Advantages of new generation Direct Acting Antivirals (DAAs)

PHC 2011

17 January 2010

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New Direct Acting Antivirals

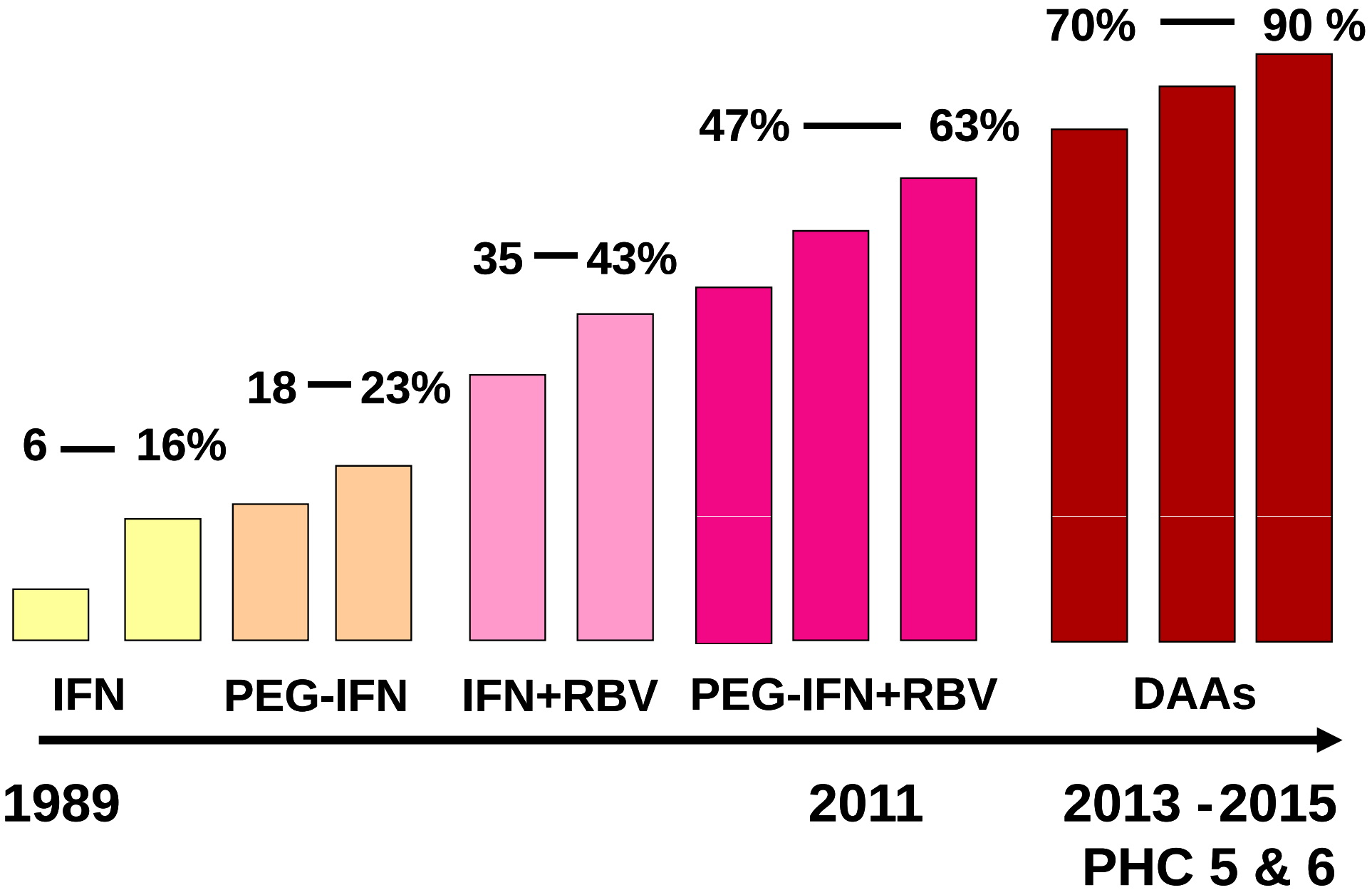
- **Introduction**
- **Advantages**
- **Limitations**
- **Conclusion**

