Supplementary Materials

eTable 1. Cognitive function in PHIV adolescents compared to controls

	PHIV	Controls				
	Mean (95%CI)	Mean (95%CI)	Coefficient (95%CI)	*p*	Adjusted coefficient (95%CI)	*p*
Intelligence Quotient	81.0 (76.8-85.1)	91.8 (87.1-96.6)	-11 (-17 to -4.6)	**<.0001**		
Processing speed	99.8 (94.8-105)	104 (99.5-108)	-3.91 (-10 to 2.5)	.225	2.58 (-3.0 to 8.2)	.362
Working memory	8.34 (7.38-9.30)	10.0 (9.0-11.1)	-1.68 (-3.0 to -0.33)	**.016**	-0.53 (-1.82 to 0.76)	.413
Executive function	-0.72 (-1.15 to -0.28)	0.00 (-0.29 to 0.28)	-0.72 (-1.22 to -0.22)	**.006**	-0.38 (-0.88 to 0.12)	.138
Learning ability	-0.44 (-1.0 to 0.13)	0.11 (-0.16 to 0.38)	-0.55 (-1.16 to 0.06)	.077	-0.15 (-0.79 to 0.49)	.633
Visual-motor function	39 (35-43)	44 (41-47)	-5.2 (-10 to -0.3)	**.040**	-0.70 (-5.3 to 3.9)	.761

The 2nd and 3rd column display the scores of specific domains of PHIV adolescents and matched controls, respectively. Lower scores represent worse performance. The results of cognitive function were standardized into Wechsler norm or scale scores, using age and sex adjusted Dutch standards. Executive function and learning ability are presented in *Z* scores based on mean of the control group within this cohort as reference values were unavailable. Unadjusted coefficient is a univariable linear regression between groups. Adjusted coefficients are multivariable linear regression adjusted for IQ. For IQ and processing speed the Wechsler Intelligence Scale for Children (WISC-III) [1] and Wechsler Adult Intelligence Scale (WAIS-III) [2] were used. The Rey Auditory Verbal Learning Test was used to assess learning ability [3]. The Beery-Buktenica Developmental Test of Visual-Motor Integretaion was used to assess visual motor function [4]. The Trail Making Test was used to assess executive function [5]. Abbreviations: CI = confidence interval

eTable 2. Comparison of regional brain volumes, white matter damage and cerebral blood flow between adopted and not-adopted participants

	Adopted (n = 28)	Not adopted (n=45)				
	mean ± SD or n(%)	mean ± SD or n(%)	beta	95%CI	*p*	*ES*
Volumetry (l)						
GM	0.707 ± 0.06	0.686 ± 0.06	0.02	-0.03 – 0.07	.405	0.38
WM	0.441 ± 0.06	0.480 ± 0.04	-0.005	-0.05 – 0.04	.813	0.73
CSF	0.192 ± 0.04	0.231 ± 0.05	-0.01	-0.06 – 0.02	.569	0.65
WM macrostructure						
WMH (any)	15 (54%)	19 (42%)			.422	
WMH volume (mm^3) log	4.1 ± 1.6	4.2 ± 1.3	0.187	-1.59 – 1.96	.831	0.08
WM microstructure						
FA	0.38 ± 0.01	0.41 ± 0.01	-0.02	-0.02 to -0.003	.125	2.07
MD (10^{-3} mm^2/s)	0.82 ± 0.02	0.78 ± 0.02	0.01	-0.004 – 0.03	.140	1.93
RD (10^{-3} mm^2/s)	0.64 ± 0.03	0.60 ± 0.02	0.01	-0.005 – 0.03	.147	1.99
AD (10^{-3} mm^2/s)	1.18 ± 0.02	1.16 ± 0.02	0.01	-0.007 – 0.03	.248	1.33
Cerebral blood flow (ratios)						
GM	0.98 ± 0.19	0.96 ± 0.23	-0.07	-0.27 – 0.14	.514	0.07
WM	0.22 ± 0.06	0.22 ± 0.07	-0.02	-0.09 – 0.04	.452	0.06
Caudate nucleus	0.94 ± 0.19	0.90 ± 0.24	0.01	-0.20 – 0.23	.913	0.17
Putamen	0.82 ± 0.17	0.82 ± 0.22	-0.02	-0.22 – 0.17	.817	0.03
Thalamus	0.83 ± 0.18	0.87 ± 0.25	-0.03	-0.25 – 0.19	.773	0.17

