Increased Tenofovir Diphosphate in Cells, but Not Tenofovir in Plasma, with Sofosbuvir and Ribavirin

Christine E. MacBrayne[1], Kristen M. Marks[2], Daniel S. Fierer[3], Susanna Naggie[4], Raymond T. Chung[5], Kimberly M. Hollabaugh[6], Michael D. Hughes[6], Diana M. Brainard[7], Sharon M. Seifert[1], Jose R. Castillo-Mancilla[8], Lane R. Bushman[1], Peter L. Anderson[1], Jennifer J. Kiser[1]

[1]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, [2] New York Presbyterian Hospital, New York, NY, [3] Icahn School of Medicine at Mount Sinai, New York, NY, [4]Duke Clinical Research Institute, Durham, NC, [5]Massachusetts General Hospital, Boston, MA, [6]Harvard T.H. Chan School of Public Health, Boston, MA, [7]Gilead Sciences, Foster City, CA, [8]University of Colorado Department of Medicine, Aurora, CO

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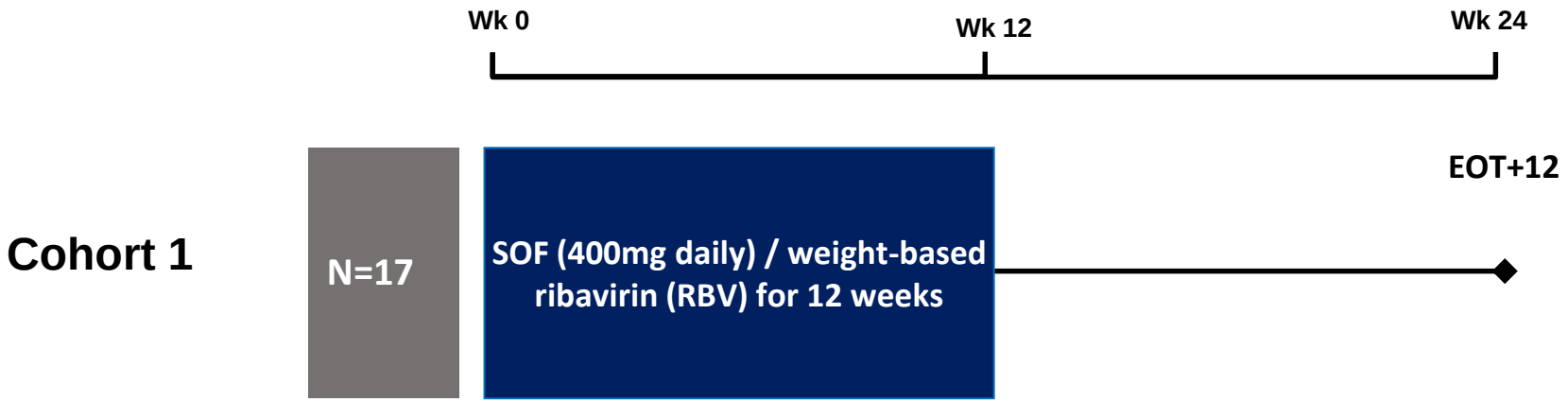
ACTG
AIDS CLINICAL TRIALS GROUP

