"Wonder pills", breakthroughs and continuing challenges – HIV and Hepatitis C antiviral treatments revisited

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Disclosures

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- Unrestricted research grant: AbbVie

Off-label Investigational Uses:

- None

Learning Objectives

- **Review key information on chronic hepatitis C**
  - Hepatitis C Virus
  - Natural history of chronic hepatitis C
  - Goals and endpoints of treatment
- **Direct Acting Antivirals (IFN-free treatment)**
  - Mechanism of action
  - Currently available IFN-free all-oral regimen
- **Current Treatment with DAA´s**
- **Upcoming new treatment regimen**

???? Questions ????

Hepatitis C Virus infection can be cured permanently by a short course of an all-oral IFN-free treatment regimen.

YES! **or** **NO!**

???? Questions ????

Daclatasvir (DCV) is an Inhibitor of the Hepatitis C Virus (HCV) NS3a-Protein.

YES! **or** **NO!**

???? Questions ????

Treatment of Hepatitis C Virus Genotype 3 (HCV-3a) with Simeprevir/Dasabuvir yields high SVR rates.

YES! **or** **NO!**

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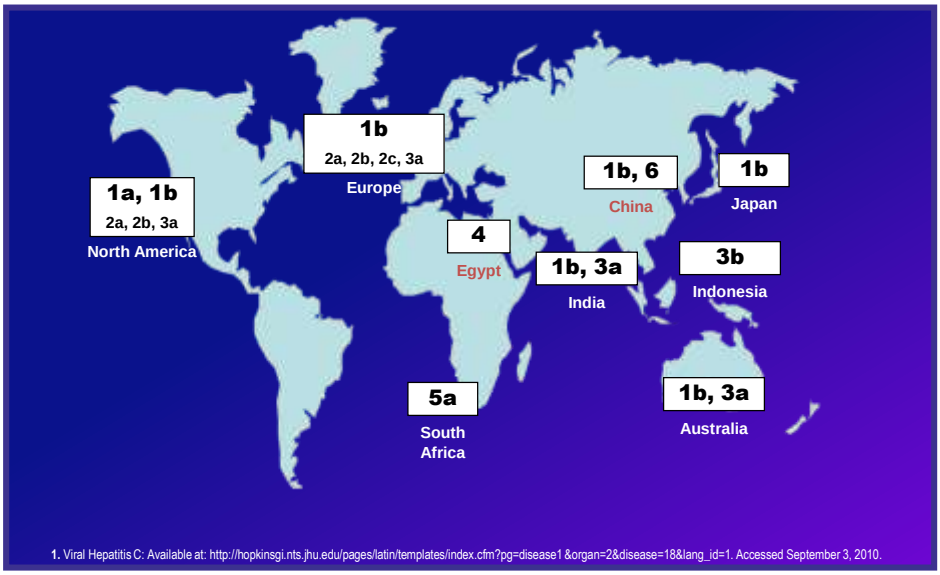
Hepatitis C Virus (HCV)

- 40-70 nm in diameter
- Envelope proteins E1, E2
- Lipid envelope derived from host cell
- Nucleocapsid containing **single-stranded viral RNA** and capsid protein
- **Identified 1989**

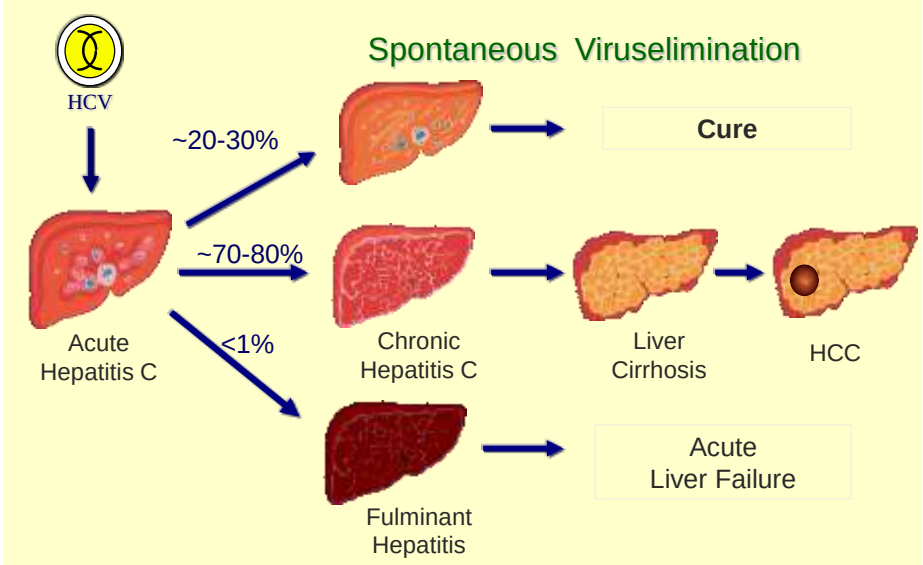
1. Moradpour D et al. *Nat Rev Microbiol*. 2007;5:453-463.

HCV-Genotype

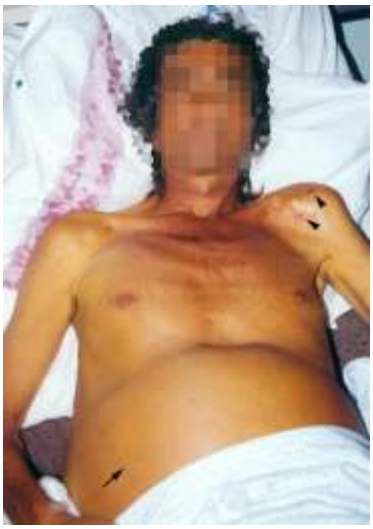


1. Viral Hepatitis C: Available at: http://hopkinsgi.nts.jhu.edu/pages/latin/templates/index.cfm?pg=disease1 &organ=2&disease=18&lang_id=1. Accessed September 3, 2010.

