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British HIV Association  
**BHIVA**

**Third Annual BHIVA Conference  
for the Management of HIV/Hepatitis Co-infection**

**Wednesday 6 October 2010**

ONE GREAT GEORGE STREET CONFERENCE CENTRE · LONDON



Third Annual BHIVA Conference for the  
Management of HIV / Hepatitis Co-infection



**Professor Yves Benhamou**  
Hôpital Pitié Salpêtrière , Paris, France

COMPETING INTEREST OF FINANCIAL VALUE $\geq$ £1,000:	
Speaker Name	Statement
Yves Benhamou:	Advisory Board, Speaker bureau, Investigator Roche, Boehringer Ingelheim, Merck, Vertex, Novartis, Idenix, Tibotec , Synxis
Date	27 September 2010

*Wednesday 6 October 2010, One Great George Street Conference Centre, London*

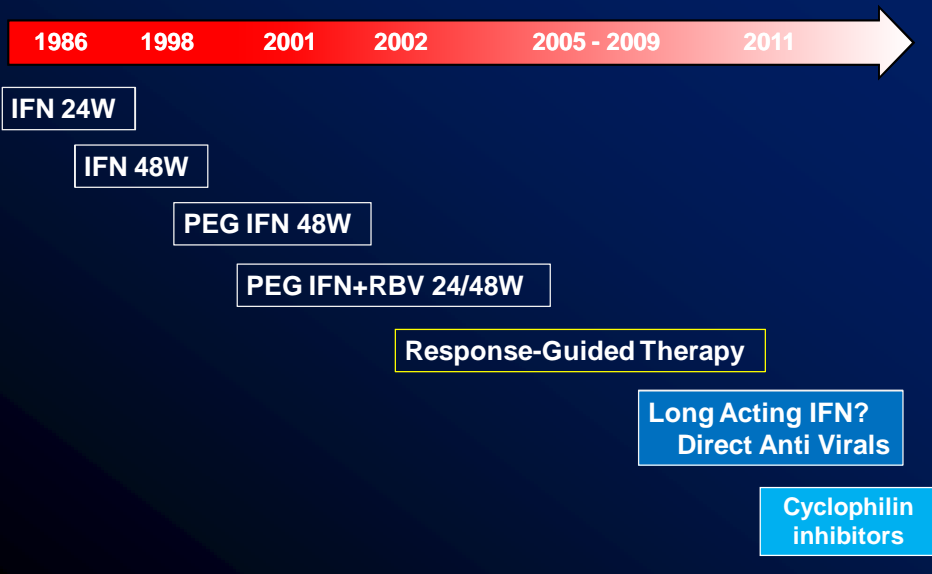
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# Future Treatment Options for Hepatitis C

Yves Benhamou

*Groupe Hospitalier Pitié Salpêtrière,  
Paris,  
France*

## Anti-HCV Therapy 1996 – 201...



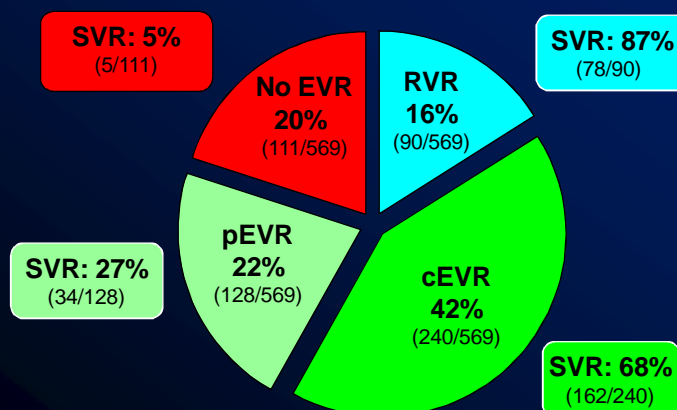
## Response-guided therapy Definitions of on-treatment response

Response	Definition
RVR*	HCV RNA negative (<50 IU/mL) at week 4
EVR**	Complete EVR HCV RNA positive at week 4 but negative at week 12
	Partial (slow) EVR HCV RNA positive at week 4 and 12 but $\geq 2 \log_{10}$ drop from baseline at week 12
Non-EVR	$< 2 \log_{10}$ drop from baseline at week 12

