New HCV Therapies

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Chronic Hepatitis C Virus Infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010

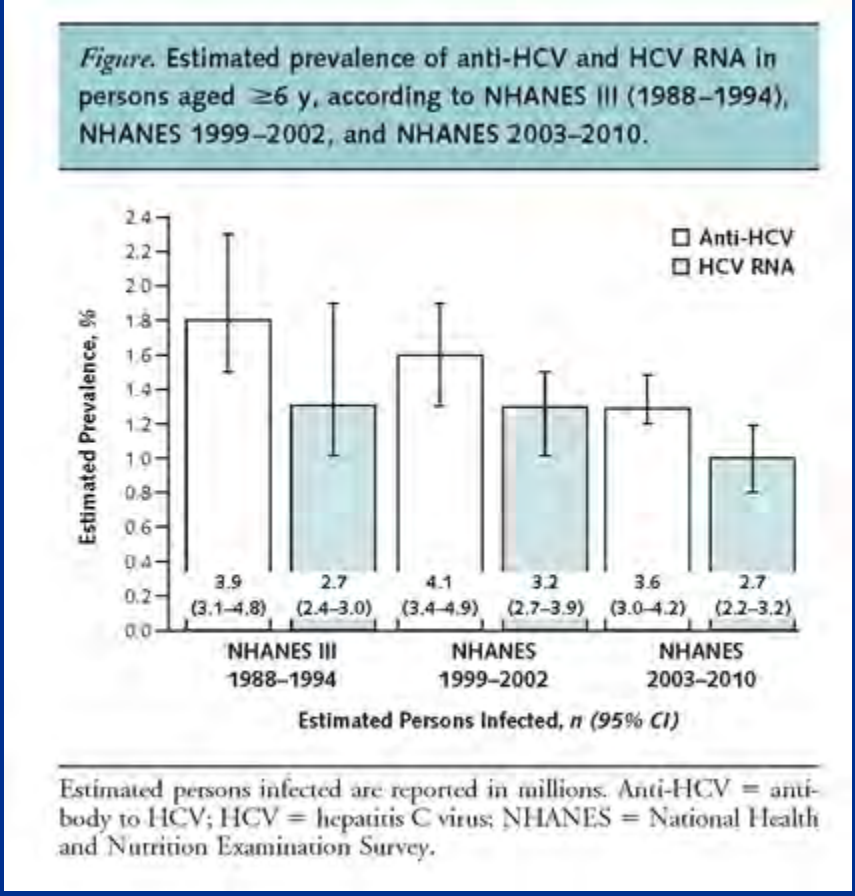


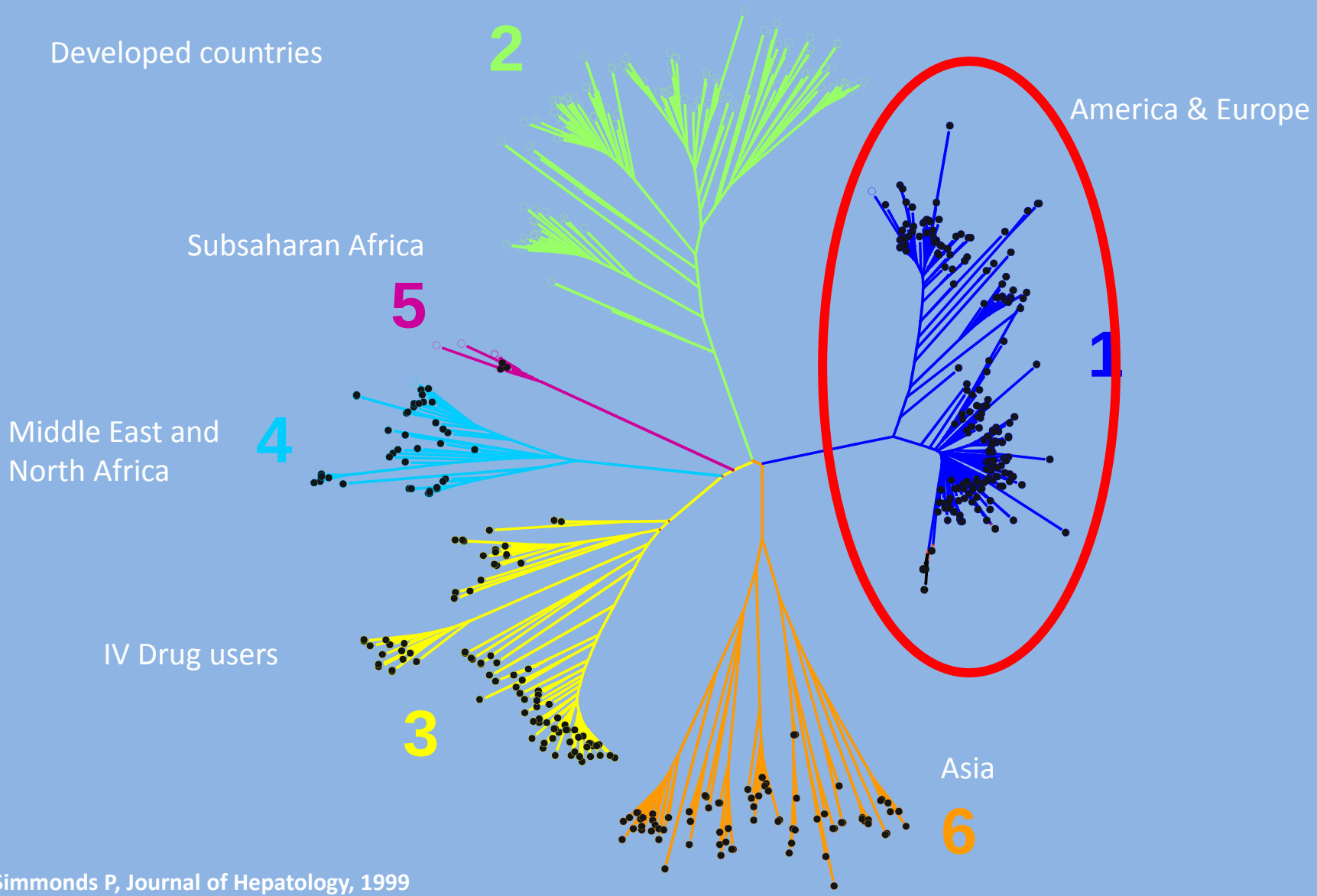
Figure. Estimated prevalence of anti-HCV and HCV RNA in persons aged ≥6 y, according to NHANES III (1988–1994), NHANES 1999–2002, and NHANES 2003–2010.

Estimated persons infected are reported in millions. Anti-HCV = antibody to HCV; HCV = hepatitis C virus; NHANES = National Health and Nutrition Examination Survey.

Risk Factors	OR
Age > 40	6-9.5
Male	1.6
Non-hispanic black	1.6
Low education	2
Family income	3.7
IVDU	8.7

Ann Int Med 2014; 160:293-300

HCV genotypes and subtypes

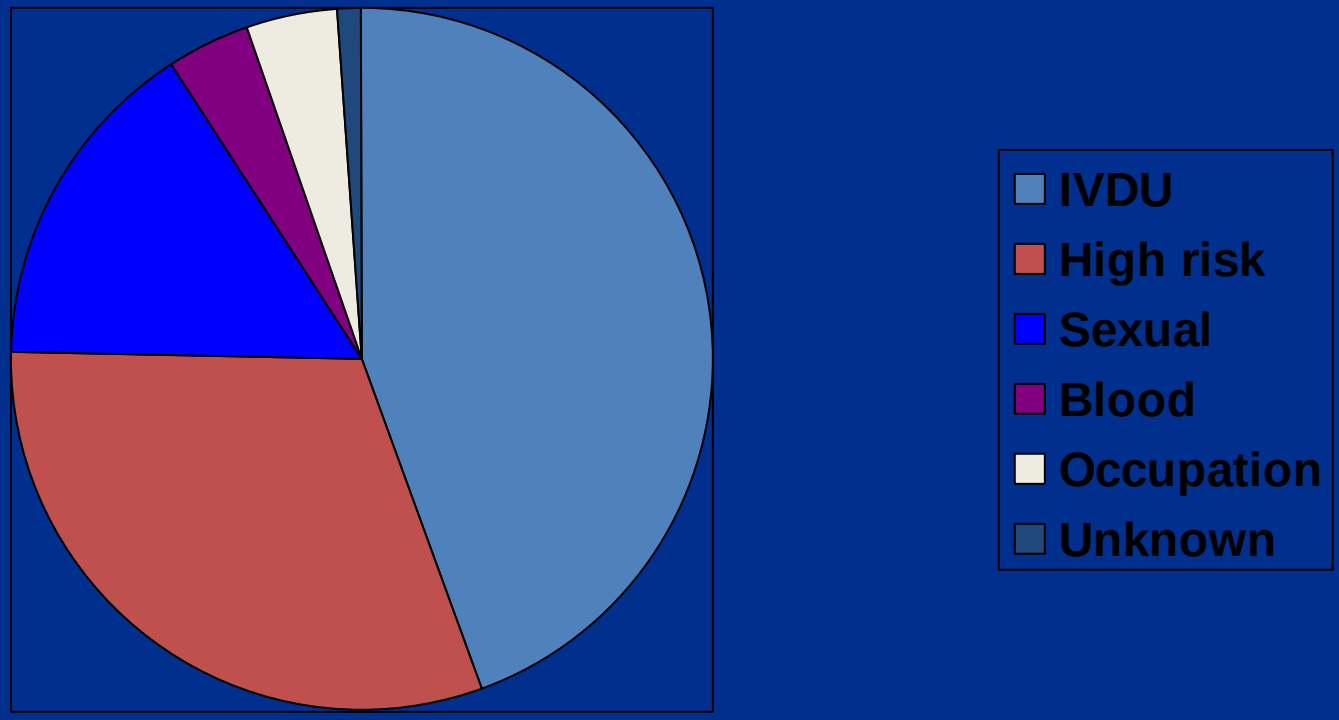


Simmonds P, Journal of Hepatology, 1999

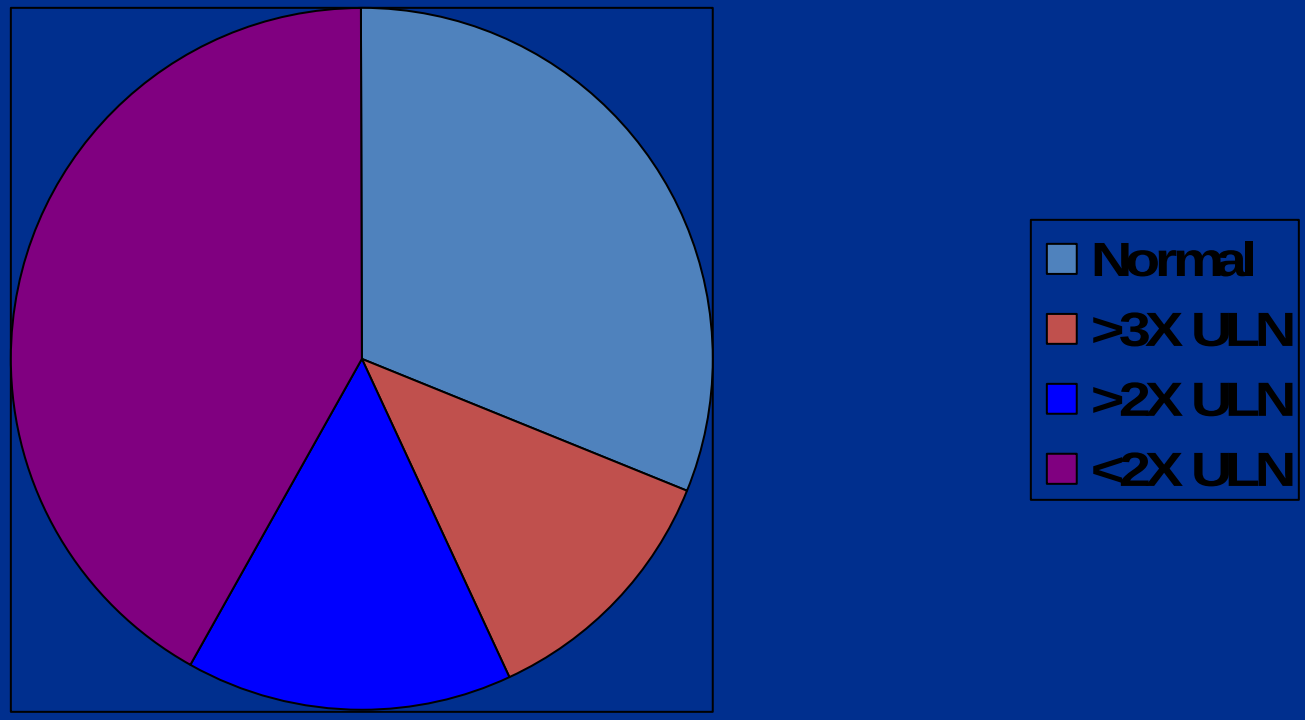
HEPATITIS C

- Agent 35 nm RNA
- Genotypes 1, 2, 3, 4, 5, 6
- Antibody HCV IgG
- Mortality 3-8%
- Chronicity 90%
- Vaccine none

