HCV Infection:
EASL Clinical Practice Guidelines 2016

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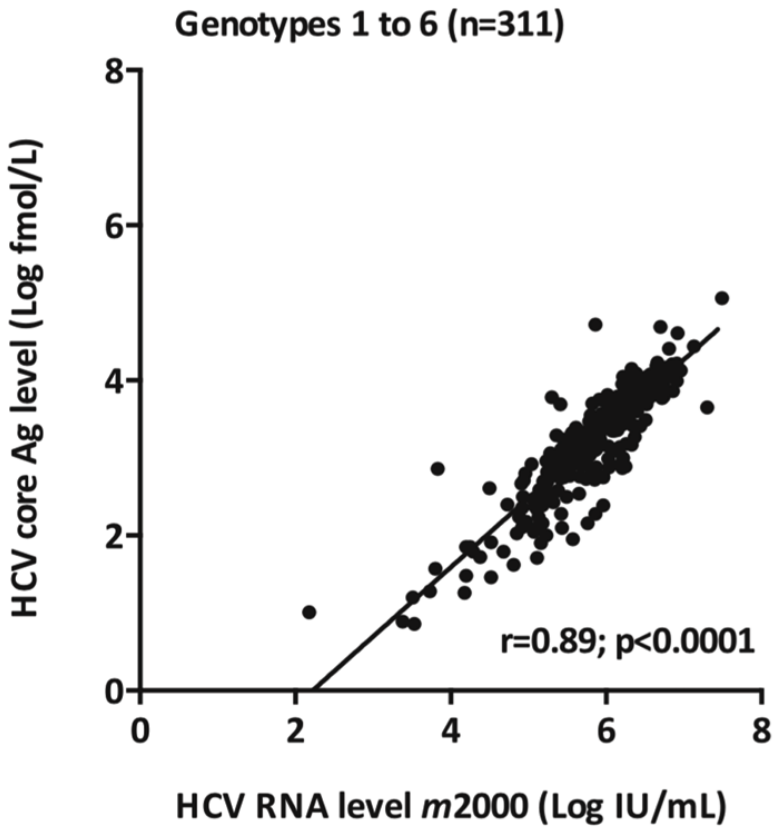
Goal of Therapy

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death
- The endpoint of therapy is undetectable HCV RNA in a sensitive assay (LOD <15 IU/mL) 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment
- Undetectable HCV core antigen 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment is an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy if HCV RNA assays are not available or not affordable

Relationship Between HCV Core Ag and HCV RNA Levels



Analytical sensitivity equivalent to 500-3000 HCV RNA IU/mL

Rare false-negatives (core Ag-negative, HCV RNA-positive)

(Chevaliez et al., J Clin Virol 2014;61:145-8)

Treatment Indications

Treatment Indications

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy

=> UNIVERSAL ACCESS TO THERAPY

Patients Who Should be Treated Without Delay

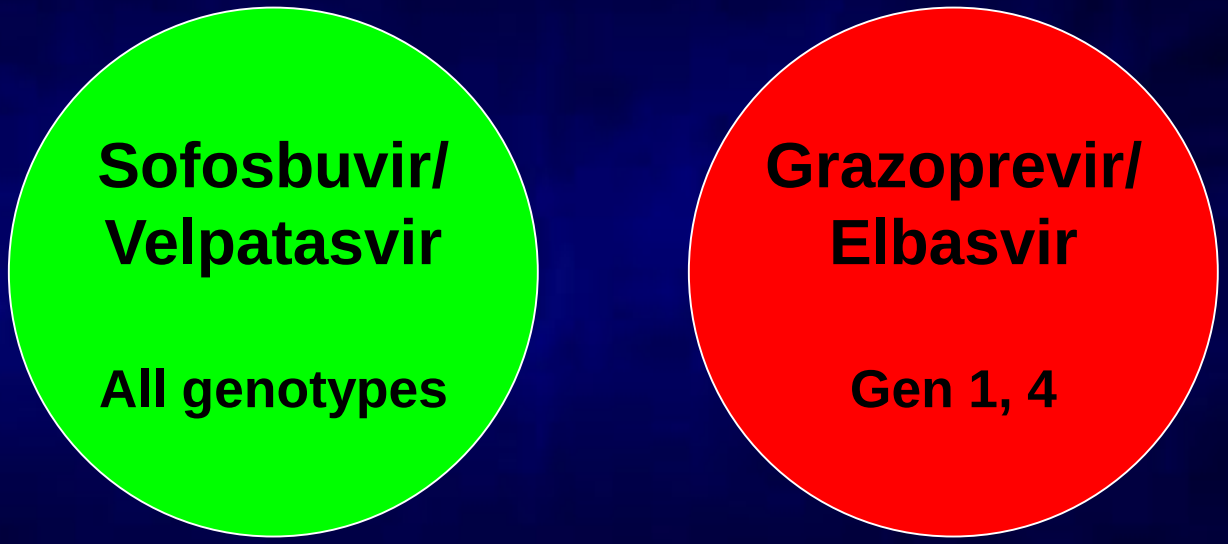
- Significant fibrosis or cirrhosis (METAVIR score F2, F3, F4), including decompensated cirrhosis
- Clinically significant extra-hepatic manifestations
- HCV recurrence after liver transplantation
- Individuals at risk of transmitting HCV
  - Active injection drug users
  - MSM with high-risk sexual practices
  - Women of child-bearing age who wish to get pregnant
  - Hemodialysis patients
  - Prison inmates

Available therapies

DAAs Approved in 2014

DAAs Approved in 2015

DAAs Approved in 2016



General Considerations

- **IFN-free regimens are the best options in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, because of their virological efficacy, ease of use and tolerability**

- **The same IFN-free treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical**

Drug-Drug Interactions

www.hep-druginteractions.org

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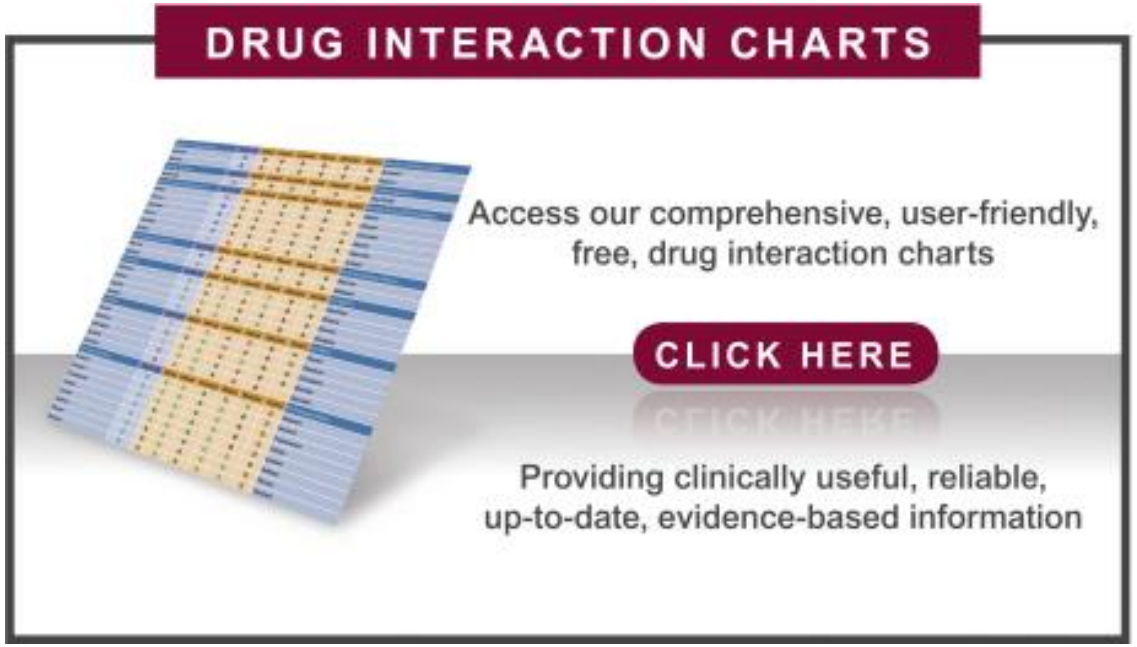


DDIs: HIV Antiretrovirals

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; Atazanavir/r; Atazanavir/Cobicistat	◆	◆*	◆*	■!	●	■	●
	Darunavir/r; Darunavir/Cobicistat	◆	◆*	◆*	■!	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