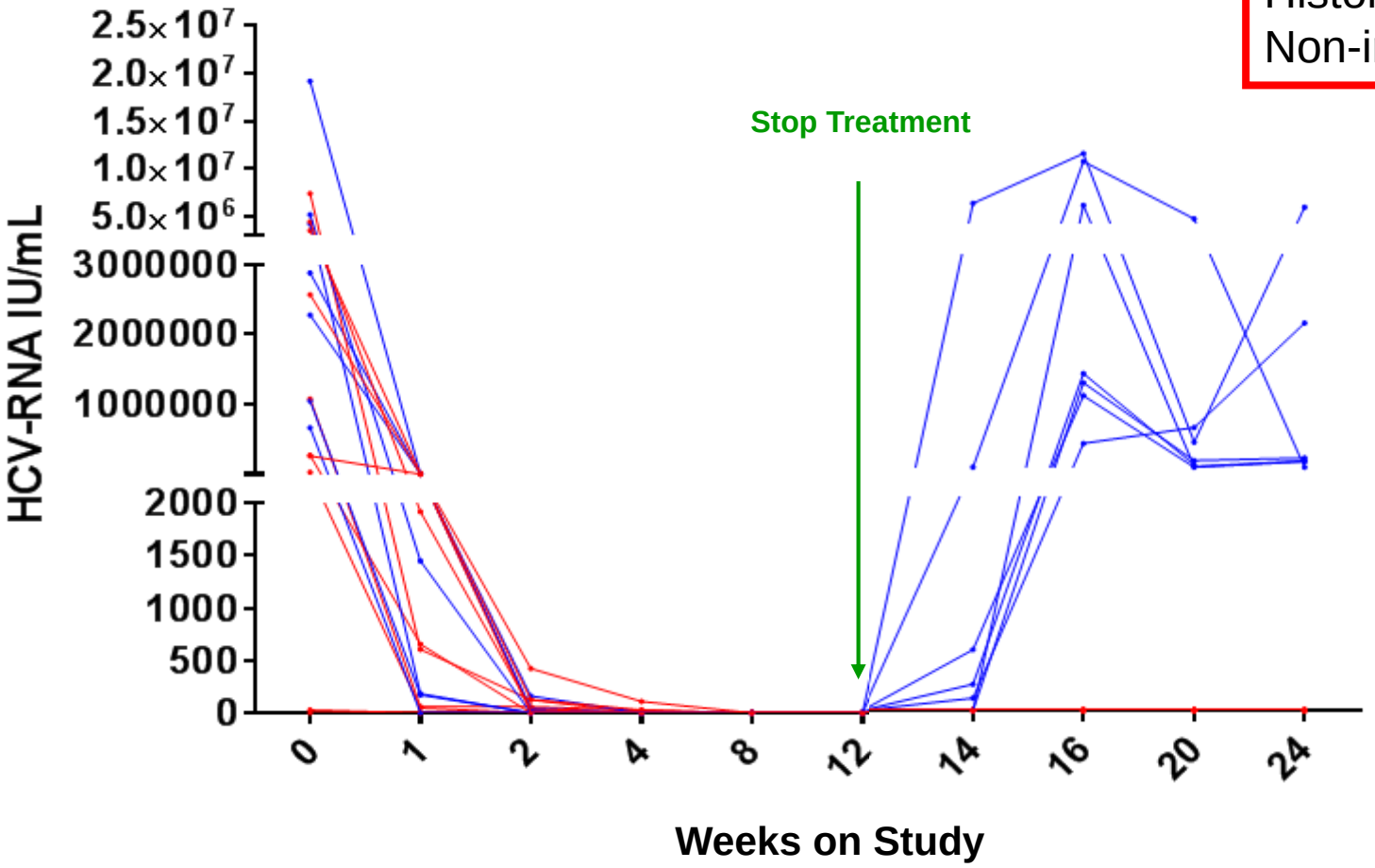
SWIFT-C (ACTG 5327) Design

- SWIFT-C is an ongoing, phase I, open-label study of sofosbuvir (SOF)-containing HCV treatment for HIV-infected individuals with acute HCV
- Two cohort study
  - data presented for Cohort 1