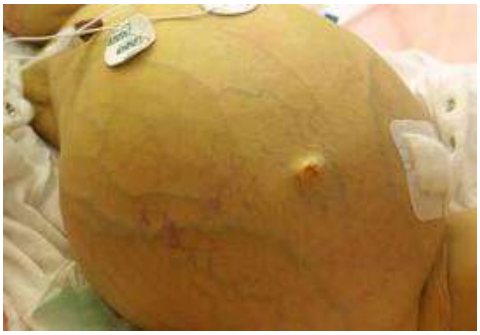
Natural Course of HCV Infection



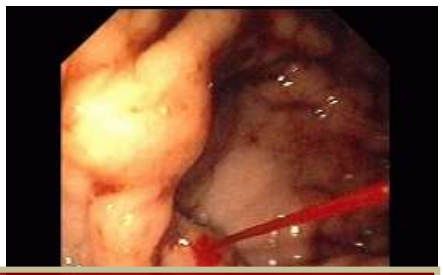
Liver Cirrhosis – end stage liver disease



Jaundice
Ascites
Portal Hypertension



Portal Hypertension – esophageal varices



Life threatening complications of liver cirrhosis
Variceal Bleeding
Hepatocellular Carcinoma
Hepatic Encelopathy
Hepatorenal Syndrome
SBP - Infections…

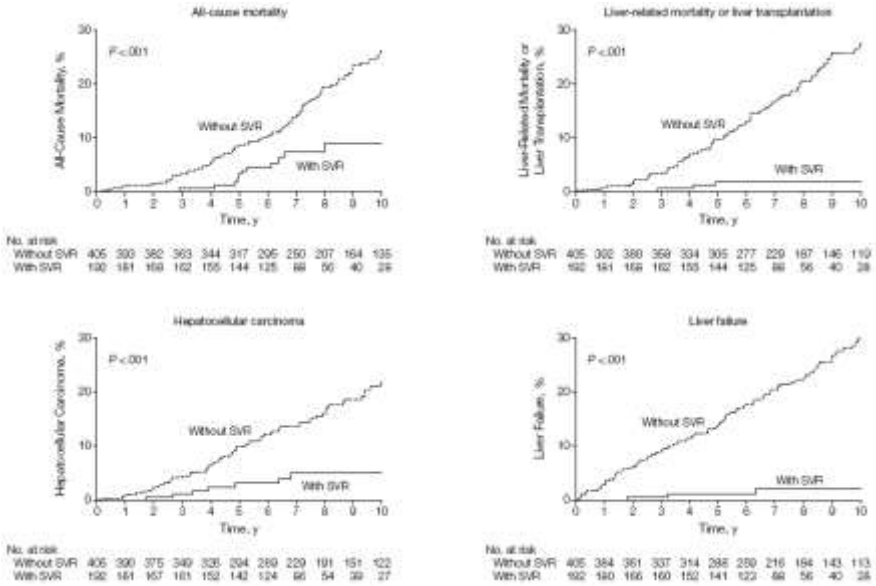
Goal and endpoint of antiviral treatment

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death **(A1)**

- The endpoint of therapy is undetectable HCV RNA in a sensitive assay (≤15 IU/ml) 12 weeks (SVR12) and 24 weeks (SVR24) after the end of treatment **(A1)**

EASL Clinical Pracrice Guidelines, 2015

Successful treatment increases Survival!



Van der Meer et al ., JAMA, 2012; 26;308(24):2584-93.

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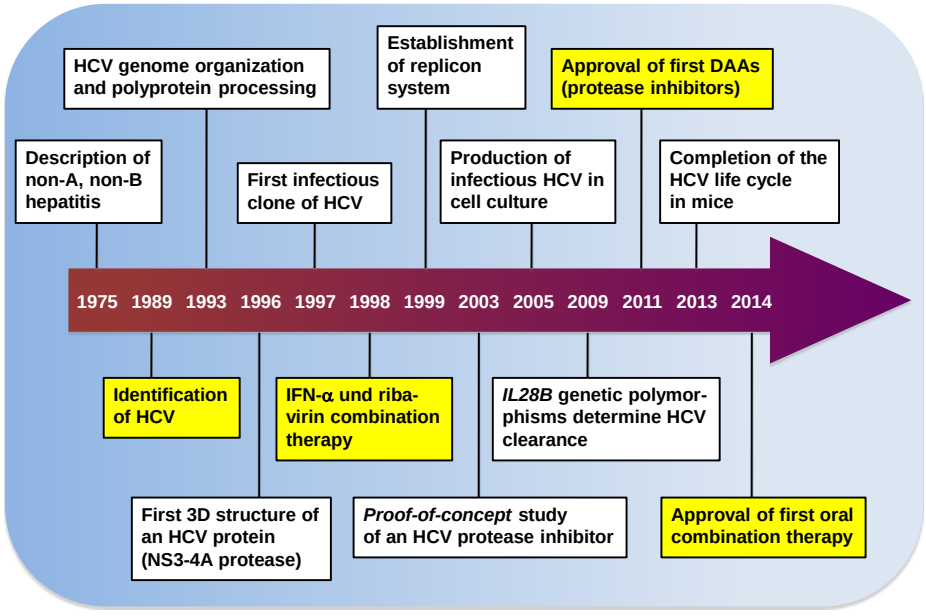
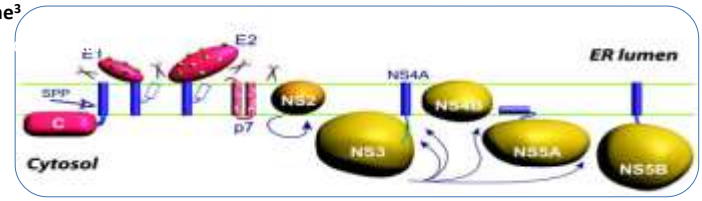
Milestones in HCV Research

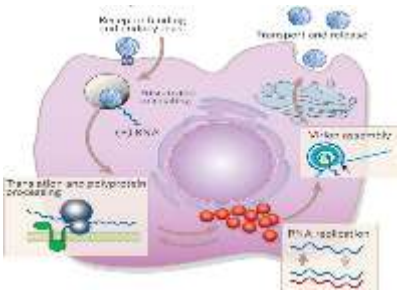


Updated from Moradpour D *et al*. Nat Rev Microbiol 2007;5:453-463

Targets of Direct Acting Antivirals

HCV Genome[3]





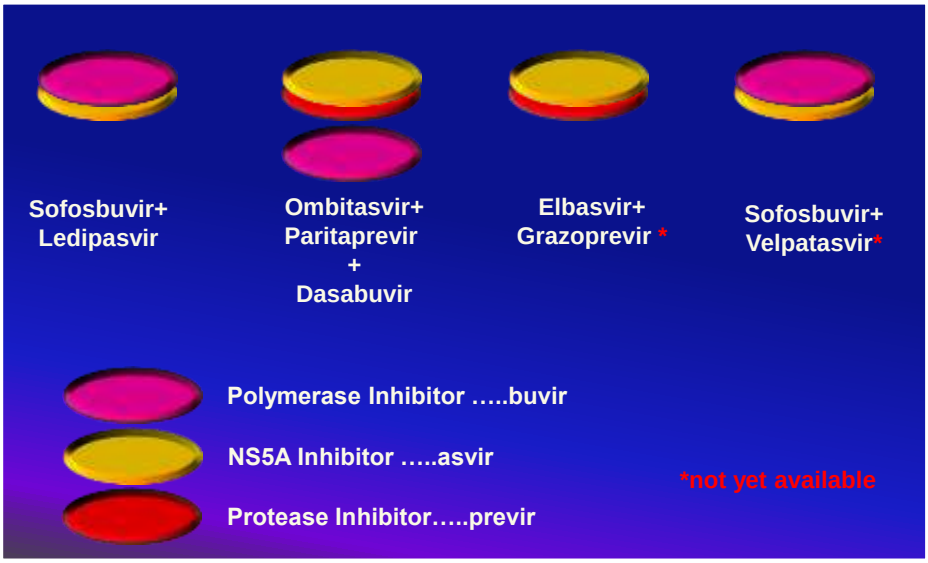
HCV Lifecycle Steps	Direct-Acting Antiviral		
	NS3	NS5A	NS5B
Viral Entry			
Translation			
Processing	✓	✓	
Replication complex		✓	
Replication		✓	✓
Assembly		✓	
Release			

