HCV Resistance and Remaining Challenges

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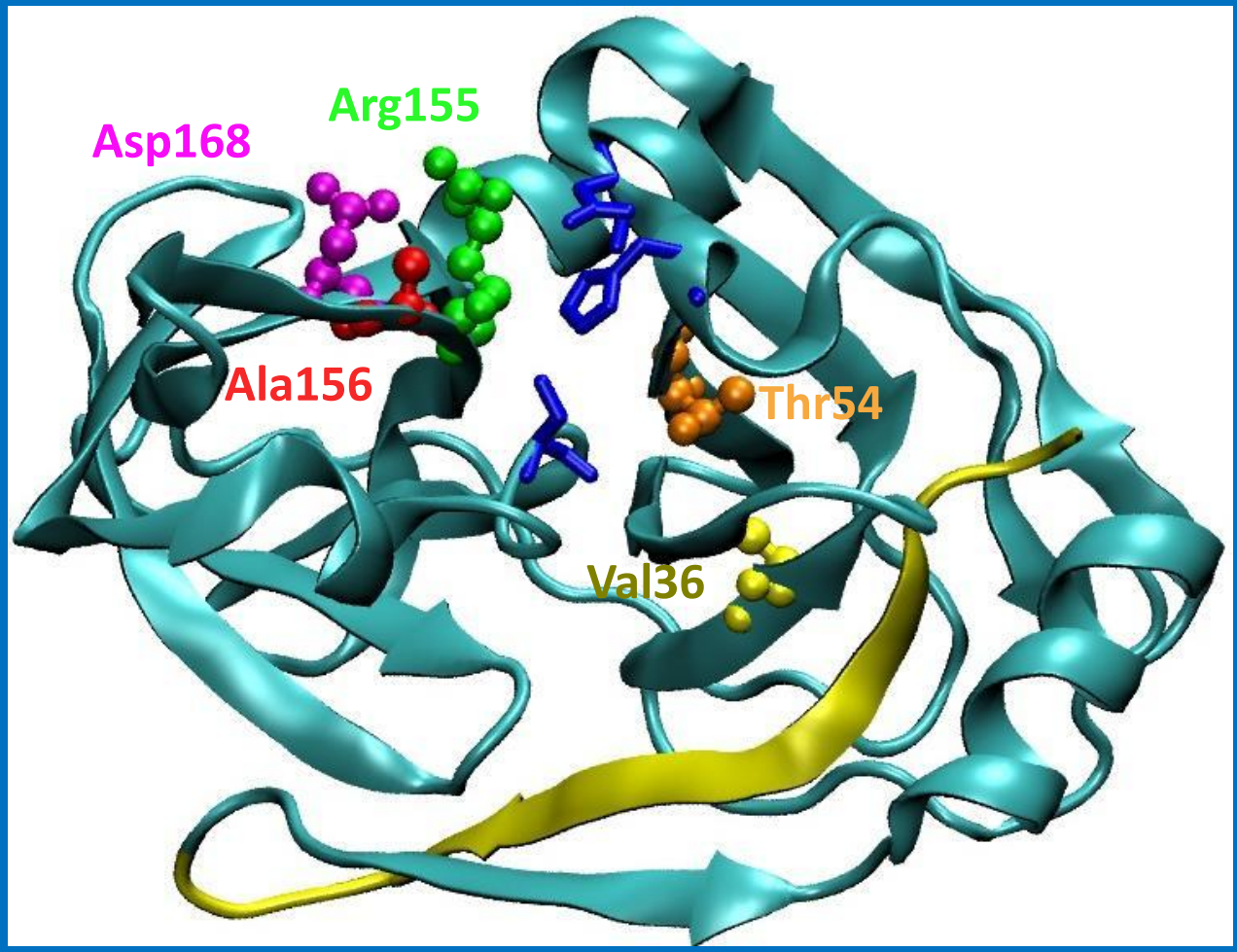
HCV Resistance

- Selection of preexisting HCV variants that are resistant to the specific drug, due to the presence of amino acid substitutions generally located within or in close vicinity to the target region, which grow according to their *in vivo* fitness and fill in the replication space