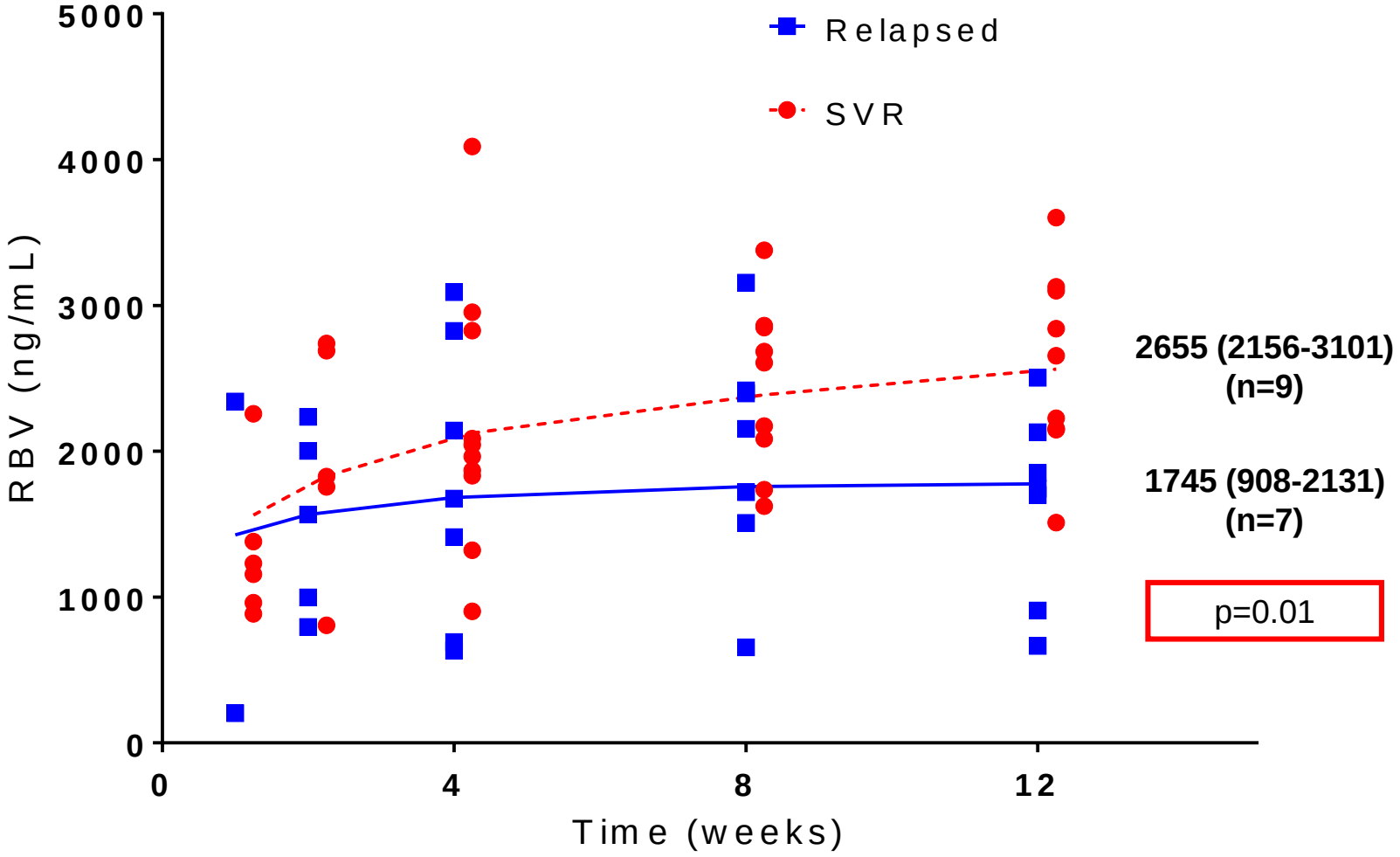
High Relapse Rate in Cohort I of SWIFT-C

SWIFT-C SOF/RBV SVR = 59%[1]
Historical SVR with PEG/RBV =60%[2]
Non-inferiority not achieved



[1]Naggie S, et al. AASLD. November 13, 2015 2015. San Francisco, CA. Abstract # 1094
[2]NEAT Consensus Panel. AIDS. 2011 Feb 20;25(4):399-409

Individuals that Relapsed had Lower Ribavirin Concentrations



May reflect reduced RBV adherence in those that relapsed.

MacBrayne CE, et al. CROI. Boston.February 22-25 2016, Abstract 99

Primary Aim

Given the reduced RBV adherence in those that relapsed, we sought to quantify antiretroviral (ARV) adherence in the study participants.

Aim : Compare tenofovir diphosphate (TFV-DP) concentrations in cells and tenofovir concentrations in plasma before, during, and after SOF/RBV treatment.

Measure of ARV Adherence

- 15/17 participants in SWIFT-C were taking Tenofovir Disoproxil Fumarate (TDF)
- Tenofovir-diphosphate (TFV-DP) has a long half life, thus concentrations in dried blood spots (DBS) are reflective of cumulative drug dosing and long-term adherence[1,2]
- Tenofovir (TFV) concentrations in plasma reflect recent dosing and short-term adherence[1]