\* RVR = rapid virological response  
\*\* EVR = early virological response

## SVR rates in genotype 1 patients

PEG 2a 180 µg/wk plus RBV 1000/1200 mg/day for 48 weeks; n=569



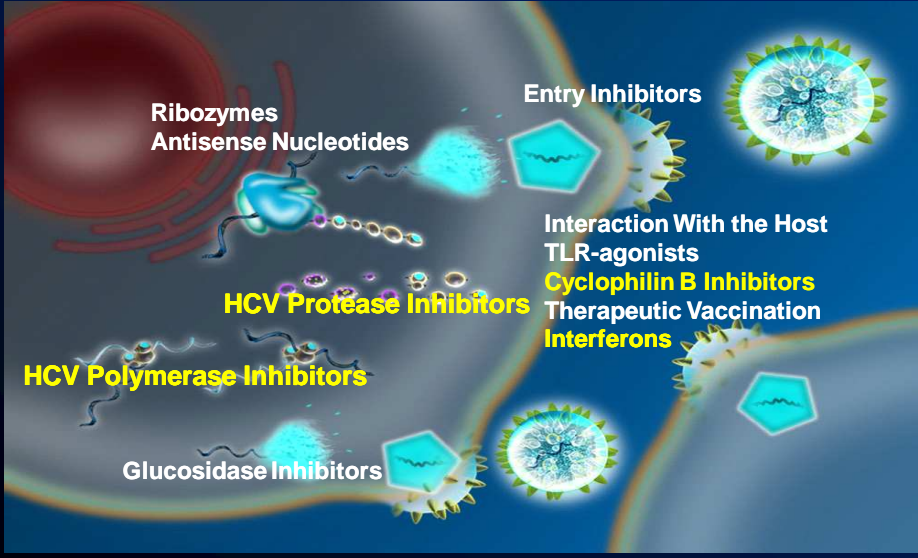
Marcellin P, et al 2008

# The RGT algorithm

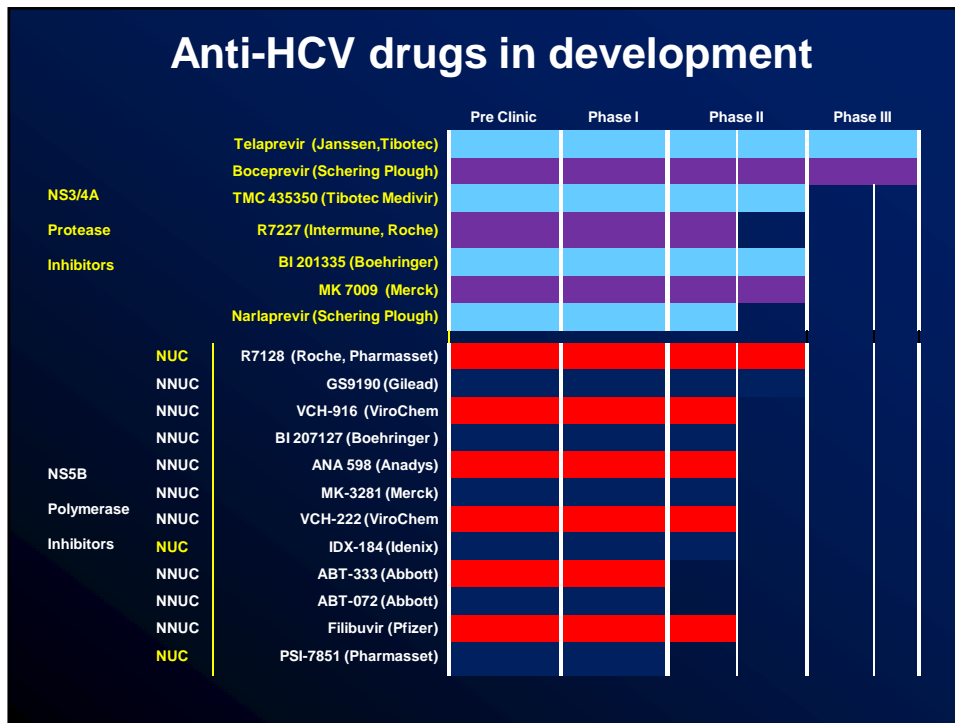
Week 4	-	+	+	+	+
Week 12	-	-	>2log	>2log	<2log
Week 24	-	-	-	+	+