I

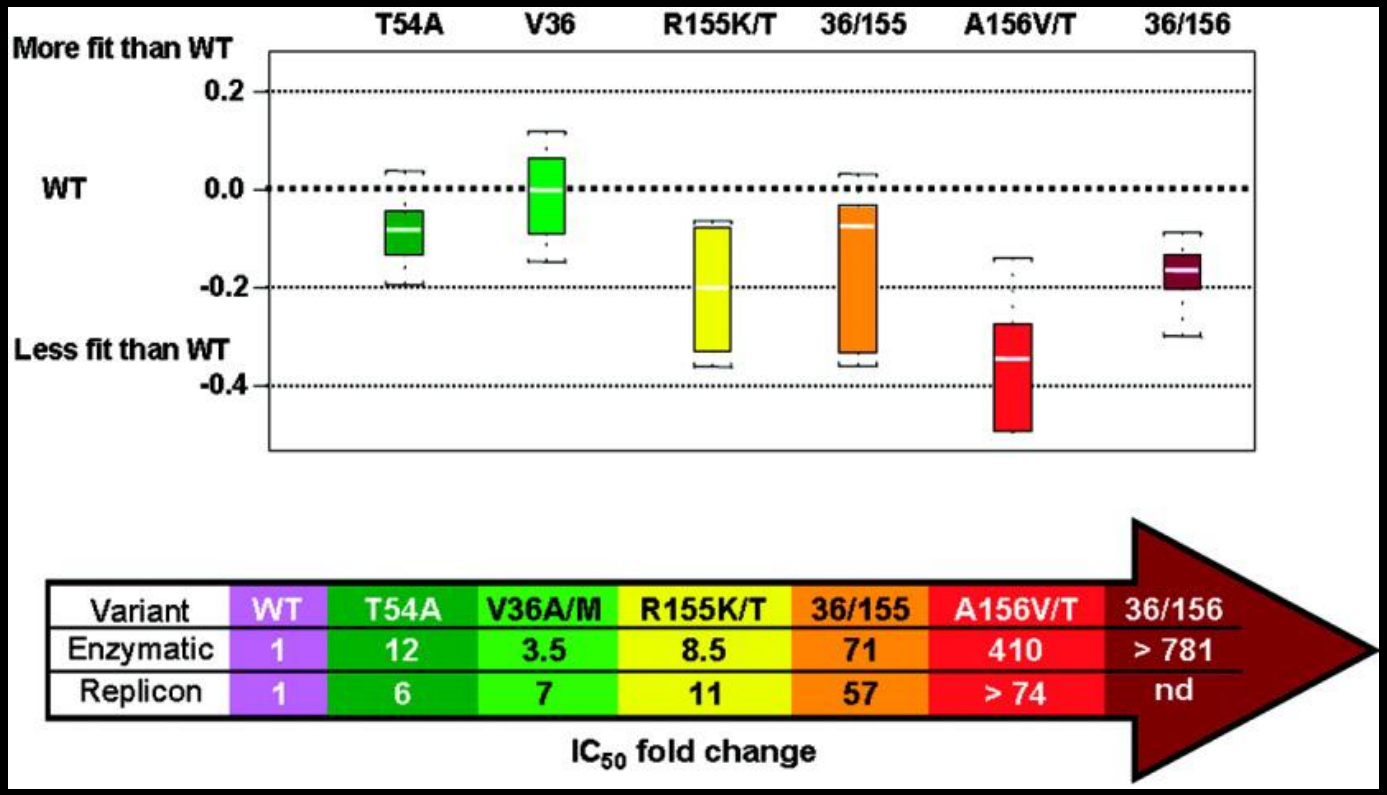
HCV Resistance to DAAs

Amino Acid Substitutions Associated with PI Resistance



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

Resistance and Fitness



Variant	WT	T54A	V36A/M	R155K/T	36/155	A156V/T	36/156
Enzymatic	1	12	3.5	8.5	71	410	> 781
Replicon	1	6	7	11	57	> 74	nd

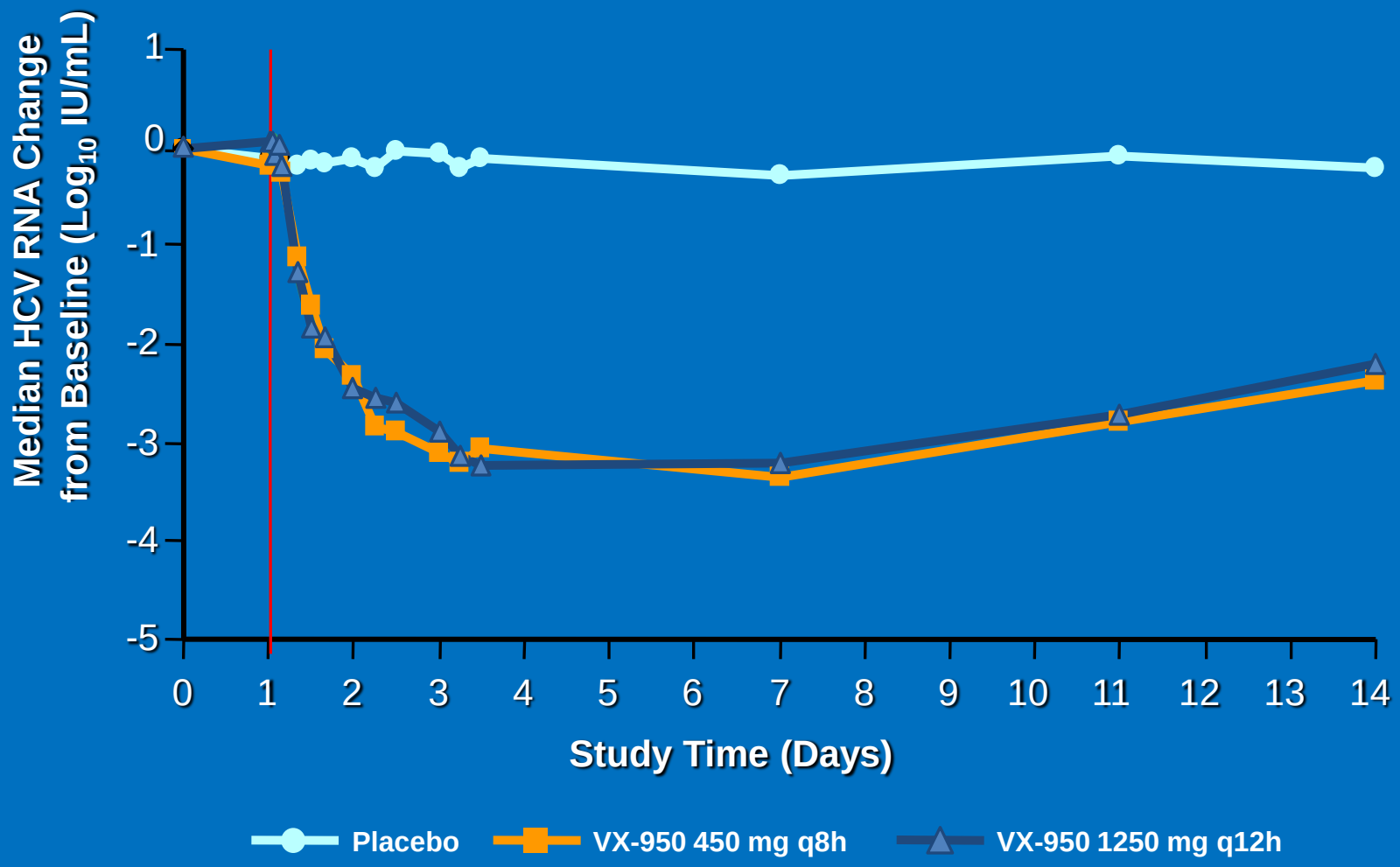
IC_{50} fold change

In vivo fitness

Resistance

(Kieffer T, et al. Hepatology 2007;46:631-9)

