

Treatment of Hepatitis C In 2014 and Beyond

Prof. Jean-Michel Pawlotsky, MD, PhD

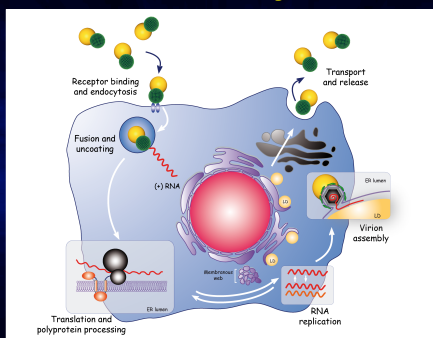


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Créteil, France

I The Toolbox

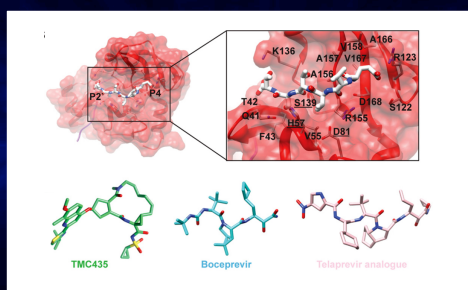
HCV Life Cycle



(Popescu & Dubuisson, *Biol Cell* 2009;102:63-74)

NS3-4A protease inhibitors

NS3/4A Protease Inhibitors

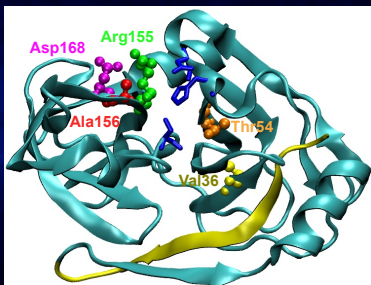


(Raney et al., *J Biol Chem* 2010;285:22725-31)

NS3/4A Protease Inhibitors

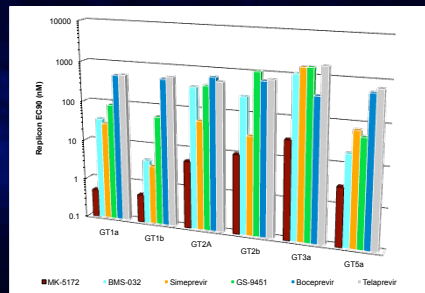
Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Telaprevir (Janssen)	Approved	750 mg q8h	14 days	-4.4
Boceprevir (Merck)	Approved	400 mg tid	7 days	-1.6
Simeprevir (Janssen)	III	200 mg qd	7 days	-4.1
Faldaprevir (BI)	III	240 mg qd	14 days	-4.0
Asunaprevir (BMS)	III	300 mg bid	3 days	-3.3
ABT-450/r (AbbVie)	III	200 mg qd	3 days	-4.1
Danoprevir (Roche)	II	200 mg q8h	14 days	-3.8
Sovaprevir (Achillion)	II	600 mg qd	5 days	-3.8
GS-9451 (Gilead)	II	400 mg qd	3 days	-3.5
IDX320 (Idenix)	II	400 mg qd	3 days	-3.3
Vaniprevir (Merck)	Japan	700 mg bid	8 days	-4.7
MK-5172 (2 nd -gen, Merck)	II	400 mg qd	7 days	-5.4
ACH-2684 (2 nd -gen, Achillion)	Ib	400 mg qd	3 days	-4.0

Amino Acid Substitutions Associated with PI Resistance



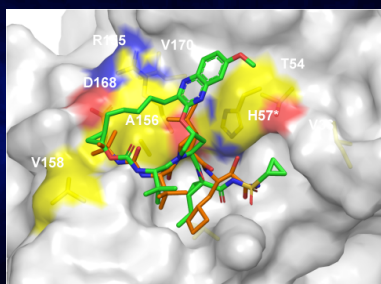
(Pawlotsky J-M, Ther Adv Gastroenterol 2009;2: 205-219)

