Hepatitis C: Aplicaciones Clínicas de la Resistencia

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DAA agents approved or in more advanced stages of clinical development

DAA family			
NS5B nucleos(t)ide analogues inhibitors	**NS5B non-nucleoside analogues inhibitors**	**NS3/4A inhibitors**	**NS5A inhibitors**
Sofosbuvir (GS-7977) †	Deleobuvir (BI-207127; NNI-site 1 inhibitor)	**Telaprevir***	Daclatasvir (BMS-790052)
Mericitabine (RG-7128) VX-135	ABT-333 (NNI-site 3 inhibitor)	**Boceprevir***	Ledipasvir (GS-5885)
IDX-184	VX-222 (NNI-site 2 inhibitor)	**Simeprevir (TMC-435)†**	ABT-267
VX-135	ABT-072 (NNI-site 3 inhibitor)	Faldaprevir (BI-2011335)	MK-8742
GS-6620	Setrobuvir (ANA-598; NNI-site 3 inhibitor)	Asunaprevir (BMS-650032)	Samatasvir (IDX-719)
INX-189	GS-9669 (NNI-site 2 inhibitor)	Vaniprevir (MK-7009)	ACH-3102
	Tegobuvir (GS-9190; NNI-site 5 inhibitor)	Danoprevir (RG-7227)	
	Filivubir (PF-868554; NNI-site 2 inhibitor)	Sovaprevir (ACH-1625)	
		ABT-450/r	
		GS-9451	
		MK-5172	

*Approved by the FDA and EMA in 2011.

† Approved by the FDA November/December 2013.

Adapted from Poveda E et al. Future Virology 2012

Rapid Evolution of HCV Regimens: Easier to take/tolerate, Short Duration, Pangenotypic, Higher SVR, Eventually Oral for all patients

2013

Genotype 2&3
P/R

Genotypes 1
Telaprevir + P/R
Boceprevir + P/R

2014

Genotype 2
Sofosbuvir+RBV 12 weeks

Genotype 3
Sofosbuvir+RBV 24 weeks

Genotypes 1-4
Sofosbuvir + P/R

Genotypes 1
Simeprevir + P/R

2015

Genotypes 1-4
Sofosbuvir+Ledipasvir ± RBV

ABT-450+ABT-267+ABT-333 +RBV

Daclatasvir+Asunaprevir

HCV Resistance to DAA

During DAA-based treatment:

- Rapid selection of resistance mutation may occur, eventually leading to viral break-through.

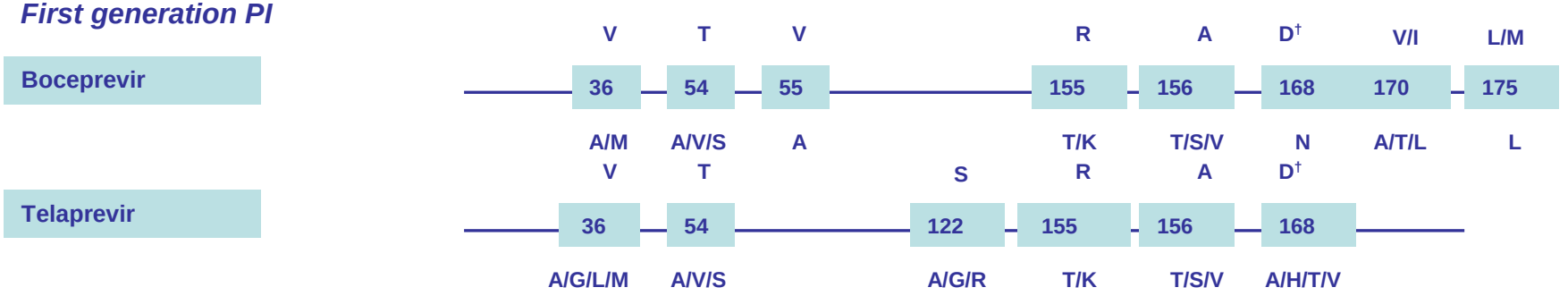
- Several changes at different positions at the NS3 protease, NS5B polymerase, and NS5A protein have been associated with loss of susceptibility to DAAs.