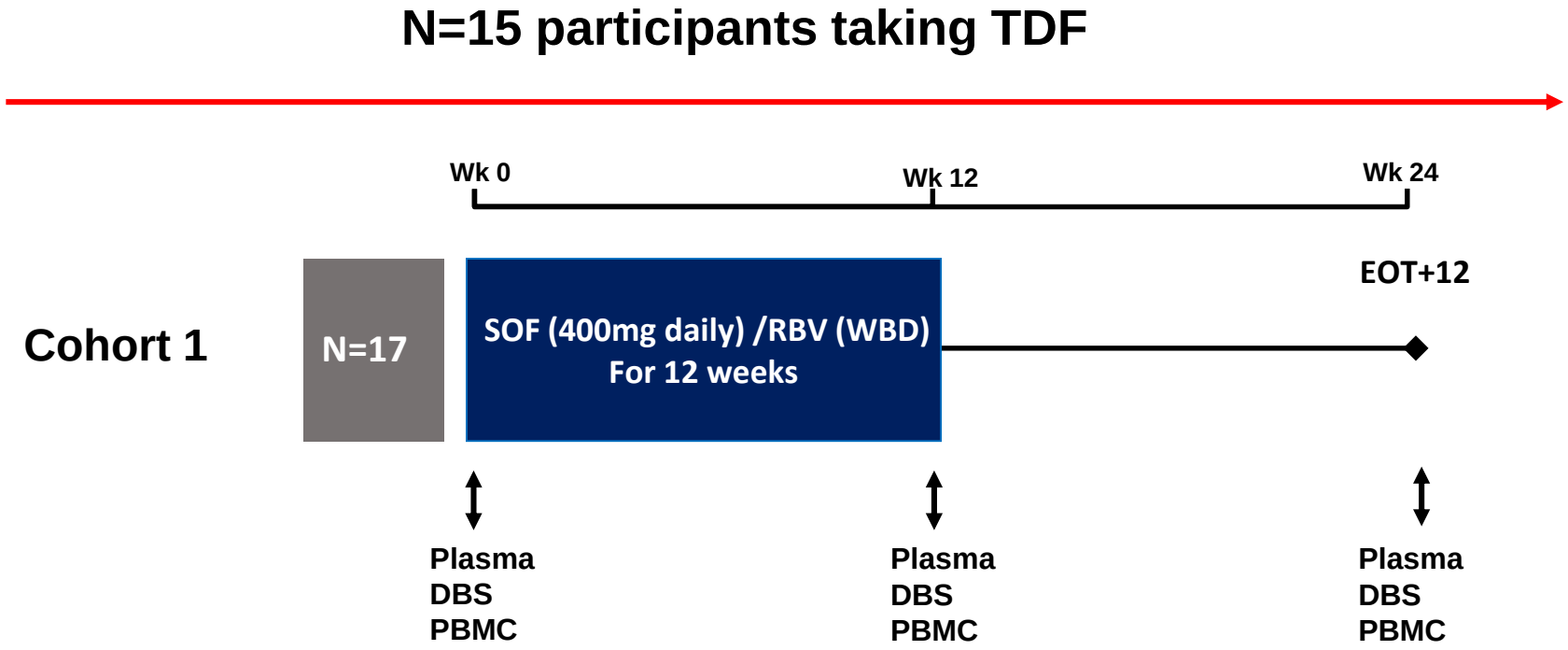
[1]Castillo-Mancilla JR. AIDS Res Hum Retroviruses 2013

Methods: SWIFT-C Inclusion/Exclusion Criteria

- Age ≥18 years
- Acute HCV*:
  - New HCV RNA in patients with documented negative serology in past 6 months or
  - Positive HCV RNA plus a new ALT elevation (>5xULN)
- No prior HCV treatment during this acute infection
- Antiretroviral therapy excluding didanosine, stavudine, zidovudine, or tipranavir/r with CD4>200 cells/mm^3

*For complete details see Naggie S, et al AASLD 2015 #1094

Methods: PK Sampling and Analytical Methodology



TFV-DP concentrations in DBS and PBMC and TFV in plasma were measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods[1,2,3,4]

