

# **Navigating Dangerous Complexities:**

## **Antiviral Strategies For Clinical Trials For Hepatitis C**

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# Treatment of Chronic HCV Infection

## 2007 PEG IFN + RBV: SVR rates in pivotal trials

	Pegasys <sup>1,2</sup>	PEG-Intron <sup>3</sup>
Overall	56% & 63%	54% (61%)
Genotype 1	46% & 52%	42% (48%)
Genotype 1, HVL	41% & 47%	30% (37%)
Genotypes 2 & 3	76% & 84%	82% (88%)

<sup>1</sup>Fried MW, et al. *N Engl J Med* 2002;347:975-982. <sup>2</sup>Hadziyannis S, et al. *Ann Intern Med* 2004;140:346-355

<sup>3</sup>Manns MP, et al. *Lancet* 2001;358:958-965 (RBV >10.6 mg/kg by post-hoc analysis)

### Established predictors of favorable response

genotype: 2 or 3 - HCV RNA: low (<800,000 IU/mL) - stage of fibrosis - ethnicity: non-African American - body weight: lighter (<85 kg) - age: younger (<40 years)

### Emerging predictors of response

steatosis / insulin resistance - adherence: good (80 / 80 / 80)  
 RBV dose- on-treatment response: RVR and EVR

# Challenges For New Oral Anti-HCV Drugs

1. Improve SVR (Naive and NR)
2. Good safety profile
3. Improve tolerability of current SOC
  1. Reduction of treatment duration
  2. Reduction of IFN and RBV doses
    1. Elimination of PEG (RBV)