DDIs: Cardiovascular Drugs

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
Antiarrhythmics	Amiodarone	●	●	●	●	■	●	■
	Digoxin	◆	■	■	■	◆	■	■
	Flecainide	◆	◆	◆	■	◆	◆	■
	Vernakalant	◆	◆	◆	■	◆	◆	◆
Antiplatelet and anticoagulants	Clopidogrel	◆	◆	◆	■	◆	■	■
	Dabigatran	◆	■	■	■	■	■	■
	Ticagrelor	◆	■	■	●	■	◆	■
	Warfarin	◆	◆	◆	◆	◆	◆	◆
Beta blockers	Atenolol	◆	◆	◆	◆	◆	◆	◆
	Bisoprolol	◆	◆	◆	■	◆	◆	■
	Carvedilol	■	■	■	■	◆	■	■
	Propranolol	◆	◆	◆	◆	◆	◆	◆
Calcium channel blockers	Amlodipine	◆	■	■	■	■	■	■
	Diltiazem	◆	■	■	■	◆	■	■
	Nifedipine	◆	◆	◆	■	◆	■	■
Hypertenstion and heart failure agents	Aliskiren	◆	■	■	●	◆	■	■
	Candesartan	◆	◆	◆	■	■	◆	◆
	Doxazosin	◆	◆	◆	■	◆	◆	■
	Enalapril	◆	◆	◆	■	◆	◆	◆

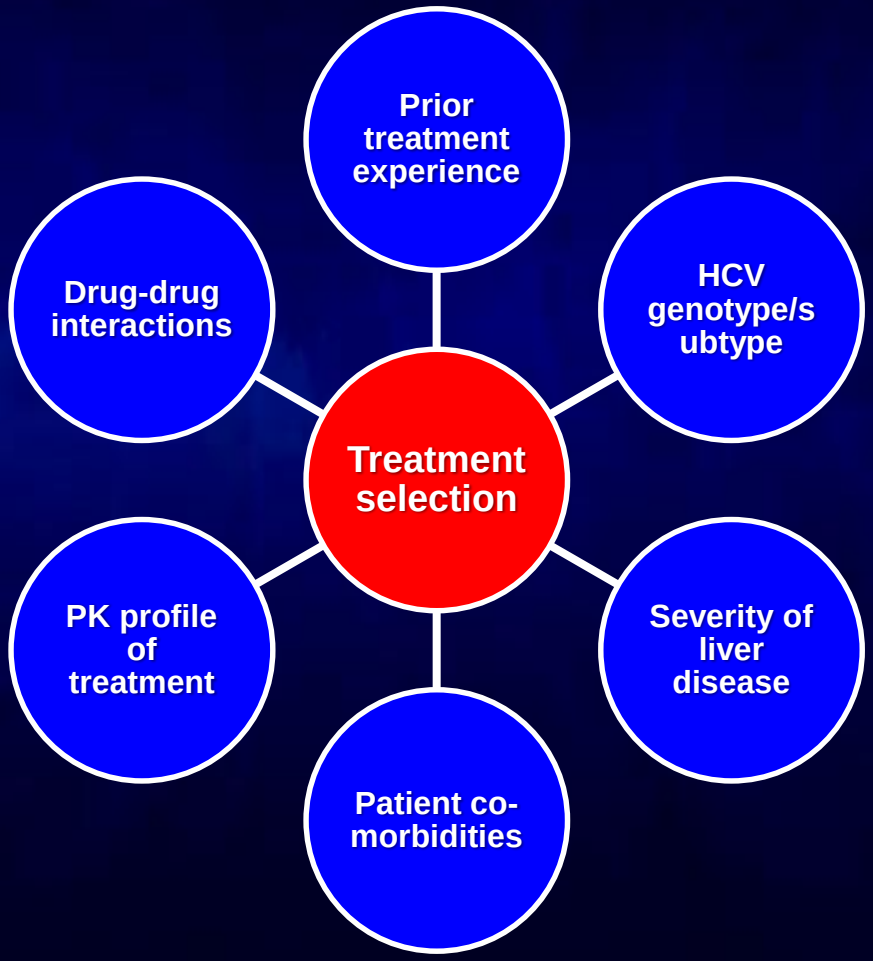
IFN-Free Treatment Options

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Yes	No	No	Yes	Yes
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No

IFN-Free Treatment Options

- These options are considered equivalent for a given genotype, and their order of presentation does not indicate any superiority of preference, unless specified so
- By convention, the combination regimens listed start with fixed-dose, single-pill combinations (sofosbuvir-based followed by sofosbuvir-free), followed by combinations of sofosbuvir with another drug in a different pill

Characteristics that Inform Treatment Option Selection



Genotype 1

Genotype 1a Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	8-12 wk	12 wk + RBV*¶	12 wk	12 wk + RBV*¶
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D) ± RBV	12 wk + RBV	12 wk + RBV	24 wk + RBV	24 wk + RBV
GZR/EBR ± RBV	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	12 wk	12 wk + RBV*¶

*24 wk without RBV if RBV contraindicated or poorly tolerated
¶Only if presence of NS5A RASs at baseline, if resistance testing available

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	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
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SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
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	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
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SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
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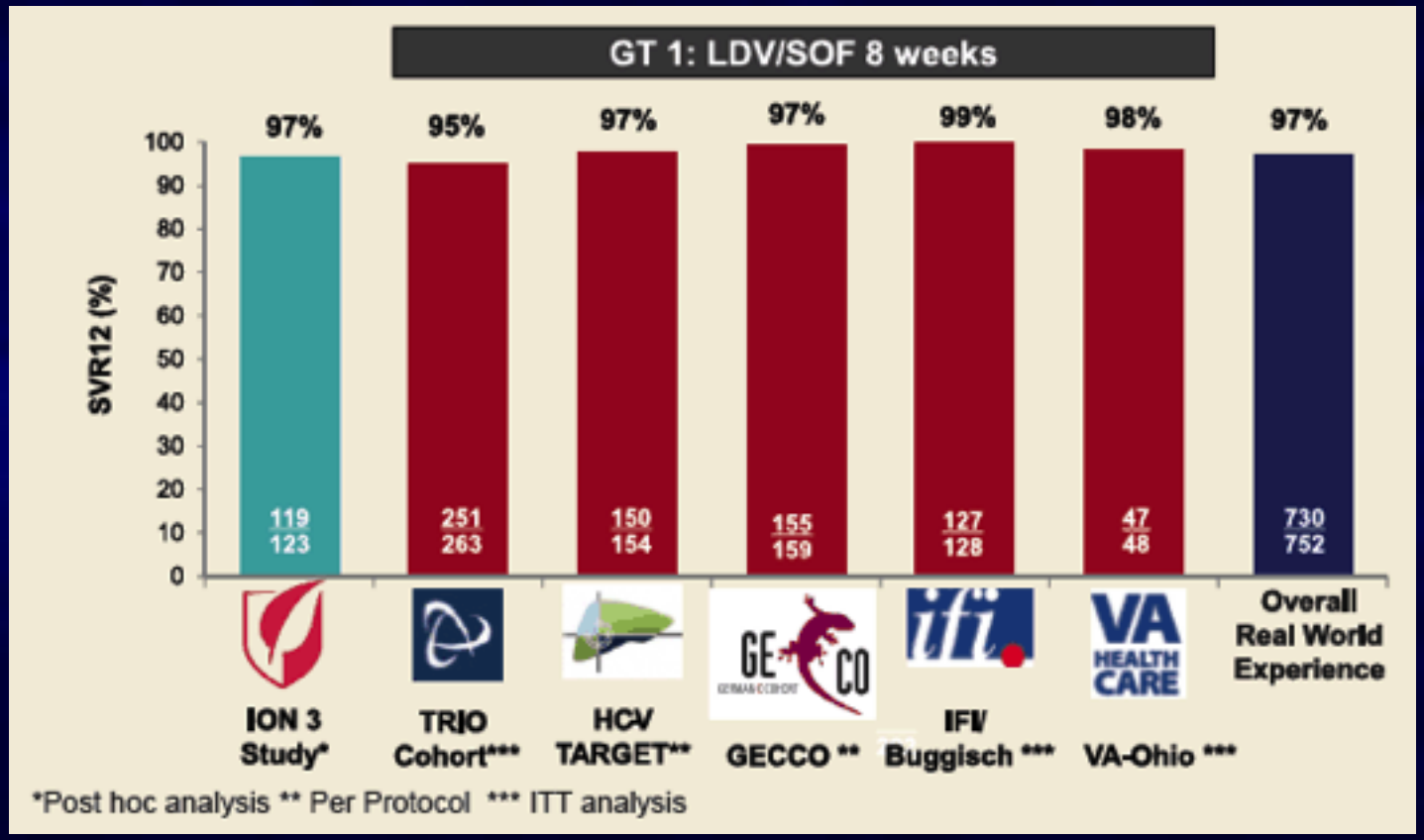
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	12 wk	12 wk + RBV*¶

