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HEPATITIS

Evolving HCV Management in Harder-to-Treat Populations

Nancy Reau, MD, FAASLD, AGAF
Chief, Section of Hepatology
Associate Director, Solid Organ Transplantation
Rush University Medical Center
Chicago, Illinois

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Faculty

Program Director

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/ Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Faculty

Nancy Reau, MD, FAASLD, AGAF
Chief, Section of Hepatology
Associate Director, Solid Organ Transplantation
Rush University Medical Center
Chicago, Illinois

Faculty Disclosures

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Considerations for "Harder-to-Treat" Populations

- Cirrhosis status
  - Compensated
  - Decompensated
- Treatment experience
- Renal status
- Genotype 3 HCV infection
- HCV/HIV coinfection

Management of HCV in Pts With Compensated Cirrhosis

AASLD/IDSA Guidance for GT1 HCV: Treatment-Naive Pts

Population	SMV + SOF	LDV/SOF	OMV/PTV/RTV + DSV	DCV + SOF
GT1a, no cirrhosis	12 wks ± RBV	12 wks	12 wks + RBV	12 wks
GT1a, compensated cirrhosis	24 wks ± RBV (without Q80K)	12 wks	24 wks + RBV	24 wks ± RBV
GT1b, no cirrhosis	12 wks	12 wks	12 wks	12 wks
GT1b, compensated cirrhosis	24 wks ± RBV	12 wks	12 wks	24 wks ± RBV

AASLD/IDSA. HCV guidelines.

AASLD/IDSA Guidance for GT1 HCV: Treatment-Experienced Pts

Previous Treatment, Cirrhosis Status	SMV + SOF	LDV/SOF	OMV/PTV/RTV + DSV	DCV + SOF
PegIFN/RBV, no cirrhosis	12 wks	12 wks	12 wks + RBV (1a) 12 wks (1b)	12 wks
PegIFN/RBV, cirrhosis	24 wks ± RBV (GT1a w/out Q80K or GT1b)*	24 wks or 12 wks + RBV	24 wks + RBV (1a) 12 wks (1b)	24 wks ± RBV
SOF + RBV, no cirrhosis	Not recommended	12 wks + RBV	Not recommended	Not recommended
SOF + RBV, cirrhosis	Not recommended	24 wks + RBV	Not recommended	Not recommended
HCV PI, + PegIFN/RBV, no cirrhosis	Not recommended	12 wks	Not recommended	12 wks
HCV PI + PegIFN/RBV, cirrhosis	Not recommended	24 wks or 12 wks + RBV	Not recommended	24 wks ± RBV
SMV + SOF, no cirrhosis	Not recommended	12 wks + RBV	Not recommended	12 wks
SMV + SOF, cirrhosis	Not recommended	24 wks + RBV	Not recommended	24 wks ± RBV

*Not recommended if both GT1a and positive for Q80K.

AASLD/IDSA. HCV guidelines.

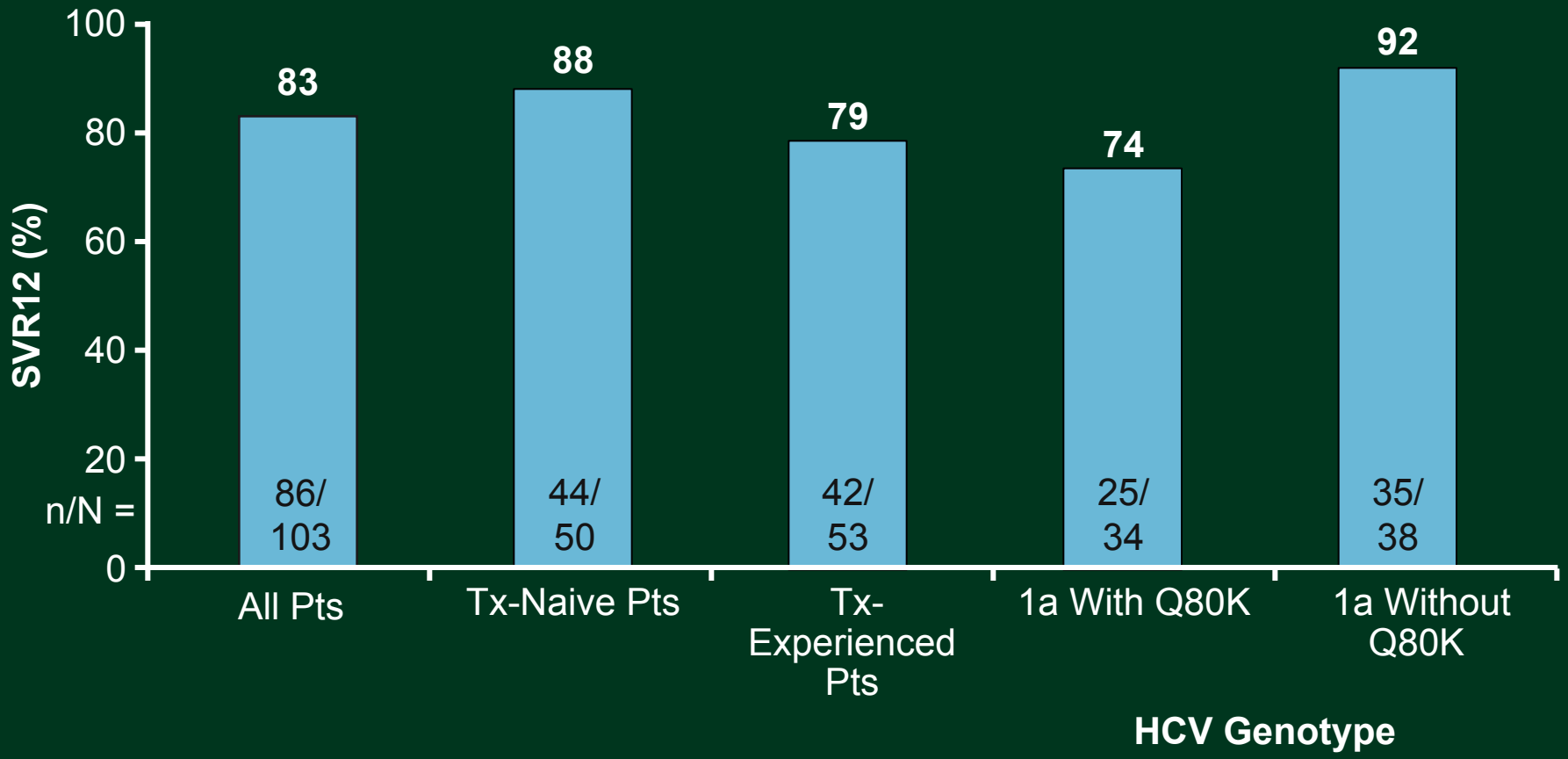
AASLD/IDSA Guidance for GT1 HCV: Previous Treatment With NS5A Inhibitor

- If minimal liver disease, defer treatment, pending further data
- If cirrhotic or treatment otherwise urgent, resistance testing for RAVs that confer decreased susceptibility to NS3 PIs, NS5As recommended
  - If both NS5A and NS3 RAVs detected, treatment within clinical trial recommended

Previous Treatment, Cirrhosis Status	DCV + SOF	LDV/SOF	OMV/PTV/RTV + DSV	SMV + SOF
NS5A, cirrhosis or urgent treatment required	Not recommended	If no NS5A RAVs: 24 wks + RBV	Not recommended	If NS5A RAVs but no NS3 RAVs: 24 wks + RBV

AASLD/IDSA. HCV guidelines.

