Brain Differences in Adolescents Living With Perinatally Acquired HIV Compared to Adoption Status Match Controls: A Cross-Sectional Study

Author(s):
Jason G. van Genderen, MD 1; Cecilia Chia 1; Malon Van den Hoof, MD, PhD 1; Henk J.M.M. Mutsaerts, MD, PhD 2; Liesbeth Reneman, MD, PhD 3; Dasja Pajkrt, MD, PhD 1; Anouk Schrantee, MSc, PhD 3

Corresponding Author:
Jason G. van Genderen, j.g.vangenderen@amsterdamumc.nl

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Affiliation Information for All Authors: 1. Department of Pediatric Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, location Academic Medical Center, Amsterdam, the Netherlands; 2. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location VU Medical Center, University of Amsterdam, Amsterdam, the Netherlands; 3. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Equal Author Contribution:

Contributions:
Jason G. van Genderen: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Cecilia Chia: Drafting/revision of the manuscript for content, including medical writing for content
Malon Van den Hof: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Henk J.M.M. Mutsaerts: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Liesbeth Reneman: Drafting/revision of the manuscript for content, including medical writing for content
Dasja Pajkrt: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Anouk Schrantee: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions: Supervision

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Abstract

Background and Objectives Despite effective combination antiretroviral therapy (cART), adolescents with perinatally acquired HIV (PHIV) exhibit cognitive impairment, of which structural changes could be the underlying pathophysiological mechanism. Prior MRI studies found lower brain volumes, more white matter (WM) hyperintensities (WMH) volume, lower WM integrity, and

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differences in cerebral blood flow (CBF). However, these findings may be confounded by adoption status, as the large portion PHIV adolescents have been adopted. Adoption has been associated with malnutrition and neglect which in turn may have affected brain development. We investigated the long-term effects of PHIV on the brain, while minimizing the confounding effect of adoption status.

**Methods** We determined whole brain gray matter (GM) and WM volume with 3D T1-weighted scans; total WMH volume with fluid-attenuated inversion recovery (FLAIR); CBF in the following regions of interest (ROIs): WM, GM and subcortical GM with arterial spin labeling (ASL); and whole brain WM microstructural markers: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) with diffusion tensor imaging (DTI) in cART treated PHIV adolescents visiting our outpatient clinic in Amsterdam and controls matched for age, sex, ethnic origin, socio-economic status, and adoption status. We assessed differences in neuroimaging parameters between PHIV adolescents and controls using linear regression models adjusted for age and sex and applied multiple comparisons correction.

**Results** 35 PHIV adolescents and 38 controls were included with a median age (years) of 14.9 (IQR: 10.7-18.5) and 15.6 (IQR:11.1-17.6), respectively with a similar rate of adoption. We found a lower overall FA (beta = -0.012; \( p<0.014, -2.4\%) \), higher MD (beta = 0.014, \( p = 0.014, 1.3\%) \) and higher RD (beta = 0.02, \( p = 0.014, 3.3\%) \) in PHIV adolescents vs. adoption-matched controls, but no differences in AD. We found comparable GM, WM and WMH volume, and CBF in ROIs between PHIV adolescents and controls. We did not find an association between cognitive profiles and WM microstructural markers in PHIV adolescents.

**Discussion** Irrespective of adoption status, PHIV adolescents exhibited subtle lower WM integrity. Our findings may point towards early-acquired WM microstructural alterations associated with HIV.

**Introduction**

Human Immunodeficiency Virus (HIV) is known for its neurotropic properties.\(^1\) Despite effective combination antiretroviral therapy (cART), children and adolescents with perinatally acquired HIV...
(PHIV) still experience neurological complications. These findings suggest structural brain changes or brain damage associated with HIV. The pathophysiological mechanisms underlying this cerebral damage are yet to be fully elucidated, however it is hypothesized to include multifactorial effects, such as lasting effects of damage acquired during untreated perinatal HIV infection, HIV-associated neuroinflammation, and toxicity associated with cART. The introduction of cART led to a substantial decrease in the incidence of severe neurological complications such as HIV-associated encephalopathy. Yet evidence suggests that despite cART, PHIV adolescents still exhibit a higher prevalence of cognitive impairment compared to uninfected peers, including lower IQ and poorer executive function.