*24 wk without RBV if RBV contraindicated or poorly tolerated
¶Only if presence of NS5A RASs at baseline, if resistance testing available

SOF/LDV Trials *vs* Real-World

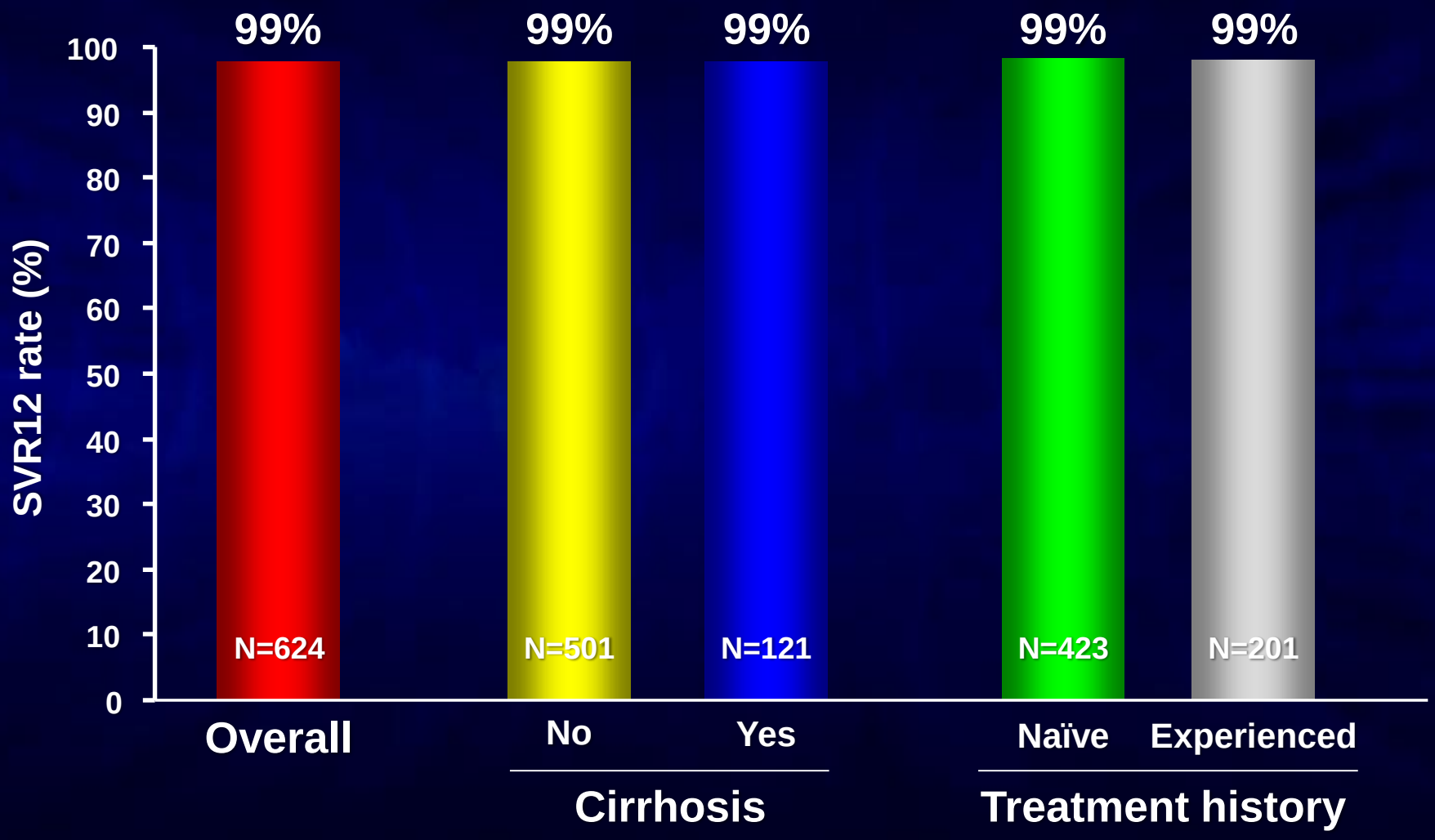
ION-3 vs Real-world, Rx-naive, No cirrhosis, VL <6 M IU/mL



(Curry et al., EASL 2016)

Sofosbuvir + Velpatasvir

ASTRAL-1– Phase III, TN and TE (32%), Gt 1,2,4,5,6, 19% cirrhosis, 12 wks



(Feld et al., N Engl J Med 2015;373:2599-607)

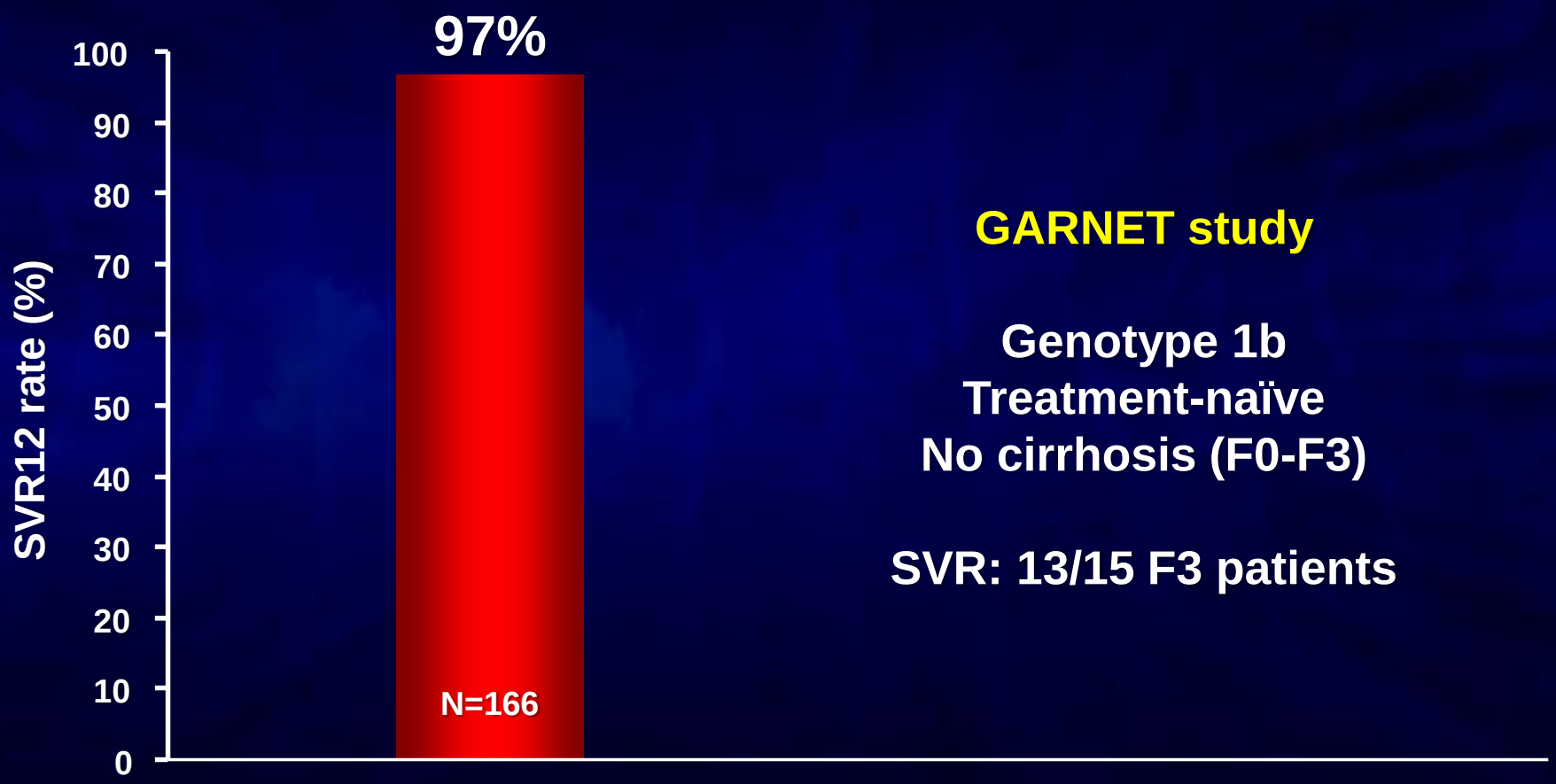
Genotype 1b Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	8-12 wk	12 wk	12 wk	12 wk
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D) ± RBV	8-12 wk	12 wk	12 wk	12 wk
GZR/EBR ± RBV	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk	12 wk	12 wk

