Pharmacokinetics of GS-331007 Triphosphate in Red Blood Cells in HCV-infected Subjects Receiving Sofosbuvir plus Ribavirin in the SPARE trial

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Abstract #8

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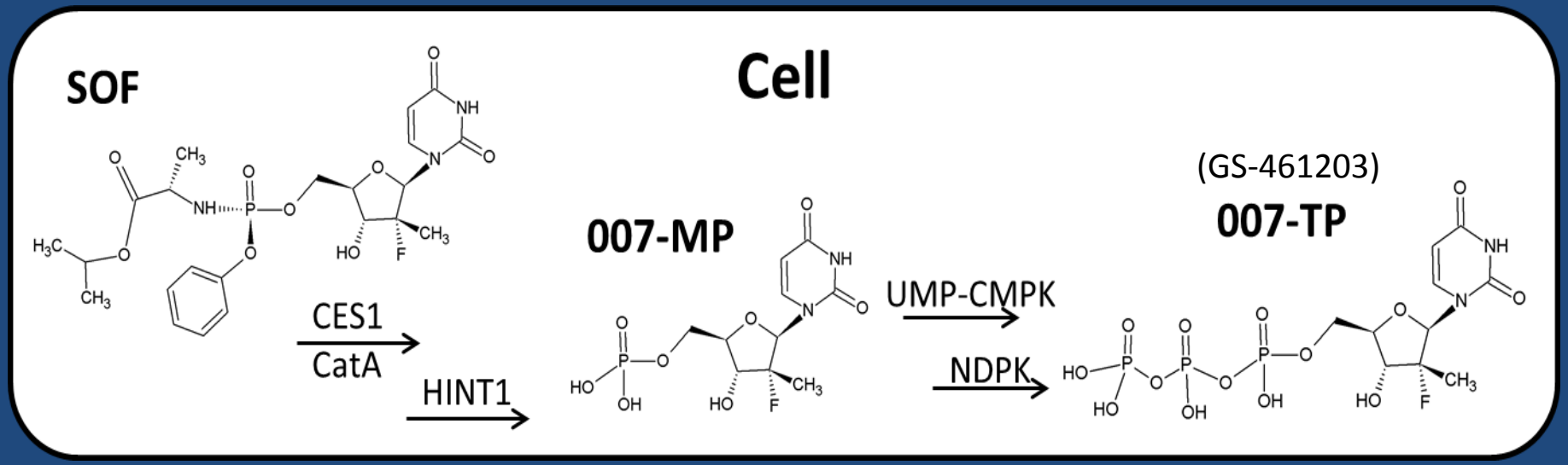
Introduction

- Sofosbuvir (SOF) is a pan-genotypic Hepatitis C virus NS5B polymerase inhibitor.
- SOF is a liver-targeted phosphoramidate pro-drug of the monophosphate (MP) form of the uridine analog GS-331007.
- The tri-phosphate (TP) is the pharmacologically active form.
- Limited data on intracellular 007 concentrations in humans.
  - PBMC: median [007-TP] of 859 fmol/10^6 cells and a 26 hour half-life[1].

