

Maraviroc-Enhanced cART Improves Cognition in Virally-Suppressed HAND: A Pilot Study

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Introduction

The prevalence of HIV-associated neurocognitive disorders (HAND) remains high despite the introduction of combined antiretroviral therapy (cART). This may reflect ongoing low-level viral replication and/or chronic inflammation in the brain

There are no clear guidelines for managing HAND in those with viral suppression in blood and CSF.

cART enhancement with maraviroc (MA) may be one option as MA can penetrate the CNS and has dual antiretroviral/anti-inflammatory activity

AIMS

- To determine whether MA-enhanced cART leads to improved neurocognition (NC) over 12 months relative to existing therapy and generate preliminary effect sizes
- To examine MA-related changes in major cerebral metabolites in the frontal white matter (FWM) and basal ganglia (BG) using single-voxel magnetic resonance spectroscopy (¹H-MRS)

Methods

Design

12 month prospective, double observer-blinded, open label pilot RCT

Randomization

1:1 MA-enhancement (MA arm) vs. existing cART (control arm)

Subjects

- 19 virally-suppressed (blood and CSF) HIV+ males on stable cART with recent progression to HAND
- 14 completed study (Table 1). 3 screen fails, 1 control withdrew for personal reasons, 1 control lost to follow-up prior to 6-months
- 2 MA, 1 control CXCR4-tropic; 1 control CCR5-tropic. Data unavailable for others

Procedures

- Brief 5-domain NC battery (see Table 2) at baseline, 6-months and 12-months
- ¹H-MRS study (Phillips Achieva 3T MRI; PRESS sequence with short TE; Figure 1) at baseline and 12-months

Outcomes and Analyses

1. NC change (global z-score averaging age-adjusted z-scores for each test) across study period
 2. Change in cerebral metabolites (LC-model) in FWM and BG from baseline to 12-months
- Mixed effects regression model with fixed effects: arm, time, arm*time interaction and subject as random effect
 - Repeated measures ANOVA with same fixed effects

Table 1. Sample Demographic and Clinical Characteristics

	MA arm (n=9)	Control arm (n=5)	p
Age (years)	52.2 (3.7)	60.0 (9.4)	.14
Gender (M:F)	9:0	5:0	1.0
Ethnicity			1.0
Caucasian	9	5	
Other	0	0	
Education (years)	12.3 (2.8)	11.6 (2.3)	.61
Premorbid IQ (NART errors)	102.2 (16.3)	104.4 (18.9)	.83
Nadir CD4	150 (220)	310 (339)	.35
Current CD4			
Baseline	499 (489.5)	980 (493)	.06
12 month	484 (270.5)	829 (574.5)	.14

