New from AASLD
Non-Nucs Regimens

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Direct-Acting Antiviral Agents (DAAs)

NS3 /4A Inhibitors (Protease inhibitor PI)

High potency

Limited genotypic coverage

Low barrier to resistance

NS5B Nucleos(t)ide Inhibitors (NI)

Intermediate potency

Pan genotypic coverage

High barrier to resistance

NS5A Inhibitors

High potency

Multi-genotypic coverage

Low barrier to resistance

NS5B Non Nucleoside Inhibitors (NNI)

Intermediate potency

Limited genotypic coverage

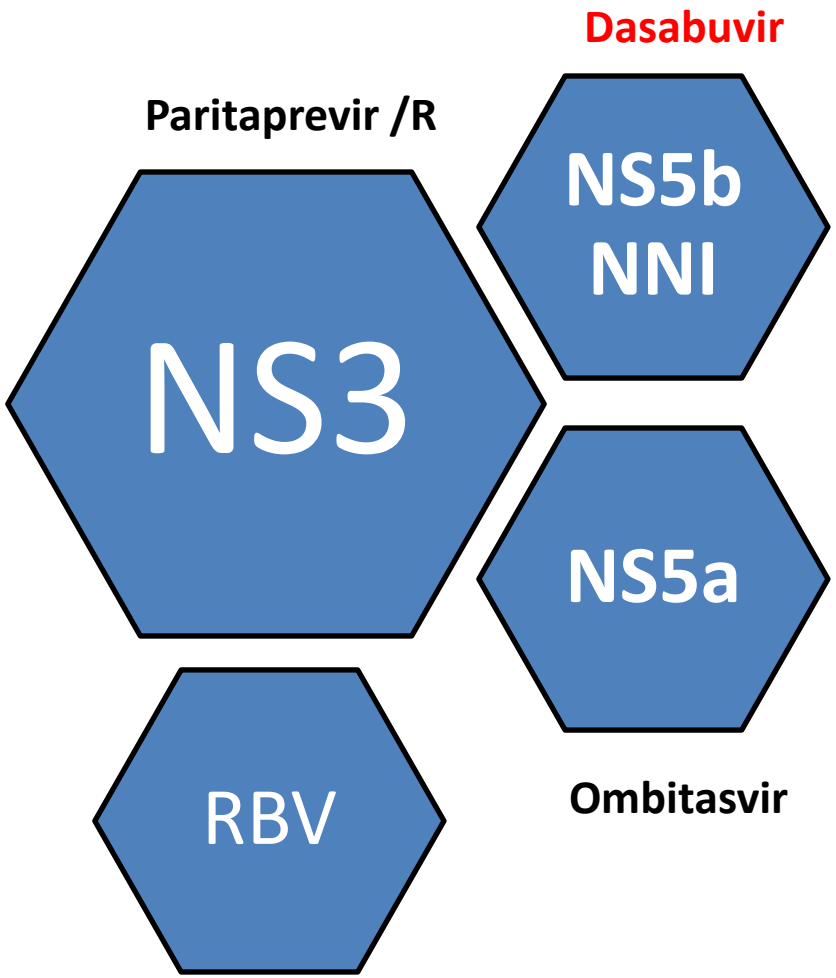
Low barrier to resistance

Phase III studies
Non-nucleoside NS5B polymerase inhibitors

- **Dasabuvir**
  - 250 mg Twice daily
  - Combination with Paritaprevir/R, and Ombitasvir
  - Activity against Genotype 1&4

- **Beclabuvir**
  - 75 mg Twice daily
  - Combination with Daclatasvir and Asunaprevir
  - Activity against genotype 1&4

AbbVie 3D regimen



Studies Phase 3: Paritaprevir/r + Ombitasvir + Dasavubir± RBV in Genotype 1 patients

Sapphire GT1a + 1b

SAPPHIRE-I[1] N=631 Naive

SAPPHIRE-II[2] N=394 Treatment Experienced

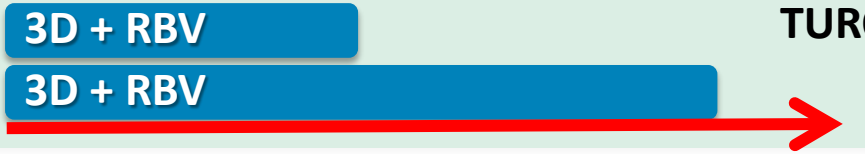
Pearl GT1a or GT1b

PEARL-II[3] N=186 1b Treatment Experienced

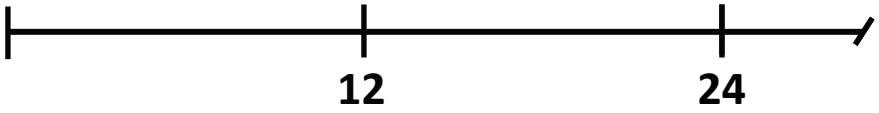
PEARL-III[4] N=419 1b Naïve (RBV Placebo)

PEARL-IV[4] N=305 1a Naïve (RBV Placebo)

Turquoise-II GT1a + 1b



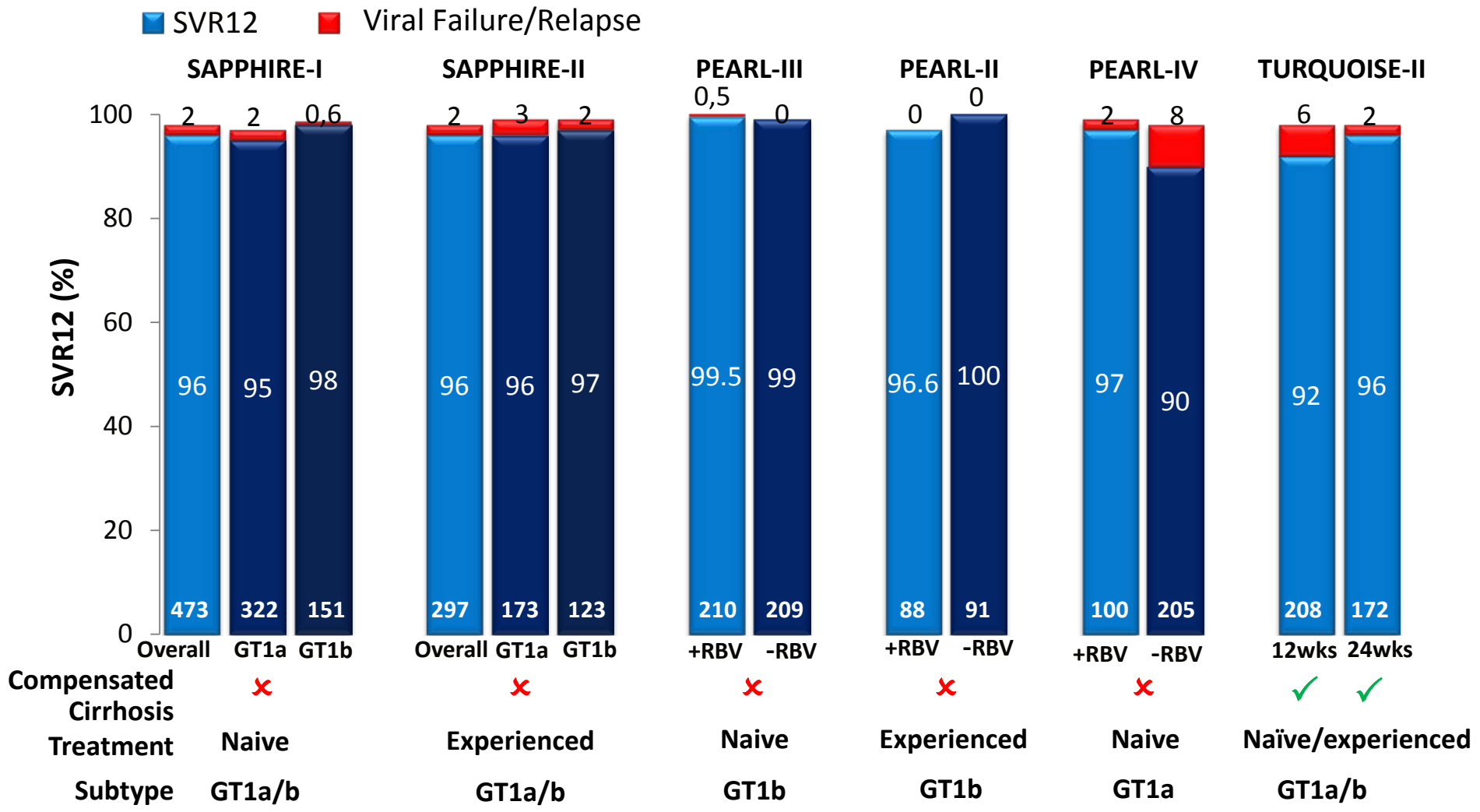
TURQUOISE-II[5] N=380 **1a/b compensated Cirrhotics**
Naïve and Treatment Experienced



3D: co-formulated ABT450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
RBV: 1000-1200 mg daily according to body weight (<75 kg and ≥75kg, respectively)

1. Feld JJ, et al. NEJM 2014; 370(17): 1594-603.
2. Zeuzem S, et al. NEJM 2014; 370(17):1604-14.
3. Andreone P, et al. Gastroenterology 2014;147:359-365.
4. Ferenci P, et al. NEJM 2014; 370(21):1983-92.
5. Poordad F, et al. NEJM 2014; 370(21):1973-82.

