Neurodevelopment in Children Exposed In Utero to Dolutegravir- or Efavirenz-Based ART in Botswana

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BACKGROUND

Little is known about the impact of *in utero* exposure to dolutegravir (DTG)- or efavirenz (EFV)-based ART on child neurodevelopmental (ND) outcomes.

METHODS

Recruitment: We prospectively enrolled 3 cohorts of 2-year-old children with differing prior *in utero* exposures: HIV-exposed/uninfected (HEU)/DTG-exposed, HEU/EFV-exposed, and HIV-unexposed/uninfected (HUU), from 3/2021-5/2023.

Measures:

- Administered by trained staff at 23-25 months of child age
- Bayley Scales of Infant & Toddler Development, 3rd Ed. (BSID-III)
- Behavior Rating Inventory of Executive Function-Preschool, Short Form (BRIEF-P-SF)
- Caregiver Reported Early Development Instruments (CREDI; Short, Social-Emotional).

Analysis Plan: ND outcomes were compared between groups using GEE models to account for twins, and adjusting for enrollment site, child sex/age at testing, maternal age/education/marital status/income, food insecurity (and for DTG vs EFV comparisons, breastfeeding and timing of first *in utero* ART exposure). Children were classified "at risk" if they scored ≥1SD below the mean or were unable to complete the BSID-III for reasons other than illness, lack of time, or other extrinsic factor.

RESULTS

	HEU/DTG (n=202)	HEU/EFV (n=202)	HUU (n=160)
Age at assmt (months), mean (SD)	25.6 (1.2)	25.7 (1.3)	25.8 (1.3)
Sex, n (%)			
Female	88 (44%)	101 (50%)	87 (54%)
Male	114 (56%)	101 (50%)	73 (46%)
ART initiation timing, n (%)			
Conception/1st trimester	179 (89%)	183 (91%)	-
2nd/3rd trimester	23 (11%)	19 (9%)	-
EGA, mean (SD)	38.5 (2.6)/103	39.4 (3.3)/109	38.5 (2.6)/100
Birth weight, mean (SD)	3086.6 (612.1)	3026.1 (547.3)	3000.5 (510.8)
Preterm (per EGA or birth weight), n (%)	27 (13%)	37 (18%)	28 (18%)
Preterm per EGA, n (%)	11 (11%)/103	17 (16%)/109	15 (15%)/100
Ever breastfed, n (%)	91 (45%)	85 (42%)	154 (96%)
Primary caregiver: mother, n (%)	154 (76%)	157 (78%)	127 (79%)
Maternal characteristics, n (%)			
Education (≤ Jr. secondary)	114 (57%)	125 (63%)	61 (38%)
Marital status (married/cohab)	70 (35%)	93 (47%)	78 (79%)
Income (none/<$40/month)	92 (46%)	91 (46%)	94 (59%)
Food insecurity (any household member skip meals bc not enough food)	52 (26%)	54 (27%)	29 (18%)

In utero **DTG-based ART exposure** is associated with **better** neurodevelopmental outcomes at 2-years compared with EFV-based ART. Longer-term follow-up is indicated.

HEU vs HUU:

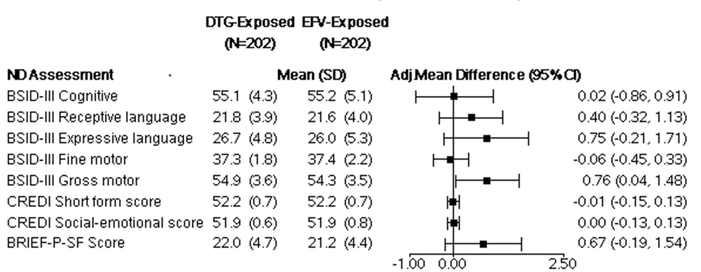
- Children in the HEU group were more likely than those in the HUU group to be classified "at risk" on the BSID-III Expressive Language domain in both unadjusted (13.0% vs. 7.0%, RR=1.89 (1.02, 3.53)) and adjusted analyses (aRR = 2.06 (1.05, 4.03)). Rates of "at risk" classification were otherwise similar across HEU and HUU groups.