[1]Rower CROI 2015

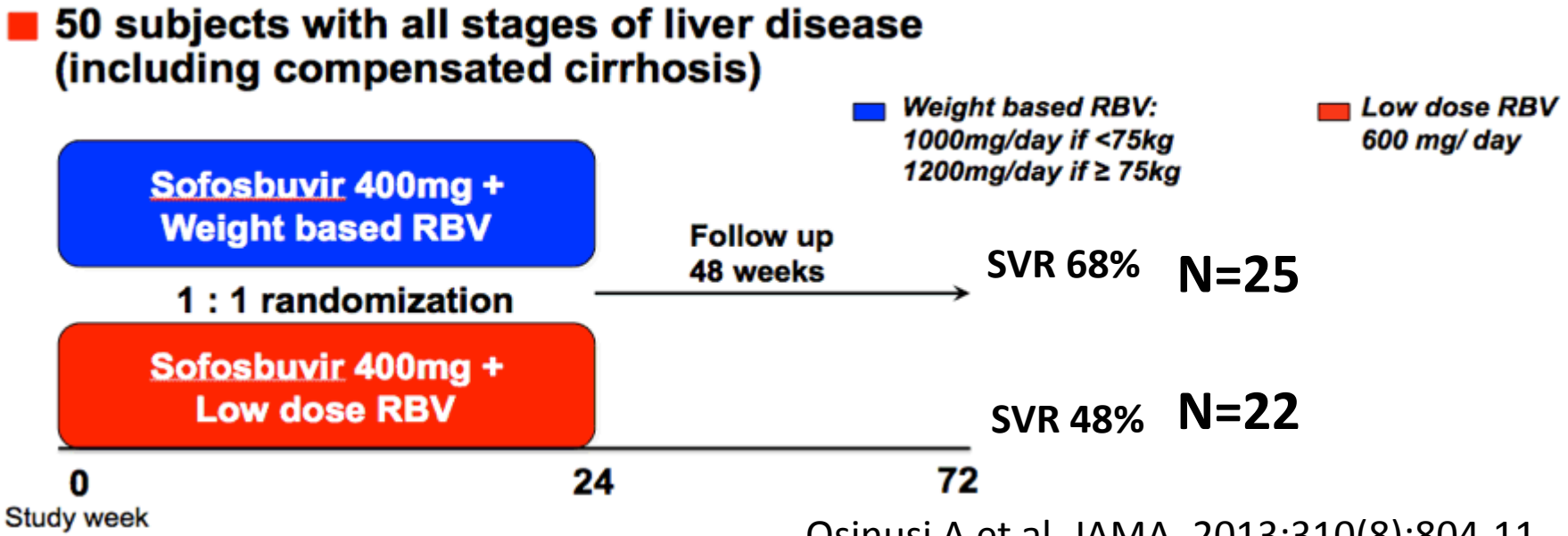


Objective

- To characterize the intracellular pharmacology of SOF (via its 007-TP metabolite) in red blood cells (RBC).
- To explore clinical covariates associated with RBC 007-TP.
- To evaluate relationships between RBC 007-TP and SVR24.

Study Design

- Study subjects received 400 mg SOF + low-dose (600 mg) or weight-based (1000 or 1200 mg) ribavirin (RBV) daily as part of the NIH/NIAID SPARE trial.
  - All subjects provided written informed consent to participate in the study.



