Resistencias a los Agentes Antivirales de Acción Directa frente al VHC

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DAA & HCV resistance

- The antiviral potency of most DAA is impressive. However, the rapid emergence of drug resistance upon failure in HCV may challenge DAA success.

- Moreover, given the large genetic variability in HCV the efficacy of these drugs can be genotype/subtype dependent. The presence of natural polymorphisms associated with reduced susceptibility to some compounds may compromise the DAA activity.

DAA in more advanced stages of clinical development

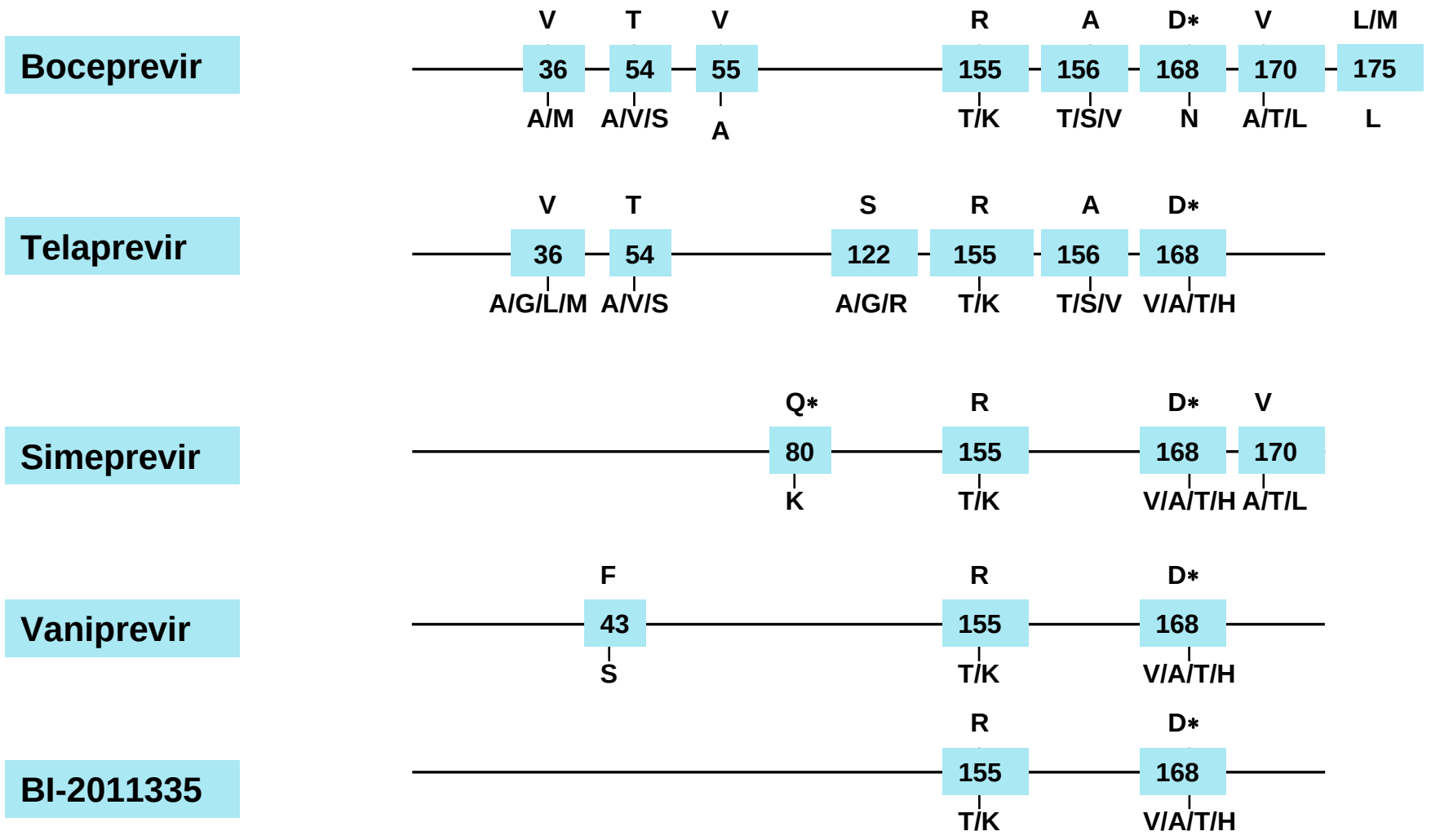
Protease inhibitors	Polymerase inhibitors		NS5A inhibitors
	Nucleoside analogues	**Non-nucleoside analogues**	
▪ Telaprevir ▪ Boceprevir ▪ Simeprevir ▪ Danoprevir ▪ Vaniprevir ▪ BI-1335 ▪ MK-5172 ▪ GS-9256 ▪ ABT-450 ▪ ACH-1625	▪ Mericitabine ▪ GS-7977 ▪ IDX-184 ▪ INX-189	▪ Tegobuvir ▪ Filibuvir ▪ BI-7127 ▪ BI-1325 ▪ Setrobuvir ▪ VX-222 ▪ VCH-759 ▪ ABT-072 ▪ GS-9669	▪ Daclatasvir ▪ GS-5885 ▪ IDX-179 ▪ ABT-267

