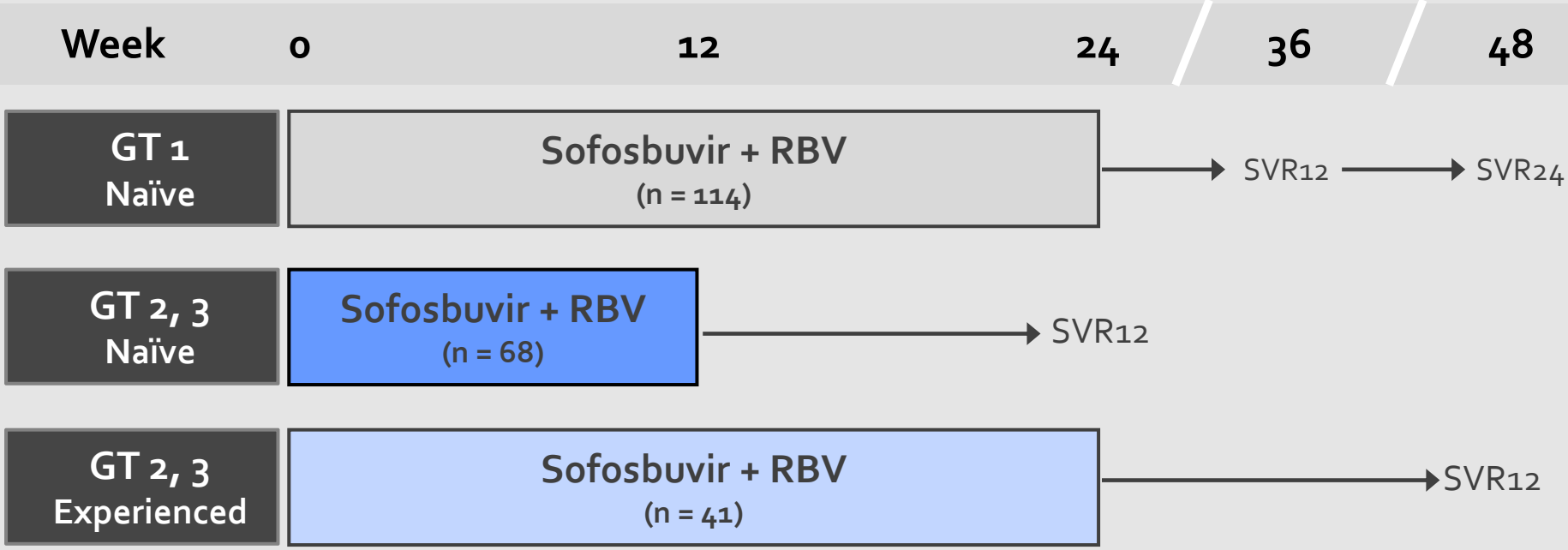
VALENCE: SVR12 by RBV dose reduction or interruption

RBV Dose Reduction or Interruption	Genotype 2	Genotype 3
Yes	6/6 (100%)	13/13 (100%)
No	62/67 (93%)	200/235 (85%)

No impact of RBV dose reduction on SVR.
Echoes similar theme from many other studies.

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

PHOTON-I: Study design (co-infected)

