LIVER AND PLASMA HCV RNA KINETICS AS ASSESSED BY SERIAL FINE NEEDLE ASPIRATES

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Disclosures

The following are my reported disclosures related to this presentation:

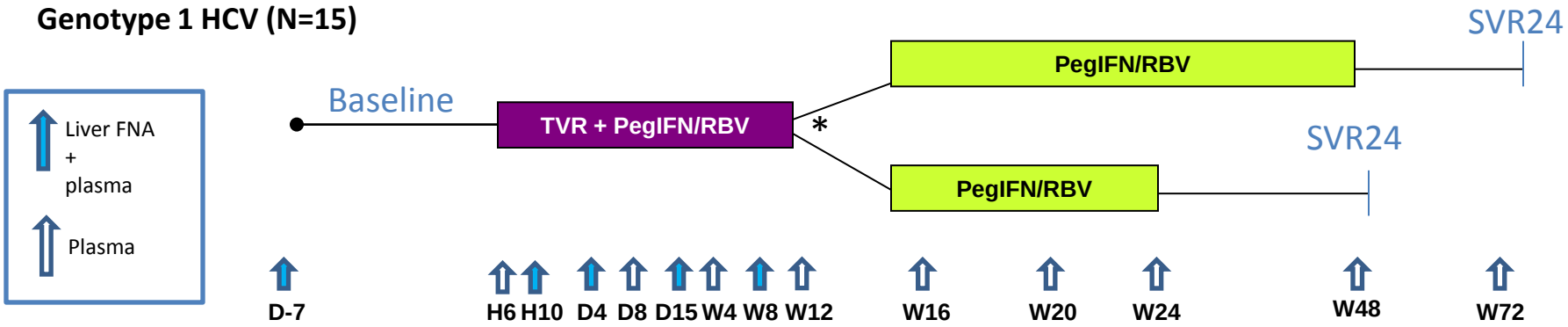
- Abbott: Research support
- Boehringer Ingelheim: Review panel member, research support
- Genentech: Speaker bureau, research support
- Gilead: Research support, advisor
- Merck: Research support, advisor
- Pfizer: Review panel member
- Vertex: Research support, advisor, speaker bureau

Background

- In response to direct acting antivirals (DAAs), HCV RNA levels decay rapidly in peripheral blood[1]
  - HCV RNA decline had not been assessed in liver
- Doses for antiviral agents have been derived largely based upon plasma measurements
  - Significant compartment differences may exist altering liver-to-plasma ratios for particular antiviral agents.
- Sampling via fine needle aspiration (FNA) offers lower morbidity and more acceptable alternative to sampling via core needle biopsy.

Study Design

Genotype 1 HCV (N=15)



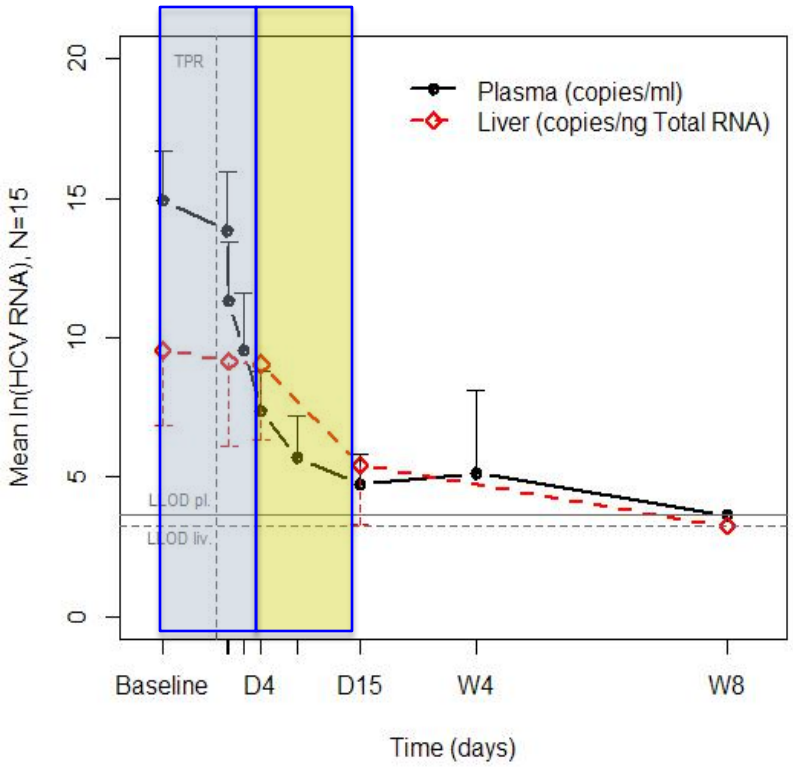
*Treatment-naïve patients with undetectable HCV RNA at Weeks 4 and 12 received 24 weeks total PR. Treatment-naïve patients with detectable HCV RNA at Weeks 4 and 12 and prior non-responders received 48 weeks total PR