Osinusi A et al. JAMA. 2013;310(8):804-11

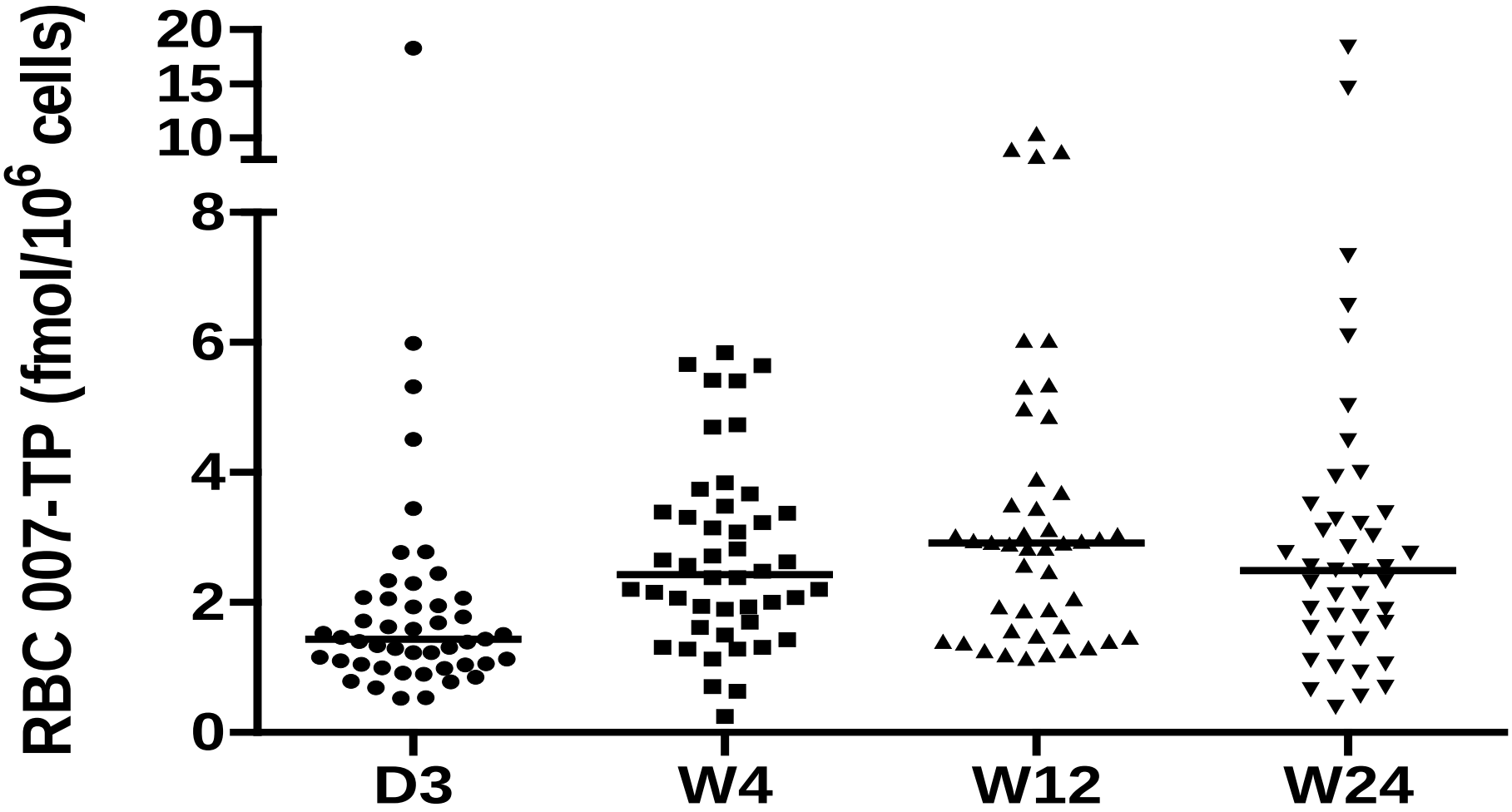
Analytical Methods

- Whole blood samples were obtained on day 3, and weeks 4, 12, and 24; and 007-TP quantified using a validated LC-MS/MS method.
  - Linear range: 50-50000 fmol/sample (typically 50 to 100x10^6 RBC/sample assayed)
  - Concentrations from whole blood samples correlated well with purified RBC samples (R^2=0.9984).
- Data were modeled using a 1 compartment model in NONMEM v7.2 to determine RBC 007-TP half-life.
- Associations between RBC 007-TP and clinical covariates analyzed using regression (continuous) in SAS v9.4 or unpaired t-tests (dichotomous).
- Predictors of SVR24 were determined using univariate and multivariable logistic regression (SAS v9.4).