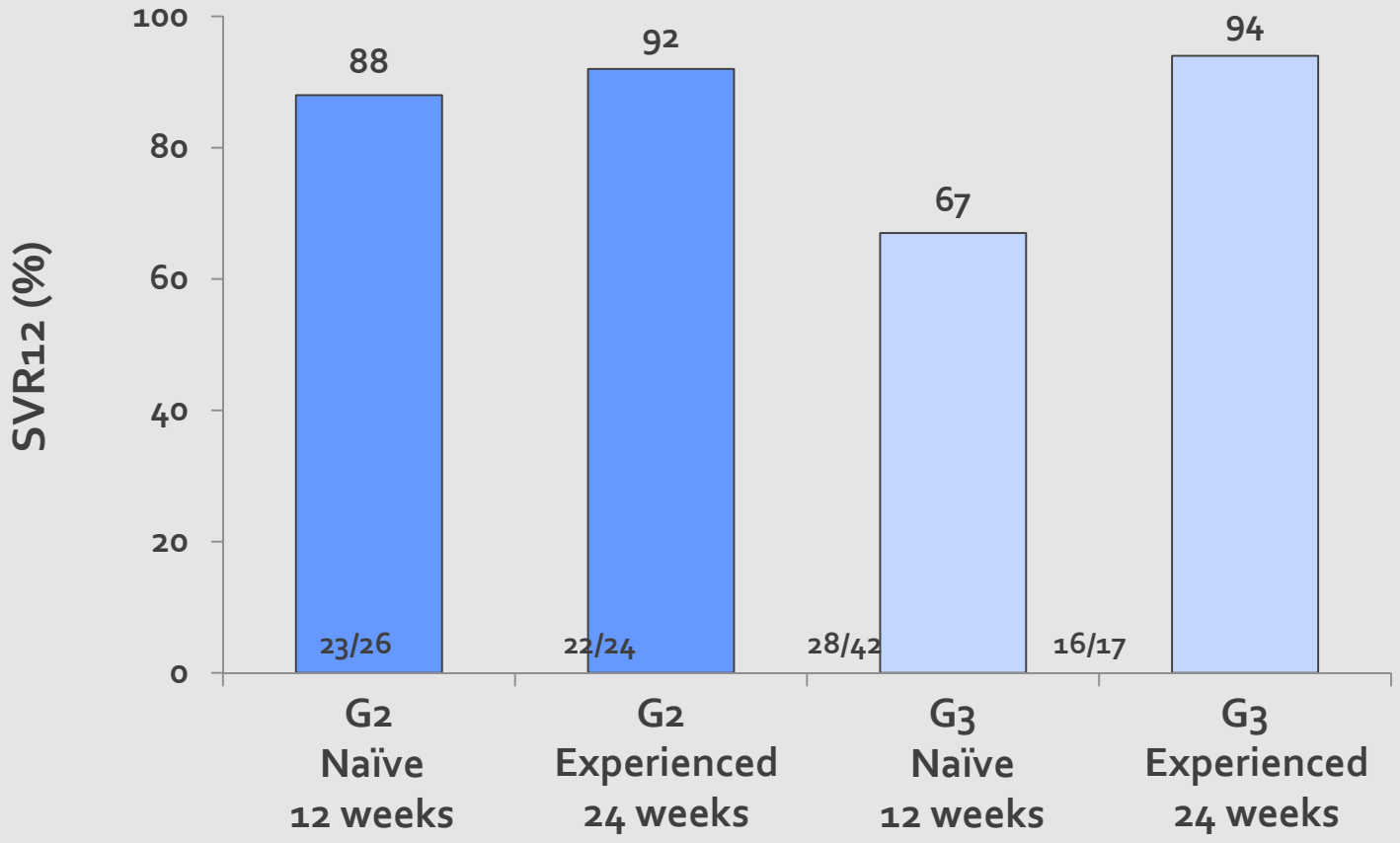


Sofosbuvir: 400 mg once daily; RBV: 1000-1200 mg/day

- Undetectable HIV RNA on stable ART or no ART with CD4 >500 cells
- Wide range of ART regimens allowed
- Compensated cirrhosis permitted (small numbers enrolled)

Naggie S, et al. 2014; CROI: Boston. #26

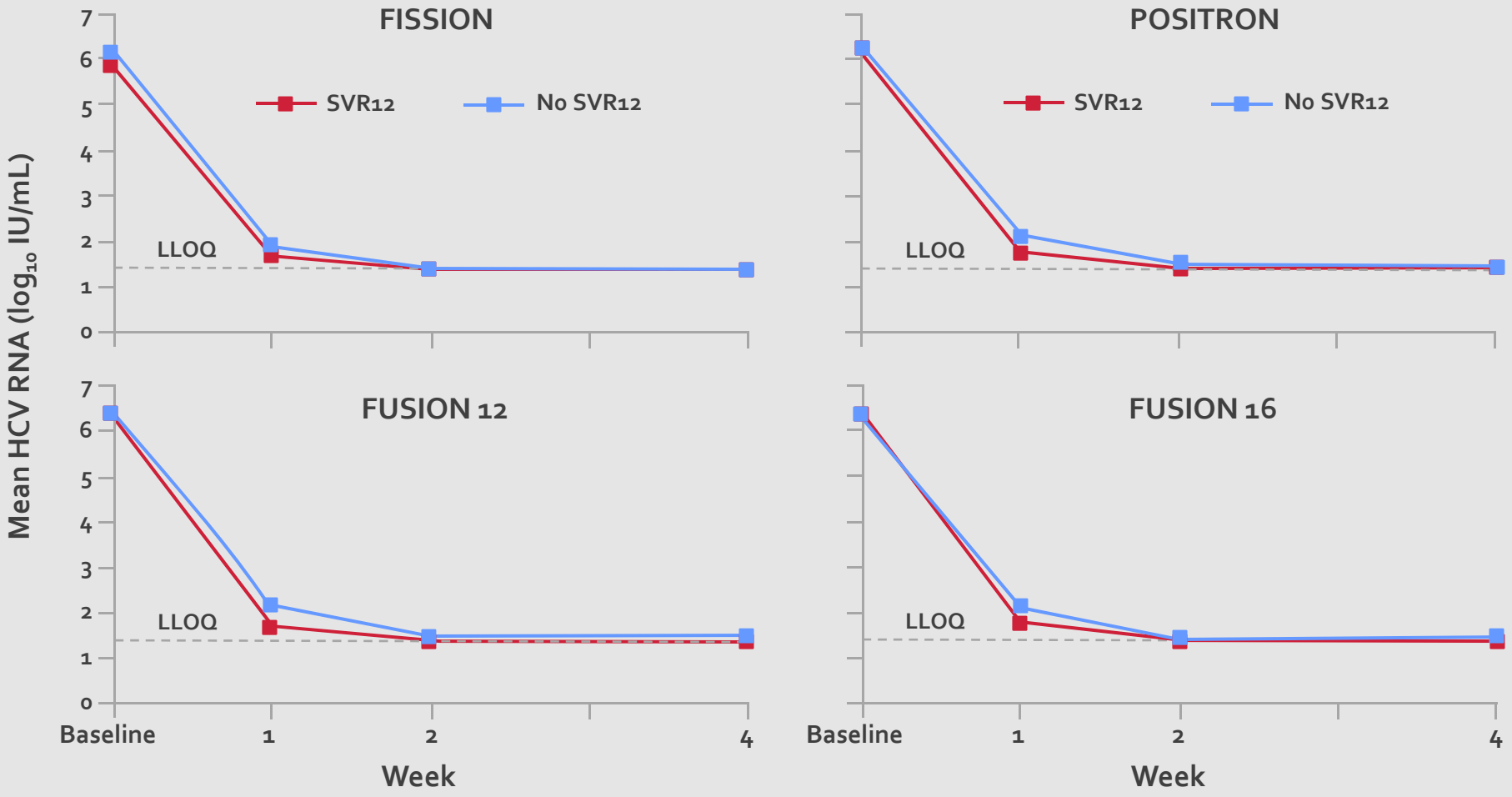
PHOTON-I: Sofosbuvir + RBV in HCV/HIV co-infected patients