OPTIMIST-2: Impact of Tx Exp, Q80K in Cirrhotic GT1 Pts (SMV + SOF for 12 Wks)

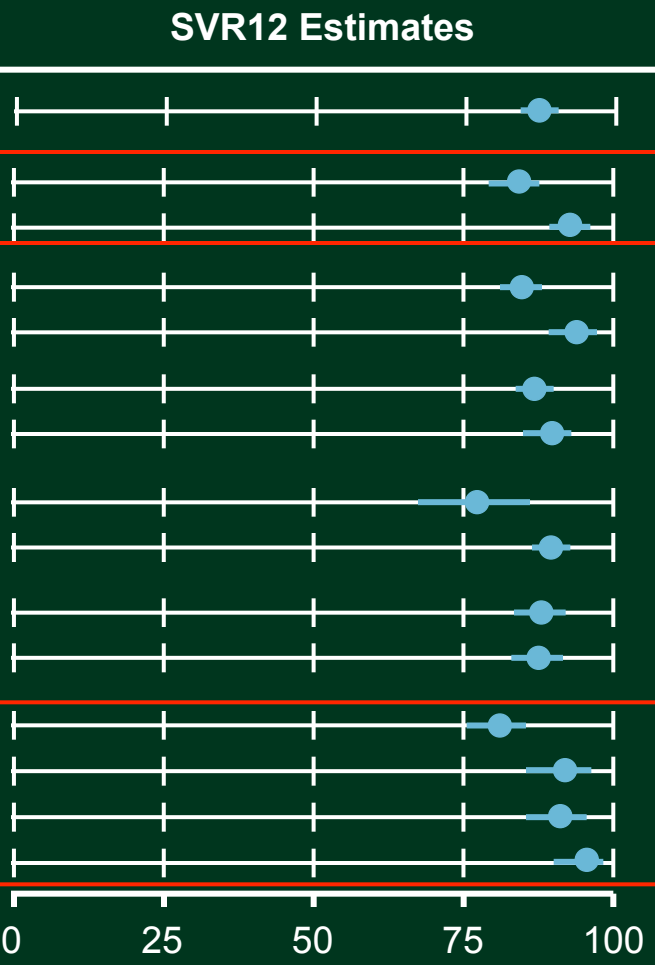


Lawitz E, et al. EASL 2015. Abstract LP04.

HCV-TARGET: Impact of Cirrhosis and Genotype (SMV + SOF)

SVR12 for Pts Treated With SMV + SOF ± RBV

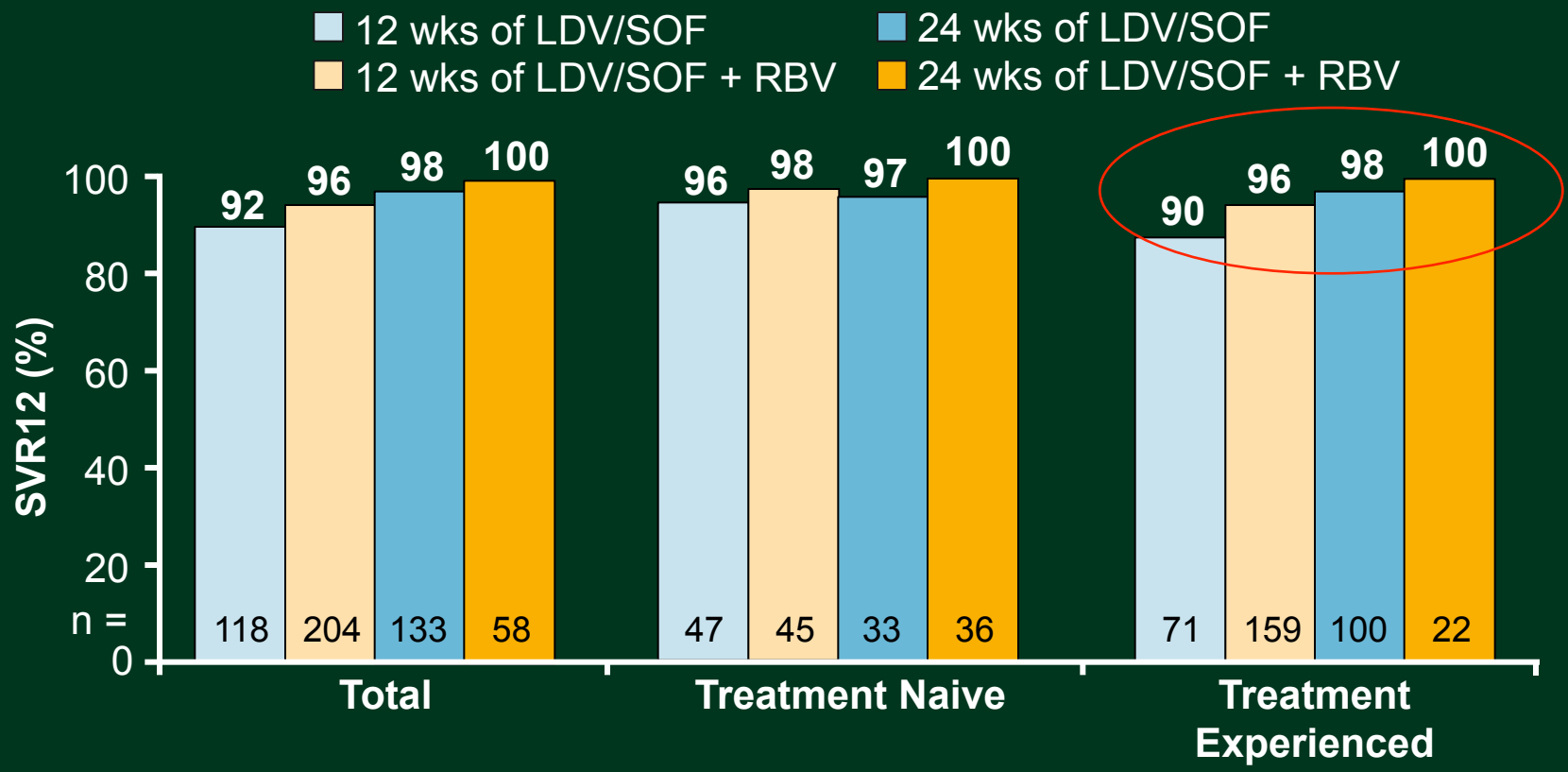
Group		N	SVR (95% CI)
Overall		715	88 (86-91)
Cirrhotic	Yes	415	85 (81-88)
	No	300	93 (9096)
Genotype	1a	483	85 (82-88)
	1b	232	94 (90-97)
Experienced	Yes	439	87 (84-90)
	No	276	90 (85-93)
Triple Failure	Yes	92	78 (68-85)
	No	623	90 (87-92)
PegIFN Failure	Yes	335	88 (84-92)
	No	380	88 (84-91)
Genotype/ Cirrhosis	1a/Cirr	289	81 (76-85)
	1b/Cirr	126	93 (85-96)
	1a/Noncirr	194	92 (86-95)
	1b/Noncirr	106	97 (90-99)



Nelson DR, et al. ISVHLD 2015.

