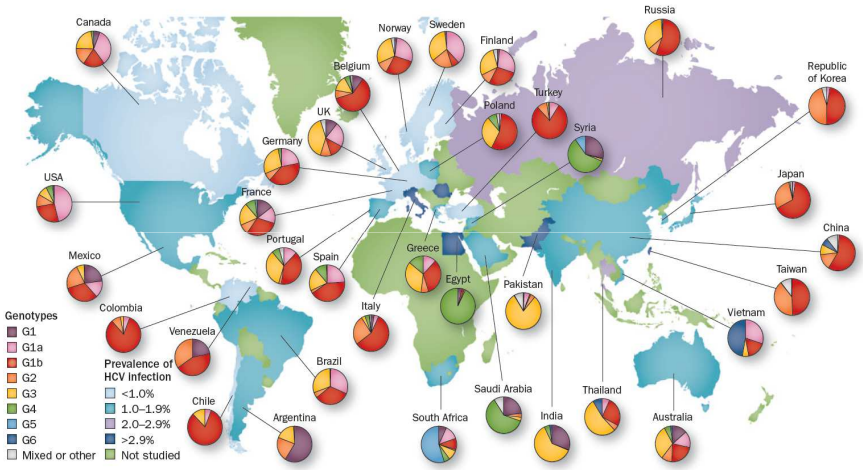
Hépatite C chronique: quoi de neuf?

Colloque MPR
18 juin 2014

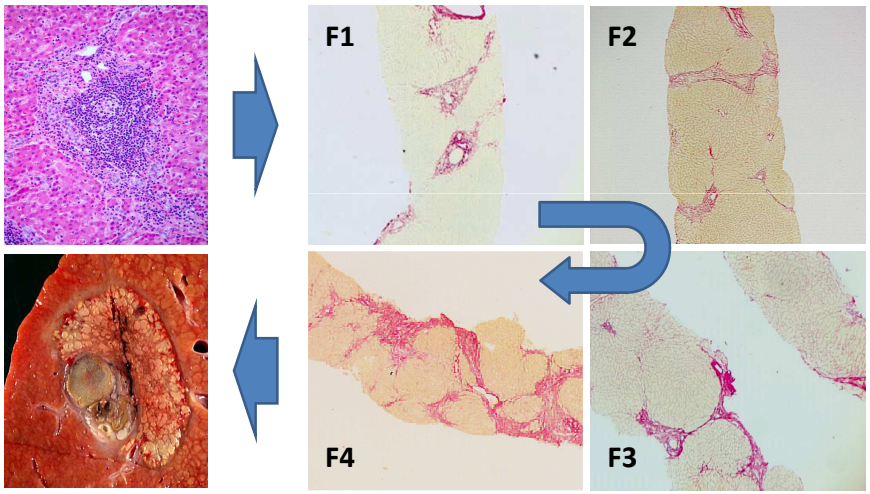
Francesco Negro
Hôpitaux Universitaires de Genève

HCV infects >185 million people worldwide

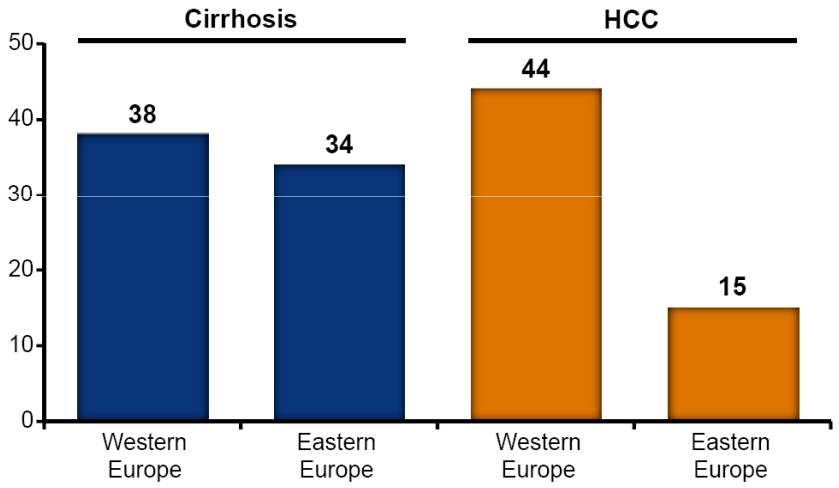


HAJARIZADEH *et al*. Nat Rev Gastroenterol Hepatol 2013;10:553-562
NEGRO and ALBERTI. Liver Int 2011;31 Suppl 2:1-3
HANAFIAH *et al*. Hepatology 2013;57:1333-1342

Hepatitis C: a chronic inflammatory liver disease leading to cirrhosis and HCC



Proportion of cirrhosis or HCC cases attributable to HCV (Europe)

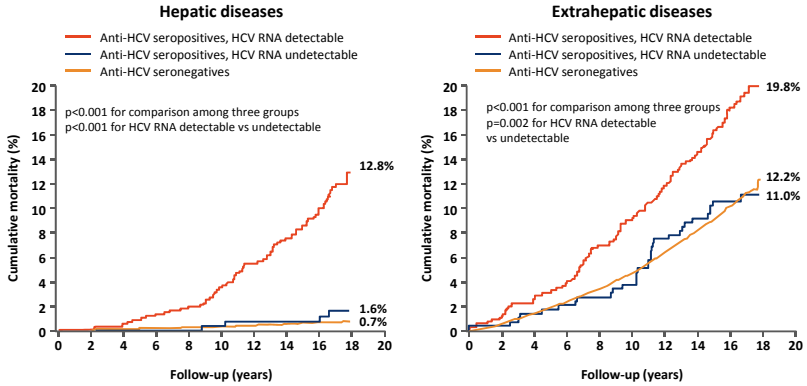


PERZ et al, *J Hepatol* 2006;45:529-38

Chronic HCV increases mortality from hepatic and non-hepatic diseases

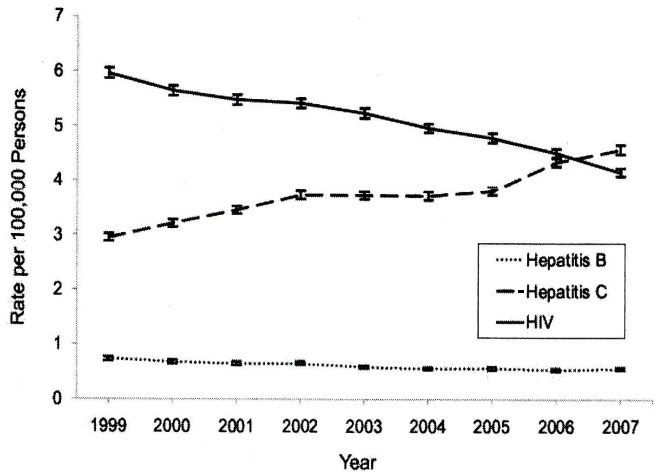
The REVEAL HCV Cohort Study

- 23 820 adults in Taiwan prospectively followed since 1991/2
- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA