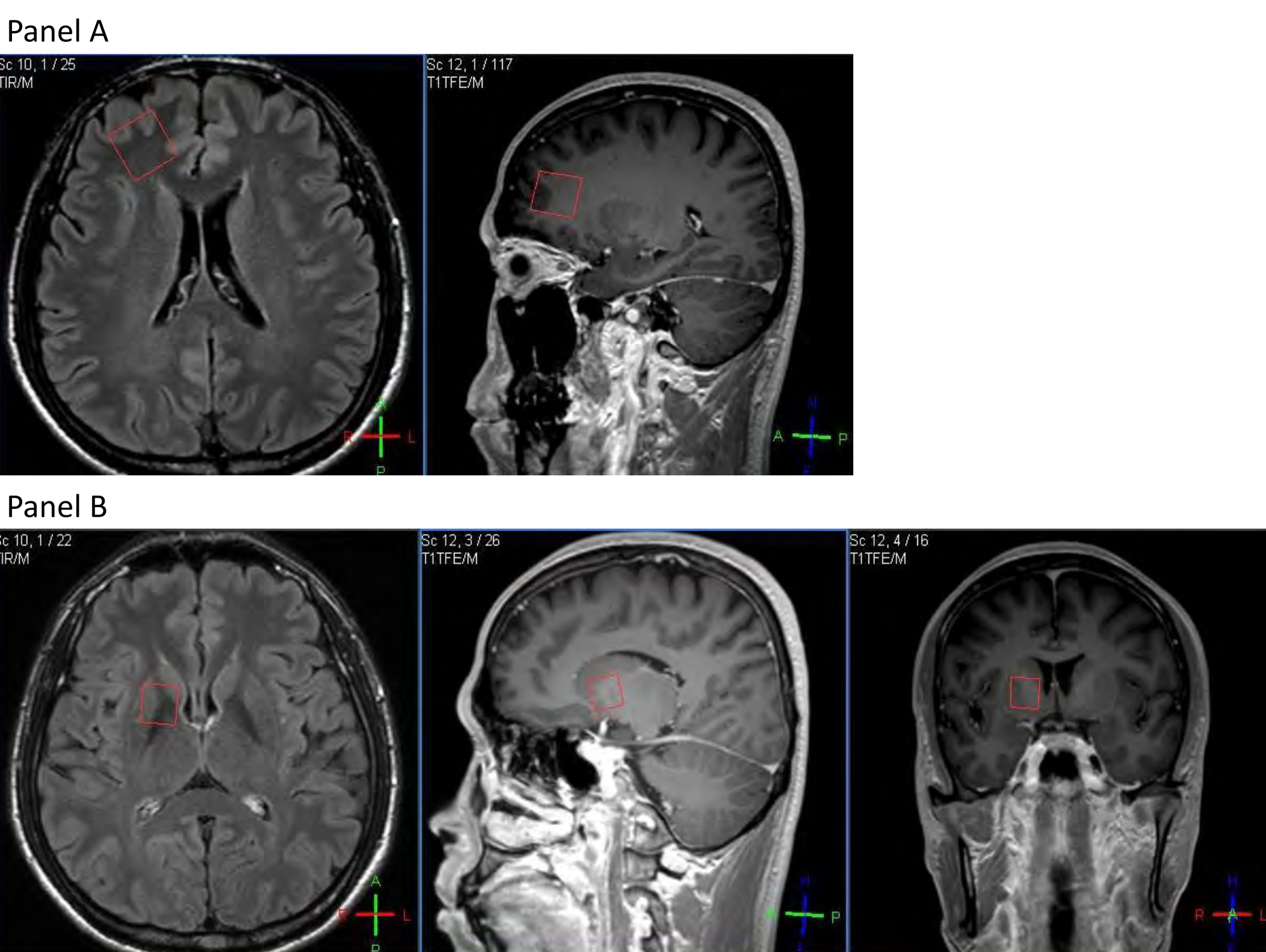


Figure 1. Voxel positioning for acquisition of FWM (size=20mm³; no. acquisitions=128; Panel A) and BG (size=15mm³; no. acquisitions=64; Panel B) spectra via PRESS (TE32/TR2000msec; 2.0kHz bandwidth).