SVR 12 in Phase 3 studies with Paritaprevir-R/ombitasvir and Dasabuvir±Ribavirin in Genotype 1 patients



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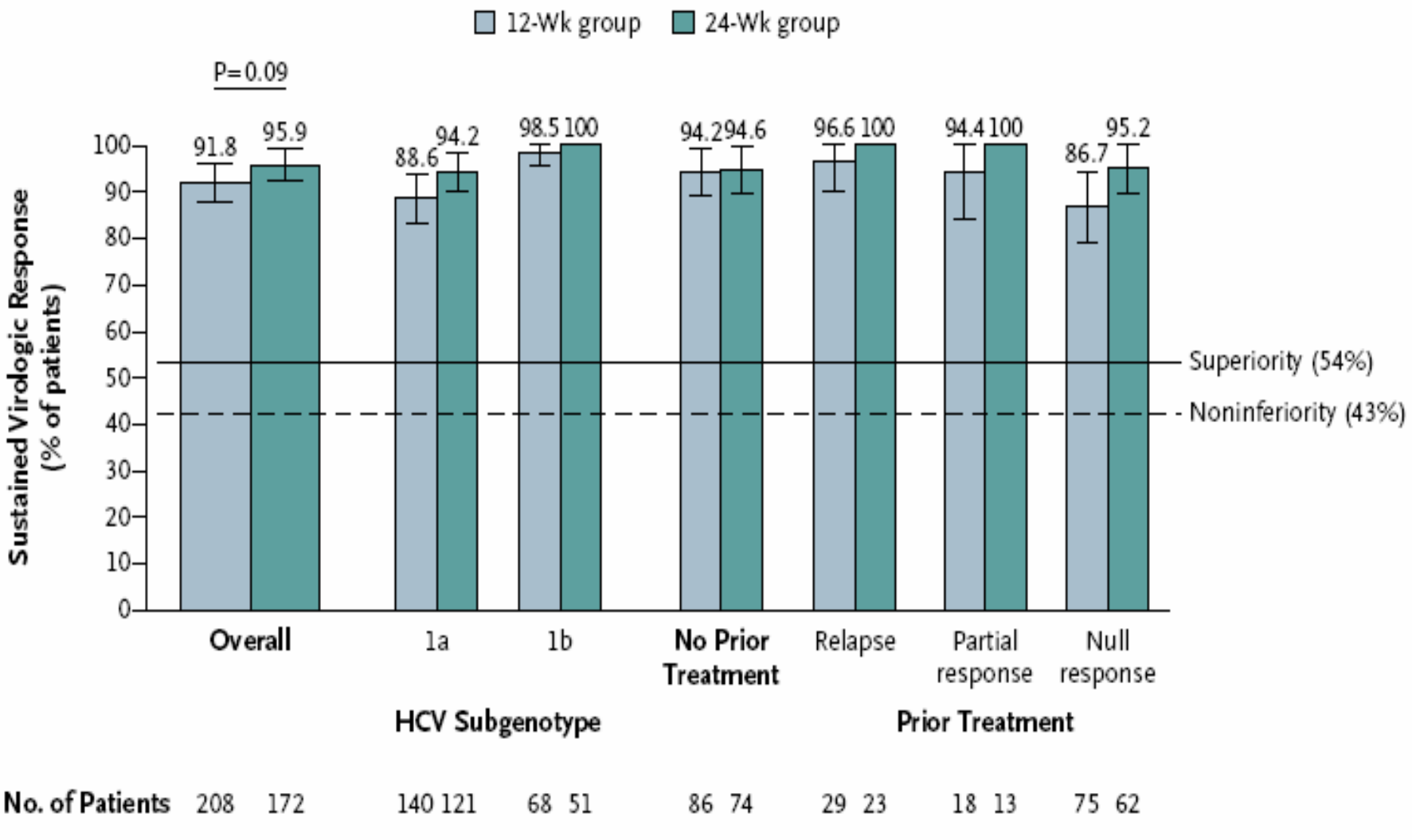
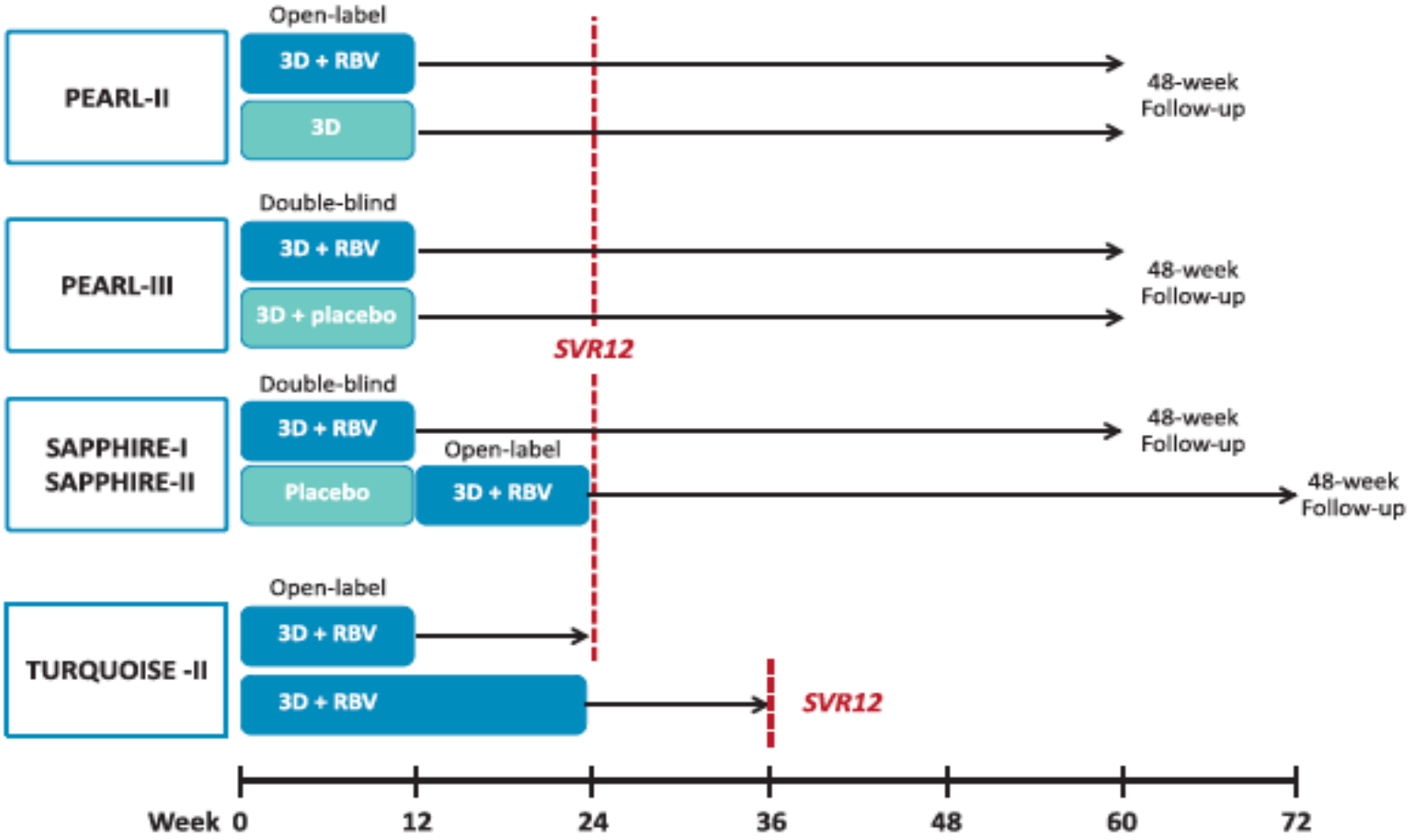
TURQUOISE-II: 3D + RBV in GT1, treatment-naive and -experienced cirrhotic patients (No=380) – SVR12 rates