LEE et al, *J Infect Dis* 2012;206:469–477

The growing burden of mortality associated with viral hepatitis in the US, 1999-2007 (CDC)



LY et al, *Ann Intern Med* 2012;156:271-8

How many die of …. ?

	Deaths in 2010
HCV	57,000
HBV	31,000
HIV	8,000

Global Burden Disease Study 2010 (COWIE *et al,* EASL 2014, oral presentation #86)

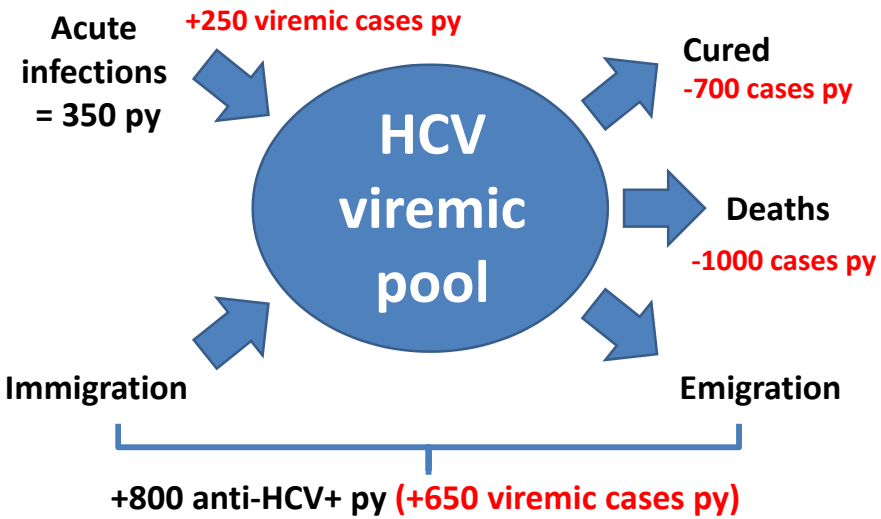
Modeling the HCV epidemic in Switzerland

Model inputs and 2013 estimates (BRUGGMANN *et al,* EASL 2014, poster 1285)

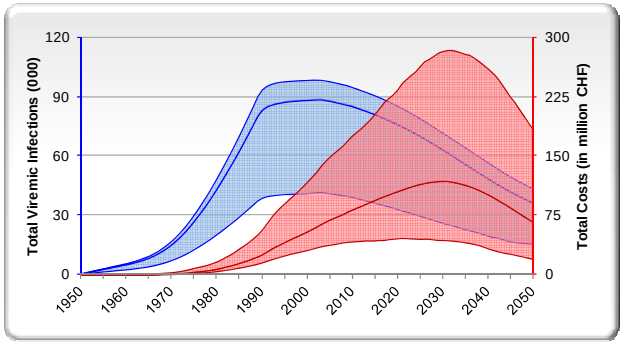
	Historical	Year	2013 (Est.)
HCV Infections	110,000 (57,000 - 128,000)	1998	104,000
Anti-HCV Prevalence	1.6% (0.8% - 1.8%)		1.3%
Total Viremic Infections	88,000 (45,400 - 102,000)	1998	82,700
Viremic Prevalence	1.2% (0.6% - 1.4%)		1.0%
Viremic Rate	79.7%		79.7%
HCV Diagnosed (Viremic)	32,900	2012	32,600
Viremic Diagnosis Rate	37.4%		39.4%
Annual Newly Diagnosed	1,050	2012	1,050
New Infections			
New Infection Rate (per 100K)			13
Treated			
Number Treated	1,100	2011	1,100
Annual Treatment Rate	1.3%		1.3%

SAGMEISTER et al, Eur J Gastroenterol Hepatol 2002; 14: 25-34
Swiss Federal Office of Public Health, http://www.bag.admin.ch/ (accessed June 3, 2013)
ARMSTRONG et al, Ann Intern Med 2006;144:705-14
IMS Health. IMS Health MIDAS Data. 2013

The input due to immigration is relevant and underestimated: the Swiss situation



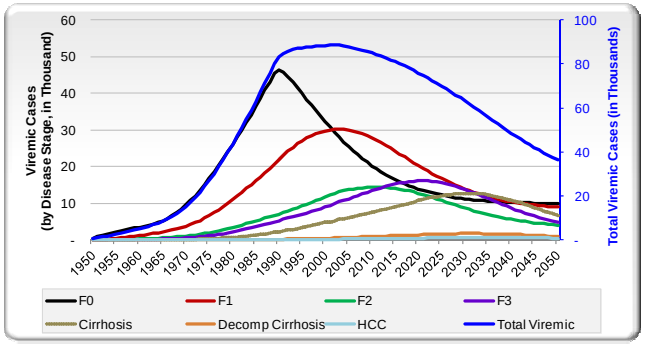
In Switzerland, HCV prevalence peaked in 2003, but HCV-associated healthcare costs (excluding treatment costs) will peak in 2030



	2013	2030
Viremic cases	82,700 (37,200 – 93,400)	63,200 (25,900 – 71,800)
HCV-related costs (excluding treatment costs)	89.6M (43.3M – 191.1M)	118.7M (43.9M – 282.9M)

BRUGGMANN *et al*, EASL 2014, poster 1285

As the infected population ages, the number of advanced liver disease cases increases