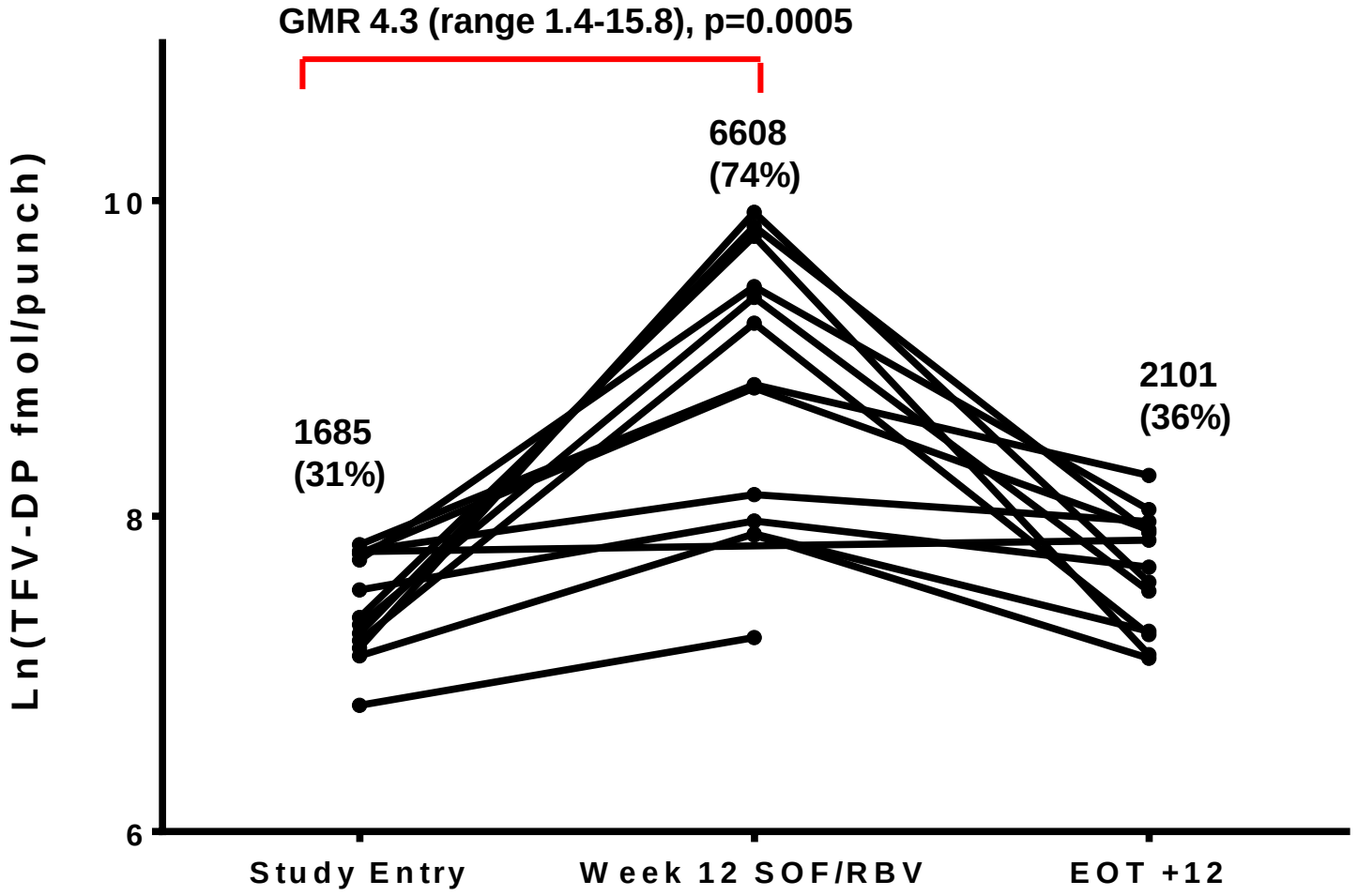
[1]Zheng JH. J Pharm Biomed Anal. 2016
[2]Zheng JH. J Pharm Biomed Anal. 2014
[3]King T. J Chromatogr B Analyt Technol Biomed Life Sci. 2006
[4]Delahunty T. J Chromatogr B Analyt Technol Biomed Life Sci. 2009

Results: Participant Characteristics (n=15) on TDF

Gender, % • Male	 100
Race • Hispanic, % • White, %	 73 27
Baseline CrCl (mL/min): mean ± SD	123.88 ± 24.34
Age (years): mean ± SD	44.3 ± 9.5
Weight (kg): mean ± SD	76.5 ± 10.3