1. Gao et al. Nature. 2010;465:96.; 2. Nettles et al. Hepatology. 2011;54:1956; 3. Chevaliez et al. In: Hepatitis C Viruses: Genomes and Molecular Biology, 2006; 4. He et al. In: Hepatitis C Viruses: Genomes and Molecular Biology, 2006; 5. Gao et al. Curr Opin Virol 2013;3:514. 6. Jazwinski et al. Gastroenterol Hepatol 2011; 7:154-162

Antivirals

		2014	2015
PEGIFN		PegIFN	
Ribavirin		RBV	
Proteaseinhibitors	...previr	Simeprevir (SMV)	Paritaprevir/r
NS5A Inhibitors	...asvir	Daclatasvir (DCV)	Ledipasvir (LPV) Ombitasvir
Nuc NS5B-Inhibitors	...buvir	Sofosbuvir (SOF)	
Non-Nuc NS5B-Inhibitors	...buvir		Dasabuvir

Fixed-Dose Combinations 2016



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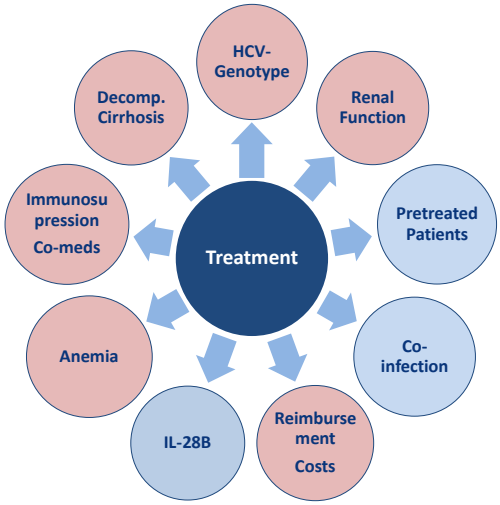
Choice of Treatment



http://www.hcvguidelines.org
http://www.easl.eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2015

Who should be treated?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	• Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis • Patients with HIV coinfection • Patients with HBV coinfection • Patients with an indication for liver transplantation • Patients with HCV recurrence after liver transplantation • Patients with clinically significant extra-hepatic manifestations • Patients with debilitating fatigue • Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
Treatment is justified	• Patients with moderate fibrosis (F2)
Treatment can be deferred	• Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	• Patients with limited life expectancy due to non-liver related comorbidities

EASL
European Association for the Study of the Liver

Journal of Hepatology **2015** vol. 63 | 199–236

EASL: IFN-free treatment of HCV-1

Non-Cirrhotic HCV-1 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naive or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV 12 wk without RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b								

Cirrhotic HCV-1 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naive or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV 12 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b								

EASL Recommendations, 2015

IFN-free treatment of HCV-1

- **Sofosbuvir/Ledipasvir FDC (+/-RBV)**
- **Paritaprevir/r,Ombitasvir,Dasabuvir (+/-RBV)**
- **Sofosbuvir+Simeprevir (+/-RBV)**
- **Sofosbuvir+Daclatasvir (+/-RBV)**

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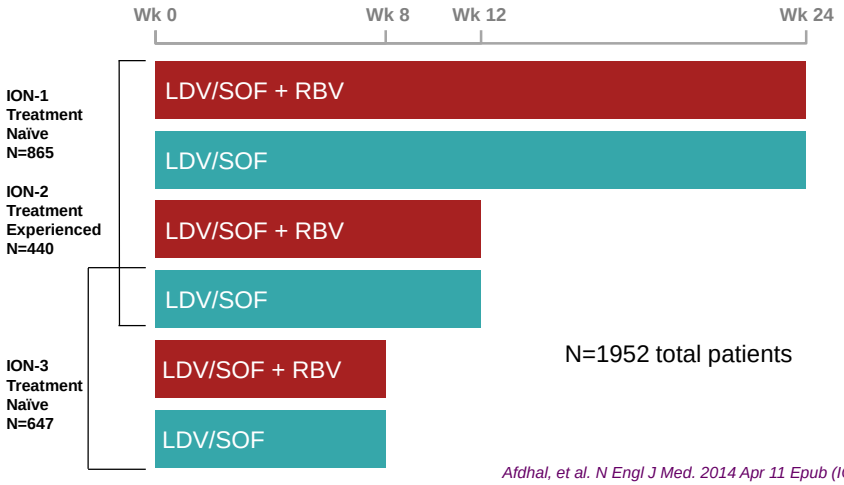
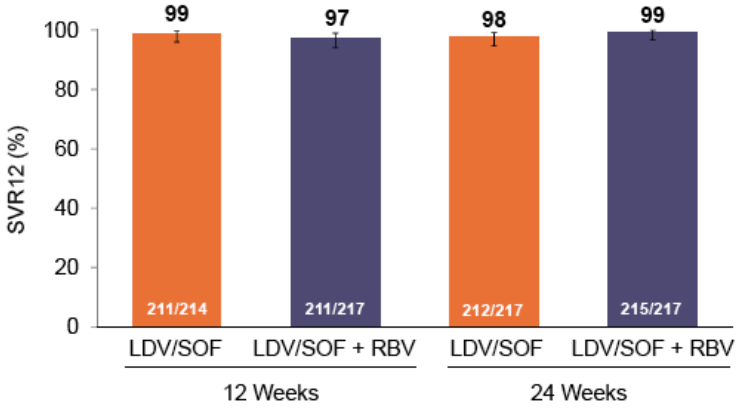
Sofosbuvir&Ledipasvir FDC: ION-1, 2, 3



Afdhal, et al. N Engl J Med. 2014 Apr 11 Epub (ION1)
Afdhal, et al. N Engl J Med. 2014; 370: 1483-93 (ION-2)
Kowdley, et al. N Engl J Med. 2014 Apr 10 Epub (ION-3)

Results: SVR12

GT 1 Treatment-Naïve (ION-1)

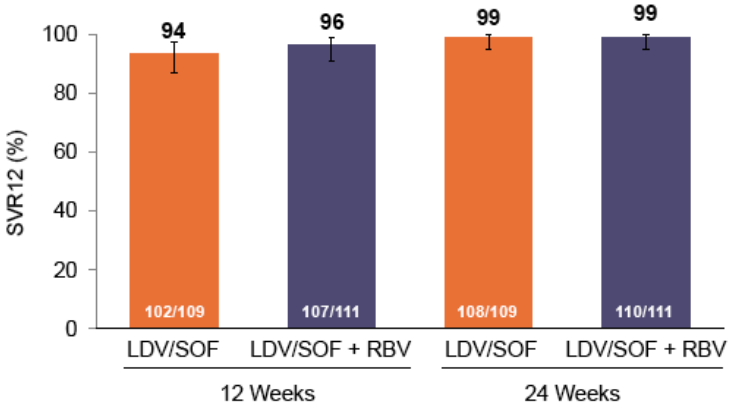


Error bars represent 95% confidence intervals.