MK-5172 Genotypic Coverage



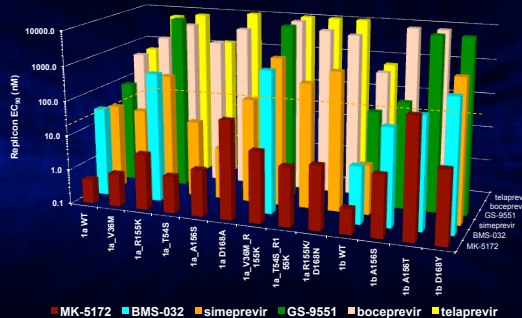
(Lahser et al., AASLD 2012)

MK-5172 and Boceprevir Resistance-Associated Variants



(Lahser et al., AASLD 2012)

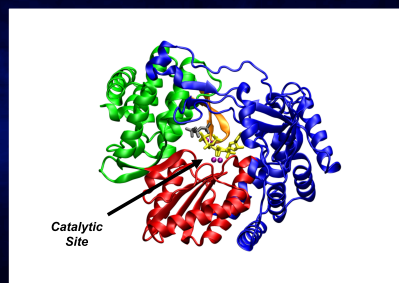
MK-5172 Resistance Profile



(Lahser et al., AASLD 2012)

Nucleoside/nucleotide analogue inhibitors of HCV RdRp

Nucleoside/Nucleotide Analogue Inhibitors of HCV RdRp

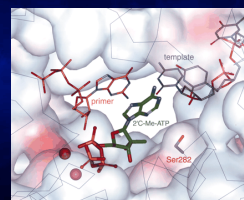


Nucleoside/Nucleotide Analogue Inhibitors of HCV RdRp

Drug	Phase	Dose	Duration	Median/mean log HCV RNA level reduction
Sofosbuvir (Gilead)	III	400 mg qd	3 days	-3.7
VX-135 (ALS-2200, Vertex)	II	200 mg qd	7 days	-4.5
Mericitabine (Roche)	II	1500 mg bid	14 days	-2.7

HCV Resistance to 2'-C-Methyl Nucleoside Inhibitors

2'-C-Me-ATP in the catalytic site



(Migliaccio et al., J Biol Chem 2003;278:49164-70)

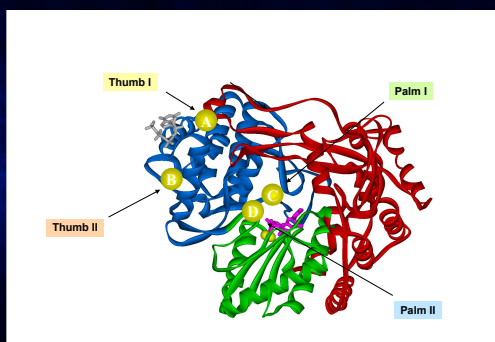
Sofosbuvir Resistance

- S282T
 - Is the only known aa substitution conferring phenotypic resistance to sofosbuvir
 - Is associated with low-level resistance (<20-fold) in vitro
 - Results in a severe reduction of replication capacity in vitro and in vivo
- No S282T variants found at baseline by population sequencing (n=1992) or deep sequencing (n=576)

(Gilead, data on file)

Non-nucleoside inhibitors of HCV RdRp

Non-Nucleoside Inhibitors (NNI)



Non-Nucleoside Inhibitors of HCV RdRp (NNIs)

Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Tegobuvir (Gilead)	II	40 mg bid	8 days	-1.4
Setrobuvir (Roche)	II	800 mg bid	3 days	-2.9
Deleobuvir (BI207127, BI)	II	800 mg q8h	3 days	-3.1
ABT-333 (AbbVie)	III	600 mg bid	2 days	-1.5
ABT-072 (AbbVie)	III	600 mg qd	3 days	-1.6
Lomibuvir (VX-222, Vertex)	II	750 mg bid	3 days	-3.7
GS-9669 (Gilead)	II	500 mg qd	3 days	-3.1
BMS-791325 (BMS)	II	?	?	?
TMC647055 (Janssen)	Ib	1000 mg bid	6 days	-3.4

Non-Nucleoside Inhibitors (NNI)