Study Population, n (%)	
Treatment experience	
Naïve	9 (60)
Prior PR null and partial responders	6 (40)
Race	
Caucasian	11 (73)
African American	3 (20)
Hispanic	1 (7)
HCV Genotype 1 a	11 (73)
IL28B genotype CC	2 (13)
Males	9 (60)
Median age (years)	55
T12PR SVR rates,	
Overall	9/15 (60)
Prior partial and null responders	2/6 (33)

TVR = telaprevir; pegIFN/RBV = peginterferon alfa-2a/ribavirin; PR = pegylated interferon/ribavirin, T/PR = telaprevir, pegylated interferon/ribavirin, D = day, W = week, H = hour; SVR24 = sustained virologic response 24 weeks after end of treatment

Results: Plasma and Liver HCV RNA levels

- **Question**: How does HCV RNA decline in liver in comparison to plasma after initiation of T/PR?



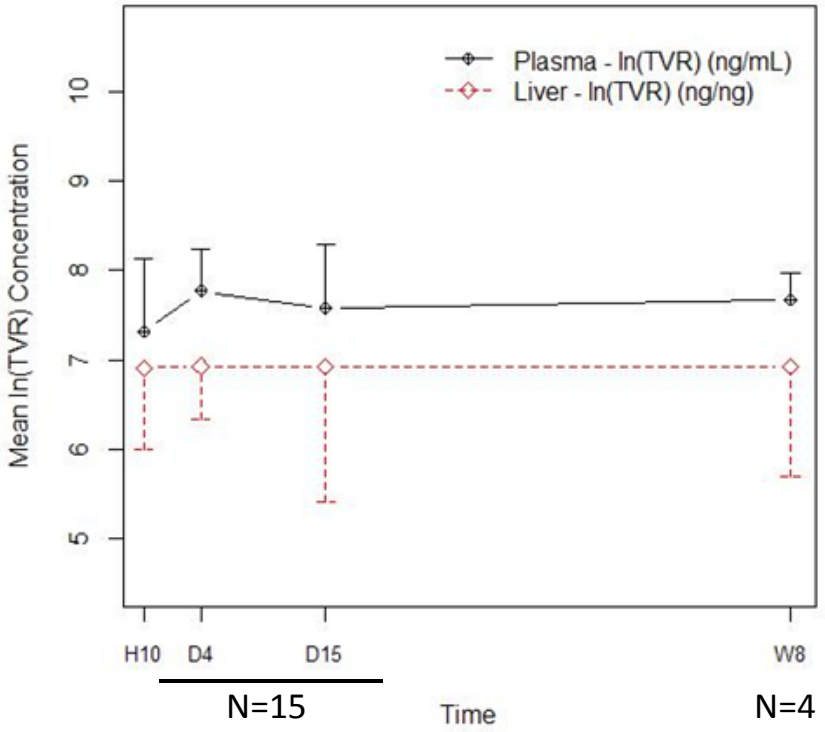
Results

- Baseline to D4 decline rate:
  - Median slope of ln(HCV RNA) decline is slower in liver than in plasma (-0.020 versus -0.664), $p<0.0001$
- D4 to D15 decline rate:
  - liver and blood were similar (p=0.1)

HCV RNA Assay
Liver, Real-Time PCR (LLOQ = 50 copies)
Plasma, Roche Cobas (LLOQ=43 , LLOD=7 IU/ml)