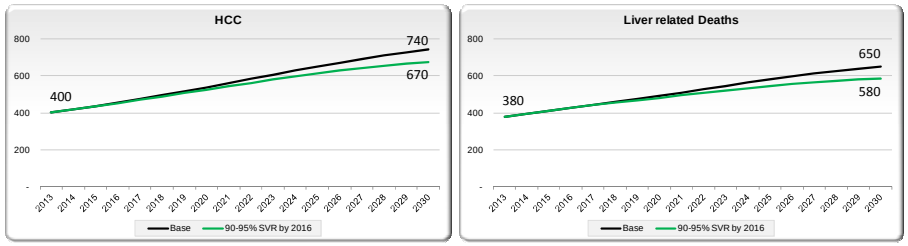


	2030 *
Decompensated cirrhosis	1,800 (+55%)
HCC	760 (+85%)
HCV liver-related deaths	650 (+70%)

*Data compared to 2013, assuming constant treatment uptake

BRUGGMANN *et al*, EASL 2014, poster 1285

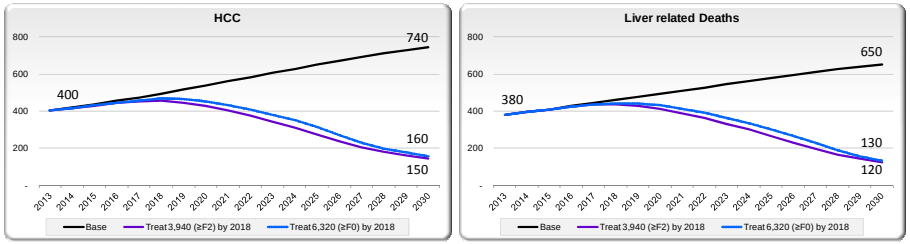
Increasing SVR to 90-95% by 2016 will decrease HCV-related HCC cases and liver-related mortality by 10% in 2030



- Increasing SVR while maintaining an annual treatment uptake of 1,100 patients will decrease HCC and liver-related mortality by 10% by 2030
- Total viremic infections will decrease by 7% vs base case

BRUGGMANN *et al*, EASL 2014, poster 1285

Increasing SVR to 90-95% by 2016 and treating 3,940 patients by 2018 will decrease HCV liver-related mortality by 80%



- To reduce HCC and liver-related mortality by 80% by 2030, 3,940 patients will have to be treated annually (≥F2) by 2018
- The proposed scenario would require the diagnosis of 4,740 new viremic infections annually by 2020 (as compared to 1,050 in 2013)
- Expanding treatment access to ≥F0 patients would require treatment of 6,320 annually by 2018 to achieve the same reduction in HCC cases and liver-related mortality
- An estimated CHF 735 M and CHF 742 M in healthcare cost savings (excluding scenario and treatment costs) was projected for the scenario treating 3,940 ≥ F2 patients and 6,320 ≥ F0 patients, respectively

BRUGGMANN *et al*, EASL 2014, poster 1285

Indications au traitement (EASL 2014)

- Tous les patients atteint d'une hépatite C (jamais traités ou ayant essuyé un échec thérapeutique) devraient être évalués pour un traitement antiviral
- Priorité: fibrose avancée (Metavir F3 ou F4)
- Le traitement est *justifié* lors d'un score Metavir F2
- L'indication au traitement et le moment de son début doivent être personnalisés si le score Metavir est F0-F1

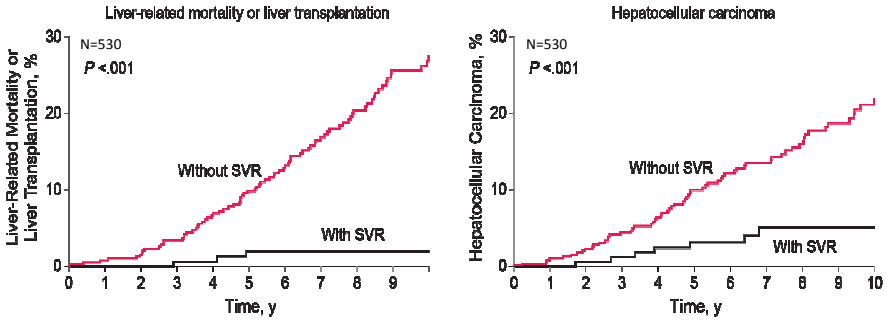
But du traitement

- Le but du traitement est l'**éradication du HCV**, afin d'arrêter l'évolution vers une cirrhose, le développement d'une insuffisance hépatique, d'un CHC, et de réduire la mortalité liée au foie
- Le patient est considéré comme étant guéri lorsque son HCV RNA est négatif 12-24 semaines après la fin du traitement (réponse virologique soutenue = RVS)
- Chez 99% des cas, la RVS est définitive, et est associée à une amélioration du pronostic

