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SWITCHING TO TAF IN EVG-BASED REGIMENS: CSF PHARMACOKINETICS AND ANTIVIRAL ACTIVITY

Qing Ma[1], Andrew J. Ocque[1], Gene D. Morse[1], Chelsea Sanders[2], Alina Burgi[2], Susan J. Little[2], Scott L. Letendre[2]

[1]University at Buffalo, Buffalo, New York, USA; [2]University of California San Diego, La Jolla, California, USA

Scott Letendre MD
University of California San Diego
San Diego, CA 92093
E-mail: sletendre@ucsd.edu

Qing Ma PharmD PhD
University at Buffalo
Buffalo, NY 14214
Email: qingma@buffalo.edu

Abstract

Background: TAF co-formulated with elvitegravir (E), cobicistat (C) and emtricitabine (F) has become a recommended regimen, replacing E/C/F/TDF due to improved renal and bone safety. Limited data are available on TAF and EVG pharmacokinetics (PK) in CSF, particularly after switching from TDF. This study aims to measure TAF, tenofovir (TFV), and EVG concentrations in CSF and compare them to HIV RNA in CSF and neurocognitive (NC) performance using a brief screening instrument.

Methods: This was a single-arm, open-label, single-center study in 14 participants. After an initial assessment, 9 participants switched from E/C/F/TDF to E/C/F/TAF and were followed for 24 weeks. At week 0 and week 24, blood was collected at 2, 4, and 6 hours after an observed dose and CSF was then collected within 1 hour of the 6-hour blood collection. Total plasma and CSF concentrations were determined by LC/MS-MS. The wild-type HIV-1 EC_{50} for EVG was 0.76 ng/ml. HIV RNA was measured in plasma and CSF by RT-PCR (lower limit of quantitation, LLQ, 20 copies/mL). NC performance was estimated by the Montreal Cognitive Assessment (MoCA) with a score <26 indicating impairment. Adherence was determined by pill count. Changes in drug concentrations between visits were analyzed using paired, two-sided signed rank tests. All concentrations are expressed in ng/ml..

	Week 0 (TDF)*	Week 24 (TAF)*	
	Median (range)	Median (range)	p
EVG Plasma	1080 (524-2123)	1608 (897-2352)	0.004
EVG CSF	4.30 (1.65-7.85)	5.58 (3.15-6.76)	0.203
EVG CPR (%)	0.380	0.278	0.359
TFV Plasma	174 (13.8-191)	14.1 (9.67-15.1)	0.004
TFV CSF	3.00 (0.528-5.48)	0.481 (0.10-1.80)	0.004
TFV CPR (%)	1.76	3.38	0.004
TAF Plasma 2h	Not taking TAF	11.05 (2.84-147.11)	--
TAF Plasma 6h	Not taking TAF	≤ 0.5	--
TAF CSF 6h	Not taking TAF	≤ 0.1	--

*Data from 9 participants switched from E/C/F/TDF to E/C/F/TAF and followed for 24 weeks.

Results: EVG concentrations in CSF remained stable (p=0.203) while they increased in plasma after the switch (p=0.004, table). TFV concentrations in both CSF (p=0.004) and plasma (p=0.004) declined over time, consistent with the lower dose of TAF compared with TDF. The CSF:plasma ratio (CPR) for EVG remained stable (p=0.359) while the TFV CPR increased (p=0.004). At 24 weeks, TAF concentrations in plasma peaked 2 h after dosing [11.05 (2.84-147.11)] but were below LLQ at 6 h. TAF was not detected in CSF at 6 h. All HIV RNA levels remained ≤ 40 copies/mL in CSF and plasma. The proportion of EVG concentrations in CSF exceeded the EC_{50} in all participants at week 0 and week 24. Three participants (3/9, 33%) had NC impairment at week 0 and 2 (2/9, 22%, p=0.50) remained impaired at week 24. Across both assessments, higher EVG CPR values (but not TFV CPR) correlated with better NC performance (r=0.343, p=0.08).

Conclusions: Switch to E/C/F/TAF was associated with reductions in TFV concentrations in CSF, as expected because of lower TFV concentrations in plasma, but stable EVG concentrations in CSF. No virological failure or significant NC changes were detected at 24 weeks following the switch.

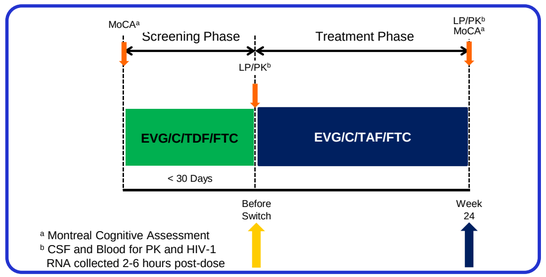
Introduction

- Tenofovir alafenamide (TAF) co-formulated with elvitegravir (EVG), cobicistat and emtricitabine (E/C/F/TAF) has become a recommended regimen, replacing E/C/F/TDF due to improved renal and bone safety in phase III studies (GS-US-292-0104 and GS-US-292-0111)[1,2]. Limited data are available on TAF and EVG pharmacokinetics (PK) in CSF, particularly after switching from E/C/F/TDF. The objectives were to measure TAF, EVG, and tenofovir (TFV) concentrations in CSF and compare them to HIV RNA in CSF and neurocognitive (NC) performance