Genotype 1b Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	8-12 wk	12 wk	12 wk	12 wk
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D) ± RBV	8-12 wk	12 wk	12 wk	12 wk
GZR/EBR ± RBV	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk	12 wk	12 wk

8 weeks of OBV/PTV/r + DSV in Genotype 1b Treatment-Naïves



GARNET study

Genotype 1b
Treatment-naïve
No cirrhosis (F0-F3)

SVR: 13/15 F3 patients

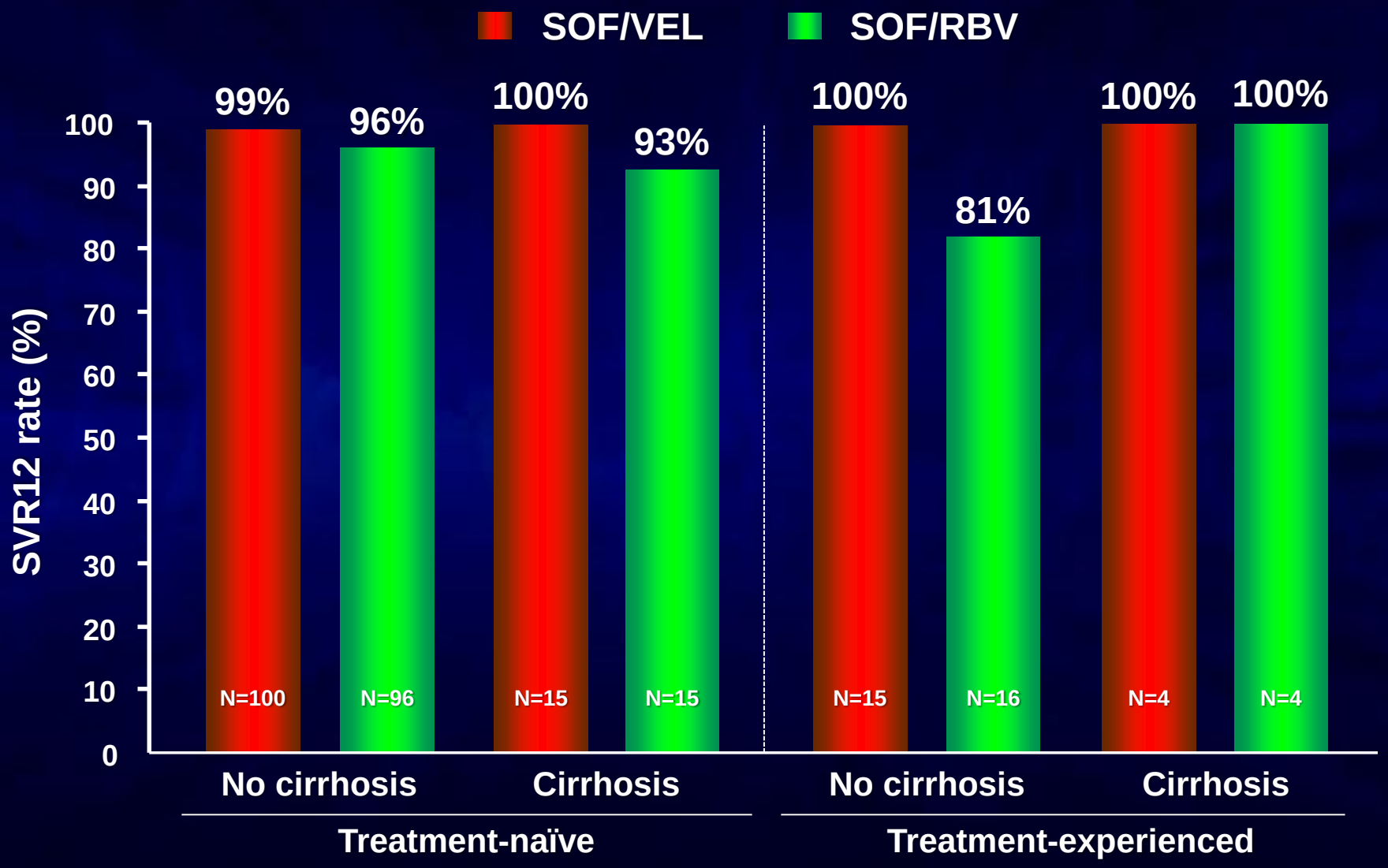
(Abbvie, presented at the EASL/AASLD Special Conference on Hepatitis C)

Genotype 2 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk	12 wk	12 wk

Sofosbuvir + Velpatasvir

ASTRAL-2– Phase III, TN and TE (14%), Gt 2, 14% cirrhosis, 12 weeks



(Foster et al., N Engl J Med 2015;373:2608-17)

Genotype 3 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/VEL ± RBV	12 wk	12 wk + RBV*¶	12 wk + RBV*¶	12 wk + RBV*¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	24 wk + RBV	24 wk + RBV

*24 wk without RBV if RBV contraindicated or poorly tolerated
¶Only if presence of NS5A RAS Y93H at baseline, if resistance testing available

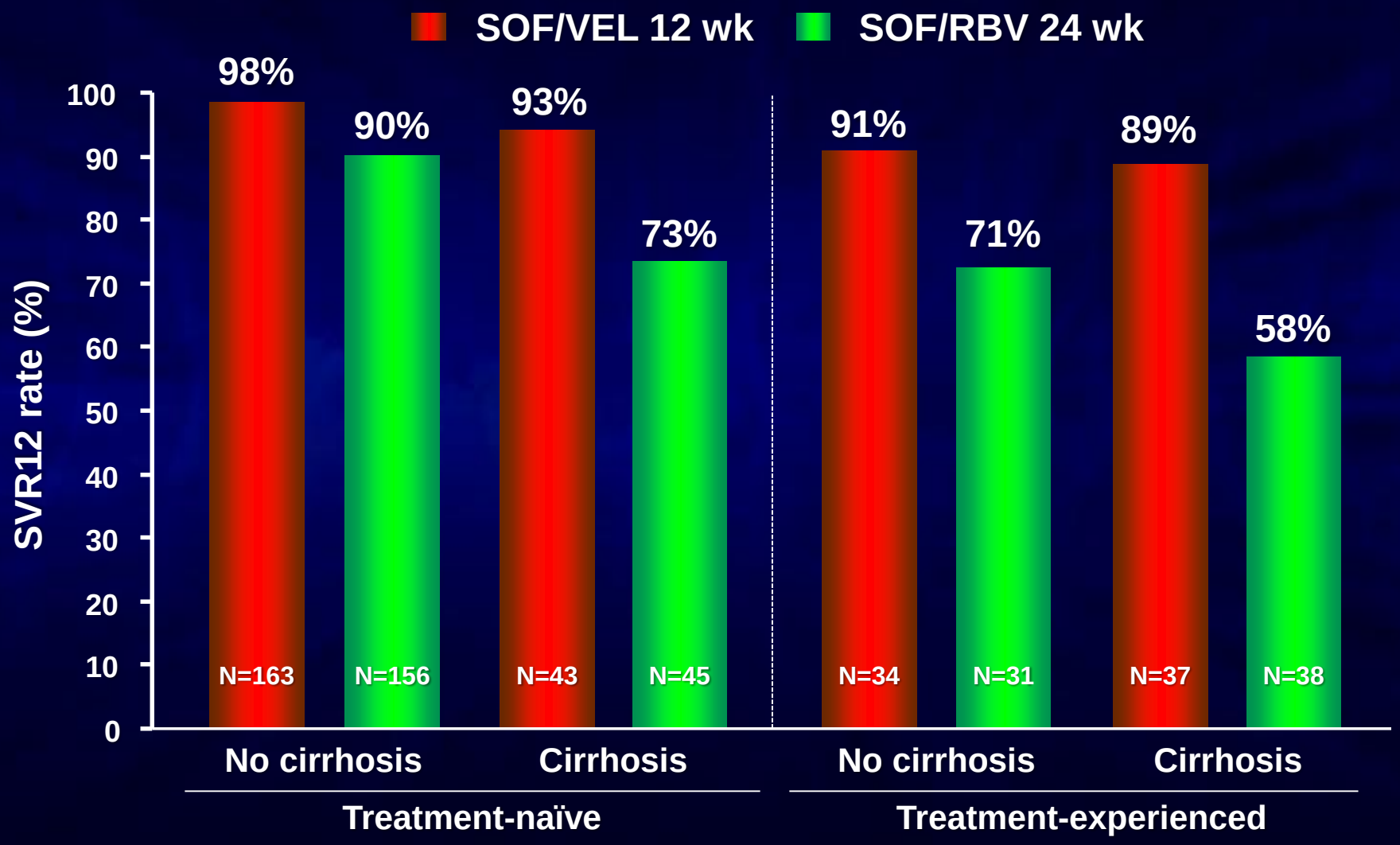
Genotype 3 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/VEL ± RBV	12 wk	12 wk + RBV*¶	12 wk + RBV*¶	12 wk + RBV*¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	24 wk + RBV	24 wk + RBV