Naggie S, et al. 2014; CROI: Boston. #26

Viral kinetics in GT 3 patients FISSION, POSITRON, and FUSION

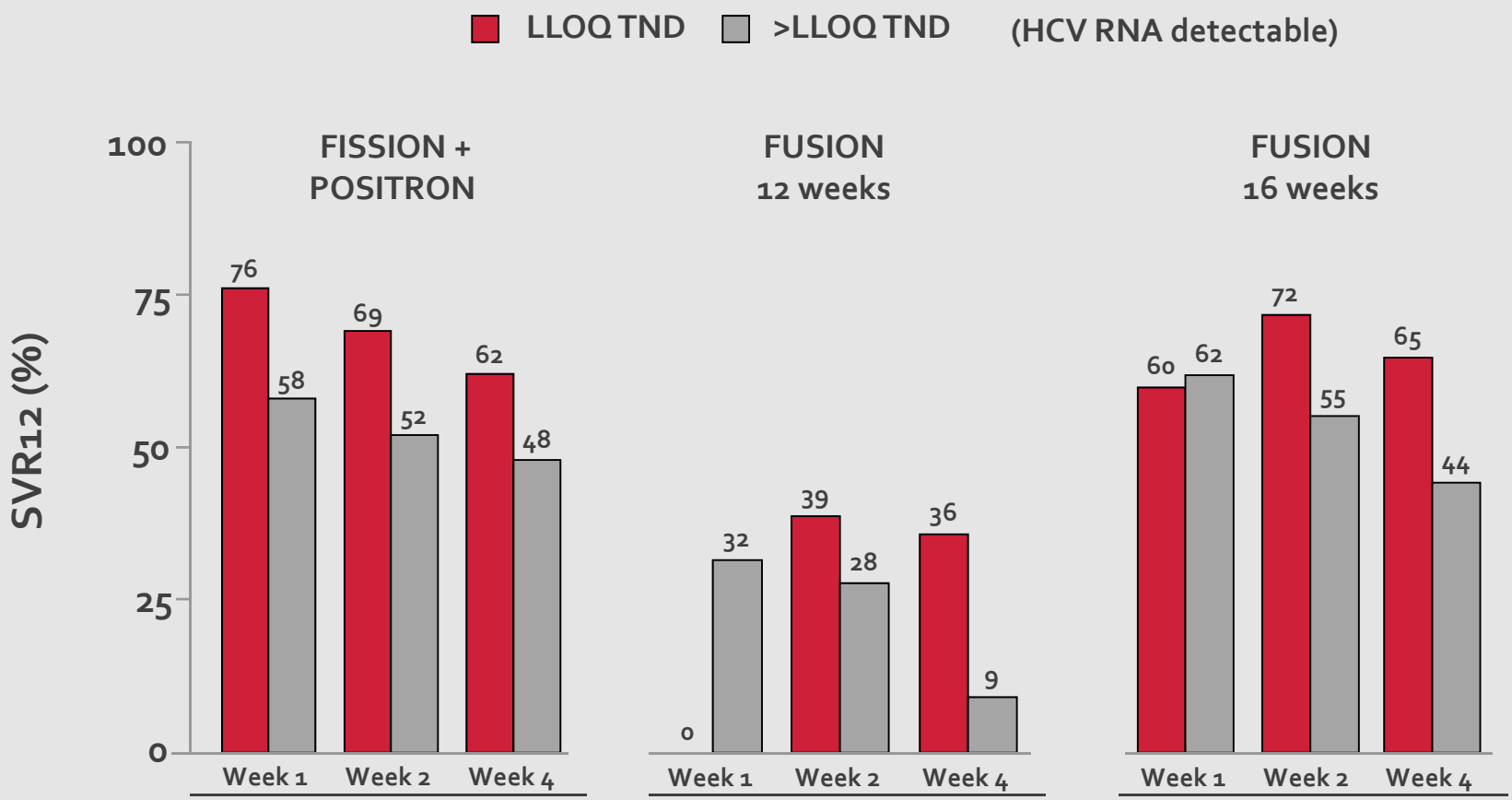
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Wyles D, et al. 2013; AASLD

SVR12 in patients with GT 3 (HCV RNA < or ≥ LLOQ TND)