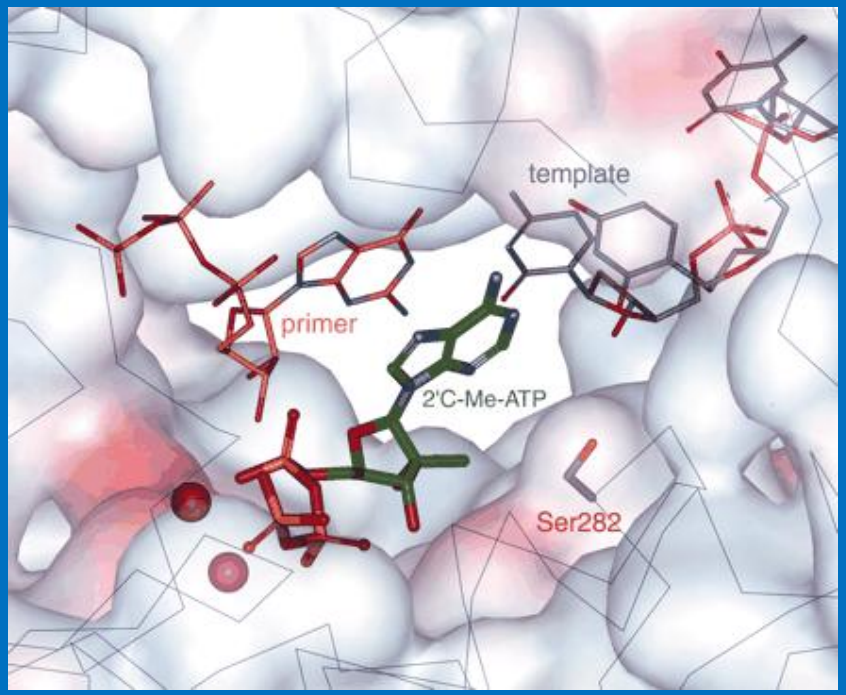
Telaprevir Resistance



(Reesink HW, et al. Gastroenterology 2006;131:997-1002)

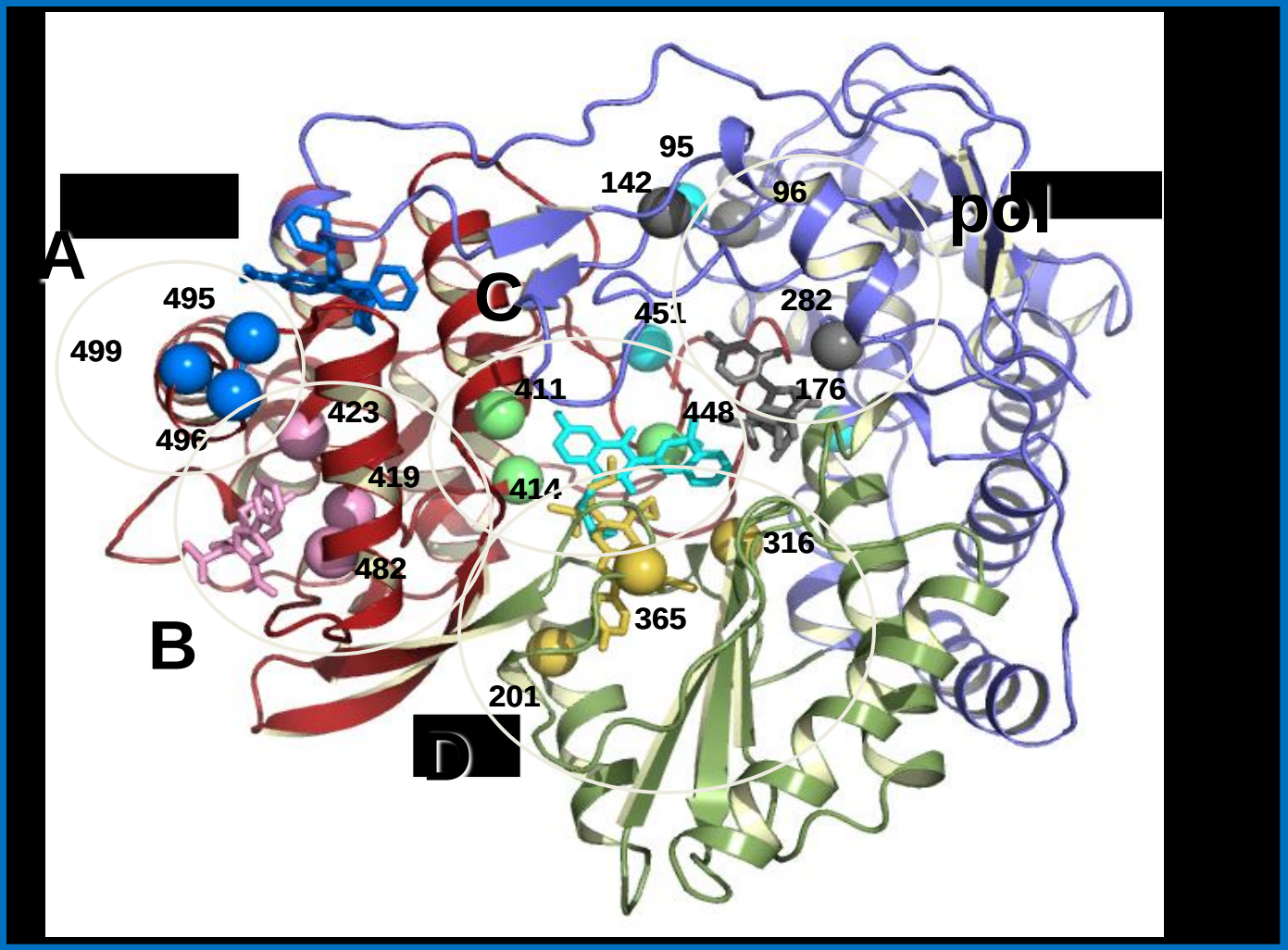
HCV Resistance to 2’-C-Methyl Nucleoside Inhibitors