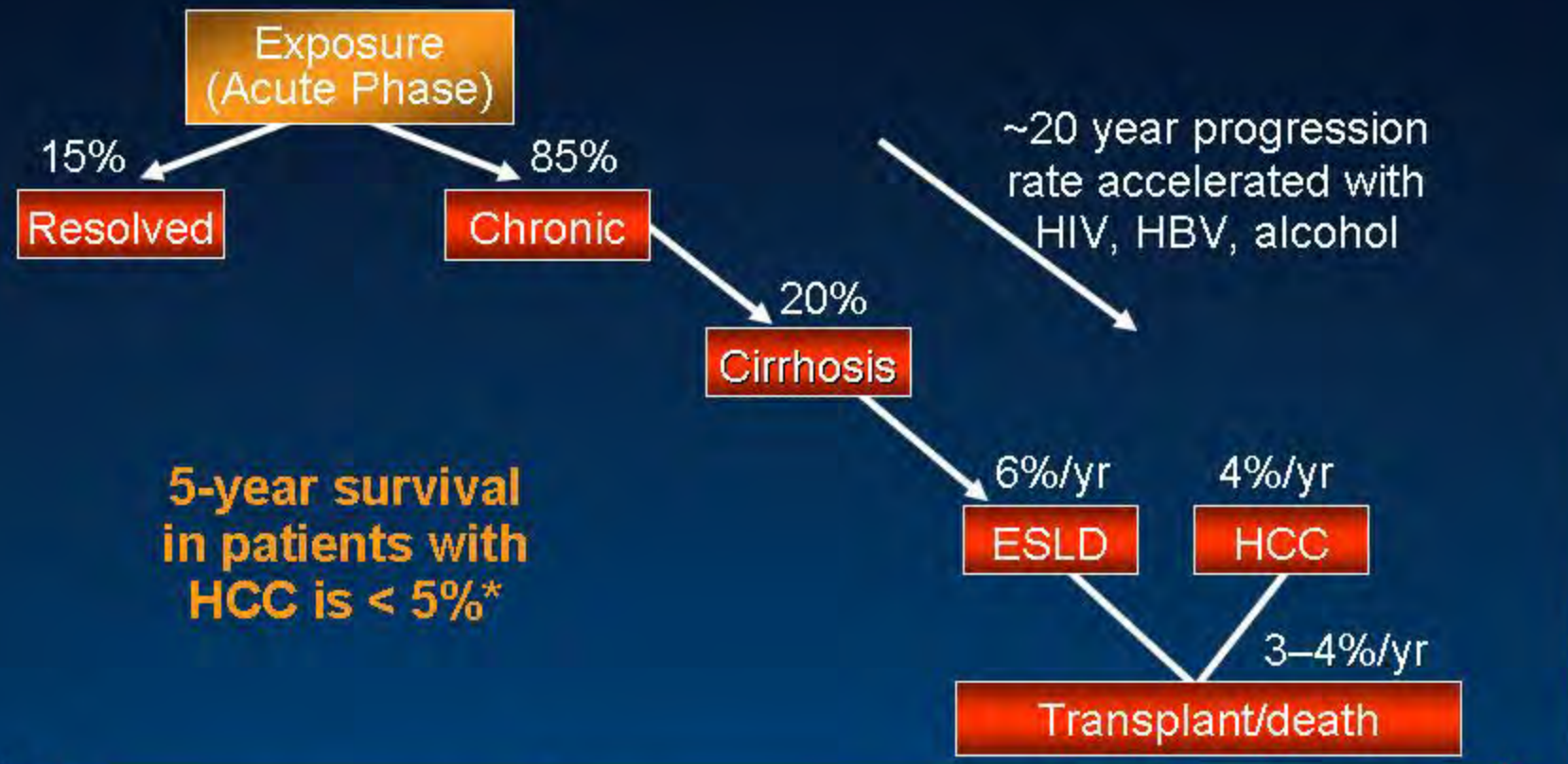
Risk Factors for Hepatitis C



Pattern of ALT Elevation



Natural History of HCV Infection



5-year survival in patients with HCC is < 5%*

HCC = hepatocellular carcinoma

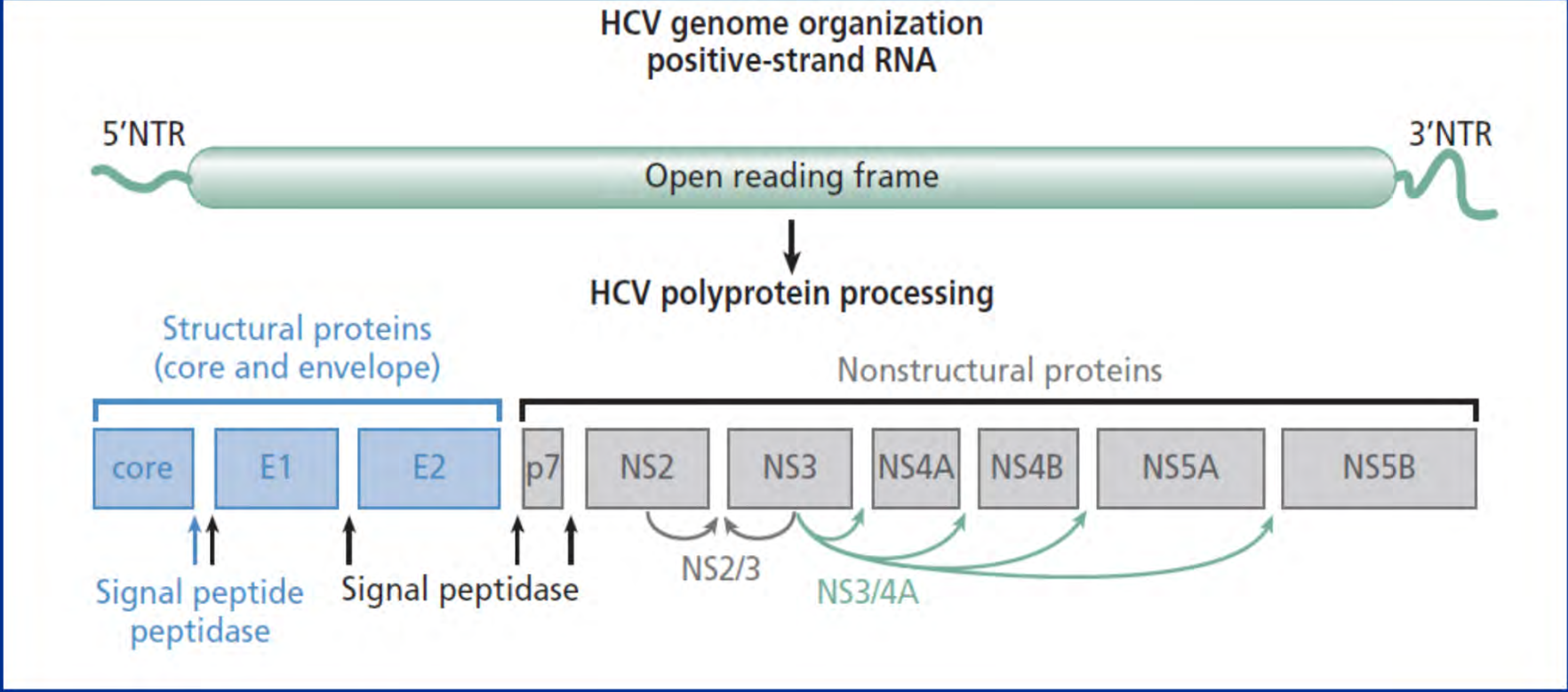
ESLD = end-stage liver disease

*NIH Consensus Statement. 2002.

Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

Hepatitis C

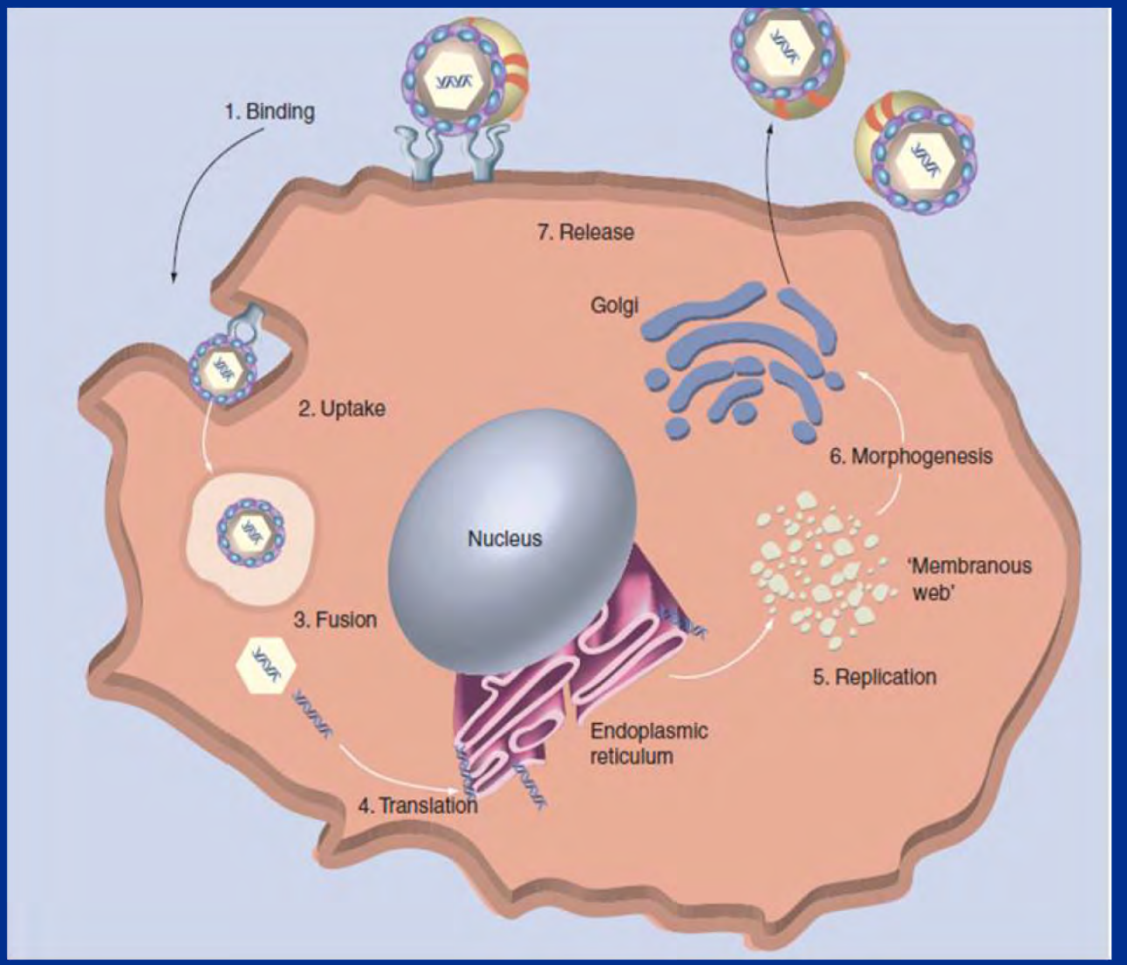
Identified in 1989 by the group of Michael Houghton as the cause of hepatitis non-A non-B-1



Top Antiviral Med. 2011:19(3):117-120

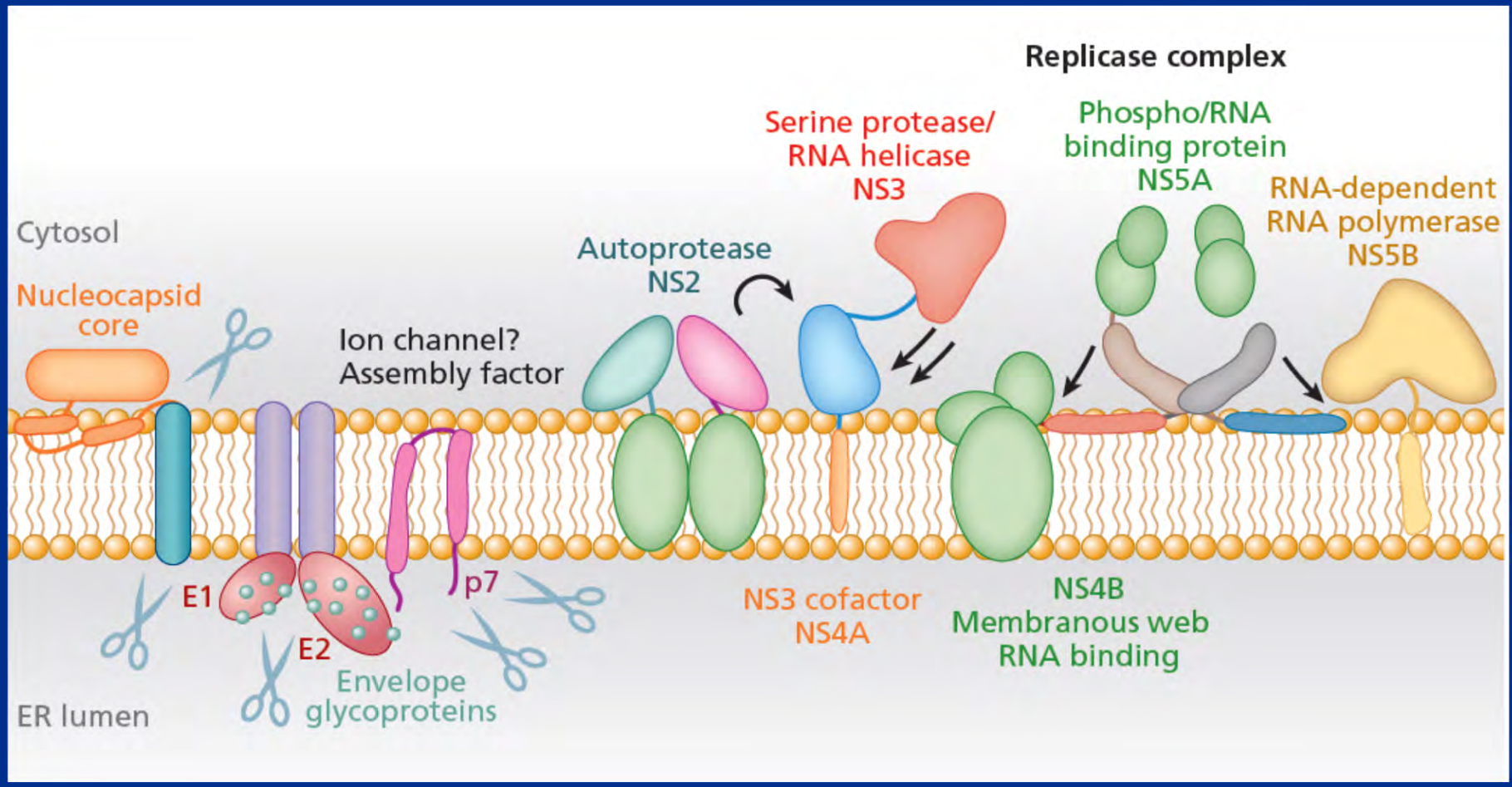
Viral Replication Cycle

The viral replication cycle can broadly be divided into three phases:
1. Entry into the host cell
2. Intracellular RNA replication
3. Assembly of new particles and their release into the blood



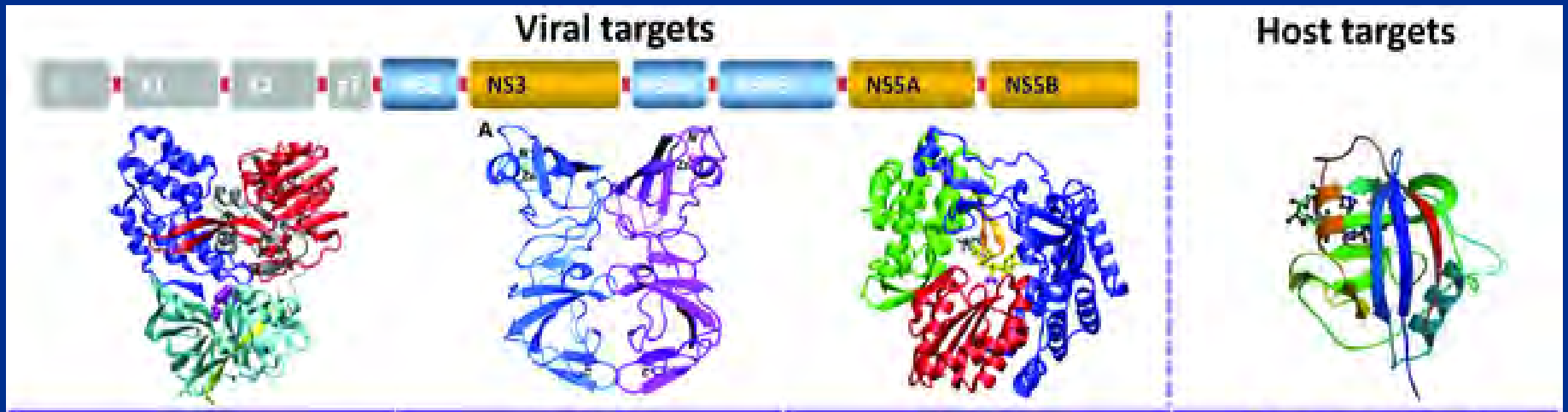
Replication Cycle – von Hahn T, Steinmann E, Ciesek S, Pietschmann T, Expert Rev Gastroenterol Hepatol. 2010 Feb;4(1):633-79.

