NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Case 3: Genotype 1

Treatment Naïve

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Case – Genotype 1, treatment-naïve

- A 54-year-old African-American male surgeon with recently diagnosed HCV genotype 1a
- Complains of moderate chronic fatigue, not sufficient to limit work hours but rests more than in the past on weekends
- PMH:
  - Hypertension, treated with lisinopril
  - Insulin resistance
- BMI 31
- No hepatosplenomegaly
- Labs:
  - ALT 82 U/L, AST 62 U/L
  - Bilirubin 0.6 mg/dL, albumin 4.4 gm/dL
  - Platelets 205,000
  - Fasting glucose 103 mg/dL
  - HA1C 6.1
  - Creatinine 0.9 mg/dL
  - HCV RNA 5.8 million IU/mL (was 2.4 million IU/mL 5 years ago)
- Ultrasound: fatty infiltration, normal liver contour, normal spleen

How Would You Evaluate Hepatic Fibrosis?

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

1. FibroSURE or the equivalent serum test
2. FibroScan
3. MR elastography
4. Serum test + elastography (e.g., FibroSURE + FibroScan)
5. Liver biopsy
6. None of the above

Case – Genotype 1, treatment-naïve

The following results were obtained:

a. FibroSURE 0.37
b. FibroScan 6.4 kPa

NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Would you obtain a liver biopsy?

What is the role of liver biopsy in patients with hepatitis C?

Is it important to distinguish NAFLD from NASH in this case?

Case – Genotype 1, treatment-naïve

How would you manage this patient?

1. Defer therapy until fibrosis progresses
2. PEG-IFN + RBV + sofosbuvir
3. Ledipasvir + sofosbuvir
4. Simeprevir + sofosbuvir
5. Paritaprevir/ritonavir/ombitasvir + dasabuvir +

Case – Genotype 1, treatment-naïve

If you selected ledipasvir and sofosbuvir, how long would you treat the patient?

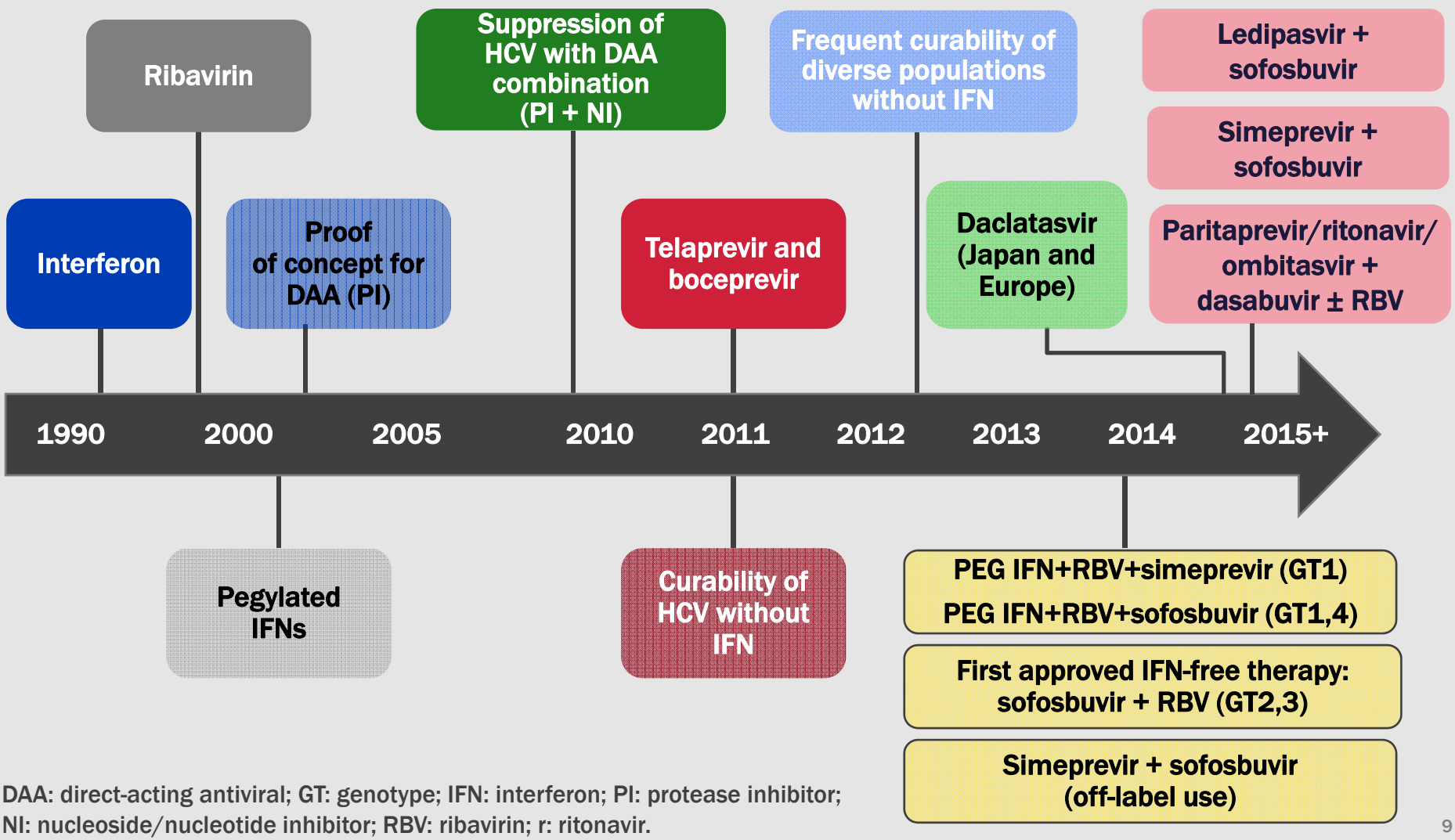
1. 8 weeks
2. 12 weeks
3. 24 weeks

Case – Genotype 1, treatment-naïve

The insurance company denies coverage because the patient does not have F3-4 fibrosis. Which of the following points would you include in your appeal?

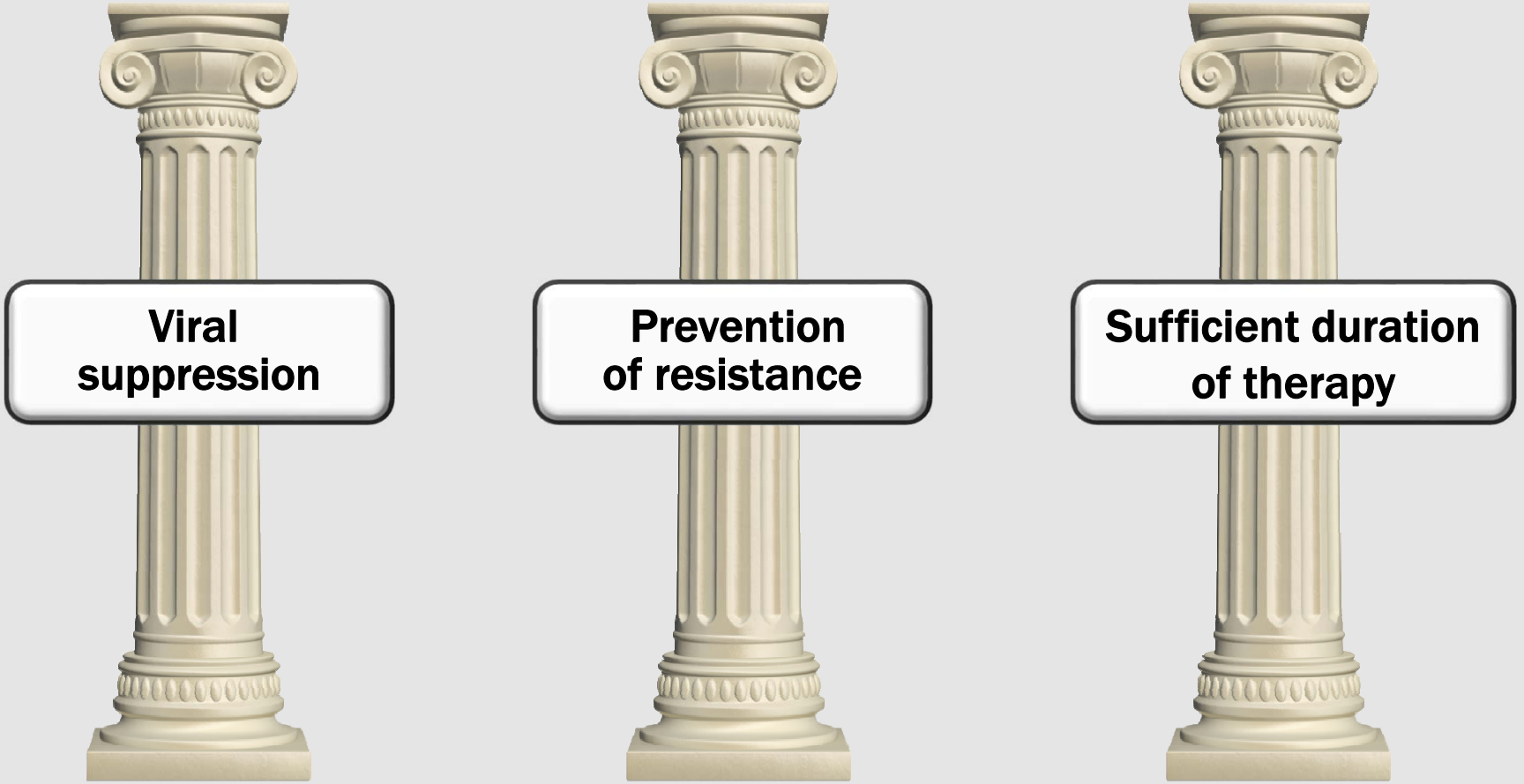
1. The patient's occupation
2. The patient's chronic fatigue
3. The patient's prediabetic state
4. The patient's steatosis
5. All of the above

HCV therapy: Past, present, and future



DAA: direct-acting antiviral; GT: genotype; IFN: interferon; PI: protease inhibitor; NI: nucleoside/nucleotide inhibitor; RBV: ribavirin; r: ritonavir.

The pillars of HCV DAA therapy



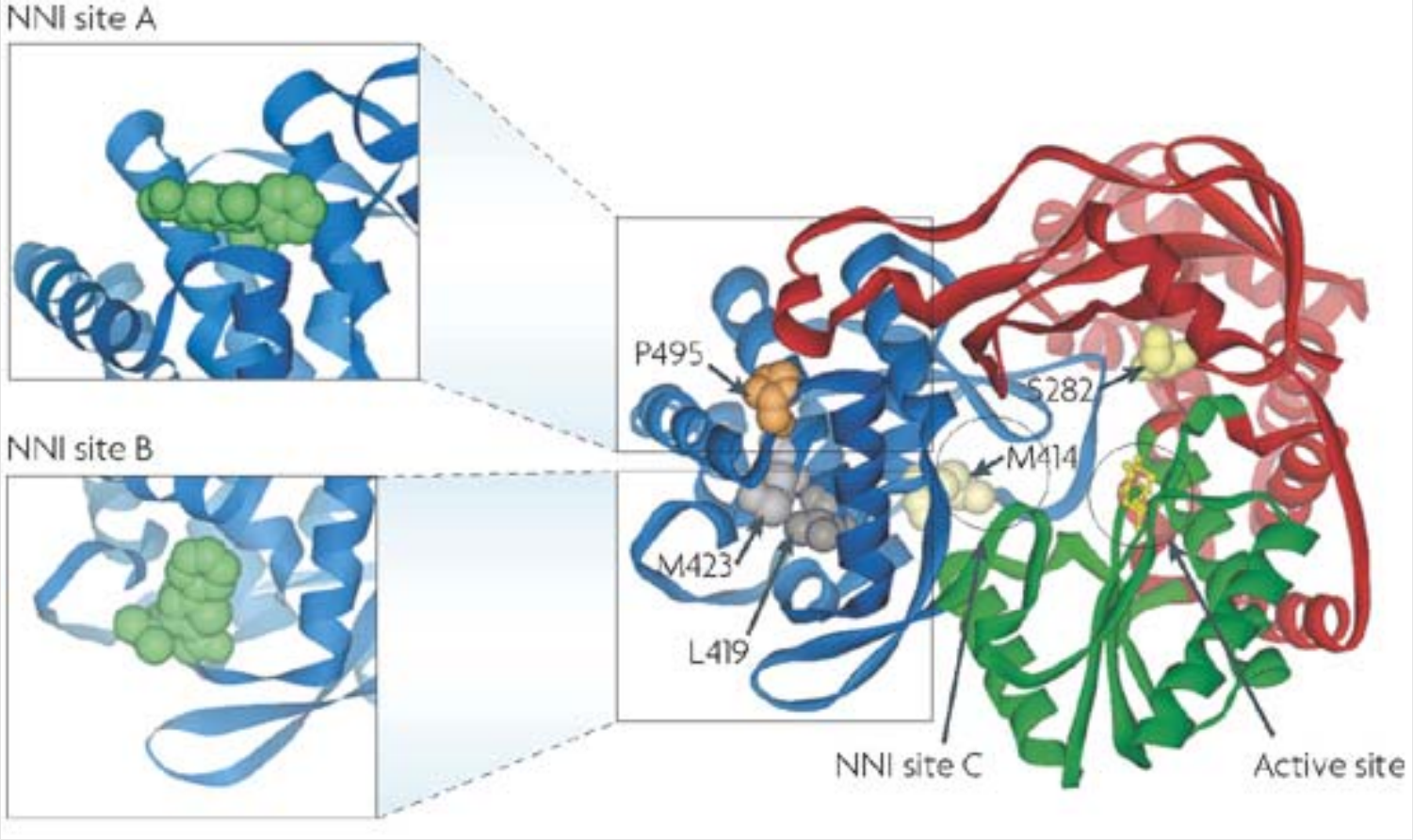
Approaches to erecting a high barrier to resistance with DAA therapy for HCV

A combination of DAAs, each with a low resistance barrier, that collectively confer a high barrier to resistance on the regimen

A combination containing a DAA with a high resistance barrier that confers a high resistance barrier on the regimen

