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Switching to Tenofovir Alafenamide in Elvitegravir-Based Regimens: Pharmacokinetics and Antiviral Activity in Cerebrospinal Fluid

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Background. Tenofovir alafenamide fumarate (TAF) co-formulated with elvitegravir (EVG; E), cobicistat (C), and emtricitabine (F), a recommended antiretroviral regimen, was evaluated for distribution and antiviral activity in cerebrospinal fluid (CSF) as well as neurocognitive (NC) performance change in participants switching from E/C/F/tenofovir disoproxil fumarate (TDF) to E/C/F/TAF.

Methods. This was a 24-week, single-arm, open-label study in treatment-experienced adults living with human immunodeficiency virus (HIV). Nine participants switched from E/C/F/TDF (150/150/200/300 mg once daily) to E/C/F/TAF (150/150/200/10 mg once daily) at week 12. CSF and total plasma concentrations of EVG, TDF, TAF, tenofovir (TFV), and HIV RNA levels were measured at baseline and week 24. NC performance was estimated by the Montreal Cognitive Assessment.

Results. EVG concentrations in CSF and the CSF:plasma ratio remained stable ($P = .203$) over time. Following the switch, TFV concentrations in CSF and plasma declined ($P = .004$), although the TFV CSF:plasma ratio increased ($P = .004$). At week 24, median TAF plasma concentration was 11.05 ng/mL (range, 2.84–147.1 ng/mL) 2 hours postdose but was below assay sensitivity 6 hours after dosing. TAF was below assay sensitivity in all CSF specimens. HIV RNA was ≤40 copies/mL in all CSF and plasma specimens. Three participants (33%) had NC impairment at baseline and 2 (22%) remained impaired at week 24.

Conclusions. Switch to E/C/F/TAF was associated with reductions in TFV concentrations in CSF but stable EVG concentrations that exceeded the 50% inhibitory concentration for wild-type HIV, suggesting that EVG achieves therapeutic concentrations in the central nervous system. No virologic failure or significant NC changes were detected following the switch.

Clinical Trials Registration. NCT02251236.

Keywords. cerebrospinal fluid; HIV; elvitegravir; tenofovir alafenamide.

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF, Genvoya) was approved in 2015 as a multiclass, single-tablet combination of drugs with potent antiretroviral activity against human immunodeficiency virus (HIV). Randomized double-blind phase 3 clinical trials demonstrated noninferiority as well as the tolerability of E/C/F/TAF compared to E/C/F/tenofovir disoproxil fumarate (E/C/F/TDF, Stribild) (GS-US-292-0104 and GS-US-292-0111) [1, 2]. Similar results have been found between E/C/F/TAF and TDF-based regimens in treatment-experienced patients with virologic suppression [3]. E/C/F/TAF has become a recommended regimen due to improved renal and bone safety [4]. The assessment of E/C/F/TAF based on the pooled data from clinical trials with a total of 866 subjects in the E/C/F/TAF arms has suggested that its components are distributed into the central nervous system (CNS), as up to 14% of participants reported relevant adverse events (AEs), such as headache, insomnia, dizziness, somnolence, or abnormal dreams [2].

Distribution of antiretroviral therapy (ART) drugs into protected compartments like the CNS is likely necessary for control of HIV replication and reduction of tissue inflammation [5]. Understanding the degree to which different components of combination ART exert activity within the CNS, a sanctuary site of HIV, may be important [6] because HIV-associated neurocognitive impairment and cerebrospinal fluid (CSF) viral escape [7] continue to occur in treated patients. The reported prevalence of CSF viral escape ranged from 4% to 20% [8, 9]. ART with better CNS distribution and higher concentrations in brain tissues and CSF may better suppress HIV in the brain and CSF than those with poor CNS distribution [8, 10]. Although it remains controversial if ART with better CNS penetration could overcome CSF escape, recent evidence has indicated that regimens with low CNS penetration effectiveness as independent predictors of CSF escape [8].