Steady-state TVR inhibitory concentration ratios

- ***A priori* hypothesis: TVR levels are higher in liver in comparison to peripheral blood based upon preclinical studies.**
- **TVR levels measured using liquid chromatography, tandem mass spectrometry**
- **TVR levels higher in plasma (2,241 ng/mL) than liver (1,594 ng/mL) at Week 8, p=0.0349.**



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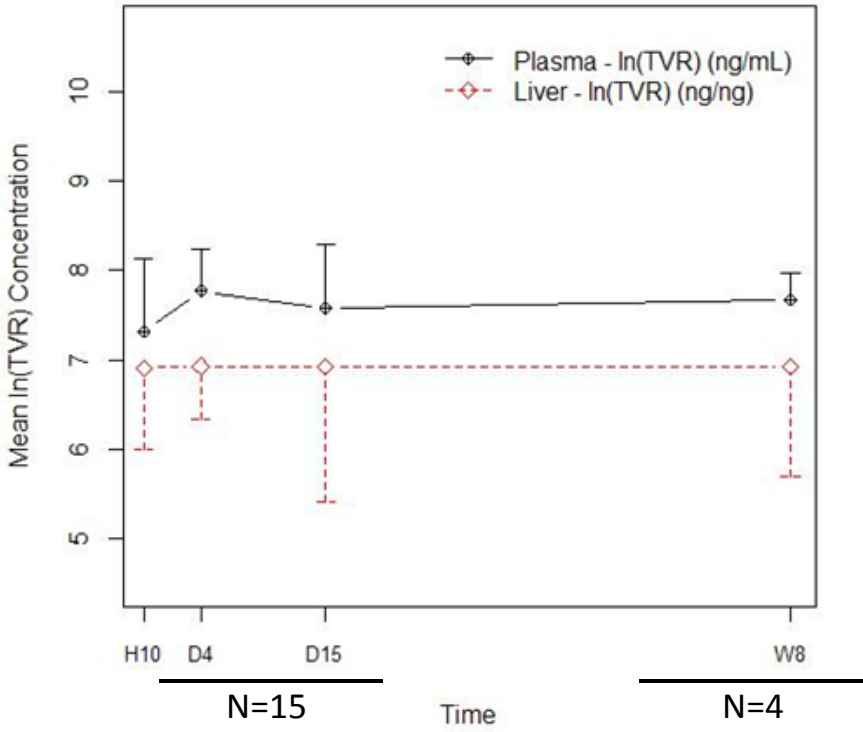
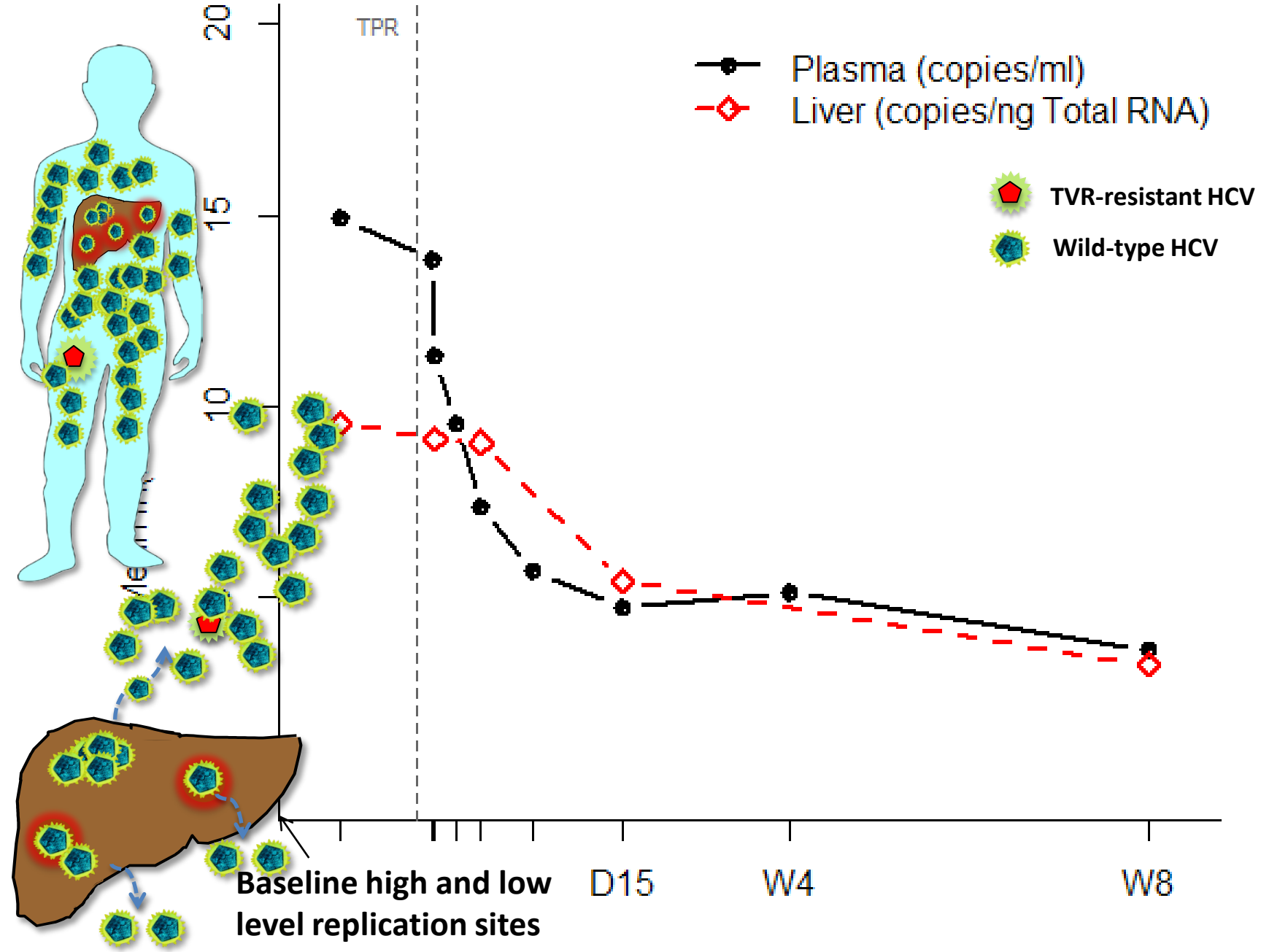
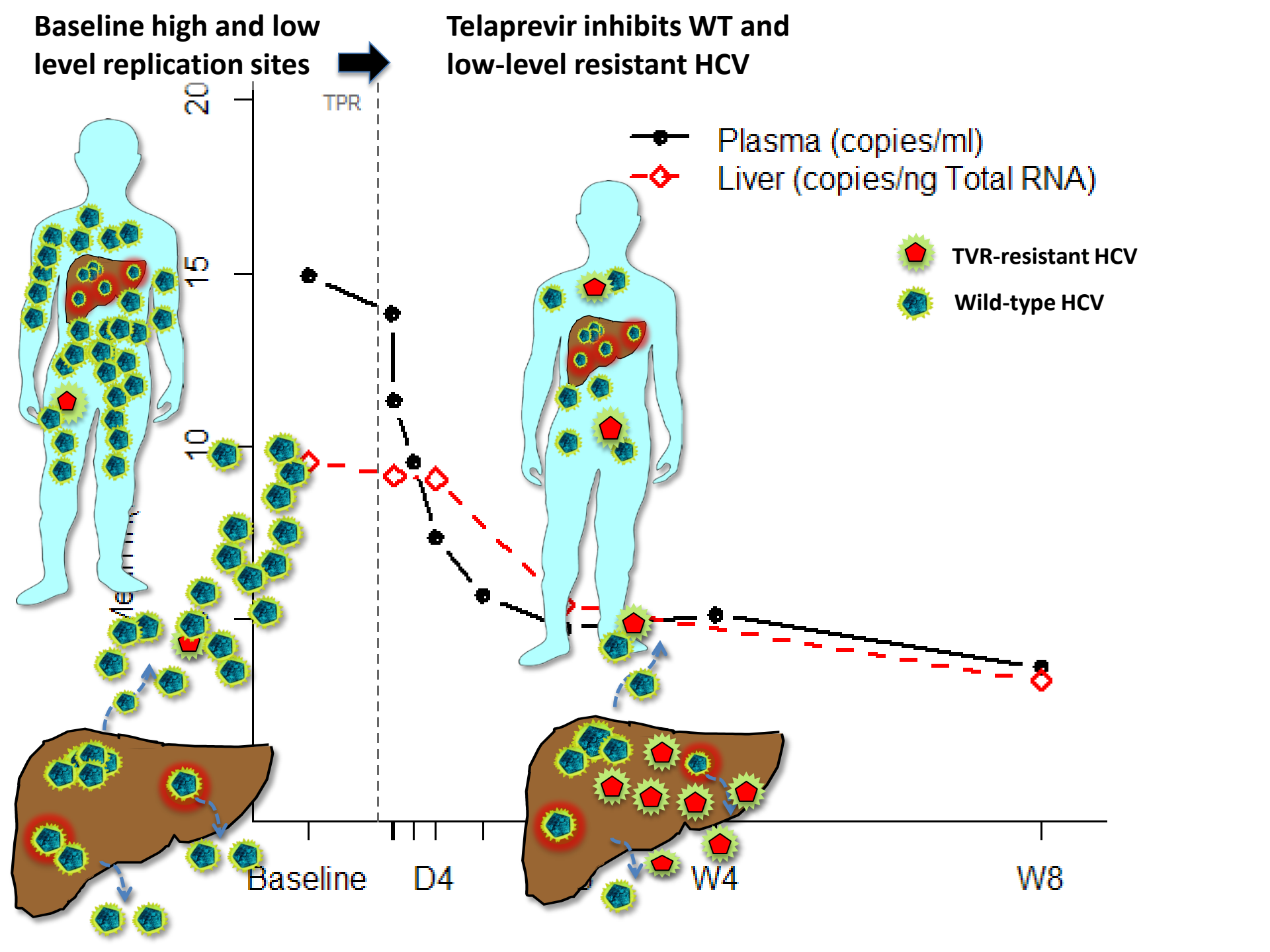


