Efavirenz Plasma Levels, Cognition and Central Nervous System Side Effects

Alice Ranzani 1, Francesco Castelli 2, Antonio Di Biagio 3, Antonella D’Arminio Monforte 4, Antonio D’Avolio 5, Alessandro Soria 1, Francesca Bai 6, Emanuele Focà 7, Lucia Taramasso 7, Andrea Calcagno 5, Paolo Bonfanti 6, Giuseppe Lapadula 8

1 San Gerardo Hospital, Monza, Italy; 2 University of Brescia, Brescia, Italy; 3 University of Genoa, Genoa, Italy; 4 University of Milan, Milan, Italy; 5 University of Turin, Turin, Italy; 6 San Paolo Hospital, Milan, Italy; 7 San Martino Hospital, Genoa, Italy; 8 University of Milano–Biocca, Milan, Italy

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 ripravirine (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 CNS domains, evaluation of depression, anxiety, quality of sleep, CNS symptoms and self-reported Cognitive Failures (CFQ). Those with altered findings repeated the tests 4 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.

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 164 ng/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=0.28; 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/NCT02042201
Author Contact Information: alice.ranzani@asst-monza.it, giuseppe.lapadula@unimib.it