Thumb I
Deleobuvir (B207127)
BMS-791525
TMC647055

Palm I
Setrobuvir
ABT-333
ABT-072

Thumb II
Filibuvir
Lomibuvir (VX-222)
GS-9669

Palm II
Tegobuvir

Filibuvir (Pfizer) Resistance-Associated Residues

filibuvir

M423 R422 M426

(Troke et al., Antimicrob Agents Chemother 2012;56:1331-41)

HCV NNI Resistance Mutations

A 499 459 423 419 482 201

B 142 95 96 451 282 411 176 448 316 365

C D

(courtesy of Isabel Najera, Roche)

NS5A inhibitors

NS5A Protein

NS5A Dimer

- Domain III
- Domain II
- Domain I

Cytosol
ER membrane
ER lumen

- Required for HCV RNA replication
- Required for HCV viral particle assembly
- May be involved in the release of HCV particles

NS5A Inhibitors

Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Daclatasvir (BMS)	III	10 mg qd	1 day	-3.2
Ledipasvir (GS-5885, Gilead)	III	30 mg qd	3 days	-3.3
PPI-461 (Presidio)	II	100 mg qd	3 days	-3.7
PPI-668 (Presidio)	II	240 mg qd	3 days	-3.7
ACH-2928 (Achillion)	II	60 mg qd	3 days	-3.7
ABT-267 (AbbVie)	III	200 mg qd	3 days	-3.1
GSK2336805 (GSK)	II	60 mg qd	1 day	-3.0
BMS824393 (BMS)	II	50 mg qd	3 days	-3.9
Samatasvir (IDX719, Idenix)	II	50 mg qd	3 days	-3.7
MK-8742 (2 nd -gen, Merck)	Ib	50 mg qd	5 days	-4.1
ACH-3102 (2 nd -gen, Achillion)	Ib	50 mg qd	1 day	-3.8
GS-5816 (2 nd -gen, Gilead)	Ib	50 mg qd	3 days	-4.0

NS5A Inhibitor Resistance

Effect of NS5A Domain I Mutations on Replication and Daclatasvir Potency

Mutation	Fold Resistance	Replication Level, %*
Wild-type	1	100
F28S	7735	125 ± 49
L31M	141	83 ± 37
C92R	98	10 ± 5
Y93H	749	81 ± 21

Means ± standard deviations from transient-transfection assays with luciferase reporter replicon.

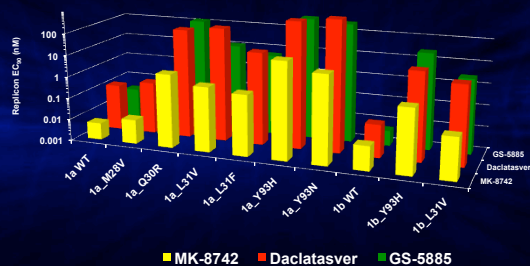
NS5A Dimer, Domain I



Primary and secondary mutation sites

(Fridell et al., Hepatology 2011;54:1924; Aghemo & De Francesco Hepatology 2013;58:428)

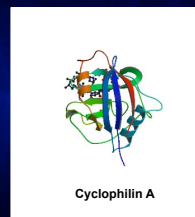
MK-8742 Resistance Profile



(Merck, unpublished data)

Cyclophilin inhibitors

Cyclophilins

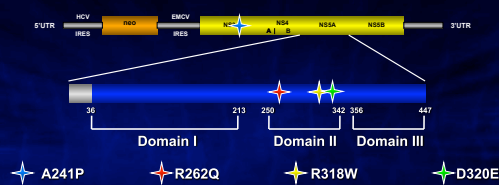


Cyclophilin A

Antiviral Efficacy of Cyclophilin Inhibitors

Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Alisporivir (DEBIO-025)	III	1200 mg bid	14 days	-3.6
SCY-465	II	900 mg qd	15 days	-2.2

