Who is the difficult-to-treat HCV patient nowadays?

11th Residential Course

on Clinical Pharmacology of Antiretrovirals,

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Conflict of Interest

- Honoraria for lectures and/or consultancies from Abbott, AbbVie, Bionor, BMS, Cipla, Gilead, Janssen, Merck, Roche, ViiV.
- Research grants from Dt. Leberstiftung, DZIF, NEAT ID.

Difficult-to-treat Hepatitis C positive populations

- Genotype 3
- HIV coinfection
- Renal impairment
- Transplant patient
- Drug and/or alcohol abuse
- Advanced cirrhosis stages
- Patient who relapsed under DAA combination therapy
- Acute HCV infection

Difficult-to-treat Hepatitis C positive populations

- Genotype 3
- **HIV coinfection: SVR12 rates in ION-4, Ally-2 and TURQUOISE >96%; no longer special patient population in guidelines**
- **Renal impairment: SVR12 rates in the C-surfer and Ruby study 97 and 99%, respectively**
- **Transplant patient: SVR12 rate >96% (unless CHILD B or C); SVR12 88% from TARGET cohort**
- **Drug and/or alcohol abuse: C-EDGE Co-star study SVR12 91.5%**
- Advanced cirrhosis stages
- Patient who relapsed under DAA combination therapy
- Acute HCV infection

Difficult-to-treat Hepatitis C positive populations

- **Genotype 3**
- **Advanced cirrhosis stages**
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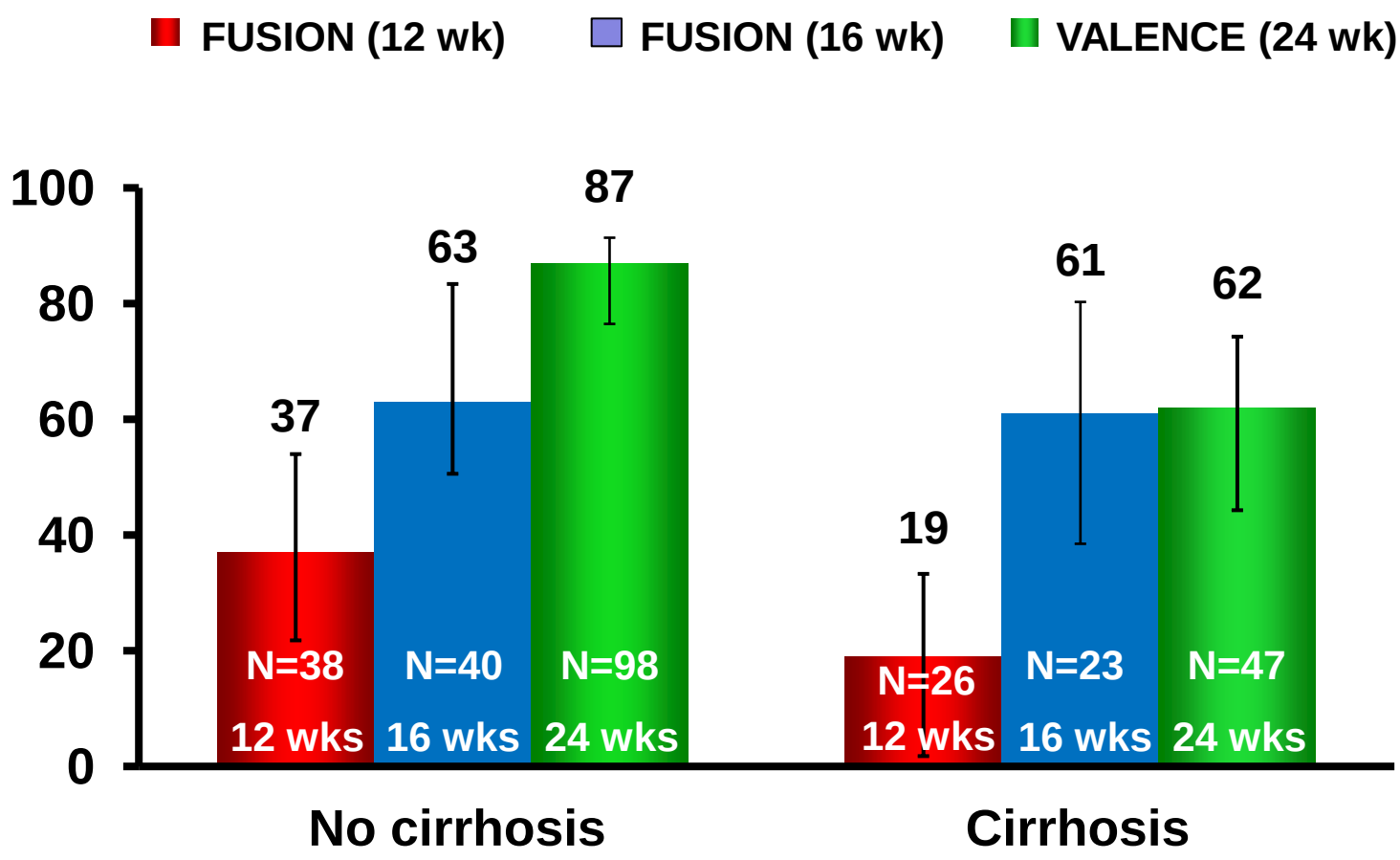
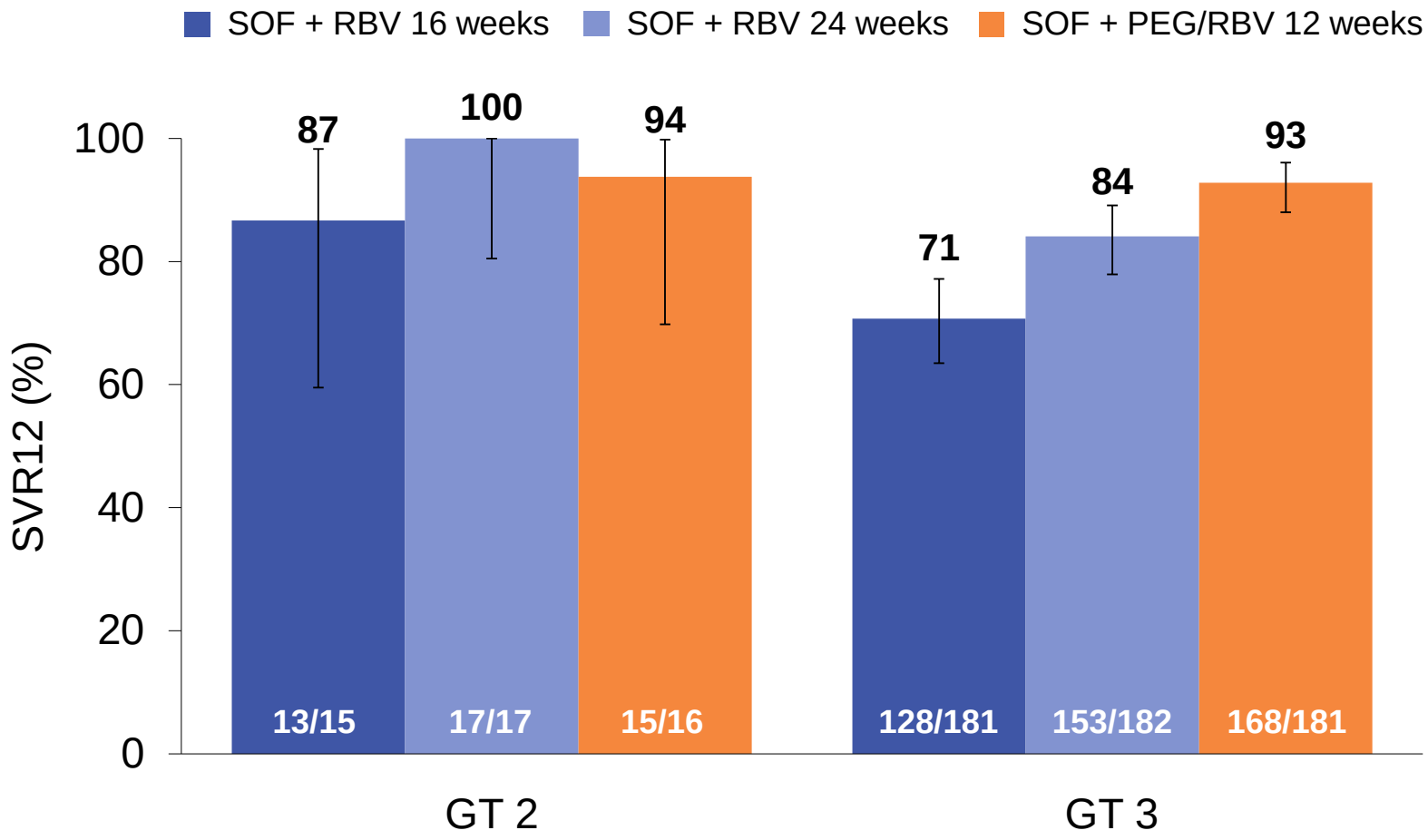
Sofosbuvir + RBV in GT 3