Sparse data are currently available on elvitegravir (EVG) or TAF pharmacokinetics in CSF, particularly after switching from

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E/C/F/TDF. No published systematic studies have yet measured EVG or TAF concentrations in human CSF or compared them to outcomes, except for a recent case report on EVG [11]. While prior studies have described low tenofovir (TFV) concentrations in CSF among adults taking TDF [12], extracellular TFV concentrations in CSF will likely decline when patients transition to TAF-containing regimens because the TAF dose is lower than the TDF dose and TAF concentrates intracellularly (Figure 1). Nevertheless, a meta-analysis revealed no significant differences in HIV RNA suppression rates or clinical safety between low doses of TAF and the standard doses of TDF, suggesting comparability of these formulations [13]. Because EVG has potent antiretroviral activity, it was hypothesized that even modest distribution into the CNS may result in therapeutic concentrations. The objectives of this project were to assess the extent of EVG and TAF into CSF and to evaluate HIV RNA in CSF and plasma and neurocognitive (NC) performance.

METHODS

Design and Study Population

This was a 24-week, single-arm, open-label, single-center study in ART-experienced adults living with HIV. Eligible participants were at least 18 years old; had at least 3 months of prior therapy with E/C/F/TDF; had undetectable HIV RNA in plasma; and provided informed consent for all study procedures. Exclusions included contraindication to lumbar puncture, >2 failed ART regimens, evidence of primary viral resistance on prior clinical screening, active US Centers for Disease Control and Prevention (CDC) category C disease (except Kaposi sarcoma), pregnancy, breastfeeding, current malignancy, recent treatment with HIV vaccines or immunomodulators, or defined laboratory values—for example, serum hepatic aminotransferase or creatinine values more than twice the upper limit of the normal range. Ethics committee approval was obtained in accordance with the principles of the 2008 Declaration of Helsinki. This study was registered at ClinicalTrials.gov (NCT02251236). Participants who switched regimens received the E/C/F/TDF (150/150/200/300 mg) combination tablet for 12 weeks before switching to E/C/F/TAF (150/150/200/10 mg) from week 12 to 24, all taken once daily. Five (n = 5) participants were already taking E/C/F/TAF at entry and continued this for 24 weeks. Data from these participants were not included in switch analyses, but are included in the Supplementary Table.

Study Endpoints

The primary endpoint was the EVG, TAF, and TFV concentrations in CSF. Secondary endpoints included the change in EVG and TFV concentrations in CSF after the switch; the relationship between EVG and TFV concentrations in CSF and those in plasma; HIV RNA levels in CSF; and blood–brain barrier permeability, as estimated by the CSF:serum albumin ratio and Montreal Cognitive Assessment (MoCA) scores. Additionally, the incidence of treatment-emergent genotypic and phenotypic resistance to EVG and other components of the regimen were assessed for any participant with protocol-defined virologic failure.

Procedures and Assessments

Study visits occurred at baseline and week 24. EVG, TFV, TAF (week 24 only), and HIV RNA were measured in specimens that were collected by venipuncture (blood plasma) or lumbar

