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Fairly normal brain structure development in perinatally HIV-positive adolescents on long-term treatment: a longitudinal neuroimaging study

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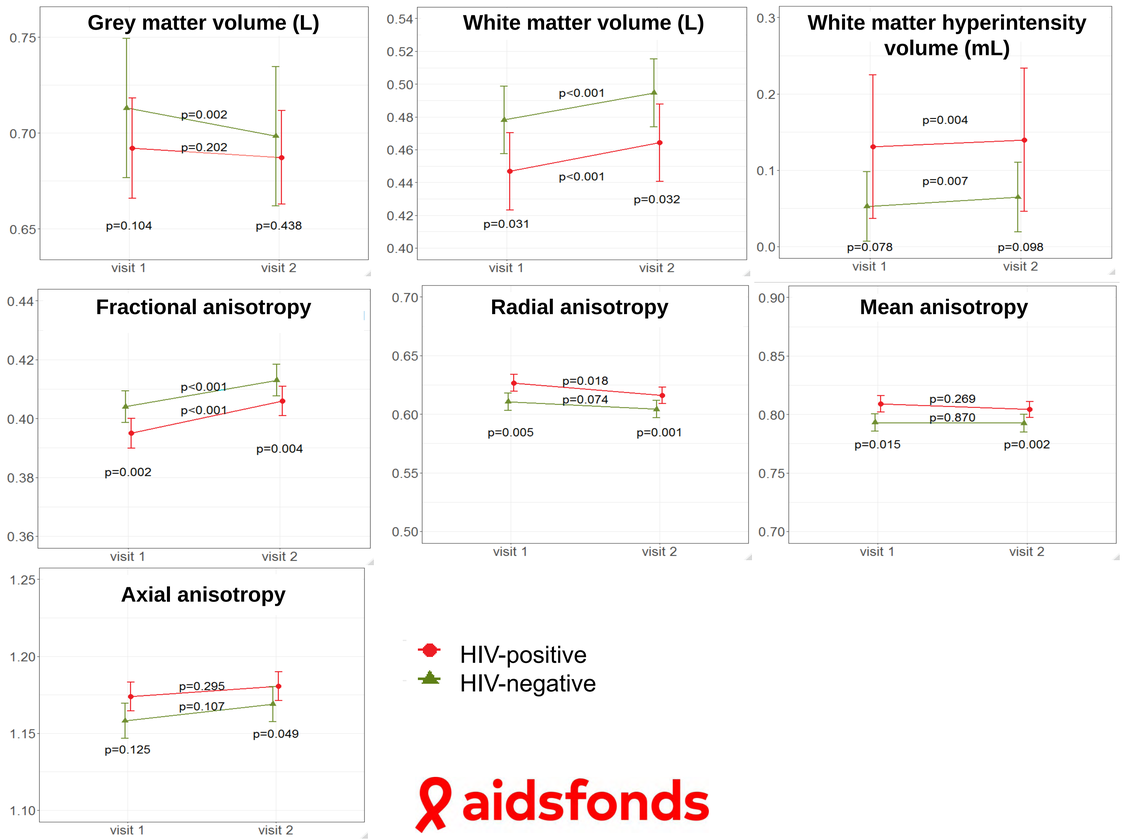
BACKGROUND

- Cross-sectional studies have revealed **lower white matter** [WM] and **grey matter** [GM] brain volumes, **more WM abnormalities** (in terms of WM hyperintensity [WMH] volume) and **poorer quality of WM** in treated PHIV-positive children.
- These differences have mainly been investigated on cross-sectional basis. This study design only provides a snapshot of the brain, and do not reveal ongoing development.
- The current study aims to answer the question whether previous found differences are subject to change over time.

METHODS

- We made use of a prospective observational cohort, **NOVICE**, in which we study neurological, visual and cognitive performance in HIV-positive children.
- At enrollment, the cohort included HIV-positive children between 8-18 years old from the outpatient department of our hospital. We recruited a group of HIV-negative controls, whom we matched for age, sex, ethnicity and socioeconomic status.
- Participants underwent advanced brain imaging, using 3 Tesla MRI. After 4-5 years of follow-up, we approached all participants to repeat brain imaging under the same conditions.
- At both time-points, we assessed **volumes of the brain**, and **the quality of the white matter.**
- For brain volumes, we assessed **GM and WM volume**, using T1-weighted MRI. Additionally, we assessed WM hyperintensities, for which we used FLAIR imaging.
- For the **quality of the white matter,** we used diffusion MRI.
- Historical data related to HIV- and ART were provided through the Dutch HIV Monitoring Foundation.
- We used linear mixed effects model analysis to analyse these outcomes, and adjusted all models for the pre-defined determinants sex and age at first MRI.

Perinatally HIV-positive adolescents appear to have normal structural brain development while using long-term therapy



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RESULTS

- We started with 31 cases and 37 controls; 20 cases and 20 controls came back for follow-up MRI. Groups were still well matched. We disregarded the data from those who did not attend follow-up.
- HIV-positive children were diagnosed at a median age of 1.5 years (IQR 0.7 – 4.1) and received cART for a median duration of 15.0 years (12.3 – 19.6). They had started cART at a median age of 2.5 years (1.2 – 4.3).
- We found a significant group-by-time interaction of GM volume (adjusted beta coefficient 0.010 L, 95% CI -0.001 to 0.020, p=0.078). Other group-by-time interactions were not statistically different between groups.
- The rate of GM decline was not associated with cognitive outcomes (p>0.149), nor with any historical HIV- and cART related factors (p>0.186).

CONCLUSIONS

- We found no large differences in brain development between positive adolescents and healthy controls over 4-5y of follow-up. Although differences persist, they do not appear to get worse over time.
- However, we do see a slower rate of the normal process of grey matter decline in HIV-positive children. We found no associations with disease markers; this needs to be further investigated.
- **In general, these outcomes suggest that brain development is broadly speaking stable while adolescents are using long-term treatment, and suggest that existing brain differences originate early in life.**
- Although follow-up was high, we realized that the relative small number of patients and controls may mean that we do not detect all differences.

ADDITIONAL KEY INFORMATION

We are very grateful to all participants of this study.

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