Updated from Soriano et al, Exp Op Pharmacother 2012

Inhibitors of NS3/4A Protease

	1st generation	2nd generation
Mechanisms of action	Covalent inhibitors	Non- covalent inhibitors
Approved agents	Telaprevir Boceprevir	None Phase IIb/III: Danoprevir, Simeprevir, Vaniprevir, BI-1335, 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 Drug Resistance Mutations to PIs



Adaptada de *Poveda et al*.17

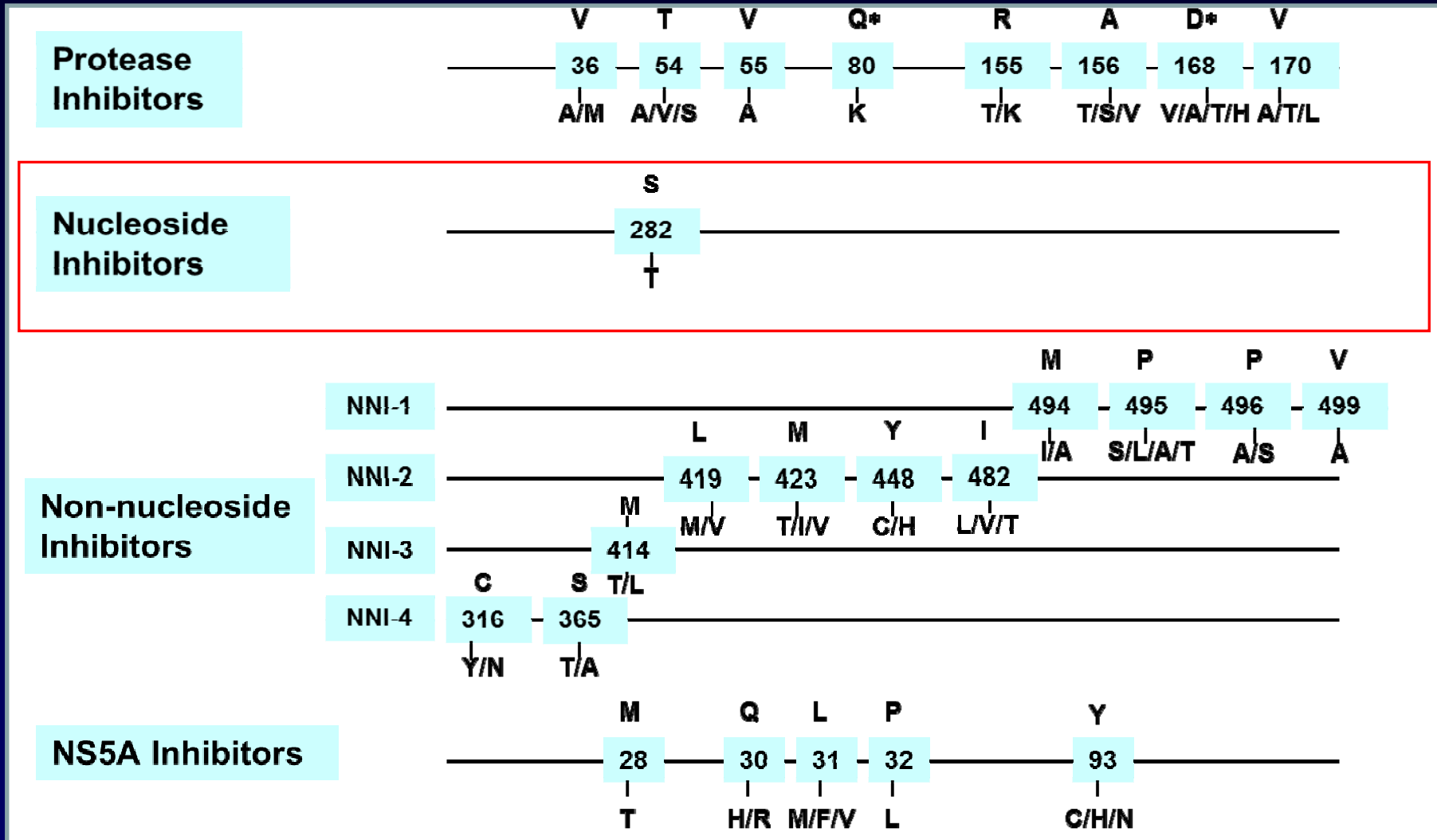
∗ Q80K es un polimorfismo natural que se encuentra entre el 25%-39% de los genotipos 1a y está asociado con resistencia a simeprevir.

