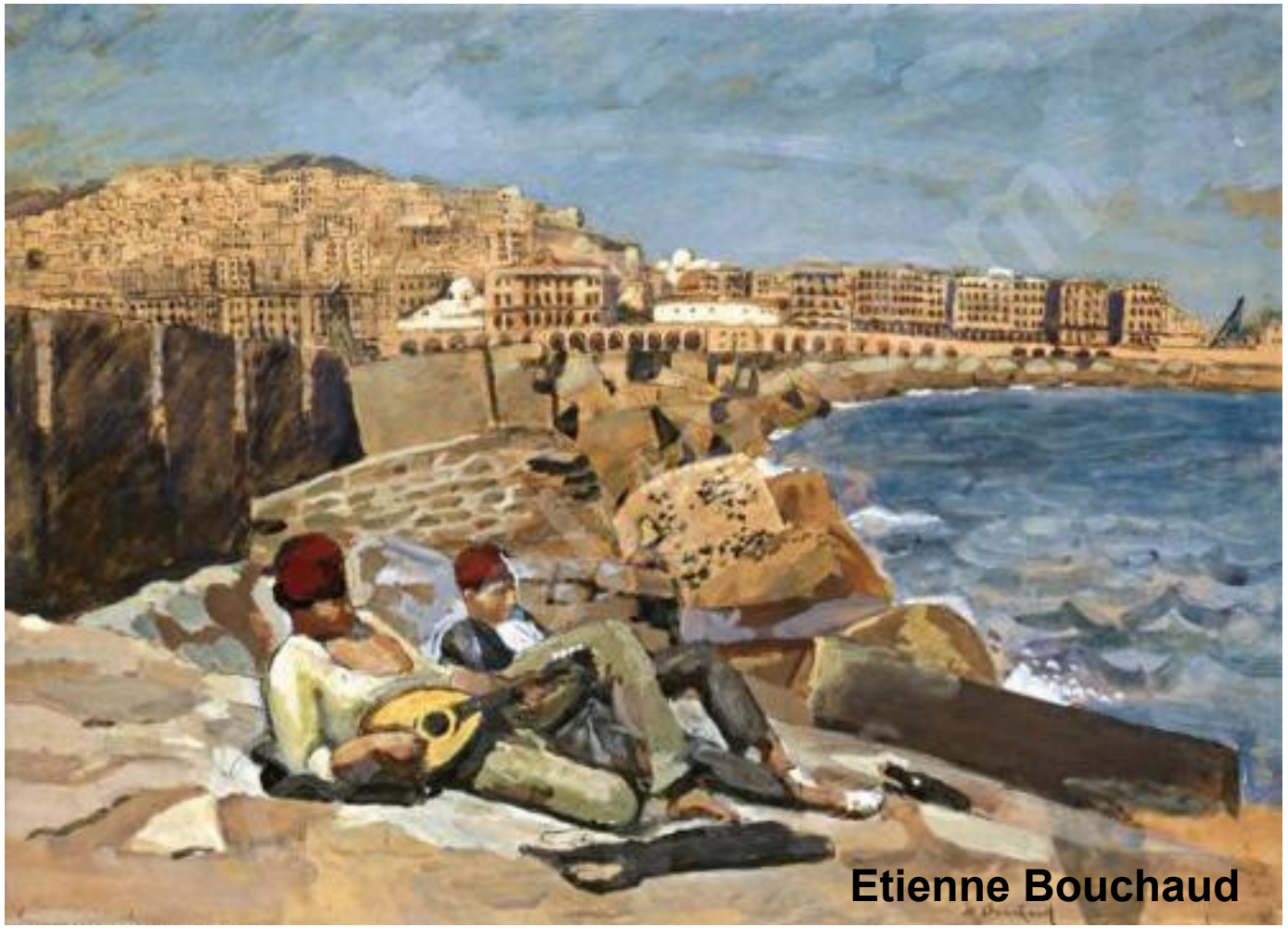
Optimizing Current Therapies & Future Perspectives for HCV



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Disclosures

- Advisory Board/Speaker Bureau member and investigator for: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and Roche

We still have a dream (back to 2011)

Martin Luther King J (1963, Washington)

Where we go : The Future (back to 2011)
Ten Commandments for the Magic Drug

1 HIGH **E**FFICACY

2 LOW **R**ESISTANCE (high genetic barrier)

3 P**A**N-GENOTYPIC ACTIVITY

7 SHORT **D**URATION

8 FAVORABLE SAFETY PROF**I**LE

9 ON**C**E A DAY (Good pharmacokinetic)

10 OR**A**L REGIMEN (IFN free)

11 FEW DRUG-DRUG IN**T**ERRACTION

12 AVA**I**LABLE FOR (ELD), CIRRHOSIS and HIV-HCV

19 L**O**W PRICE (access program)

HCV ERADICATION WORLWIDE

Asselah et al. Direct acting antivirals for the treatment of chronic hepatitis C: ***One pill a day for tomorrow****. Liver Int 2012;32 Suppl 1:88-102.*

The goal of this lecture will be to summarize results obtained with recently approved oral DAAs combinations for HCV treatment to discuss future perspectives.

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Introduction (Direct-Acting Antivirals)

Recently approved treatment

- Ledipasvir/Sofosbuvir
- Paritaprevir/Ombitasvir/Dasabuvir
- Optimization (simplification)

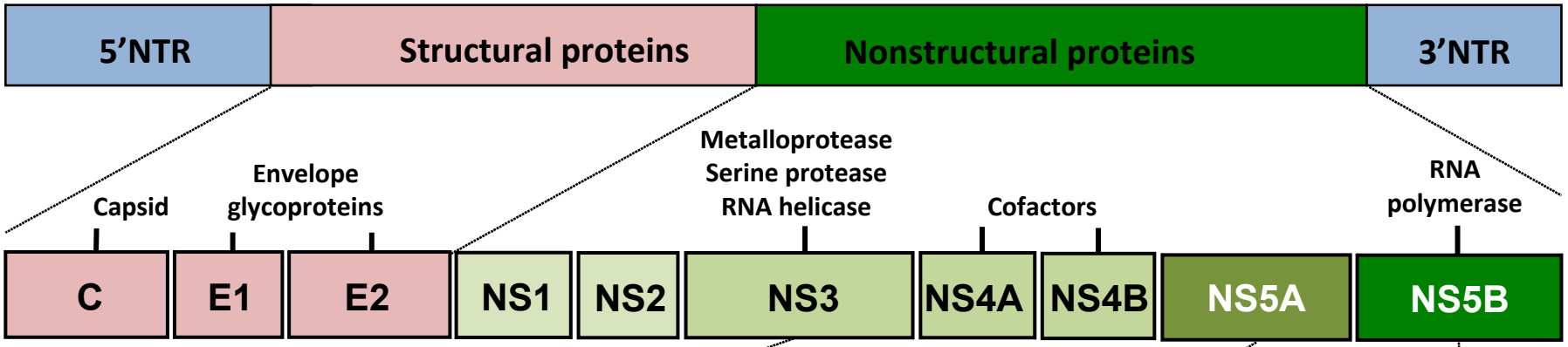
Available soon

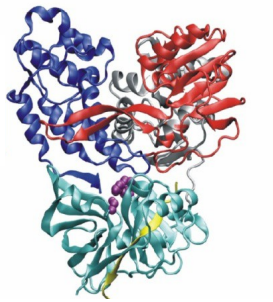
- Grazoprevir/elbasvir
- Velpatasvir/Ledipasvir
- AbbVie 2nd Generation

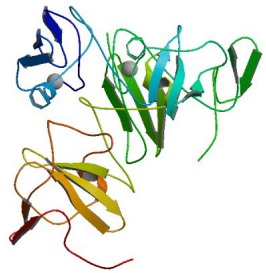
Perspectives

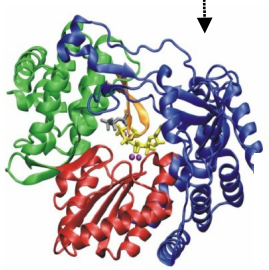
- Shorten treatment duration
- Future Challenges (ELD, RAVs, DDI….)

Direct-acting antivirals (DAAs)









Protease Inhibitors
« …previr »

- Telaprevir
- Boceprevir
- Simeprevir
- Paritaprevir
- ABT 493
- Grazoprevir
- GS-9857
- Sovaprevir
- ACH-2684

NS5A Inhibitors
« ….asvir »

- Daclatasvir
- Ledipasvir
- Velpatasvir (GS-5816)
- Ombitasvir
- ABT 530
- Elbasvir
- MK-8408
- Samatasvir
- Odalasvir (ACH-3102)

Polymerase Inhibitors
« …..buvir »

Nucs

- Sofosbuvir
- MK 3682
- ACH-3422
- ALS-335

Non-Nucs

- Dasabuvir
- GS-9669
- MK-8876

Asselah et al. Liver Int 2016.

Direct-Acting Antivirals: Mode of Action

	Nucleotide NS5B inhibitors	Non-nucleoside NS5B inhibitors	NS5A replication complex inhibitors	Protease inhibitors
Gilead	Sofosbuvir	GS-9669	Ledipasvir Velpatasvir	GS-9857
AbbVie		Dasabuvir	Ombitasvir ABT-530	Paritaprevir/r ABT-493
Merck (MSD)	MK-3682	MK-8876	Elbasvir MK-8408 Samatasvir	Boceprevir Grazoprevir
Janssen/ Achilleon	ACH-3422 AL-335		Odalasvir (ACH-3102)	Simeprevir Sovaprevir

