Resistance to DAAs: is it a real issue ?

Today yes

Tomorrow may be no

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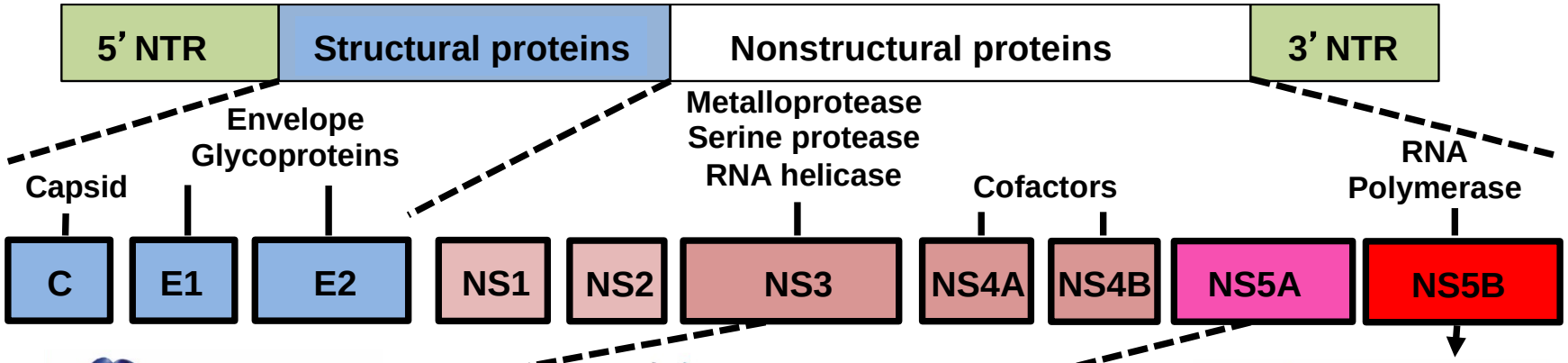
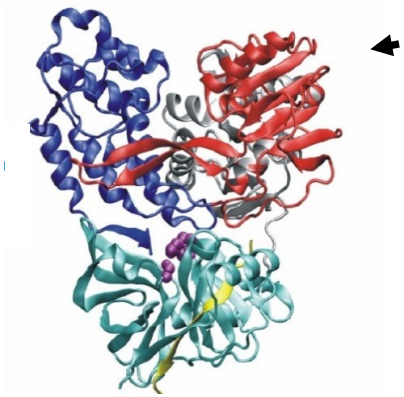
Progress in the Treatment of Hepatitis C

	HBV	HIV	HCV
Genome	DNA	RNA	RNA
Mutation rate	+	+++	+++
Daily viral production	1013	1010	1012
Viral Reservoir	cccDNA	Integrated c DNA	None
Therapeutic strategy	Single	Multiple	Multiple
recovery	No	No	Yes

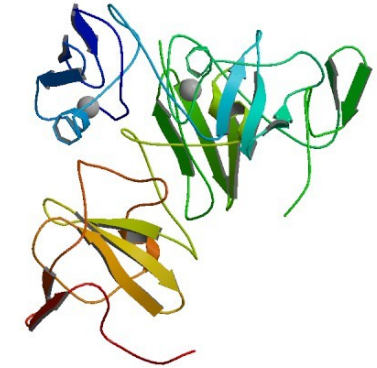
Targets for DAAs





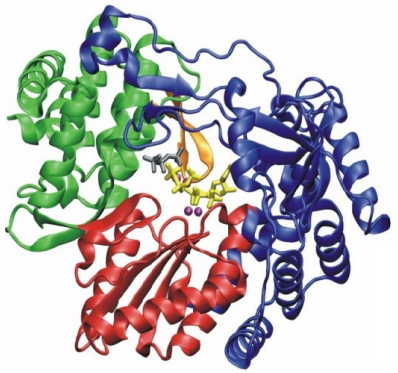
Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir
ABT-450
MK-5172
Sovaprevir
ACH-2684



NS5A Inhibitors

Daclatasvir
Ledipasvir
ABT-267
GS-5816
ACH-3102
PPI-668
GSK-2336805
Samatasvir
MK-8742



Polymerase Inhibitors

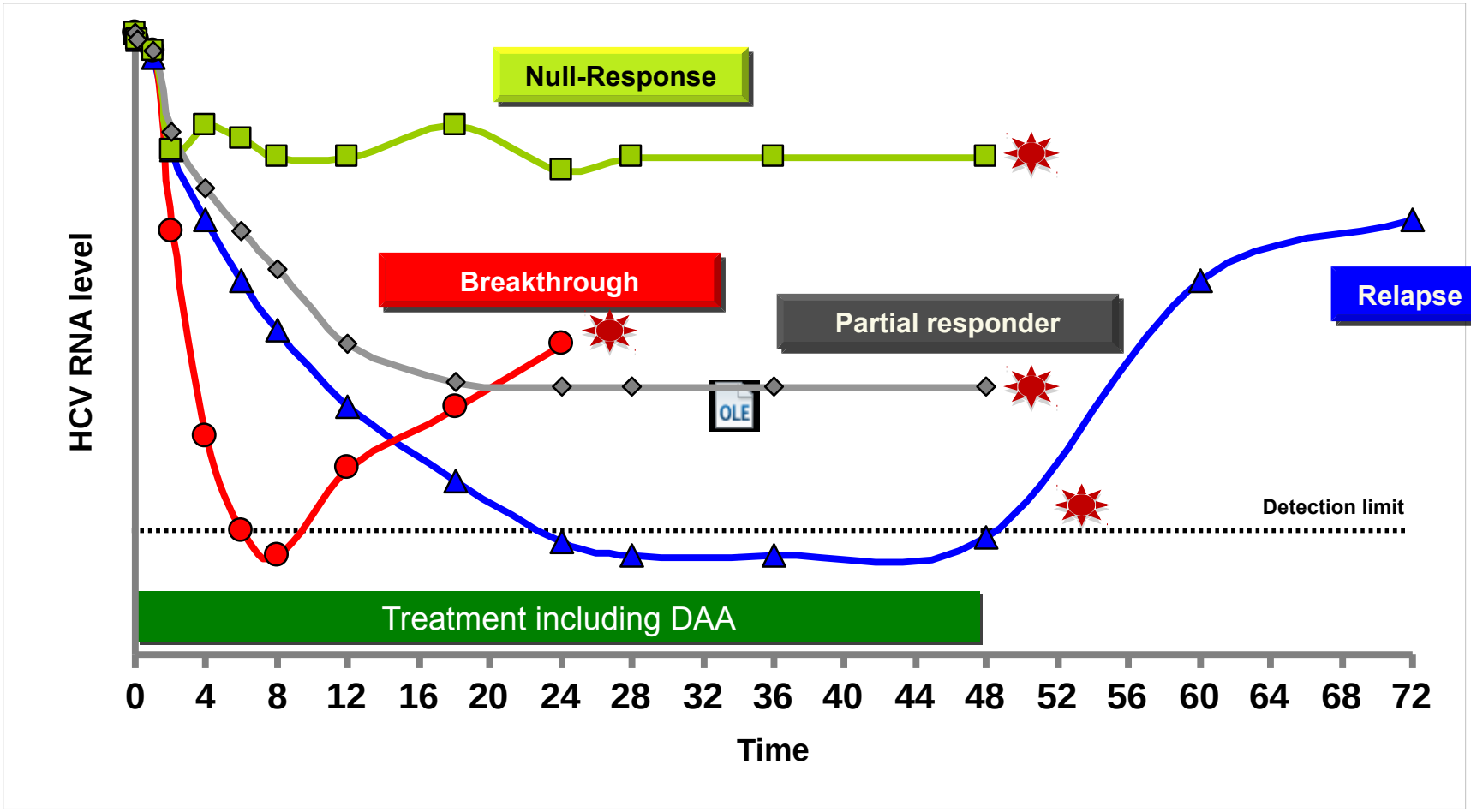
Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	Deleobuvir
IDX-20963	BMS-791325
ACH-3422	PPI-383
	GS-9669
	TMC-647055