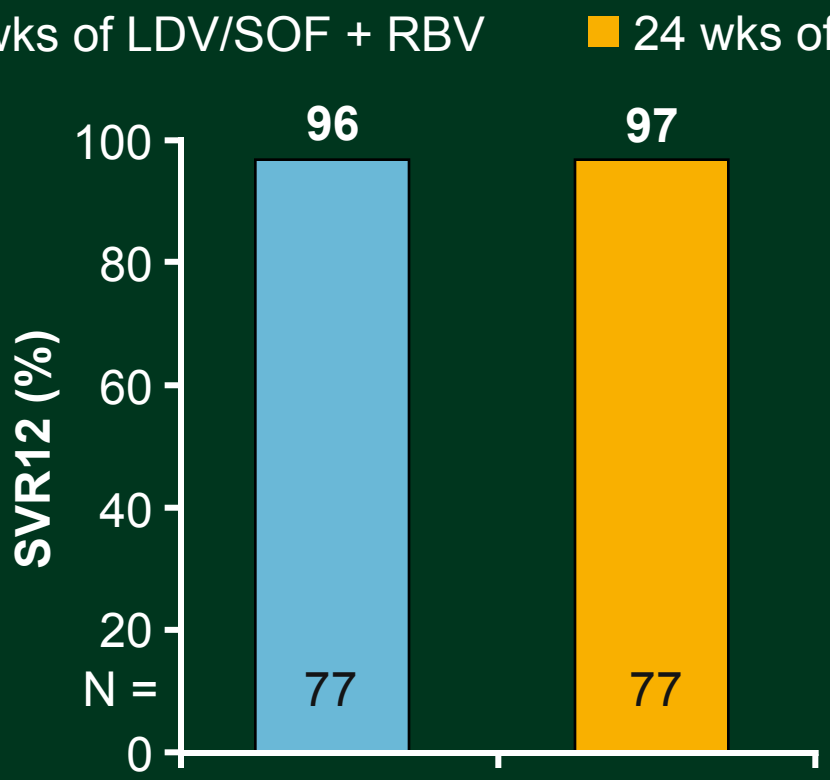
Pooled Data: Impact of Tx Duration and RBV in Cirrhotic GT1 Pts (LDV/SOF)

- Pooled data (ONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS)
- No difference in SVR rate by HCV subtype



Reddy KR, et al. Hepatology. 2015;62:79-86.

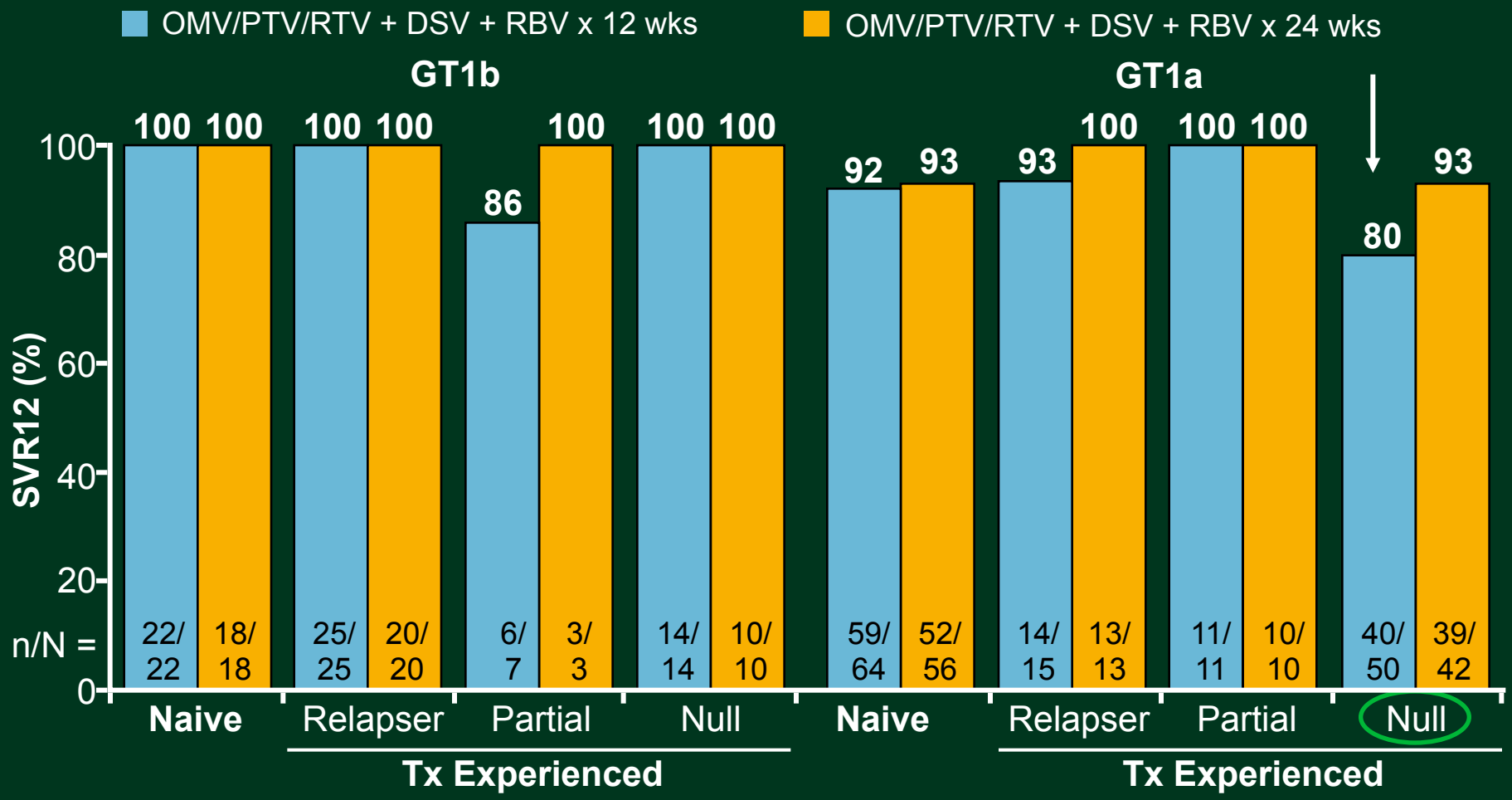
SIRIUS: Impact of Tx Duration and RBV in Cirrhotic, PI-Exp'd, GT1 Pts (LDV/SOF)



- Pts with previous boceprevir, telaprevir, simeprevir, or faldaprevir

Bourlière M, et al. Lancet Infect Dis. 2015;15:397-404.

TURQUOISE II: Impact of Tx Duration in Cirrhotic GT1 Pts (OMV/PTV/RTV + DSV)



Poordad F, et al. N Engl J Med. 2014;370:1973-1982. Poordad F, et al. EASL 2014. Abstract O163.

Daclatasvir and Sofosbuvir ± RBV in Pts With GT 1 HCV

Phase	Regimen	GT1 SVR, %	GT1 Baseline Cirrhosis, %
III	12 wks DCV + SOF + RBV (ALLY-1)[1]	**82** (advanced cirrhosis) **95** (posttransplantation)	100
III	8-12 wks DCV + SOF (ALLY-2)[2]	**76** (8 wks; naive) **96** (12 wks; naive) **98** (12 wks; tx exp'd)	< 18
IIb	12-24 wks DCV + SOF ± RBV[3]	**98** (12 wks; naive) **100** (24 wks; naive) **98** (24 wks; tx exp'd)	16

1. Poordad F, et al. EASL 2015. Abstract LO8. 2. Wyles DL, et al. CROI 2015. Abstract 151LB.
3. Sulkowski M, et al. N Engl J Med. 2014;370:211-221.