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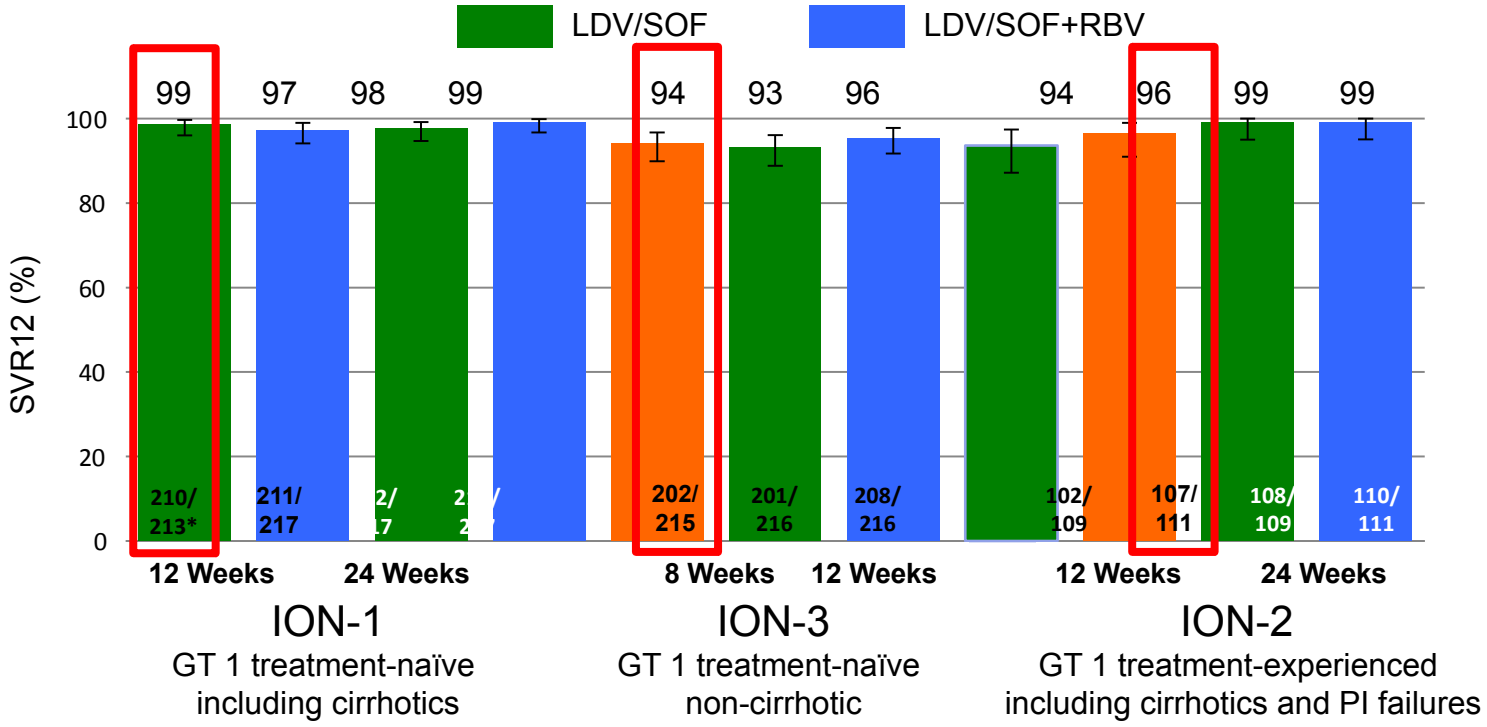
Sofosbuvir/ledipasvir



Afdhal et al. N Engl J Med 2014; 370: 1889–98.
Afdhal et al. N Engl J Med 2014; 370: 1483–93.
Kowdley et al. N Engl J Med 2014; 370: 1879–88.

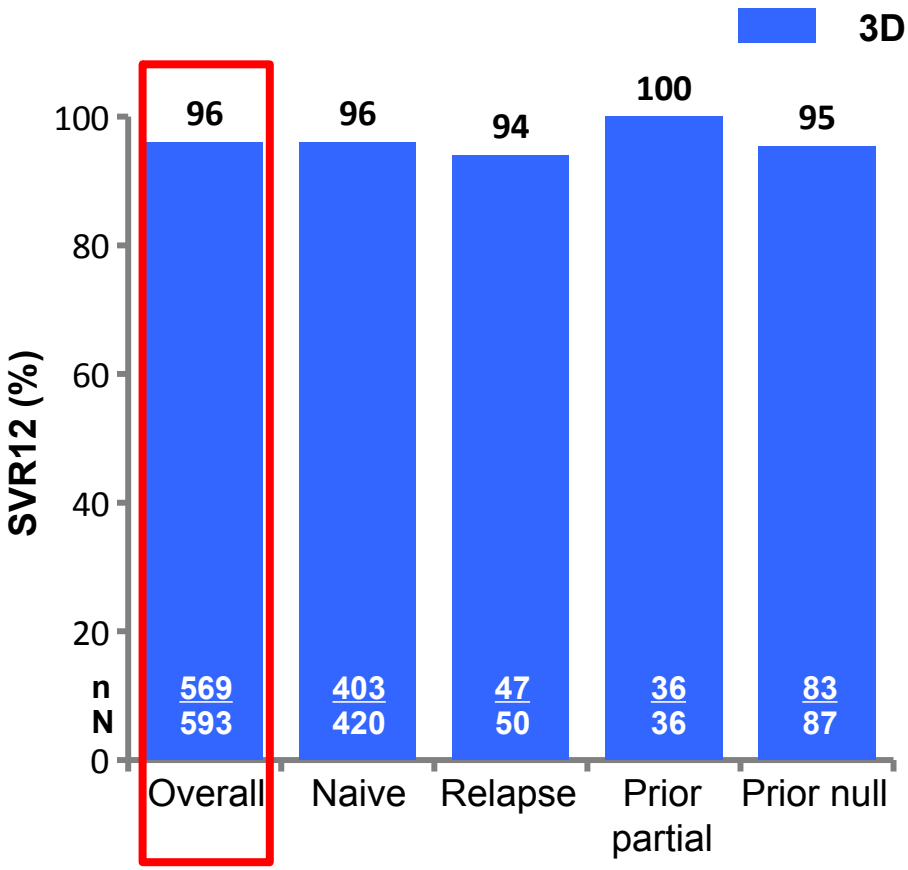
Sofosbuvir/ledipasvir

Treatment Status	Cirrhosis Status	Duration (Wks)	ITT SVR
Treatment Naïve	Non-Cirrhotic	8	94.0%
		12	95.4%
	Cirrhotic	12	94.1%
		24	93.9%
Treatment Experienced	Non-Cirrhotic	12	95.4%
		24	98.9%
	Cirrhotic	12	86.4%
		24	100.0%

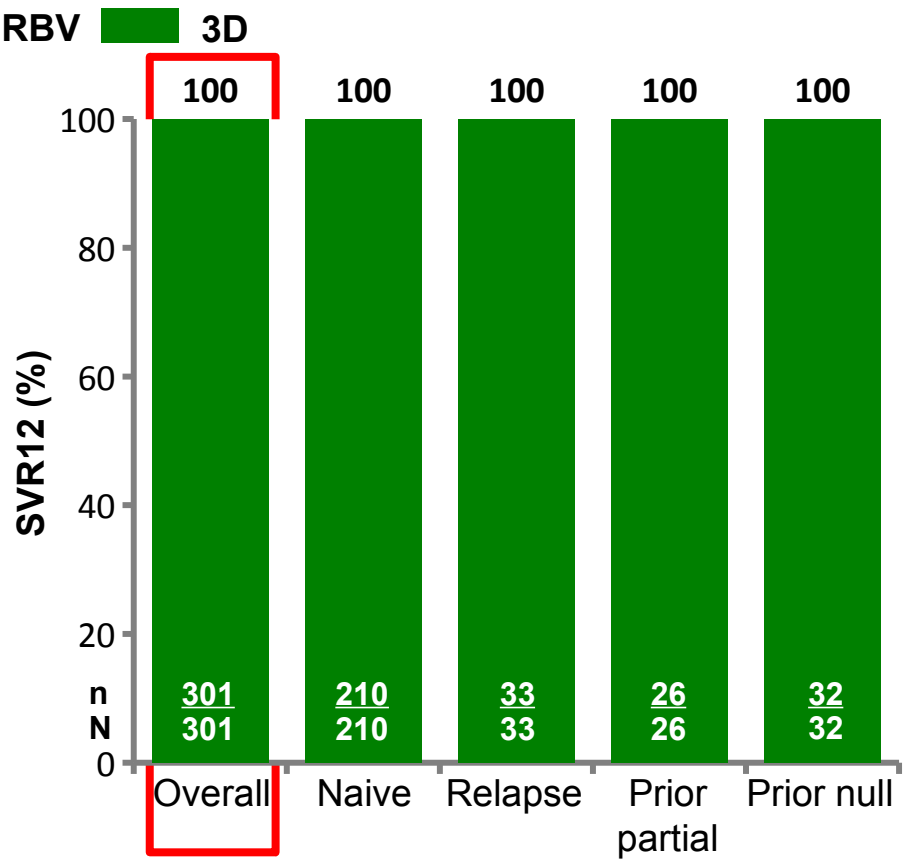
Gilead Sciences Ltd. Harvoni (ledipasvir/sofosbuvir), Summary of Product Characteristics, November 2014.