Magnetic resonance imaging (MRI) biomarkers are sensitive in detecting early HIV-related brain changes. For example, a large study found lower gray matter (GM) and white matter (WM) volume in PHIV children compared to healthy controls. In addition, WM damage can be investigated by determining WM hyperintensities (WMH) typically assessed using fluid-attenuated inversion recovery (FLAIR) MRI sequence. Current evidence concerning WMH volume in PHIV children on cART is scarce and contrasting: one study reported a higher volume of WMH, whereas most studies found no differences compared to controls in volume or presence. In adults, evidence suggests that a positive HIV status is associated with higher WMH volume as compared to healthy adults, which in turn is associated with cognitive impairment. To further examine WM microstructure, diffusion tensor imaging (DTI) – which assesses the diffusion of water in WM – can be used. In PHIV children and adolescents, both longitudinal and cross-sectional studies report (persistent) lower whole brain fractional anisotropy (FA) compared to controls, suggesting lower WM integrity.

As WMH are presumed to be part of the small vessel disease spectrum, it is of interest to assess cerebral perfusion as well. This can be investigated non-invasively using arterial spin labeling (ASL) MRI, which measures cerebral blood flow (CBF) using arterial blood water as endogenous tracer. Despite initially higher CBF in putamen and caudate nucleus in PHIV adolescents as compared to matched healthy controls, we reported comparable CBF development over time in PHIV adolescents and matched controls.
While evidence suggests that PHIV children and adolescents manifest subtle brain alterations compared to healthy controls, these studies did not match for, or report differences in, early life characteristics, such as nutrition history or adoption status.8–10,14,16 These factors are important as brain maturation is at a critical stage in early life17 and adoption has been associated with malnutrition and neglect,18 which in turn have been associated with altered brain development.19,20 In the Netherlands, the vast majority of PHIV adolescents has been adopted.21 While minimizing the confounding effect of adoption status – and associated early life characteristics – we compared brain alterations in PHIV adolescents to HIV negative status controls, matched for age, sex, ethnic origin, socio-economic, and adoption status. We hypothesized that, even when controlling for early life characteristics associated with adoption status, PHIV adolescents will still have more brain alterations compared to controls, related to their HIV status.

**Methods**

**Study participants**

We used anonymized data from participants who enrolled in the Neurological, cOgnitive and VIsual performance in perinatally HIV infected ChildrEn (NOVICE) study between February 2017 and July 2018. The NOVICE study is a cohort study investigating the neurological, cognitive and ophthalmological outcomes of PHIV adolescents compared to controls, who were frequency matched for age, sex, ethnic origin, socio-economic status, and additionally for international adoption status.22 PHIV adolescents visiting the outpatient clinic of the Emma Children’s Hospital (Amsterdam) or previously participated in our study were approached for participation. This outpatient clinic is one of four Dutch pediatric HIV centers that PHIV adolescents visit biannually for a check-up. Internationally adopted HIV-negative controls were recruited through two government licensed organizations, for these organizations arrange adoptions from the Sub-Saharan region. The following exclusion criteria were used: current or past neurological or psychiatric disorders not associated with
HIV, a history of traumatic brain injury resulting a loss of consciousness of more than 30 minutes, intracerebral neoplasms and MRI contraindications including metal implants or claustrophobia; the complete criteria for non-inclusion have been previously published in detail.\(^9\)

*Standard Protocol Approvals, Registrations, and Patient Consents*

The Institutional Review Board of the Academic Medical Center, part of the Amsterdam University Medical Center, approved the study with registration number: NL58216.018.016 on 21 October 2016. The NOVICE study is registered at the Dutch Trial Registry (registration number: NL6813). We adhered to the Declaration of Helsinki and obtained written informed consent from all participants older than 12 years and from participants’ parents younger than 18 years of age.

*MRI data acquisition and image processing*

We performed an MRI scan of the brain of all participants using a 3T MRI scanner (Ingenia, Philips, Best, The Netherlands) equipped with a 16-channel phased-array head coil.

3D T1-weighted

We measured brain volumes using sagittal 3D T1-weighted (T1\(_w\)) scans with a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following scanning parameters: echo time (TE) = 3.18 ms, repetition time (TR) = 7.0 ms, field of view (FOV) = 256 × 240 × 180 mm\(^3\), flip angle = 9\(^\circ\), isotropic voxel size = 1 mm\(^3\). Computational Anatomy Toolbox 12 (CAT12) was used to segment GM, WM and cerebrospinal fluid (CSF),\(^{23}\) implemented within the ExploreASL (version 1.2.0) toolbox.\(^{24}\)