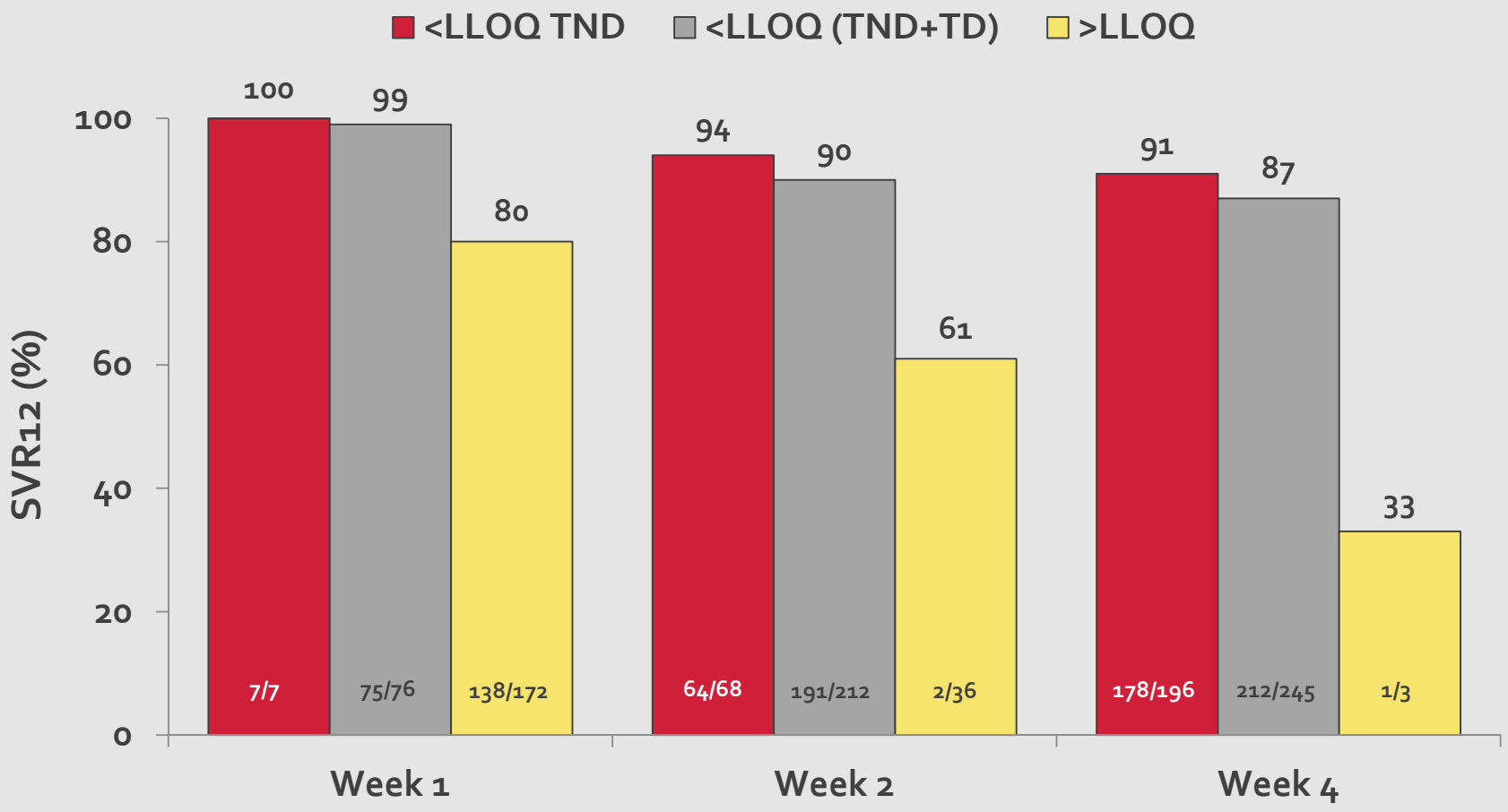
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Wyles D, et al. 2013; AASLD

VALENCE: Viral kinetics and SVR12 rates

Genotype 3



Zeuzem S, et al. 2014; EASL: London

No resistance to SOF in combination therapy for genotypes 2 and 3

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Study*	SOF + RBV
FISSION[1] (n=74)	0%
FUSION[2] (n=72)	0%
POSITRON[2] (n=40)	0%
VALENCE[3]	0%

- S282T is the "signature mutation" in vitro
- No SOF resistance mutations in NS5B detected by deep or population sequencing in any subject receiving SOF + RBV or SOF + PEG-IFN + RBV in Phase 2 and 3 studies
- No "virologic price to pay" for failure
- Implications for ability to retreat with SOF

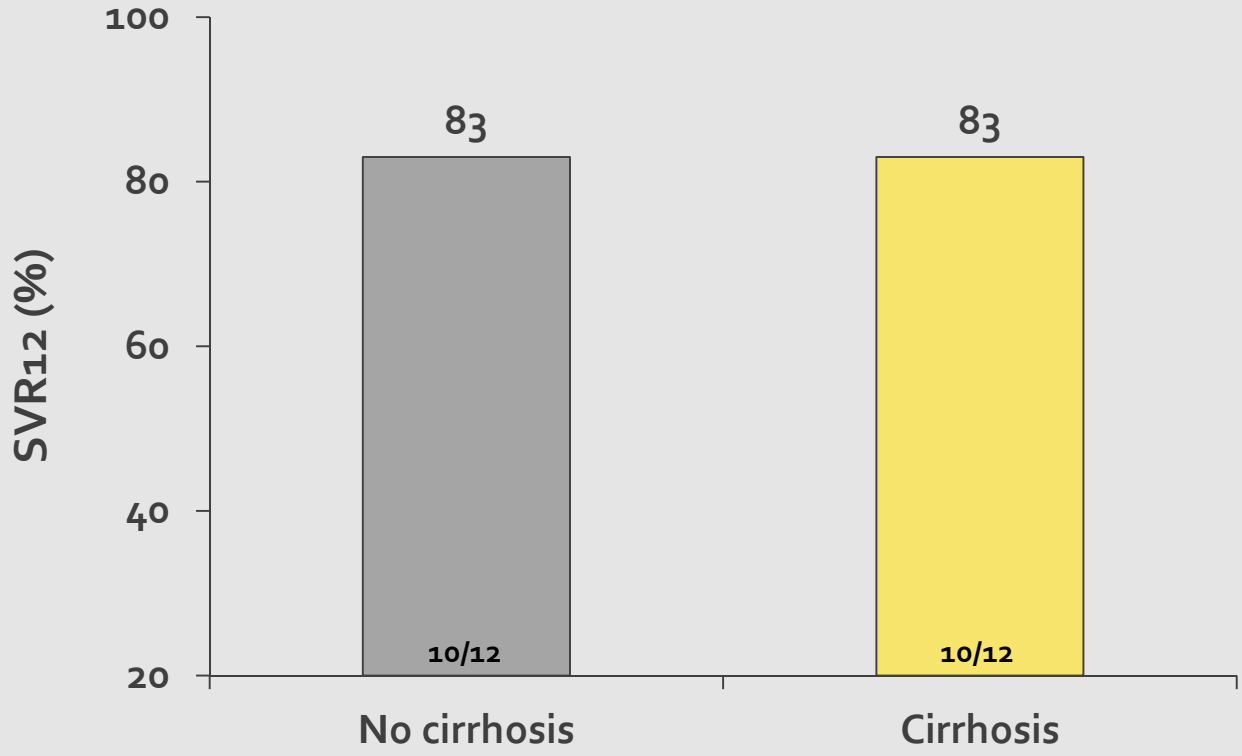
*n = number of patients analyzed for resistance