Poordad F, et al. N Engl J Med 2014

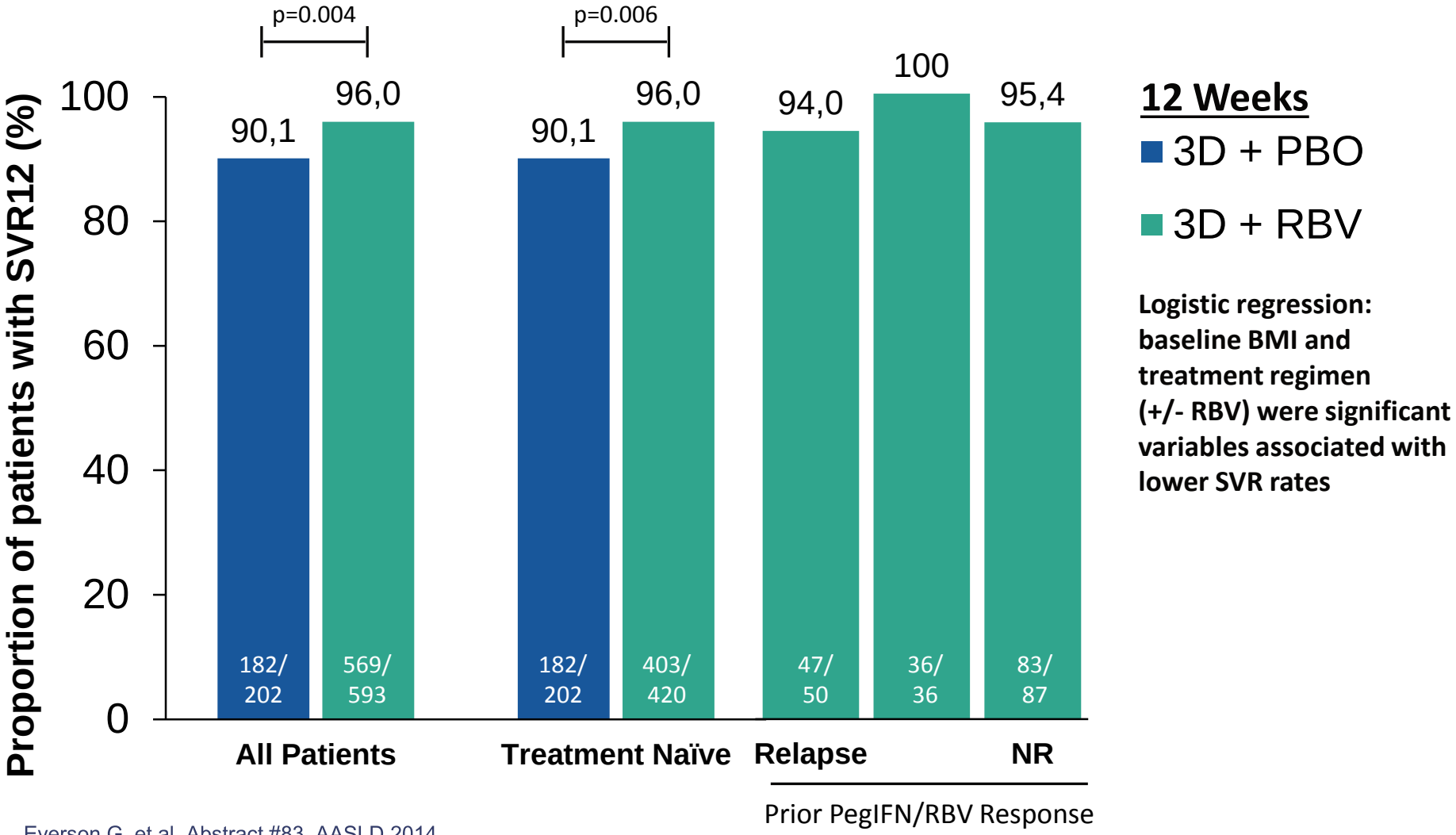
An integrated anaylsis of the Studies with the 3 D regimens

Figure 1. Study Designs



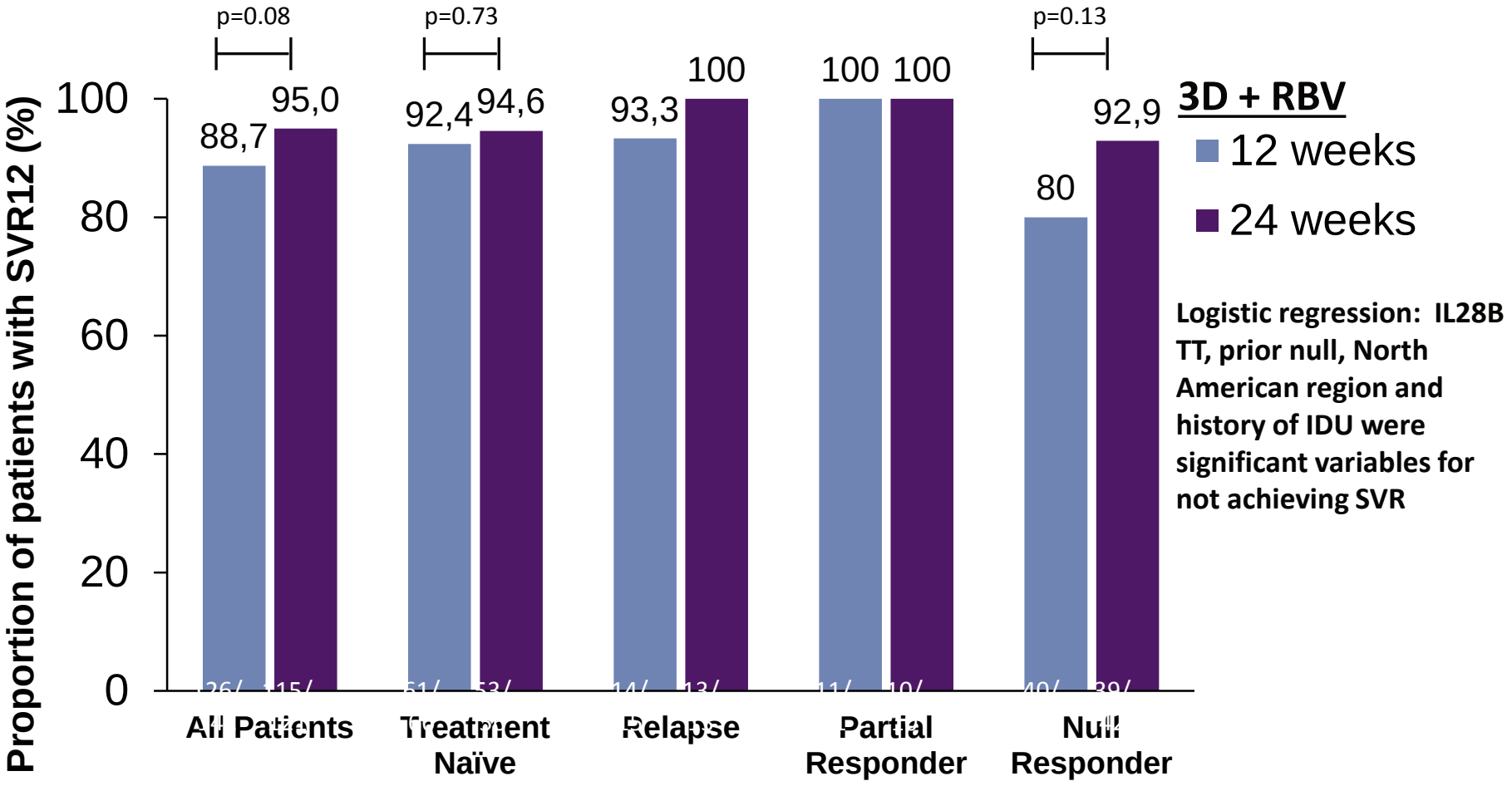
Integrated efficacy analysis of Phase 3 studies in G1a patients treated with 3 regimen ± RBV for 12 weeks.