*24 wk without RBV if RBV contraindicated or poorly tolerated
¶Only if presence of NS5A RAS Y93H at baseline, if resistance testing available

Sofosbuvir + Velpatasvir

ASTRAL-3– Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks

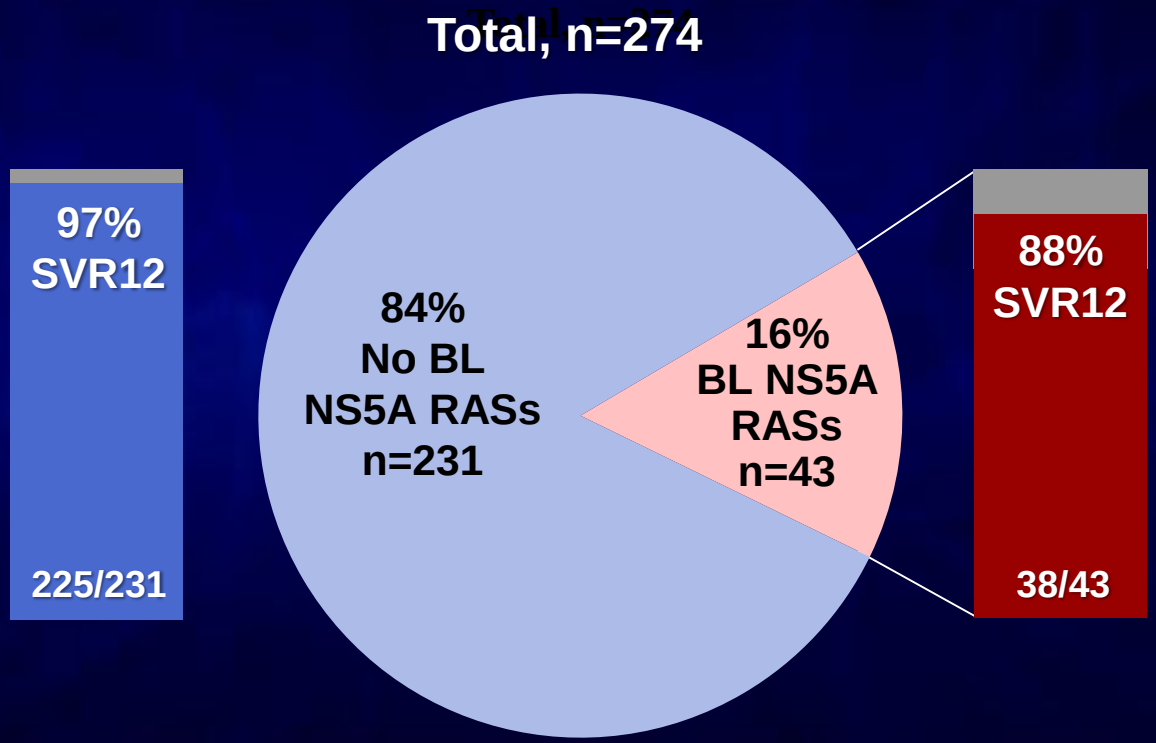


(Foster et al., N Engl J Med 2015;373:2608-17)

Sofosbuvir + Velpatasvir

ASTRAL-3– Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks

Resistance analysis (1% cutoff, deep sequencing)



- **SVR12 was 84% (21/25) in patients with Y93H**

(Foster et al., N Engl J Med 2015;373:2608-17)

Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D) ± RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF + SIM ±RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D) ± RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF + SIM ±RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

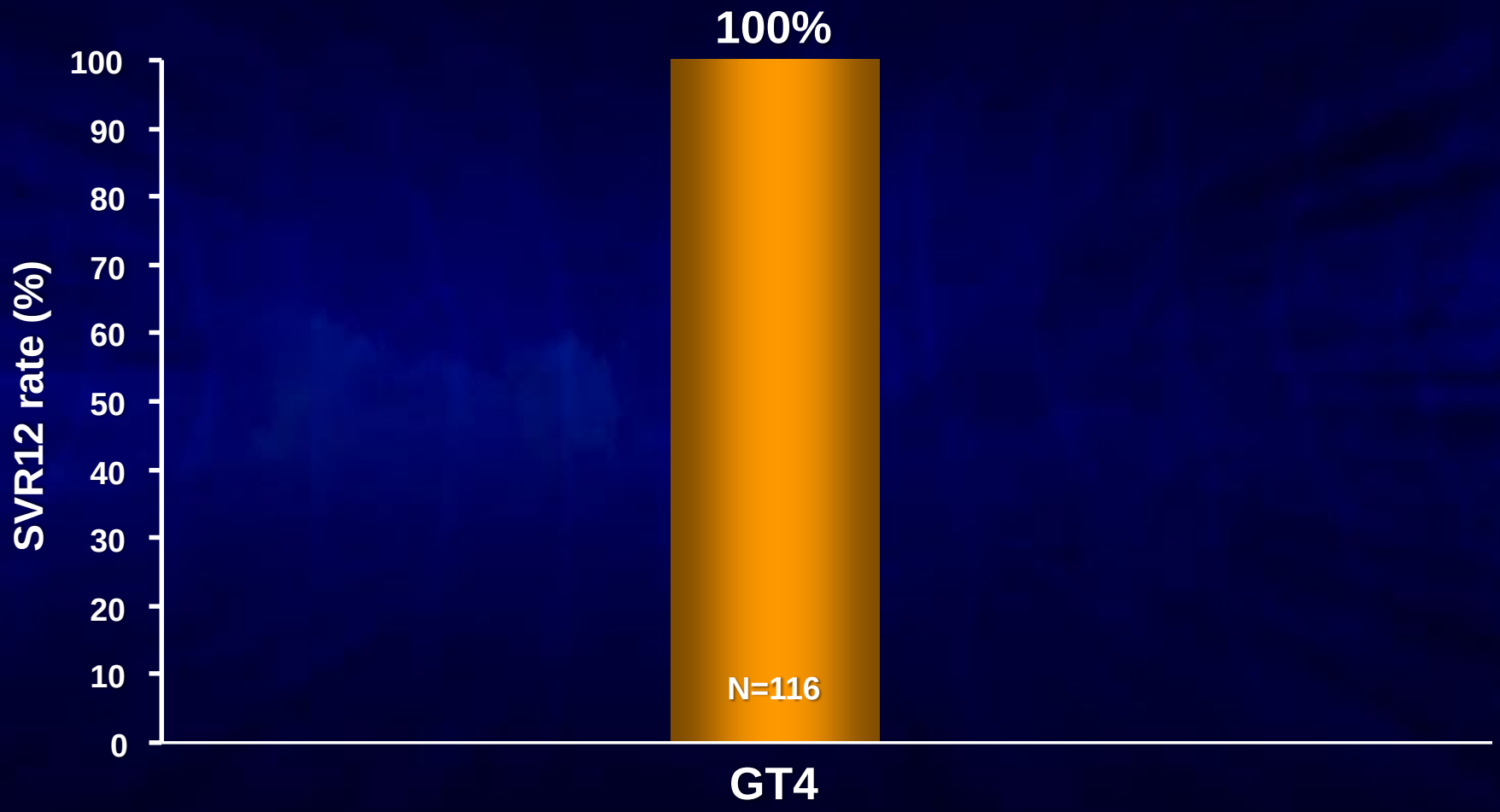
Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D) ± RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF + SIM ±RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