	Unadjusted			Adjusted	
	HEU scores (N=404)	HUU scores (N=160)	Estimated mean difference (95% CI)	p-value	Estimated mean difference (95% CI)	p-value
BSID-III Cognitive	55.1 (4.7)	55.5 (4.5)	-0.40 (-1.25, 0.43)	0.34	-0.23 (-1.13, 0.67)	0.62
BSID-III Rec language	21.7 (3.9)	21.9 (4.0)	-0.24 (-0.97, 0.50)	0.53	0.04 (-0.75, 0.84)	0.92
BSID-III Exp language	26.3 (5.1)	27.5 (4.5)	**-1.15 (-2.02, -0.27)**	**0.010**	-0.80 (-1.81, 0.20)	0.12
BSID-III Fine motor	37.3 (2.0)	37.6 (2.0)	-0.26 (-0.62, 0.11)	0.17	-0.11 (-0.49, 0.28)	0.58
BSID-III Gross motor	**54.6 (3.6)**	**55.6 (4.3)**	**-0.93 (-1.69, -0.17)**	**0.017**	**-0.87 (-1.72, -0.01)**	**0.046**
CREDI Short Form	52.2 (0.7)	52.3 (0.6)	-0.04 (-0.17, 0.08)	0.52	0.02 (-0.12, 0.16)	0.80
CREDI Social-Emotional	51.9 (0.7)	51.8 (0.6)	0.07 (-0.05, 0.18)	0.26	0.09 (-0.04, 0.22)	0.16
BRIEF-P-SF	21.6 (4.6)	22.3 (4.5)	-0.73 (-1.56, 0.10)	0.085	-0.57 (-1.43, 0.29)	0.19

DTG vs EFV:

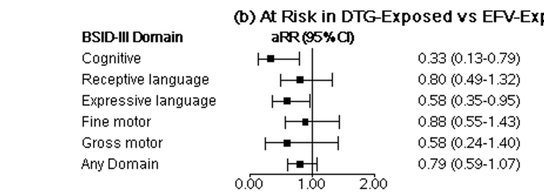
- Mean BSID-III Gross Motor scores were lower among children who were EFV-exposed vs DTG-exposed.

(a) Mean ND Outcomes in DTG-Exposed vs EFV-Exposed



DTG vs EFV *(continued)*:

(b) At Risk in DTG-Exposed vs EFV-Exposed



- Children in the EFV group were more likely than those in the DTG group to be classified "at risk" on the BSID-III Cognitive and Expressive Language domains.

EFV (vs HUU):

- Lower mean Expressive Language scores (adj estd mean diff = -1.28)
- Slightly fewer parent-report executive function problems (adj estd mean diff = -1.03)
- Greater relative risk of "at risk" Expressive Language classification (aRR = 2.11 (1.02, 4.38))

DTG (vs HUU): no significant differences

CONCLUSIONS

Two-year ND outcomes among HEU and HUU children were mostly comparable. However, HEU status was associated with a higher risk of adverse expressive language outcomes.

Children exposed *in utero* to EFV-based ART were at higher risk of adverse cognitive and expressive language outcomes than those exposed to DTG-based ART. We also observed lower mean scores in the gross motor domain for children in the EFV- (vs DTG)-based ART group, but these differences were small and of unclear clinical significance. **Children exposed to DTG-based ART performed comparably to children HUU on all ND measures.**

Longer-term ND follow-up is needed to examine the possibility of increased ND burden as children who are HEU-/ART-exposed enter school-age.

ACKNOWLEDGEMENTS: Funding for this study was provided by NIH/NIMH 5R01MH121191. The authors thank the children and caregivers who participated in this study and the entire Motheo Study team.

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