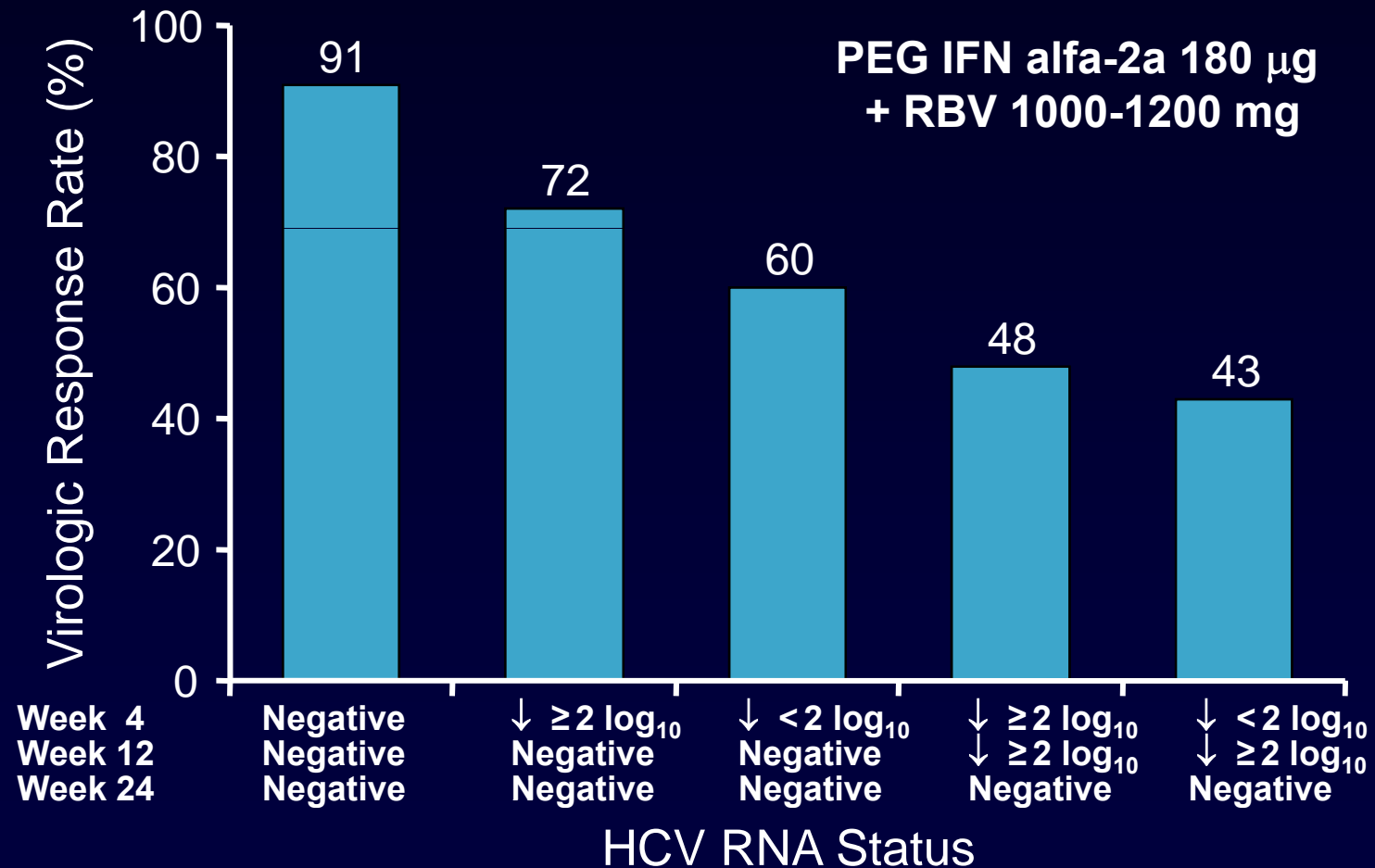
## Major limitations

- Toxicity and resistance

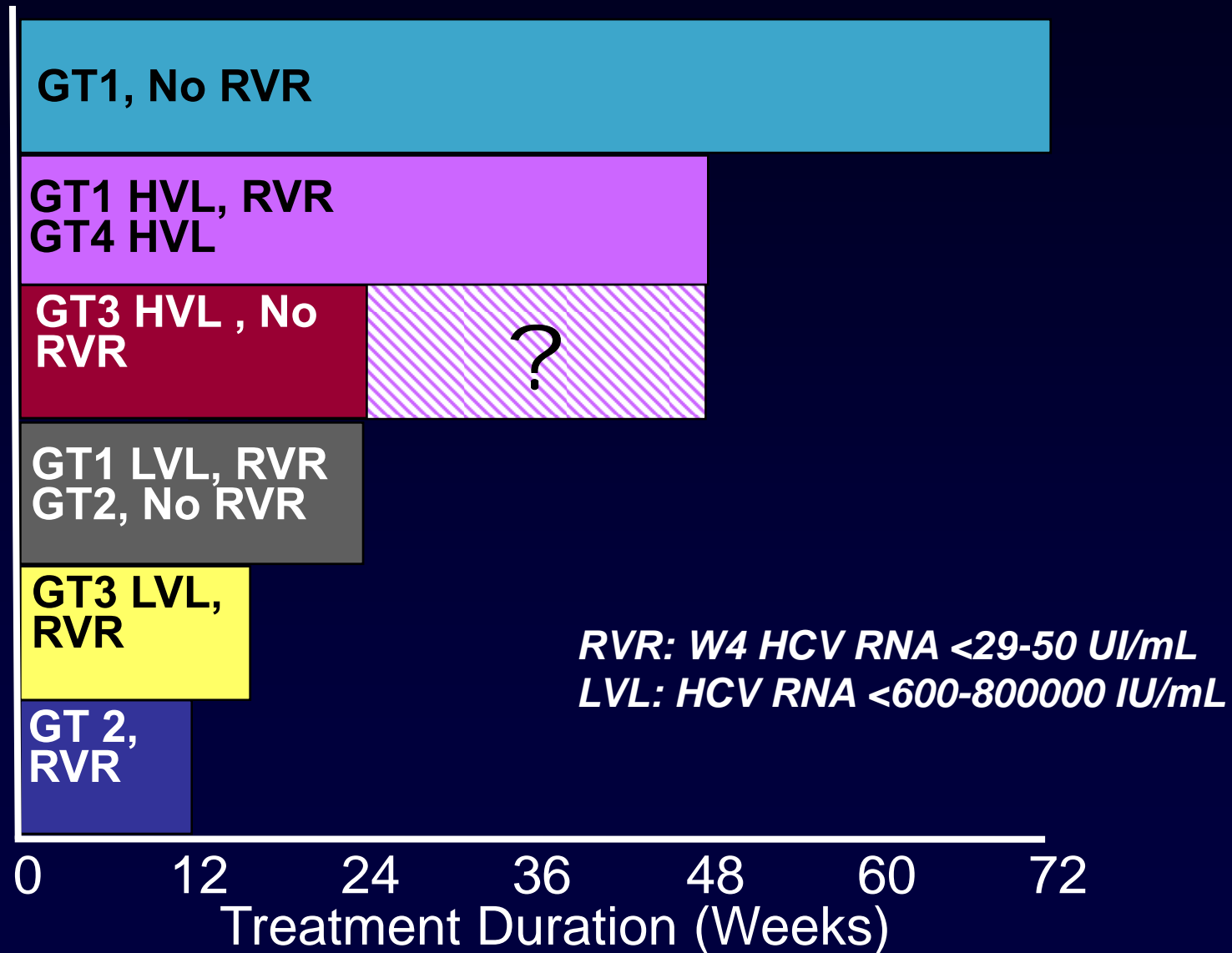
# Lessons From HCV Therapy With PEG IFN + RBV

- Individualized therapy:
  - Role of genotype and baseline viral load
  - On-treatment responses crucial
    - Rapid virological response (RVR): W4
    - Early virological response (EVR): W12
  - Remains true with oral anti-HCV?