Asselah T et al. Liver International 2013

Resistance to specific HCV inhibitors

- **Selection of viral variants bearing amino acid substitutions alters the drug target and thereby confers reduced susceptibility to the drug**

Resistance to specific HCV inhibitors



Resistance mutants

DAA – Direct acting antiviral agents

Adapted from Zoulim F, PHC 2012

Factors influencing viral resistance with DAA

Viral Factors

- Level of viral replication (1012/day)
- Low fidelity of polymerase
- Impact of mutations on fitness
- Viral quasi-species
- Half-life of infected hepatocytes

Resistance

Pharmacological Factors

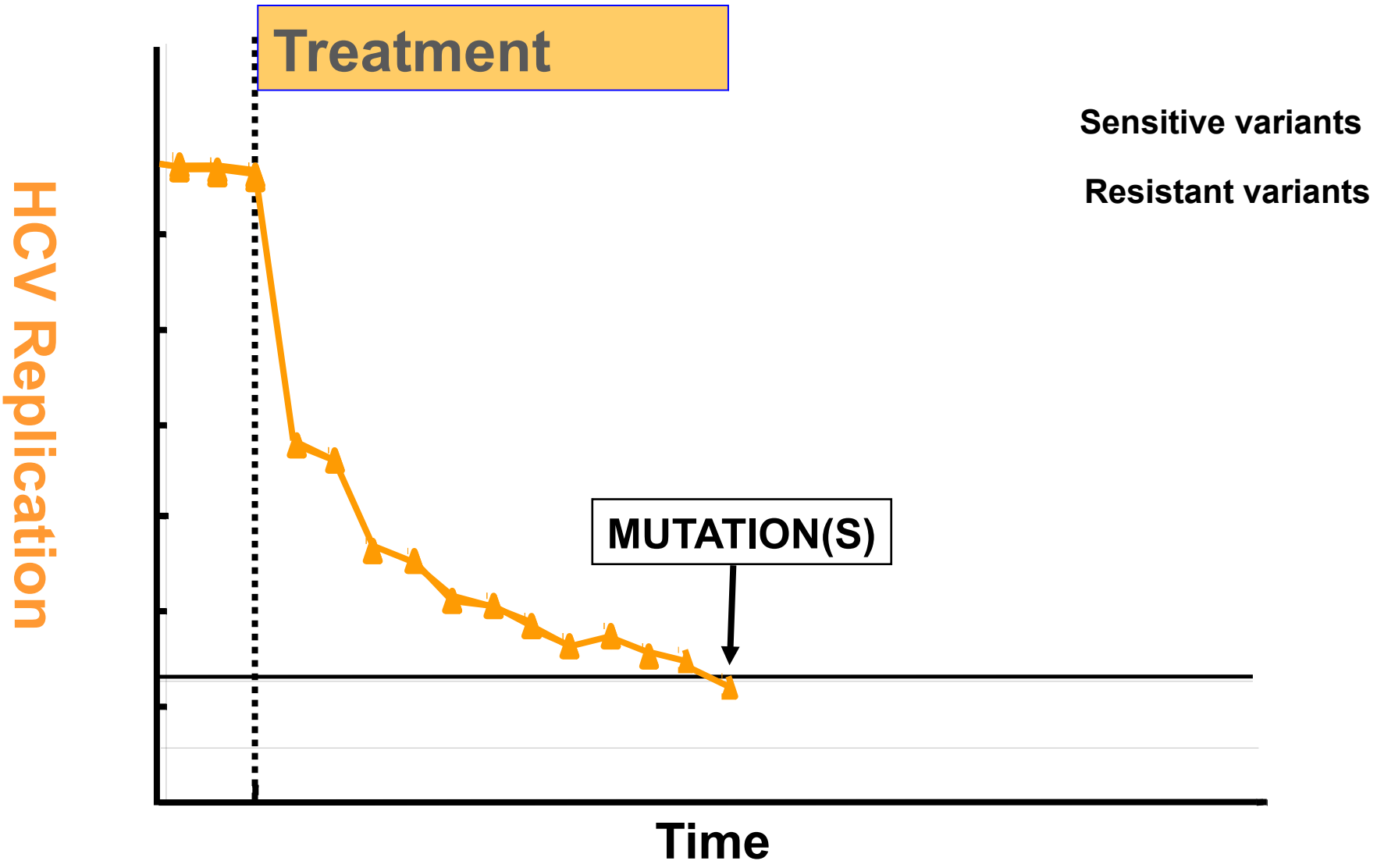
- Drug potency
- Genetic barrier
- Pharmacokinetic

Host Factors

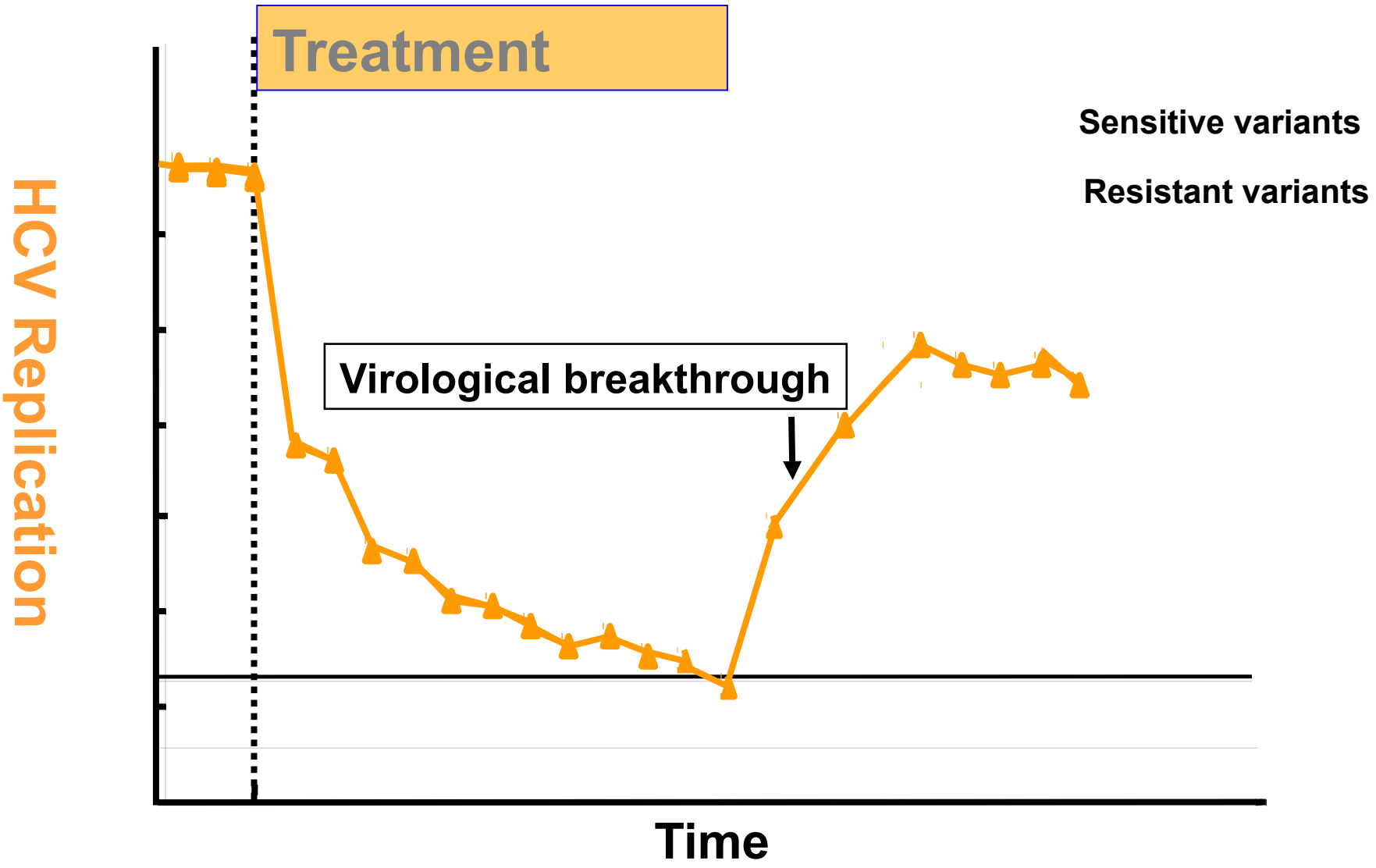
- Compliance
- Immune system
- Replication space
- Activity of protein kinase
- Nucleos(t)ide