1. Lawitz E, et al. *N Engl J Med*. 2013;368:1878–1887.
2. Jacobson IM, et al. *N Engl J Med*. 2013;368:1867–1877.
3. Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001.

Sofosbuvir + PEG-IFN + RBV in genotype 3 treatment-experienced patients

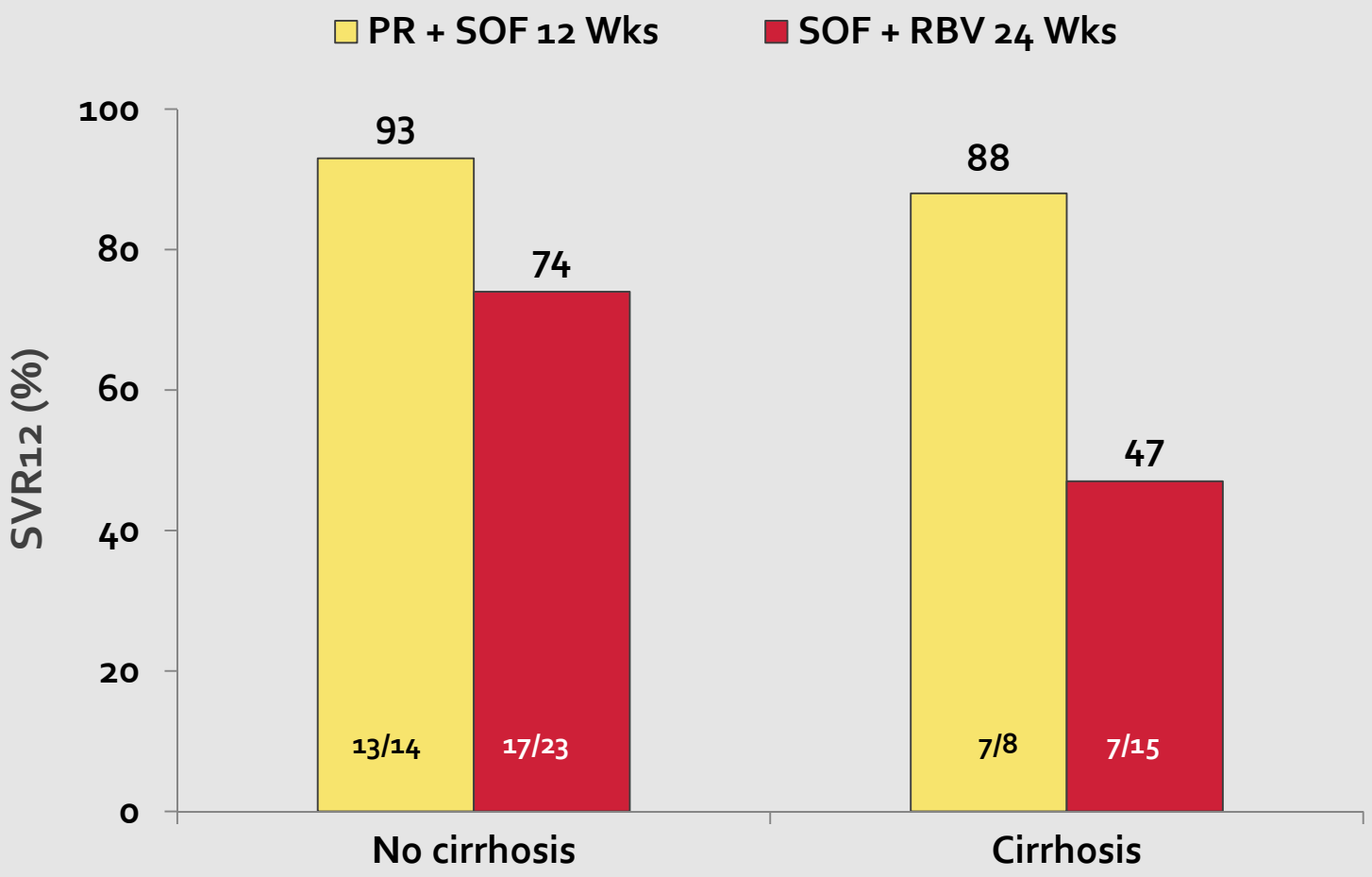
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

