CNS Outcomes of cART vs. cART plus Maraviroc and Raltegravir Intensification During Acute HIV

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Abstract

Background: Within weeks of HIV infection, HIV RNA is found in cerebrospinal fluid (CSF) with accompanying changes in brain parenchyma by magnetic resonance spectroscopy (MRS) supporting theories of early CNS seeding with virus. Intensification of cART with CCR5 and integrase inhibitors is strategized to limit HIV reservoirs when instituted early after HIV infection. The impact of cART intensification on CNS outcomes, when instituted during the earliest stages of infection is not known. We investigated change in inflammatory markers using MRS and CSF cytokines among subjects randomized to cART (efavirenz (EFV), tenofovir (TFV), emtricitabine (FTC), n=25) vs. cART+ (cART + raltegravir (RAL) and maraviroc (MVC)).

Methods: 62 acute HIV subjects (31 cART and 31 cART+) underwent MRS for N-acetyl aspartate (NAA), choline (CHO), myoinositol (MI), and glutamate/glutamine (Glx) at basal ganglia (BG), parietal gray matter (PG), frontal white matter (FW), and frontal gray matter (FG) during acute HIV (Fiebig stage I-IV) then at 12 and 24 weeks after cART vs. cART+ randomization. Subjects intolerant to EFV (n=3) or with resistance (n-=1) in the cART arm were switched to RAL whereas EFV was discontinued for those intolerant (n=5) or resistant (n=1) in the cART+ arm. CSF was sampled for HIV RNA, IL-6, IP-10, MCP-1 and neopterin at baseline and 24 weeks after randomization. Comparisons employed regression models across visits for MRS and comparison of baseline to last sampling for MRS and $\log_{10}$ transformed cytokines.

Results: Enrollment occurred a mean (range) of 17 (4-40) days after estimated HIV exposure. Mean (SD) age was 29 (7.3) years and 94% were male with no differences by arm. 45 cases underwent MRS at baseline (25 cART and 20 cART+) and 43 at week 24 (25 cART and 18 cART+). 31 had baseline CSF sampling (14 cART and 17 cART+) and 27 at week 24 (13 cART and 14 cART+). Increased NAA in PG (p=.03), FW (p=.005), and FG (p=.04) was observed over 24 weeks and decreased CHO in BG (p=.0005), but no differences were observed by arm. Mean cytokine levels declined in nearly all subjects. Baseline cytokine levels were associated with degree of change in each measure; however, treatment arm was not.

Conclusions: Intensification of cART with CCR5 and integrase inhibitors was not associated with differences in CSF cytokines or MRS markers of inflammation during acute HIV. Improved CNS markers of increased NAA, decreased tCHO and decreased inflammatory cytokines were noted in both groups, regardless of intensification.

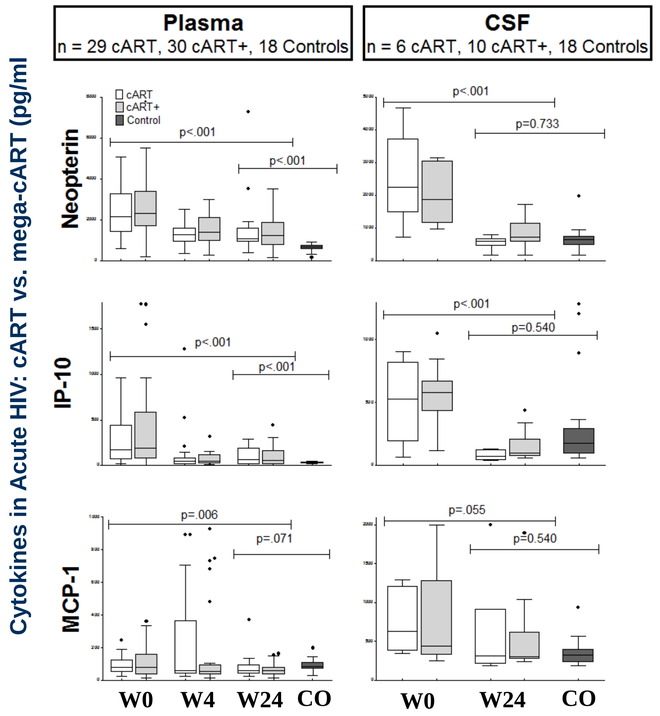

Figure 1: Boxplots* of change in plasma and CSF cytokines in cART (white) vs. cART+ (grey) compared to controls (black). We examined neopterin, IP-10, MCP-1 and IL-6. IL-6 is not displayed because it was constitutively undetectable (controls) and seldom elevated in HIV, particularly in plasma.