Like any dogma, liver fibrosis is reversible

D'AMBROSIO et al, *Hepatology* 2012;56:532-43

SVR is associated with a reduction in liver-related mortality and risk of HCC



VAN DER MEER et al, *JAMA* 2012;308:2584-2593

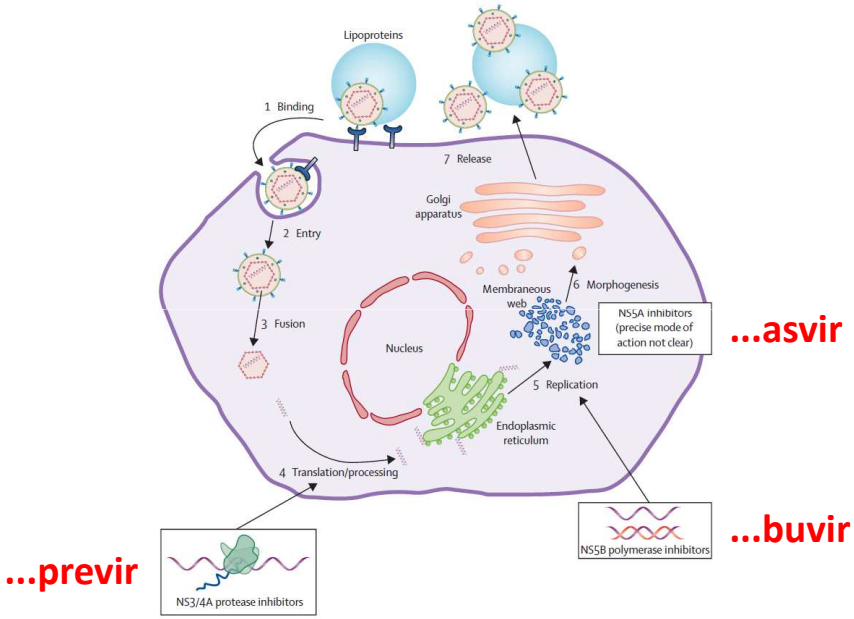
1986 Interferon-α

1998 Interferon-α + Ribavirin

2001 Pegylated Interferon-α + Ribavirin

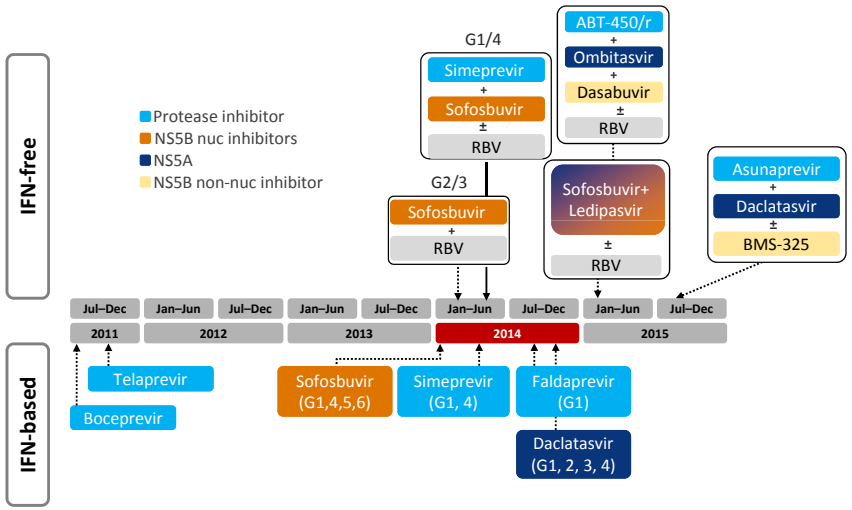
2011 Pegylated Interferon-α + Ribavirin + First generation protease inhibitors

2014 Interferon-α-free regimens

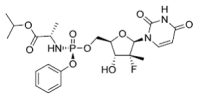


CORNBERG & MANNS, Lancet Infect Dis 2013;13:378-9

Direct-acting antivirals against HCV: a rich pipeline

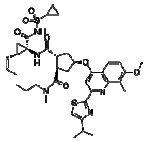


2014



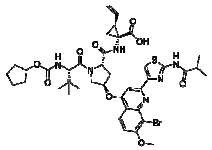
Sofosbuvir (Sovaldi™)

Nucleotide polymerase inhibitor
400 mg qd, all genotypes
High barrier to resistance



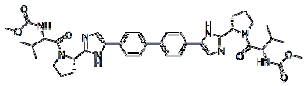
Simeprevir (Olysio™)

NS3/NS4A serine protease inhibitor
150 mg qd, genotypes 1 and 4
Low barrier to resistance



Faldaprevir

NS3/NS4A serine protease inhibitor
120-240 mg qd, genotypes 1, 2, 4, 5 and 6
Low barrier to resistance

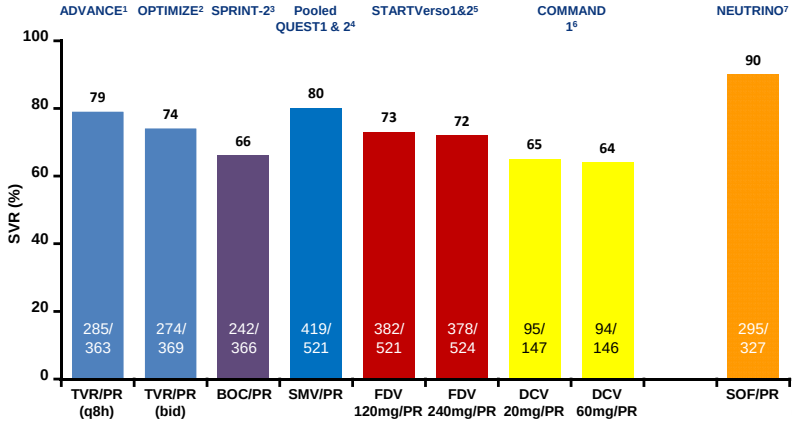


Daclatasvir (Daklinza™)

NS5A inhibitor
60 mg qd, all genotypes
Low barrier to resistance

HCV-1, jamais traités

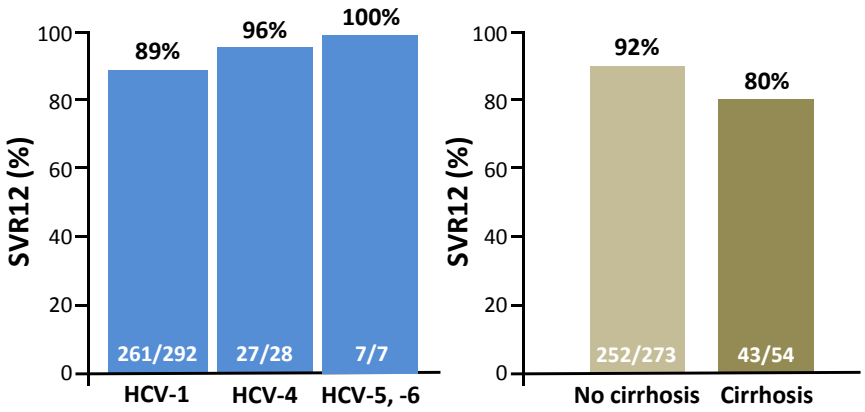
IFN-based options for HCV genotype 1 treatment-naïve patients



1. Telaprevir EU SmPC; 2. Buti M, Gastroenterology 2014;146:744–53
3. Boceprevir SmPC; 4. Jacobson I, et al. AASLD 2013. Poster 1122
5. Jensen DM, et al. AASLD 2013. Abstract 1088
6. Hézode, et al. AASLD 2012: Abstract 755; 7. Lawitz E, et al. N Engl J Med 2013;368:1878–87