SOF 400 mg QD + PEG-IFN + RBV 1000–1200 mg for 12 weeks



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

Retreatment of genotype 3 sofosbuvir + RBV failures



Esteban R, et al. 2014; EASL: London. #08

Variable EC_{50s} for NS5A inhibitors against genotype 3: EC_{50} (nM) in replicons

Drug	1a	1b	3a	4a
Daclatasvir	0.02	0.004	0.15	0.012
Ledipasvir	0.034	0.004	35	0.11
GS-5816	0.011	0.009	0.012	0.009
MK-8742	0.004	0.003	0.03	0.003
ACH-3102	0.02	0.007	<0.2	<0.2
IDX-719	0.0062	0.0024	0.017	0.002

Gao M. *Curr Opin Virol.* 2013;3:514-520

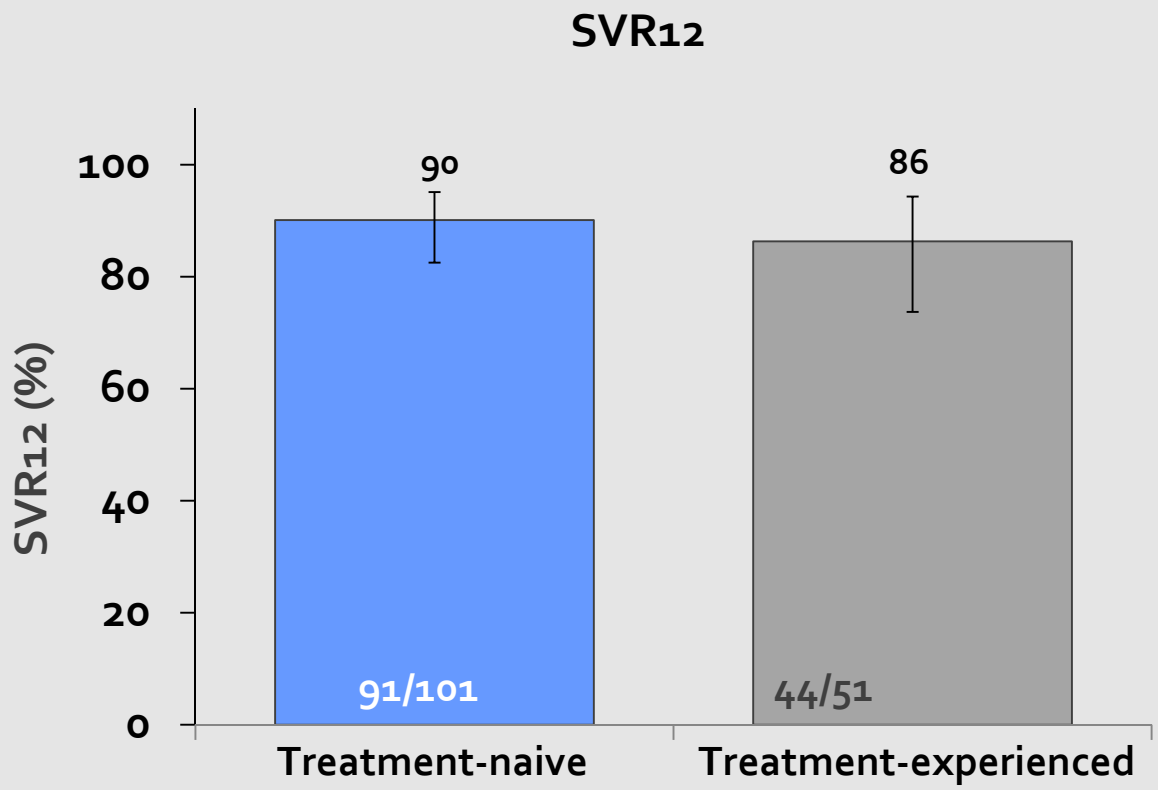
ALLY-3 Study: 12-week combination treatment with DCV + SOF without RBV for HCV G3

Demographic and baseline characteristics

Parameter	Tx-naive (n=101)	Tx-experienced (n=51)
Age, median years	53 (24–67)	58 (40–73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
Asian	5 (5)	2 (4)
Other	0	2 (4)
HCV RNA, n (%)		
<800,000 IU/mL	31 (31)	13 (25)
≥800,000 IU/mL	70 (69)	38 (75)
Cirrhosis, n (%)	19 (19)	13 (25)
IL28B genotype, n (%)		
CC	40 (40)	20 (39)
Non-CC	61 (60)	31 (61)