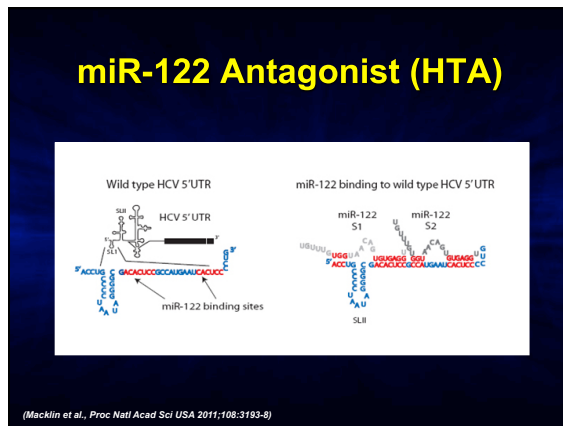
Alisporivir Resistance *in vitro*



	A241P + R262Q	A241P + R318W	R262Q + R318W	R318W + D320E	A241P + R262Q + R318W	A241P + R262Q + R318W + D320E
Fold-change vs wt	1.02	1.58	1.37	3.67	1.72	3.89

(Coilmont et al., EASL, 2009)

miR-122 antagonists



Antiviral Efficacy of miRNA-122 Antagonists

Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Miravirsen (Santaris)	II	7 mg/kg	29days	-3.0

- ### Barrier to Resistance
- Low barrier to resistance
 - First-generation protease inhibitors
 - Non-nucleoside inhibitors of RdRp
 - NS5A inhibitors (subtype 1a)
 - High barrier to resistance
 - Nucleoside/nucleotide analogues
 - Cyclophilin inhibitors
 - miRNA-122 antagonist
 - NS5A inhibitors (subtypes other than 1a)
 - 2nd/3rd-generation protease and NS5A inhibitors

II Hepatitis C Treatment, Today and Tomorrow

Before 2011

Our Good Old Friends



Pegylated IFN- α



Ribavirin

Since 2011

HCV Genotype non-1

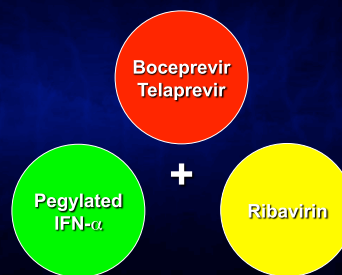


Pegylated IFN- α

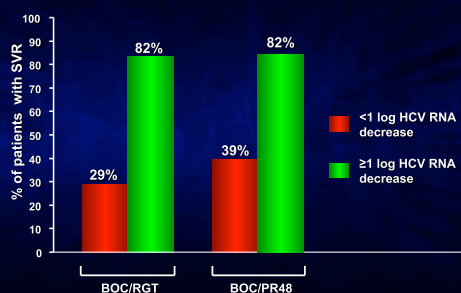


Ribavirin

Standard-of-Care for HCV Genotype 1






SVR According to Lead-in (SPRINT-2, non-black)

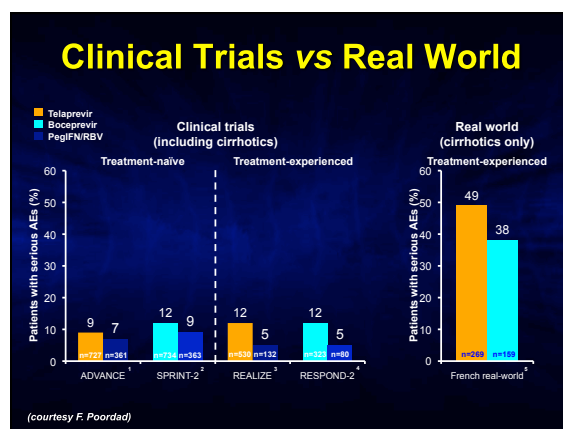
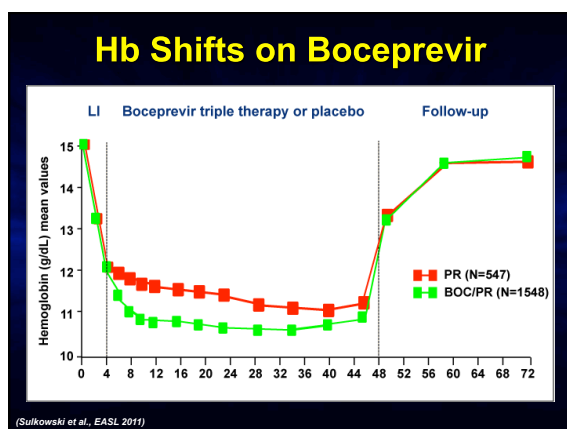