2’C-Me-ATP in the catalytic site



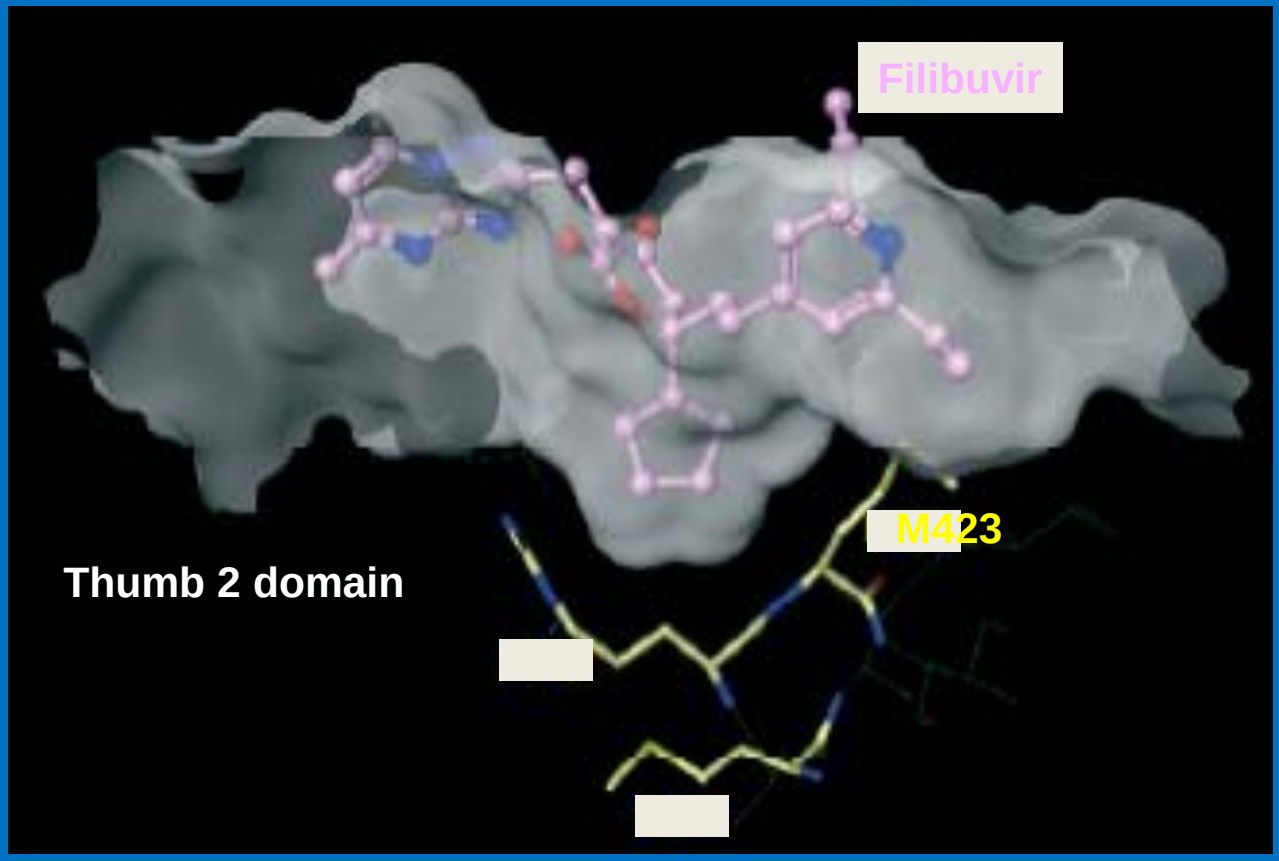
(Migliaccio et al., J Biol Chem 2003;278:49164-70)

RdRp Resistance Mutations



(courtesy of Isabel Najera, Roche)

Filibuvir (Pfizer) Resistance in IFN Null-Responders



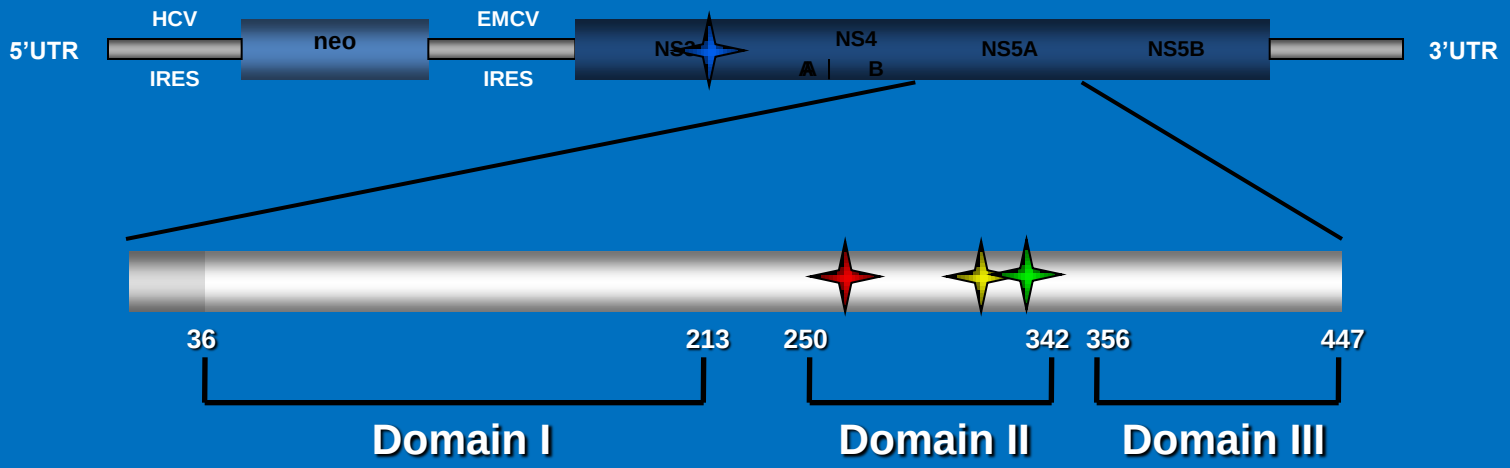
(Mori et al., EASL 2010)