Afdahl et al, NEJM 2014

Results: SVR12

GT 1 Treatment-Experienced (ION-2)

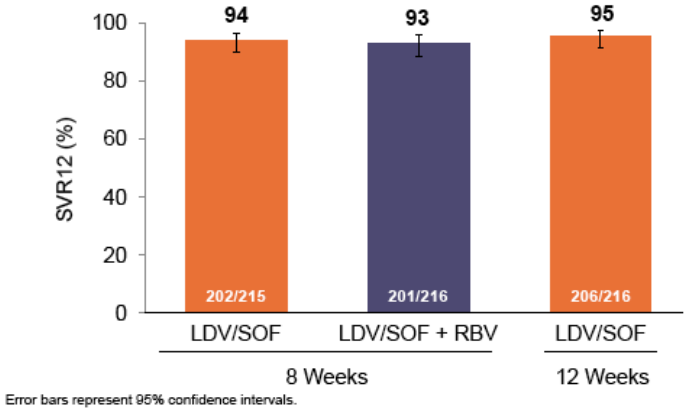


Error bars represent 95% confidence intervals.

Afdahl et al, NEJM 2014

Results: SVR12

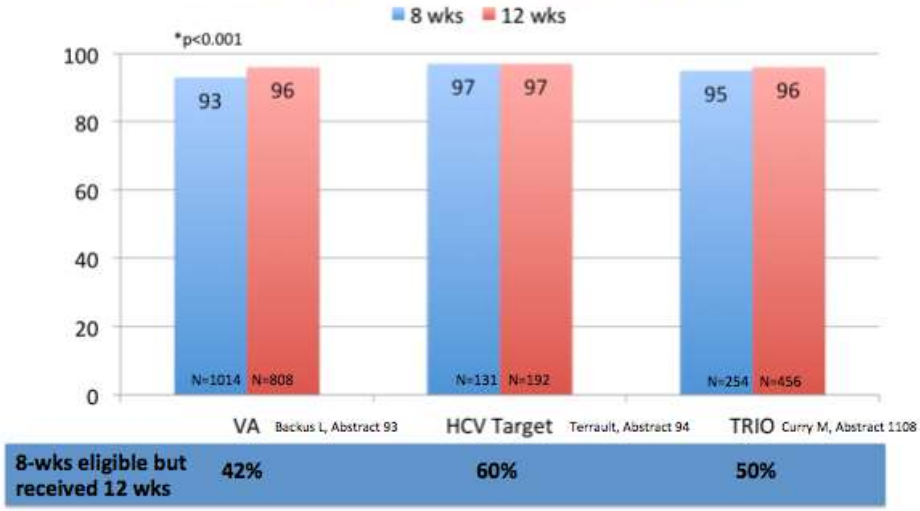
GT 1 Treatment-Naïve (ION-3)



Error bars represent 95% confidence intervals.

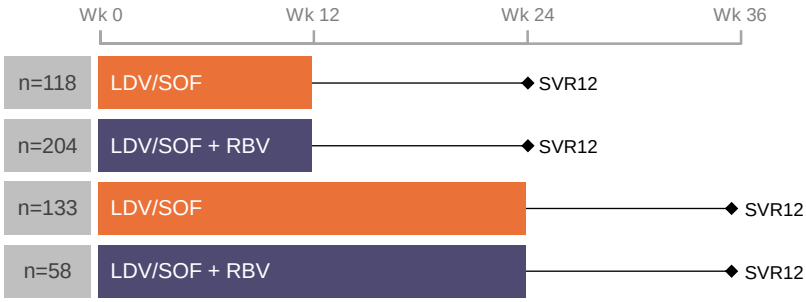
Kowdley et al, NEJM 2014

Real-World Experience with LDV-SOF of Genotype 1 Treatment Naïve, Non-Cirrhotics with HCV VL <6 million IU/mL



SOF/LPV: compensated cirrhosis

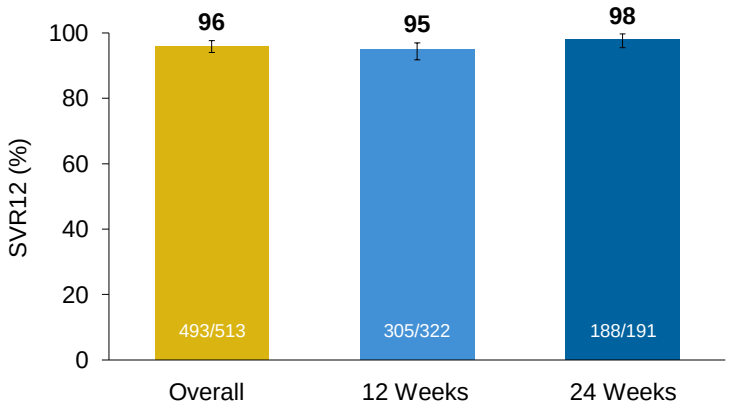
Reddy et al., Hepatology,2015 Apr 4. doi: 10.1002/hep.27826. [Epub].



- 513 patients with HCV GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS
- Primary efficacy endpoint: SVR12

SOF/LPV: compensated cirrhosis

Reddy et al., Hepatology,2015 Apr 4. doi: 10.1002/hep.27826. [Epub].



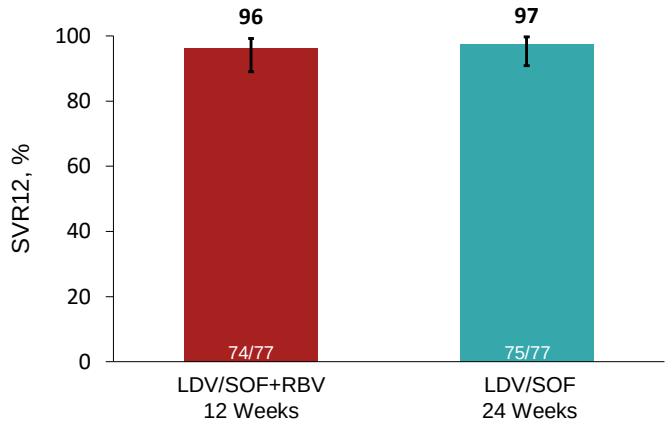
SOF/LPV: compensated cirrhosis

Reddy et al., Hepatology,2015 Apr 4. doi: 10.1002/hep.27826. [Epub].