# Rapidity of Viral Clearance Predicts SVR with PEG IFN + RBV



# HCV Treatment Individualization

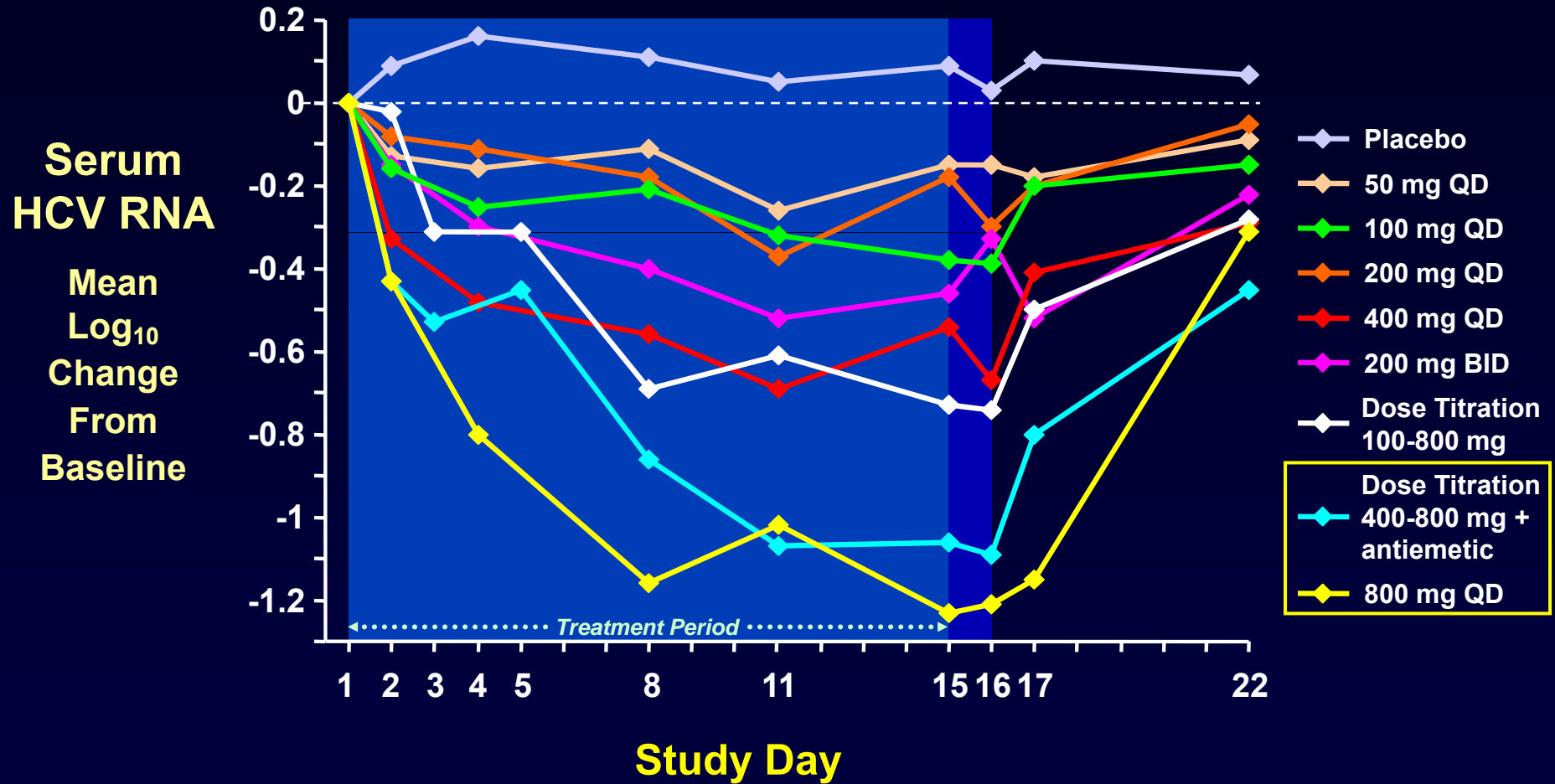


## **Lessons From Oral Anti-HCV Studies**

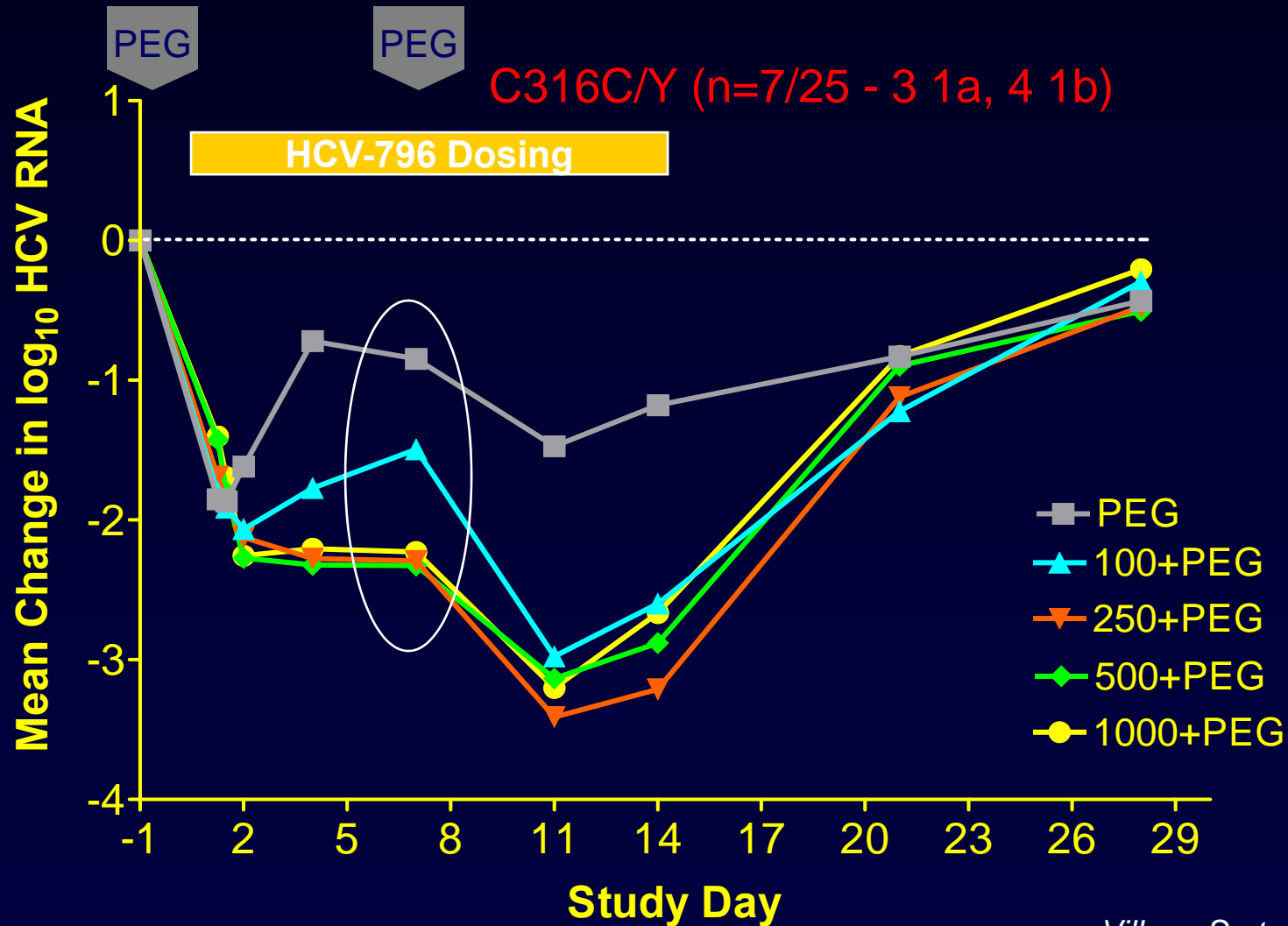
- **Monotherapy with new oral agents will not improve SVR**
  - **Lack of efficacy**
  - **Rapid development of resistance (1st week of therapy)**

# Lessons From Oral Anti-HCV Studies

## Valopicitabine: HCV-GT1



# Lessons From Oral Anti-HCV Studies HCV 796 GT1



# Lessons From Oral Anti-HCV Studies

## Boceprevir HCV GT1 NR

### Peg-IFN alone

- Mean 1.1

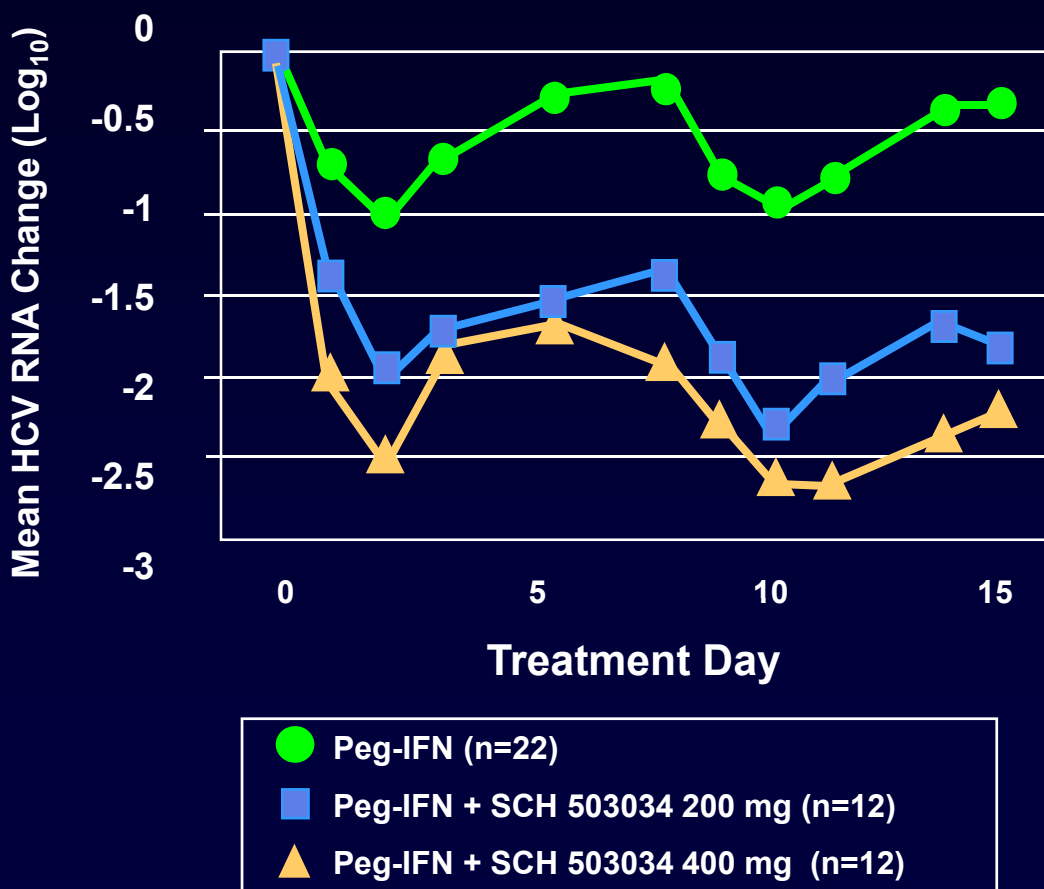
### SCH 503034 alone

- 200 mg TID monotherapy: Range 0.4 – 1.77
- 400 mg TID monotherapy: Range 0.5 – 2.5