Sofosbuvir + Velpatasvir

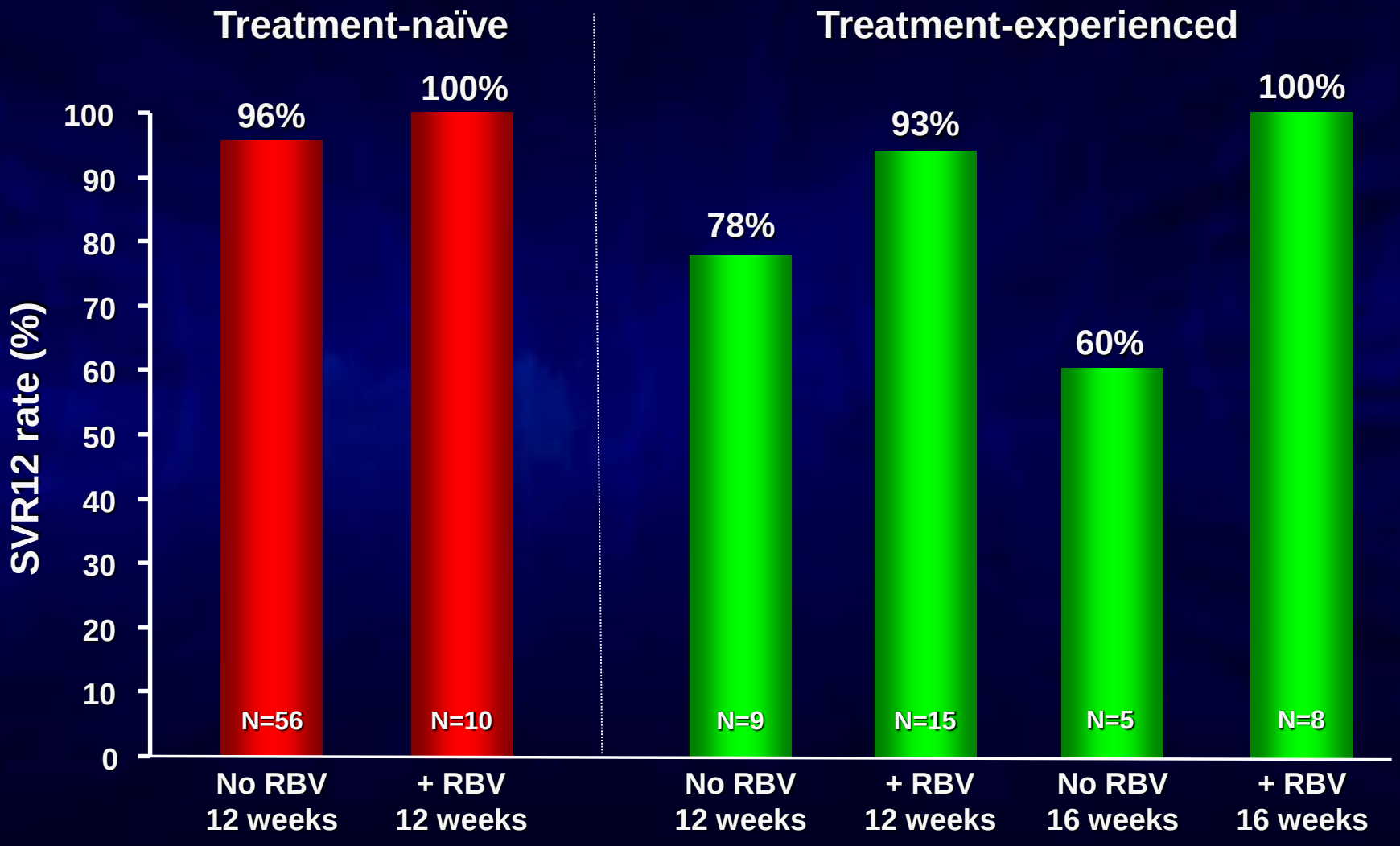
ASTRAL-1– Phase III, TN and TE (32%), Gt 4, 19% cirrhosis, 12 wks



(Feld et al., N Engl J Med 2015;373:2599-607)

Grazoprevir + Elbasvir

Integrated analysis of Phase II and III trials, Gt 4, w/o cirrhosis



(Asselah et al., AASLD 2015)

Genotype 5-6 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

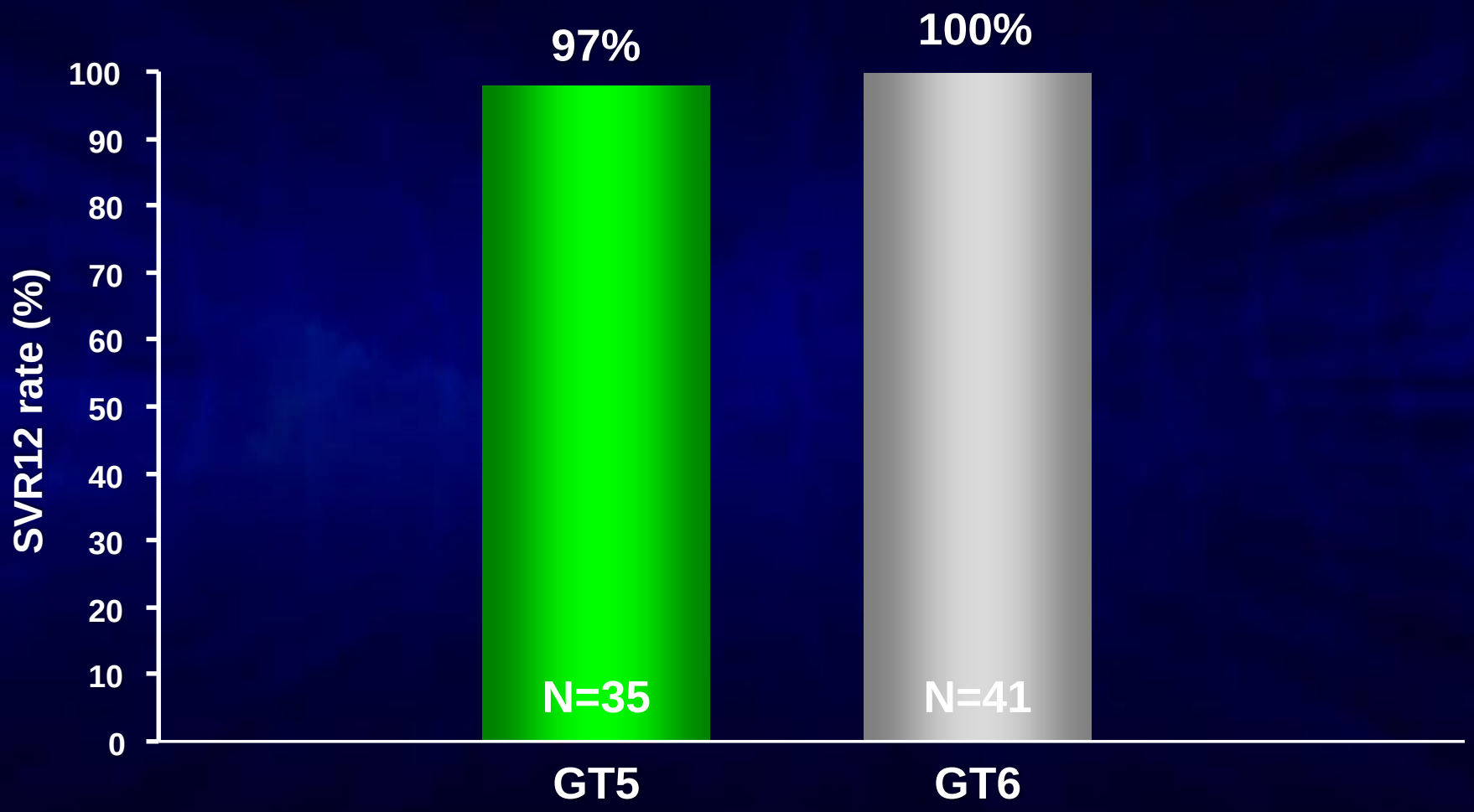
Genotype 5-6 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