HCV RNA polymerase

vfm2

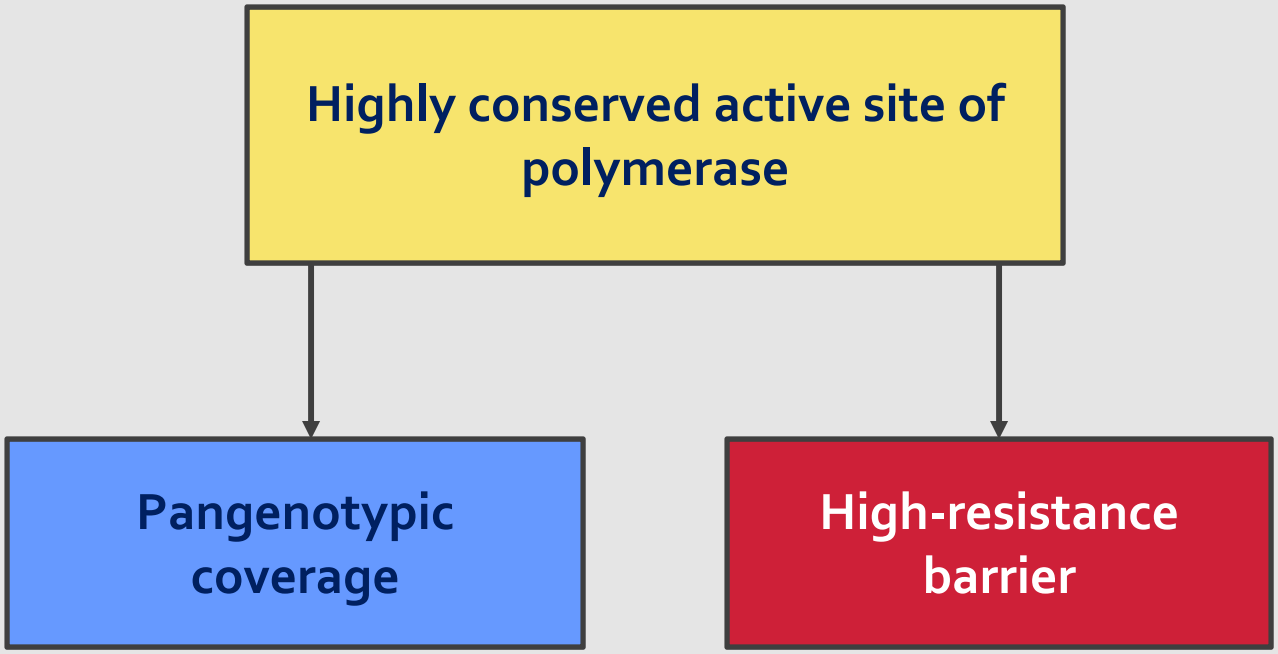


Manns M, et al. *Nat Rev Drug Discov*. 2007;6:991-1000
Accessed at www.nature.com/nrd/journal/v6/n12/fig_tab/nrd2411_F5.html

vfm2 The way forward in HCV treatment--finding the right path.

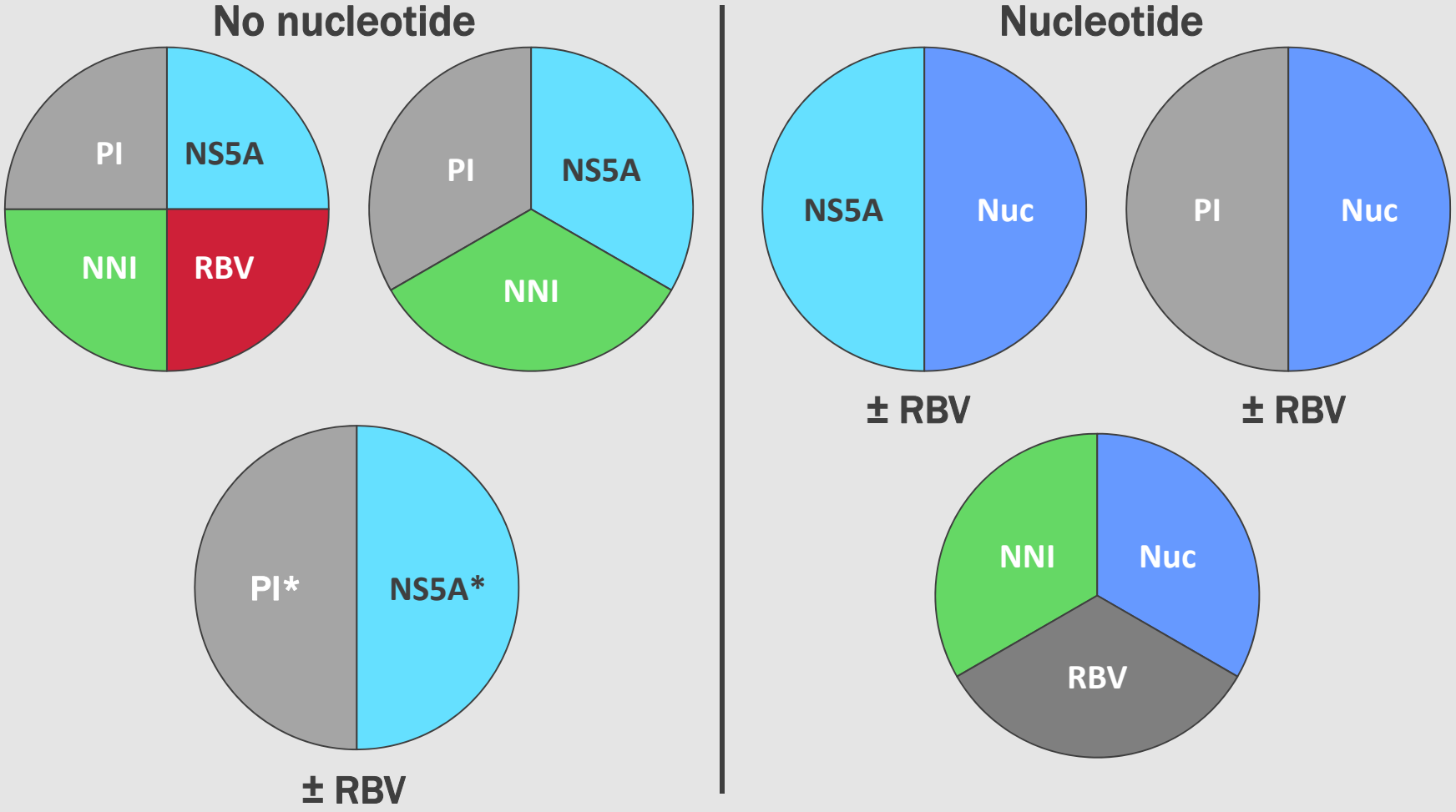
vfm, 12/8/2014

Nucleotide polymerase inhibitors



Oral regimens with ≥90% SVR for GT1 patients

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

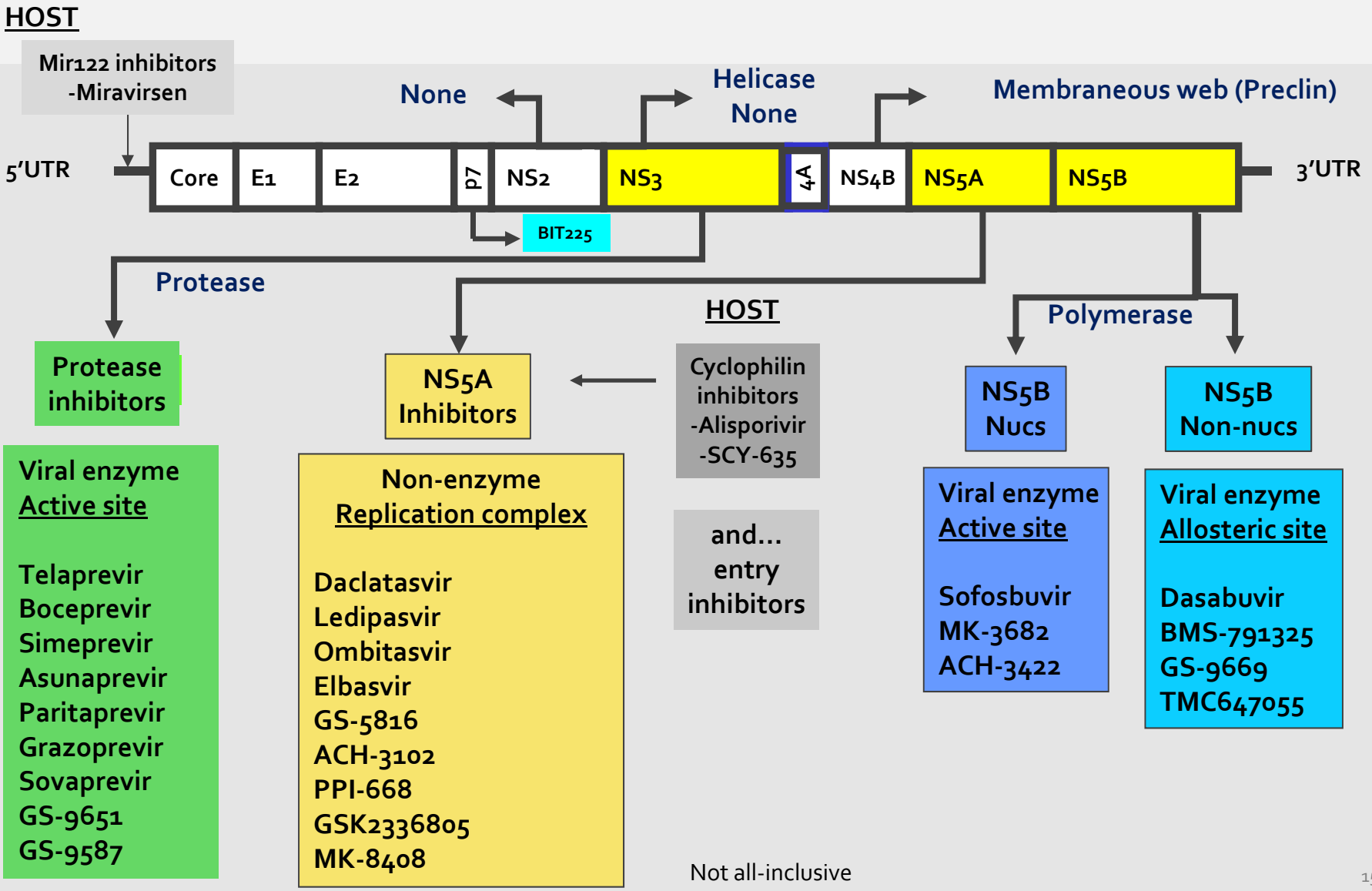


*"Second generation"

NNI, non-nucleoside inhibitor; Nuc, nucleotide inhibitor; PI, protease inhibitor

Multiple validated drug targets

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Not all-inclusive

NEW OPTIONS IN HCV THERAPY:

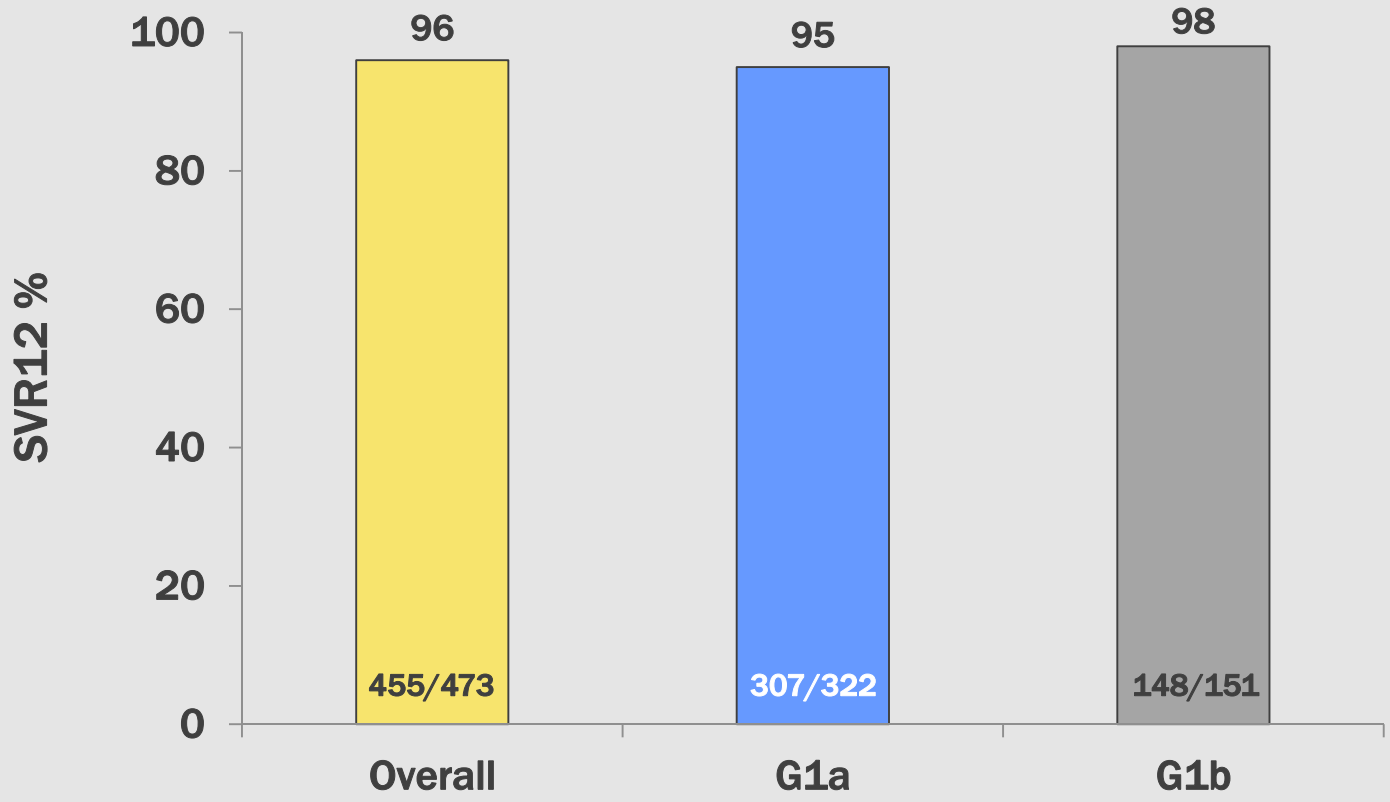
UPDATE FROM AASLD 2014

Interferon-Free, Direct-Acting Antiviral Regimens for Genotype 1

No Nucleotide

Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV: SAPPHIRE-I

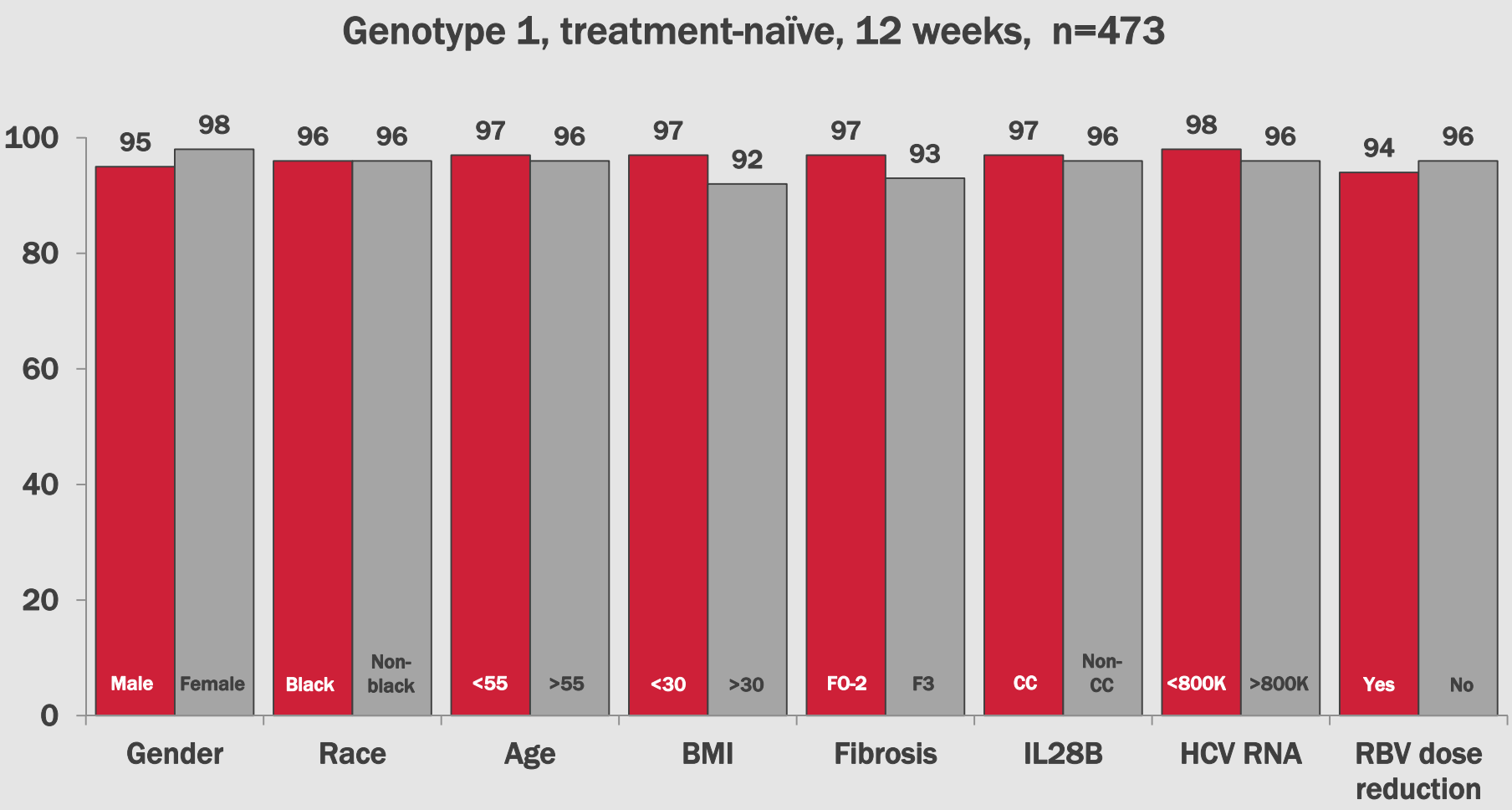
Genotype 1, treatment-naïve, non-cirrhotic, 12 weeks, n=473



Feld JJ, et al. *N Engl J Med.* 2014;370:1594-1603

ABT-450/r-ombitasvir + dasabuvir + RBV SAPPHIRE-I

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Feld JJ, et al. *N Engl J Med.* 2014;370:1594-1603

SAPPHIRE-I: Reasons for non-SVR12

Event, n/N (%)	3D + RBV (N=473)
SVR12	455/473 (96.2)
Non-SVR12	18/473 (3.8)
Virologic failure	
Breakthrough	1/473 (0.2)
Relapse	7/463 (1.5)
Prematurely discontinued study drug*	7/473 (1.5)
Lost to follow-up after completion of treatment	3/473 (0.6)

*Patients (n=7) who prematurely discontinued without breakthrough; 2 due to adverse events, 5 withdrew consent/lost to follow-up.

Adapted from the presentation by Jordan Feld at ILC/EAST on April 11, 2014.

SAPPHIRE-I: Adverse events occurring in >10% of patients in either group

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Event, n (%)	3D + RBV (N=473)	Placebo (N=158)	*P* Value
Any AE	414 (87.5)	116 (73.4)	<0.05
Fatigue	164 (34.7)	45 (28.5)	NS
Headache	156 (33.0)	42 (26.6)	NS
Nausea	112 (23.7)	21 (13.3)	>0.05
Pruritus	80 (16.9)	6 (3.8)	<0.05
Insomnia	66 (14.0)	12 (7.6)	<0.05
Diarrhea	65 (13.7)	11 (7.0)	<0.05
Asthenia	57 (12.1)	6 (3.8)	<0.05
Rash	51 (10.8)	9 (5.7)	NS

AEs were generally mild.
Adapted from the presentation by Jordan Feld at ILC/EAST on April 11, 2014.

SAPPHIRE-I: Laboratory abnormalities

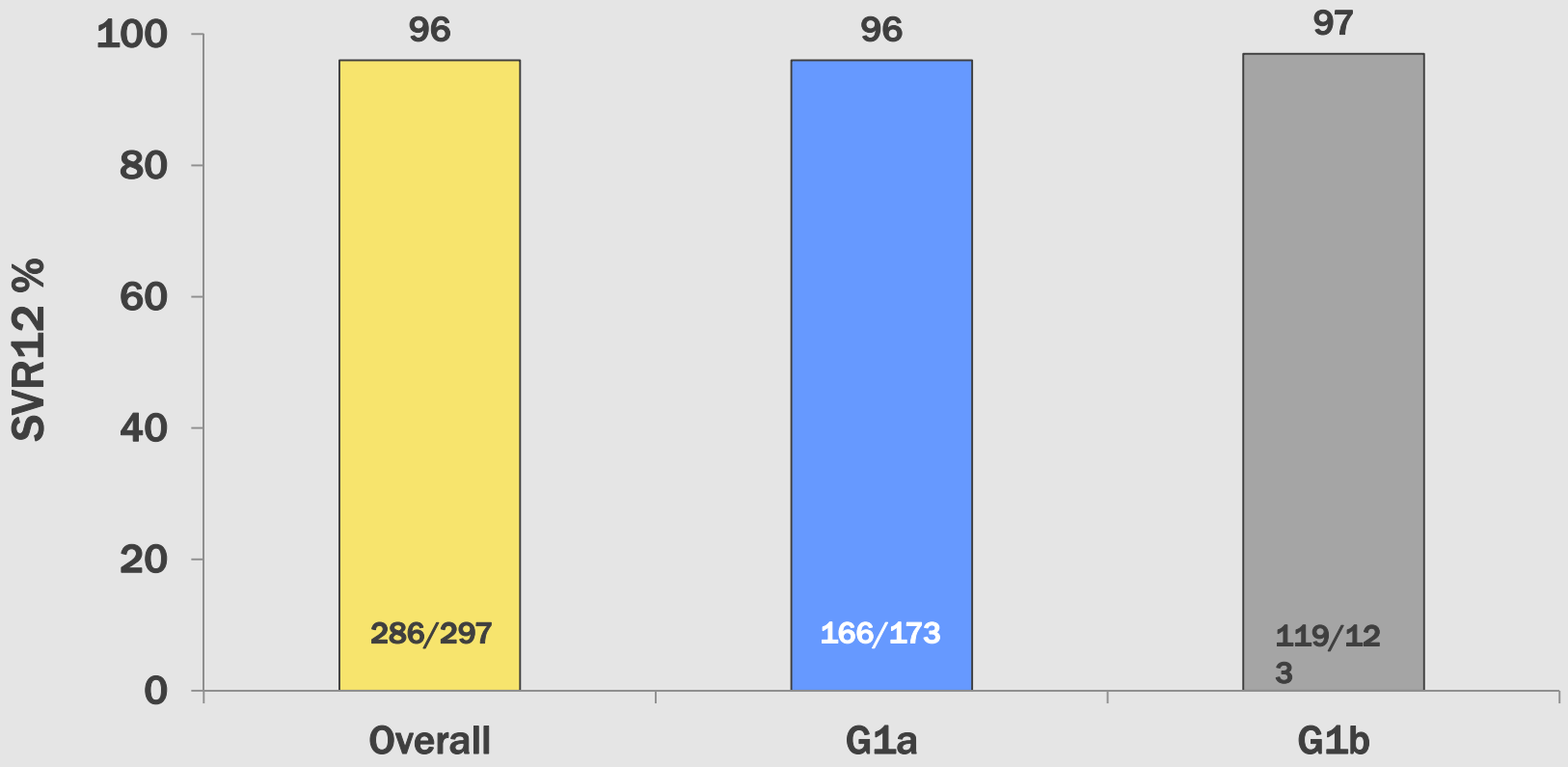
Event, n (%)	3D + RBV (N=469)
ALT >5X ULN	4 (0.9)
Ast >5x ULN	3 (0.6)
Alkaline phosphatase >5X ULN	0
Total bilirubin >3X ULN	13 (2.8)
Hemoglobin	
<10-8.0 g/dL	27 (5.8)
<8.0-6.5 g/dL	0
<6.5 g/dL	0

There were no discontinuations due to laboratory abnormalities.
Elevations in total bilirubin were mainly transient and predominantly indirect bilirubin; no cases consistent with the Hy's law.
One patient received EPO; no patient was transfused.

Adapted from the presentation by Jordan Feld at ILC/EAST on April 11, 2014.

Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV: SAPPHIRE-II

Genotype 1, treatment-experienced, non-cirrhotic, 12 weeks, n=394



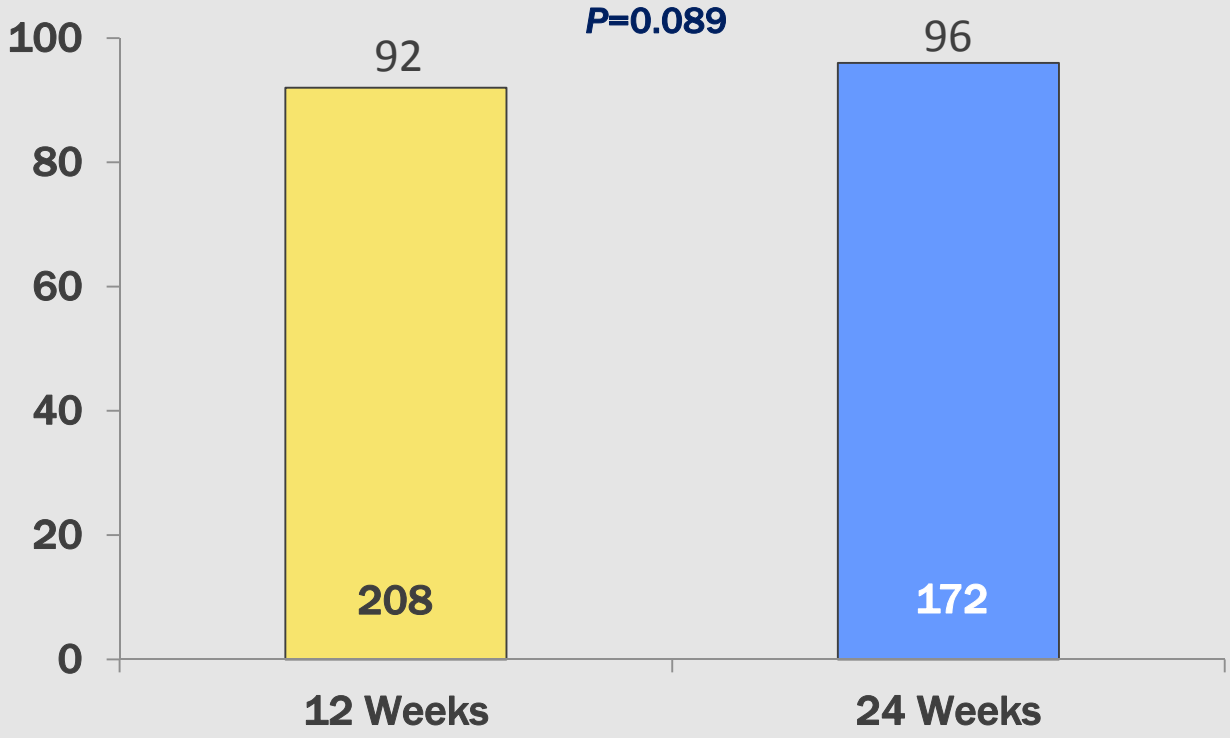
Zeuzem S, et al. *N Engl J Med*. 2014;370:1604-1614

TURQUOISE II: ABT-450/r-ombitasvir + datasubuvir ± RBV

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Genotype 1 patients, with compensated cirrhosis