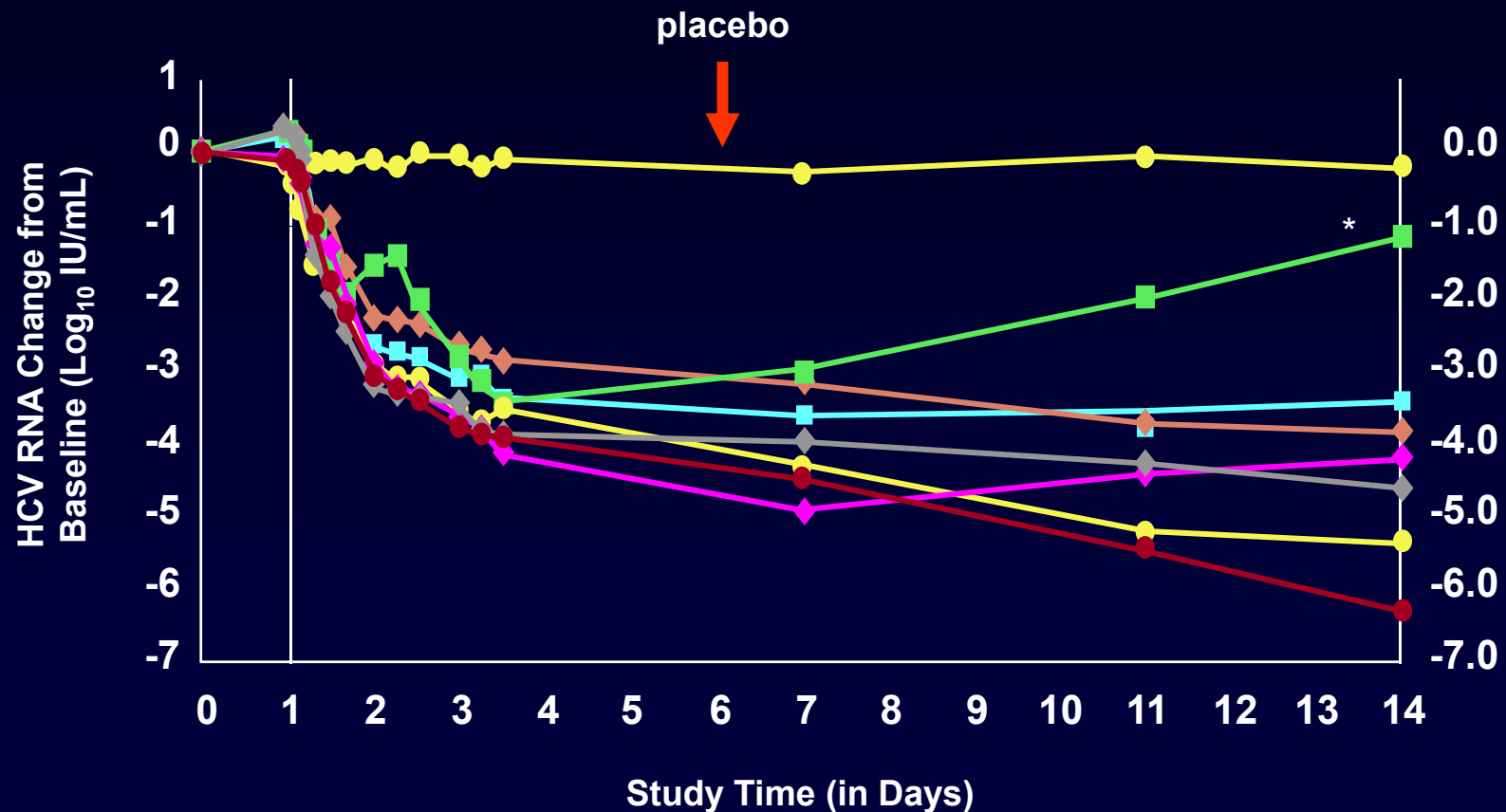
### SCH 503034 + Peg-IFN -2b

- 200 mg: Mean 2.4 (1 – 4.5)
- 400 mg: Mean 2.9 (2.3 – 4.1)

Antiviral Activity of SCH 503034 in Combination with Peg-IFN vs Peg-IFN Alone in HCV-1 Patients