Main Findings:

- Neopterin and IP-10 remain elevated in plasma after 24 weeks on ART.
- CSF cytokines decrease with treatment and appear similar to controls, though these findings are underpowered.
- No differences in cytokine response is noted by arm

*Tukey whisker plots shown using established guidelines: Q3+(1.5*IQR) < Outlier < Q1-(1.5*IQR)

Participants

	cART	cART+	Control
Enrollment	31	31	18
Age, mean (SD) years	31 (7)	28 (7)	34 (7)
Education, mean (SD) years	17 (3.3)	16 (3.6)	11.3 (4.6)
Gender, n (%) male	29 (94)	29 (94)	9 (50)
Baseline CD4 T-lymphocyte count, median (IQR)	352 (264)	392 (213)	--
Change in CD4 T-lymphocyte count, median (IQR)	256 (225)	206 (207)	--
Baseline Plasma viral load, mean log10 (SD)	5.5 (1.08)	5.5 (1.19)	--
Drop in Plasma viral load, mean log10 (SD)	3.78 (1.06)	3.71 (1.34)	--
Baseline CSF viral load, mean log10 (SD)	3.0 (1.31)	3.4 (1.07)	--
Drop in CSF Viral Load, mean log10 (SD)	1.99 (1.48)	1.79 (.9)	--

Table 1: Demographic/clinical comparison by arm. No significant difference between HIV+ arms was found.

Neuropsychological Assessment

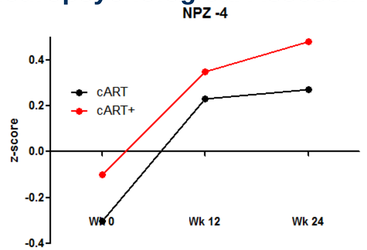

Figure 2: A comparison of neuropsychological test performance by arm. Mean (SD) change in Thai-normalized z-scores from pre-cART to 24 weeks post-cART. Scores do not differ by arm when adjusted for baseline value.

	cART	Mega-cART	p-value
Color Trails I	.98 (1.50)	1.26 (1.21)	0.169
Color Trails II	.60 (.62)	.33 (1.29)	0.379
Grooved Pegboard	.19 (1.16)	.35 (.61)	0.430
Trail Making A	.53 (1.35)	.63 (.91)	0.474
NPZ-4	.58 (.65)	.64 (.62)	0.534

MRS Progression in Acute HIV

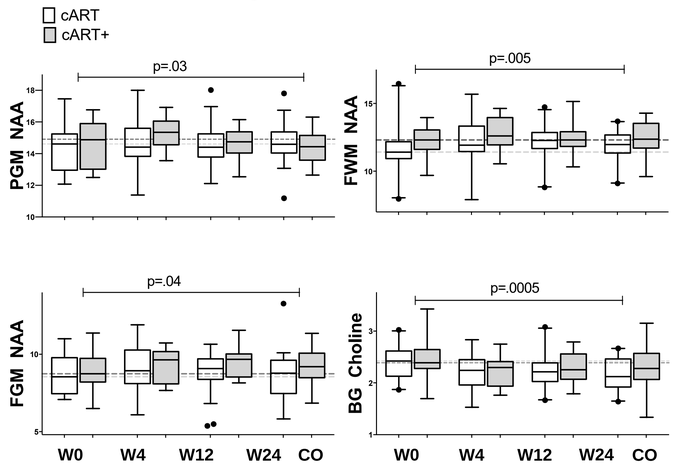

Figure 3: **A comparison of MRS by arm**. Among all metabolites, only NAA and CHO had statistically significant changes over time and only among voxels presented; no difference was noted by study arm.

Conclusions

- Early treatment with cART during acute HIV markedly decreases inflammation as measured by cytokines in plasma and CSF as well as MR spectroscopy.
- Neuropsychological testing performance improves with cART during acute HIV; we identify no difference by arm
- We identified no difference by arm in cytokine and MRS outcomes at 24 weeks.
- At 24 weeks post-cART, evidence of monocyte related inflammation remains as noted by elevated plasma neopterin (p<.001), and IP-10 (p<.001).

Acknowledgements

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