		Total	Treatment Naïve	Treatment Experienced
Overall SVR12		96%	98%	95%
Duration	12 wk	95%	97%	94%
	24 wk	98%	99%	98%
Regimen	LDV/SOF	95%	96%	95%
	LDV/SOF + RBV	97%	99%	96%
Duration/ ± RBV	LDV/SOF 12 wk	92%	96%	90%
	LDV/SOF + RBV 12 wk	96%	98%	96%
	LDV/SOF 24 wk	98%	97%	98%
	LDV/SOF + RBV 24 wk	100%	100%	100%

SIRIUS: TE Cirrhotics (PI-failures)

Bourlière et al., Lancet Infect Dis, 2015 Apr;15(4):397-404.



TE cirrhotics had a similar response to LDV/SOF+RBV for 12 weeks and LDV/SOF for 24 weeks

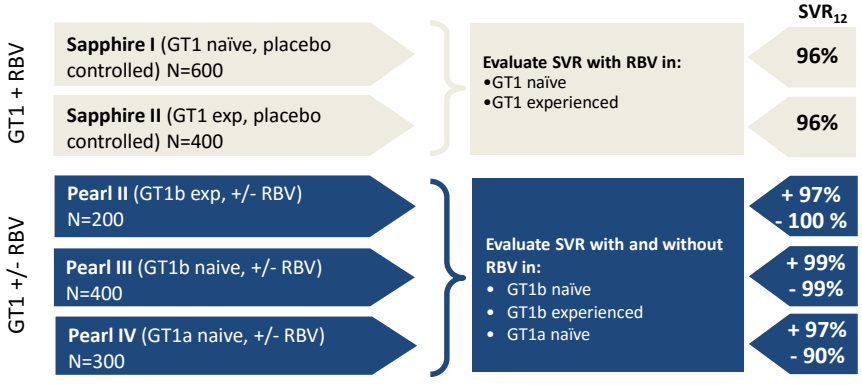
Error bars represent 95% confidence intervals.

IFN-free treatment of HCV-1

- Sofosbuvir/Ledipasvir FDC (+/-RBV)
- **Paritaprevir/r,Ombitasvir,Dasabuvir (+/-RBV)**
- Sofosbuvir+Simeprevir (+/-RBV)
- Sofosbuvir+Daclatasvir (+/-RBV)

3D-Combination (Phase II & III)

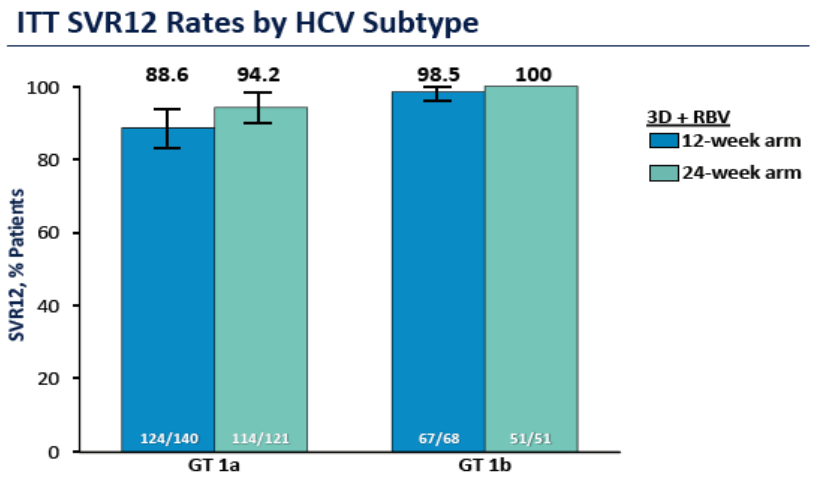
12 Weeks: Paritaprevir/r, Ombitasvir, Dasabuvir+/-RBV



Feld J, *et al. N Engl J Med* 2014; **370:**1594–1603;
Zeuzem S, *et al. N Engl J Med* 2014; **370:**1604–1614;
Andreone P, *et al. Gastroenterol* 2014; **147:**359–365;
Ferenci P, *et al. N Engl J Med* 2014; **370:**1983–1992.

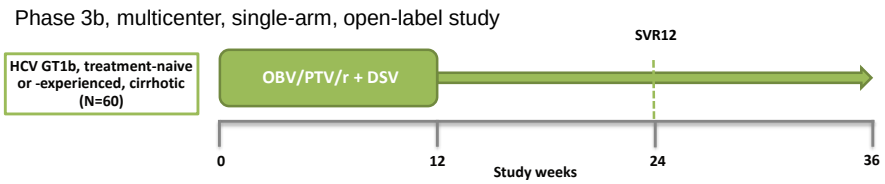
3D+RBV: Tourquise-II: Cirrhotics

Poordad et al., N Engl J Med, 2014 May 22;370(21):1973-82.



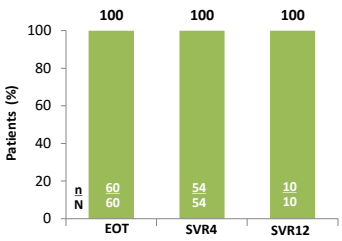
TURQUOISE-III: SAFETY AND EFFICACY OF 12-WEEK RIBAVIRIN-FREE TREATMENT FOR PATIENTS WITH HCV GENOTYPE 1B AND CIRRHOSIS

Phase 3b, multicenter, single-arm, open-label study



Study population, %	HCV GT1b cirrhosis OBV/PTV/r + DSV (N=60)
Male	62
PegIFN/RBV treatment-experienced	55
IL28B non-CC genotype	83
Platelet <90 x 10^9/L	22
Albumin <3.5 g/dL	17

Preliminary results



Safety

- Adverse events (AEs) were generally mild
- Only one patient (1.7%) experienced a serious AE and there were no premature treatment discontinuations.
- No clinically significant laboratory abnormalities were observed.

IFN-free treatment of HCV-1

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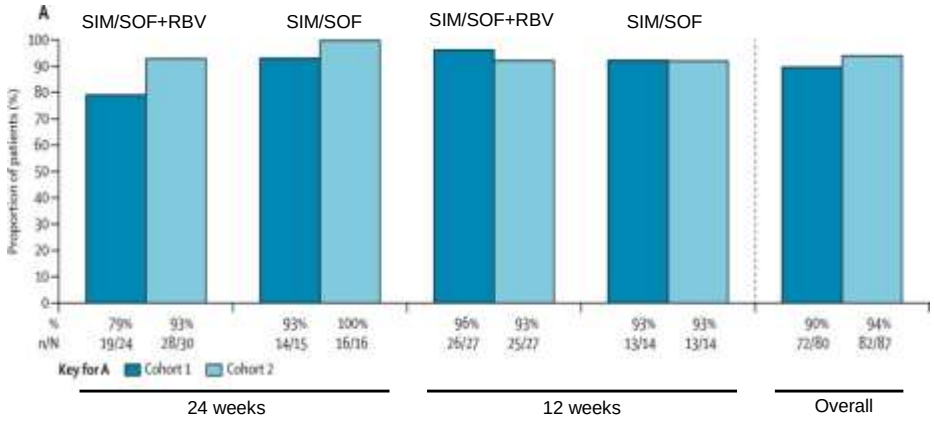
- Paritaprevir/r,Ombitasvir,Dasabuvir (+/-RBV)
- **Sofosbuvir+Simeprevir (+/-RBV)**
- Sofosbuvir+Daclatasvir (+/-RBV)

Cosmos: SOF+SIM±RBV

Lawitz et al., Lancet 2014 Nov 15;384(9956):1756-65.