∗ D168Q se encuentra en la mayor parte de las variantes VHC genotipo 3.

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

Mechanisms of action	Inhibition of NS5B polymerase synthesis by targeting the active site
Approved agents	None Phase IIb/III: Mericitabine, Sofosbuvir (GS-7977)
Combination Therapy	pegIFN/RBV Other DAAs
Genotype activity	Across all
Resistance barrier	**HIGH**
Cross-resistance	LOW

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.

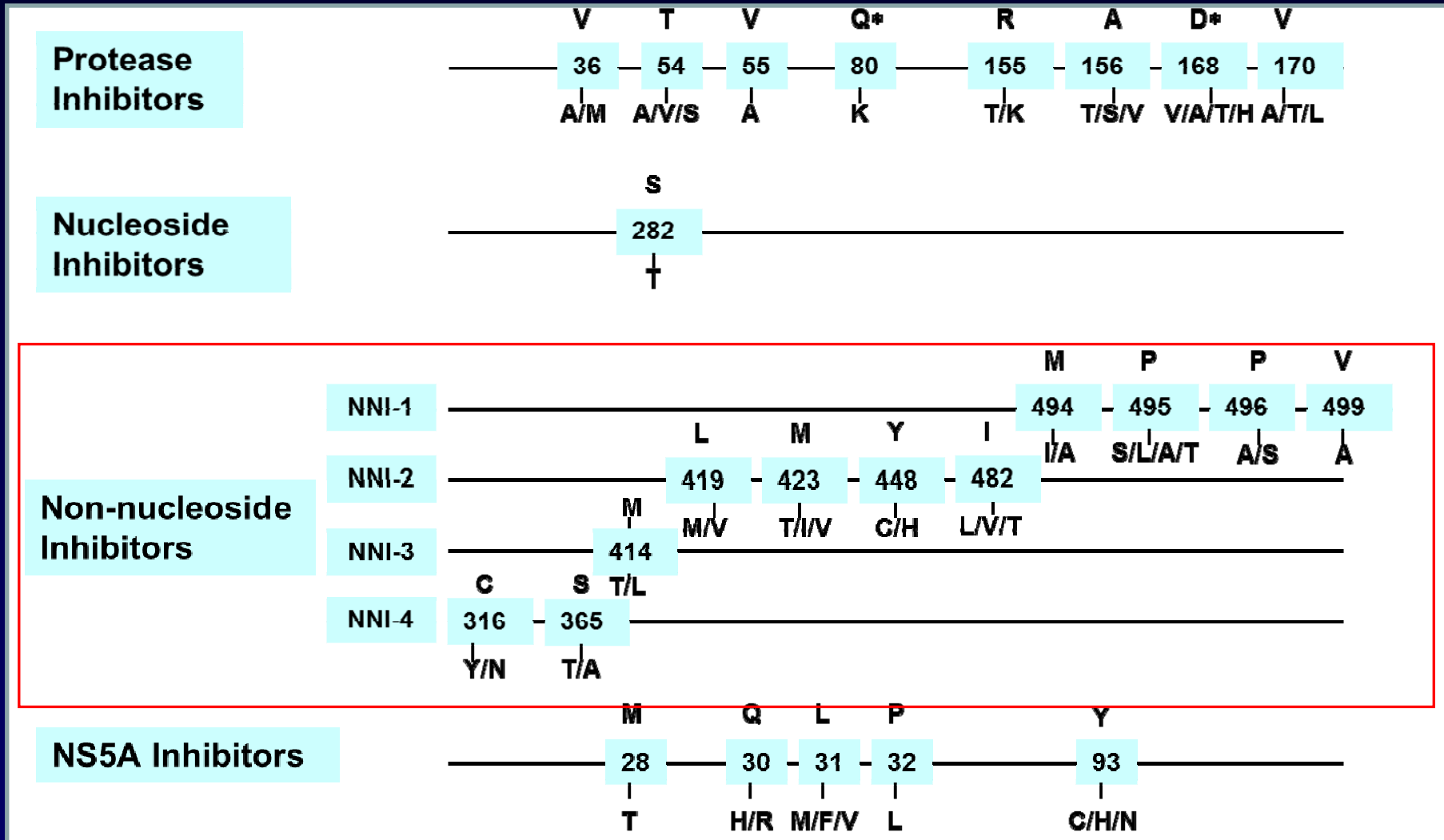
*Protease D168Q is found in all HCV-3 variants.