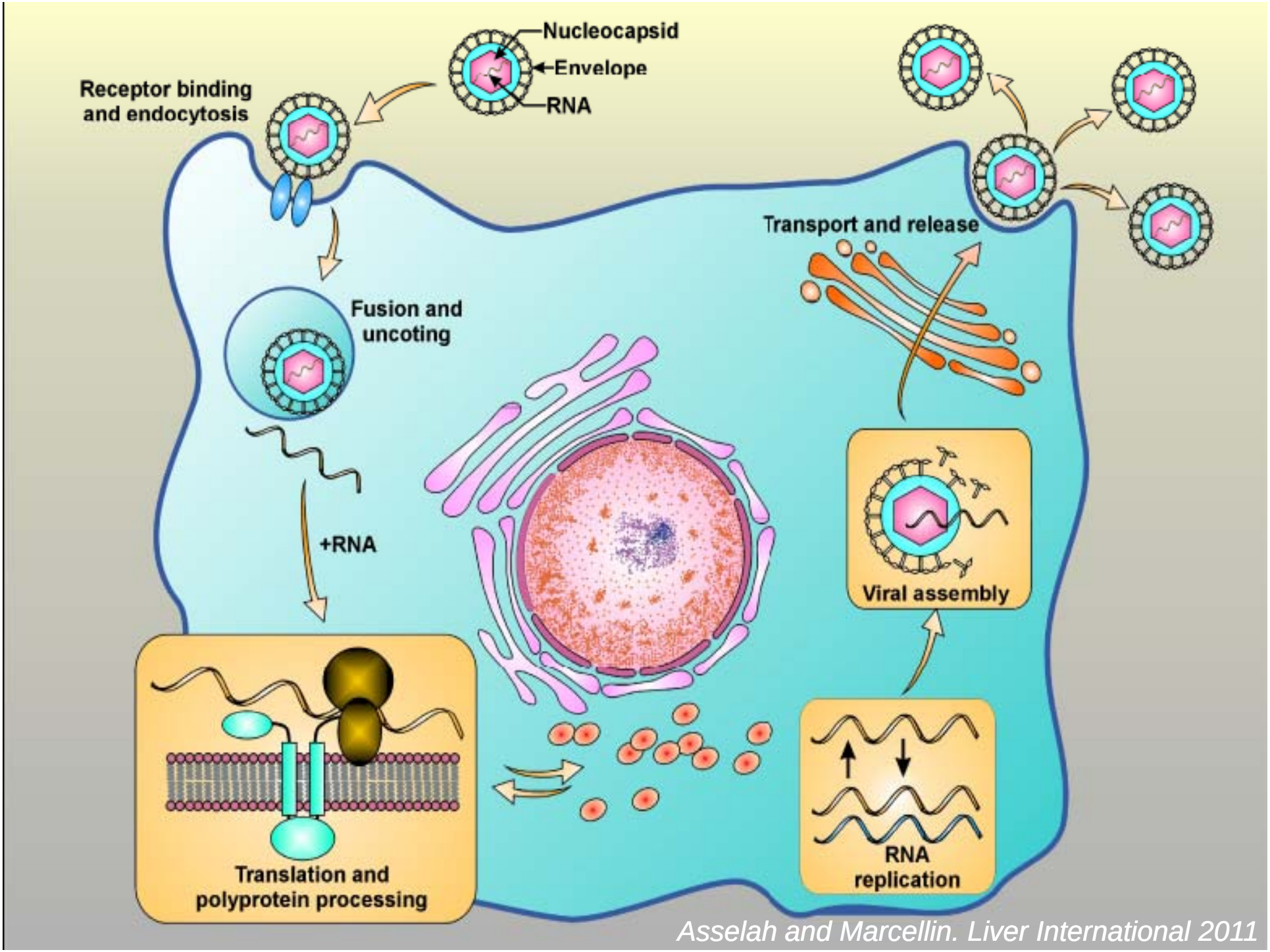
Chronic Hepatitis C
Goals of Therapy

- Eradicate the virus (HCV clearance)
- Reduce Necroinflammation
- Stop Fibrosis progression
- Prevent cirrhosis devlopment
- Prevent complications
- Prevent HCC
- Increase survival