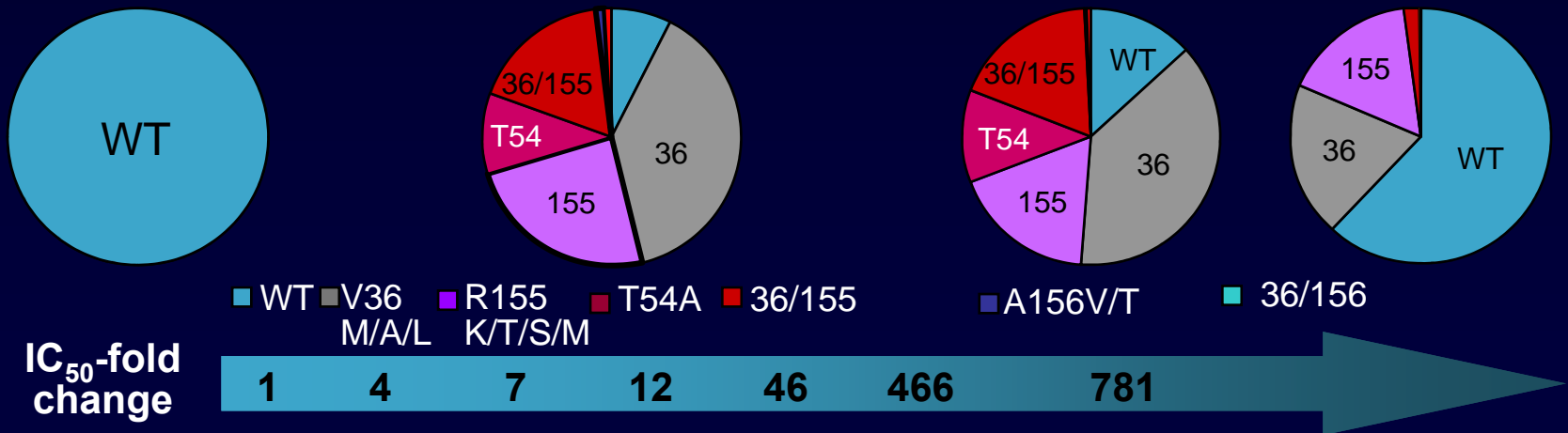
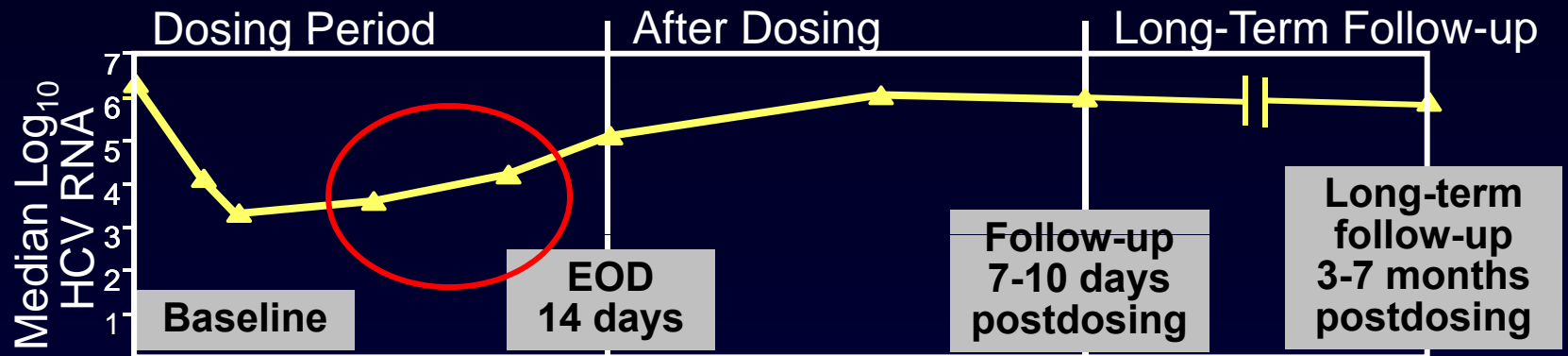


# Lessons From Oral Anti-HCV Studies Telaprevir (750 mg q8h) HCV GT1



\*Lowest VX-950 exposure in dose group

# Lessons From Oral Anti-HCV Studies Telaprevir (750 mg q8h) HCV GT1

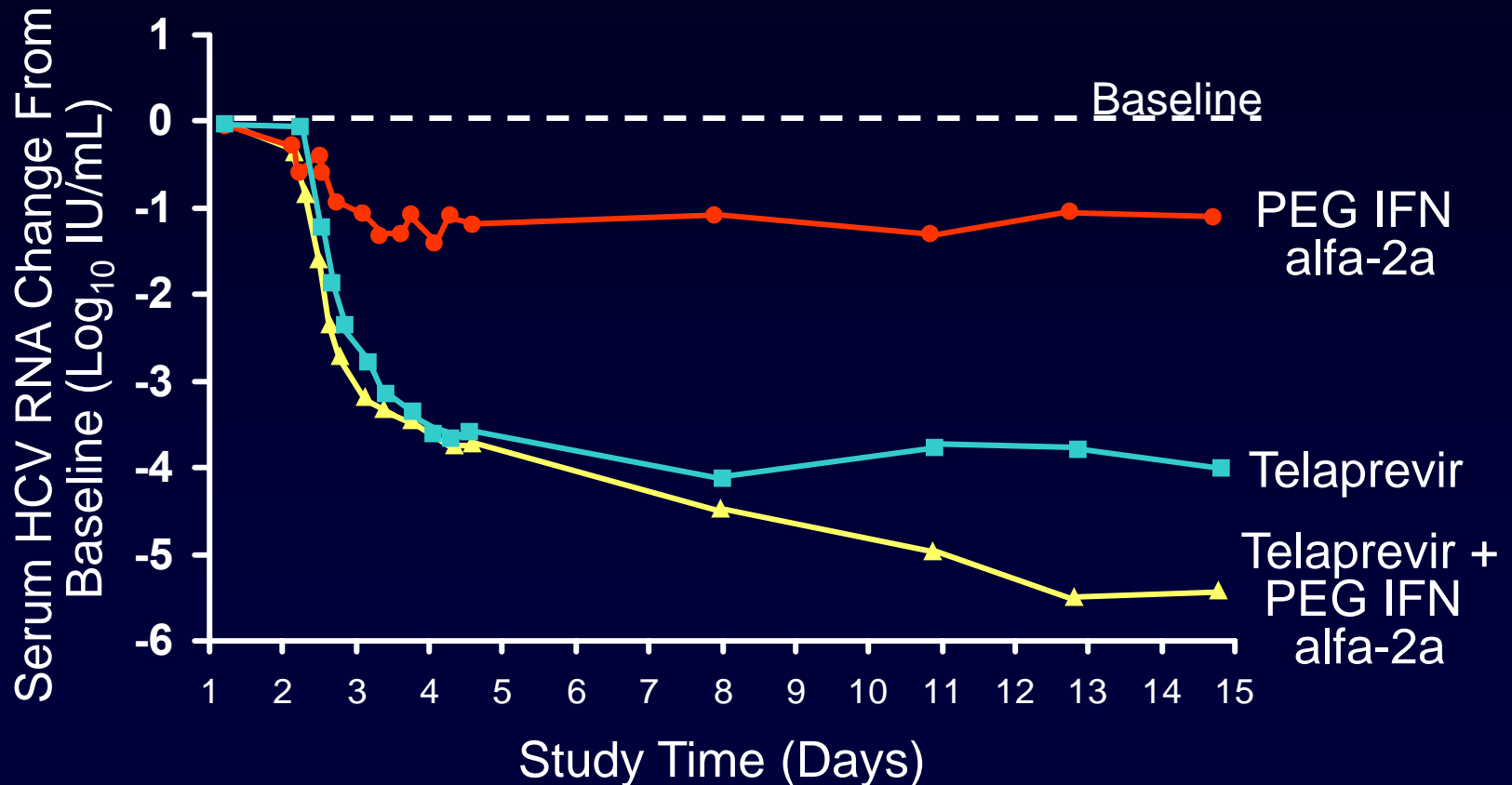


# Lessons From Oral Anti-HCV Studies

- Monotherapy with new oral agents will not improve SVR
- Initial development must be done in combination with IFN **AND** RBV
  - Improve anti-viral activity
  - Reduction of the risk of resistance
  - Reduction of relapses (RBV)