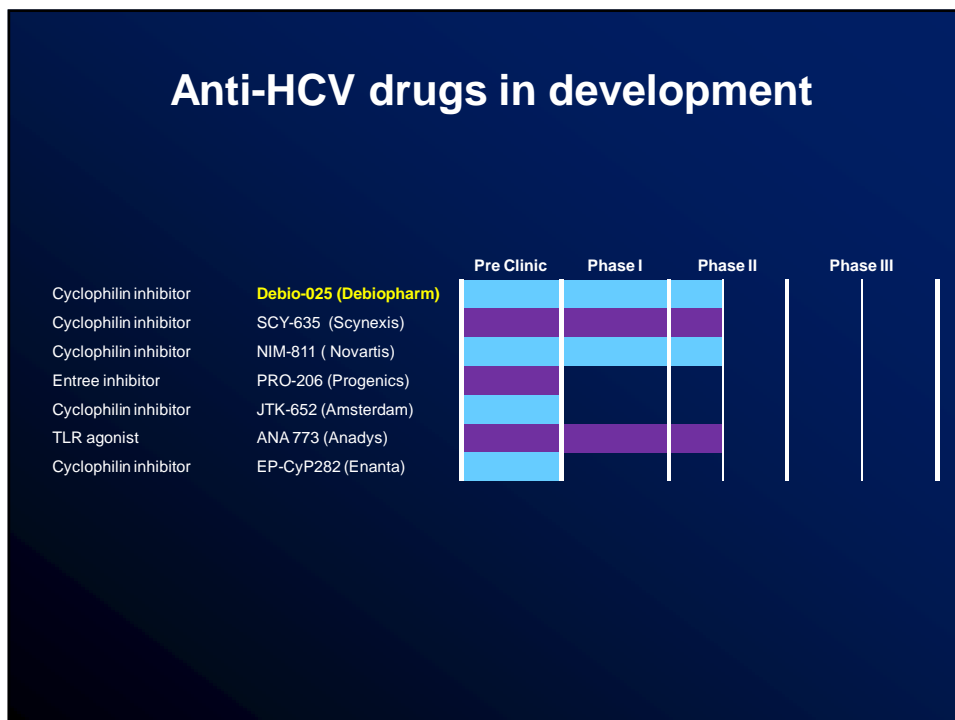
# Future HCV Treatment Paradigms: Drugs



## Anti-HCV drugs in development



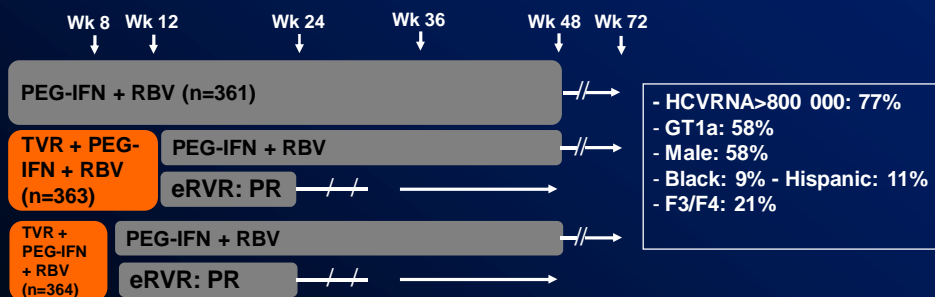
## Anti-HCV drugs in development



# Protease Inhibitors

- Potency
  - HCV RNA decline: 2 – 4 log in 1-4 wk
- Low genetic barrier for resistance
- Dosing: QD – TID
- 1st « generation » : Telaprevir – Boceprevir
- 2<sup>nd</sup> « generation » : TMC 435 – BI 201335

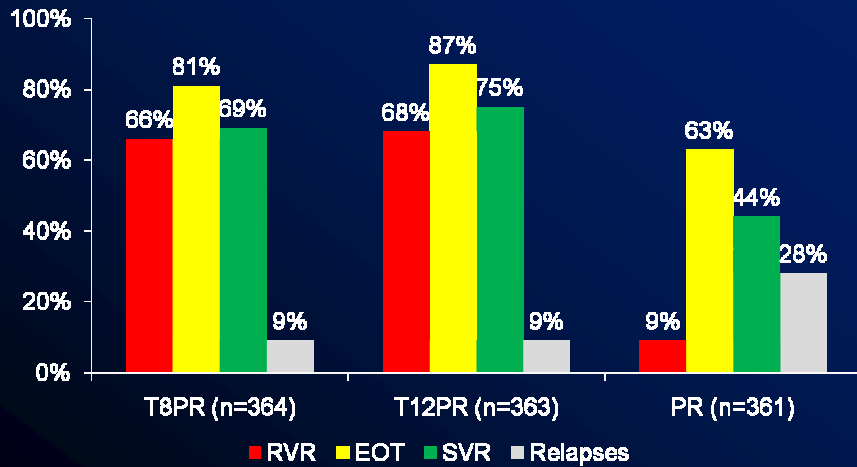
## ADVANCE: Telaprevir Naïve GT 1 Patients



TVR, telaprevir 750mg q8h; PEG-IFNα-2ab 180 µg/wk + RBV 1000-1200 mg/d.  
 Patients had to achieve undetectable HCV RNA at wk 4 (<10 IU/mL) and at last test before stopping therapy at 12 or 24 wk.

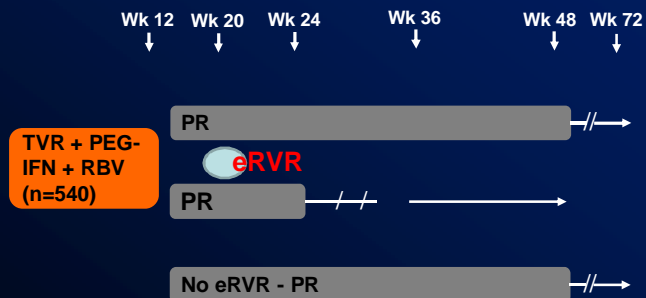
Jacobson IM et al. AASLD 2010

## ADVANCE: Telaprevir Naïve GT 1 Patients



Jacobson IM et al. AASLD 2010

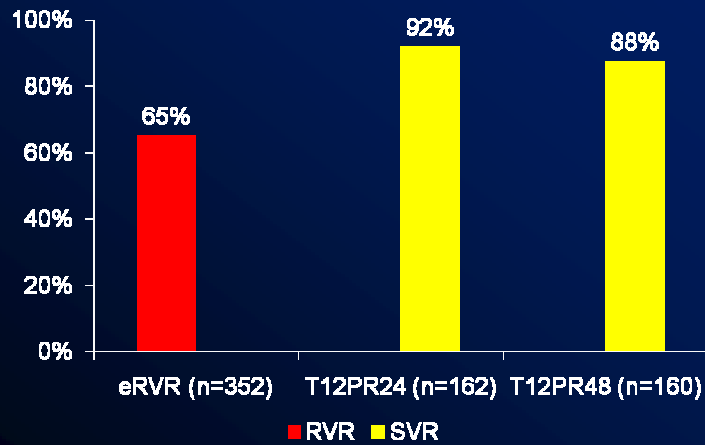
## ILLUMINATE: Telaprevir Naïve GT 1 Patients 24 vs 48 W in Patients with eRVR



TVR, telaprevir 750mg q8h; PEG-IFN $\alpha$ -2ab 180  $\mu$ g/wk + RBV 1000-1200 mg/d.  
Patients had to achieve undetectable HCV RNA at wk 4 (<10 IU/mL) and at last test before stopping therapy at 12 or 24 wk.

Sherman KE et al. AASLD 2010.

## ILLUMINATE: Telaprevir Naïve GT 1 Patients 24 vs 48 W in Patients with eRVR



Sherman KE et al. AASLD 2010.