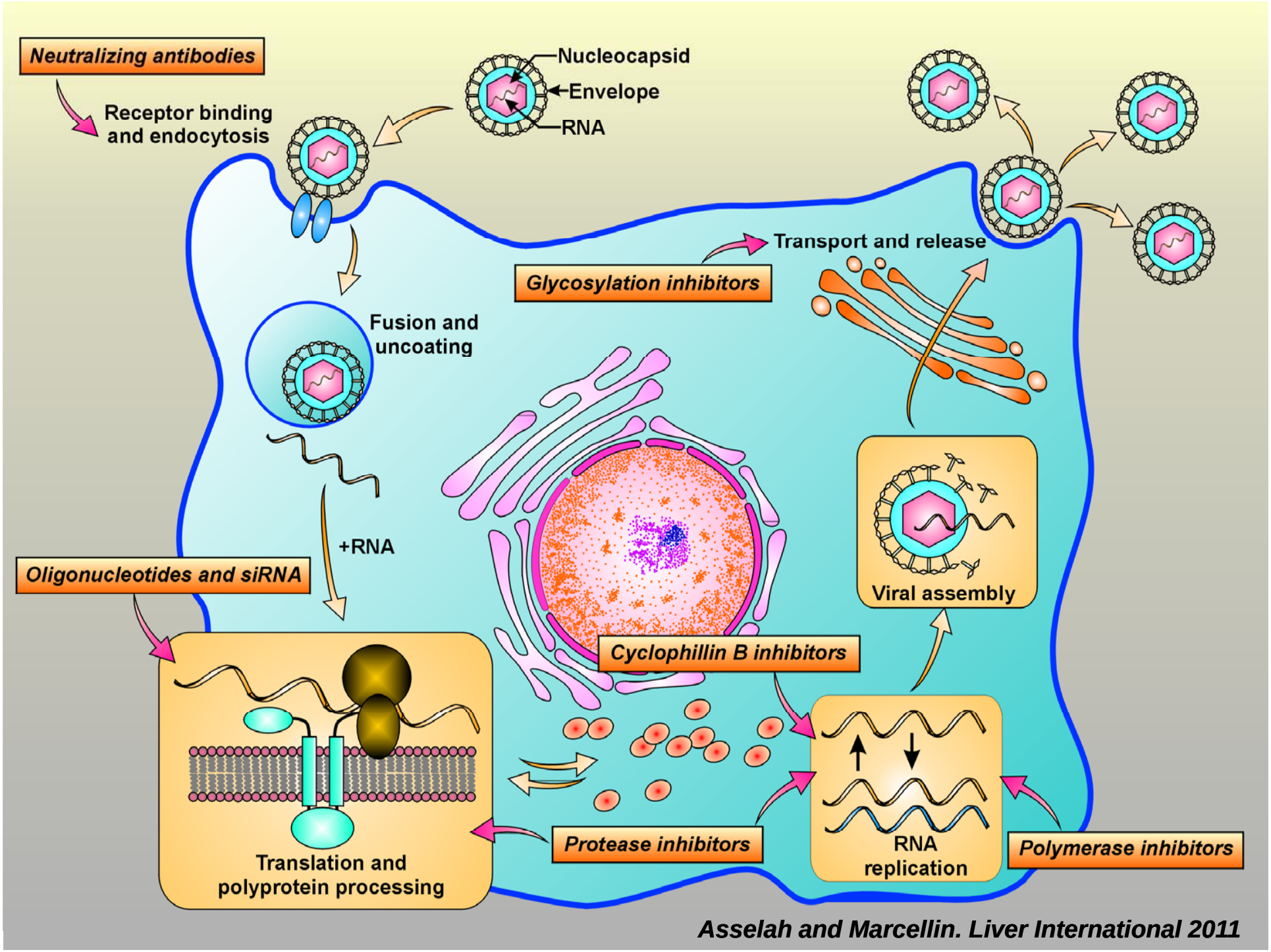
Maylin et al. Gastroenterology 2008

Progress in the Treatment of Hepatitis C





Asselah and Marcellin. Liver International 2011


Neutralizing antibodies
Receptor binding and endocytosis
Nucleocapsid
Envelope
RNA
Transport and release
Glycosylation inhibitors
Fusion and uncoating
+RNA
Oligonucleotides and siRNA
Viral assembly
Cyclophillin B inhibitors
Translation and polyprotein processing
Protease inhibitors
RNA replication
Polymerase inhibitors
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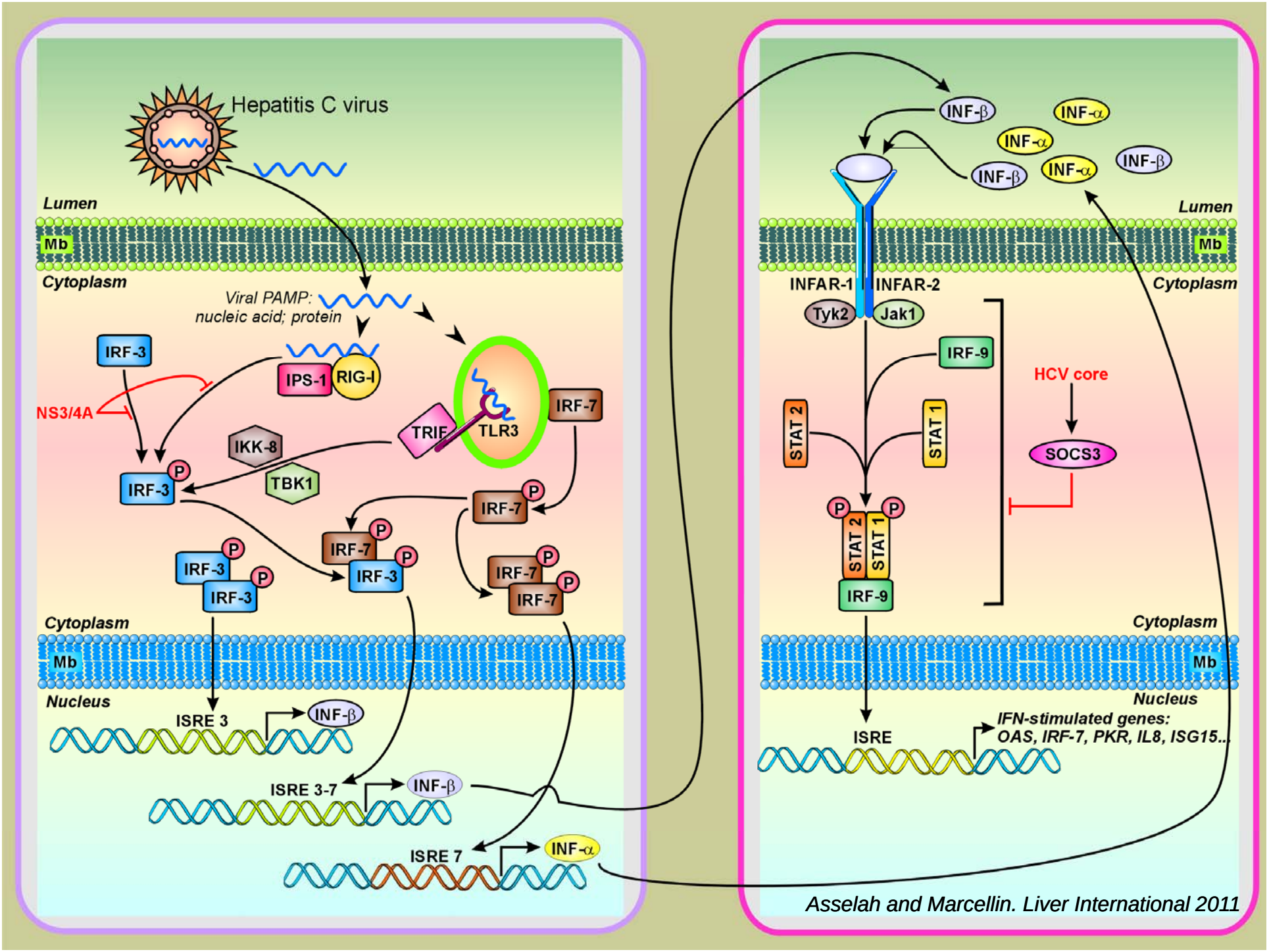