(Poordad et al., N Engl J Med 2011;364:1195-206)

Rash Grading

Mild rash	Moderate rash	Severe rash
Localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body)	Diffuse rash involving ≤50% of body surface area	Extent of rash >50% of body surface area or with: •Significant systemic symptoms •Mucous membrane ulceration •Target lesions •Epidermal detachment
		
36.8%	13.8%	4.8%

(Cacoub et al., J Hepatol 2012;56:455-63)



Medicines that are Contraindicated with Boceprevir and Telaprevir

Drug class	Contraindicated with boceprevir	Contraindicated with telaprevir
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Antiretrovirals	EFV, all RTV-boosted PIs	DRV/RTV, FPV/RTV, LPV/RTV
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	<i>Hypericum perforatum</i> (St John's wort)	<i>Hypericum perforatum</i>
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

(Boceprevir package insert; Telaprevir package insert)

2014-2015

Two DAAs Approved in 2014

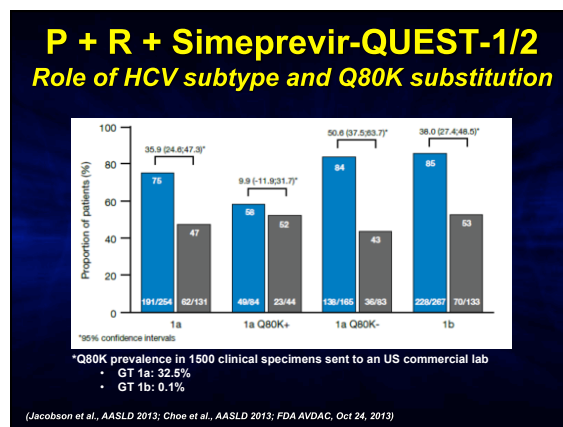
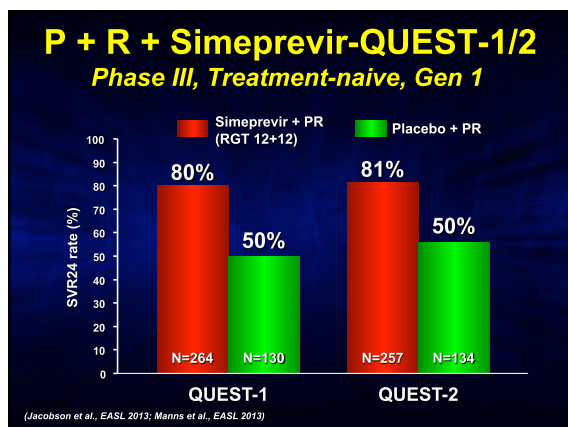
Simeprevir