3D FLAIR

Sagittal 3D FLAIR scans were obtained using the following parameters: TR/TE = 4,800/356 ms, TI = 1,650 ms, FOV = 250 mm × 250 × 180 mm\(^3\), voxel size = 1.1 × 1.1 × 0.56 mm\(^3\). To determine the presence of any WMH, one investigator (JvG) reviewed and manually segmented all FLAIR scans with supervision of an experienced neuroradiologist (LR) using segmentation software ITK-SNAP version 3.4.0 (Philadelphia, PA and Salt Lake City, UT, USA).\(^{25}\) ITK-SNAP computed the total WMH.
volume after manual segmentation. We excluded scans in which WMH could not be identified due to severe head motion, as defined by the neuroradiologist. To determine the intra-rater reliability, twenty FLAIR scans were randomly selected and rated twice. Intra-rater reliability was assessed using percentual agreement and Cohen’s weighted κ coefficient.

**ASL**

CBF maps were obtained using 2D EPI pseudo-continuous ASL (pCASL) with TE/TR 16/4000 ms, FOV = 240 × 240 mm², voxel size 3 × 3 × 6.6 mm³, 20 axial 6 mm slices with 0.6 mm slice gap, labeling duration = 1650 ms, post labeling delay = 1525–2230 ms, 30 control and label pairs. We used ExploreASL (version 1.2.0) to process ASL images. We chose the following regions of interest (ROIs): cortical GM, WM and subcortical GM regions: caudate nucleus, putamen and thalamus, due to cerebral injury in PHIV children mostly occurring in GM, WM and subcortical regions, and because of the association between subcortical brain volume and cognitive impairment.426 There were no statistically significant hematocrit differences, adjusted for age and sex, between PHIV adolescents and controls (p=.910); hence we assumed the same blood T1 values for quantification in both groups.27 Due to a scanner software upgrade, we used individual CBF ratios to allow methodological correct comparison, in line with our previous publication on CBF in PHIV adolescents.16 We calculated CBF ratios of ROIs by dividing the CBF value of an ROI (in mL/100g/min) by the mean GM CBF of controls (in mL/100g/min). We excluded scans in case of insufficient quality due to head motion or artifacts, which was done in agreement between two investigators (JvG and HJMMM).

**DTI**

In line with our previous analyses, we assessed WM microstructure using the following whole brain parameters: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). We used the following acquisition sequence: spin-echo single-shot echoplanar imaging along 64 directions with b = 1,000 seconds/mm² and 4 averages with b = 0 seconds/mm²; TE/TR = 92/9,476 ms, FOV = 224 x 224 mm², 70 slices and an isotropic voxel size of 2.0 mm³. We used FMRIB Software Library (FSL) 4.1.6 (University of Oxford, Oxford, UK) to analyze the DTI.
We denoised the data and corrected for eddy currents using MRtrix3 and Eddy (FSL), respectively. We replaced outliers defined by head motion equal or more than three standard deviations by Gaussian Process predicted values. Diffusion weighted volumes \((b>0)\) were rigid-body registered to the non-diffusion weighted volume \((b=0)\). Next, Gibbs artifacts were corrected using an in-house Matlab script. We used FSL’s DTIFIT to fit the tensors to the diffusion data to create FA, MD, AD and RD maps. These maps were analyzed using FSL’s Tract-Based Spatial Statistics (TBSS), using the most representative study-specific FA image as target image. A mean FA skeleton, which represented the center of all study-specific common WM tracts, with a threshold of \(p>0.20\) was created after resampling into the common space. To create skeletonized data, FA images of all participants were projected onto the mean FA skeleton. Whole-brain FA, MD, AD and RD values were calculated by averaging the entire WM skeleton for each subject.

**Demographic and HIV related variables**

The following (historical) cART- and HIV related characteristics of the PHIV participants were collected from patient records or provided by the Dutch HIV monitoring foundation: peak HIV viral load (zenith), CD4+ T-cell nadir, cART use, duration of treatment and HIV historical classification.

We defined cART as the use of at least three antiretroviral drugs from a minimum of two drug classes. In all controls we confirmed HIV negative status as reported previously.