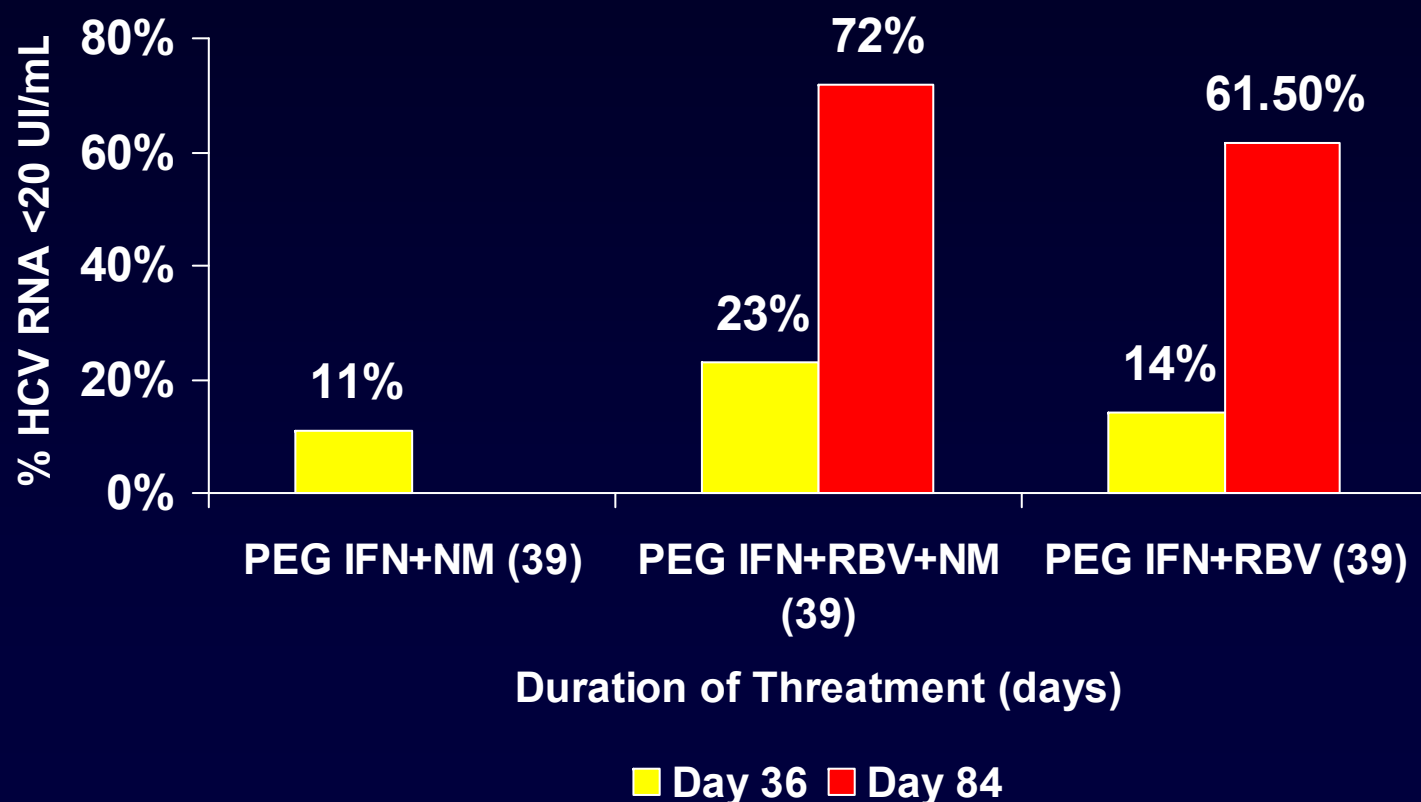
# Lessons From Oral Anti-HCV Studies

## Telaprevir (750 mg q8h) HCV GT1



# Lessons From Oral Anti-HCV Studies

## Valopicitabine: HCV-GT1 Naive



# Lessons From Oral Anti-HCV Studies

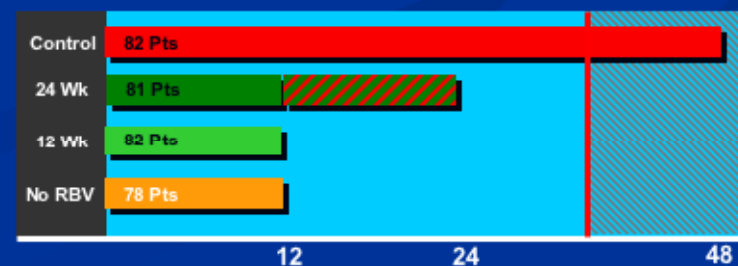
## Telaprevir: HCV-GT1 Naïve (PROVE 2)

Treatment Arm	Endpoint	Result
Control Arm N=82	Ongoing	
24 Week Arm n=81	SVR12	65%
12 Week Arm n=82	SVR24*	59%
No RBV Arm n=78	SVR24**	29%