Protease
Gen 1, 4

Sofosbuvir

Nucleotide
All gen

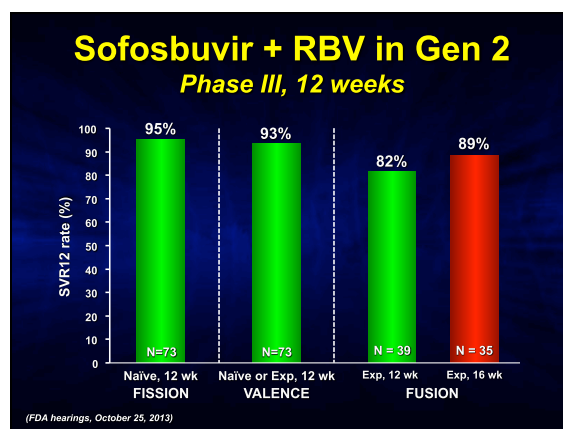
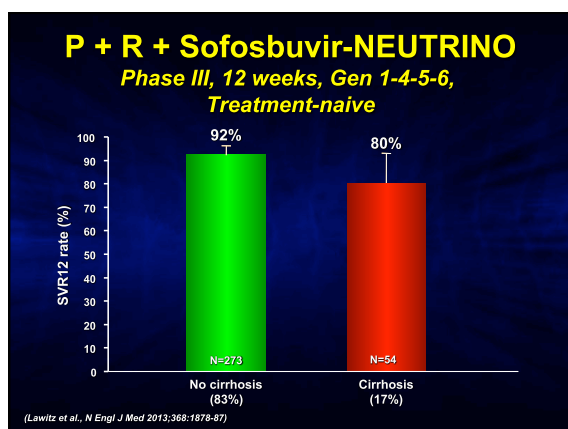
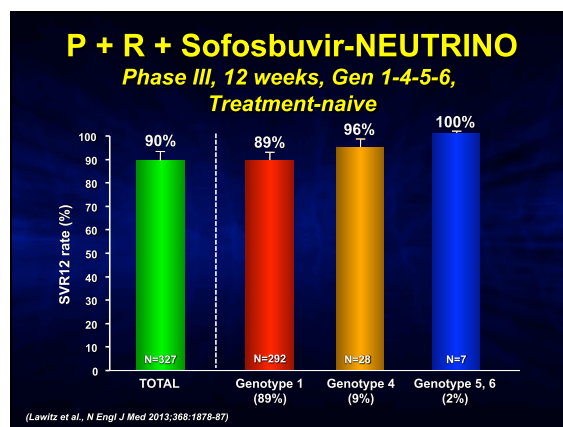
- ### Four Options in 2014
- Simeprevir + Peg-IFN α + ribavirin (gen 1, 4)
 - Sofosbuvir + Peg-IFN α + ribavirin (gen 1, 4, 5, 6)
 - Sofosbuvir + ribavirin (gen 2, 3)
 - Sofosbuvir + simeprevir (gen 1, 4)

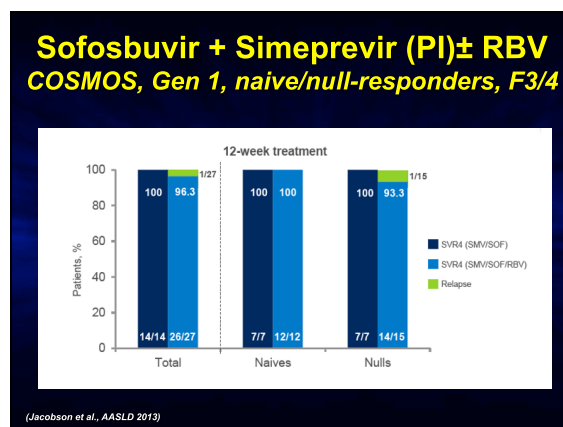
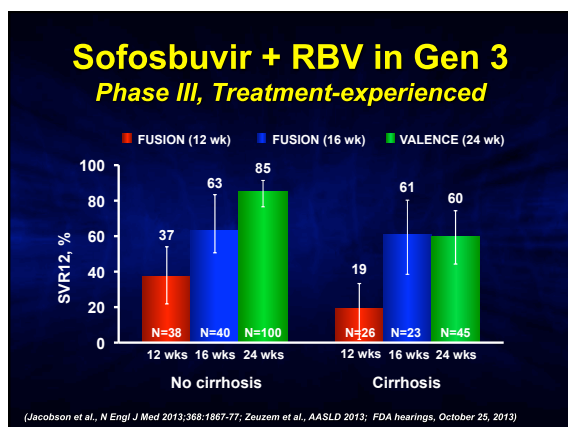
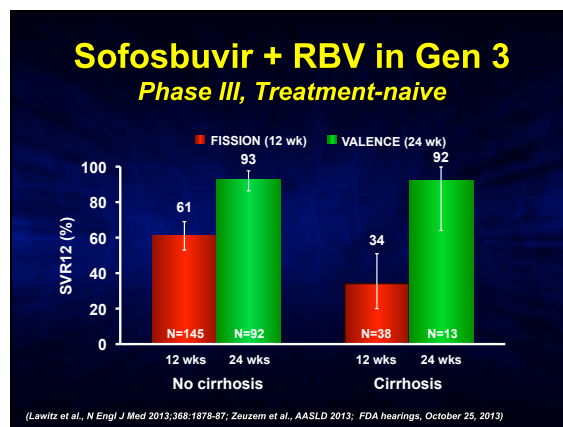
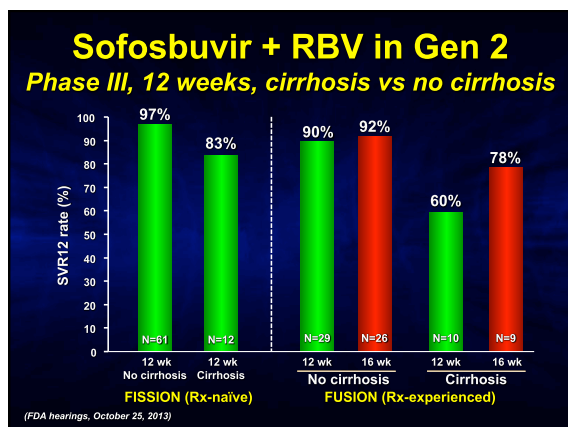