Asselah and Marcellin. Liver International 2011

Prediction of SVR with Molecular Signature

2 genes (IFI27 et CXCL9)

↓

SVR/NR correctly predicted in 78%

Asselah et al. GUT 2008

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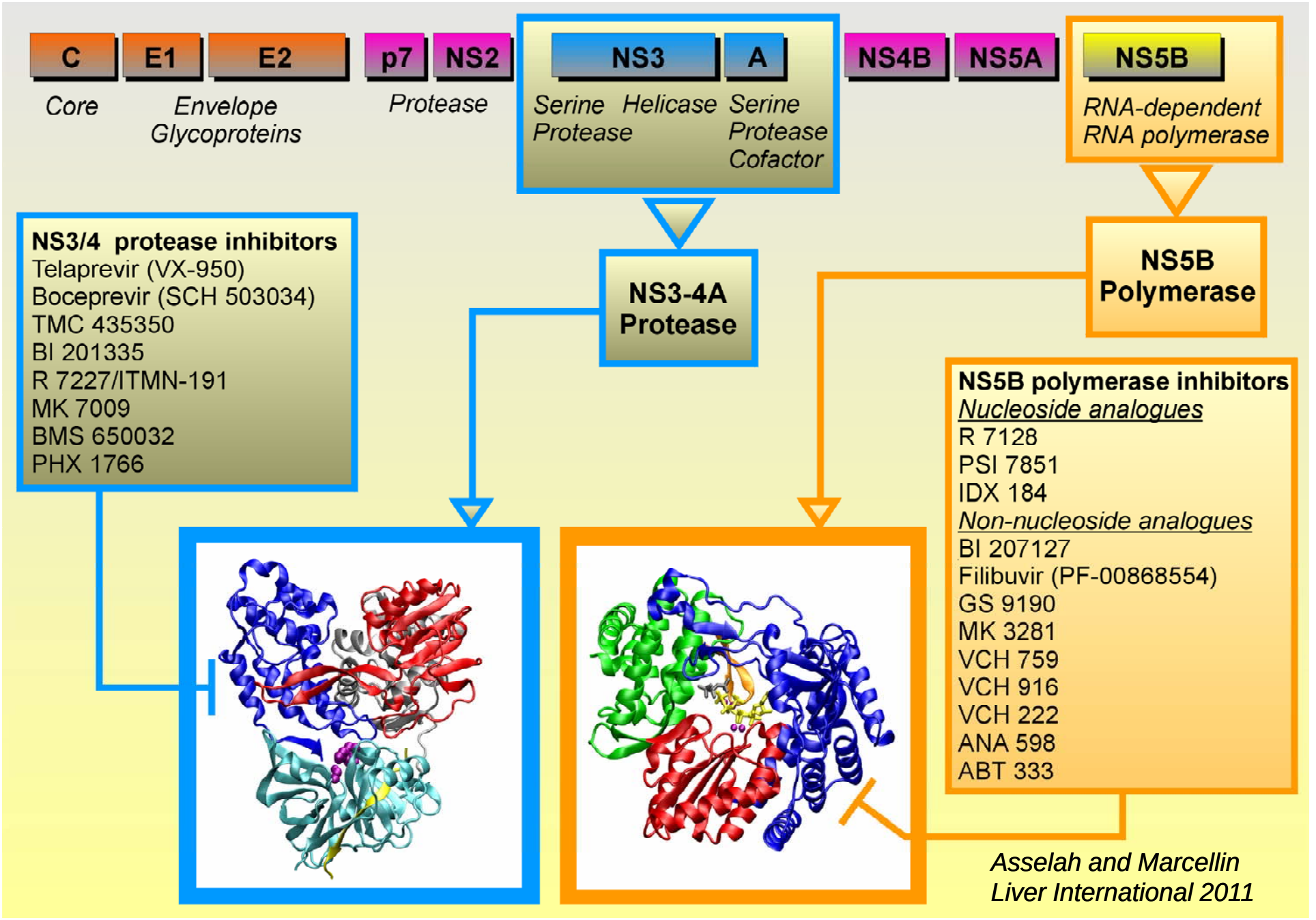
Direct Acting Antivirals Target Virus Enzymes