**Cognitive function**

A neuropsychologist performed neuropsychological assessments using a test battery adapted to the Dutch language to assess various cognitive domains including intelligence quotient (IQ), processing speed, learning ability, visual-motor function and executive function. For IQ and processing speed the Wechsler Intelligence Scale for Children (WISC-III) and Wechsler Adult Intelligence Scale (WAIS-III) were used. The Rey Auditory Verbal Learning Test was used to assess learning ability. The Beery-
Buktenica Developmental Test of Visual-Motor Integration was used to assess visual motor function. The Trail Making Test was used to assess executive function. \(^{22}\)

**Statistical analyses**

Statistical analyses were performed using R version 3.5.1 (R Core team, Vienna, Austria),\(^{33}\) and a value of \(p < 0.05\) was considered statistically significant. We compared demographic variables between PHIV adolescents and controls using the Mann-Whitney \(U\) test (non-normally distributed) or Students’ \(t\) test (normally distributed) for continuous data and Fisher’s exact test for categorical data. We assessed differences in whole brain GM and WM volume, WM microstructural differences: FA, MD, AD and RD, WMH volume and CBF in GM, WM, caudate nucleus, putamen and thalamus between PHIV adolescents and controls using linear regression models adjusted for age and sex. We also assessed these differences between adopted and non-adopted participants using linear regression models adjusted for age, sex and HIV status. We additionally adjusted the model for WMH volume for WM volume. We assessed differences in IQ, processing speed, learning ability, visual motor function and executive function between PHIV adolescents and controls using linear regression models while adjusting for age, sex, and IQ (the latter was added in the model for all domains except IQ). In PHIV adolescents, we assessed associations between MRI parameters and the following HIV related characteristics: peak HIV viral load (zenith), CD4\(^+\) T-cell nadir, cART use, duration of treatment and HIV historical classification, as well as cognitive profiles. To control for multiple comparison, we applied Benjamini-Hochberg adjustments,\(^{34}\) using the `p.adjust` function in R. We calculated the effect size magnitude using Cohen’s \(d\) with R package `effsize` and considered the following thresholds: \(|d| (0.01) = \text{very small},|d| (0.2) = \text{small},|d| (0.5) = \text{medium},|d| (0.8) = \text{large}.\(^{35}\)

**Data Availability**

Anonymized data not published within this article will be made available by request from any qualified investigator.

**Results**
We approached 53 PHIV adolescents and 52 controls. We included 35 PHIV adolescents and 38 matched HIV negative status controls with a median age at enrollment of 14.9 years (IQR: 10.7-18.5) and 15.6 (IQR: 11.1-17.6), respectively. Reasons for non-inclusion were inability to reach or no interest in participation (13 PHIV and 14 controls), 2 PHIV were excluded based on criteria and 3 PHIV relocated. In both groups we had similar numbers of MRIs with good quality for assessment. There were no differences in baseline characteristics between PHIV adolescents and matched controls at enrollment (Table 1). 21 PHIV adolescents and 23 controls were previously enrolled in another cross-sectional study conducted between 2012 and 2014. The data presented here were obtained in a separate study four to five years later between 2017 and 2018, so there is no overlap in the data presented here with our previous study.

MRI parameters and cognitive profiles in PHIV adolescents
PHIV adolescents had significant lower FA, and higher MD and RD compared to matched controls with a medium effect size (Figure 1 and Table 2). We found no differences in GM, WM and WMH volume between PHIV adolescents and matched controls. There were no differences in WMH count between groups (eTable 4). Intra-rater reliability of WMH segmentation was 90% with a Cohen’s weighted $\kappa$ of 0.83. CBF in all ROIs was also comparable between groups. We additionally found no differences in all MRI parameters between adopted and non-adopted participants (eTable 2). PHIV adolescents had a significant lower IQ (81 vs. 92, $p < 0.001$) compared to controls (eTable 1).

Factors associated with MRI parameters
We found no associations between WM microstructural markers and historical HIV-associated characteristics (Table 3). We found that a higher age at cART initiation was associated with a higher WMH volume and a longer duration of cART was associated with a lower WMH volume (eTable 3A).

No significant associations were found between other MRI parameters and HIV characteristics (eTable 3A and 3B). We also did not find an association between IQ and other cognitive profiles and WM microstructural markers in PHIV adolescents (Table 3 and eTable 5).
**Discussion**

In this study, we investigated brain MRI biomarker differences between PHIV adolescents and controls, while controlling for adoption status. We found that PHIV adolescents had lower FA and a higher MD and RD than controls, suggesting lower WM integrity in PHIV adolescents, irrespective of adoption status. In contrast, we did not find group differences in GM, WM and WMH volume, or in CBF.