Management of HCV in GT1 Pts With Decompensated Cirrhosis

AASLD/IDSA Guidance for Pts With Decompensated Cirrhosis

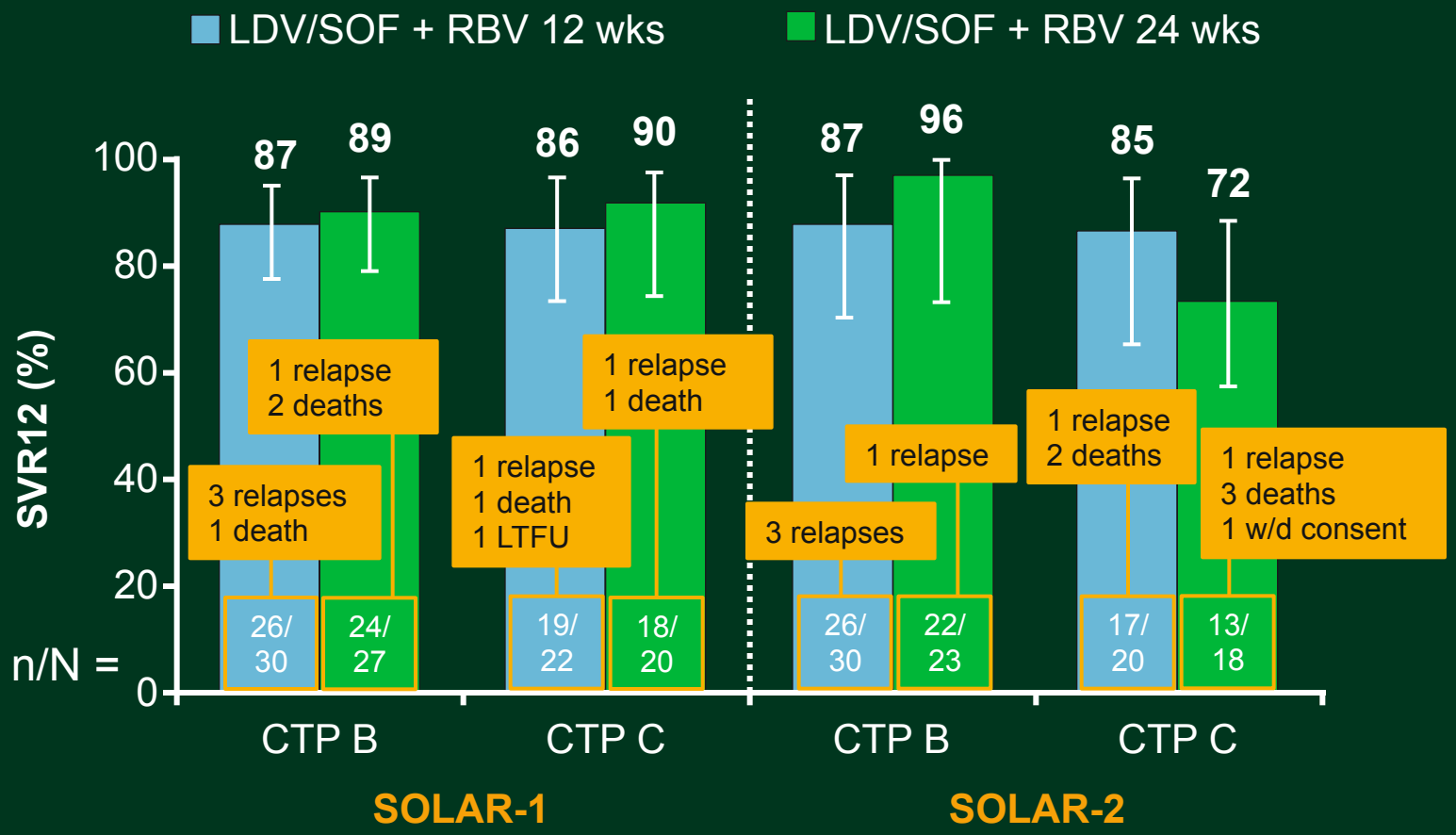
- Refer to experienced HCV practitioner (ideally liver transplant center)
- Avoid IFN, TVR, BOC, SMV, OMV/PTV/RTV + DSV, or monotherapy with RBV or DAA

Population	RBV Eligible		RBV Ineligible
	DCV + SOF	LDV/SOF	DCV + SOF
GT1/4	12 wks + low-dose RBV*	12 wks + low-dose RBV*	24 wks
GT1/4, SOF failure	Not recommended	24 wks + low-dose RBV*	Not recommended

*Initial dose of 600 mg/day, increased as tolerated.

AASLD/IDSA. HCV guidelines.

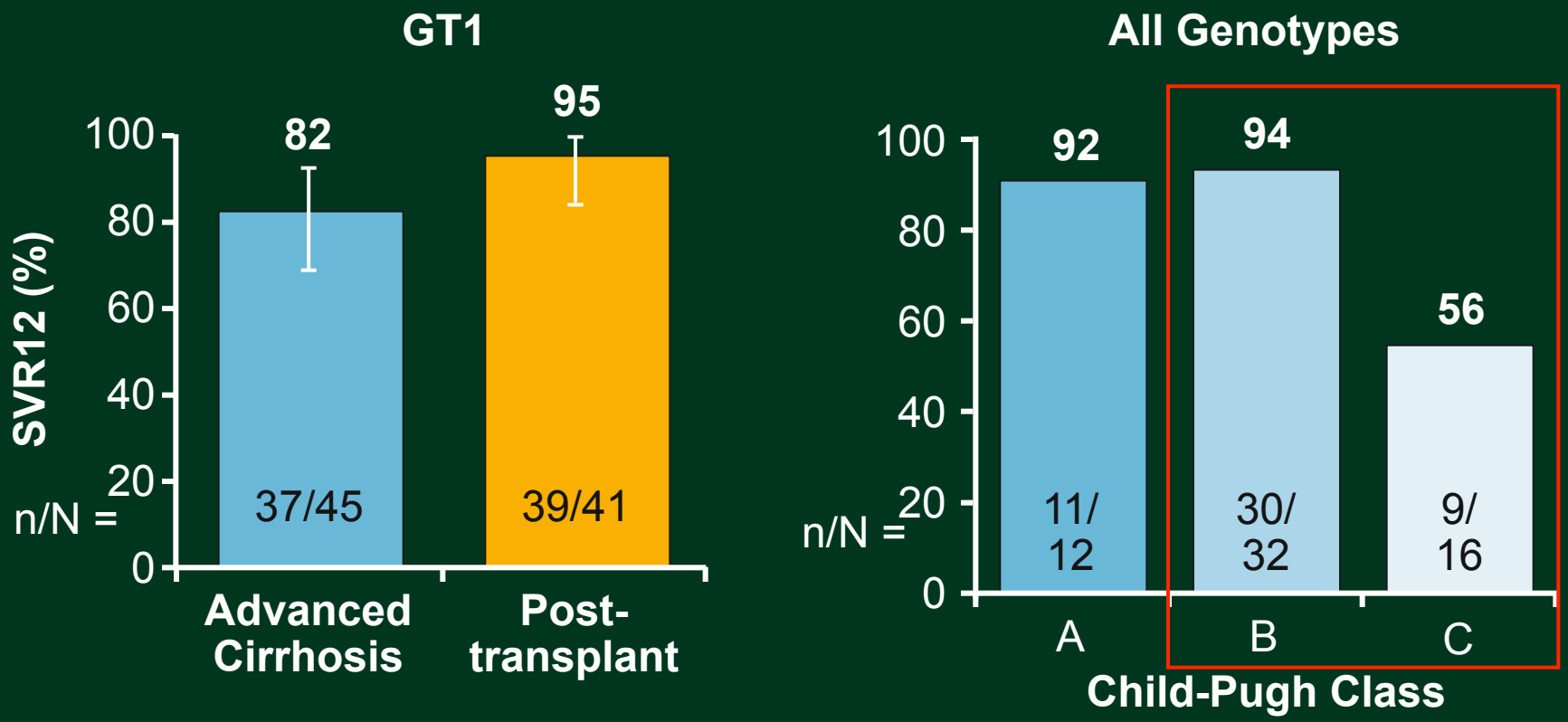
SOLAR-1 and -2: Impact of Tx Duration in Decompensated Cirrhosis (LDV/SOF + RBV)



Error bars represent 90% CIs.