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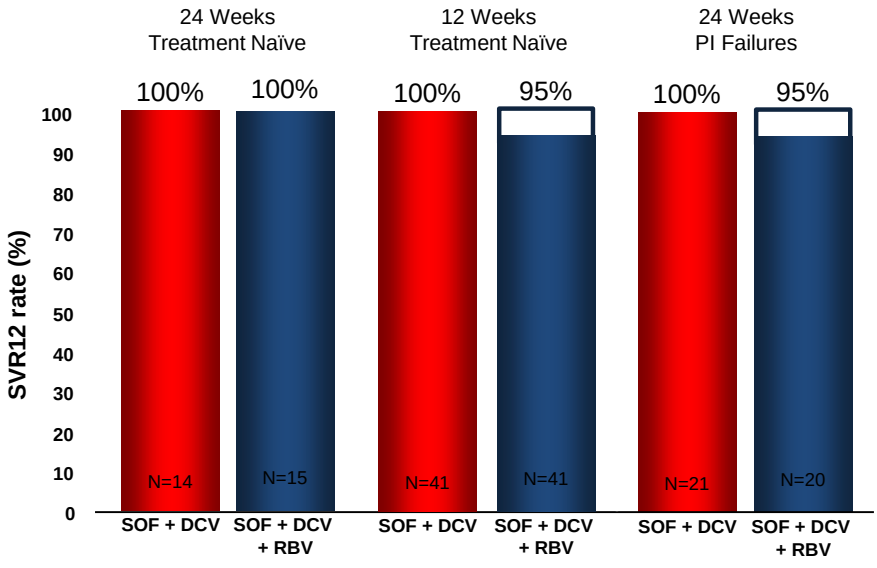
SOF+DCV±RBV



Sulkowski et al., N Engl J Med 2014;370:211-21

EASL: IFN-free treatment of HCV-2

Non-Cirrhotic HCV-2 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV

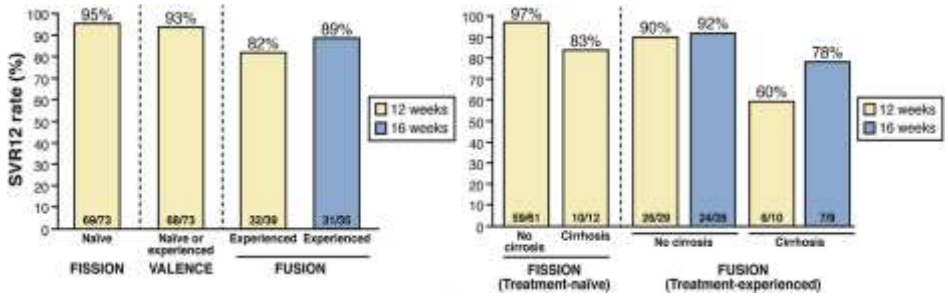
Cirrhotic HCV-2 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV

EASL Recommendations, 2015

SVR in HCV-genotype 2 patients

IFN-free therapy: FISSION, FUSION, VALENCE (SOF/RBV)



Pawlotsky JM. Gastroenterology 2014;146:1176-1192

EASL: IFN-free treatment of HCV-3

Non-Cirrhotic HCV-3 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV

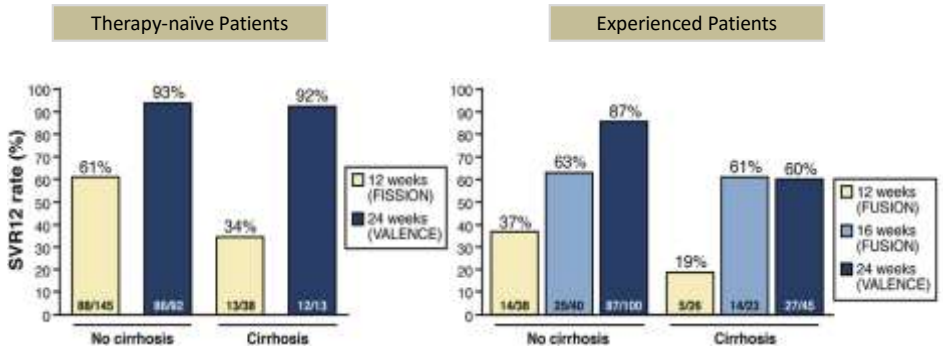
Cirrhotic HCV-3 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV

EASL Recommendations, 2015

IFN free: SVR in HCV-genotyp 3 patients

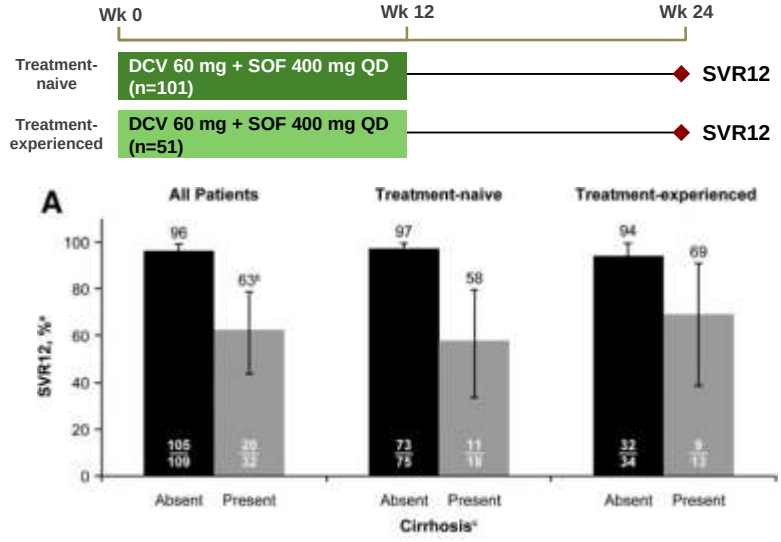
IFN-free Therapy: FISSION, FUSION, VALENCE (SOF/RBV)



Pawlotsky JM. Gastroenterology 2014;146:1176-1192

SOF/DAC in GT3 patients (ALLY-3)

Nelson et al., Hepatology, 2015 Apr;61(4):1127-35. doi: 10.1002/hep.27726.



