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INTRODUCTION & OBJECTIVES

- Access to newer and more effective antiretroviral drugs for use in pregnancy have contributed to reduced vertical transmission of HIV, resulting in a growing population of children who are HIV-exposed and uninfected (CHEU).
- Volumes of the basal ganglia (caudate and putamen) have been shown to be reduced in CHEU in comparison to their uninfected counterparts^{1,2}.
- There is a critical need to evaluate the effect of dolutegravir (DTG) on neurodevelopmental outcomes in children given is now established as a first-line treatment for pregnant mothers in South Africa, however there is limited data available on the effect of specific ART on the developing brain.
- We aimed to use magnetic resonance imaging (MRI) to compare the brain structure in CHEU and their HIV-unexposed counterparts (CHU) with a particular focus on the differential impact of antiretroviral therapy (ART), comparing DTG- and efavirenz-based (EFV) regimens, on brain development in early childhood.

METHODS

- We collected high-resolution magnetic resonance (T1-weighted) scans of children aged 39 to 54 months from DolPHIN-2 Plus, an infant follow-up study of the completed DolPHIN-2 trial (NCT03249181).
- DolPHIN-2 was a randomized open-label trial evaluating the efficacy and safety of DTG in comparison to EFV and enrolled mothers living with untreated HIV in the 3rd trimester of pregnancy
- Global and regional brain volumes were extracted for analysis and multiple linear regression models, adjusting for age at scan, sex, and total intracranial volume, were used to investigate the effect of ART and HIV exposure on brain morphology.
- Significance threshold was $p = < 0.05$