Inhibitors of NS3/4A Protease

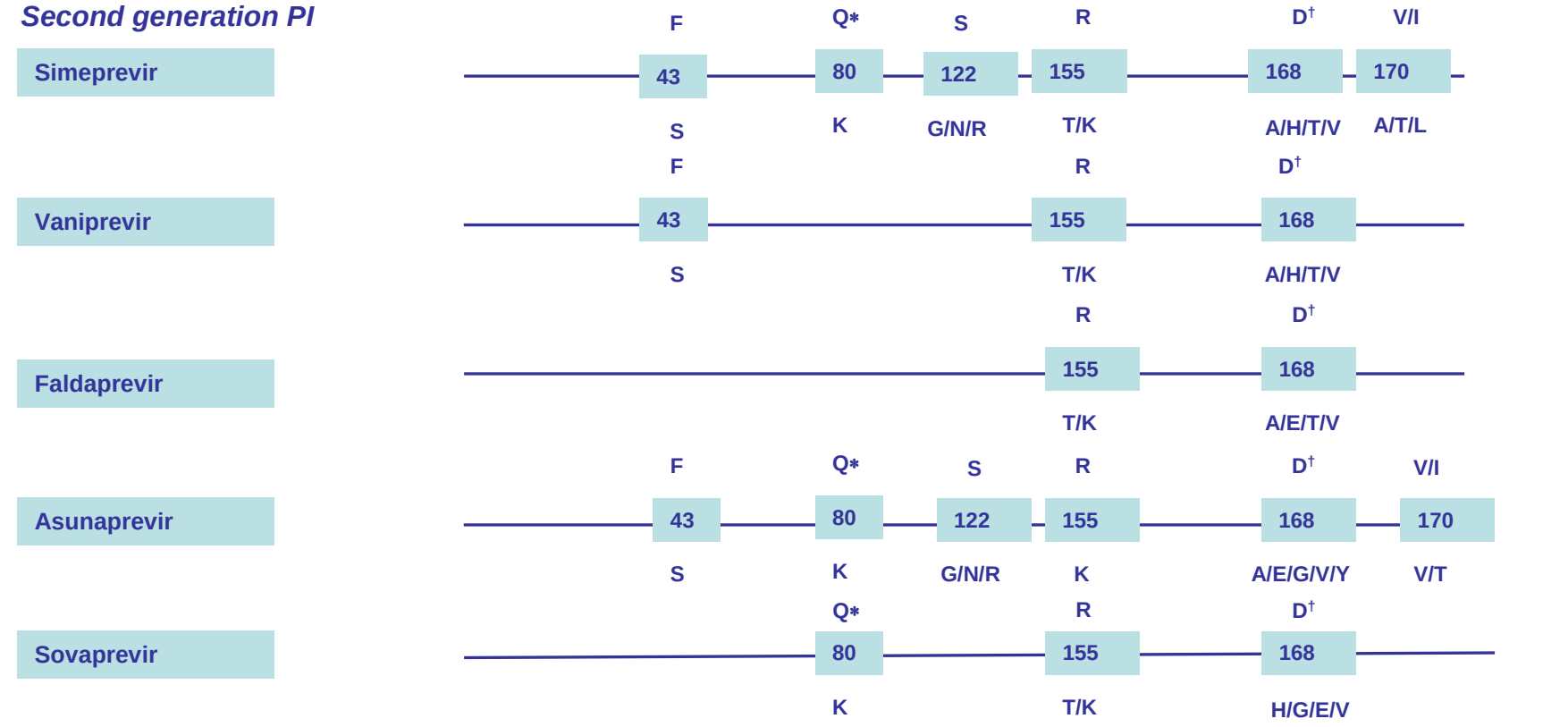
	1st generation	2nd generation
Mechanisms of action	Covalent inhibitors	Non- covalent inhibitors
Approved agents	**Telaprevir** **Boceprevir**	**Simeprevir** Phase IIb/III: Faldaprevir, Vaniprevir, Asunaprevir, Sovaprevir, MK-5172
Combination Therapy	pegIFN/RBV	pegIFN/RBV and/or Other DAA
Genotype activity	Genotype 1 (G1b >G1a)	Across all (but G3; D168Q)
Resistance barrier	**LOW (G1b >G1a)**	**LOW (G1b >G1a)**
Cross-resistance	HIGH	HIGH MK-5172: activity againts viruses with resistance to other PIs

Main resistance mutations associated with first and second generation of protease inhibitors

