Ledipasvir/Sofosbuvir Raises Tenofovir Diphosphate Concentrations in Red Cells

Christine E. MacBrayne[1], Daniel S. Fierer[2], Kristen M. Marks[3], Peter L. Anderson[1], Lane R. Bushman[1], Kimberly M. Hollabaugh[4], Michael D. Hughes[4], Raymond T. Chung[5], Susanna Naggie[6], Jennifer J. Kiser[1]

[1]University of Colorado-AMC, [2]Icahn School of Medicine at Mount Sinai, [3]Weill Cornell Medicine, [4]Harvard T. H. Chan School of Public Health, [5]MGH, [6]Duke University

Skaggs School of Pharmacy and Pharmaceutical Sciences
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

ACTG AIDS CLINICAL TRIALS GROUP

#404

Abstract

Background: ACTG 5327 ("SWIFT-C") is an ongoing study of sofosbuvir (SOF)-based treatment of acute Hepatitis C virus (HCV) in HIV-infected individuals. We previously reported that participants in Cohort 1 of SWIFT-C taking SOF and ribavirin had 4.3-fold (range 1.4-15.8) higher intracellular tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS), but there are no data with SOF and the HCV NS5A inhibitor, ledipasvir (LDV). The objective of this analysis was to compare TFV-DP concentrations in red blood cells (RBC) measured with DBS and tenofovir (TFV) concentrations in plasma before, during, and after LDV/SOF treatment in participants in Cohort 2 of SWIFT-C.

Methods: Plasma and DBS were obtained from participants taking tenofovir disoproxil fumarate (TDF). TFV-DP was measured in those with available samples at entry, weeks 2 and 8 of LDV/SOF treatment and 2 (EOT+2), 4 (EOT+4), 8 (EOT+8), and 12 weeks (EOT+12) following completion of LDV/SOF treatment. For the 12 participants with data through EOT+12, TFV-DP was also measured at weeks 1 and 4 to provide additional information on the kinetics of the interaction. TFV in plasma was measured at entry, week 8 and EOT+12. TFV and TFV-DP were log transformed for analysis and compared at each visit to study entry using paired t-tests.

Results: 19 participants (5 Hispanic, mean ± SD age 43.7±8.4yrs, weight 77.4±10.2kg, and CrCl 106.1±24.4 mL/min) were taking a TDF-based antiretroviral (ARV) regimen prior to commencing 8 weeks of LDV/SOF. At weeks 1, 2, 4 and 8 of LDV/SOF treatment, TFV-DP was 7.1, 9.7, 16.7 and 16.6-fold higher in DBS, respectively compared with study entry (all $p < 0.001$). By EOT + 12, TFV-DP concentrations were similar to baseline (p=0.39). Plasma TFV levels were 1.9 fold higher at week 8 vs. study entry (P=0.0014) and similar between study entry and EOT+12 (P=0.56).

Conclusions: After 8 weeks of LDV/SOF treatment, TFV-DP concentrations in DBS were increased 16.6-fold and TFV in plasma was increased 1.9 fold. TFV-DP accumulated rapidly in DBS after starting LDV/SOF (more than doubling within the first week), but declined consistent with the 17-day half-life in RBC after LDV/SOF therapy was completed. This suggests enhanced RBC loading during LDV/SOF therapy. Additional studies are needed to determine the mechanism, magnitude in other cell types, and clinical significance of this interaction.

Background

- ACTG 5327 ("SWIFT-C") is an ongoing study of sofosbuvir (SOF)-based treatment of acute Hepatitis C virus (HCV) in HIV-infected individuals.[1]
- We previously reported that participants in Cohort 1 of SWIFT-C taking SOF and ribavirin had 4.3-fold (range 1.4-15.8) higher intracellular tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS)[2], but there are no data with SOF and the HCV NS5A inhibitor, ledipasvir (LDV).

Objective

The objective of this analysis was to compare TFV-DP concentrations in red blood cells (RBC) measured with DBS and tenofovir (TFV) concentrations in plasma before, during, and after LDV/SOF treatment in participants in Cohort 2 of SWIFT-C.

Methods

- Cohort 2 of SWIFT-C included HIV-infected participants who were at least 18 years of age with acute HCV.[1]
- Participants taking TDF before, during, and after LDV/SOF treatment were eligible for this analysis.
- TFV-DP was measured in DBS samples at study entry, week 1, 2, 4 and 8 of LDV/SOF treatment as well as 2, 4, 8 and 12 weeks following the end of LDV/SOF treatment (EOT).
- Plasma TFV samples were measured at study entry, week 8 of LDV/SOF treatment and 12 weeks following the end of treatment (EOT+12).
- TFV-DP concentrations in DBS and tenofovir in plasma were measured using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methods.[3,4]
- TFV-DP and TFV concentrations were log transformed to reduce skew and compared to baseline using paired t-tests.

Results

Table 1: Demographics of the study participants.