Flamm SL, et al. AASLD 2014. Abstract 239. Manns M, et al. EASL 2015. Abstract P0774

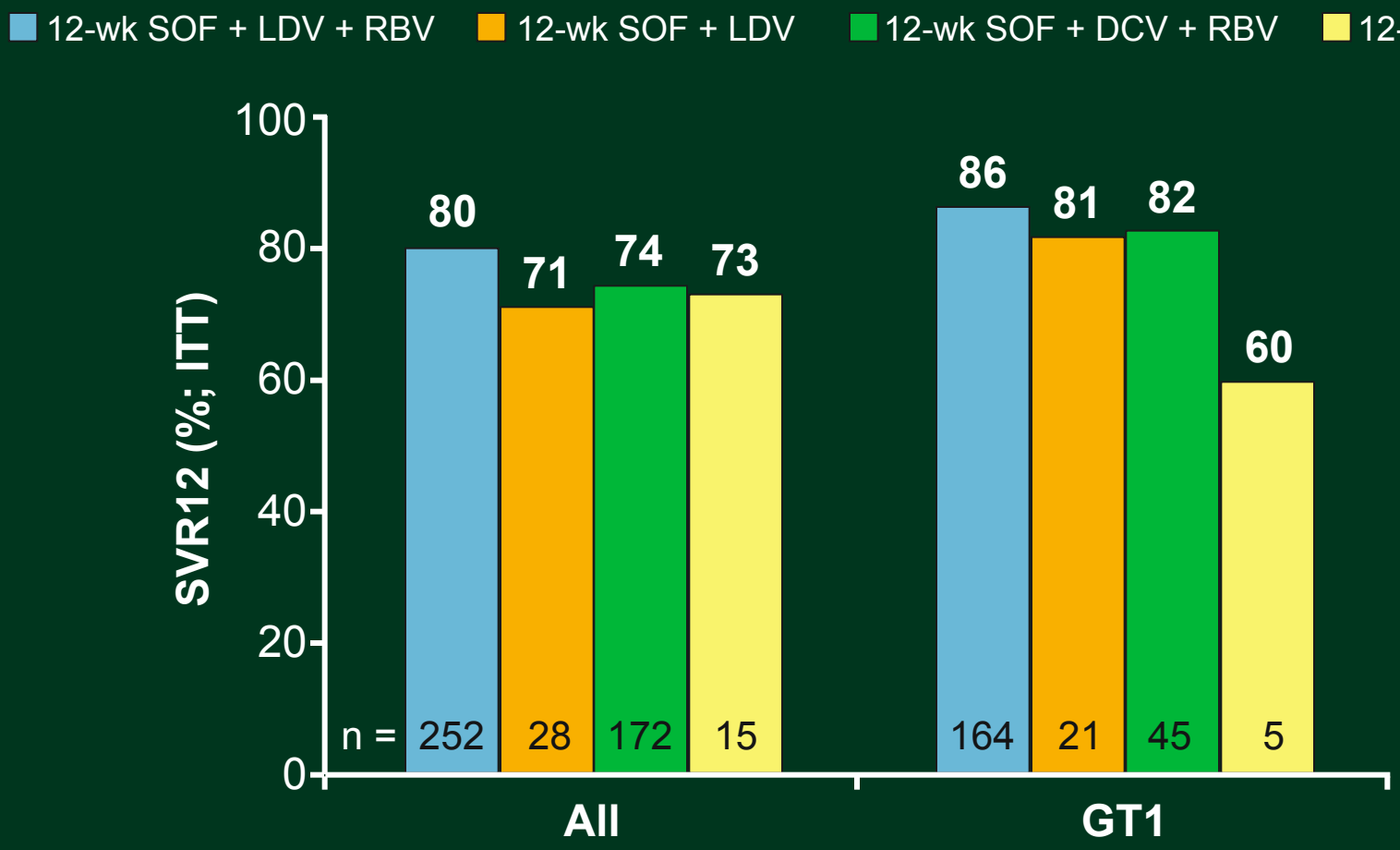
ALLY-1: SOF + DCV + RBV for 12 Wks in Pts With HCV and Cirrhosis



- Treatment naive or treatment experienced

Poordad F, et al. EASL 2015. Abstract LO8.

SOF + NS5A Inhibitors ± RBV for 12 Wks in GT1 Pts With Decompensated Cirrhosis



Foster GR, et al. EASL 2015. Abstract O002.

Management of HCV in Patients With Renal Impairment

AASLD/IDSA Dosing Considerations for Pts With Renal Impairment

eGFR/CrCl	OMV/PTV/RTV + DSV[1]	LDV/SOF[2]	SMV + SOF,[3] DCV + SOF[4]	RBV[5]
30-50 mL/min	No adjustment needed	No adjustment needed	No adjustment needed	Alternating 200 mg and 400 mg every other day
15-30 mL/min	**No adjustment needed**	Safety and efficacy not established	**No adjustment needed for SMV or DCV;** Safety and efficacy of SOF not established	200 mg/day
< 15 mL/min or hemodialysis	Safety and efficacy not established	Safety and efficacy not established	Safety and efficacy not established	200 mg/day

In noncirrhotic pts for whom tx is urgent and renal transplant not an immediate option:

■ Recommended ■ Recommended if RBV intolerant/ineligible, in consultation with expert[3]

1. OMV/PTV/RTV + DSV [package insert]. 2. LDV/SOF [package insert]. 3. AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. 4. DCV [package insert]. 5. RBV [package insert]. 6. AASLD/IDSA. HCV guidelines.

RUBY-1: OMV/PTV/RTV + DSV ± RBV in Tx-Naive, Noncirrhotic GT1 Pts With CKD

- SVR4: 10/10 pts reaching posttreatment Wk 4
  - SVR12: 2/2 pts reaching posttreatment Wk 12
  - No virologic failures observed as of time of reporting

Pt	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
GT	1a	1a	1a	1a	1b	1a	1a	1a	1a	1a	1b	1a	1a	1a	1b	1b	1b	1b	1b	1a
Renal Stage	4	4	5	5	5	5	5	4	5	5	5	5	4	4	5	4	5	5	5	5
BL (x 1000)	746	25300	17100	3520	2980	429	1730	43300	12600	6670	9820	292	6980	2570	3680	383	1230	6500	1850	4210
W1																				
W2																				
W4																				
W8																				
W12EOT																				
PTW4																				
PTW12																				
PTW24																				

HCV RNA: ≥ 25 IU/mL < 25 IU/mL Undetectable

Pockros PJ, et al. EASL 2015. Abstract L01.