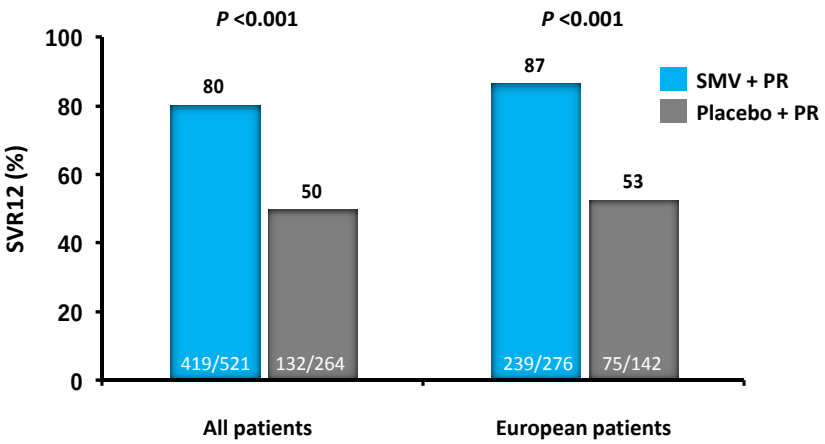
P + R + sofosbuvir (NEUTRINO study)

(HCV genotypes 1, 4-6; treatment-naive; 12-week triple treatment flat duration)



LAWITZ *et al,* N Eng J Med 2013

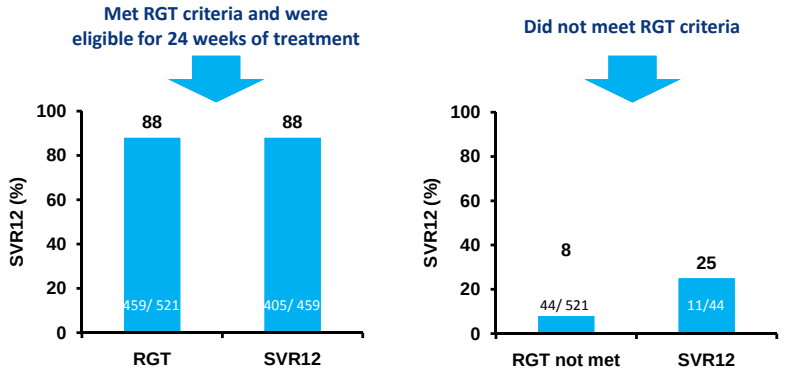
Pooled QUEST 1 & 2: SVR12 in all *vs* European patients



FOSTER et al, EASL 2014, Poster P1127

SMV + PR: pooled QUEST 1&2

Response-guided treatment*:
Early extended virological response allows a 24-week course of treatment

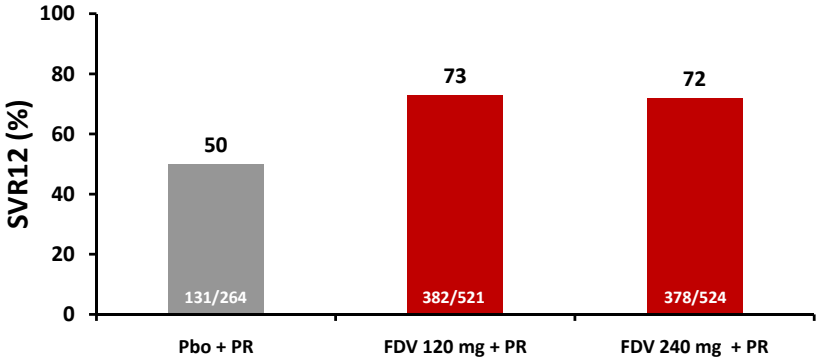


*Patients were eligible to stop therapy at Week 24 if HCV RNA <25 IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Week 12

JACOBSON *et al*, AASLD 2013, Poster 1122

STARTVerso1&2

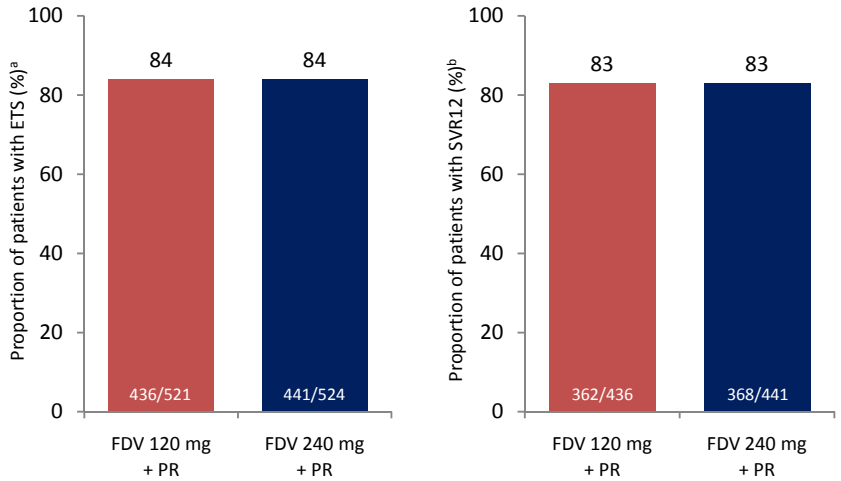
SVR12 according to faldaprevir dose



JENSEN *et al*, AASLD 2013, Abstract 1088

STARTVerso1&2

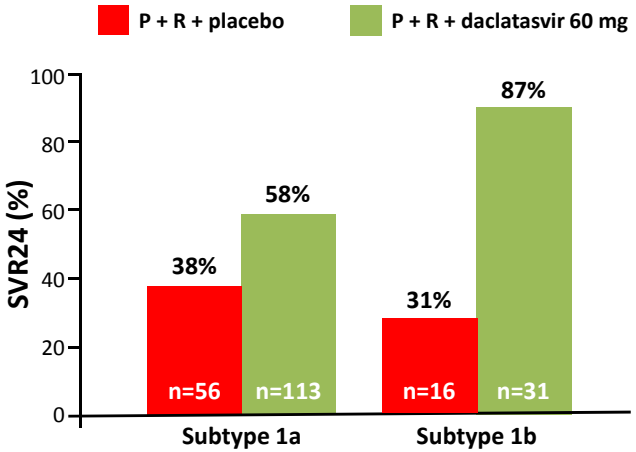
Patients who achieve ETS* can be treated 24 weeks



*ETS: HCV RNA <25 IU/mL (detected or undetected) at week 4 and <25 IU/mL (undetected) at week 8