BMS-790052 Resistance *in vitro*

Subtype	Sustitution	EC50	Fold-change	Replication level (% wt)
1b replicon	wt	2.6±0.3	1	100
	L31V	61±15	24	144±47
	Y93H	49±13	19	20±7
1a replicon	wt	5.9±3.7	1	100
	M28T	4,100±360	360	31±23
	Q30H	8,700±1,900	1,900	75±31
	Q30R	7,300±1,100	1,100	41±16
	L31M	2,100±610	610	55±15
	L31V	20,000±6,000	6,000	117±29
	Y93C	11,000±4,000	4,000	11±7

(Gao et al., Nature 2010;465:96-100)

Alisporivir Resistance *in vitro*



A241P R262Q R318W D320E

	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

(Coelmont et al., EASL 2009)

II

Failure of the Triple Combination of PegIFNα, Ribavirin and a PI to Eradicate HCV

Treatment Failures on Triple Combination with a DAA

- Treatment-Naïve: 20-30%
- Treatment-experienced: 40-50%

Expected Higher Failure Rates in Difficult-to-Treat Patients

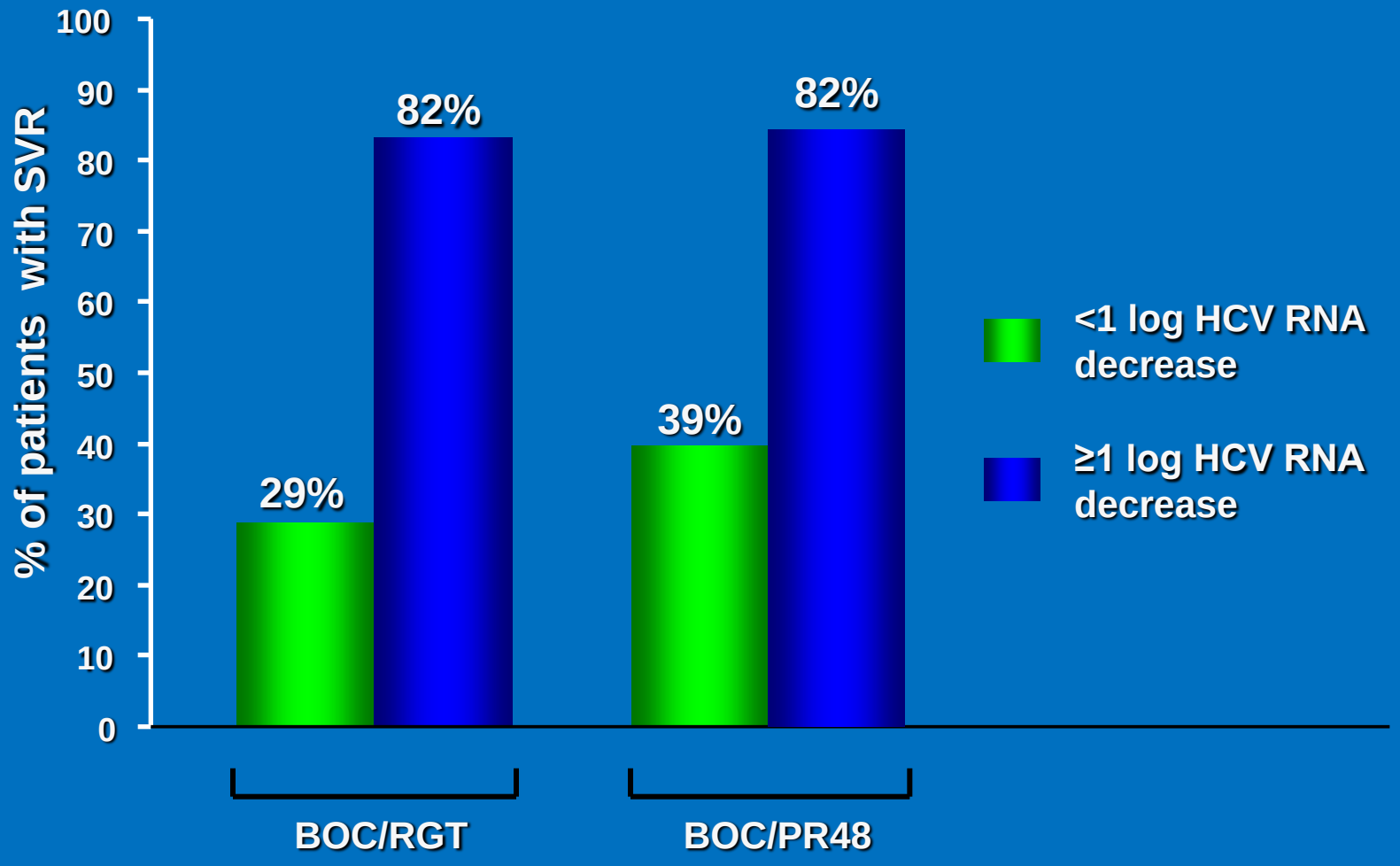
- Advanced liver disease
- Liver transplant
- HIV coinfected
- Hemodialysis
- Immunosuppressed patients
- African Americans
- etc…

