Efavirenz Plasma Levels, Cognition and Central Nervous System Side Effects

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BACKGROUND

Efavirenz (EFV) plasma concentration has been associated with central nervous system (CNS) side-effects; in vitro data suggest neurotoxicity may be mediated by 8-hydroxy(OH)-EFV. Whether drug plasma concentrations are associated with neurocognitive impairment or whether 8-OH-EFV is a more accurate predictor of CNS abnormalities is still debated.

METHODS

- Morning EFV and 8-OH-EFV plasma concentrations were measured by HPLC on frozen plasma samples collected during the screening of a randomized trial evaluating neurocognitive function after switching from EFV to rilpivirine (RPV) (Swear Study).
- All participants were on stable therapy with tenofovir/emtricitabine/EFV at bedtime and had HIV-RNA <50 copies/ml for at least 6 months.
- Participants underwent comprehensive neurocognitive assessment of 6 cognitive domains, evaluation of depression, anxiety, quality of sleep, CNS symptoms and self-reported Cognitive Failures (CFQ). Those with altered findings repeated the tests 24 weeks after switching away from EFV.
- EFV and 8-OH-EFV plasma concentrations were compared using Mann-Whitney test according to the presence of impairment in the different assessments.
- Correlations between drug plasma concentrations and scores (baseline and 24-week changes) were explored with Spearman's test.

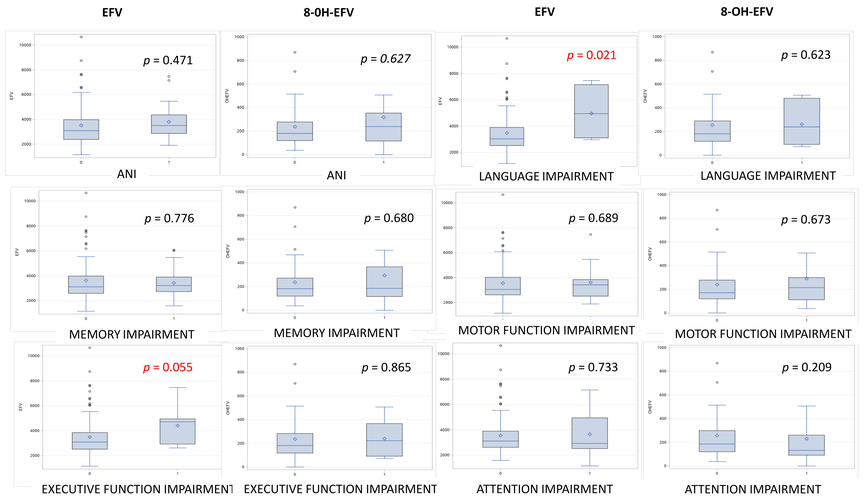
8-OH-EFV plasma concentration is associated with ***SNC side effects*** and can be useful to identify patients who could benefit from ***EFV discontinuation.***

EFV plasma concentration is mildly associated with ***neurocognitive performance***.

Table 1. Characteristics of the participants enrolled in the study (N=104).

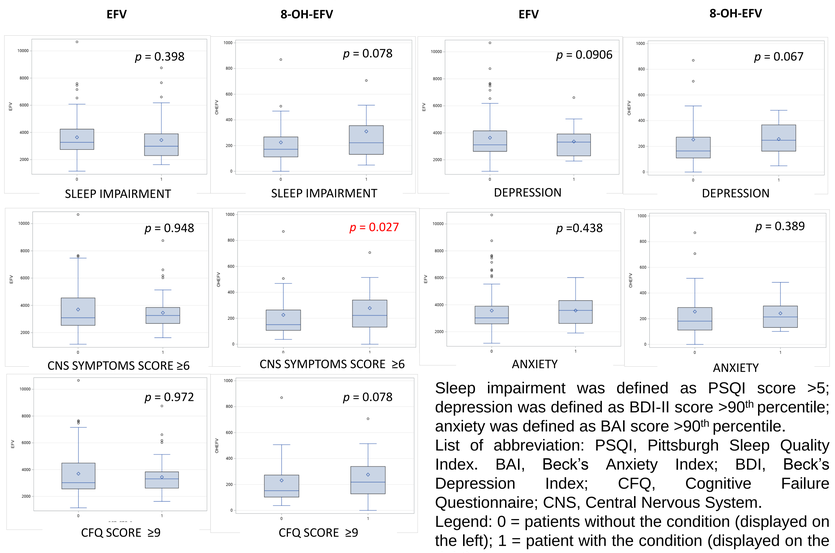
	N (104)
Male	90 (86.5)
Age, median (IQR)	46.9 (40-54)
Nationality, n (%)	
Italian	94 (90.4)
Education, n (%)	
≤ 5 years	4 (3.8)
8-13 years	84 (80.8)
Higher education	16 (15.4)
CDC class C, n (%)	26 (25)