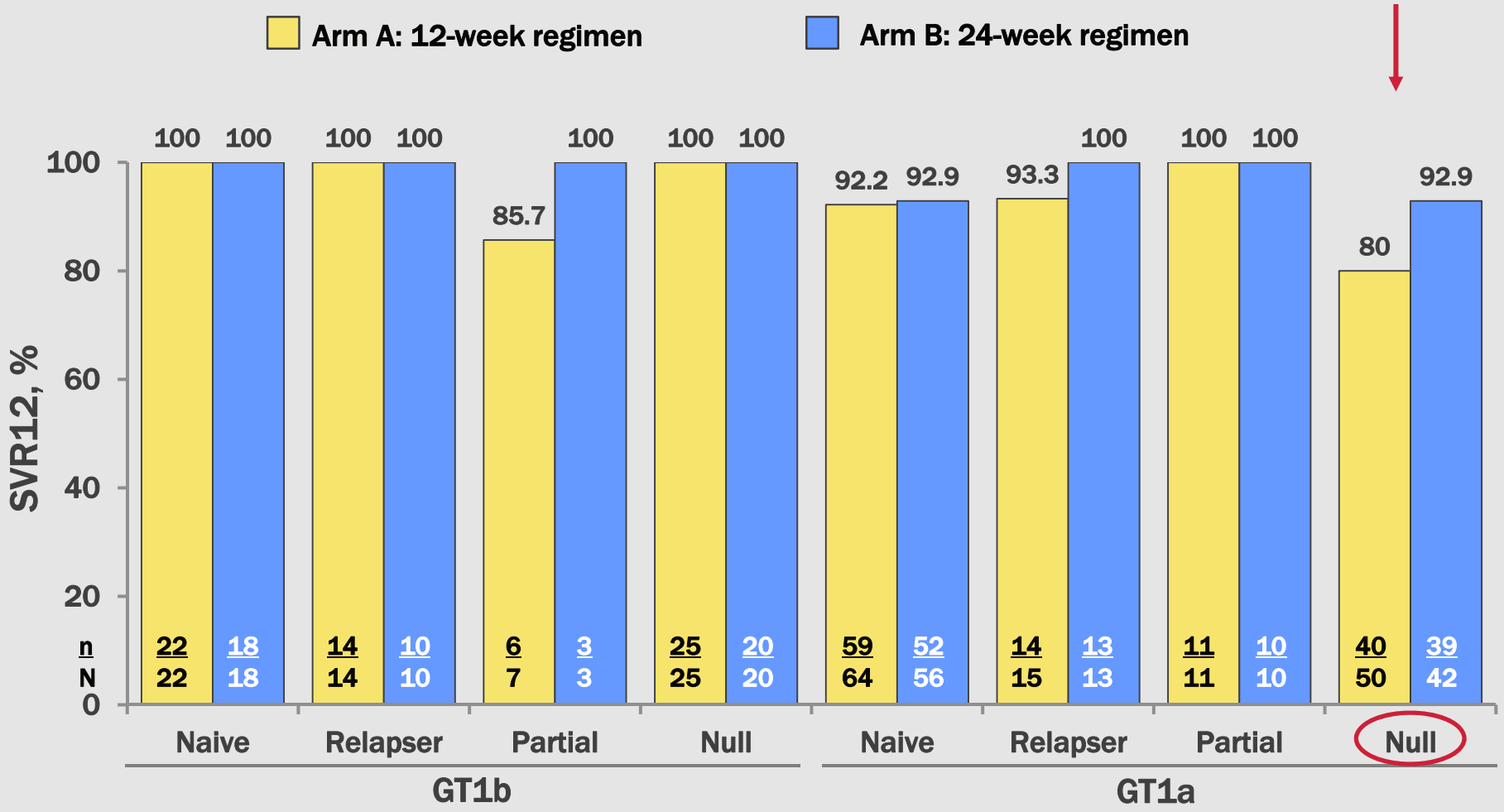
Treatment-Naïve and Treatment-Experienced



- Relapse/viral breakthrough in 6% (12 weeks) and 2% (24 weeks)

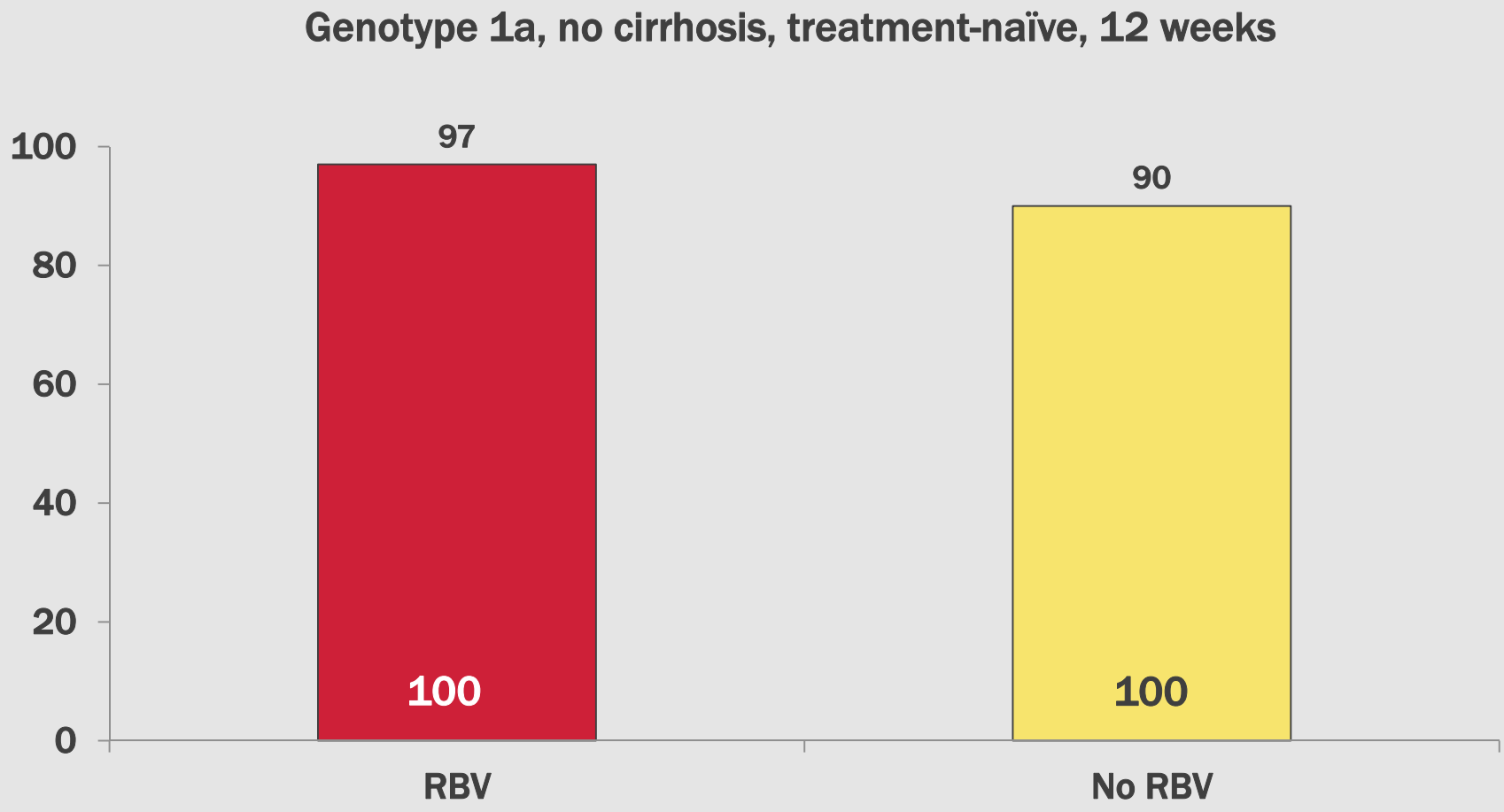
Poordad F, et al. *N Engl J Med.* 2014;370:1973-1982

Which population drove the difference between 12 and 24 weeks in TURQUOISE-II?



Poordad F, et al. *N Engl J Med.* 2014;370:1973-1982

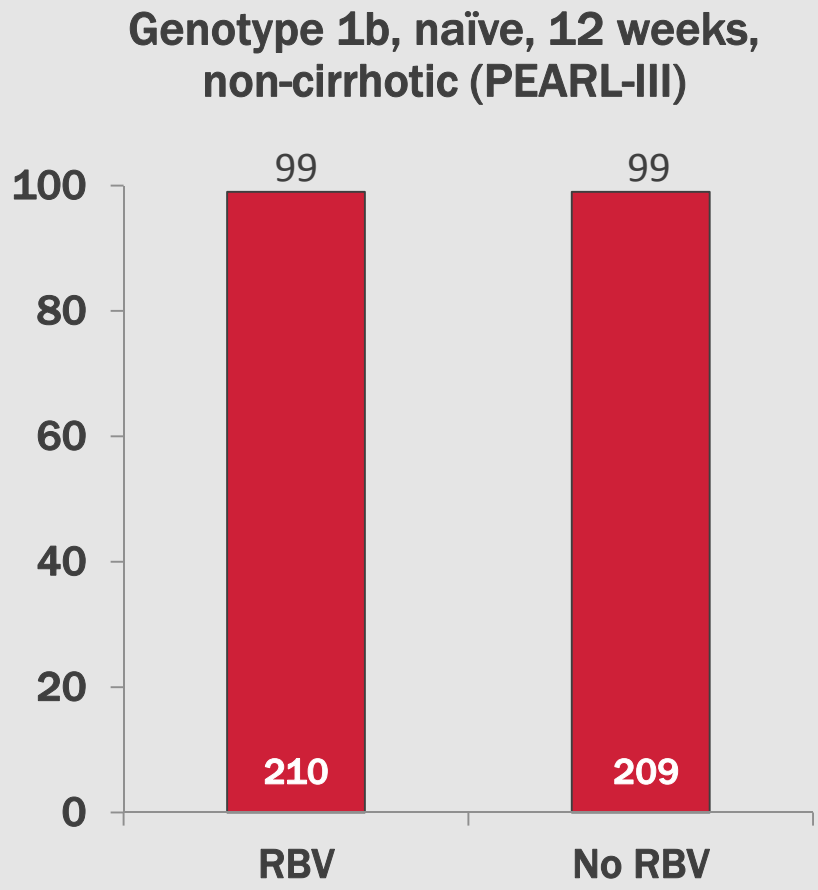
Paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin: PEARL-4

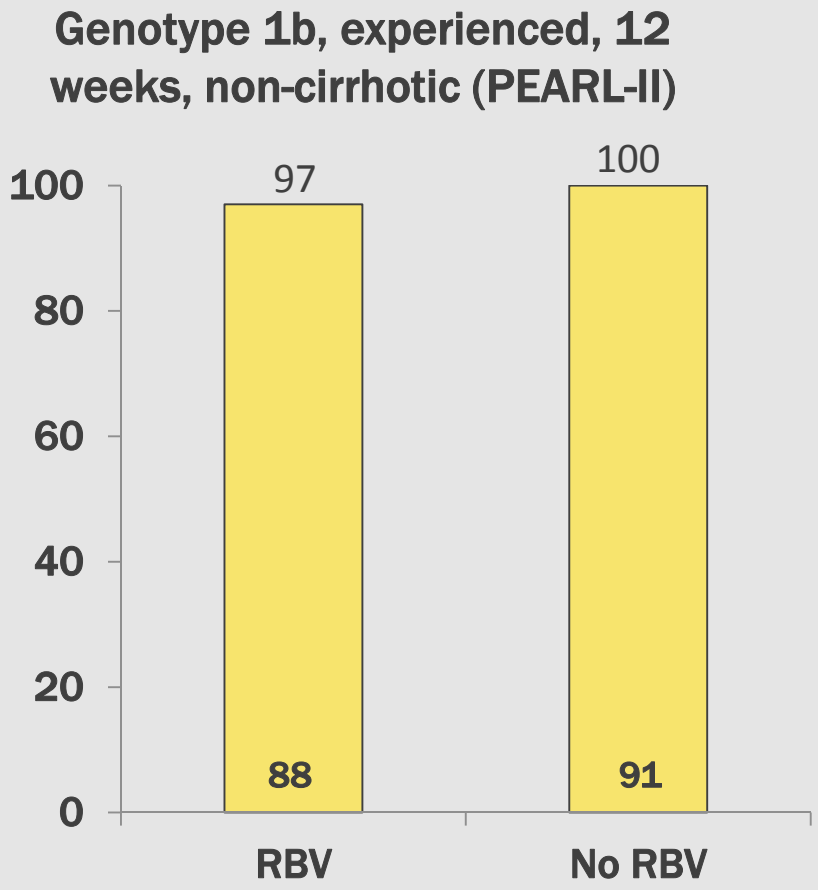


Ferenci P, et al. *N Engl J Med*. 2014;370:1983-1992

Paritaprevir/ritonavir/ombitasvir + dasabuvir ± RBV in genotype 1b

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014





Ferenci P, et al. *N Engl J Med.* 2014;370:1983-1992

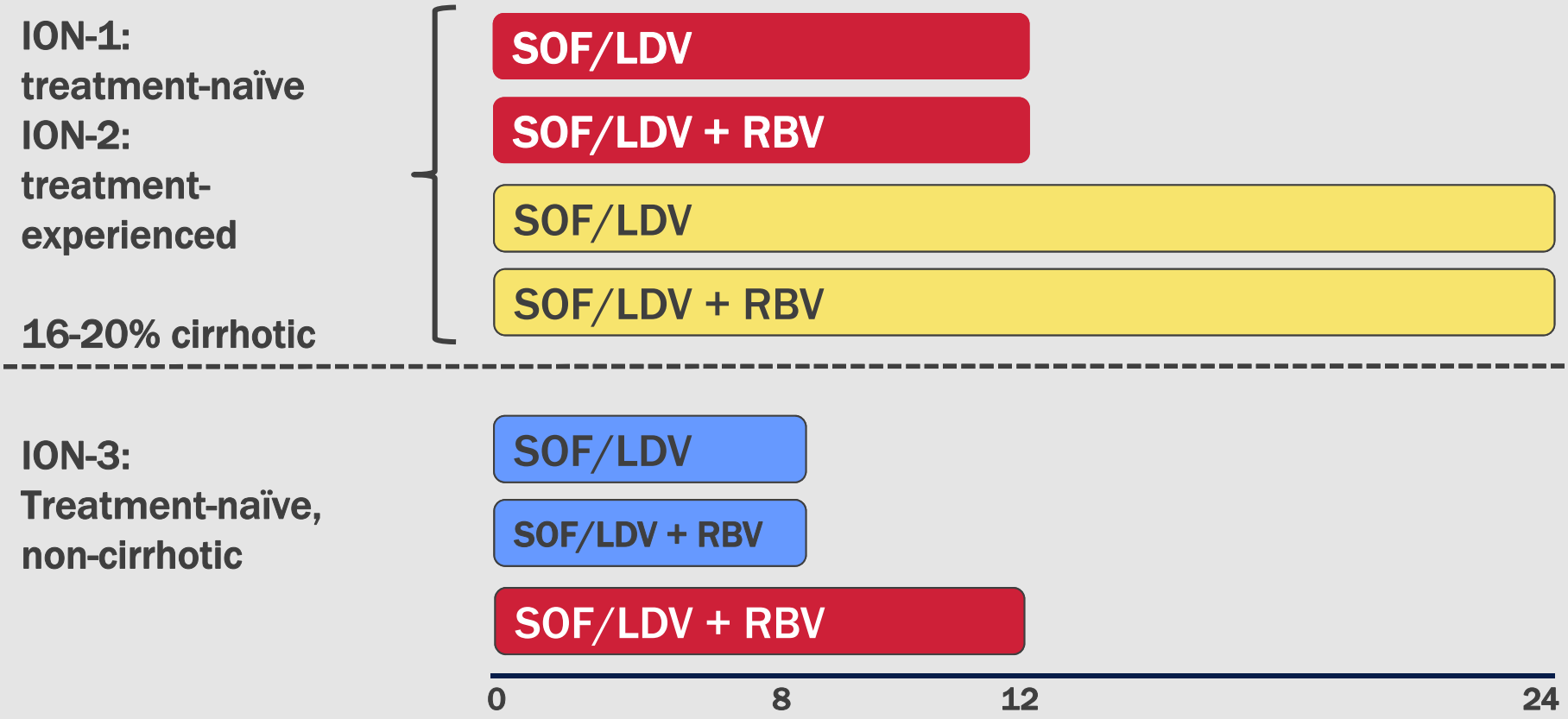
NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Interferon-Free Direct-Acting Antiviral Regimens for Genotype 1