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 II: Tegobuvir, filibuvir, BI-7127
Combination Therapy	pegIFN/RBV Other DAAs
Genotype activity	Genotype 1 (G1b >G1a) Highly genotype/subtype dependent
Resistance barrier	**LOW**
Cross-resistance	Split into families

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.

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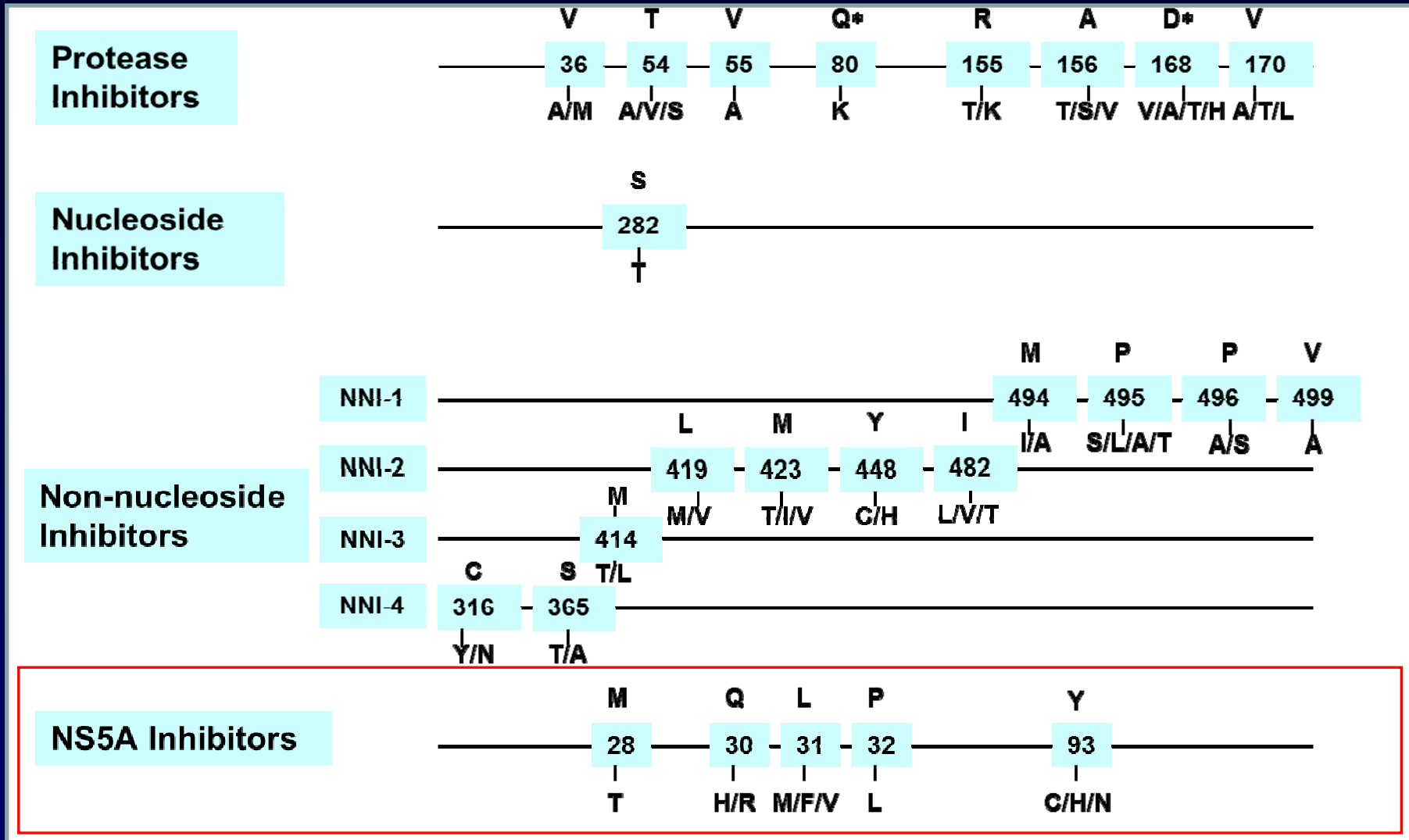
Poveda et al, Future Virology 2012