JENSEN *et al*, AASLD 2013, Abstract 1088

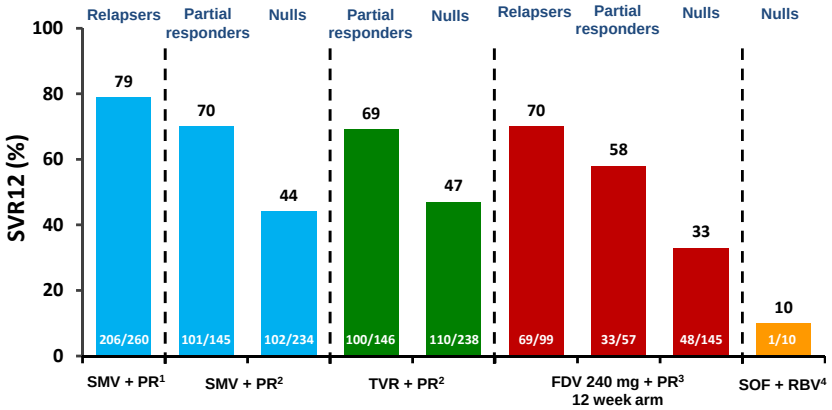
P + R + daclatasvir
(treatment-naïve HCV-1: COMMAND-1, phase 2b study)



HEZODE *et al,* Hepatology 2012;56(suppl):553A

HCV-1, échecs thérapeutiques

Overview of DAA + PR in treatment-experienced patients



1. Forns X et al Gastroenterology 2014;146:1669–1679
2. Reddy KR, et al. APASL 2014. Oral presentation
3. Jacobson I, et al. AASLD 2013. Abstract 1100
4. Gane EJ, et al. AASLD 2013. Abstract 73

Benefits of the *second wave* PIs

Regimen	Trial	HCV genotype/ population	N	F4 (%)	Grade 3–4 AE (%)	SAEs	Disc. due to AEs (%)	Notable AEs*
TVR + PR[1]	OPTIMIZE	G1 TN	740	14	40	9%	17	Nausea, pruritus, rash and anaemia
BOC + PR[2]	SPRINT-2	G1 TN	1097	5	–	11%	12	Increased anaemia and dysgeusia
SMV + PR[3]	Pooled analysis Phase 2b/3	G1 TN & TE	924	11	31	5.5%	4	Increased bilirubin, rash, photosensitivity
FDV + PR[4]	STARTVerso	G1 TN	524	10	–	8%	3	Increased bilirubin, rash, GI

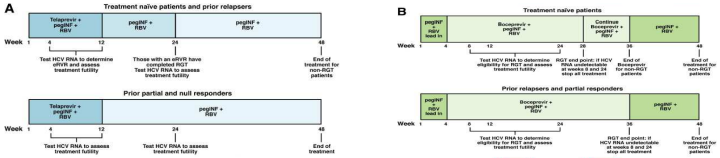
Cross comparison of studies cannot be carried out
*Occurring more frequently vs PR alone

1. Buti. Gastroenterology 2014;146:744–53. 2. Poordad et al. N Engl J Med 2011;364:1195–206. 3. Manns et al. Hep DART 2013. Poster 57. 4. Jensen et al. AASLD 2013. Poster 1088

Telaprevir and boceprevir led to increased efficacy in HCV genotype 1 (63-75% SVR)

- Increased complexity, safety issues, pill burden
- Still associated with IFN-α and RBV

For physicians: lead-in, response-guided therapy



For patients:

Pill burden

BOC = 12/day
RBV = 4-7/day

TVR = 6/day
RBV = 4-7/day

Food requirement

CUPIC: SVR12 and risk of occurrence of severe complications

		Platelet count ≤ 100 G/L	Platelet count > 100 G/L
Albumin < 35 g/L	n Complications, n (%) SVR12, n (%)	**37** **19 (51.4%)** **10 (27.0%)**	**31** **5 (16.1%)** **9 (29.0%)**
Albumin ≥ 35 g/L	n Complications, n (%) SVR12, n (%)	**74** **9 (12.2%)** **27 (36.5%)**	**305** **19 (6.2%)** **168 (54.9%)**

HEZODE *et al*, J Hepatol 2013;59:434-441
FONTAINE *et al*, AFEF 2013

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.

PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

CARE
COMING SOON: In Whom and When to Initiate Treatment
INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT
RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

Read more>>

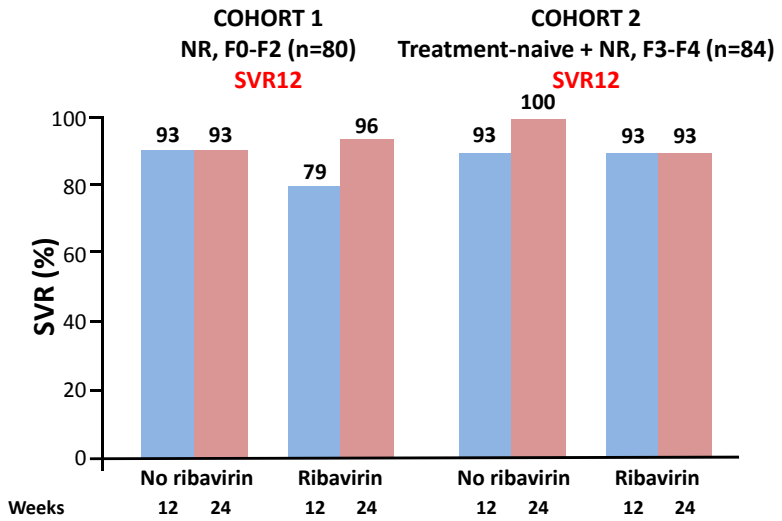
Methods Table 2. Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Recommendations are based on scientific evidence and expert opinion.

www.hcvguidelines.org (accessed April 6, 2014)