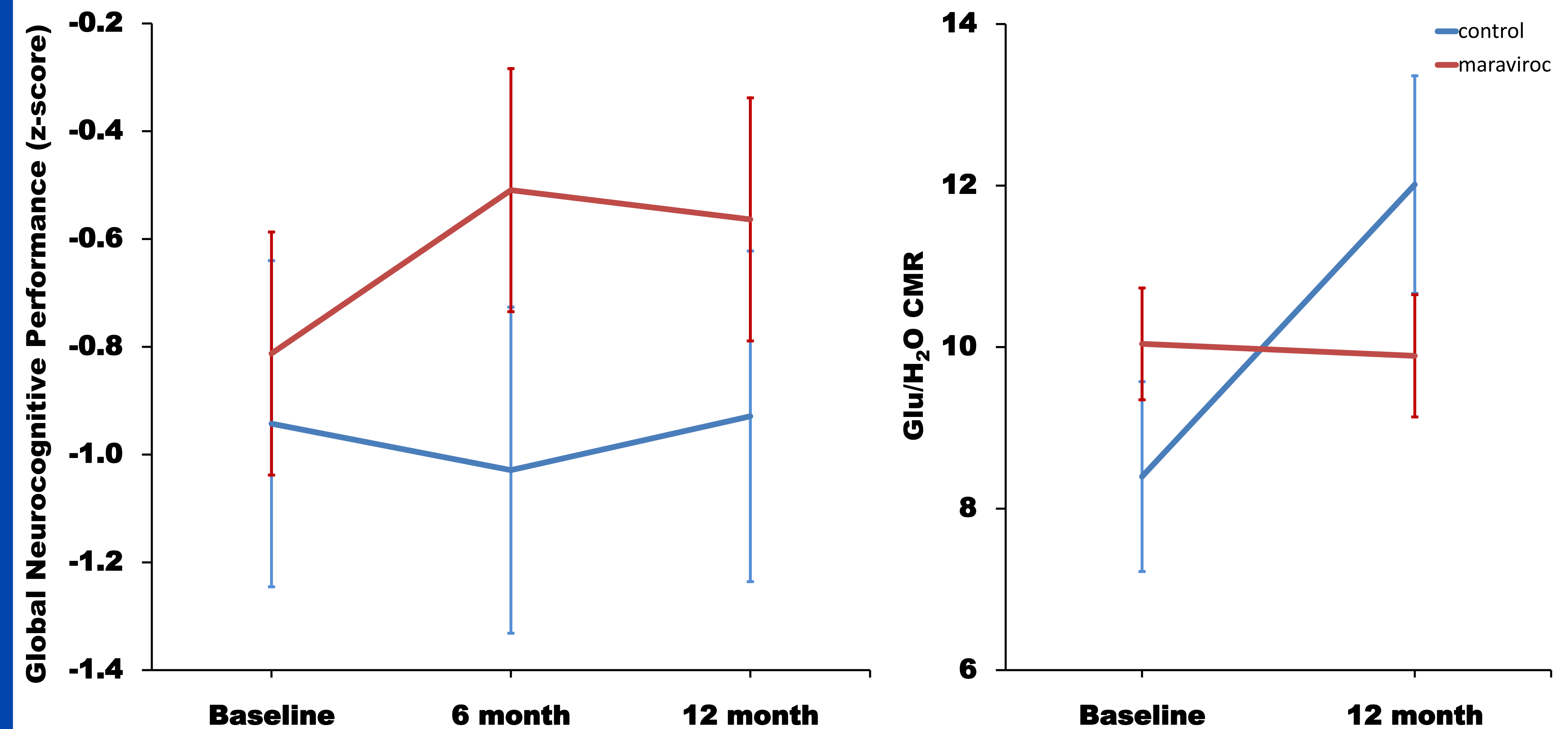


Figure 2. (Left) Mean (SE) global NC performance over time based on model least mean squares and adjusted for attrition (arm*time interaction p<.05; 6-months: d=.77, 90%CI=-.19,1.71; 12-months: d=.55, 90%CI=-.47,1.55) (41 data-points; MA: n=27, control: n=14); (Right) Mean (SE) change in glutamate concentration over time (arm*time interaction: Std β=-.40, 90%CI=-.04,-.78; p<.07) (data-points: MA: n=9 pairs; control: n=4 pairs)

Results

- Clinically relevant effect sizes detected in favour of improved global NC in MA arm over time, with a large effect at 6-months and moderate effect at 12-months
- Glutamate concentration (a marker of excitotoxicity) in BG was stable in MA arm but increased in control arm at 12-months

Table 2. Tests included in brief NC battery.

Cognitive Domain	Tests
Speed of information processing	CogState™ Detection Task
	CogState™ Identification Task
	Trail Making Test – Part A
	Trail-Making Test – Part B
	WAIS-III Digit-Symbol Coding
Attention/working memory	CogState™ 1-Back Task
	CogState™ 2-Back Task
	Grooved Pegboard – Dominant Hand
Motor Functioning	Grooved Pegboard – Non-Dominant Hand
Verbal Learning	CogState™ International Shopping List Task: Learning
Verbal Memory	CogState™ International Shopping List Task: Delayed Recall

Conclusion

- This pilot study provides feasibility, tolerability, proof-of-concept and preliminary evidence for clinically relevant improvement with MA-enhanced cART in virally suppressed HAND patients
- If replicated in a larger study, these findings have important implications for managing HAND by supporting MA enhancement over cautious monitoring of patients over time

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