Demographics

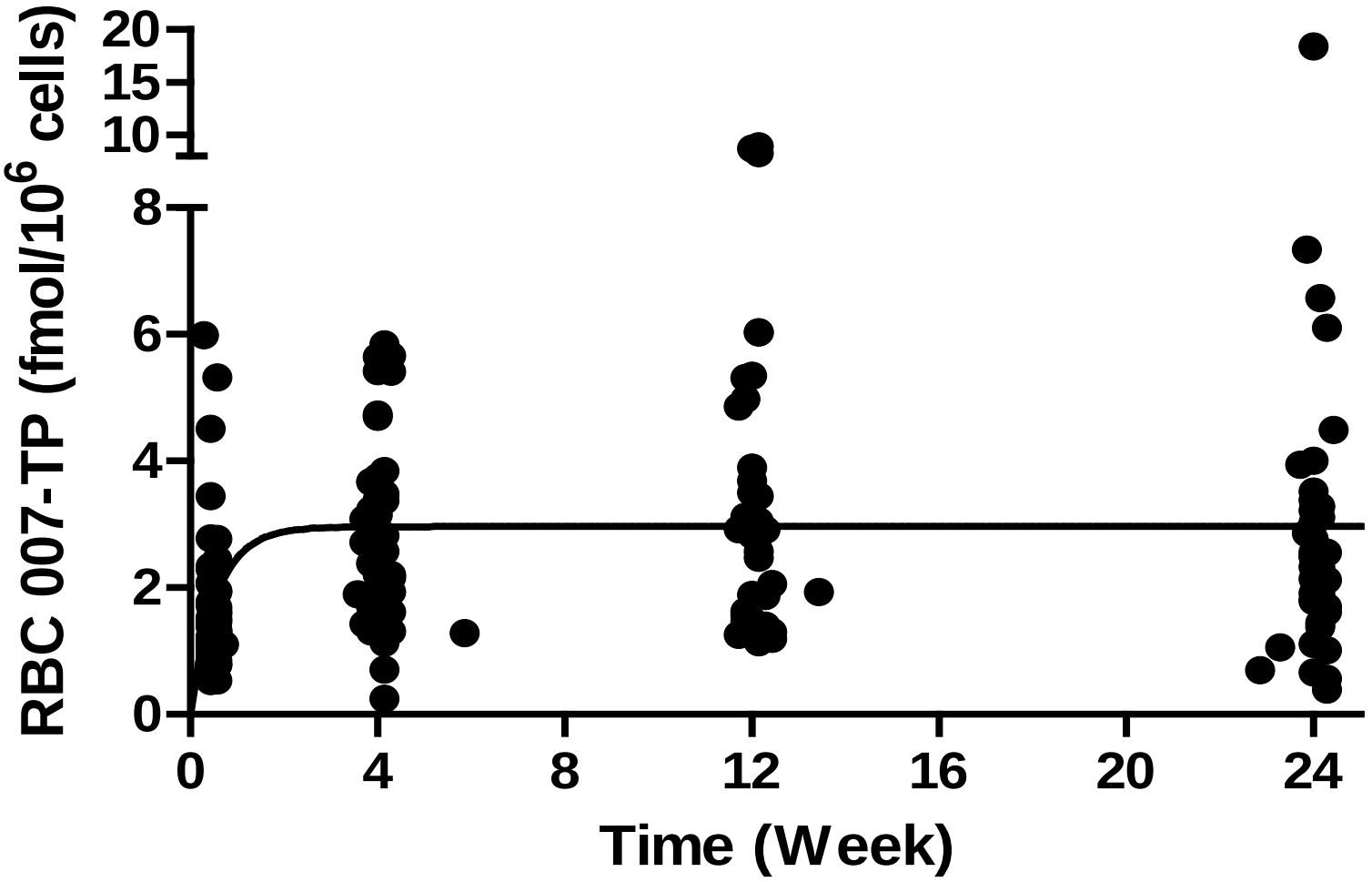
Subjects	47 (180 samples)
Sex	**32 men (68%)**, 15 women
Race	**37 African-American (79%)** 10 non African-American
Fibrosis	0: 11, 1: 21, 2: 1, **3: 12, 4: 2 (30%: F3-4)**
SVR24	**Achieved: 29 (62%)** Relapse: 18
RBV Dosing	**Low Dose: 22 (47%)** Weight Based: 25
RBC RBV-TP C_{ss} (pmol/10^6 cells) (Median (Range))	122 (33.4, 320)
Baseline HCV RNA (log IU/mL) (Median (Range))	6.19 (2.84, 7.06)