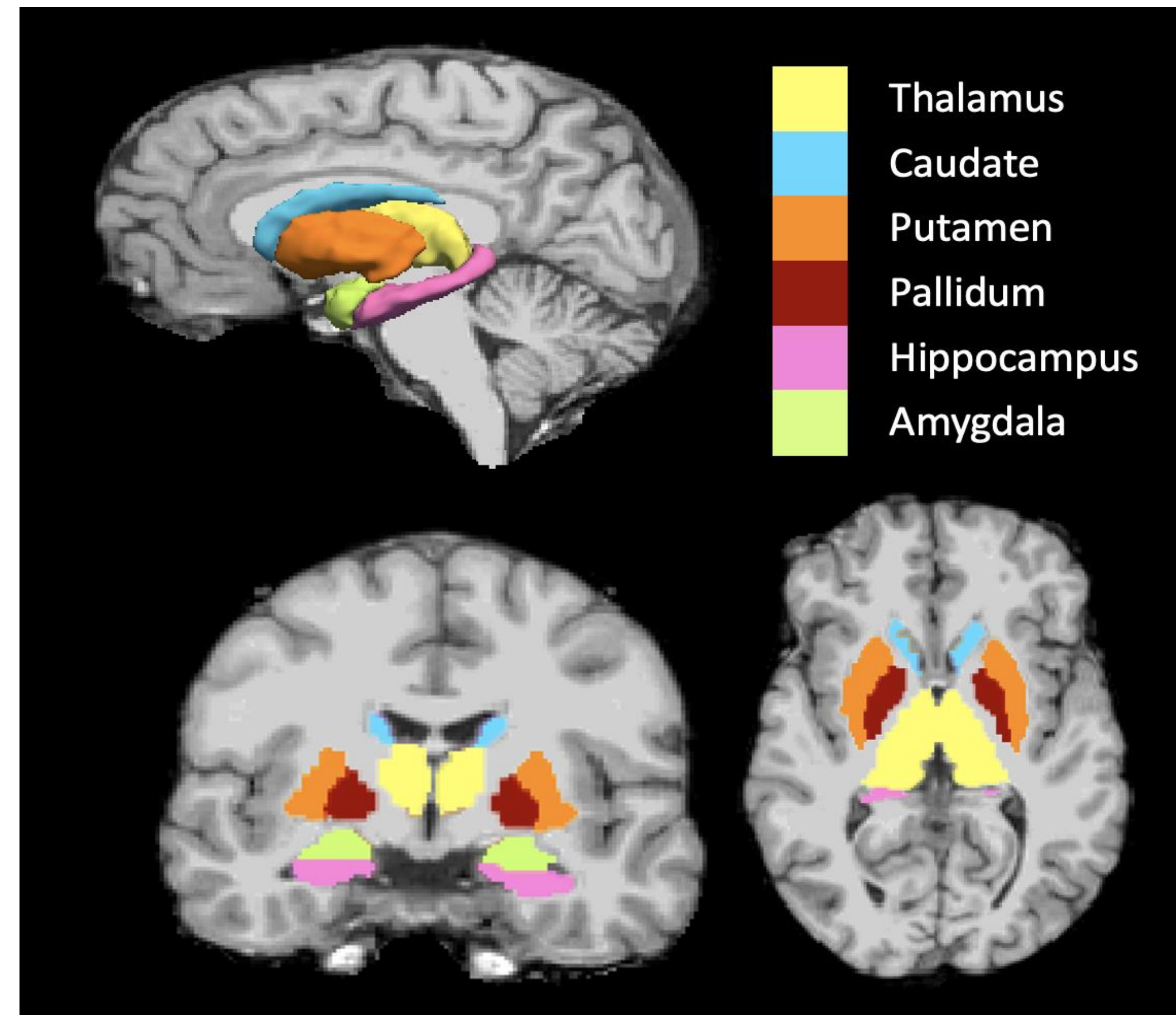


Figure 3. Subcortical regions of interest included in analysis.

No significant differences in brain volume were found in CHEU aged 3-4 years born to mothers receiving dolutegravir versus efavirenz-based ART