Paritaprevir/Ombitasvir/Dasabuvir

GT1a-infected, non-cirrhotic patients
SAPPHIRE-I, -II, PEARL-IV

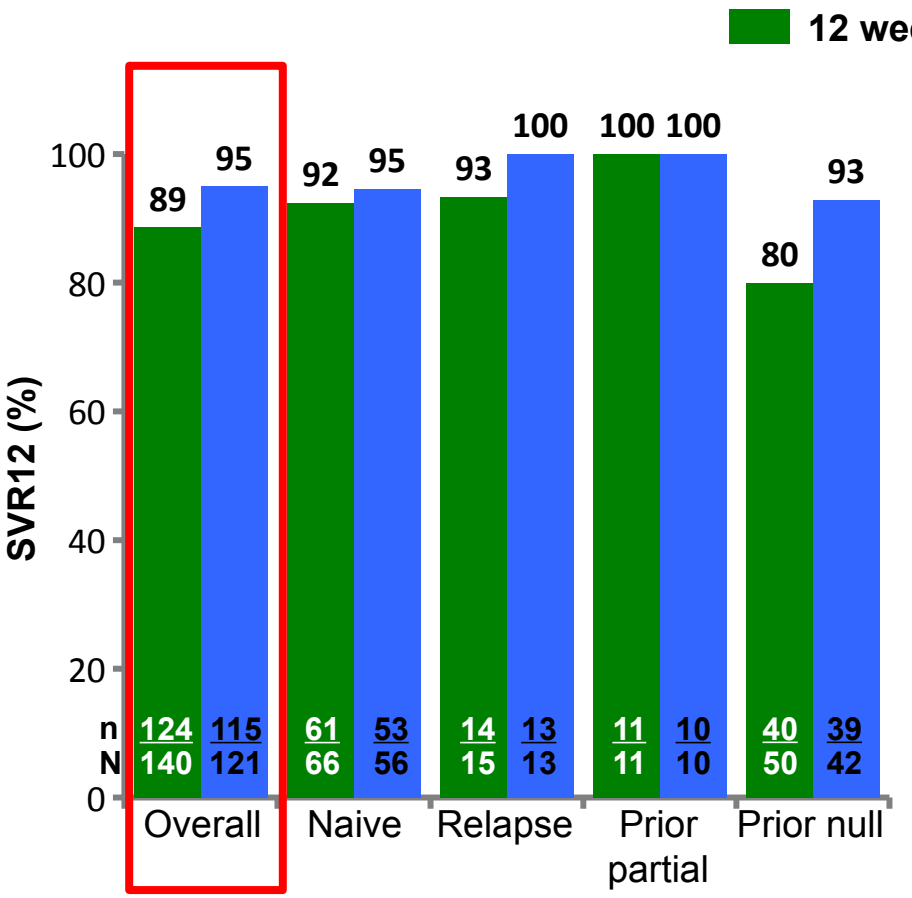


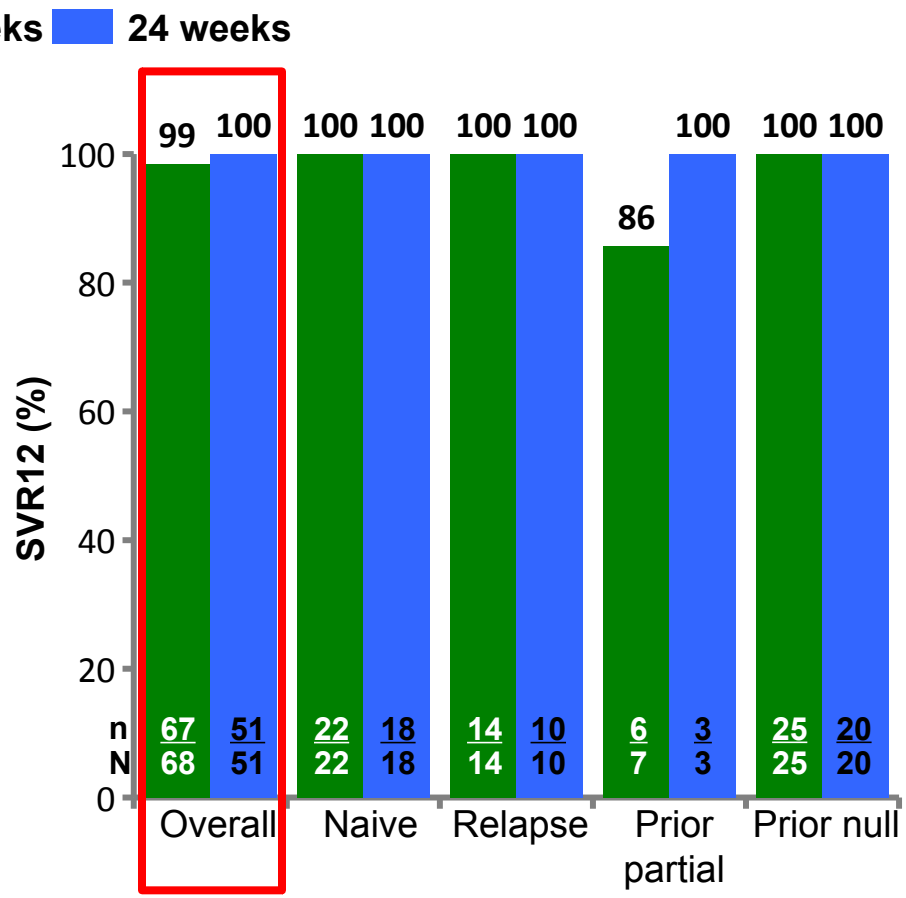
GT1b-infected, non-cirrhotic patients
SAPPHIRE-I, -II, PEARL-II, -III



Everson et al. Hepatology 2014; 60 S: 239–240A.
Colombo et al. Hepatology 2014; 60 S: 1131A.

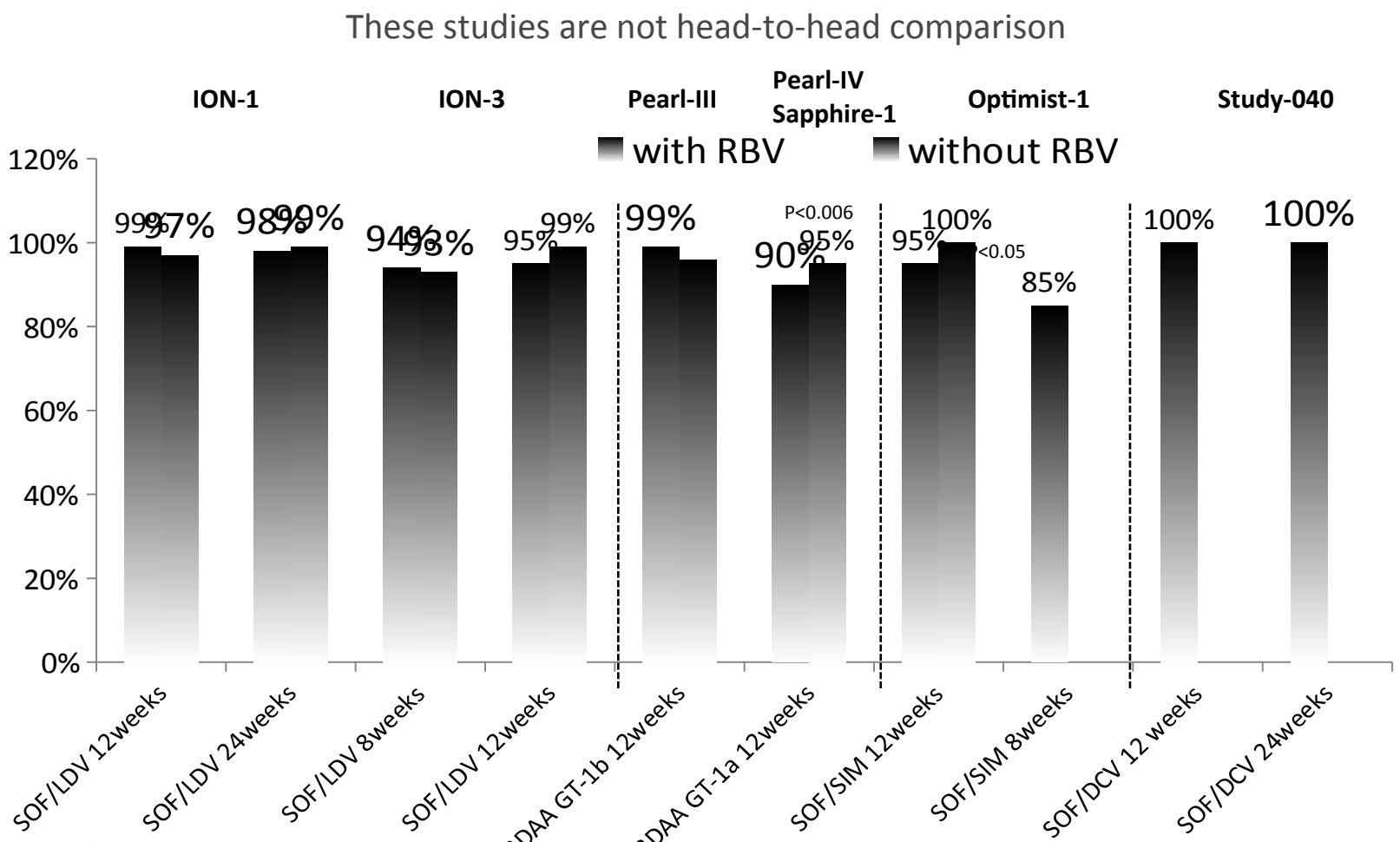
Paritaprevir/Ombitasvir/Dasabuvir





Everson et al. Hepatology 2014; 60 S: 239–240A.
Colombo et al. Hepatology 2014; 60 S: 1131A.

Genotype 1: High SVR rates for treatment-naïve patients in clinical trials



3D, peritaprevir/ritonavir + ombitasvir + dasabuvir; ASV, asunaprevir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

Afdhal N, et al. N Engl J Med 2014;370:1483–1493, Kowdley KV et al. N Engl J Med 2014; 370: 1879-88, Ferenci P et al. N Engl J Med 2014; 370: 1983-92, Feld JJ. N Engl J Med 2014; 370: 1594-1603, Everson GT et al. AASLD 2014: abst 53, Kwo P et al. EASL 2015: abst LB 14, Sulkowski et al. N Engl J Med 2014;370:211–21.

Optimization, Simplification

Sofosbuvir/Ledipasvir : Shortening treatment durations		
Patients Population	Treatment	Duration
Genotype 1, without cirrhosis	Sofosbuvir/Ledipasvir	8 weeks

Optimization, Simplification

Sofosbuvir/Ledipasvir : Shortening treatment durations		
Patients Population	Treatment	Duration
Genotype 1, without cirrhosis	Sofosbuvir/Ledipasvir	8 weeks
Genotype 4, without cirrhosis	Sofosbuvir/Ledipasvir	8 weeks

Asselah et al. Liver Int 2016.

Optimization, Simplification

Paritaprevir based regimen : Shortening treatment duration or avoiding ribavirin		
Patients Population	Treatment	Duration
Genotype 1b, without cirrhosis	Viekira Pak; (Viekirax + Exviera)	8 weeks
Genotype 1b, with compensated cirrhosis	Viekira Pak; (Viekirax + Exviera)	12 weeks

Optimization, Simplification

Paritaprevir based regimen : Shortening treatment duration or avoiding ribavirin		
Patients Population	Treatment	Duration
Genotype 1b, without cirrhosis	Viekira Pak; (Viekirax + Exviera)	8 weeks
Genotype 1b, with compensated cirrhosis	Viekira Pak; (Viekirax + Exviera)	12 weeks
Genotype 4, without cirrhosis	Viekirax (Technivie)	12 weeks
Genotype 4, with compensated cirrhosis	Viekirax + ribavirine	12 weeks

Asselah et al. Liver Int 2016.