First generation PI



Second generation PI



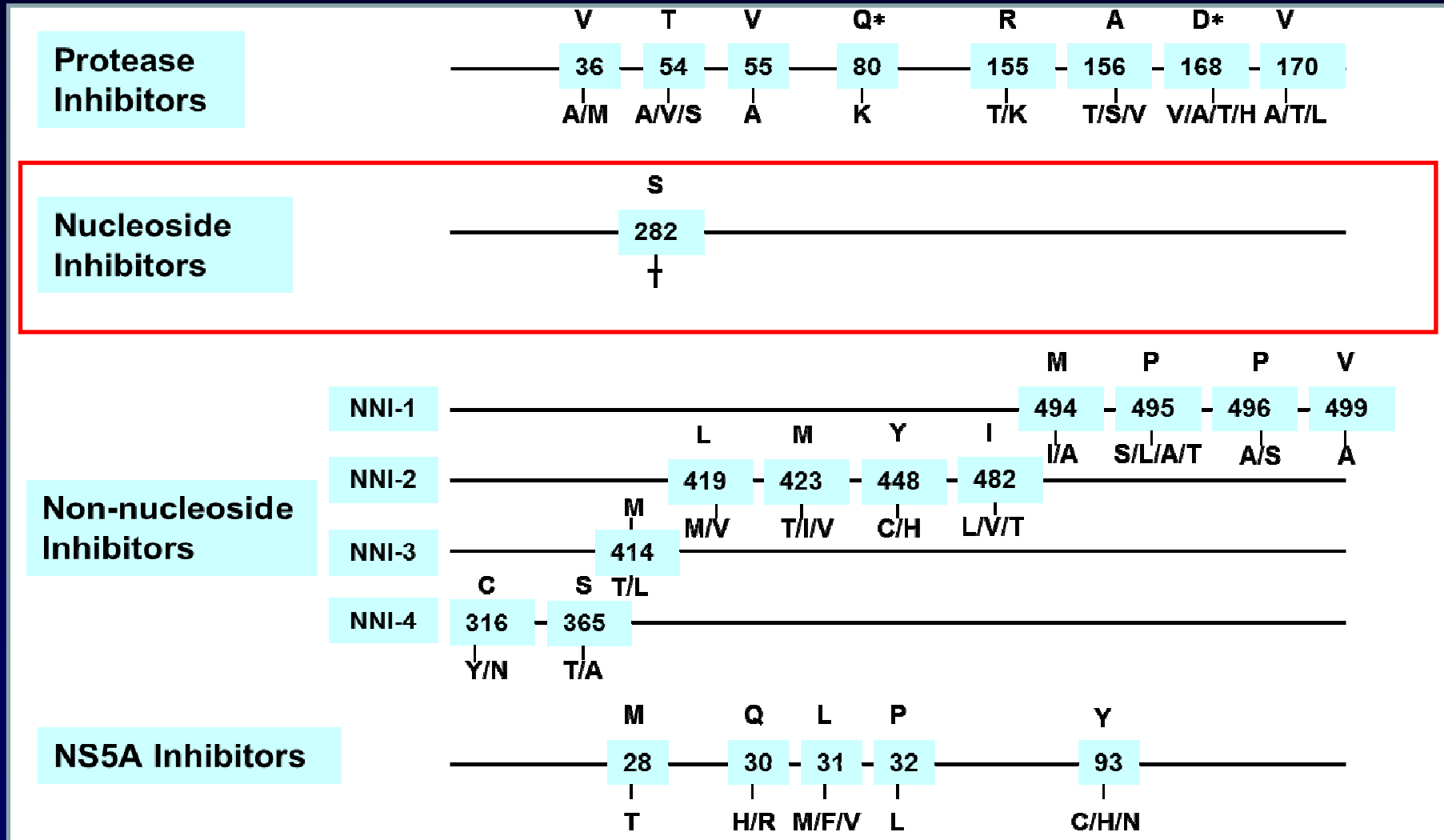
⁎ Q80K is a natural polymorphism found in 25%-39% of HCV genotype 1a and is associated with low level resistance to simeprevir, asunaprevir and sovaprevir. † D168Q is found in almost all HCV genotype 3 conferring natural resistance to most protease inhibitors.

Updated from Poveda et al., Future Virology 2012

Inhibitors of NS5B polymerase: nucleos(t)ide analogues (NIs)

Mechanisms of action	Inhibition of NS5B polymerase synthesis by targeting the active site
Approved agents	**Sofosbuvir** Phase IIb/III: Mericitabine, VX-135
Combination Therapy	pegIFN/RBV RBV Other DAAs
Genotype activity	**Across all** Sofosbuvir displays less antiviral activity againts G3 (treatment duration 24 weeks)
Resistance barrier	**HIGH**
Cross-resistance	HIGH

Main Drug Resistance Mutations to DAA



*Protease Q80K is a natural polymorphism found in ~44% of HCV-1a and is associated with resistance to simeprevir.

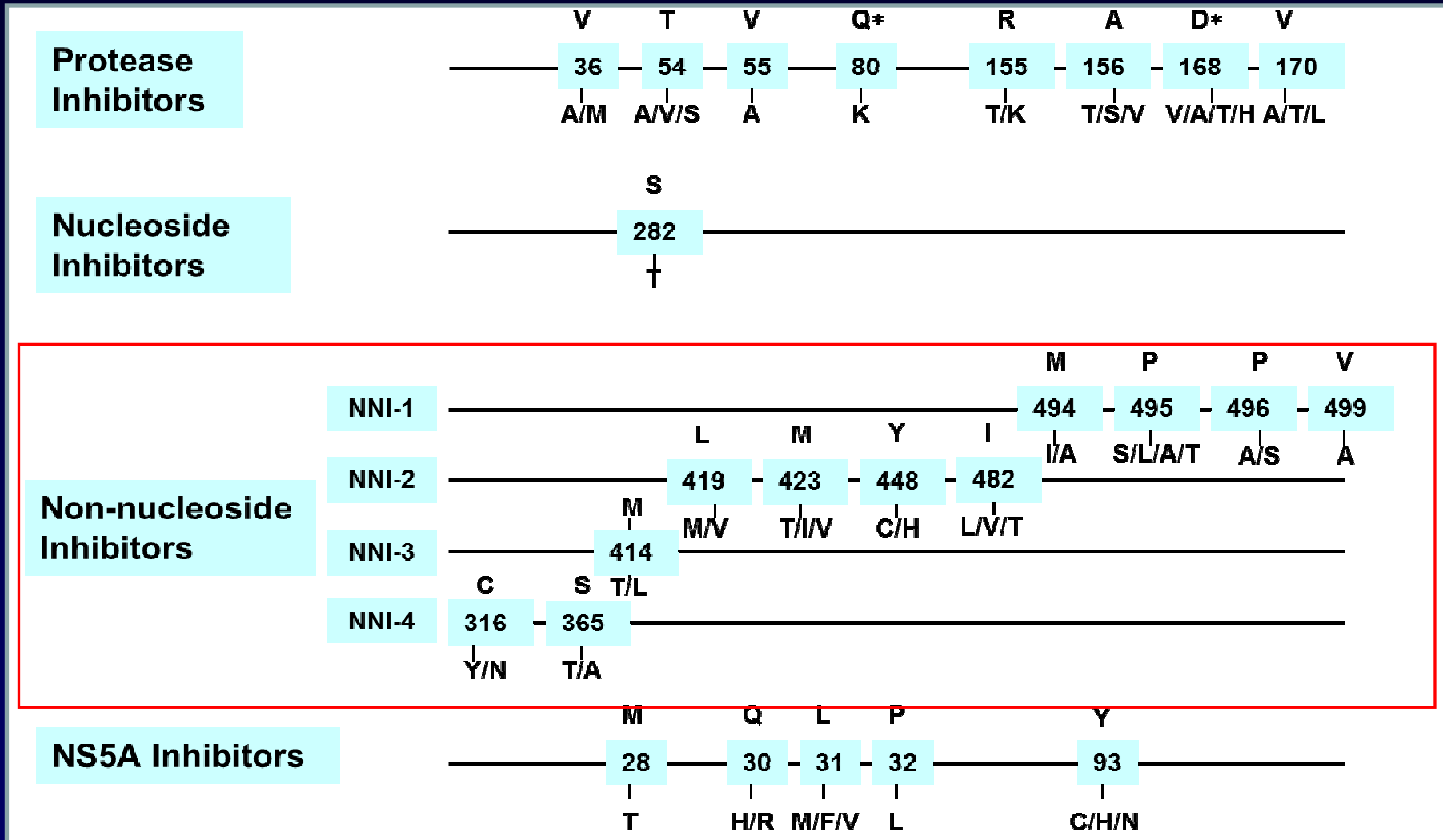
*Protease D168Q is found in all HCV-3 variants.