Sofosbuvir + Velpatasvir

ASTRAL-1– Phase III, TN and TE (32%), Gt 1,2,4,5,6, 19% cirrhosis, 12 wks



(Feld et al., N Engl J Med 2015;373:2599-607)

Utility of HCV resistance testing prior to first-line therapy

HCV RAS Testing Prior to First-line Therapy

- Systematic testing for HCV resistance prior to treatment is NOT recommended. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information

- Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions

- The test should be based on population sequencing (reporting RASs as “present” or “absent”) or deep sequencing with a cutoff of 15% (only RASs that are present in more than 15% of the sequences generated must be considered)

HCV Resistance Testing Prior to First-Line DAA Therapy

Not available

↓

Optimize therapy to avoid treatment failure

↓

- **SOF/LDV, SOF/DCV, SOF/SIM: Add RBV in G1a-4-5-6 TE**
- **SOF/VEL: Add RBV in G3 TE patients and cirrhotics**
- **GZR/EBR: use 16 weeks with RBV in GT1a**

Available, reliable, interpretable, understandable*

***recommended for GZR/EBR for US patients with GT1a**

↓

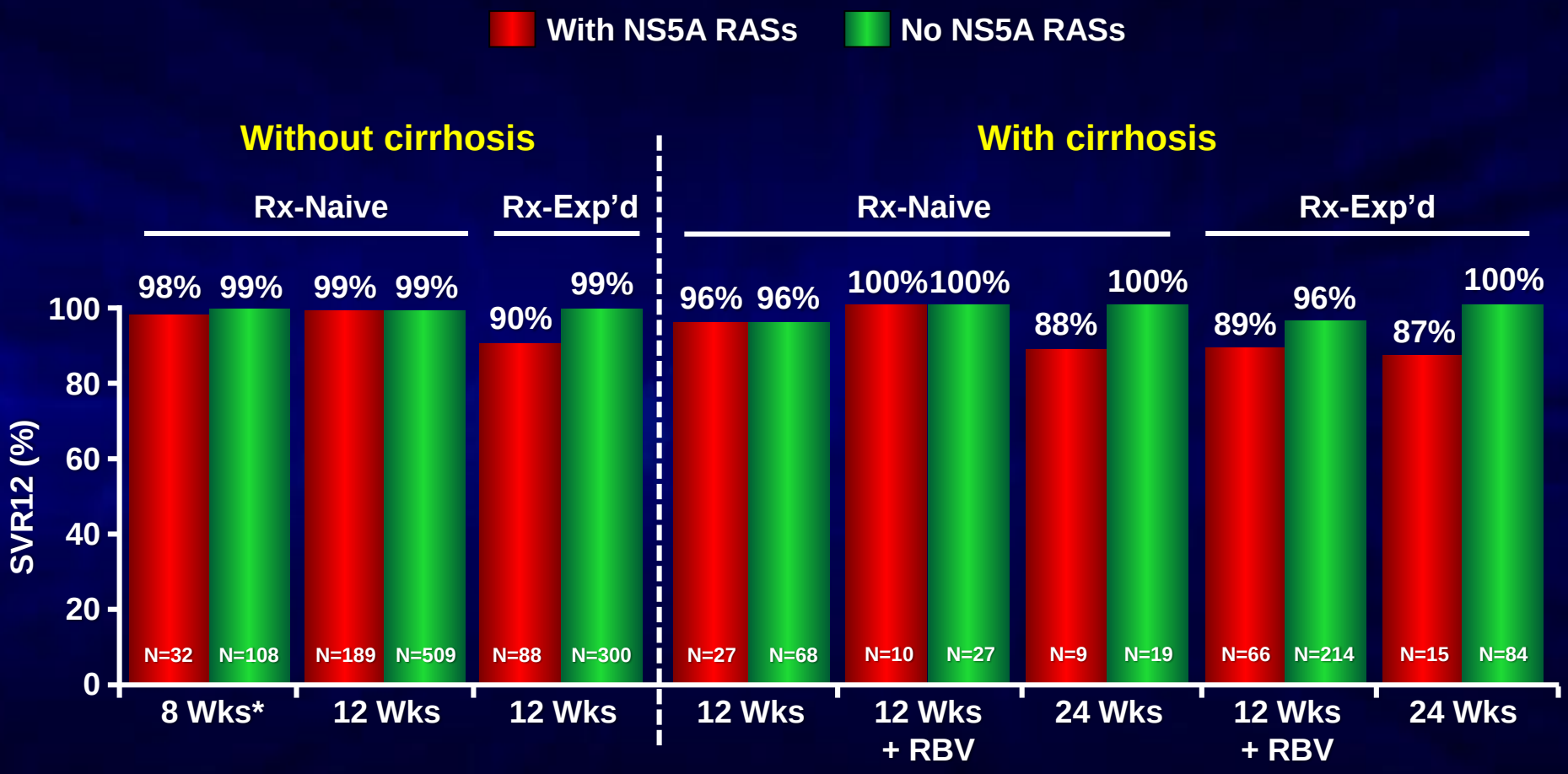
Presence of NS5As RASs conferring high-level resistance (pop seq or >15%)

↓

Add ribavirin and/or increase treatment duration in patients with NS5A RASs

SVR According to Baseline NS5A RASs

GT1, SOF/LDV, guidelines-recommended

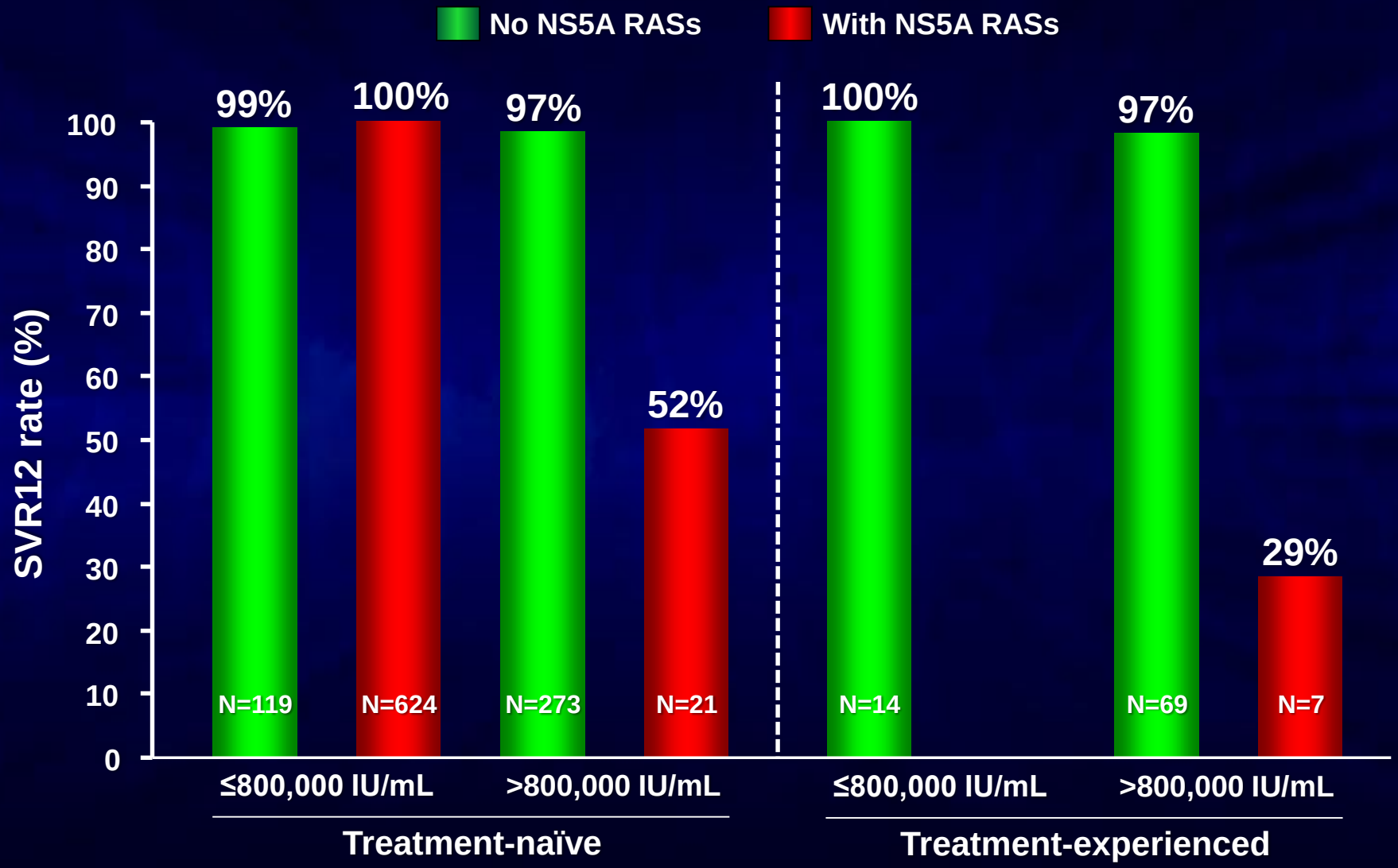


*HCV RNA < 6 million IU/mL

(Zeuzem et al., AASLD 2015)