Phase III, Treatment-experienced



Jacobson et al., N Engl J Med 2013;368:1867-77; Zeuzem et al., N Engl J Med 2014; 370(:1993-2001

SVR12 in GT 2 vs GT 3 in the BOSAN trial

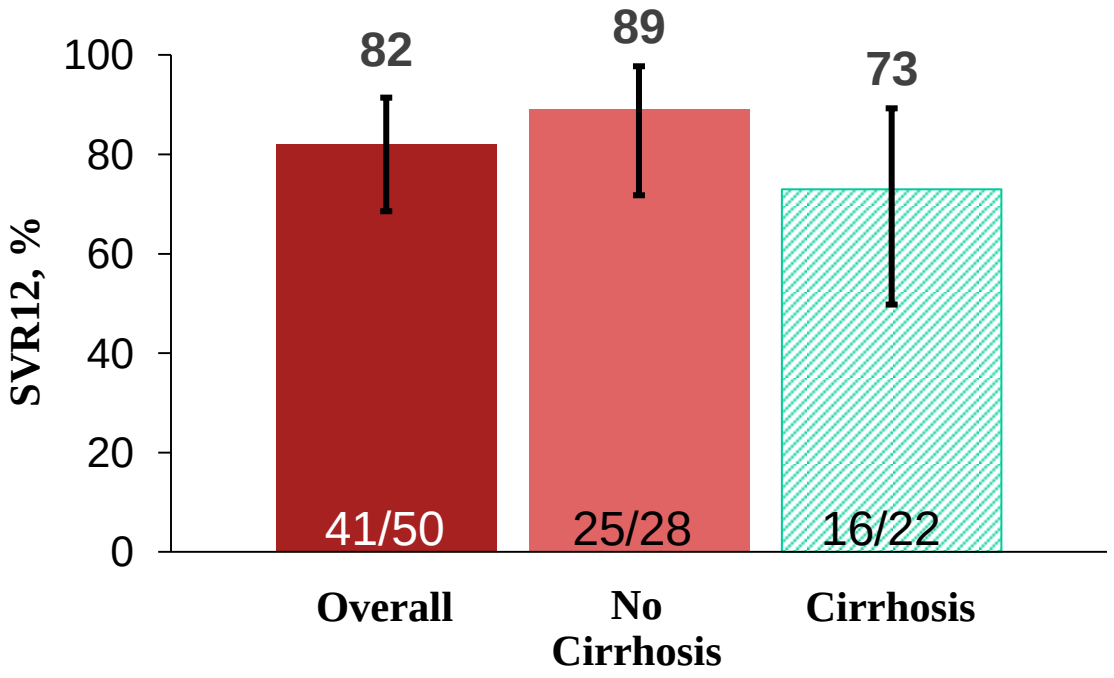


Error bars represent 95% confidence intervals.

Foster G et al., EASL 2015

ELECTRON-2:

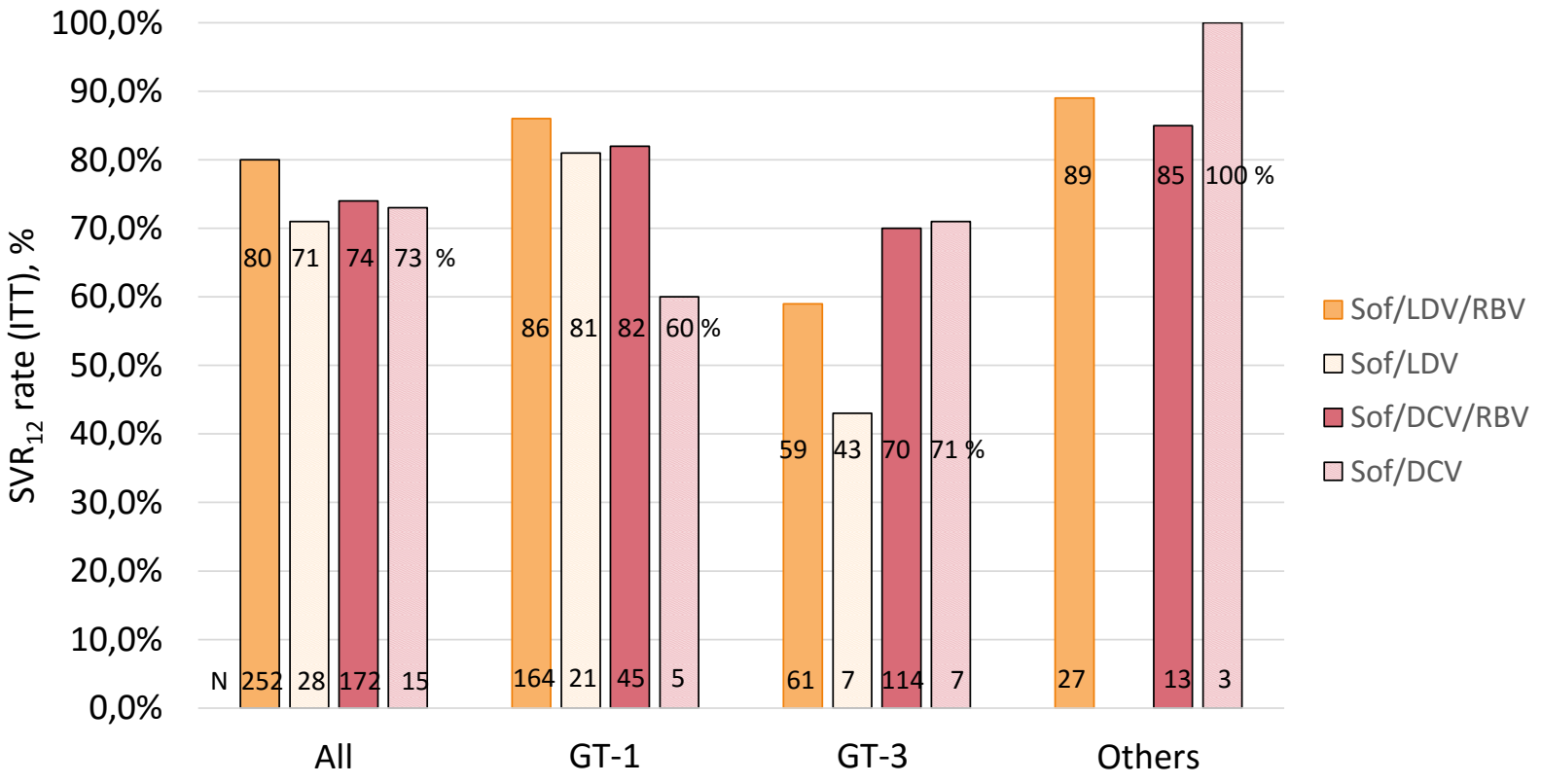
LDV/SOF + RBV for 12 Weeks for HCV GT 3 Treatment-Experienced