Antiretroviral Regimen, %
• NNRTI
• Integrase
• Boosted
  • COBI
  • RTV
	
	47
	33
	33
	20
	13

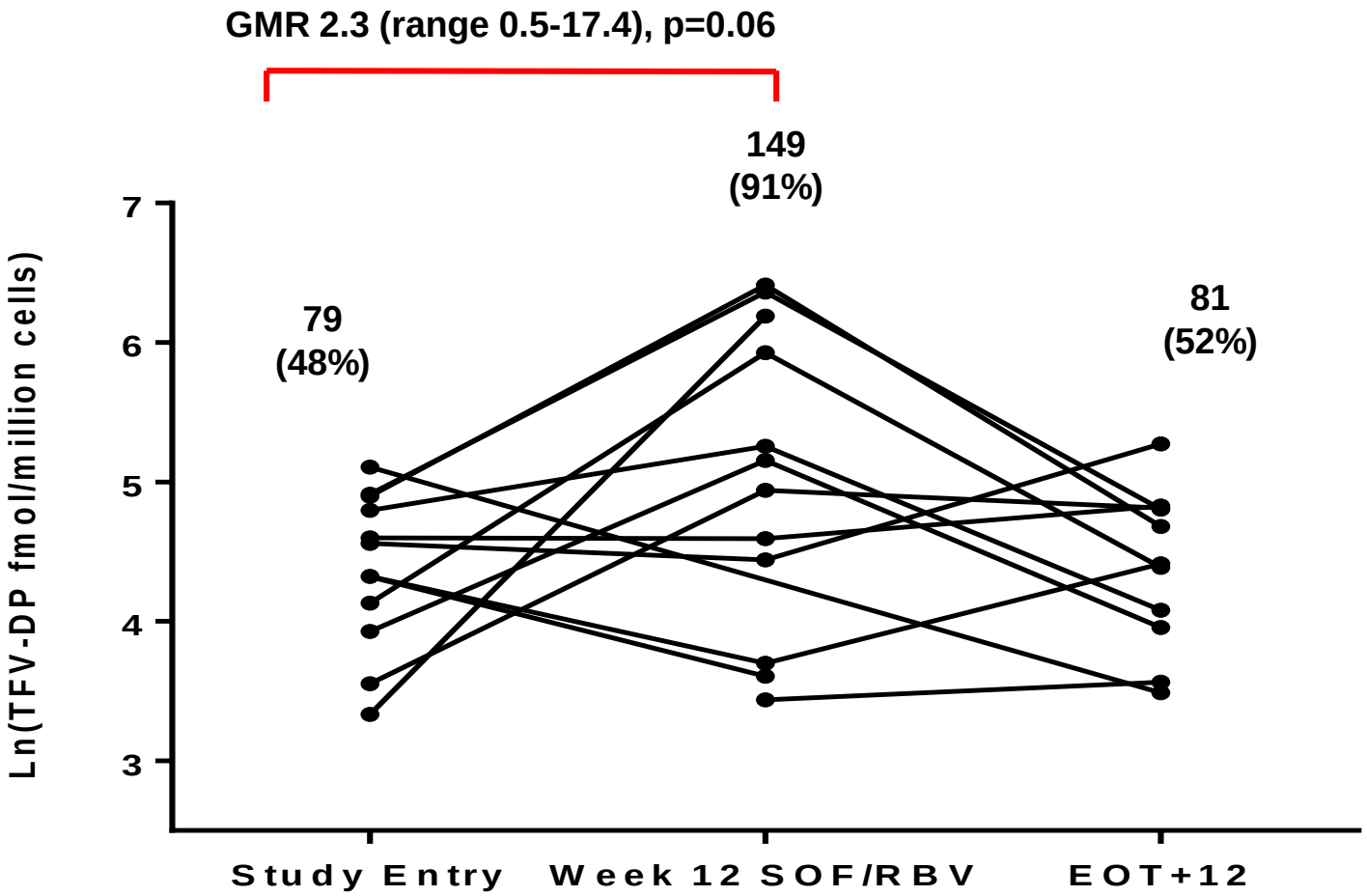
Results : TFV-DP Concentration in DBS



From study entry to EOT + 12 there was a difference p=0.01

* Wilcoxin signed rank test