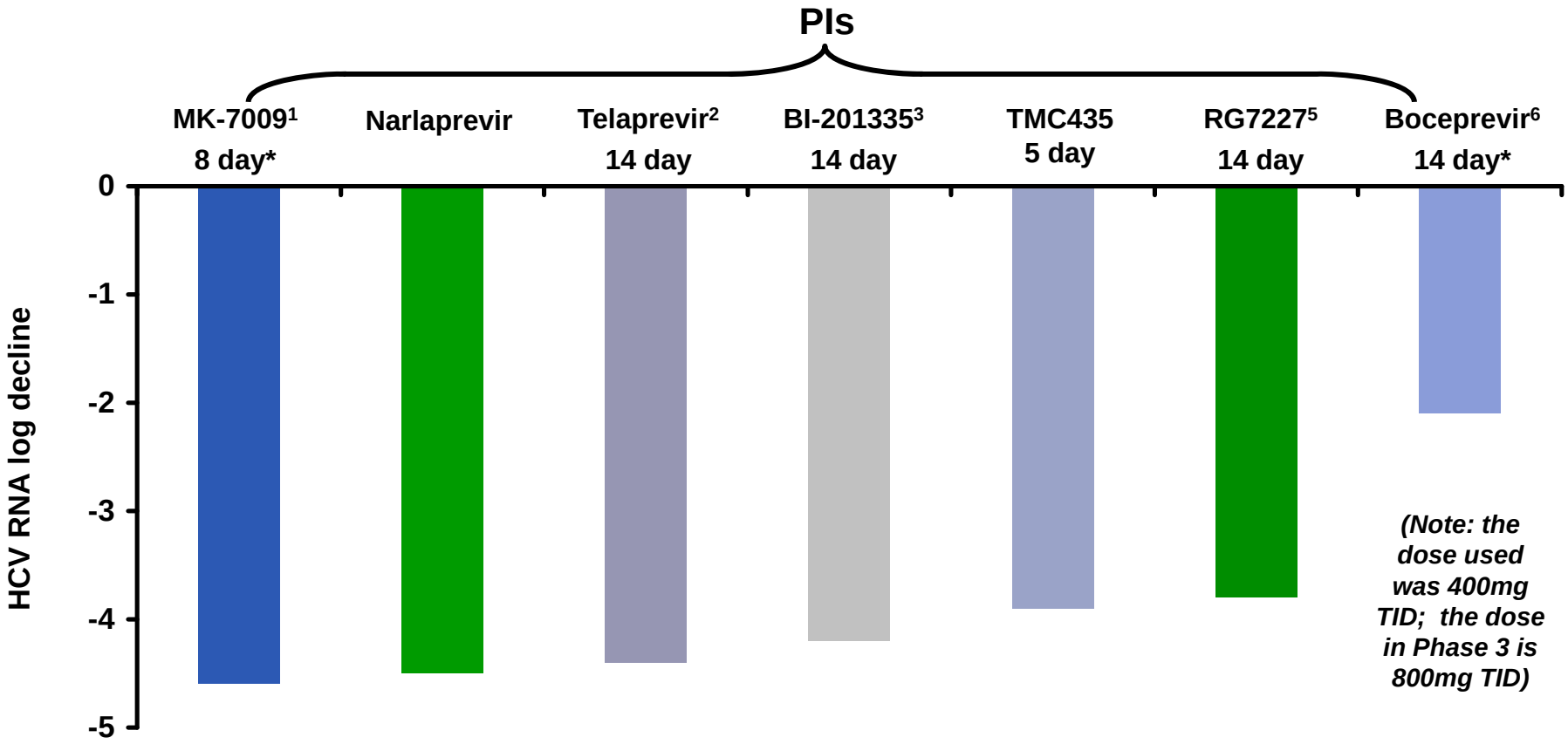


Direct Acting Antivirals in Devlopment

Drug name	Company	Study phase
NS3/4 serine protease inhibitors		
Telaprevir (VX-950)	Vertex	Phase 3
Boceprevir (SCH 503034)	Schering-Plough/Merck	Phase 3
TMC 435350	Tibotec/Medavir	Phase 2
BI 201335	Boehringer Ingelheim	Phase 2
R 7227/ITMN 191	InterMune/Roche	Phase 2
MK 7009	Merck	Phase 2
BMS 650032	Bristol-Myers Squibb	Phase 1
PHX 1766	Phenomix	Phase 1
NS5B RNA-dependent RNA-polymerase inhibitors		
Nucleoside analogues		
R 7128 (Prodrug of PSI-6130)	Roche/Pharmasset	Phase 2
PS -7851	Pharmasset	Phase 1
IDX 184	Idenix	Phase 1
Non-nucleoside analogues		
BI 207127	Boehringer Ingelheim	Phase 2
Filibuvir (PF-00868554)	Pfizer	Phase 2
GS 9190	Gilead	Phase 1
MK 3281	Merck	Phase 1
VCH 759	ViroChem Pharma	Phase 1
VCH 916	ViroChem Pharma	Phase 1
VCH 222	ViroChem Pharma	Phase 1
ANA 598	Anadys	Phase 1
ABT 333	Abbott	Phase 1