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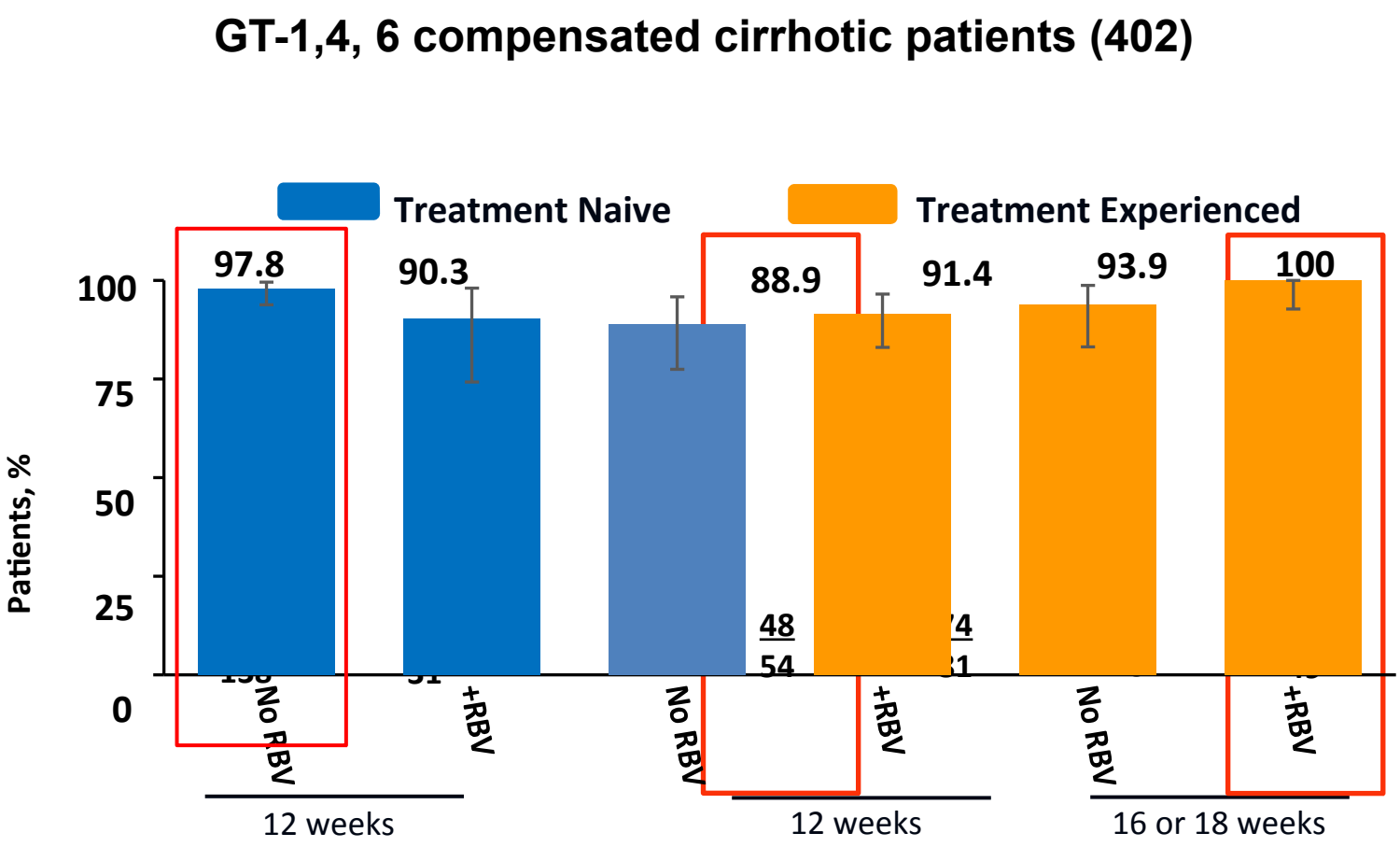
- Future Challenges (ELD, RAVs, DDI….)