## Telaprevir Naïve GT 1 Patients: Tolerability (ADVANCE)

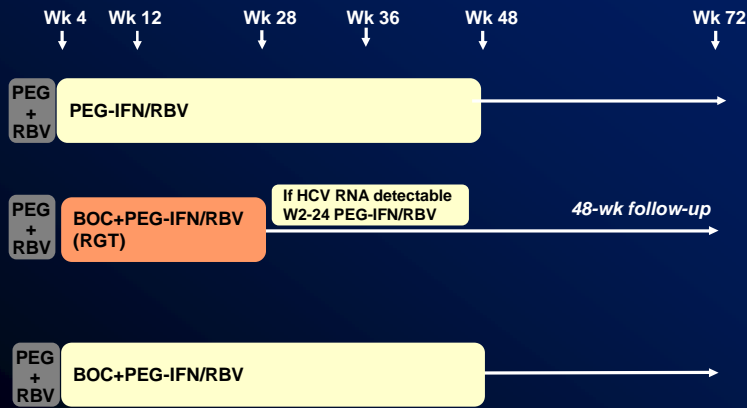
	T8PR	T12PR	PR
DC due to Aes	8%	7%	4%
DC due to Rash	0.5%	1.4%	0
DC due to Anemia	3.3%	0.8%	0.6%

### AEs in Telaprevir arms (>25%):

- Pruritus, rash, diarrhea, nausea, anemia,
- Fatigue, influenza like, insomnia, headache,

Jacobson IM et al. AASLD 2010

## Boceprevir: Lead-in With IFN/RBV in Naïve GT 1 Patients



SPRINT-2 study  
 BOC, boceprevir 800 mg TID; PEG-IFN $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 600-1400 mg/d.  
 Poordad F et al. AASLD 2010

## Boceprevir: in Naïve GT 1 Patients

	Non Black			Black		
	48P/R	RGT	LI+44BOC/P/R	48P/R	RGT	LI+44BOC/P/R
N	311	316	311	52	52	55
SVR, n(%)	125 (40)	211 (67)	213 (68)	12 (23)	22 (42)	29 (53)
End of therapy response, n (%)	176 (57)	235 (74)	241 (77)	15 (29)	26 (50)	36 (65)
Relapse, n/m (%)	37/162 (23)	21/232 (9)	18/230 (8)	2/14 (14)	3/25 (12)	6/35 (17)

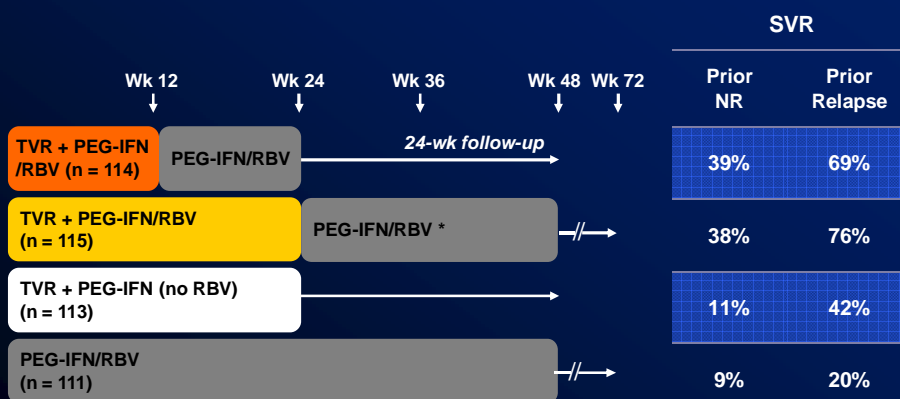
SPRINT-2 study  
 BOC, boceprevir 800 mg TID; PEG-IFN $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 600-1400 mg/d.  
 Poordad F et al. AASLD 2010

## Boceprevir Naïve GT 1 Patients: Tolerability (SPRINT-2)

	48PR	BOC Arms
DC due to Aes	16%	12%-16%
Anemia	29%	49%
. Dc	1%	2%
. Dose reduction	13%	21%
DC due to Anemia	3.3%	0.6%

Poordad F et al. AASLD 2010

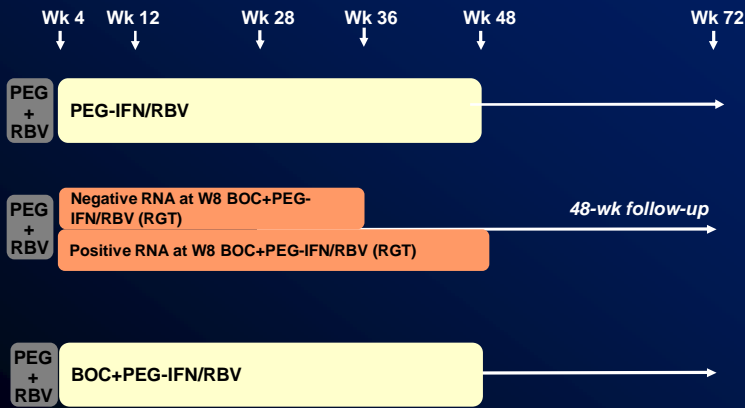
## Telaprevir: SVR Rates for Prior Non Responder or Relapser GT 1 Patients



PROVE 3 study

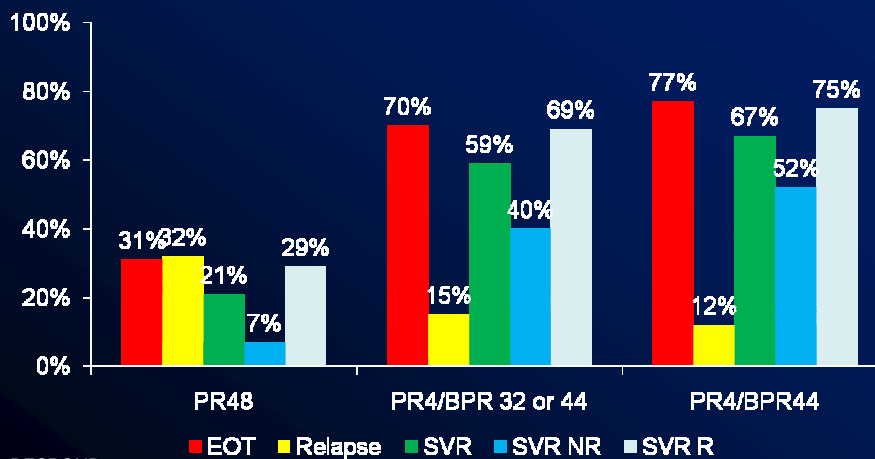
TVR, telaprevir 750 q8h, PEG-IFN $\alpha$ -2a 180  $\mu$ g qwk + RBV 1000–1200 mg/d.  
McHutchison JG et al. AASLD 2009 ; Manns M et al. *J Hepatol.* 2009;50(suppl 1):S379.