Emergence of resistance during antiviral therapy

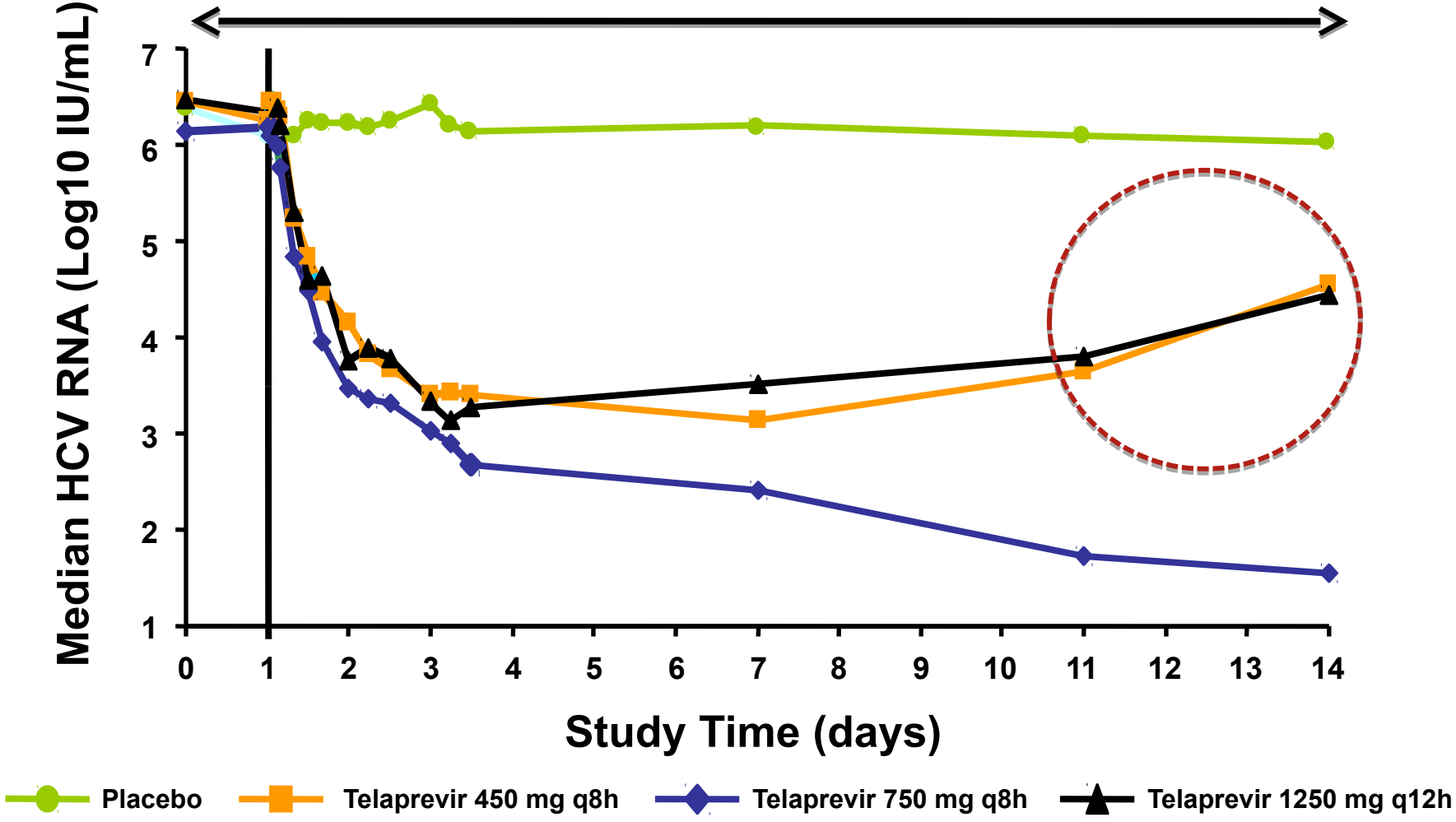
Emergence of resistance during antiviral therapy



Emergence of resistance during antiviral therapy



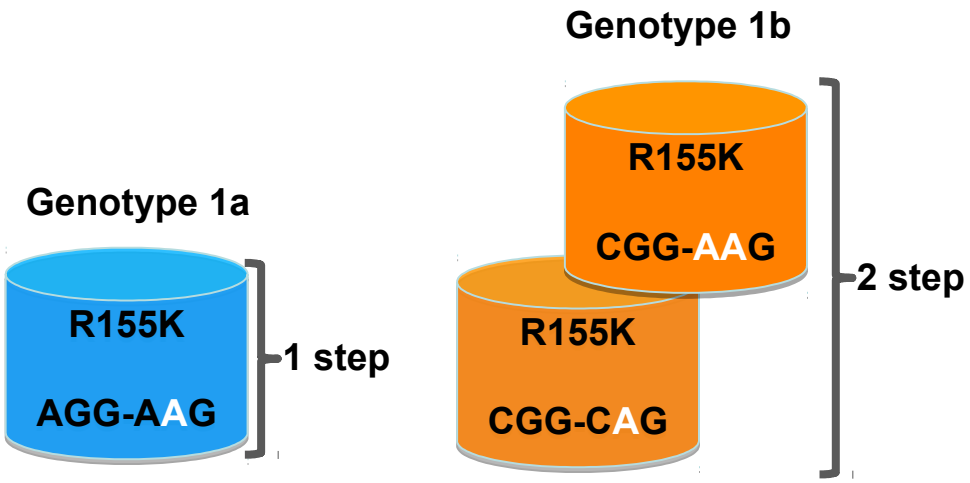
Resistant-associated viruses (RAVs) are rapidly selected by Telaprevir alone