Summary of Simeprevir Resistance Data

- Baseline Q80K polymorphism
 - Present in 41% of patients with genotype 1a infection
 - Associated with lower SVR12 rate in QUEST-1
- Selection of NS3 protease substitutions in >90% of patients without SVR
 - Genotype 1a: R155K alone, with mutations at positions 80 and/or 168;
 - Genotype 1b: most common substitutions: D168V, Q80R+D168E

(Jacobson et al., EASL 2013; Manns et al., EASL 2013)

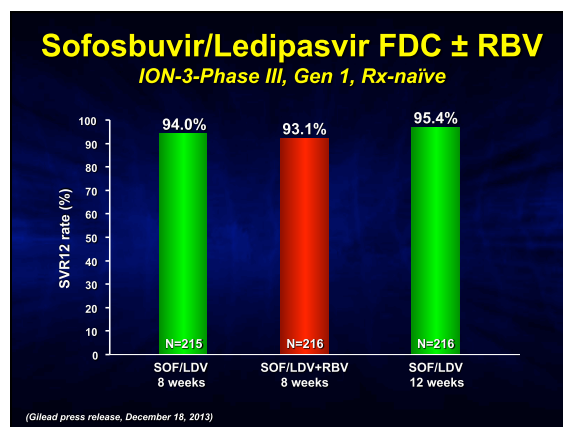
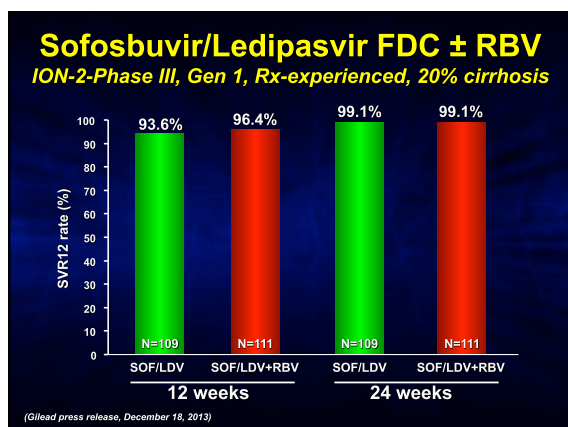
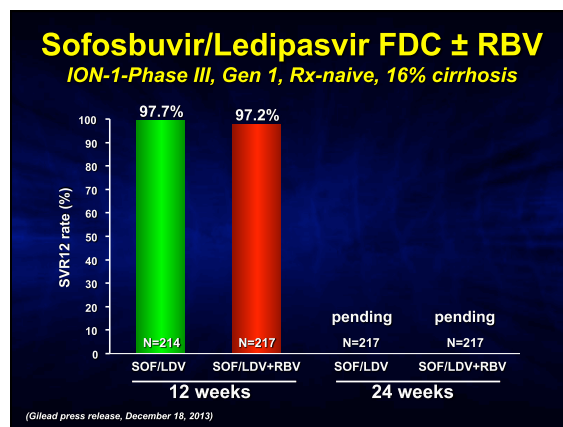
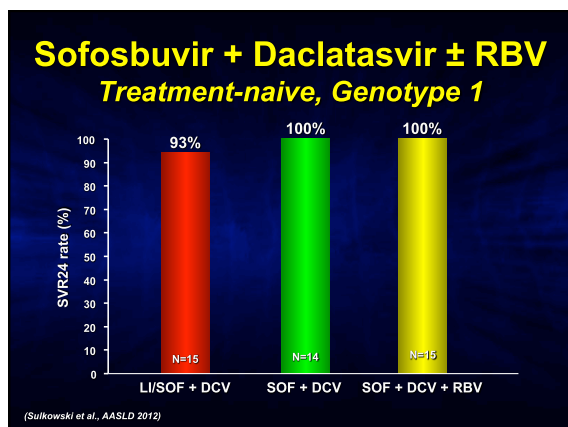