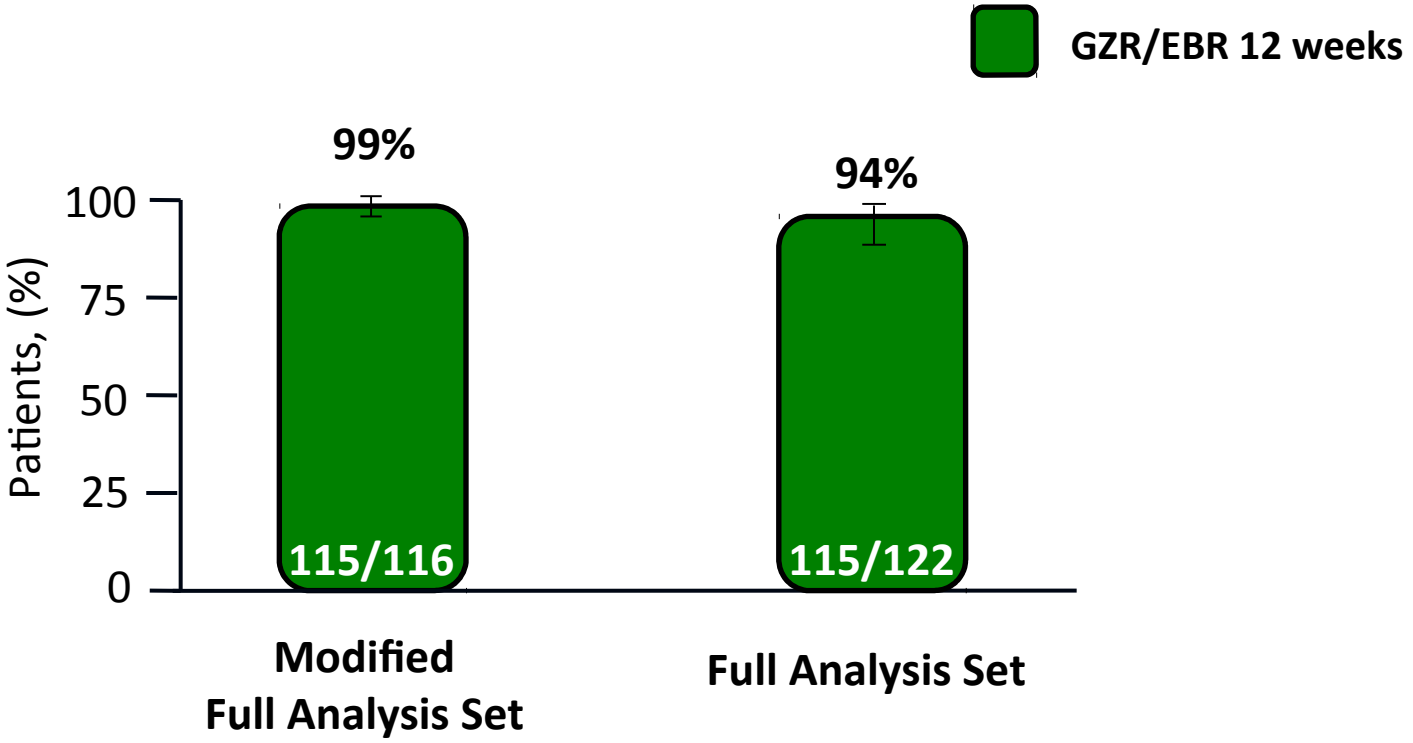
Grazoprevir/elbasvir



Jacobson I et al. AASLD 2015, Abs. 42

Grazoprevir/elbasvir

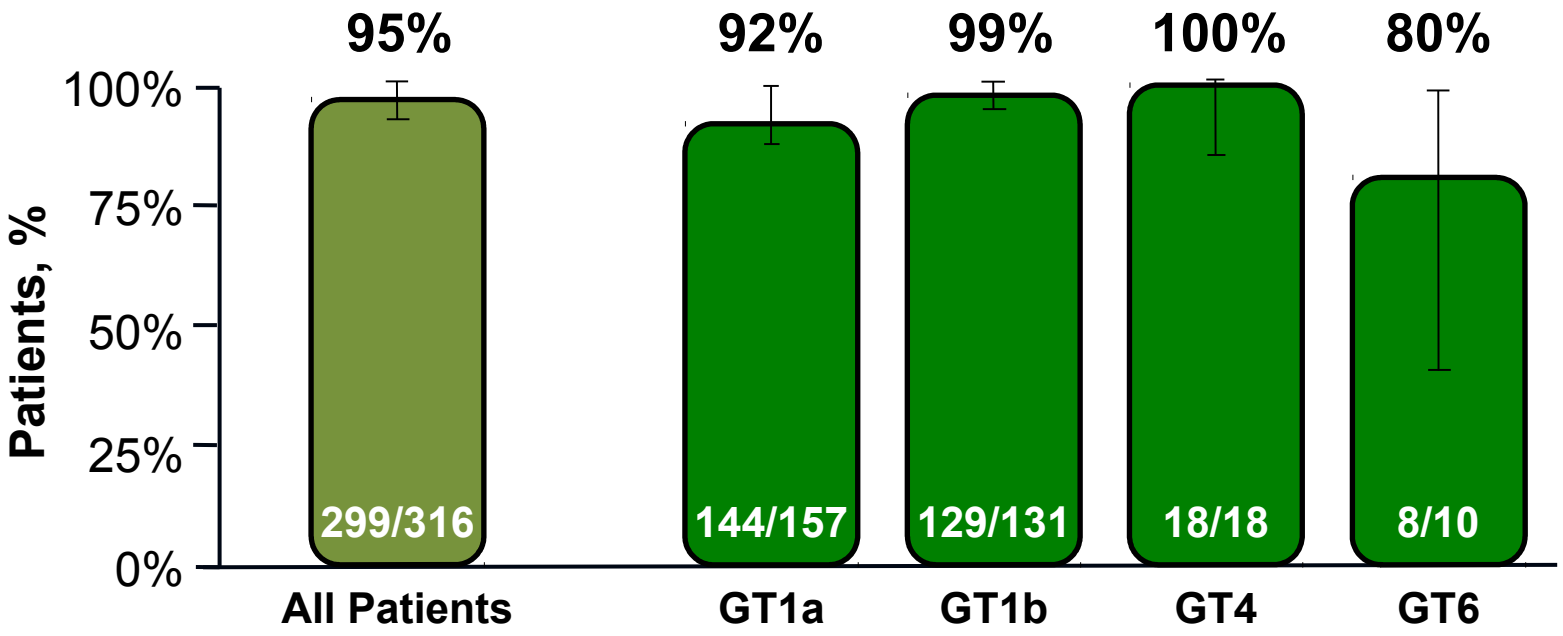
Chronic Kidney Disease (CKD) stage 4/5



Roth et al. Lancet, 2015

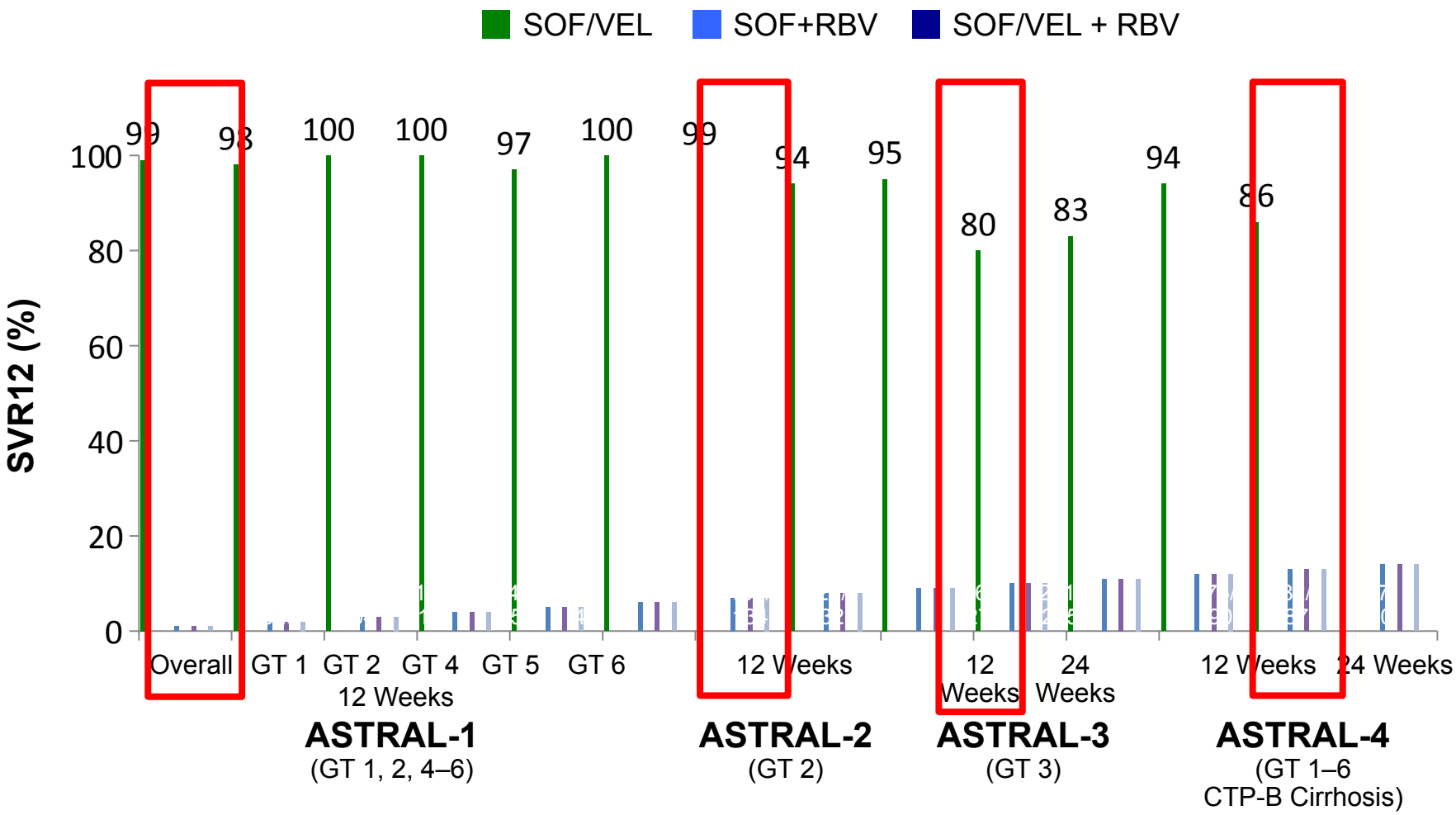
Grazoprevir/elbasvir

People Who Inject Drugs (PWID)



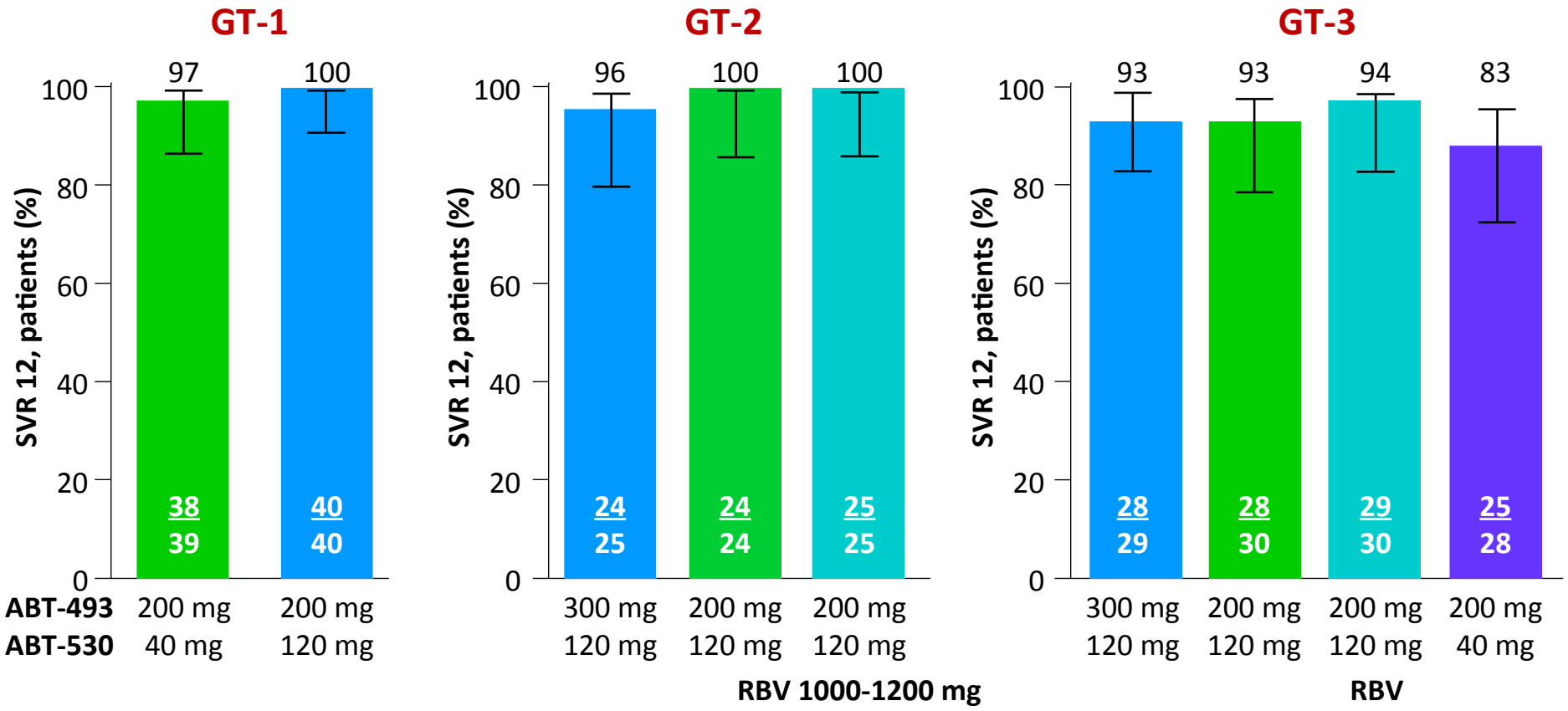
Zeuzem et al. Ann Intern Med 2015; 163: 1–13.

Velpatasvir/Sofosbuvir



Feld et al. N Engl J Med 2015.
Foster et al. N Engl J Med 2015.

ABT-493/ABT-530



Poordad F et al. , AASLD 2015, A41 ; Wyles DL et al. AASLD 2015, A250 ; Kwo P et al AASLD 2015, A248,

