ALTERED BRAIN FRONTAL WHITE MATTER CELLULAR ENERGY IN CHRONIC HIV INFECTION

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Disclosures

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HIV-associated Neurocognitive Disorders (HAND)

	Acquired Impairment in ≥2 Cognitive Abilities	Interferes with Daily Functioning	
Asymptomatic Neurocognitive Impairment (ANI)	YES	NO	No Dementia
Mild Neurocognitive Disorder (MND)	YES	MILD	No Dementia
HIV-Associated Dementia (HAD)	MARKED	MARKED	Dementia

Fracati HAND Diagnostic Criteria., Neurology 2007

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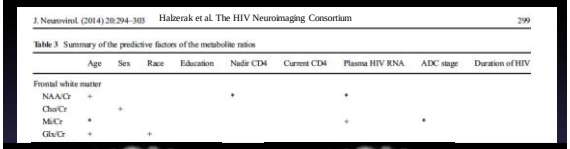
Background

Long-term brain neurochemical changes are not clearly understood in HIV-infected adults who are aging and are otherwise clinically stable.



J. Neurovirol. (2014) 20:294–303 Halzerak et al. The HIV Neuroimaging Consortium 299

Table 3 Summary of the predictive factors of the metabolite ratios

	Age	Sex	Race	Education	Nadir CD4	Current CD4	Plasma HIV RNA	ADC stage	Duration of HIV
Frontal white matter									
NAA/Cr	+				*		*		
Cho/Cr		+							
Mi/Cr	*						+	*	
Glx/Cr	+		+						

Cysique et al., 2013 Plos One

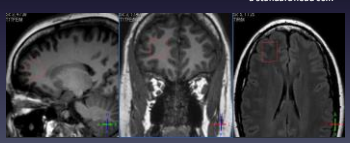
Single Voxel Proton Magnetic Resonance Spectroscopy (SVS) was acquired at baseline and 18 months follow-up

- Single voxel 1H MRS Data acquisition was conducted on 3T scanner at St. Vincent's Hospital Imaging department under supervision of KM.
- All spectroscopy data will be acquired using the Philips SMART Brain software allowing accurate repeatable positioning of the voxel

Our protocol

- PRESS
- TE = 30
- TR = 2000
- CHESS
- 2nd ordershimming
- Ratio to water

MR scans are acquired on a Philips 3T Achieva Quasar Dual imaging system (Philips Medical Systems) with a standard head coil.

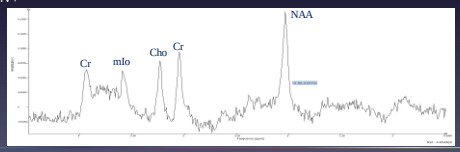


Voxel size: 2cm³ Frontal white matter

- *Prior to analysis*
  - QA Visual inspection in frequency domain while fitting is processed within the time domain
- SVS Fitting
  - Removal of H_2O
  - Quantitation using AMARES
  - H_2O reference fitting
  - Amplitudes are recorded.

Frontal white matter spectra

HIV+



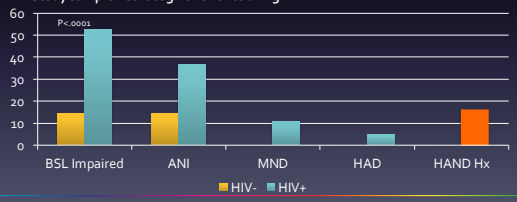
Plausible physiological significance of main brain metabolites for HIV-related brain injury

Metabolites	Chemical Shift Normal concentration range	Physiological significance
***N*-Acetyl-Aspartate** **NAA**	2.03 ppm 7.8 mM (6.5-9.7)	Neuronal and axonal integrity/density
Choline **Cho**	3.2 ppm 1.3 mM (0.8-1.6)	Membrane turnover Acute neuroinflammation
Creatine ***Cr***	3.0 ppm 4.5 mM (3.4-5.5)	Cellular energetic marker
***Myo*-Inositol** **mIo**	3.56 ppm (short TE only) 3.8 mM (2.2-6.8)	Glial cell marker Chronic neuroinflammation

Baseline Study Samples' Characteristics

Study sample demographics	HIV-	HIV+	p
N (*all males*)	42	84	-
Age (years)	53.5	54.6	.36
Education level (years)	15	14	.03
White English-Australian background	95%	99%	.26

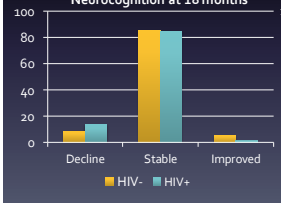
Study sample neurocognitive functioning



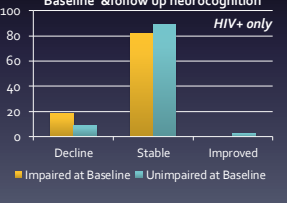
Follow-up Study Samples' Characteristics