EASL: IFN-free treatment of HCV-4

Non-Cirrhotic HCV-4 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV

Cirrhotic (CHILD A) HCV-4 patients:

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV

EASL Recommendations, 2015

IFN-free Combinations

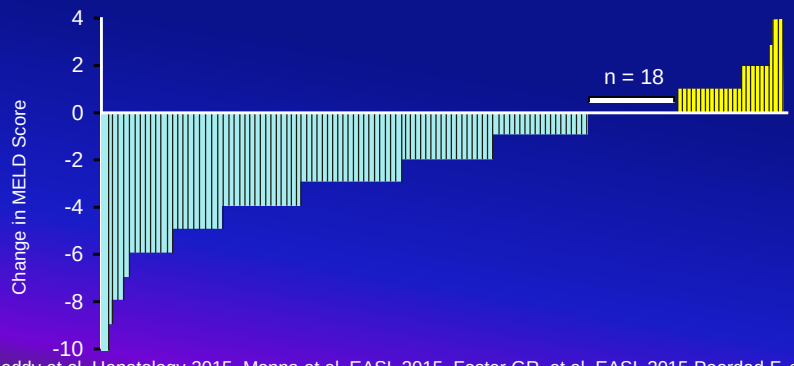
– **Sofosbuvir/Ribavirin** (GT2&3)
– **Sofosbuvir/Simeprevir±Ribavirin** (GT1/4)
– **Sofosbuvir/Daclatasvir±Ribavirin** (GT1-4)
– **Sofosbuvir/Ledipasvir FDC±Ribavirin** (GT1/4)
– **Paritaprevir/r,Ombitasvir,Dasabuvir±RBV** (GT1)
– **Paritaprevir/r,Ombitasvir±RBV** (GT4)

Special Populations

- HCV/HIV, HCV/HBV Co-infection
- Renal Impairment
  - 3D-Combination
  - SOF: CrCl>30ml/min, Toxicity of RBV
- Non-liver Organ transplantation
- Liver transplantation
- Decompensated Cirrhosis
- DDI´s

Decompensated Cirrhosis (Child B/C)

- SOLAR 1: SVR: 86-90%
- SOLAR 2: SVR: 72-96%
- GB CUP: SVR: 71-80%
- ALLY-1: 82%
- C-SALT (CPB): 90%
- ASTRAL-4: 83-94%



Reddy et al, Hepatology 2015, Manns et al, EASL 2015, Foster GR, et al. EASL 2015 Poordad F, et al. EASL 2015. Abstract LO8, Jacobson et al., 2015 EASL,

TABLE 1. Use of DAAs in Patients With Advanced Liver Disease and Immunosuppressive Drugs

Drug	CTP B	CTP C	CsA	TAC
SOF	NDA	NDA	NDA	NDA
SMV	AUC↑ 2.4-fold NR	AUC↑ 5.2-fold NR	SMV-AUC↑ 5.8-fold NR	NDA
Paritaprevir/r	AUC↑ 62% NR	AUC↑ 9209% NR	CsA-AUC↑ 5.8-fold Adjust CsA dose	TAC-AUC↑ 58-fold Adjust tacrolimus dose
GZV (Yeh et al.[7] [2015])	AUC↑ 5-fold Decrease GZV dose	No data	GZV-AUC↑ 15-fold NR	NDA
Daclatasvir	NDA	NDA	NDA	NDA
Ledipasvir	NDA	NDA	NDA	NDA
Ombitasvir	NDA	NDA	NDA	NDA
Elbasvir	NDA	NDA	No data	No data
Dasabuvir	NDA	NDA	NDA	NDA

NOTE: Modified from Gambato et al.[1] (2014).

	SIM	DCV	SOF	SOF/ LDV	3D
Azathioprine	•	•	•	•	•
Cyclosporine	•	•	•	•	•
Etanercept	•	•	•	•	•
Everolimus	•	•	•	•	•
Mycophenolate	•	•	•	•	•
Sirolimus	•	•	•	•	•
Tacrolimus	•	•	•	•	•

EASL
European Association for the Study of the Liver

Drug-Drug Interactions

Amiodarone

Sofosbuvir/Ledipasvir –
Sofosbuvir/Daclatasvir

www.hep-druginteractions.org

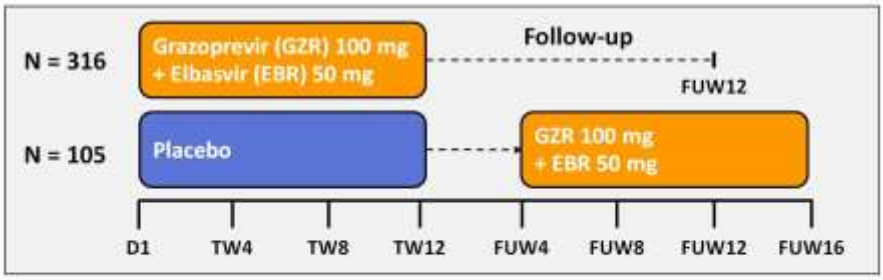
Don´t trust your memory!

Learning Objectives

- **Review key information on chronic hepatitis C**
  - Hepatitis C Virus
  - Natural history of chronic hepatitis C
  - Goal and endpoints of treatment
- **Direct Acting Antivirals (IFN-free treatment)**
  - Mechanism of action
  - Currently available IFN-free all-oral regimen
- **Current Treatment with DAA´s**
- **Upcoming new treatment regimen**

Grazoprevir/Elbasvir (naïve pts)

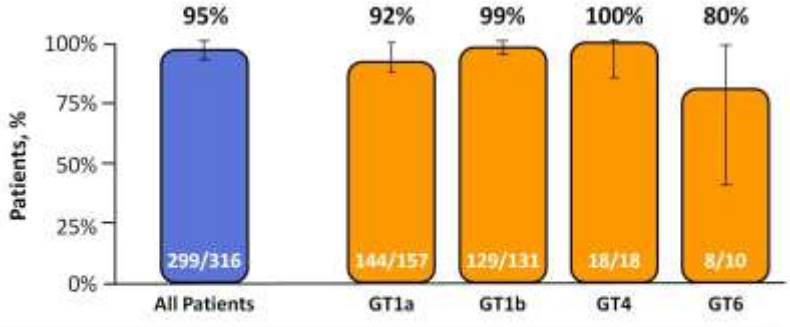
Ann Intern Med. 2015 Jul 7;163(1):1-13. doi: 10.7326/M15-0785.