HCV-1, intolérants à l'IFN ou si l'IFN est contre-indiqué

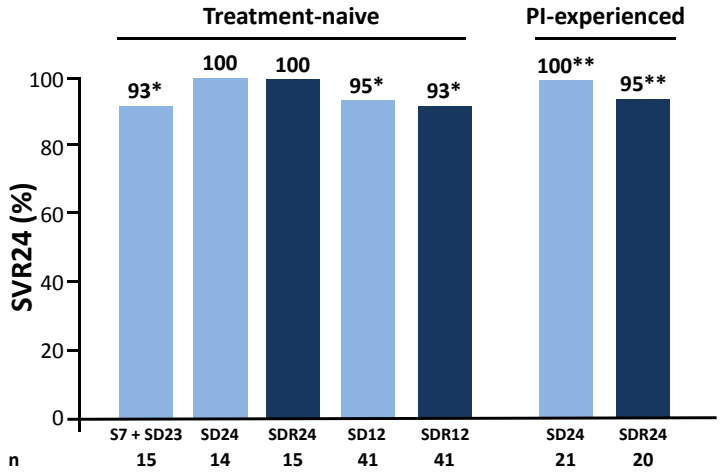
SMV + SOF ± RBV in treatment-naive and prior null responders, HCV-1 (COSMOS phase II study)



SULKOWSKI *et al*, EASL 2014; LAWITZ *et al*, EASL 2014

Sofosbuvir + Daclatasvir ± Ribavirin in HCV-1

(126 naive + 41 PI-experienced; no cirrhotics; AI444040 phase II study)

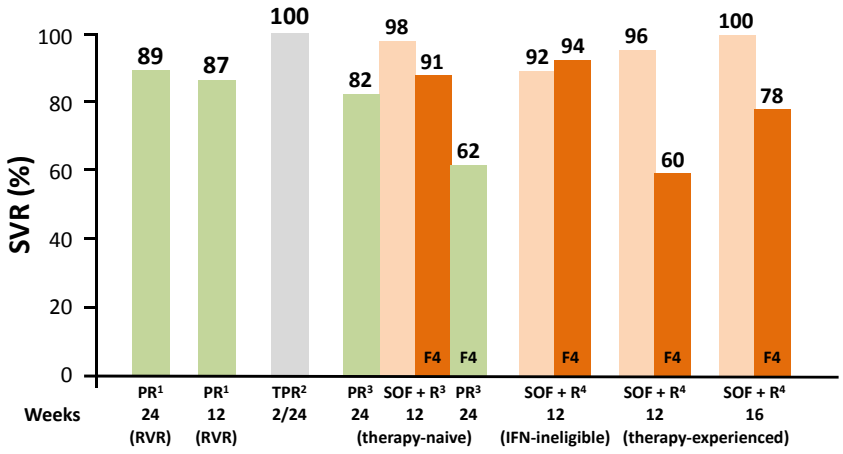


*Considering 4 SVR36 and 1 reinfection, true SVR = 99% (125/126)
**SVR12 available only; considering 1 SVR24, true SVR = 100%

SULKOWSKI *et al*, N Engl J Med 2014 Jan 16 [ePub ahead of print]

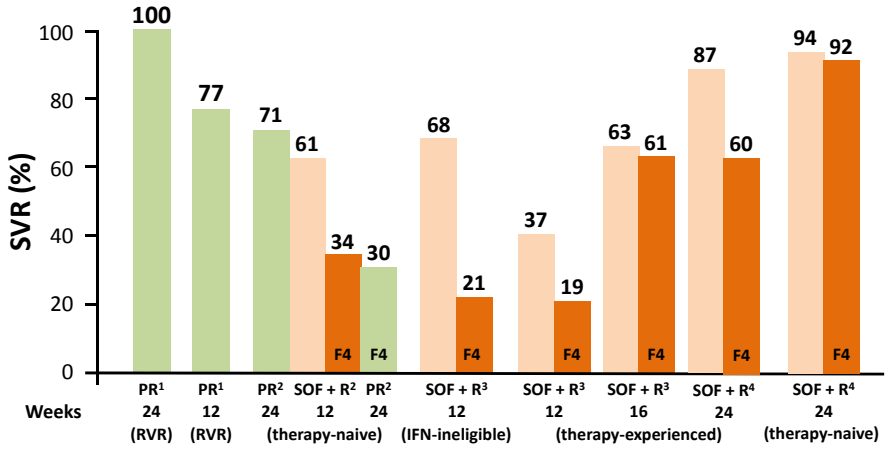
Les génotypes 2 à 4

2014: the different options for HCV-2



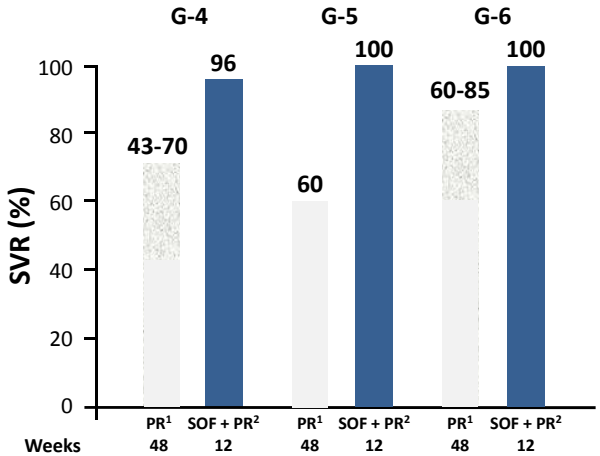
1. MANGIA *et al*, N Engl J Med 2005;352:2609-17; 2. FOSTER *et al*, Gastroenterology 2011;141:881-9
3. LAWITZ *et al*, N Engl J Med 2013;368:1878-87; 4. JACOBSON *et al*, N Engl J Med 2013;368:1867-77

2014: the different options for HCV-3



1. MANGIA *et al*, N Engl J Med 2005;352:2609-17; 2. LAWITZ *et al*, N Engl J Med 2013;368:1878-87
3. JACOBSON *et al*, N Engl J Med 2013;368:1867-77; 4. ZEUZEM *et al*, N Engl J Med 2014

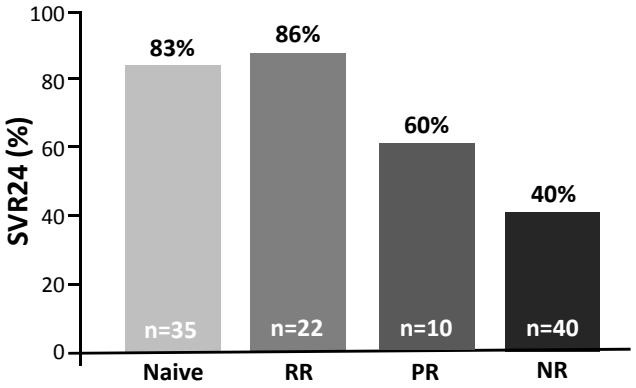
In 2014, all SOF-based options for treatment-naive HCV-4 to 6 will still contain PR