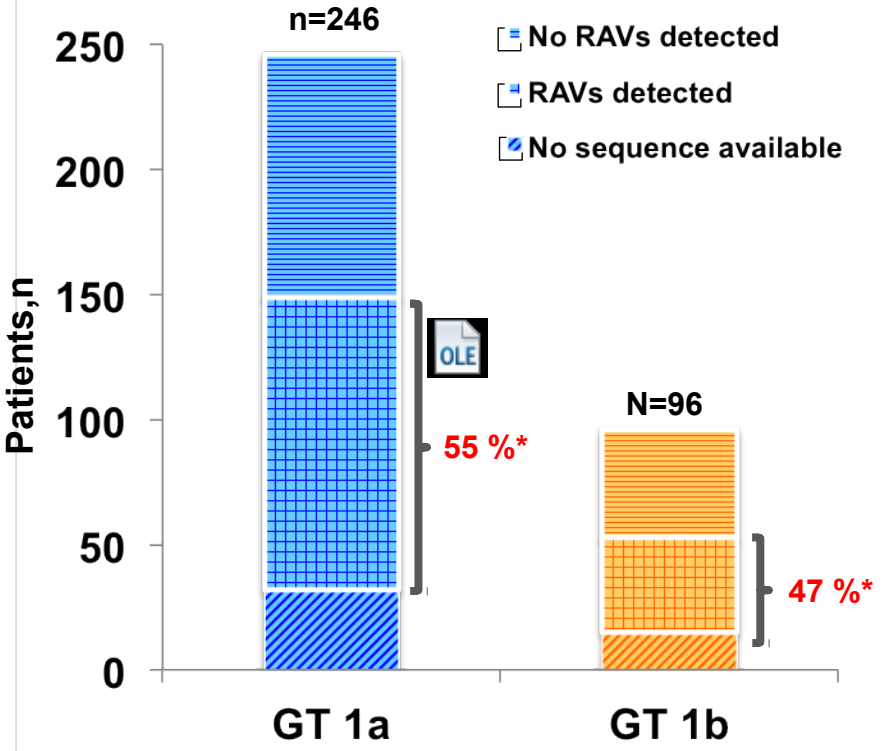
Reesink HW, et al. Hepatology. 2005;42:234A.

Subtype impacts the genetic barrier to resistance to Protease Inhibitors (PI)

Number of nucleotide substitutions needed according subtype



RAVs in GT1 patients who failed to BOC PR treatment (Sprint-2 and Respond-2)