Management of HCV in Patients With Genotype 3

AASLD/IDSA Guidance for Treatment-Naive or Treatment-Experienced GT3 Pts

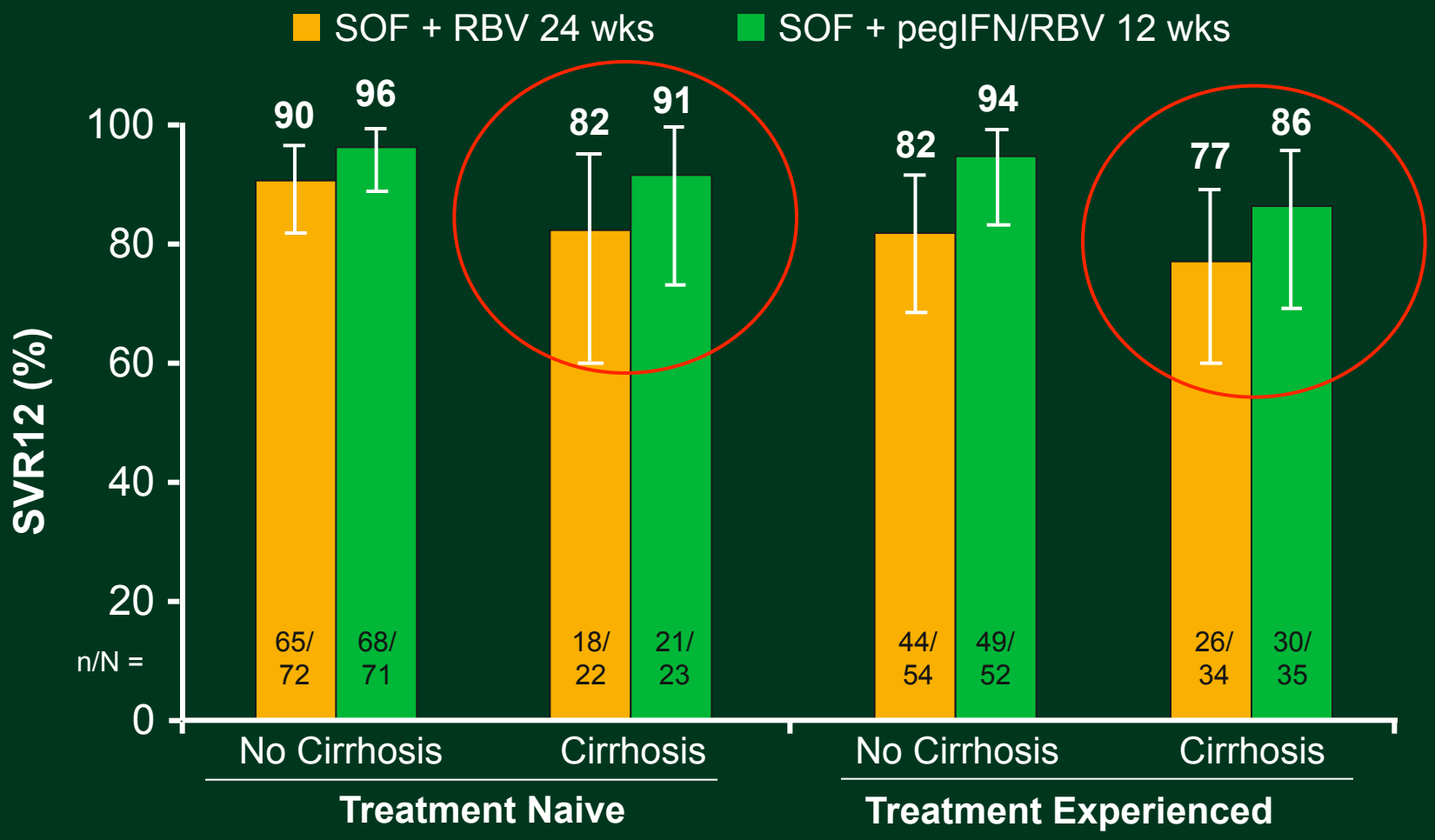
Population	Recommended		Alternative
	DCV + SOF	SOF + RBV	SOF + RBV
Naive, no cirrhosis	12 wks	12 wks + pegIFN	24 wks†
Naive, cirrhosis	24 wks ± RBV	12 wks + pegIFN	24 wks†
P/R failure, no cirrhosis	12 wks	12 wks + pegIFN	Not recommended
P/R failure with cirrhosis, or SOF/RBV failure	24 wks + RBV†	12 wks + pegIFN	Not recommended
Decompensated cirrhosis‡	12 wks + low-dose RBV	Up to 48 wks*	Not recommended

- LDV/SOF or OMV/PTV/RTV + DSV not recommended for GT3

*RBV dosed 1000-1200 mg/day based on weight, with consideration for pt's CrCl and hemoglobin. †For IFN-ineligible pts. ‡Pts with GT3 HCV decompensated cirrhosis should be referred to a medical practitioner with expertise in that condition

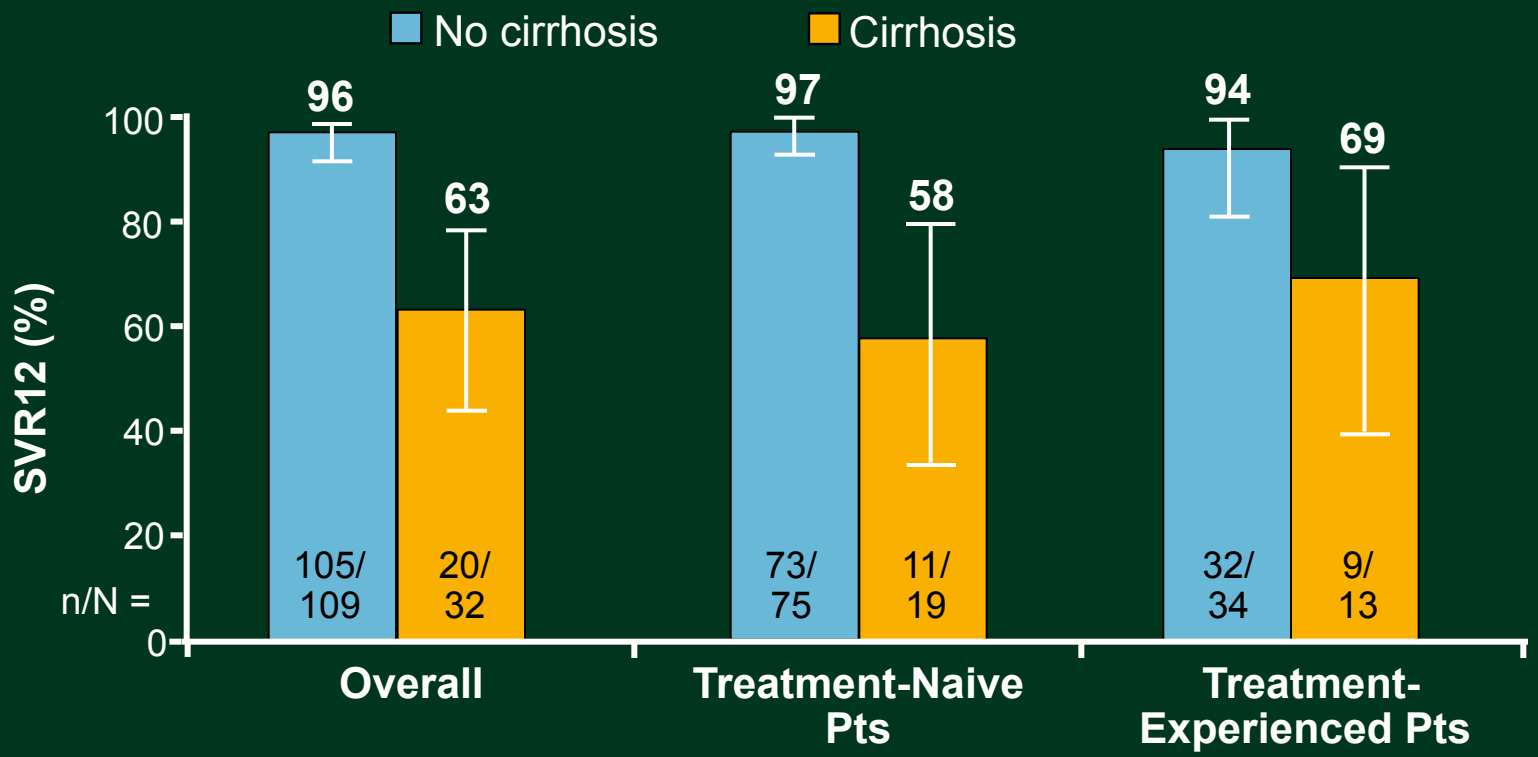
AASLD/IDSA. HCV guidelines.

BOSON: Is SOF + PegIFN/RBV for 12 Wks Superior to SOF + RBV for 24 Wks in GT3?