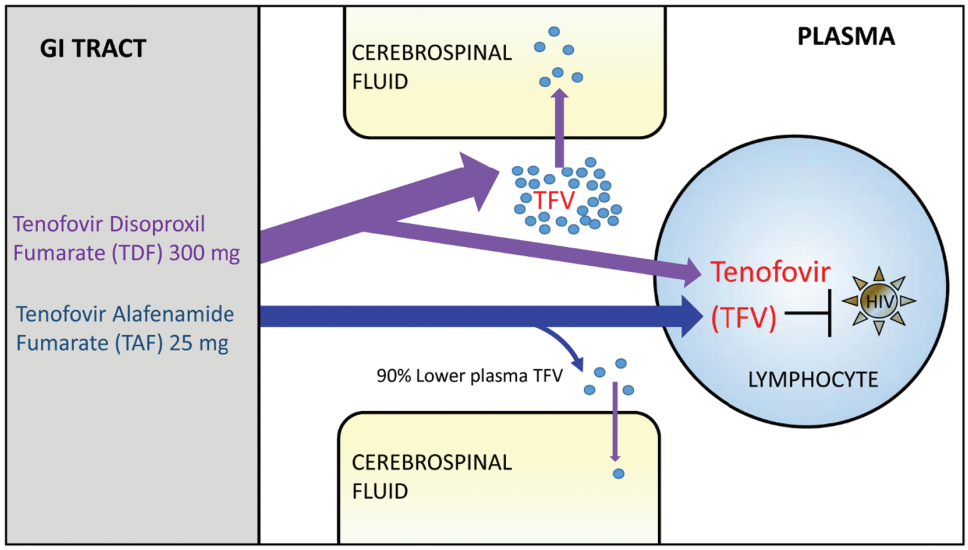

Figure 1. Distribution of tenofovir alafenamide fumarate (TAF) into plasma and cerebrospinal fluid: comparison with tenofovir disoproxil fumarate (TDF). TAF and TDF are prodrugs of tenofovir. TAF has been developed to produce the comparable potency as TDF combined with an improved safety profile. TAF has longer plasma half-life and greater plasma stability (~90 minutes) than TDF (~0.4 minute) [14, 15]. Abbreviations: GI, gastrointestinal; HIV, human immunodeficiency virus; TFV, tenofovir.

puncture (CSF). Plasma specimens were collected 2 hours and 6 hours after the dose, and CSF specimens were collected within 1 hour of the 6-hour plasma specimen. HIV RNA was measured using the Roche Amplicor Real Time HIV PCR assay (lower limit of quantification 40 copies/mL). $CD4^+$ T-cell count was determined by flow cytometry. Clinical chemistry panels and cell counts (blood, CSF) were performed by standard clinical methods. MoCA was performed at baseline and week 24 to screen for cognitive impairment [16].

EVG, TAF, and TFV concentrations were measured using validated analytical methods based on protein precipitation or solid phase extraction followed by high-performance liquid chromatography–tandem mass spectrometry [17, 18]. For plasma, the lower limit of quantification was 10 ng/mL (EVG) and 0.50 ng/mL (TFV, TAF), and the upper limit was 5000 ng/mL (EVG) and 500 ng/mL (TFV, TAF). Total CSF concentrations had a lower limit of quantification of 1 ng/mL (EVG) and 0.100 ng/mL (TFV, TAF) and an upper limit of 25.0 ng/mL (EVG) and 50.0 ng/mL (TFV, TAF).

Safety was assessed by standardized monitoring of vital signs, laboratory results, and AEs. The AEs were assessed and graded according to the Division of AIDS toxicity scales [19].

Statistical Analyses

This was a single-arm study to assess the distribution of EVG and TAF into the CSF compartment that did not include statistics to test a hypothesis. Drug concentrations were compared in plasma and CSF using Pearson correlation coefficient. Virologic suppression was determined by the last available HIV RNA while the subject was receiving treatment. Descriptive statistics summarized absolute values and change from baseline in plasma and CSF EVG, TAF, and TFV concentrations; HIV RNA (plasma and CSF) and $CD4^+$ T-cell counts; and the incidence and severity of serious AEs (SAEs), AEs leading to withdrawal, or graded laboratory abnormalities; and MoCA performance. The assessments of EVG, TAF, and TFV concentrations in plasma and CSF, and of CSF HIV RNA responses, were based on all available data.

RESULTS

Of 14 subjects screened and enrolled, 9 completed the 24-week study by switching to E/C/F/TAF after 12 weeks of E/C/F/TDF. Most participants were white men (89%), 5 (56%) were of Hispanic ethnicity, and median age was 34 years (range, 23–54 years). One participant was a woman of African ancestry. Baseline characteristics are summarized in Table 1. At the week 24 analysis, no subjects had premature withdrawal due to SAEs or virologic failure (ie, plasma HIV RNA >200 copies/mL).