Inhibitors of NS5A protein

Mechanisms of action	Inhibits HCV replication complex by unclear mechanisms involving interaction with the NS5A protein.
Approved agents	None Phase III: Daclatasvir, GS-5885
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

DAA activity is geno/subtype dependent

	NS3 protease inhibitors	NS5B polymerase nucleoside analogues	NS5B polymerase non-nucleoside analogues	NS5A inhibitors
Genotype activity	G1 (1b>1a) 2nd PI generation: Across all, but G3	Across all	G1 (1b >1a)	Across all (1b >1a)
Resistance barrier	LOW (1b>1a)	HIGH	LOW	LOW (1b>1a)
Cross-resistance	HIGH	LOW	Split out in 4 families	HIGH
Main drug resistance mutations	1a: R155K, V36M 1b: T54A/S, A156S, I170A	S282T	Specific for each family	M28T,Q30H/R L31M/F/V, P32L, Y93C/H/N

Poveda et al, Future Virol 2012

Natural polymorphisms influencing DAA susceptibility

Drug family	Key mutations associated with DAA resistance*	1a	1b	2	3	4	DAA affected by specific polymorphisms
NS3 protease inhibitors (no. NS3 sequences: 1612†)	T54A/S	1.4% S	0	0	0	5.5% S	Telaprevir, boceprevir
	V55A	1.2% A	0	0	0	0	Boceprevir
	Q80K	39.7% K	0	0	0	0	Simeprevir
	D168A/H/T/V/Q	0	0	0	99.2% Q	0	Simeprevir
NS5B non- nucleoside analogues (no. NS5B sequences: 1025†)	C316Y/N	0	36% N	0	0	0	ABT-333 (NNI-4) ABT-072 (NNI-4)
	M414T/L	0	0	0	0	34.2%L	Setrobuvir (NNI-3)
	L419M/V	0	0	2.7% V	0	0	VCH-759 (NNI-2)
	M423T/I/V	1.8 I	0	0	0	0	Filibuvir (NNI-2) VCH-759 (NNI-2) VHC-916 (NNI-2)
	I482L/V/T	0	0	100% L	100% L	100% L	VCH-759 (NNI-2)
	V494I/A	0	0	100% A	5.2%A	0	VCH-759 (NNI-2)
	V499A**	96.2% A	10.5%A	91% A	100%A	100%A	Tegobuvir (NNI-1) BI-7127 (NNI-1)
NS5A inhibitors (no. NS5a sequences: 3153†)	Q30H/R	0	0	0	0	51.3% R	Daclatasvir
	L31M/V/F	0	0	83.5 % M	0	92% M	Daclatasvir
	Y93C/H/N	0	2% H	0	0	5.4%H	Daclatasvir

Poveda et al, ICVH NYC 2012

HCV isolates containing Q80K displayed significantly reduced susceptibility to TMC-435