Our diffusion MRI findings suggest lower WM integrity in PHIV adolescents, and are in line with previous studies in younger PHIV children and adolescents with similar age. Our results add to the prior literature by demonstrating that these differences are unlikely to be due to adoption status. This is important as adopted children might endure psychosocial deprivation and malnutrition, both affecting WM integrity in children, and previous studies did not match for or report differences in adoption or associated early life characteristics. WM maturation is at a critical stage in the first years of life, thus coinciding with diagnosis and treatment initiation of perinatal HIV infection. Our findings might implicate that these differences in WM integrity could originate from that critical early life period and reflect the inability of the brain to undo the lasting effects of early WM damage caused by HIV itself. This is substantiated by another study in PHIV children demonstrated that starting cART as early as possible may reduce HIV-associated WM damage. Alternatively, lower WM integrity in our participants could hint at previous neurotoxic effects of cART. However, we did not find an association between WM integrity and cART characteristics. Moreover, our previous longitudinal DTI assessment suggests that despite potential early damage, there is no progressive decrease of WM integrity in PHIV adolescents while on effective treatment. Taken together, our studies do not suggest that cART induced changes in WM integrity. FA is a very sensitive but not very specific biomarker of WM integrity, thus the underlying pathophysiological mechanisms remain unknown. On the other hand, higher MD and RD – in the presence of abnormal FA – have previously been associated with edema or necrosis and higher demyelination, respectively.
However, if these processes underlie our findings, we suspect them to be subtle, otherwise we would have detected larger WMH volume and/or more severe clinical symptoms, which is not the case in the PHIV adolescents in our study.

While PHIV had lower IQ, we did not find an association between WM integrity and IQ, in contrast to a previous study in children without neurological disease. This could be a result of the fact that we used whole brain averages of DTI parameters instead of investigating specific WM fiber bundles, or it might be that the reduced WM integrity in our participants was too small to affect cognitive function. Alternatively, the lack of association could be due to the narrow IQ range in our sample. In sum, the exact pathophysiological mechanisms underlying the lower WM integrity and its clinical consequences remain to be completely elucidated.

We found no difference in presence of any WMH between PHIV adolescents and controls, which is in contrast with an earlier study from a partially overlapping cohort performed at a different timepoint. Reasons for this difference are difficult to pinpoint, but could include controlling for adoption status, sampling variation or cohort differences, such as lower CDC-B and -C classification in PHIV adolescents in our study (15/35 vs. 22/35). Our current finding of comparable WMH presence is in line with a previous study investigating PHIV children in Zambia. Yet, compared to that study, we found a higher mean WMH presence, which could be explained by the use of a higher MRI field strength in our study (3T vs 1.5T) resulting in a higher detection sensitivity of WMH. In adults with HIV, there is contrasting evidence as to whether HIV is an independent contributor to WMH. Surprisingly, we found a high percentage of controls with WMH (57%), which could reflect a better matched control group and indicate that WMH in PHIV adolescents might not solely be a complication of a perinatal HIV infection. Moreover, WMH presence itself does not provide information about the extent of WMH. In this study, the relatively high presence of any WMH is accompanied with low absolute WMH volume in PHIV adolescents (mean: 0.09 ml) and controls (mean: 0.05 ml) which probably impedes the clinical consequences at this moment. The lack of clinical consequences of WMH in children is also reported in studies investigating WMH presence in
healthy cohorts\textsuperscript{43} or pediatric patients with morbidities other than HIV (reported WMH presence up to 30\%).\textsuperscript{44,45} All studies had different MRI scan parameters, which may have affected WMH detection sensitivity. Altogether, follow-up is warranted to further understand the association between HIV and WMH, and its relevance in PHIV adolescents could still emerge, as WMH have been associated with cognitive impairment at older age.\textsuperscript{46} Lastly, we explored the relation between cART and WMH. We found that older age at cART initiation or shorter duration of cART was associated with higher WMH volume. While HIV status was not associated with a significant higher WMH volume in our cohort, these associations could however implicate that WMH in PHIV adolescents partially originated from the period prior to treatment initiation. Therefore, starting cART as early as possible could mitigate the presence of higher WMH volume in at least a portion of PHIV patients.

We found comparable CBF between groups, in contrast to our previous cross-sectional study, which demonstrated higher CBF in WM and subcortical regions.\textsuperscript{47} This difference could be inherent to the younger age in the previous cross-sectional assessment leading to interindividual physiological effects in adolescents, as CBF swiftly declines in different brain regions during adolescence.\textsuperscript{48} This is underscored by our longitudinal CBF assessment in which we found comparable changes in CBF between groups after a follow-up of 4.6 years.\textsuperscript{16} Another explanation could be the variability in CBF, as CBF highly dynamic and could be influenced by many factors.\textsuperscript{49}