Paired CSF and plasma pharmacokinetic samples were available from all 9 subjects at baseline and week 24. The EVG concentrations in CSF and plasma are shown in Table 2.

Table 1. Characteristics at Baseline and Week 24 in the Intention-to-Treat Exposed Population (n = 9)

Characteristic	Baseline	Week 24
Age, y, median (range)	34 (23–54)	…
Sex, female	1 (11)	…
Race/ethnicity		
White	3 (33)	…
Hispanic	5 (56)	…
African American	1 (11)	…
Plasma HIV-1 RNA		
≤40 copies/mL	9 (100)	9 (100)
CSF HIV-1 RNA		
≤40 copies/mL	9 (100)	9 (100)
$CD4^+$ count, cells/μL		
Mean (SD)	750 (246)	817 (307)
Median (range)	601 (537–1023)	799 (518–1139)
Nonreactive hepatitis B and C test results[a]	9 (100)	…
Montreal Cognitive Assessment score		
Mean (SD)	26 (3)	27 (3)
Median (range)	27 (24–29)	28 (26–30)
CDC category[b]		
A	8 (89)	…
B	1 (11)	…

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: CDC, US Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HIV-1, human immunodeficiency virus type 1; SD, standard deviation.

[a]Nonreactive results showed neither hepatitis B nor hepatitis C.

[b]CDC category A is defined as asymptomatic, lymphadenopathy, or acute HIV infection; and category B is defined as symptomatic, not AIDS.

The median EVG concentration in CSF was 4.30 ng/mL (range, 3.11–5.20 ng/mL) at baseline and 5.90 ng/mL (interquartile range [IQR], 4.44–6.60 ng/mL) at week 24. Concentrations of EVG in CSF were low compared with plasma with median fractional penetrance of 0.38% (range, 0.27%–0.43%) at baseline and 0.28% (range, 0.26%–0.37%) (P = .359) at week 24. The EVG concentration in CSF in all participants exceeded the in vitro 50% inhibitory concentration (IC_{50}, non–protein binding adjusted) of 0.76 ng/mL against wild-type HIV [20] (Figure 2A).

As expected, regimen switch was associated with reduction in extracellular TFV concentrations in CSF and plasma at week 24 (Table 2). Median TFV concentration in CSF was 3.03 ng/mL (range, 2.13–4.84 ng/mL) at baseline and 0.507 ng/mL (IQR, 0.344–1.197 ng/mL) at week 24, both of which were below the in vitro IC_{50} (11.5 ng/mL, non–protein binding adjusted) against wild-type HIV [21] (Figure 2B). While extracellular TFV concentrations declined in plasma and CSF, TFV fractional penetrance rose from 1.97% (range, 1.31%–2.45%) at baseline to 3.03% (range, 2.43%–3.99%) at week 24 (P = .004; Figure 3). Median TAF concentration in plasma was 11.1 ng/mL (IQR, 6.9–21.4 ng/mL) 2 hours after dosing but was below assay sensitivity 6 hours after dosing. All TAF concentrations in CSF were below assay sensitivity. At week 24, total EVG concentrations in CSF correlated with those in plasma (r = 0.775, P = .02). TFV

Table 2. Elvitegravir and Tenofovir Concentrations in Plasma and Cerebrospinal Fluid (n = 9)

	Baseline		Week 24		
Drug	Mean (SD)	Median (Range)	Mean (SD)	Median (IQR)	*P* Value (Week 24 vs Baseline)
Elvitegravir					
Plasma total, ng/mL	1249 (500)	1219 (817–1557)	1775 (439)	1757 (1419–2215)	.004
CSF total, ng/mL	4.30 (1.80)	4.30 (3.11–5.20)	5.47 (1.25)	5.90 (4.44–6.60)	.203
Tenofovir					
Plasma total, ng/mL	188 (56)	179 (157–189)	27.0 (42.1)	14.5 (10.1–15.1)	.004
CSF total, ng/mL	3.52 (2.05)	3.03 (2.13–4.84)	0.895 (1.039)	0.507 (0.344–1.197)	.004
TAF[a]					
Plasma total, ng/mL	NP	NP	26.9 (45.5)	11.1 (6.9–21.4)	

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; NP, not performed; SD, standard deviation; TAF, tenofovir alafenamide.