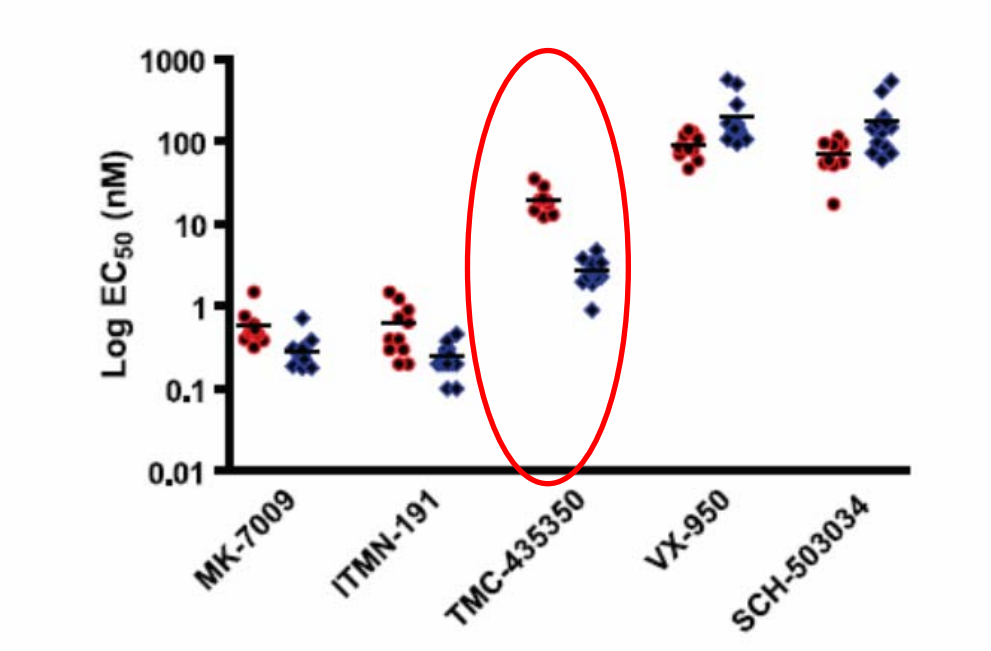


TABLE 4. Susceptibilities of mutants generated by site-directed mutagenesis

NS3 mutant	Fold change in EC_{50}[a]				
	VX-950	SCH-503034	TMC-435350	MK-7009	ITMN-191
T54S	**5.6**	**4.7**	0.7	0.5	1.0
Q80K	1.0	0.9	**10.9**	**6.6**	**6.3**
Q80K/T54S	2.3	1.7	**7.3**	**3.7**	**5.3**

[a] Fold change in EC_{50} = chimeric mutant replicon EC_{50}/wild-type replicon EC_{50}. The values represent the means from 2 or 3 independent experiments; the values in boldface represent >3-fold increases in the EC_{50}.

Bae et al, Antimicrob Agents Chemother 2010

ASPIRE trial (**TMC435**+pegIFN/RBV, IFN-experienced)

SVR to TMC435 based on HCV subtype (G1a vs. G1b) and presence or absence of Q80K polymorphism.

	G1a	GT1a with Q80K	G1a no Q80K	G1b
TMC100mg+ P/R N=197	45/81 (55.6)	5/23 (21.7)	40/57 (70.2)	83/113 (73.5)
TMC150mg+ P/R N=199	53/84 (63.1)	14/23 (60.9)	39/59 (66.1)	90/112 (80.4)
Placebo+P/R N=66	5/27 (18.5)	1/5 (20)	4/22 (18.2)	10/39 (25.6)

Lenz et al, EASL Barcelona 2012

Lack of activity of TMC435 against G3 due to the presence of D168Q polymorphism.

- Antiviral activity of TMC435 (monotherapy/7days) in 37 treatment-naive patients infected with HCV GT2 (6), G3 (8), G4 (8), G5 (7), G6 (8).

- Mean HCV RNA changes from baseline at day 3/8:

  G2: -2.02 / -2.73 log (V36L, Q80G, S122R) TMC435 activity in 3/6

  G3a: -0.16 / -0.04 log (V36L, D168Q)

  G4: -3.43 / -3.52 log (V36L, S122T, I170V) TMC435 activity in 2/8

  G5: -2.71 / -2.19 log (V36L, Q80K-all, S122A/G-some) TMC435 activity in all

  G6: -3.57 / -4.35 log (V36L, Q80K, or I170V-some, S122T/N-all) 2/8

- Resistance profile to G2, 4, 5 and 6 was similar to G1 (Q80R/K, R155K, and D168E/V, alone or in combination).