Poveda et al, Future Virology 2012

Inhibitors of NS5B polymerase: non-nucleoside analogues (NNIs)

Mechanisms of action	Inhibition of NS5B polymerase function by targeting one of at least four allosteric sites (thumb 1,2; palm 1,2) Heterogeneous group of agents
Approved agents	None Phase IIB/III: Setrobuvir, ABT-333, ABT-072, VX-222
Combination Therapy	pegIFN/RBV Other DAAs
Genotype activity	Genotype 1 (G1b >G1a) Highly genotype/subtype dependent
Resistance barrier	**LOW**
Cross-resistance	LOW/Split into families

Main Drug Resistance Mutations to DAA



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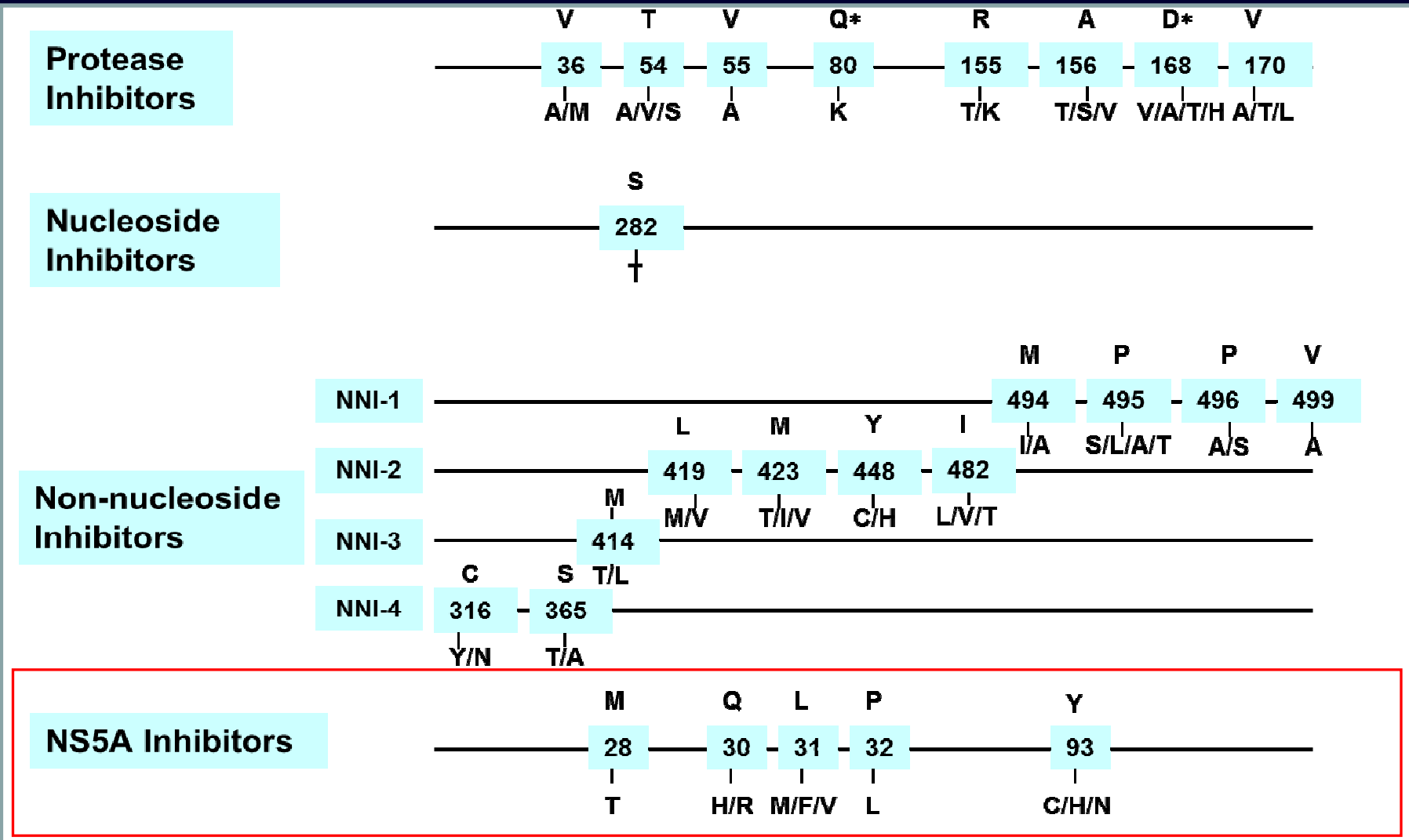
Poveda et al, Future Virology 2012