Treatment Failures on Triple Combination with a DAA

- Insufficient response to Peg-IFNα and ribavirin
- Uncontrolled outgrowth of DAA-resistant HCV variants

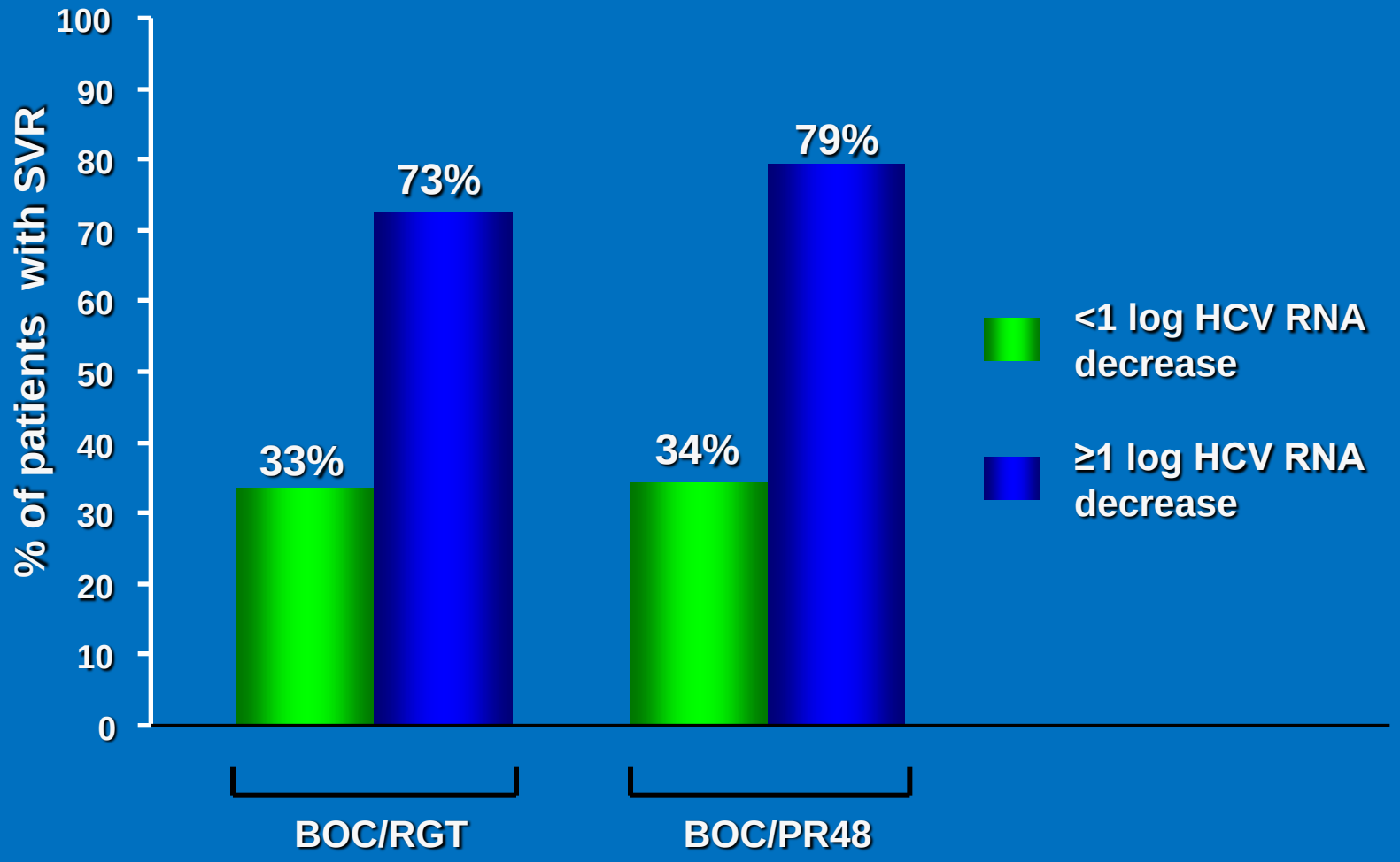
SVR According to Lead-in

(SPRINT-2, non-black)