Viral Targets of antiviral drugs



Top Antiviral Med. 2011:19(3):117-120

Different classes of direct-acting antiviral drugs (DAAs)



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease	Multifunctional phosphoprotein, component of the HCV-RNA replication complex	RNA-dependent RNA polymerase	Host protein interacting with NS5A and the NS5B
Boceprevir **Telaprevir** ABT-450/r, ACH-1625 Asunaprevir, TMC-435 (Simeprevir), BI-201335 Danoprevir/r, GS-9451 MK-5172	Daclatasvir GS-5885 ABT-267 PPI-668 MK	Nucleos(t)ide analogue GS-7977 (Sofosbuvir), Mericitabine, IDX-184 Non-nucleoside analogue BI-207127, ABT-333 ABT-072, BMS-791325 Tegobuvir, Setrobuvir VX-222, Filibuvir	Alisporivir SCY-635

Liver International
pages 18-23, 23 DEC 2013 DOI: 10.1111/liv.12405

Table 1. DAAs and HTAs in Clinical Development at the Beginning of 2014

Agent class	Generation	Compound	Manufacturer	Phase of clinical development
NS3–4A protease inhibitors	First-wave, first-generation	Telaprevir	Vertex, Janssen, Mitsubishi	Approved
		Boceprevir	Merck	Approved
	Second-wave, first-generation	Simeprevir	Janssen	Approved
		Faldaprevir	Boehringer-Ingelheim	III
		Asunaprevir	Bristol-Myers Squibb	III
		ABT-450/r	Abbvie	III
		Danoprevir/r	Roche	II
		Sovaprevir	Achillion	II[a]
		Vedroprevir	Gilead	II
		IDX320	Idenix	II
		Vaniprevir	Merck	III (Japan)
	Second-generation	MK-5172	Merck	III
		ACH-2684	Achillion	II
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir	Gilead	Approved
		VX-135	Vertex	II[b]
	Nucleoside analogue	Mericitabine	Roche	II
Non-nucleoside inhibitors of the HCV RdRp	Thumb domain I inhibitors	BMS-791325	Bristol-Myers Squibb	III
		TMC647055	Janssen	II
	Thumb domain II inhibitors	Lomibuvir	Vertex	II
		GS-9669	Gilead	II
	Palm domain I inhibitors	Dasabuvir	Abbvie	III
		ABT-072	Abbvie	II
		Setrobuvir	Roche	II
NS5A inhibitors	First-generation	Daclatasvir	Bristol-Myers Squibb	III
		Ledipasvir	Gilead	III
		Ombitasvir	Abbvie	III
		PPI-668	Presidio	II
		PPI-461	Presidio	II
		ACH-2928	Achillion	II
		GSK2336805	GlaxoSmithKline	II
		BMS824393	Bristol-Myers Squibb	II
		Samatasvir	Idenix	II
	Second-generation	MK-8742	Merck	II
		ACH-3102	Achillion	II
		GS-5816	Gilead	II

Table 2. All-Oral, IFN-Free HCV Therapeutic Agents in Clinical Development, 2014–2015

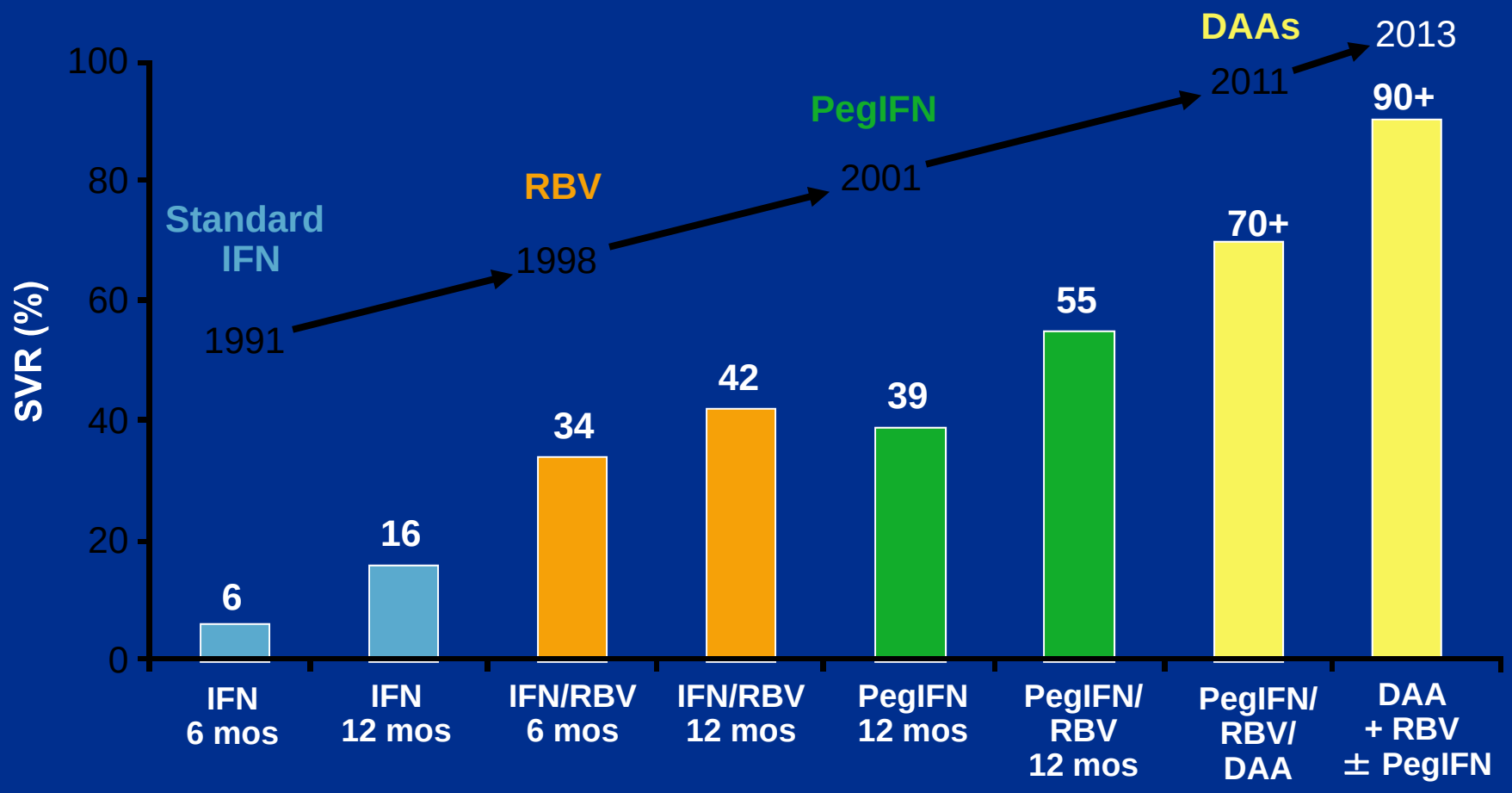
Strategy	Company	Nucleoside/ nucleotide analogue	NS3-4A protease inhibitor	NS5A inhibitor	Non-nucleoside inhibitor of HCV RdRp	Cyclophilin inhibitor	Ribavirin
Nucleoside/nucleotide analogue-based strategy	Gilead	Sofosbuvir		Ledipasvir			±
	Gilead	Sofosbuvir		GS-5816			±
	Gilead	Sofosbuvir		Ledipasvir	GS-9669		-
	Gilead	Sofosbuvir	Vedroprevir	Ledipasvir			-
	Gilead/Janssen	Sofosbuvir	Simeprevir				±
	Gilead/Bristol-Myers Squibb	Sofosbuvir		Daclatasvir			±
	Vertex	VX-135			Lomibuvir		
	Vertex/Janssen	VX-135	Simeprevir				±
	Vertex/Bristol-Myers Squibb	VX-135		Daclatasvir			±
	Roche (emerging markets)	Mericitabine	Danoprevir/r		Setrobuvir		±
Nucleoside-free triple combo strategy	Abbvie		ABT-450/r	Ombitasvir	Dasabuvir		±
	Bristol-Myers Squibb		Asunaprevir	Daclatasvir	BMS791325		±
	Boehringer-Ingelheim/Presidio		Faldaprevir	PPI-668	? [a]		±
	Janssen/GlaxoSmithKline		Simeprevir	GSK2336805	TMC647055		±
	Janssen/Idenix		Simeprevir	Samatasvir	TMC647055		±
Nucleoside-free double combo strategy with a high-barrier-to-resistance drug	Merck		MK-5172	MK-8742			±
	Achillion		ACH-2684	ACH-3102			±
	Novartis					Alisporivir	±

/r, ritonavir-boosted.
[a] Deleobuvir development was halted in January 2014 owing to digestive toxicity.

Summary of Investigational HCV Agents

Class	Drug	Dosing
NS3/4A protease inhibitor	ABT-450/RTV	150/100 mg
NS3 protease inhibitor	Asunaprevir	200 mg BID
NS3/4A protease inhibitor	Faldaprevir	120 mg or 240 mg QD
NS3 protease inhibitor	GS-9451	200 mg QD
NS3/4A protease inhibitor	MK-5172	100 mg QD
NS3/4A protease inhibitor	Simeprevir	150 mg QD
NS5B nonnucleoside polymerase inhibitor	ABT-333	400 mg BID
NS5B nonnucleoside polymerase inhibitor	BMS-791325	75 mg or 150 mg BID
NS5B nonnucleoside polymerase inhibitor	Deleobuvir	600 mg BID
NS5B nonnucleoside polymerase inhibitor	GS-9669	500 mg QD
NS5B nucleotide polymerase inhibitor	Sofosbuvir	400 mg QD
NS5A inhibitor	ABT-267	25 mg QD
NS5A inhibitor	Daclatasvir	30 mg BID or 60 mg QD
NS5A inhibitor	Ledipasvir	90 mg QD
NS5A inhibitor	MK-8742	20 or 50 mg QD
NS5A inhibitor	PI-688	200 mg QD

The Good News

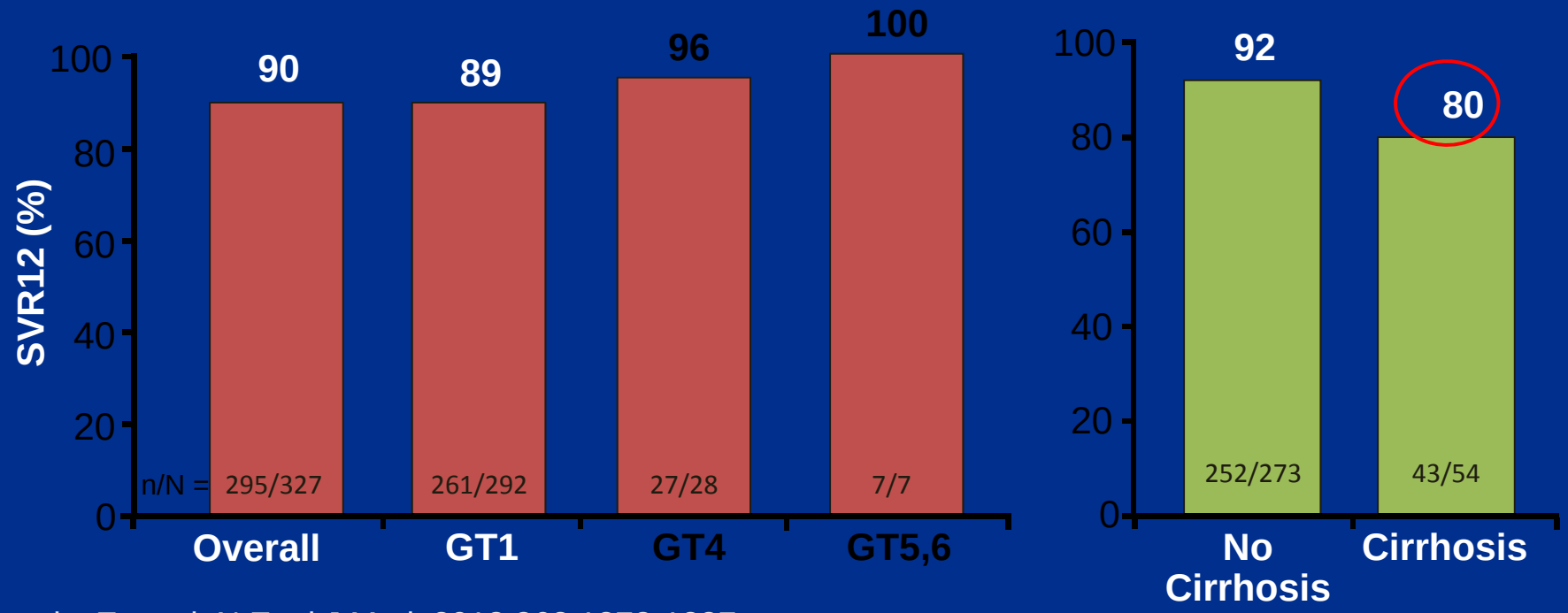


Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

GENOTYPE 1

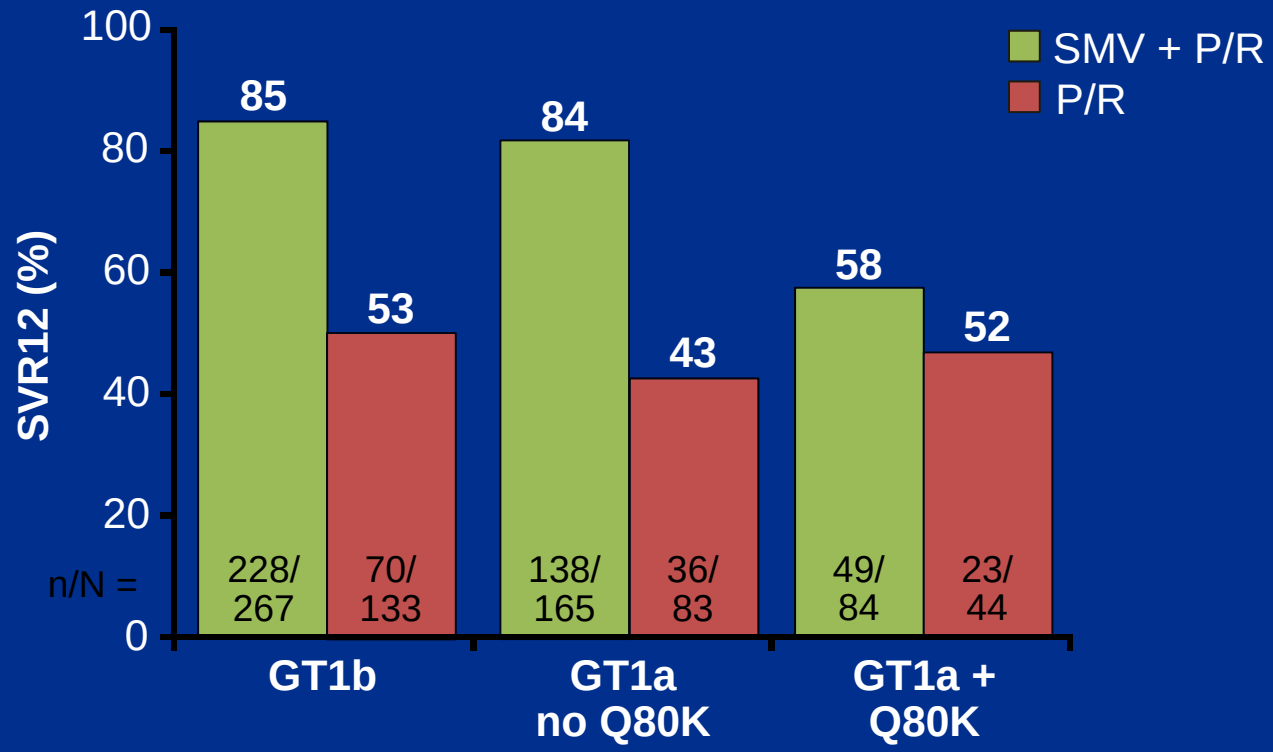
NEUTRINO: Sofosbuvir + P/R for 12 Weeks in Treatment-Naive GT 1/4/5/6 HCV

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 weeks in treatment-naive patients with GT1/4/5/6 HCV
  - 17% cirrhosis; 89% GT1; 9% GT4; < 1% GT5; 2% GT6



Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

QUEST: Simeprevir + P/R

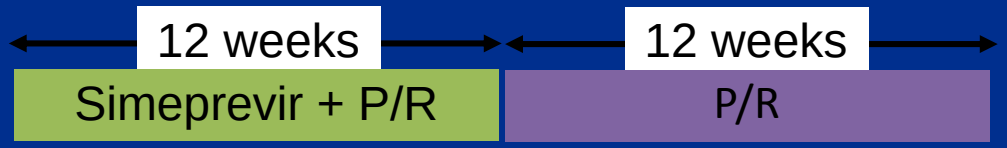


Q80K present in 34% of GT1a patients
No benefit of simeprevir if Q80K positive

Jacobson I, et al. AASLD 2013. Abstract 1122.