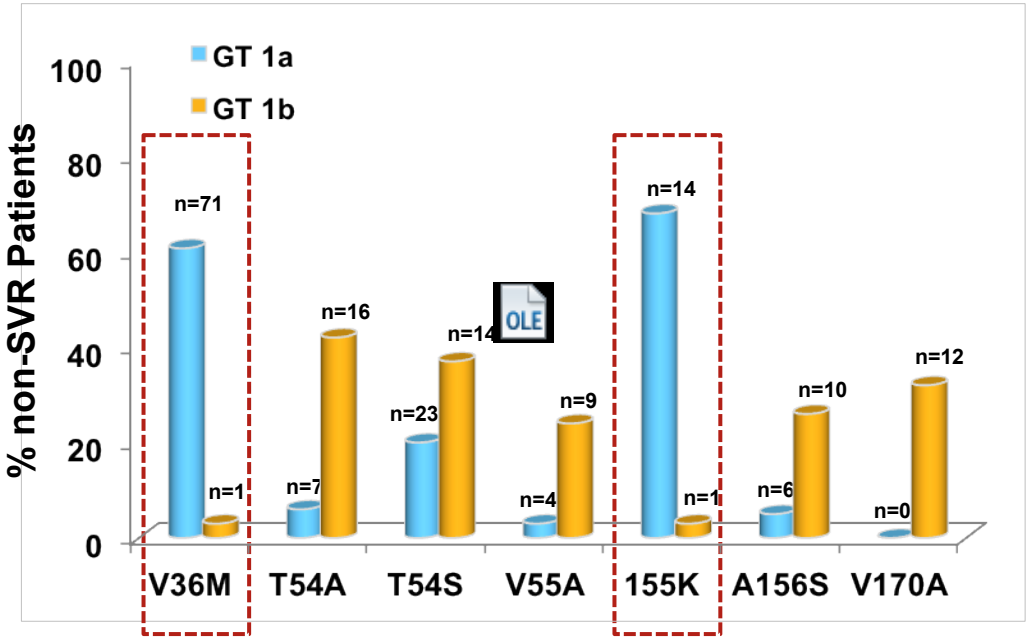


Patients with HCV GT1a showed a higher rate of RAVs than GT1b

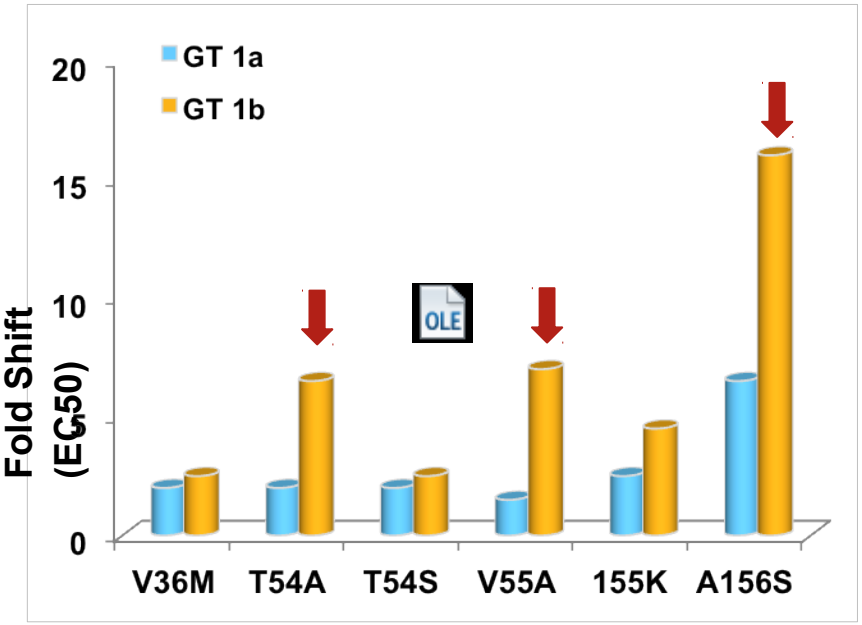
Ogert et al. AASLD 2013, Abst. 927

Different patterns of Resistance to BOC in GT1a vs GT1b

Frequency of the most common RAVs in GT1a and GT1b infected patients



In vitro Characterization of Boceprevir RAVs in HCV replicons



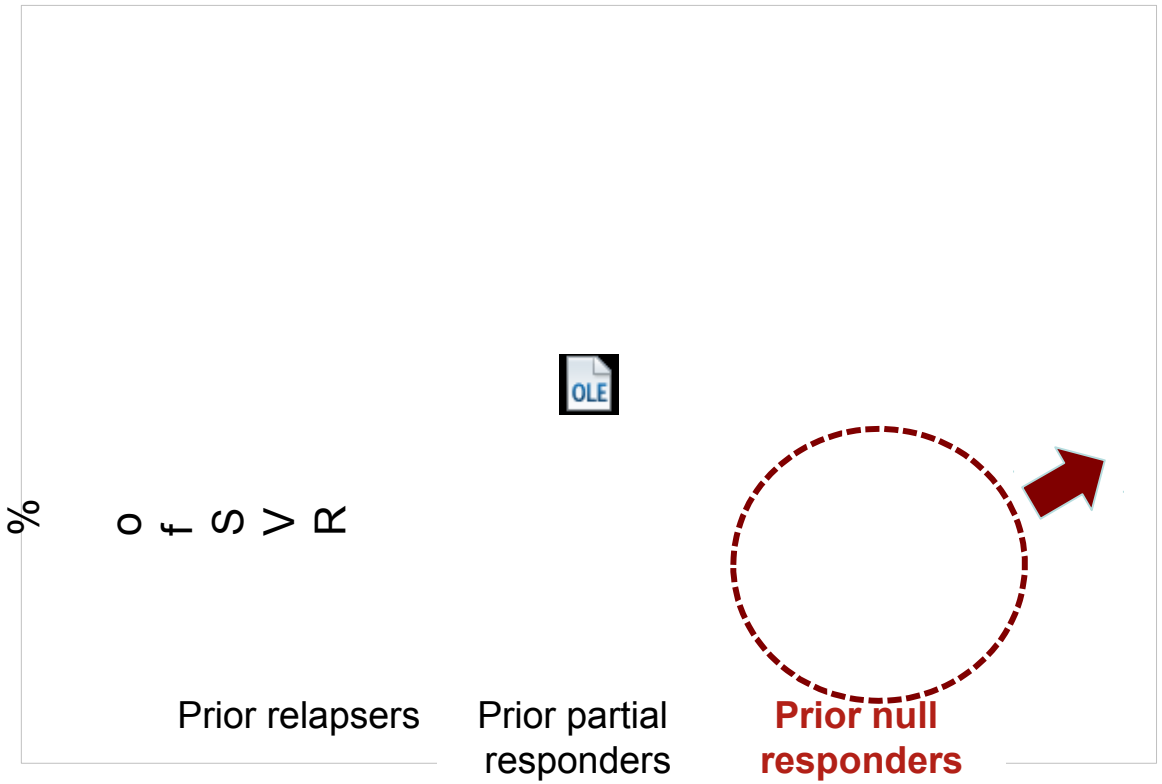
Differential patterns of RAVs were observed in GT1a vs GT1b patients who dis not achieve SVR.

RAVs found in GT1b appear to have higher level of resistance than those in GT1a

Ogert et al. AASLD 2013, Abst. 927

The subgroup of Prior null responders: Selection of RAVs

REALIZE trial (Telaprevir)



Only 14% of Prior Null responders with cirrhosis achieved SVR

Zeuzem et al. NEJM 2011

The subgroup of Prior null responders: Selection of RAVs

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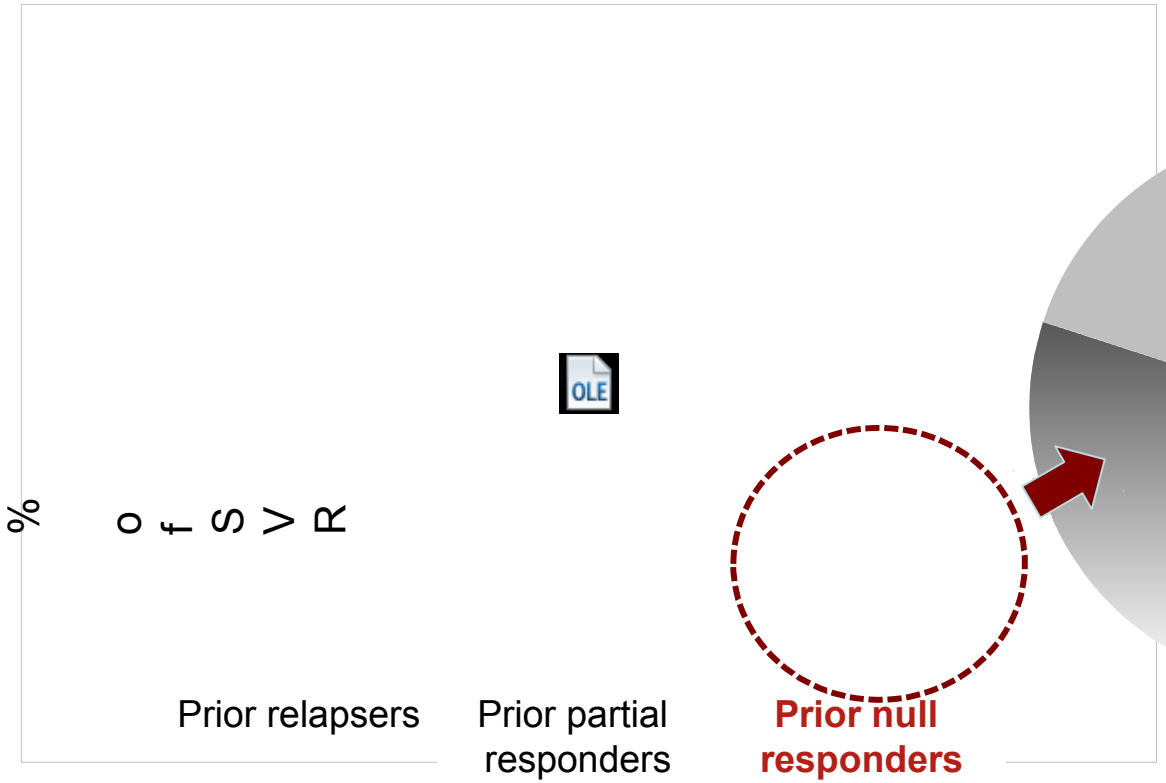
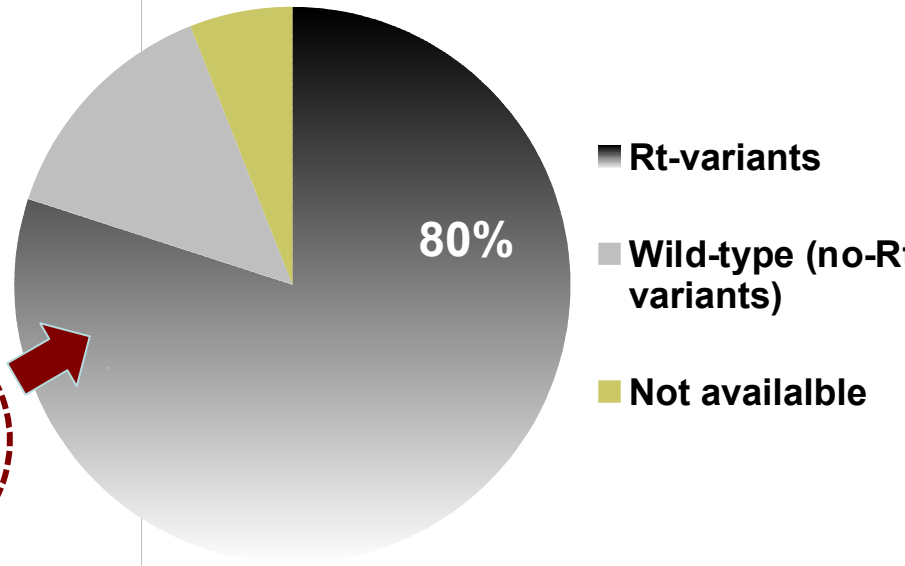


Characterization of Viral Variants in prior null responders without SVR.