Lenz et al, IDRW Los Cabos, México 2011

Natural polymorphisms influencing DAA susceptibility

Drug family	Key mutations associated with DAA resistance*	1a	1b	2	3	4	DAA affected by specific polymorphisms
NS3 protease inhibitors (no. NS3 sequences: 1612†)	T54A/S	1.4% S	0	0	0	5.5% S	Telaprevir, boceprevir
	V55A	1.2% A	0	0	0	0	Boceprevir
	Q80K	39.7% K	0	0	0	0	Simeprevir
	D168A/H/T/V/Q	0	0	0	99.2% Q	0	Simeprevir
NS5B non- nucleoside analogues (no. NS5B sequences: 1025†)	C316Y/N	0	36% N	0	0	0	ABT-333 (NNI-4) ABT-072 (NNI-4)
	M414T/L	0	0	0	0	34.2%L	Setrobuvir (NNI-3)
	L419M/V	0	0	2.7% V	0	0	VCH-759 (NNI-2)
	M423T/I/V	1.8 I	0	0	0	0	Filibuvir (NNI-2) VCH-759 (NNI-2) VHC-916 (NNI-2)
	I482L/V/T	0	0	100% L	100% L	100% L	VCH-759 (NNI-2)
	V494I/A	0	0	100% A	5.2%A	0	VCH-759 (NNI-2)
	V499A**	96.2% A	10.5%A	91% A	100%A	100%A	Tegobuvir (NNI-1) BI-7127 (NNI-1)
NS5A inhibitors (no. NS5a sequences: 3153†)	Q30H/R	0	0	0	0	51.3% R	Daclatasvir
	L31M/V/F	0	0	83.5 % M	0	92% M	Daclatasvir
	Y93C/H/N	0	2% H	0	0	5.4%H	Daclatasvir

Poveda et al, ICVH NYC 2012

Natural polymorphisms at NS5A protein

Drug family	Key mutations associated with DAA resistance*	1a	1b	2	3	4	DAA affected by specific polymorphisms
NS5A inhibitors (no. NS5a sequences: 3153†)	Q30H/R	0	0	0	0	51.3% R	Daclatasvir
	L31M/V/F	0	0	83.5 % M	0	92% M	Daclatasvir
	Y93C/H/N	0	2% H	0	0	5.4% H	Daclatasvir

Antiviral Therapy 2012; 17:921–926 (doi: 10.3851/IMP2091)

Short communication

Prevalence of natural polymorphisms at the HCV NS5A gene associated with resistance to daclatasvir, an NS5A inhibitor

*Zulema Plaza[1], Vincent Soriano[1], Eugenia Vispo[1], Maria del Mar Gonzalez[1], Pablo Barreiro[1], Eduardo Seclén[1], Eva Poveda[1]**

[1]Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain

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

Abstract 795. Characterization of HCV NS5A resistance variants in naive patients infected with genotypes 2 and 3 receiving short-term treatment of daclatasvir in combination with pegylated interferon-alfa and ribavirin. *McPhee F et al.*

□ Plasma samples from 47 G2 and 53 G3 receiving DCV (60 mg QD) in combination with IFN-PEG/RBV were collected at baseline and at on-treatment time points when HCV-RNA was >1000 IU/mL. 85% SVR at week 12.

Conclusions

■ NS5A RAVs associated with DCV resistance in G1-infected patients were detected in *50% of G2* and *16% of G3* at baseline. However, virologic failure only ocurred in 3/100 patients, suggesting that detection of these pre-existing variants does not predict failure in G2 and 3.

Y93H was detected in G2 vB and in two G3 with detectable HCVRNA at wk12.

McPhee et al, AASLD, Boston 2102

SPRINT-2 & RESPOND-2 (BOC):