This study has some limitations. Our small sample size reduced the generalizability of results and possibly hampered the detection of subtle associations. The cross-sectional design does not allow us to investigate causal effects or assess disease progression. Moreover, we assumed that adoption status may be associated with early life adversity, such as malnutrition. However, we do not have medical records of children containing details prior to adoption, therefore we do not know if and to what extent the participants were affected. Although we did not assess HIV clades as possible confounding factor to our results, another study showed WM microstructural damage to occur irrespective of HIV clade.\textsuperscript{50}

\textbf{Conclusion}

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Despite effective treatment, PHIV adolescents exhibit lower WM integrity compared to matched controls, regardless of international adoption status. These results underscore the neuropathogenicity of HIV, or to lesser extent, its treatment. Although, GM, WM and WMH volume and CBF in ROIs did not differ between groups, these findings warrant follow-up as PHIV adolescents – frequently affected by cognitive impairment – grow into adulthood and experience lifelong disease and treatment.

**Figure 1.**

Scatter dot plots display WM integrity variables for PHIV adolescents (blue) and HIV-negative matched controls (red). An asterisk (*) indicates a significant difference, ns = not significant. Unit for MD, RD and AD = mm^2/s. The colored horizontal line indicates the mean value and the black error bars indicate ± one standard deviation. Abbreviations: AD = axial diffusivity; FA = fractional anisotropy; HIV = human immunodeficiency virus; MD = mean diffusivity; RD = radial diffusivity.
### Table 1. Participants’ characteristics at enrollment

<table>
<thead>
<tr>
<th></th>
<th>PHIV (n = 35)</th>
<th>CONTROLS (n=38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>35 14.9 (10.7-18.5)</td>
<td>38 15.6 (11.1-17.6)</td>
<td>.855*</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>35 18 (51%)</td>
<td>38 22 (58%)</td>
<td>.642*</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>35 30 (86%)</td>
<td>38 29 (76%)</td>
<td>.102*</td>
</tr>
<tr>
<td>Other</td>
<td>5 (14%)</td>
<td>9 (24%)</td>
<td></td>
</tr>
<tr>
<td><strong>International adoption</strong></td>
<td>35 16 (46%)</td>
<td>38 12 (32%)</td>
<td>.238*</td>
</tr>
<tr>
<td><strong>Age at adoption (years)</strong></td>
<td>16 3.3 (2.5-4.8)</td>
<td>12 2.9 (1.2-5.2)</td>
<td>.745*</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>33 1.59 (1.46-1.68)</td>
<td>38 1.63 (1.52-1.73)</td>
<td>.450*</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>33 50 (36-64)</td>
<td>38 56 (41-67)</td>
<td>.284*</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>33 19.0 (17.6-21.9)</td>
<td>38 20.2 (18.5-23.4)</td>
<td>.131*</td>
</tr>
<tr>
<td><strong>Hematocrit (l/l)</strong></td>
<td>34 0.40 (0.39-0.45)</td>
<td>38 0.41 (0.39-0.43)</td>
<td>.910*</td>
</tr>
<tr>
<td><strong>Age at HIV diagnosis (years)</strong></td>
<td>35 2.1 (0.6-3.8)</td>
<td>38 2.1 (0.6-3.8)</td>
<td></td>
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<tr>
<td><strong>CDC HIV category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>20 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>9 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nadir CD4⁺ T-cell Z score</strong></td>
<td>33 -0.85 (0.56)</td>
<td>38 -0.9 (0.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Zenith HIV viral load (10¹⁰log)</strong></td>
<td>32 5.3 (4.7-5.7)</td>
<td>38 5.2 (4.9-5.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at cART initiation</strong></td>
<td>32 2.8 (1.1-5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of cART</strong></td>
<td>32 9.0 (7.0-15.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Undetectable viral load at assessment</strong></td>
<td>35 33 (94%)</td>
<td>38 33 (94%)</td>
<td></td>
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<tr>
<td><strong>MRI of good quality for assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1w</td>
<td>35 30 (86%)</td>
<td>38 29 (76%)</td>
<td>.380*</td>
</tr>
<tr>
<td>DTI</td>
<td>35 27 (77%)</td>
<td>38 29 (76%)</td>
<td>.999*</td>
</tr>
<tr>
<td>FLAIR</td>
<td>35 31 (89%)</td>
<td>38 28 (74%)</td>
<td>.141*</td>
</tr>
<tr>
<td>ASL</td>
<td>35 30 (86%)</td>
<td>38 29 (76%)</td>
<td>.380*</td>
</tr>
</tbody>
</table>