Inhibitors of NS5A protein

Mechanisms of action	Inhibits HCV replication complex by unclear mechanisms involving interaction with the NS5A protein.
Approved agents	None Phase IIb/III: Daclatasvir, Ledipasvir, ABT-267, MK-8742
Combination Therapy	pegIFN/RBV Other DAAs
Genotype activity	Across all (G1b>G1a)
Resistance barrier	**LOW**
Cross-resistance	HIGH (L31M; Y93H)

Main Drug Resistance Mutations to DAA



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Poveda et al, Future Virology 2012

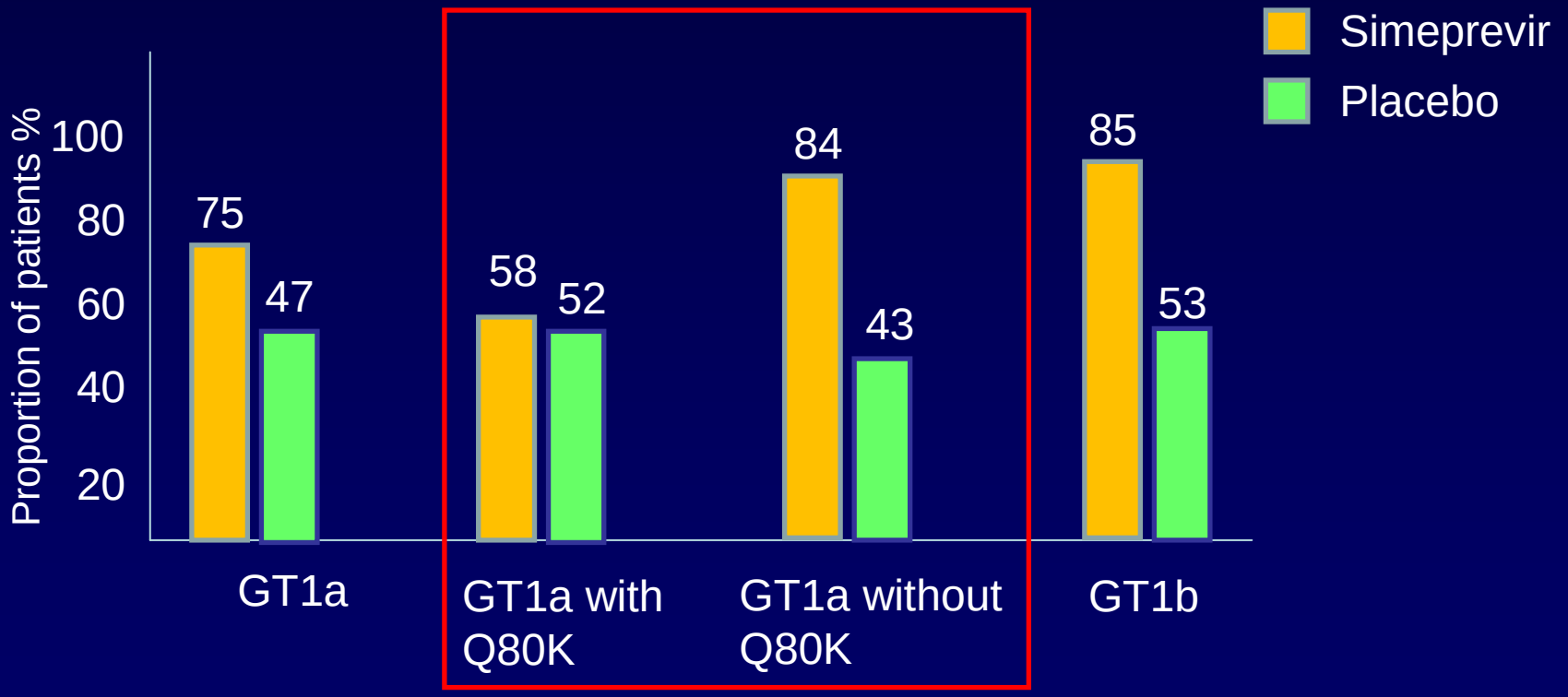
Key polymorphims at NS3, NS5B and NS5A sequences associated with resistance to DAA