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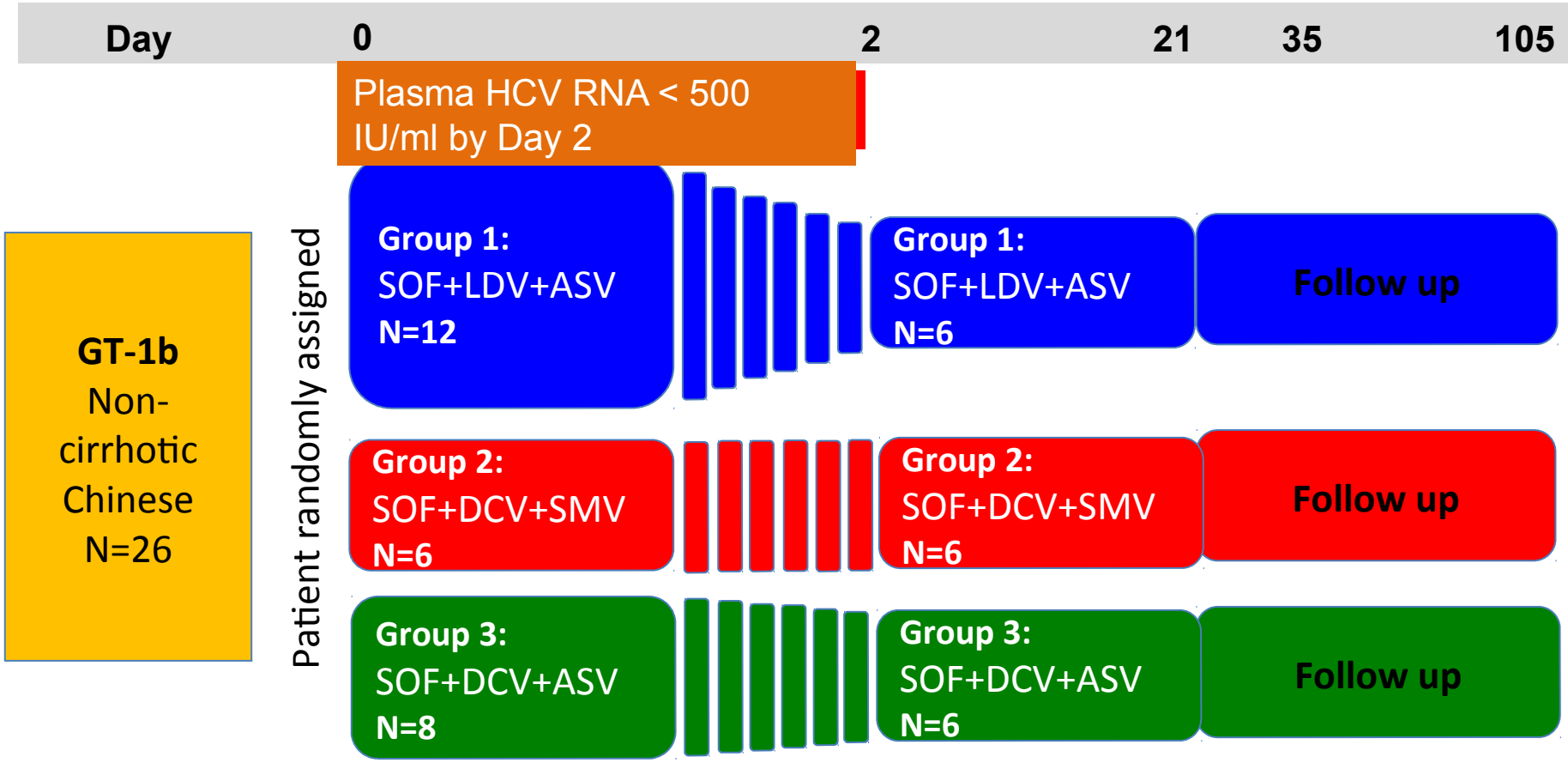
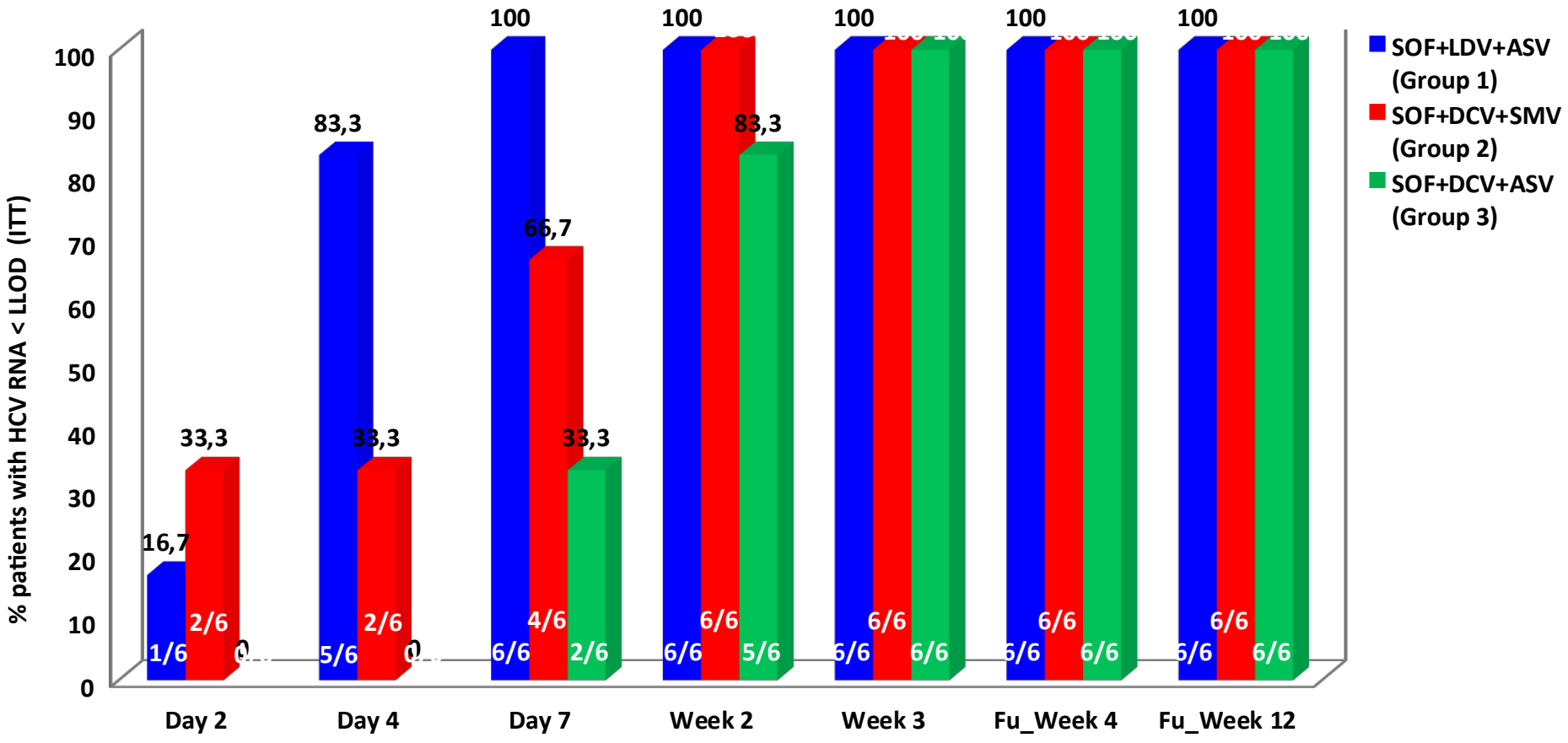
- **Future Challenges (ELD, RAVs, DDI….)**

SODAPI study : Response-Guided Therapy



Lau G et al . AASLD 2015 : LB23

SODAPI study : Response-Guided Therapy

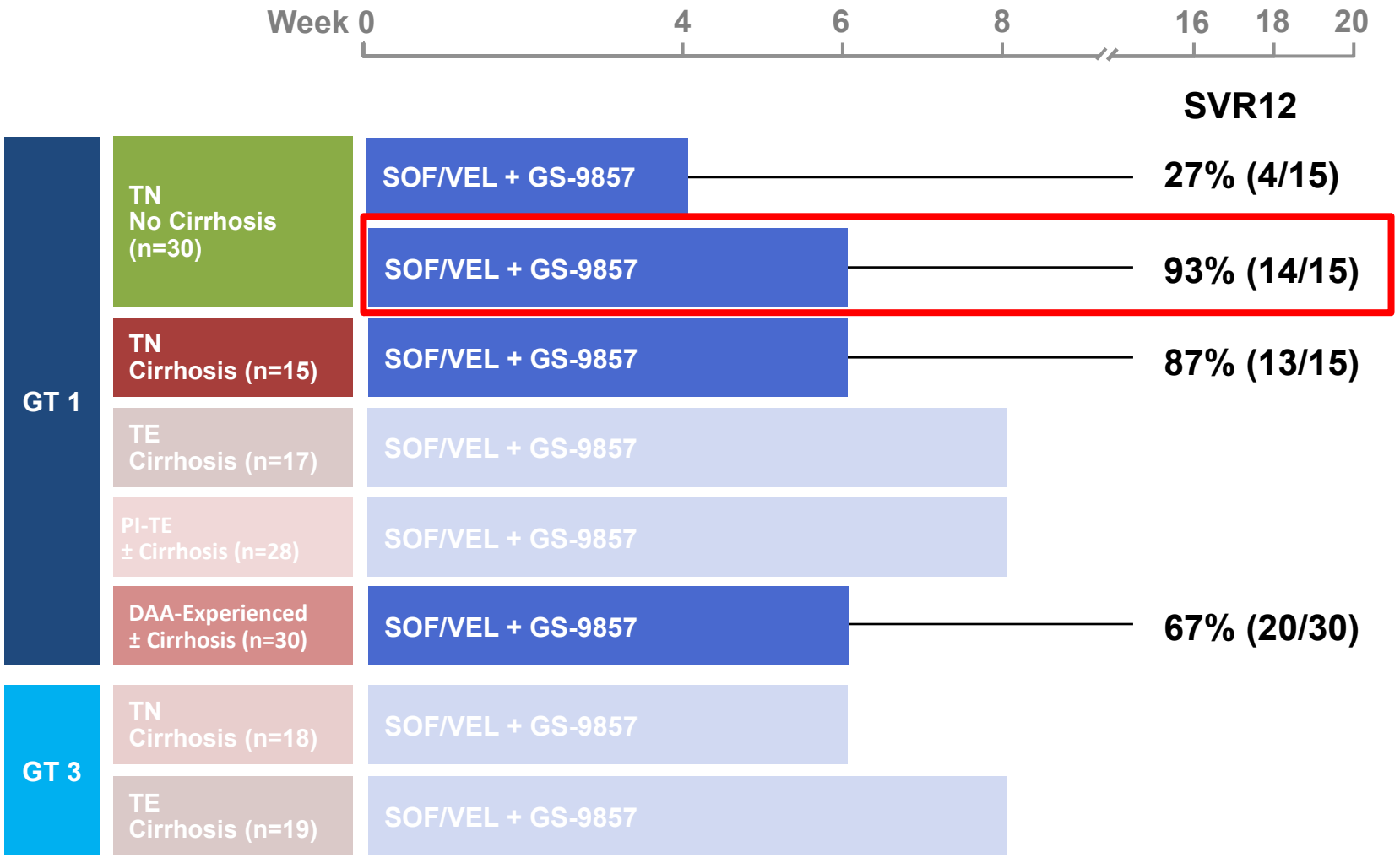


RVR in 69% (N=18)