SVR12 in GT 1a **Non-cirrhotic Patients**



Everson G, et al. Abstract #83, AASLD 2014

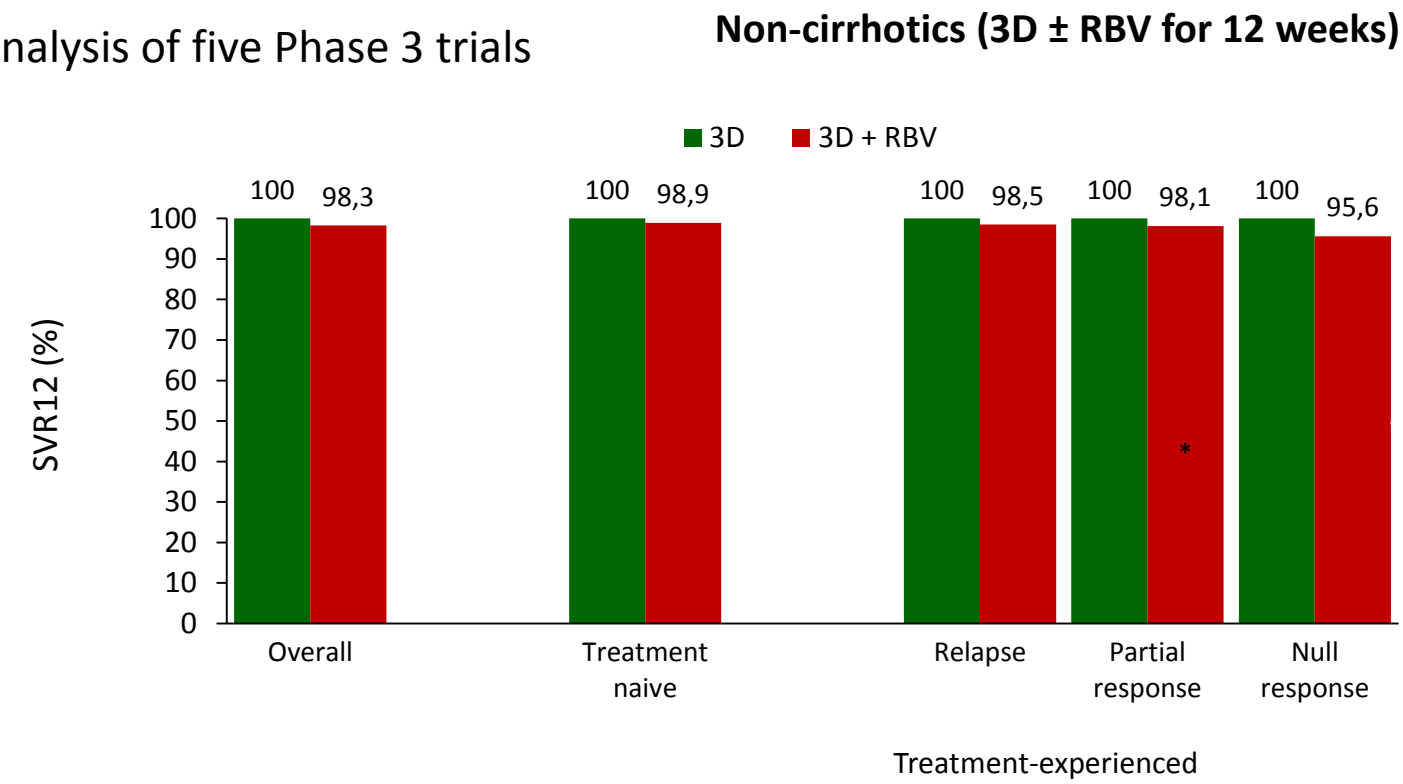
SVR12 in GT 1a **Cirrhotic Patients**: 3D Regimen + RBV for 12 vs 24 Weeks



Fried M, et al. Abstract #81, AASLD 2014

High SVR12 rates in 992 G1b Non-Cirrhotics patients treated with Paritaprevir-r/ombitasvir + dasabuvir ± RBV

- Pooled analysis of five Phase 3 trials



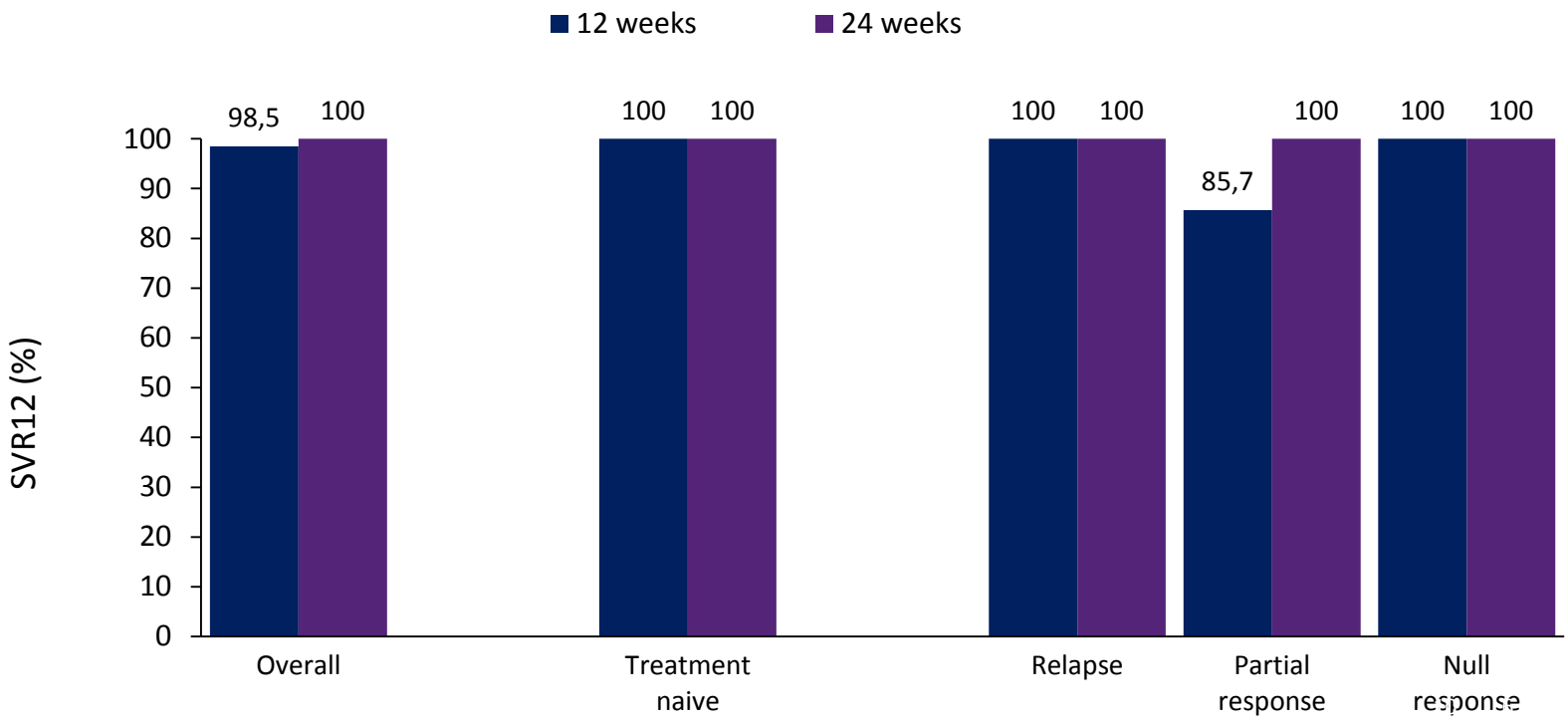
12 weeks of 3D regimen achieved a high SVR rates
RBV is not needed in non cirrhotics G1 b patients

Colombo M, et al. AASLD 2014, Boston. #1931

SVR12 rate of 98.6% in 992 G1b Cirrhotics treated with Paritaprevir/r/ombitasvir + dasabuvir ± RBV