Drug family	Mutation	1a	1b	2	3	4	DAA agents potentially affected by specific polymorphisms
NS3/4A protease inhibitors	Q80K	25-39.7%	0	0	0	0	Simeprevir Asunaprevir Sovaprevir
	D168Q	0	0	0	99.2%	0	Second PI generation
NS5B non-nucleoside analogs inhibitors	C316N		13,3%				Setrobuvir (NNI-site 3 inhibitors) ABT-072 (NNI-site 3 inhibitors) ABT-333 (NNI-site 3 inhibitors)
	L419V			13%			Filibuvir (NNI-site 2 inhibitors) VX-222 (NNI-site 2 inhibitors) GS-9669 (NNI-site 2 inhibitors)
NS5A inhibitors	L31M		7%	83,5%		92%	Daclatasvir Ledipasvir
	Y93H		6-12,5%			5,4%	Daclatasvir Ledipasvir

Poveda E et al. Future Virology 2012

Lower SVR12 rates to Simeprevir among patients with G1a Q80K polymorphism at baseline

1122: Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naive patients: efficacy in difficult-to-treat patient sub-populations in the QUEST-1 and 2 Phase III trials. *Jacobson I et al.*



Prevalence of Q80K and across different regions in simeprevir phase IIB/III studies

	All HCV GT	HCV GT1a	HCV GT1b
Overall	13.7%	29.5%	0.5%
Europe	6.1%	19.4%	0.3%
North America	34.4%	48.1%	0%
South America	3.3%	9.1%	0%

Lenz O et al. AASLD 2013. Abstract 1101

Impact of Q80K among HCV G1a infected patients

OLYSIO (simeprevir) capsules, for oral use
Initial U.S. Approval – 2013

----------INDICATIONS AND USAGE----------

OLYSIO is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. (1)

- OLYSIO efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis). (1, 14)
- OLYSIO must not be used as monotherapy. (1)
- Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism. (1, 12, 14)

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA

Infectious Diseases Society of America

HCV Guidance

Wednesday, January 29, 2014

The Recommendations for Testing, Managing, and Treating Hepatitis C are now available.

The most current version of the HCV Guidance exists on *Recommendations for Testing, Managing, and Treating Hepatitis C*. (http://www.hcvguidelines.org)

Recommendations for patients who are initiating therapy for HCV infection or who experienced relapse after prior PEG/RBV therapy

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
			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

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

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Press Release

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LabCorp Announces the Availability of Hepatitis C Virus Q80k Polymorphism Screening for the Newly Approved Drug OLYSIO™ (simeprevir)

BURLINGTON, N.C.--(BUSINESS WIRE)--Dec. 3, 2013-- Laboratory Corporation of America® Holdings (LabCorp®) (NYSE: LH) announced today the immediate availability of an enhanced version of its HCV GenoSure® NS3/4, a drug resistance test that screens for the Q80K polymorphism. Q80K is a naturally occurring polymorphism that develops in certain strains of HCV, making the virus less susceptible to Janssen Therapeutics' OLYSIO™ (simeprevir), which was recently approved by the U.S. Food and Drug Administration for the treatment of certain adult patients diagnosed with genotype 1chronic hepatitis C (HCV). In clinical trials, patients with HCV genotype 1 containing the Q80K polymorphism demonstrated significantly lower response rates to treatment with OLYSIO. Approximately one-third of HCV patients have virus with Q80K polymorphism. Given the high frequency of the Q80K polymorphism and its significant impact on OLYSIO's success rate, it is recommended that patients be screened for the Q80K polymorphism prior to treatment.

LabCorp and Monogram Biosciences, Inc., a member of the LabCorp Specialty Testing Group, were the first to launch an HCV drug resistance test for NS3/4A protease inhibitors. In addition to OLYSIO, LabCorp's HCVGenoSure NS3/4A test also provides resistance information for the drugs VICTRELIS® (boceprevir) and INCIVEK® (telaprevir). With the inclusion of all three FDA approved protease inhibitors, HCV GenoSure NS3/4A enables healthcare providers to select the most appropriate therapy regimen for their patients.

Daclatasvir+RBV+pegIFN *alfa-2a vs. alfa-2b* in treatment-naive and IFN-experienced HCV G1 infected patients.

- N=36 patients (18 treatment naive; 18 IFN-experienced):

  9 experienced virological failure

- Patient's profile at failure:

Treatment naive (n=1):

- Baseline polymorphism: Y93H
- Non-CC IL28

IFN-experienced (n=8):