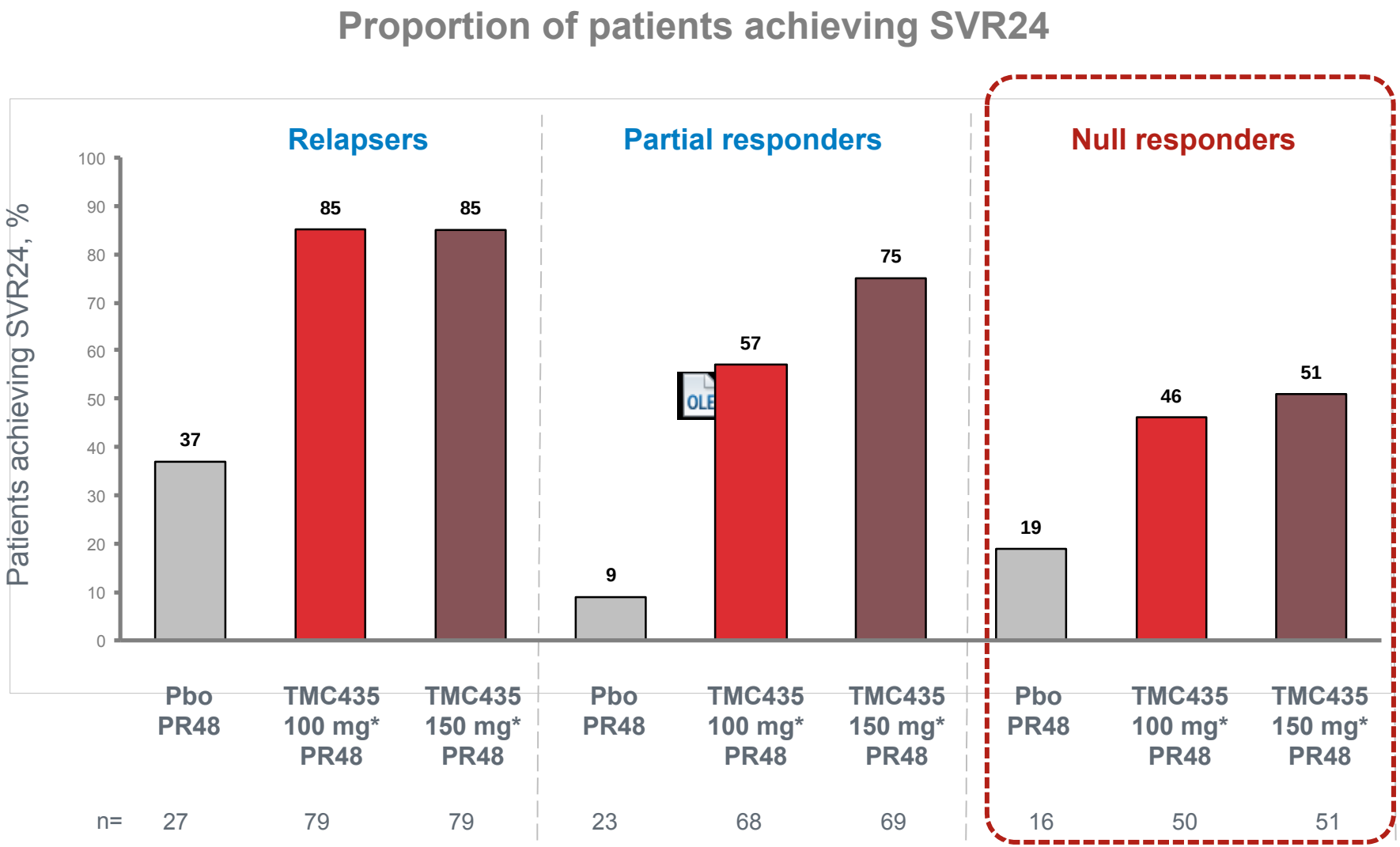
- **So, the poor response favors the growth of resistant virus selected by telaprevir or boceprevir.**

Zeuzem et al. NEJM 2011

De Meyer et al. Hepatology 2012

PI 2nd generation : TMC435 (ASPIRE trial):

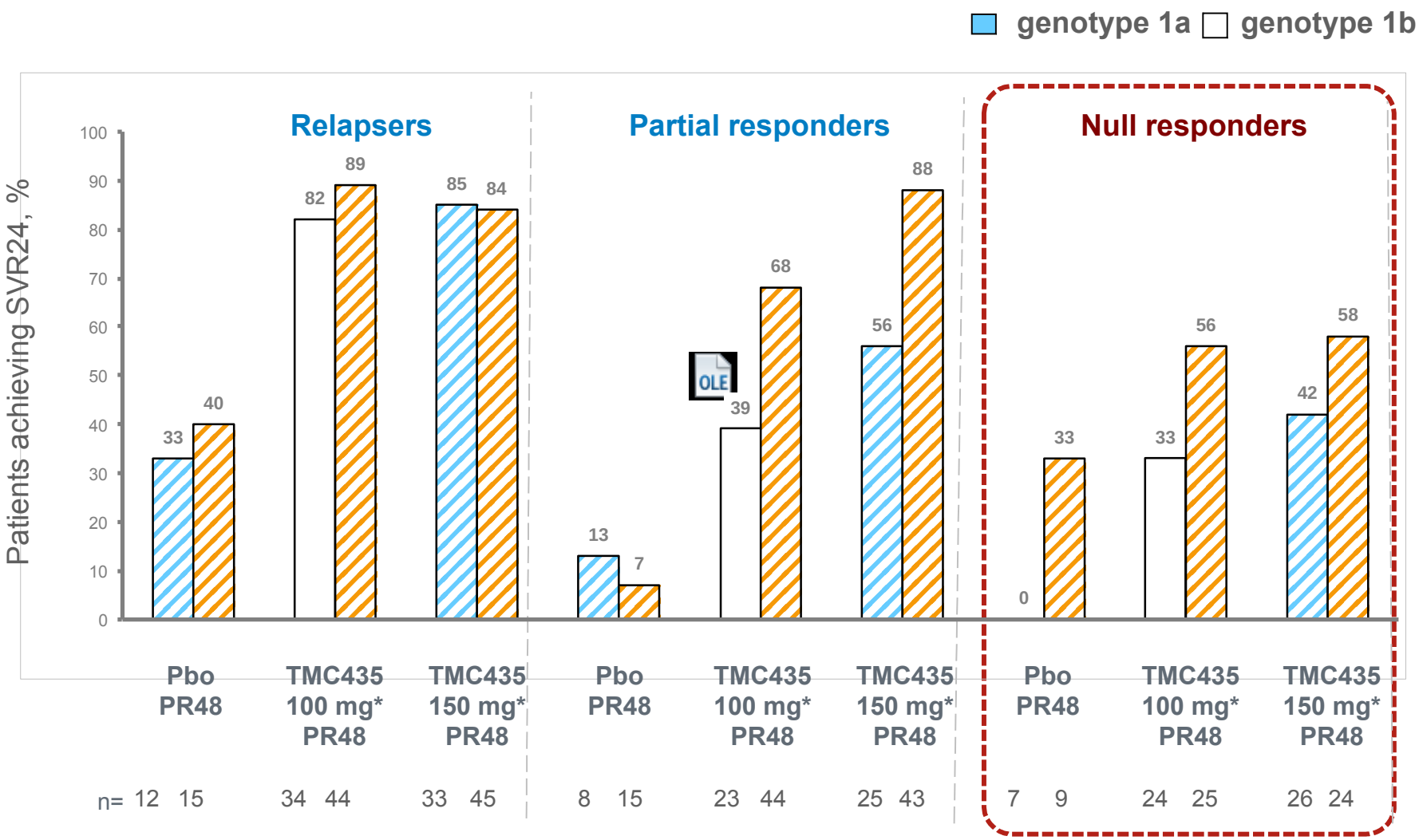
ASPIRE trial: n= 411 HCV GT 1 patients who had failed to respond or relapsed following pegIFN/RBV therapy.