## Boceprevir: Lead-in With IFN/RBV in previous NR and Relapsers GT 1 Patients



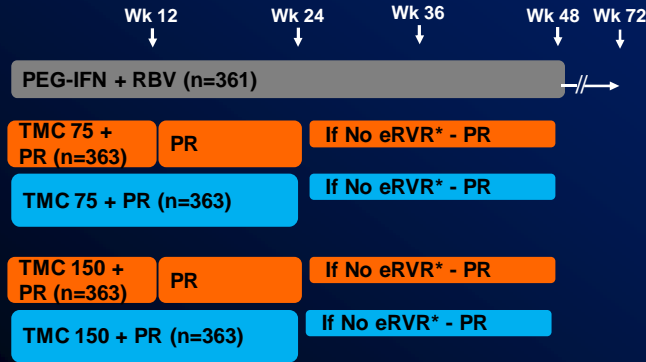
RESPOND-2  
 BOC, boceprevir 800 mg TID; PEG-IFN $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 600-1400 mg/d.  
 Bacon BR et al. AASLD 2010

## Boceprevir: Lead-in With IFN/RBV in previous NR and Relapsers GT 1 Patients



RESPOND-2  
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 Bacon BR et al. AASLD 2010

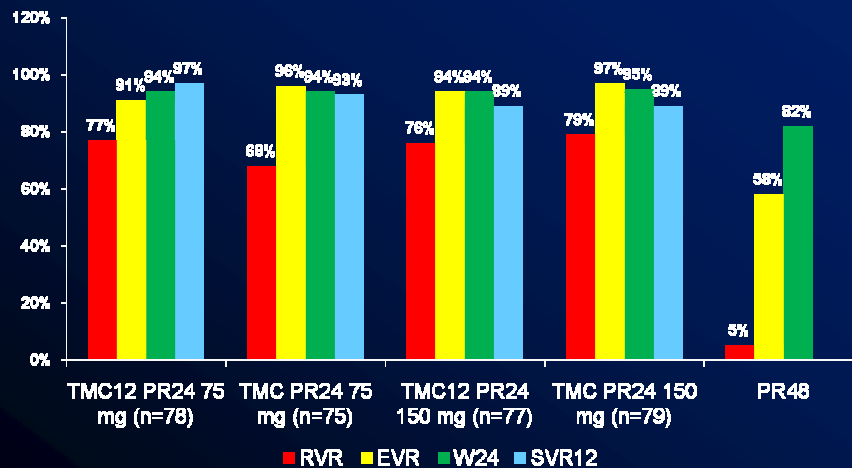
## PILLAR: TMC 435 With IFN/RBV GT 1 Naïve Patients



TMC 435 QD. PEG-IFN $\alpha$ -2ab 180  $\mu$ g/wk + RBV 1000-1200 mg/d.  
eRVR: Patients had to achieve undetectable HCV RNA at wk 4 <25 and at wk 12, 16 and 20 <15 IU/mL IU/mL) and at last test before stopping therapy at 12 or 24 wk.

Fried LW et al. AASLD 2010

## PILLAR: TMC 435 With IFN/RBV GT 1 Naïve Patients

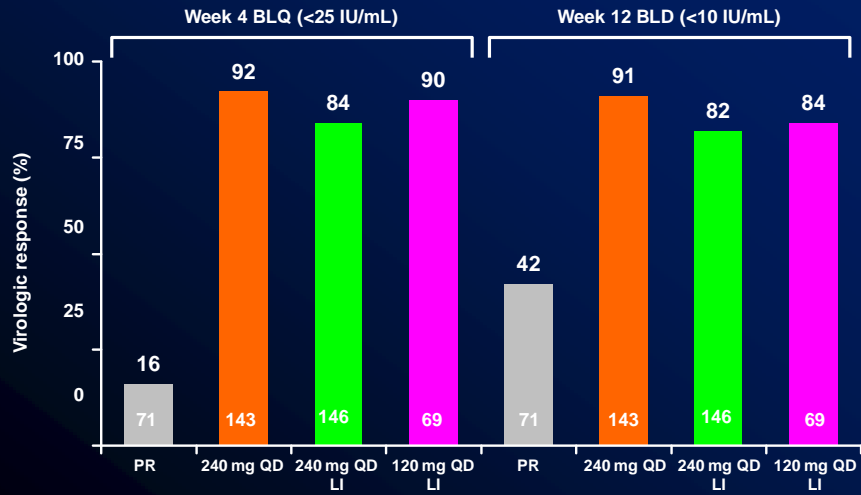


TMC 435 QD. PEG-IFN $\alpha$ -2ab 180  $\mu$ g/wk + RBV 1000-1200 mg/d.