Simeprevir + P/R for GT1 HCV: Approved Indications

- Simeprevir 150 mg/day with food, administered with P/R
  - Fixed duration (no RGT)
- Treatment-naive patients and relapsers (including cirrhotic patients
- Previous partial or null responders (including cirrhotic patients)



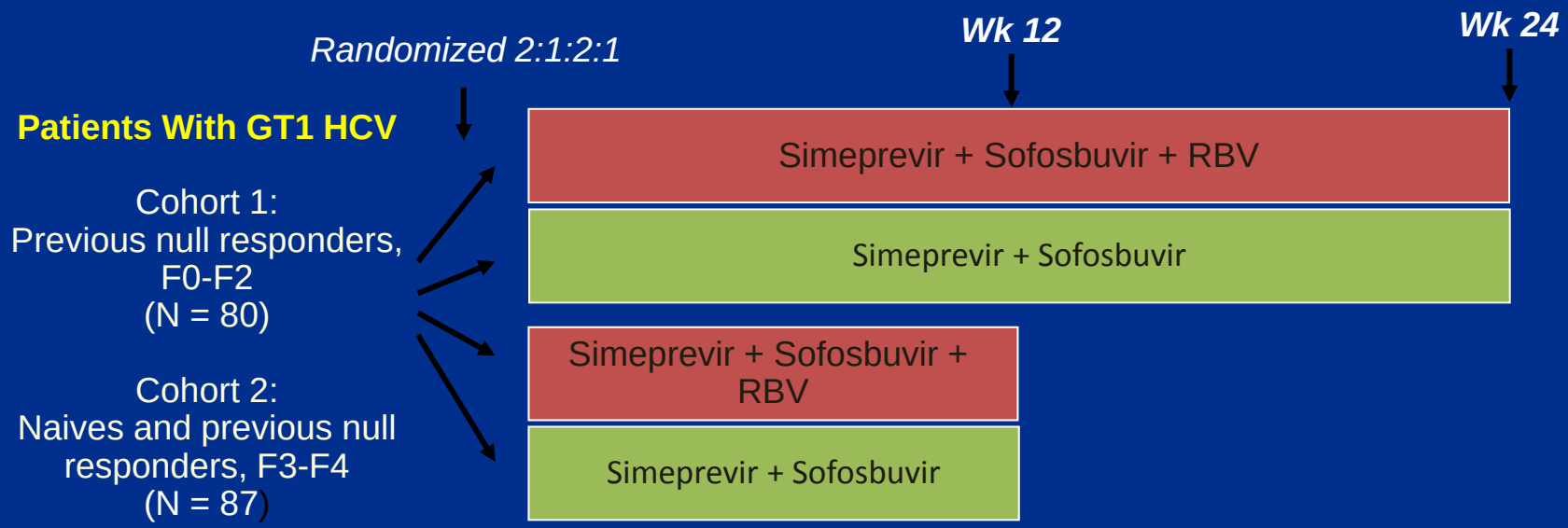
Treatment Wk	HCV RNA (IU/mL)	Action
4	≥ 25	Discontinue simeprevir, pegIFN, and RBV
12	≥ 25	Discontinue pegIFN and RBV (SMV stops at 12 wks)
24	≥ 25	Discontinue pegIFN and RBV

Simeprevir [package insert]. November 2013.

INTERFERON FREE GENOTYPE 1

COSMOS: Simeprevir + Sofosbuvir ± RBV in Genotype 1 HCV Patients

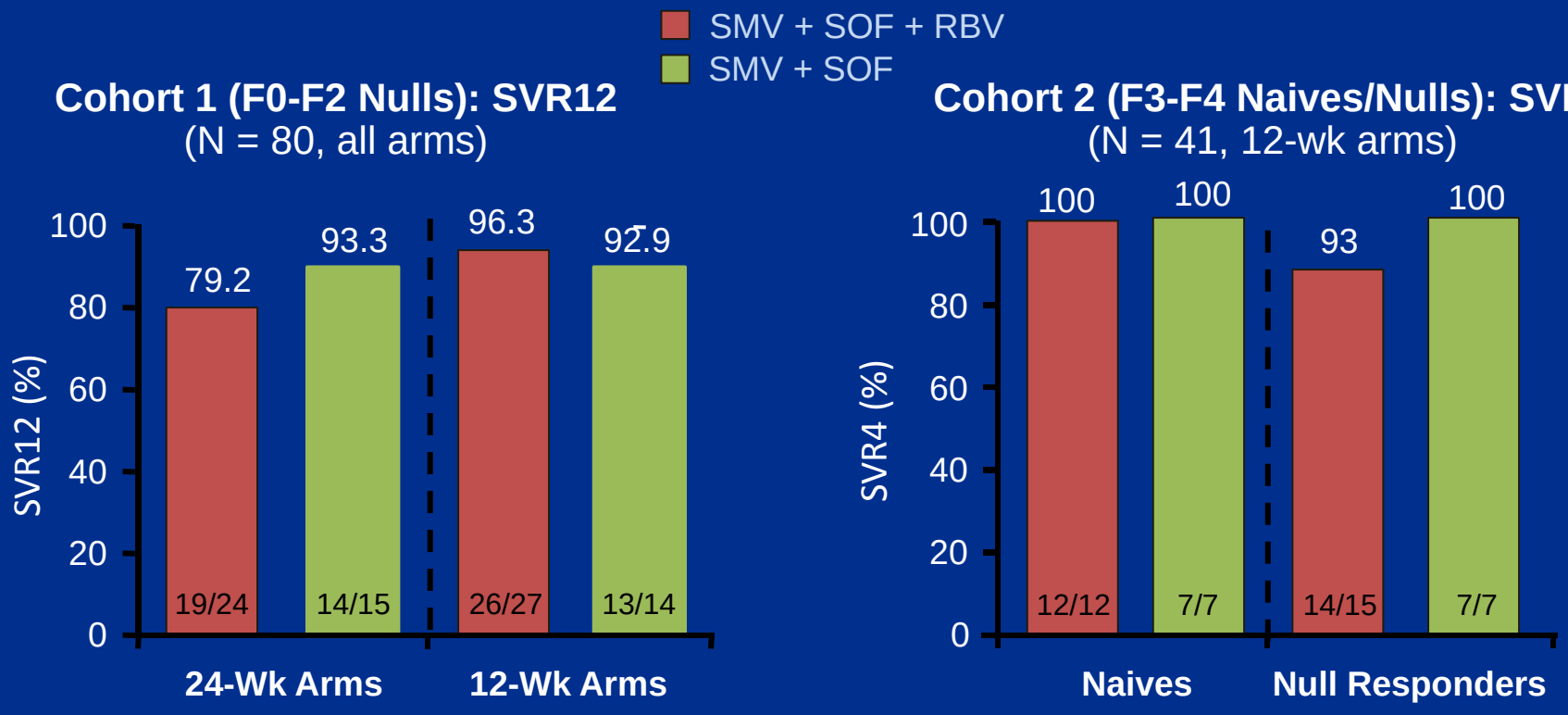
- Planned interim analysis of randomized phase IIa study
- 2 cohorts with same study design evaluating impact of duration and RBV
- Primary endpoint: SVR12



Simeprevir 150 mg QD; sofosbuvir 400 mg QD; weight-based RBV 1000-1200 mg/day.

Jacobson I, et al. AASLD 2013. Abstract LB-3.

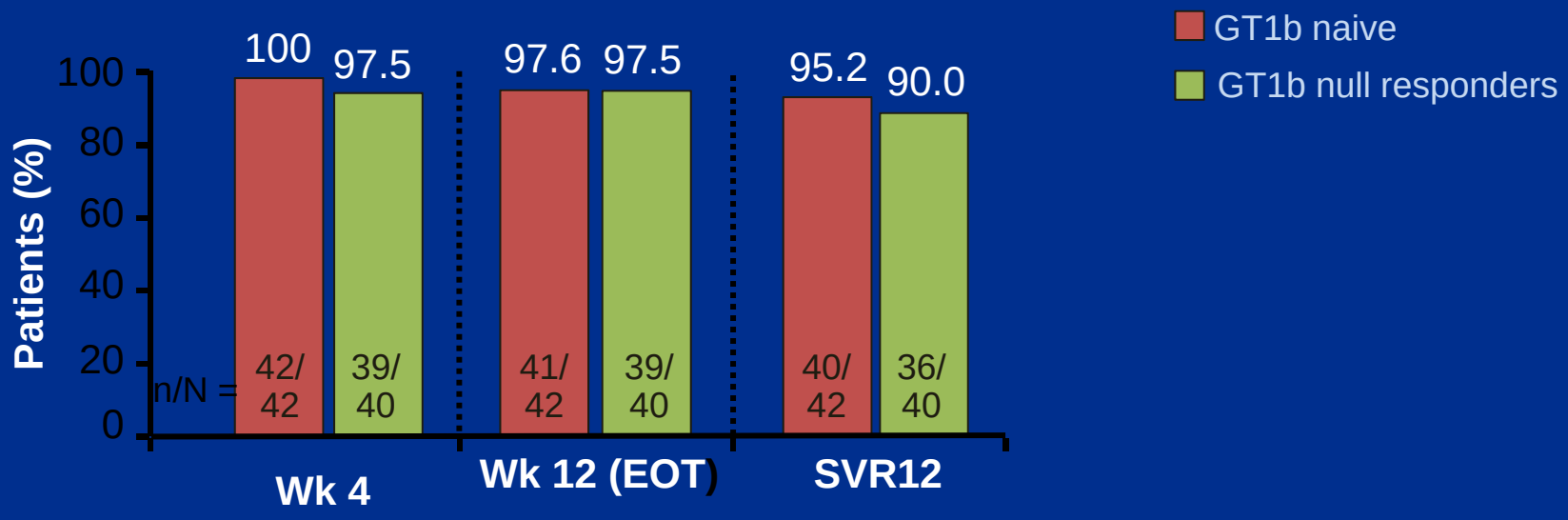
COSMOS: SVR12 in F0-F2 Pts (All Arms) and SVR4 in F3-F4 Pts (12-Wk Arms Only)



- Relapse in 3 pts in Cohort 1 and 1 pt in Cohort 2; all with GT1a and Q80K polymorphism at BL
- AEs (anemia and indirect bilirubin increases) largely confined to RBV arms

Jacobson I, et al. AASLD 2013. Abstract LB-3.

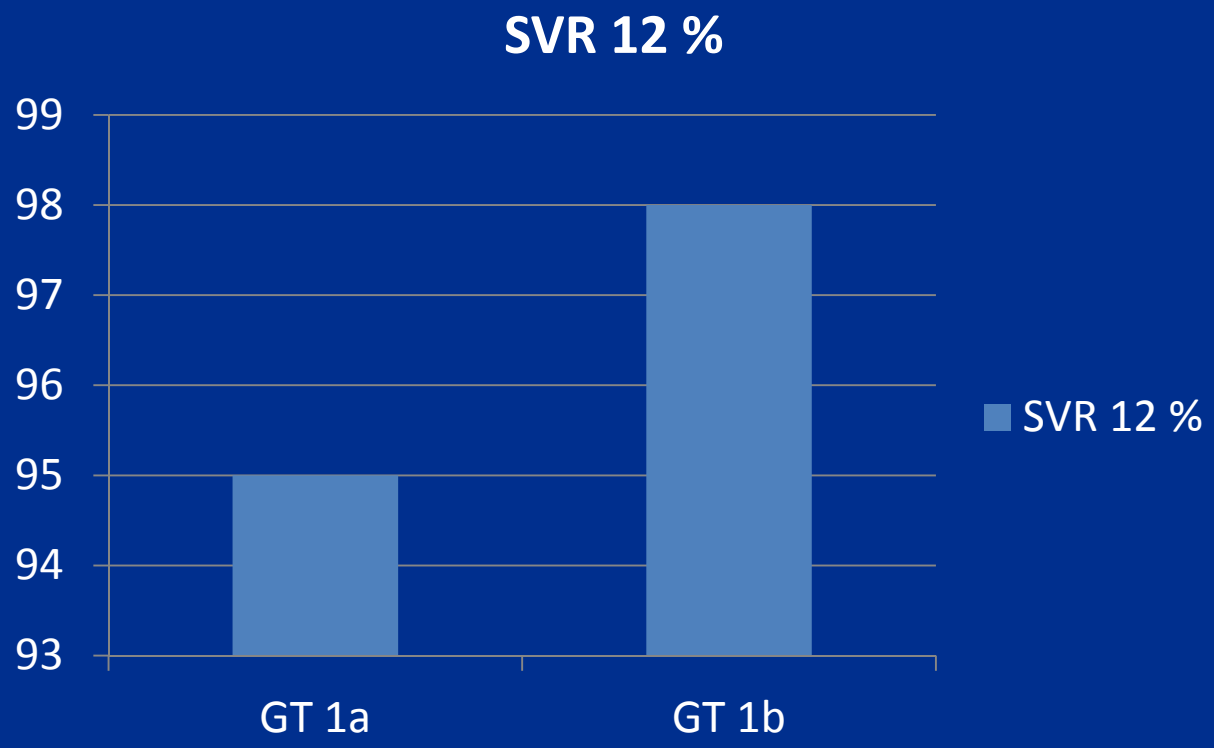
PEARL-I: Virologic Response Rates With ABT-450/RTV + ABT-267 in GT1b Pts



- No discontinuations due to AEs or laboratory abnormalities
- No virologic failures in naive patients; 4 virologic failures in null responders (1 viral breakthrough and 3 relapses)

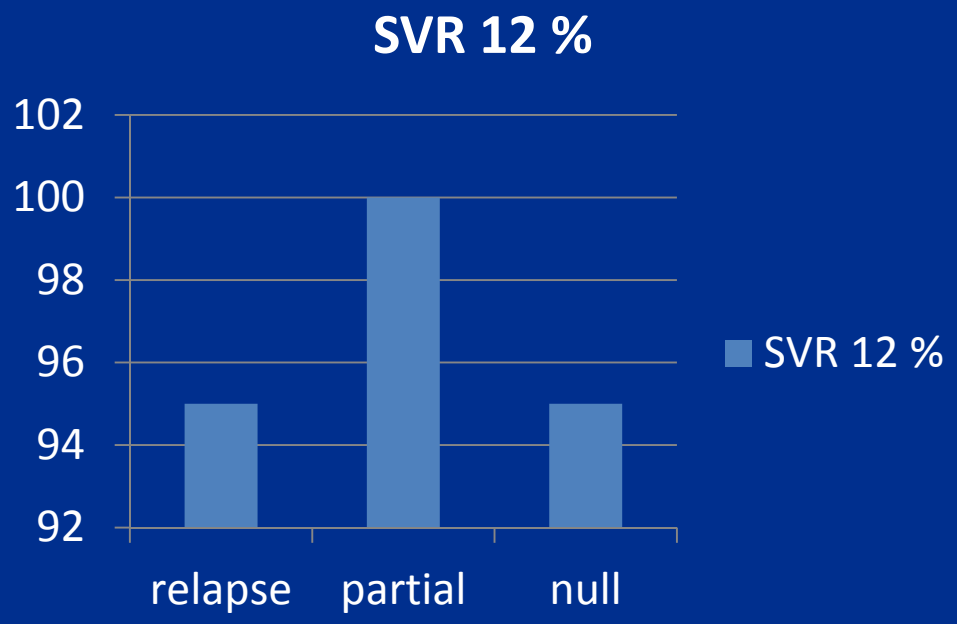
Lawitz E, et al. AASLD 2013. Abstract 75.