Zeuzem et al. Abst 2998. EASL 2011

* Duration groups pooled; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after the end of ttt

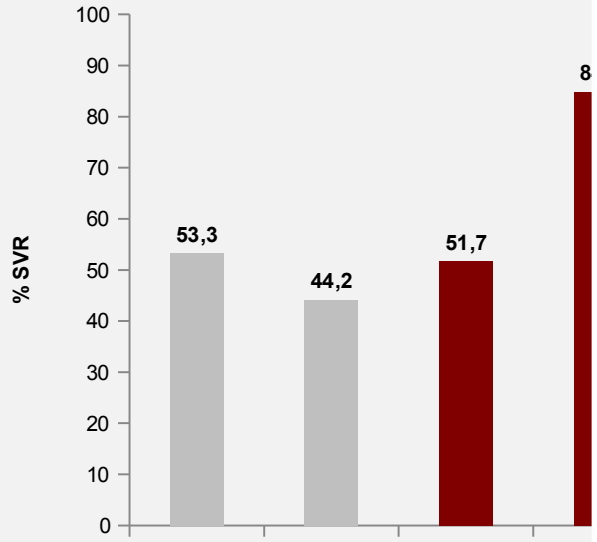
ASPIRE: SVR24 by prior response and HCV genotype subtype



Zeuzem et al. Abst 2998. EASL 2011

* Duration groups pooled; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after the end of ttt

Q80K mutation observed in Naïve HCV GT1 patients treated with TMC-435



Author of study (year)	Genotype 1a – prevalence of baseline Q80k polymorphism	Data source*	Total
Bae 2010	45.1%	Susceptibility testing on samples from Los Alamos and Gilead Sciences databases	N=268 isolates (1a) N=372 isolates (1b)
Kirst 2011	53% *	Sequencing analysis	N=22 (1a=15, 1b=7) subjects
Bartels 2013	38%	Sequencing analysis on patients from Phase II-III trials of telaprevir	N=3447 patients
SMV C08/C216 pooled analysis	48.1%	TMC435 phase 3 naïve clinical trials	North America region (US, Canada, Mexico)
Author of study (year)	**prevalence of baseline Q80k polymorphism**	**Data source***	**Total**
Gaudieri 2011 (Germany)	22.6% *	Sequencing analysis on patients within the Munich and ATAHC cohorts	N=500 subjects
Paolucci 2012 (Italy	29%	Direct sequencing of HCV NS3/4A protease was performed	in 156 HCV patients naïve to PIs
Vicenti 2011 (Italy)	16%	Sequencing analysis	N=109 (1a=67, 1b=42)
Plaza 2012 (Spain)	39.7%	Sequencing analysis on patients from Los Alamos Database	N=5790 HCV sequences (of which NS3 protease = 1612)
Trevinio 2011 (Spain	17.1%	All individuals newly diagnosed with HIV-1 at several clinics in Madrid between 2000 and 2010 were tested for serum HCV antibody and HCV RNA.	

Lower SVR12 rates are observed in patients with baseline Q80K compared to subjects without Q80K

Prevalence of Q80K baseline polymorphism in HCV genotype 1a – in USA or HCV genotype 1a /1b in Europe.

Problem of Cross-Resistance to PI!

NS3/4A Protease Inhibitors	V36 M	T54 S	V55 A	Q80 R/K	R155 K/T/ Q	A156 S	A156 T/V	D168 A/E/ G/H/ T/Y	V170 A/T
Telaprevir	●	●			●	●	●		
Boceprevir	●	●	●		●	●	●		●
Narlaprevir	●	●			●	●	●		
Danoprevir					●			●	
TMC435				●	●		●	●	
BI201335					●		●	●	
Vaniprevir					●			●	
Asunaprivir				●	●			●	
ABT-450					●			●	
GS-9451					●			●	

Many new therapeutic strategy with or without IFN include a Protease Inhibitor

Resistance Profile need to be determined after virological failure and before retreatment !

How to retreat the subgroup of experienced-patients with Prior Null response to PEG+ RIBA or/and resistance to Telaprevir and Boceprevir ?

Quadruple-Therapies for null responders

Null-responders genotype 1 patients, n=20

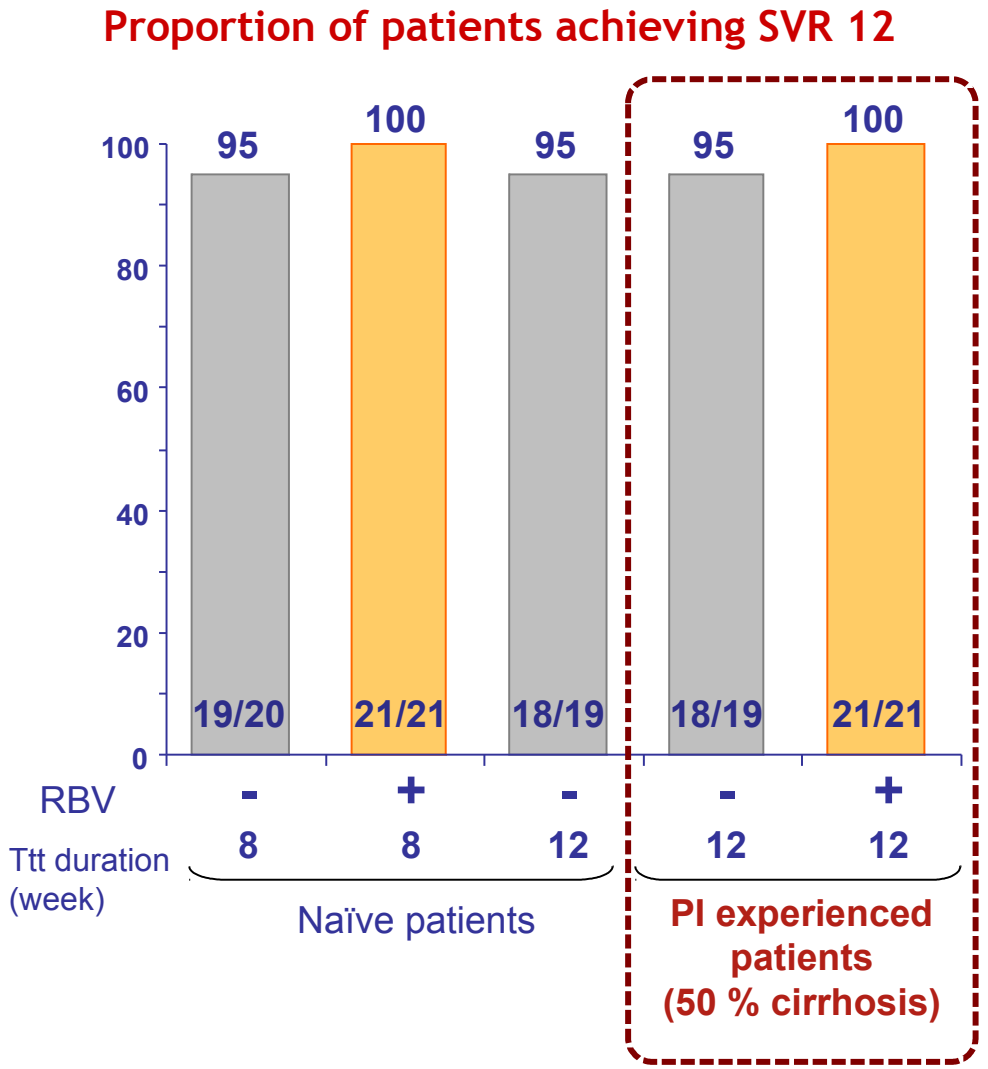
(NS5A Inh Daclatasvir + PI Asunaprevir with PEG2a + R for 24 weeks)