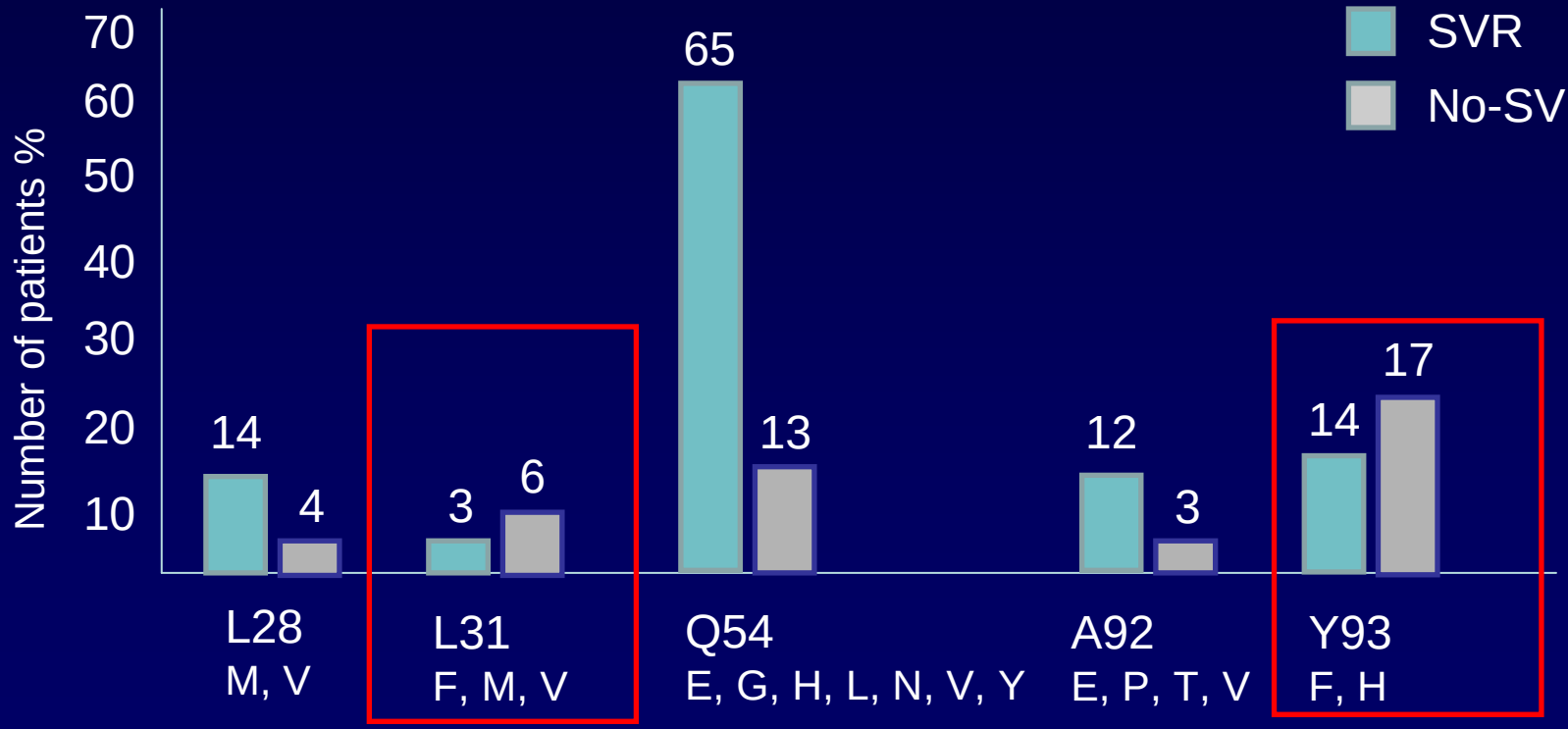
- 7 non-CC IL28B
- All baseline polymorphisms :L28M(1),L31V/M(2), R30Q(1), Q54H(5), Q62R(1), A92T(1).

- The most common emergent variants associated with DCV resistance were: L31V/M and Y93H.

McPhee et al, EASL Barcelona 2012

Baseline polymorphisms at NS5A positions L31 or Y93 were uncommon but present in more patients who did not achieve SVR

1111: Analysis of HCV resistance variants in a phase 3 trial of Daclatasvir combined with asunaprevir for Japanese patients with Genotype 1b infection. *McPhee et al.*



McPhee et al., AASLD Washington 2013

Impact of baseline polymorphism know to confer loss of susceptibility to Daclatasvir among patients receiving Daclatasvir plus Sofosbuvir.

Prevalence of baseline polymorphisms:

8% of G1 untreated patients
8% of G1 treated patients
61% of G2
28% of G3

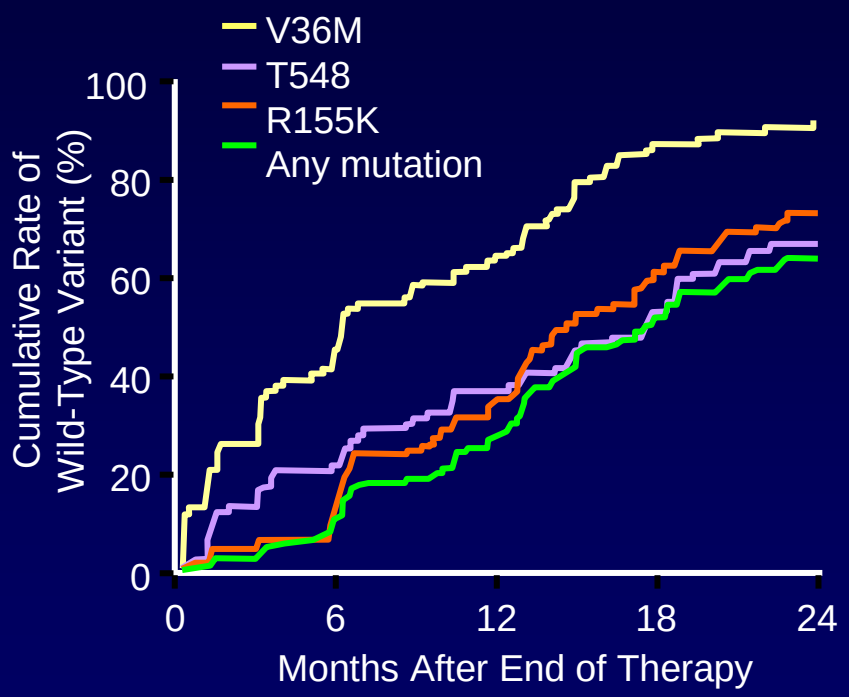
All patients but one with preexisting daclatasvir resistance variants had a sustained virologic response