1. ANTAKI *et al*, Liver Int 2010;30:342-55
2. LAWITZ *et al*, N Engl J Med 2013;368:1878-87

P + R + Simeprevir

(treatment-naive or -experienced HCV-4: Phase III RESTORE trial)



MORENO *et al*, EASL 2014, late breaking poster 1319

2015

IFN-free combination options*

	NI	PI	NS5A	NNI	RBV	Genotype
Nucleotide analogue-based						
Gilead	Sofosbuvir	GS-9451	Ledipasvir		±	1-4
Roche	Mericitabine	Danoprevir/r		Setrobuvir	±	1, 4
Nucleos(t)ide-free triple combo						
AbbVie		ABT-450/r	ABT-267	ABT-333	±	1
BMS		Asunaprevir	Daclatasvir	BMS791325	±	1, 4
Janssen/GSK		Simeprevir	GSK2336805	TMC647055	±	1
Nucleos(t)ide-free second generation double combo						
Merck		MK-5172	MK-8742		±	1, 2, 4-6
Achillion		ACH-2684	ACH-3102		±	1
Off-label options						
(na)	Sofosbuvir	Simeprevir			-	1
(na)	Sofosbuvir		Daclatasvir		-	1-3

*VX-135 and deleobuvir are not shown since currently on hold

Sofosbuvir/ledipasvir (single pill, once a day) ± RBV

Results of phase III studies

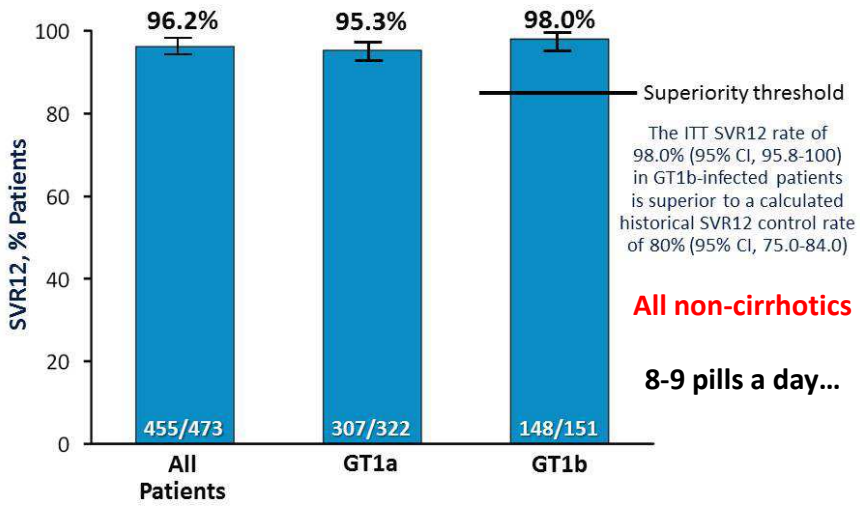
Study	Population	Treatment	Duration	SVR12
ION-1	HCV-1 treatment-naive (incl. 136/865 or 15.7% with cirrhosis)	SOF/LDV	12 weeks	**99%**
		SOF/LDV + RBV	12 weeks	**97%**
		SOF/LDV	24 weeks	**98%**
		SOF/LDV + RBV	24 weeks	**99%**
ION-2	HCV-1 treatment-experienced (including 88/440 or 20% with cirrhosis)*	SOF/LDV	12 weeks	**94%**
		SOF/LDV + RBV	12 weeks	**96%**
		SOF/LDV	24 weeks	**99%**
		SOF/LDV + RBV	24 weeks	**99%**
ION-3	HCV-1 treatment-naive (all non-cirrhotics)	SOF/LDV	8 weeks	**94%**
		SOF/LDV + RBV	8 weeks	**93%**
		SOF/LDV	12 weeks	**95%**

*Includes patients treated with PI-containing regimens

AFDAHL *et al,* N Engl J Med 2014; AFDAHL *et al,* N Engl J Med 2014
KOWDLEY *et al,* EASL 2014

ABT-450/r/ombitasvir qd + dasabuvir bid + R bid, 12 weeks

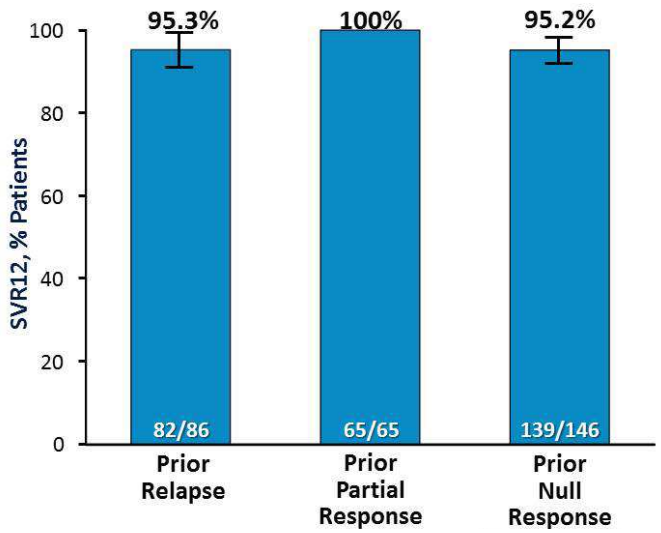
(SAPPHIRE-1 phase 3 study, HCV-1, n = 631 treatment-naive)



FELD et al, EASL 2014

ABT-450/r/ombitasvir qd + dasabuvir bid + R bid, 12 weeks

(SAPPHIRE-2 phase 3 study, HCV-1, n = 394 treatment-experienced)



ZEUZEM et al, EASL 2014

Les traitements sans interféron, en peu de mots

- Très efficaces (RVS >90%)
- Presque pas d'effets secondaires
- Schémas thérapeutiques simplifiés
  - Courte durée, peu de comprimés
  - Pas besoin de surveiller la réponse pendant traitement
  - Peu d'influence de la part des caractéristiques au basal (cirrhose, HCV-3)
- Presque pas de résistance