Asselah and Marcellin. Liver International 2011

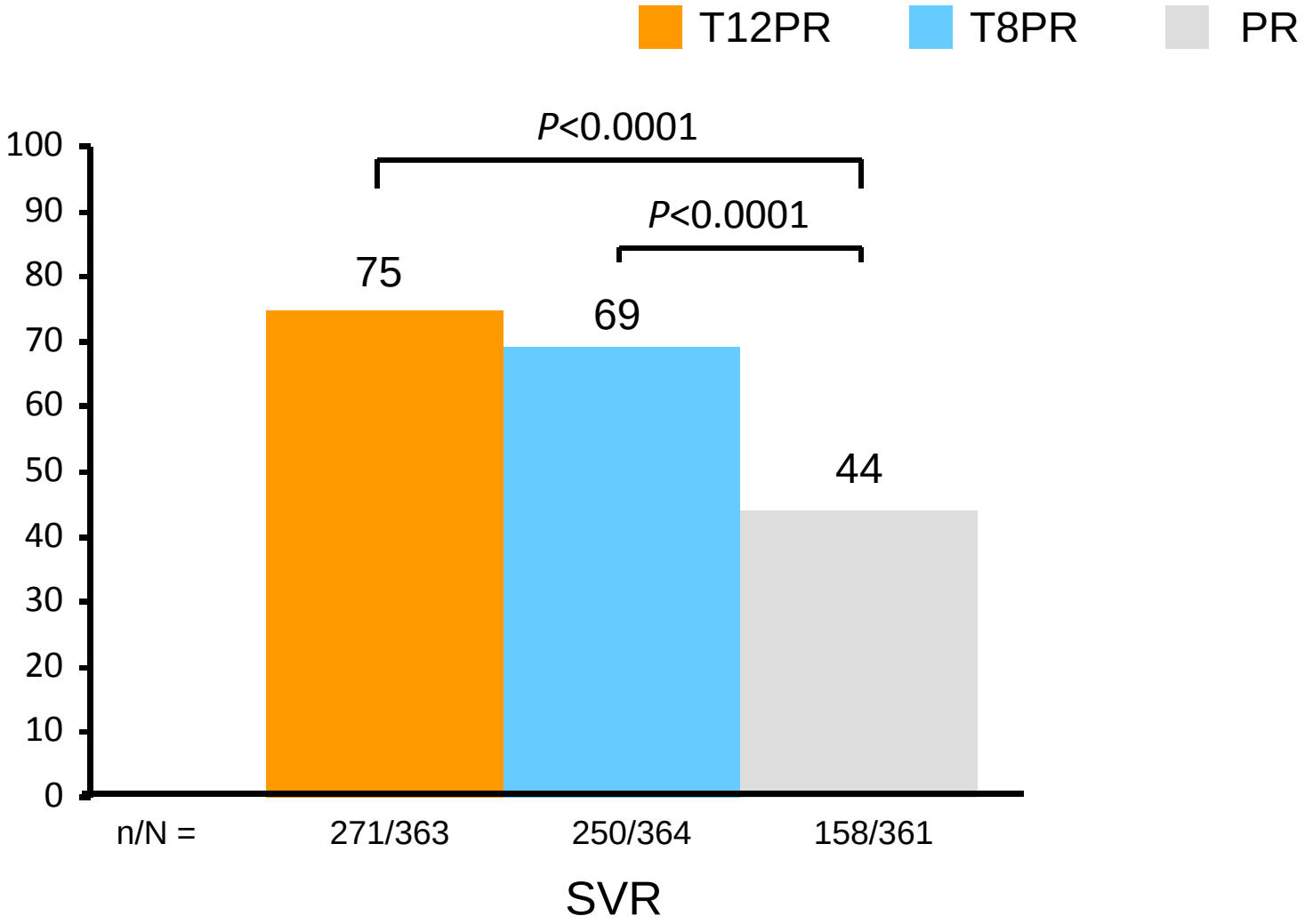
Protease inhibitors: viral load reduction (monotherapy 5-14 days)



Note: no head-to-head trials have been conducted to date
***Mean decline**

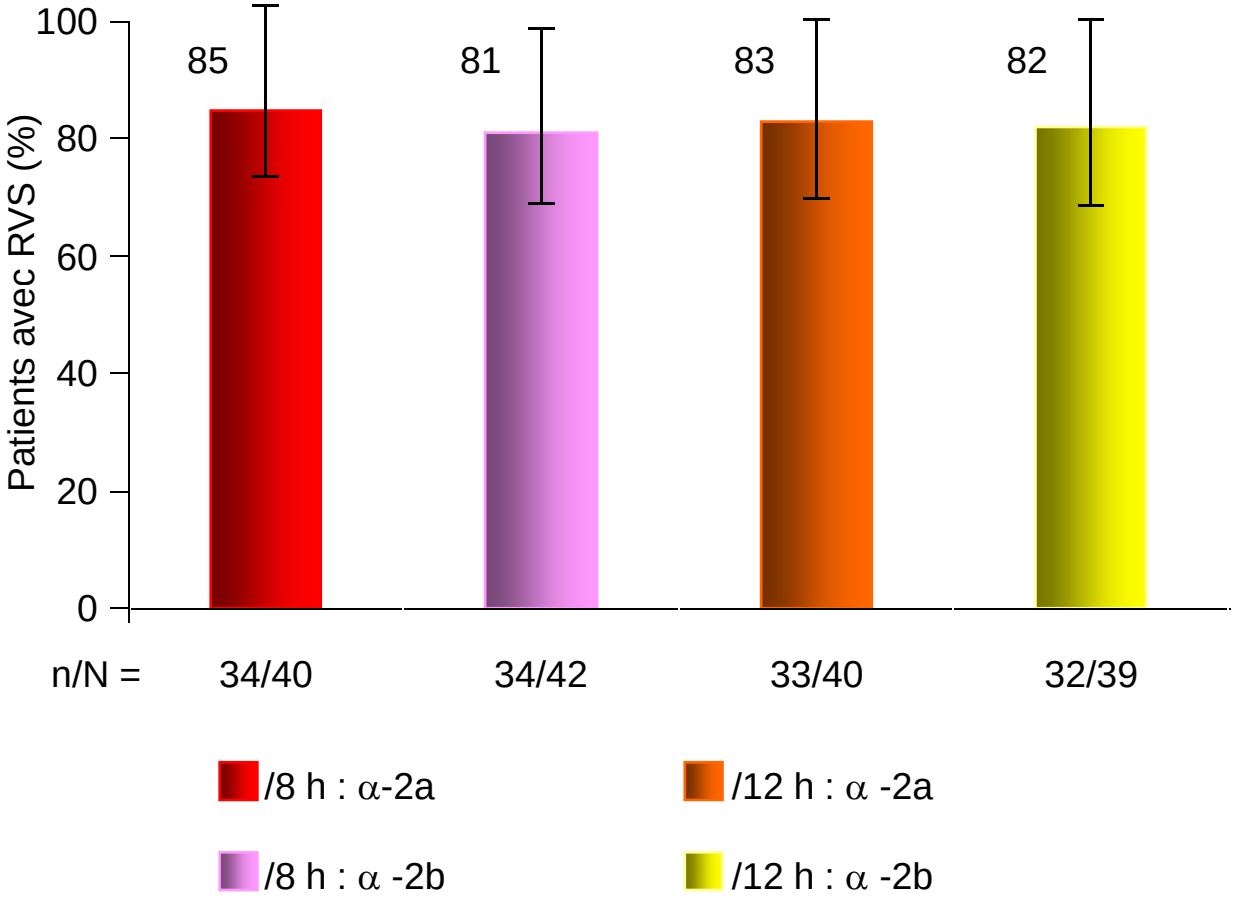
1. Lawitz E, et al. 59th AASLD 2008, San Francisco, CA, October 31–November 4 2008; 2. Reesink H, et al. 56th AASLD 2005, San Francisco, CA, November 11–15 2005; 3. Manns M, et al. 59th AASLD 2008, San Francisco, CA, October 31–November 4 2008; 4. Reesink H, et al. 43rd EASL 2008, Milan, Italy, April 23–27 2008; 5. Forestier N, et al. 59th AASLD 2008, San Francisco, CA, October 31–November 4 2008; 6. Zeuzem S, et al. 56th AASLD 2005, San Francisco, CA, November 11–15 2005