Fried LW et al. AASLD 2010

## BI 201335 + PEG 2a+RBV: Naive G1

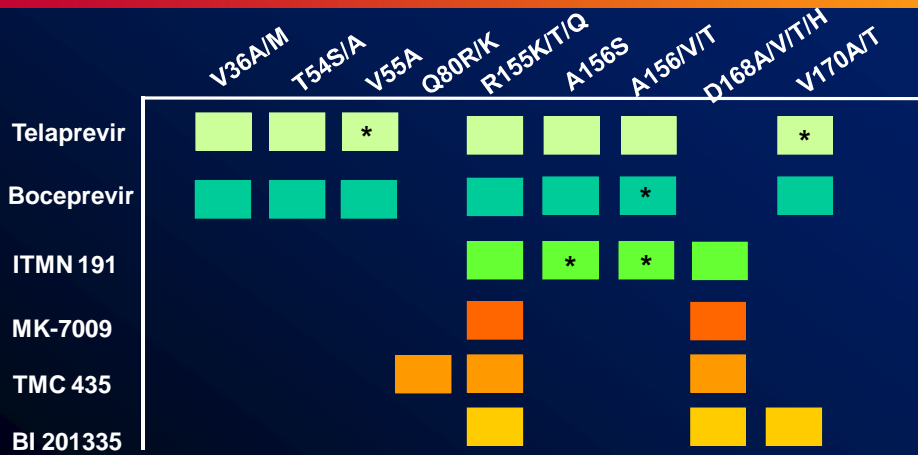
SILEN-C1: GT-1 naïve; 12-weeks BI 201335 QD plus PR ± 3-day PR lead-in



BLQ = below limit of quantification; BLD = below limit of detection; LI = 3-day lead-in

Sulkowski M, et al. AASLD 2009

## Cross-resistance of NS3 protease inhibitors

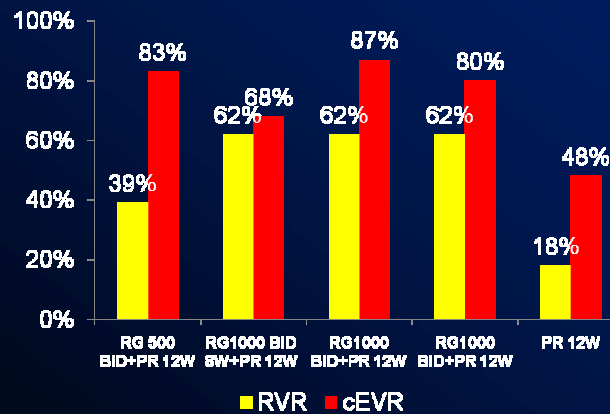


\*Mutations associated with resistance in vitro but were not described in patients

Susser S et al. Hepatology 2009; 50: 1709-1718. Sarrazin C et al. Gastroenterology 2010

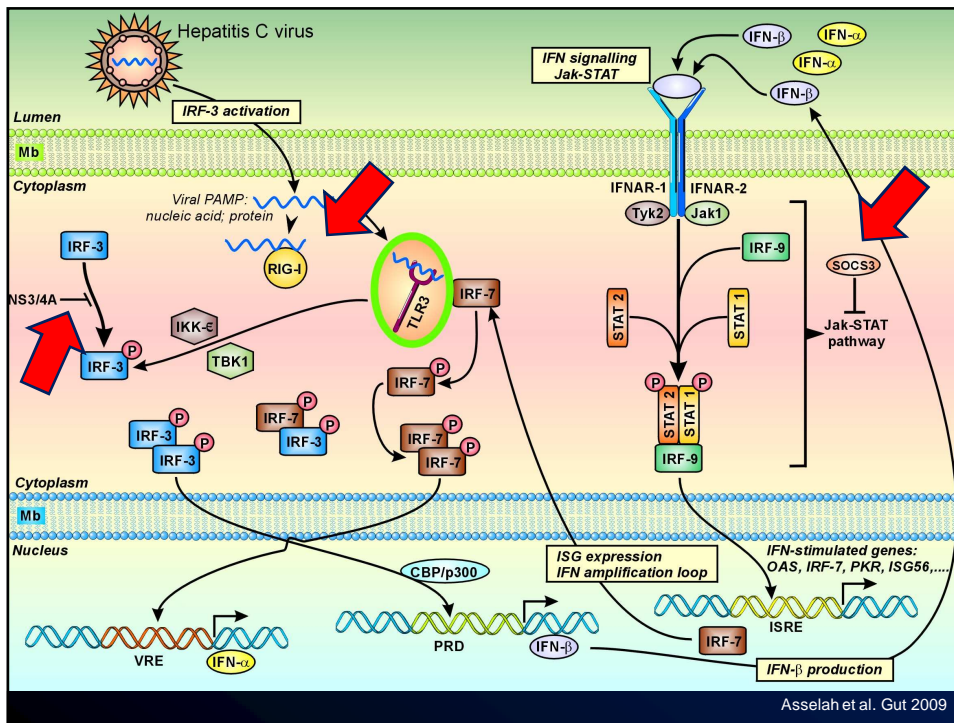
## R7128: NS5B polymerase inhibitors (NUCS) HCV GT 1/4 naive