Nelson DR, et al. 2014; AASLD: Boston. #LB-3

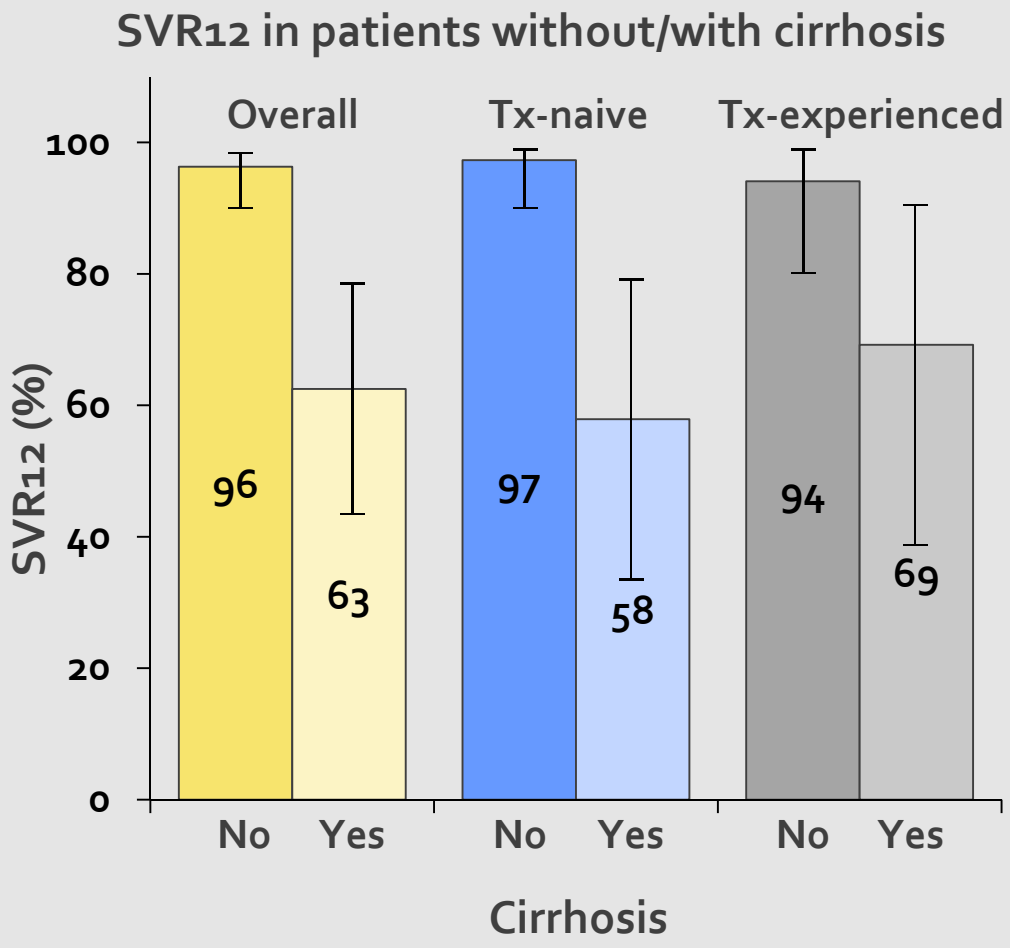
ALLY-3 study: 12-week combination treatment with DCV + SOF for HCV G3



Nelson DR, et al. 2014; AASLD: Boston. #LB-3

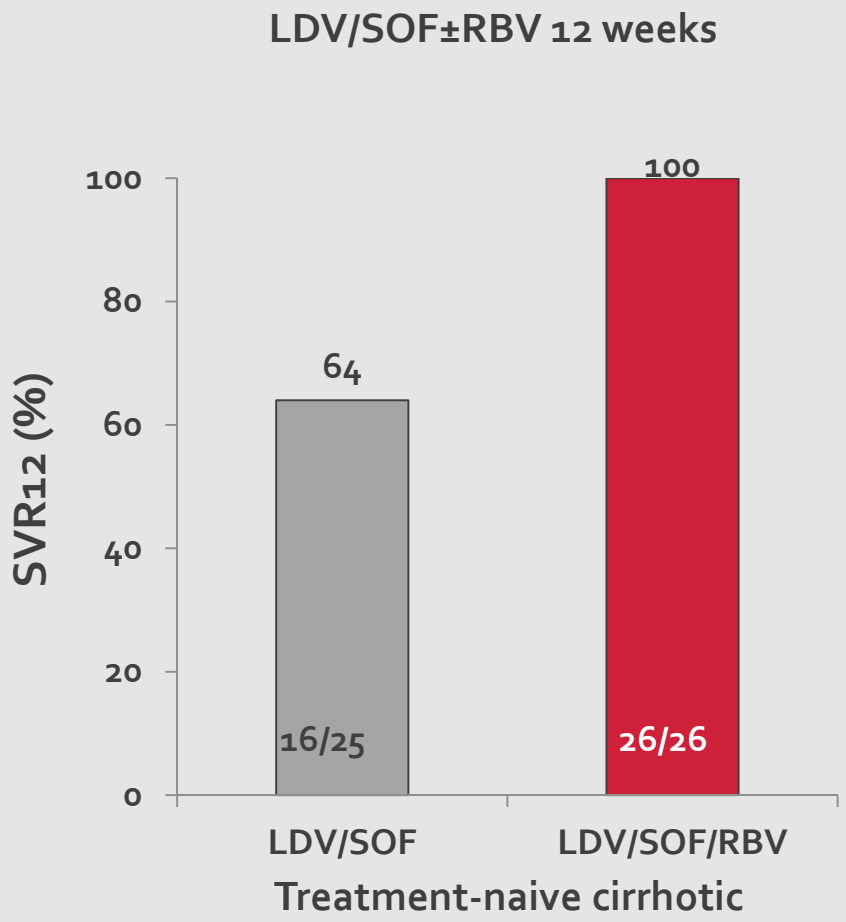
ALLY-3 study: 12-week combination treatment with DCV + SOF for HCV G3 (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Nelson DR, et al. 2014; AASLD: Boston. #LB-3