Results



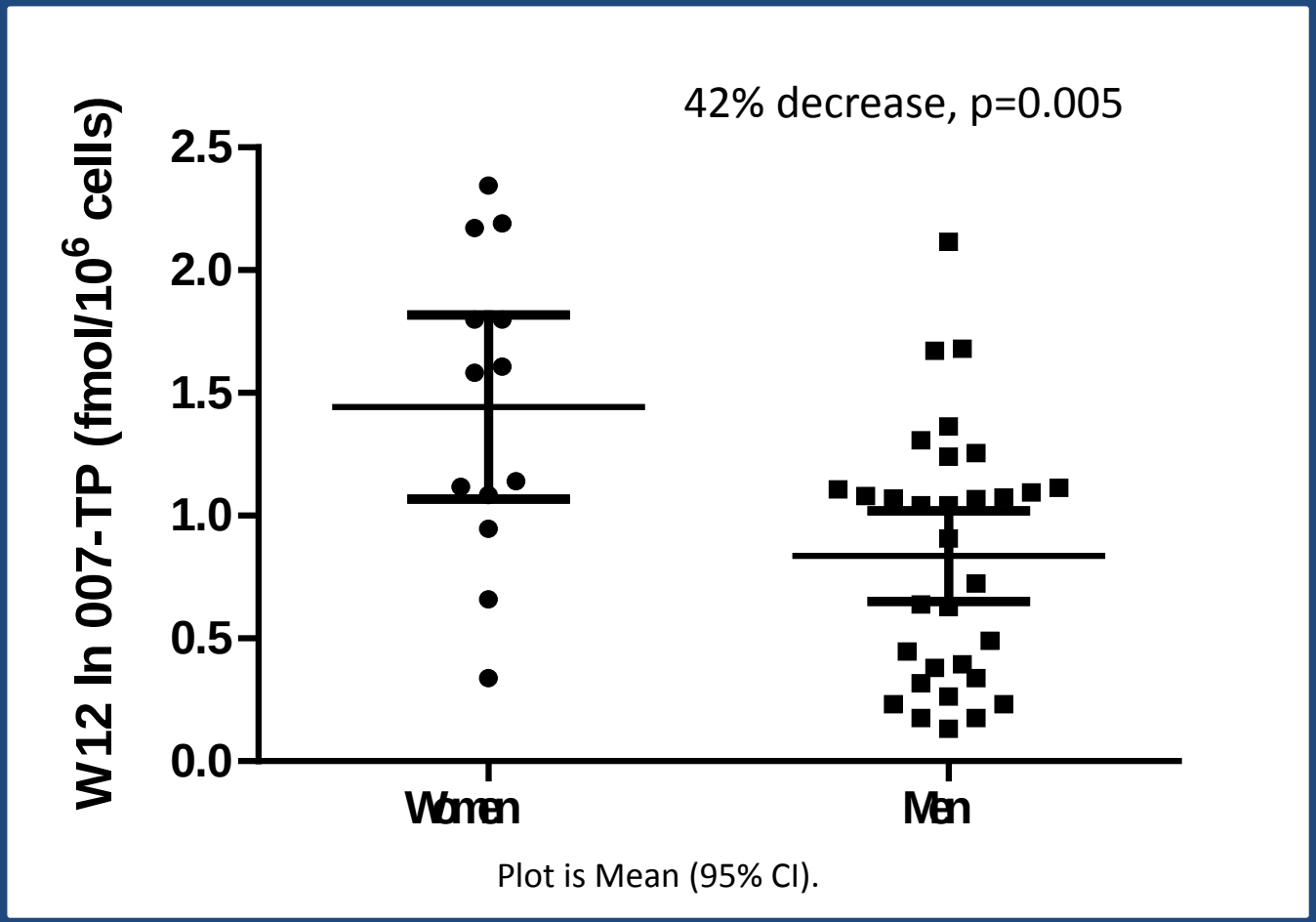
	D3	W4	W12	W24
Median (Range) (fmol/10^6 cells)	1.44 (0.527, 18.3)	2.43 (0.251, 5.84)	2.91 (1.14, 10.4)	2.50 (0.393, 18.4)