Nucleotide in Regimen

ION-1, ION-2, and ION-3 phase 3 studies: sofosbuvir/ledipasvir ± RBV in HCV genotype 1



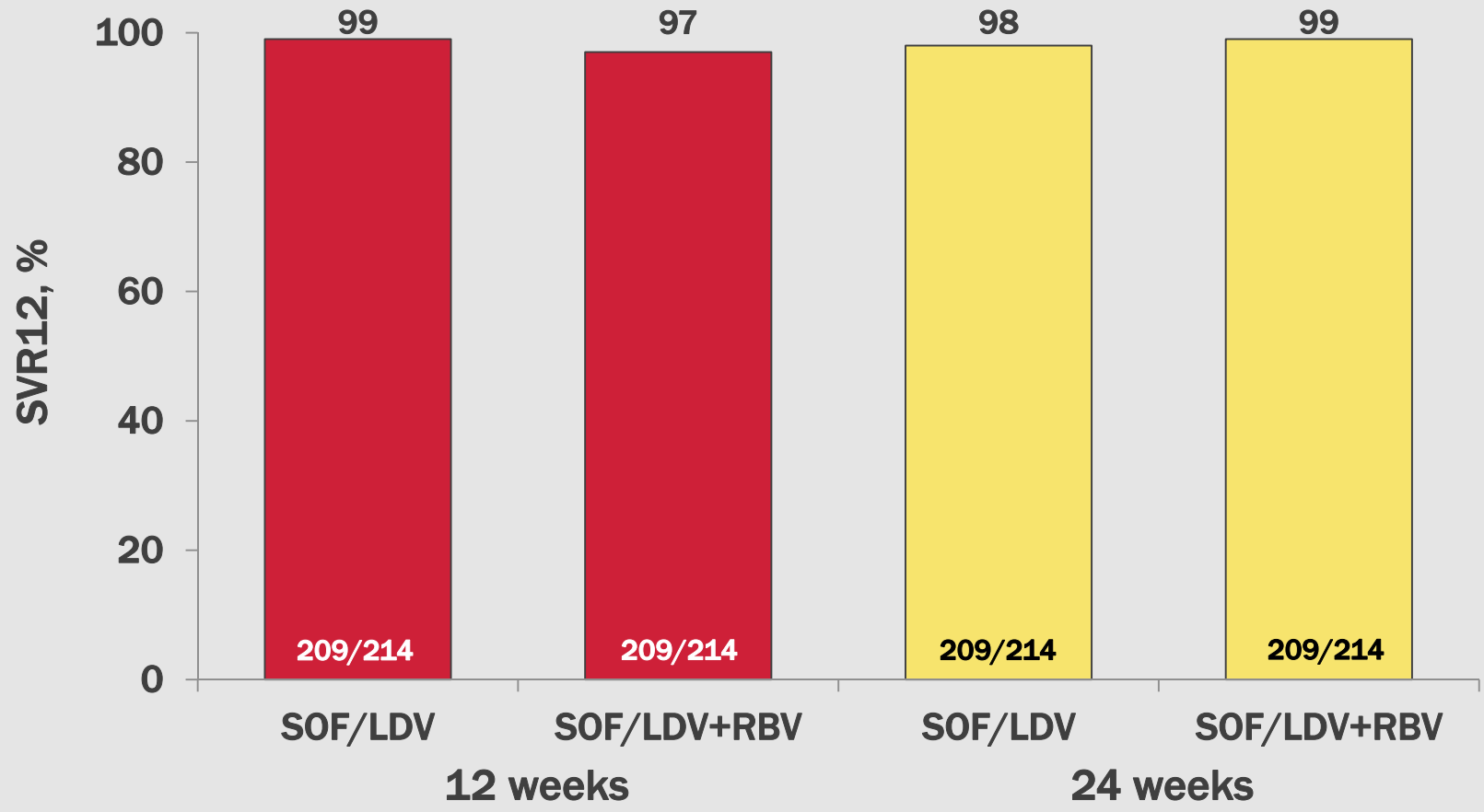
Sofosbuvir/ledipasvir 400/90 mg qd; RBV (weight-based 1000 or 1200 mg/day).

Afdhal N, et al. *N Engl J Med*. 2014;370:1889-1898. Afdhal N, et al. *N Engl J Med*. 2014;370:1483-1493.
Kowdley KV, et al. *N Engl J Med*. 2014;370:1879-1888.

ION-1: Sofosbuvir + ledipasvir ± RBV genotype 1: treatment-naïve, n=865

Cirrhosis in 16%

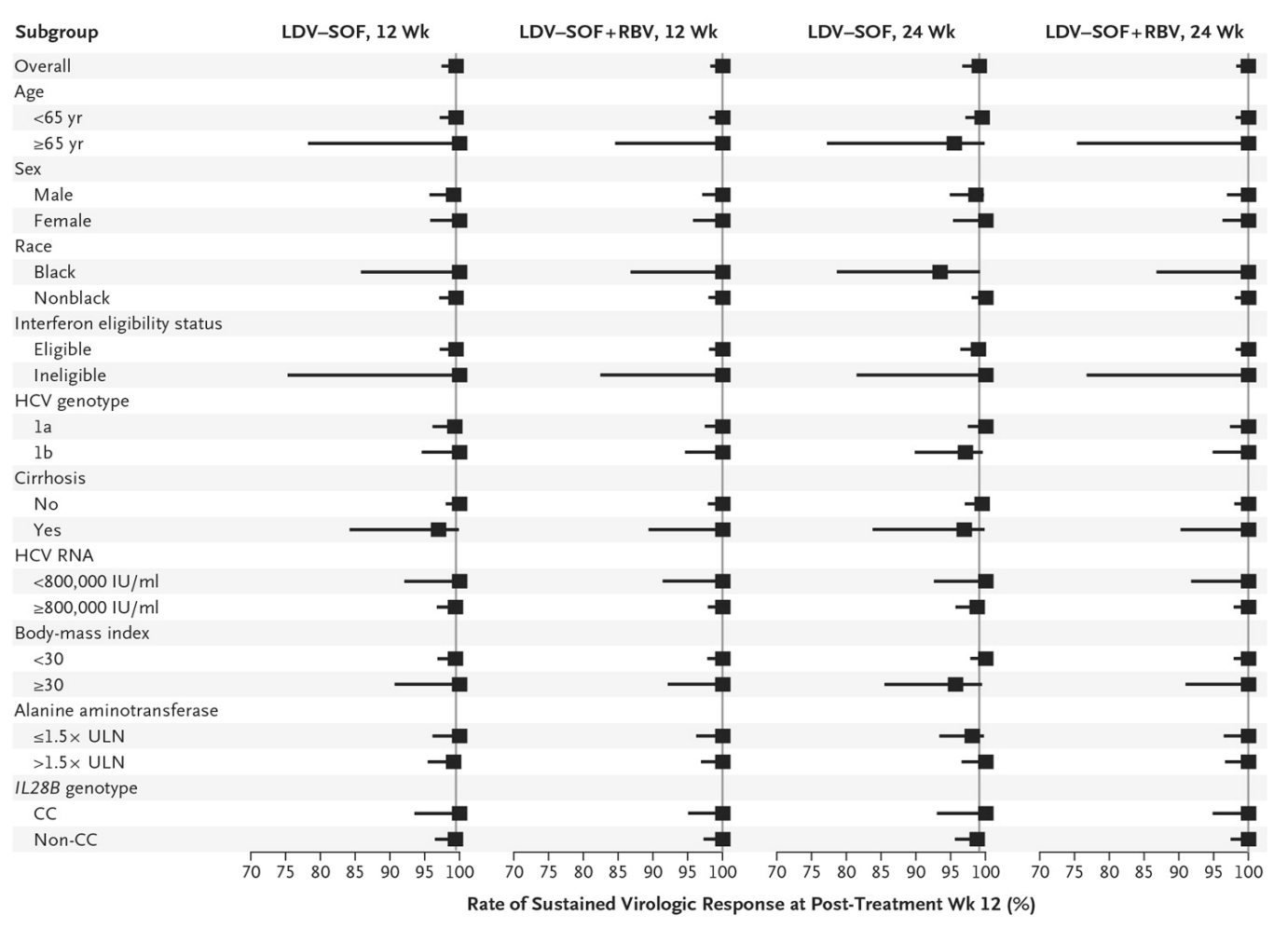
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Afdhal N, et al. *N Engl J Med.* 2014;370:1889-1898

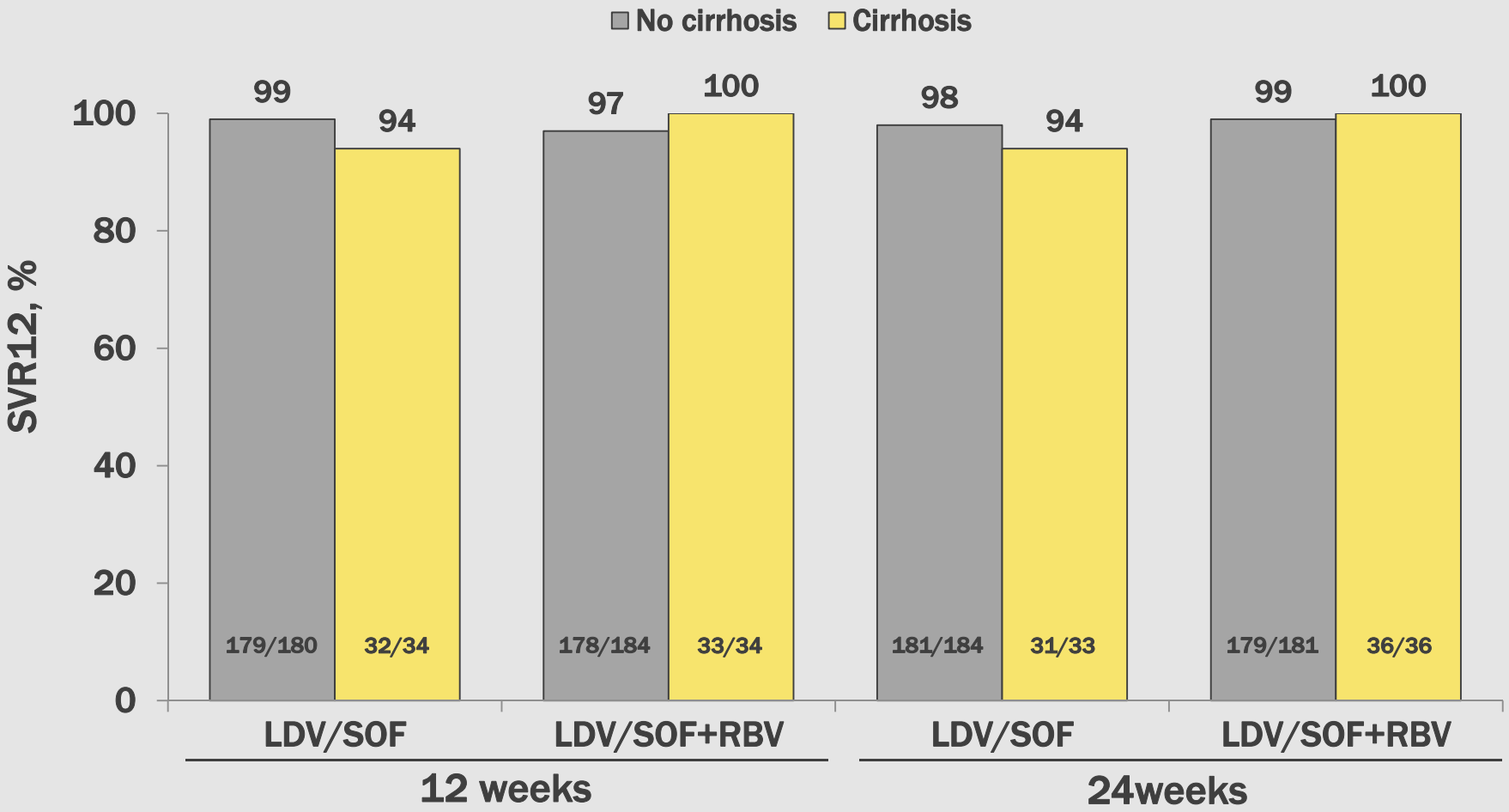
ION-1: Rates of sustained virologic response according to subgroup

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Afdhal N, et al. *N Engl J Med.* 2014;370:1889-1898

ION-1: Non-cirrhotic vs cirrhotic patients



Afdhal N, et al. *N Engl J Med*. 2014;370:1889-1898
Afdhal N, et al. 2014; EASL

ION-1: Reasons for failure to attain SVR

	12 Weeks		24 Weeks	
	LDV-SOF	LDV-SOF+RBV	LDV-SOF	LDV-SOF+RBV
On-treatment failure	0	0	1*	0
Relapse	1	0	1	0
Lost to follow-up	2	4	2	2
Withdrew consent	0	2	1	0