- Phase 3, randomized, placebo-controlled trial
- GZR/EBR fixed-dose combination tablet given once daily, without ribavirin, for 12 weeks
- After a 4-week follow-up period, placebo recipients were unblinded and received open-label GZR/EBR
- Stratification by cirrhosis and HCV geno/subtype

Grazoprevir/Elbasvir (naïve pts)

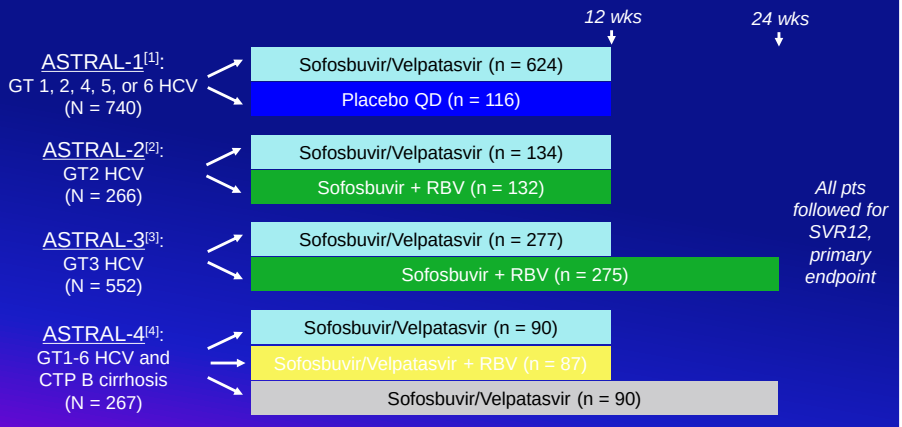
Ann Intern Med. 2015 Jul 7;163(1):1-13. doi: 10.7326/M15-0785.



Non-virologic failure	4	3	1	0	0
Breakthrough	1	1	0	0	0
Relapse	12	9	1	0	2

ASTRAL: Sofosbuvir/Velpatasvir

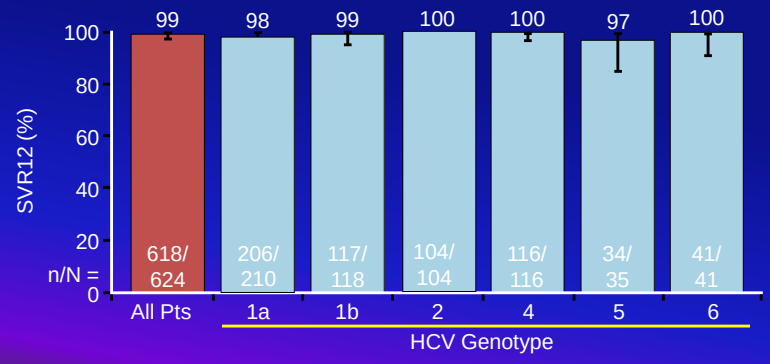
- Multicenter, randomized phase III trials in Tx-naive and Tx-experienced pts



Foster et al., N Engl J Med., 2015 Dec 31;373(27): 2608-17
Feld et al., N Engl J Med. 2015 Dec 31;373(27):2599-607
Curry et al., N Engl J Med. 2015 Dec 31;373(27):2618-28

ASTRAL-1: Sofosbuvir/Velpatasvir

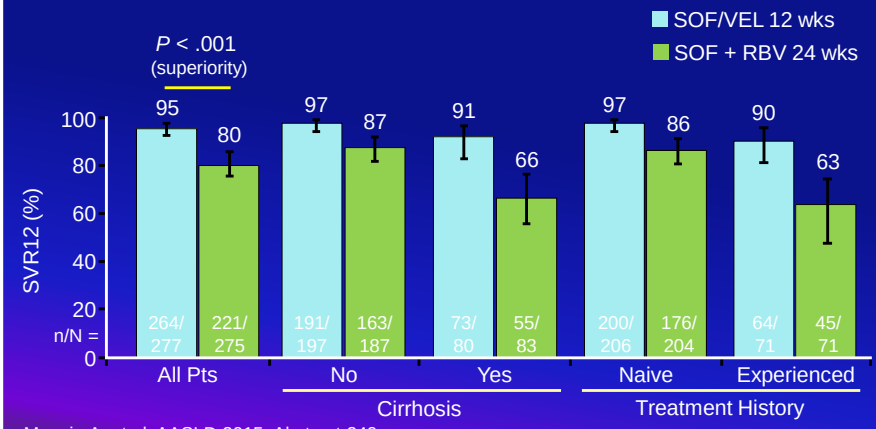
- Double-blind, placebo-controlled trial
  - All pts with GT5 HCV allocated to active Tx because few pts in this group (n = 35)
  - Key baseline characteristics: cirrhosis 19%; Tx exp'd 32%; BL NS5A RAVs 42%
- No impact of cirrhosis, Tx experience, BL NS5A RAVs on SVR rates



Feld JJ, et al. N Engl J Med. 2015.

ASTRAL-3: SOF/VEL in GT3 Pts

- SVR12 rate numerically lower with vs without BL NS5A RAVs (88% vs 97%)
- Safety profile similar to ASTRAL-1



Mangia A, et al. AASLD 2015. Abstract 249.
Foster GR, et al. N Engl J Med. 2015.

Conclusion

- True paradigm change in HCV treatment!
- High efficacy of IFN-free treatment regimens.
- Excellent safety profile.
- Treatment of difficult-to-treat patient groups:
  Patients with advanced/decompensated liver disease, liver transplantation, Co-infection..
- Real-life data show similar results to Phase III.
- GT3 remains a challenge with current regimen

???? Questions ????

Hepatitis C Virus infection can be cured permanently by a short course of an all-oral IFN-free treatment regimen.

YES! **or** NO!

???? Questions ????

Daclatasvir (DCV) is an Inhibitor of the Hepatitis C Virus (HCV) NS3a-Protein.

YES! **or** **NO!**

???? Questions ????

Treatment of Hepatitis C Virus Genotype 3 (HCV-3a) with Simeprevir/Dasabuvir yields high SVR rates.

YES! **or** NO!

"Wonder pills", breakthroughs and continuing challenges – HIV and Hepatitis C antiviral treatments revisited

Harald Hofer

Thank you for your attention!

MEDIZINISCHE UNIVERSITÄT WIEN

Klinische Abteilung für Gastroenterologie und Hepatologie
Univ.Klinik für Innere Medizin III

AASLD Guidance on HCV/HIV DDIs

	SMV + SOF	SOF	LDV/SOF	DCV + SOF	OMV/PTV/RTV + DSV
Atazanavir + RTV	X	√	≈	≈	√
Darunavir + RTV	X	√	≈	√	X
Lopinavir/RTV	X	√	≈	√	X
Tipranavir + RTV	X	X	X	X	X
Efavirenz	X	√	≈	≈	X
Rilpivirine	√	√	√	√	X
Etravirine	≈	√	√	≈	≈
Raltegravir	√	√	√	√	√
Elvitegravir + COBI	X	≈	≈	≈	≈
Dolutegravir	√	√	√	√	√
Maraviroc	√	√	√	√	≈
Tenofovir DF	√	√	≈ nephrotoxicity	√	√

- No clinically significant interaction expected
- Potential interaction may require adjustment to dosage, timing of administration, or monitoring
- Do not coadminister

AASLD/IDSA. HCV guidelines. December 2015.