LDV/SOF+RBV for 12 weeks resulted in high SVR rates in TE GT3

Gane, AASLD, 2014, Poster #LB-11

SVR12 by Genotype and Regime from the English EAP study

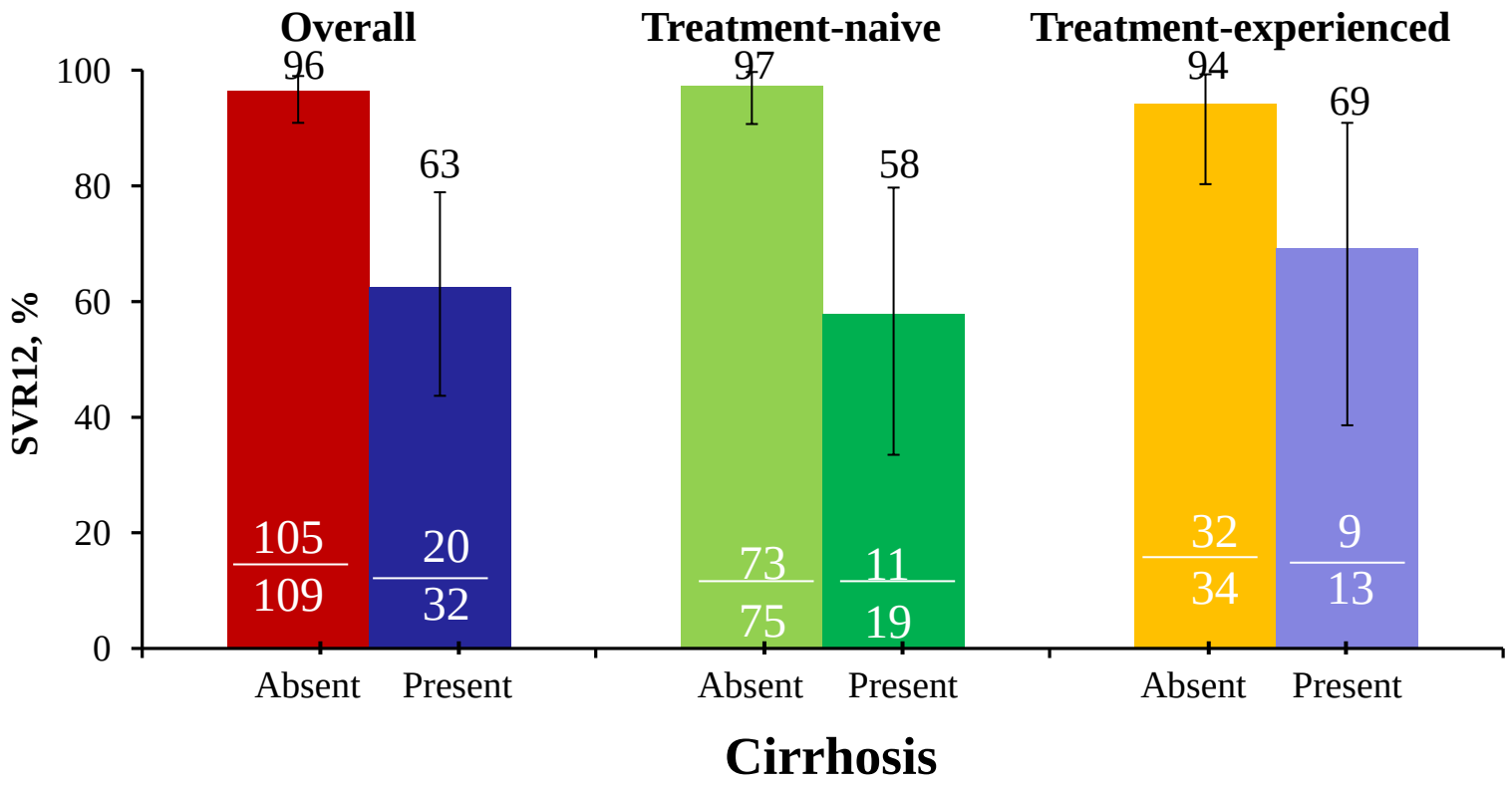


SVR12 defined as HCV RNA at 12 weeks post-treatment < 30 IU/mL.
ITT, intention to treat.

Foster G et al., EASL 2015

Ally-3: DCV 60 mg + SOF 400 mg QD: Results

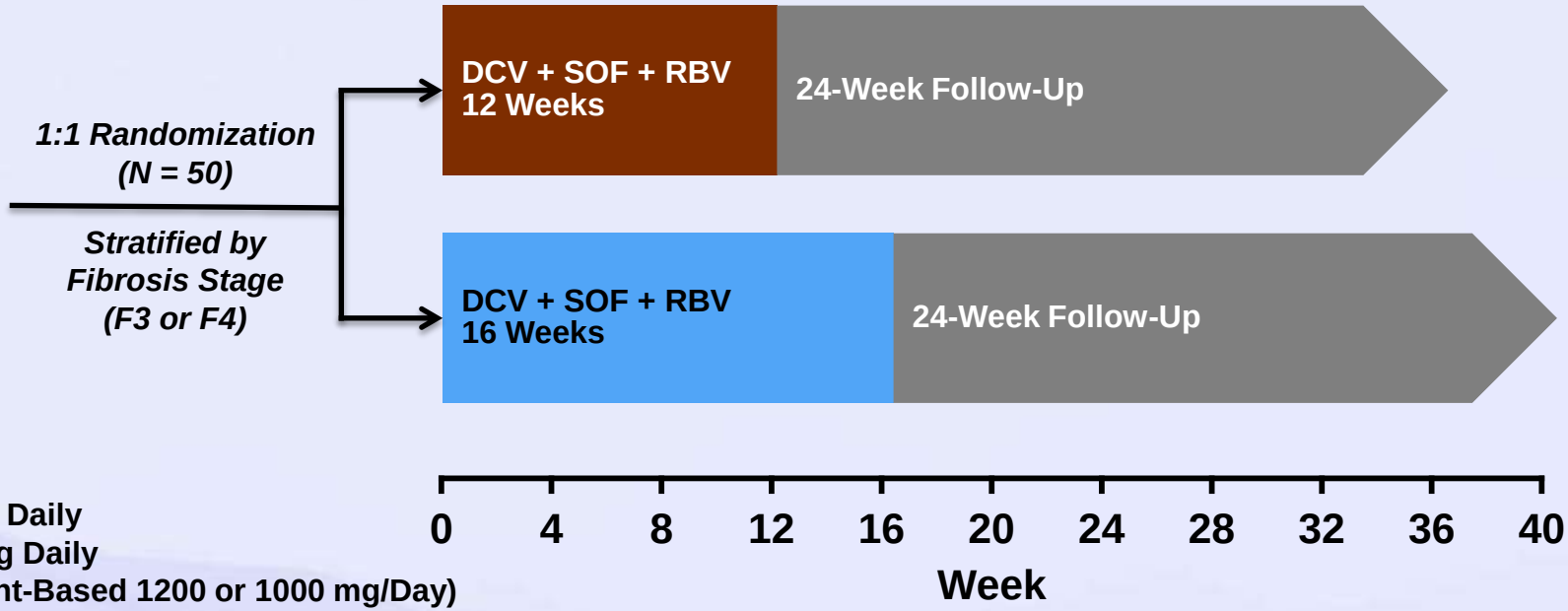
SVR12 in Patients with Cirrhosis



Nelson D, et al. Hepatology. 2015;61:1127-35.