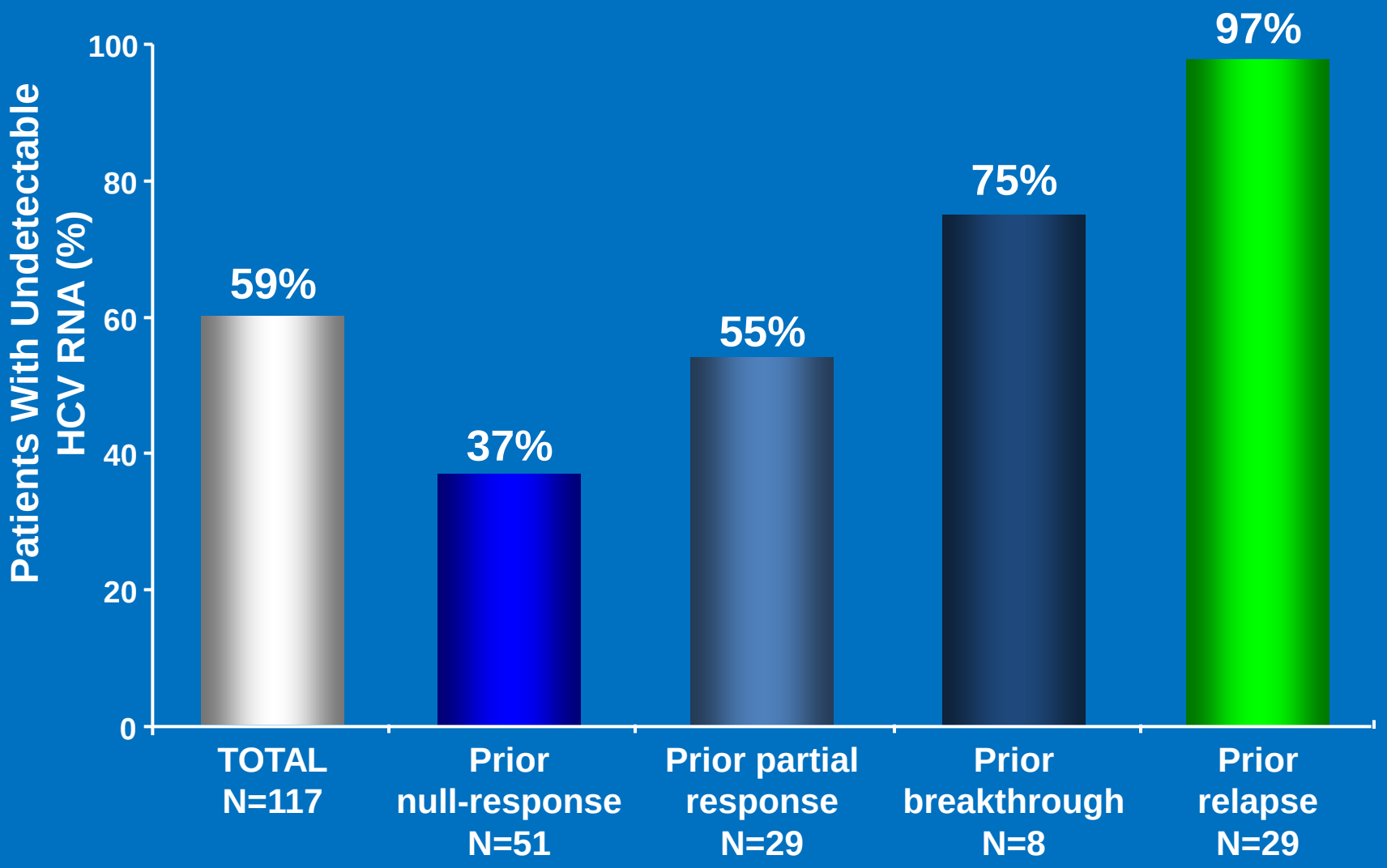
(Poordad et al., AASLD 2010)

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



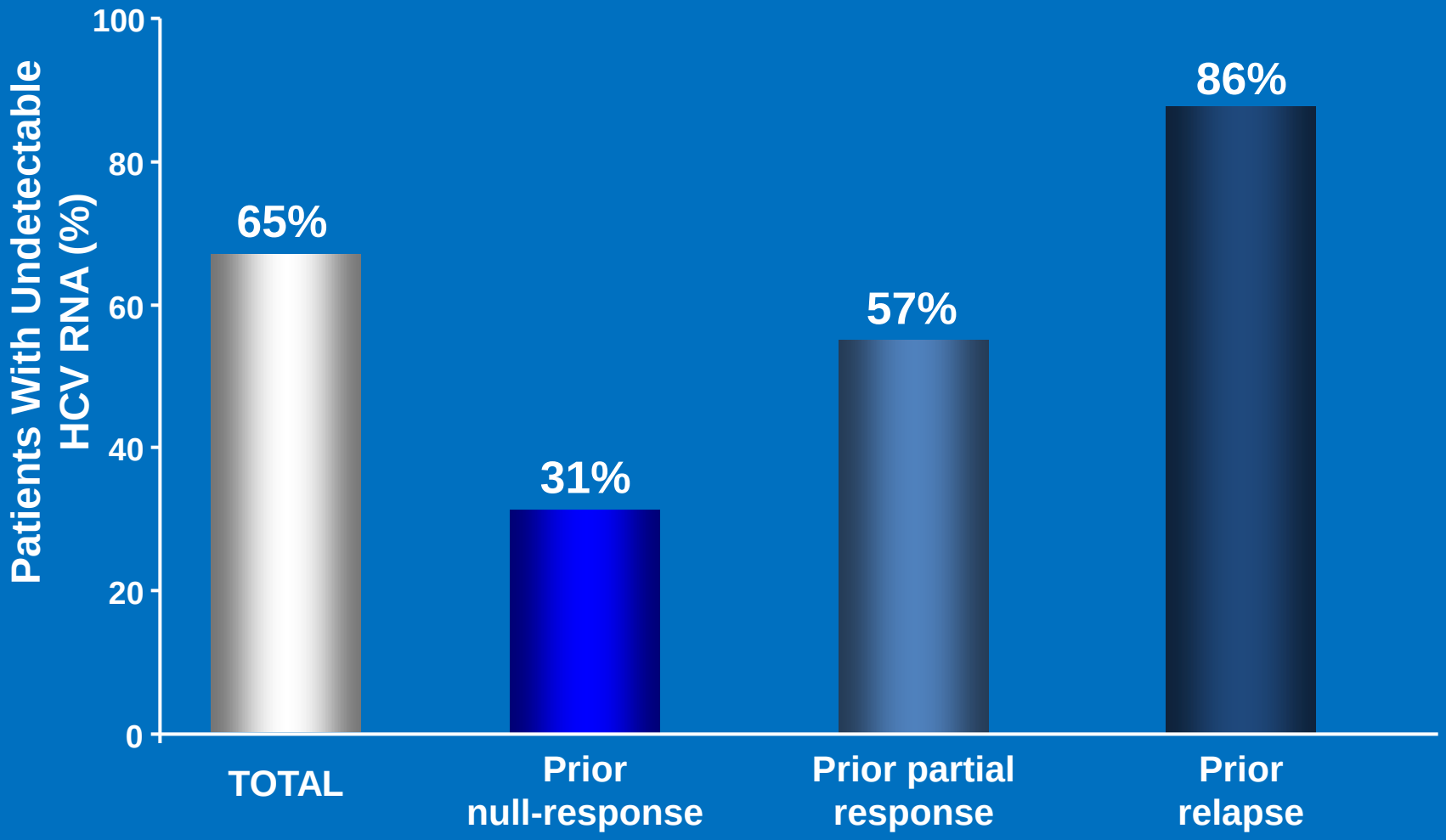
(Bacon et al., AASLD 2010)

