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

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on behalf of the SEARCH 010/RV254 Study Group

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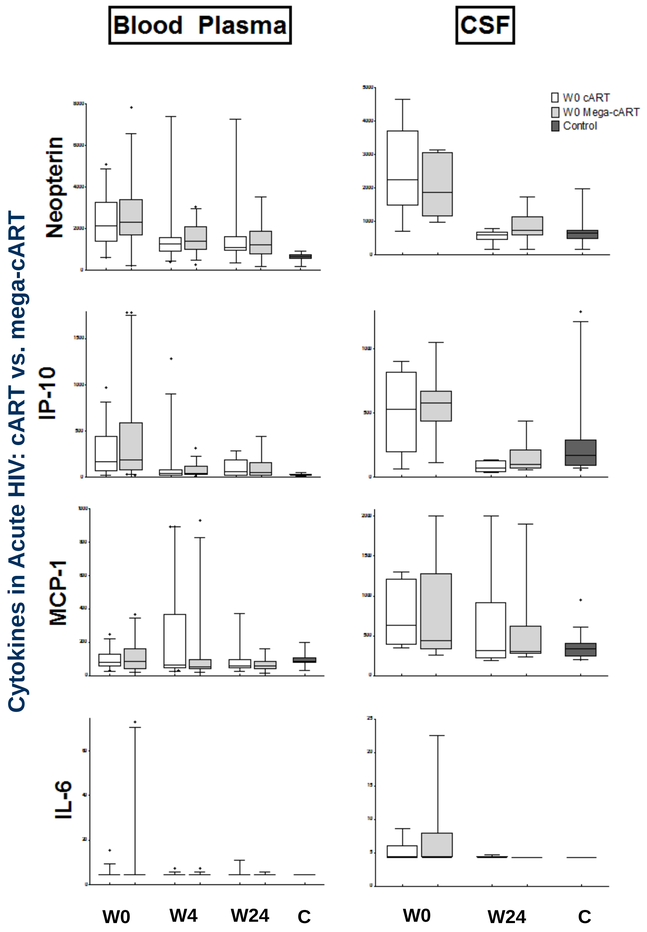
Abstract

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.



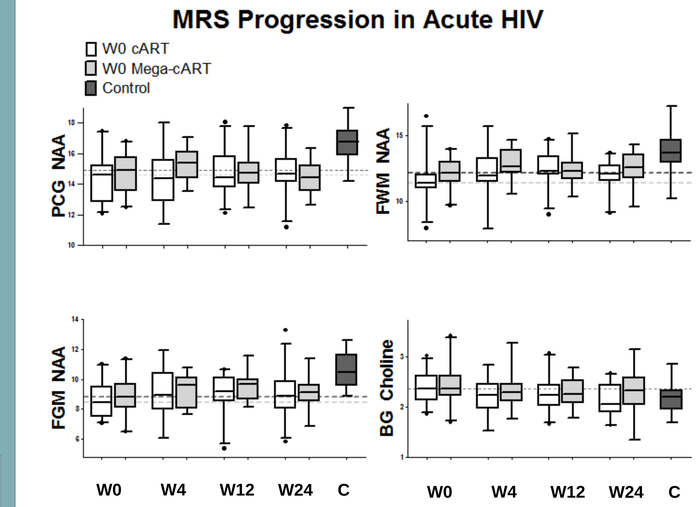
Participants

Demographic/Clinical Comparison	cART	Mega-cART	p-value
Age, mean (SD) years	30.5 (7.3)	27.9 (7.1)	0.18
Education, mean (SD) years	16.9 (3.31)	16.1 3.57	0.36
Gender, n (%) male	29 (94)	29 (94)	1.0
Baseline CD4 T-lymphocyte count, median (IQR)			
Change in CD4 T-lymphocyte count, median (IQR)	256 (225)	206 (207)	0.879
Drop in Plasma viral load, mean log10 (SD)	3.78 (1.06)	3.71 (1.34)	0.8006
Drop in CSF Viral Load, mean log10 (SD)	1.99 (1.48)	1.79 (.9)	0.3916

Neuropsychological Assessment

NP Testing W0 v. W24 Comparison	cART	Mega-cART	p-value
Change zColor Trails I, mean (SD)	.98 (1.50)	1.26 (1.21)	0.5121
Change zColor Trails II, mean (SD)	.60 (.62)	.33 (1.29)	0.3928
Change zGrooved Pegboard, mean (SD)	.19 (1.16)	.35 (.61)	0.5882
Change zTrails-Making A, mean (SD)	.53 (1.35)	.63 (.91)	0.7796
Change in NPZ Global, mean (SD)	.58 (.65)	.64 (.62)	0.7428

Table 1: A comparison of performance on an abridged neuropsychological assessment broken down by arm and task.



References

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