ALLY-3+: Study Design

Phase 3b, Open-Label, Randomized Study

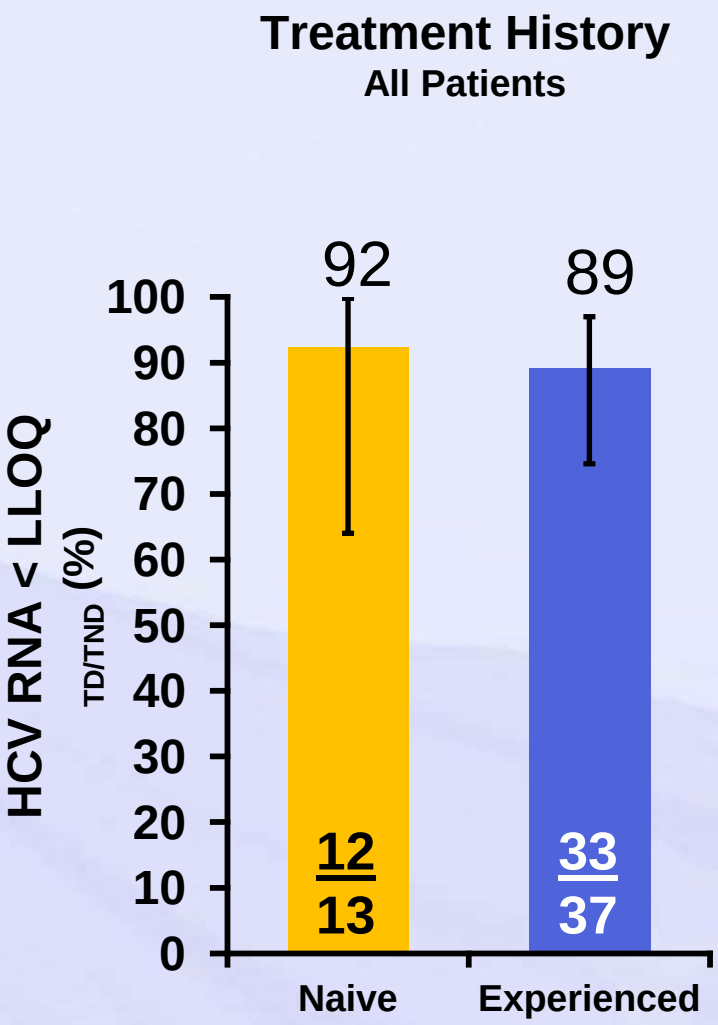


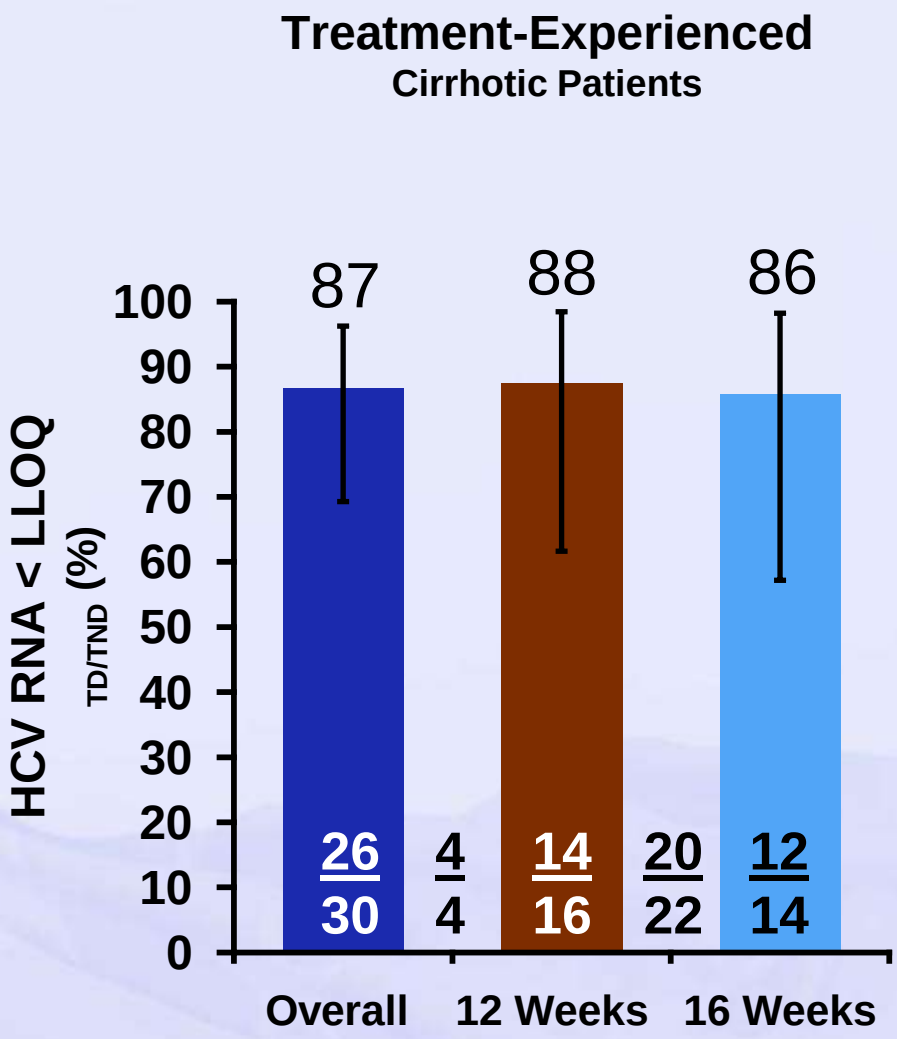
DCV 60 mg Daily
SOF 400 mg Daily
RBV (Weight-Based 1200 or 1000 mg/Day)

- Primary Efficacy Endpoint: SVR12
  - HCV RNA <$LLOQ_{TD/TND}$ (next observation carried backward) by Roche COBAS TaqMan v2.0 assay (LLOQ 25 IU/mL)
- Safety Endpoints
  - Frequencies of serious AEs, discontinuations due to AEs, grade 3/4 AEs, and laboratory abnormalities

Leroy V, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-3.

ALLY-3+: SVR12 (ITT) by Prior Treatment

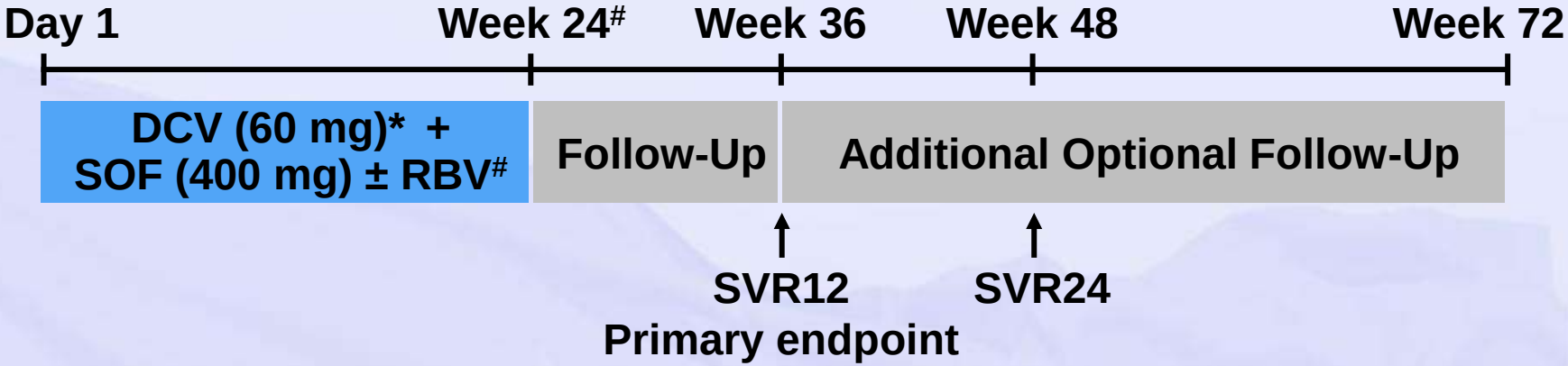




Leroy V, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-3.