[a]Pharmacokinetic samples collected at 2 hours postdose.

concentrations in CSF and plasma were also correlated with each other ($r = 0.881$, $P < .001$). The CSF:serum albumin ratio did not significantly change during the study (baseline median, 3.875 vs 24-week median, 4.573; $P = .215$).

Regarding antiviral efficacy, all HIV RNA levels were <40 copies/mL in CSF and plasma at baseline and remained <40 copies/mL in both fluids after 24 weeks. The median $CD4^+$ T-cell count increased from 601 cells/μL (interquartile range [IQR], 537–1023 cells/μL) at baseline to 799 cells/μL (IQR, 518–1139 cells/μL) at week 24 ($P = .125$). Neither EVG nor TFV concentrations in plasma correlated with changes from baseline in $CD4^+$ cell count at week 24.

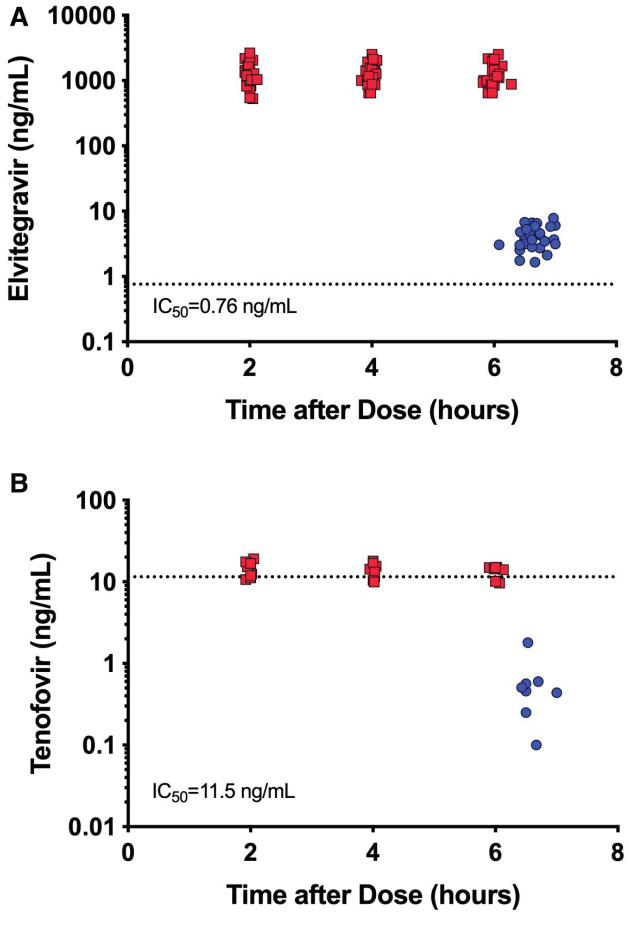

Figure 2. *A*, Elvitegravir concentrations in plasma and cerebrospinal fluid (CSF). *B*, Tenofovir concentrations in plasma and CSF. Abbreviation: IC_{50}, half maximal inhibitory concentration.

Regarding NC performance, median MoCA value increased modestly from 27 (IQR, 24–28.5) at baseline to 28 (IQR, 25.5–30) ($P = .065$) at week 24. At baseline, 3 of 9 (33%) participants had NC impairment (MoCA value <26) and the 2 who had the lowest baseline MoCA values remained impaired at week 24. Neither EVG nor TFV CSF concentrations correlated with NC performance at week 24.

Regarding safety, the regimen switch was well tolerated with no clinically significant trends in AEs or laboratory abnormalities and no participant reporting a new or recurrent CDC category B or C condition. AEs were reported from 5 (56%) participants, most of which were grade 1 or 2. Two grade 3 AEs were reported and resolved during the study, including a headache following the baseline lumbar puncture and a grade 3 creatinine clearance that was present at baseline but improved to grade 2 by week 24. The only drug-related AEs reported in 2 participants (22%) were grade 1 low bicarbonate levels at week 24, which resolved on repeat testing. No deaths occurred and no participant prematurely withdrew from the trial.