Sapphire-1: ABT-450/RTV/Ombitasvir + Dasabuvir + Riba. GT1 Naïve Patients



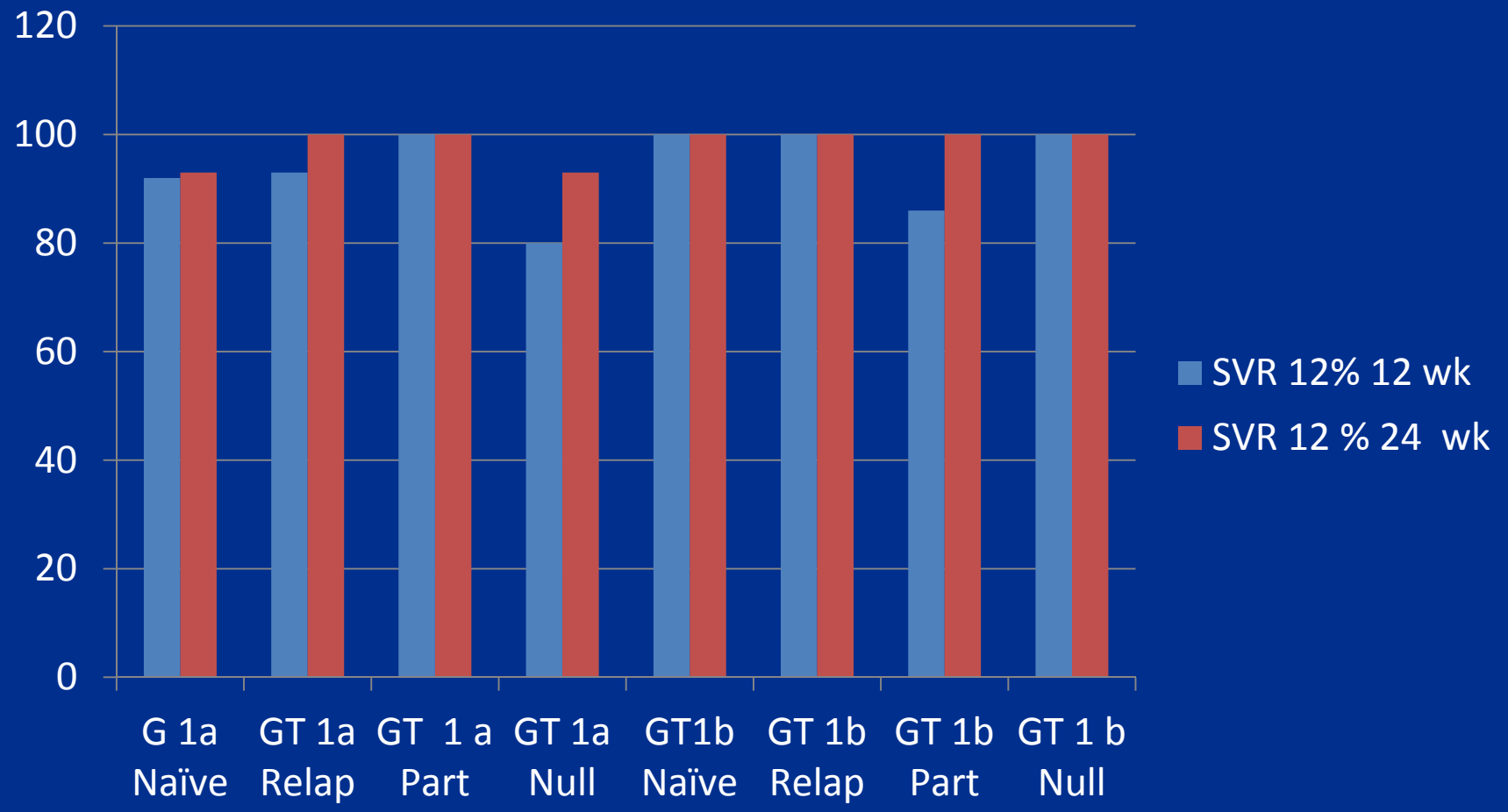
ABT/RTV NS3/4A PI, Ombitasvir NS5A, Dasabuvir NS5B PI
N=473 pts, 57% males, 90% Cau
SVR and fibrosis 0-1 97%, F2 94%, F3 93%
SAE fatigue 34%, HA 33%
Feld JJ. EASL 2014

Sapphire II: ABT-450/RTV/Ombitasvir + Dasabuvir + Riba. GT 1 Treatment Experienced



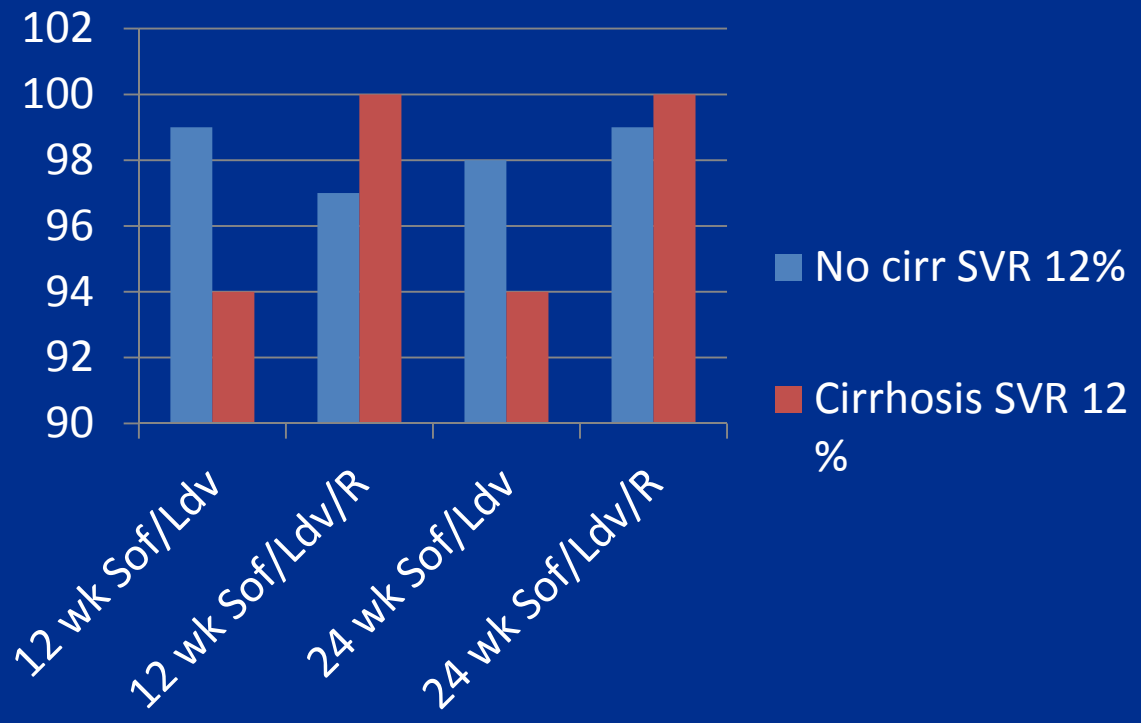
12 week treatment course, n=394 patients
Relapse 29%, Partial 22%, Null 49%
No difference in response in GT 1a or 1b.
Zeuzem S. EASL 2014

Turquoise II: Cirrhotic Genotype 1 Treated ABT 450/RTV/Ombitasvir + Dasabuvir + Riba



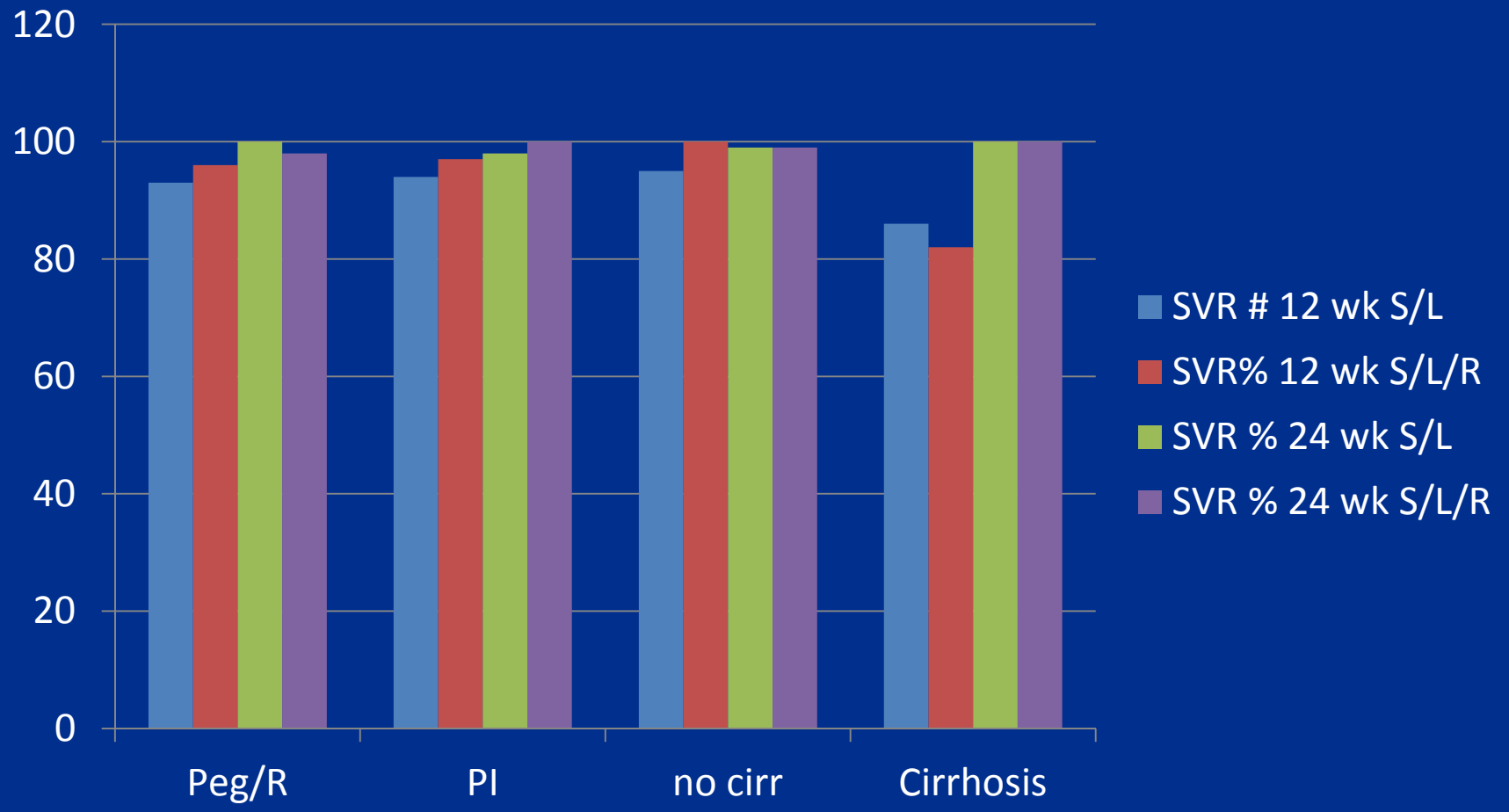
Naïve 42%, Relapse 13%, Partial 7%, Null 36%. Poordad F. EASL 2014

ION 1: Sofosbuvir/Ledipasvir +/- Riba GT1 Naive



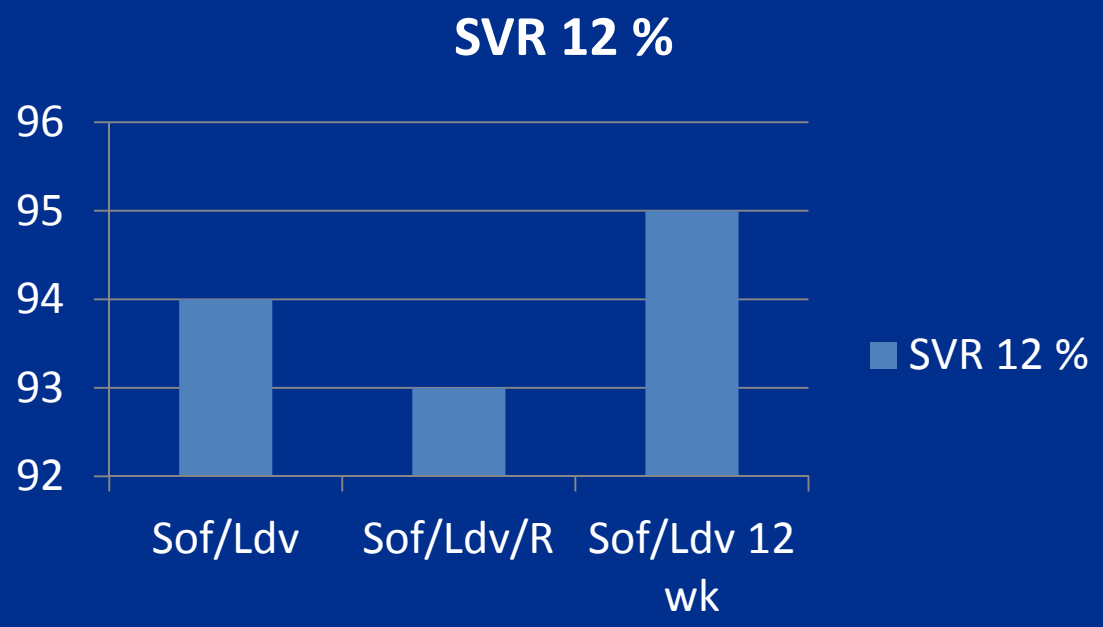
Sofosbuvir NS5B PI, Ledipasvir NS5A inhibitor
12 Weeks of treatment, n=865 patients, 16% cirrhosis
Fatigue 21-36%, Headache 23-30% SAE
Mangia A, EASL 2014

ION 2: Sofosbuvir/Ledipasvir +/- Riba. Treatment Experienced GT 1



n=440 patients, nonresponder 45%, PI failure 46-61%, Cirrhosis 30%
Afdhal N. EASL 2014

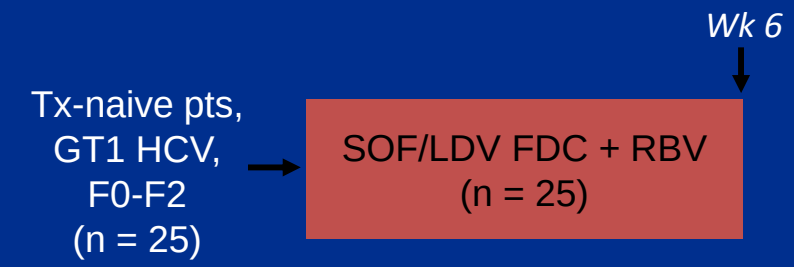
ION 3: Sofosbuvir/Ledipasvir 8 wk GT1 Naive



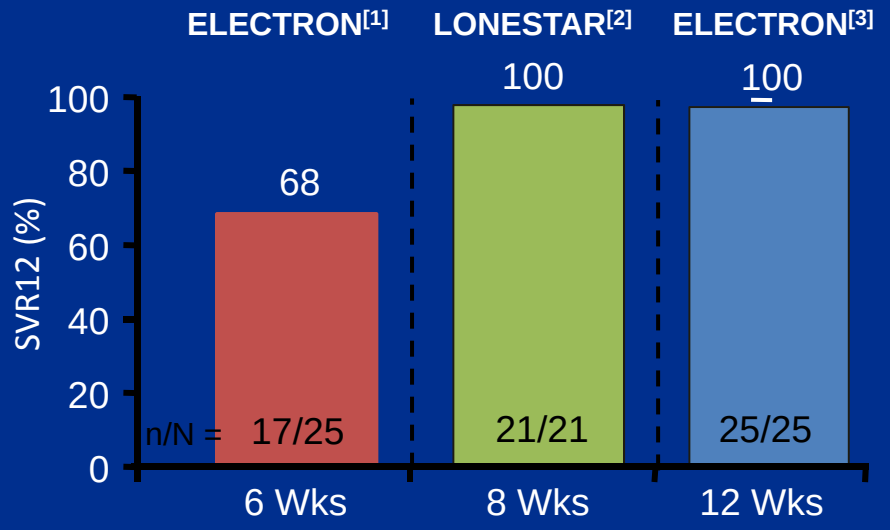
N= 647 patients, 8 week vs 12 week Sof/Ldv +/ R, noncirrhotic naïve
Kowdley KV. EASL 2014.