Foster GR, et al. EASL 2015. Abstract LO5.

ALLY-3: SOF + DCV for 12 Wks in Pts With GT3 HCV Infection



- Of 16 pts with relapse, 11 had cirrhosis
- 1 of 16 relapses occurred between posttreatment Wks 4 and 12

Nelson DR, et al. Hepatology. 2015;61:1127-1135.

Management of HCV in HCV/HIV-Coinfected Patients

AASLD/IDSA Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected pts, but consider drug–drug interactions
  - Avoid combination of LDV and tenofovir DF if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PIs
  - When LDV/SOF and tenofovir DF are coadministered with antiretrovirals, monitor for nephrotoxicity
  - Adjust/withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Adjust DCV with atazanavir/RTV, efavirenz, or etravirine
- DCV + SOF ± RBV is recommended when ART regimen changes cannot be made to accommodate other DAAs
- Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org, hep-druginteractions.org

AASLD/IDSA. HCV guidelines.

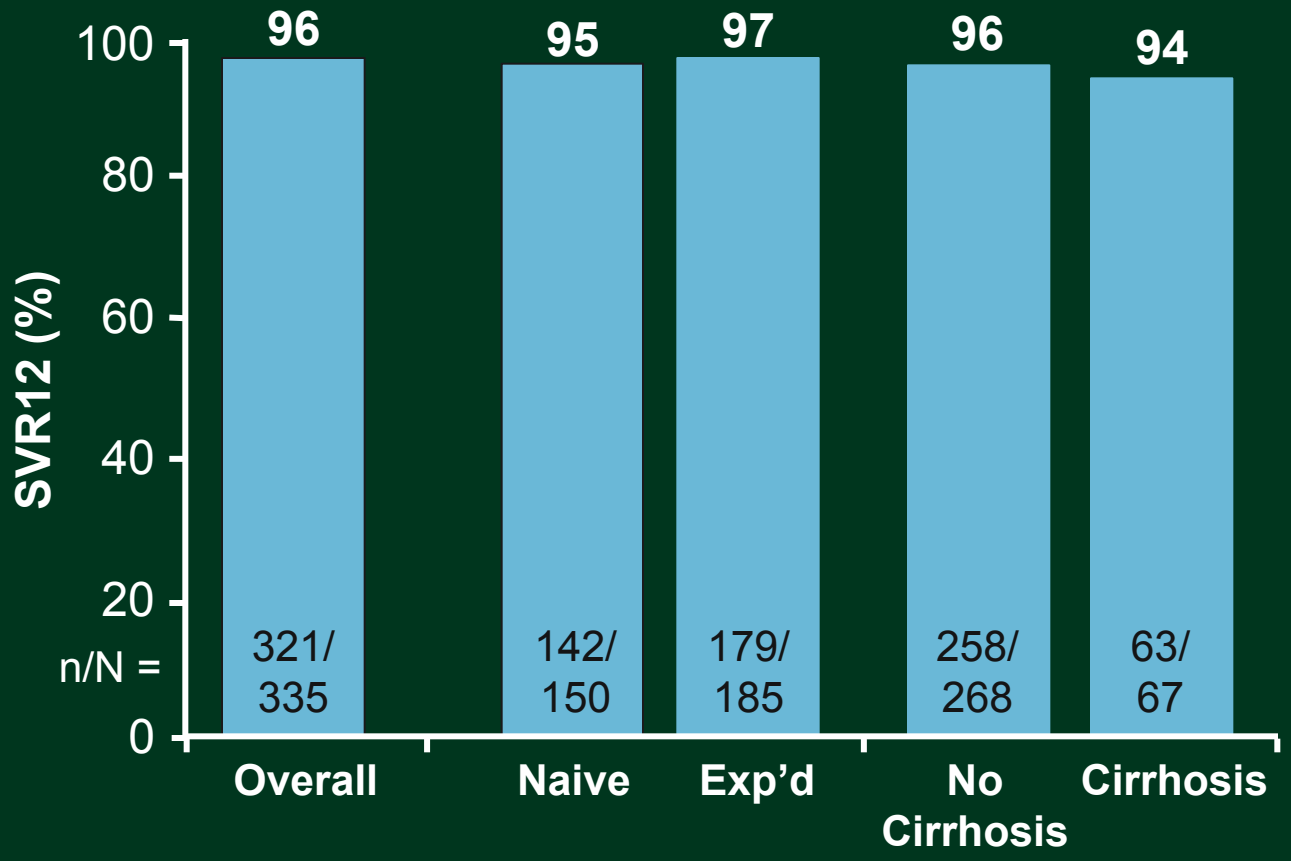
AASLD Guidance on HCV/HIV Drug–Drug Interactions

	SMV	SOF	LDV	DCV	OMV/PTV/RTV + DSV
ATV/RTV	No data	No data	LDV↑; ATV↑	DCV↑	PTV↑; ATV↑
DRV/RTV	SMV↑; DRV↔	SOF↑; DRV↔	LDV↑; DRV↔	DCV↑; DRV↔	PTV ↓/↑; DRV↓
LPV/RTV	No data	No data	No data	DCV↑; LPV↔	PTV↑; LPV↔
Tipranavir/RTV	No data	No data	No data	No data	No data
EFV	SMV↓; EFV↔	SOF↔; EFV↔	LDV↓; EFV↓	DCV↓	No PK data
RPV	SMV↔; RPV↔	SOF↔; RPV↔	LDV↔; RPV↔	No data	PTV↑; RPV↑
Etravirine	No data	No data	No data	DCV↓	No data
RAL	SMV↔; RAL↔	SOF↔; RAL↔	LDV↔; RAL↔	No data	OMV/PTV/RTV + DSV↔; ↑RAL
EVG/COBI	No data	COBI↑; SOF↑	COBI↑; LDV↑	No data	No data
DTG	No data	No data	LDV↔; DTG↔	DCV↔; DTG↑	PTV↓ DTG↑
Maraviroc	No data	No data	No data	No data	No data
TDF	SMV↔; TDF↔	SOF↔; TDF↔	LDV↔; TDF↑	DCV↔; TDF↔	OMV/PTV/RTV + DSV↔; TDF↔

AASLD/IDSA. HCV guidelines.

