DO AGE AND LONG-TERM HIV INFECTION CONTROL AFFECT BRAIN METABOLITES?

C. Rae[1], L. A. Cysique[2], J. M. Lee[3], T. Lane[4], K. Moffat[5], A. Carr[6], and B. J. Brew[7]

[1]Neurosciences Research Australia, University of New South Wales, Sydney, NSW, Australia, [2]Brain Sciences, University of New South Wales, Sydney, NSW, Australia, [3]Neurosciences Research Australia, University of New South Wales, Sydney, Australia, [4]Psychology, Macquarie University, Sydney, Australia, [5]Medical Imaging, St. Vincent's Hospital, Sydney, Australia, [6]Immunology and Infectious Diseases, St. Vincent's Hospital, Sydney, Australia, [7]Neurology, St. Vincent's Hospital, Sydney, Australia

Purpose: HIV epidemic is characterized by an aging population; age-related diseases such as cardio-vascular diseases and a chronic form of HIV-associated neurocognitive disorder (HAND) that is dissociated from traditional HIV disease biomarkers. The current study was designed to address three questions: 1. Is chronic HIV-infection and age >45y associated with an increased risk of neurocognitive disorders and brain metabolic abnormalities? 2. If HIV-infected (HIV+) individuals show any brain metabolic abnormalities, does this involve traditionally affected regions of the brain (subcortical areas and frontal white matter) or does it also extend to regions usually affected in pathological aging (e.g., posterior cingulate cortex)? 3. Are brain metabolic abnormalities associated with cardio-vascular risks?

Outline of Content: We present the baseline results of a prospective study investigating the effects of HIV and aging on brain functions in a cohort of clinically stable HIV+ individuals aged 45+. Sixty-one HIV+ individuals were enrolled with historically advanced disease (nadir CD4 lymphocyte count $\leq$ 350 cells/µl; and current stable cART $\geq$ 6 months. The median HIV duration was 19 years. Sixteen HIV-negative (HIV-) aged 45+ were enrolled as controls (see Table 1). All participants had no neurological disorder, brain trauma, psychiatric disorder on the psychotic axis or substance use disorder. In the HIV+ group, 97% had virus controlled (HIV RNA <50 copies/ml) in the plasma and 96% in the cerebrospinal fluid among the patients who had a lumbar puncture (N=28).

Table 1: Demographic characteristics for the HIV- and HIV+ groups

	HIV-	HIV+	p
N	16	61	-
Age	54.5 ± 6.4	56.8 ± 7.4	.22
Education	15.7 ± 2.1	14.1 ± 3.0	.02
Gender (% males)	12%	3%	.13
Estimated Pre-morbid IQ	116 ± 7	113 ± 10	.10
Depressive complaints	0%	18%	.06
Neurocognitive impairment	0.0%	23%	<.02

Figure 1: 2.0cm³ voxel placement in the posterior cingulate area

Figure 2: AMARES fit of ¹H MRS from posterior cingulate

Neurocognitive exam: All participants underwent a standard neuropsychological evaluation to assess attention/working memory; verbal learning and memory, verbal generativity; fine-motor coordination; mental flexibility and speed of information processing. Neuropsychological scores were converted into demographically corrected T-scores using published normative data and deficit scores to compute overall impairment rate and domain specific performance scores (Heaton et al., 2004; Carey et al., 2004). Mood status was assessed with a standard instrument (Beck Depression Inventory-II).

Single voxel ¹-H MRS: Spectra were acquired from the right frontal white matter (FWM), posterior cingulate cortex (PCC) and right caudate nucleus area (Caud) at 3T (Philips Achieva) using an eight-channel head coil. Scanning parameters: CHESS-suppressed PRESS; TE 31ms, TR 2000 ms; 2.0 cm³ voxel size except for the caudate area which was 1.5 cm³; 128 scans for caudate and 64 for all other ROIs. Spectra were analyzed using jMRUI, version 3.0). All spectra were pre-processed with baseline correction, and water removal (HLSVD). AMARES was used to fit relative concentrations of *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), *myo*-inositol (mI), and glutamine/glutamate (Glx). All metabolites were expressed as ratios over unsuppressed H_2O signal or Cr.

Data analysis: Brain metabolite concentrations were compared between HIV- and HIV+ group using t-test (α = 0.05). Cohen's d effect sizes (ES) were computed and ES >.40 were included in subsequent analyzes. Univariate regression models with a non-linear term (interaction between age * HIV status) were used to test whether there was an amplified age effect in older HIV+ individuals on overall neurocognitive performance and on brain metabolites with ES>.40. Standard linear regression models were built to test biomarkers of HIV (nadir CD4; Blood current CD4 & CD8 counts, HIV duration, adjusted for current cART duration) and cardiovascular risk (Framingham score and radial artery stiffness derived from peripheral radial artery tonometry). Statistical analyses were conducted using JMP 8 (SAS, Inc).
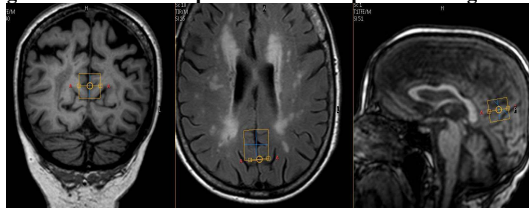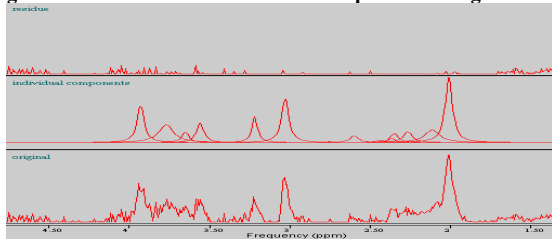
Summary:

- A greater HIV duration was predictive of reduced Caud NAA (β=-.34, SE = .0008; *p*<.03).
- A lower nadir CD4 was associated with lower NAA concentration in the PCC (β=.38, se= .0009; p<.03).
- A higher Framingham cardio-vascular risks score was associated with reduced NAA in the PCC (β=-.27, se = .42; p<.03).
- No direct association between metabolites and neurocognitive impairment in the HIV+ group, but a higher Framingham score was associated with worse fine motor-coordination performance (r=-.46; p<.003).
- Higher depressive complaints were associated with reduced Caud NAA (p<.04).
- There was no age * HIV status interaction (p>.30) on both neuropsychological impairment and abnormal metabolite concentrations.

Chronic HIV brain infection is marked by altered neuronal density/function, reduced metabolism (Glx) and abnormal mI/Cr. We here identify involvement of the posterior cingulated cortex, a region known to be affected by aging. The duration of HIV infection and history of immune impairment relate strongly to metabolic outcomes. Together with cardiovascular risk, these factors are increasingly impacting the etiology of brain injury in persons with HIV infection.

Figure 3: In HIV+ individuals, NAA concentration was reduced (p<.02) in the PCC (d=.55) and Caud (d=.57); mIo/Cr was increased (p<.02; d=.59) and Glx is decreased (p=.12; d=.44) in the PCC. mI/Cr comprised lower Cr/H_2O and higher mI/H_2O in HIV+. Reduced PCC NAA was associated with lower PCC Glx (p<.0001) and higher mI/Cr (p<.03).