*Undetectable drug levels

Afdhal N, et al. *N Engl J Med*. 2014;370:1889-1898

ION-1: Safety and tolerability

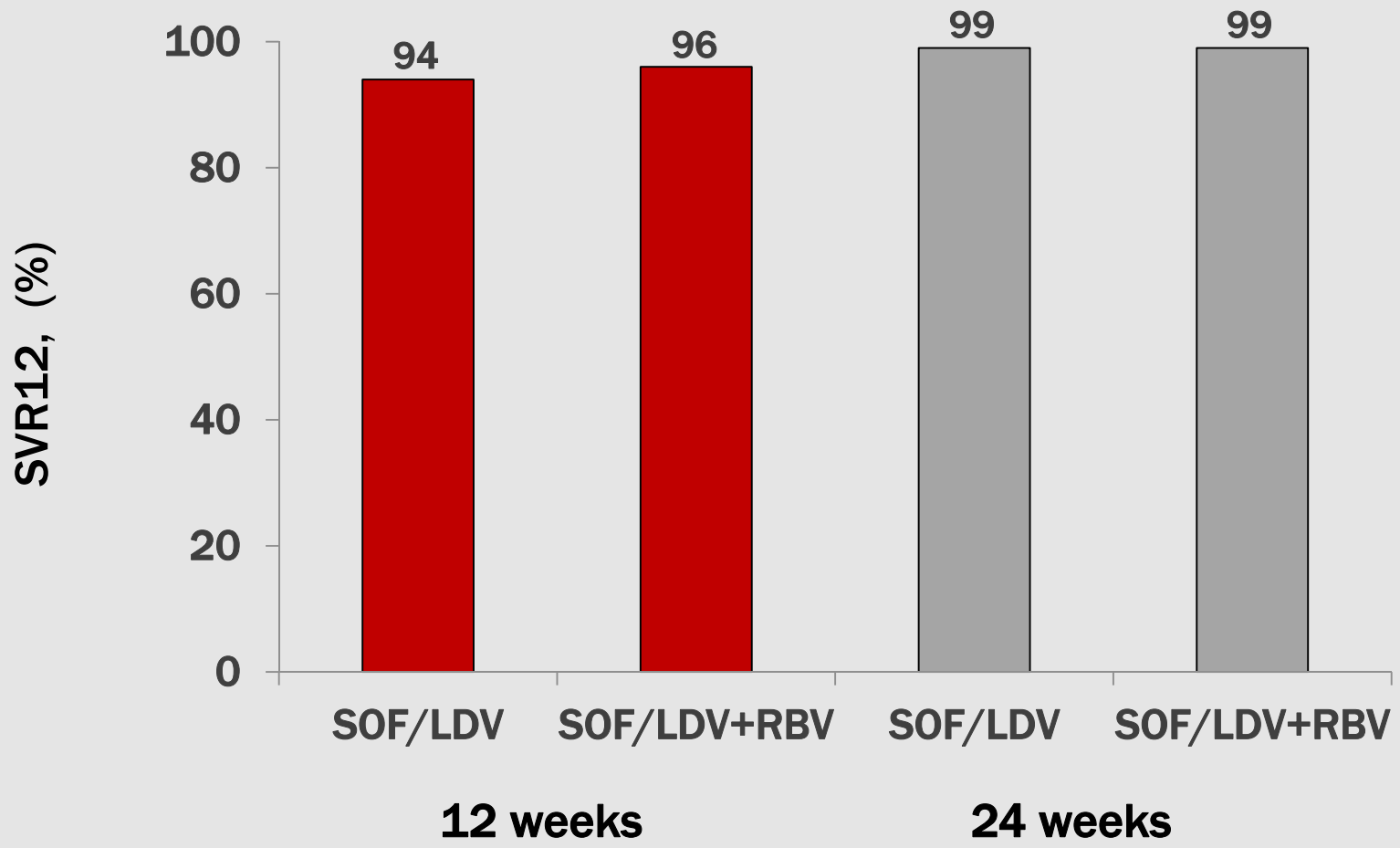
	12 Weeks		24 Weeks	
	LDV-SOF (%)	LDV-SOF+RBV (%)	LDV-SOF (%)	LDV-SOF+RBV(%)
D/C for AEs	0	0	2	3
SAEs	<1	3	8	3
Fatigue	21	36	24	38
Headache	25	23	25	30
Insomnia	8	21	12	22
Nausea	11	17	13	15
Cough	3	10	7	12
Rash	7	10	7	12
Pruritus	5	10	4	9
Anemia	0	12	0	10
Hgb<10 gm/dl	0	9	0	7
Bilirubin>2.5x	0	4	<1	3

List of AEs is not all-inclusive

Afdhal N, et al. *N Engl J Med*. 2014;370:1889-1898

ION-2: Sofosbuvir + ledipasvir ± RBV
Genotype 1, treatment-experienced:
Cirrhosis in 20%

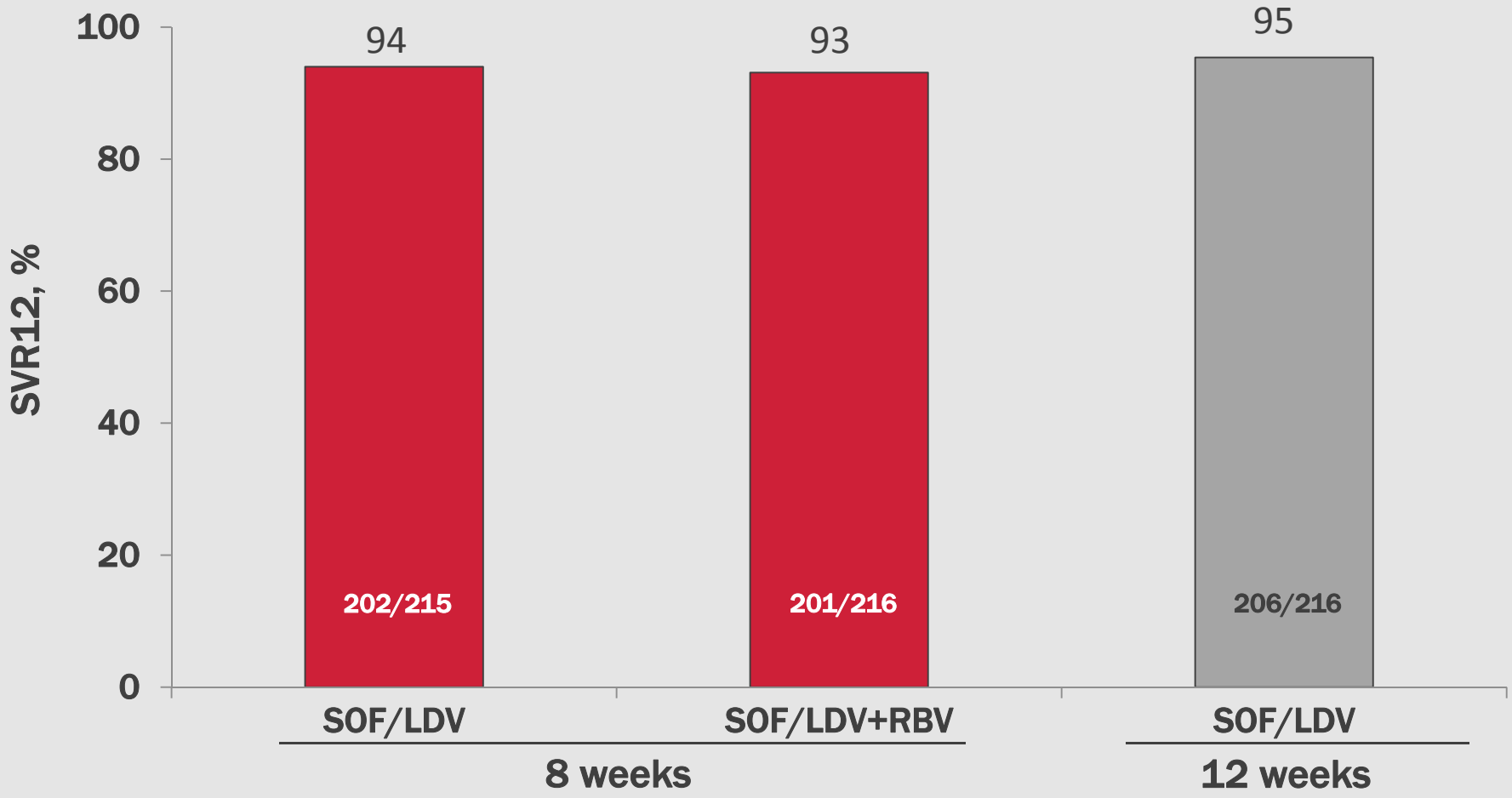
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Afdhal N, et al. *N Engl J Med*. 2014;370:1483-1493

ION-3: Sofosbuvir + ledipasvir + RBV
Genotype 1, treatment-naïve, non-cirrhotic:
8 weeks vs 12 weeks

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Kowdley KV, et al. *N Engl J Med.* 2014:370:1879-1888

Does ION-3 establish 8 weeks as standard duration for G1 non-cirrhotic?

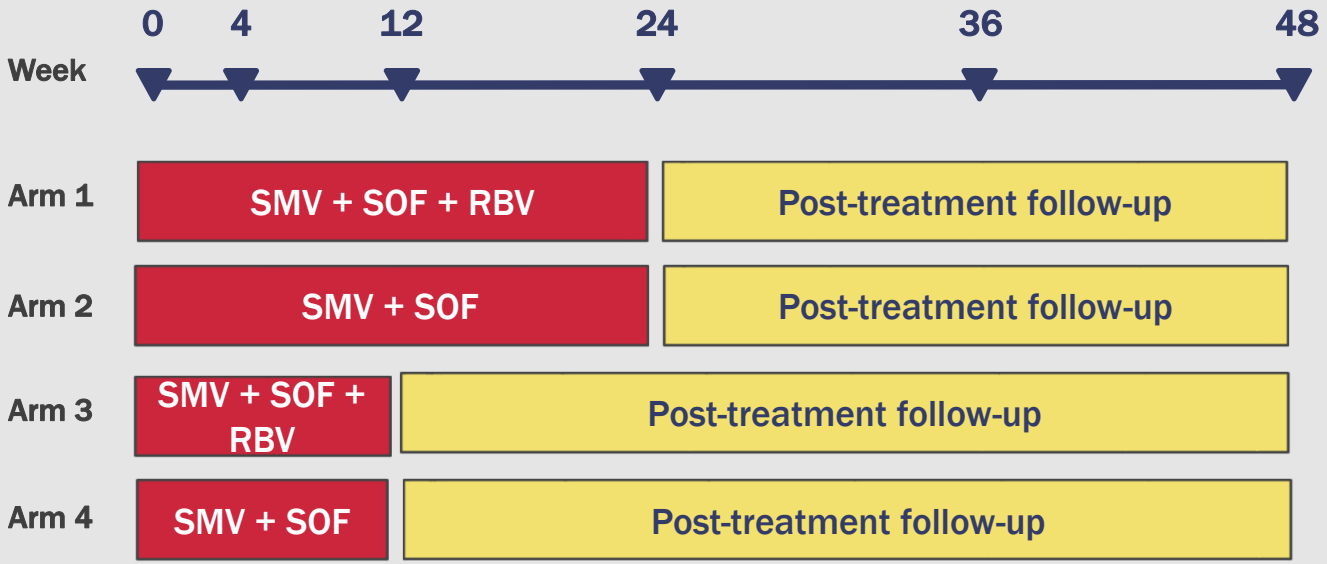
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

	LDV/SOF 8 weeks	LDV/SOF 12 weeks
SVR – overall	94% (202/215)	96% (208/216)
Relapse – overall	5% (11/215)	1% (3/216)
HCV RNA <6M	2% (2/123)	2% (2/131)
HCV RNA ≥6M	10% (9/92)	1% (1/85)

- ~60% of patients had baseline HCV RNA <6M IU/mL
  - Relapse rates identical
  - SVR12: 97% with LDV/SOF 8 weeks, 96% 12 weeks

Package Insert for Harvoni (LDV/SOF). Kowdley KV, et al. *N Engl J Med.* 2014:370:1879-1888

Simeprevir + sofosbuvir + RBV for prior null responders and naïve patients (COSMOS)



Enrollment ratio 2:1:2:1

- Cohort 1: Prior null responders (METAVIR F0-F2)
  - Final SVR12 for all arms
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)
  - Interim SVR4 for Arms 3 and 4
- Total n=167

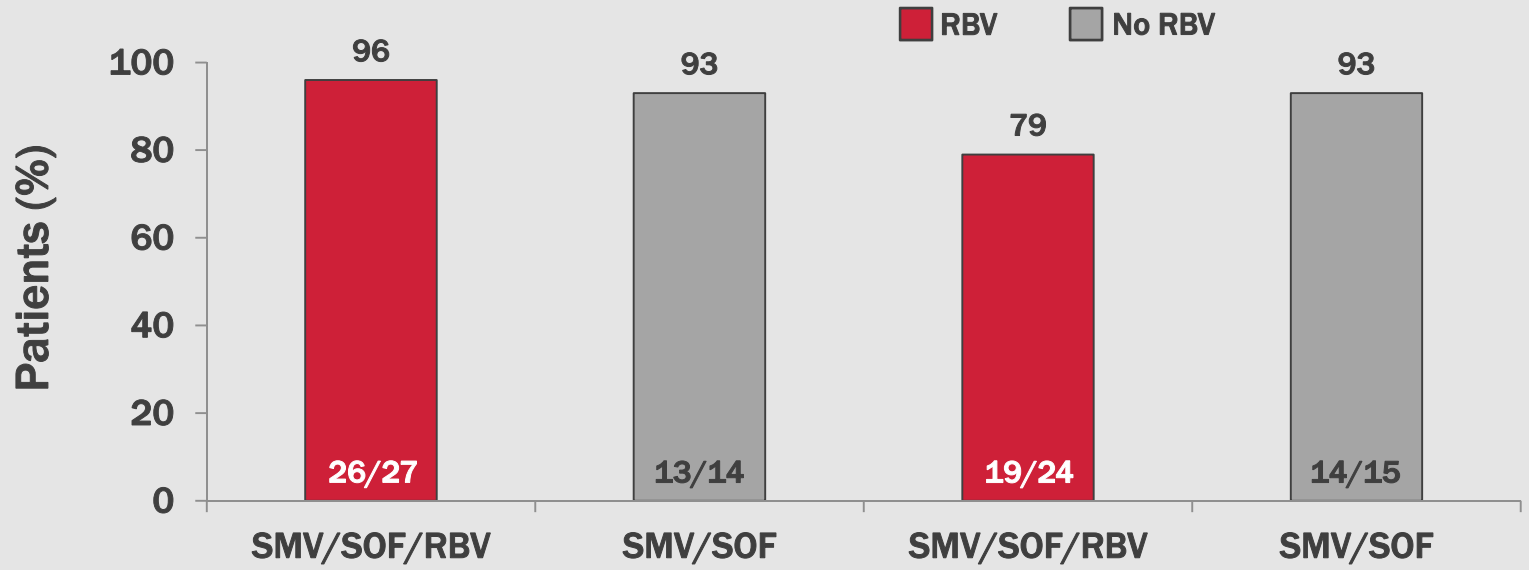
Jacobson IM, et al. 2013; AASLD #LB-3
Lawitz E, *Lancet.* July 26, 2014 epub

COSMOS study: SMV + SOF ± RBV

Final results in cohort 1 (F0-2), n=80 (ITT)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- 80 null responders to PR with F0–2
- 61% male, 29% AA, 78% G1a (half with Q80K)



	12-week treatment		24-week treatment	
Relapse	1/27	1/14	1/24	0/15
Non-virologic failure	0/27	0/14	4/24	1/15