- Pooled analysis of five Phase 3 trials
- Cirrhotics in the TURQUOISE-II received 3D + RBV for either 12 or 24 wks)

Cirrhotics (3D + RBV for 12 or 24 weeks)

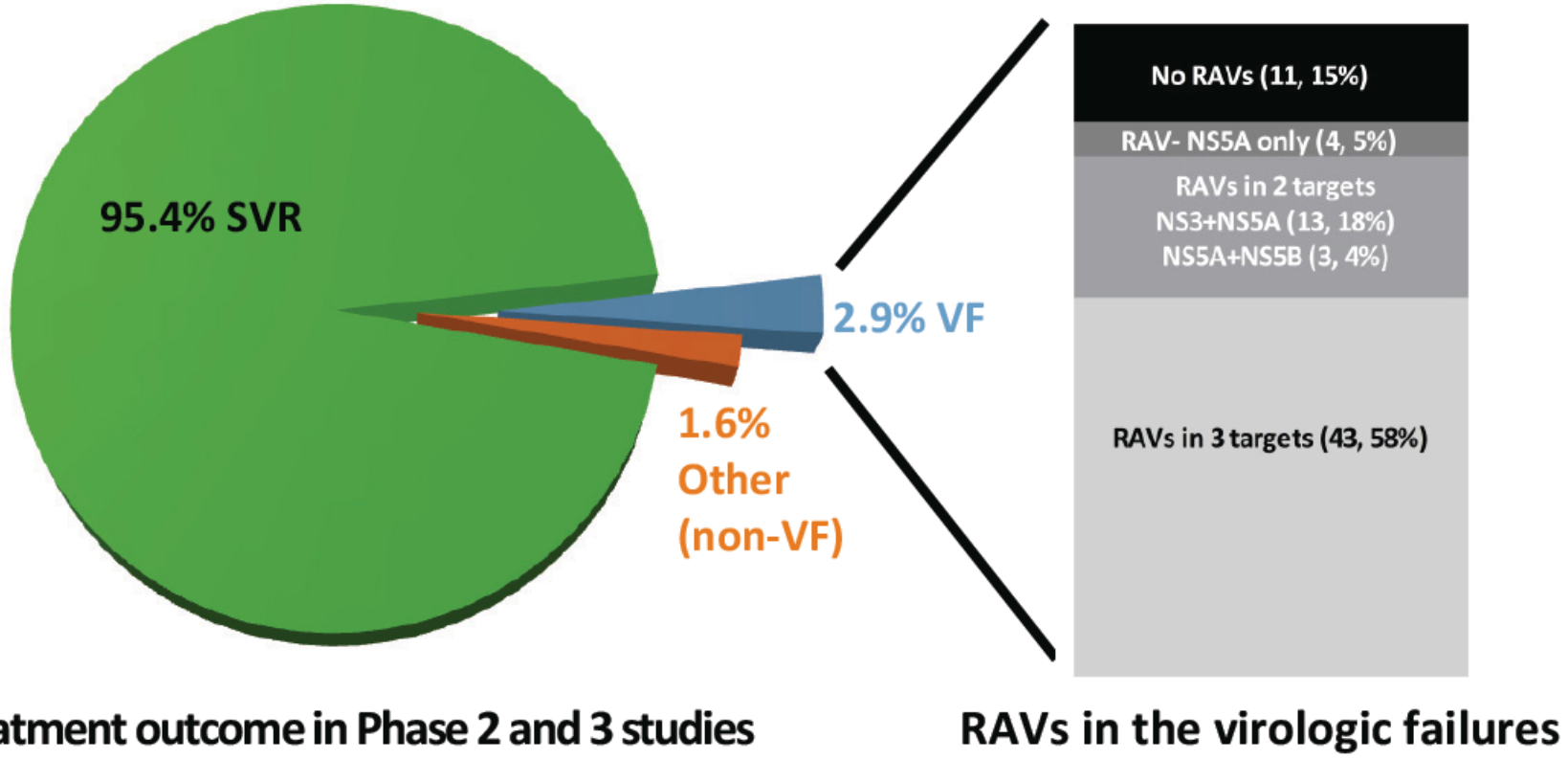


All Patients with Ribavirin
24 weeks is not superior to 12 wks regimen

Colombo M, et al. AASLD 2014, Boston. #1931

Pooled Analysis of Resistance in Patients Treated With 3D regimen ±Ribavirin in Phase 2 and Phase 3 Clinical Trials

2509 HCV genotype 1 patients were treated in the 3 Phase 2 and 6 Phase 3 clinical trials, there were a total of 74 virologic failures (67 GT 1a and 7 GT 1b), including 20 on-treatment virologic failures and 54 relapsers



Treatment outcome in Phase 2 and 3 studies

RAVs in the virologic failures

Krishnan P et al. AASLD 2014

Conclusions

GT 1a patients without cirrhosis benefit from RBV inclusion in 12 week treatment regimen (SVR12=96%)

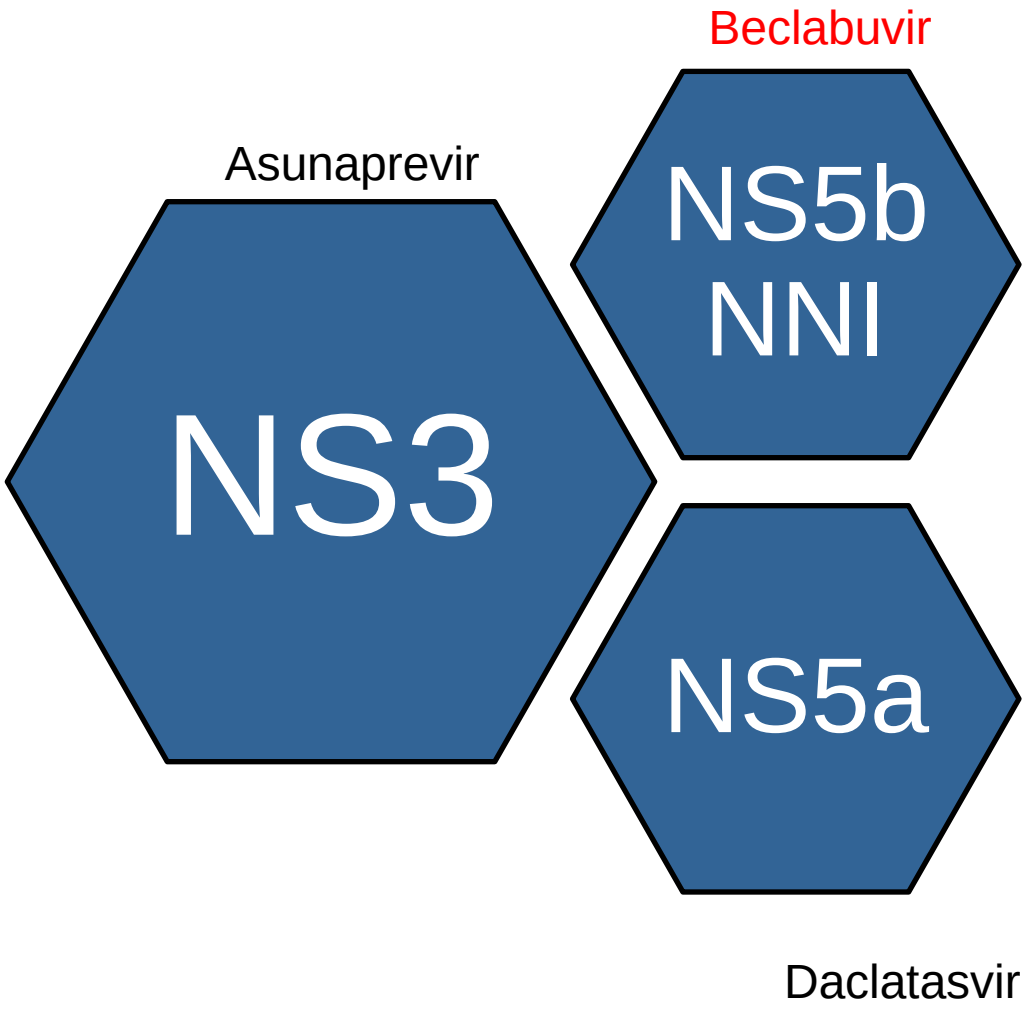
GT 1a patients with cirrhosis achieved SVR12 rates >90% with 3D + RBV regimen for 12 wks