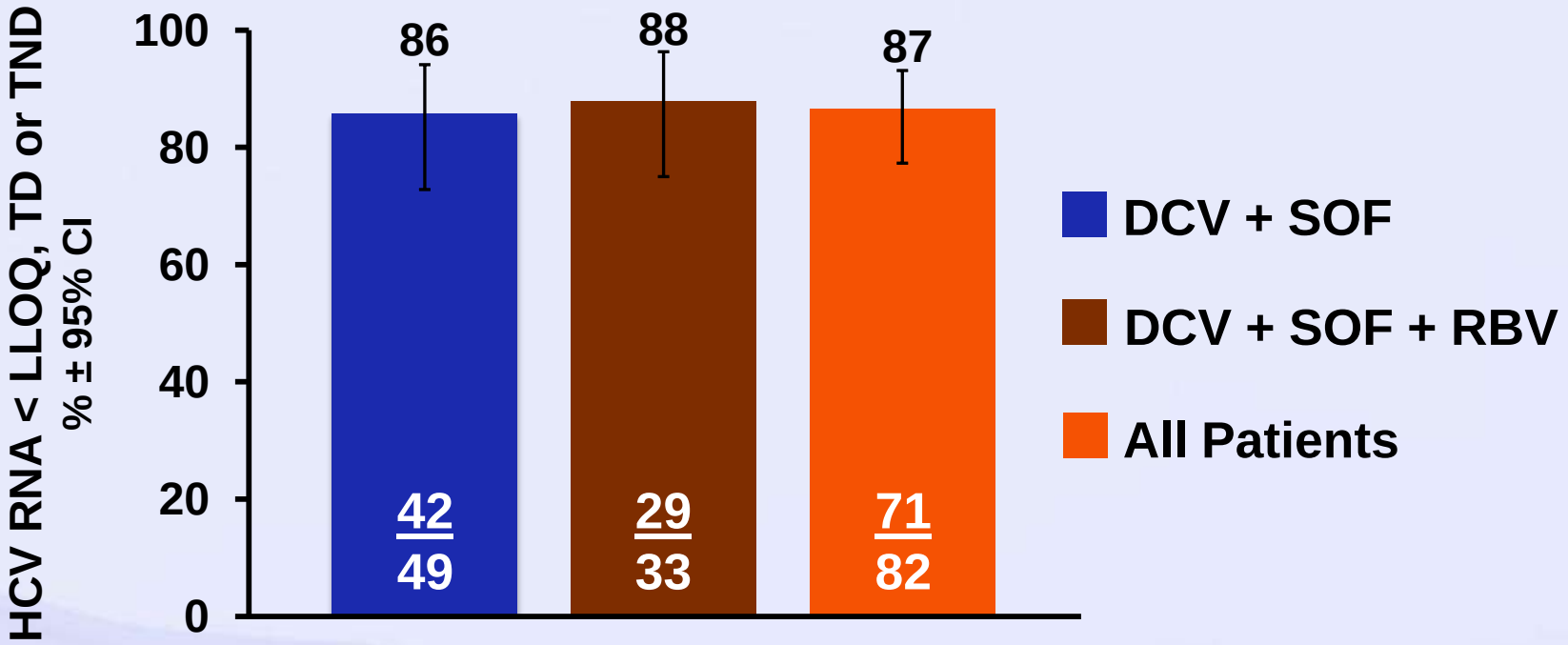
European DCV Compassionate Use Program

- Inclusion criteria
  - Age ≥ 18 years with no treatment options
  - High risk of hepatic decompensation or death within 12 months if left untreated
    - Or urgent need of viral clearance (extrahepatic manifestations/comorbidities)



Welzel T, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 37.

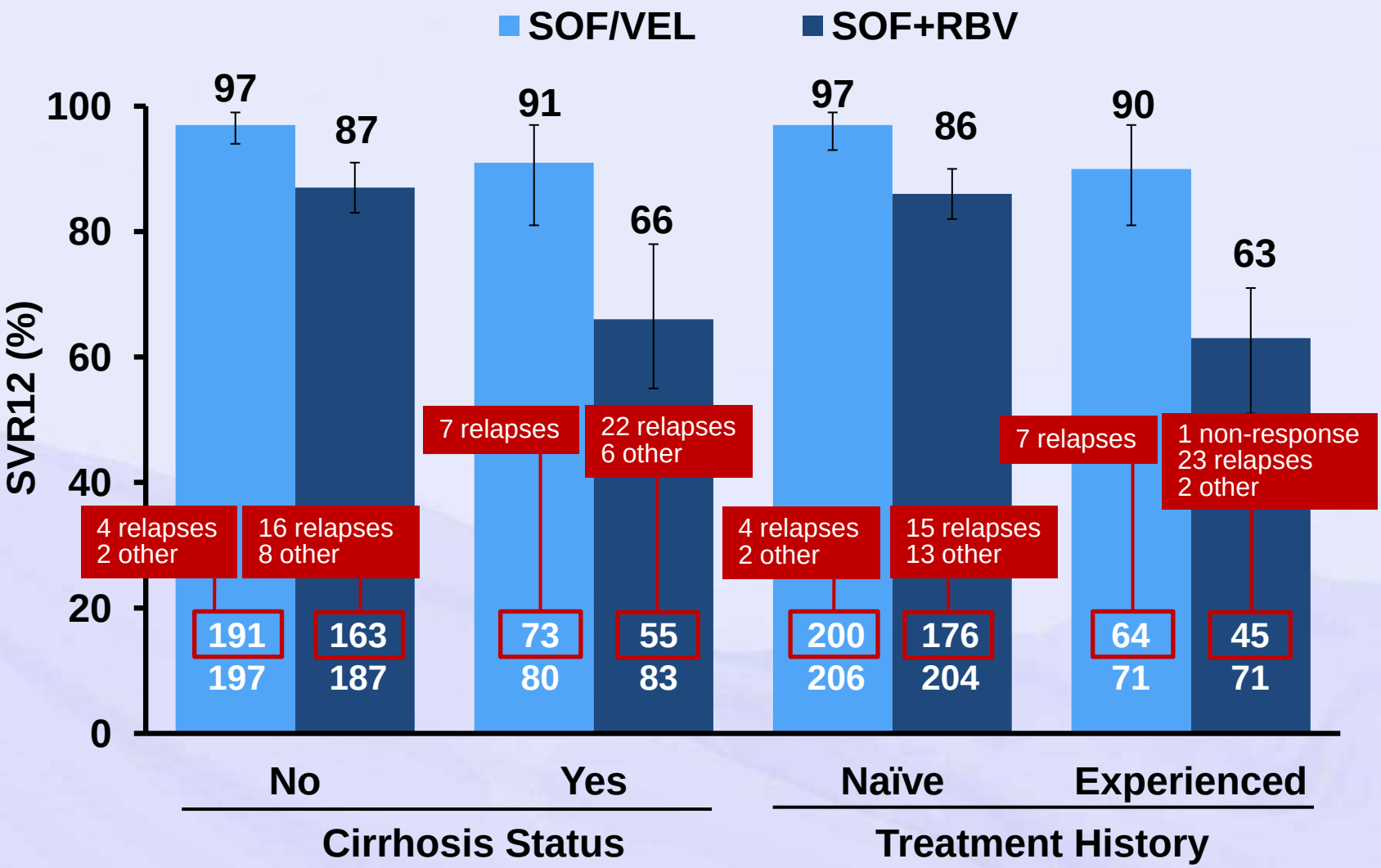
Primary Efficacy Analysis – SVR12 (mITT) in GT3 Patients



Not Achieving SVR12	7	4	11
Breakthrough	1	0	1
Relapse	3	3	6
Discontinuation (AE)	0	1	1
Death	3	0	3

Welzel T, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 37.

ASTRAL-3: SOF/VEL FDC Daily for 12 Weeks Versus SOF/RBV for 24 Weeks in Patients with HCV Genotype 3 Infection



Mangia A, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 249.