ELECTRON: Sofosbuvir/Ledipasvir FDC + RBV for 6 Wks in Naive GT1 HCV Pts

- Open-label phase II trial in GT1 HCV pts
- 68% SVR12 rate with 6 wks of SOF/LDV FDC + RBV lower[1] than SVR rates previously achieved with 8 wks[2] or 12 wks[3] treatment with this regimen



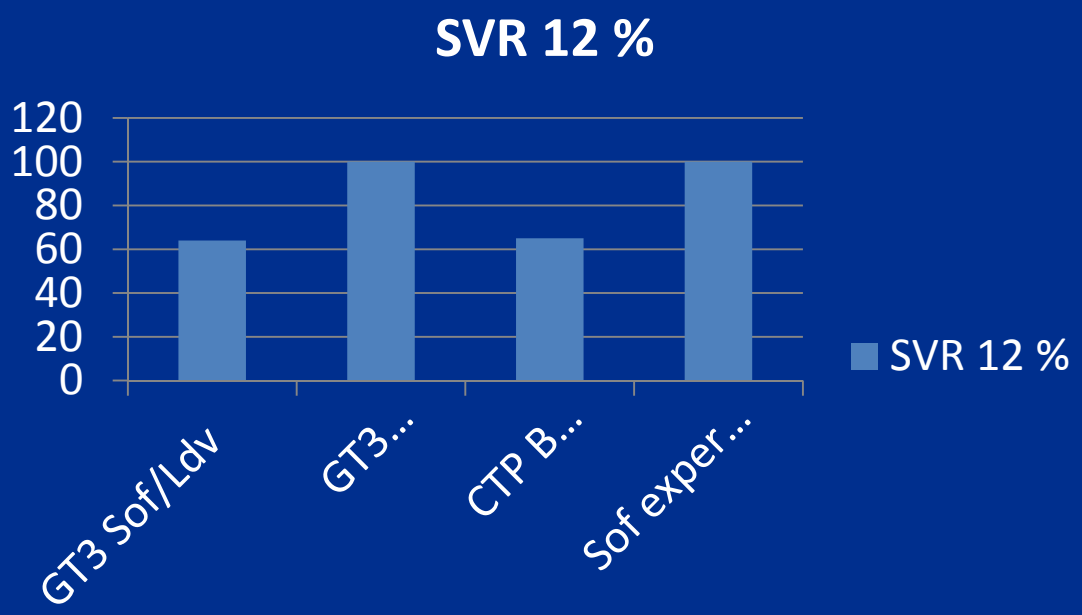
Sofosbuvir 400 mg QD;/ledipasvir 90 mg QD; weight-based RBV 1000-1200 mg/day



Duration of SOF/LDV + RBV in Tx-Naive Pts

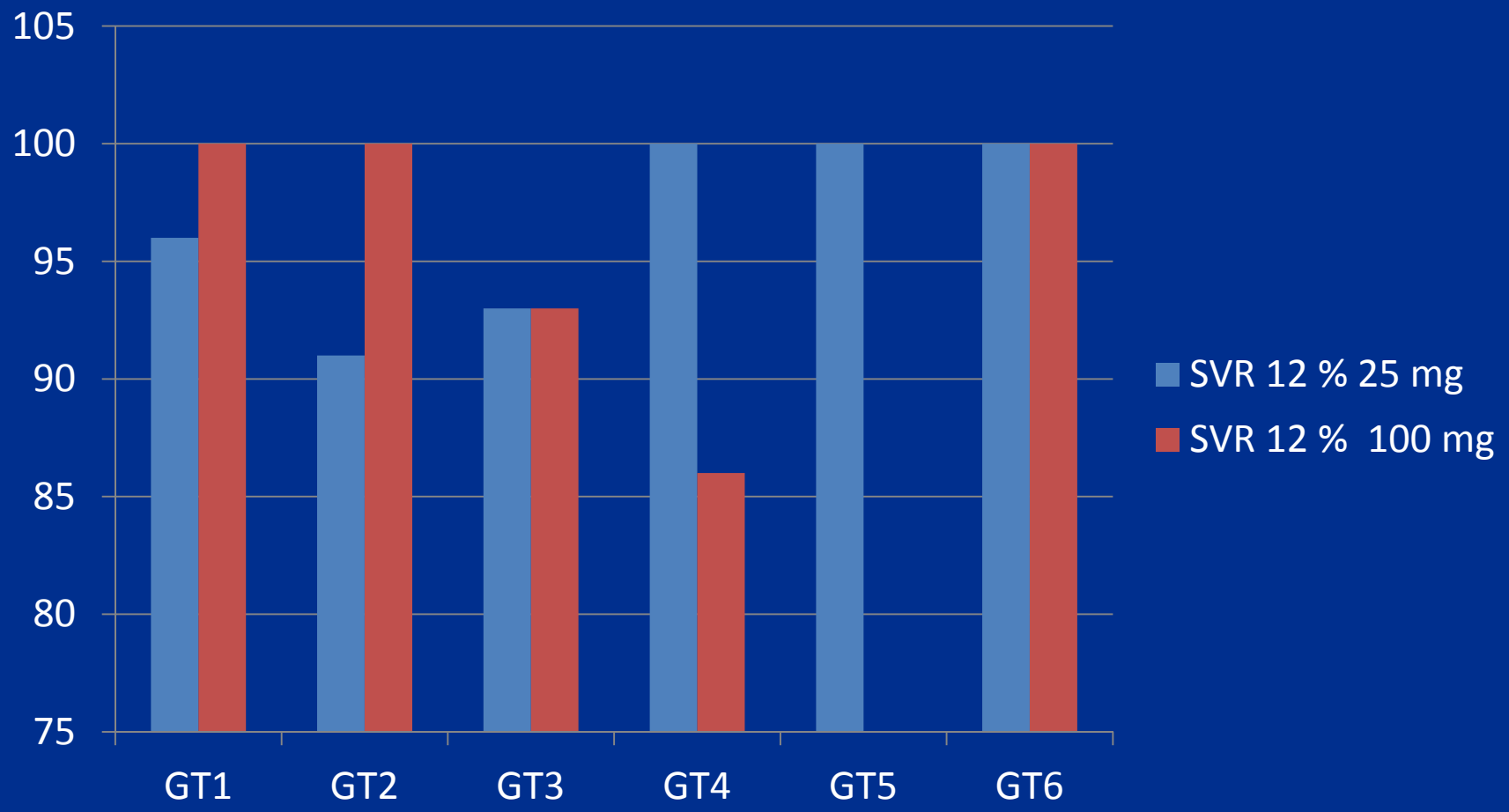
1. Gane EJ, et al. AASLD 2013. Abstract 73.
2. Lawitz E, et al. AASLD 2013. Abstract 215. 3. Gane EJ, et al. EASL 2013. Abstract 14.

ELECTRON 2: Sofosbuvir/Ledipasvir +/ Riba. Difficult to Treat Patients



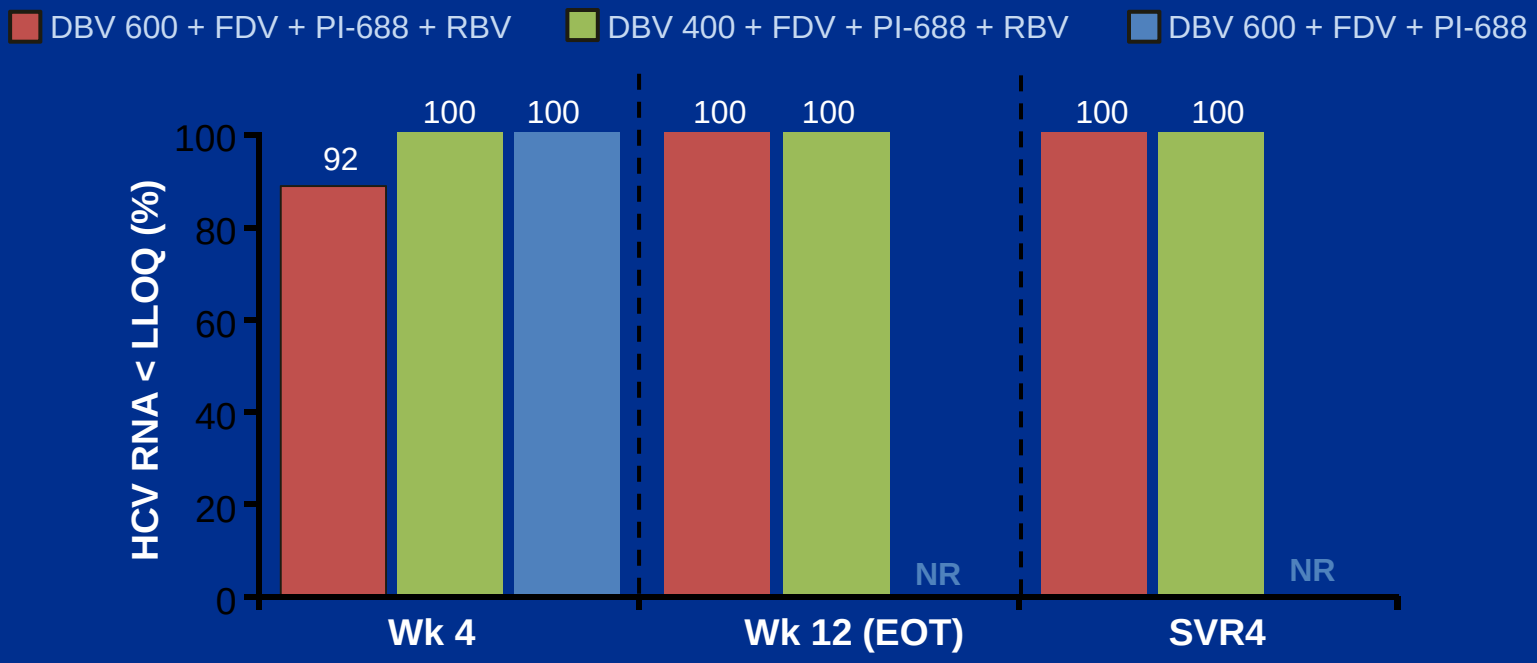
GT3 n=51, GT1 CTP B n=20, Sof failure GT1 n=19
Gane EJ. EASL 2014

Sofosbuvir + GS-5816 Genotype 1-6 Naive



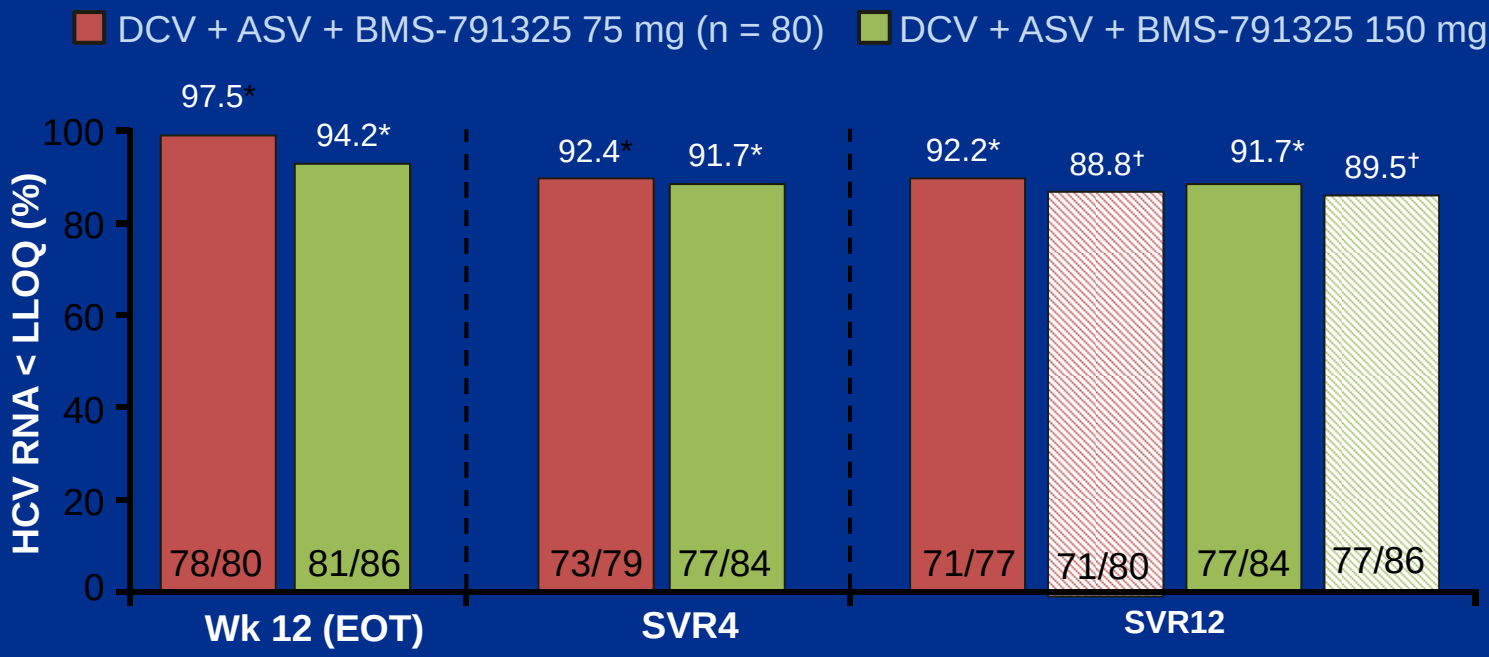
Virologic Response Rates With Faldaprevir + Deleobuvir + PPI-688 ± RBV

- Very high early response rates with all-oral therapy with or without RBV
- Only 1 severe AE and 1 discontinuation for AE
- Frequent bilirubin elevations ≥ grade 1, consistent with FDV inhibition of UGT1A1



Lalezari J, et al. AASLD 2013. Abstract LB-20.

AI443-014: Virologic Response Rates With Daclatasvir + Asunaprevir + BMS-791325

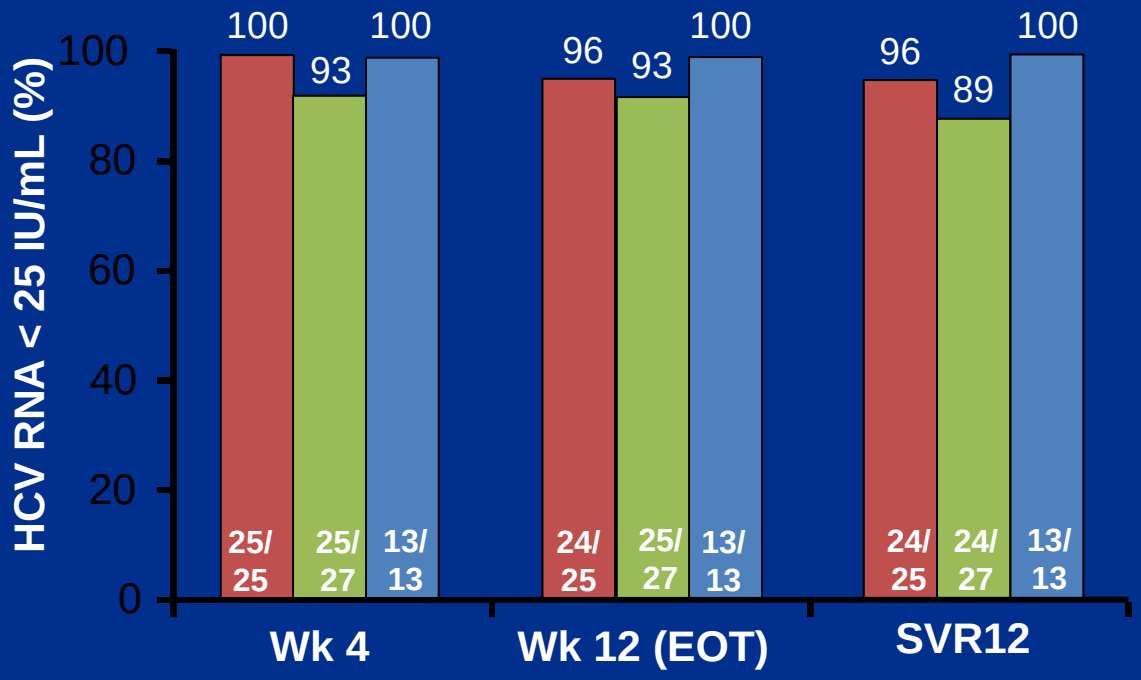


*Observed analysis: breakthrough, relapse, or addition of P/R equals failure.
†Modified ITT analysis: missing data, breakthrough, relapse, or addition of P/R equals failure.

