LONGITUDINAL STUDY OF NEUROCOGNITIVE DISORDERS AND ASSOCIATED STRUCTURAL BRAIN CHANGES IN ADOLESCENT HIV

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BACKGROUND

Neurocognitive disorders (NCD) despite ART are well known in perinatally-infected HIV+ adolescents (PHIV) but there are few data on longitudinal changes in NCD and brain structure in PHIV over time.

METHODS

Within this sub-study of the Cape Town Adolescent Antiretroviral Cohort, PHIV on ART >6m completed baseline and 3-year follow-up assessments including a comprehensive neurocognitive battery assessing function in 10 domains. We applied the youth HIV-associated NCD diagnostic criteria to classify each as having either a major NCD, a minor NCD, or no impairment. Diffusion tensor imaging and structural brain magnetic resonance imaging was done to determine fractional anisotropy (FA), mean diffusivity (MD), grey and white matter volumes, cortical thickness and cortical surface area. In analysis we examined changes over the 3-year period in NCD and neurostructural measures in PHIV compared to age- and sex-matched HIV- controls.

Table 1: Demographic and clinical parameters of children with HIV (n = 122) at baseline (9 -11 yo) and 3-year follow-up (12-15 yo)

Variable	Baseline mean (SD)	Follow-up mean (SD)	Statistic	P-value
Age	10.4	13.11	T = 3.90	< 0.001
Sex (Male/Female)	60/62	60/62	N/A	N/A
CD4 (cells/mm^3)	934.21 (495.02)	980.23 (540.23)	T = 0.99	0.16
Viral load (median, copies/ml)	40	40	N/A	N/A
Number of virally unsuppressed (%)	20 (16,4 %)	17 (13,9%)	T = 0.43	0.63

Table 2: Significant differences in white matter microstructure between HIV+ adolescents (n=122) and healthy controls (n=37) at 3-year follow-up compared to baseline (p < 0.05; FDR-corrected)

White matter measurement	Post-hoc direction of change	Anatomical region	F-value	P-value
Axial diffusivity	Follow-up > Baseline HIV > CON	RH Anterior limb of internal capsule	8.087	0.005
		LH Posterior limb of internal capsule	6.138	0.014
	Baseline > Follow-up CON > HIV	RH Cingulum	4.819	0.029
Mean diffusivity	Baseline > Follow-up HIV > CON	RH Cerebral peduncle	4.781	0.030
		RH Anterior limb of internal capsule	5.779	0.017
		RH Cingulum	4.980	0.027
Radial diffusivity	Baseline > Follow-up HIV > CON	RH Cingulum	4.769	0.030

Neurocognitive disorders and Brain macro-and microstructural alterations increase over 3 year follow-up among perinatally-infected HIV+ adolescents, despite sustained viral suppression

RESULTS

Overall 122 PHIV ages 9-12 years (mean CD4 cell count 953 cells/μL and 85.3% VL<50 copies/mL) and 37 age-matched HIV- controls completed baseline and 3-year follow-up assessments.

Majority of participants had sustained viral suppression over the 3 year period.

At baseline 83,6% were virally suppressed, and 86,1% at 3 year follow-up.

48% PHIV had a NCD at baseline and 60% at follow-up

NCD diagnosis was stable over time in 60 (49%) of participants, 22 (18%) improved NCD status and 40 (33%) deteriorated.

At baseline, PHIV with major NCD showed the highest whole brain MD (p=.007); at follow-up whole brain grey (p=.004) and white matter volumes (p=.032) were lowest in PHIV, with whole brain MD remaining highest in PHIV with a major NCD (p=.02). Higher MD is suggestive of inflammation and myelin loss. In addition significant regional brain changes were observed at follow-up compared to baseline in PHIV vs controls. Structural changes over time were observed mainly in cortical surface area of the bilateral orbitofrontal, anterior cingulate, medial orbitofrontal, middle frontal, superior temporal, transverse temporal gyri and insula (all p<.05). White matter microstructural changes over time were observed in the internal capsule, cerebral peduncle and the cingulum (all p<.05).