\* No relapse between SVR 12 and 24

\*\* One relapse between SVR 12 and 24

Intent-To-Treat Analysis

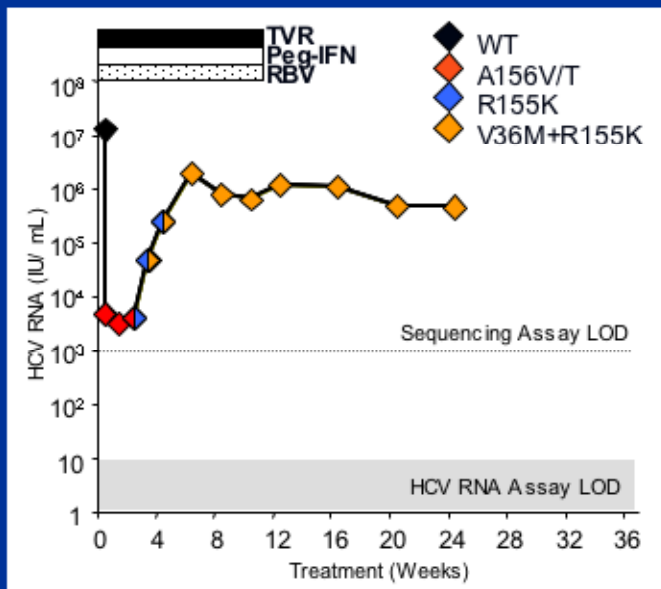


# Lessons From Oral Anti-HCV Studies Telaprevir: HCV-GT1 Naïve (PROVE 2)

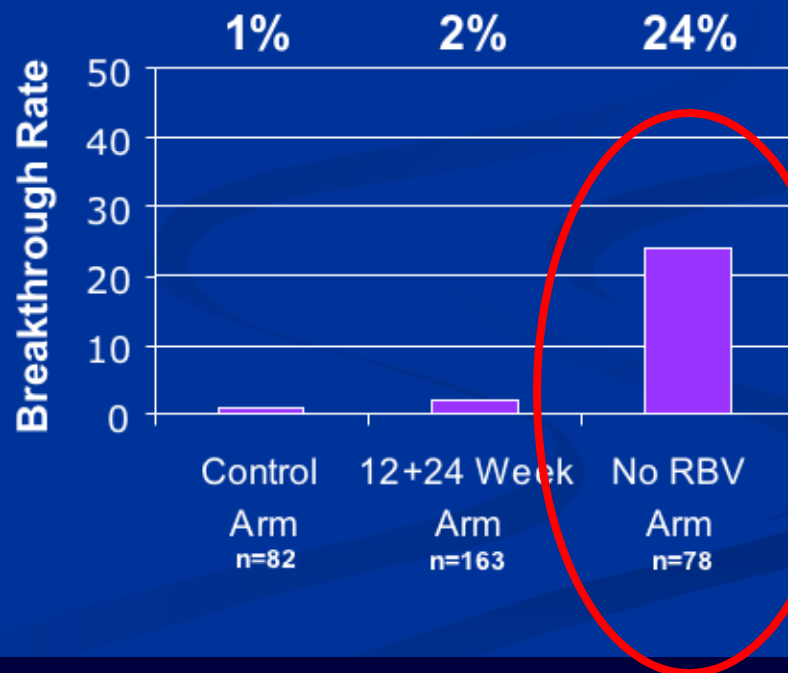
**Viral breakthrough (increase in HCV RNA on treatment):**

- increase of  $> 1$ -log above HCV RNA nadir
- increase to  $>100$  IU/mL in previously undetectable patients

*Representative example*



*From Poster LB8*



# Lessons From Oral Anti-HCV Studies

- **Importance of W4 response (RVR)**
  - **To predict SVR**
    - **Resistance**
    - **Relapses**
  - **To individualize treatment duration?**

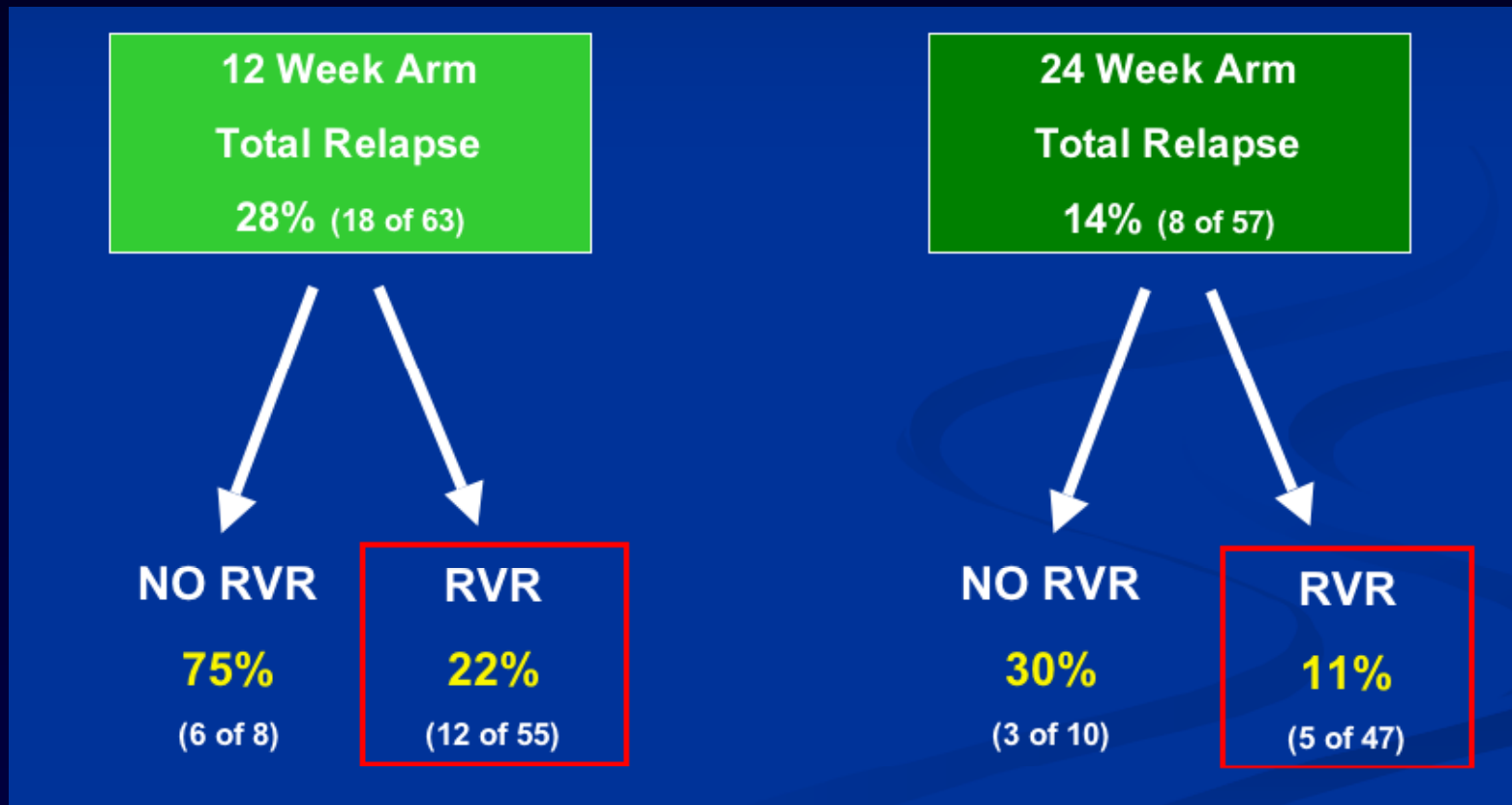
# Lessons From Oral Anti-HCV Studies

## Telaprevir: HCV-GT1 Naïve (PROVE 1)

Fourteen subjects experienced viral breakthrough

- 2 in control group (3%)
- 12 in TVR groups (7%)
  - All but one breakthrough in the TVR groups occurred within first 4 weeks
  - 9 of 12 breakthroughs occurred in patients who never became undetectable
  - All associated with high level TVR-resistant viral variants

