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A Randomised Controlled Trial of Maraviroc Intensified bPI ART on Cognitive Function

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Background

- Neuroinflammation may be one of the pathogenic processes underlying cognitive impairment in HIV disease
- In addition to antiretroviral activity, maraviroc may have anti-inflammatory activity. Therefore maraviroc-intensified ART could have anti neuroinflammatory properties resulting in cognitive benefits
- We assessed maraviroc-intensified ART in antiretroviral naïve subjects electively commencing therapy in an exploratory, 48 week, randomised controlled study

Methods; Study design

- Therapy naïve, neurologically asymptomatic, HIV-positive patients were eligible
- Those with existing neurological or significant psychiatric co-morbidities were excluded. Eligible subjects were HLA B5701 negative. Viral tropism testing was not an inclusion criteria
- Subjects were randomised on a 1:1 basis to arm1 or arm2:
  1) TDF/FTC plus atazanavir/r (300/100mg) once daily
  2) ABC/3TC plus darunavir/r/maraviorc (800/100/150mg) all once daily
- We specifically chose to compare two different boosted protease inhibitor containing regimens given the low rates of neuropsychiatric adverse events generally reported with boosted protease inhibitor regimens

Methods; Study procedures

- Cognitive function was assessed at screening, baseline and after 12, 24, 36 and 48 weeks (CogState™ battery). This included a detailed assessment of 11 cognitive domains
- Cerebral metabolite ratios were measured using proton spectroscopy in the right frontal white matter (FWM) at baseline. Metabolite ratios assessed included N-acetyle-aspartate/Creatine (NAA/Cr) ratio

Methods; Statistical considerations

- Primary endpoint was difference in overall cognitive function after 48 weeks between the study treatment arms
- All subjects with at least two cognitive function test results were included in the primary analysis with missing values imputed
- Overall cognitive function score was derived as an aggregated variable from the z-standardised individual domain score. Factors associated with changes in cognitive function were assessed via regression models

Results; Baseline Characteristics		Arm 1	Arm 2	Total
number		30	30	60
gender	male	29	29	58
age	median (IQR), years	31 (27 to 38)	35 (28 to 41)	33 (28 to 40)
baseline HIV RNA	median (IQR), copies/mL x 10^3	45 (22 to 70)	51 (26 to 76)	46 (21 to 76)
CD4+ lymphocyte	mean (SD), cells/uL	453 (218)	429 (240)	441 (227)
ethnicity	white	23	22	45
	black	5	6	11
	mixed race/other	2	2	
education	university degree or above	13	15	28
current smoker	yes	9	12	21
recreational drug use	yes (past 6 months)	8	7	15

Week 48; Clinical outcomes		Arm 1	Arm 2	Total
Number completed week 48 visit		27	29	56
CD4+ lymphocyte	mean (SD), cells/uL	607 (218)	622 (244)	615 (229)
plasma HIV RNA	< 50 copies/mL	27/27	29/29	
remain on randomised therapy	number	27/27	28/29	

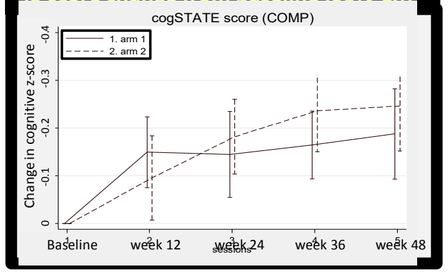
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Overall cognitive z-score (SD)

	baseline	week 12	week 24	week 36	week 48
Arm 1	-0.147 (0.67)	0.008 (0.64)	0.04 (0.71)	0.059 (0.69)	0.062 (0.64)
Arm 2	-0.169 (0.63)	-0.032 (0.67)	0.050 (063)	0.060 (0.66)	0.78 (0.70)

Change in overall cognitive function (z-score change from baseline (95% CI))



Multivariate models

Variable	Model 1	Model 2
Baseline cognitive function	0.77***	0.81***
Treatment arm (2 versus 1)	0.0009	0.1725
FWM NAA/Cr		0.51*

Correlation coefficients shown
* p<0.05; *** p<0.001

Conclusions

- In neurologically asymptomatic antiretroviral naïve subjects, a maraviroc intensified boosted protease inhibitor regimen did not demonstrate benefits on overall cognitive performance over 48 weeks
- We observed the greatest improvement in cognitive function in subjects initiating antiretroviral therapy with higher baseline cerebral function markers (higher cognitive performance and higher neuronal metabolites [NAA/Cr ratio])
- Importantly our study did not assess the effects of maraviroc intensified treatment regimens in subjects with symptomatic cognitive impairment