2015 and onwards

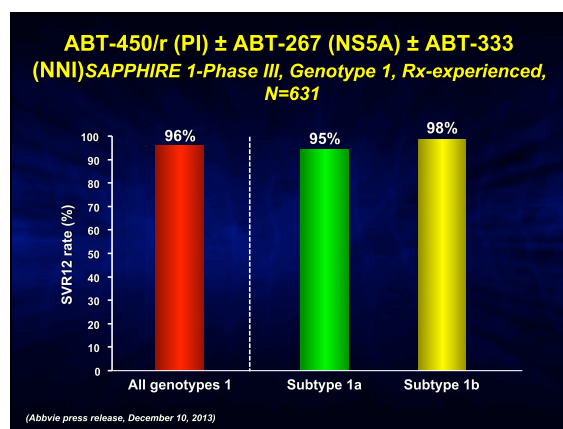
IFN-Free Combination Options

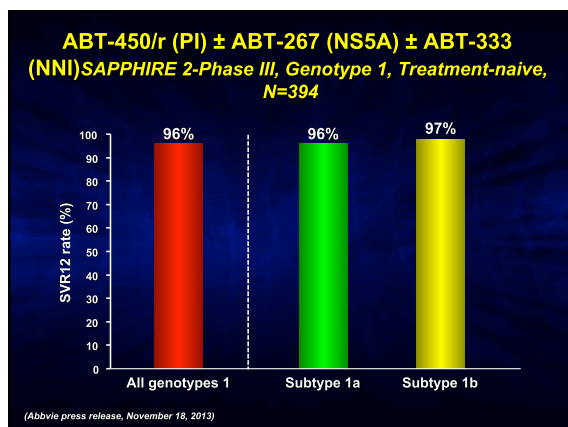
	NI	PI	N5SA	NNI	RBV
Nucleos(t)ide analogue-based strategies					
Gilead	Sofosbuvir		Ledipasvir	GS-9669	±
Vertex/others	VX-135	Simeprevir	Daclatasvir		±
Roche	Mericitabine	Danoprevir		Setrobuvir	±
Nucleoside-free triple combo strategies					
Abbvie		ABT-350/r	ABT-267	ABT-333	±
BMS		Asunaprevir	Daclatasvir	BMS791325	±
BI/Presidio		Faldaprevir	PPI-668	Deleobuvir	±
Janssen/GSK		Simeprevir	GSK2336805	TMC647055	±
Nucleoside-free, second-generation double combo strategies					
Merck		MK-5172	MK-8742		±
Achillion		ACH-2684	ACH-3102		±



IFN-Free Combination Options

	NI	PI	NS5A	NNI	RBV
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Vertex/others	VX-135	Simeprevir	Daclatasvir		±
Roche	Mericitabine	Danoprevir		Setrobuvir	±
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	NI	PI	NS5A	NNI	RBV
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Gilead	Sofosbuvir		Ledipasvir	GS-9669	±
Vertex/others	VX-135	Simeprevir	Daclatasvir		±
Roche	Mericitabine	Danoprevir/r		Setrobuvir	±
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Merck		MK-5172	MK-8742		±
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