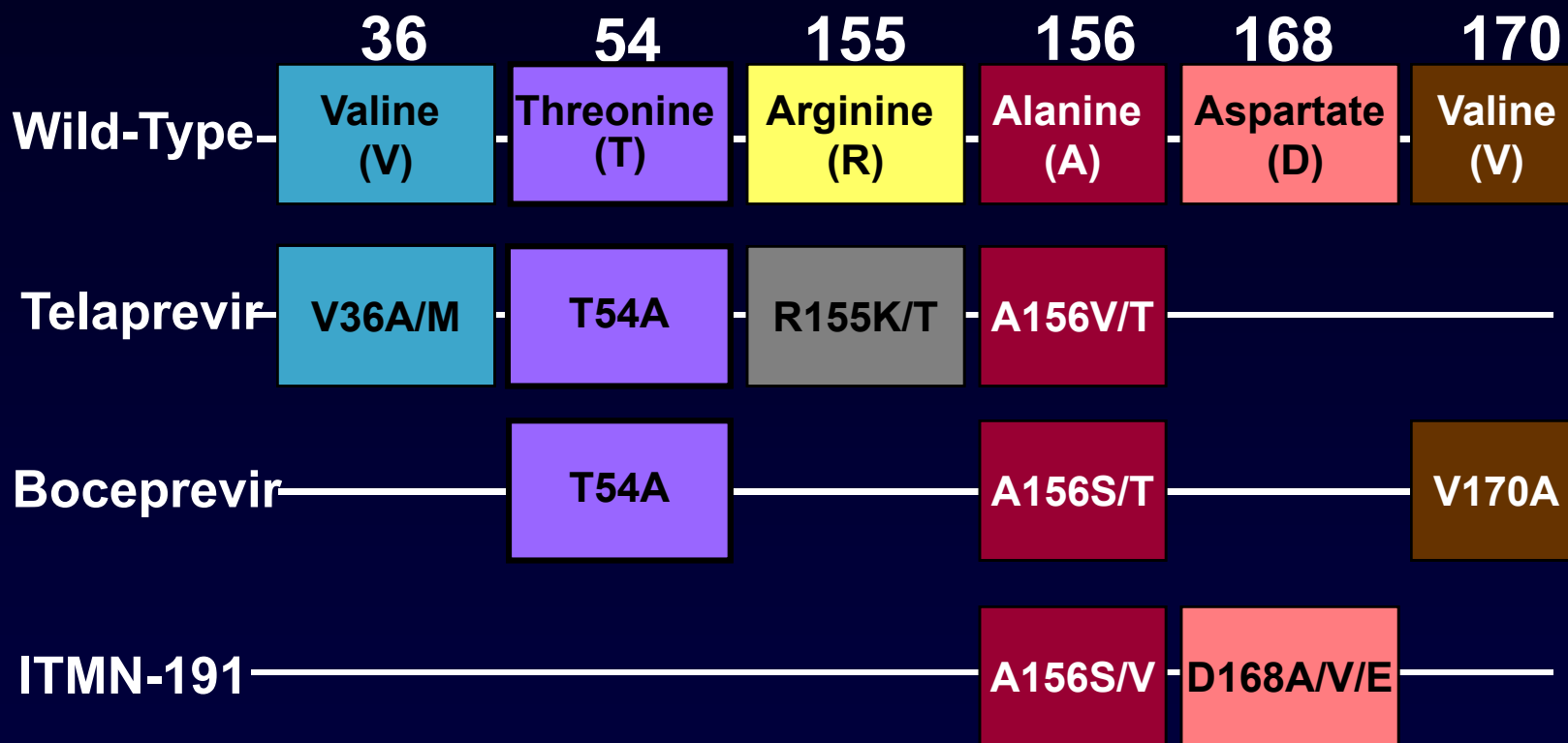
# Lessons From Oral Anti-HCV Studies



# Lessons From Oral Anti-HCV Studies Summary

- Monotherapy studies (POC) should exceed not 5-7 days
  - Enough to measure anti viral activity
  - Minimize risk of emergence of resistance (cross resistance)
- No oral anti-HCV will be developed without combination with IFN **AND** RBV
  - For many years or ever ?
- RVR (W4) is the most important end point to predict SVR, resistance and to optimize treatment duration
  - W2 virological response (**VRVR?**) may be more interesting predictors of SVR?

# Lessons From Oral Anti-HCV Studies In Vitro Resistance To Protease Inhibitors



*Adapted from Kieffer et al. Hepatology. 2007;46(3):631-639. Graphic courtesy of Dr Ira M. Jacobson.*

# Oral Anti-HCV Studies ???

- **Naive patients**
  - Monotherapy < 6 days
  - Triple combo
    - RVR : 24 weeks?
    - No RVR and EVR: 48 weeks?
    - Lead dose with IFN/RBV for poor resistance profile / modest efficacy drugs
- **Non Responders**
  - No monotherapy
  - Lead dose with IFN/RBV?
  - RVR: 48 weeks?
  - No RVR and EVR: 72 weeks?
- **Combination therapies**
  - For the all duration?
  - Until PCR negativation (+4 W)?
    - Reduction of the exposure to new drugs may reduce risk of toxicity?
  - Discont. if no negative PCR at W12

## Oral Anti-HCV Studies

- Combinations of oral anti-HCV with different MOA and no cross resistance
  - Should be considered early in the development
  - Will improve RVR – SVR and minimize the risk of resistance
  - May help to eliminate IFN (and RBV?) from the regimen

# Combinations With Complementary MOA

## *Supported by In Vitro Studies*

Polymerase Inhibitors (NS5B)	Protease Inhibitors (NS3)	Other MOA
NM107*	Boceprevir	
NM107*		NIM811 (cyclophilin inhibitor)
NM107*	Telaprevir	ACH806 (NS4A antagonist)
HCV-796	Boceprevir	<b>Results</b> Additive-to-synergistic antiviral efficacy Decreased emergence of resistant variants
R1479**	ITMN-191	
R1479**	Telaprevir	

\*NM283; \*\*R1626

# CONCLUSION

- **Antiviral strategies for clinical trials for HCV**
  - 1<sup>st</sup> objective: SVR > vs SOC (more important than reduction of Rx duration)
  - Safety and efficacy must be studied in triple combo regimen
  - Duration of therapy will be clearly driven by the initial (2-4 weeks) anti-viral response
    - RVR may help to individualize treatment duration and optimized SVR
  - Trial to identify the best **SVR / Rx duration** must be designed, powered and performed prospectively (avoid sub analyses)
  - Drug resistance profile
    - Key point for the decision of the development strategy
    - Is predictable and should be extensively studied in vitro (HIV)
    - Adherence will be critical to prevent resistance (pk profile, tolerability ...)
- **Future therapy will involve combinations of antiviral drugs with one another and/or with IFN-based therapy**

# **One Trial For One objective Supported by a **Simple Design****

*« Appearance requires art and subtlety, truth calm and simplicity » (E Kant)*

*« A complex system that works is invariably found to have evolved from a simple system that works » (J Gaule)*

**WHEN DESIGNING A TRIAL, MOST IMPORTANT  
OBJECTIVE IS NOT TO MAKE A DRUG  
APPROVED BUT TO CURE MORE PATIENTS**