Neurocognitive and neurometabolic effects of switch from efavirenz to ritonavir-boosted lopinavir

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Introduction

The aetiology of cognitive impairment in HIV infection is incompletely understood, and the role of HAART modification remains controversial. Efavirenz (EFV) is associated with early neuropsychiatric side effects, and recent observational studies have suggested that chronic EFV use may additionally be associated with cognitive impairment. RCTs of initial HAART have suggested that the neurometabolic effects of EFV may differ from other HAART. Animal and *in vitro* models suggest that EFV may have adverse neurocognitive effects.

The aim of this study was assess whether cessation of chronic EFV therapy was associated with beneficial cognitive or neurometabolic effects.

Methods

Trial Design. Open-label phase IV pilot study.

Participants. Adult HIV-infected patients, unselected with respect to the presence or absence of CNS symptoms. Subjects were on suppressive HAART for at least 12 months and on EFV for at least 6 months.

Interventions. All subjects switched from EFV to LPV/r (Kaletra®). Participants had study observations performed at baseline and 10 weeks after switch.

Measurements.
A computerised neurocognitive testing battery (CogState®) was performed comprising of: Detection (DET, psychomotor function / speed of processing), Identification (IDN, visual attention / vigilance), One card learning (OCL, visual learning and memory), One back (ONB, attention / working memory), Continuous paired associate learning (CPAL, visual learning and memory), and Groton maze learning (GML, executive function / spatial problem solving).

Proton magnetic resonance spectroscopy (^{1}H-MRS) was performed with voxels in frontal white matter (FWM), frontal grey matter (FC), and basal ganglia (BG). N-acetylaspartate (NAA) and choline (Cho) concentrations were expressed relative to creatine (Cre). Task-based (attentional processing) functional magnetic resonance imaging (fMRI) assessed response to incongruent visual stimuli in the Stroop paradigm.

Sleep was assessed by self-completion of a two week sleep diary, Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI).

Results

Subject characteristics: 17 participants were recruited of whom 16 completed the study (3F / 13M). Median duration of diagnosed HIV infection was 6.7 years. Subjects had been receiving EFV for a median of 4.5 years. Median CD4 count at baseline was 660 cells/μL, and median nadir CD4 count was 237. Subjects frequently reported neurocognitive symptoms at baseline: memory problems (81%), vivid / intrusive dreams (75%), fatigue (69%), concentration difficulties (63%), sleep problems (56%), low mood (50%), and anxiety (44%).

Neurocognitive performance: No change in neurocognitive performance was observed **(Table 1).**

^{1}H-MRS: No changes were observed for any metabolite in any voxel **(Table 2).**

fMRI: Three clusters of significant activation with the incongruent stimulus of the Stroop task were identified, in an anatomical distribution corresponding to that expected for this test paradigm **(Figure 1).** There was no change in brain activation between the two study time-points.

Sleep: There was no change in daytime sleepiness (ESS), or hours of sleep. There was an improvement in sleep quality (PSQI) **(Table 3).**