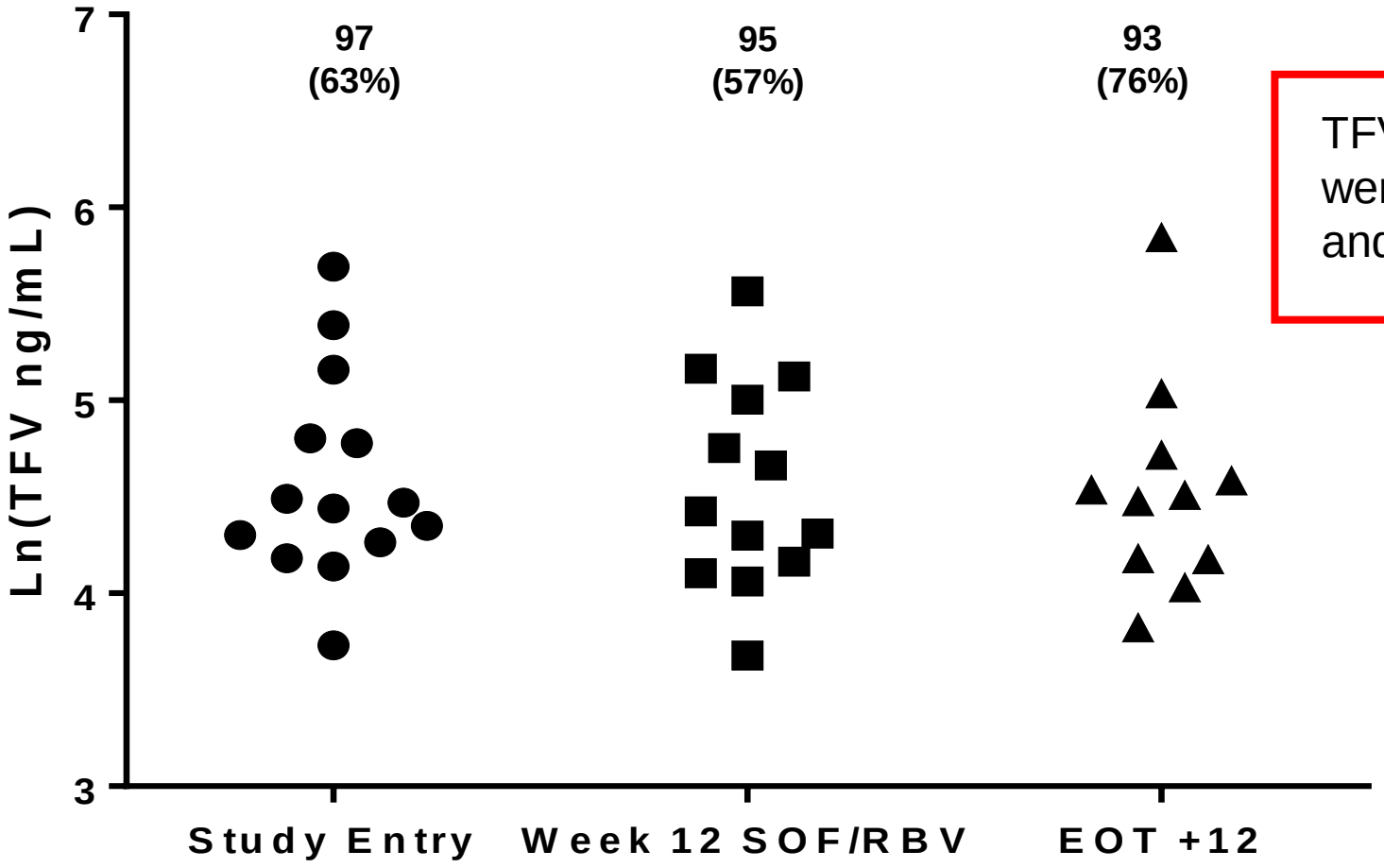
Results : TFV-DP Concentration in PBMC



From study entry to EOT+12 there was no difference
P =0.84

* Wilcoxin signed rank test

Results : TFV Concentration in Plasma



TFV concentrations in plasma were similar to historical data and unchanged across visits.