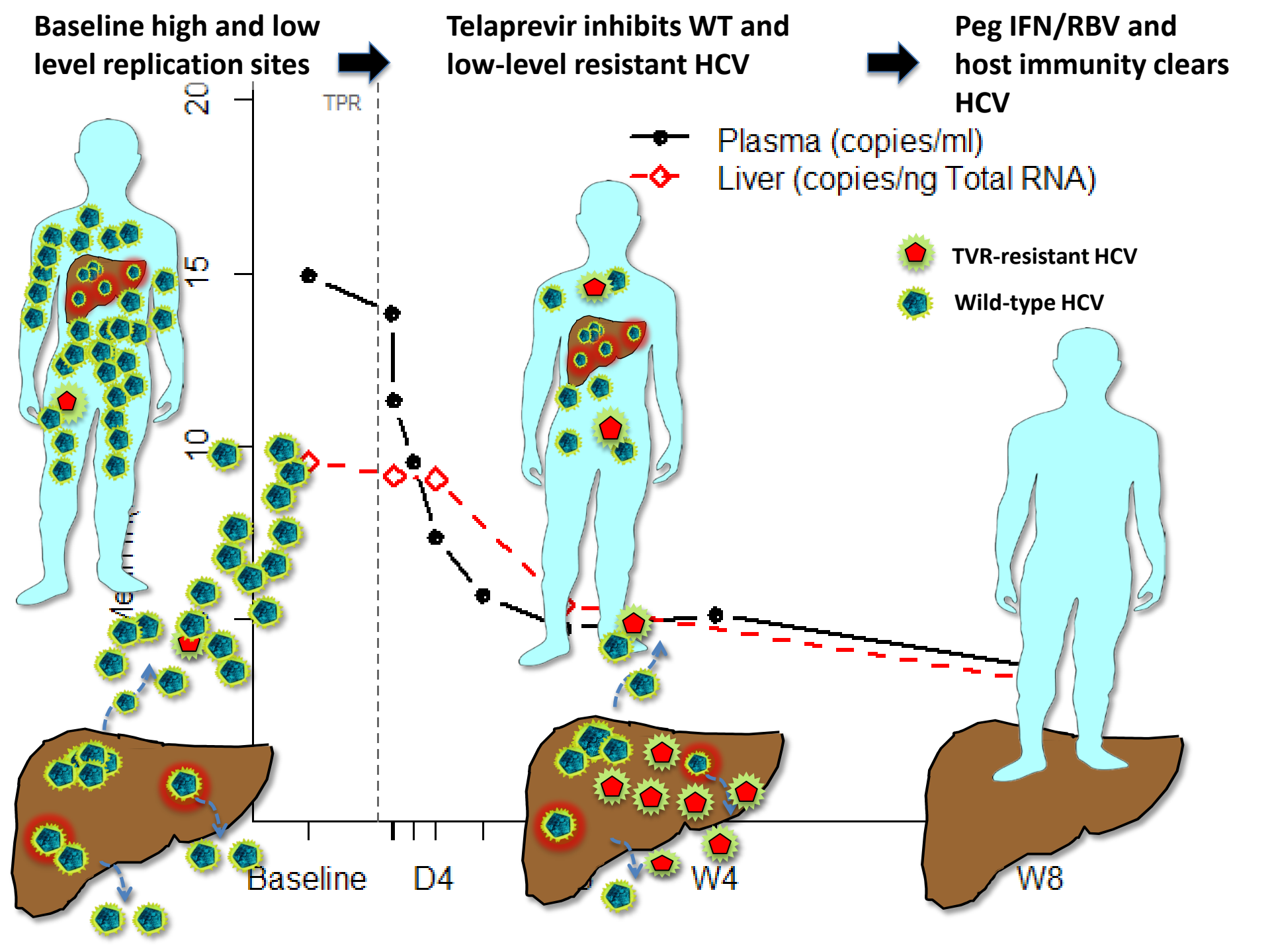
Inhibitory concentration (IC) ratios (min, max) of Week 8 TVR over WT