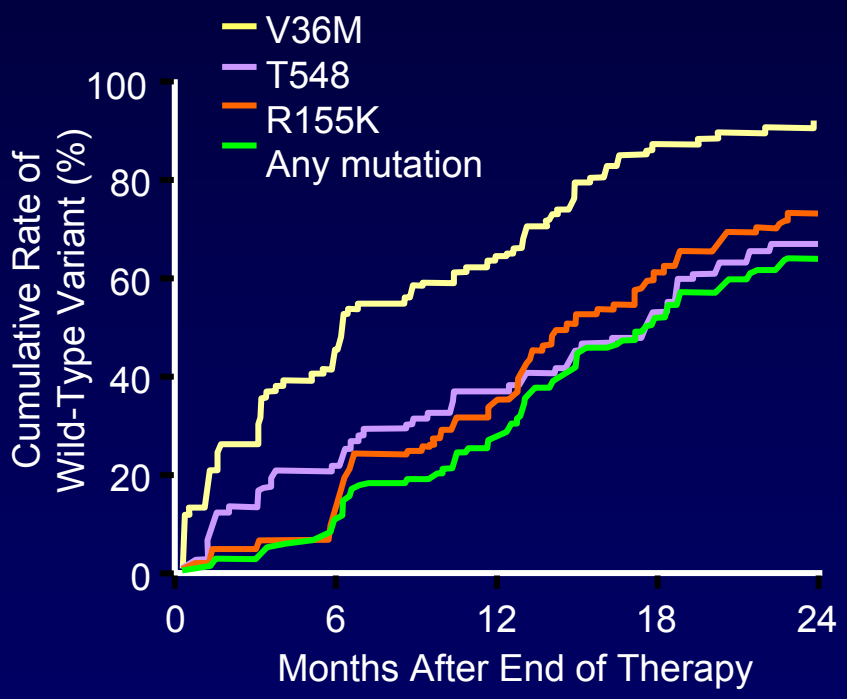
SVR rates by treatment week 4 response among patients with or without baseline RAVs detected

	Total†	Interferon Responders‡		Poor Interferon Responders§	
		Patient n	SVR (%)	Patients n	SVR (%)
Patients without Baseline RAVs	902	648	79%	254	34%
Patients with Baseline RAVs	64	51	76%	13	23%
Other Baseline RAVs	21	15	80%	6	50%
V36M, R155K, T54S/A and V55A	43	36	78%	7	0%

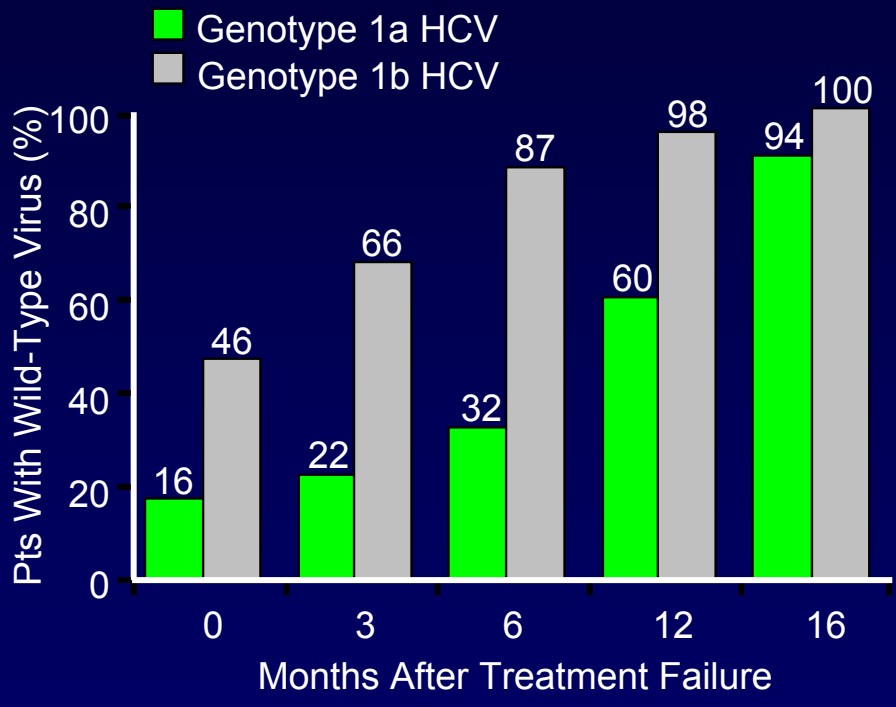
Brass et al, EASL Berlín 2011

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.

Conclusions & Clinical implications

□ The rate of natural polymorphisms associated with resistance to DAA is highly dependent of agents and HCV geno/subtypes (i.e. Q80K 25-40% G1a; simeprevir).

□ At baseline, the presence of RAVs and/or polymorphisms associated with resistance to DAA might be clinically relevant specially in ***IFN non-responders, genotype 1a,*** *and* ***non-CC IL28***. In these settings, baseline drug resistance testing might be justified before prescribing specific DAA agents.

□ In rescue interventions, the harmful impact of selected mutants to a given agent and cross-resistance to others could be minimized or removed after 16-24 months of the end of treatment.