Challenges

- Not all currently available DAAs have genotype 3 antiviral activity
- Efficacy particularly lower in cirrhotics and previous HCV treatment failure
- Role of ribavirin in particular in the sofosbuvir and daclatasvir combination not well defined; even in newer more active combinations such as SOF/VEL role of RBV will need to be explored

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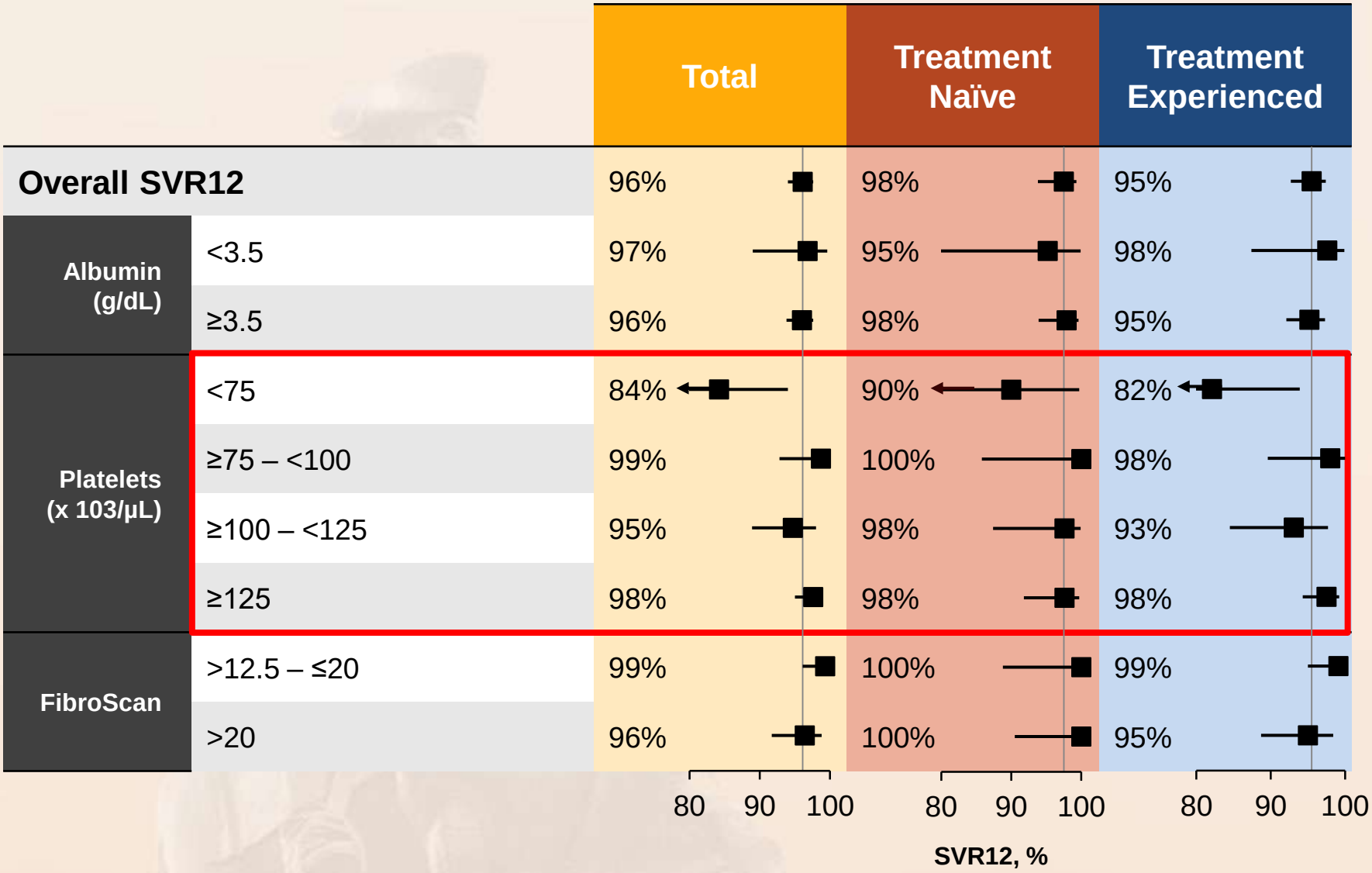
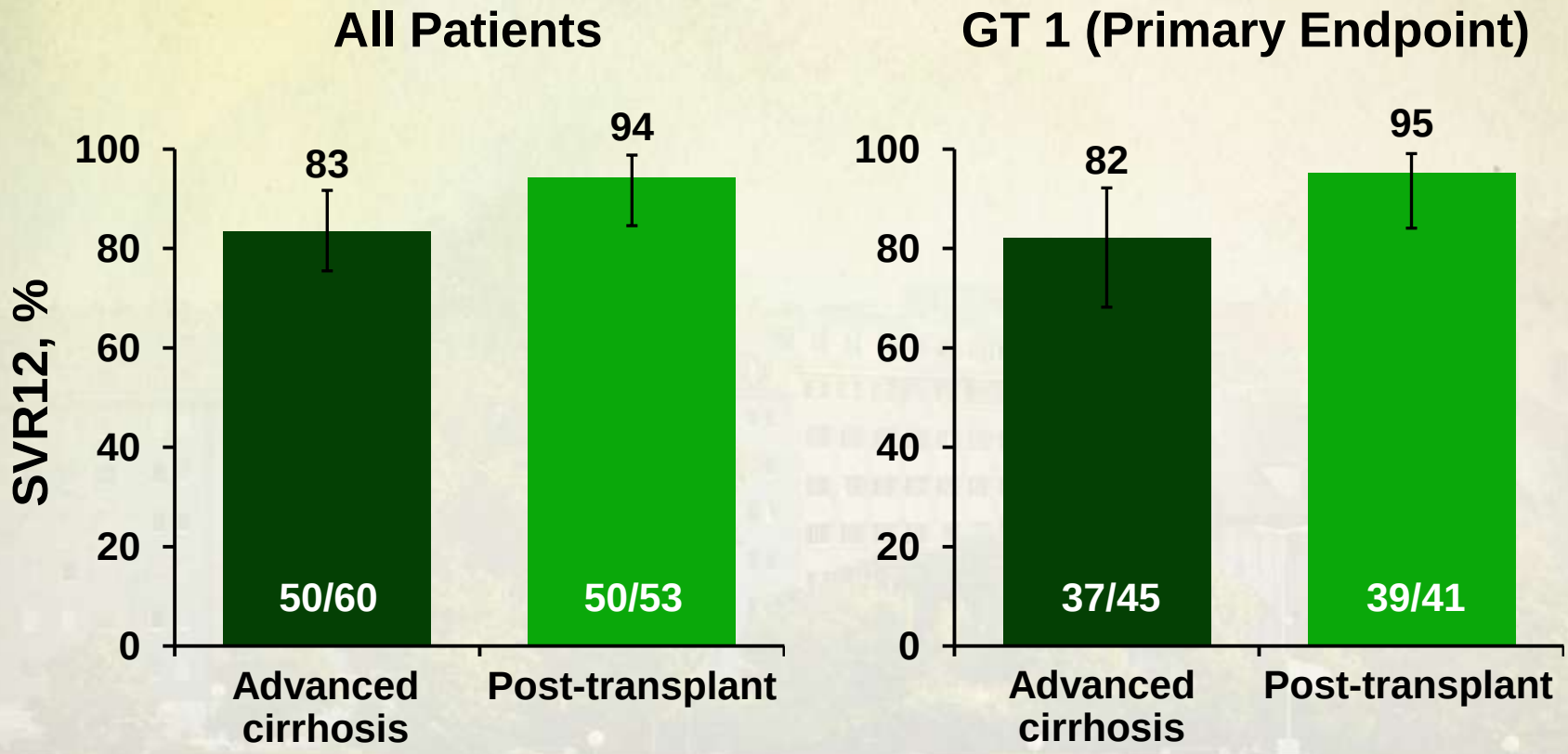
Results: SVR12 by Baseline Characteristics (Ledipasvir/Sofosbuvir) in cirrhotics



Bourliere M, et al. 65th AASLD; Boston, MA; November 7-11, 2014. Abst. 82.