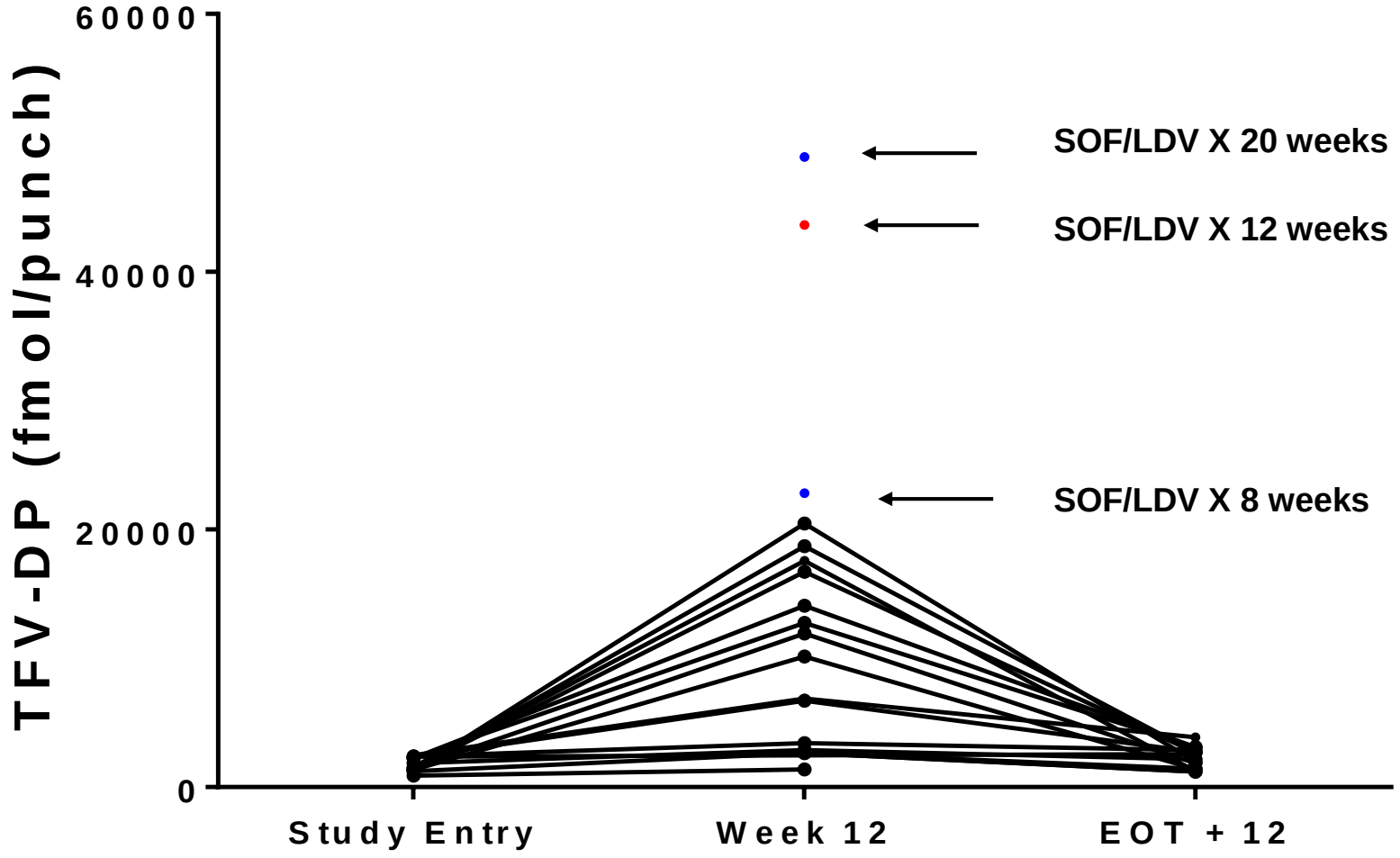
TFV-DP vs Historical Data

Patient Population	TFV-DP in DBS fmol/punch	TFV-DP in PBMC fmol/10^6 cells	Comments
SWIFT-C Week 12; Geometric mean (CV%)	6608 (74%)	148 (91%)	N=15; acute HCV and HIV co-infection
Healthy Participants[1]; Median (CV%)	1560 (30%)	Mean (CV%) 97.9 (30%)	N=17; taking TDF/FTC for 30 days
HIV Infected Women[2]; Median (CV%)	1874 (39%)	125 (49%)	N=35; 23% of women had less than daily adherence
HIV Infected Adult Participants[3]; Geometric mean (CV%)	2070 (39%)	94 (72%)	N=44; 21 old and 23 young

During SOF/RBV treatment, average TFV-DP concentrations in the patients in Cohort 1 of SWIFT-C were ~4 and 2 times higher than what has been previously observed in RBC and PBMC, respectively

[1]Castillo-Mancilla JR. AIDS Res Hum Retroviruses. 2013
[2]Castillo-Mancilla JR. AIDS Res Hum Retroviruses. 2015
[3]Seifert SM. 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; Washington D.C. June 2016. Abstract O_09

Is SOF or RBV the Perpetrator?



What is the Mechanism?

- SOF (or its metabolites) increase cellular uptake of TDF or TFV?
- SOF (or its metabolites) enhance phosphorylation of TFV, or perhaps inhibit TFV-DP dephosphorylation?
- SOF (or its metabolites) reduce the cellular efflux of TFV or TFV-DP?

Does this interaction have clinical relevance?

- Use of TDF has been associated with renal toxicity including declines in glomerular filtration rate, proximal tubular damage, and acute kidney injury[1,2] as well as declines in bone mineral density[3]
  - Studies suggest these toxicities are concentration-dependent[4-6]
- CrCl unchanged in this Cohort, and no other measures of renal function were collected
  - Study Entry = 123.8 mL/min, week 12 of SOF/RBV = 118.1 mL/min
- Perhaps not for HCV since treatment is finite, but implications for other nucleotide analogs which may require longer durations of treatment?
- What is the correct moiety to study?

[1]Hall AM. Am J Kidney Dis. 2011
[2]Monteiro N. J Int AIDS Soc. 2014
[3]Casado JL. AIDS. 2016
[4]Rodriguez-Novoa S. AIDS. 2010
[5]Moss DM. Front Pharmacol. 2014
[6]Poizot-Martin IJ. Acquir Immune Defic Syndr. 2013

Summary

- The intent of this work was to assess ARV adherence, however these data suggest a new type of drug interaction at the cellular level.

- After 12 weeks of SOF/RBV treatment, TFV-DP concentrations in DBS and PBMC were increased approximately 4 and 2-fold respectively despite no change in TFV plasma levels.

- Additional studies are needed to determine the mechanism and clinical significance.

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- Study participants

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