Results



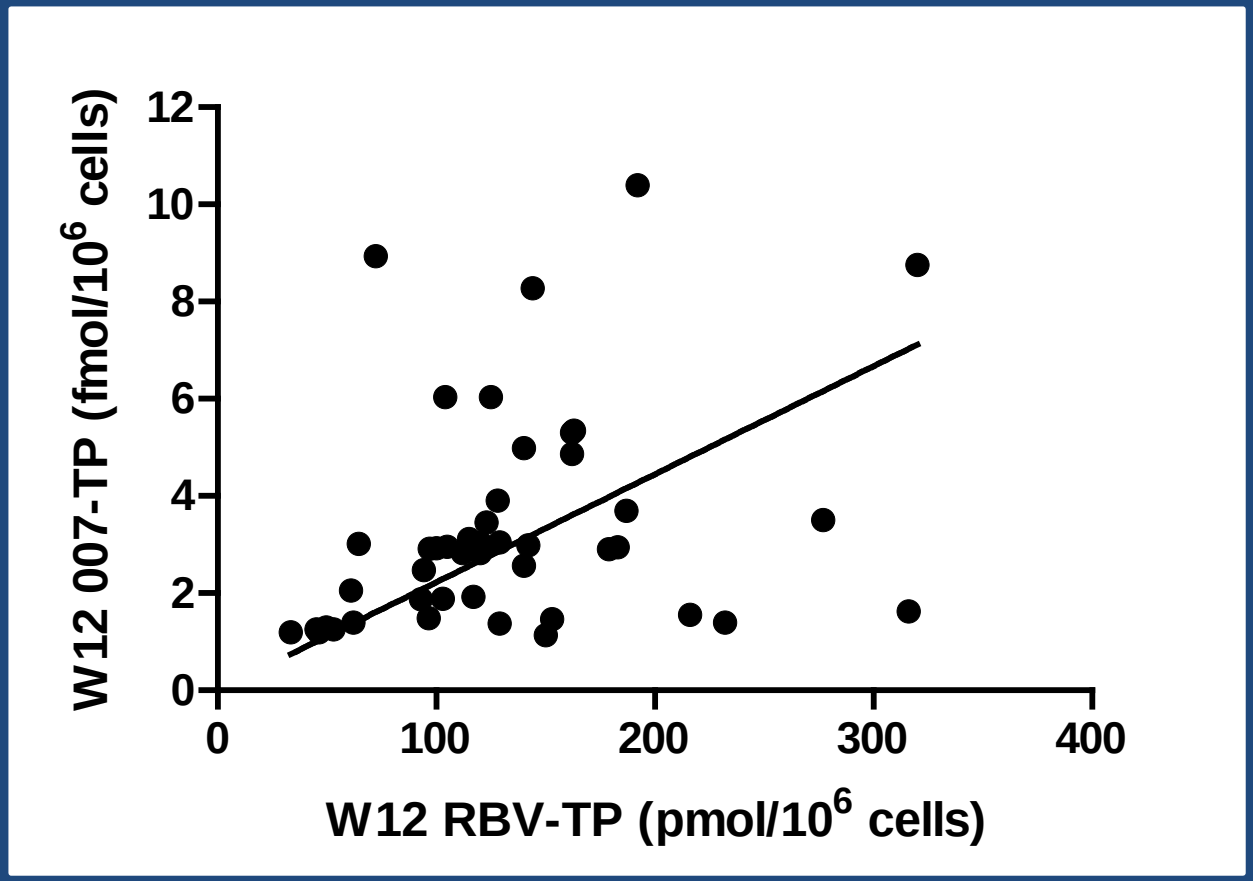
- Modeled accumulation phase half-life: 69 hours.

Results



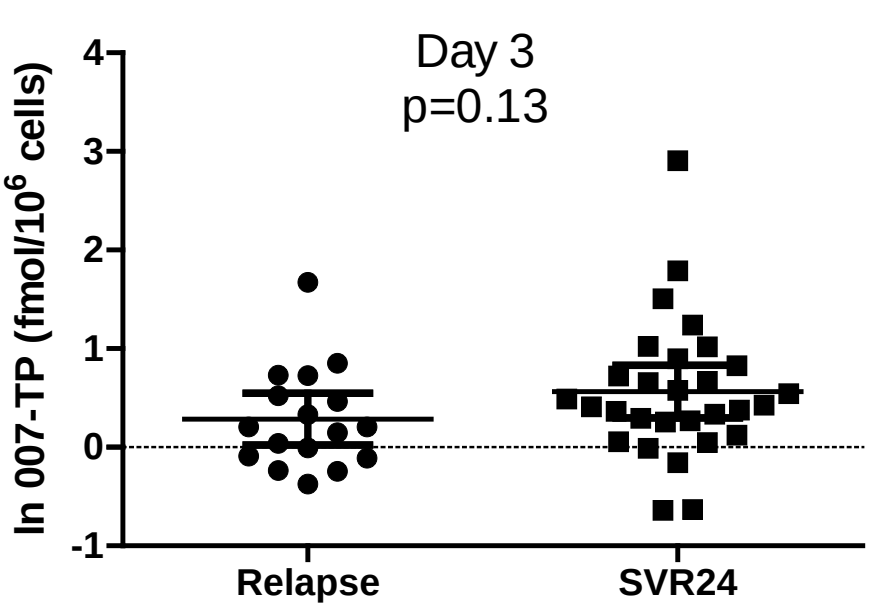
- Sex was associated with steady-state RBC 007-TP concentrations.