Figure 1. Efavirenz and 8-hydroxy-efavirenz plasma levels in study participants with and without neurocognitive impairment (N=104).



Asymptomatic neurocognitive impairment (ANI) was defined as z-scores below -1 in ≥2 cognitive domains. Single domain impairment was defined as a z-score below -1.
Legend: 0 = patients without the condition (displayed on the left); 1 = patient with the condition (displayed on the right)

Figure 2. Efavirenz and 8-hydroxy-efavirenz plasma levels in study participants with and without selected clinical conditions (N=104).



Sleep impairment was defined as PSQI score >5; depression was defined as BDI-II score >90th percentile; anxiety was defined as BAI score >90th percentile.
List of abbreviation: PSQI, Pittsburgh Sleep Quality Index. BAI, Beck's Anxiety Index; BDI, Beck's Depression Index; CFQ, Cognitive Failure Questionnaire; CNS, Central Nervous System.
Legend: 0 = patients without the condition (displayed on the left); 1 = patient with the condition (displayed on the right).

RESULTS

- Characteristics of the 104 patients enrolled in the study are shown in Table 1. Median EFV and 8-OH-EFV plasma concentrations were 3108 (IQR 2559-3946) and 184 (IQR 118–289) ng/ml.
- EFV and 8-OH-EFV plasma concentrations did not significantly differ in participants with or without asymptomatic neurocognitive impairment (Figure 1), although higher EFV plasma concentrations were observed in participants with impaired executive function (4719 *vs* 3058 ng/ml, *p*=0.055*)* and language (4949 ng/ml *vs* 3022 ng/ml, *p*=0.021).
- Conversely, participants with more CNS side-effects, high CFQ score, depressive symptoms and low-quality sleep had higher 8-OH-EFV (but not EFV) plasma concentration (222 *vs* 151 ng/ml, *p*=0.027; 218 *vs* 152 ng/ml, *p*=0.078; 247 *vs* 164ng/ml, *p*=0.067 and 222 *vs* 171, *p*= 0.078, respectively; Figure 2).
- A trend to a weak correlation between EFV plasma concentration and lower executive function (R=-0.18; P=0.059), motor function (R=-0.19; P=0.054), attention (R=-0.17; P=0.082) and language (R=-0.17; P=0.093) *z*-scores was observed.
- Conversely, 8-OH-EFV plasma concentration was correlated with higher CNS symptom score (R=0.26; p=0.007), CFQ score (R=0.18; P=0.066) and PSQI score (R=0.22; p=0.021).
- Seventy participants were enrolled in the Swear Study and repeated the neurocognitive assessment 24 weeks after switching to RPV.
- Baseline EFV plasma concentration was not associated with changes in neurocognitive scores after EFV discontinuation, whereas participants with high 8-OH-EFV plasma concentration (≥184 ng/ml) were more likely to experience CNS symptom improvement (CNS symptom score -8[-11 to -1] vs -1[-5 to 2]; P<0.001).

CONCLUSIONS

Higher 8-OH-EFV plasma concentration is associated with CNS side effects. Therefore, such marker can be useful to identify people living with HIV who could benefit the most from EFV discontinuation. Conversely, EFV but not 8-OH-EFV plasma concentrations were marginally associated with neurocognitive performances.
These findings suggest possible different pathways in determining detrimental effects on cognitive function.

ADDITIONAL KEY INFORMATION

Additional Resources:
Swear study protocol, https://clinicaltrials.gov/ct2/show/NCT02042001
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