	Fold over IC_{50}	Fold over IC_{90}
Liver	2.3, 14.9	0.7, 6.3
Plasma	5.5, 14.4	2.3, 6.1

Integrated Model of HCV replication



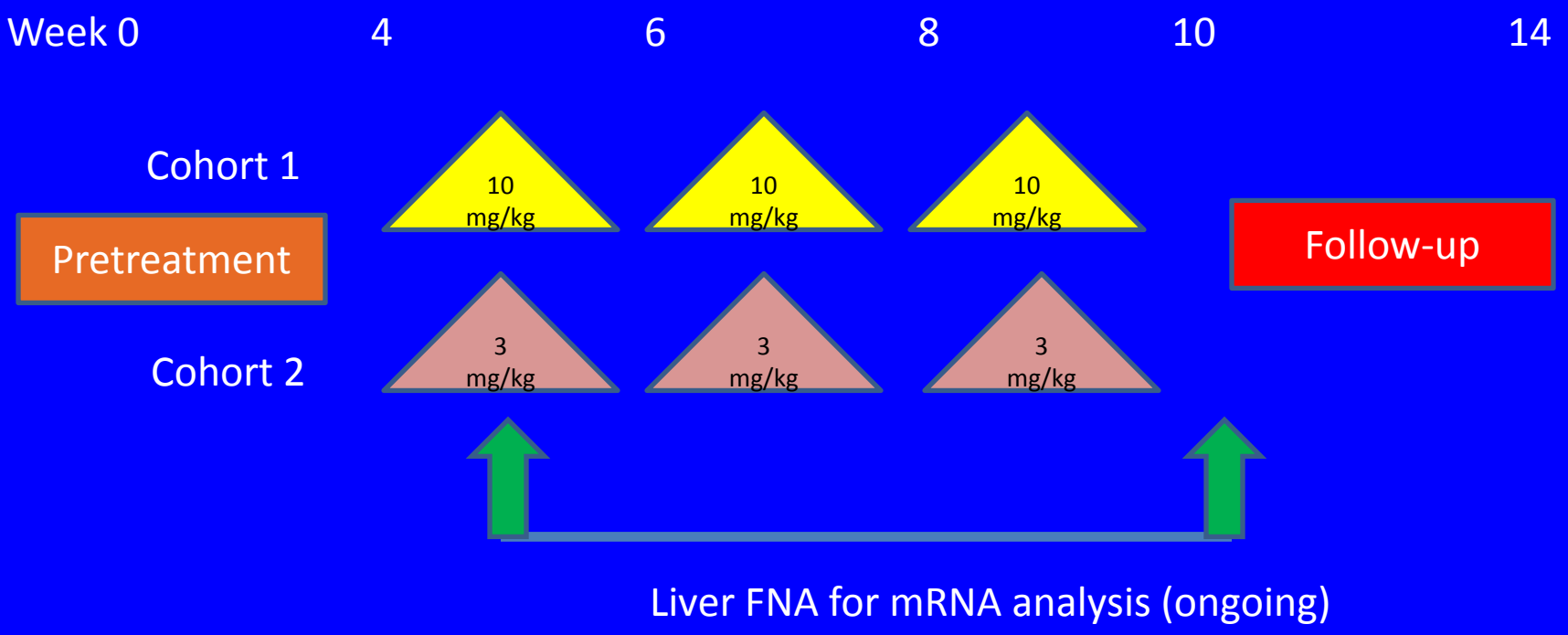

Baseline high and low level replication sites
Telaprevir inhibits WT and low-level resistant HCV
TPR
20
15
10
Plasma (copies/ml)
Liver (copies/ng Total RNA)
TVR-resistant HCV
Wild-type HCV
Baseline