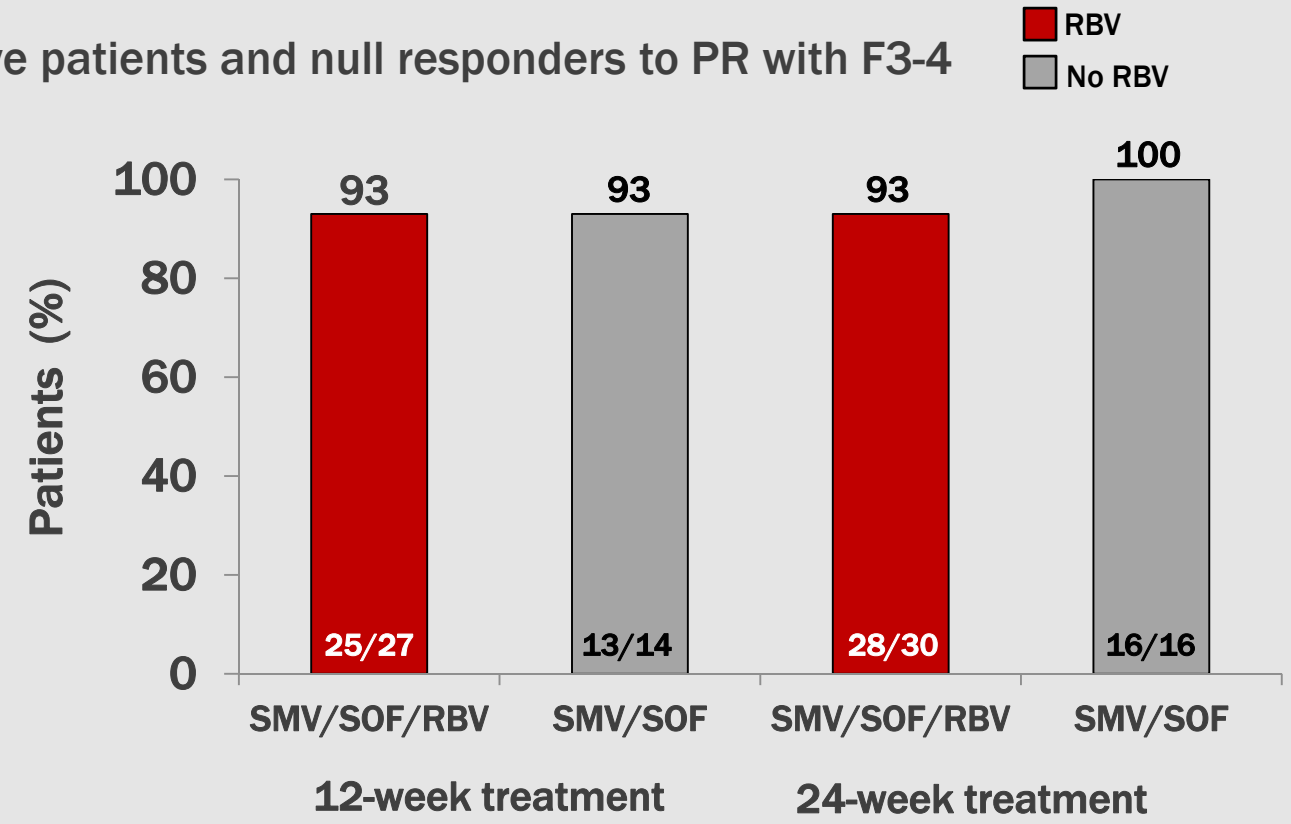
Sulkowski M, et al. 2014; EASL: London #07. Lawitz E, et al. *Lancet*. July 26 2014 epub

COSMOS Study: SMV + SOF ± RBV

Final results in cohort 2 (F3-4), n=87 (ITT)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- 87 naïve patients and null responders to PR with F3-4

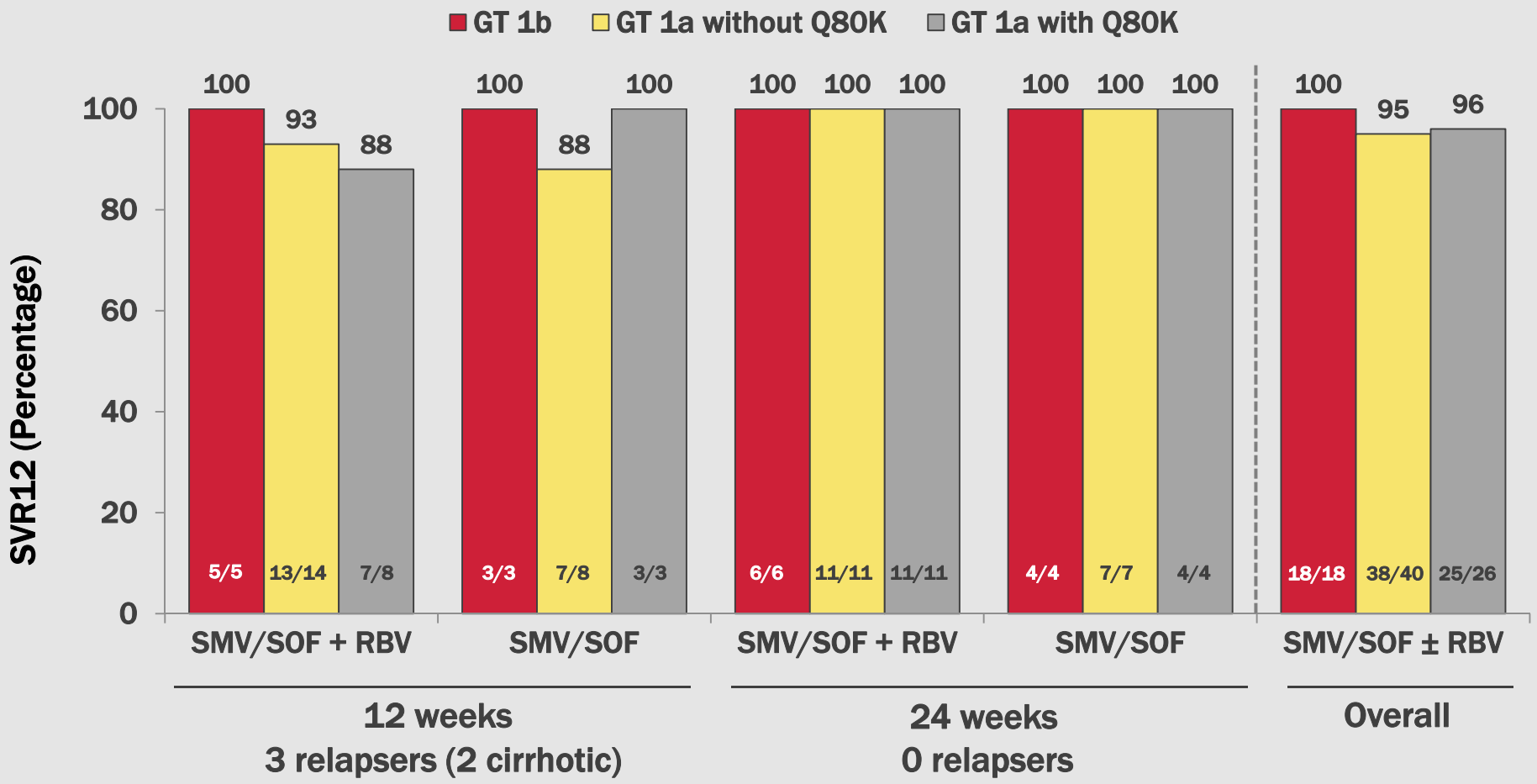


Relapse	2/27	1/14	0/30	0/16
Non-virologic failure	0/27	0/14	2/30	0/15

Sulkowski M, et al. EASL 2014, London. #07

COSMOS: Final results in cohort 2

(Excludes non-virologic failures)



Lawitz E, et al. 2014; EASL #0165

COSMOS study (cohort 2): Safety with simeprevir + sofosbuvir ± RBV

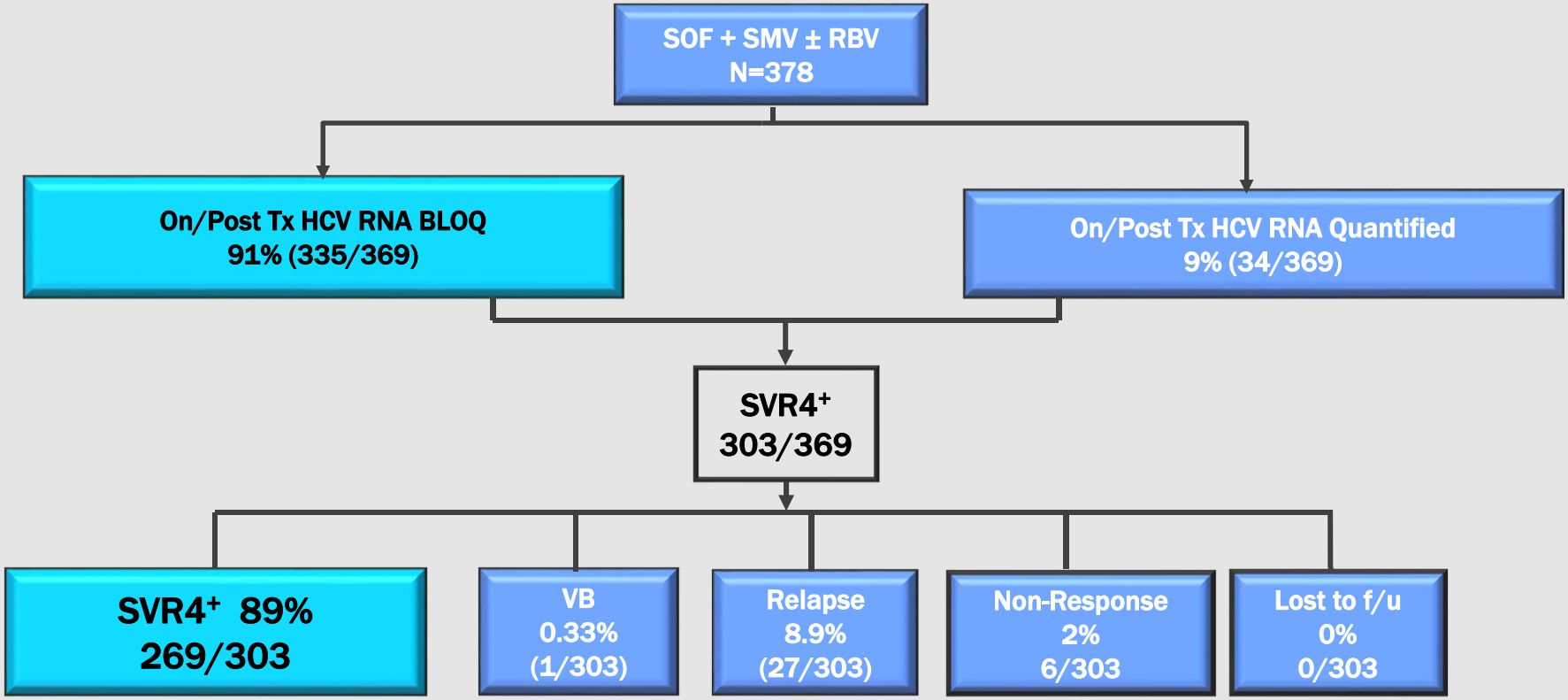
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

	12 Weeks		24 Weeks	
	Simeprevir Sofosbuvir RBV (n=30)	Simeprevir Sofosbuvir – (n=16)	Simeprevir Sofosbuvir RBV (n=27)	Simeprevir Sofosbuvir – (n=14)
Grade 3/4 events (%)				
Adverse events	16.7	12.5	3.7	7.1
Hyperbilirubinemia*	13.3	6.3	3.7	7.1
Discontinuations due to adverse events (%)	0	6.3	0	0
Common adverse events (%)				
Fatigue	50	38	33	21
Headache	23	18	19	14
Nausea	20	19	15	14
Anemia	23	6	11	0
Pruritus	17	6	11	14
Dizziness	13	19	11	7
Rash	13	0	19	7

*Simeprevir interacts with bilirubin transporters

Lawitz E, et al. *Lancet.* 2014;384:1756-1765.

HCV RNA outcomes for SOF/SMV+/-RBV: G1



SVR4+

No cirrhosis:	92% (113/123)	G1a:	89% (47/53)
Cirrhosis:	87% (156/180)	G1b:	95% (88/93)

Cohort of patients with treatment start on or before 4/15/14; BLOQ=below level of quantitation.