CONCLUSIONS

NCD and brain structural alterations in PHIV increased over the 3 years of follow-up compared to HIV- controls, despite sustained viral suppression in >80% of participants. Studying the participants who improved vs deteriorated over time may provide insight into future interventions for NCD in PHIV.

Table 3: Significant differences in cortical thickness, surface area and subcortical volume between HIV+ adolescents (n=122) and healthy controls (n=37) at 3-year follow-up compared to baseline (p < 0.05; FDR-corrected)

Structural measurement	Post-hoc direction of change	Anatomical region	F-value	P-value
Subcortical volume	Follow-up > Baseline HIV > CON	LH Accumbens	11.595	0.001
Cortical thickness	Baseline > Follow-up CON > HIV	RH Postcentral gyrus	5.303	0.022
Surface area	Baseline > Follow-up CON > HIV	LH Lateral orbitofrontal	4.708	0.031
		RH Lateral orbitofrontal	7.017	0.009
		LH Medial orbitofrontal	8.593	0.004
		LH Rostral anterior cingulate	4.522	0.034
		LH Rostral anterior cingulate	3.983	0.047
		RH Rostral middle frontal	4.150	0.043
		RH Superior temporal	4.366	0.038
		RH Transverse temporal	5.106	0.025
	Follow-up > Baseline CON > HIV	RH Insula	6.977	0.009

Abbreviations: **HIV:** HIV+ adolescents; **CON:** Healthy controls; **LH:** Left hemisphere; **RH:** Right hemisphere

Table 4: Differences in whole brain structure based on neurocognitive disorder classification in PHIV+ adolescents at baseline age (9-11 years old) FROM CTAAC

Structural measurement	Controls (n=37)	HIV+ No neurocognitive impairment (n=63)	HIV+ Minor cognitive disorder (n=55)	HIV+ Major neurocognitive disorder (n=4)	F	P
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Grey matter volume	655925 (80150)	657165 (58934)	638901 (97352)	612506 (67317)	0.596	0.619
White matter volume	383486 (52976)	379709 (45733)	367959 (64452)	338471 (61880)	0.863	0.463
Mean cortical thickness	2.64 (0.13)	2.68 (0.12)	2.63 (0.14)	2.67 (0.13)	1.197	0.315
Mean FA	0.302 (0.22)	0.289 (0.28)	0.296 (0.03)	0.277 (0.05)	1.101	0.353
Mean MD	8.50E-4 (5.3E-5)	8.58E-4 (4.2E-5)	8.61E-4 (4.7E-5)	9.96E-4 (1.6E-5)	4.342	0.007*

*Results were significant at p < 0.05. Covariates of no interest included age, sex and ethnicity.

Table 5: Differences in whole brain structure based on neurocognitive disorder classification in HIV+ adolescents at follow-up age (12-15 years old) FROM CTAAC

Structural measurement	Controls (n=37)	HIV+ No neurocognitive impairment (n=48)	HIV+ Minor cognitive disorder (n=67)	HIV+ Major neurocognitive disorder (n=7)	F	P
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Grey matter volume	643463 (81835)	598184 (98876)	613222 (103730)	603981 (91917)	3.379	0.004*
White matter volume	414895 (65160)	376536 (86675)	380517 (87216)	373752 (75226)	2.401	0.032*
Mean cortical thickness	2.56 (0.11)	2.56 (0.14)	2.54 (0.15)	2.56 (0.12)	0.320	0.925
Mean FA	0.432 (0.01)	0.426 (0.02)	0.423 (0.02)	0.414 (0.02)	1.665	0.137
Mean MD	7.82E-4 (2.9E-5)	7.94E-4 (3.2E-5)	7.96E-4 (2.8E-5)	8.27E-4 (3.4E-5)	2.648	0.020*

*Results were significant at p < 0.05. Covariates of no interest included age, sex and ethnicity.

ADDITIONAL INFORMATION

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