Number of Patients	HCV Genotype	Polymorphism(s) at NS5A Amino Acid Positions	Virologic Outcome
1	1a	30H/R	SVR_{48}
1	1a	M28T	SVR_{24}
1	1a	Q30H-Y93H	SVR_{12}
1	1a	Q30E, Y93N	SVR_{48}
1	1a	Y93C	SVR_{36}
1	1a	Q30H	SVR_{36}
1	1a	L31M	SVR_4, then lost to follow-up
1	1a	Q30H-L31M	SVR_{36}
1	1a	Y93N	SVR_{48}
1	1b	R30Q-L31M	SVR_{48}
2	1b	L31M	SVR_{12}, SVR_{36}
1	1b	Y93H	SVR_{36}
13	2	L31M	SVR_{48} (all)
1	2	L31M-P58S	SVR_{24}
1	3	A30K	Relapse
1	3	A30K, L31M	SVR_{48}
3	3	Y93H	SVR_{48} (all)

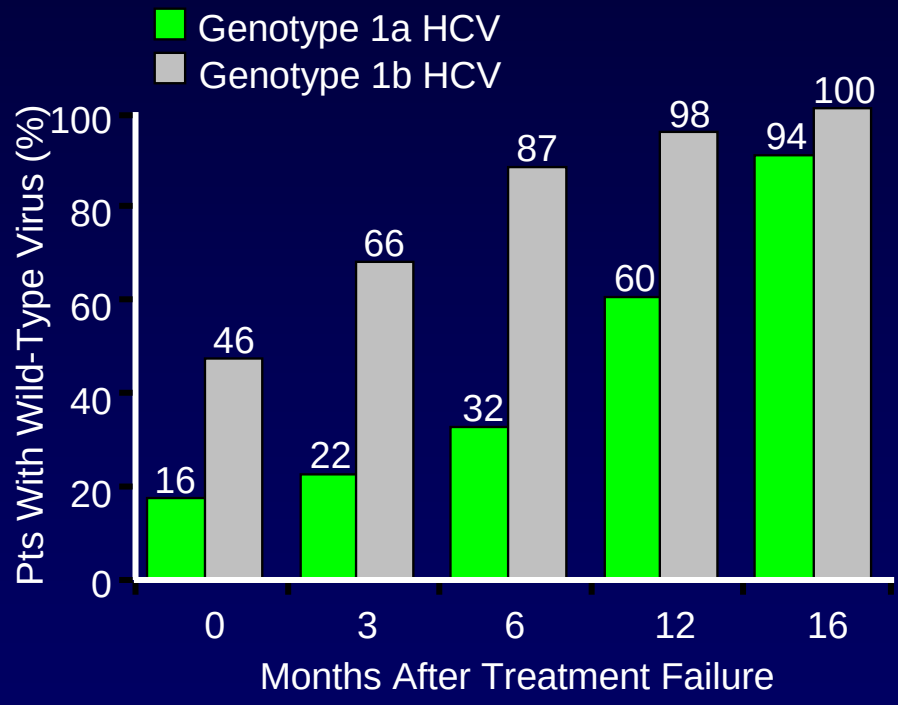
Sulkowski et al., N Engl J Med 2014; 370:211-21

Loss of Detectable Resistance in Patients Stopping BOC or TVR + PegIFN/RBV

Boceprevir*[1]



Telaprevir[2]



*Data from phase II studies.

1. Vierling JM, et al. EASL 2010. Abstract 2016.
2. Sullivan J, et al. EASL 2011. Abstract 8.

Recommendations for patients in whom previous PEG/RBV treatment has failed

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

*** Non-responder is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naive (see Initial Treatment section)

†† 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.

AASLD HCV Guidance, January 29, 2014

The Role of HCV resistance in DAA-based therapies

■ The rates of polymorphisms associated with resistance to DAA is especially relevant among HCV genotype 1 patients and mainly affect the susceptibility to protease and NS5A inhibitors.

■ The Q80K polymorphism is associated with lower rates of virological responses to simeprevir and is highly prevalent among HCV genotypes 1a infected patients. Baseline screening for Q80K polymorphism is strongly recommended for HCV genotype 1a patients before initiate a simeprevir-based therapy.

■ The clinical relevance of baseline polymorphisms associated with resistance to protease and NS5A inhibitors might be depending on virological (i.e. HCV subtype 1a), host (i.e. *non-CC IL28)*, and clinical (i.e. *IFN non-responders)* features. HCV treatment strategies must be optimized considering all these characteristics.

■ Selected mutants to protease inhibitors tend to dissappear after 16-24 months of the end of treatment. However, considering the high degree of cross-resistance existing between compounds belonging to the same family it is NOT recommended the use of simeprevir in patients with previous telaprevir or boceprevir exposure.