For the 5 participants who received E/C/F/TAF at entry and continued for 24 weeks, all HIV RNA levels were <20 copies/mL in CSF and plasma in week 24. The median $CD4^+$ T-cell count was 784 cells/μL (IQR, 466–895 cells/μL) at baseline and remained at 783 cells/μL (IQR, 534–954 cells/μL) at week 24. Their plasma and CSF concentration profiles of EVG, TAF, and TFV in week 24 were similar to those obtained from the 9 participants in the regimen switch group.

DISCUSSION

Distribution of ART drugs to the CNS is likely essential for suppressing HIV replication in the brain. Evolution of drug resistance mutations in the CNS has been reported, suggesting

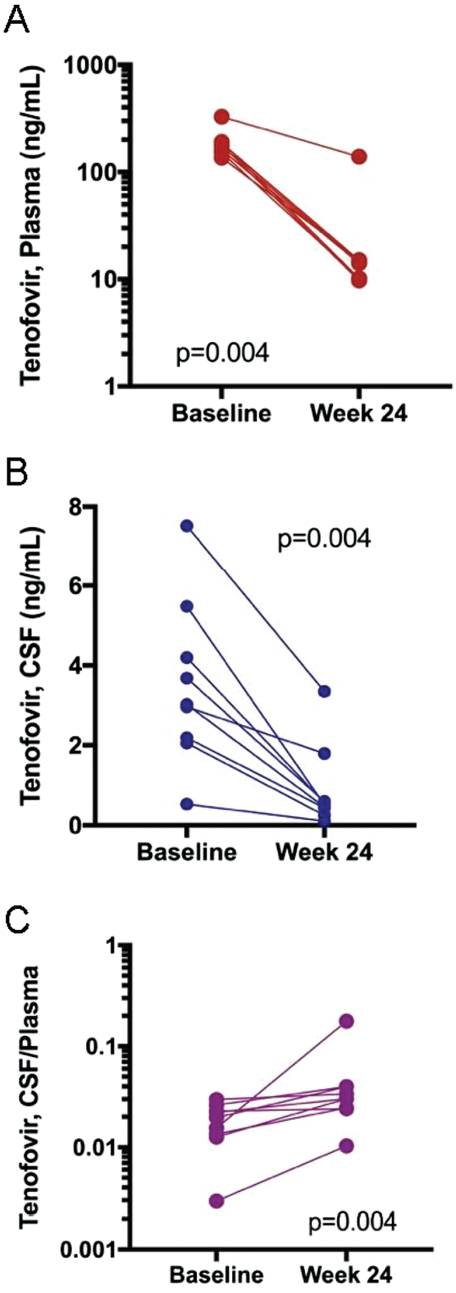

Figure 3. Changes in tenofovir (TFV) concentrations. *A*, TFV concentrations in plasma. *B*, TFV concentrations in cerebrospinal fluid (CSF). *C*, TFV CSF-to-plasma concentration ratio.