SVR in 100% in those with RVR

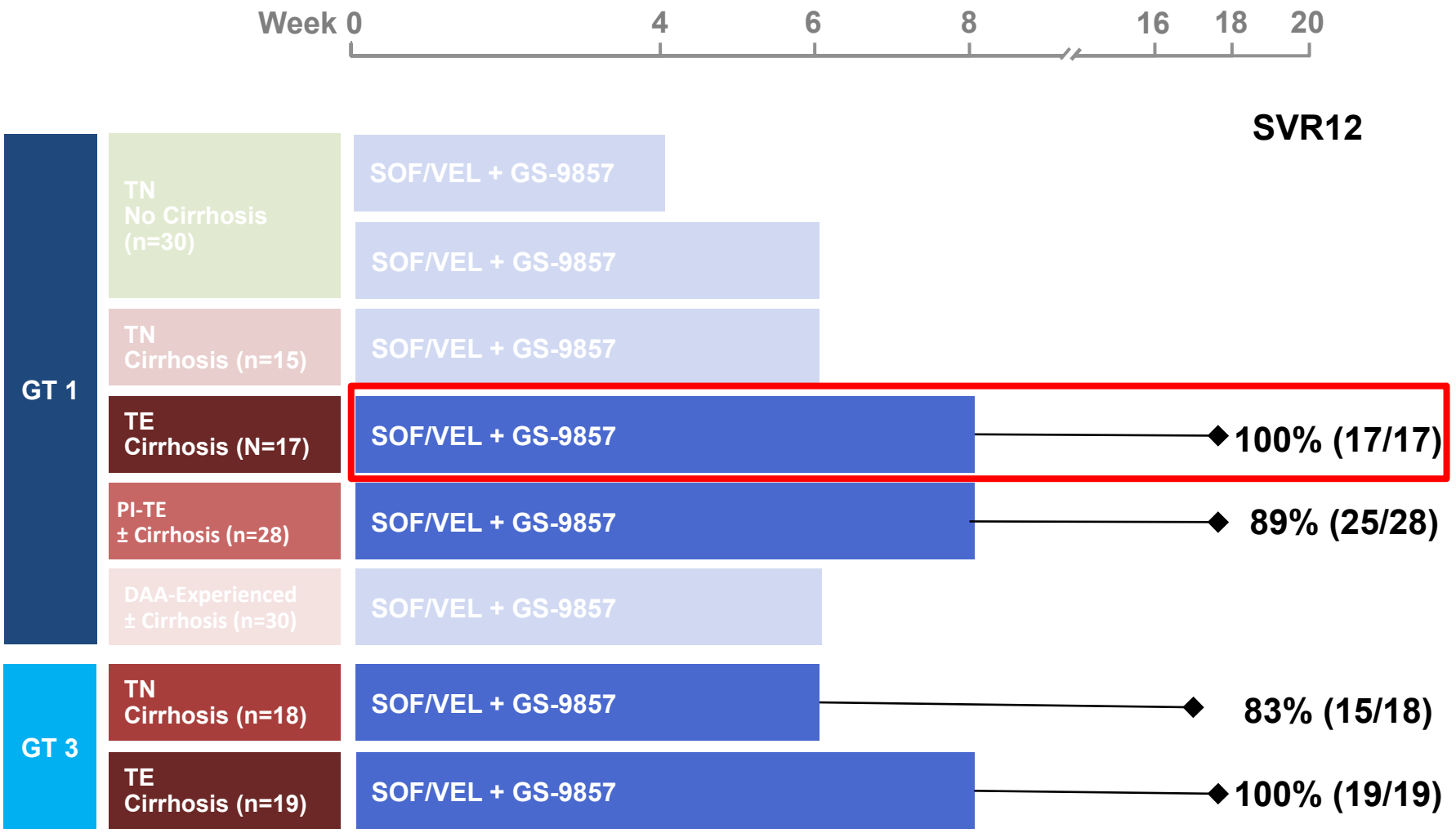
Lau G et al . AASLD 2015 : LB23

Sofosbuvir/Velpatasvir/GS-9857



Gane E, et al. EASL 2015, poster LP03.

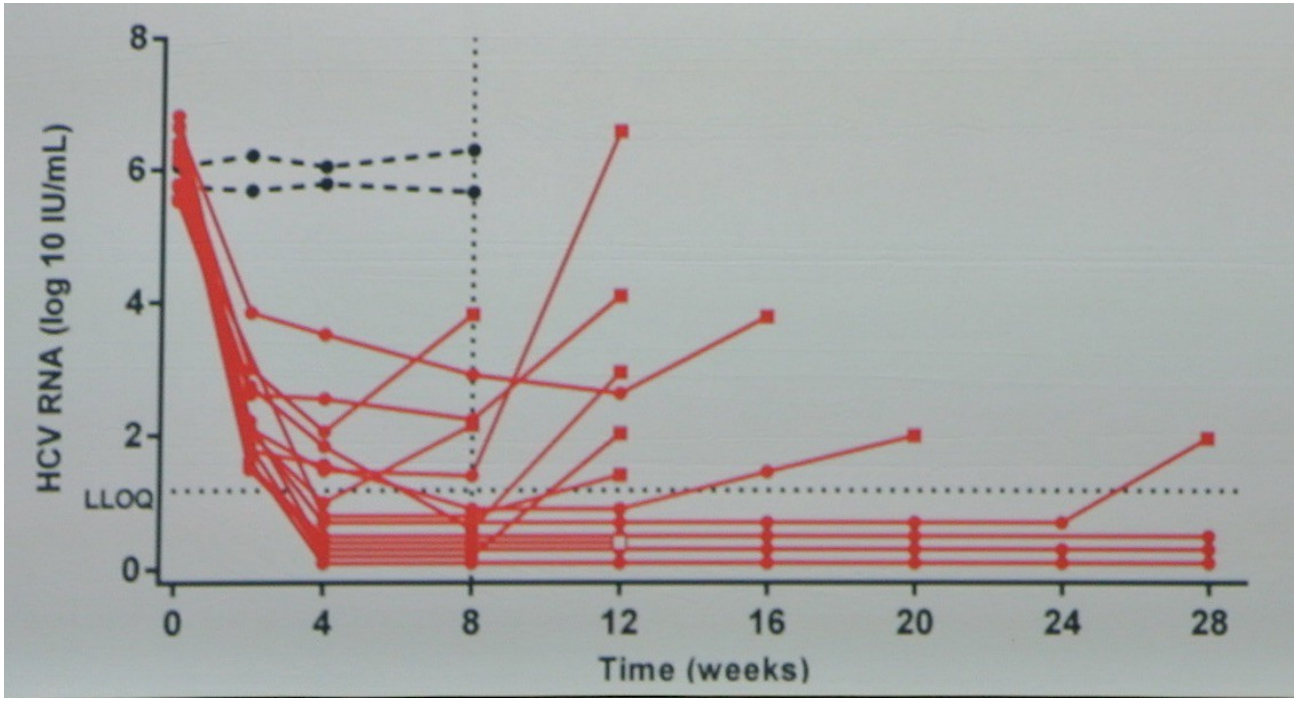
Sofosbuvir/Velpatasvir/GS-9857



Gane E, et al. AASLD 2015, Abst 38.

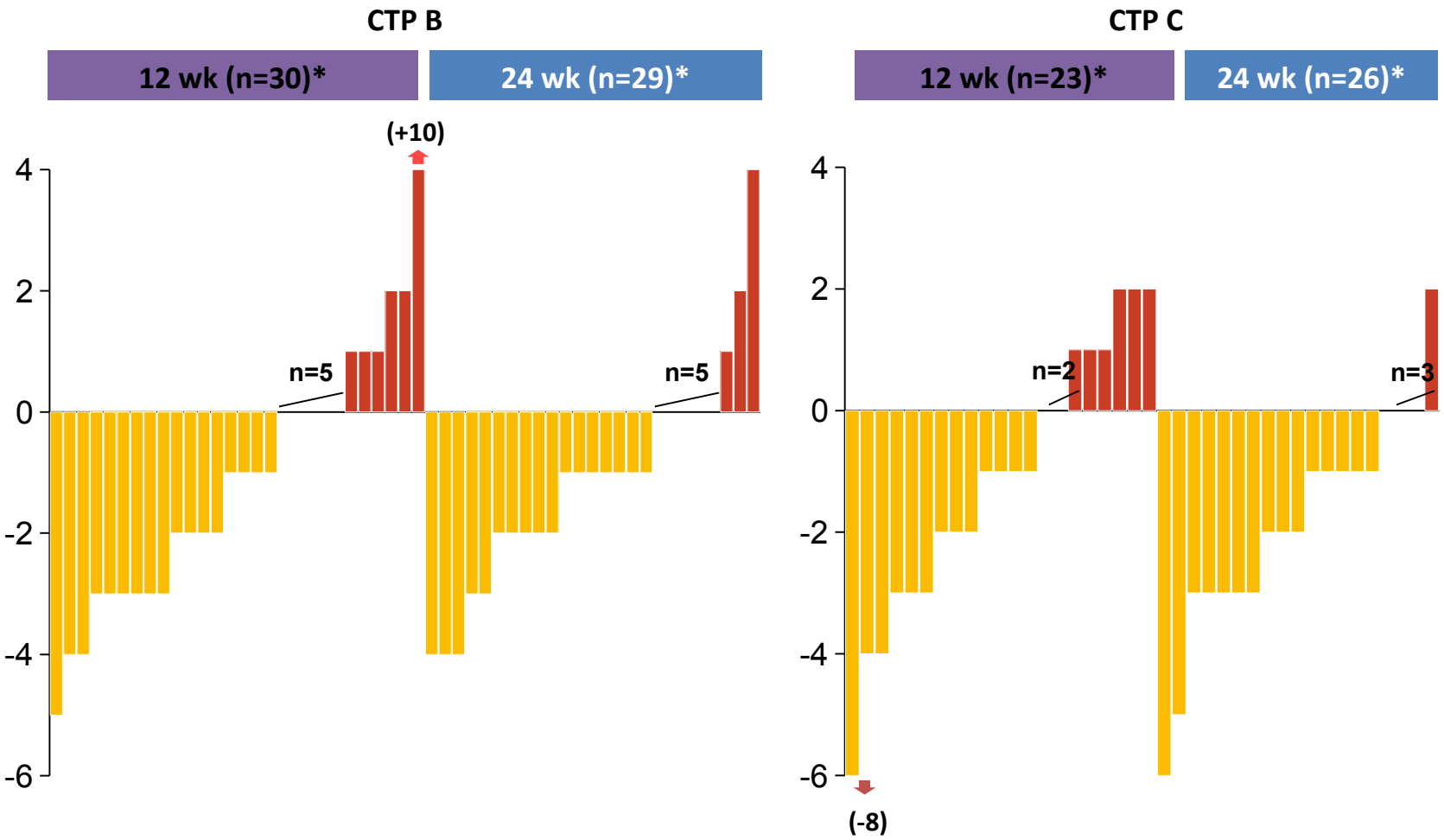
Single s.c dose of RG-101: anti-miR-122.I

28 patients dosed and 4 placebo



Van der Ree MH et al. AASLD 2015; abst 208

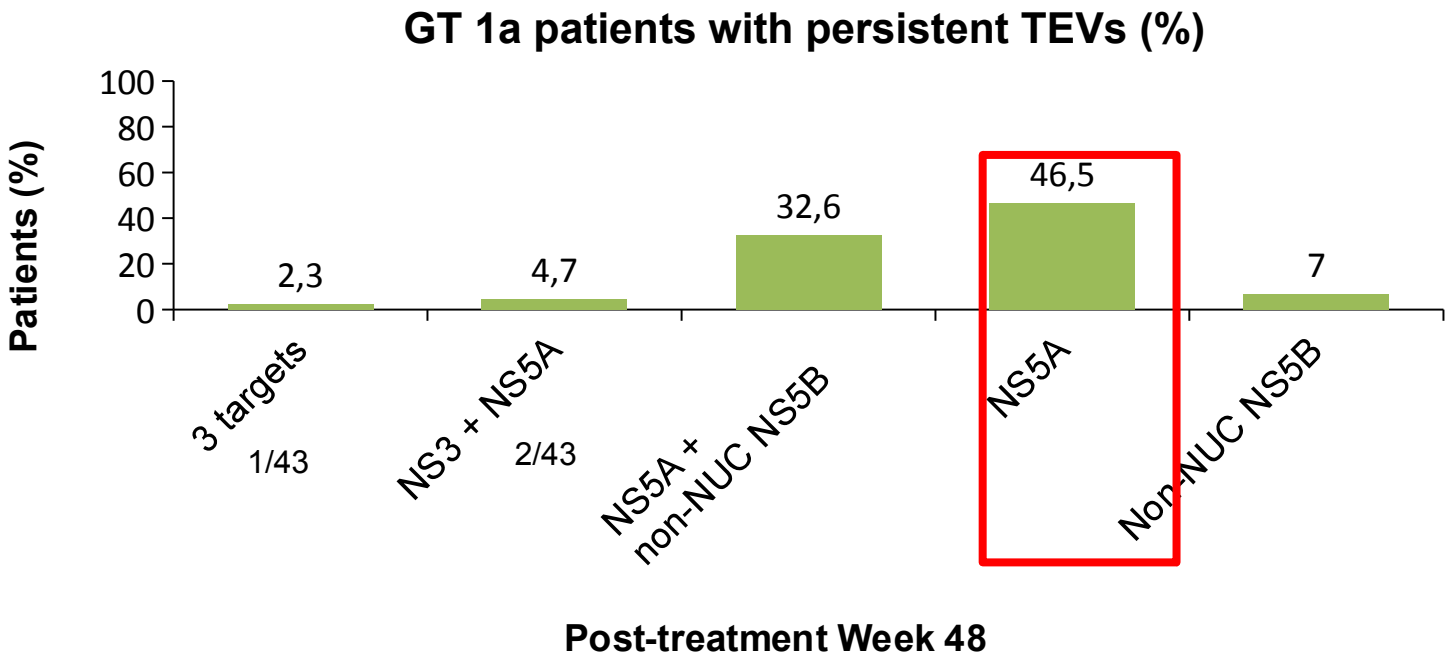
Decompensated cirrhosis: Point of no return



Flamm S, et al. AASLD 2014; Oral #239.