D4
W4
W8


Baseline high and low level replication sites
Telaprevir inhibits WT and low-level resistant HCV
Peg IFN/RBV and host immunity clears HCV
TPR
Plasma (copies/ml)
Liver (copies/ng Total RNA)
TVR-resistant HCV
Wild-type HCV
20
15
10
Baseline
D4
W4
W8

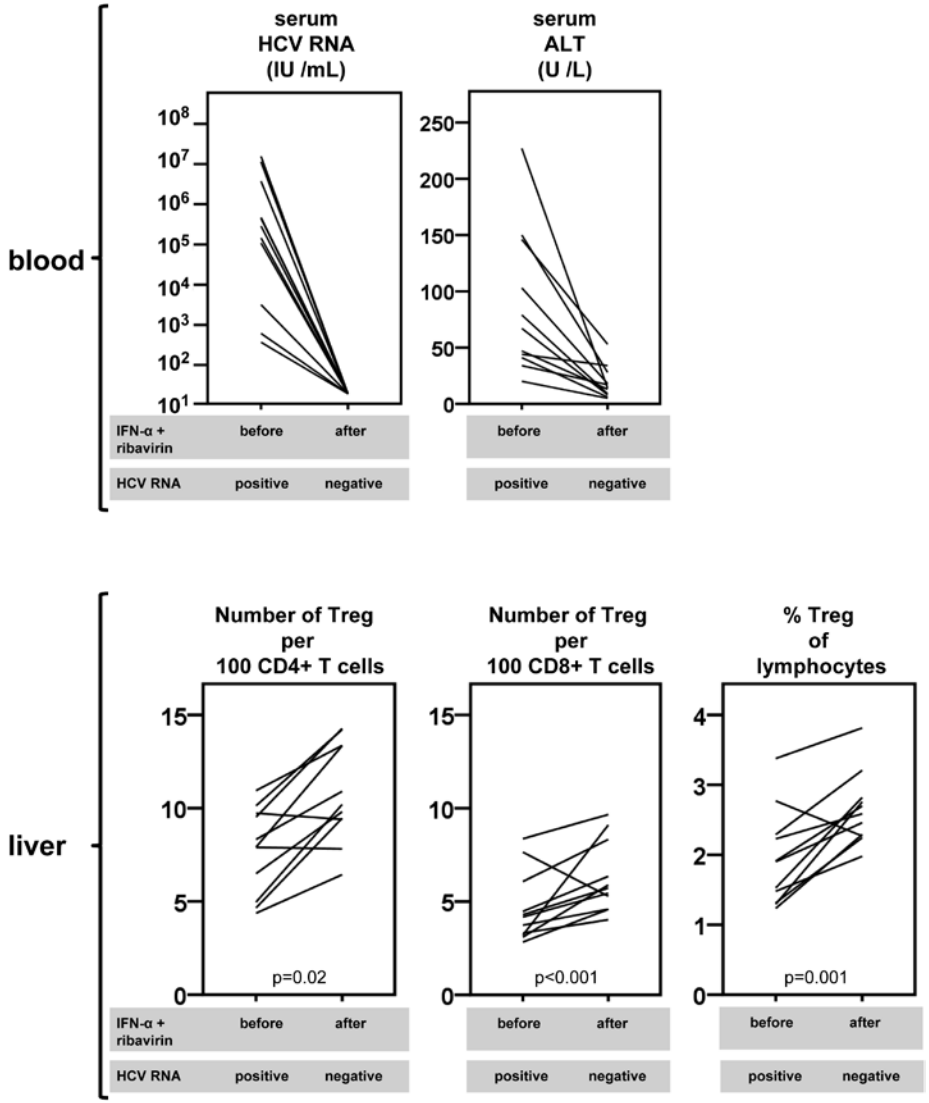
Hepatic mRNA Analysis in Patients Treated with Simtuzumab