ADVANCE STUDY : SVR rates in Telaprevir Compared to PEG-IFN/Ribavirin Alone



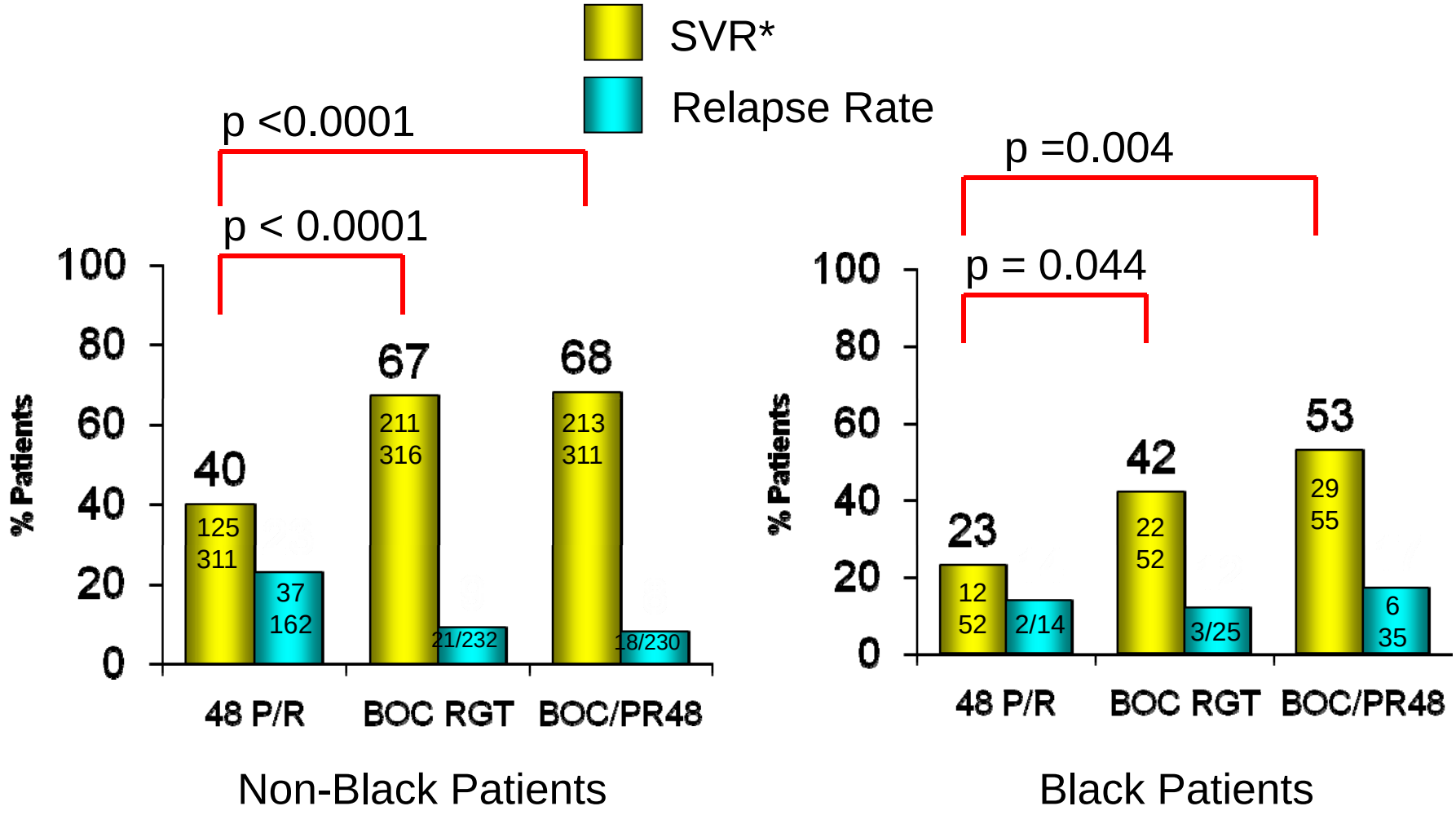
Jacobson et al. AASLD 2010; Abstract 211

Triple therapy with Telaprevir : Similar efficacy of PEG-IFN a-2a vs 2b *(C-208)*