Values noted are either the median (with interquartile range) or number (with percentage). Y = Mann-Whitney U test, Z = Fisher’s exact test. Abbreviations: ASL = arterial spin labeling; BMI = body mass index; cART = combination antiretroviral therapy; CDC = Center for Disease Control & Prevention. NA = no or minimal symptoms; B = moderate symptoms; C = severe symptoms or (brain) AIDS; DTI = diffusion tensor imaging; FLAIR = fluid-attenuated inversion recovery; HIV = Human Immunodeficiency Virus; kg = kilogram; l = liter; m = meter; MRI = magnetic resonance imaging; * according to criteria outlined in the methods.
Table 2. Comparison of regional brain volumes, white matter damage and cerebral blood flow between PHIV adolescents and matched controls.

<table>
<thead>
<tr>
<th></th>
<th>PHIV</th>
<th>Controls</th>
<th>beta</th>
<th>95% CI</th>
<th>p</th>
<th>*BH</th>
<th>ES</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD or n(%)</td>
<td>mean ± SD or n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volumetry (l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>0.699 ± 0.06</td>
<td>0.689 ± 0.06</td>
<td>0.010</td>
<td>-0.02 to 0.04</td>
<td>.486</td>
<td>.681</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>WM</td>
<td>0.460 ± 0.05</td>
<td>0.467 ± 0.05</td>
<td>-0.008</td>
<td>-0.03 to 0.02</td>
<td>.491</td>
<td>.681</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>0.201 ± 0.05</td>
<td>0.215 ± 0.05</td>
<td>-0.007</td>
<td>-0.03 to 0.02</td>
<td>.535</td>
<td>.681</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td><strong>WM macrostructure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH (any)</td>
<td>18 (58%)</td>
<td>16 (57%)</td>
<td></td>
<td></td>
<td>.999</td>
<td>.999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume (mm&lt;sup&gt;3&lt;/sup&gt;) log</td>
<td>4.5 ± 1.5</td>
<td>3.9 ± 1.3</td>
<td>0.564</td>
<td>-0.43 to 1.56</td>
<td>.256</td>
<td>.554</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td><strong>WM microstructure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>0.40 ± 0.02</td>
<td>0.41 ± 0.02</td>
<td>-0.012</td>
<td>-0.018 to -0.005</td>
<td>&lt;.001</td>
<td>.014</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>MD (10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</td>
<td>0.80 ± 0.03</td>
<td>0.79 ± 0.03</td>
<td>0.014</td>
<td>0.005 to 0.024</td>
<td>.003</td>
<td>.014</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>RD (10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</td>
<td>0.62 ± 0.03</td>
<td>0.60 ± 0.03</td>
<td>0.02</td>
<td>0.007 to 0.03</td>
<td>.002</td>
<td>.014</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>AD (10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</td>
<td>1.17 ± 0.02</td>
<td>1.16 ± 0.02</td>
<td>0.009</td>
<td>-0.0004 to 0.024</td>
<td>.061</td>
<td>.214</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral blood flow (ratios)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>0.93 ± 0.21</td>
<td>1.00 ± 0.22</td>
<td>-0.06</td>
<td>-0.17 to 0.05</td>
<td>.277</td>
<td>.554</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>WM</td>
<td>0.21 ± 0.06</td>
<td>0.23 ± 0.07</td>
<td>-0.02</td>
<td>-0.06 to 0.01</td>
<td>.246</td>
<td>.554</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.92 ± 0.20</td>
<td>0.91 ± 0.24</td>
<td>0.007</td>
<td>-0.11 to 0.13</td>
<td>.902</td>
<td>.972</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>0.82 ± 0.19</td>
<td>0.82 ± 0.22</td>
<td>0.007</td>
<td>-0.10 to 0.11</td>
<td>.903</td>
<td>.972</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.83 ± 0.22</td>
<td>0.88 ± 0.23</td>
<td>-0.05</td>
<td>-0.18 to 0.07</td>
<td>.366</td>
<td>.641</td>
<td>.23</td>
<td></td>
</tr>
</tbody>
</table>

Values in the second and third column are either mean ± SD or number(percentage). *BH p = adjusted p value with Benjamini-Hochberg method. Any WMH presence was compared with Fisher’s exact test. Differences were assessed by performing multivariable linear regression. We adjusted all models for age and sex. WMH (any) is defined as presence of any WMH lesion. WMH volume (mm<sup>3</sup>) 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.
Table 3. Association analyses between WM microstructure and PHIV characteristics