Values in the second and third column are either mean ± standard deviation or number(percentage). WMH (any present) was compared with Fisher's exact test. Differences were assessed by performing multivariable linear regression. All models were adjusted for age, sex and HIV status. WMH is defined as presence of any WMH lesion. WMH volume (mm^3) was logarithmically transformed to approach a normal distribution and the regression model was additionally adjusted for WM volume. MD, RD and AD were multiplied with 10^3 for interpretation purposes of coefficients. Cerebral blood flow are ratios of individual CBF of ROI (in mL/100g/min) to mean GM blood flow in controls (in mL/100g/min). Effect size thresholds: |d| (0.01) = very small, |d| (0.2) = small, |d| (0.5) = medium, |d| (0.8) = large Abbreviations: AD = axial diffusivity; ES = effect size; FA = fractional anisotropy; GM = gray matter; MD = mean diffusivity; RD = radial diffusivity; SD = standard deviation; WM = white matter; WMH = white matter hyperintensities

eTable 3A. Association analyses between MRI parameters and PHIV characteristics

	GM volume (l)		WM volume (l)		CSF volume (l)		WMH burden (any present)		WMH volume (ml)		AD (10^{-3} mm^2/s)	
	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*
HIV VL zenith log (copies/ml)	0.01 (-0.01 – 0.02)	.453	0.001 (-0.02 – 0.02)	.883	-0.01 (-0.02 – 0.01)	.489	-0.02 (-0.20 – 0.16)	.790	0.061 (-0.11 – 0.23)	.440	-0.001 (-0.008 – 0.006)	.837
$CD4^+$ T-cell *Z* score nadir	0.03 (0.002 – 0.07)	.039	0.03 (-0.003 – 0.06)	.070	-0.01 (-0.05 – 0.02)	.453	0.02 (-0.34 – 0.38)	.904	0.16 (-0.15 – 0.47)	.291	-0.01 (-0.02 – 0.01)	.391
CDC HIV category												
B	-0.05 (-0.11 – 0.02)	.127	-0.05 (-0.12 – 0.01)	.105	0.003 (-0.06 – 0.07)	.934	-0.22 (-0.90 – 0.44)	.486	-0.01 (-0.62 – 0.59)	.960	-0.0004 (-0.03 – 0.03)	.971
C	0.01 (-0.05 – 0.08)	.669	-0.01 (-0.08 – 0.05)	.696	0.01 (-0.06 – 0.08)	.767	-0.08 (-0.76 – 0.60)	.809	-0.14 (-0.73 – 0.44)	.604	0.004 (-0.02 – 0.03)	.717
Current cART use (yes/no)	0.02 (-0.10 – 0.13)	.764	0.05 (-0.06 – 0.16)	.322	0.06 (-0.04 – 0.17)	.229	0.73 (-0.34 – 1.79)	.172	NA*		0.003 (-0.04 – 0.04)	.883
Undetectable VL at assessment (yes/no)	-0.04 (-0.12 – 0.05)	.386	-0.02 (-0.1 – 0.06)	.584	-0.06 (-0.14 – 0.01)	.110	-0.62 (-1.40 – 0.15)	.111	NA*		-0.009 (-0.04 – 0.02)	.508
Age at treatment initiation (years)	-0.001 (-0.01 – 0.004)	.822	0.002 (-0.003 – 0.01)	.374	-0.002 (-0.007 – 0.004)	.592	-0.02 (-0.08 – 0.04)	.534	0.06 (0.13 – 0.1)	.017	-0.023 (-0.23 – 0.18)	.817
Duration of treatment (years)	0.001 (-0.01 – 0.01)	.822	-0.002 (-0.01 – 0.003)	.375	0.002 (-0.004 – 0.007)	.593	0.02 (-0.04 – 0.08)	.536	-0.06 (-0.1 – -0.01)	.018	0.0002 (-0.002 – 0.002)	.826

Association analyses using multivariable linear regression. All models were adjusted for age and sex. HIV viral load zenith was logarithmically transformed to approach a normal distribution. AD was multiplied with 10^5 to better interpretation of coefficients. *NA = not able to calculate this analysis due to all participants in this subset on treatment and undetectable viral load; CDC = Center for Disease Control & Prevention; B = moderate symptoms; C = severe symptoms or (brain) AIDS.