Grazoprevir/Elbasvir

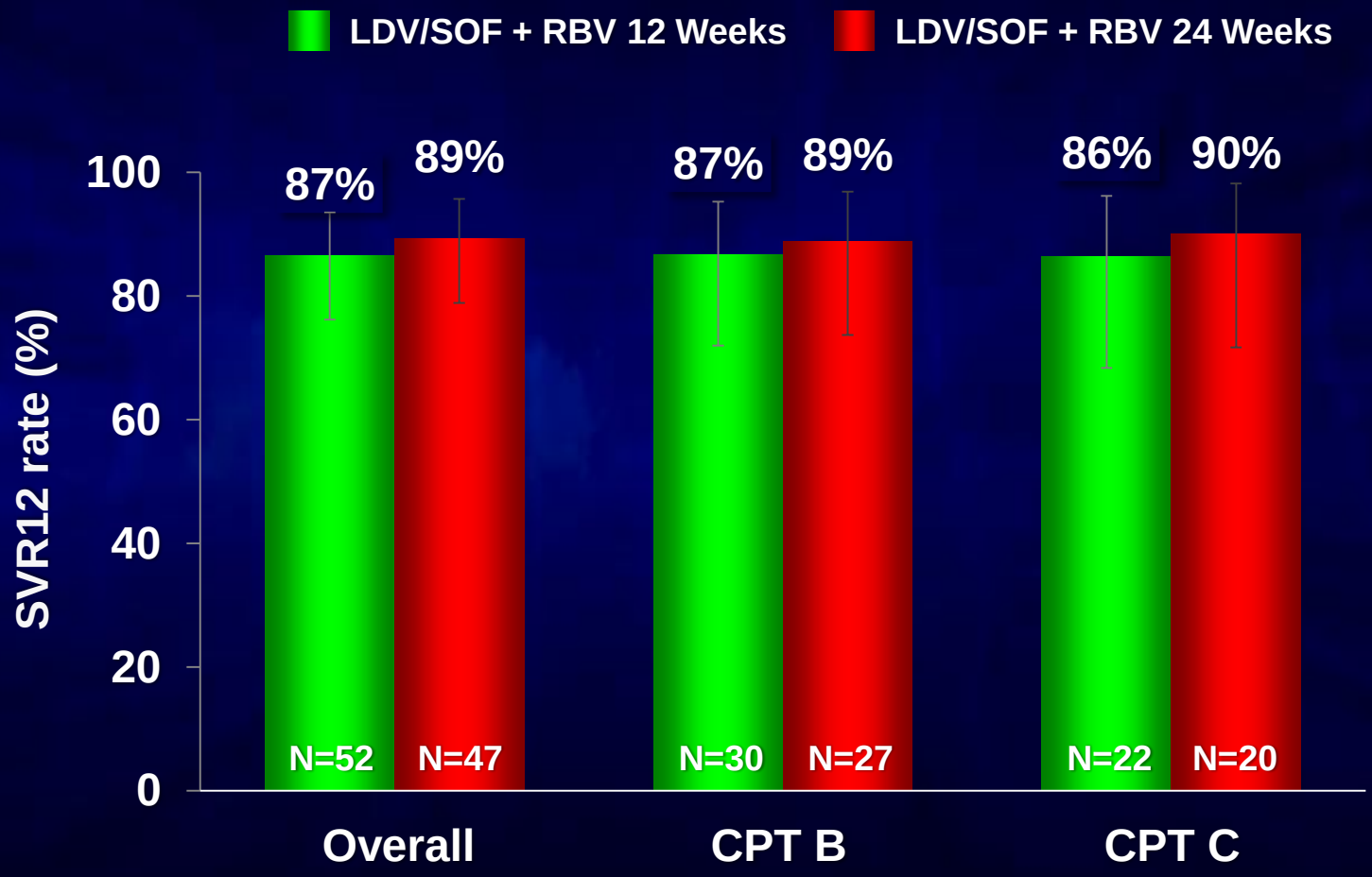
Pooled efficacy population-Phase II and III trials, GT1a, 12 weeks, no RBV



(Merck, communicated to the panel)

Sofosbuvir/Ledipasvir FDC + RBV

SOLAR-1- Genotype 1, decompensated cirrhosis

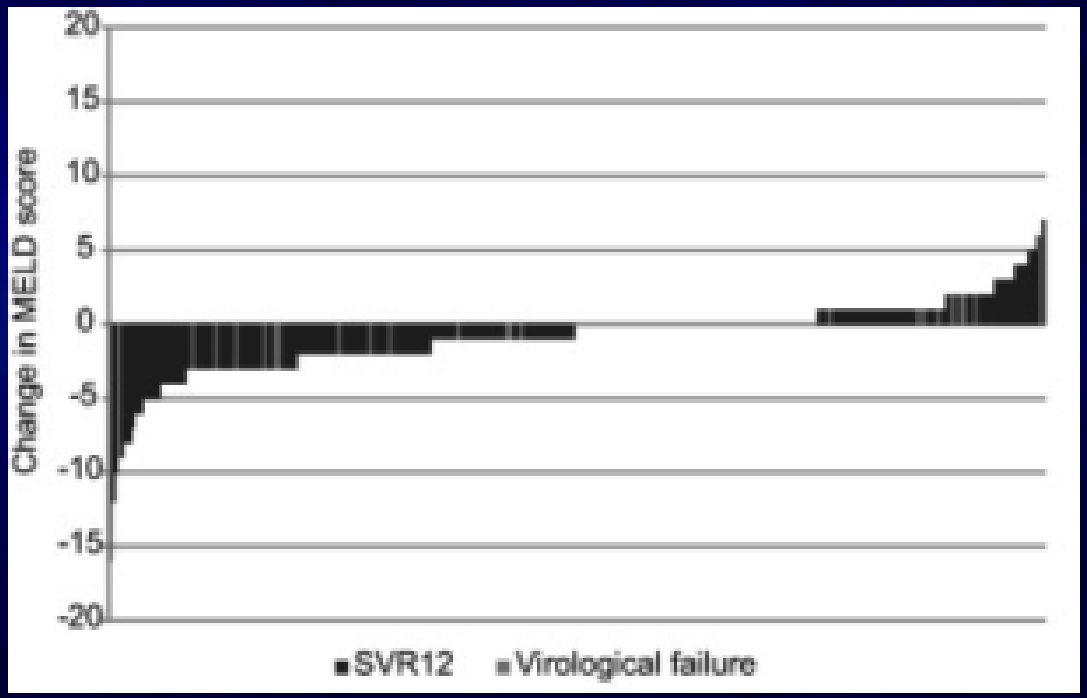


(Charlton et al., Gastroenterology 2015;149:649-59)

SOF/LDV or SOF+DCV ± RBV

Real-life UK EAP, Decompensated cirrhosis (CPT ≥7), All GTs

Change in MELD score



(Foster et al., J Hepatol 2016;64:1224-31)

Patients with Decompensated Cirrhosis Without an Indication for LT

- Patients with decompensated cirrhosis (CPT-B or CPT-C) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival should be treated urgently
- Protease inhibitors should not be used in patients with Child-Pugh B and are contraindicated in patients with Child-Pugh C decompensated cirrhosis
- Frequent clinical and laboratory assessment is necessary