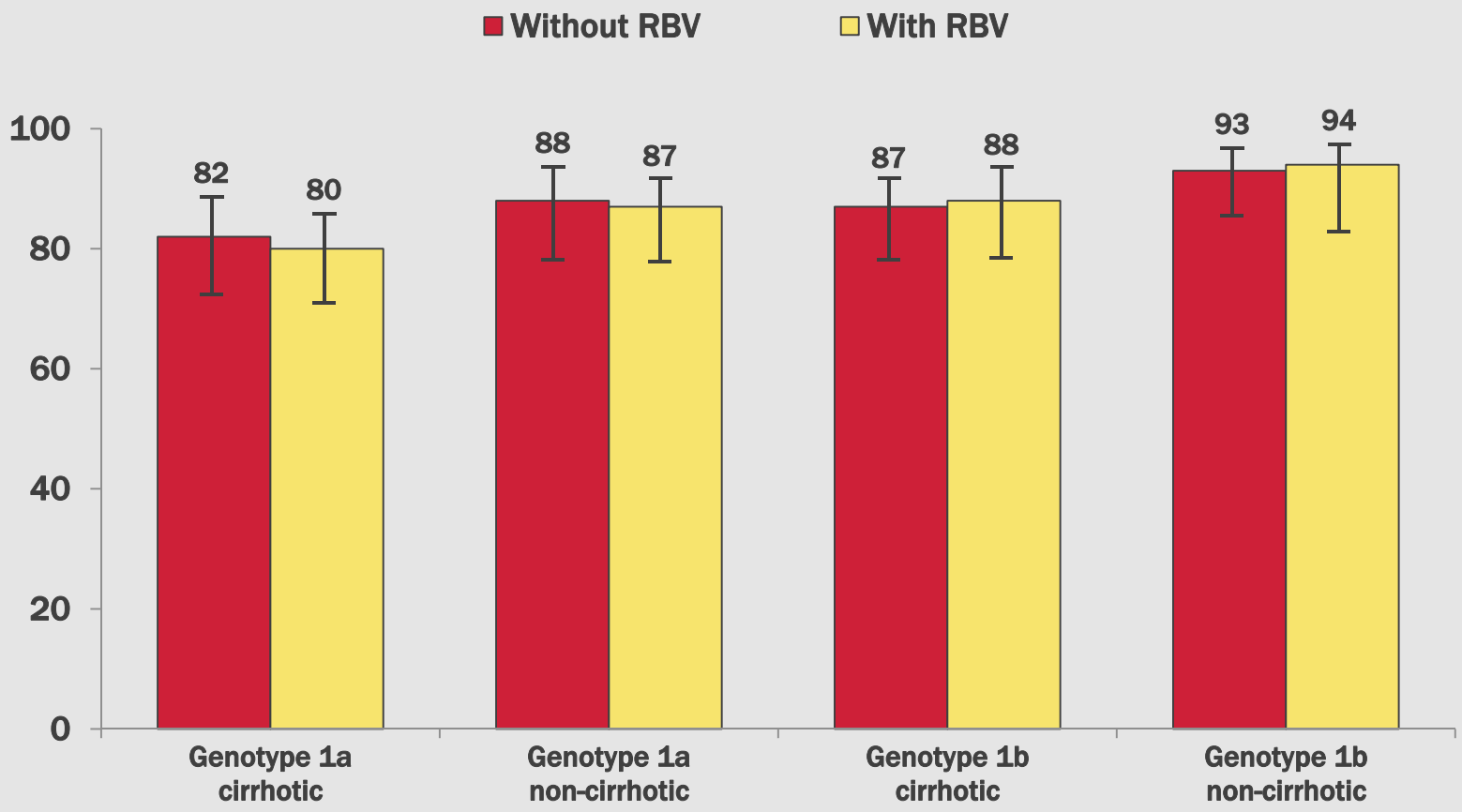
Sulkowski M, et al. 2014; AASLD

HCV-TARGET

SOF Containing Regimens

TARGET SIM/SOF

Adjusted SVR4 by RBV, G1 subtype, and cirrhosis

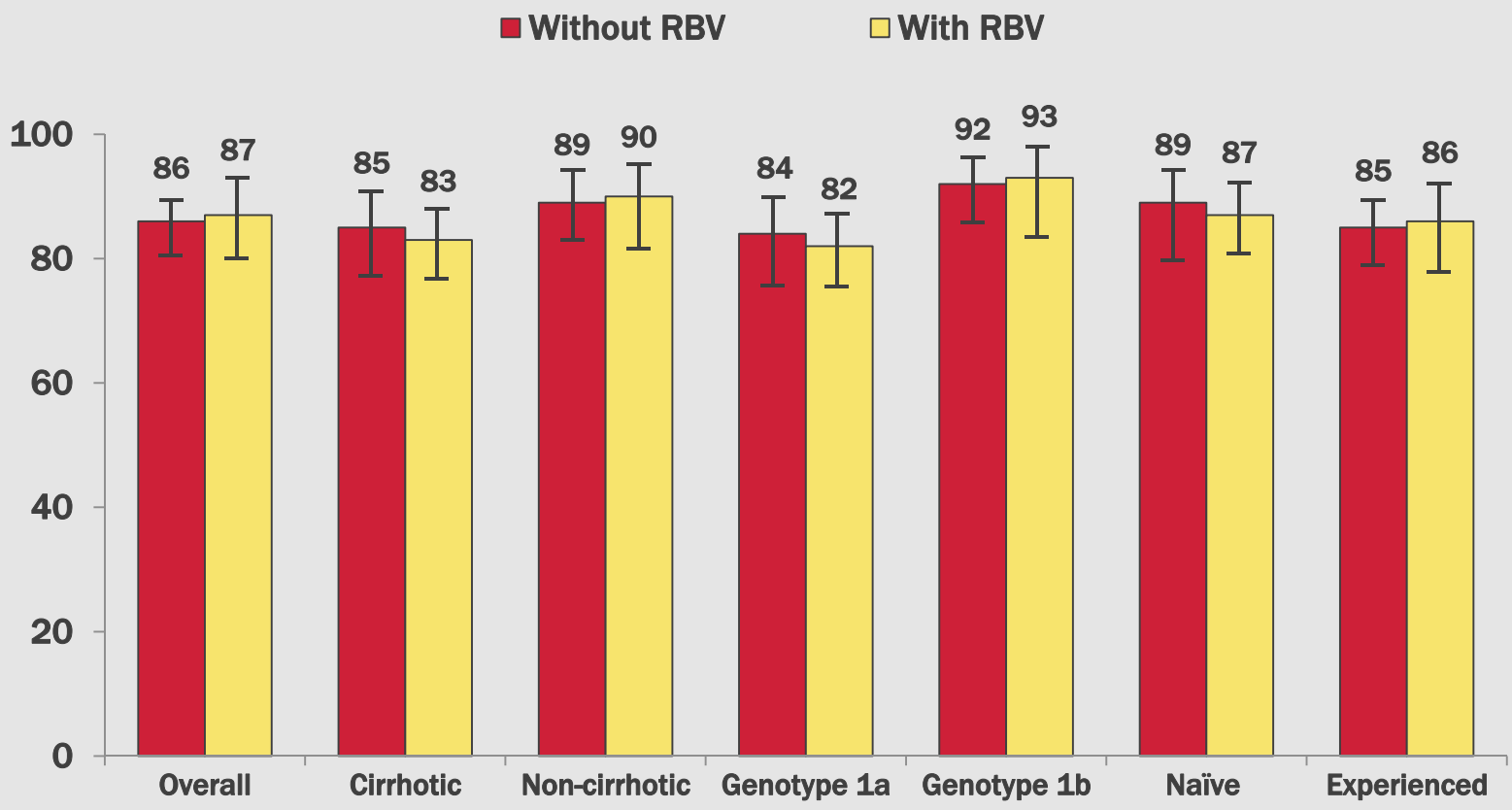


Is the difference between GT1a and 1b related to Q80K?

Sulkowski M, et al. 2014; AASLD

TARGET SIM/SOF

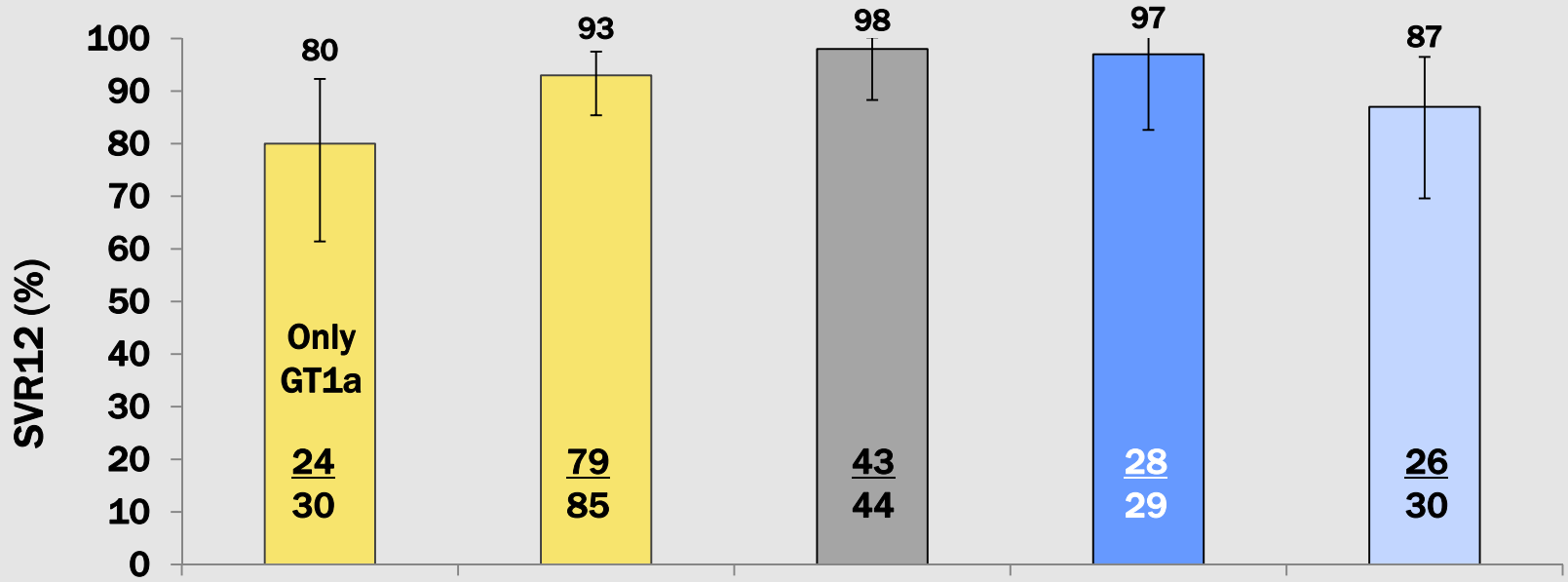
SVR4 rates by subgroups: No impact of ribavirin



Sulkowski M, et al. 2014; AASLD

Grazoprevir + elbasvir ± ribavirin in HCV mono-infected and HIV/HCV co-infected, treatment-naïve, non-cirrhotic patients with HCV GT1 infection: The C-WORTHY study

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



	HCV Mono-infected			HIV/HCV Co-infected	
Treatment Duration	8 weeks	12 weeks	12 weeks	12 weeks	12 weeks
RBV	+ RBV	+ RBV	No RBV	+ RBV	No RBV
LTFU* or discontinued early not due to virologic failure	1	3	0	0	2
Breakthrough	0	1†	0	0	2
Relapse	5	2‡	1	1	0

*LTFU=Lost to follow-up; †Breakthrough was due to HCV GT2b (minor GT2b variant at baseline); ‡One of the patients who relapsed did not receive grazoprevir and received only elbasvir + RBV for the first month of treatment. Regimens not yet FDA approved.

Sulkowski M, et al. *Lancet*. Available online November 11, 2014. DOI: 10.1016/S0140-6736(14)61793-1t

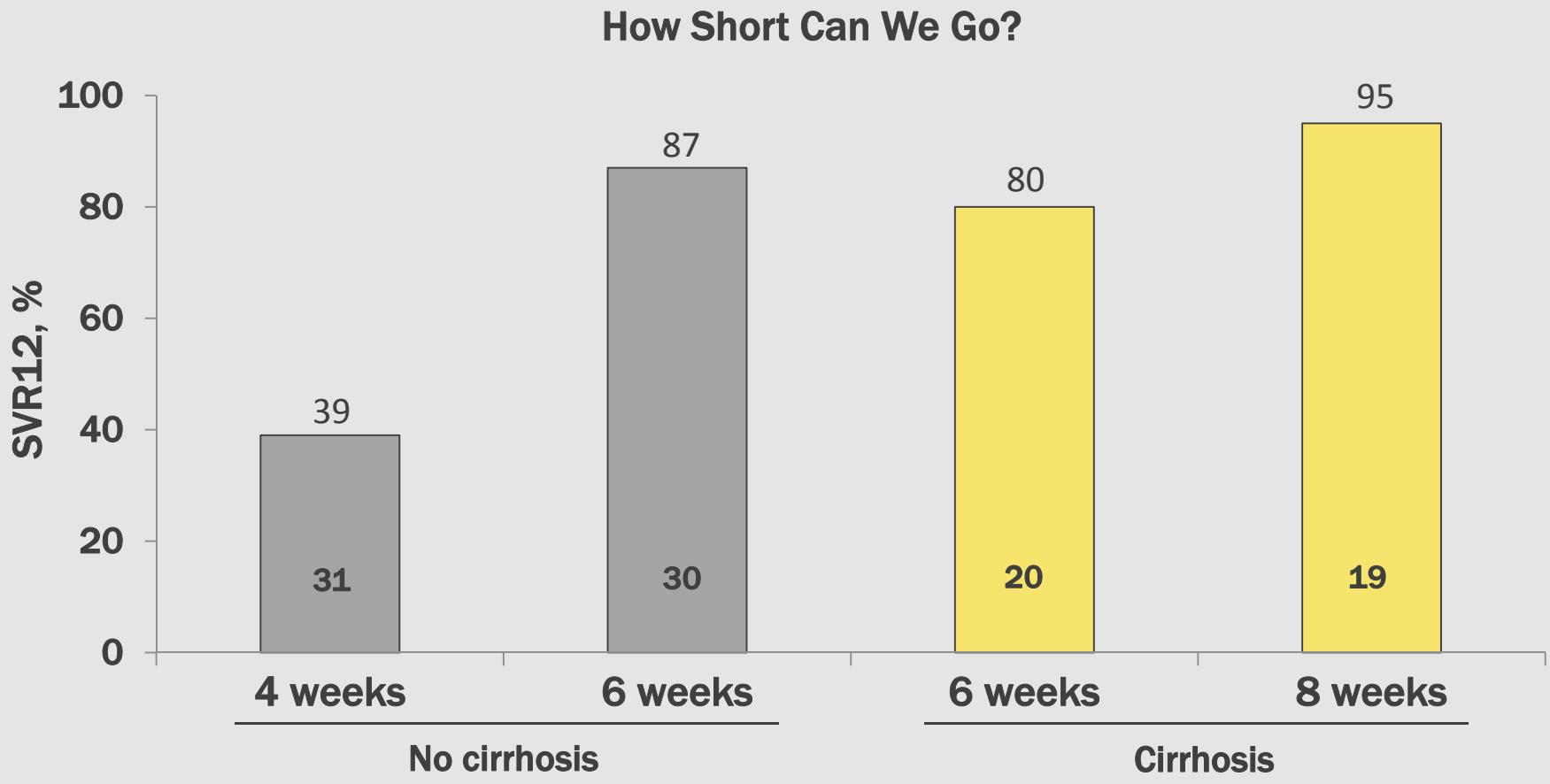
C-WORTHY STUDY: Adverse event and laboratory safety summary during treatment

	HCV Mono-infected		HIV/HCV Co-infected	
	Grazoprevir + Elbasvir + RBV N=116*	Grazoprevir + Elbasvir (No RBV) N=43*	Grazoprevir + Elbasvir + RBV N=29	Grazoprevir + Elbasvir (No RBV) N=30
Serious adverse event	1† (1%)	0 (0%)	1‡ (3%)	1§ (3%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemoglobin <10 g/dL	10 (9%)	0 (0%)	1 (3%)	0 (0%)
Total bilirubin >5xULN	0 (0%)	0 (0%)	2 (7%)	0 (0%)
ALT/AST >2x to ≤5xULN after initial normalization	1 (1%)	1 (2%)	0 (0%)	1 (3%)
ALT/AST >5xULN after initial normalization	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Change in CD4 from baseline (cells/mm^3, mean (SD))	N/A	N/A	-47 (176)	52 (178)
HIV breakthrough	N/A	N/A	0 (0%)	0 (0%)

*One patient received RBV but was assigned the RBV-free arm. For the analysis of safety, this patient is in the + RBV group.
Serious AEs were: †nausea (related to study drug); ‡ asthenia (related to study drug);
§ Staphylococcal infection (not related to study drug)

Sulkowski M, et al. *Lancet*. Available online November 11, 2014. DOI: 10.1016/S0140-6736(14)61793-1t

C-SWIFT study: Grazoprevir + elbatasvir + sofosbuvir for 4, 6, or 8 weeks



Regimens not yet FDA approved

Lawitz E, et al. 2014; AASLD

Potential drivers of regimen choices in GT1 patients

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014