Marcellin et al. Gastroenterology 2010

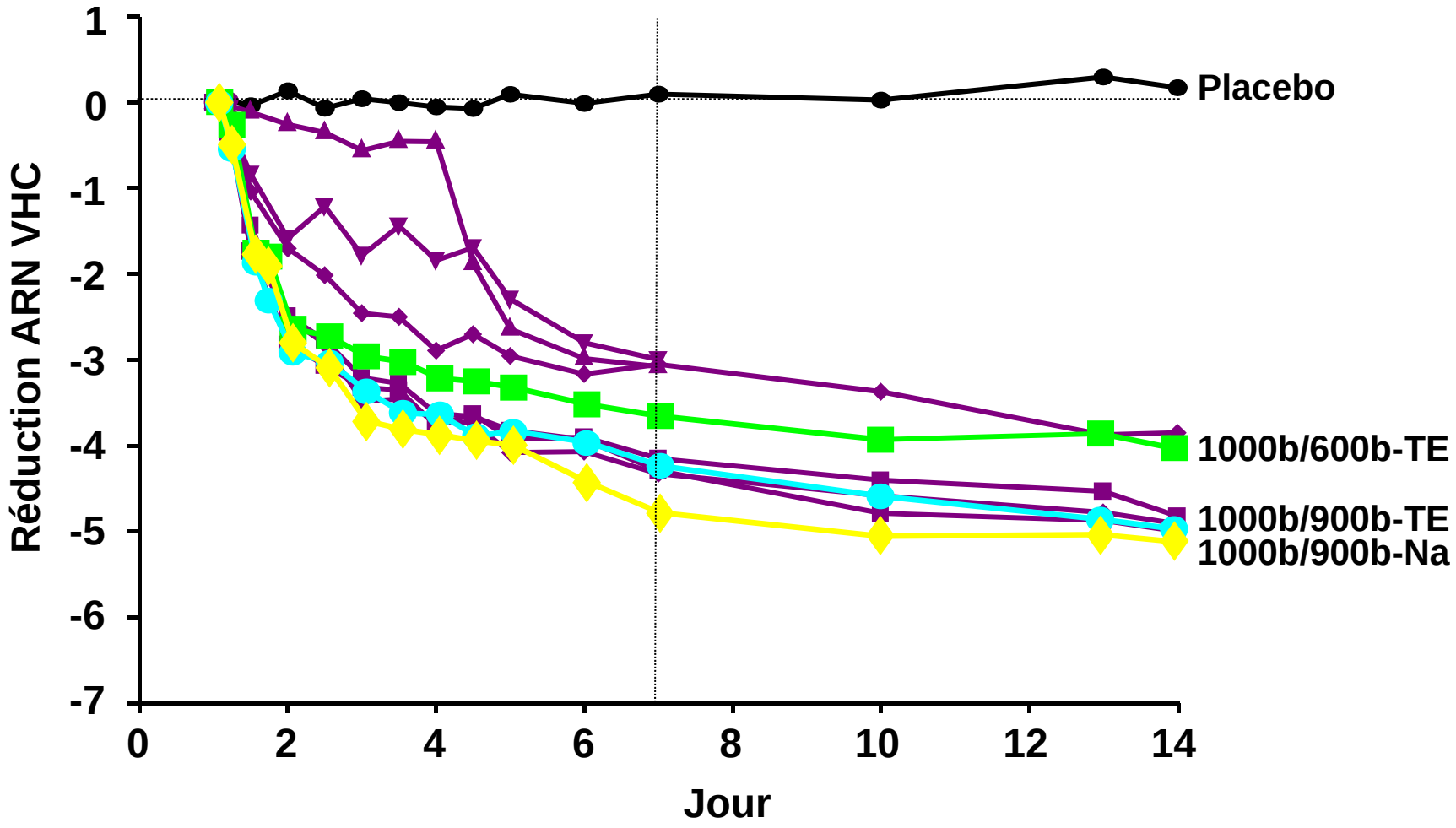
SPRINT 2: SVR rates in Boceprevir compared to PEG-IFN/Ribavirin Alone



*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

Poordad F et al. Hepatology 2010; 52: 402A (abstract)

INFORM-1: Antiviral Activity in HCV G1 Interferon-Naïve and Null Responders with a BID Regimen of RG7128 + RG7227



Gane E, et al. Lancet 2010

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Side effects

Telaprevir	Boceprevir
Rash	Anemia
Anemia	Dysgeusia
	Vomiting

HCV resistance

	V36A/M	T54S/A	V55A	Q80R/K	R155K/T/Q	A156S	A156T/V	D168A/V/T/H	V170A/T
Telaprevir (linear)			*						*
Boceprevir (linear)							*		
SCH900518 (linear)									
BILN-2061** (macrocyclic)									
ITMN191/R7227 (macrocyclic)						*	*		
MK7009 (macrocyclic)									
TMC435350 (macrocyclic)									
BI-201335 (macrocyclic?)									

* Mutations associated with resistance in vitro but not seen in patients
** Mutations associated with resistance in vitro

Sarrazin and Zeuzem. Gastroenterology 2010

New Direct Acting Antivirals
Advantages : summary

- **Potent anti-virals, increasing SVR**
- **Different targets : combinations of DAAs**
- **Shorten duration of treatment**
- **IFN free regimen**
- **HCV might become the first chronic viral infection eradicate worldwide with a finite duration of treatment, without vaccination.**

New Direct Acting Antivirals
Limitations : summary

- **Side effects**
  - Frequent physical examinations and laboratory testing for rash, anemia and other AE's
  - Potential hepatotoxicities of a number of DAAs, drug interactions
- **Adherence, medical education**
- **Resistance**
  - **Frequently test for virologic breakthrough**
  - **Early discontinuation for 1-log increase in viral load on therapy**
- **Special Population: Genotype non 1, HIV-HCV coinfected, Transplanted patients, etc…**
- **Cost**