Methods

- Key eligibility criteria: HIV-1 infected adults (≥18 years old), no more than 2 failed ART regimens, ≥3 months on E/C/F/TDF, undetectable screening plasma HIV-1 RNA, and no contraindication to lumbar puncture
- All 9 participants received E/C/F/TDF (EVG 150 mg, COBI 150 mg, FTC 200 mg and TDF 300 mg combination tablet) QD for 12 weeks and switched to E/C/F/TAF (EVG 150 mg, COBI 150 mg, FTC 200 mg and TAF 10 mg) QD from week 12 to 24. Five (n=5) participants received E/C/F/TAF for 24 weeks (excluded from the final analyses)
- Plasma and CSF samples were collected as in Figure 1. Before switching and at Week 24, plasma PK samples were collected at 2, 4, and 6 hours post-dose
- CSF PK samples were collected within 1 hour of the 6-hour plasma sampling. Additional plasma HIV-1 RNA assessments occurred at week 12
- Montreal Cognitive Assessment (MoCA) was performed at baseline and week 24
- Safety assessments including adverse event reporting and assessment of laboratory abnormalities

Figure 1. Study Design



Results

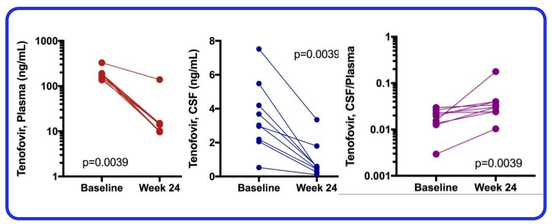
Table 1. Pharmacology, Virologic, and Immunologic Response Data in Plasma and CSF

	Plasma EVG (ng/ml)		CSF EVG (ng/ml)		EVG C/P Ratio (%)		Plasma TFV (ng/mL)		CSF TFV (ng/mL)		TFV C/P Ratio (%)		Plasma TAF 2h	MoCA (Total Calculated)		HIV-1 RNA (c/mL) W24		CD4+ Cell Count (cells/mm³)		
ID	W0	W24	W0	W24	W0	W24	W0	W24	W0	W24	W0	W24	W24	Baseline	W24	Plasma	CSF	Baseline	W24	Change
A	534	1488	1.65	4.09	0.309	0.275	136	15.1	3.03	0.458	2.22	3.03	23.5	30	30	≤20	≤20	519	799	+280
B	664	1349	2.56	6.76	0.385	0.501	161	14.1	4.20	0.563	2.62	4.00	4.24	29	30	≤20	≤20	566	508	-58
C	1219	1608	3.65	6.06	0.300	0.377	174	14.5	2.19	0.437	1.26	3.02	9.87	24	28	≤20	≤20	502	488	-14
D	1080	1122	4.48	3.15	0.415	0.280	152	10.2	2.06	0.251	1.35	2.47	19.3	28	30	≤20	≤20	892	944	+52
E	1558	1757	7.85	4.79	0.503	0.272	184	15.0	5.48	0.507	2.98	3.38	14.7	28	28	≤20	≤20	1071	1200	+129
F	2123	2352	4.55	5.90	0.214	0.251	179	9.67	0.53	0.100	0.29	1.03	147	21	22	40	≤20	1049	1238	+189
G	911	897	2.72	--	0.298	--	13.8	11.8	--	0.481	--	4.09	6.24	26	29	≤20	≤20	650	853	+203
H	1538	2078	5.84	5.27	0.380	0.254	191	10.1	2.97	1.80	1.55	17.75	9.64	24	25	≤20	≤20	601	527	-74
I	969	1813	4.30	6.52	0.444	0.360	187	15.0	3.69	0.598	1.97	3.99	11.1	27	28	≤20	≤20	997	1077	+80

*All concentrations are expressed in ng/ml

- EVG concentrations observed in CSF exceeded the in vitro EC_{50} against wild-type HIV (0.76 ng/mL)[3] for all participants (100%) at baseline and Week 24
- The switch was associated with a reductions in TFV concentrations in CSF and plasma, but an increase in CPR (Figure 2)
- Correlations between week 24 CSF and plasma concentrations were 0.775 (p=0.02) for EVG and 0.881 (p<0.0001) for TFV
- HIV-1 RNA remained undetectable in the CSF and plasma after the regimen switch
  - All participants had CSF HIV-1 RNA ≤20 c/mL at Week 24
  - Eight (89%) participants had plasma HIV-1 RNA ≤ 20 c/mL at Week 24
  - Participant F, who had detectable plasma HIV-1 RNA of 40 c/mL at Week 24, had CSF HIV-1 RNA below 20 c/mL
- CD4+ T-cell count of most (6, 67%) increased after the regimen switch
  - CD4+ T-cell count increased from a mean of 761 to a mean of 848 cells/mm^3 at week 24 (p=0.066) after the switch

Figure 2. Tenofovir Concentrations and CPR



- The blood-brain barrier permeability remained unchanged
  - The mean CSF:serum albumin ratio was 3.86 before switching and 4.86 at week 24
- No clinically significant trends in NC or post-dose laboratory abnormalities were observed
  - For instance, the average serum glucose concentration was 94 mg/dL at baseline vs. 95 at week 24 after the regimen switch
  - Three participants (3/9, 33%) had NC impairment at week 0 and 2 (2/9, 22%) remained impaired at week 24 (p=0.50)

Conclusions

- EVG achieves CSF concentrations exceeding reported EC_{50} in the majority after the regimen switch
- Switch from TDF (300 mg) to TAF (10 mg) reduced TFV concentrations in CSF and plasma
- Given the short half-life of TAF, undetectable concentrations were expected in plasma or CSF at 6 hours
- CSF concentrations of EVG and TFV correlated with the plasma concentrations of each drug
- Switching from E/C/F/TDF to E/C/F/TAF maintained virologic suppression in CSF and plasma
- No significant changes in blood-brain barrier permeability or neurocognitive performance were observed
- **In this small, 24-week, open-label project, switching from E/C/F/TDF to E/C/F/TAF was safe and effective in the central nervous system**

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The State University of New York

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