May have less resistance – Active in all HCV genotypes



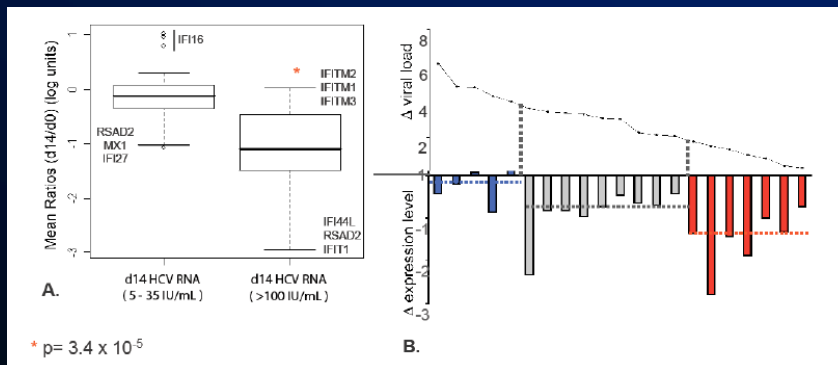
DM Jensen et al. AASLD 2010

# Can We Cure Hepatitis C Without Interferon?



## Anti Viral Activity of PI (Telaprevir) Resolves Expression of an HCV Gene Signature

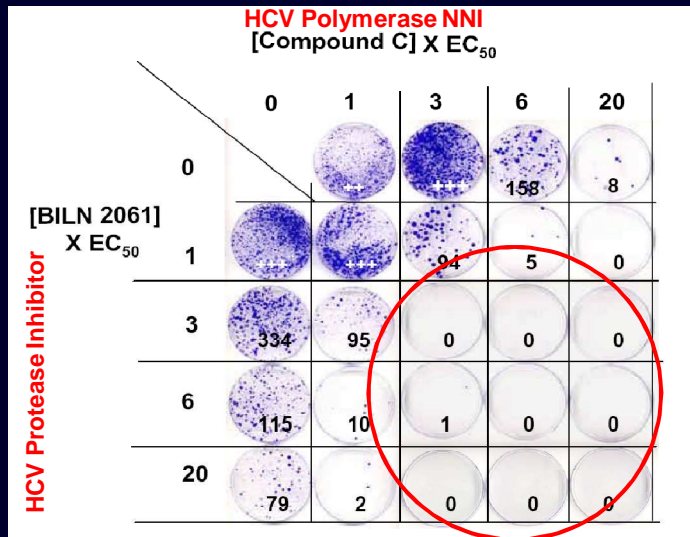
Sustained levels of IFN Sensitive Genes correlates with the reduction in plasma HCV RNA levels



- Plasma clearance of HCV RNA and elimination of virus particles results in normalization of genes expression signatures
- Inhibition of NS3/4A restore IFN signaling

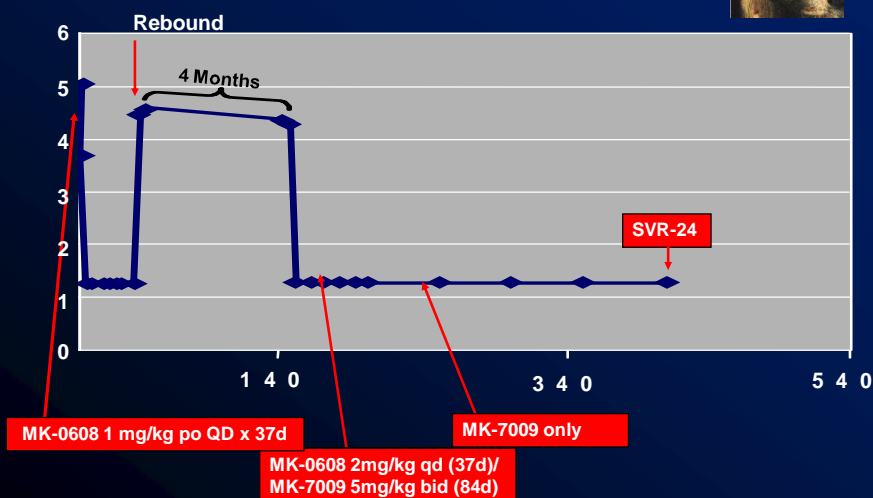
Ramachandran R et al. EASL 2006

## Prevention of Resistance DAA combination (*in vitro*)



Kukolj et al., 2005 J. Biol. Chem. 280: 39260-7

## IFN/RBV Free regimen POC in Chimpanzee



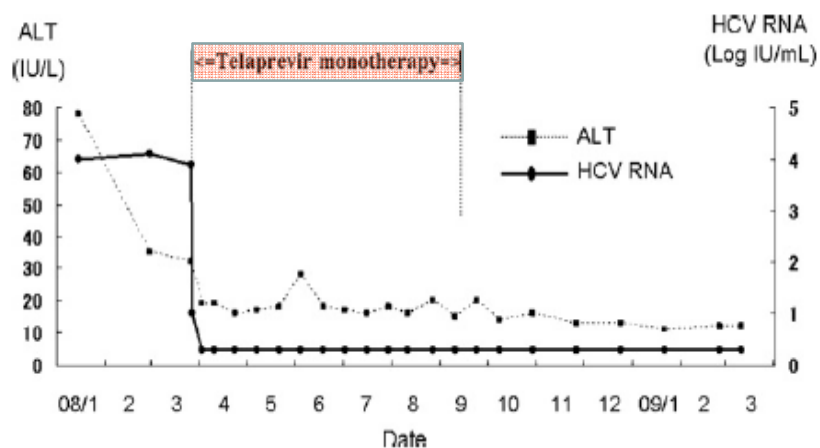
MK-0608: Nucleoside analog (7-deaza-2'-C-Methyl-adenosine) MK-7009: Protease inhibitor

## IFN/RBV Free regimen POC in Human

- 58 years old Japanese Men
  - Biopsy: A1 – F2
  - HCV Naive
  - GT1b
- Baseline
  - HCV RNA 3.9 logs IU/mL
  - ALT 46 IU/L
- Telaprevir monotherapy (750 mg q8h) 24 weeks