incomplete suppression, which may be due to subtherapeutic drug concentrations in the CNS and drug selection pressure [19, 22, 23]. In this study, EVG concentrations in CSF exceeded the IC_{50} against wild-type HIV (0.76 ng/mL) [20] by 6- to 7-fold, suggesting that concentrations in CSF were therapeutic. EVG in CSF may exhibit slow clearance from the CNS, similar to other integrase inhibitors such as dolutegravir [24] and raltegravir [25]. Regarding TFV, our prior study of TDF found low extracellular TFV concentrations in CSF that were frequently (~80%) below the wild-type IC_{50} [13]. In the present study, the regimen switch from TDF (300 mg) to TAF (10 mg) reduced TFV concentrations in CSF (6-fold) and plasma (12-fold). Such a reduction was anticipated because TAF has better oral bioavailability and cell membrane permeability, which results in more rapid intracellular delivery and clearance from the extracellular space than TDF [26]. Given the short half-life of TAF (0.5 hour), undetectable concentrations were expected in CSF and plasma at 6 hours postdose, which is consistent with prior reports on TAF pharmacokinetics [27]. Even with low concentrations in CSF, ART drugs may reach therapeutic concentrations in brain tissue [28]. While we did not measure emtricitabine concentrations in this trial, it has previously been shown to distribute well into the CNS [29]. The combination of these 3 drugs, whether with TDF or TAF, was sufficient to maintain HIV below the lower limit of quantification in all participants. The duration of the present study was decided primarily based on pharmacokinetics of EVG and TAF that steady state would be achieved during the 24-week study period.

Elvitegravir is highly protein bound in plasma (98%–99%) [30]. While only total EVG concentrations were measured in CSF and plasma, the impact of protein binding on unbound EVG concentrations in the CSF might be small because of the lower concentrations of binding proteins (eg, albumin) in CSF than in plasma (100-fold lower) [31]. This was supported by findings from our previous studies on highly protein-bound dolutegravir (>99%) [32] demonstrating similar dolutegravir concentrations in CSF and unbound concentrations in plasma [24].

In comparison to raltegravir, the distribution of EVG into CSF was relatively low with fractional penetrance of 0.3%–0.4% vs 6% for raltegravir [25], but similar to that of dolutegravir (0.5%) [24]. The greater potency of EVG resulted in a higher CSF inhibitory quotient (ratio of CSF concentrations to IC_{50}) than raltegravir: 6- to 7-fold for EVG vs 4.5-fold for raltegravir [32]. While the CSF and plasma TFV concentrations were low after the regimen switch, intracellular concentrations of TFV diphosphate were not measured in this study. Because TAF is activated and concentrated intracellularly, measurement of unphosphorylated extracellular TFV may underestimate the antiviral efficacy of TAF. In addition to the comparable efficacy of 10 mg TAF to that of 300 mg TDF [2], the long intracellular half-life of active TFV diphosphate (150–180 hours) supports slow clearance after TAF is activated in target cells [26]. This was supported by our findings that HIV RNA remained undetectable in CSF in all participants after the regimen switch despite substantially reduced extracellular TFV concentrations.

The neurocognitive effects of E/C/F/TAF were also assessed in this study using the MoCA. Most participants (~70%) had modest NC improvement at week 24 from baseline ($P = .067$), which could be due to learning (practice effect). NC improvement was also observed following initiation of a raltegravir-containing regimen among treatment-naive participants, but

whether this reflects practice effect or benefits from HIV suppression, immune recovery, or raltegravir itself remains to be determined [33, 34]. No statistically significant correlations between drug concentrations and MoCA values were found in this study, but the MoCA was primarily performed as a safety assessment, and our small study was not powered to detect statistically significant correlations.

In general, the regimen switch was well tolerated in the ART-experienced, HIV-infected participants in this study. Nearly all AEs were mild and resolved without intervention. Overall, the safety profile of E/C/F/TAF in these participants was consistent with findings of larger phase 3 studies [2, 4]. One participant had a grade 3 headache, which was temporally related to lumbar puncture and resolved with conservative management. One participant had renal insufficiency at baseline, which was improved after the regimen switch, consistent with the known benefits of TAF compared with TDF [35].

In conclusion, this small 24-week open-label study demonstrated that switching from E/C/F/TDF to E/C/F/TAF was safe and effective in the CNS. EVG concentrations in CSF were in the therapeutic range. As expected, TAF concentrations in CSF were below assay sensitivity. While TFV concentrations in CSF were detectable, they were lower than the IC_{50} against wild-type HIV type 1 in vitro. The clinical implications of this are unclear, however, as TFV concentrations may be higher in brain tissue than in CSF and all participants maintained viral suppression in CSF after switching to this TAF-containing regimen.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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