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
<th></th>
<th>MD</th>
<th></th>
<th>RD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta (95%CI)</td>
<td>p</td>
<td>beta (95%CI)</td>
<td>p</td>
<td>beta (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>HIV VL zenith log (copies/ml)</td>
<td>0.0004</td>
<td>.873</td>
<td>-0.001</td>
<td>.630</td>
<td>-0.002</td>
<td>.590</td>
</tr>
<tr>
<td></td>
<td>(-0.005 – 0.006)</td>
<td>(-0.01 – 0.006)</td>
<td>(-0.01 – 0.006)</td>
<td>(.001 – 0.006)</td>
<td>(-0.01 – 0.006)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>CD4⁺ T-cell Z score nadir</td>
<td>0.004</td>
<td>.500</td>
<td>-0.01</td>
<td>.335</td>
<td>-0.01</td>
<td>.364</td>
</tr>
<tr>
<td></td>
<td>(-0.007 – 0.01)</td>
<td>(-0.02 – 0.01)</td>
<td>(-0.03 – 0.01)</td>
<td>(.001 – 0.006)</td>
<td>(-0.03 – 0.01)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>CDC HIV category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>-0.01</td>
<td>.274</td>
<td>0.01</td>
<td>.573</td>
<td>0.01</td>
<td>.457</td>
</tr>
<tr>
<td></td>
<td>(-0.03 – 0.01)</td>
<td>(-0.02 – 0.04)</td>
<td>(-0.02 – 0.05)</td>
<td>(.001 – 0.006)</td>
<td>(-0.02 – 0.05)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>C</td>
<td>-0.01</td>
<td>.346</td>
<td>0.01</td>
<td>.491</td>
<td>0.01</td>
<td>.450</td>
</tr>
<tr>
<td></td>
<td>(-0.03 – 0.01)</td>
<td>(-0.02 – 0.04)</td>
<td>(-0.02 – 0.05)</td>
<td>(.001 – 0.006)</td>
<td>(-0.02 – 0.05)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>Current cART use</td>
<td>0.01 (-0.02 – 0.05)</td>
<td>.372</td>
<td>-0.01 (-0.05 – 0.04)</td>
<td>.790</td>
<td>-.01 (-0.06 – 0.04)</td>
<td>.689</td>
</tr>
<tr>
<td>Undetectable VL at assessment</td>
<td>-0.003</td>
<td>.803</td>
<td>-0.005</td>
<td>.768</td>
<td>-0.002</td>
<td>.900</td>
</tr>
<tr>
<td></td>
<td>(-0.03 – 0.02)</td>
<td>(-0.04 – 0.03)</td>
<td>(-0.04 – 0.03)</td>
<td>(.001 – 0.006)</td>
<td>(-0.04 – 0.03)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>Age at treatment initiation (years)</td>
<td>0.001</td>
<td>.227</td>
<td>-0.001</td>
<td>.454</td>
<td>-0.001</td>
<td>.381</td>
</tr>
<tr>
<td></td>
<td>(-0.001 – 0.003)</td>
<td>(-0.003 – 0.001)</td>
<td>(-0.004 – 0.002)</td>
<td>(.001 – 0.006)</td>
<td>(-0.004 – 0.002)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>Duration of treatment (years)</td>
<td>-0.001</td>
<td>.230</td>
<td>0.001</td>
<td>.460</td>
<td>0.001</td>
<td>.385</td>
</tr>
<tr>
<td></td>
<td>(-0.003 – 0.001)</td>
<td>(-0.001 – 0.003)</td>
<td>(-0.002 – 0.004)</td>
<td>(.001 – 0.006)</td>
<td>(-0.002 – 0.004)</td>
<td>(.001 – 0.006)</td>
</tr>
<tr>
<td>IQ*</td>
<td>0.01 (-0.37 – 0.39)</td>
<td>.272</td>
<td>0.39 (-2.4 – 3.2)</td>
<td>.777</td>
<td>0.28 (-2.2 – 2.7)</td>
<td>.814</td>
</tr>
</tbody>
</table>

Association analyses using multivariable linear regression. We adjusted all models for age and sex. HIV viral load zenith was logarithmically transformed to approach a normal distribution. MD and RD were multiplied with 10³ for interpretation purposes of coefficients. *Despite this depiction, IQ was used as outcome variable and coefficients were multiplied with a factor 10⁵ for interpretation purposes. CDC = Center for Disease Control & Prevention; NA = no or minimal symptoms; 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.
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Brain Differences in Adolescents Living With Perinatally Acquired HIV Compared to Adoption Status Match Controls: A Cross-Sectional Study


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