- Simtuzumab (GS-6624) is a humanized immunoglobulin-G_4 monoclonal antibody against Lysyl Oxidase-Like 2 (LOXL2) enzyme.
  - LOXL2 promotes cross-linking of type 1 collagen
  - A core regulator of fibrogenesis.
- Two sequential cohorts of liver disease patients (n=10, each) were treated with 3 infusions over a 4 week period of either 10 mg/kg or 3 mg/kg

Study Design



$CD4^+CD25^+FoxP3^+$ Treg remain present in the liver of subjects after therapy-induced clearance of HCV



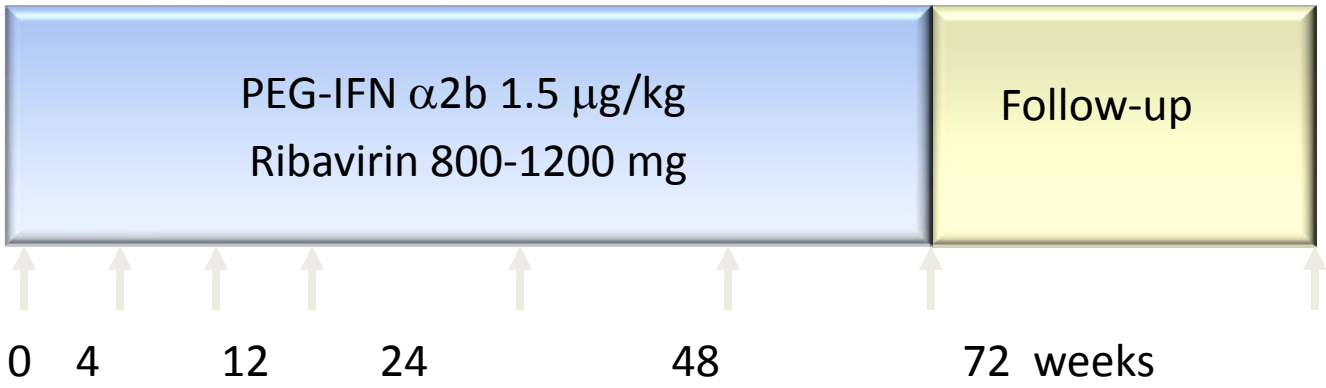
4wk FU
24wk FU

How does IFN/riba treatment affect the HCV-specific T cell response?

CIRES study – Erasmus MC (Janssen/ Boonstra)

20 HCV genotype 1 infected therapy naïve patients

30 HCV genotype 1 infected previous non-responders



Claassen, Janssen, Boonstra.
J Hepatology 2010; J Virol 2011; Plos One 2012

Telaprevir Modulation of HCV Specific Immune Responses?

- *Collaboration with Erasmus MC: Andre Boonstra and Michelle Spaan*
- *Study in 25 chronic HCV patients treated with peginterferon, ribavirin and telaprevir*
- *Before, during and after therapy taking FNA at 4 time points + blood samples to investigate*
  - *NK and T cell phenotype and functionality*
  - *Gene expression*
  - *Differences between responders and non-responders.*

Other FNA-based collaborations

- Assessment of T cell epitopes and functional characteristics in liver and blood
  - Collaboration with Ray Chung and Georg Lauer
- Assessment of MK7009 levels in samples obtained by FNA
  - Collaboration with Merck

Conclusion and Discussion Points

- Liver FNA-Relatively safe method to serially sample liver
- Preliminary uses to date
  - Viral kinetics/resistant variants
  - Drug concentration
  - Host gene analysis
  - Immunological parameters
- Potential other uses?