Brain structure of South African HEU children exposed to dolutegravir versus efavirenz

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BACKGROUND

- Children who are HIV-exposed and uninfected (CHEU) may be at risk for neurodevelopmental delay and altered structural brain development compared to children who are HIV-unexposed (CHU).
- Factors driving this association and the potential role of specific antiretroviral regimens are poorly understood.
- Volumes of the basal ganglia (caudate and putamen) have been shown to be reduced in HEU vs HU neonates[1,2].
- There is no research published on the structural brain outcomes of children born to mothers on dolutegravir-based ART.

METHODS

- Fifty-eight children from DolPHIN-2 Plus (D2+) were included in this analysis.
- D2+ is an open-label follow-up to the DolPHIN-2 trial (NCT03249181) in which mothers were enrolled in the third trimester of pregnancy, prior to ART initiation.
- Participants had high-resolution T1-weighted MRI at 3T.
- Total cortical grey matter, white matter and subcortical grey matter volumes were compared between CHEU and CHU groups using linear regression adjusting for age, sex, maternal education and total intracranial volume, and additionally CD4 in the dolutegravir (DTG) vs efavirenz (EFV) group.
- Within the CHEU group, brain volumes were compared between children who were born to mothers who received DTG and EFV-based ART.
- Significance threshold was p= < 0.05

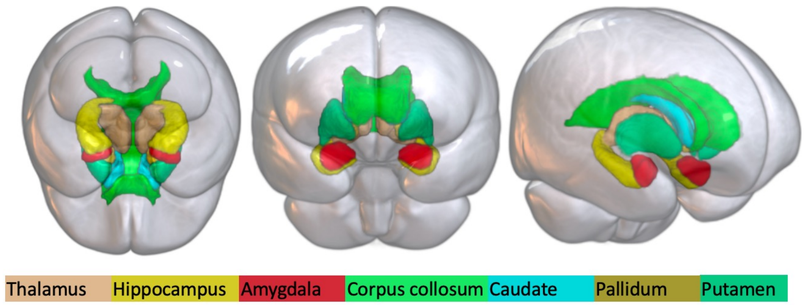


Figure 1: Subcortical brain structures included in analyses

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

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=0.043). In the DTG group, 12 mothers (92.3%) had a detectable viral load (≥40 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 6 (50%) at delivery.
- In unadjusted and adjusted analyses, there was no evidence for an effect of HIV exposure on total grey matter (adjusted p=0.833, β = 0.01), subcortical grey matter (p=0.467, β =-0.07), or cerebral white matter (p=0.837, β =0.02), although there were smaller absolute mean volumes in several subcortical regions including the corpus collosum, caudate, putamen, pallidum, hippocampus and amygdala in CHEU compared to CHU (Figure 1).
- Similarly, ART exposure showed no association with total grey matter (adjusted p=0.459, β =0.06), subcortical grey matter (p=0.7, β =-0.07), or cerebral white matter (p= 0.196, β =-0.16), although there were larger absolute mean subcortical volumes in the corpus collosum, caudate, putamen and pallidum in the DTG compared to EFV groups (Figure 2). The largest adjusted effect size was seen in the putamen (p=0.332, β =0.23).

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.
- These are the first data comparing brain volumes in HEU children born to mothers receiving DTG- versus EFV-based ART in pregnancy.
- While there were no differences by ART regimen in this small sample, larger absolute mean subcortical volumes, particularly in basal ganglia regions, in DTG-exposed children in this requires further investigation
- Next steps will include developmental outcomes and how this relates to neuroimaging findings

Demographic Variables	CHU	CHEU		
		Total	DTG	EFV
Sample size (N)	33	25	13	12
Sex - Male - Female	 17 (52%) 16 (49%)	 13 (52%) 12 (48%)	 7 (54%) 6 (46.%)	 6 (50%) 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 vs CHU and DTG vs EFV sample groups

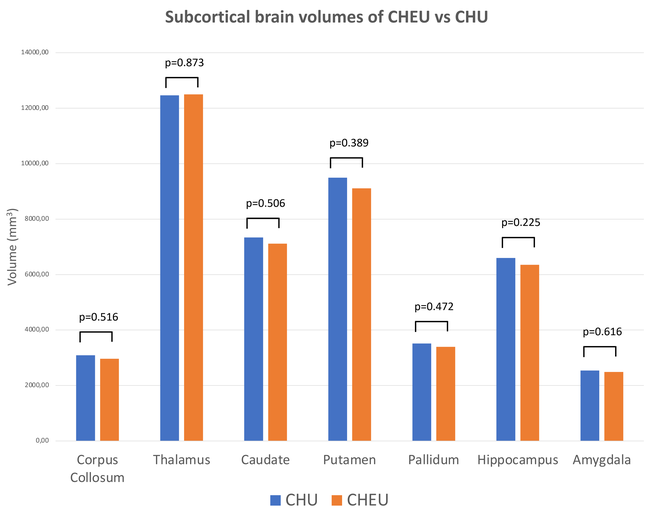


Figure 1: Mean subcortical brain volumes and adjusted p-values in CHEU vs CHU

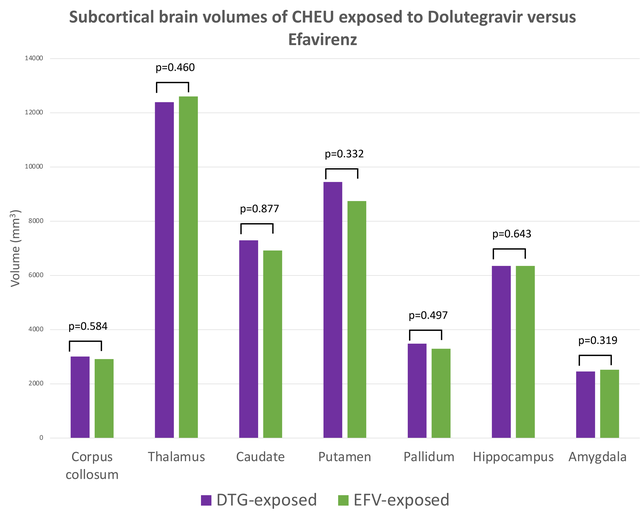


Figure 2: Mean subcortical brain volumes and adjusted p-values in DTG vs EFV

References:

1. Wedderburn CJ, Groenewold NA, Roos A, et al. Early structural brain development in infants exposed to HIV and antiretroviral therapy in utero in a South African birth cohort. *J Int Aids Soc* 2022; **25**(1)
2. Ibrahim A, Warton FL, Fry S, et al. Maternal ART throughout gestation prevents caudate volume reductions in neonates who are HIV exposed but uninfected. *Front Neurosci* 2023; **17**: 1085589.

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