- 3 pts with virologic breakthrough in 150-mg arm
  - Both GT1a; 2 intensified treatment with P/R

Everson GT, et al. AASLD 2013. Abstract LB-1.

C-WORTHY: Virologic Response Rates With MK-5172 + MK-8742 ± RBV



MK-5172 100 mg + MK-8742 20 mg + RBV (n = 25)

MK-5172 100 mg + MK-8742 50 mg + RBV (n = 27)

MK-5172 100 mg + MK-8742 50 mg (n = 13)

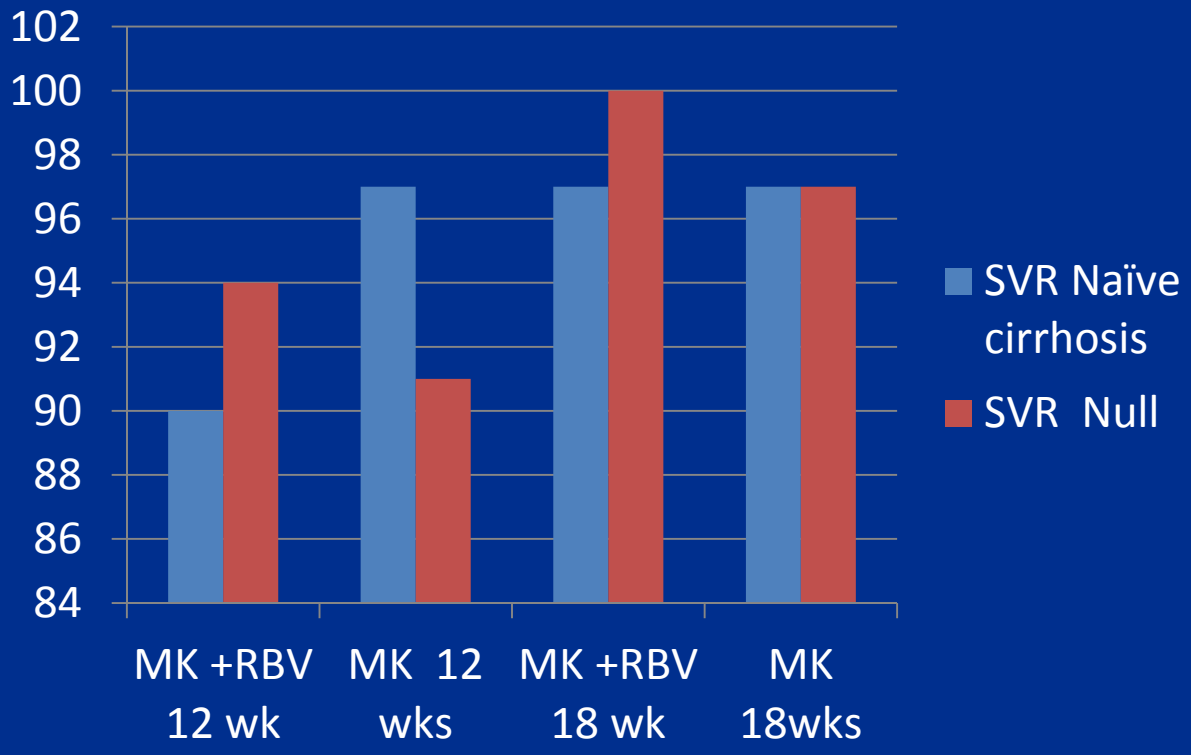
MK 5172 NS3/4A PI, MK8742 NS 5A inhibitor

All treatment regimens safe and well tolerated

No early discontinuations due to drug-related AEs

Lawitz E, et al. AASLD 2013. Abstract 76.

C-WORTHY: MK 5172 + MK 8742 +/ RBV. GT1 +/- Cirrhosis and Null Responders



MK 5172 NS3/4 A PI, MK 8742 NS5a inhibitor

N=253 patients

SVR GT1a cirrotic naïve 94%, GT 1b 100%, Null cirrhotics GT1 a 94%, GT 1b 100%

Lawitz E. EASL 2014.

Interferon Free trials for Genotype 1-treatment Naïve Patients

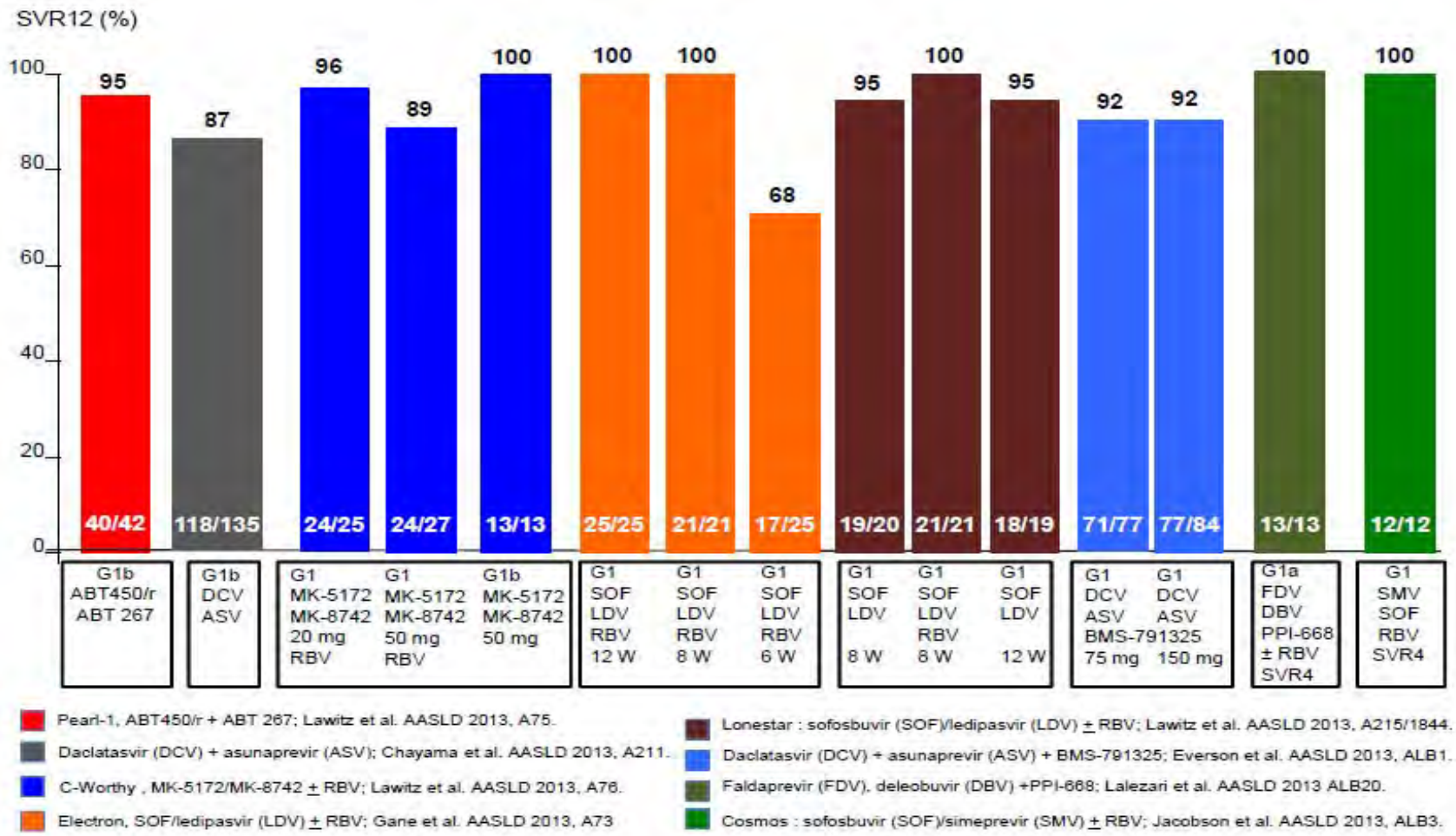


Fig. 2. IFN-free trials for genotype 1-naïve subjects.

Schinazi et al. Liver Int. 2014 Feb;34 Suppl 1:69-78.

Interferon Free trials for Genotype 1-treatment experienced Patients

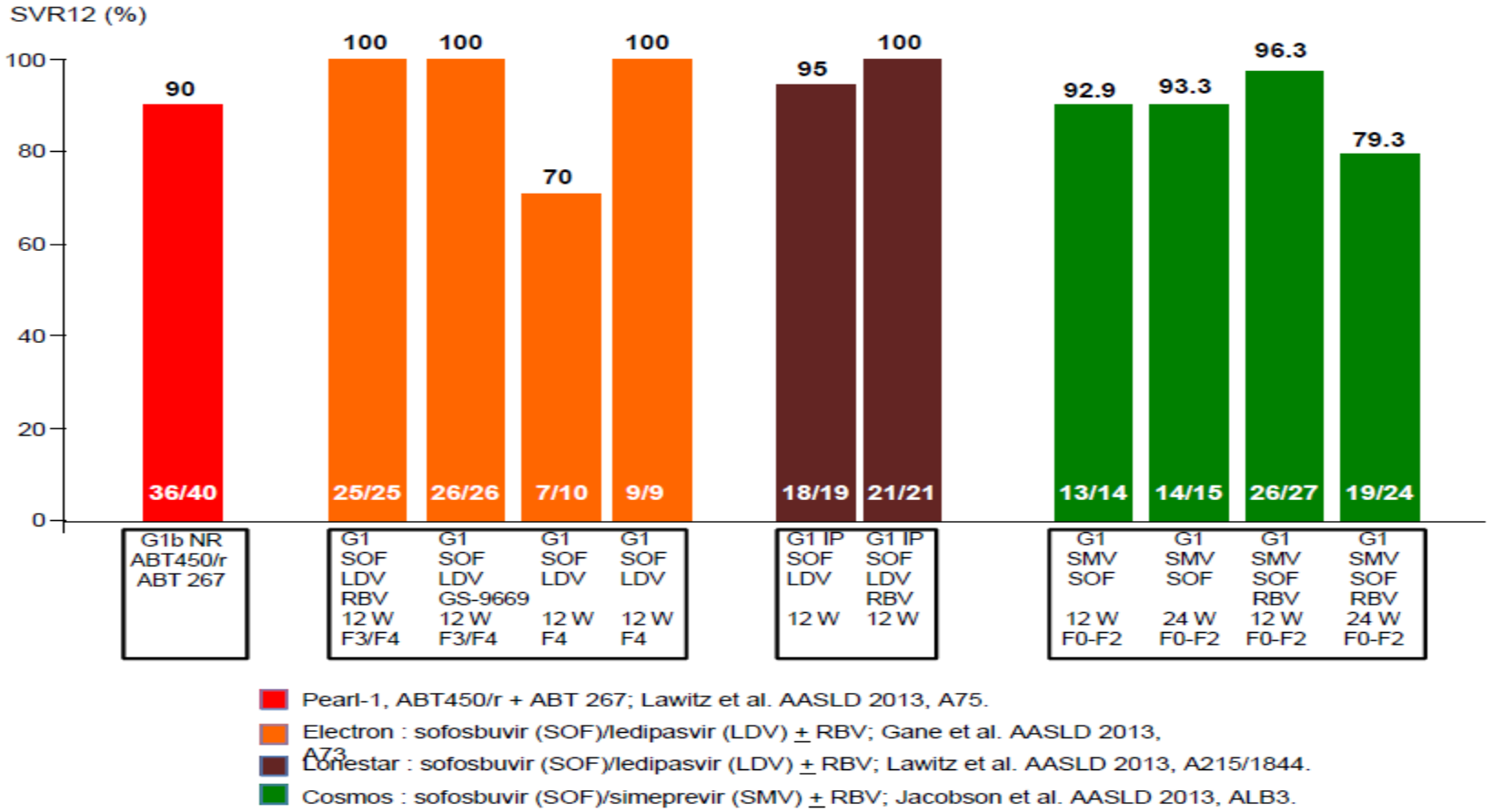
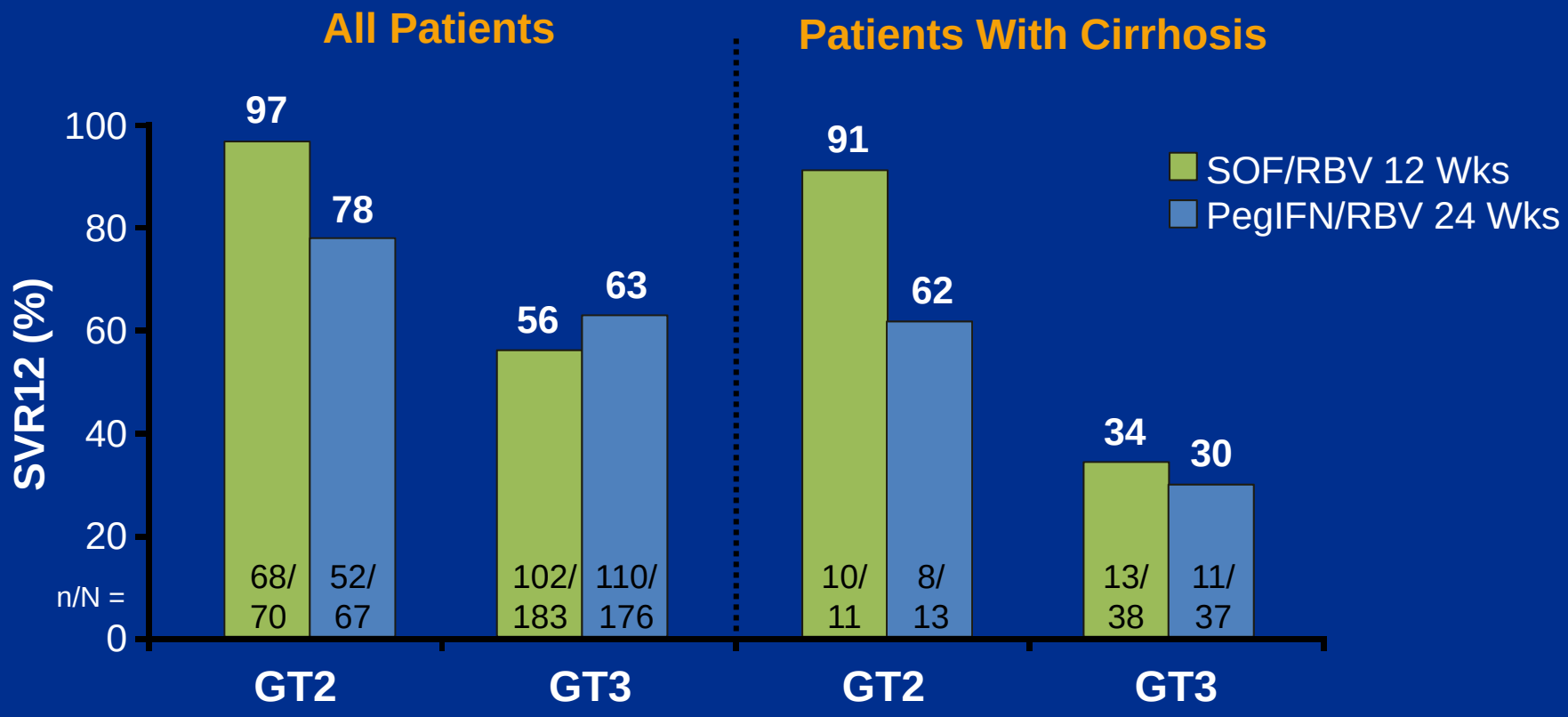


Fig. 3. IFN-free trials for genotype 1 experienced subjects.