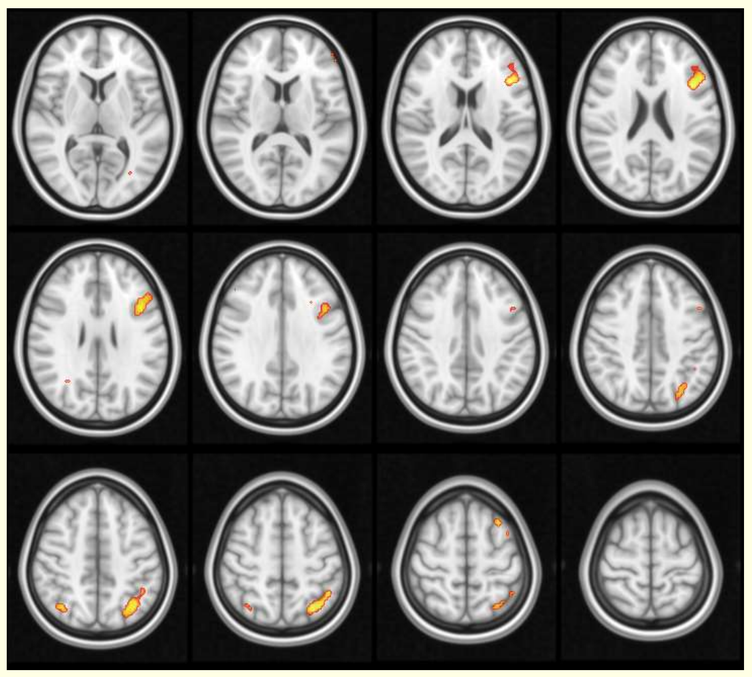

Figure 1. Neuroanatomical regions of activation during incongruent task compared with neutral task during Stroop fMRI paradigm. Three clusters of activity were identified (with peak T scores for each region): BA45 (6.78), BA8 (4.45) and BA46 (4.32) (p <0.001); BA20 (6.14), BA7 (5.82) and BA40 (5.52) (p <0.001); BA7 (5.25) (p 0.028). BA, Broca area.

No changes in brain activation were observed between baseline and follow-up visits.

		Baseline (EFV)	Follow-up (LPV/r)	Change
Task	n	Mean (SD)	Mean (SD)	Mean (95% CI)
DET	16	2.56 (0.08)	2.59 (0.10)	-0.03 (-0.09, 0.04)
IDN	16	2.78 (0.07)	2.75 (0.07)	0.03 (-0.02, 0.07)
OCL	16	0.92 (0.11)	0.96 (0.11)	0.03 (-0.004, 0.07)
ONB	16	1.3 (0.13)	1.3 (0.14)	-0.001 (-0.07, 0.07)
CPAL	16	121 (46.6)	107.4 (60.1)	13.6 (-9.8, 37.0)
GML	16	62.8 (22.4)	59.8 (24.7)	9.(-3.5, 9.4)

Table 1. Change in cognitive function (CogState®) between baseline and follow-up visits. Change scores are expressed such that positive score indicates improvement.

		Baseline (EFV)			Follow-up (LPV/r)			Change		
		n	Mean	SD	n	Mean	SD	n	Mean	95% CI
FC	Cho/Cre	14	0.26	0.03	14	0.27	0.03	14	0.01	-0.01, 0.02
	NAA/Cre	14	1.8	0.27	14	1.96	0.35	14	0.16	-0.13, 0.44
FWM	Cho/Cre	13	0.25	0.05	11	0.3	0.07	11	0.03	-0.02, 0.08
	NAA/Cre	13	1.38	0.33	11	1.51	0.22	11	0.11	-0.12, 0.33
BG	Cho/Cre	9	0.22	0.09	9	0.23	0.04	8	0.04	-0.02, 0.10
	NAA/Cre	9	2.34	0.78	9	2.13	0.31	8	0.03	-0.32, 0.38

Table 2. Change in brain metabolites by ^{1}H-MRS between baseline and follow-up visits.

Table 3. Change in sleep between baseline and follow-up visits. A decrease indicates improvement in score for ESS and PSQI.

	Baseline (EFV)			Follow-up (LPV/r)			Change		
	n	Mean	SD	n	Mean	SD	n	Mean	95%CI
ESS score	16	9.8	5.9	16	8.9	5.1	16	-0.9	-2.7, 0.9
PSQI score	15	8.5	6.5	15	5.8	5.5	14	-3.4	-6.0, -0.7
sleep duration (hr)	16	7.3	2.1	15	7.5	1.2	15	0.1	-0.7, 1.0

Conclusions

- Despite a high prevalence of neurocognitive symptoms at baseline, in patients on stable suppressive chronic EFV therapy there were no beneficial changes in cognitive performance or in brain metabolites on switching away from EFV.
- An improvement in sleep quality was however observed.
- Although study size was small, it is unlikely that clinically meaningful effect sizes would have been missed.
- Previous observational studies associating EFV with worse cognitive performance may have been affected by confounding factors which will have been controlled for in our paired study design.
- Switching away from EFV is unlikely to improve neurocognitive function in most otherwise stable HAART-treated patients.

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References

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