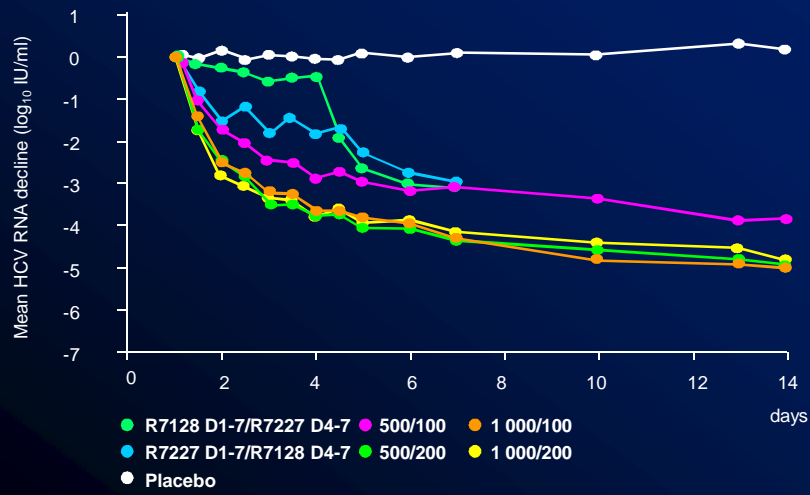
Fumikata S et al J Clin Virol 2009

## IFN/RBV Free regimen POC in Human



Suzuki F et al. J Clin Virol 2009

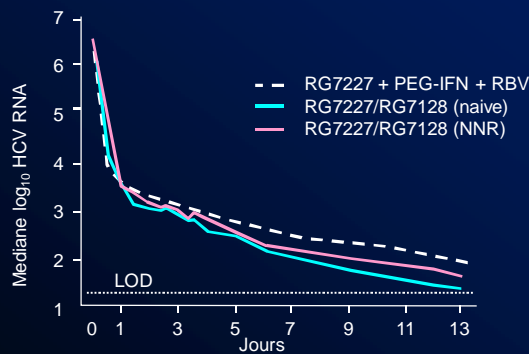
**PEG IFN/RBV sparing regimen  
Protease + Polymerase inhibitor for the treatment  
of HCV  
INFORM-1: GT1 Naive patients**



**No treatment-emergent resistance identified**

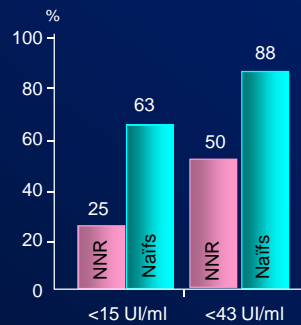
Gane EJ. et al. EASL 2009

**PEG IFN + RBV sparing regimen  
Protease (R7227) + Polymerase inhibitor (R7128) for the  
INFORM-1: GT1 Rx experienced patients**



RG7128 1000 mg x 2/j + RG7227 900 mg x 2/j

**W2 Response**



**No treatment-emergent resistance identified**

Null Non Resonders NNR = HCV RNA decline < 1 log<sub>10</sub> UI/ml at W4 or < 2 log<sub>10</sub> UI/ml at W12

Gane JE, et al. AASLD 2009

**PEG IFN sparing regimen  
Protease (BI 1335) + Polymerase inhibitor (BI  
7127) for HCV GT1 Naive patients**

	Day 8	Day 15	Day 22	Day 29
400 mg TID BI 207127 + BI 201335 + RBV	4/15	6/15	10/15	11/15
600 mg TID BI 207127 + BI 201335 + RBV	3/17	14/17	17/17	17/17

S. Zeuzem et al. AASLD 2010

**Can We Cure Hepatitis C Without Interferon?**

**IFN**

**DAA**

**Antiviral activity**

**More potent  
antiviral activity**

**Immune  
modulation**

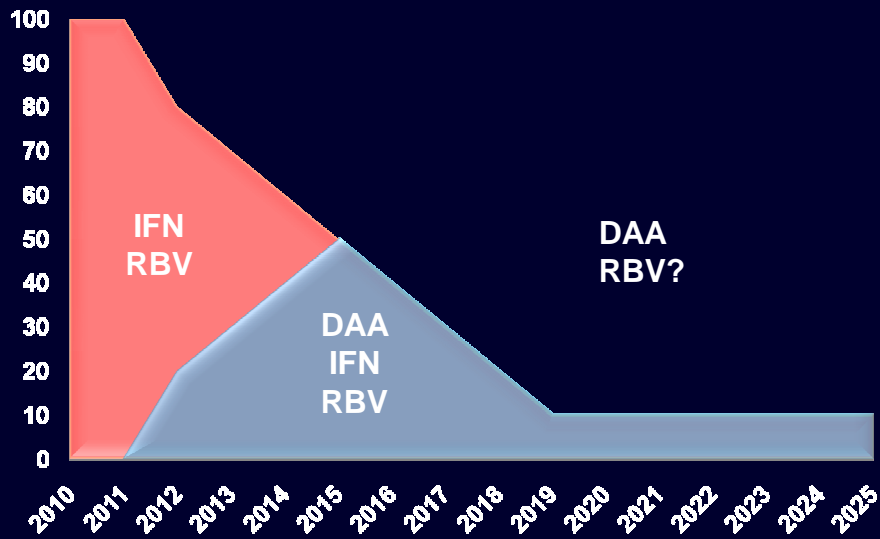
**Cells self defence  
restoration**

**No resistance**

**DAA  
combinations**

**RBV ?**

## Can We Cure Hepatitis C Without Interferon?



## Conclusion

- Improve SVR and Reduce duration of therapy
- IFN/RBV Backbone of anti HCV therapy for...?
  - « Tolerability »: same or even worse
- Challenges: Resistance
- 2011:
  - Q2 – 3: Telaprevir / Boceprevir
    - Improve efficacy (GT1)
- 2013: 2<sup>nd</sup> DAA generation
- 20???: IFN free regimens?