Subcortical Brain Volumes of CHU exposed to DTG vs. EFV

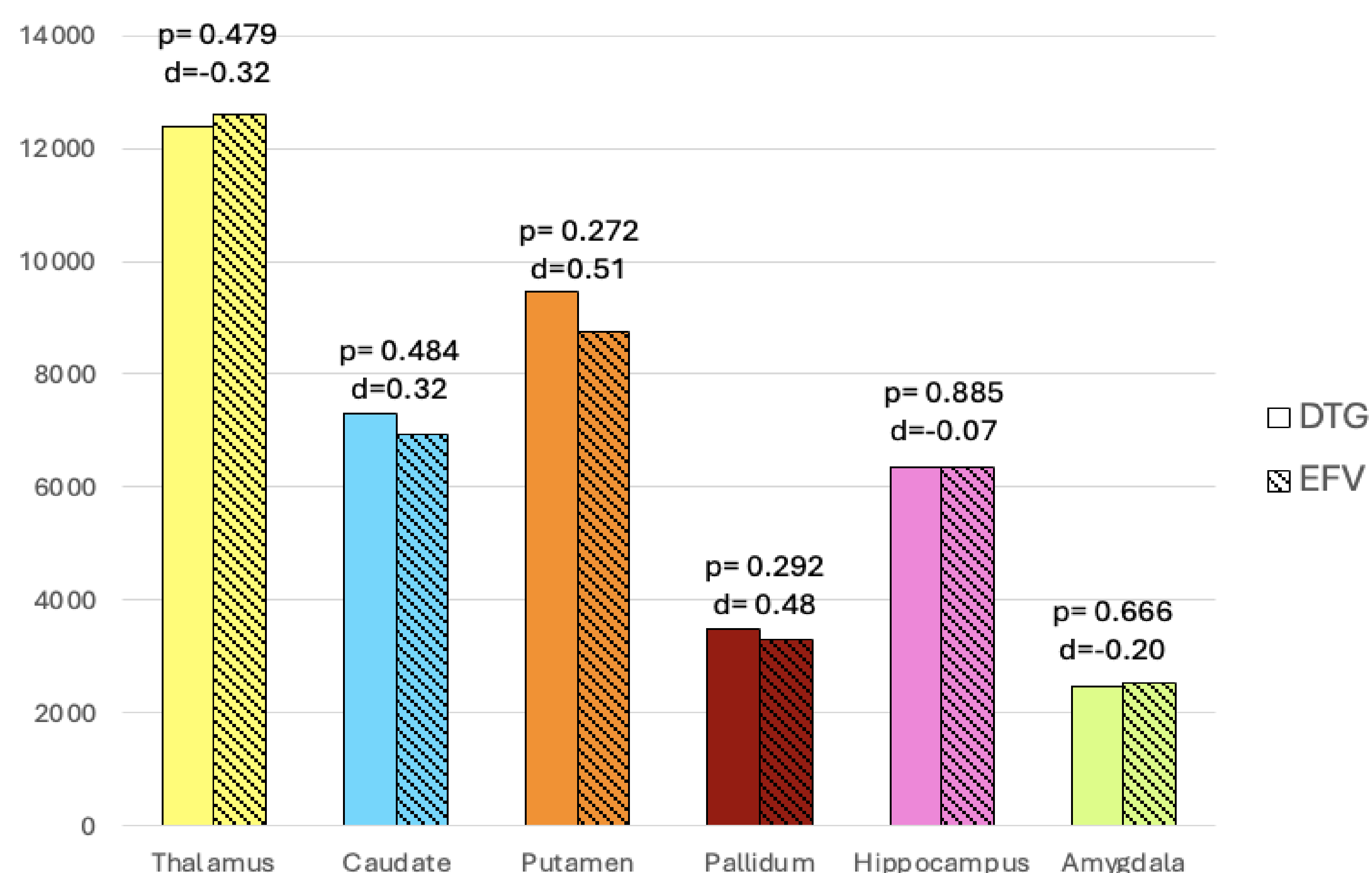


Figure 2. Mean subcortical brain volumes with adjusted p-values and Cohen's d effect size in CHEU exposed to DTG vs. EFV.

RESULTS

- Between 2021 and 2023, 25 CHEU born in the DolPHIN-2 trial were enrolled and scanned at 3-4 years along with 33 CHU. Demographic characteristics were similar for CHEU vs CHU and DTG vs. EFV (Table 1).
- Maternal CD4 count at enrolment was lower in the DTG group ($p=0.039$). In the DTG group, 11 mothers (84.6%) had a detectable viral load (≥ 50 copies/ml) at enrolment prior to ART initiation versus 2 (15.4%) at delivery. In the EFV group, 12 mothers (100%) had a detectable viral load at enrolment versus 4 (33.3%) at delivery.
- In unadjusted and adjusted analyses, ART exposure showed no association with total grey matter (adjusted $p=0.861$, effect size [Cohen's d] = -0.08) or cerebral white matter ($p=0.158$, $d=0.66$), although there were larger absolute mean subcortical volumes in several subcortical regions including the caudate, putamen and pallidum in the DTG group (Figure 2). A moderate effect size was seen in the putamen ($p=0.272$, Cohen's $d=0.51$).
- Similarly, there was no significant association between HIV exposure and brain volume for total grey matter ($p=0.775$, effect size [Cohen's d] = 0.08), cerebral white matter ($p=0.703$, $d=0.10$) or subcortical regions.

CONCLUSIONS

- Brain volumes were similar in CHEU vs CHU, and within the CHEU group, in children at 3-4 years of age in this sample.
- In this sample, the findings suggest that DTG is comparable to EFV in terms of its association with brain structure in early childhood, offering novel data on this new first-line treatment in comparison to the previously widely used efavirenz.
- Further longitudinal studies with larger sample sizes are warranted to clarify the effects of prenatal exposure of HIV and specific ART regimens on brain development

References

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Demographic Variables	CHU	CHEU		
		Total	DTG	EFV
Sample size (N)	33	25	13	12
Sex				
- Male	17 (52%)	13 (52%)	7 (54%)	6 (50%)
- Female	16 (49%)	12 (48%)	6 (46%)	6 (50%)
Mean Age (months)	47.00	45.48	45.69	45.25
Maternal Education (Completed secondary school)	14 (42%)	9 (36%)	3 (23%)	6 (50%)
Maternal Employment Status (Employed)	9 (27%)	12 (48%)	5 (39%)	7 (58%)
Maternal alcohol use during pregnancy	11 (33%)	8 (32%)	2 (15%)	6 (50%)
Maternal Depression	6 (18%)	2 (8%)	1 (8%)	1 (8%)

Table 1: Demographic characteristics of CHEU versus CHU and DTG versus EFV sample groups