Telaprevir Rollover Study 107



(Berg et al., EASL 2010)

REALIZE Trial-Telaprevir Arms



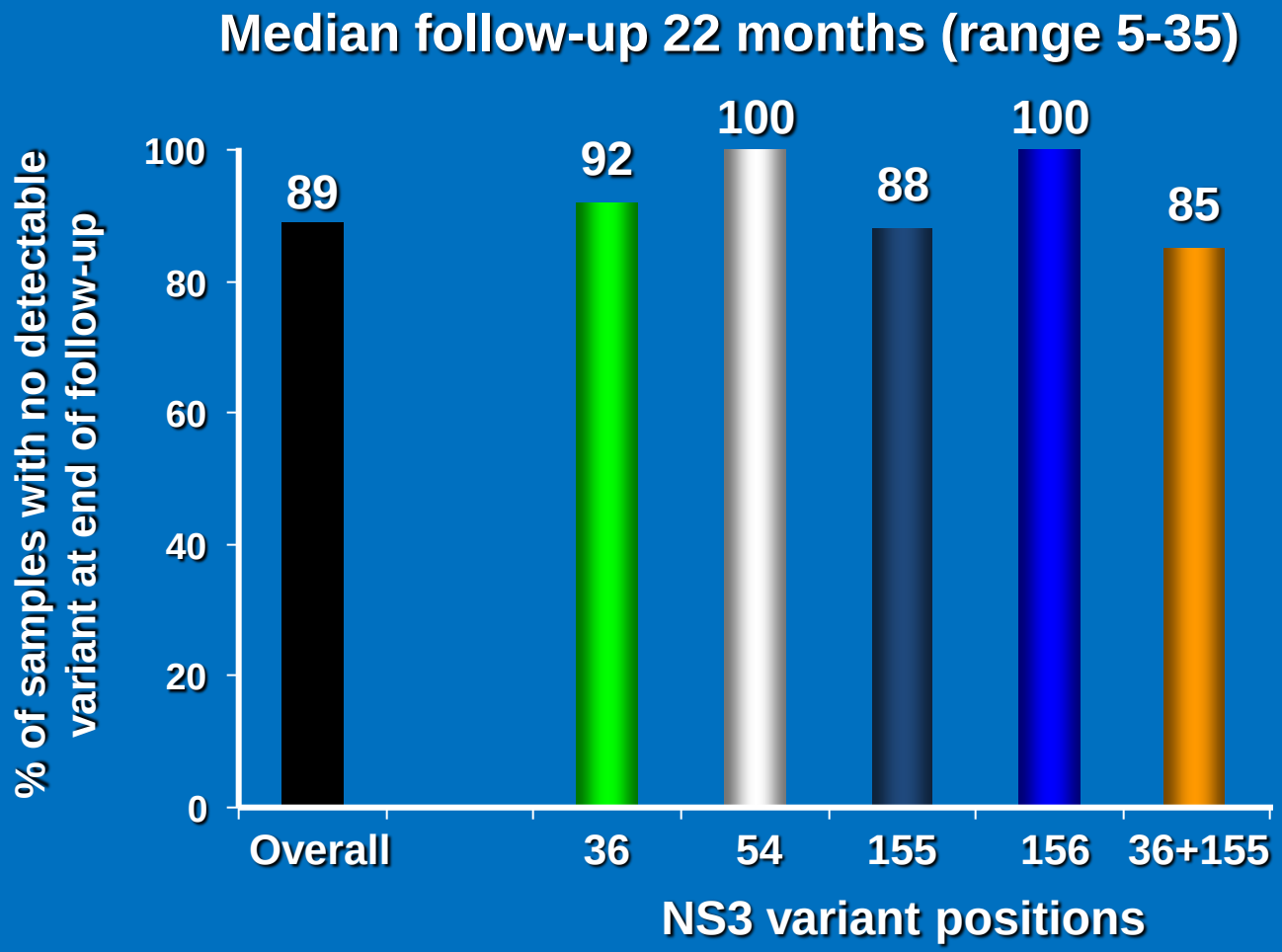
(Vertex press release, Sept 7, 2010)

Incidence of HCV resistance

Arm	Event	N	VL <LOD	Wild-type	Low-level resistance	High-level resistance
T12PR24	Breakthrough	4	-	-	-	4
	Relapse	8	-	1	4	3
T12PR12	Breakthrough	1	-	1	-	-
	Relapse	19	3	1	13	2
T12P12	Breakthrough	19	2	-	9	8
	Relapse	22	4	-	16	2

(Hézode et al., N Engl J Med 2009;360:1839-50)

Long-Term Follow-Up After Treatment Failure (EXTEND)



(Zeuzem et al., AASLD 2010)

Conclusions

- The administration of DAAs is always associated with the selection of resistant HCV variants
- In combination regimens, the antiviral effect of pegylated IFNα and ribavirin prevents the growth of DAA-resistant variants and leads to viral eradication
- Treatment failure with the triple combination of pegylated IFNα, ribavirin and a DAA is due to an insufficient antiviral response to IFNα and ribavirin

Conclusions

- Treatment failure is characterized by the outgrowth of DAA-resistant HCV variants, as a result of virtual monotherapy with the DAA

- Prevention of treatment failure in patients with an insufficient response to pegylated IFN and ribavirin is based on:
    - An accurate assessment of IFN responsiveness (lead-in phase, baseline parameters)
    - Alternative options for true IFN null responders that must be assessed in prospective clinical trials