*Missing FU-4: n=2 CTP B 12 wk; n=4 CTP B 24 wk; n=2 CTP C 12 wk; n=7 CTP C 24 wk; BL: baseline

Most NS5A RAVs persist post-treatment



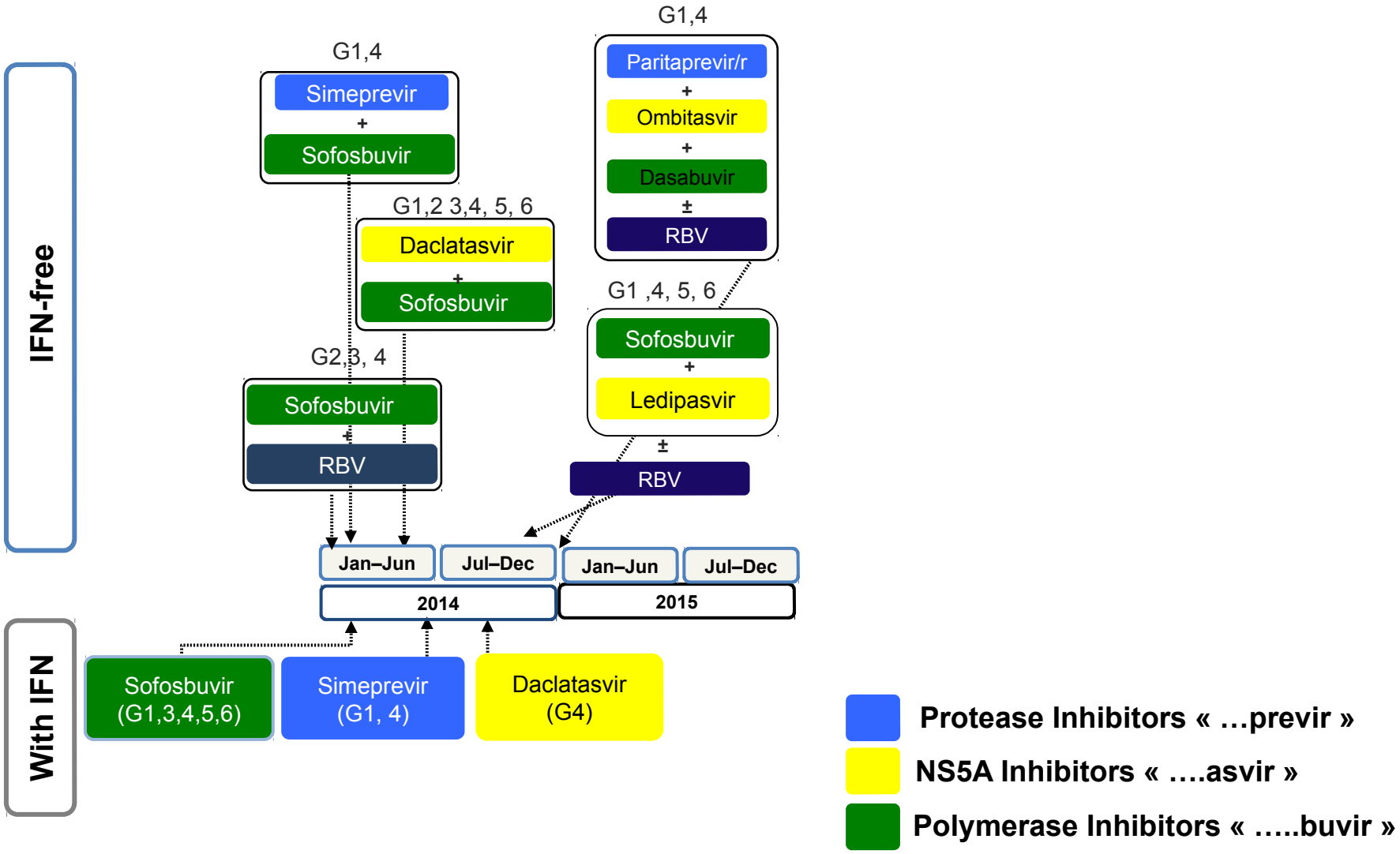
Patients with TEVs by population sequencing (cut-off 20%) in nine OMV/PTV/RTV + DSV ± RBV trials

In GT 1a patients, NS3 (9%), NS5A (96%) and non-NUC NS5B (57%) TEVs were still detectable through to post-treatment Week 48

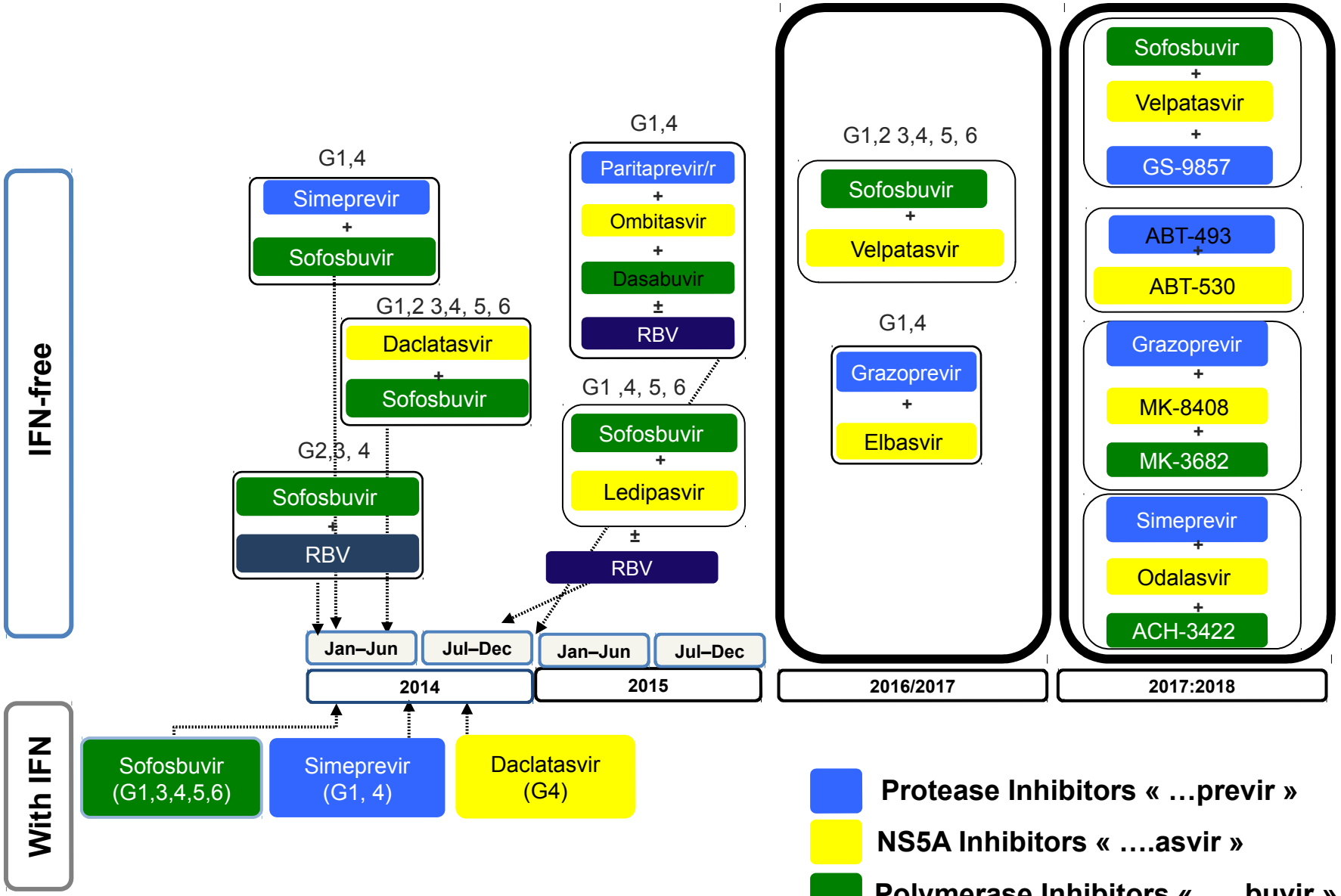
Krishnan P, et al. EASL 2015; Oral #057

NA: nucleos(t)ide analogue;
TEV: treatment-emergent resistance-associated variants

Perspectives



Perspectives



Asselah et al. Liver Int 2016.

Future Challenges
Ten Commandments for the Magic Drug

1 **E**ducation (medical education, sciences)

2 **R**esistance (salvage therapy, RAVs)

3 **A**ccess to Treatment (major issue)

7 **D**uration (shorten, 6 or 8 weeks)

8 **I**ncreasing Screening (worldwide)

9 **C**ompliance

10 **A** la carte or Universal Treatment

11 **T**reatment Interraction (DDI)

12 **I**mproving Survival (HCC, ELD)

13 **O**ther populations (PWID, Decompensated cirrhosis,…

HCV ERADICATION WORLWIDE

Centre de Recherche sur l'Inflammation
PARIS MONTMARTRE

THANK YOU

PHYSIOPATHOLOGY AND TREATMENT OF VIRAL HEPATITIS

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