Abbreviations: cART = combination antiretroviral therapy; FA = fractional anisotropy; GM = gray matter; MD = mean diffusivity; RD = radial diffusivity; VL = viral load

eTable 3B. Association analyses between MRI parameters and PHIV characteristics

	GM CBF		WM CBF		Caudate nucleus		Putamen		Thalamus	
	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*
HIV VL zenith log (copies/ml)	0.02 (-0.06 – 0.1)	.624	-0.002 (-0.03 – 0.02)	.827	0.03 (-0.04 – 0.12)	.310	0.02 (-0.05 – 0.09)	.509	0.02 (-0.06 – 0.11)	.617
$CD4^+$ T-cell *Z* score nadir	-0.03 (-0.19 – 0.12)	.657	0.01 (-0.03 – 0.06)	.600	-0.01 (-0.16 – 0.15)	.911	-0.02 (-0.15 – 0.12)	.821	-0.11 (-0.27 – 0.05)	.168
CDC HIV category										
B	0.13 (-0.12 – 0.38)	.303	-0.02 (-0.10 – 0.06)	.563	0.08 (-0.17 – 0.34)	.508	0.08 (-0.14 – 0.30)	.469	0.19 (-0.07 – 0.46)	.150
C	0.02 (-0.24 – 0.28)	.873	-0.04 (-0.12 – 0.04)	.309	0.02 (-0.25 – 0.28)	.899	0.01 (-0.23 – 0.24)	.957	0.18 (-0.10 – 0.46)	.202
Current cART use	-0.32 (-0.78 – 0.14)	.169	-0.05 (-0.18 – 0.09)	.479	-0.28 (-0.73 – 0.18)	.224	-0.25 (-0.66 – 0.17)	.233	-0.24 (-0.73 – 0.25)	.322
Undetectable VL at assessment	0.14 (-0.20 – 0.48)	.406	0.03 (-0.07 – 0.13)	.501	-0.28 (-0.73 – 0.18)	.224	0.15 (-0.15 – 0.45)	.313	0.08 (-0.29 – 0.44)	.671
Age at treatment initiation (years)	-0.01 (-0.04 – 0.02)	.436	-0.0002 (-0.007 – 0.007)	.956	-0.01 (-0.02 – 0.02)	.363	-0.008 (-0.03 – 0.02)	.509	-0.02 (-0.04 – 0.01)	.246
Duration of treatment (years)	0.01 (-0.02 – 0.04)	.440	-0.0002 (-0.01 – 0.01)	.958	0.01 (-0.01 – 0.04)	.364	0.007 (-0.02 – 0.03)	.512	0.02 (-0.01 – 0.04)	.250

Association analyses using multivariable linear regression. All models were adjusted for age and sex. HIV viral load zenith was logarithmically transformed to approach a normal distribution. AD was multiplied with 10^5 to better interpretation of coefficients. CDC = Center for Disease Control & Prevention; B = moderate symptoms; C = severe symptoms or (brain) AIDS. Abbreviations: cART = combination antiretroviral therapy; FA = fractional anisotropy; GM = gray matter; MD = mean diffusivity; RD = radial diffusivity; VL = viral load

eTable 4. Additional analysis in participants with WMH

	PHIV	Controls	
			p
WMH count category			.906
1-4	7	8	
5-9	6	5	
10+	5	3	
Total WMH count	6 (2.5 – 11)	4 (2 – 8.3)	.477

WMH count is the number of WMH lesions per participants. Differences between groups in WMH count categories were assessed with Fisher's exact test. Total WMH count is depicted with median and interquartile range. Group difference was assessed with Mann-Whitney U test.

Abbreviations: WMH = white matter hyperintensities

eTable 5. Associations between DTI parameters and cognitive profiles in PHIV adolescents

	FA		MD		RD	
	beta (95%CI)	*p*	beta (95%CI)	*p*	beta (95%CI)	*p*
IQ	0.01 (-0.37 – 0.39)	.272	0.39 (-2.4 – 3.2)	.777	0.28 (-2.2 – 2.7)	.814
Processing speed	0.07 (-0.35 – 0.49)	.727	-0.25 (-3.36 – 2.85)	.867	-3.34 (-29.9 – 23.2)	.797
Working memory	0.05 (-0.04 – 0.13)	.261	-0.32 (-0.94 – 0.29)	.287	-2.7 (-8.0 – 2.52)	.292
Executive function	0.02 (-0.04 – 0.08)	.463	-0.07 (-0.51 – 0.37)	.751	-0.82 (-4.61 – 2.95)	.654
Learning ability	0.04 (-0.01 – 0.10)	.130	-0.33 (-0.73 – 0.07)	.104	-2.70 (-6.15 – 0.75)	.119
Visual motor function	0.01 (-0.31 – 0.33)	.942	0.57 (-1.81 – 2.94)	.625	3.0 (-17 – 23)	.763

Multivariable linear regression models were adjusted for age and sex. All cognitive profiles were used as outcome variables.

Values of FA were multiplied with 10^2 and MD and RD with 10^5 for better interpretation of coefficients.

Abbreviations: FA = fractional anisotropy, MD = mean diffusivity; PHIV = perinatally acquired HIV; RD = radial diffusivity

References

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