- Prior PR null responders may benefit from longer treatment duration

GT1b patients without cirrhosis achieved higher SVR with 12 wks and without ribavirin

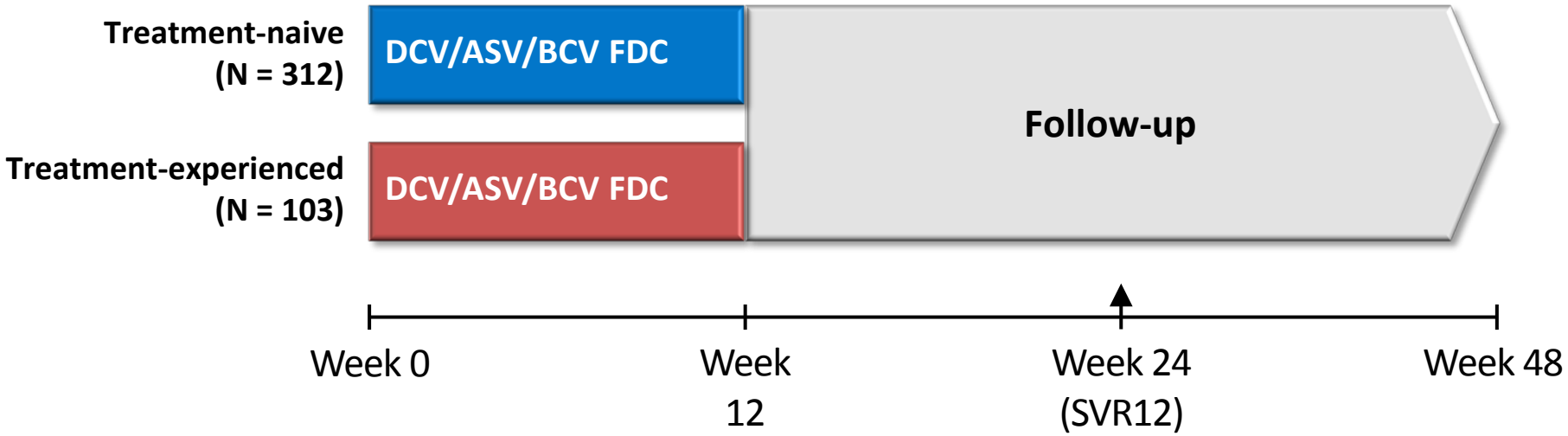
GT1b patients with cirrhosis can be treated with 12 weeks 3D regimen and Ribavirin

All Oral Daclatasvir Trio regimen



DCV / ASV / BCV co-formulated as twice-daily fixed-dose combination (FDC)

UNITY-1 Study Design (AI443-102)
Non-Cirrhotics Genotype 1



Primary Endpoint

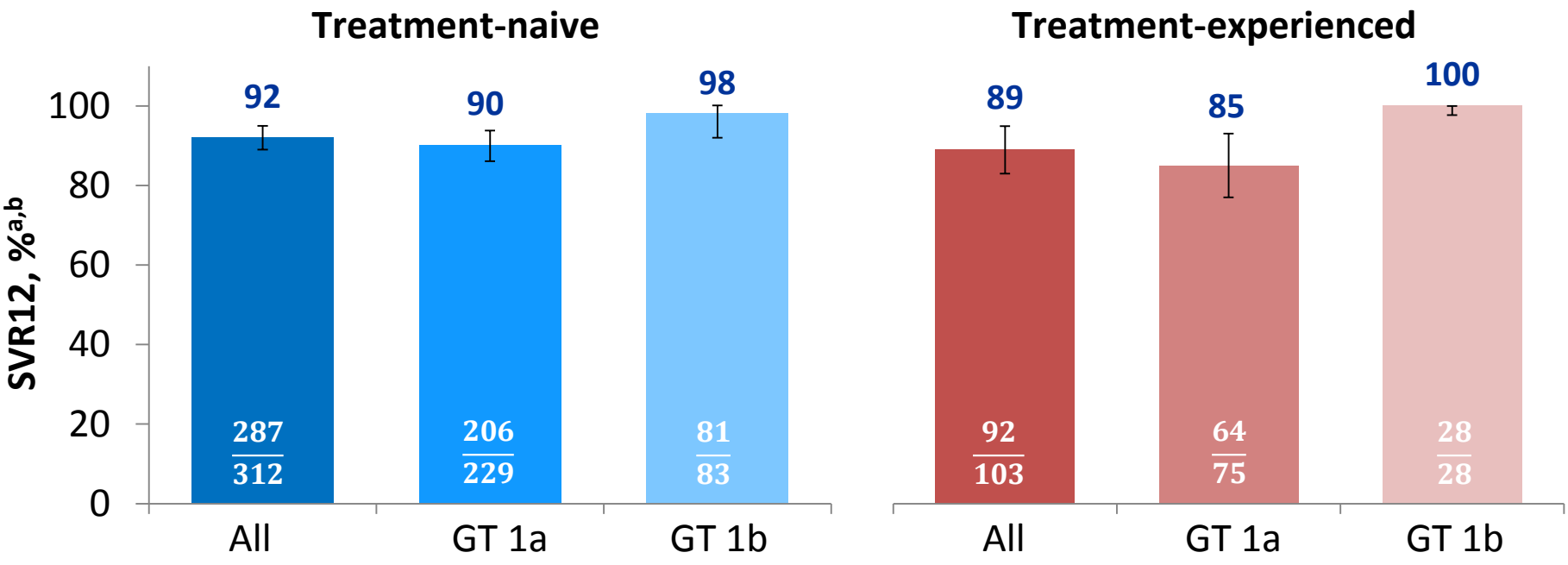
- SVR12 in treatment-naive patients
  - HCV RNA < lower limit of quantitation (LLOQ) at posttreatment Week 12
  - Demonstrate SVR12 is significantly greater than historical threshold of 79% (based on an analysis of sofosbuvir plus peginterferon/ribavirin data)
  - Assessed using the Roche HCV COBAS TaqMan® test v2.0 (LLOQ, 25 IU/mL)

Treatment regimen

- Twice-daily, fixed-dose combination tablet (DCV-TRIO)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg

Poordad F *et al. AASLD* 2014. Poster LB-7

SVR12 Rates by Patient Population

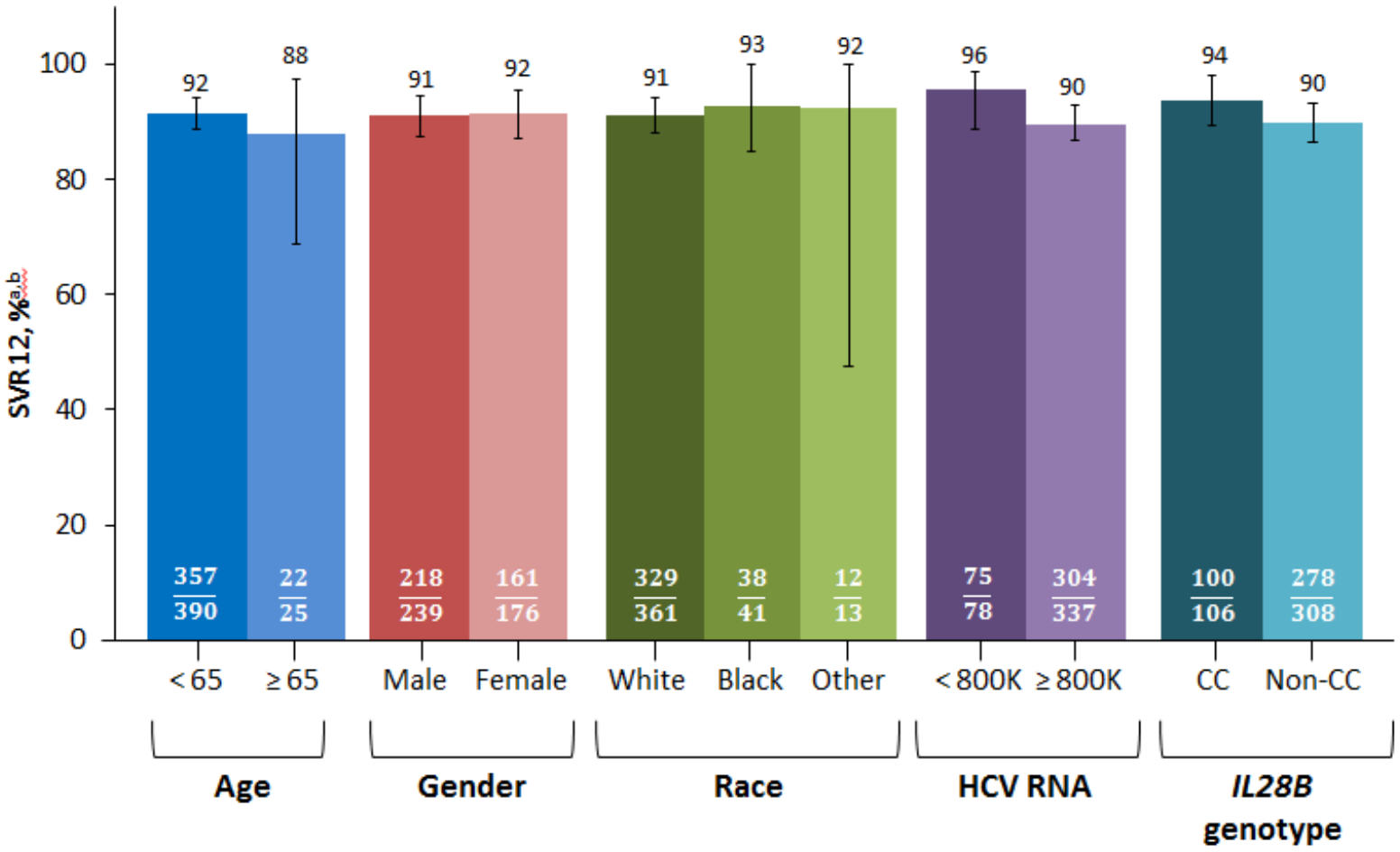


- High SVR12 rates (98–100%) were observed in treatment-naive and treatment-experienced patients infected with HCV GT 1b

[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

Poordad F *et al. AASLD* 2014. Poster LB-7

SVR12 by Baseline Factors



- SVR12 rates were high across patient subgroups based on baseline characteristics

[a] HCV RNA < LLOQ (25 IU/mL); patients with missing SVR12 data counted as treatment failures.
[b] Error bars reflect 95% CI.

Poordad F *et al. AASLD* 2014. Poster LB-7

On-Treatment Safety

Parameter, n (%)	All patients (N = 415)
Death[a]	1 (0.2)
Serious AEs[b]	7 (2)
AEs leading to discontinuation[c]	3 (0.7)
Any AE	328 (79)
Most frequent AEs (≥ 10% of patients)	
Headache	107 (26)
Fatigue	69 (17)
Diarrhea	58 (14)
Nausea	56 (13)
Grade 3/4 laboratory abnormalities	
Hemoglobin < 9.0 g/dL	0
Absolute neutrophils < 0.75×10^9 /L	2 (0.5)
Absolute lymphocytes < 0.5×10^9 /L	1 (0.2)
Platelets < 50×10^9 /L	0
Alanine aminotransferase > 5 × ULN	19 (5)
Aspartate aminotransferase > 5 × ULN	9 (2)
Total bilirubin > 2.5 × ULN	0
Total lipase > 3.0 × ULN	16 (4)

AE, adverse event; ULN, upper limit of normal.

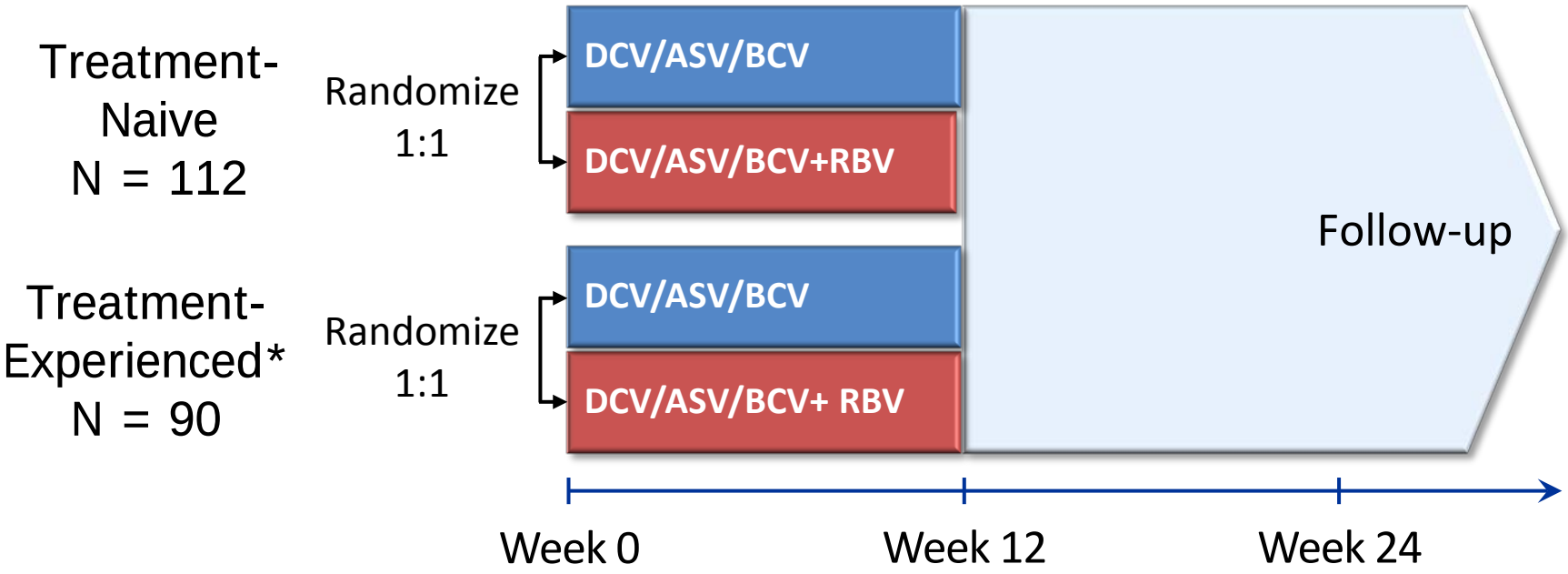
[a] One death was reported at posttreatment Week 3 due to a heroin overdose and was not considered related to treatment.

[b] All serious AEs were not considered related to study medication.

[c] All patients discontinued due to a treatment-related AE (insomnia, ALT elevation, ALT/AST elevation); all achieved SVR12.

Poordad F *et al. AASLD* 2014. Poster LB-7

UNITY-2: Randomized, Double-Blind, Phase 3 Study in HCV-1 Patients with Cirrhosis