Quadruple 90% SVR

Lok et al., NEJM 2012

IFN FREE : Sofosbuvir (anti-NS5B)+Ledipasvir (anti-NS5A) +/-ribavirin in HCV GT1: LONESTAR

- GT1 naïve patients (n = 60)
  - SOF/LDV ± RBV 8 weeks
  - Or SOF/LDV 12 weeks
- Patients with prior non response to PI (n = 40)
  - Cirrhosis, n = 22
  - SOF/LDV ± RBV during 12 weeks



Lawitz E ,Etats-Unis, AASLD 2013, Abs. 215/1844, actualisés

In vitro analysis of HCV NS5B 282T mutants

Replication capacity of 282T mutants to their corresponding wild type

- S282T mutants across all HCV genotypes showed reduced replication capacity compared to their corresponding WT HCV strain.

Susceptibility of 282T mutants to sofosbuvir and ribavirin

- The S282T mutant EC50 values were 2.4 to 16.2 fold higher than their corresponding WT.
- S282T mutants in multiple HCV genotype show low level of reduced sensibility to sofosbuvir and no resistance to ribavirin.

Han, Etats-Unis, AASLD 2013, Abs. 1078

In vitro cross-resistance assessment to other classes of DAA

Susceptibility of NS5 282T to nonnucleoside NS5B inhibitors (NNIs) GS-9669 and tegobuvir (GS-9190)

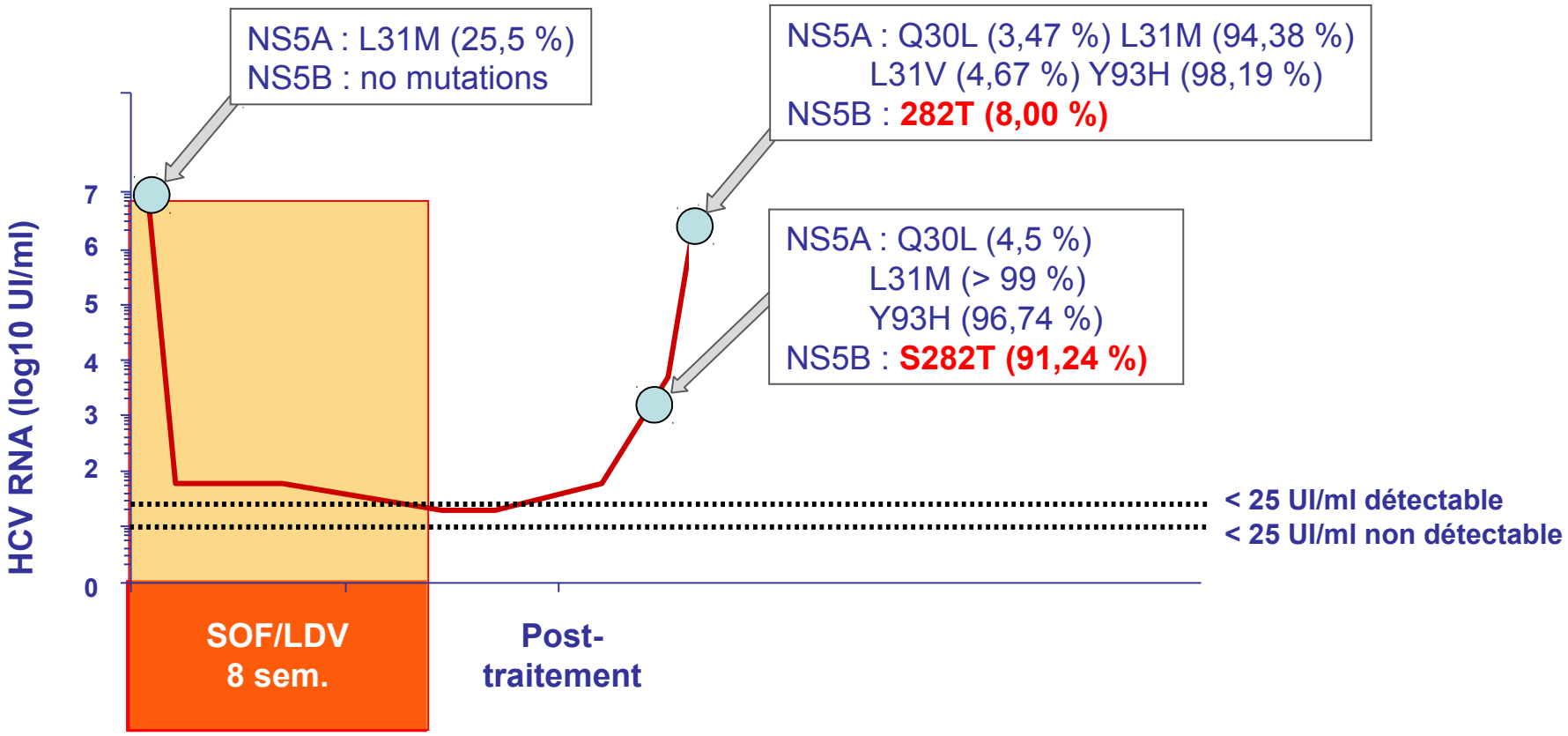
Susceptibility of NS5 282T to protease ihnibitors (GS-9451) and NS5A inhibitors (GS-5885)

- **S282T mutants remained sensitive to other class of DAA including NS5A inhibitors , Nonnucleoside NS5B inhibitors, NS3 protease Inhibitors and Ribavirin.**

Han, Etats-Unis, AASLD 2013, Abs. 1078, actualisés

Re-treatment of patients who relapsed after 8 weeks of sofosbuvir + ledipasvir

Patient from LONESTAR study



Lawitz E ,Etats-Unis, AASLD 2013, Abs. 215/1844, actualisés

Conclusions: Resistance to protease inhibitors: is it a real issue ?

- **Today: Yes**
  - **Importance of adherence**
  - **Impact of subtype (1a/1b) on genetic barrier**
  - **The subgroup of Null-responders (with or without cirrhosis).**
  - **Retreatment of patients with resistance to Telaprevir or Boceprevir**
  - **Determination of cross resistance profile**
- **Tomorrow: may be no**
  - **Development of new combination therapy**