Demographics	N=19
% Male	100%
Race	26% Hispanic 74% White
Age (years): mean ± SD	43.7 ± 8.4
Weight (Kg): mean ± SD	77.4 ± 10.2
CrCl (ml/min): mean ± SD	106.1 ± 24.4
Genotype • 1a • 1b • 1(unknown) • 4	 14 2 2 1

Table 2: Geometric Mean TFV-DP and TFV Concentrations

	TFV-DP in DBS		TFV in Plasma	
Visit	**Number of participants samples analyzed**	**Geometric Mean (%CV) TFV-DP in DBS**	**Number of participants samples analyzed**	**Geometric Mean (%CV) TFV in Plasma**
Entry	19	1533.0 (35.9)	17	75.9 (77.9)
Week 1	12	10,850.9 (71.9)		
Week 2	19	14,838.8 (61.0)		
Week 4	12	25,547.6 (66.5)		
Week 8	17	25,519.5 (54.4)	15	144.6 (129.2)
EOT + 2	11	15,138.6 (48.5)		
EOT + 4	16	8,333.2 (69.8)		
EOT + 8	12	3,893.3 (55.9)		
EOT + 12	12	1,970.4 (47.4)	11	76.9 (47.5)

Figure 1: TFV-DP concentrations at weeks 1, 2, 4 and 8 of LDV/SOF treatment were 7.1, 9.7, 16.7 and 16.6-fold higher in DBS, respectively compared with study entry (all $p < 0.001$). By EOT + 12, TFV-DP concentrations were similar to baseline (p=0.39).

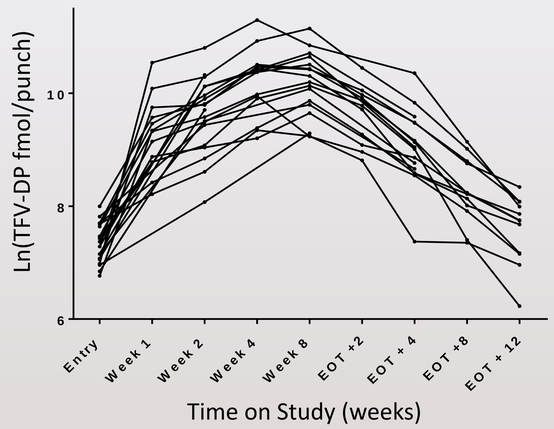
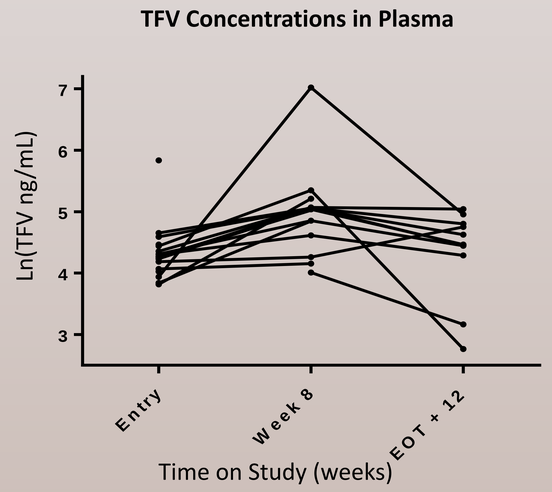
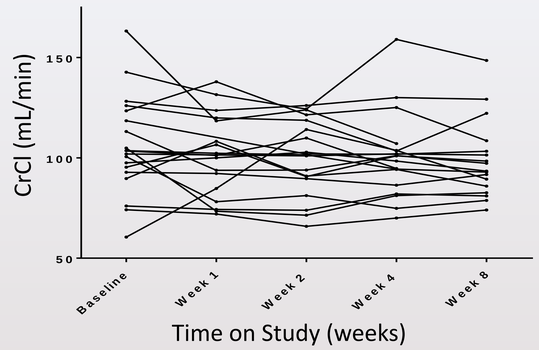


Figure 2: Plasma TFV levels were 1.9 fold higher at week 8 vs. study entry (P=0.0014) and similar between study entry and EOT+12 (P=0.56).



Results Continued

Figure 3: CrCl was similar across study visits



Conclusions

After 8 weeks of LDV/SOF treatment, TFV-DP concentrations in DBS were increased 16.6-fold and TFV in plasma was increased 1.9 fold.

TFV-DP accumulated rapidly in DBS after starting LDV/SOF (more than doubling within the first week), but declined consistent with the 17-day half-life in RBC after LDV/SOF therapy was completed; potentially suggesting enhanced RBC loading during LDV/SOF therapy.

Additional studies are needed to determine the mechanism, magnitude in other cell types, and clinical significance of this interaction.

Acknowledgements and References

We wish to acknowledge the study participants, the principal investigators and study personnel at the following ACTG sites: UCSF HIV/AIDS, Weill Cornell Uptown, Cornell Chelsea, Whitman-Walker Health, Massachusetts General hospital, UCSD Antiviral Research Center, Rush University, Cincinnati and Northwestern University, the ACTG 5327 Protocol Team, and members of the Colorado Antiviral Pharmacology Laboratory.

1. Naggie S, et al. Clinical Infectious Disease. [Accepted].
2. MacBrayne CE, et al. 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. Washington, DC. June 8-10, 2016. Abstract# O_19.
3. Delahunty T, et al. J Chromatogr B Analyt Technol Biomed Life Sci 2006,830:6-12.
4. Zheng JH, et al. J Pharm Biomed Anal 2016,122:16-20.

Conference on Retroviruses and Opportunistic Infections, Feb 13-16, Seattle, WA. 2017