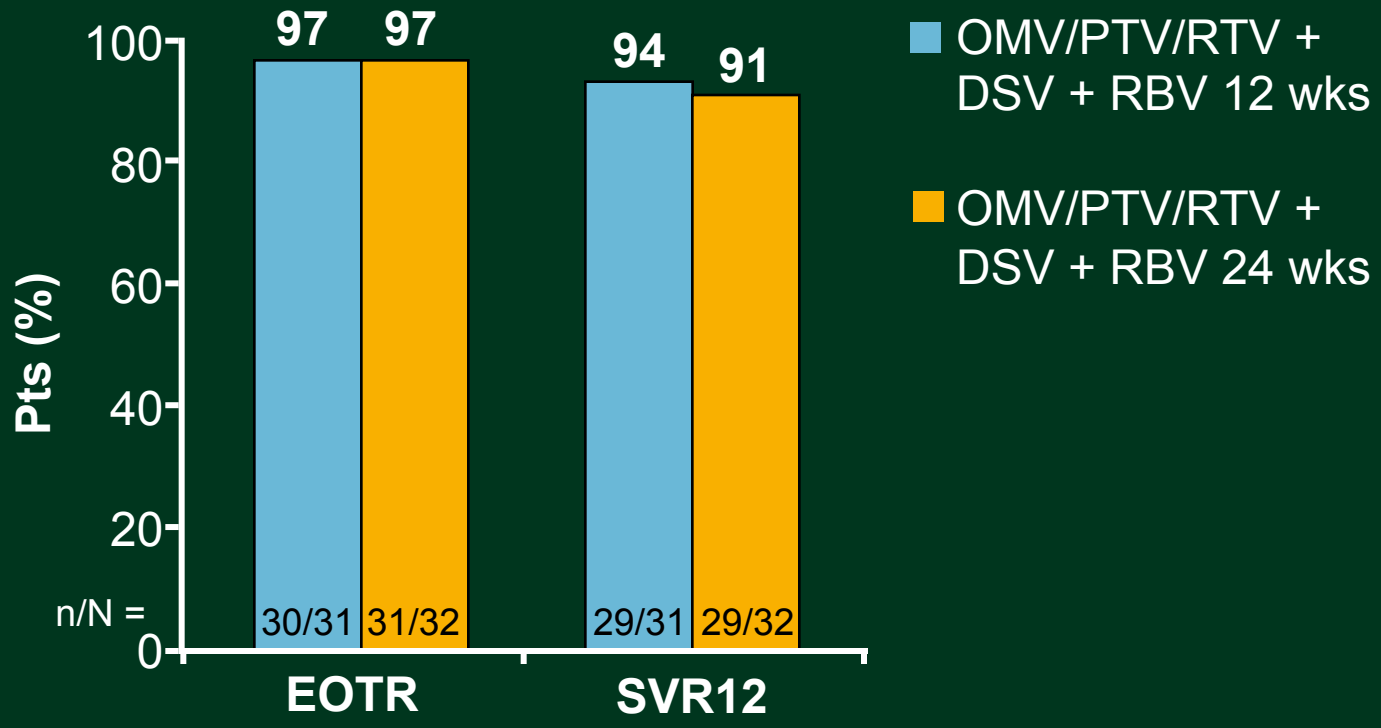
ION-4: LDV/SOF for 12 Wks in HCV/HIV-Coinfected Pts

- GT1 or 4 HCV, 20% with compensated cirrhosis, 55% treatment experienced



Naggie S, et al. CROI 2015. Abstract 152LB.

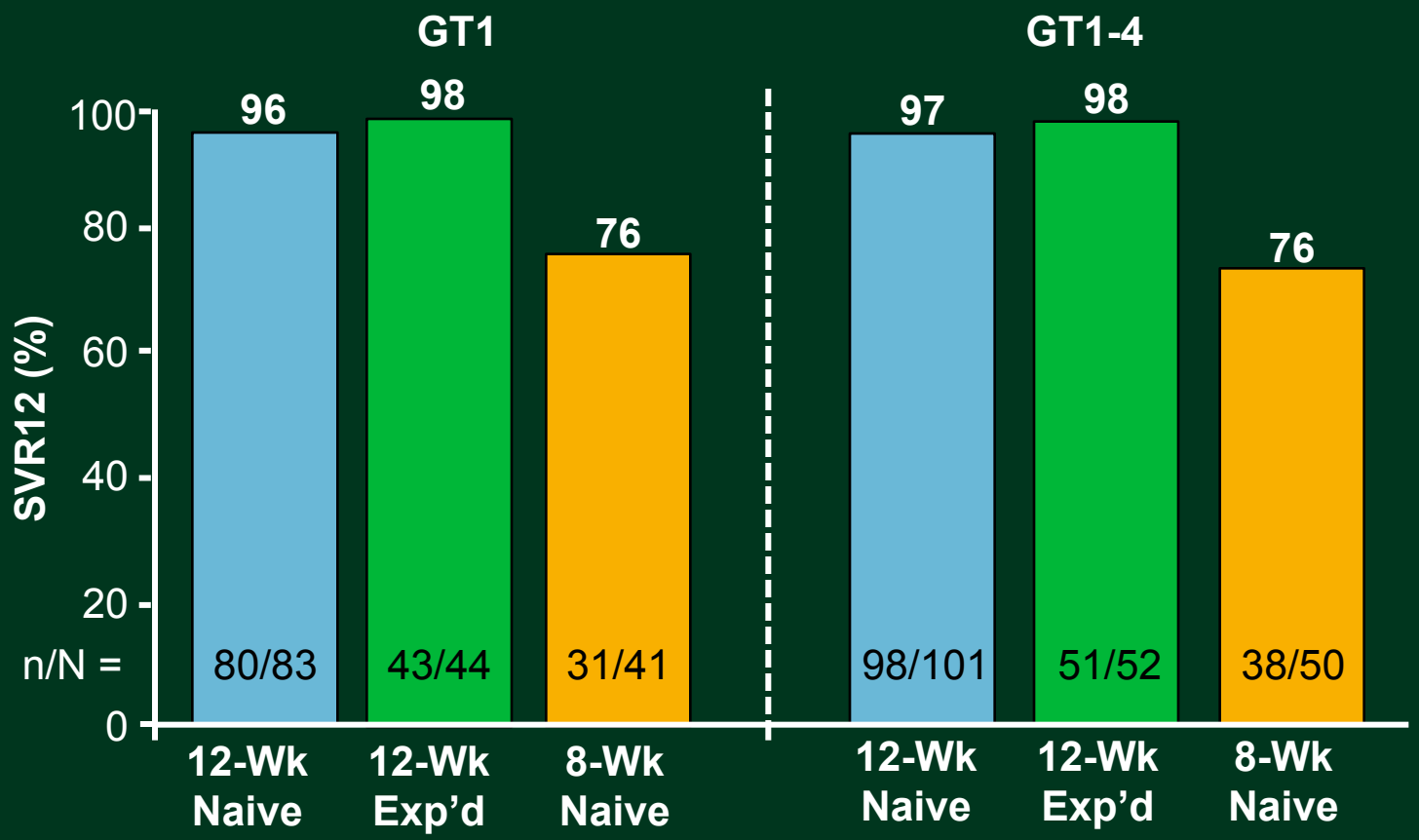
TURQUOISE-1: OMV/PTV/RTV + DSV + RBV for 12 vs 24 Wks in GT1 HCV/HIV Coinfection



- 65% HCV treatment–naive pts in 12-wk arm, 69% in 24-wk arm
- 19% pts with METAVIR F4 fibrosis

Sulkowski M, et al. JAMA. 2015;313:1223-1231.

ALLY-2: SOF + DCV in HCV/HIV-Coinfected Pts



- 12 pts with relapse, 10 in 8-wk arm

Wyles DL, et al. CROI 2015. Abstract 151.

Investigational Agents

Population	Regimen	Trial	Phase	SVR12, %
GT1 HCV + stage 4/5 CKD	12 wks of grazoprevir/elbasvir	C-SURFER[1]	III	99
GT3 HCV (treatment-naive, noncirrhotic or cirrhotic)	8-12 wks grazoprevir/elbasvir + SOF	C-SWIFT[2]	II	91-100
GT1, 4, 6 HCV + HIV coinfection	12 wks of grazoprevir/elbasvir	C-EDGE[3]	III	96
GT3 HCV (treatment-naive, noncirrhotic)	8 wks of SOF + GS-5816 ± RBV	ELECTRON-2[4]	II	88-100

1. Roth D, et al. EASL 2015. Abstract LP02. 2. Poordad F, et al. EASL 2015. Abstract O006.
3. Rockstroh JK, et al. EASL 2015. Abstract P0887. 4. Gane EJ, et al. AASLD 2014. Abstract 79.

Summary

- All-oral HCV therapy has significantly improved tolerability and efficacy, but challenging populations remain
- Cirrhotics may require addition of RBV or longer duration with current therapy to achieve SVR rates comparable to noncirrhotics
- GT3 pts remain a challenging population although the recent availability of DCV introduces a new, IFN-free option in this population
- HIV-coinfected individuals can now achieve SVR rates comparable to monoinfected, but drug–drug interactions must be carefully considered

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