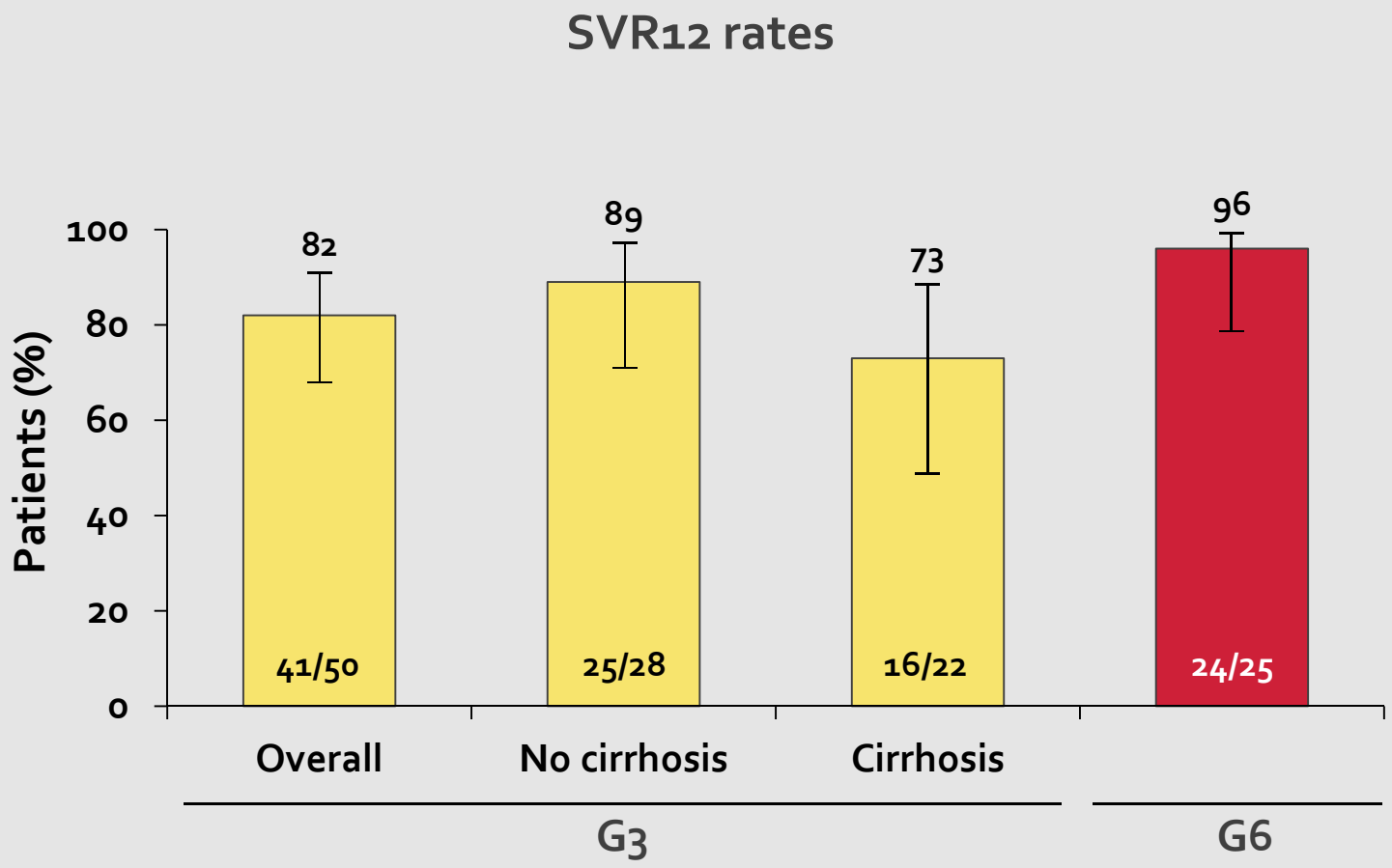
Ledipasvir/sofosbuvir ± RBV for treatment-naïve HCV G3 patients



Gane EJ, et al. 2014; EASL

High efficacy of LDV/SOF regimens for patients with HCV genotype 3 or 6

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Gane EJ, et al. 2014; AASLD: Boston. #LB-11

Once-daily SOF with GS-5816 for 8 weeks ± RBV in treatment-naive G3 non-cirrhotics: The ELECTRON-2 study

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

4 arms: 2 doses of 5816 with/without RBV

	SOF + GS-5816 25 mg	SOF + GS-5816 25 mg + RBV	SOF + GS-5816 100 mg	SOF + GS-5816 100 mg + RBV
n	27	24	27	26
RVR n/N (%)	26/27 (96)	22/23 (96)	24/26 (92)	25/26 (96)
SVR4 n/N (%)	27/27 (100)	21/24 (88)	26/27 (96)	26/26 (100)
SVR12 n/N (%)	**27/27 (100)**	**21/24 (88)**	**26/27** (96)**	**26/26 (100)**
Relapse n/N (%)	0 (0)	2* (8)	0 (0)	0 (0)
LTFU n/N (%)	0 (0)	1 (4)	1 (4)	0 (0)

Gane EJ, et al. 2014; Boston: AASLD. #79

Conclusions: Genotype 3

- Sofosbuvur + ribavirin for 24 weeks remains the approved regimen in the U.S.
- Ledipasvir + SOF + RBV appears to be effective against genotype 3
  - Suboptimal but SVR rates still unexpectedly high in light of poor in vitro activity
  - Probably difficult to access at present
- Daclatasvir + SOF 24 effective in non-cirrhotics, less in cirrhotics
  - "Should work" because has intrinsic activity vs G3
  - Perhaps 24 weeks ± RBV would improve SVR in cirrhotics
- The future of therapy for genotype 3 is likely to be a pangenotypic NS5A (or PI) + a nucleotide