Schinazi et al. Liver Int. 2014 Feb;34 Suppl 1:69-78.

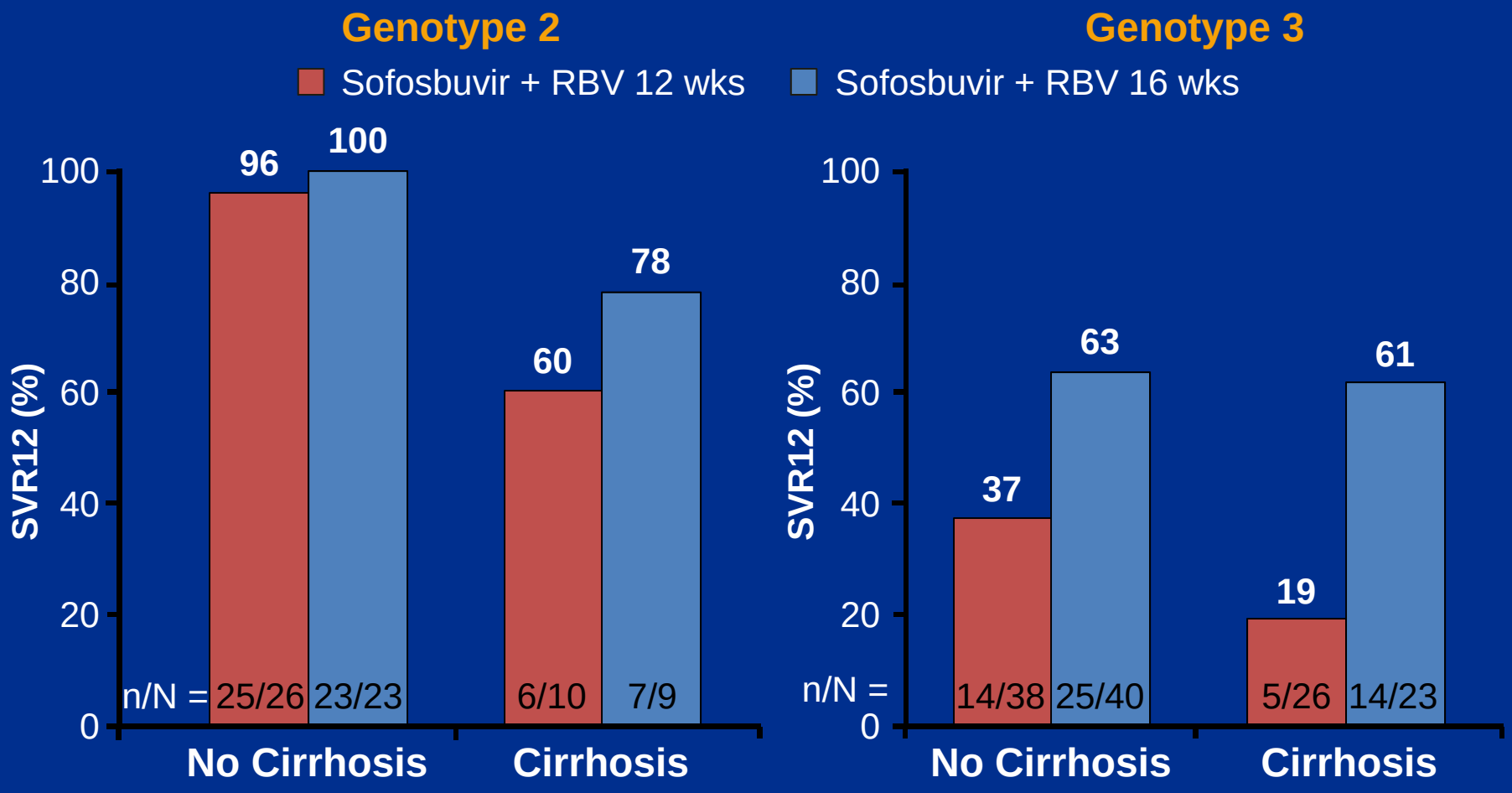
GENOTYPE 2/3

Fission: SOF/RBV in GT2 and GT3 Naives



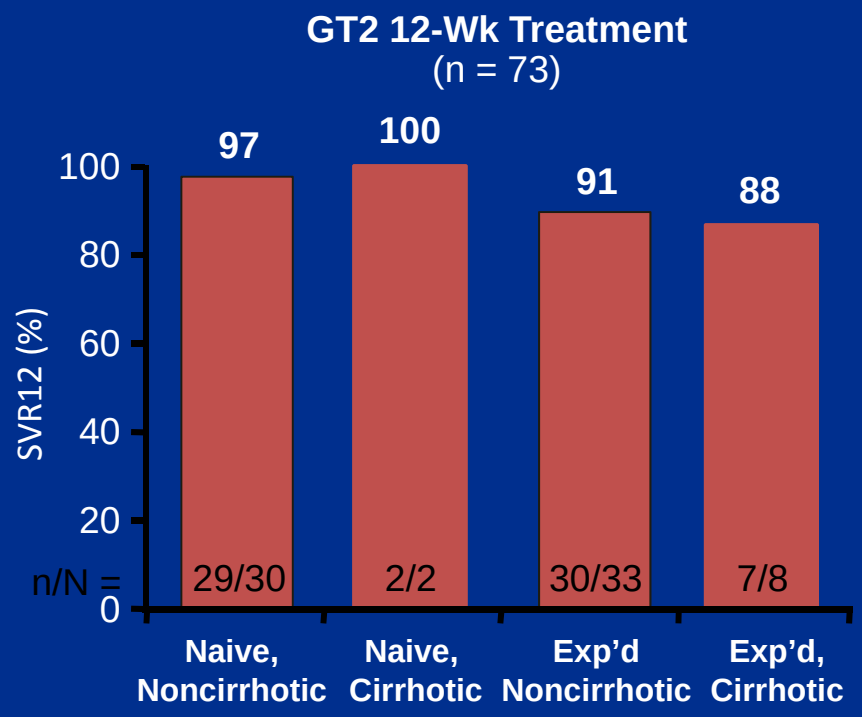
Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

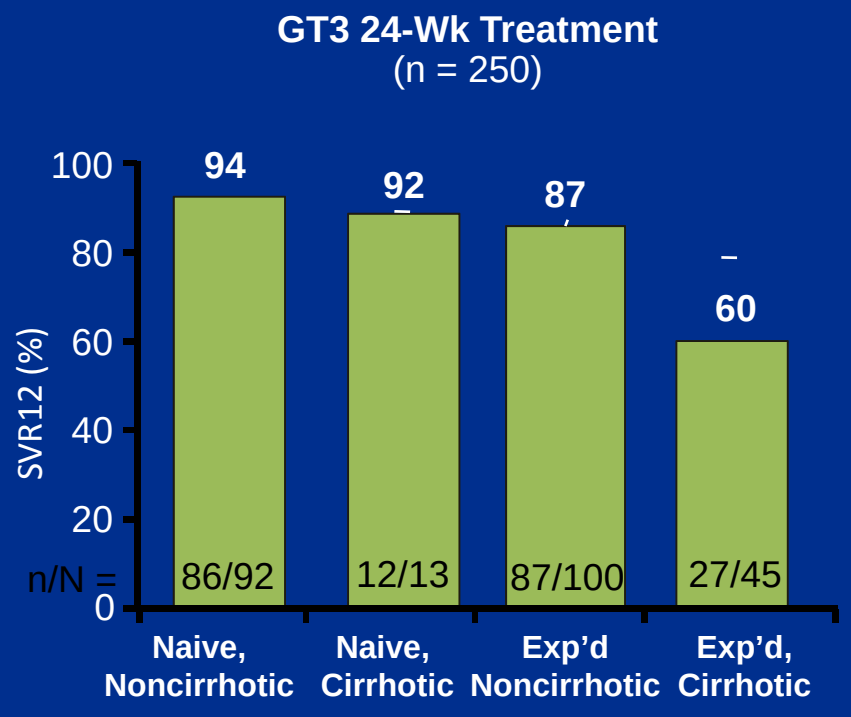
FUSION: Impact of Cirrhosis and Duration on SVR Rates



Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

VALENCE: SVR12 With 12 or 24 Wks of SOF + RBV in GT2 and GT3 Pts

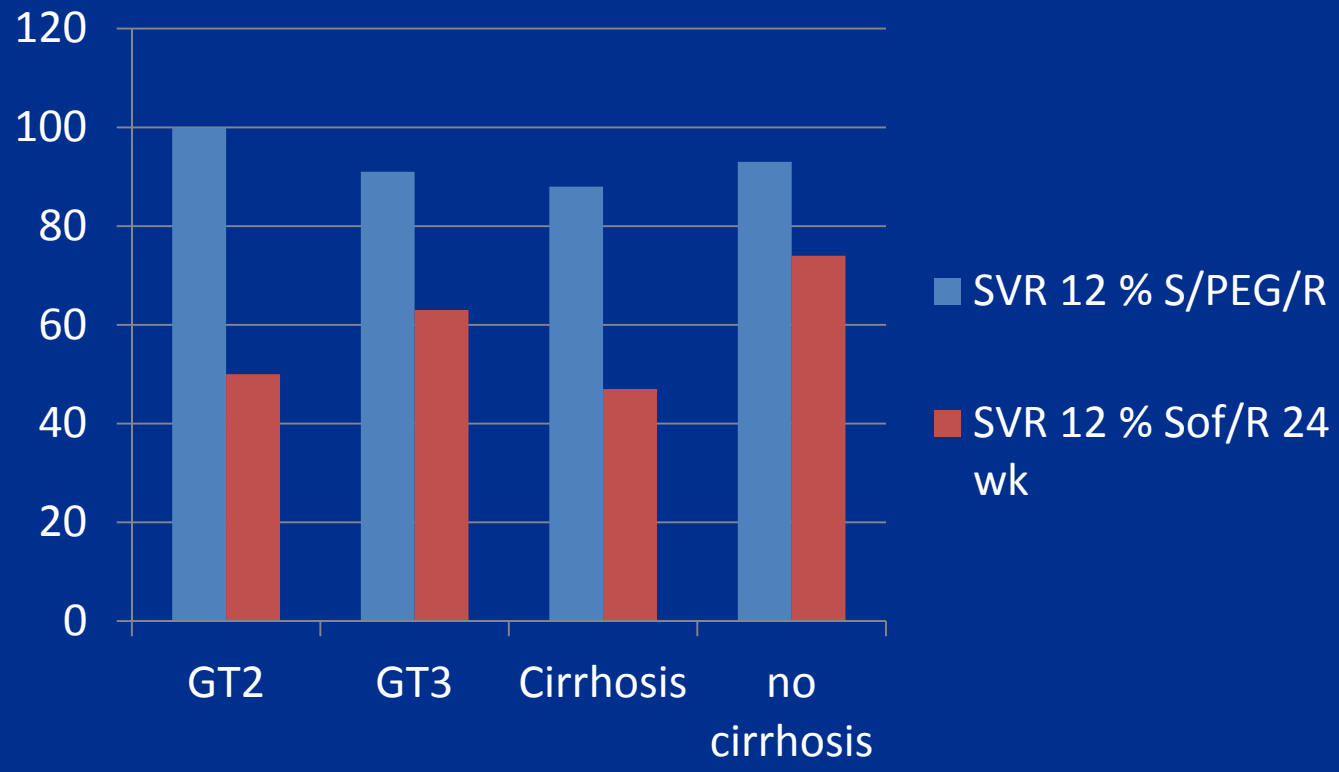




- No increase in AEs seen with longer duration treatment
  - AEs seen consistent with RBV

Zeuzem S, et al. AASLD 2013. Abstract 1085.

Retreatment Sofosbuvir/RBV or add PEG INF GT2, 3 prior failure of Sofosbuvir/RBV



GT2 S/Peg/R 18%, GT3 82%, GT2 S/R 24 wks 7%, GT3 93%
Esteban R. EASL 2014

INITIAL TREATMENT

Genotype	Recommended	Alternative	NOT Recommended
1	**IFN eligible:** SOF + PEG/RBV x 12 weeks IFN ineligible: SOF + SMV ± RBV x 12 weeks	**IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* IFN ineligible: SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	**IFN eligible:** SOF + PEG/RBV x 12 weeks IFN ineligible: SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

HCVguidelines.org-AASLD+IDSA

Retreatment of Hepatitis C

Retreatment Box. Recommendations for Patients in Whom Previous PEG/RBV Treatment Has Failed†

Genotype	Recommended	Alternative	NOT Recommended
Patients in whom previous PEG/RBV has failed*			
1	SOF + SMV ± RBV x 12 weeks	SOF x 12 weeks + PEG/RBV 12 weeks SMV x 12 weeks + PEG/RBV x 24 weeks**	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a direct-acting antiviral agent Do not treat decompensated cirrhosis with PEG
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± any current protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
4	SOF x 12 weeks + PEG/RBV 12 weeks SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
5 or 6	SOF x 12 weeks + PEG/RBV 12 weeks	SOF + RBV x 24 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA

Retreatment of Hepatitis C

Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed †† †††***			
1a	SOF x 12 weeks + PEG/RBV x 24 weeks	SOF + RBV x 24 weeks	PEG/RBV ± telaprevir or boceprevir or SMV Monotherapy with PEG, RBV, or a DAA
1b	SOF x 12 weeks + PEG/RBV x 12-24 weeks	SOF + RBV x 24 weeks	Do not treat decompensated cirrhosis with PEG or SMV

†† A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistant resistance to protease inhibitor treatment.

Monitoring During Treatment

- Follow usual monitoring with INF/R
- Without INF, no specific guideline
- Personal experience:
- Pre: genotype, HCV RNA level, TSH, Pregnancy testing, CBC, CMP
- During treatment: q 2 wks (CBC, Hepatic panel) ??? HCV level (2 wks)
- HCV 12 weeks post treatment

Drug-Drug Interactions

- Sofosbuvir
  - Rifampin and St Johns Wort (decrease SOF)

Drug-Drug Interactions SMV

	Increase	decrease
Antibiotics/antifungal	↑ SMV	
Calcium Channel blockers	↑ Ca channel blocker level	
herbals	↑ SMV (milk thistle)	↓ SMV (St John wart)
HIV	↑ SMV	↓ SMV
HMG CO A	↑ HMG CO A levels	
Immunosupression	↑ CSA	↓ FK
Midazolam/Triazolam	↑ drug levels	

HCV Post Transplant RX

EOT HCV RNA Negative

Genotype	Peg/Sof/R	Sof + Sim	Sof + R
GT1	4/4 neg	2/2 neg	1/1 neg
	4 pending	14 pending	2 pending
GT 2			4/4 neg
GT 3 (24 wks)			
			4/4 pending

As of 6/6/14, UNMC

Future ??

Future HCV Treatment?