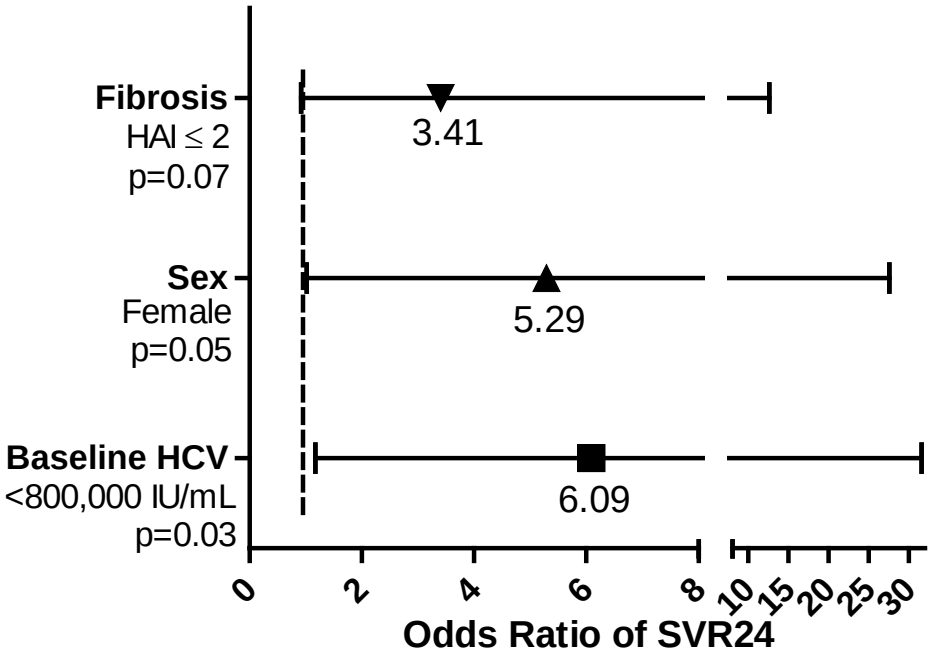
Results



- RBC RBV-TP concentrations (1.3 fmol/10^6 cells increase per 100 pmol/10^6 cells RBV-TP, p=0.04) were associated with steady-state RBC 007-TP concentrations.

Results





Plots are mean (95% CI)

- SVR24 trended towards association with RBC 007-TP concentrations.
- Baseline HCV (<800,000 IU/mL), sex (female), and fibrosis (≤2) were also univariate predictors of SVR24 (similar to initial SPARE findings).
- Fibrosis (p=0.04) and baseline HCV-RNA (p=0.02) remained significant in a multivariable model.

Conclusions

- 007-TP in RBC were ~300 fold lower than PBMC, and longer lived (69 vs. 26 hours).
  - SOF transport/phosphorylation in RBC is not as efficient as in PBMC; potentially because SOF is a uridine analog[1].
- Increased RBC RBV-TP concentrations were associated with increased RBC 007-TP.
  - RBC transport/phosphorylation of SOF and RBV are complex processes, but may be mediated with similar efficiencies.

[1]Durand-Gasselin, L et al. AAC. 2007 51(6):2105-2111.

Conclusions

- Increased 007-TP and female sex were associated with increased SVR24 odds.
  - RBC 007-TP may be useful as a predictive measure of treatment success.

- Baseline HCV-RNA <800,000 IU/mL and fibrosis stage ≤2 were associated with increased SVR24 odds.
  - Decreased liver disease severity at treatment start may result in better SOF-based treatment outcomes.
  - Supports need for early HCV diagnosis and treatment.

Limitations

- Subjects were on concomitant RBV, which has previously been shown to be associated with SVR24[1].

- Retrospective study with small subject population, suggesting need for replication of these results.

[1]Rower JE et al. JAC. 2015 epub

Unanswered Questions

1. Is there an RBC 007-TP threshold that predicts SVR24 vs. relapse?

2. Is SVR24 associated with 007-TP in more potent regimens (ie SOF/ledipasvir)?

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