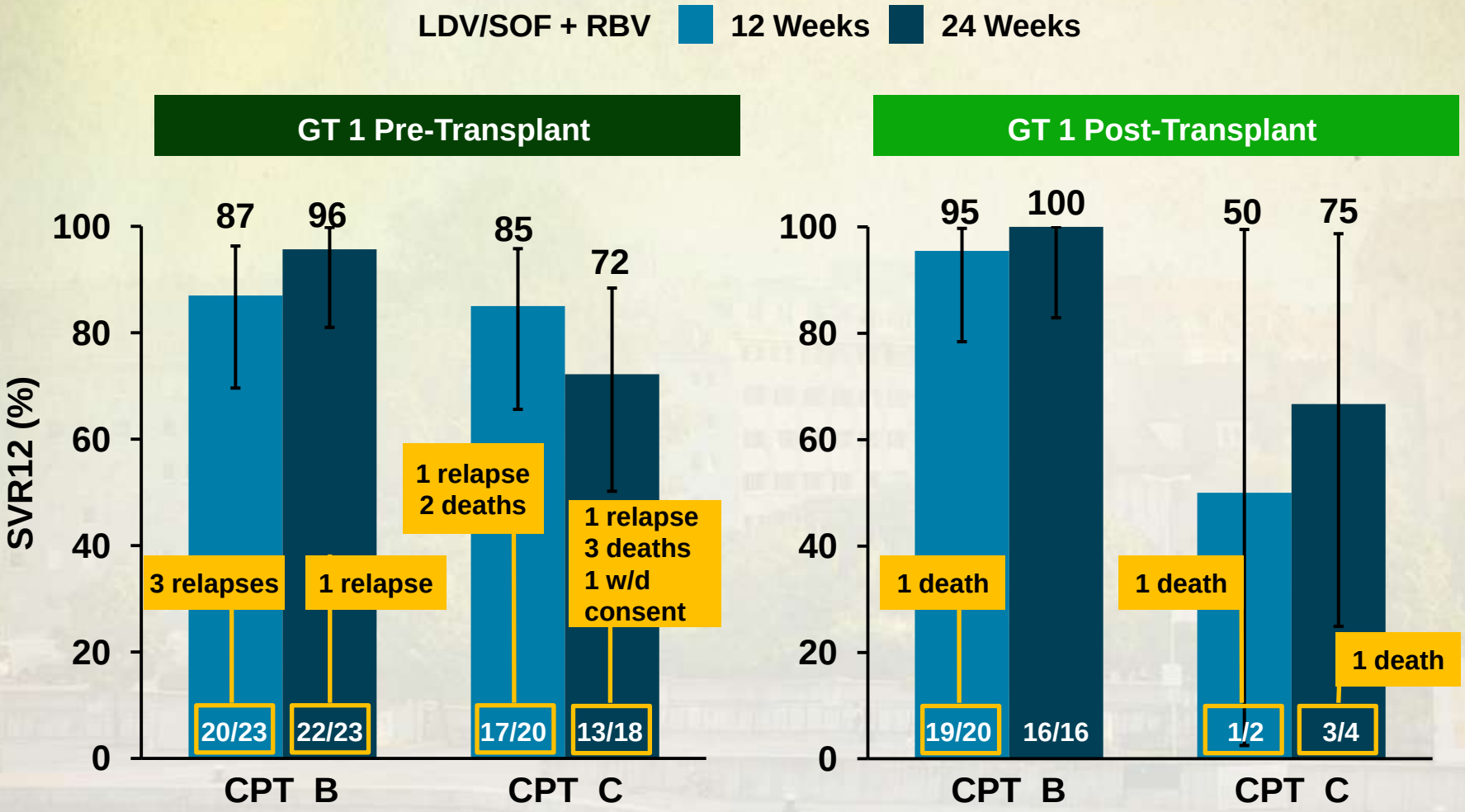
ALLY-1: SVR12 Results (by Cohort)



- In a regression analysis, no difference by gender, age, *IL28B*, or HCV RNA in the advanced cirrhosis cohort with GT 1

Poordad F, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LO8.

SOLAR-2: SVR12 Results (GT1)
Pre- and Post-Transplant CPT B and C



Manns M, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0774.

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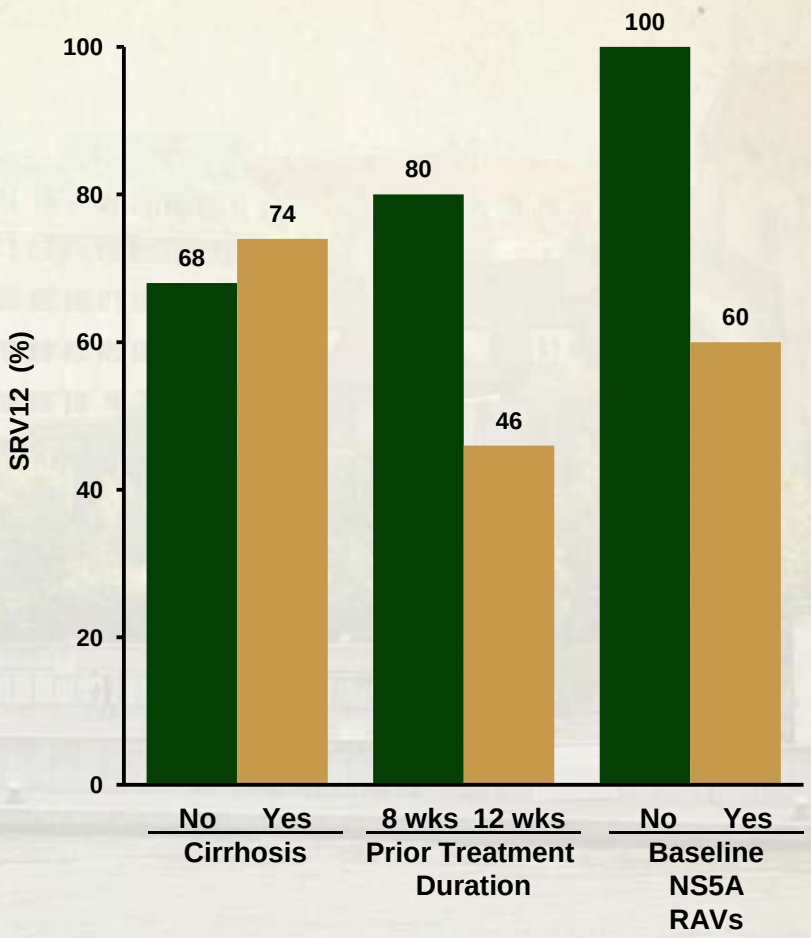
Lawitz: Retreatment of Patients Who Failed 8 or 12 Weeks of LDV/SOF-Based Regimens With LDV/SOF for 24 Weeks