HIV+ only	No Follow-up	Follow-up	p
N	11	73	-
Age (years)	52	55	.20
Education level (years)	13.3	14.1	.43
Baseline Impaired	54.5%	52.5%	.88
Always undetectable during study	54.5%	92%	.006

Neurocognition at 18 months



Baseline &follow up neurocognition *HIV+ only*



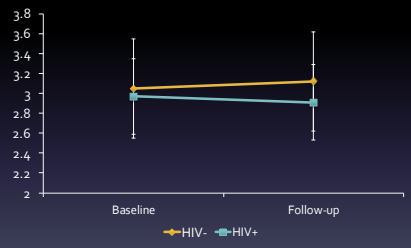
HIV+ sample clinical characteristics

Baseline	
Median Nadir CD_4	180 [IQR:42-284]
Median Current CD_4	560 [IQR:362-723]
Plasma HIVRNA <50 cp/mL (Undetectable)	97.2%
CSF HIVRNA <50 cp/mL (Undetectable)	97.2% (35/36)
Median HIV duration (years)	19 [IQR:13-15]
Historical AIDS%	33%
Only Nadir < 200	28%
Median Current cART duration	28 [IQR:18-56]

Follow up	
Median Current CD_4	638 [IQR:438-832] *
New ADIs	-
Plasma HIVRNA <50 cp/mL (Undetectable)	94.5%
Always undetectable	91.8%

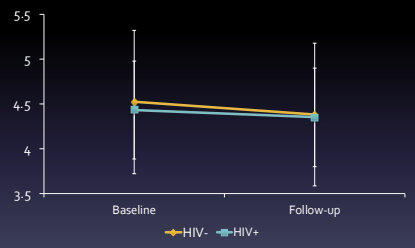
* p<.0001 difference with baseline

FWM *Creatine*: Cellular energy marker



Group effect: P<.002

FWM *NAA*: neuronal integrity marker



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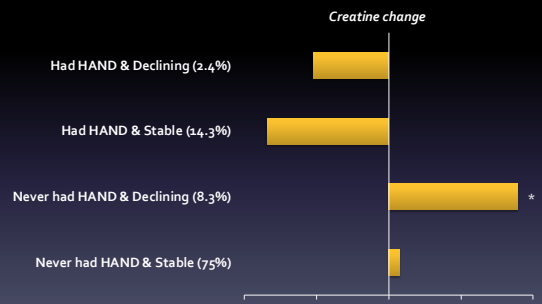
A History of HAND and neurocognitive decline yield distinct brain cellular energy profiles



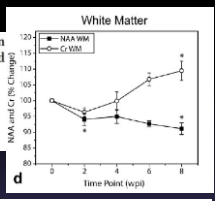
* Associated with increased in CSF neopterin

Creatine alterations in the NeuroAIDS literature

Brain Creatine Elevation and *N*-Acetylaspartate Reduction Indicates Neuronal Dysfunction in the Setting of Enhanced Glial Energy Metabolism in a Macaque Model of NeuroAIDS

Magnetic Resonance in Medicine 66:625–634 (2011)

Eva-Maria Ratai,[1] Lakshmanan Annamalai,[2†] Tricia Burdo,[3] Chan-Gyu Joo,[1] Jeffrey P. Bombardier,[1] Robert Fell,[1] Reza Hakimelahi,[1] Julian He,[1] Margaret R. Lentz,[1] Jennifer Campbell,[3] Elizabeth Curran,[2] Ilkan F. Halpern,[4] Eliezer Masliah,[5] Susan. V. Westmoreland,[2] Kenneth C. Williams,[2] and R. Gilberto Gonzalez[1]*



Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy

Assawin Gongvatana · Jaroslaw Harezlak · Steven Buchthal · Eric Daar · Giovanni Schifitto · Thomas Campbell · Michael Taylor · Elyse Singer · Jeffrey Algers · Jianhui Zhong · Mark Brown · Deborah McMahon · Yuen T. So · Deming Mi · Robert Heaton · Kevin Robertson · Constantin Yiannoutsos · Ronald A. Cohen · Bradford Navia · HIV Neuroimaging Consortium

		Rate	*p* value
Absolute concentrations			
FWM	NAA	−2.95 %	*0.0009*
	Cr	−0.43 %	0.4787
	Cho	−2.61 %	*0.0001*
	MI	−1.38 %	0.1194
	Glx	−1.90 %	0.0516
MFC	NAA	−1.89 %	*0.0007*
	Cr	−1.84 %	*0.0059*

Conclusions

- Longer-term studies of neurochemical changes in chronic HIV infection are needed to understand the prognostic of Creatine changes at 18 months
- The majority of aging HIV+ persons on stable cART are doing well
- But a non-negligible minority have ongoing disease with two main patterns:
  - Abnormal cellular energy that may reflect initial steps of slow neurodegenerative processes
  - Ongoing HIV-related injury that is associated with low-grade chronic neuroinflammation
- *We only presented data in the frontal white matter, therefore these results are partial as we also scanned the Posterior Cingulate Cortex and the Caudate area*

Acknowledgements

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