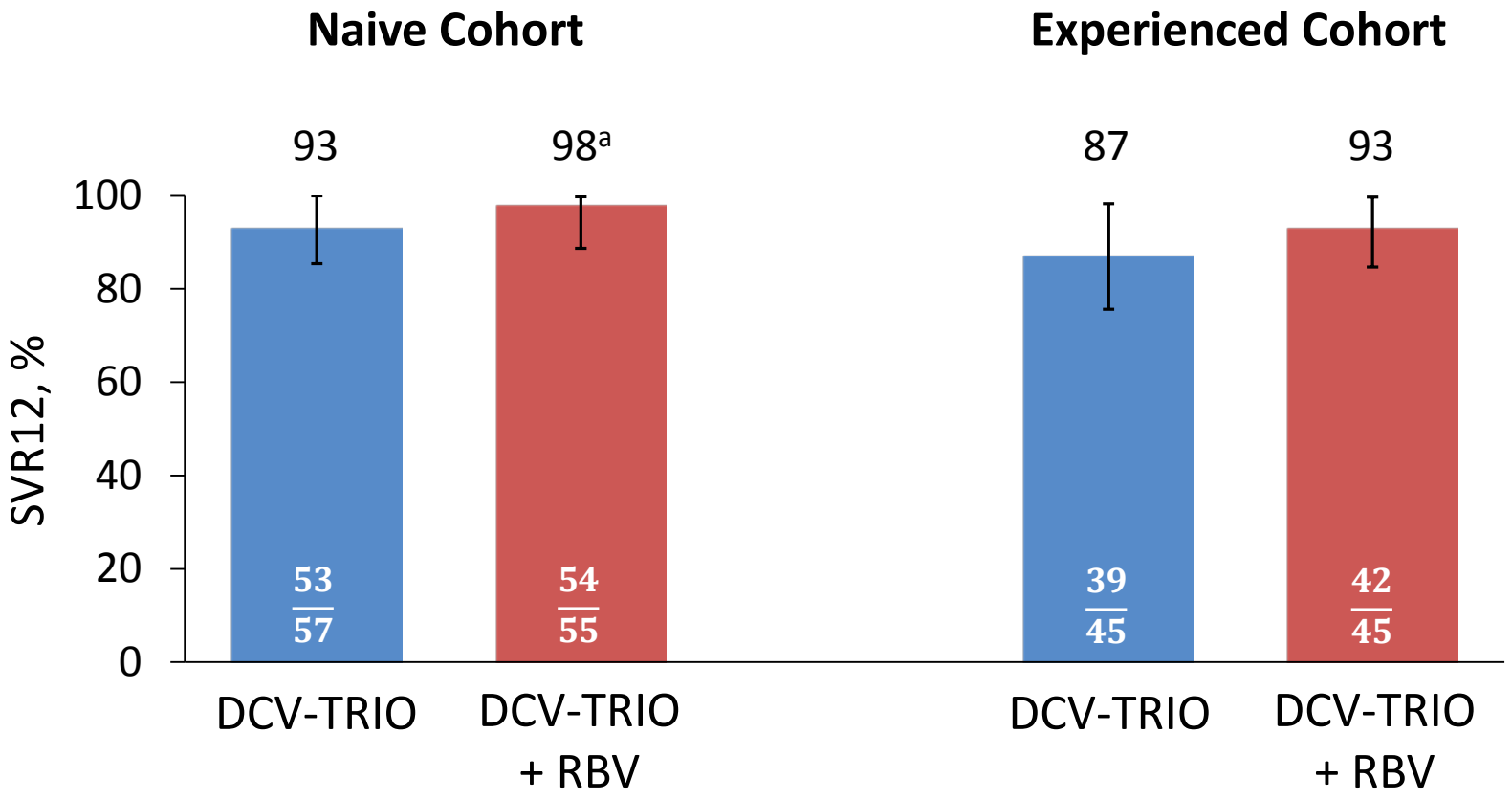


- Primary efficacy assessment: SVR12
  - HCV RNA < LLOQ (25 IU/mL) TD or TND at posttreatment Week 12
- Twice-daily fixed-dose combination (FDC)
  - DCV 30 mg / ASV 200 mg / BCV 75 mg
  - With or without weight-based ribavirin twice-daily

* PegIFN and Ribavirin TD, target detected; TND, target not detected

Muir et al. AASLD 2014, LB-2.

SVR12 (mITT)

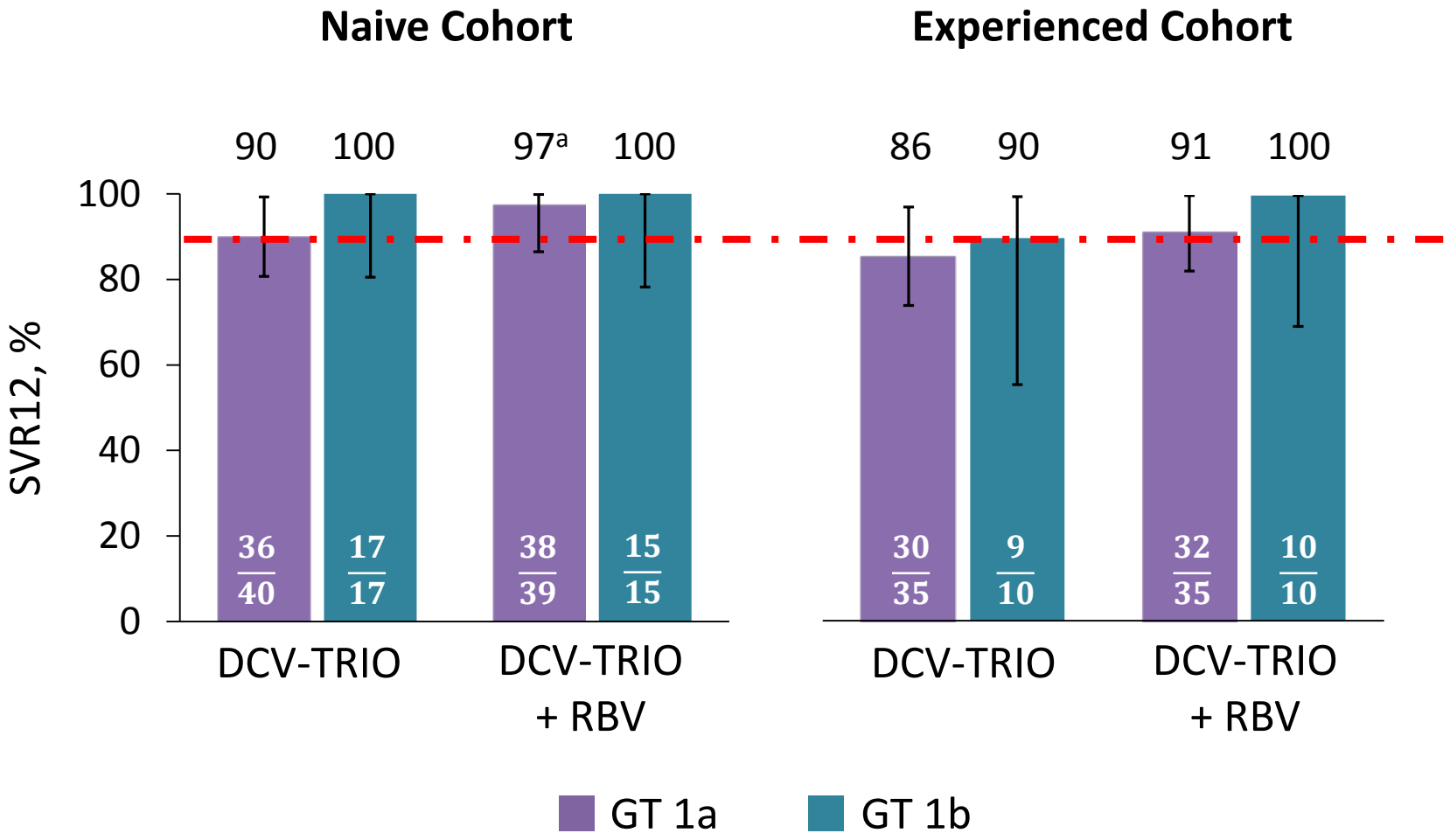


[a]One patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 97.5% confidence intervals.

Muir et al. AASLD 2014, LB-2.

SVR12 by GT 1 Subtype



[a]One patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 95% confidence intervals.

Muir et al. AASLD 2014, LB-2.

Resistance Analyses

Resistance-associated variants (RAVs) at baseline[a]

- NS5A (28, 30, 31, 93) and NS3 (168) RAVs do not appear to impact SVR12
  - 26/28 patients with NS5A RAVs achieved SVR12
  - 2/2 patients with NS3 RAVs achieved SVR12
- NS5B-P495 variants not detected at baseline

Emergent RAVs in virologic failures[a]

- Sequencing data are currently available for 8 of 13 virologic failures

Patient	GT	Outcome	NS5A	NS3	NS5B
1	1a	On-treatment failure	Q30R/H	None	None
2	1a	On-treatment failure	Q30E	R155K	P495P/L
3	1a	On-treatment failure	Q30E	R155K	P495S
4	1a	Relapse	None	None	None
5	1a	Relapse	Q30H	R155K	None
6	1a	Relapse	Y93N	R155K	None
7	1a	Relapse	Q30R, L31M/I	R155K/R, D168D/E	A421V
8	1b	Relapse	Y93H	None	None

[a] Population sequencing

Muir et al. AASLD 2014, LB-2.

Summary

- High SVR12 rates after 12 weeks of treatment with DCV/ASV/BCV fixed-dose combination (DCV-TRIO), with or without RBV, in patients with GT 1 with and without and compensated cirrhosis
  - 98% in naive, 93% in experienced patients with DCV-TRIO + RBV
  - 92-93% in naive, 87-89% in experienced patients with DCV-TRIO alone
- Addition of RBV decreased relapse frequency in GT 1a
- Baseline RAVS do not appear to impact response
- DCV-TRIO ± RBV was generally safe and well tolerated