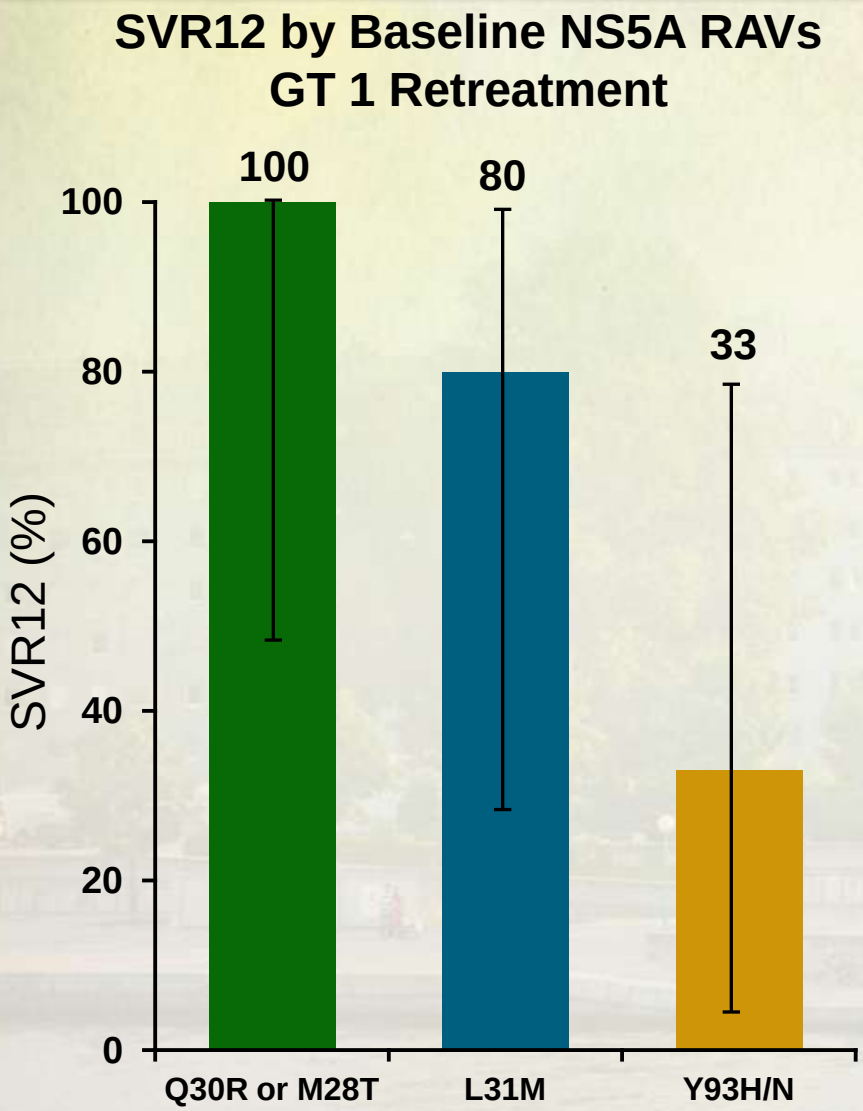
	LDV/SOF 24 Weeks N=41
Mean age, y (range)	58 (35-71)
Male, n (%)	34 (83)
Black/African American, n (%)	10 (24)
IL28B non-CC, n (%)	38 (93)
GT 1a, n (%)	34 (83)
Mean HCV RNA, log_{10}IU/mL (range)	6.2 (4.5-7.4)
Cirrhosis, n (%)	19 (46)
Presence of NS5A RAVs	15 (79)
Prior HCV treatment, n (%)	
LDV/SOF ± RBV	33 (80)
LDV/SOF + GS-9669	8 (20)
Prior HCV treatment duration, n (%)	
8 weeks	30 (73)
Presence of NS5A RAVs	19 (63)
12 weeks	11 (27)
Presence of NS5A RAVs	11 (100)

SVR according to baseline parameters



Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

Lawitz: Results and Analysis



- Prior to re-treat
  - No NS5B resistance associated (S282T) or treatment-emergent (L159F, V321A) variants were detected
- At second virologic failure
  - 4 of 12 (33%) patients had NS5B variants detected
    - S282T (n=2)
    - L159F (n=1)
    - Double-mutant S282T + L159F (n=1)

Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

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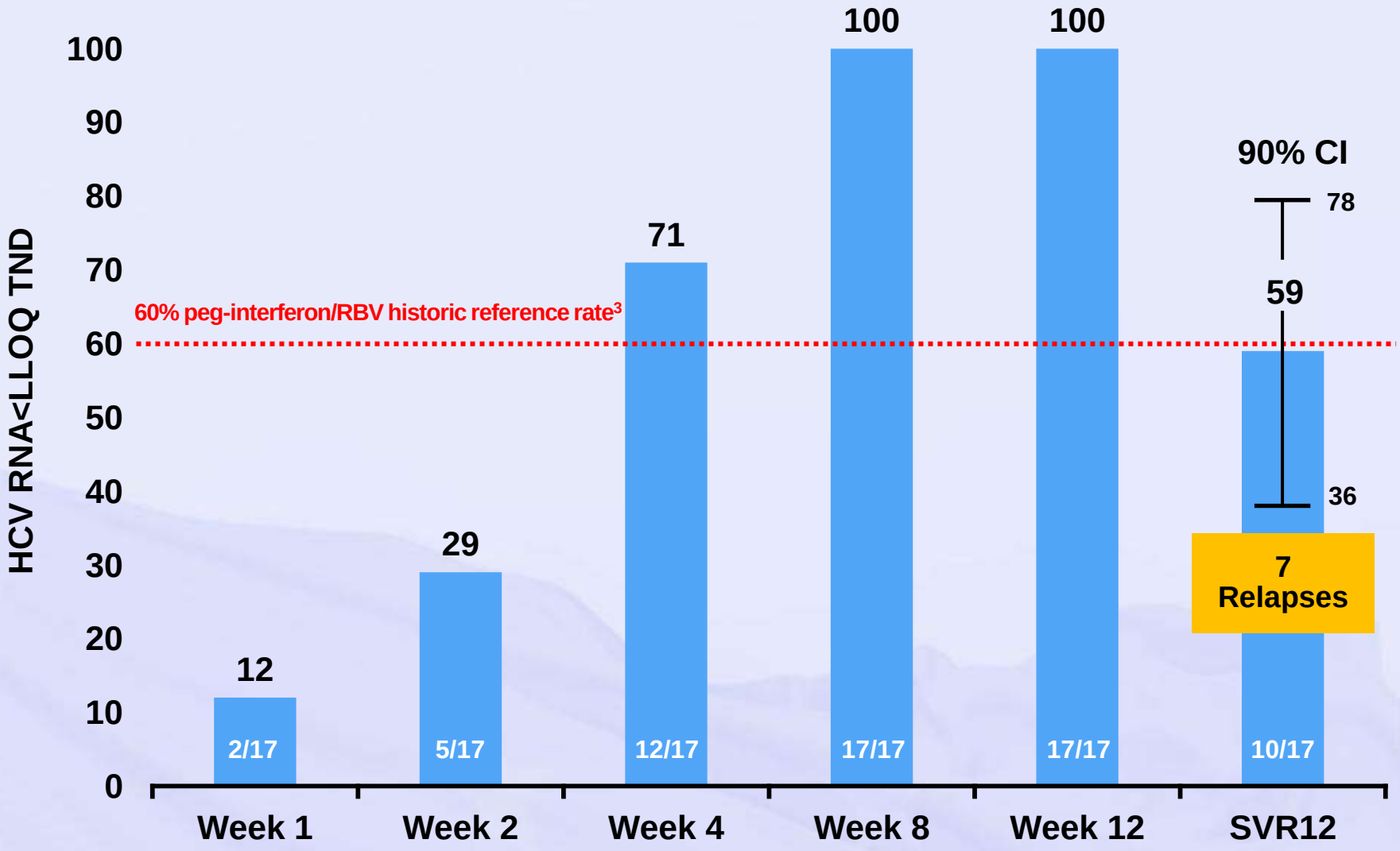
SWIFT-C: Viral Suppression Rates under SOF/RBV for acute HCV



Naggie S, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 1094.

SOF/LDV vs. SOF + SIM for Acute Hepatitis C: Results

Undetectable	Group A SOF + LDV N=14	Group SOF + SIM N=15
Day 7, n, %	13/14, 92.9%	13/15, 86.67%
4 Weeks, n %	14/14, 100% **(ETVR)**	14/15, 93.3% (1 dropped started IV drug use)
8 Weeks, n, %	14/14, 100%	14/15, 93.3% **(ETVR)**
16 Weeks, n, %	14/14, 100%, **SVR12**	14/15, 93.3%
20 Weeks, n, % (per protocol)	(1 dropped, transferred to the prison)	13/13, 100%, **SVR12** (one was lost to follow-up-homeless)
Retention	13/14, 92.9%	13/15, 86.67%

Basu P, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 1074.

Summary

- Genotype 3 has become the new difficult to treat HCV genotype in the DAA era
- Patients with decompensated cirrhosis have lower SVR rates and complications may occur; impact on MEL score needs to be considered
- Guidance on retreatment of DAA failures is scarce; genotypic resistance testing warranted
- DAA therapy in acute HCV still needs to be defined